Abstracts

International Academy of Cardiology
Annual Scientific Sessions 2014
19th World Congress on Heart Disease

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Each abstract was graded by at least nine expert reviewers. Acceptance for presentation was based on the average score of all reviewers. A large number of excellent contributions were received and we thank both contributors and reviewers for their support, interest and effort.

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NEW INSIGHTS INTO THE PATHOGENESIS AND TREATMENT OF CARDIOMYOPATHIES

001
THE INTERACTIVE ROLE OF CYTOKINES IN CARDIOMYOCYTE SURVIVAL
P.K. Singal
Institute of Cardiovascular Sciences, St. Boniface Hospital Research Centre, Faculty of Medicine, University of Manitoba, Winnipeg, Canada

Heart failure subsequent to myocardial infarction is associated with an increase in tumor necrosis factor-alpha (TNF-alpha) and a decrease in interleukin-10 (IL-10). In isolated cardiomyocytes, IL-10 has been shown to antagonize the pro-apoptotic effect of TNF-alpha. Although the anti-apoptotic action of IL-10 in cardiomyocytes is now generally accepted, its molecular basis is not yet well understood. We studied the role of Toll-like Receptor 4 (TLR4) and its downstream signals in the survival of adult cardiomyocytes in the presence of IL-10. In IL-10 stimulated cardiomyocytes, TLR4 expression followed the upregulation of myeloid differentiation primary gene 88 (MyD88). Its activation led to IRF3 dimerization and phosphorylation which augmented IL-1beta translatinal activity. Degradation of Ikk suggested that IkkB is an activating kinase for IRF3-regulated NF-kB activation and its nuclear translocation. There was an activation of Bcl-xL which attenuated the proteolytic activity of Caspase3 and PARP cleavage. Inhibition of MyD88 modulated IL-10 induced expression of TLR4, IRF3-dependent IL-1beta production and NFkB p65 phosphorylation and translocation. There was a significant decrease in Bcl-xL expression leading to PARP cleavage. These data suggest that anti-apoptotic function of IL-10 through TLR4 activation, requires MyD88 activation for the cardiomyocyte survival signal. (Supported by CIHR.)
NEW INSIGHTS INTO THE PATHOGENESIS AND TREATMENT OF CARDIOMYOPATHIES

002
MITOCHONDRIAL DIVISION/MITOPHAGY INHIBITOR (MDIVI) AMELIORATES PRESSURE OVERLOAD INDUCED HEART FAILURE
S.C. Tyagi
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We have previously reported the role of anti-angiogenic factors in inducing the transition from compensatory cardiac hypertrophy to heart failure and the significance of MMP-9 and TIMP-3 in promoting this process during pressure overload hemodynamic stress. Several studies reported the evidence of cardiac autophagy, involving removal of cellular organelles like mitochondria (mitophagy), peroxisomes etc., in the pathogenesis of heart failure. However, little is known regarding the therapeutic role of mitochondrial division inhibitor (Mdivi) in the pressure overload induced heart failure. We hypothesize that treatment with mitochondrial division inhibitor (Mdivi) inhibits abnormal mitophagy in a pressure overload heart and thus ameliorates heart failure condition.

Materials and Methods: To verify this, ascending aortic banding was done in wild type mice to create pressure overload induced heart failure and then treated with Mdivi and compared with vehicle treated controls.

Results: Expression of MMP-2, vascular endothelial growth factor, CD31, was increased, while expression of anti angiogenic factors like endostatin and angiostatin along with MMP-9, TIMP-3 was reduced in Mdivi treated AB 8 weeks mice compared to vehicle treated controls. Expression of mitophagy markers like LC3 and p62 was decreased in Mdivi treated mice compared to controls. Cardiac functional status assessed by echocardiography showed improvement and there is also a decrease in the deposition of fibrosis in Mdivi treated mice compared to controls.

Conclusion: Above results suggest that Mdivi inhibits the abnormal cardiac mitophagy response during sustained pressure overload stress and propose the novel therapeutic role of Mdivi in ameliorating heart failure.
NEW INSIGHTS INTO THE PATHOGENESIS AND TREATMENT OF CARDIOMYOPATHIES

003

IMPROVING ENERGY SUPPLY TO MEND A SICK HEART?
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Substrate supply to the heart plays an essential role in maintaining cardiac performance. Perturbations in energy metabolism have been linked to pathological cardiac hypertrophy and failure. However, our understanding of the regulation of substrate utilization in the adult heart remains poor. Liver X Receptors (LXRα and β) are members of the nuclear receptor superfamily that play roles in transcriptional regulation of lipid and cholesterol metabolism. Our previous study showed that LXRα is a negative regulator of cardiac hypertrophy via its anti-inflammatory effect. However, it remains unclear if LXRα may protect the heart through transcriptional regulation of myocardial energy supply. The current study on a mouse line of tamoxifen inducible, cardiomyocyte-restricted knockout of the LXRα further uncovers the essential role of this nuclear receptor in the cardiac pathophysiology via regulating energy metabolism. LXRα deficiency in adult hearts led to cardiac dysfunction and myocardial hypertrophic remodeling. Moreover, LXRα deficiency in cardiomyocytes attenuated expression of genes for fatty acid and glucose metabolism, and cholesterol efflux. Consequently, LXRα deficiency perturbed myocardial energy metabolism and mitochondrial oxidative function due to diminished fatty acid and glucose utilization, elevated cholesterol, and especially mitochondrial membrane cholesterol content. As a result, LXRα deficient hearts showed increased cell death, and subsequent cardiac hypertrophy and remodeling. Interestingly, endoplasmic reticulum (ER) stress and autophagic flux were upregulated, preventing the LXRα deficient heart from further pathological development. On the other hand, treatment of T1317, a dual ligand, not only activates LXRα but also LXRβ, could at least partially rescue the above metabolic defects in cultured cardiomyocytes from LXRα deficient hearts. Therefore, these results indicate that LXRα plays an essential role in the heart for fuel utilization and cholesterol efflux. Cardiac selective LXRα activation may help improve energy substrate supply to the heart and rescue cardiac function.
NEW INSIGHTS INTO THE PATHOGENESIS AND TREATMENT OF CARDIOMYOPATHIES

004  
EFFECTS OF LONG-TERM THERAPY WITH BENDAVIA (MTP-131), A NOVEL MITOCHONDRIA-TARGETING PEPTIDE, ON SKELETAL MUSCLE FIBER TYPE COMPOSITION IN DOGS WITH CHRONIC HEART FAILURE  

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Background: Chronic heart failure (HF) is associated with a shift in skeletal muscle (SM) fiber type composition manifested by a decline in the number of aerobic, slow-twitch, fatigue-resistant type-1 fibers and an increase in the number of glycolytic, fast-twitch type-2 fibers. This adaptation may be responsible, in part, for the exercise intolerance that characterizes the HF state. Previous studies in rats with HF showed a decrease in SM citrate synthase activity and SM mitochondrial respiration without changes in SM capillary density and fiber bundle diameter, findings indicative of SM mitochondrial dysfunction in HF. Bendavia (MTP-131), a novel, first in class, mitochondria-targeting peptide, improves LV systolic function in dogs with chronic HF and has been shown to restores ATP synthesis in multiple organs in other animal models of disease. In aging mice, Bendavia was shown to improve SM mitochondrial ATP synthesis and phosphocreatine (PCr) to ATP ratio. We tested the hypothesis that long-term therapy with Bendavia can reverse the maladaptive SM fiber type shift in dogs with chronic HF.

Methods: Studies were performed in triceps SM samples of 14 HF dogs produced by intracoronary microembolizations (LV ejection fraction ~30%) and from 9 normal dogs. HF dogs were randomized to 3 months therapy with subcutaneous injections of Bendavia (0.5 mg/kg once daily, n=7) or saline (Control, n=7). SM type-1 and -2 fibers were differentiated histologically by myofibrillar adenosine triphosphatase staining.

Results: The proportion of SM type-1 fibers was lower and type-2 fibers higher in HF-Controls compared to normals. Treatment with Bendavia restored a near normal fiber type composition. There were no differences in fiber CSA among study groups.

Conclusions: Therapy with Bendavia reverses abnormalities of SM fiber type without influencing SM CSA. Reversal of this SM maladaptations following therapy with Bendavia can lead to improved exercise tolerance in HF.
NEW INSIGHTS INTO THE PATHOGENESIS AND TREATMENT OF CARDIOMYOPATHIES

005
ROLE OF OXIDATIVE PROTEIN MODIFICATIONS IN REGULATING KINASE PATHWAYS IN HEART FAILURE: ROLE IN THERAPY
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Background: Emerging evidence suggests that oxidative posttranslational modifications (Ox-PTMs) may work in concert with phosphorylation to determine the ultimate biological outcome and cell phenotype. In this context, it seems that cross-talk between PTMs represent a complex regulatory network with characteristics of a dynamic code. Recently, we showed that glycogen synthase kinase 3 beta (GSK3beta) is involved in modulating the myofilament contractility via novel phosphorylation in cardiac resynchronization therapy (CRT) which is sensitive to redox.

Objectives: To explore the cross-talk between protein cysteine oxidative modifications and protein kinase network. Specifically, we investigate how NO through s-nitrosylation (SNO) of GSK3beta to regulate its activity and how this will influence the cardiovascular disease progression and therapy.

Methods and results: Treatment of isolated rat heart myofilament and HEK293 cells with 100 microM GSNO and CysNO, respectively, induces SNO of GSK3beta by biotin switch assay. Mass spectrometry identified SNO of GSK3beta at multiple sites including Cys76, 199 and 317. SNO of GSK3beta negatively correlated to its kinase activity as indicated by the significant drop of the phosphosylation level of its well known downstream target, glycogen synthase 1 (Gys1) in HEK293 cells. The inhibition of GSK3beta kinase activity by SNO is independent of the ser9 phosphorylation status. We tested this hypothesis in CRT and found that CRT increases SNO of GSK3beta in the t myofilament as compare to the control and dyssynchronous heart failure (DHF) dogs while CRT decrease the GSK3beta SNO level in the cytosol.

Conclusions: SNO of GSK3beta inhibit its kinase activity and this inhibition is independent from the ser9 phosphorylation pathway. NO signaling may shed light onto heart failure therapy by regulating protein kinase network.
NEW INSIGHTS INTO THE PATHOGENESIS AND TREATMENT OF CARDIOMYOPATHIES

006
MOLECULAR TARGETING OF DCM
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The E2F/Pocket protein pathway regulates cardiac growth, differentiation, and death. Modulating its activity presents intriguing possibilities for targeting cardiac disease. E2F activation leads to hypertrophy and apoptosis. We fine tuned modulation of E2F activity by suppression through E2F6. E2F6 transgenic (tg) mice develop dcm in the absence of hypertrophy. Modulation of the E2F pathway by E2F6 clearly impacted the phenotype and we investigated if and how the E2Fs may potentially integrate with beta adrenergic signals to define the hypertrophic response. Hypertrophy was induced in wt and E2F6 tg mice via delivery of isoproterenol (iso) at low or high dose. Mice were analyzed by echocardiography, and hearts were collected for biochemical and histological analysis. No difference in left ventricle (lv) mass: body weight were observed in wt and tg saline treated mice, but tg mice treated with the low dose of iso exhibited a 30% increase in lv mass while wt only display a 15% increase. Both wt and tg mice treated with the higher dose of iso exhibit 40% increases in lv mass. QPCR revealed wt mice treated with isop display an up-regulation of fetal gene program markers ANP, BNP, and &beta-MHC. Tg mice treated with saline only display an increase in fetal gene program markers, but display no further increase in response to iso. Western blot analysis revealed that beta-adrenergic receptors were decreased in wt mice treated with iso, but not in tgs. E2F6-tg mice develop dcm and heart failure in the absence of hypertrophy but are more sensitive to low dosage of iso than their wt counterparts. The increased sensitivity of tg mice to beta adrenergic stimulation may be linked to an inability to down-regulate beta receptor levels in response to iso. A unique role for E2Fs in beta adrenergic signaling is implied.
NEW INSIGHTS INTO THE PATHOGENESIS AND TREATMENT OF CARDIOMYOPATHIES

007
TRANSFOMING T3 TREATMENT OF HEART FAILURE FROM BENCH TO BEDSIDE: FINALLY, A SAFE TREATMENT/MONITORING PROTOCOL THAT SHOULD WORK!
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The idea of treating heart failure with thyroid hormones (THs) is not new. Unfortunately, cardiovascular clinical studies mostly using TH analogs at excessive doses demonstrated an increased incidence of arrhythmias and have largely deterred further studies. At the heart of the problem, no one has clearly demonstrated potential benefits using a therapeutic TH treatment/monitoring protocol that can be safely translated to humans. Over the past few years, our lab has investigated the pathophysiological consequences of low oral doses of T3 in animal models of diabetic cardiomyopathy (DM), myocardial infarction (MI), and hypertension. In each model, a T3 dose that produced mild feedback inhibition of T4 and/or TSH was used with insignificant changes in serum T3. Cardiac tissue T3 levels were depressed in untreated rats and restored to normal with T3 in all disease models. Results were remarkable. T3 prevented decline in LV function and arteriolar remodeling in DM. T3 treatment of MI dramatically improved LV systolic and diastolic function, reduced sensitivity to arrhythmia induction, increased myocyte survival, and reduced the incidence of RV hypertrophy, suggesting improved pulmonary function. One year of T3 treatment in Spontaneously Hypertensive Heart Failure rats did not affect the degree of hypertension but improved diastolic function and tended to reduce fibrosis. No adverse effects were observed in any T3 treated model. It appears that re-expression of the fetal gene program, ubiquitous in diseases leading to heart failure and also hypothyroidism, may reflect low cardiac tissue T3 levels. In conclusion, safe restoration of low cardiac T3 levels in heart diseases leading to heart failure may lead to dramatic improvement in cardiac function and remodeling. The approach employed in these studies provides a safe and effective treatment/monitoring protocol that should be easily translatable to humans.
NEW INSIGHTS INTO THE PATHOGENESIS AND TREATMENT OF CARDIOMYOPATHIES

008
DIFFERENCE IN SERUM AMYLOID A LEVELS BETWEEN PATIENTS WITH LEFT VENTRICULAR DYSFUNCTION OF ISCHEMIC AND NON ISCHEMIC ORIGIN
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The activation of the immune response in heart failure and myocardial infarction has already been demonstrated, even if the patterns of this activation are not well described. Therefore it is interesting the exploration and the understanding of the factors that regulate immune response at long interval of time from acute phase.

For this reason we decided to study Serum Amyloid A (SAA) as a marker of acute phase, already demonstrated as elevated in acute myocardial infarction, also in chronic patients.

We have studied a group of patients, 25 subjects (20 males and 5 females), mean age 61 years (SD 9) with left ventricular dysfunction caused by different cardiac disorders: 9 patients with LV dysfunction of non-ischemic origin; 8 patients with LV dysfunction of ischemic origin; 8 patients with acute myocardial infarction (AMI).

The levels of SAA were analysed (Siemens Health Care Diagnostics- immunonephelometric assay; reference range: 1-10 mg/L, from manufacturer), and statistical analysis performed for groups.

The results have been the following: there were statistically significant differences in the levels of SAA between non ischemic and chronic ischemic and AMI patients while the difference between chronic ischemic and AMI patients was not significant.

There were no statistically significant differences among groups for NYHA class nor for ejection fraction of the left ventricle, measured by Simpson formula on 2D echo. Table 1, Figure 1.

Table 1. Mann Whitney test for groups.

<table>
<thead>
<tr>
<th>PATIENTS</th>
<th>N</th>
<th>SAA level Mean (mg/L); SD</th>
<th>SAA level Median (mg/L)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-ischemic</td>
<td>9</td>
<td>12,24; 17,37</td>
<td>5,06</td>
<td>vs Ischemic chronic p=0,013 vs AMI p=0,027</td>
</tr>
<tr>
<td>Ischemic-chronic</td>
<td>8</td>
<td>125,07; 223,33</td>
<td>33,5</td>
<td>vs AMI p=ns</td>
</tr>
<tr>
<td>AMI</td>
<td>8</td>
<td>104,85; 113,77</td>
<td>47,5</td>
<td>vs ischemic chronic p=ns</td>
</tr>
</tbody>
</table>

Figure 1. Levels of SAA in studied groups (Non ischemic –NON ISCH; Ischemic chronic –ISCH; AMI).
Echocardiography has today become the most widely used technique in the noninvasive assessment of cardiac disease entities. It began in the fifties and sixties as A-mode and M-mode echocardiography in which a pencil-thin ultrasound beam was sent to the heart by placing a small transducer on the chest wall and images of very small portions of cardiac structures were obtained at any given time. Subsequently, in the seventies echo transducers were developed which moved the ultrasound beam rapidly so that more than one cardiac structure could be visualized simultaneously. This development of real time two-dimensional echocardiography revolutionized the field of cardiac imaging and with further development of conventional and color Doppler resulted in echocardiography becoming the most cost effective noninvasive imaging modality for the assessment of various cardiovascular lesions in both adult and pediatric patients. Subsequently, contrast, stress and transesophageal echocardiographic techniques added new dimensions by supplementing information provided by conventional two-dimensional echocardiography. Live/real time three-dimensional transthoracic and transesophageal echocardiography represent more recent advances that are further changing the clinical practice of cardiology. They provide a valuable adjunct to the two-dimensional technique because of their ability to view cardiac structures in three dimensions. They are beginning to be used extensively in the cardiac catheterization laboratory for percutaneous interventional procedures and in the intraoperative setting for valvular and congenital heart disease. Three-dimensional speckle tracking echocardiography has also been developed and has provided new insights in the assessment of systolic as well as diastolic ventricular function.
ADVANCES IN CARDIOVASCULAR IMAGING

010
PRESENT AND FUTURE OF NUCLEAR CARDIOLOGY AND CARDIAC CT IN CAD: VALUE-BASED IMAGING

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The future use SPECT or PET, and cardiac CT will be based on their providing value by improving quality (e.g., reducing events) or decreasing costs. For prevention, coronary calcium scanning can provide value, guiding management more effectively than risk factors or other biomarkers. In patients with suspected CAD, CCTA is emerging as a potential first test of choice, based on its high sensitivity and specificity and strong prognostic value. In patients with acute chest pain, four randomized clinical trials have demonstrated that CCTA reduces time to diagnosis and safely increases rates of discharge from the emergency department, while saving or not increasing cost. In patients with known CAD or with extensive coronary calcification, CCTA is less useful, and SPECT myocardial perfusion imaging (MPI) has been shown to reduce admissions and costs. In the patient with stable symptoms and a low-intermediate likelihood of CAD, CCTA is playing an increasing role as the first diagnostic test. A normal CCTA examination has a “warranty” of at least 7 years, with almost no cardiac deaths over this period. While management of the patient with normal, non-obstructive or critically obstructed proximal vessels is clear, management of patients with lower-risk stenosis is not. In patients with a low-intermediate likelihood of CAD, CCTA likely will reduce costs with little effect on outcomes. In patients with a high likelihood of CAD, anatomic assessment by CCTA may be associated with increased costs and little effect on outcomes, thus not providing value. SPECT and PET MPI are most likely to have value in patients with a high likelihood of CAD, by decreasing revascularization in patients with no/minimal ischemia; however, in patients with low-intermediate/intermediate likelihood of CAD, MPI tests will likely increase costs and not affect outcomes. With both modalities, combined anatomic/physiologic assessment will expand their value and decrease layered testing.
STRESS-ONLY IMAGING; A NEW PARADIGM FOR PERFORMING STRESS MYOCARDIAL PERFUSION IMAGING

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Background: There have been continued efforts over the past several years to utilize a patient-centered imaging approach when performing stress myocardial perfusion imaging (MPI). One such approach has been to choose a single day stress/rest imaging strategy so that if the stress study is normal, rest imaging is unnecessary. By performing so-called “stress-only imaging”, radiation exposure to the patient can be markedly reduced by avoiding the higher rest radiopharmaceutical dose. In addition stress-only imaging affords improved laboratory efficiency, conservation of Tc-99m radiotracers, convenience for the patient and reduction in cost by eliminating the higher rest radiotracer dose.

Methods/Results: Several recent studies have determined the safety of stress-only imaging. In a study by our group, 16,854 patients with a normal stress MPI were followed for a median of 4.5 years with the primary endpoint of all-cause mortality. Event rates were similar in those who underwent stress-only (n=8,034) vs. stress-rest (n=8,820) MPI, and irrespective of gender, coronary artery disease status, stressor utilized or history of diabetes mellitus. In addition 60% of subjects received < 5mSv radiation dose with stress-only imaging. Similar findings were observed by Duvall et al. In a recent randomized study, we compared cardiac computed tomography (CTA) to stress MPI in low to intermediate risk patients evaluated in the emergency department with chest pain of uncertain cardiac etiology. By utilizing stress-only imaging, radiation exposure was significantly less with MPI vs. CTA (10.9+ 4.4 vs. 12.7+4.9mSv, p<0.001) with no difference in hospital cost, time to diagnosis or diagnostic accuracy.

Conclusion: A stress-rest MPI protocol affords the use of stress-only imaging which enhances patient throughput with less radiation exposure without sacrificing long term patient safety.
Angiotensin II (AII), an octapeptide member of the renin-angiotensin system (RAS), is formed by the enzyme angiotensin converting enzyme (ACE) and exerts adverse cellular effects through an interaction with its type 1 receptor (AT1R). Both ACE inhibitors and angiotensin receptor blockers (ARB) mitigate the vasoconstrictive, proliferative, proinflammatory, proapototic and profibrotic effects of AII and are widely used as effective antiremodeling agents in clinical practice. Prediction of individual response to these agents, however, remains problematic and is influenced by many factors including race, gender and genotype. In addition, systemic and tissue RAS activity do not correlate closely. Non-invasive determination of tissue ACE activity and AT1R expression using novel nuclear tracers may improve treatment of heart failure through more selective pharmacologic intervention and better dose titration of available drugs while avoiding unnecessary drug toxicity and side effects. Such imaging techniques would also be another step forward in attempts towards personalized approaches to management of advanced heart disease.
HAND HELD CARDIAC ULTRASOUND: ROLE IN CLINICAL PRACTICE

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Technologic advances have resulted in miniaturization of ultrasound systems. Battery-operated, hand-held cardiac ultrasound devices (HHCU) devices weigh less than one pound, fit into the pocket of a laboratory coat, and have been approved by the FDA for cardiac imaging. HHCU are inexpensive compared to full-size ultrasound systems and represent a growing sector of the market. HHCU do not provide zoom functions, spectral Doppler, velocity or time measurements, or electrocardiography interface, and thus, allow limited quantitative information. HHCU have been used to provide point-of-care assessment cardiac assessment in rural and remote community settings. In a health camp in India, studies were uploaded to a cloud-based web server and images reviewed and reports completed by physicians working remotely. Feasibility was excellent; the utility of HHCU in expediting care in remote areas was demonstrated. In a prospective study of 190 adults undergoing comprehensive transthoracic echocardiography, experienced sonographers performed a detailed examination with HHCU. Expert echocardiographers independently viewed images from the comprehensive transthoracic study and from HHCU and findings were compared. Concordance was good for left ventricular dimensions and chamber size. However, discordant findings were present in 27% of patients. Regional wall motion abnormalities were the most common discordance. HHCU tended to underestimate pathology. The American Society of Echocardiography has recommended that HHCU is most appropriately used as an extension of the physical examination, to address one of several specific clinical questions (e.g., is there left ventricular systolic dysfunction?), and applied when standard echocardiography is not immediately available. Training is required and HHCU must be differentiated from limited transthoracic ultrasound.

Summary: In the hands of experienced users, HHCU correlates well with standard transthoracic echocardiography for certain findings but tends to underestimate the severity of pathology. It is most appropriate as an extension of the physical examination, or when standard transthoracic echocardiography is unavailable.
ADVANCES IN CARDIOVASCULAR IMAGING

014
IMPACT OF CORONARY CT ANGIOGRAPHY ON PATIENT MANAGEMENT AND CARDIOVASCULAR OUTCOMES: HOW TO INTEGRATE TEST RESULTS IN PATIENT CARE

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Coronary computed tomography angiography (CTA) offers a non-invasive approach to visualize coronary atherosclerosis and can be used to accurately exclude the possibility of coronary stenosis. In order for this test to be used effectively, it is essential for clinicians to understand the implications of various CTA findings and how to integrate the CTA results in patient care. While patients who have no plaque or stenosis have an excellent prognosis and do not require further testing, individuals who are found to have CAD may require additional therapies or testing. Among such patients, the severity and extent of plaque can be used to inform the risk of future cardiovascular events, such as myocardial infarction or death, and provide data which is incremental to traditional risk approaches. Reflecting the increased recognition that coronary plaque is associated with increased risk, multiple studies have shown that CTA findings have a significant impact on medical management, as patients who are found to have disease are more likely to be prescribed new (or more potent) lipid lowering agents and aspirin. Importantly, even patients who have non-obstructive CAD, (the type of disease that would not be expected to result in any functional impairment to coronary flow) may have an increased risk of MI or cardiovascular death, especially if there is extensive plaque which involves multiple coronary segments. Since the presence of anatomical stenosis has a limited capacity to identify ischemia, there is concern that CTA findings may lead to excess invasive cardiac procedures. Therefore, some patients who are found to have stenosis and are being considered for coronary revascularization should first have an evaluation for ischemia. In conclusion, optimal integration of CTA test results can lead to improved patient management by targeting preventive therapies to at-risk individuals while avoiding further downstream testing in the majority of individuals tested.
ADVANCES IN CARDIOVASCULAR IMAGING

015

FUNCTIONAL AND ANATOMICAL CARDIAC IMAGING IN PATIENTS WITH CORONARY ARTERY STENTS

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Coronary artery stenting has been shown to improve myocardial function, and ameliorate angina. The number of complex interventional procedures has recently increased due to technical advances. However, myocardial perfusion may be compromised after coronary stenting by acute thrombosis or the development of fibrointimal hyperplasia leading to decline in left ventricular function and increased risk of myocardial infarction. The diagnosis of in stent stenosis is a clinically important, though a challenging task, particularly in patients with no cardiac symptoms. Although, coronary angiography is considered the golden standard, the associated risk and cost prohibits its routine use for that purpose.

Cardiac stress imaging techniques play important clinical role in evaluation of in stent stenosis and assessing adequacy of revascularization. Stress echocardiography with exercise or dobutamine is widely used and provides fair accuracy. The use of myocardial contrast agents improves accuracy and allows detection of perfusion abnormalities. Stress radionuclide imaging is widely available and accurately predicts extent of coronary artery disease. Small studies showed lower specificity shortly after stenting. Stress imaging techniques provide incremental prognostic information after coronary stenting. Stress echocardiography and radionuclide imaging are appropriately indicated in symptomatic patients and in those with incomplete revascularization. Cardiac CT angiography is highly sensitive for diagnosis of coronary artery stenosis. Average sensitivity and specificity for diagnosis of in stent stenosis in pooled data are 79% and 81% respectively. Feasibility is very limited in small (<3 mm) stents and in stents with thick struts.

In conclusion, non-invasive imaging modalities provide useful functional and anatomical information after coronary stenting. The choice of particular modality depends on recognition of advantages and limitations of each technique, and expertise with particular type of imaging.
ADVANCES IN CARDIOVASCULAR IMAGING

016
DIAGNOSTIC AND PROGNOSTIC ROLE OF NONINVASIVE CORONARY FLOW RESERVE
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Coronary flow reserve (CFR) can be abnormal into one third of patients with angiographically normal coronary arteries for (functional and/or anatomic) microvascular disease, and can be normal in up to 50% of patients with anatomically significant coronary artery stenosis. Dipyridamole has been demonstrated to be a suitable tool for dual imaging stress echocardiography. Adding CFR to regional wall motion allows us to have, in the same sitting, high specificity (regional wall motion) and a high sensitivity (coronary flow reserve) diagnostic marker, with an obvious improvement in overall diagnostic accuracy. CFR was defined as the ratio between peak diastolic flow velocity in LAD at maximal vasodilation and at rest. With the advent of CFR in the stress echo lab, a striking amount of information became available through large-scale multicenter studies, showing the impressuve prognostic value in patients with stable angina, patients with intermediate stenosis of single vessel disease, and in several other challenging subsets characterized by negative wall motion response during stress echo, such as patients with normal coronary arteries, diabetes, under antianginal therapy, dilated cardiomyopathy, hypertrophic cardiomyopathy or heart transplant. The evaluation CFR on LAD has limitations of dependence upon operator expertise and patient acoustic window, and is highly feasible only on LAD district. It has the advantage to be non-invasive, radiation-free nature also make it ideally suited for research-oriented studies, especially when each subject or patient acts as his/her own control, allowing establishment of acute or chronic changes in coronary flow reserve. At present, CFR on LAD is a feasible, useful, and prognostically validated tool to be considered with standard wall motion analysis for the “two birds with one stone” approach of dual imaging in stress echo. As such, it is currently recommended as the state-of-the art method with vasodilatory stress echo when adequate technology and expertise are available.
017
CARDIAC MAGNETIC RESONANCE IMAGING FOR CORONARY ARTERY DISEASE
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2. Cardiothoracic Centre, CCM, Monaco

Stress cardiac magnetic resonance imaging (CMR), has been shown to have excellent diagnostic accuracy for detection of significant coronary artery disease (CAD). In addition, CMR provides valuable clinical data, including details on left ventricular function, the presence of late gadolinium enhancement, and whether there is structural or valvular heart disease. As a result, stress CMR is increasingly being used to assess chest pain in patients with known or suspected CAD. CMR potentials derive from its high-spatial resolution, image contrast, lack of ionizing radiation and excellent depiction of wall motion. An essential characteristic of stress modalities is their negative prognostic value. The detection of myocardial ischemia with stress CMR is typically based on first-pass perfusion imaging, with the acquisition of high-spatial-resolution images during the injection of a bolus of a gadolinium-based contrast agent to search for inducible perfusion defects, or on wall motion abnormality imaging, based on iterative collection of cine images allowing the identification of inducible impairment of regional systolic function. Previous reports on stress CMR showed good diagnostic accuracy for the detection of significant CAD. Patients with normal stress-CMR have been reported to have a low event rate at short- and intermediate-term follow-up. Prognostic validation of stress CMR is critical because a negative stress CMR can be reassuring that the patient has a very low risk for major adverse cardiovascular events though the patients risk for cardiovascular events is intermediate or high. In the current environment of escalating medical costs, the prognostic performance of stress CMR may also help justify its use compared with more commonly used stress modalities such as stress echocardiography and stress nuclear perfusion imaging.
018
FRACTIONAL FLOW RESERVE
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University of Colorado, Aurora, CO, USA

Objectives: Understanding the technical aspects of Fractional Flow Reserve (FFR) as it applies to
daily clinical practice and its use during complex cases.

Background: FFR is a pressure derived physiologic testing that uses hyperemia to assess the
significance of a coronary lesion. FFR use in multi-vessel disease facilitates percutaneous coronary
intervention (PCI) guidance.

Methods: FFR allows for the evaluation of coronary lesions while facilitating decision making
during PCI. Moreover, its use during complex cases allows for the evaluation of ischemia and
dictates the need for further interventional needs in ostial disease, bifurcation disease, jailed side
branches and/or diffuse disease.

Conclusions: FFR is now considered the gold standard for the evaluation ischemia in coronary
disease.
019
PROGNOSTIC VALUE OF MICROVASCULAR OBSTRUCTION ON MULTIDETECTOR COMPUTED TOMOGRAPHY AFTER PRIMARY PERCUTANEOUS CORONARY INTERVENTION IN ACUTE MYOCARDIAL INFARCTION
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2. Ogaki Municipal Hospital, Ogaki, Japan
3. Nagoya University Graduate School of Medicine, Nagoya, Japan

Background: Recent research has suggested that patients with greater delayed contrast-enhanced size (as assessed by multidetector computed tomography (MDCT) without an additional contrast agent immediately after PCI) are more likely to experience adverse cardiac events and have poor prognoses over the long term. The defect area in the delayed contrast-enhanced effect indicates impaired contrast penetration, called microvascular obstruction (MVO). The outcomes of patients with MVO detected by MDCT have not been clear. We examined the clinical importance of MVO detected by delayed contrast-enhanced MDCT after percutaneous coronary intervention (PCI) in patients with acute myocardial infarction.

Methods and Results: In 80 patients with acute myocardial infarction, MDCT was performed immediately after primary PCI. We investigated the outcomes of the patients with MVO detected by MDCT. MVO was observed in 14 patients (17.5%). All 14 of these patients with MVO had a transmural infarction, and their infarct volume was significantly higher than those of the patients without MVO (n=66). During the median follow-up period of 308.5 days, the appearance of MVO was associated with the presence of slow flow/no-reflow, time from onset to reperfusion ≥6 hours, aging, smoking, chronic kidney disease, and hyper-low-density lipoprotein cholesterolemia. The incidence of major adverse cardiovascular events (MACE) was significantly higher in the patients with MVO compared to those without MVO, regardless of the myocardial infarct volume.

Conclusions: These results indicate that the presence of MVO in delayed contrast-enhanced MDCT after PCI as well as the extent of infarct area are important predictors of MACE.
NOVEL THERAPIES FOR ATHEROSCLEROSIS

020
GUIDING PRINCIPLES IN STATINS UTILIZATION: EMERGING CLINICAL AND PUBLIC HEALTH CHALLENGES
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The current totality of evidence on statins in treatment and prevention of cardiovascular disease (CVD) includes 170,000 secondary prevention and high risk primary prevention patients. Those assigned at random to a statin had statistically significant and clinically important reductions in myocardial infarction of 30%, stroke of 15%, the need for stents and coronary artery bypass grafts of 25% and coronary death of 22%. In analyses of an additional 40,000 randomized patients assigned to more or less intensive statin therapy, more intensive therapy produced incremental clinical benefits on various manifestations of CVD. The results of more recent subgroup analyses among randomized subjects with 5-year risks lower than 10% were markedly consistent with those in secondary prevention and high risk primary prevention patients. This large and robust totality of evidence provides clinicians with challenges and opportunities to more widely prescribe statins in treatment and prevention of CVD. In secondary prevention and high risk primary prevention, the challenge is to more widely prescribe statins as the first line drug of choice. In low risk primary prevention subjects previously considered ineligible, the available totality of evidence provides clinicians the opportunity to expand statin utilization. The more widespread and appropriate utilization of statins, as adjuncts, not alternatives to therapeutic lifestyle changes (TLCs), will yield net benefits even in low risk primary prevention subjects unwilling or unable to adopt TLCs. The decision to prescribe statins should be an individual clinical judgment that includes all the risk factors of the patient, not just those in any risk algorithm. Finally, following these guiding principles will lead to greater and more appropriate utilization of statins. This, in turn, will lead to greater net clinical and public health benefits in the treatment and prevention of CVD.
NOVEL THERAPIES FOR ATHEROSCLEROSIS

021
HDL AND THE HDL HYPOTHESIS: WHERE DO WE STAND NOW?
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There is robust epidemiological evidence dating back to the original Framingham Heart Study from 1977 that indicates an important inverse relationship between high-density lipoprotein cholesterol (HDL-C) and risk of incident coronary artery disease (CAD). Despite this body of scientific information demonstrating that low levels of HDL-C are an independent predictor of subsequent CAD events, multiple therapeutic attempts to raise HDL-C levels have failed to demonstrate a consistent reduction in prognostically important endpoints such as death, myocardial infarction (MI), and stroke. Recently, several major randomized trials using different therapeutic interventions have raised appropriate concerns about our basic understanding of HDL-C and whether the "HDL hypothesis" of lowering cardiovascular events through therapeutic interventions directed at raising HDL-C is a scientifically viable one. While two recent randomized controlled trials (AIM-HIGH and HPS2-THRIVE) failed to show a reduction in cardiovascular events in patients treated to optimally low levels of low-density lipoprotein cholesterol (LDL-C) at baseline with extended-release niacin on a background of simvastatin, these clinical trials studied specific populations of stable ischemic heart disease patients. The data from these two contemporary trials cannot be extrapolated to all patient populations, such as those with acute coronary syndromes or myocardial infarction or those with significant residual mixed dyslipidemia not treated with optimal doses of intensive statin therapy, as these patients were excluded by trial design in both studies. Therefore, at the present time, there is insufficient evidence from clinical trials to recommend HDL-targeted therapy for additional event reduction in CAD patients. However, we will review the relevant data from recent major trials (AIM-HIGH, HPS2-THRIVE, ILLUMINATE, and dal-OUTCOMES) and highlight the potential clinical implications of these trials in modern pharmacotherapy as it relates to HDL-C raising and potential cardiovascular event reduction.
NOVEL THERAPIES FOR ATHEROSCLEROSIS

022
TRANSLATION OF HDL FUNCTIONALITY IN CLINICAL PRACTICE

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HDL is conventionally quantified by the cholesterol cargo transported in these protein rich lipoprotein particles. In prospective population studies and clinical trials with low to moderate intensity statins, HDL cholesterol (HDL-C) is biomarker of atherosclerotic cardiovascular disease (ASCVD) risk. However, the reduced CVD risk associated with high HDL-C levels is attenuated in models that adjust for associated excess apolipoprotein (apo) B-containing lipoproteins or in trials that use high-potency statins, which are more effective in lowering apoB levels than low to moderate intensity statins. In these analyses, NMR-measured HDL particles retain their inverse association with ASCVD risk. Thus, the concentration of HDL particles is a more robust measure of ASCVD risk than the cholesterol content transported by HDL particles. HDL particles are heterogeneous in their protein (proteome) and lipid (lipidome) constituents. Small HDL particles contain proteins that contribute to the HDL functions in protecting LDL against oxidation, suppression of proinflammatory pathways, endothelial protection and repair, reduced apoptosis and reduced prothrombotic state. When the HDL particles increase in size due to increased cholesterol content, the proteome is altered resulting in atheroprotective particles. Therapeutic interventions directed at increasing HDL have been directly directed to increasing the cholesterol carried in HDL particles rather than expanding the number of HDL particles and the functionality of those particles. Future investigations into HDL therapies need to be directed towards increasing the numbers of atheroprotective HDL particles or preventing the formation of dysfunctional HDL particles. Currently, delipidation of HDL particles or infusions of apo A-I/phospholipid complexes hold the most promise to reducing HDL associated residual risk.
NOVEL THERAPIES FOR ATHEROSCLEROSIS

023
RESIDUAL VASCULAR RISK AFTER STATIN THERAPY: THE PROMISE OF NOVEL LIPOPROTEIN BIOMARKERS

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Objectives: Statins are the most widely used lipid-lowering agents and the standard of care for individuals with dyslipidemia, prior CVD, or at high-risk for CVD. However, the risk among statin-treated individuals remains high and has been termed “residual risk”. The rate of a major CVD event occurring during 5 years of follow-up among statin-treated patients in randomized clinical trials was 1 in 5 for individuals with prior CVD and 1 in 10 for those without prior CVD.

Methods and Results: The Treating to New Targets study (N=9251) showed that clinical risk factors account for a substantial proportion of residual risk in individuals with prior CVD. However, the c-index of 0.679 suggested that other factors are determinants of residual risk. In the JUPITER trial of individuals without prior CVD or diabetes who were recruited based on low LDL-cholesterol and elevated high-sensitivity C-reactive protein, we examined whether two promising lipoprotein biomarkers are significant determinants of residual risk: 1) lipoprotein(a), and 2) HDL particle number (HDL-P). In approximately 10,000 JUPITER participants with baseline and one-year levels of lipoprotein(a), on-statin concentrations were associated with residual risk (adjusted hazard ratio per 1-standard deviation: 1.27, 95% CI 1.01-1.59, p=0.04), which was independent of LDL-cholesterol and other risk factors. In another analysis from JUPITER, on-statin concentrations of HDL-P were also significant determinants (inversely) of residual risk (adjusted hazard ratio per 1-standard deviation: 0.73, 95% CI 0.57-0.93, p=0.01), stronger than the association of on-statin HDL-cholesterol (0.82, 95% CI 0.63-1.08, p=0.16) or apolipoprotein A-I (0.86, 95% CI 0.67-1.10, p=0.22) with residual risk.

Conclusions: Thus, a multi-faceted prevention approach targeting modifiable risk factors should be underscored as the cornerstone of optimal residual risk assessment and prevention. In addition, future studies are needed to directly assess the impact of specifically modifying lipoprotein(a) or HDL-P concentrations for potentially reducing residual risk.
Numerous studies in man and in animals support the relation between low or turbulent shear stress and atherosclerotic plaque location. However, little is known regarding the role of shear stress on the progression and composition of pre-established plaques. A recent prospective study in patients revealed that atherosclerosis regression is a realistic goal in patients, and it can be achieved through increased shear stress. We have used a model of arteriovenous fistula (AVF) developed in the lab, connecting the right common carotid artery with the jugular vein, to increase blood flow over established plaques in the brachiocephalic artery of LDL receptor knockout mice. Animals are placed on a high-fat diet for 12 weeks (wk0-wk12), then divided in three groups: control, sham, or AVF. Sham and AVF animals are maintained on high-fat for 4 weeks post-surgery. Atherosclerotic plaque size in the brachiocephalic artery progresses between wk12 (control animals) and wk16 (sham), whereas it actually regresses by 53% in AVF in the same timeline. Relative smooth muscle cell, macrophage, and collagen content are equivalent between groups, but matrix metalloproteinase (MMP) activity is enhanced in the AVF mice, suggesting that these enzymes might participate in the remodeling process. Indeed, in mice treated with MMP inhibitors and TIMP plasmids, MMP expression and activity diminish, and AVF fails to reduce plaque size. Hence, a favorable local shear stress may reverse the atherosclerotic process through a process involving metalloproteinases.
025

BIOPHYSICS OF MYELOPEROXIDASE INTERACTIONS WITH HDL: AN INDEX OF FUNCTIONALITY?

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Bioassays of HDL function are better predictors of cardiovascular disease (CVD) than HDL cholesterol (HDL-C). However, bioassays are difficult to perform and very time-consuming, thus making them impractical as a routine clinical assay. The Octet Red is an automated biolayer interferometer that quantifies rates of association/dissociation between proteins. Differences in the rates of association/dissociation can reveal subtle changes in the structure of proteins without knowledge of the modifying species. HDL interactions with myeloperoxidase (MPO) have been shown to impair HDL-C metabolism and increase inflammation. However, it is unclear whether increased MPO binding to HDL is a consequence or cause of CVD. In this report, we hypothesize that oxidative modification of HDL proteins increases MPO interactions with the HDL particle. To test this hypothesis, human HDL was modified with HOCl, 4-HNE, MDA or simply incubated at 37oC overnight and rates of MPO binding determined. In addition, HDL in plasma from hypercholesterolemic mice, fructose-fed hamsters and humans diagnosed with CVD was immunocaptured and rates of MPO binding determined. Our studies show that HOCl-mediated oxidation of HDL increases initial rates of MPO binding. Further, oxidative modification of HDL with 4-HNE, MDA or by heating at 37oC induces distinct differences in MPO association rates. HDL immunocaptured from rodent models of hypercholesterolemia and metabolic syndrome also exhibits higher rates of MPO association. Finally, HDL isolated from human subjects with documented CVD exhibits higher rates of MPO association than control HDL. Taken together, these data suggest that oxidative stress modifies the molecular structure of HDL and alters the biophysical interactions between HDL and MPO such that initial rates of MPO association are increased. As this assay can be automated and performed in less than 7 minutes, biolayer interferometry may be a valuable clinical assay for reference laboratories for more accurately determining the risk of developing CVD.
NOVEL THERAPIES FOR ATHEROSCLEROSIS

026
LDL CARBAMYLATION IN CHRONIC UREMIA: IS THERE A ROLE FOR MYELOID PEROXIDASE?

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Background and Objective: Carbamylated LDL (cLDL), a product of non-enzymatic modification of LDL by urea-derived cyanate, was demonstrated to induce atherosclerosis during chronic kidney disease (CKD) associated with uremia. cLDL may also be generated by cyanate produced through the oxidation of thiocyanate in reaction catalyzed by myeloid peroxidase (MPO). The current study was aimed to dissect whether or not MPO-dependent mechanism of LDL carbamylation is involved in atherosclerosis induced by chronic uremia in mice.

Methods: The experiments were performed using MPO knockout mice and their wild-type littermates as controls. To induce atherosclerosis, mice were fed with a high fat diet. Chronic uremia was induced by urea supplementation, unilateral nephrectomy (UNX) or by electrocoagulation model of chronic renal failure (CRF). Plasma cLDL and oxidized LDL were measured by ELISA.

Results: Our data suggest that both MPO and urea mechanisms may lead to cLDL production, while elevated urea level alone causes drastic surge in cLDL production. MPO mechanism leads mainly to LDL oxidation. MPO did not have significant impact on plasma cLDL under physiological conditions or during CRF. cLDL was produced in the absence of MPO, and chronic uremia solely caused significant increase cLDL in mouse circulation.

Conclusions: This direct comparison of the two pathways showed that majority of circulated cLDL is likely to be induced by chronic uremia rather than MPO. Although it possible that MPO catalyzes the cLDL production in vascular walls, it is not an obligatory component for LDL carbamylation and its activity results in both LDL carbamylation and oxidation.
NOVEL THERAPIES FOR ATHEROSCLEROSIS

027
RANDOMIZED PHASE II TRIAL TO ASSESS SAFETY AND EFFICACY OF CAPRE IN MILD-TO-SEVERE HYPERTRIGLYCERIDEMIC PATIENTS
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2. St-Jerome Medical Research, St-Jerome, QC, Canada
3. CSSS Vallee De L’Or, Val D’Or, QC, Canada
4. Medical Clinic of Grand Mere, Grand Mere, QC, Canada
5. IRCM, Montreal, QC, Canada
6. JSS Medical Research, Montreal, QC, Canada

Objectives: To evaluate the safety and efficacy of CaPre to reduce fasting plasma TG (200-877 mg/dL) after 4 and 8 weeks versus Standard Of Care (SOC). Secondary endpoints were changes in TC, LDL-C, HDL-C, non-HDL-C, and HbA1c. Serum apolipoproteins (Apo-CIII, Apo-AI) were also assessed.

Background: Long-chain polyunsaturated omega-3 fatty acids, eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) have been shown to reduce hepatic secretion of TG-rich lipoproteins and plasma TG levels. CaPre® is a novel highly purified omega-3 krill oil extract with a high content of phospholipid-conjugated EPA and DHA.

Methods: 288 patients aged 18-75 from 34 centers were randomized in an open-label study to SOC, or CaPre given daily for 8 weeks with dose-doubling at week 4 for 0.5g, 1g, and 2g groups while 4g group was dosed for 8 weeks. Standard safety assessments were conducted. Statistical analysis was performed using ANOVA followed by post-hoc contrast analysis assessing % change between CaPre baseline, week 4 and 8 versus SOC.

Results: CaPre SOC-adjusted 4-week TG % difference was -8% (p=NS), -16% (p=0.007), -13% (p=0.025) and -18% (p=0.002), for 0.5g, 1g, 2g, and 4g, respectively. The SOC-adjusted 8-week TG % difference was 2% (p=NS), 16% (p=0.021), -6% (p=NS) and -14% (p=0.038), for 0.5g, 1g, 2g, and 4g, respectively. CaPre 4g SOC-adjusted 8-week TC % difference was -7% (p=0.06) and non-HDL-C was -10% (p=0.036). Similarly to beneficial lipid effects, HbA1c was significantly lowered with CaPre 2g (-18%, p=0.013) and 4g (-15%, p=0.039). Additionally 4-week treatment with 4g CaPre significantly lowered serum Apo-CIII by 25% (p<0.01) while 1g CaPre significantly increased serum Apo-AI by 17% (p<0.05).

Conclusions: CaPre at daily doses of 1g-4g was effective in reducing serum triglycerides and increasing HDL-C without deleterious effects on LDL-C in mild-to-high hypertriglyceridemia patients. CaPre was safe, well-tolerated, with incidence of AEs similar to SOC (NCT01516151).
INFLUENCE OF STATINS ON CIRCULATING MICRORNAS DURING PROLONGED AEROBIC EXERCISE

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2. Cardiovascular Performance Program, Massachusetts General Hospital, Harvard Medical School, Boston, MA, USA, Division of Cardiology, Hartford Hospital, Hartford, CT, USA, Boston Athletic Association, Boston, MA, USA, Cardiology Division, Department of Internal Medicine, Gangnam Severance Hospital, Yonsei University College of Medicine, Seoul, Korea

Objectives: We sought to investigate whether certain c-miRNAs could serve as real-time markers of statin-induced muscle damage during prolonged exercise.

Background: Statins can exacerbate exercise-induced skeletal muscle injury. Circulating microRNAs (c-miRNAs) may serve as real-time markers of exercise-induced tissue adaptation, but their response to statin-associated muscle injury remains unknown.

Methods: We measured levels of muscle-specific microRNAs (miR-1, miR-133a, miR-206, and miR-499-5p) in circulating plasma from 21 statin-using participants (15 men, age 54.0 years) and 21 controls (16 men, age 56.6 years) before (PRE), immediately (FINISH), and 24 hours (POST-24) after a 42-km foot race (the marathon).

Results and Conclusions: Baseline (PRE) levels of candidate c-miRNAs were low and did not differ between groups. Age, body mass index, and finishing time showed no significant correlation in relation to c-miRNAs levels at any time point. Levels of c-miR-1, c-miR-133a, and c-miR-206 demonstrated similar elevations at FINISH in statin and non-statin runners followed by near-complete clearance at POST-24. In contrast, c-miR-499-5p was increased significantly at FINISH, and remained elevated at POST-24 rather than returned to baseline level in both subject groups, but the increase was greater in statin users. Specifically, when comparing statin users with non-statin users, c-miR-499-5p increased 5.5 ± 2.2 vs. 1.7 ± 0.4 fold, p = 0.051 at FINISH and 5.9 ± 1.7 vs. 2.2 ± 0.4 fold, p = 0.048 at POST-24. These findings suggest a role of c-miR-499-5p as real-time biomarker of muscle damage after prolonged exercise in statin users.
CHEST COMPRESSIONS DURING SUSTAINED INFLATIONS: A NOVEL TECHNIQUE OF NEONATAL RESUSCITATION THAT IMPROVES RECOVERY AND SURVIVAL IN A NEONATAL PORCINE MODEL

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Background: Guidelines on neonatal resuscitation recommend 90 chest compressions (CC) and 30 manual inflations (3:1) per minute in newborn infants. However, the optimal compressions to inflations ratio remains unknown.

Objective: The study aimed to determine if CCs during sustained inflations (SI) improves return of spontaneous circulation (ROSC) of asphyxiated newborn piglets compared to coordinated 3:1 resuscitation.

Methods and Results: Term newborn piglets (n=8/group) were anesthetized, intubated, instrumented and exposed to 45-minute normocapnic hypoxia followed by asphyxia. Protocolized resuscitation was initiated when heart rate decreased to 25% of baseline. Piglets were randomized to receive either 3:1 resuscitation (3:1 group) or CCs during SIs (SI group). Piglets randomized to the SI group received a SI with a peak inflating pressure of 30 cm H2O for 30 sec. During the SI, CCs were provided at a rate of 120 per minute. SI was interrupted after 30 sec for one second before a further 30 sec SI was provided. During the whole time CCs were continued. CC and SIs were continued until ROSC. Continuous respiratory parameters, cardiac output, systemic and pulmonary artery pressures, and regional blood flows were measured.

Results: Median (IQR) time for ROSC was significantly reduced in the SI group vs. 3:1 group [38 (23-44) sec vs. 143 (84-303) sec, respectively, p=0.0008]. In the SI group, administration of oxygen and epinephrine was significantly lower, whilst minute ventilation and exhaled CO2 were significantly increased. The SI group had significantly higher mean systemic and pulmonary arterial pressures during resuscitation compared to the 3:1 group [51(10) vs. 31(5) mmHg; 41(7) vs. 31(7) mmHg, respectively; all p<0.05], with improved cardiac output and common carotid blood flow.

Conclusions: Combining CCs and SI significantly improved ROSC with better hemodynamic recovery in asphyxiated newborn piglets when compared to the standard coordinated 3:1 resuscitation.
Objective. Noonan syndrome (NS) is the second most common genetic syndrome associated with cardiac abnormalities, including, most notably, pulmonary stenosis (PS) and hypertrophic cardiomyopathy (HCM). Little is known about the natural history of heart disease in this unique subset of patients. We sought to contribute information on the natural history of NS by looking at how the cardiac disease progresses with time.

Design. This is a retrospective review of the medical records of patients with NS seen at our institution between 1963 and 2011.

Results. Records were available for 113 patients. Average length of follow-up was 14.16 years (2 months to 44 years, median 12.5 years). Sixty-six percent (75/113) of our patients had PS; within this subset, 57% (43) were classified as mild, 9% (7) moderate, and 33% (25) severe. None of the cases of mild PS worsened with time. All of the severe cases had an intervention, as did some moderate cases. Fourteen percent (16/113) of our patients had HCM; 56% (9/16) were mild, diagnosed at an average age of 3.8 years. Seven of these were stable with time, while one did progress. Forty-four percent (7/16) of cases were classified as severe, diagnosed at an average age of 4.2 months, and all were managed medically, surgically, or both. Our cohort had seven deaths (ages 6 months and 6, 10, 20, 40, 49, and 50 years).

Conclusion. Mild PS in patients with NS is nonprogressive. Severe, and in some cases moderate, PS will invariably require a therapeutic intervention. It is uncommon for HCM to progress or have new onset beyond early childhood. Prognosis of heart disease in NS is influenced most by the findings on presentation.
Echocardiographic Assessment of Unicuspid Aortic Valve


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Objectives/Background: Unicuspid aortic valve (UAV) is a rare congenital abnormality of the aortic valve with an estimated incidence of 0.02%. The aim of this study was to describe the natural history, assess the valve hemodynamics at the time of diagnosis and intervention, and determine disease associations for patients with unicuspid aortic valve by echocardiography.

Methods: We identified 29 patients diagnosed with UAV at Mayo Clinic by echocardiography between 1982 and 2012. Sixteen of the patients presented as adults (age 18-38), and 13 as infants, children or adolescents.

Results: Age at diagnosis showed a bimodal distribution with age peaks between 0-5 and 25-40 years. Table displays demographic and aortic valve hemodynamic data at diagnosis and at intervention. At initial diagnosis, aortic stenosis was severe in 14 patients (6 children, 8 adults). Aortic valve repair was performed in 7 patients (4 children, 3 adults) and valve replacement in 10 patients (2 children, 8 adults). Coarctation was present in 4 children, 2 requiring surgical treatment, and dilatation of the ascending aorta was present in 21 patients (8 children, 13 adults), 11 patients requiring grafting.

Conclusions: Diagnosis of UAV occurs when the aortic valve gradient is severely increased. The majority of patients have an associated thoracic aortopathy.

<table>
<thead>
<tr>
<th>Table</th>
<th>All Patients</th>
<th>Pediatric</th>
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<tbody>
<tr>
<td></td>
<td>Adult</td>
<td>Pediatric</td>
</tr>
<tr>
<td>Number of Patients, n</td>
<td>16</td>
<td>4</td>
</tr>
<tr>
<td>Age at Diagnosis</td>
<td>33.0 ± 7.0</td>
<td>5.1 ± 6.3</td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>9 (66)</td>
<td>9 (69)</td>
</tr>
<tr>
<td>Aortic Valve Area (cm²)</td>
<td>1.32 ± 0.53</td>
<td>1.34 ± 0.53</td>
</tr>
<tr>
<td>Aortic Valve Gradient (mmHg)</td>
<td>44 ± 13</td>
<td>40 ± 35</td>
</tr>
<tr>
<td>Associated Aortopathy, n (%)</td>
<td>13 (81)</td>
<td>8 (62)</td>
</tr>
<tr>
<td>Associated Coarctation, n (%)</td>
<td>0 (0)</td>
<td>4 (31)</td>
</tr>
<tr>
<td>Diameter of Proximal Ascending Aorta (mm)</td>
<td>43 ± 4</td>
<td>-</td>
</tr>
<tr>
<td>Number requiring intervention, n (%)</td>
<td>11 (69)</td>
<td>8 (62)</td>
</tr>
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<table>
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<tr>
<th>Patients Requiring Intervention</th>
<th>Adult</th>
<th>Pediatric</th>
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<tr>
<td>Aortic Valve Replacement</td>
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<tr>
<td>Aortic Valve Repair</td>
<td>3</td>
<td>2</td>
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<tr>
<td>Aortic Valve Gradient (mmHg)</td>
<td>22.08 ± 3.58</td>
<td>1.10 ± 0.57</td>
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<tr>
<td>Associated Aortopathy, n (%)</td>
<td>13 (81)</td>
<td>0 (0)</td>
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<tr>
<td>Associated Coarctation, n (%)</td>
<td>0 (0)</td>
<td>4 (31)</td>
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<tr>
<td>Diameter of Proximal Ascending Aorta (mm)</td>
<td>44 ± 5</td>
<td>47 ± 5</td>
</tr>
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*One adult patient had repair followed by subsequent replacement. Echo data prior to each procedure was included in its respective category
**Only one patient had gradient measured
†Operative information was unavailable for one adult and one pediatric procedure
032
PROGNOSIS FOR PATIENTS WITH HEART FAILURE AFTER PALLIATIVE SURGERY FOR SINGLE VENTRICLE CARDIAC DISEASE
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Objective: Elucidate prognostic factors affecting patients with single ventricle congenital heart disease (SV-CHD) who develop heart failure after cardiac surgery.

Background: The outcomes for infants with SV-CHD have improved considerably over the past 3 decades. The risk factors for poor outcome are well described, but the specific prognosis for patients with postoperative heart failure is not well described.

Methods: We retrospectively reviewed our center’s Society of Thoracic Surgeons (STS) database over a 7 year period, filtered for SV-CHD patients who developed heart failure or low cardiac output. After manually excluding patients who had systemic to pulmonary artery shunts placed or other indication other than SV-CHD, 185 records from 174 unique patients were included in our study. The electronic medical records of each of these subjects were then reviewed.

Results: Between 2004 and 2010, 1038 surgeries were performed on patients with SV-CHD. 258 cases resulted in heart failure or low cardiac output, representing approximately 25% (258/1038) of cases. Overall survival for the 174 patients was 74.8%, 67.0%, 63.2%, and 55.0% at 2 months, 1 year, 2 years, and 4 years respectively. Patients who were inotrope dependent for >1 week had an ongoing risk of death, even long after discharge, with a 50% mortality at 2 years postop. Patients with persistent systemic ventricular dysfunction on echocardiogram at postoperative day 7 had a survival disadvantage proportional to the degree of dysfunction; with extremely poor survival of patients with moderate or greater dysfunction, 100% mortality at 18 months.

Conclusions: 25% of single ventricle heart surgeries resulted in at least transient heart failure or low cardiac output, by STS database criteria. This population is at disproportionate risk of poor outcome. A patient’s ability to recover cardiac function is not completely reassuring, as the population retains persistent mortality risk for years afterwards.
033
IMPROVED RESYNCHRONIZATION PACING EFFICACY AMONG CONGENITAL HEART DISEASE PATIENTS WITH REFRACTORY HEART FAILURE

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Introduction: Many patients (pts) with congenital heart disease (CHD) will require heart transplant (HT) for heart failure (HF). Since CHD pts have added co-morbidities and published cardiac resynchronization pacing therapy (CRT) guidelines do not apply in CHD, better pt selection are needed. The purpose of this study was to evaluate a new screening selection protocol for CRT implant among CHD pts with HF.

Methods: From 1998-2013, 103 CHD pts were considered for HT (NYHA 3-4). During HT listing, 25 of these (mean age 22y) had additional cardiac catheterization studies with ventricular paced hemodynamics, including contractility indices (dP/dt, dP/dt/p). CHD included tetralogy of Fallot, transposition, and single ventricle; 20/25 pts had preexisting pacemakers. A positive CRT response was defined as a >15% increase in indices over baseline. Based on the pre-implant evaluation, pts either did or did not receive CRT and all were followed from 1-144 months (mean 36).

Results: Of 25 pts, 17 (68%) had a positive response (mean dP/dt 551 vs 823mmHg-sec, p<0.006) and received CRT. During follow-up, all improved in NYHA class and better cardiac ejection fraction (36% vs 52%, p < 0.01). Of these pts, 4 underwent eventual HT (mean 56 mos later), 3 died (2 noncompliance (NC)) and 10 remain clinically stable (NYHA class 1-3), off the HT list (repeat dP/dt mean 843mmHg-sec). Of the 8 pts with a negative acute CRT response (mean dP/dt 635 vs 662mmHg-sec, p=NS), 2 received HT (mean 12 mos later) and both died within 6y post HT, 2 died awaiting HT (NC), and 4 remain on the HT list (NYHA 3-4).

Conclusions: Pt response to CRT is often equivocal. CHD pts have co-morbidities that may complicate CRT. Pre-selecting CHD pts by direct paced contractility response assures greater CRT efficacy, can delay need for HT and improve pt well-being.
VELOCITY TIME INTEGRAL OF THORACIC AORTA: A MEASURE TO ASSESS SYSTOLIC FUNCTION OF THE SYSTEMIC RIGHT VENTRICLE IN PATIENTS WITH TRANSPOSITION OF THE GREAT VESSELS

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Objectives: The aim of our study was to investigate velocity time integral of descending thoracic aorta (DTA VTI) as an alternative, more reproducible and technically feasible echocardiographic parameter for assessment of systemic right ventricular function (SRVF) in patients with complete transposition of the great arteries (dTGA).

Background: Echocardiography (TTE) is a readily available and noninvasive modality for assessment of cardiac function. However, the complex 3-dimensional anatomy of the right ventricle (RV) creates significant inter- and intra-observer variability in the measurement of RV ejection fraction in patients with d-TGA. Cardiac MRI remains the gold standard for assessment of SRVF, but is cumbersome and limited to patients without cardiac and other metallic implants.

Methods: A retrospective review of TTEs was performed on 49 patients (men=29, women=20, mean age 33 ± 8 years) with dTGA and atrial switch (Senning=14, Mustard=33). DTA VTI (mean= 21.1 ± 5.5), minute distance (1438.6 ± 341.3), TAPSE (mean 1.49 ± 0.4), single plane end diastolic and end systolic volume index (70 ± 34.1 and 40 ± 25.1, respectively) and ejection fraction (45% ± 12.1) of RV were calculated.

Results: DTA VTI ≥ 20.1 predicted EF ≥ 55 with 92% sensitivity and 54% specificity (area under curve: 0.83, p=0.001) whereas TAPSE ≥ 1.75 predicted EF ≥ 55 with a sensitivity of 75% and specificity of 86% (area under the curve=0.85, p=0.0001). Furthermore, DTA VTI was positively correlated with both TAPSE (r=0.43, p=0.002) and EF (r=0.52, p= 0.0001). Of all the measured parameters, DTA VTI had least intra- observer variability and maximum reproducibility.

Conclusions: The acquisition and analysis of DTA VTI are independent of the complex RV anatomy and function in patients with dTGA. DTA VTIs significantly more reproducible than TAPSE and EF and holds promise as an accurate measure of SRVF.
035
PREDICTION OF PULMONARY REGURGE AND RIGHT VENTRICULAR FUNCTION IN ASYMPTOMATIC REPAIRED TETRALOGY OF FALLOT PATIENTS IN DEVELOPING COUNTRIES; A COMPARISON TO CARDIAC MRI
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2. Cairo University Hospitals, Radiology, Cairo, Egypt
3. Cairo University Hospitals, Cardio-thoracic surgery, Cairo, Egypt

Background: Although long-term outcome of Tetralogy of Fallot (TOF) surgical repair in developing countries is still unknown, pulmonary regurgitation (PR) remains the most important post repair lesion influencing earlier morbidities. We aimed at comparing echocardiographic measurements for quantification of PR and right ventricular (RV) function to those in cardiac MRI (CMR).

Methods: 25 asymptomatic corrected TOF patients (9.2 ± 4 years) were compared with 20 age and sex matched healthy children. RV functions were assessed by myocardial performance index (MPI) obtained by TDI and myocardial tissue velocities.

Results were compared to RV volumes and ejection fraction (RVEF) by CMR. Echo variables for quantification of PR were: (1)PR jet width /PA diameter, (2)Pulmonary pressure half time, (3)Pulmonary regurge index (PRi); PR duration to diastole duration, (4)No flow time; diastole duration- PR duration and (5)diastole systole time velocity integral ratio (DSTVI). Those variables were compared to regurgitant fraction (RF %) obtained by CMR. Results: By logistic regression, PRi and no flow time had the best prediction for severity of PR. ROC curve analysis using RF % as a gold standard, showed sensitivity= 86.36%, specificity=100% and cut-off value=0.8 for PRi, and a sensitivity= 81%, specificity=100% and cut-off value= 64msec for no flow time. RV myocardial velocities were significantly lower while E/ E’ ratio and MPI were significantly higher than in normal controls. No significant correlation between TDI and CMR measurements for RV functions was shown in our study.

Conclusion: Echocardiography may offer a readily available and accurate complementary approach for prediction of severity of PR and assessment of RV function in corrected TOF patients in developing countries, where routine follow up with CMR may be challenging.
ISOPROTERENOL-ASSOCIATED RISK STRATIFICATION FOR SUDDEN DEATH AMONG PEDIATRIC PATIENTS WITH WOLFF-PARKINSON-WHITE SYNDROME: LOCATION-BASED ACCESSORY PATHWAY REFRACTORY PERIODS

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Introduction: During electrophysiology studies (EPS), isoproterenol (Iso) evaluates accessory pathway effective refractory periods (APERP) in patients (pts) with Wolff-Parkinson-White (WPW) and supraventricular tachycardia (SVT). APERP ≤ 250ms is associated with risk for sudden death. However, there is limited information of Iso effects on AP locations (APloc). The purpose of this study was to compare Iso effects on RP by APloc.

Method: 143 pts (male 53%, mean 14.2y, 95% with normal cardiac anatomy) with WPW underwent EPS over 6 years. Based on clinical findings, Iso (0.1 mcg/kg/min) was used in 94 EPS. APERP at baseline (b) and during Iso infusion (i) were compared and categorized based on the APloc (RAS-right anterior septal, RA-right anterior, RPL-right posterior/lateral, S-septal, LL-Left lateral, LP-Left posterior).

Results: Demographic data were comparable regardless of APloc. Asymptomatic WPW accounted for 30% of pts. All symptomatic pts presented with sensed tachycardia. Syncope was presented in 12 pts (18%). All b-APERPs were comparable and shortened with Iso regardless of APloc (p< 0.05). However, APERPs ≤ 250 ms were found only with S and RAS APloc (Table). SVT was induced in all pts, 32% generating to flutter/fib with rapid ventricular response (43% septal vs 17% non septal, p < 0.05).APloc.

Conclusions: APERP are related to location. Iso aids in unmasking AP with ERP ≤ 250ms. RAS and S APs locations confirm a higher risk for sudden death.

<table>
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<th>APloc (n=94)</th>
<th>S** (n=9)</th>
<th>RAS** (n=17)</th>
<th>RA (n=20)</th>
<th>RPL (n=11)</th>
<th>LL (n=14)</th>
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<td>343 ± 74</td>
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</table>

** APERP difference with Iso;** APERP ≤ 250ms with Iso
INDEXES OF MYOCARDIAL REPOLARIZATION ARE ASSOCIATED WITH LEFT TO RIGHT SHUNTS IN VENTRICULAR SEPTAL DEFECT

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Background: The QT variability index, calculated between Q and the T wave end (QT), is an index of temporal myocardial repolarization lability associated with cardiac events in damaged myocardium. Little is known about temporal variability in congenital heart disease and the other two temporal myocardial repolarization descriptors obtained from J-Tpeak (JTp) and Tpeak-Tend intervals (Tp-e). We therefore investigated differences between these indexes in ventricular septal defect (VSD) patients, and in those who performed radical surgery or not.

Methods and Results: We enrolled 74 patients (age:4.3±4.0, M:F= 37:37, surgical practice:17 patients, age 1.7±2.1, M:F=8:9) with VSD all of whom had been followed out patient clinic. After we obtained informed consent from parents, performed ECG and echo-sonography recordings from patients. We calculated RR, QRS, JTend, JTp, corrected JTp (JTpc, by Fridericia formula), Tp-e, and variability Index of JTp (JTpVI) and left to right shunt ratios (Qp/Qs) by doppler echo-sonogram analysis. We then subdivided data patients into two groups, performed surgical operation (OPE), and not performed (NOPE). The controls were 37 age-matched subjects. The linear regression analysis for the correlation between Qp/Qs and ECG indexes, Tukey-Kramer honestly significant difference test were conducted. p-values <0.05 were considered statistically significant. Qp/Qs had significant correlations with JTpc, JTp/JT, JTpVI and Tp-e/QT. In higher correlation indexes, JTpc were significantly shorter in OPE than NOPE (p<0.05), there was no significant difference between the control and NOPE. JTp/JT were significantly lower in OPE than in the control group and NOPE (p<0.05, respectively). JTpVI increased in OPE than in the control group and NOPE (p<0.05, respectively).

Conclusions: Our data show that the shunt ratio significantly contributes to JT peak interval indexes in patients with radical surgery. Further studies should investigate whether these indexes might help stratify the pathophysiological condition and determination of surgical indications in VSD.
038
ELECTROCARDIOGRAPHIC CHANGES, TROPONIN ELEVATION AND LENGTH OF STAY AMONG COCAINE USERS ADMITTED FOR CHEST PAIN
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2. American Heart Association Liaison with Interamerican Society of Cardiology

Background: Chest pain visits to emergency rooms (ER) by cocaine abusers are frequent, but a better risk stratification system needs to be established. The aim of this study is to identify higher-risk patients with electrocardiogram (EKG) findings due to cocaine-related chest pain, and the impact to the length of stay (LOS) in Hispanic and African American (AA) patients.

Method: We reviewed EKGs of Hispanic and AA cocaine users admitted for chest pain after their arrival to the ER. We identified EKG changes suggestive of ischemia and troponin elevation. We looked for associations among those EKG changes, troponin elevation and LOS. Statistical analyses were performed by Fisher’s exact test.

Results: There were 44 cocaine users, 95% male, mean age (SD) 49.7 (1.1) years, 64% Hispanics and 36% AA. Sinus rhythm was present in 42/44. EKG changes suggestive of ischemia were noted in 26/44 (59%). T wave inversions (TWI) were seen in 25/26 (20% of the 25 presented ST depression), and the remaining subject showed ST elevation. Troponin elevation was found in 9/44 patients [6 had TWI/ST depression (2/6 also had ST depression)], two had no ischemic EKG changes, and one had ST elevation. Mean LOS (SD) was 1.5 days (1.17). LOS ≥3 days were seen in 8/44 (18%). All of these 8 showed TWI, and 75 % presented troponin elevation. TWI and troponin elevation was associated with prolonged hospitalization (P= 0.017 and P= 0.0003 respectively).

Conclusions: EKG changes were found in 59% of the Hispanic and AA cocaine users admitted with chest pain, where the most common EKG change was TWI (20% with concomitant ST depressions). No statistical difference was found between different EKG changes and troponin elevation, although EKG changes and troponin elevation were significantly associated with a longer hospitalization.
Objective: The study purpose is to examine the role of collagen in the enhancement of platelet aggregability and impact of 5HT on adverse events after percutaneous coronary intervention (PCI).

Background: Adverse cardiac events after the PCI remained frequently problematic especially stent thrombosis and in-stent restenosis. Dual antiplatelet therapy suppresses platelet aggregation via arachidonic acid and adenosine-5'-diphosphate (ADP) inhibition; however, residual platelet aggregation-induced substrates remained undersuppressed. Collagen is one of the strong platelet activators found in injured coronary arteries. Collagen stimulates serotonin (5HT) release from activated platelets resulting in a strong vasoconstrictor effect via direct action on Rho/Rho kinase in vascular smooth muscle cells.

Methods: We prospectively studied platelet aggregation in 31 acute coronary syndrome patients undergoing PCI and had been on dual antiplatelets prior to the procedure. Plasma serotonin level (5HT) and platelet aggregation responses to collagen (COL) were measured within 24-48 hours after PCI by uilltrasensitive ELISA and optical aggregometry. Adverse events (AE) within 30 days after the PCI (death, non-fatal myocardial infarction (MI), stent thrombosis, target vessels revascularization, and readmission) were collected.

Results: Five (16.1%) adverse events were observed. Univariate analysis showed that history of prior PCI is associated with AE (p=0.031). 5-HT in AE group was higher than non-AE group (81.2+20.2 versus 66.8+34.6 ng/mL [mean+SD]) with 21.6% difference. COL also showed similar trend (35.3+20.0% versus 27.6+21.3%) with 27.9% difference.

Conclusions: 5-HT and COL in PCI patients potentially serve as a surrogate marker to predict adverse events after PCI.
THE PLAQUE AND ACUTE CORONARY SYNDROMES

040
DECASES AFTER TAKOTSUBO
Easton Hospital, Easton, PA, USA

Background: Takotsubo Cardiomyopathy (TC) is a relatively new diagnosis first described in 1991. It can mimic Acute Coronary Syndrome (ACS), particularly STEMI, in its clinical presentation. Extensive literature has been published documenting the suspected pathophysiology, clinical manifestations, and acute recovery of cardiac function. Few studies, however, have focused on its long term prognosis.

Results: We diagnosed TC based on the Modified Mayo Criteria which includes akinesia of mid-distal Left Ventricle, nonobstructive Coronary Artery Disease (CAD), new electrocardiogram (ECG) changes, and absence of myocarditis or pheochromocytoma. Regarding the nine study patients: 89% were female, 67% (6/9) had hypertension, 45% (4/9) had history of CAD, 67% (6/7) had hyperlipidemia, 44% had some preceding emotional trauma, and 44% had some physical/physiological stress. Over two-thirds had a positive family history for CAD. All patients presented with substernal chest pain, an unremarkable physical exam, and elevated troponin levels. Cardiac catheterization revealed apical hypokinesis in 7/9 patients along with decreased ejection fraction (EF) and mild CAD. Patients were followed with Therapeutic Lifestyle Changes (TLC) and Guideline Directed Medical Therapy (GDMT) for aggressive risk factor reduction. TLC included diet, exercise and cardiac rehabilitation. GDMT often included Aspirin, Metoprolol (or Carvedilol), Lisinopril, and Lipitor. Follow-up echocardiograms showed an improvement of EF of 10-25% from their initial presentation along with normalization of cardiac contractility. All of the patients survived and there were few recurrences of non-cardiac chest pain.

Conclusion: The long term follow-up of nine patients diagnosed with TC with mild CAD demonstrates that aggressive risk factor reduction with TLC and GDMT appears to be very effective. The improvement in ejection fraction was maintained on long term follow-up. All nine patients are still alive and none have documented CAD. The long term prognosis of TC is excellent with optimal medical management.
BIOCHEMICAL MARKERS FOR RISK ASSESSMENT IN CARDIOVASCULAR DISEASE

041
DELAYED REDUCTION IN CYSTATIN C-BASED GFR AFTER PCI IS A PREDICTOR OF ADVERSE OUTCOMES IN PATIENTS WITH PRESERVED RENAL FUNCTION

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Background: Cystatin C has emerged as not only an early sensitive marker for acute kidney injury but also as a prognostic marker for coronary artery disease. We evaluated whether delayed reduction in cystatin-based glomerular filtration rate (GFR) after percutaneous coronary artery intervention (PCI) can also serve as a prognostic marker for adverse clinical outcomes.

Method: A total of 343 patients undergoing elective PCI were prospectively enrolled. After exclusion of 48 patients with MDRD GFR of <60 mL/min, 295 patients with preserved renal function were analyzed. Serum cystatin C and creatinine (Cr) were measured before and 24h and 48h after PCI. We calculated modification of diet in renal disease (MDRD) GFR and Cystatin C-based GFR (cystatin-GFR). Patients were grouped according to degree of (≥30% versus <30%) reduction in cystatin-GFR at 24h and 48h after PCI. The primary endpoint was major adverse cardiovascular event (MACE), a composit of death, myocardial infarction, stroke, and repeat revascularization.

Result: Change in serum Cr or cystatin C level at 24h and 48h were not able to predict MACE. Reduction in cystatin-GFR at 24h also could not predict MACE after PCI. However, Patients with reduction >30% in cystatin-GFR at 48h (n=11) showed significantly reduced MACE-free survival compared to those with less reduced cystatin-GFR (p<0.0001). Hazard ratio of prolonged reduction >30% in cystatin-GFR for MACE was 8.2 (p=0.003, 95% Confidence Interval 2.02 to 33.2) on multivariate cox regression analysis.

Conclusion: Delayed reduction in cystatin-GFR was a significant predictor of MACE after PCI in patients despite with preserved renal function.
POST STEMI LEFT VENTRICULAR EJECTION FRACTION AND INFARCT SIZE ESTIMATION – ARE SERUM TROPONIN T LEVELS HELPFUL???

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2. Rashid Hospital, Dubai, UAE
3. Sialkot Medical Complex, Sialkot, Pakistan

**Background:** Troponin T is used as biomarker for diagnosis of Acute Myocardial Infarction (AMI). Data revealing relationship between Troponin T and infarct size in patients with Acute ST segment elevation Myocardial Infarction (STEMI) and Left Ventricular LV Ejection Fraction (LVEF) are limited.

**Objective:** Evaluating relationship between Troponin T levels with infarct size measured by Electrocardiography (ECG) and LVEF measured by Echocardiography (Echo) in patients with STEMI.

**Methods:** A single centered, prospective analysis of 116 patients with Acute STEMI. Their ECGs were recorded at time of their presentation and Troponin T levels were measured at 12 hours and then 2D Echo was done 48 hours post admission. The relationship between infarct size and LVEF with serum Troponin T levels was evaluated.

**Results:** A total of 116 consecutive patients (age, 58 ± 17 years; 18% women) with STEMI were studied. Areas of infarction determined by ECG were inferior wall (IWMI) in 37%, Anteroseptal wall (ASMI) in 19%, Anterolateral wall (ALMI) in 18%, Extensive anterior in 13%, posterior wall (PWMI) in 4% and 2% were having global infarction. Regarding levels of Troponin T, 48% had high positive, i.e >2.0ng/ml, 52% had quantitative readings (20% had 1.5-2.0ng/ml, 18% had 1.0-1.5ng/ml and 14% had 0.5-1.0ng/ml). The mean value of Troponin T in PWMI is 1.1ng/ml, IWMI is 1.2ng/ml, LWMI is 1.3ng/ml, ASMI is 1.6ng/ml and for ALMI, Extensive MI and global MI is >2.0ng/ml. The mean value of Troponin T in patients with LVEF>50 is 1.3ng/ml, LVEF between 40%-50% is 1.68ng/ml and with LVEF <40% is 1.89ng/ml respectively.

**Conclusion:** Troponin T is a reliable and cost effective tool at 12 hours post STEMI to determine infarct size as measured by an ECG and LVEF by 2D Echocardiography. The higher values are indicative of more area of infarction with a negative correlation with the LVEF.
043

DOES PRIOR ASPIRIN USE PREDICT THE DEGREE OF PEAK TROPONIN LEVELS IN PATIENTS WITH ACUTE CORONARY SYNDROME?

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Background: Aspirin has long been used for primary and secondary prevention as well as for the treatment of acute coronary syndromes (ACS). In the setting of ACS, peak troponin levels have been shown to predict infarct size, left ventricular function, in-hospital mortality and future major cardiac events.

Objective: We investigated if a history of aspirin use prior to admission could predict the degree of troponin release in patients who presented with ACS including unstable angina, non-ST elevation myocardial infarction (NSTEMI) or ST elevation myocardial infarction (STEMI).

Methods: Electronic medical records of 697 patients undergoing cardiac catheterization (CC) from 2010-2012 were reviewed retrospectively to collect the data on variables related to CC indications, patient demographics, cardiovascular risk factors, aspirin use prior to hospitalization, lab data and angiographic findings. A total of 215 patients with acute coronary syndromes were analyzed including those who underwent percutaneous coronary intervention (PCI) as well as those who did not undergo PCI. Mean peak troponin levels during hospitalization were calculated for these patients. Univariate, binary logistic and binary linear regression analyses were done.

Results: Patients with prior aspirin use (n = 106) had mean peak troponin 11.25 ± 24.56 ng/ml, whereas patients with no prior aspirin use (n = 109) had mean peak troponin 42.12 ± 65.01 ng/ml (difference of mean: 95% CI 17.69 – 44.06; p = 0.001). Prior aspirin was independently associated (p = 0.001) with mean peak troponin levels on linear regression.

Conclusion: Our study shows an association between prior aspirin use and degree of peak troponin elevation in ACS. Patients with ACS who present with no history of prior aspirin use should be monitored closely for complications associated with high peak troponin levels. Further research is needed to determine the relationship between pre-admission aspirin use and morbidities associated with peak troponin elevation.
BIOCHEMICAL MARKERS FOR RISK ASSESSMENT IN CARDIOVASCULAR DISEASE

044
PLASMA PRO-BNP IS NOT A SPECIFIC MARKER FOR TRANSIENT MYOCARDIAL ISCHEMIA

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1Baystate Medical Center, Tufts University School of Medicine, Springfield, MA, USA

Objectives: To study plasma pro-BNP as a marker of transient myocardial ischemia.

Background: Plasma pro-BNP levels are increased in patients with acute myocardial infarction. Previous studies have shown conflicting data on the effect of transient myocardial ischemia on plasma BNP levels. We designed the current study to examine plasma pro-BNP levels in patients with transient myocardial ischemia during a percutaneous coronary intervention (PCI).

Methods and results: We enrolled 49 consecutive patients with a history of angina or abnormal stress test who presented for cardiac catheterization. We obtained plasma pro-BNP levels in all patients at a) arterial access (pro-BNP 1), b) the end of the procedure (pro-BNP 2) and c) 4 hours after procedure (pro-BNP 3). Hotelling’s T-squared test was used to evaluate the equality of means. Log transforms of pro-BNP were used to impart data normality. 22 patients underwent diagnostic catheterization (DCA group) and 27 underwent PCI (PCI group). Both groups had normal left ventricular function and a baseline creatinine < 2 mg/dl. Baseline log (pro-BNP) was 4.7 ± 0.99 (units) and rose significantly at 4 hours in both groups (p<0.02), with no difference in rate of change.

Figure: Change in pro-BNP level over time in PCI and DCA (no PCI) groups.

Conclusions: Plasma pro-BNP was increased in both DCA and PCI groups which limits its utility to identify transient myocardial ischemia. The etiology of increase in pro-BNP is both groups is speculative and maybe related to injection of radiographic contrast media into the coronary artery which leads to microcirculatory impairment resulting in myocardial tissue hypoxia and transient increase in left ventricular pressure, however, further evaluation is required.
BIOCHEMICAL MARKERS FOR RISK ASSESSMENT IN CARDIOVASCULAR DISEASE

045
INCREMENTAL VALUE OF HIGH SENSITIVITY TROPONIN IN ACUTE CORONARY SYNDROME
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Dept of Cardiology, Kims Hospital, Trivandrum, Kerala, India

Aim: To find the sensitivity and specificity of High sensitive Troponin T in Acute coronary syndromes.

Methods: Inclusion criteria:
400 consecutive patients who came to our Emergency department with chest pain since Jan 2013 were included.
Exclusion criteria:
Renal failure
Sepsis

Conclusion:
1. Single Trop .T- HS value of <25 pg/ml rules out clinical CAD with high NPV of 85.18 % (P<0.00001).
2. Trop T- HS value of > 100 pg/ml has high specificity of 91.3 % and 100% for predicting Coronary Artery Disease biochemically and by Coronary angiogram (p<0.00001 & p=0.05) respectively.
3. In patients with initial HS- Troponin value between 25-100 pg/ml, who underwent CAG, 91% had coronary artery disease.
4. Among patients having a rising HS-Troponin value, patients with initial value 25-100 pg/ml had significantly higher CAD than patients with Hs -Troponin <25 pg/ml.
5. Sensitivity of HS – Troponin among patients with initial value between 25-100 pg/ml with incremental values, for diagnosing CAD is 81.82% (p=0.0003).
ANTIPLATELET AND ANTITHROMBOTIC THERAPIES IN ACUTE CORONARY SYNDROMES

046
SAFETY OF ADJUNCTIVE ANTICOAGULATION DURING PRIMARY PERCUTANEOUS CORONARY INTERVENTION IN PATIENTS WITH THERAPEUTIC ORAL ANTICOAGULATION
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1. The Wright Center for Graduate Medical Education, Scranton, PA, USA,
2. The Commonwealth Medical College, Scranton, PA, USA

Background: There are no data suggesting safety of concomitant intravenous anticoagulation management in patients on therapeutic levels of oral anticoagulation presenting with ST-elevation myocardial infarction (STEMI) undergoing primary percutaneous coronary intervention (PCI).

Methods: Total of 1210 consecutive patients from 01/2006 to 12/2011 presenting with STEMI who underwent primary PCI in a community medical center were retrospectively reviewed. Total of eight interventional cardiologists with average experience of 10 years performed the procedure in two institutions.

Results: Total of 11 patients underwent primary PCI for STEMI while on therapeutic anticoagulation. Table-1 showed the baseline and procedural characteristics of all patients. All patients were on Coumadin prior to the procedure and continued during hospital stay. Seven patients received intra-procedural intravenous anticoagulation at the discretion of the interventionists. Eight patients received intravenous bivaluridin, two patients received intracoronary abciximab and three patients received intravenous unfractionated heparin. Only two patients developed access site hematoma which did not require any surgical intervention. No incident of any major bleeding or inhospital mortality. Majority of the patients were discharged on aspirin and clopidogrel along with Coumadin.

Conclusion: PPCI for STEMI in pts on therapeutic OAC can be performed safely and with excellent outcomes by experienced operators. Optimal adjunctive anticoagulation during PPCI requires further study.

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<td>Anterior</td>
<td>LAD</td>
<td>BMS</td>
<td>2.2</td>
<td>Rad 5F</td>
<td>Heparin + abciximab</td>
<td>No</td>
</tr>
<tr>
<td>71/M</td>
<td>Afib</td>
<td>Coumadin</td>
<td>Inferior</td>
<td>RCA</td>
<td>DES</td>
<td>2.4</td>
<td>Fem 6F</td>
<td>bivaluridin</td>
<td>No</td>
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<tr>
<td>74/M</td>
<td>Afib/AfM</td>
<td>Coumadin</td>
<td>Anterior</td>
<td>LAD</td>
<td>DES</td>
<td>2.4</td>
<td>Fem 6F</td>
<td>bivaluridin</td>
<td>No</td>
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</table>
Objectives: Percutaneous Coronary Intervention (PCI) is a common treatment option for patients with Acute Coronary Syndrome (ACS) or Stable Angina (SA). The current 2011 ACCF/AHA/SCAI guidelines for PCI recommend the use of anticoagulants in combination with a dual antiplatelet regimen (aspirin + P2Y12 inhibitor or GPIib/iiia inhibitor) in patients undergoing PCI. Cangrelor, a novel, rapid-reversible and acting IV P2Y12 agent which has been shown in the CHAMPION PHOENIX (CP) trial to reduce ischemic events vs. clopidogrel. The aim of our analysis was to quantify the annual clinical value of using cangrelor in PCI patients from a US hospital perspective.

Methods: A decision analytic model based on current clinical practice was developed to estimate the potential annual clinical value of using cangrelor during PCI. Data from RCTs were used to estimate event rates (mortality, Myocardial Infarction (MI), Stent Thrombosis (ST), Ischemia Driven Revascularization (IDR), Major and Minor Bleeding). Ischemic event costs were informed by analysis of 1,117 US hospital bills from the CP trial. Demographics and drug mix were informed by analysis of Premier’s Perspective database. Bleeding costs came from a targeted literature review. Drug costs were 2013 wholesale acquisition costs. Clinical value of cangrelor was estimated by setting the drug costs to $0. This model excludes additional value from eliminating the need to bridge to surgery.

Results: For a hypothetical US hospital treating 1,000 PCI patients/year (patient mix: 27%=STEMI, 31%=NSTEMI/UA and 42%=SA), the use of cangrelor resulted in $385,000 in clinical value. The total costs in the base case are estimated to be $6.35MM vs. the scenario case of $5.97MM. Cost offsets were derived from eliminating GPIs, lower GPI bailout rates and lower ischemic rates (MI, ST and IDR).

Conclusions: Using cangrelor in PCI is estimated to deliver clinical value of at least $385 per PCI-patient.
048

COMPLICATIONS OF INTRACORONARY ABCIXIMAB BOLUS-ONLY VERSUS STANDARD PROTOCOL DURING PERCUTANEOUS CORONARY INTERVENTION IN ACUTE CORONARY SYNDROME

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Background: Abciximab reduces major adverse cardiac events in patients with ST elevation myocardial infarction undergoing primary percutaneous coronary intervention (pPCI). Standard protocol is intravenous abciximab bolus during PCI plus abciximab infusion for 12-18 hours post pPCI. Intracoronary (IC) abciximab bolus administration results in high local drug concentrations and hence it should have higher antiplatelet effect. In this study, we assess the short-term efficacy and safety of IC compared to IV bolus of abciximab in ACS patients during pPCI.

Methods: We compared the clinical outcomes between the IC (n 56) and standard protocol (n 170) group of patients. Primary endpoints included bleeding/vascular/ischemic complications and MACE.

Results: The two groups were similar with respect to baseline characteristics. IC abciximab bolus only reduced bleeding complications, with no moderate bleed versus 7.2% in standard protocol group (p value 0.04). Ischemic/vascular complications had statistically insignificant difference between the two groups.

Conclusion: We found no significant difference between IC abciximab bolus only and standard abciximab therapy in terms of ischemic/vascular complications and MACE. But there was higher risk of moderate bleed in standard therapy group. The IC bolus route of abciximab may be superior to the intravenous route. Prospective randomized trials are warranted to validate these findings.
DIABETES MELLITUS, OBESITY, THE METABOLIC SYNDROME AND ATHEROSCLEROSIS: BASIC AND CLINICAL

049
MEDITERRANEAN DIET, ADIPONECTIN LEVELS, GENETIC POLYMORPHISMS AND INCIDENCE OF CARDIOVASCULAR DISEASES IN THE PREDIMED-VALENCIA STUDY
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3. Department of Computer Languages and Systems, University Jaume I, Castellon, Spain

Background and aims: Epidemiological evidence supports a relevant role of the Mediterranean Diet (MedDiet) in the prevention of cardiovascular diseases (CVD). However, the underlying mechanisms remain unknown. One of these mechanisms may involve adiponectin. Adiponectin is an adipocytokine that can suppress atherosclerosis development via various anti-inflammatory effects. Accordingly, some studies have reported an increase of plasma adiponectin levels in response to a MedDiet. However, the results are controversial. Likewise, the association between adiponectin gene (ADIPOQ) variation and CVD remains to be clarified and the effect of the MedDiet on this association has not been investigated. Present study aimed to analyze the influence of the MedDiet and ADIPOQ polymorphisms on adiponectin levels as well as the association between these polymorphism and CVD after intervention with MedDiet.

Methods: We studied all the participants (n=1094) in the PREDIMED-Valencia Study, a randomized controlled trial testing the effect of the MedDiet versus a control diet in the primary prevention of CVD. Plasma adiponectin was measured and three ADIPOQ polymorphisms were determined. Incidence of CVD was assessed with a median follow-up of 4.5 years.

Results: Carriers of the minor allele of the rs17300539 polymorphism in the ADIPOQ promoter had higher adiponectin concentrations at baseline (P=0.001). Also higher levels were observed in homozygous subjects for the minor allele of the rs1501299 G>T (P=0.012), and no significance was detected for the rs2241766 (P=0.571). Adherence to MedDiet was not associated with adiponectin levels at baseline. Only the rs1501299 polymorphism was significantly associated with CVD incidence. This association was more evident in women. In a multivariable Cox regression model adjusted for age, diabetes, obesity, dietary intervention (MedDiet versus control), smoking, and drinking, carriers of the minor allele had higher CVD risk than non-carriers (P=0.034)

Conclusions: Intervention with MedDiet did not modify the association of the rs1501299 polymorphism with CVD.
050
RELATIONSHIP BETWEEN ADMISSION BLOOD GLUCOSE LEVEL AND LONG-TERM CLINICAL OUTCOME IN ACUTE MYOCARDIAL INFARCTION
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Objective: The aim of this study was to examined the association between acute hyperglycemia and mortality in acute myocardial infarction (AMI). The long-term prognostic impact of hyperglycemia remains unclear.

Methods and Results: This study included total of 377 subjects who underwent primary percutaneous coronary intervention. Patients were divided into two groups according to median glucose level (10 mmol/L). Glucose ≥ 10 mmol/L patients were 145 and glucose < 10 mmol/L patients were 232. All-cause mortality and major adverse cardiac events (MACE) were compared between two groups. 12.7% patients had died. Patients with hyperglycemia that was defined as admission glucose ≥ 10 mmol/L had a significantly higher long-term mortality compared to patients without hyperglycemia (6.9% vs 5.8%, P = 0.0017). Univariable cox regression indicated that acute hyperglycemia was positive correlated with all-cause death and MACE. Multivariable cox regression found that acute hyperglycemia was an independent prediction for death (HR = 2.01, P = 0.013) and MACE (HR = 1.62, P = 0.045).

Conclusions: Hyperglycemia at presentation is related to the MACE and all-cause death.
DO WE REACH BETTER LIPID CONTROL IN DIABETIC PATIENTS AFTER PERCUTANEOUS CORONARY INTERVENTION?

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Objectives: To assess the control of total (T) cholesterol (C), LDL-C, HDL-C, and triglycerides (TG) in patients (P) undergoing percutaneous coronary intervention (PCI), and to compare results in diabetic (DM) and non-diabetic (non-DM) P.

Methods and Results: We analyzed 1087 lipid level determinations of 96 DM-P vs. 165 non-DM-P. Before PCI, DM-P had lower levels of TC (188±40 vs. 202±39 mg/dL; p<.02) and LDL-C (108±33 vs. 123±33 mg/dL; p<.003), similar levels of HDL-C (47±15 vs. 49±13 mg/dL) but higher of TG (172±114 vs. 142±81 mg/dL) than non-DM-P. At the end of follow-up (45±16 months) the lipid profile was better in both DM and non-DM-P, but still with lower levels of TC (153±35 vs. 169±38 mg/dL; p<.001), LDL-C (79±27 vs. 95±31 mg/dL; p<.005) and of HDL-C (43±12 mg/dL vs. 48±12 mg/dL; p<.001) in the DM group compared to non-DM, without differences in TG (157±85 vs. 138±107 mg/dL, n.s.). We analyzed 422 and 665 determinations of LDL-C from DM and non-DM-P. Considering a target level of <70 and <100 mg/dL, this was achieved in only 39% and 82% of the DM-P measurements and in 22% and 66% of non-DM-P analyses. In DM-P, the change in therapeutic strategy was appropriate only in 42% and 80% of cases considering target levels of LDL-C <70 and 100 mg/dL, respectively. In non-DM-P, physicians were less aggressive, and the therapeutic strategy was appropriate only in 31% and 68% of cases, respectively.

Conclusions: After PCI, despite a high rate of statin therapy (95%) and a significant reduction in mean lipid levels, a high proportion of P does not achieve the target level of LDL-C. DM-P are better treated than non-DM-P suggesting a more intensive management of lipid lowering therapy in DM-P and undertreatment of non-DM-P. Thus, in usual practice, guidelines are not followed properly, especially in non-DM-P.
Objectives: Progression to target organ damage and cardiovascular (CVD) risk are more closely associated with ambulatory (ABPM) than clinic blood pressure (BP) measurements. Moreover, the sleep-time BP mean is a better predictor of CVD risk than the awake or 24h BP means. Nighttime hypertension and non-dipper BP patterning are highly prevalent in diabetes and they have been consistently associated with their increased CVD risk. However, whether elevated ABPM provides prognostic value for predicting the development of diabetes has scarcely been investigated.

Methods: We evaluated 2656 subjects without diabetes, 1292 men/1364 women, 50.6+/-14.3 years of age, with baseline ambulatory BP ranging from normotension to hypertension. At baseline and annually (or more frequently if hypertension treatment was adjusted) thereafter, ambulatory BP and physical activity (wrist actigraphy) were simultaneously monitored for 48h to accurately derive the awake and asleep BP means.

Results: During a 5.6-year median follow-up, 190 participants developed diabetes. The asleep, but not awake, systolic BP (SBP) mean was a highly significant predictor of new-onset diabetes in a Cox proportional-hazard model adjusted for the significant confounding variables of age, waist perimeter, glucose, and chronic kidney disease (for each 1-SD elevation, hazard ratio 1.30, [95%CI: 1.13-1.48] for asleep SBP, P<0.001; 1.12 [0.97-1.29] for awake SBP, P=0.128). Exploration of the combined contribution of multiple BP parameters indicated clinic SBP had no predicting value when corrected by asleep SBP mean (1.10 [0.94-1.29], P=0.210).

Conclusions: Sleep-time SBP mean, but not daytime clinic BP measurement or ABPM-derived awake BP mean, is a highly significant and independent prognostic marker of new-onset diabetes. Alteration in nighttime BP regulation, highly frequent in diabetes, seems to precede diabetes, rather than to be a consequence of this condition. These findings indicate ABPM is a clinical necessity to accurately detect abnormal sleep-time BP and evaluate the risk of progression to diabetes.
**DIABETES MELLITUS, OBESITY, THE METABOLIC SYNDROME AND ATHEROSCLEROSIS: BASIC AND CLINICAL**

**053**

**INFLUENCE OF TIME OF DAY OF BLOOD PRESSURE-LOWERING TREATMENT ON THE RISK OF DEVELOPING NEW-ONSET DIABETES**

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**Objectives:** In hypertension, ingesting one or more blood pressure (BP)-lowering medications at bedtime is associated with significant reduction of sleep-time BP, a sensitive prognostic marker of cardiovascular disease (CVD) risk, also identified as a marker for the risk of new-onset diabetes (DM). This randomized trial investigated if bedtime therapy with the entire dose of at least one hypertension medication exerts greater reduction in the risk for developing DM than conventional, morning-time therapy with all medications.

**Methods:** We conducted a prospective, open-label, blinded endpoint trial on 2012 hypertensive patients without DM, 976 men/1036 women, 52.7+/-13.6 years of age, randomized to ingest all their prescribed hypertension medications upon awakening or the entire daily dose of at least 1 of them at bedtime. At baseline and annually (or more frequently if hypertension treatment was adjusted) thereafter, BP and physical activity (wrist actigraphy) were simultaneously monitored for 48h to accurately derive the awake and asleep BP means.

**Results:** During a 5.6-year median follow-up, 171 participants developed DM. The Kaplan-Meier survival curves indicated a highly significant difference between treatment-time groups in event-free survival (log-rank 28.0, P<0.001). Participants ingesting BP-lowering medications at bedtime showed a significantly lower hazard ratio (HR) of new-onset DM (adjusted by the significant influential characteristics of glucose, waist perimeter, sleep-time systolic BP decline, and chronic kidney disease) than those ingesting all medications upon awakening (0.43 [95%CI: 0.31-0.61]; event-rate 4.8 vs. 12.1%; P<0.001). There was an even further benefit in preventing DM among patients ingesting not just one but all BP-lowering medications at bedtime (event-rate 6.1 vs. 3.7%).

**Conclusions:** In non-diabetic hypertensive patients, treatment with at least one BP-lowering medication at bedtime, compared to ingestion of all medications upon-awakening, resulted in improved ambulatory BP control (significant decreases of asleep BP and enhanced sleep-time relative BP decline) and markedly reduced prevalence of new-onset DM.
054
THE ASSOCIATION OF EDUCATION AND OBESITY AS DETERMINANTS OF PULSE PRESSURE IN A DIABETIC POPULATION
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The aim of this analysis is to examine the association between education and obesity status predicting high pulse pressure (HPP, pulse pressure >60mmHg) in diabetic and non-diabetic US populations.

Research has pointed to various physical and social determinants of blood pressure and cardiovascular health, however no explicit relationship between education levels as a measure of pulse pressure (PP) in diabetic populations has been observed.

A total of 4596 adults aged 25-55 from the National Health and Nutrition Examination Survey (NHANES) 2009-2010 were included for this analysis. Based on self-reported completed education levels, participants were grouped as: less than grade 9, grade 9-11, high school, some college, and college graduate (analytic reference). The measured body mass index (BMI= kg/m2) was used to categorize individuals as underweight (UW =30.0), with NW as the analytical reference group. Participants were also categorized by diabetic status as having: pre-diabetes, diabetes, or none using fasting serum glucose concentration. Multiple logistic regression models were constructed to evaluate the odds of HPP for levels of education and obesity category according to their diabetic status.

In the original population, compared to college graduates the ORs (95% CI) of having a high pulse pressure was non-significant with less than grade 9 education, 1.85 (1.07, 3.20) with grade 9-11, 2.10 (1.27, 3.46) with high school, and 3.01 (2.10, 4.30) with some college. In this group, obese individuals had no significantly increased odds with 1.71 (0.99, 3.02). When the models were modified excluding diabetic/pre-diabetic patients, the grade 9-11 education groups no longer had significant odds increase, and obese individuals did have significantly increased odds of high pulse pressure with 1.84 (1.07, 3.17) and 1.91 (1.09, 3.32) greater odds respectively in non-diabetic and non-pre/ non-diabetic populations. Therefore the effect of obesity on pulse pressure may be dependent on individuals’ diabetic status.
THE RELATIONSHIP BETWEEN JOB ENRICHMENT AND ABDOMINAL OBESITY: A LONGITUDINAL FIELD STUDY OF APPARENTLY HEALTHY INDIVIDUALS
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Obesity has become an epidemic in modern society. However, there is a paucity of research about how job context affects obesity. To enhance our knowledge we used a large, heterogeneous sample of apparently healthy employees (n = 1,949) across two time periods with an average of close to 3.5 years between measures. We tested a hypothesized curvilinear effect of job enrichment on changes in two stress related indicators of abdominal obesity over time: waist circumference (WC) and waist-hip ratio (WHR). Job enrichment consisted of the job dimensions of variety, identity, significance, autonomy, and feedback, and in our analysis we controlled for demographics and health related behaviors, including weekly sports activity, number of cigarettes smoked per day, and weekly alcohol consumption. The results supported the hypothesized U-shaped relationship between job enrichment and changes in both indicators of abdominal obesity over time, such that the level of abdominal obesity was reduced when job enrichment was moderate and was increased when job enrichment was either high or low. As expected, no such association was observed for the general obesity measure of body mass index (BMI). We discuss the theoretical and practical implications of these results.
DIABETES MELLITUS, OBESITY, THE METABOLIC SYNDROME AND ATHEROSCLEROSIS: BASIC AND CLINICAL

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PREVALENCE OF CORONARY ATHEROSCLEROSIS IN AN ASIAN POPULATION: FINDINGS FROM CORONARY CT ANGIOGRAPHY

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Objectives: The purpose of this study was to estimate the prevalence of coronary atherosclerosis in an Asian population.

Background: There are limited data regarding the prevalence of coronary atherosclerosis on coronary computed tomographic angiography (CCTA) in Asian populations.

Methods and Results: We analyzed 6,311 consecutive asymptomatic individuals aged 40 and older with no prior history of coronary heart disease who voluntarily underwent CCTA evaluation as a general health examination. The mean age of the study population was 54.7±7.4 years and 72.8% were male. After adjustment with age and gender, the prevalence of plaque was 40.5% (95% CI [confidence interval], 38.1–42.9); significant CAD (coronary artery disease) was observed in 9.0% (95% CI, 7.7–10.2); multi-vessel disease in 2.2% (95% CI, 1.7–2.8); significant CAD in the left main or proximal left anterior descending artery in 3.2% (95% CI, 2.5–3.9). After adjustment with age and gender, there was a greater prevalence of significant CAD in individuals with diabetes mellitus (standardized rate ratio [SPR], 2.66 [95% CI, 1.93–3.68], p<0.001), hypertension (SPR, 2.24 [95% CI, 1.69–2.97], p<0.001), hyperlipidemia (SPR, 1.65 [95% CI, 1.25–2.17], p<0.001), intermediate and high Framingham risk (SPR, 5.91 [95% CI, 2.34–14.95], p<0.001), or high atherosclerotic cardiovascular disease risk (SPR, 8.04 [95% CI, 3.04–21.23], p<0.001), but current smoking was not significantly associated with a higher prevalence of significant CAD (SPR, 1.74 [95% CI, 0.78–3.88], p=0.176).

Conclusions: The prevalence of coronary atherosclerosis in an Asian population was not negligible and associated with cardiovascular risk factors.
IT CAN BE DONE: REDUCTION OF OBESITY & CARDIOVASCULAR DISEASE RISK IN A HIGH RISK POPULATION BY LIFESTYLE CHANGES

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Background: Obesity and the metabolic syndrome is an emerging public health problem worldwide as children and adolescents are being afflicted. This report examined the distribution of cardiovascular disease (CVD) risk factors and effect of life-style changes on coronary heart disease risk reduction in a high risk population.

Methods: We examine the baseline distribution of CVD risk factors in 515 obese African Americans, with BMI of 42.96.8 kg/m2, and evaluate the effect of 6 month diet-exercise program on risk reduction.

Results: The prevalence of hypertension was 57%, dyslipidemia 27% and diabetes mellitus 24%. Metabolic syndrome was present in 36% of the subject and 39% had two features of the syndrome. Forty-four percent were nocturnal blood pressure nondippers. BMI impacts negatively on blood pressure dipping. In addition, BMI and the metabolic syndrome impacts negatively on arterial compliance as reflected in a higher pulsepressure. The 10-year risk prediction for developing CHD ranged from 4% to 17% for women and 6% to 29% for men. After 6-months of life-style changes, the risk scores reduced on average from 6% to 4% for women and 16% to 13% for men.

Conclusion: The high prevalence and increasing incidence of obesity and associated CVD risk factors emphasizes the need to focus on obesity reduction in this high risk population.
OPTIMAL CUTOFF OF WAIST CIRCUMFERENCE AND WAIST TO HIP RATIO FOR THE KOREAN POSTMENOPAUSAL WOMEN

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Objectives: The purpose of this study was to evaluate the optimal cutoff value of Waist circumference (WC) and Waist to hip ratio (WHR) for identifying metabolic syndrome (MS), metabolic obesity (MO) and its component.

Background: In Korea, the cutoff value of WC for identification of MS was suggested to be 85Cm for women based on the analysis in adults. The usefulness of WC and WHR to predict MS and MO in the postmenopausal women has not been studied yet.

Methods: Two hundred and thirty postmenopausal women in the age of fifties and sixties were included in this cross-sectional study. MS and MO were defined by the modified NECP-ATP III criteria except WC. We diagnosed as MS when subject have 2 and more these metabolic factors, and as MO with 1 and more factors without WC criteria. A Receive operating characteristic (ROC) curve analysis was use to assess the accuracy of WC, WHR for identifying MS, MO and its components. The optimal cutoff values were obtained both from the point on the ROC curve which was closest to (0, 1) and from the Youden’s index.

Results: Among the subjects, 38.3% and 79.1% were classified as MS and MO without WC criteria. And 24.3% and 80.9% were classified as MS and MO with WC. The area under the ROC curve (AUC) value of WC, WHR for MS were 0.744, 0.685 and for MO were 0.705, 0.732. The optimal cutoff value of WC, WHR for MS were 76.8Cm, 0.87 and for MO were 76.3Cm, 0.84.

Conclusion: To identify the MS more correctly, WC criteria (85Cm) for the Korean postmenopausal women should be lowered. But to obtain age specific optimal cutoff values more studies are needed.

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EXPERIENCE WITH VENO-VENOUS ECMO IN PATIENTS WITH SEVERE ARDS
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Introduction: Extracorporeal membrane oxygenation (ECMO) is often the last resort for serious acute respiratory distress syndrome (ARDS) when all non-invasive treatment options have failed to improve the patient’s pulmonary condition.

Methods: We retrospectively evaluated all patients who underwent veno-venous ECMO in the observation period between 2010 and 2012 at our university hospital. Our main attention was in particular turned to the indication, the runtime, the weaning protocol and the outcome.

Results: Veno-venous ECMO was performed in 39 cases at our center in the last 3 years. 27 patients were men with a mean age of 53.4±16.4 years (range 26.5–75.0 years) at the time of ECMO implantation. The mean age for the 12 females was 44.8±15.2 years (range 24.6–69.7 years). The main reason for ECMO support was severe pneumonia (n=33; 84.6%), in 6 cases multiple traumas were the implantation causes. The middle runtime of the ECMO lay with 12.7±10.9 days (range 0.5–46 days). The 30-day mortality was 24/39 (61.5%); the 1-year mortality was 29/39 (74.4%).

Conclusions: Our data in this study were comparable to the literature regarding the most favorable timing for the initiation and the weaning of ECMO as well as the outcome. There many reports on ECMO therapy from other cardiac centers, nevertheless the role and adequate use of ECMO for patients with ARDS have not been definitively established.
060
OBESITY IN PULMONARY ARTERIAL HYPERTENSION: IMPACT OF BODY MASS INDEX (BMI) ON SEVERITY AND OUTCOME
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Background: Body Mass Index (BMI) in Pulmonary Arterial Hypertension (PAH) patients in the REVEAL-PAH registry was reported to be similar to normal controls. The impact of BMI on outcome in patients with PAH has not been studied.

Objectives: To determine (i) BMI in patients with PAH and (ii) whether BMI has an effect on severity and survival.

Methods: Records of 75 PAH (Group 1) patients at the Pulmonary Hypertension Center in our institution were reviewed. Data obtained included weight, height, and mean pulmonary artery pressure (mPAP), at initial evaluation. Body mass index (BMI) was calculated using formula: BMI=Weight (kg)/Height (m) square. Number of patients alive versus expired during period of follow-up was noted. Pearson’s test for linear correlation was performed to assess correlation of BMI with mPAP and survival. p < 0.05 was deemed statistically significant.

Results: Mean mPAP was 35.2±12 mmHg; mean BMI 28±6 kg/sq.m. Three percent were underweight (BMI <18); 29% had a normal BMI; 32% were overweight (BMI 25-30); 36% were obese (BMI>30). During follow-up of 2-5 years, 18 (24%) patients expired. Of 49 patients with BMI> 25, 8 expired (16%); of 26 patients with BMI < 25, 10 (38%) expired (p<0.05). mPA for BMI>25 was 45±13 mmHg; for BMI<25 was 36±10 mmHg (p=0.003). Pearson’s test for linear correlation revealed a significant correlation between BMI and survival (r=0.248, p=0.032) and BMI and mPA (r=0.317; p=0.006).

Conclusion: A significant proportion of patients (68%) with PAH are overweight and obese, with BMI>25. Despite having a significantly higher mPA, these patients surprisingly have a better survival than patients with normal or low BMI (BMI<25). Further studies are needed to determine whether obesity is a risk factor for PAH and its effect on mortality in PAH patients.
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CORRELATION BETWEEN PULMONARY ARTERY DIAMETER AND MEAN PULMONARY ARTERY PRESSURE IN PULMONARY ARTERIAL HYPERTENSION ASSOCIATED WITH SCLERODERMA

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Background: Pulmonary Artery Hypertension (PAH) in Scleroderma has a prevalence rate of 30-60%. Studies exist on pulmonary artery diameter (PA-Dia) as an indicator of increased mean Pulmonary Artery Pressure (mPAP) in PAH but variable results are reported in patients with pulmonary fibrosis. The relation of PA-Dia on CT with mPAP in patients with Pulmonary Artery Hypertension associated with Scleroderma (Scl-PAH), who often have associated pulmonary fibrosis, has not been studied.

Objective: To determine whether mPAP and Pulmonary Vascular Resistance (PVR) correlates with PA-Dia in patients with Scl-PAH.

Methods: Records of 26 patients with Scl-PAH being followed at our institution were reviewed. Patient demographics, mPAP, and PVR on initial right heart catheterization (RHC) were obtained. CT scans at initial evaluation were reviewed with a radiologist. PA-Dia was measured in the axial sections on mediastinal window settings, 1cm above the level of the bifurcation of the main pulmonary artery, using electronic calipers. Using Pearson’s test for linear correlation, correlation coefficient (r) for PA-Dia versus mPAP and PVR respectively, was calculated.

Results: Mean age was 64.4 +/- 11 years; 88% of patients were females. Mean mPAP was 34 plus-minus 8.5 mm Hg; mean PVR was 398 plus-minus 177 dynes/sec/cm5. Eighty-four percent patients had evidence of pulmonary fibrosis of varying degrees on CT chest. Mean PA-Dia was 3.2 plus-minus 0.6cm. Absolute measures of PA-Dia correlated strongly with mPAP (r= 0.516; p=0.003) as well as with PVR (r= 0.57; p=0.001).

Conclusions: In patients with Scl-PAH, majority of whom had pulmonary fibrosis of varying degrees, PA-Dia on CT correlated strongly with mPAP and PVR. Larger studies should confirm if there is a significant difference in the PA-Dia in Scleroderma patients with and without PAH and whether PA-Dia can be used to identify which Scleroderma patients should be referred for RHC.
PROCESS/OUTCOME MEASURES OF ADULT VENOUS THROMBOEMBOLUS (VTE) & PULMONARY EMBOLUS (PE) PROPHYLAXIS

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Background: VTE and PE are potentially serious cardiovascular complications of surgery.

Methods: Medicare’s Quality Improvement Organization Program reviews nationwide all-payer samples of medical records data. For surgical patients meeting specific criteria, ordering and receipt of mechanical or pharmacologic VTE/PE prophylaxis were tracked. Data on VTE/PE coded as secondary discharge diagnoses/1,000 surgical discharges meeting specific criteria came from the Healthcare Cost and Utilization Project’s administrative databases designed to generate nationwide adjusted outcome rates.

Results: Percentages (standard errors) of surgical patients with VTE/PE prophylaxis ORDERED increased from 93.3% (0.0%) in 2009 to 97.6% (0.02%) in 2011. Percentages of patients RECEIVING prophylaxis rose from 91.3% to 96.8%. State-specific ranges for prophylaxis ordering rose from 88.9%-97.6 in 2009 to 95.1%-98.6% in 2011. State-specific ranges for prophylaxis receipt rose from 84.9%-96.3% to 94.1%-98.0%. For men, ordering rose from 92.2% to 97.3%; receipt rose from 90.1% to 96.2%. For women, ordering rose from 94.0% to 97.8%; receipt rose from 92.1% to 97.1%. For whites, ordering rose from 93.6% to 97.8%; receipt rose from 91.5% to 96.9%. Among minority groups, ordering rates ranges rose from 90.4%-93.2% in 2009 to 95.2%-97.6% in 2011. Receipt ranges rose from 88.6%-91.6% to 94.8%-96.9%. Ordering among patients <65 years old rose from 91.9% to 97.3%. Ranges for sub-groups 65+ rose from 94.3%-94.6% to 97.4%-98.2%. Nationwide, adjusted VTE/PE rates fell from 8.9 (0.02)/1,000 discharges in 2009 to 7.8 (0.02 /1,000 in 2011. Male rates fell from 10.7/1,000 to 9.5/1,000. Female rates fell from 7.5/1,000 to 6.6/1,000. Racial variation was modest.

Conclusions: VTE/PE prophylaxis receipt lagged slightly behind prophylaxis ordering; both improved over time. Gaps among states/sub-groups in ordering and receipt, and gaps between ordering and receipt all narrowed. Remaining variations may indicate modest quality improvement opportunities. Declining post-operative VTE/PE occurrence seen in complementary datasets is encouraging; its relationship to increasing prophylaxis is unclear.
RIGHT VENTRICULAR MYOCARDIAL STRAIN TO QUANTIFY DYSFUNCTION IN SUBMASSIVE PULMONARY EMBOLISM

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Objective: A study is in progress to demonstrate that thrombolytic therapy resolves right ventricular (RV) dysfunction within 72 hours of treatment, lowering the risk of persistent RV dysfunction or chronic pulmonary hypertension. RV strain by echocardiography is utilized to assess RV dysfunction.

Background: Persistent RV dysfunction at discharge in patients presenting with submassive pulmonary embolism (PE) is associated with 8 times the recurrence and 4 times the mortality of patients with resolved RV dysfunction. Echocardiography can quantify RV myocardial strain and systolic function.

Methods: Potential participants present with hemodynamic stability and acute, symptomatic PE, with embolus involving at least one main or lower lobe pulmonary artery. Thrombolytic treatment is instituted within 24 hours of presentation. The patients receive an echocardiogram at baseline, 72 hours post-treatment, and 90 days post treatment. Each echocardiogram includes standard images, with additional focus on the RV fractional area change (RVFAC) and RV strain.

Results: The current data shows improvement in the RV strain, RVFAC, and right ventricular systolic pressure (RVSP). The data thus far demonstrates a positive response to treatment.

Conclusions: RV myocardial strain is significantly improved. This therapy has resolved RV dysfunction, according to RV strain measurement, by the 72 hour post treatment echocardiogram.
CARDIOVASCULAR ASPECTS IN RENAL DISEASE

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HIGHER CYSTATIN C LEVEL PREDICTS CONTRAST INDUCED NEPHROPATHY IN PATIENTS WITH PERIPHERAL ARTERIAL DISEASE WITH PRESERVED NORMAL KIDNEY FUNCTION

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Objectives: The association of cystatin C, known as novel marker for kidney function, with risk for developing contrast induced nephropathy (CIN) and adverse clinical events in patients with peripheral artery disease (PAD) has not been examined, especially in patients with normal kidney function.

Materials and Methods: We evaluated 141 patients who were treated with percutaneous transluminal angioplasty (PTA) for PAD from September 2010 to May 2013 in Severance Cardiovascular Hospital. CIN was defined as increase ≥ 25% and/or ≥ 0.5 mg/dl in serum creatinine at 48 h after PTA vs. baseline. Preserved renal function was defined estimated glomerular filtration rate (eGFR) is more than 60 ml/min. Baseline clinical and laboratory characteristics including cystatin C and serum creatinine level were measured before the procedure. Multivariable logistic regression analysis was then performed to identify independent predictors of CIN. Additionally, we evaluate the prevalence of adverse clinical events such as overall mortality, bypass surgery, amputation and re-PTA according to the initial cystatin C level.

Results: We evaluated 141 patients and mean follow up duration was 423 days. The incidence of CIN was 6.5% and we set cut-off value of cystatin C level as 1.03 mg/dl calculated by ROC curve with sensitivity 78% and specificity 65%. The AUC was greater when using cystatin C level than using creatinine level (0.73 vs. 0.58). Baseline level of cystatin C above 1.03 mg/dl was reported as an independently significant risk factor for CIN in both uni-variate and multi-variate analysis. (Hazard ratio 5.85, 95% CI 1.09 - 31.4). The adverse outcome was not different according to the baseline cystatin C level.

Conclusion: Elevated concentrations of cystatin C were independent predictive value of CIN in patients with PAD and with preserved renal function.
OBJECTIVES: We focused on the effect of semaphorin 3C on endoMT in a PKD mouse model.

Background: Renal fibrosis is the main cause of end stage renal failure. Among the sources of fibroblasts, endothelial cell-derived fibroblasts are very important as well as epithelial cell-derived cells. Polycystic kidney disease (PKD) is a genetic disease featured by formation of cysts in the kidney. Research groups generated various animal models mimicking human PKD, and jck mice is the one of those models that carries missense mutation in Nek8 gene. These mice can live for 100 days and show onset of cyst formation at 25 days after birth. This mouse model is good for us to trace the progression of cystogenesis and renal fibrosis. In vertebrates, semaphorins are categorized into five classes. Among them, semaphorin class 3 is the only secreted protein which binds to NRP/Plexin co-receptor. In previous study, semaphorin 3C stimulated proliferation and migration of mouse glomerular endothelial cells.

Methods: The jck and age-matched wild-type littermates were sacrificed at indicated time points. Isolated kidneys were used for immunostaining to find lesions with endoMT. At those lesion, expression pattern of semaphorin 3C was evaluated.

Results: Compared to age-matched wild-type littermates, kidney of the jck mice contained more positive cells for endoMT. Also, it was found that semaphorin 3C expression was correlated with endoMT progression.

Conclusions: EndoMT is the one of contributors to PKD progression, which is related with semaphorin 3C.
Background: In cardiac arrest, admission serum potassium (K) may be misleadingly elevated due to acidosis, thus underestimating total potassium deficits.

Methods: We investigated laboratory and clinical data in 41 consecutive cardiac arrest patients (13 females, 60 +/- 32 years old, 6 with diabetes, 7 with chronic kidney disease, and 8 with history of cardiovascular disease) treated with therapeutic hypothermia. Expected serum K was calculated as $K_{exp} = (7.40 - \text{admission pH}) \times 0.5 + 4$. Total K deficit was calculated as $K_{def} = (4 - K_{exp}) \times 0.4 \times \text{weight, kg}$. ANOVA, chi-square, Kaplan-Meier, and logistic regression analyses were used.

Results: Improved survival was noted in lower admission K (75% survival in K<4 vs. 47% in K>4 mEq/L, p=0.096) and higher pH (47% per 0.1 increase in pH, 95%CI 22-99, p=0.048). Consequently, survivors had higher admission pH (7.27 +/- 0.12 vs. 7.13 +/- 0.16 in deceased, p<.027), lower $K_{exp}$ (4.1 +/- .06 vs. 4.1 +/- .08 in deceased, p<.027), and higher $K_{def}$ (-2.2 +/- 1.9 vs -4.1 +/- 2.32 in deceased, p<.055). In accord with these, shockable rhythms - ventricular tachycardia or fibrillation (VT-VF) - were more common in patients with K<4 (70% vs. 14%, p=0.001). Correlation between admission K and pH ($R^2$= 0.06) or between K requirements and calculated K deficit ($R^2$=0.007) were poor. Admission pH was similar in VT-VF and pulseless electrical activity-asystole patients (7.23 +/- 0.13 vs. 7.19 +/- 0.19, respectively, p=0.5). The difference in measured and $K_{exp}$ was not predictive of mortality (0.464 +/- 1.28 in survivors vs 0.403 +/- 0.799 in deceased, p<.899).

Conclusions: We have observed an improved survival in cardiac arrest patients treated with therapeutic hypothermia with lower admission K and higher admission pH. However, admission pH appears to be a better predictor of hospital outcomes than measured or expected potassium levels in cardiac arrest survivors treated with therapeutic hypothermia.
UTILITY OF T-WAVE-ALTERNANS AND HEART RATE VARIABILITY FOR RISK ASSESSMENT IN BRUGADA SYNDROME

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Objectives: We aim to evaluate the efficacy of T-wave-alternans (TWA) and heart rate variability (HRV) using 24-hour multichannel Holter ECG (24-M-ECG) in patients with Brugada syndrome (BS) as markers for risk stratification.

Background: The prognostic value of TWA and HRV for risk stratification in patients with BS is still unclear.

Methods: From April 2012 to January 2014, we enrolled a total of 136 consecutive patients with BS (VF; n = 17, Syncope; n = 10, and Asymptomatic; n = 109) and 11 control subjects. A 12-channel ECG monitoring was performed in all individuals for 24-hour period. On 24-M-ECG, the precordial electrodes were attached at the standard position in leads V2 and V5 (4L-V2, 4L-V5) and the third intercostal space in lead V2 (3L-V2). We measured the maximum TWA in 4 time zones (0-6 am, 6-12 am, 0-6 pm, and 6-12 pm) by using the time-domain modified moving average method. We calculated very low (24-VLF), low (24-LF), high frequency power (24-HF), and LF/HF power ratio (24-LF/HF) with power spectral analysis.

Results: In VF and Syncope groups, max-TWA at 3L-V2 was significantly larger during 0-6 am, 6-12 am, and 6-12 pm, and very low frequency power (VLF) was significantly smaller than Asymptomatic and control groups. Sixteen patients experienced VF episodes during a mean follow up period of 66±38 months. The new combined score for predicting VF episodes was defined as having met 24-VLF <726 msec2 and 2 or more of the following of maximum TWA at 3L-V2 in the 3 time zones; (0-6am: >20, 6-12am: >27, and 6-12pm: >35 microV). Multivariate analysis showed that the new combined score and documented VF were independent markers for VF episodes.

Conclusion: The combination of TWA and HRV may be suitable for risk stratification in patients with BS.
TH has been proven to be effective in the realm of cardiac arrest (CA); two randomized studies have shown improved neurologic outcomes in patient’s experiencing cardiac arrest in which spontaneous circulation has been restored. Vasopressor use during TH is variable and based upon the arterial pressure status pressure related to the protocol. Neurologic outcome based on vasopressor use during TH has not been previously studied. A retrospective analysis was performed on 331 consecutive cardiac arrest patients admitted to a tertiary medical center from December 2006 to October 2012. Patients were categorized into two groups: patients who good neurological outcome (CPC score 1-2) and those with poor neurological outcome (CPC score 3-5). Data was collected on age, gender, mean arterial blood pressure, and use of vasopressors. Data obtained in this single institution retrospective analysis identified after cox regression that use of vasopressors is associated with worse neurological outcomes in those with shockable rhythm CA undergoing TH. We also found that in the shockable rhythm cohort, there was an association of older age, history of DM, longer time to ROSC, and out-of-hospital CA with worse neurological outcomes. In this same cohort, longer time to hypothermia showed a statistically significant association with better neurological outcomes. This single-center study is one of the first to investigate vasopressor use in TH and its association with neurological outcomes. We found that in the post-CA survivors with shockable rhythms, vasopressor use in TH is associated with worse neurological outcomes along with older age, history of diabetes mellitus, longer time to ROSC and out-of-hospital cardiac arrest. Lastly, we found a significant association of longer time to target temperature as being associated with better neurological outcomes in this cohort. These associations present a possibility to provide accurate prognostic tools for clinicians treating patients with TH.
SYNCOPE AND SUDDEN DEATH: RISK ASSESSMENT AND MANAGEMENT

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A POTENT DOMINANT NEGATIVE MUTATION IN HERG IN A CHINESE FAMILY EXPERIENCING LONG QT SYNDROME, EPILEPSY, AND UNEXPECTED SUDDEN DEATH
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Objectives: We aimed to screen the mutation in a Chinese family experiencing long QT syndrome, syncope and unexpected sudden death. Additionally, we also investigated the functional role of the mutation and its potential contribution to the disease phenotype.

Background: Inherited long-QT syndromes (LQTS) are electrical heart disorders characterized by torsade de pointes, syncope and cardiac sudden death. Mutations in the human ether-a-go-go-related gene (hERG) are responsible for the type 2 LQTS (LQT2).

Methods: Regular physical examinations were conducted to exclude the structural heart diseases. Direct sequencing of candidate gene hERG was performed. The mutant A561V-hERG plasmid was constructed and transfected into HEK293 cells. Western blotting and immunostaining experiments were conducted to evaluate the A561V-hERG protein expression. Whole cell patch clamp was performed to investigate the function of A561V-hERG channels. Additionally, different concentrations of the mutant A561V-hERG plasmids were transfected into the HEK293 cells stably expressing wide type hERG (WT-hERG) to simulate the heterozygous mutation.

Results: Based on the characteristics of the ECG, we identified a heterozygous missense mutation in the S5/pore region of the hERG protein that leads to the substitution of the amino acid alanine by valine (A561V). A561V-hERG protein could not travel to the plasma membrane and failed to generate functioning hERG currents in homozygous cells. When A561V-hERG was expressed simultaneously with WT-hERG, it resulted in obvious retention of WT-hERG channel protein in the endoplasmic reticulum and reduced its expression on the membrane. Additionally, A561V-hERG suppressed WT-hERG currents in a concentration-dependent manner and changed the gating properties of the channel.

Conclusion: A561V produced a non-function protein. Additionally, it suppressed WT-hERG channels expression and functional via a dominant-negative effect. This may explain, in part, the clinical manifestations in the Chinese family with the mutation.
Introduction: Despite tremendous advances in the management of cardiovascular diseases and cardiac arrest in particular, there is paucity of information regarding sudden cardiac death (SCD) in sub-Saharan Africa. We present a two-year review of cases of SCD among patients managed at a tertiary hospital in north-eastern Nigeria.

Subjects and methods: Patients admitted from January 2012 through December 2013 were followed-up and SCD identified. Definition of SCD was based on records of events preceding death, direct interviewing of attending physician/nurses, and family members/eye witnesses for out-of-hospital SCD. Demographic and clinical profiles were obtained from case notes. Cause of death were obtained from the death certificate for cases of in-hospital SCD.

Results: Three hundred and eighty eight patients comprising 171 males and 217 females with a mean age of 42.22±19.30 years were admitted during the period, out of whom 56 (14.4%) died. Twenty three (41.1%) with M:F of 1:1.1 were attributed to SCD, with 61% in NYHA class I and II. Fourteen (60.9%) occurred in-hospital. The predominant aetiology is ischaemic cardiomyopathy, followed by peripartum cardiomyopathy and dilated cardiomyopathy (figure 1). Age-based distribution of the various aetiologies is illustrated in figure 2.

Conclusion: SCD is common among patients admitted with cardiovascular diseases. The predominance of ischaemic cardiomyopathy reflects its emerging role in the epidemiology of Non communicable diseases.
SYNCOPE AND SUDDEN DEATH: RISK ASSESSMENT AND MANAGEMENT

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TRANIENT EPISODES OF UNRESPONSIVENESS IN A PATIENT ON METHADONE
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Introduction: Methadone, a synthetic opioid, mostly used in drug rehabilitation and pain management is known to cause polymorphic ventricular tachycardia (PVT).

Case Report: A 59-year-old man, with chronic pain syndrome due to osteosarcoma, requiring high dose of morphine and methadone for pain, presented with recurrent transient episodes of unresponsiveness, after suffering from flu-like symptoms and diarrhea for which he was treated with doxycycline. His 12-lead-EKG was significant for prolonged QT-interval (550 msec) and several short runs of premature ventricular complexes. While in the emergency room, he developed PVT requiring immediate cardioversion and intravenous magnesium sulfate. He also had severe hypokalemia (2.7mEq/dl), requiring correction. Methadone was discontinued. However his corrected QT-interval remained at 600 msec. He was cardioverted several times for recurrent sustained PVT, which preceded with episodes of transient sinus bradycardia, requiring temporary trans-venous pacing for over-drive suppression. His cardiac evaluation included a normal echocardiogram, fixed inferior perfusion defect on SPECT imaging and no significant coronary artery disease on cardiac catheterization. Cardiac MRI was unremarkable. As methadone has a long half-life of 8-59 hours, prolonging QT-interval, he was discharged with an external ICD life vest. Within few weeks, his QT interval was shortened and his life vest was discontinued. He had no further cardiac symptoms during the last 6 months of follow up.

Discussion: Methadone causes QT prolongation by blocking the potassium efflux during repolarization phase. Also due to negative chronotropic effects, methadone can facilitate bradycardia dependent torsade de pointes, especially in association with electrolyte disturbances and concomitant use of medications like certain antibiotics, antihistamines, antimalarials and antidepressants, which are also metabolized by cytochrome-P450-system.

Conclusion: With increasing use of methadone in clinical practice, physicians should be aware of its association with malignant arrhythmias. Due to potential drug-drug interactions, it should be used cautiously in patients at risk for electrolyte abnormalities.
Cardiovascular Disease Prevention and Risk Factors

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GENDER DISPARITY IN CORONARY HEART DISEASE: BIAS, BIOLOGY, OR BOTH?

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Cardiovascular disease remains a major cause of mortality for women both in industrialized economies and in developing nations. A stunning improvement has occurred in cardiovascular disease mortality for U.S. women between 2000 and 2010, attributable both to application of evidence-based therapies of established cardiovascular disease and to preventive interventions; these likely derived from research studies of cardiovascular disease in women. Despite these salutatory findings, women remain underrepresented in clinical trials of cardiovascular disease and cardiovascular therapies resulting in substantial gender disparities in preventive interventions, diagnostic procedures, and application of guideline-based therapeutic strategies, with consequent adverse outcomes for women. This presentation explores the potential contributions of gender differences in biologic characteristics and of gender bias in coronary heart disease: in the application of preventive interventions; and the management of stable ischemic heart disease, acute coronary syndromes, myocardial infarction, and myocardial revascularization procedures. Gender-specific basic and clinical cardiovascular research is needed to address these issues, with rigorous application required for the emerging knowledge. These approaches offer promise to improve cardiovascular outcomes for women and are the rationale for gender-based evaluation of pathophysiology, preventive interventions, clinical presentations, and medical and revascularization therapies.
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TIME TO FOCUS ON CARDIOVASCULAR HEALTH (NOT CV DISEASE)

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Despite rapidly advancing technologies in the treatment of CV diseases the current status of healthcare economics and global epidemiologic trends related to non-communicable diseases are unsustainable. A healthcare transformation is needed with a greater focus on CV health promotion and disease prevention.

Importantly, a better understanding of the definition of CV health is needed, in addition to tools and approaches to predict, promote, and impact CV health. At present ideal CV health is not prevalent. The need for comprehensive and complementary CV prevention programs focused on environmental and systems changes are needed. There are societal and systems challenges to overcome with the potential for significant impact.
The Framingham Heart Study first noted that risk functions for predicting cardiovascular disease (CVD) risk provide an efficient way for identifying persons at high risk who need preventive therapy; this led to future recommendations regarding the targeting of the intensity of therapy to a patient’s global risk. Risk scores including those of Framingham, PROCAM, and European SCORE provide estimates for 10-year risk of hard or total CHD or CVD events. The ACC/AHA 2013 guidelines for CVD risk assessment specify use of a Pooled Cohort Equations score for predicting 10-year and lifetime risk of ASCVD including both nonfatal and fatal myocardial infarction and stroke and are recommended for use in those aged 40-79 years of age; those aged 20-59 years of age with a low estimated risk are recommended to be evaluated with lifetime risk as well. When the treatment decision is uncertain, the guidelines recommend consideration of use of premature family history of CVD, hs-C-reactive protein, ankle brachial index, or coronary calcium scoring to further stratify the person’s risk of CVD. A positive premature family history with CVD <55 years of age in a male first degree relative or <65 years of age in a female first degree relative, a hs-CRP of >2 mg/L, ankle brachial index <0.9, or coronary calcium score of >=300 or >=75%tile for age, ethnicity and gender are suitable to stratify the individual’s CVD risk upward for consideration of initiation or intensification of therapy. Incorporation of global risk scoring into electronic medical records systems for rapid accessibility to the healthcare provider when seeing the patient, as well as accessibility to required measures and further testing will be key in successful implementation of the recent recommendations for CVD risk assessment.
Heart disease is the most common cause of death in patients with chronic kidney disease (CKD), particularly in those receiving dialysis. Atherosclerotic cardiovascular (CV) disease (CVD) accounts for a large number of these deaths. Atherosclerosis is accelerated in patients with CKD due predominantly to the high prevalence of traditional CVD risk factors in the CKD population. CKD aggravates pre-existent traditional risk factors such as hypertension and dyslipidemia due to secondary renal parenchymal hypertension and secondary dyslipidemia. In addition, a variety of non-traditional risk factors that occur commonly in CKD patients contribute to CV risk. These include hyperhomocysteinemia, increased oxidative stress, endothelial cell dysfunction, inflammation, activation of the renin-angiotensin-aldosterone and sympathetic nervous systems and vascular calcification. Recent studies suggest that CKD itself may be an independent risk factor for CVD, particularly coronary heart disease. Many therapies aimed at CV risk factor modification that have been successful in reducing CV risk in the general population are less effective or ineffective in favorably modifying CV risk in CKD.
THE INFLUENZA VACCINE- PREVENTING CARDIOVASCULAR EVENTS IN HIGH-RISK PATIENTS

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Background: Recent influenza infection is associated with an increased risk of cardiovascular events. We evaluated whether influenza vaccination reduces the risk of major adverse cardiovascular events.

Methods: We performed a systematic review and meta-analysis of Medline, Embase, and the Cochrane central registry (inception – August 2013) for randomized trials comparing influenza vaccine to standard care/placebo in patients with, or at high risk of, cardiovascular disease. A composite cardiovascular endpoint, mortality, and individual cardiovascular events were detected either as efficacy or safety events in trials with >50 patients. Analyses were stratified by subgroups of patients with and without a recent acute coronary syndrome (ACS).

Results: Six randomized controlled trials of 6,735 patients (mean age 67 years, 51% women, 36% with a cardiac history, mean duration of follow-up 8.9 months) were included. Influenza vaccine reduced the risk of composite cardiovascular events (2.7% vs. 4.6%; RR 0.64, 95% CI, 0.49-0.84; P=0.001) with a directionally consistent trend for individual endpoints, including cardiovascular mortality, all-cause mortality, myocardial infarction, stroke, heart failure, unstable angina, and coronary revascularization. A treatment interaction was detected between patients with (RR 0.46, 95% CI, 0.33-0.64) and without (RR 0.91, 95% CI, 0.54-1.54) a recent ACS (P-interaction=0.03). Results remained significant when an additional 6 trials comprising 16,857 patients randomized to experimental versus standard influenza vaccination were included.

Conclusion: Influenza vaccine reduced major adverse cardiovascular events and may reduce cardiovascular mortality in patients with, or at risk of, cardiovascular disease. A large multicenter trial is warranted to address these findings and inform policy.
C Reactive protein (CRP) is a prototypic acute phase reactant very well known and used to identify and monitor inflammatory and infective conditions. Because of the robustness of the protein and of the analytical assessment, CRP has become a standard markers in rheumatology and infections. With the mounting evidence that atherosclerosis is an inflammatory disease, the interest of cardiologist shifted toward CRP twenty years ago when Liuzzo and coll. published the first paper demonstrating the clinical role of CRP in acute coronary syndromes (ACS). Soon, studies from Ridker and coll. confirmed the importance of CRP also in primary prevention and showed that CRP could represent a valid biomarker for primary risk stratification and for initiation of a treatment with statins. These evidences have been criticized on the basis of the uncertain pathogenic role of CRP and of its being a no-specific marker of risk reflecting the total risk burden. However recent studies have confirmed and expanded previous results, showing in large cohorts the independent and additive role of CRP in risk stratification. Elevated levels of CRP are significantly associated with outcome also in diabetics, in heart failure pts and in those undergoing implantation of an ICD. Very importantly CRP can be used as a marker of total atherosclerotic burden in general populations but also in those undergoing ICD implantation end in large populations from different countries. More importantly, however, recent studies have raised the possibility that elevated CRP levels might address the opportunity of novel therapies with cytokine antagonist or anti-inflammatory drugs.
ASSOCIATION BETWEEN OBSTRUCTIVE SLEEP APNEA AND CORONARY ARTERY DISEASE

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Much attention has recently been paid to links between sleep disordered breathing (SDB) and cardiovascular diseases, including hypertension, arrhythmia, coronary artery disease (CAD), heart failure, aortic dissection, pulmonary hypertension, and stroke. Obstructive sleep apnea (OSA), which is a chronic condition characterized by repetitive episodes of upper airway collapse, apnea, and arousal during sleep, is the most frequent SDB, with an approximate prevalence of 10 - 20% (defined as an apnea-hypopnea index of 5 or greater) in the general adult population. The prevalence of OSA is up to 2-fold greater in subjects with CAD than in those without CAD. OSA is also frequently observed in subjects with coronary spastic angina. Physicians should therefore proactively screen for OSA in patients with CAD. OSA may be associated with nocturnal myocardial ischemia, nocturnal onset of acute coronary syndrome, and increased mortality and morbidity in subjects with CAD. OSA-induced hypoxia (hypoxia-reoxygenation), hypercapnea, sympathetic nervous activation, and hemodynamic stress (excessively negative intrathoracic pressure and resultant increased cardiac transmural pressure) can cause inflammation, oxidative stress, and vascular endothelial injury, all of which can contribute to the development of atherosclerosis and an increased risk for cardiovascular mortality and morbidity. Nasal continuous positive airway pressure therapy (CPAP), the first-line therapy for OSA, may reduce cardiovascular events in OSA subjects with CAD. However, there is no prospective, randomized, controlled trial of the effects of treatment of OSA on the risks of developing CAD and the cardiovascular mortality and morbidity in CAD patients, and such trials are ethically quite difficult to be undertaken. The precise effects of OSA on CAD and the merits of the treatment of OSA with CPAP in CAD patients with OSA remain to be further clarified.
INTegrative AND Complementary MEDICINE IN CARDIOLOGY: NEW HOPE OR JUST “HIP” AND “HYPE”?  
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Objectives: To review rigorous scientific evidence of benefit and effective treatments in integrative medicine (IM) for cardiovascular disease (CVD). IM integrates traditional medicine with non-conventional therapeutic modalities referred to as complementary alternative medicine (CAM).

Background: CAM use is widespread in the world’s population (38%). The demography of CAM users includes younger age, more educated, and wealthier population. Only 20% discuss CAM use with their physicians. Increasing prevalence of IM warrants elucidating the mechanism of action for benefit, and magnitude of efficacy in CVD for rationale and appropriate use.

Methods: Systematic review of meta-analysis and bibliographic computerized databases was conducted for CAM studies in CVD for efficacy and mechanism of action.

Results: Robust data is lacking for herbal supplementation, the most utilized CAM modality in CVD. Physician referral for acupuncture (AP) worldwide is >40%, but < 5% for CVD. AP benefit in hypertension reduces systolic BP by a small significant 5-10 mmHg with attenuation of sympathetic outflow in animal models. AP efficacy in angina is mixed with small studies, and moderate-high risk of bias based on Cochrane Collaboration analysis. Mind-body CAM using transcendental meditation (TM) has the strongest evidence for reduction in CVD morbidity (hypertension, ischemia on treadmill p<0.001) and all-cause mortality (23% reduction, p< 0.04) in small trials of elderly with control group design. Stress, a major CVD risk factor, influences TM’s mechanism of benefit via BP reduction and heart rate variability.

Conclusions: No established benefit exists in CVD with herbal supplements, the most common CAM. AP and mind-body therapies such as TM are infrequently used and may be overlooked for CVD and need larger studies for conclusive evidence. Current evidence warrants further investigation to augment the therapeutic armamentarium of cardiologists. Elucidation of scientific mechanisms, will encourage physician referral for effective CAM, and foster improved communication between patients and physicians.
Cardiovascular disease remains the leading killer of both men and women in the United States. However, compared to men, women have higher rates of morbidity and mortality secondary to cardiovascular disease. Whether these differences are due to excess sex-specific risk factors can be debated. Studies showing excess sex-specific risk for cardiovascular events, in part due to traditional risk factors as well as novel biomarkers, will be reviewed. We will discuss the excess relative risk from diabetes in predicting incidence of cardiovascular events as well as discuss sex-specific differences in lipids. The role of novel biomarkers of coagulation and fibrinolysis and diagnostic testing, such as endothelial function testing, will be discussed. Recent trial evidence also suggests that strategies for primary prevention in women might be different than in men. Future clinical trials need to address the sex-based differences in the prevalence, etiology, and treatment of heart disease in men and women.
**ASSOCIATION BETWEEN SERUM VITMAIN D LEVELS AND ATHEROSCLEROSIS: A META ANALYSIS**

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**Background:** Prevalence of Vitamin D deficiency (VDD) has increased worldwide. Recent studies have shown VDD as an independent risk factor for adverse cardiovascular events. VDD leads to increased production of proinflammatory cytokines and underexpression of matrix metalloproteinase inhibitors leading to formation and destabilization of atherosclerotic plaques. The objective of this study is to conduct a meta-analysis to evaluate the association between serum Vitamin D level and carotid intima-media thickness (CIMT), a preclinical marker for atherosclerosis.

**Methods:** We searched MEDLINE, CINHAL and COCHRANE LIBRARY for studies reporting serum vitamin D levels and CIMT in the study population. We included case controls, cohort and cross-sectional studies. We calculated the weighted standardized mean difference (SMD) between the CIMT in the >30 mg/dl and <30 mg/dl vitamin D group.

**Results:** Our search strategy yielded 61 studies and we included for this analysis only 8 cross-sectional studies enrolling 4234 participants. The median age of the normal vitamin D group was 59 yrs (31.5 – 66.7) compared to 58.9 yrs (32.2 – 64.3) in the low vitamin D group. The median % of female population in the normal vitamin D group was 34.5% (18 -100) compared to 44% ( 22- 100) in the low vitamin D. The unweighted median CIMT of the normal vitamin D group was 0.755mm (0.07 – 0.945) compared to 0.916mm (0.06 – 1.1) in the low vitamin D. The SMD of CIMT was -0.23 (95% CI -0.29- -0.17) p<0.01 comparing those with normal vitamin D and low vitamin D.

**Conclusion:** VDD shows a strong association with increased CIMT. Current findings warrant the need to further investigate the role of Vitamin D in the prevention and progression of atherosclerosis.
PREDICTION AND PREVENTION OF SUDDEN CARDIAC DEATH

082 POTENTIAL THERAPY FOR THE PREVENTION OF SUDDEN CARDIAC DEATH
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Objectives: Although sudden cardiac death is a leading cause of mortality, the mechanisms for its pathogenesis as well as therapy for prevention are poorly understood.

Background: Since overactivation of sympathetic nervous system is invariably seen in subjects with high risk for sudden cardiac death, elevated levels of circulating catecholamine levels are considered to result in lethal ventricular arrhythmias and subsequent sudden cardiac death. Such arrhythmogenic effects of catecholamines are generally believed to occur by their actions on α-adrenoceptors in coronary arteries for inducing coronary spasm and subsequent myocardial ischemia as well as on β-adrenoceptors in cardiomyocytes for stimulating cardiac function and producing defects in intracellular Ca\(^{2+}\)-handling.

Methods and Results: Experimental evidence from our laboratory has revealed that excessive amounts of circulating catecholamines are oxidized to aminochromes, which are highly reactive quinine compounds. These oxidation products of catecholamines have been demonstrated to produce subcellular alterations, intracellular Ca\(^{2+}\)-overload, coronary spasm, myocardial cell damage, depletion of high energy stores and ventricular arrhythmias. Furthermore, catecholamine-induced arrhythmias and ventricular fibrillation were associated with elevated levels of plasma adrenochromes; however, these changes were markedly attenuated by treatment of animals with different antioxidants.

Conclusions: The results suggest that oxidation of catecholamines under stressful conditions may result in sudden cardiac death and thus different antioxidants may be considered as potential therapy for its prevention.
Between 184,000 and 462,000 Americans die suddenly each year. Fifty to seventy percent of these deaths are due to ventricular tachycardia/fibrillation (VT/VF). We tested whether hibernating myocardium or myocardial sympathetic denervation identifies patients at high-risk for developing VT/VF independently of EF. Positron emission tomography (PET) was used to quantify myocardial sympathetic denervation (11C-meta-hydroxyephedrine, 11C-HED), perfusion (13N-ammonia, 13NH3), and viability (insulin-stimulated 18F-2-deoxyglucose, 18FDG) in patients with ischemic cardiomyopathy (EF<35%) eligible for a primary prevention implantable cardioverter defibrillator (ICD). The primary end-point was sudden cardiac arrest (SCA) defined as arrhythmic death or ICD discharge for VT/VF >240 bpm. Volumes of total denervated (p=0.001) and viable denervated myocardium (11C-HED-18FDG mismatch, p=0.03) predicted SCA, while hibernating and infarcted myocardium did not. Multivariate analysis identified four independent predictors of SCA: denervated myocardium >37.6% LV, LV end-diastolic volume >98 ml/m2, creatinine >1.49 mg/dl, and no ACE- inhibition therapy. Denervated myocardium had a hazard ratio of 3.5 for SCA (10.3%/year vs. 3.0%/year, p=0.001). Absence of all four factors predicted low risk (44% of cohort; SCA <1%/year) while ≥2 identified subjects at high-risk (20% of cohort; SCA 12%/year). Denervated myocardium quantified using PET strongly predicts risk of SCA, and is independent of EF, infarct volume, and other clinical variables.
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CLINICAL EFFECTIVENESS OF CRT AND ICD THERAPY IN PATIENTS WITH HEART FAILURE BY RACE AND GENDER: FINDINGS FROM IMPROVE HF
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Background: Clinical trials have demonstrated benefit for cardiac resynchronization therapy (CRT) and implantable cardioverter defibrillator (ICD) therapies in patients with heart failure (HF) and reduced ejection fraction (EF), yet questions have been raised with regard to the benefit of device therapy for women and minorities.

Methods: IMPROVE HF was a prospective evaluation of an outpatient practice-based performance improvement intervention to increase the use of guideline-recommended care for eligible patients with HF. Data were analyzed by device status as well as sex and race among guideline-eligible patients where vital status (alive/dead) at 24 months was the outcome of interest. Multivariate GEE analyses of device therapy and sex/race were conducted adjusting for baseline patient and practice characteristics.

Results: Among 7748 eligible patients (5485 men, 71%), those with ICD/CRT-D were less likely to die at 2 years compared to those without (20.4% vs. 27.8%, odds ratio (OR) 0.66, 95% confidence intervals (CI) 0.58-0.74, p<0.0001). The benefit associated with ICD/CRT-D therapy was similar in men and women (OR 0.64, 95% CI 0.55-0.75, p<0.0001 and OR 0.65, 95% CI 0.53-0.79, p<0.0001, respectively). CRT-P/CRT-D therapy also showed a survival benefit (28.8% vs. 38.3%, OR 0.63, 95% CI 0.48-0.84, p=0.0017), with similar outcomes in men (OR 0.67, 95% CI 0.49-0.92, p=0.0133) and women (OR 0.53, 95% CI 0.31-0.91, p=0.0227). Regarding race, there was also benefit associated with ICD/CRT-D therapy (OR 0.64, 95% CI 0.52-0.79, p=0.0002 for 24-month mortality) and CRT-P/CRT-D therapy (OR 0.55, 95% CI 0.33-0.91, P=0.0222), which was of similar proportion in white, black, and other minority/not documented patients.

Conclusions: The use of guideline-directed CRT and ICD therapy was associated with substantially reduced 24 month mortality regardless of sex and race. Device therapies should be offered to all eligible HF patients, without restriction based on sex or race.
MITOCHONDRIAL DYSFUNCTION AND ARRHYTHMIC RISK: POSSIBLE NEW THERAPIES FOR SUDDEN DEATH
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Mitochondria are essential to providing ATP thereby satisfying the energy demand of the incessant electrical activity and contractile action of cardiac muscle. Emerging evidence indicates that mitochondrial dysfunction can adversely affect cardiac electrical functioning by impairing the intracellular ion homeostasis and membrane excitability through reduced ATP production and excessive reactive oxidative species (ROS) generation, resulting in increased propensity to cardiac arrhythmias. Recent work by our group has demonstrated that increased cytosolic NADH, because of cardiomyopathy and mitochondria dysfunction, results in decreased INa. This work suggests a link between metabolism and INa. The deleterious effect of NADH accumulation on INa can be ameliorated with NAD+, the oxidized form of the nucleotide. NAD+ supplementation acts via a membrane surface receptor to decrease mitochondrial ROS and raise sodium channel levels. Myocardial infarction (MI) and angiotensin II are also associated with mitochondrial ROS production and decreased expression of Cx43, the principal gap junction protein responsible for propagating current in ventricles. Inhibition of mitochondrial ROS or downstream, activated c-Src improved Cx43 levels and conduction velocity and lowered arrhythmia inducibility in arrhythmic mouse models. These results suggest that myocardial injury is associated with decreased conduction velocity secondary to reduced INa and Cx43. Raising these ion channel levels by reducing mitochondrial ROS production may be a new paradigm of antiarrhythmic therapy.
Sudden death during sports is often the first and definitive manifestation of an underlying cardiovascular disease. Medical evaluation before competition offers the potential to detect still asymptomatic athletes with life-threatening heart diseases and to protect them from sudden cardiac death (SCD). The risk of SCD in young people engaged in regular training and athletic competition has been estimated to be approximately three times the risk among their nonathletic counterparts. Arrhythmic cardiac arrest may be precipitated by the interaction between exercise-induced adrenergic stimulation and underlying cardiovascular diseases, such as cardiomyopathies (mostly hypertrophic cardiomyopathy and arrhythmogenic right ventricular cardiomyopathy) and cardiac ion-channel disorders. A positive family history, an abnormal physical examination, or premonitory symptoms are present in only a minority of young competitive athletes who die suddenly — with sudden cardiac arrest often the first manifestation of previously unsuspected heart disease. Preparticipation screening that relies solely on medical history and physical examination is of only marginal value for the detection of athletes at risk for SCD. The addition of ECG substantially enhances the power of screening for early detection of the leading causes of SCD, which are commonly manifested as ECG abnormalities. The analysis of data coming from the long-running Italian experience indicates that ECG screening has provided adequate sensitivity and specificity for detection of lethal cardiomyopathy or arrhythmias and has led to substantial reduction of mortality of young competitive athletes by approximately 90%. The Italian screening program was feasible thanks to the National Health System, which is developed in terms of health care and prevention services and because of the limited costs of cardiovascular evaluation in the setting of a mass program. On the basis of current scientific evidence the implementation of a mass-screening program aimed to prevent athletic-field sudden cardiac death should be at least carefully considered by public health administrators worldwide.
THE SHORT QT SYNDROME AND SUDDEN CARDIAC DEATH
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The Short QT Syndrome is a genetic disorder characterized by an abbreviated QT interval and vulnerability to atrial and ventricular arrhythmias. The diagnostic criteria for SQTS suggest a QTc of less than 370 ms may signal the presence of this condition, although like LQTS, overlap likely exists with the QT range of a healthy population. Causative genes for this disorder include the same genes that are causative for LQTS, although as opposed to a loss-of-function in LQTS mutations causing SQTS lead to an increase in repolarizing current.
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ABLASTION OF IDIOPATHIC VENTRICULAR TACHYCARDIA
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Idiopathic ventricular tachycardia occurs when ventricular tachycardia occurs in the absence of detectable heart disease. Other than syncope they can cause cardiomyopathy if Premature Ventricular Contraction is frequent. Medications are partially effective but ablation when done carefully is effective over 90% of the time. Most of these arrhythmia is concentrated around the outflow tracts. Implantable cardiac defibrillator (ICD) is generally not indicated and successful ablation is curative.
A CASE OF ORTHOSTATIC HYPOTENSION AND RECENT ADVANCES
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JM is a 78 year old man who had a history of hypertension and developed an ascending aortic aneurysm while under treatment. He presented to the hospital for elective prostate operation and was seen by Cardiology for evaluation of atypical chest pain. The patient gave a history of recurrent syncope over the past 6 years with syncope every 1-2 years. He described one incident as sitting at a stop light in his car driving home after shopping in a mall. The next thing he remembered was being awakened by EMS. Another incident was in the morning getting up to brush his teeth and his wife heard a thump and found him on the bathroom floor.

Orthostatic hypotension is a common cause of syncope, dizziness, angina or less commonly, stroke; and is estimated to have a population prevalence of 5-20%. The main pathophysiologic impairment is during autonomic dysfunction or marked intravascular volume depletion when standing or in an upright posture. A related condition, post-prandial hypotension which occurs after eating and being upright seated or standing between 15-90 minutes after a meal is also common in the elderly. The evaluation should include a good history and physical examination that includes orthostatics even if the patient is asymptomatic at the time of the examination. A thorough medication history is essential, including use of OTC agents that may lead to volume loss. An ECG and echocardiogram to rule out structural heart disease and ambulatory ECG monitoring for a sufficient amount of time to capture a rhythm strip during an event. This may include extended event monitors repeated over several months or an implantable loop recorder (which usually has a 2-3-year life of monitoring) and can be interrogated. A tilt table test can help to rule out postural tachycardia syndrome, neutrally medicated syncope or autonomic failure. Blood tests to rule out electrolyte disorders and adrenal insufficiency.

Management will depend on diagnoses. For orthostatic hypotension that is neutrally medicated, conservative measure like eliminating offending medications, rising slowly from a seated or supine position, support hosiery, and maintaining hydration, and avoiding maneuvers that decrease venous return are recommended. Fludrocortisone is recommended as first line treatment. If unable to tolerate, fludrocortisone, then midodrine can be used.
PREDICTION AND PREVENTION OF SUDDEN CARDIAC DEATH

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NON-INVASIVE RISK STRATIFICATION IN BRUGADA SYNDROME WITHOUT HISTORY OF CARDIAC ARREST: PROGNOSTIC VALUE OF J-WAVE AND ST-SEGMENT MORPHOLOGY
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Introduction: Risk stratification in patients with Brugada syndrome (BrS) without cardiac arrest has not been clearly determined. We evaluated the prognostic value of a J-wave and ST-segment morphology after J wave in infero-lateral leads as non-invasive markers in a large Japanese cohort of BrS.

Methods and Results: A total of 402 consecutive BrS patients without previous cardiac arrest (mean age 52±17; 14 years, 375 males) were enrolled. Clinical and ECG characteristics, including the location of leads showing a J wave, ST-segment, and clinical outcomes, were evaluated in patients with syncope without documented VF (N = 122), and asymptomatic subjects (N = 280). The prevalence of J wave at inferior and/or lateral leads was 10%, which was not different between the 2 groups. The incidence of cardiac events (sudden death orVF) during a mean follow-up period of 57±34 months was 8.2% and 1.8% in syncope and asymptomatic groups, respectively (p=0.003), and was significantly higher in patients with symptoms, spontaneous type 1 ECG, and the combination of a J wave in both inferior and lateral leads with horizontal ST-segment after the J wave, as determined by univariate and multivariate analysis. The combination of a J wave in both inferior and lateral leads with horizontal ST-segment yielded a higher hazard ratio than the other parameters. Inducible VT/VF and family history of sudden cardiac death were of no predictive values.

Conclusion: Presence of a J wave in multiple leads and horizontal ST-segment after the J wave may indicate a highly arrhythmogenic substrate in BrS patients without previous cardiac arrest.
INFLAMMATION AND CARDIOVASCULAR DISEASE MECHANISMS

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INNATE IMMUNITY AND HEART DISEASE
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The innate immune system is a primitive, rapid immune response that responds to detected threats by producing a rapid inflammatory response. A series of pattern recognition receptors (PRR) recognizes molecular patterns (pathogen associated molecular patterns or PAMPs) that are common to microbes and to danger signals (damage-associated molecular patterns or DAMPs) from injured cells. These signals can activate specific toll-like receptors (TLRs), which then activate a rapid inflammatory response. Innate immunity is essential, as adaptive immunity, which produces antibodies, takes 4-5 days for a complete response. The heart contains TLRs, of which TLR2 and 4 have been most studied. TLR2 and 4 can be activated by proteins and other molecules released by injured or stressed cardiac myocytes. In the failing rat heart heat shock protein (HSP) 60 is present on the surface of cardiac myocytes. We have previously shown that heat shock HSP60 activates TLR4 leading to NFkB activation and the production of inflammatory cytokines, which in turn causes apoptosis in other cardiac myocytes. Ischemia/reperfusion releases a host of molecules, which can lead to local activation of innate immunity, compounding injury. Thus, innate immunity is an important factor in the heart disease and the progression of heart failure.
INFLAMMATION AND CARDIOVASCULAR DISEASE MECHANISMS

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ROLE OF ENDOTHELIN-1 AND CAMKINASE II SIGNALING IN CARDIOVASCULAR COMPLICATIONS
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Vasoactive peptides such as angiotensin II and endothelin-1 as well as growth factors regulate vascular homeostasis through signaling pathways that are triggered in both normal and disease states. These vasoactive peptides and growth factors also increase the cellular levels of calcium which, through calcium binding effector systems initiates the downstream signaling and physiological responses in target cells. A multifunctional calcium-calmodulin-dependent protein kinase II (CaMKII) has emerged as an important transducer of vasoactive peptide-induced responses in vascular smooth muscle cells (VSMC). Endothelin-1 (ET-1), a potent vasoactive peptide with a pathogenic role in vascular diseases, has been shown to induce the activation of ERK1/2, PKB and the expression of a transcriptional regulator, the early growth response 1 (Egr-1), key mediators of hypertrophic and proliferative responses in VSMC. Here, by utilizing pharmacological inhibitors of calmodulin (CaM) and CaMK, and by CaMKII knockdown techniques, we have investigated the contribution of CaM and CaMKII in ET-1-induced ERK1/2 and PKB signaling, Egr-1 expression and hypertrophic and proliferative responses in VSMC. W-7 and calmidazolium, antagonists of CaM, as well as KN-93, an inhibitor of CaMKII activity, attenuated ET-1-induced ERK1/2 and PKB phosphorylation. In addition, transfection of VSMC with a CaMKII inhibitory peptide suppressed ET-1-evoked ERK1/2 and PKB phosphorylation. Similarly, siRNA-mediated CaMKII silencing reduced ET-1-produced ERK1/2 and PKB phosphorylation. CaM and CaMKII blockade also significantly lowered the ET-1-induced protein and DNA synthesis as well as Egr-1 expression. These findings demonstrate that CaMKII by regulating ET-1-induced growth promoting signaling pathways and hypertrophic as well as proliferative responses plays a key role in vascular pathophysiology.

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INFLAMMATION AND POST-ISCHEMIC CARDIAC REMODELING: MOLECULAR MECHANISMS AND THERAPEUTIC PERSPECTIVES

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Various types of inflammatory cells are recruited to ischemic sites, where they play an active role in vascular and tissue remodeling in the context of myocardial infarction (MI). The overall effect of the various actors of the inflammatory component depends on the local environment, the activation and differentiation states of each cell type of inflammatory cells. Hence, monocytes constitute a heterogeneous population with two major subtypes in mice: Ly6ChighCCR2+CX3CR1low monocytes and Ly6ClowCCR2-CX3CR1high monocytes corresponding in humans to the CD14+CD16- and CD14lowCD16+ subpopulations, respectively. These two subtypes of monocytes are recruited sequentially to the ischemic tissue and display different functions. They have similar capacities for the phagocytosis of dead cell debris, but Ly6Chigh monocytes trigger adverse ventricular remodeling whereas Ly6Clow monocytes express VEGF strongly and participate to the positive outcome after MI. Similarly, two subtypes of macrophage (M) can be distinguished on the basis of various markers and functional criteria and it is widely agreed that the M2 population favors tissue regeneration. In addition, the inflammatory reaction within the infarcted heart is promoted by both innate and adaptive immunity. After acute MI in mice, mature B lymphocytes selectively produce Ccl7 and induce Ly6Chigh monocyte mobilization and recruitment to the heart, leading to enhanced tissue injury and deterioration of myocardial function. Genetic (Baff receptor deficiency) or antibody-mediated (CD20- or Baff-specific antibody) depletion of mature B lymphocytes impeded Ccl7 production and monocyte mobilization, limited myocardial injury and improved heart function. These effects were recapitulated in mice with B cell-selective Ccl7 deficiency. Of interest, high circulating concentrations of CCL7 and BAFF in patients with acute myocardial infarction predict increased risk of death or recurrent myocardial infarction. Hence, a crucial interaction between mature B lymphocytes and monocytes occurs after MI, identifying new therapeutic targets for patients with acute MI.
Vascular endothelial dysfunction and inflammation are hallmarks of atherosclerosis. Increasing evidence supports that laminar blood flow activates several genes that play important roles in maintaining endothelial function, inhibiting vascular inflammation, and preventing atherosclerotic development. In particular, Krüppel-like factor 2 (KLF2) and endothelial nitric oxide synthase (eNOS) are key mediators in laminar flow anti-inflammatory and anti-atherosclerotic actions. However, the molecular mechanisms by which laminar flow mediates atheroprotective gene expression remain poorly understood. We have found that histone deacetylase 5 (HDAC5) inhibited flow-mediated KLF2 and eNOS expression in endothelial cells. Fluid shear stress generated by laminar flow stimulated HDAC5 phosphorylation and nuclear export in endothelial cells through a calcium/calmodulin-dependent pathway. Consequently, laminar flow induced the dissociation of HDAC5 and myocyte enhancer factor-2 (MEF2) and KLF2, and enhanced both MEF2 and KLF2 transcriptional activity, which leads to expression of KLF2 and eNOS in endothelial cells. HDAC5 depletion by HDAC5 siRNA transfection exhibits a significant enhancement in endogenous eNOS expression in endothelial cells. Importantly, adenoviral overexpression of a HDAC5 phosphorylation-defective and nucleus-localized mutant attenuated the laminar flow-mediated KLF2 and eNOS expression and laminar flow inhibitory effects on monocyte adhesion to endothelial cells. Collectively, our studies define a novel role of HDAC5 in regulation of flow-mediated KLF2 and eNOS gene expression. Our findings suggest that HDAC5 could be a new molecular target to prevent vascular inflammation and endothelial dysfunction associated with cardiovascular disease.
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NOVEL ALTERNATIVE MECHANISMS OF CARDIOVASCULAR CALCIFICATION
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The global impact of the spectrum calcific cardiovascular diseases is serious but underappreciated health problem in the developed world. Cardiovascular calcification is an independent risk factor for cardiovascular morbidity and mortality. Recent studies showed that small (sub)cellular size calcification/microcalcifications contribute to plaque failure. However, the derivation of microcalcifications is poorly understood due to the inability to monitor calcification nucleation in vivo. Here we present optical molecular imaging as a promising tool that simultaneously detects pathobiological processes associated with inflammation and microcalcification in vivo at the (sub)cellular levels. Research into treatment of cardiovascular calcification is lacking, as shown by clinical trials that have failed to demonstrate the reduction of calcific aortic stenosis. Hence the need to elucidate the pathways that contribute to cardiovascular calcification and to develop new therapeutic strategies to prevent or reverse calcification has driven our investigations. We previously showed that early calcification/microcalcification associates with macrophage accumulation in vulnerable atherosclerotic plaques. Chronic renal disease (CRD) accelerates calcification and the subsequent release of matrix vesicles (MVs) — precursors of microcalcifications. We tested the hypothesis that macrophage-derived MVs contribute directly to microcalcifications. We showed that macrophages associated with regions of calcified vesicular structures in human carotid plaque samples (n=136 patients). In vitro, macrophages released MVs with high calcification potential. MVs expressed exosomal markers (CD9 and TSG101), and contained S100A9 and annexin V (Anx5). Silencing S100A9 in vitro and genetic deficiency in S100A9-/- mice reduced MV calcification, while stimulation with S100A9 increased calcification potential. Externalization of phosphatidylserine (PS) after Ca/P stimulation, and interaction of S100A9 and Anx5, indicated that a PS–Anx5–S100A9 membrane complex facilitates hydroxyapatite nucleation within the macrophage-derived MV membrane. These results supported the novel concept that macrophages release calcifying MVs, which contribute to accelerated formation of microcalcification, thus providing an alternative mechanism of calcification as opposed to osteogenic differentiation.
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PHARMACOLOGICAL MODULATION OF ANGIOTENSIN-II-INDUCED ARTERIAL MONONUCLEAR CELL ADHESION BY NUCLEAR RECEPTORS ACTIVATION
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Objective: The need of effective strategies to treat and prevent atherosclerosis led us to investigate the effect of combined concentrations of Rosuvastatin (Rosu) and bexarotene (Bex) on angiotensin II (Ang-II)-induced arterial mononuclear cell (MC) recruitment.

Background: MC infiltration into the arterial subendothelium constitutes an early event of the atherogenic process. Rosu or Bex exert anti-inflammatory activity but concerns regarding the development of serious adverse effects have risen.

Methods: MC-endothelium interactions were evaluated in vitro using the dynamic flow chamber assay and human umbilical arterial endothelial cells (HUAEC). In vivo, arteriolar leukocyte adhesion was determined by intravital microscopy.

Results and conclusions: HUAEC were stimulated with Ang-II (1 μM) for 4h. Rosu (10-30 nM), Bex (0.3-1 μM) or different combinations of both, were added to plates 20h before Ang-II challenge. Surprisingly, a combination of Rosu (10 nM)+Bex (0.3 μM) which did not affect Ang-II-induced MC recruitment when either stimulus was assayed alone, significantly reduced this response. This effect was accompanied by diminished Ang-II-induced ICAM-1, VCAM-1 and CX3CL1 endothelial expression as well as CXCL1, CXCL8, CCL2 and CCL5 synthesis. Rosu+Bex HUAEC preincubation caused a drastic inhibition of RhoA activation by Ang-II and RhoA knockdown prevented Ang-II-induced arterial MC arrest. Increased RXRα, PPARα and PPARγ expression was detected in Bex+Rosu preincubated HUAEC and further stimulated with Ang-II. HUAEC transfection with RXRα, PPARα or PPARγ specific siRNA reversed the Bex+Rosu inhibitory response. In vivo, chronic administration of Ang-II to mice (500 ng/kg/min, 14 days) increased cremasteric arteriolar leukocyte adhesion. While chronic Rosu (1.25 mg/kg/day) or Bex (10 mg/kg/day) administration did not exert any significant effect on this parameter, their combined administration ameliorated it by 65%. These data indicate that combined administration of Rosu+Bex at suboptimal doses may constitute an alternative therapy in the control of the vascular inflammation minimizing the appearance of drug-associated adverse effects.
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TRAINING OF CARDIOVASCULAR PHYSICIAN-SCIENTISTS: RESULTS OF SPECIFIC TRAINING PATHWAYS

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Objectives: Determine factors that predict successful career development for physician-scientists mediated by three programs: MD-PhD, Physician-Scientist Residency, and NIH-funded K-awards.

Background: Physician-scientists play a crucial role in biomedical research in the United States. However, the number and portion of MD’s who commit a major portion of their professional time to research and who receive major external funding is diminishing.

Methods: National data on outcomes and career success rates for three physician-scientist development programs were examined (MD-PhD, American Board of Internal Medicine Research Pathway, and NIH K-award programs.) The intersection of these programs for trainees and their subsequent career success rate was determined.

Results: MD-PhD programs have expanded over ten years (2002-2012) by 40%, with 73% of matriculants actually receiving both the MD and PhD. Predictors of attrition from the PhD program include MCAT score <34, age >23 at matriculation, and being at an institution that does not have NIH support for the MD-PhD program. Having received an MD-PhD is an important element for entering an Internal Medicine Research Pathway, as 60% of program members have a PhD and 13% a Master’s degree. Earning a PhD prior to residency is the strongest predictor of future success in a funded research career. An additional strong predictor is having received personal external grant funding, notably a K-award from the NIH. Funding of research career development awards from the NIH have been declining since 2006. NIH K08 and K23 award success rate is 35-42%; at the NHLBI the current rate is 25-30%.

Conclusion: Completing an MD-PhD prior to residency and receiving a K award from the NIH are key elements that predict research career success. MD-PhD programs have recently expanded. Research Pathway trainees are few, and K award funding is declining.
Various studies showed that extracellular matrix proteins influence inflammatory reactions. Interestingly, our previously studies suggested that suppressing different leukocyte subsets significantly affected composition of scar. Therefore, we hypothesized that different inflammatory responses might lead to different composition of extracellular matrix and might be responsible for various outcomes after MI. To study the relation between the different leukocyte subsets and extracellular matrix protein, we induced myocardial infarction in different knockout models, such as CCR1−/− (reduced neutrophils), CCR2−/− (reduced inflammatory monocyte), CCR5−/− (reduced T cells) and CX3CR1−/− mice (reduced reparatory monocyte). After healing, the function, the infarction size, stiffness (atomic force microscopy) and composition were analyzed. Scar tissue from CCR1−/− presented higher mRNA expression of collagen 11, moderate collagen 19 and low collagen 13 and 26 compared with other groups. CCR2−/− scar tissue showed higher level of collagen 13, while CX3CR1−/− scars expressed high level of collagen 19 and collagen 26 compared with other mice. In order to study possible mechanisms and involved signaling pathways, isolate myofibroblasts were stimulated with TGF-β1 and co-incubated with different leukocyte subsets under normoxic/hypoxic conditions. Co-incubation with inflammatory cells dramatically changed the mRNA expression of most collagens, biglican and fibronectin in myofibroblasts. While co-incubation with neutrophils increased the mRNA level of biglican and fibronectin and reduced the level of collagen 1, 3, 5, 16, 23, co-incubation with monocytes did not change biglican and fibronectin, and reduced moderate, but still significant the level of collagen 5 and 16. Neutrophils seemed to increase the inflammatory-, differentiation-, migration-, angiogenesis-related genes. Monocytes increased proliferation-, and remodeling-related genes, while inhibited the migration- and inflammation-related genes. These results demonstrate for the first time that inflammatory cells are able to influence protein synthesis in myofibroblasts, thus interfering active in extracellular matrix deposition and scar formation.
REGULATION OF ENDO THELIAL VCAM-1 EXPRESSION VIA MODULATION OF ANTI-OX IDANT PATHWAY

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Objectives: The Purpose of this study was to determine if TSP-1 utilizes Nrf2-driven antioxidant pathway in regulating the expression of adhesion molecules on vascular endothelial cells (ECs).

Background: Thrombospondin-1 (TSP-1) is a matrix protein with a pro-inflammatory role described in acute inflammatory condition, but an anti-inflammatory role in chronic inflammation. Vascular ECs express two TSP-1 receptors namely CD36 and CD47, known to induce different signaling pathways. Inflammatory cytokine IL-17 induces increased expression of VCAM-1 and also induces oxidative stress.

Methods: Vascular endothelial cells (2H-11) treated with TNFa or IL-17 (10 ng/ml) or TSP-1 derived peptides (CD36 or CD47 binding) were stained with antibodies against ICAM-1, VCAM-1, Nrf2 and TSP-1 followed by fluorescence-conjugated secondary antibodies. Stained ECs were evaluated using fluorescence microscopy. Leukocyte adhesion assay was performed using CFSE-labeled mouse lymph node cells. Fluorescence of EC-adherent cells was measured using a fluorescence reader.

Results: To evaluate possible TSP-1 dependent regulation of adhesion molecules on vascular endothelium during chronic inflammation we examined the expression of VCAM-1 and TSP-1 in 2H-11 ECs treated with IL-17. While VCAM-1 immunostaining was enhanced, that of TSP-1 was reduced in ECs treated with IL-17 as compared to the untreated control cells. We used TSP-1 derived peptides that specifically bind CD47 or CD36 receptor on ECs. While CD47 ligation on ECs reduced CD36 ligation enhanced IL-17-induced VCAM-1 staining. This difference correlated with an enhanced staining of a transcription factor associated with anti-oxidant pathway, Nrf2, upon CD47 ligation and reduced staining of the same upon CD36 ligation on ECs. These results suggest a differential regulation of VCAM-1 expression on ECs possibly via Nrf2-driven antioxidant pathway.

Conclusions: Our results suggest a TSP-1-mediated differential regulation of inflammation-induced expression of adhesion molecules in vascular endothelium via anti-oxidant pathway possibly explaining the contradictory role of TSP-1 in acute vs. chronic vascular inflammatory responses.
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CHRONIC KIDNEY DISEASE AUGMENTS CARDIOVASCULAR RISK: MODULATION OF MYOCARDIAL BLOOD FLOW REGULATION AND CYP450 ARACHIDONIC ACID METABOLITES

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Chronic kidney disease (CKD) increases cardiovascular risk. Metabolites of the arachidonic acid released by vascular and inflammatory cells via cytochrome P-450 (CYP450) pathways can affect vessel tone and contribute to vascular disease. In this study, we 1- evaluated myocardial blood flow (MBF) regulation and its transmural distribution during increased cardiac work, and 2- measured CYP450 metabolites in heart, liver and kidney biopsies in dogs with CKD. CKD was produced by a two-stage subtotal nephrectomy; control (CTR) dogs underwent a sham procedure. Serum creatinine and blood urea nitrogen were evaluated weekly along with systemic blood pressures. After 5 weeks, CKD dogs were staged (as per International Renal Interest Society guidelines); all dogs were anesthetized and prepared for blood flow studies. Cardiac work was increased using dobutamine (5 and 10 µg/Kg/min IV); MBF was measured with neutron-activated microspheres. At the end of each experiment tissues were harvested, washed in cold PBS and snap frozen. ELISA kits were used to assess 20-hydroxyeicosatetraenoic acid (20-HETE-vasoconstrictor) and 14,15-dihydroxyeicosatetraenoic acid (14,15-DHET-vasodilator). All data are mean±1SD; hemoglobin levels were 11.3±1.7 g/dL in CTR versus 7.3±1.0 g/dL (p less than 0.05) in CKD (stage 2) dogs. In CTR dogs, MBF increased 2.6±0.9-fold at the highest dobutamine dose while in CKD dogs maximum responses (3.8±1.5-fold) were obtained with 5 µg/Kg/min dobutamine. Results indicate that coronary reserve is easily exhausted when cardiac work is increased. Cardiac 20-HETE/14,15-DHET ratios decreased in CKD (1.03±0.14; p less than 0.05) compared to CTR dogs (1.2±0.04). In liver tissues, 20-HETE/14,15-DHET ratios were 0.97±0.03 versus 1.04±0.06 (p less than 0.05) in CTR and CKD dogs; no change was observed in remnant kidney biopsies from either group. In conclusion, we report significant reduction of coronary vascular reserve and MBF regulation during CKD. Production of CYP450 metabolites is also altered; however, their contribution to MBF regulation, particularly with respect to progressive kidney disease, remains unknown.
INFLAMMATION AND CARDIOVASCULAR DISEASE MECHANISMS

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ROLE OF NON-GENOMIC SIGNALING IN THE TISSUE SPECIFIC AND VASCULAR PROTECTIVE EFFECTS OF ESTROGEN
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Clinical and mouse model studies indicate that estrogen can protect against vascular disease and damage by binding to the Estrogen Receptor alpha (ER alpha) transcription factor. However, the effects of estrogen differ greatly between tissues (e.g. also promoting thrombosis and breast cancer in post-menopausal women). 17-beta estradiol (E2)-bound ER can regulate transcription by binding to ERE elements on DNA ("genomic" signaling), but can also activate cellular kinases including PI3K, Akt, Src and ERK ("rapid signaling"), which could potentially alter the activities of other transcription factors. The functions of rapid signaling in mediating the vascular effects of E2, and the mechanisms underlying its tissue specific effects, however, are largely unknown.

Using novel rapid signaling-deficient transgenic mice, we find that rapid signaling is required for the ability of E2 to reduce remodeling after vascular injury in vivo, inhibit smooth muscle cell growth and promote endothelial cell migration. We also find that rapid signaling is involved in the regulation of a large number of genes by E2 in aorta. In other recent studies, we find that E2 regulates very different sets of genes, and that ER alpha binds to very different genome wide locations on chromatin, in mouse aorta versus liver. Interestingly, aorta-specific E2-downregulated genes are not significantly associated with nearby ER alpha binding sites, but show strong promoter enrichment of consensus binding sites for transcription factors other than ER, many of which are targets of rapid signaling kinases.

These observations indicate that rapid signaling is required for the protective effects of E2 in vascular injury, and that a relatively strong role for rapid signaling could underlie vascular- versus liver-specific regulatory responses to E2. Interestingly, one aorta-specific E2 response was the down-regulation of inflammatory genes, suggesting that E2 may specifically protect against vascular damage by limiting inflammation.
NEW DIRECTIONS IN CARDIOVASCULAR SURGERY

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CHALLENGE OF READMISSIONS IN THE LVAD SUPPORTED HEART FAILURE POPULATION
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Purpose: The purpose of this retrospective study was to characterize readmissions for patients supported by continuous flow left ventricular assist devices (LVADs) to expand our understanding of the patient population, guide future practice decisions, and prepare for potential changes in reimbursement and regulatory practices. Our primary objective was to quantify heart failure (HF) associated readmissions that fell within 30 days of discharge from a previous HF associated admission.

Methods and Procedures: ED visits, readmissions per year of LVAD support, and all readmissions, including HF flagged readmissions, were characterized. Inferential statistics were used to compare readmissions rates for patients with average vs. extended length of stay (LOS), INTERMACS profile and LOS, INTERMACS profile and readmissions, and LOS and LVAD indication (i.e. bridge-to-transplant vs. destination therapy).

Results: For 121 LVAD patients cumulatively supported for 74,229 days, 252 readmissions were categorized into 26 groups. Top causes included GI bleed (23.8%), CVA or TIA symptoms (7.5%), VT and/or AICD fire (6.7%), hemolysis (5.2%) and “other infection” (5.2%). Average number of readmissions per year was 1.1 by yr 1, 1.7 by yr 2, and 3.2 by yr 3. Between years 2-3 of support, patients with ≤;28 days LOS had significantly less readmissions compared to those with >28 days LOS (2 vs. 5.5 readmissions, respectively, p=0.01). Readmission rate was independent of LVAD indication and INTERMACS profile. LOS was independent of INTERMACS profile. 49% of ED visits resulted in admissions. 9.9% of readmissions were associated with HF. 1.6% of readmissions constituted HF associated readmissions within 30 days of a HF discharge for the same patient.

Conclusion: Only 1.6% of all readmissions for LVAD patients constituted HF related readmissions within 30 days of discharge. INTERMACS profile and LVAD indication did not influence readmissions. Average LOS following LVAD implantation influenced readmissions (2-3 yr support).
CAN BLOOD TYPE O PATIENTS ON LVADS BE AT INCREASED RISK FOR GI BLEEDS?

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Purpose: Literature suggests patients with blood type O have decreased levels of von Willebrand Factor (VWF). Alteration of VWF levels is thought to be associated with increased predisposition to gastrointestinal (GI) bleeding in continuous flow left ventricular assist device (LVAD) patients. The primary purpose of this retrospective study was to determine if LVAD patients with blood type O experienced significantly more GI bleeding. The secondary objective was to determine if age, gender, INTERMACS profile, and continuous flow LVAD type are associated with increased GI bleeding.

Methods and Procedures: Data was analyzed for 118 discharged continuous flow LVAD patients. The chi-square test was performed to test for statistical independence (p<0.05) between the Non-GI bleed group, GI bleed group and categorical variables (e.g. blood type, gender, INTERMACS profile, device type). A t-test was performed to test for significance (p<0.05) between groups for age.

Results: Blood type, gender and INTERMACS profile were not associated with significant incidence of GI bleeding. Patients supported by the HeartMate II (HMII) LVAD experienced more GI bleeding than patients supported by the HeartWare LVAD (p=0.009). Age was a significant factor for GI bleeding (p=0.0004). HMII LVAD patients who experienced GI bleeding had a mean age of 59.8 years vs. 55.7 years for HMII LVAD patients in the Non-GI bleed group.

Conclusion: Not finding a significant correlation between blood type and GI bleeding may be an important piece of information as we continue to study the association between VWF and GI bleeding in LVAD patients. The fact that HMII LVAD patients had significantly more GI bleeding was not surprising, due to high shear stress to blood components from high speed and small gap distance between the impeller and pump housing. Increased age has been reported to be associated with greater GI bleeding in LVAD patients.
Background: Paradoxical association of smoking and in-hospital mortality among heart failure patients is well known. We aimed to ascertain the relationship between smoking and clinical outcomes among heart transplant recipients from a national database.

Methods: Of 13,961 heart transplant recipients within the Nationwide Inpatient Sample datasets 2003-2010, 1,048 (7.5%) were current or previous smokers (defined by ICD-9 codes 305.1 and V15.82). Multivariable logistic regression models were used to measure the association of smoking and outcomes among these patients.

Results: Prevalence of smoking decreased from 12% in 2003 to 5% in 2010 among heart transplant recipients. Smokers were more likely to be older males with hypertension and history of substance abuse but less likely to have complicated diabetes mellitus and had similar renal failure. The in-hospital mortality risk was less in smokers (1.3 vs. 5.5%, $P < 0.001$). After adjustment for important patient and hospital characteristics, smokers still had lower in-hospital mortality risk (Odds ratio; 0.28, 95% confidence interval; 0.16-0.48, $P < 0.001$). Smoking was also associated with shorter length of stay and lower hospital charge (Table).

Conclusion: Among heart transplant recipients, those who were current or previous smokers had lower risk adjusted in-hospital mortality compared with non-smokers. These observations extend the well-known smokers’ paradox and may have implications for the selection of heart transplant recipients.

<table>
<thead>
<tr>
<th>Table: In-hospital outcomes by smoking status among heart transplant recipients at Nationwide Inpatient Sample databases 2003-2010 (N=13,961)</th>
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<tbody>
<tr>
<td>In-hospital outcomes</td>
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<td>----------------------</td>
</tr>
<tr>
<td>No smoking (N=12,913)</td>
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<tr>
<td>Mortality</td>
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<tr>
<td>Length of stay ≥ median 21 days</td>
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<tr>
<td>Total charge ≥ median $370,502</td>
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*Adjusted for age, sex, comorbidities, payment status, median household income, hospital region and hospital bed size.
NEW DIRECTIONS IN CARDIOVASCULAR SURGERY

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PROENKEPHALIN PREDICTS ACUTE KIDNEY INJURY IN CARDIAC SURGERY PATIENTS
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Background: Acute kidney injury (AKI) occurs in up to 40% of patients undergoing cardiac surgery. Proenkephalin A 119-159 (pro-ENK) is a novel stable surrogate biomarker for enkephalins, endogenous opioids involved in various physiological processes including neurohormonal stress.

Methods: 92 patients undergoing cardiac surgery at the Veterans Affairs San Diego Healthcare System were retrospectively studied for the ability of pro-ENK to predict AKI as well as to compare it against other risk factors for development of AKI.

Results: Of 92 patients, 20 patients developed AKI post-operatively. Pro-ENK levels were significantly elevated in patients who develop AKI. Log pro-ENK value pre-operatively has a hazards ratio of 23.8 (p=0.011, 95% CI = 2-270) in its association with AKI. Pro-ENK performs similarly to baseline creatinine in its ability to predict post-operative AKI. Additionally, changes in pro-ENK level from pre-op to 12 hours post-operatively have greatest area under curve by ROC analysis for AKI after post-op day 1.

Conclusion: Pro-ENK is associated with prediction of AKI in patients undergoing cardiac surgery. Future studies utilizing this novel biomarker should be considered to further elucidate its clinical utility in cardiorenal syndromes and to better understand mechanisms of renal injury.
NEW DIRECTIONS IN CARDIOVASCULAR SURGERY

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QUALITY OF LIFE OUTCOMES IN ELDERLY PATIENTS UNDERGOING CORONARY ARTERY BYPASS GRAFT SURGERY: WHAT IS THE EVIDENCE?
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Background: The ageing population of developed countries has increased the population of elderly patients undergoing coronary artery bypass graft surgery (CABG). Contemporary series have demonstrated that elderly patients can achieve good peri-operatives and have long-term outcomes comparable to the age-adjusted population. There is considerably less evidence, however, on the health-related quality of life (HRQOL) outcomes after CABG in elderly patients.

Methods: We performed a comprehensive review of clinical studies published after January 2000 which evaluated HRQOL in the elderly after CABG. Strict inclusion and exclusion criteria were applied. Quality appraisal and data extraction was performed using pre-defined criteria. HRQOL results were synthesized and the results of all studies were critically appraised.

Results: Eighteen studies satisfied the selection criteria. HRQOL improvements were shown across most domains in different HRQOL instruments. Elderly patients experience rapid symptomatic relief and good early HRQOL. Although this recovery may be slower than younger patients, they can achieve equivalent HRQOL at one year. Long-term follow-up shows elderly patients have improved HRQOL compared to their pre-operative state and also to an age-matched general population. This benefit is persistent although there may be an eventual natural age-dependent decline in physical health. The majority of these patients were willing to undergo surgery again. In addition, there appears to be considerable benefits for preserving independence, increasing daily activities and exercise, increased enjoyment of life, less anxiety about having sudden death, and good treatment satisfaction. There was a diverse range of study designs, methods and follow-up times which limited direct comparison between studies.

Conclusion: CABG results in significant HRQOL benefits across a broad range of health domains in elderly patients. Hence, age should not preclude patients from undergoing CABG surgery.
NEW DIRECTIONS IN CARDIOVASCULAR SURGERY

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RELATIONSHIP BETWEEN THE ANGIOGRAPHICALLY DERIVED SYNTAX SCORE AND OUTCOMES IN HIGH-RISK PATIENTS UNDERGOING PERCUTANEOUS CORONARY INTERVENTION
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Introduction: Numerous risk scores have been designed to predict the outcome of percutaneous coronary intervention (PCI). The Synergy between Percutaneous Coronary Intervention with Taxus and Cardiac Surgery (SYNTAX) score has been shown to predict outcome in patients with severe coronary artery disease (CAD) randomized to PCI or bypass surgery, but its utility in patients with less severe CAD is less well established.

Methods: We calculated the SYNTAX score in 482 patients with diabetes mellitus or chronic kidney disease (serum creatinine >1.5 mg/ml) undergoing non-emergency PCI. The study endpoint was 3-year all-cause mortality or repeat revascularization.

Results: The mean age was 69+11 years, 44% were women, 82% had diabetes and they had 1.82±0.78 diseased vessels. The mean creatinine clearance was 67.3±37.2 ml/min. The mean SYNTAX score was 11±8, median of 9 (5-15), tertiles <7, 7-12 and >12. There was good inter-observer concordance (0.784 and 0.816, P<0.01, respectively among two pairs of observers). The 3-year estimated survival rate was 0.85 (95% CI 0.82-0.88). By multivariable analysis, creatinine clearance (HR 0.82 per 10 ml/min, P<0.001), ejection fraction (HR 0.82 per 10%, P=0.004) and prior infarction (HR 1.7, P=0.03) were the only predictors of death. The SYNTAX score did not predict mortality. The incidence of repeat PCI by increasing tertiles of SYNTAX score was 19.2%, 32.2% and 33.2%, respectively, P<0.001.

Conclusion: In patients at high-risk for ischemic events without severe CAD, the SYNTAX score is not associated with mortality at 3 years.
NEW DIRECTIONS IN CARDIOVASCULAR SURGERY

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MANAGEMENT OF HEPARIN INDUCED THROMBOCYTOPENIA AND LEFT VENTRICULAR THROMBUS IN A PATIENT WITH CARDIOGENIC SHOCK
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Background: Anticoagulation with heparin is the standard of care during cardiopulmonary bypass (CPB) for mechanical circulatory support (MCS) surgery. However, patients with active Left Ventricular (LV) apical thrombus and heparin-induced thrombocytopenia (HIT) pose a special challenge. We report a case of a patient with LV thrombus and HIT who required MCS.

Case: Forty-year-old female presented with cardiogenic shock secondary to ST-elevation myocardial infarction. She was treated with thrombectomy and drug eluting stent (DES) of the left main coronary artery. She was anticoagulated with intravenous heparin, as well as aspirin and clopidogrel for her DES. Initial transthoracic echocardiogram (TTE) indicated an ejection fraction of 10% and no evidence of LV apical thrombus. Her clinical condition continued to deteriorate requiring inotropes and an intraaortic balloon pump (IABP). Repeat TTE demonstrated a large LV apical thrombus. Decision was made to place a left-sided centrifugal pump. Postoperatively, however, patient was found to be HIT positive with an optical density of 2.6. Heparin was discontinued and patient was started on argatroban. A month later, after her optical density came down to 0.6, she was implanted with a HeartMate II left ventricular assist device (LVAD). Intraoperative heparin was utilized again and patient was immediately started on postoperative argatroban bridging with coumadin. She made progressive recovery and underwent heart transplantation.

Conclusion: To the best of our knowledge, this is the first reported case of a patient with HIT and LV thrombus, who underwent sequential temporary and durable LVAD placement while receiving intraoperative heparin. We demonstrate that patients who are HIT positive with an LV apical thrombi requiring an LVAD may still undergo CPB on heparin anticoagulation.
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IS PRIOR CORONARY REVASCULARIZATION RELATED TO HIGHER MORTALITY RATE IN A HIGH RISK US VETERAN POPULATION?
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Background: Generally it is perceived that patients with prior revascularization will have higher mortality rates compared to those with no prior revascularization. We sought to investigate this relationship in a US veteran population with atherothrombotic risk factors.

Methods: We conducted a retrospective study of 1002 consecutive patients (Oct 2001 to July 2004) at a Veteran Affairs (VA) health care facility. All-cause mortality rates were determined at the end of the follow-up period, May 2013.

Results: Mean age was 63.1±10.8 years with 98% male. Mean body mass index (BMI) was 29±6. The prevalence of selected risk factors were: hypertension (HTN) (87%), diabetes (DM) (44%), hyperlipidemia (HLP) (79%), and smoking (40%). The baseline serum creatinine was 1.14±0.89 mg/dL, with 14.9% patients having chronic kidney disease (CKD). The mean serum glucose was 129±61 mg/dL and the mean total cholesterol was 180±46 mg/dL with 77% patients on statins. Mean left ventricular ejection fraction (LVEF) was 47%±13%. Of the 1002 patients, 369 (37%) had prior revascularization and 633 (63%) had no prior revascularization. The non-adjusted mortality rate was higher in the revascularized group (50.7% vs 43.0%, p=0.018 with chi square test). However, adjusted for 10 univariate risk factors (Age, BMI, CKD, DM, HLP, HTN, LVEF, LVH, Peripheral vascular disease, and Smoking), prior revascularization was not an independent predictor of mortality (odds ratio = 1.16 [95% CI = 0.83 to 1.62], p = 0.38).

Conclusion: Prior coronary revascularization does not confer a higher mortality rate when adjusted for common risk factors found in cardiovascular patients. These findings corroborate the current body of evidence regarding coronary artery disease management.
AORTOESOPHAGEAL FISTULA AFTER THORACIC ENDOVASCULAR AORTIC STENT-GRAFT PLACEMENT: A POTENTIAL FATAL COMPLICATION

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Aorta-Esophageal fistula (AEF) with Thoracic aorta pseudo aneurysm (TAPA) is infrequently considered as a differential diagnosis in patients presenting with epigastric pain and hematemesis. AEF/TAPA, if left untreated can lead to rupture and potential death. Thoracic endovascular aortic repair (TEVAR) has been a safer alternative approach to open surgical repair. Surgical repair is associated with high mortality rates. An 80 year old female with history of coronary artery disease, hypertension and chronic obstructive pulmonary disease was transferred from another facility with complaints of epigastric pain and hematemesis. An esophagogastroduodenoscopy (EGD) showed a mass compressing the distal esophagus with a proximal ulcer. A computerized tomography (CT) scan highlighted a TAPA greater than 5cm compressing the esophagus and aortoesophageal fistula (AEF). A TEVAR approach placed a stent in the descending thoracic aorta and a repeat EGD did not show extravasation of contrast. Blood cultures were negative but sputum cultures identified methicillin resistant staphylococcus aureus (MRSA). The patient was treated empirically with intravenous antibiotics for six weeks. Patient returned six weeks later with complaints of weight loss and new onset hematemesis. Patient had leukocytosis with blood cultures identifying MRSA and treated with daptomycin. A repeat CT scan showed extraluminal air around the thoracic graft indicating infection. An EGD identified AEF. Due to the patient’s high risk for open surgical repair, a fully covered esophageal wall stent was placed with no further extravasation of contrast into the aorta. A diagnosis of sepsis and AEF secondary to an infected thoracic stent was made. The patient survived for approximately twelve weeks after TEVAR. TEVAR can be beneficial in patients who are poor candidates for open surgical repair from immediate rupture of TAPA with AEF. However, the risk of infection and sepsis persists. AEF is a rare but fatal complication with risk of recurrence after TEVAR.
GENETIC DISRUPTION OF NPR1 UPREGULATES CARDIAC EXPRESSION OF PROINFLAMMATORY MEDIATORS

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Proinflammatory cytokines play a central role in the pathophysiology and development of endothelial dysfunction, cardiac hypertrophy, and heart failure in experimental animal models and humans. We have examined whether genetically determined differences in guanylyl cyclase/natriuretic peptide receptor-A (GC-A/NPRA) gene (Npr1) affect cardiac expression of proinflammatory cytokines, hypertrophic markers, and nuclear factor kappa-B (NF-kB) in a Npr1 gene-dose-dependent manner. Gene-disrupted Npr1−/− mice showed 41 mmHg higher systolic blood pressure (SBP) and 60% greater heart weight/body weight (HW/BW) ratio compared with Npr1+/+ wild-type mice. Significant up-regulation of proinflammatory cytokines and hypertrophic markers gene expression along with enhanced NF-kB binding activities were observed in Npr1 gene-disrupted mice hearts. On the other hand, the expression of hypertrophic markers and proinflammatory cytokine genes along with NF-kB binding activities were markedly decreased in Npr1 gene-duplicated (Npr1++/++) mice hearts. The guanylyl cyclase activity and intracellular cGMP levels in ventricular tissues were reduced by 97% and 90%, respectively, in Npr1 gene-disrupted mice, but these parameters were increased by 3.0-fold and 3.8-fold, respectively, in Npr1 gene-duplicated mice hearts compared with wild-type mice hearts. M-mode echocardiographic analysis indicated that the fractional shorting was greatly reduced in Npr1 gene-disrupted mice, while significantly enhanced in Npr1 gene-duplicated mice compared with wild-type mice hearts. It is implicated that the Npr1 gene represses the expression of cardiac proinflammatory mediators, hypertrophic markers, and NF-kB-mediated mechanisms to enhance the cardiac function and protection of heart in the disease states.
Platelet activation pathways reflecting hemostasis and thrombosis are the underlying substrate for many cardiovascular diseases and related acute events. Genome wide association studies (GWAS) have provided many genetic loci that are associated with platelet function, but the mechanisms of how genes control platelet function remain unclear. Our own GWAS study uncovered more than 50 loci associated with platelet aggregation at genome-wide significance (p<5x10^-8), with many replicated in both white and African American subjects. Most genetic signals occurred in intergenic regions (38%), or in introns (55%), neither of which are translated into proteins, with only 1.6% producing missense mutations in exons. Mechanistic interpretation is limited by uncertainty as to which gene(s) are up- or down-regulated in the presence of most SNP modifications. In this study, we are creating pluripotent stem cells (iPS) from peripheral blood mononuclear cells of subjects with known genetic variants. We are then differentiating these stem cells into megakaryocytes (Mks), the precursor for platelets, and characterizing all of the genetic mRNA transcripts up- and down-regulated in the Mks using NextGen Sequencing (RNAseq). This will allow us to examine mRNA expression patterns for each GWAS signal to determine known and novel functional pathway(s) involved in platelet aggregation. We are particularly interested in the platelet membrane receptors PEAR1 and MET, for which intronic GWAS variants are associated with aggregation to multiple agonists. It is unknown whether these intronic loci, which presumably represent genetic regulatory regions, influence the amount of mRNA transcribed in these genes or in other genes in aggregation pathways. These studies should result in a better understanding of platelet biology and potentially in new therapeutic targets to modify platelet aggregation in appropriate individuals.
GENETIC ASPECTS OF CARDIOVASCULAR DISEASE / STEM CELL AND GENE THERAPY

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STEM CELL AND GENE THERAPY FOR HEART FAILURE
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The number of patients with advanced heart failure who are still symptomatic despite optimized medical therapy continues to increase. Therapeutic options for this population have been limited to heart transplant or use of LVADs. The most promising new therapy is use of stem cells or genes to improved myocardial function and vascularity. This field has progressed rapidly with identification of many new types, sources, and delivery methods leading to an increasing number of clinical trials. Two of the most important advances include identification of the mesenchymal stem cell that can be given without the need for immunosuppression, and use of early cell sources such as from umbilical cords. Similar progress has been made in the number and type of genes in clinical trial. In addition there has been major advances in understanding mechanisms of benefit. Stem cell and gene therapy will be a prominent therapeutic option for all forms of CV disease in the near future.
Atherosclerosis is the major underlying cause of myocardial infarction and stroke and preferentially occurs in arterial regions exposed to disturbed flow (d-flow) by mechanisms involving broad changes in gene expression. We have shown that D-flow rapidly induces atherosclerosis in vivo using a mouse partial carotid ligation model. In addition, we developed a novel intimal RNA preparation method using this animal model and identified numerous mecanosensitive endothelial genes that change in response to d-flow. Some of these mecanosensitive genes are regulated by microRNAs (miRNAs). While miRNAs are known to regulate various aspects of cardiovascular biology and disease, their role in atherosclerosis is unclear. Recently, we identified novel mecanosensitive miRNAs using the same mouse model and endothelial miRNA array. Here we identified that atypically derived mecanosensitive microRNA, miR-712, as the most shear-sensitive miRNA upregulated by d-flow both in vivo and in vitro. Mechanistically, d-flow-induced miR-712 directly downregulates tissue inhibitor of metalloproteinase 3 (TIMP3) expression that in turn activates the downstream metalloproteinases and stimulate pro-atherogenic responses and endothelial inflammation. Further, subcutaneously injected anti-miR-712 silences miR-712 and rescues TIMP3 expression, and prevents atherosclerosis in two independent murine models of atherosclerosis. Localized overexpression of TIMP3 also inhibits lesion development supporting the critical role of TIMP3 in atherosclerosis. Our results suggest that targeting mecanosensitive "athero-miRs" with anti-miR-based approaches may provide a new treatment paradigm in atherosclerosis.
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CARBON NANOTUBES SCAFFOLDS AS A NEW BASIS FOR CARDIAC TISSUE ENGINEERING
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In our previously published work we reported that MWCNTs used as growth supports for culturing neonatal rat ventricular myocytes (NRVM) increase myocyte proliferation and induce a more negative resting potential, suggesting that carbon nanotubes promote cardiomyocyte maturation. However, the mechanistic link between the enhanced cardiomyocyte proliferation and maturation and carbon nanotubes interaction was unknown. We subsequently investigated the gene program of the cardiac myocytes cultured with the CNTs and have found that the exposure to CNTs not only induces the expression of more mature, adult genes, but also prevents the induction of the pathologic gene program when these cells are exposed to the hypertrophic agonist Phenylephrine. In an effort to explore the effects on the entirety of the NRVM gene profile we have recently performed a series of transcriptome analyses on myocytes cultured in the presence or absence of CNTs and also in response to Phenylephrine. Preliminary bioinformatics analysis of these results confirms the pro-proliferative response for the myocytes cultured on CNTs and promotion of a more “normal” gene program. Based on these findings, we propose that the consistent and unique effects of carbon nanotubes on myocardial cells may have very important potential for clinical applications in the currently challenging field of regenerative medicine as applied to striated muscle.
We previously showed that circulating cells with smooth muscle outgrowth potential exist in the peripheral circulation and that bone marrow derived precursor cells contribute to smooth muscle cells within murine and human atherosclerotic plaque. More recently we have defined a myeloid subpopulation of cells that undergo smooth muscle cell differentiation following signalling through the CX3CR1 chemokine receptor. We have shown in rodent models that competence of this CX3CR1 receptor is critical for myeloid smooth muscle cell transition within healing plaque in response to injury. Moreover receptor competence is essential in angiogenesis with respect to microvessel integrity and perivascular smooth muscle cell investment. This may have significant implications for drugs targeting both angiogenesis in general and CX3CR1 pathway in particular. More recently we have shown that this chemokine receptor pathway can be therapeutically antagonised with potent inhibition of intimal hyperplasia within stents and differential saving of endothelium. Together these data suggest new avenues for drug targeting in atherosclerosis and its treatment with interventional devices that presents both a therapeutic challenge in terms of unanticipated side effects and an opportunity in terms of selective cell targeting.
GENETIC ASPECTS OF CARDIOVASCULAR DISEASE / STEM CELL AND GENE THERAPY

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GENETIC FACTORS INFLUENCING CAROTID ARTERY SIZE IN AMERICAN INDIANS
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While carotid artery lumen diameter is strongly influence by age, blood pressure (BP) and body size, a significant proportion of the variability in carotid artery lumen diameter is attributable to genetic factors. Among American Indians participants in the Strong Heart Family Study (SHFS), we found that the heritability (h²) of carotid artery lumen diameter is 0.44 (SE=0.07), after adjusting for covariates, suggesting that a moderate proportion of the inter-individual variability in carotid artery size is due to additive effects of genes. We recently conducted genome-wide linkage analysis of carotid artery lumen diameter to identify chromosomal regions that may harbor novel genes associated with inter-individual variation in carotid artery lumen diameter in the American Indian participants in the SHFS. Genome-wide linkage analysis revealed the highest LOD score for left carotid artery diastolic and systolic lumen diameter in Arizona SHFS participants in chromosome 7 at 120 cM (LOD=4.85 and 3.77, respectively, after sex and age adjustment and LOD=3.33 and 3.00, respectively, after adjustment for sex, age, height, weight, systolic and diastolic blood pressure and current smoking). Other regions with suggestive linkage for left carotid artery diastolic and systolic lumen diameter was found in chromosome 12 at 153 cM (LOD=2.48 and 2.18, respectively, after full covariate adjustment) in Arizona SHFS participants; suggestive linkage for right carotid artery diastolic and systolic lumen diameter was found in chromosome 9 at 154 cM (LOD=2.72 and 3.19, respectively after sex and age adjustment and LOD=2.34 and 2.29, respectively, after full covariate adjustment) in Oklahoma SHFS participants. In summary, we found significant linkage of carotid artery lumen diameter in chromosome 7q and suggestive linkage in chromosome 12q and chromosome 9q. Identification of genes influencing carotid artery size may provide insight into mechanisms involved in aortic aneurysm formation.
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GENETIC DISCOVERY OF CVD IN DIABETIC PATIENTS

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Diabetes is associated with an elevated risk of coronary heart disease (CHD). Previous studies have suggested that the genetic factors predisposing to excess cardiovascular risk may be different in diabetic and non-diabetic participants. We studied five independent studies, including in total of 1,517 CHD cases and 2,671 CHD-negative controls, all with type 2 diabetes. We identified a variant on chromosome 1q25 (rs10911021) consistently associated with an 36% increased CHD risk among diabetic participants. No association between this variant and CHD was detected among non-diabetic participants. The SNP was associated with the expression of the neighboring glutamate-ammonia ligase (GLUL) gene in human endothelial cells and a decreased ratio between plasma levels of gamma-glutamyl cycle intermediates pyroglutamic and glutamic acid.
CILIA AND CONGENITAL HEART DISEASE: WHAT IS THE CONNECTION?

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Motile cilia at the embryonic node and in the respiratory tract are required for left-right patterning and for muco-ciliary clearance from the respiratory tract, respectively. The heart is one of the most asymmetric organs in the body in order to support two separate circulation systems, the pulmonary and systemic circulation, in parallel. Hence defects in ciliary function could contribute to abnormal heart development resulting in congenital heart disease (CHD) as well as increased respiratory complications. This dual role is exemplified by patients with primary ciliary dyskinesia (PCD) in which patients have abnormal respiratory ciliary function leading to severe respiratory complications over time as well as ~50% of patients having complete reversal of visceral organ situs or situs inversus totalis.

Heterotaxy is characterized by randomized variation of left-right patterning in thoraco-abdominal visceral situs. We have shown that patients with heterotaxy and CHD have a high prevalence of ciliary motion abnormalities as demonstrated by abnormally low nasal nitric oxide (nNO) levels as well as high-speed video-microscopy of ciliated nasal epithelial tissue. These patients had increased respiratory symptoms reminiscent of PCD patients as well as were enriched for mutations in genes typically associated with PCD. We have also extended this work with studies on patients with transposition of the great arteries (TGA), both D- and L-TGA, and show that these patients, similar to heterotaxy patients, have a high prevalence of abnormal ciliary motion, borderline or PCD level abnormal nNO levels, increased respiratory symptoms as compared to TGA patients without ciliary motion abnormalities, and are enriched for novel or rare coding variants in the genes typically associated with PCD.

Our studies support a possible underlying mechanism leading to development of CHD involving mutations in genes relating to cilia structure or function. Screening patient with CHD for ciliary dysfunction might allow for prophylactic treatment of such patients in order to decrease their risk of post-operative infection and complications, which typically have been attributed to their CHD in the past.
MECHANISMS OF ACUTE CORONARY SYNDROME: FROM BENCH TO BEDSIDE

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TOLL-LIKE RECEPTOR 9 REGULATION OF COAGULATION IN ACUTE CORONARY ARTERY DISEASE
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Bacteriemia has recently been reported to be associated with increased risk of acute coronary artery disease and stroke. Bacterial DNA containing unmethylated CpG dinucleotide motifs is potent inducer of immune responses predominantly through Toll-like receptor 9 (TLR9). Bacterial DNA has been detected in atherosclerotic plaques in human coronary arteries and can persist in tissues and contribute to ongoing inflammation even in the absence of bacteria. Endothelial cells of human atherosclerotic plaques express TLR9. Human coronary artery cells (HCAEC) constitutively express TLR9 intracellularly, but not on the cell surface. Bacterial DNA, but not eukaryotic DNA, evoked concentration-dependent increases in the expression of tissue factor (TF), a key initiator of coagulation. Bacterial DNA enhanced TF gene transcription through induction of NF-κB and increased TF activity on the surface of HCAEC. Furthermore, bacterial DNA attenuated transcription of tissue factor pathway inhibitor (TFPI), reduced intracellular TFPI level and TFPI activity of the cell surface. Pharmacological blockade with telomere-derived TLR9 inhibitory oligodeoxynucleotide or transient knockdown of TLR9 with siRNA markedly attenuated HCAEC response to bacterial DNA. Methylation of cytosines in CpG motifs in bacterial DNA resulted in complete loss of activity on HCAEC, lending additional support for involvement of TLR9. Our results provide a novel mechanism by which bacterial DNA may contribute to a hypercoagulable state in the coronary circulation. These results also identify TLR9 inhibitory oligonucleotides as potential therapeutic agents for the prevention of coagulation in acute coronary artery disease where bacterial DNA may abundantly be present.

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Cardiac troponin I and T (cTnI and cTnT) are components of the cardiac myocyte myofibrillar apparatus that are released when these cells are injured. Current assays set “normal” at levels that incorporate 99% of the non-diseased population, with usual upper limits in the range of 0.05ug/ml. Troponin elevations are useful in diagnosing acute coronary syndrome (ACS) in conjunction with clinical, electrocardiographic, and imaging data. Numerous other systemic processes that directly injure myocytes, or alter the supply-demand balance, can cause elevation of cTn, including ESRD, heart failure, sepsis, myocarditis, tachycardia, and hypertension. Distinguishing ACS from other causes can be difficult. In our retrospective study of low-risk troponinemia, 140 patients without clinical ACS but with a cTnI between 0.06 and 2.0 ug/ml were referred for cardiac catheterization to define the cause of elevated cTnI. Only 16 patients (11%) had significant CAD, with no patients under the age of 49 having CAD. Predictors of CAD included diabetes or presentation with an arrhythmia or syncope. Patients without CAD most frequently had conditions associated with increased cardiac wall stress. High-sensitivity troponin (hs-cTn) can detect levels of troponin in the order of 10 ng/ml. This increased sensitivity may speed the diagnosis of true ACS with minimal elevations of troponin, but may also result in a greater number of non-ACS patients being identified and treated. For example, 100% of patients with ESRD have an elevated cTnT – although this signifies increased risk for future cardiovascular events, should all these patients be identified as potentially having ACS? The decreased specificity of hs-cTn has slowed the adoption of this assay in the United States, but it's eventual use will likely increase the prevalence of troponinemia with unknown consequences for risk assessment, diagnosis and treatment.
Abrupt rupture is the predominant event leading to acute coronary syndromes (ACS). It occurs under the influence of a multitude of genetic, inflammatory, hemodynamic, and rheolytic factors. Once the vascular endothelium has been disrupted, an intense thrombotic process ensues. Platelets are the first to congregate at the site of plaque rupture. The adhesion of the platelets to the injured endothelium engenders platelet activation, aggregation and subsequent generation of thrombin. These elements ultimately coalesce into a stable thrombus which occludes the culprit vessel. From the above description of the pathophysiology of ACS it is intuitive that antiplatelet therapy can play a major role in modulating the vascular response to plaque rupture. While inhibition of adhesion would be endangering overall hemostasis in the body, the processes of activation and aggregation are excellent targets for pharmacological intervention. Platelet activation serves as an amplification cascade, such that activated platelets degranulate and secrete pro-inflammatory and pro-thrombotic compounds that promote more platelet activation. In the process, the platelets change their shape and exteriorize the glycoprotein (GP) IIb/IIIa receptor – the final common pathway towards platelet aggregation. Aspirin inhibits thromboxane-mediated activation. Heparin and direct thrombin inhibitors address thrombin-mediated platelet activation. Antagonists of the P2Y12 receptors specifically block ADP-mediated platelet activation, a pathway particularly relevant in conditions of increased shear stress. Intravenous GP inhibitors completely eliminate platelet aggregation. In a graded fashion, addition of any antiplatelet agent decreases the incidence MACE in ACS. Aspirin – compared to placebo – reduces events by ~20%, dual antiplatelet therapy with aspirin and clopidogrel produces a further 20% reduction (CURE), while novel P2Y12 antagonists added to aspirin reduce MACE by an additional 20% in comparison with aspirin and clopidogrel (TRITON-TIMI-38 and PLATO). These major advances – as well as prompt revascularization – have led to a dramatic reduction (>60%) in-hospital events in this important group of patients.
INTRODUCTION OF A MOUSE MODEL THAT REFLECTS HUMANATHEROSCLEROTIC PLAQUE INSTABILITY AND RUPTURE: A UNIQUE TOOLFOR DISCOVERY OF STRATEGIES TOWARDS PLAQUE PACIFICATION ANDULTIMATELY PREVENTION OF MYOCARDIAL INFARCTION

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The high morbidity and mortality of atherosclerosis is typically precipitated by plaque rupture and consequent thrombosis and vessel closure. However, research on underlying mechanisms and therapeutic approaches is limited by the lack of animal models that reproduce plaque instability observed in humans. We aimed to develop and utilize a mouse model of plaque rupture that reflects the end stage of human atherosclerosis. Based on flow measurements and computational fluid dynamics, we applied a tandem stenosis to the carotid artery of ApoE-/- mice on high fat diet. At 7 weeks postoperatively, we observed intraplaque hemorrhage in ~50% of mice, as well as disruption of fibrous caps, intraluminal thrombosis, neovascularization and further characteristics typically seen in human unstable plaques. Administration of atorvastatin was associated with plaque stabilization and down regulation of MCP-1 and ubiquitin. Microarray profiling of mRNA and microRNA and in particular its combined analysis demonstrated major differences in the hierarchical clustering of genes and microRNAs between non-atherosclerotic arteries, stable and unstable plaques and allows the identification of distinct genes/microRNAs, potentially representing novel therapeutic targets for plaque stabilization. The feasibility of the described animal model as a discovery tool was established in a pilot approach, identifying ADAMTS4 and miR-322 as potential pathogenic factors of plaque instability in mice and validated in human plaques. Overall, the newly described mouse model reflects human atherosclerotic plaque instability and represents a discovery tool towards the development and testing of therapeutic strategies aimed at preventing plaque rupture. Distinctly expressed genes and microRNAs have been linked to plaque instability and are thus identified as potential therapeutic targets. In addition, the novel mouse model of plaque instability has been instrumental to develop molecular imaging methods that allow the identification of unstable, rupture-prone atherosclerotic plaques.
MECHANISMS OF ACUTE CORONARY SYNDROME: FROM BENCH TO BEDSIDE

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IMPAIRED ENDOGENOUS THROMBOLYSIS- A NOVEL, POINT-OF-CARE BIOMARKER PREDICTIVE OF ADVERSE CARDIOVASCULAR EVENTS

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The clinical outcome of a thrombotic event is determined by the balance between thrombus formation and efficacy of endogenous thrombolytic processes. Spontaneous lysis is an important defense mechanism against lasting vessel occlusion. The ideal assessment of thrombotic risk should not only assess platelet function, but also endogenous thrombolytic status. Although individual components of the fibrinolytic system can be measured (PAI-1, TAFI), overall fibrinolytic status has traditionally been difficult to ascertain. Furthermore, clot structure (density and structure of fibrin fibres) is also an important determinant of endogenous thrombolysis. The Global Thrombosis Test is a novel automated point-of-care test that can assess endogenous thrombolysis using native blood. Endogenous thrombolysis is frequently impaired in patients with acute coronary syndrome and is a significant and independent predictor of major adverse cardiovascular events, including cardiovascular death and nonfatal MI. Some 40% of patients with end-stage renal disease exhibit impaired endogenous thrombolysis, which is associated with a 4-fold increase in MACE, driven by AMI and CV death, and 9-fold increase in peripheral vascular events including fistula thrombosis. In patients presenting with ST-elevation MI, enhanced (rapid) endogenous thrombolysis is associated with spontaneous ST-segment resolution, TIMI 3 flow pre-PPCI and favourable outcome. Conventional antiplatelet agents (aspirin, P2Y12 inhibitors) have no effect on fibrinolysis inhibitors (TAFI, PAI-1) or clot structure; and thus do not affect endogenous thrombolytic activity. Thrombin inhibitors inhibit TAFI and alter clot structure, making the clot more accessible to lysis and may favorably alter endogenous thrombolytic status. Impaired endogenous thrombolysis is an easy to measure, novel risk factor for adverse cardiovascular events, whose clinical usefulness in identifying patients at risk of thrombosis and bleeding requires further studies. Favorably modifying the thrombotic profile of those with impaired endogenous thrombolysis through pharmacological interventions, and the effect of this on clinical outcomes, requires further exploration.
Atherosclerotic cardiovascular events result from two separate phases of mechanistic processes. Whereas lipid accumulation and chronic latent inflammation lead to development of atherosclerotic plaques over a period of years, certain internal or external factors can “trigger” the transformation of stable plaques into unstable plaques within hours to weeks, causing an acute coronary syndrome (ACS).

Many triggers act by stimulating the sympathetic nervous system or imposing extra physiologic, hemodynamic, or psychological stress, thereby inducing thrombosis, vascular inflammation, or rupture of high-risk, vulnerable plaques.

Such triggers can arise from a variety of situations and can be categorized as external (ie, natural disasters, cocaine, infectious organisms, emotional stress) or internal (ie, circadian variations). High-risk atherosclerotic plaques are commonly present but are not a prerequisite for trigger-induced ACS events. Cocaine abuse is a well-known trigger for acute coronary events and can exert its effects even in the absence of atherosclerotic lesions.

Infections are well-known triggers of ACS and have been studied rather extensively in this setting. Influenza, pneumonia, bacteremia, urinary tract infection, and other types of infection are associated with an increased risk of ACS. This fact is not surprising, given the critical role inflammation plays in the pathogenesis of ACS. Influenza vaccination has been proven to prevent ACS, and antiviral therapy after influenza infection has been suggested to prevent ACS and stroke. Despite the important role of triggers in the pathogenesis of ACS, there is little consensus about how to develop and implement a comprehensive plan to control these factors. Rigorous basic, preclinical, and clinical studies are needed to identify and develop preventive and therapeutic measures against different triggers as a new approach to preventing cardiovascular events.
Atherosclerosis, characterized by complex cellular and lipid-rich plaques resident within the artery wall, remains a major public health concern. Mechanistically, pathological studies have identified important biological markers, such as inflammation, that define plaques at heightened risk for future adverse cardiovascular events. However, despite a detailed knowledge of high-risk plaque biology, clinical tools able to discriminate which patients or plaques are at greatest risk for complications are lacking. Current atherosclerosis clinical testing modalities, including state-of-the-art intravascular imaging approaches, largely describe morphologic vascular features. Therefore, to improve risk assessment there is a significant need for new strategies that report on the key biology underlying high-risk plaques. Intravascular near-infrared fluorescence (NIRF) molecular imaging is a new, promising translational approach to identify inflamed coronary artery plaques in vivo. Optical Intravascular NIRF imaging can detect NIRF plaque signal at good sensitivity through flowing blood without vessel flushing. Using targeted molecular imaging agents (e.g. Prosense VM110, Indocyanine Green), intravascular NIRF imaging has successfully demonstrated enhanced atherosclerotic plaque macrophage content and protease activity in lipid-rich atheroma, and revealed early patterns of stent strut inflammation during coronary stent healing. Recently, intravascular NIRF molecular imaging has been combined with optical coherence tomography (OCT) structural imaging in a dual-modality catheter with exact image co-registration to enable simultaneous high-resolution light-based detection of molecular and structural plaque features. By exposing new significant plaque biology in vivo, intravascular NIRF molecular imaging of inflammation has the potential to alter current treatment paradigms and inform clinical decision making.
Evolving Role of Platelet Function Testing in Acute Coronary Syndromes

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The substantial reduction in ischemic events provided by the dual anti-platelet regimen with aspirin and clopidogrel is extensively published in patients with acute coronary syndrome and patient’s undergoing percutaneous coronary intervention (PCI). Recently there have been several “boxed warning” on clopidogrel and its variable response which lead to intense controversy on pharmacokinetic and pharmacodynamic and pharmacogenomic issues of anti-platelet drugs especially clopidogrel. Research use of platelet function testing has been successfully validated in identifying the new anti-platelet drugs like prasugrel and ticagrelor. These platelet function assays are not regarded as just a laboratory phenomenon anymore; rather a tool shown to predict mortality in several clinical trials. It is believed that sub optimal response to anti platelet regimen (pharmacodynamic effect) may be associated with cardiovascular, cerebrovascular and peripheral artery events. There has been intense controversy about this variable response of anti platelet drugs and role of platelet function testing to guide anti platelet therapy. While the importance of routine platelet functions testing may be uncertain, it may be useful in high risk patients such as diabetes mellitus, diffuse three vessels coronary artery disease, left main stenosis, diffuse atherosclerotic disease and chronic renal failure, undergoing PCI and in patient with suspected pharmacodynamic interaction with other drugs to assure the adequacy of platelet inhibition. While we wait for definitive trials, a predictive prognostic algorithm is necessary to individualize anti platelet therapy with P2Y12 inhibitors based on platelet function assays and genetic testing.
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RISK STRATIFICATION OF VERY LATE DES FAILURE BY THE EVALUATION OF NEOATHEROSCLEROSIS

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Although the incidence of very late DES failure has decreased in the second-generation DES compared with the first-generation DES, it still exists and continues to occur after its implantation. However, BMS rarely suffers very late stent failure until 5 to 10 years after implantation when it occasionally suffers acute coronary syndrome. On the other hand, angioscopy can identify intracoronary thrombus and vulnerable yellow plaques that will become thrombogenic by its disruption. After BMS implantation, the stent and yellow plaque under the stent are usually completely covered by white thick neointima at one year; however, the neointima comes to have disrupted yellow plaque with thrombus again when it causes acute coronary syndrome 5 to 10 years after implantation. In native coronary arteries, having yellow plaques is known as the risk of future event of acute coronary syndrome. Because it is very rare that the stented lesion still have thrombus at one year when second-generation DES is used, the thrombotic event after one year should be caused by newly formed thrombogenic lesion, i.e., newly disrupted yellow plaque. Cypher stent is known to have poor neointima coverage, yellow plaque, and thrombus at one year, while Endeavor stent is known to have coverage by white thick neointima without yellow plaque or thrombus. Indeed, Endeavor stent had better outcome at long-term follow-up although it had worse outcome at short-term follow-up in a large clinical trial. Therefore, we believe that the presence of in-stent yellow plaque at one year is the risk of future stent failure after second-generation DES implantation as in native coronary arteries.
VALVULAR HEART DISEASE: MECHANISMS AND TREATMENT OPTIONS

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SEVERE LEFT VENTRICULAR DYSFUNCTION IS NOT A CONTRAINDICATION TO AORTIC VALVE REPLACEMENT FOR AORTIC INSUFFICIENCY
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Objective: Left Ventricular (LV) dysfunction is an indication for surgery in patients with aortic insufficiency (AI). However, it is not well understood in which patients with severe LV dysfunction surgical intervention for AI should not be performed. The current study assesses outcomes and risk factors for aortic valve replacement (AVR) for AI in the setting of severe LV dysfunction compared to mild LV dysfunction and normal LV function.

Methods: Between 01/02-06/13, 546 consecutive patients underwent AVR for severe AI. Overall, 41/546 (8%) patients had an LV Ejection Fraction (EF) ≤ 35% (severe); 150/546 (27%) patients had an LVEF of 36-50% (mild) and 355/546 (65%) patients had an LVEF≥50% (preserved). The main outcomes of interest – postoperative complications and operative mortality, were compared between groups. Cox proportional hazard modeling was used to evaluate postoperative survival.

Results: Preoperative characteristics were similar across the groups, except the severe group was older (66.2+/−14.2yr, vs. mild 58.3+/−15.7yr; p=0.007, vs. preserved 56.4+/−14.3yr; p=0.001). Operative mortality for the entire cohort was 2.7% (15/546) and similar across groups (2.4%: 1/41 in the severe group, 2%: 3/150 in the mild group, 3.1%:11/355 in the preserved group, all p>0.5). All groups had similar rates of postoperative complications. Cox proportional hazard modeling indicated that age, preoperative creatinine, reoperation, coronary artery disease, and LV end-diastolic diameter (all p<0.05) significantly affected postoperative survival; LVEF was not found to be predictive (p=0.670).

Conclusion: Patients with severe LV dysfunction (LVEF≤35%), had similar post-operative outcomes and mortality as patients with better or preserved LV function. Our survival analysis indicates that other preoperative risk factors such as age, renal function, previous surgery, and degree of LV enlargement may be more relevant to long term outcomes, than degree of LV function as indicated by LVEF.
VALVULAR HEART DISEASE: MECHANISMS AND TREATMENT OPTIONS

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OUTCOMES OF A HYBRID APPROACH OF PERCUTANEOUS CORONARY INTERVENTION FOLLOWED BY MINIMALLY INVASIVE AORTIC VALVE REPLACEMENT
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Objective: To evaluate the short- and mid-term outcomes of hybrid percutaneous coronary intervention (PCI) followed by minimally invasive aortic valve replacement (MI-AVR).

Background: A sub-set of patients requiring coronary revascularization and aortic valve replacement (AVR) may benefit from a hybrid approach of PCI followed by MI-AVR, rather than combined median sternotomy coronary artery bypass graft and AVR. We evaluated the outcomes of this hybrid approach in such patients.

Methods: We retrospectively evaluated the outcomes of 103 consecutive patients with significant coronary artery and aortic valve disease who underwent PCI followed by elective MI-AVR at our institution between February 2009 and July 2013. A Kaplan-Meier analysis was performed to estimate mid-term survival.

Results: A total of 103 patients, 69 males and 34 females were identified, with mean age of 75.45 ± 8.3 years. Drug-eluting stents were used in 66.9% of the patients, and 68% were on dual anti-platelet therapy at the time of MI-AVR. Within a median of 40 days (IQR 28-64), 85.4% patients underwent primary and 14.6% underwent re-operative MI-AVR. Post-operatively, there was 1 (1%) cerebrovascular accident, 1 (1%) patient required re-operation due to bleeding, and 2 (1.9%) had renal failure. The operative mortality was 1.9%. Follow-up was available for 96.1% of the patients. At a mean follow-up period of 16.2 ± 12.8 months, 3.9% of the patients had an acute coronary syndrome (ACS) and 1% required a target vessel revascularization (TVR). The survival rate at 1- and 3-years was 92.2% and 88.3% respectively.

Conclusions: In a select group of patients with coronary artery and aortic valve disease, a hybrid approach of PCI followed by MI-AVR can be safely performed with excellent short- and mid-term outcomes.
DOES VALVULOARTERIAL IMPEDANCE IMPACT PROGNOSIS AFTER SURGERY FOR SEVERE AORTIC STENOSIS IN THE ELDERLY?

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Background: Valvulo arterial impedance (Zva) was introduced as a prognostic measure in patients with aortic stenosis (AS). However, it is unclear whether Zva has a prognostic impact on survival after aortic valve replacement (AVR) in patients with preserved ejection fraction (EF) and severe AS.

Methods: We retrospectively reviewed medical records of 929 consecutive patients who underwent AVR. We selected 169 elderly patients (age > 65 yrs) who had AVR secondary to severe AS (mean gradient ≥ 40 mmHg; AVA ≤ 1 cm²; peak velocity ≥ 4 m/sec). Patients with EF < 50%, greater than moderate aortic regurgitation, prior heart surgery, concomitant mitral or tricuspid valve surgery were excluded. Zva ((systolic blood pressure + mean arterial gradient) / stroke volume index) was calculated and the patients were divided into 3 groups; Low Zva, Zva ≤ 3.5 (n = 30), Moderate Zva, 3.5 < Zva < 4.5 (n = 66), High Zva, Zva ≥ 4.5 (n = 73). Post-operative survival curves were calculated according to Kaplan-Meier method and comparisons were made with the log-rank test.

Results: Age (77 ± 6 yrs, 76 ± 6 yrs, 76 ± 6 yrs; p = 0.79), prevalence of hypertension (70%, 77%, 75%; p = 0.77), prevalence of symptoms (33%, 23%, 26%; p=0.55), EF (65 ± 6%, 65 ± 7%, 65 ± 7%; p = 0.78) were not different between the groups. At 5 years, survival was not different between the groups (64% for Low Zva, 74% for Moderate Zva, 81% for High Zva; p = 0.42) (Figure)

Conclusion: Our study findings suggest that preoperative Zva does not have prognostic impact on post operative survival in elderly severe AS patients with preserved EF. Larger studies are needed to confirm our findings.
NATIONWIDE TRENDS IN THE INCIDENCE AND OUTCOMES OF ACUTE RHEUMATIC FEVER IN THE UNITED STATES

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**Background:** Over the past fifty years, the incidence and mortality from acute rheumatic fever (ARF) and chronic rheumatic heart disease have been declining in the developed world. There are limited data on the epidemiology and outcome of acute rheumatic fever in the last decade from the developed countries.

**Methods:** We used the 2003-2011 Nationwide Inpatient Sample databases to identify all patients with a primary diagnosis of ARF (ICD-9-CM codes 390-392). Temporal trends in overall, age-, gender-, and region-wise incidence and outcomes (in-hospital mortality, length of stay, and total hospital charges) of ARF were analyzed.

**Results:** From 2003 to 2011, 10,851 patients were hospitalized with ARF in the United States. The overall incidence was 0.40/100,000 persons. The incidence was higher in patients aged >40 years (0.51/100,000 persons), women (0.42/100,000 persons), and in the Northeast (0.55 per 100,000 population). During the study period, the incidence of ARF significantly declined from 0.46 to 0.30/100,000 persons (p<0.001). This declining trend was seen in both men (0.43 to 0.33/100,000 persons; p<0.007) and women (0.49 to 0.28/100,000 persons; p<0.002), as well as in the South (0.43 to 0.30/100,000 persons; p<0.001) and the West (0.30 to 0.22/100,000 persons; p<0.001). The overall in-hospital mortality in patients with ARF was 3.1%. There was a significant decrease in in-hospital mortality from 4.3% in 2003 to 1.1% in 2011 (p=0.002). The mean length of stay decreased (7.39±8.59 to 5.71±6.65 days, p<0.001), and total hospital charges increased (38,649±60,147 to 48,763±120,352, p<0.001) during the study period.

**Conclusions:** From 2003 to 2011, the incidence of ARF has declined in the United States. The overall incidence is higher in patients aged >40 years, women, and in the Northeast. In-hospital mortality, and length of stay have decreased, whereas total hospital charges have increased during the study period.
HYBRID APPROACH OF PERCUTANEOUS CORONARY INTERVENTION AND MINIMALLY INVASIVE MITRAL VALVE SURGERY IN PATIENTS WITH CORONARY ARTERY AND MITRAL VALVE DISEASE

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\textbf{Objectives:} The aim of this study was to evaluate the outcomes of a hybrid approach of percutaneous coronary intervention (PCI) followed by minimally invasive mitral valve surgery in patients with concomitant coronary artery and mitral valve disease.

\textbf{Background:} A sub-set of patients requiring coronary revascularization and mitral valve surgery may benefit from a hybrid approach, rather than the standard combined median sternotomy coronary artery bypass graft and mitral valve surgery, which often confers a higher surgical risk.

\textbf{Methods:} We retrospectively evaluated 82 consecutive patients with coronary artery and mitral valve disease who underwent percutaneous coronary intervention followed by elective minimally invasive mitral valve surgery at our institution between February 2009 and August 2013.

\textbf{Results:} A total of 45 men and 37 women were identified. The mean age was 73 \pm 8 years, with 59 (72\%) having 1-vessel, 22 (27\%) 2-vessel, and 1 (1\%) 3-vessel PCI. Within a median of 45 days (interquartile range [IQR] 18-74), 69 (84\%) patients underwent primary and 13 (16\%) underwent re-operative valve surgery, consisting of 50 (61\%) replacements and 32 (39\%) repairs. The operative mortality was 4 (5\%) and the average requirement of red blood cell products during the post-operative period was 1.5 \pm 2.6 units. At a mean follow-up of 15.3 \pm 13.2 months, 3 (4\%) patients required target-vessel revascularization, while stroke and renal failure occurred in 2 (2\%) patients each. Survival at 1 and 3 years was 89\% and 85\%, respectively.

\textbf{Conclusions:} The hybrid approach of percutaneous coronary intervention followed by minimally invasive mitral valve surgery, for either primary or re-intervention, can be safely performed with satisfactory outcomes. Further prospective, comparative studies should be performed.
MINIMALLY INVASIVE ISOLATED AORTIC VALVE REPLACEMENT IN OCTOGENARIANS

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Background: Octogenarian patients are considered high risk for surgical valve replacement and the advanced age is a major predictor of poor outcomes in patients undergoing valve surgery. Minimally invasive valve surgery approach has shown better outcomes than standard median sternotomy, with reduced morbidity and mortality in older patients. We evaluated outcomes after minimally invasive isolated aortic valve replacement surgery in low to medium risk octogenarian patients.

Methods: We retrospectively reviewed records between January 2008 and December 2012 among consecutive heart operations at our institution and identified 236 patients aged 80 yrs or greater, who underwent minimally invasive isolated aortic valve replacement surgery. The patients were risk stratified utilizing The Society of Thoracic Surgeons (STS) risk score.

Results: Mean age at surgery was 83.8 yrs (range 80-95), and 123 patients (52%) were male. 29 patients (12.3%) had prior cardiac surgery. The median STS score for mortality (3.2%), with inter-quartile range of 2-14 was predictive of 30-day mortality in this cohort of patients. The median postoperative length of stay was 7 days (IQR 6-34) and intensive care unit length of stay was 61 hours (IQR 14-449). In-hospital mortality was 6 (2.54%) and composite post-operative morbidity and mortality occurred in 74 (31.3%) patients. Post-operative complications included stroke in 3 (1.3%), prolonged ventilation in 46 (19.5%), re-operation for bleeding in 6 (2.5%), renal failure in 8 (3.4%) and wound infection in 5 patients (2.1%). Follow up was available in 234 patients (99%) and has extended up to 5 years. Overall, Operative and one year cumulative mortality was 2.54% and 5.6% and long term survival at one year was 94.4%.

Conclusion: Minimally invasive surgery for isolated aortic valve lesions in octogenarian patients yields a lower morbidity and mortality. The mortality with this procedure in low to medium risk octogenarians are comparable to age and gender matched general population.
FACTORS ASSOCIATED WITH PROCEDURAL FAILURE AND COMPLICATIONS FOLLOWING TRANSCATHETER AORTIC VALVE REPLACEMENT

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Background: Transcatheter aortic valve replacement (TAVR) is an emerging therapy for patients with high operative risk. The purpose of this study is to elucidate demographic and echocardiographic factors associated with procedural failure.

Methods: We retrospectively reviewed 67 consecutive patients undergoing TAVR with Edwards-SAPIEN (n=17) or Medtronic-CoreValve (n=50) from March 2011 to 2013. Aortic valve (AV) leaflet calcification pattern was determined by reviewing short axis views on transesophageal echocardiograms. AV calcification grade was assessed using contrasted CT images. Institutional experience (IE) was defined as number of days from the first TAVR at our hospital to capture the impact of experience over time. The primary endpoint was procedural failure, defined as death on index admission or moderate to severe paravalvular aortic insufficiency up to six months. The secondary endpoint was periprocedural morbidity, defined as hemorrhage, shock, heart block, stroke, and 60-day readmission.

Results: The mean age of the cohort was 80±10.8; 45% female. The primary endpoint occurred in 34% of patients. Younger age (OR .93, p=.024), diabetes (OR 5.3, p=.02), and use of CoreValve device (OR 47, p=.004) were associated with procedural failure as were predominantly right- or left-sided AV cusp calcification (OR .2, p=.02) and severe AV calcification (OR 19, p=.005). Baseline mitral regurgitation grade, replacement valve size, and vascular access site were not associated with failure. More IE was associated with periprocedural morbidity (OR .89, p=.04), but a lower readmission risk (OR 1.06, p=.05).

Conclusion: Younger patients with diabetes undergoing replacement with CoreValve suffered more procedural failure. Right or left-sided AV cusp calcification and severe AV calcification were also associated with failure. Diminished IE paradoxically protects against periprocedural morbidity, which may be a function of patient selection. These findings should be studied prospectively to formulate a predictive model to identify patients at greatest risk of post-TAVR complications.
THE EFFECT OF LOW EJECTION FRACTION IN ISOLATED AORTIC INSUFFICIENCY ON LEFT VENTRICULAR REMODELING AFTER AORTIC VALVE REPLACEMENT

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Background: The aim of this study was to evaluate impaired ventricular function and structure due to isolated aortic valve regurgitation, remodeling process after aortic valve replacement and the effect of low ejection fraction on remodeling and quality of life.

Methods: Between 1993 and 2013, 113 patients, with isolated aortic regurgitation (AR) undergoing AVR at our clinic, were analyzed retrospectively. These patients were divided into two groups according to their EF. Group I (n:45, mean age 34.86 ±14.3 years) had an EF of less than 50%, whereas Group II (n:68, mean age 35.7±15.9 years) had an EF equal or greater than 50%. Preoperative and postoperative echocardiographic examinations were evaluated. Echocardiography is performed to assess left ventricular (LV) dimensions, LV mass and volume, EF, interventricular septum (IVS) and posterior wall thickness (PWT).

Results: There was a significant difference between EF and LVESD in preoperative TTE assessment of two groups, whereas there were no significant differences in any other parameters. An increase in EF occurred in both groups after AVR. Unlike group II (p=0.407), this increase was significant in group I (p<0.001). There was no significant reduction of IVS and PWT in both groups. In addition, there was significant regression of LVESD and LVEDD between pre- and postoperative assessments of patients. There was a significant difference between pre LV mass and postoperative LV mass of both groups with p<0.001. Functional capacity was increased in both groups.

Conclusions: Patients with isolated AR and low EF most likely to benefit from surgery. Left ventricular dysfunction does not affect early in-hospital mortality. There is a significant improvement of functional capacity in these patients after operation. Although preoperative low EF generally appears to affect outcome of successful AVR, we also suggest surgery in patients with severe AR.
MINIMALLY INVASIVE AORTIC VALVE REPLACEMENT IMPROVES OUTCOMES OF REOPERATIVE AORTIC VALVE REPLACEMENT

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Background: The advantages of minimally invasive aortic valve replacement (AVR) are well documented, but whether the benefits of mini-AVR influence the outcomes of subsequent reoperative aortic valve surgery is unknown. The current study compares in-hospital outcomes and long-term survival following reoperative aortic valve replacement between patients who had previous minimally invasive or full sternotomy AVR.

Methods: We examined all reoperative, isolated aortic valve replacement cases between 1997 and 2012. Patients with previous aortic valve replacement with concomitant procedure were excluded. Outcomes included perioperative complications, transfusion requirements, ventilation and ICU times, LOS, and survival.

Results: We identified 96 cases meeting inclusion criteria: 32 with previous mini-AVR and 64 with previous sAVR. Patients were similar in age, gender, and preoperative risk factors. Bioprostheses were explanted in 78% mini-AVR and 73% sAVR (p=1.0) and implanted in 43% vs 36% (p=0.509). Trend towards shorter skin-to-skin operative times was noted for mini-AVR (335 min vs 354 min, p=0.088). Postoperatively, mini-AVR patients had shorter ventilation times (5hr vs. 8hr, p=0.003), ICU stays (37hr vs. 61hr, p≤0.001) and LOS (6.5d vs. 8d, p=0.031). Statistically significant overall transfusion requirement (p=0.034) and a trend towards increased intraoperative pRBC transfusion for sAVR (45.3% vs. 28.1% p=0.125) were noted. Chest tube output was similar between the two groups. Midterm survival at 1 and 5 years was 100(±0) and 100(±0) for mini-AVR and 100(±0) and 98% (+/-3.6) for sAVR (p=0.05).

Conclusions: This study shows that a previous mini-AVR provides benefits at the time of reoperation with less transfusions, shorter hospital times and improved long-term survival. These findings suggest that mini-AVR may be beneficial for patients at risk for aortic valve reoperations and offer another advantage of this well established technique.
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THE PROFOUND IMPACT OF DILATED LEFT VENTRICULAR OUTFLOW TRACT ON DOPPLER STROKE VOLUME AND AORTIC VALVE AREA ESTIMATION
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Background: Echo has become the modality of choice for hemodynamic assessment and clinical decision-making in patients with aortic stenosis (AS). Left ventricular outflow tract (LVOT) measurement is known to influence the aortic valve area (AVA) derived by the continuity equation. However, the accuracy of AVA estimation in patients with dilated-LVOT (DOT) has not been specifically evaluated.

Methods: From our echo database we retrospectively identified 15 patients with severe AS (defined by peak aortic velocity >4m/s), and markedly DOT (≥2.5 cm in the setting of bicuspid aortic valve), and 15 control AS patients without DOT, matched for age, BSA, and aortic velocity. We also analyzed 15 non-AS patients with DOT and 15 non-AS patients without DOT. Patients with left ventricular systolic dysfunction, or more than mild valvular regurgitation were excluded. We compared Doppler vs. Teichholz derived stroke volume (SV) and calculations of AVA.

Results: Among the 60 patients, the Doppler SV overestimated Teichholz SV in the DOT group by 59% (119 vs. 75mL, p<0.0001), but was similar in the non-DOT group (80 vs. 73mL, p=0.14). Consequently, those with DOT in the severe AS group had larger AVA (1.09 vs. 0.76 cm²), and more frequently had AVA>1.0cm² (11/15 vs. 0/15) despite similar aortic velocity (4.60 vs. 4.58m/s, p= 0.92 and mean gradient (49.7 vs. 48.8 mmHg, p=0.85). The presence of a bicuspid valve, severe AS, and dilated annulus was confirmed in 13/15 DOT patients who underwent surgery for symptomatic AS. The prosthetic valve was larger in the DOT group (26 vs. 23mm, p<0.001).

Conclusion: In patients with severe AS, bicuspid valve and markedly DOT, the continuity derived AVA frequently underestimates stenosis severity and should not guide clinical decision-making. This discrepancy is attributable to overestimation of the Doppler SV component of the continuity equation. The peak aortic velocity and mean gradient more accurately reflect AS severity in this setting.
A NEW AORTOTOMY TECHNIQUE FOR AORTIC VALVE REPLACEMENT: REVERSE ‘U’ AORTOTOMY (KIRALI INCISION)

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Introduction: Aortic valve replacement is one of the most common procedures in cardiac surgery. Oblique and transverse incisions should be made to access aortic valve in aortic valve replacement procedure. Both incisions have some technical difficulties and complications. In addition that with those incisions during re-operations, especially in patients having previous CABG surgery, aortic location of proximal anastomoses cause extra problems and difficulties. Patent coronary graft may confront high risk of damage, as a result patient may suffer from various complications. We developed a new aortotomy incision technique to gain access to aortic valve, which eludes these technical difficulties that mentioned above. We performed this technique in 4 patients.

Surgical technique: The incision of the aorta was started approximately 2 cm above aortic annulus and continued down at both sides. Incision of the aorta the right and left side were lengthened until near the aortic annulus. This reverse U shaped flap of the aorta was retracted anterior with a 5-0 suture to expose the aortic valve. In patients who underwent CABG, the incision was started approximately 1 cm above the upper proximal anastomosis and continued down at both sides. Native aortic valve was resected and bileaflet mechanical valve was inserted easily. The aortotomy was closed in the usual manner. One patient underwent primary operation for aortic valve replacement (AVR). 3 patients underwent secondary operation for aortic valve replacement. In these cases, two patients had undergone coronary artery bypass grafting operation before current AVR. And one patient had undergone david 1 procedure before current AVR.

Conclusion: Reverse U Aortotomy (Kirali Incision) provides technical ease at both primary operations and re-operations. Especially in re-operations with previous patent coronary graft, this new technique ensures graft protection.
A SYSTEMATIC REVIEW ON THE QUALITY OF LIFE BENEFITS AFTER AORTIC VALVE REPLACEMENT SURGERY IN THE ELDERLY

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Background: Surgical aortic valve replacement (AVR) is being increasingly performed on elderly patients with good peri-operative outcomes and long-term survival. Evidence is limited on health-related quality of life (HRQOL) following AVR which is an important measure of operative success in the elderly.

Methods: A systematic review of clinical studies after January 2000 was performed to identify HRQOL in the elderly after AVR. Strict inclusion and exclusion criteria were applied. Quality appraisal of each study was also performed using pre-defined criteria. HRQOL results were synthesised through a narrative review with full tabulation of results of all included studies.

Results: HRQOL improvements were shown across most or all domains in different HRQOL instruments. Elderly patients experienced marked symptomatic improvement. HRQOL was equivalent or superior to both an age-matched population as well as younger patients undergoing identical procedures. There were excellent functional gains after surgery, but elderly patients remain susceptible to geriatric issues and mood problems. Concomitant coronary artery bypass did not impact on HRQOL. There was a diverse range of study designs, methods and follow-up times which limited direct comparison between studies.

Conclusion: AVR results in significant HRQOL benefits across a broad range of health domains in elderly patients. Age alone should not be a precluding factor for surgery. Data is heterogeneous and mostly retrospective. We recommend future studies based on consistent guidelines provided in this systematic review.
HYPERTENSION WAS NOT A PREDICTOR OF CLINICAL EVENTS AT ONE-YEAR IN PATIENTS WITH ACUTE ST-ELEVATION MYOCARDIAL INFARCTION WHO UNDERWENT PRIMARY CORONARY INTERVENTION

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Background: Hypertension is a well-known risk factor for atherosclerosis. However, data on the effect of hypertension in patients with acute ST-elevation myocardial infarction (STEMI) are inconsistent. This study aimed to evaluate the effect of hypertension on outcomes in patients with STEMI undergoing primary percutaneous coronary intervention (PCI).

Methods: A total of 10,302 patients with STEMI who underwent primary PCI were retrieved from the Korea Working Group on Myocardial Infarction registry from 2005 through 2012. Primary study endpoint was the composite of major adverse clinical outcomes (MACE; defined as death, myocardial infarction, or revascularization) at one-year.

Results: Hypertension was present in 4,783 (46.4%) patients. Patients with history of hypertension were associated with more male (p<0.001), more anterior infarct (p<0.001), more advanced Killip class (p<0.001), and more incidence of previous coronary heart disease (p<0.001), diabetes (P<0.001), and dyslipidemia (p<0.001), compared to patients without it. Primary study endpoint was significantly higher in patients with history of hypertension than in patients without it (12.8% vs. 10.6%, p<0.001). In multivariable analysis after correcting confounding factors, the presence of hypertension was not an independent predictor for the composite of MACE at one-year (HR 2.839, CI 0.577-13.971, p=0.199). Furthermore, high blood pressure at arrival in emergency department was not associated with increased composite of MACE regardless of the presence of history of hypertension. High blood pressure at arrival had a tendency decreasing the incidence (10.1% vs. 12.5%) and risk (HR 0.869, CI 0.719-1.05, p=0.146) of the composite of MACE at one-year, compared to normal or low blood pressure at arrival. Conclusions: This study showed that the presence of hypertension was not a predictor of clinical events at one-year after PCI in patients with STEMI. Furthermore, high blood pressure at arrival had a tendency decreasing clinical events at one-year compared to normal or low blood pressure at arrival.
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ASLEEP BLOOD PRESSURE IS AN INDEPENDENT PREDICTOR OF CARDIOVASCULAR EVENTS: THE HYGIA PROJECT
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Objectives: Recent guidelines suggest relying on the awake blood pressure (BP) derived from ambulatory BP monitoring (ABPM) to corroborate the diagnosis of hypertension suspected by elevated clinic BP measurement. However, several ABPM studies have found elevated sleep-time BP is a better predictor of CVD risk than awake BP mean. We quantified the combined contribution to CVD risk of clinic, awake, and asleep BP among the participants in the Hygia Project, designed to evaluate prospectively CVD risk by ABPM in primary care centers of Northwest Spain.

Methods: This study involved 11255 subjects, 6028 men/5227 women, 58.9 +/- 14.5 years of age, with baseline BP ranging from normotension to sustained hypertension according to ABPM criteria, prospectively evaluated throughout a 4.0-year mean follow-up. BP was measured for 48h. The CVD outcome was defined as the composite of CVD death, myocardial infarction, coronary revascularization, heart failure, and stroke.

Results: The hazard ratios (HR) for each 1-SD elevation in clinic, awake, and asleep systolic BP (SBP) analyzed separately (adjusted for the significant influential characteristics of age, sex, diabetes, chronic kidney disease, cigarette smoking, waist perimeter, and history of previous CVD event) were 1.14 [95%CI: 1.08-1.22]; 1.21 [1.14-1.29], and 1.37 [1.29-1.44], respectively (always P<0.001). Exploration of the combined contribution of all three BP measurements revealed elevation in asleep SBP (HR=1.57 [1.42-1.72], P<0.001) but not in clinic BP (1.05 [0.97-1.13], P=0.217) or awake BP (0.81 [0.73-0.91], P<0.001, reflecting the enhanced CVD risk associated with decreased dipper patterning) was the only significant marker of increased CVD risk.

Conclusions: Sleep-time SBP mean, but not daytime clinic BP measurement or ABPM-derived awake BP mean, is a significant and independent prognostic marker of CVD morbidity and mortality. These findings indicate ABPM is a clinical necessity to accurately detect abnormal sleep-time BP and assess CVD risk.
SYSTEMIC AND PULMONARY HYPERTENSION, BASIC AND CLINICAL

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UNCONTROLLED HYPERTENSION IN UGANDA: A COMPARATIVE CROSS SECTIONAL STUDY
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Background: Uncontrolled hypertension is a risk factor for cardiovascular disease morbidity and mortality. The aim of this study was to investigate the prevalence of and risk factors for uncontrolled hypertension (HT) and its subtypes; isolated systolic hypertension (ISH), isolated diastolic hypertension (IDH), and combined systolic and diastolic hypertension (SDH) in a general population in two districts in Uganda.

Methods: In a cross-sectional survey, we selected 4432 persons aged 15 years and older in two districts in Uganda. We measured blood pressure and assessed known predictors for hypertension. Subtypes of hypertension were defined based on systolic blood pressure (SBP) ≥140mmHg or/and diastolic blood pressure (DBP) ≥90mmHg. Predictors for isolated ISH, IDH and SDH were assessed using bivariate and multivariate logistic regression.

Results: The prevalence of uncontrolled HT was 20.2% and the subgroups ISH, IDH and SDH were 7.2%, 4.2% and 8.8% respectively. No difference was observed between sexes. For all HT subtypes, middle (35-49 yrs) and older age groups (50+) had a higher prevalence (all p<0.001) compared to the young (15-34 yrs). However, IDH prevalence in older age was not higher compared to young age (p=0.417).

After adjusting for sex, age, residential status, education status, alcohol consumption and BMI, middle age was a predictor for all the subtypes [ISH; aOR:1.95;95%CI:1.35-2.82, IDH; aOR:2.04,95%CI:1.45-2.87 and SDH; aOR:3.97,95%CI:2.95-5.34] and old age was a predictor for ISH and SDH (ISH; aOR:11.9;95%CI:8.82-16.25, IDH; aOR:1.32;95%CI:0.81-2.14 and SDH; aOR:10.3,95%CI:7.65-13.9). Urban residents had a higher risk of IDH and SDH compared to their rural counterparts (IDH; aOR:1.59;95%CI:1.16-2.19 and SDH; OR:1.66;95%CI:1.30-2.13). Low education predicted ISH (aOR:1.39;95%CI:1.04-1.86). Alcohol consumption predicted IDH (aOR:1.58;95%CI:1.16-2.16) and SDH (aOR:1.48;95%CI:1.17-1.88). Being overweight/obese was significantly associated with ISH and SDH (aOR:2.56;95%CI:1.97-3.32)

Conclusion: More than one in five of adults in this population have uncontrolled hypertension. Preventive interventions are urgently needed to reduce the prevalence of uncontrolled hypertension.
CYP2D6 GENETIC INFORMATION-GUIDED METOPROLOL USE IN A CARDIOLOGY CLINIC – A PERSPECTIVE STUDY

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Background: Metoprolol is primarily metabolized (inactivated) by CYP2D6, an enzyme with close to 100 genetic polymorphisms, which give rise to four phenotypic categories of the enzyme: Extensive-Metabolizers (EM, normal capacity), Intermediate-Metabolizers (IM, reduced capacity), Poor-Metabolizers (PM, diminished capacity) and Ultra-extensive-Metabolizers (UM, higher than average capacity). Peak plasma metoprolol concentrations can be 2.1-/4.6-fold greater in the IM/PM groups as compared with the EM group.

Objectives: To evaluate CYP2D6 genetic variations and clinical outcomes of genetic information-guided metoprolol dosing.

Methods: DNA sequences of CYP2D6 are analyzed in 304 patients in our clinic. Phenotypes are analyzed, and individual metoprolol recommendation and follow up plan are made.

Results: Distribution of CYP2D6 phenotypes in our patients are (expressed as phenotype: patient number): EM:122, IM:140, PM:39 and UM:3. Distribution of the 166(54.6%) patients who are on metoprolol are: EM:64, IM:76, PM:24 and UM:2. In the IM/PM groups, metoprolol was decreased in dose in 44 patients and switched to atenolol in 17 patients. Dose is unchanged in 39 patients who are either already on a low dose or tolerating current dose. Doses are increased in UM patients. For those who’re not on metoprolol but phenotypically abnormal (IM:56 and PM:15), “metoprolol caution” is documented. All patients are then followed up for one year with primary endpoints of 1) ACS-or-CHF-related hospitalization, 2) cardiac death and 3) symptomatic bradycardia, hypotension or syncope.

Conclusions/Discussion: Metoprolol should be used with caution in patients with CYP2D6 variants due to the marked pharmacokinetics effect. Prevalence of IM, PM and RM phenotypes are substantial (combined 60%). Lowing dose or switching to beta-blocker that is not metabolized by CYP2D6 in IM/PM patient should decrease major side effects, whereas increasing dose in RM patients should increase clinical efficacy. These predicted clinical outcomes will be tested in the following year.
GASTRIN AND D1 DOPAMINE RECEPTOR INTERACT TO INDUCE NATRIURESIS AND DIURESIS

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Oral NaCl produces a greater natriuresis and diuresis than the intravenous infusion of the same amount of NaCl. Gastrin is the major gastrointestinal hormone taken up by renal proximal tubule (RPT) cells. We hypothesized that renal gastrin and dopamine receptors interact to synergistically increase sodium excretion, an impaired interaction of which may be involved in the pathogenesis of hypertension. In Wistar-Kyoto (WKY) rats, infusion of gastrin induced natriuresis and diuresis, which was abrogated in the presence of a gastrin (CCKBR; CI-988) or D1-like receptor antagonist (SCH23390). Similarly, the natriuretic and diuretic effects of fenoldopam, a D1-like receptor agonist, were blocked by SCH23390, as well as by CI-988. However, the natriuretic effects of gastrin and fenoldopam were not observed in spontaneously hypertensive rats (SHRs). The gastrin/D1-like receptor interaction was also confirmed in RPT cells. In RPT cells from WKY but not SHRs, stimulation of either D1-like or gastrin receptor inhibited Na+-K+-ATPase activity, an effect that was blocked in the presence of SCH23390 or CI-988. In RPT cells from WKY and SHRs, CCKBR and D1 receptor (D1R) co-immunoprecipitated, which was increased after stimulation of either D1R or CCKBR in RPT cells from WKY rats; stimulation of one receptor increased RPT cell membrane expression of the other receptor, effects that were not observed in SHRs. These data suggest that there is a synergism between CCKBR and D1-like receptors to increase sodium excretion. An aberrant interaction between the renal CCKBR and D1-like receptors (e.g., D1R) may play a role in the pathogenesis of hypertension.
COMPARISON OF ILOPROST AND NITRIC OXIDE FOR TREATMENT OF PULMONARY HYPERTENSION IN THE SETTING OF CARDIOVASCULAR SURGERY-A META-ANALYSIS

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Background: Patients undergoing a cardiac surgery (insertion of left ventricular assist device (LVAD), mitral valve repair, cardiopulmonary bypass, heart transplant) are at risk of developing right ventricular failure from increased pulmonary vascular resistance. Pulmonary hypertension is a risk factor for premature death after heart transplantation. Iloprost (IL) and Nitric oxide (NO) have been used in randomized control trials to decrease pulmonary hypertension. The aim of this study was to identify any significant difference for treatment of pulmonary hypertension in cardiovascular surgery using NO vs. IL.

Methods: We performed a meta-analysis of studies comparing IL and NO for treatment of pulmonary hypertension after cardiac surgery. We calculated the weighted standardized mean difference (SMD) in mean pulmonary artery pressure after treatment with IL and NO using the DeSirmonian and Laird method.

Results: Seven clinical trials were selected from the databases MEDLINE, PUBMED, Cochrane and EMBASE with a total of 201 subjects. Three trials randomized the subjects into NO and IL group and in four studies, subjects received both Nitric oxide and Iloprost and comparison of efficacy was done over time. The median dosage of NO was 20 ppm (range 20-40) and the median dosage of IL was 17.5mcg (range 10-50). The median pulmonary artery pressure for NO was 28 mmHg (range 25-55) and for IL was 35 mmHg (range 25-52). The SMD of mean pulmonary pressure was -0.52; 95% CI (-1.2-0.1) p = 0.148.

Conclusion: NO or IL are equally efficacious in reducing the mean pulmonary artery pressure after a cardiac surgery. In light of these findings, IL seems to be a cost effective, selective pulmonary artery vasodilator, and can be an acceptable alternative to NO.
SLEEP-TIME, NOT AWAKE BLOOD PRESSURE, DETERMINES THE TRUE PROGNOSTIC VALUE OF MASKED HYPERTENSION

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Objectives: Numerous studies consistently reveal cardiovascular disease (CVD) events are better predicted by the asleep than awake or 24h blood pressure (BP) means. However, discrepancies in the diagnosis of hypertension between office and ambulatory (ABPM) measurements are frequently defined by comparing clinic with only awake BP. We evaluated the impact of sleep-time BP in the prognostic value of out-of-office hypertension among the participants in the Hygia Project.

Methods: This study involved 11255 subjects, 6028 men/5227 women, 58.9+/−14.5 years of age, with baseline BP ranging from normotension to sustained hypertension according to ABPM criteria, prospectively evaluated throughout a 4.0-year mean follow-up. BP was measured for 48 consecutive hours. The CVD outcome was defined as the composite of CVD death, myocardial infarction, coronary revascularization, heart failure, and stroke.

Results: When clinic BP was compared to awake BP mean for classification, the adjusted hazard ratio (HR) of CVD events was equivalent between subjects with normotension, masked normotension (elevated clinic and normal awake BP), and masked hypertension (normal clinic and elevated awake BP), and only significantly elevated in subjects with sustained hypertension (HR=1.56 [95%CI: 1.31-1.86], P<0.001). When the classification was based on the comparison between clinic and asleep BP mean, CVD risk was equivalent between normotension and masked normotension (HR=0.94 [0.74-1.20], P=0.611), but highly significantly elevated in masked (1.69 [1.33-2.14], P<0.001) and sustained hypertension (2.07 [1.70-2.51], P<0.001; P=0.127 for the comparison between the later two groups).

Conclusions: Subjects with elevated sleep-time BP are at high CVD risk, independent of either daytime clinic or ABPM-derived awake BP measurements. Sleep-time BP mean, and not awake or 24h BP means as stated in many current international guidelines, should be used for proper identification of out-of-office hypertension, a condition associated with markedly increased CVD risk compared to ABPM-determined normotension.
Background. The generally accepted definition of white coat hypertension (WCH), that of higher blood pressure recorded in the doctor’s office than in the home, is too narrow and superficial, not recognizing the multiplicities revealed by analysis of the ambulatory blood pressure recording (ABPR) in susceptible persons.

Objectives. This study reviews two decades of ABPR, providing a more comprehensive definition, describing four characteristic periods in the 24 hour recordings, exploring triggers of the WCH episode, considering the complex circumstances of the nighttime pressure dip and postulating the benign nature of WCH.

Results. The first period, the attaching of the recording device in the hospital setting, is characterized by the highest pressures, usually mimicking the office pressures. These decline in bimodal fashion to normal or below. During the waking hours, elevations in blood pressure are produced by exercise and aggravation and during the night, by awakening to void. None of these incidents produce as extreme a pressure elevation as further WCH stimuli, like visiting a cardiologist’s office. This further provocation has been studied in detail to discover the actual events that trigger the WCH response. The episodic nature of WCH obviates the increased cardiovascular risk associated with ‘blunted dipping’ of the pressure during sleep. Arguments will be presented to support the concept that WCH is benign, separate from and not morphing into essential hypertension. Pressure recording examples will illustrate all these issues.

Conclusion. ABPR provides a more comprehensive and detailed description of WCH than the accepted standard definition.
ANTIHYPERTENSIVE EFFICACY OF CHLOROTHALIDONE- VERSUS HYDROCHLOROTHIAZIDE- ANGIOTENSIN RECEPTOR BLOCKER COMBINATION THERAPY: A META-ANALYSIS OF RANDOMIZED TRIALS

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**Background:** Numerous clinical trials have demonstrated greater antihypertensive efficacy of chlorthalidone (CTD) compared to hydrochlorothiazide (HCTZ). However, many recent studies have compared the efficacy of combination therapy of each agent with angiotensin receptor blockers (ARBs). The purpose of this study was to perform a meta-analysis to evaluate the antihypertensive efficacy of the combination CTD/ARB versus HCTZ/ARB.

**Methods:** A search of the PubMed and Cochrane databases was performed as well as manual searches of bibliographies of key relevant articles. All clinical trials in which the blood pressure lowering effects of CTD/ARB were compared directly to that of HCTZ/ARB were selected. We calculated the weighted standardized mean difference (SMD) using the DerSimonian and Laird method.

**Results:** Our search strategy yielded 40 studies, of which only 4 were randomized, head-to-head trials and therefore used for purposes of this analysis. The studies comprised a total of 1,839 patients with stage 1 - 2 essential hypertension either previously treated with other antihypertensive agents or treatment-naïve. All patients (mean age 56 years; mean systolic blood pressure 163.5 mmHg; 14.3% diabetics) on previous hypertensive medication regimens went through an appropriate wash-out period prior to initiating any of the studies. The overall SMD was -0.45 (95% CI, -0.56 to -0.35) in favor of CTD combined with ARBs over HCTZ combined with ARBs. CTD/ARB was found to have significantly greater antihypertensive effects as compared to the HCTZ/ARB treatment arms (p =0.049).

**Conclusion:** Chlorthalidone is often compared to HCTZ and has equal, if not superior antihypertensive effects. When combined with angiotensin receptor blockers, CTD (in comparable doses) continues to demonstrate greater antihypertensive efficacy over HCTZ/ARB combinations, thus making it a strong treatment option for patients with essential hypertension.
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INFLUENCE OF LONG TERM THERAPY WITH VALSARTAN, EPROSARTAN OR LOSARTAN ON DIASTOLIC DYSFUNCTION AND NT-PROBNP LEVEL IN HYPERTENSIVES
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Objective: To compare the effects of an angiotensin receptor blockers (ARB)-based regimen valsartan, eprosartan or losartan on diastolic function and NT-proBNP levels in patients with hypertension and diastolic dysfunction.

Background: This study was a prospective, randomised trial, which enrolled 75 patients with essential hypertension and diastolic dysfunction, NYHA I-III class (53\% men; mean±SD age, 48,9±6 years).

Methods All patients with a systolic blood pressure (SBP) ≥ 140 mmHg, a left ventricular ejection fraction ≥ 50\% and echocardiographic evidence of diastolic dysfunction were randomly assigned to treatment with valsartan (V group, n=25), eprosartan (E group, n=27), losartan (L group, n=23). Echocardiography including tissue Doppler imaging, and NT-proBNP assessment were performed at baseline and after 24 months. Results The baseline blood pressure levels were similar among the three groups, but post-therapeutic SBP were more reduced in the E group (p<0,001). Diastolic function was comparable in the all three groups at baseline and post-treatment, and was correlation between changes in SBP mean E\textsuperscript{1} (r=-0,48; p<0,001) and NT-proBNP levels (r=-0,5; p<0,001). The NT-proBNP levels more decreased in the E group (p<0,001), in the V and L group reduced similar (p<0,01). Changes in SBP was related to the changes in NT-proBNP levels (r=0,39; p<0,01).

Conclusion: Our findings suggest that, therapy with valsartan, eprosartan or losartan in hypertensive patients with diastolic dysfunction improved diastolic indices after 24 months of treatment and was associated with a greater decrease of SBP and NT-proBNP levels in the eprosartan group.
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LEFT VENTRICULAR SYSTOLIC AND DIASTOLIC FUNCTION DURING PERMISSIVE HYPERTENSION IN ACUTE ISCHEMIC STROKE
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Background: The aim of this study was to evaluate the acute effects of permissive hypertension on left ventricular systolic and diastolic function measured by transthoracic echocardiogram (TTE) across three time periods (Baseline, Day 3, and Day 14) among adult patients admitted for acute ischemic stroke.

Methods: This is a prospective, cohort, double-blinded study among adult patients with radiologically-proven acute infarction who underwent permissive hypertension. Between August to November 2013, 21 subjects (mean age: 60 ± 13 years, M : F = 13 : 8) admitted at the Acute Stroke Unit in a tertiary care hospital were enrolled. Baseline TTE and follow-up studies were done upon admission and on the 3rd and 14th day. 13 subjects completed follow-up until Day 14. A subgroup analysis was done between patients who were able to attain permissive hypertension goals on the first day of admission (11 versus 10).

Results: There were no statistically significant differences on E-point septal separation, mitral valve inflow E/A and E/e’ ratios, and deceleration time across the specified time periods for all patients in the study. Isovolumic relaxation times were prolonged at baseline (104.05 ± 24.99 ms), and a strong negative linear relationship with average mean arterial pressures was also demonstrated (rs = -0.760, p-value <0.01.). Ejection fraction measured by Simpson's remained within normal values but decreased significantly from Day 1 to Day 14 (62.23% versus 58.13%, p-value <0.05).

Conclusion: There was no significant evidence of left ventricular diastolic dysfunction throughout the first two weeks among patients with acute ischemic stroke who underwent permissive hypertension during the first 24 hours. Systolic function decreased significantly by the 14th day measured via left ventricular ejection fraction, albeit remaining within normal values.
A RETROSPECTIVE CHART REVIEW TO DETERMINE PROPER STRESS TEST UTILIZATION IN LOW RISK CHEST PAIN PATIENTS

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Background: Non-cardiac chest pain assessment can be challenging and it can result in excessive and unnecessary stress testing leading to increased health care costs.

Objectives: First to examine the utilization of inpatient stress tests in low risk chest pain admissions and second to determine if proper risk stratification is utilized at admission to order stress tests. Clinical outcomes were compared between patients who did or did not have an inpatient stress test.

Methods: It is a retrospective observational study. Patients were included if they had atypical chest pain, no prior history of coronary artery disease (CAD) and a normal initial EKG and first troponin. Patients were stratified by TIMI risk score from 0 to a maximum score of 4 since three of the higher risk criteria (positive troponins, EKG changes and history of CAD) were already excluded based on the inclusion criteria.

Results: 164 consecutive low risk chest pain patients were included based on the inclusion criteria. Fig 1a shows TIMI risk stratification of the population. A stress test was performed in 48% of the patients. Patient’s with higher TIMI scores did not have more stress test ordered and there was no association between TIMI risk scores and utilization of the stress test (p = 0.494) (fig 1b). None of the stress tests were true positive. There were no acute coronary syndromes, deaths or 30 day re-hospitalizations due to cardiac events in these patients whether they did or did not have an inpatient stress test.

Conclusion: Stress testing was over utilized independent of patient’s risk. A proportional increase in stress test utilization compared to risk was not seen. A proper risk stratification on admission can decrease stress test utilization for very low risk patients TIMI scores 0-2.
INFLUENCE OF PROCEDURE TIME ON HEMOGLOBIN DROP AS A COMPONENT OF MAJOR BLEEDING DEFINITION IN PRIMARY PERCUTANEOUS CORONARY INTERVENTION IN US ACADEMIC CENTER

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Background: There is lot of heterogeneity in the bleeding point definitions across various trials specifically involving hemoglobin drop without overt bleeding. Here we wanted to test if “four gram (4gm) drop in hemoglobin without overt bleeding” is related to complexity/duration of the procedure rather than complication of procedure.

Methods: We did a retrospective analysis of 123 out of 139 patients who did not have any “major bleeding” according to CathPCI registry bleeding definition. We compared the procedure times on those who had 4gm hemoglobin drop with those who did not. We also compared 30 day mortality and length of hospital stay on both of these groups.

Results: Baseline and procedural characteristics shown in the table. The mean procedure time in those patients who had 4gm hemoglobin drop was 112.2 minutes (7.94) and in those patients who did not was 90.6 minutes (3.52)(P=0.017). There was 0% mortality rate on both groups (P=1). The mean length of stay was 3.8 days in the former and 3.2 days in the later group (P=0.9).

Conclusions: In this single center observational analysis of PPCI patients, there is a significant interaction between procedure duration and four gram hemoglobin drop without overt source of bleeding. There was no significant difference in short term mortality as well as length of stay. Based on this, we need to carefully interpret the results of clinical trials which had “4gm drop in hemoglobin without overt bleeding” as a bleeding endpoint.
US ACADEMIC CENTER EXPERIENCE IN DOING PRIMARY PERCUTANEOUS CORONARY INTERVENTION USING VARIOUS BLEEDING AVOIDANCE STRATEGIES
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Background: We aimed to carry out comparison of different bleeding avoidance strategies in doing primary percutaneous coronary intervention (PPCI) using either radial or femoral as access of choice and either bivalirudin or unfractionated heparin as anticoagulant of choice.

Methods: We did a retrospective analysis of 139 patients with ST-segment elevation myocardial infarction (STEMI) who had PPCI in our academic center from January 2010 till May 2013. The primary outcome at 30 days was a composite of death; stent thrombosis and non-Coronary artery bypass grafting (CABG) related major bleeding (CathPCI registry definition).

Results: Baseline, procedural characteristics and primary outcomes for subgroups were shown in the table. The overall rate of primary outcome was 18%. The overall rate of major bleeding was 11.5%. There was tendency for lesser major bleeding (7 % vs. 12.6%; P=0.53) and lesser access site bleeding (0% vs. 4.5%; P=0.58) in radial arm. Also, there was tendency for lesser major bleeding (10.8% vs. 12.7 %; P=0.78) and lesser non-access site bleeding (6% vs. 11%: P=0.51) in bivalirudin group. The Glycoprotein IIb/IIIa inhibitor usage was 96% in bivalirudin arm. The rate for stent thrombosis in bivalirudin vs. heparin group was 3.2% vs. 2.1% (P=1). 

Conclusions: As Primary PCI bleeding avoidance strategies have become very important to optimize the clinical benefit, the combination of bivalirudin and radial approach deserves adequately powered randomized trial comparing other strategies.
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STUDY THE HEMODYNAMIC COMPONENTS OF ICU (INTENSIVE CARE UNIT) PATIENTS WITH USCOM

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Hemodynamic monitoring has a critical role in the assessment of patients in intensive care unit (ICU). Thermodilution cardiac output measurements have been routinely performed as part of evaluation of patients in the ICU but it’s an invasive method. Ultrasonic Cardiac Output Monitor (USCOM) is a non-invasive device that determines cardiac output by continuous-wave Doppler ultrasound.

The aim of this study was to evaluate USCOM data in the ICU of Tehran teaching hospitals.

Material and Methods: Measurements by USCOM were performed in 40 patients who has admitted to the ICU because of the Coronary artery bypass graft (CABG), Mitral Valve Replacement (MVR), Chronic obstructive pulmonary disease (COPD), congestive heart failure (CHF), sepsis and norepinephrin therapy, from October to December 2013. Evaluation of cardiac output, cardiac index, stroke volume and systemic vascular resistance, performed by USCOM in all of them. At the end, the data were analyzed by SPSS and ANOVA method.

Results: 40 measurements were obtained. 52% of patients were male. The average age, BMI, Hgb and APACHE II were 51.25, 23.8, 11.8 and 13.3 respectively. Measurements showed the average Heart Rate (bpm) 74.6, Stroke Volume (cm³) 79.3, Stroke Volume Variation (%) 30.6%, cardiac output (l/min) 46.4, cardiac index (l/min/m²) 4.3 and 1070 systemic vascular resistance (ds/cm²). The mean data in the patients with low cardiac output such as congestive heart failure patients, were more closer with the previous study and other methods for assessing the cardiac output.

Conclusion: The USCOM monitor can be used as suitable and safe device for assessment of cardiac output and other hemodynamic components in ICU patients, it may be more precise for patients with low cardiac output.
LIPID LEVELS IN PATIENTS AFTER PERCUTANEOUS CORONARY INTERVENTION IN THE REAL LIFE


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Objectives: To assess the control of total cholesterol (TC), LDL-C, HDL-C, and triglycerides (TG) in patients undergoing percutaneous coronary intervention (PCI) and if treatment changes during follow-up were appropriate or not according to the values of LDL achieved.

Methods and Results: we analyzed data of 307 consecutive patients undergoing PCI from Jan-2007 to Sep-2009. During follow-up we evaluated all available lipid plasma levels and the incidence of cardiovascular (CV) events (myocardial infarction, stroke, readmission for ACS, or new revascularization procedure), CV mortality, and overall mortality. We also tested if the treatment strategy was appropriate or not, according to the LDL-C value achieved in every control with two target levels (70 and 100 mg/dL). Mean follow-up was 44±16 months. After PCI 293/307 patients (95.4%) were treated with statins. Before PCI, the mean values were: TC 195±41 mg/dL, LDL-C 115±348 mg/dL, HDL-C 48±14 mg/dL, and TG 155±96 mg/dL. At the end of follow-up they were: TC 163±38 mg/dL, LDL-C 89±31 mg/dL, HDL-C 46±12 mg/dL and TG 145±99 mg/dL. In 46 patients there was not any LDL-C determination after PCI (20 deaths, and 26 lost of follow-up). We analyzed 1.087 determinations of LDL-C from 261 patients. Considering a target level of LDL-C <70 mg/dl and of <100 mg/dl, this was only achieved in 28.97% and in 72.4% of cases, respectively. We analyzed the therapeutic strategy adopted by the physician in 1.008 cases. Considering the target levels of LDL-C of <70 mg/dl and of <100 mg/dl, the change in the therapeutic strategy was appropriate only in 34.92% and 72.4% of cases, respectively.

Conclusions: After PCI, despite a high rate of statin therapy and a significant reduction in mean values of lipid levels, a high proportion of patients did not achieve the target level of LDL-C. Thus, in usual practice, guidelines are not followed properly.
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TYPE D PERSONALITY PREDICTS RISK FACTORS AND CLINICAL OUTCOMES IN POST ACUTE CORONARY SYNDROME PATIENTS

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Background: Evidence suggests that psychological factors can affect longevity via their influence in cardiovascular (CV) diseases. The “distressed” personality type or “type D” refers to those individuals who simultaneously tend to experience negative emotions and inhibit their self-expression. Type D personality has been associated with more adverse CV events in coronary heart disease (CHD) patients. However, the mechanism through which type D personality influences clinical outcomes is still not clear.

Objectives and methods: The aim of our research was investigating the pathophysiological pathways through which type D personality leads to worse CV prognosis in CHD patients. We investigated 99 post-acute coronary syndrome (ACS) patients. All patients completed the DS-14 personality scale. Patients underwent coronary angiography and percutaneous coronary intervention if necessary. Anthropometric measures and fasting blood samples including lipid profile were taken within 3 days after the CV event.

Results: Patients who had type D personality tended to have 1) more obstructed arteries, 2) more stents placed, 3) larger waist/hip ratio, 4) more triglycerides (TG), 5) less high-density lipoprotein (HDL), 6) more urea, and 7) more platelets. After controlling for relevant clinical factors, type D personality remained a significant predictor of the number of obstructed arteries (B=.02, p=.0009), the number of stents placed (B=.03, p=.014), platelets (B=1.61, p=.031), and high-density lipoprotein (B=-.27, p=.043). High-density lipoprotein partially mediated the relationship between D personality and 1) the number of obstructed arteries, and 2) the number of stents. In particular, patients who were more distressed had lower levels of good cholesterol and in turn more obstructed arteries and stents placed.

Conclusions: These results suggest that post-ACS patients who are more “distressed” tend to have more CV risk factors (lower HDL levels, more TG, urea, and platelets) and more obstructed coronary arteries and stents placed. This might be due to an unhealthier lifestyle (e.g., higher waist to hip ratio), which may contribute to their worse clinical outcomes.
PSYCHOLOGICAL DISTRESS AND RECURRENT CARDIAC EVENTS AFTER PERCUTANEOUS CORONARY INTERVENTION

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Background: Psychological distress can be as detrimental to the recovery of disease among patients with confirmed cardiac events as to the disease development. The purpose of this study was to examine the association between psychological distress and recurrent cardiac events after percutaneous coronary interventions.

Methods: This prospective study included 133 coronary artery disease patients (mean age 57.3 [standard deviation 10.0] yr, 78.2% male sex) undergoing percutaneous coronary intervention. Psychological distress were measured using Hospital Anxiety and Depression Scale (anxiety and depression) and a single-item visual analog scale (perceived stress). Recurrent cardiac events (included revascularizations, or rehospitalisation, or emergency room visits, and mortality) were noted for 12 months after discharge and confirmed by review of hospital record and patients interview by telephone.

Results: During the 12-month follow-up period, 20 patients (15%) were rehospitalization or visited emergency departments for complaints of chest pain or shortness of breath. Anxiety (odds ratio [OR] 1.30, 95% confidence interval [CI] 1.07-1.58) and depression (OR 1.27, 95% CI 1.02-1.58) were independent predictors of recurrent cardiac events after other risk factors were controlled for.

Conclusions: Psychological distress was associated with increased risk of recurrent cardiac events in patients with percutaneous coronary intervention. Intervention to reduce anxiety and depression may improve health outcomes in coronary artery disease patients.
Background: Paradoxically, smokers have lower mortality after acute coronary syndrome than non-smokers. This has been attributed to the younger age, lower co-morbidity, more aggressive treatment, and lower risk profile of smokers. Most of the conducted studies assess the impact of smoking using a categorical variable (i.e. smoker vs. non-smoker) and do not take into account the amount of consumed tobacco. In this study we sought to assess whether the extent of tobacco consumption (the number of cigarettes per day) was related to the extension of the coronary artery disease in patients suffering a first acute coronary syndrome (ACS).

Methods: Participants were 98 consecutive patients that underwent a coronary angiography because of a first ACS. Standardized questionnaires were used to determine participants’ past medical history, medication, and cardiovascular risk factor, including the average number of cigarettes per day. All coronary angiographies were checked by two experienced interventional cardiologist. A coronary stenosis of more than 50% in a main coronary branch was considered an obstructed vessel, and the sum of the total obstructed coronary vessels per patient was calculated.

Results: The number of cigarettes was negatively correlated with the age of the patients ($r=-0.40; p<0.001$). A negative significant association was found between the number of cigarettes per day and the number of obstructed vessels (OR=0.94; $p=0.05$). When the age of the patient was included in the model, the association disappeared ($p=0.10$).

Conclusions: Our results are in agreement with previous studies suggesting that tobacco consumption might be related to an earlier development of plaque unstabilization and the presentation of an earlier acute coronary event. Therefore, when a first coronary angiography is performed on a patient who is a smoker, he is usually younger and has fewer obstructed coronary arteries, as atherosclerotic plaques might not have had enough time to develop. The presence of fewer obstructed coronary arteries at the start of secondary prevention might explain a part of the smoker paradox.
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TRANSITIONAL NURSING CARE PROGRAM FOR PATIENTS UNDERGOING PERCUTANEOUS CORONARY INTERVENTION

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Objectives: The purpose of this study was to develop a theory-based, evidence-informed nursing program for patients undergoing percutaneous coronary intervention (PCI) to facilitate self-care and quality of life.

Background: Patients with PCI require a secondary prevention program to prevent recurrent cardiac events. Despite documented benefits of secondary prevention program, adherence to programs is suboptimal with moderate dropout rate. An intervention is required to facilitate healthy transition for appropriate self-care for PCI patients.

Methods: Guided by the transitional theory, we identified key PCI-specific nursing issues related to PCI care provision. Informed by current evidence and focus group interview with cardiology nurses, transitional nursing care program for patients with PCI was created. For clinical validity verification of developed program, a nonequivalent control group, pre-post test experimental research design was conducted for 37 patients undergoing PCI. The transitional nursing care program was only offered to the experimental group (n=20) for four weeks.

Results: We developed the transitional nursing care program to promote self-care ability for prevention of recurrent cardiac events for PCI patients. The program has potential to improve the self-efficacy (p=0.025) and experiences (p=0.015) for patients with PCI.

Conclusions: The transitional nursing care program developed in this study for PCI patients offers nurses a concise, evidence-informed and practical point-of-care tool to facilitate positive transition experience and self-efficacy for prevention of recurrent cardiac events. Pilot testing will offer insight as to its utility and potential for modification for national use.
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A COMPARISON OF THE SIX MINUTE WALK TEST AND THE SUB MAXIMAL STRESS TEST FOR ASSESSMENT OF FUNCTIONAL STATUS PRIOR TO PARTICIPATION IN CARDIAC REHABILITATION

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Background: Prior to initiation of a Phase II cardiac rehabilitation program, the Six Minute Walk Test (6MWT) or the Sub Maximal Stress Test (SMST) is performed to assess the clinical, functional, and electrocardiographic status of the patient. This study will determine which test is easiest to administer, can reliably predict exercise capacity, and sufficiently identifies patients at risk for cardiovascular events during rehabilitation.

Methods: A retrospective study was conducted evaluating forty (40) past participants of cardiac rehabilitation at the Memorial Herman Wellness Institute from September 2009 to August 2011. The participants were randomly selected and completed either the 6MWT or SMST prior to their enrollment in the Phase II cardiac rehabilitation program. The continuous variables obtained from each participant included age, blood pressure, and heart rate. The continuous variables were analyzed using Continuous T Tests to evaluate for statistical differences between the two groups. The categorical variables obtained from each subject included gender, race, cardiac history, cardiovascular events while participating in cardiac rehabilitation requiring re-hospitalization, and an assessment of return to prior functional status after completion of the program. The categorical variables were analyzed using the Fisher Exact Test to determine the p values for this study.

Results: There were no statistically significant differences in patient outcomes between the two testing modalities, and both tests were equally effective for determining functional capacity of participants prior to their enrollment in cardiac rehabilitation.

Conclusions: Our retrospective study found that both the 6MWT and the SMST were effective in determining functional status for patients prior to their enrollment in cardiac rehabilitation. However, due to the high cost and specialized personnel and equipment needed to administer the SMST, practitioners should consider utilizing the 6MWT preferentially for assessment of functional status prior to enrollment in Phase II cardiac rehabilitation.

Endpoints of Study

A: Return to prior functional status but finished rehab (p = 0.34)
B: Return to prior functional status and ended rehab (p = 1)
C: Ischemic events during rehab (p = 1)
D: Re-hospitalization but finished rehab (p = 1)
E: Re-hospitalization and did not finish rehab (p = 1)
EXERCISE AND THE CARDIOVASCULAR SYSTEM

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EXERCISE IMPROVES CARDIAC FUNCTION IN DIABETIC RATS
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Background: Type 2 diabetes leads to hyperglycemia, hyperlipidemia, and pathological cardiac hypertrophy. The beneficial effects of aerobic and resistance exercises on these cardiac alterations are poorly understood. The aim of this study was to determine the effects of aerobic and resistance exercise training on cardiac structure and function in a diabetic animal model.

Methods: The effect of aerobic or resistance exercise on the heart of the OLETF diabetic rat was investigated by glucose tolerance tests, lipid profiles, echocardiography, and mitochondrial functional studies.

Results: Both exercise groups had significantly improved blood glucose tolerance and lipid profiles compared to sedentary diabetic rats. Many abnormalities of the diabetic heart were improved in both exercise groups, but resistance exercise training was more effective than aerobic training in improving certain cardiac functions, including the ejection fraction and fractional shortening. Mitochondrial oxygen consumption rate, reactive oxygen species (ROS) production, and membrane potential improved with resistance exercise, but aerobic exercise improved only ROS production.

Conclusions: Both aerobic and resistance exercise training improved cardiac performance, but resistance exercise improved in glucose tolerance, cardiac contractility, and mitochondrial function more than aerobic exercise.
THE EFFECTS OF PSYCHOLOGICAL STRESS IN BLOOD PRESSURE DURING EXERCISE TESTING

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To determine the effects of psychological stress (PS) in blood pressure (BP) during exercise testing in adolescents. This study was carried out in a random sample of schools from Maracaibo, Venezuela. The participants were 416 adolescents, males (n= 197) and females (n=219), age-mean = 14, 71 years and standard deviation =1, 7. Each adolescent was performed exercise testing and completed the scale of Drs. Holmes and Rahe where if the individual has experienced a stress (S) level of 250 or more in the last year, even within "normal" you can find yourself in a situation of "over-stress (OS)." People with a "low stress tolerance" can be found in over-stress levels of 150 or less. The One-way ANOVA was used to study the effects of PS in BP during exercise testing. The presence of OS was 62, 7% (n=261) and S was 37, 3% (n=155). ANOVA’s results showed a significant effect for D factor in (SBP stage3 min2: F = 1,413 p= 0.020); (DBP stage4 min2: F = 1,578 p= 0.030); (MaxSBP F = 1,451 p= 0.009); (MaxDBP F = 1,445 p= 0.010) (SBP min3 recuperation: F = 1,626 p= 0.001); (SBP min5 recuperation: F = 1,838 p= 0.000) and (DBP min5 recuperation: F = 1,660 p= 0.001). Conclusions: The results provide evidence for an effect of PS in BP during exercise testing, which would mean that PS may influence BP in this group that is more vulnerable to PS due to hard changes typical of their life stage.
MODIFIED HATCH SCORE PREDICTS 6-MONTH RECURRENCE OF ATRIAL FIBRILLATION AFTER PULMONARY VEIN ISOLATION: DATA FROM THE UNIVERSITY OF MASSACHUSETTS ATRIAL FIBRILLATION REGISTRY

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**Aims:** Pre-procedural identification of patients with atrial fibrillation (AF) who will benefit most from pulmonary vein isolation remains challenging. The HATCH score \([\text{Hypertension x1 + Age greater than or equal to 75 x1 + Thrombo-embolic event x2, COPD x1, Heart failure x2}]\) has been associated with progression of AF and recently with adverse outcomes after catheter ablation. However, data regarding the HATCH score are limited. This study aimed to evaluate the performance of a modified HATCH scoring system, including pre-procedural obstructive sleep apnea as an additional risk element, compared to the CHADS risk score as a predictor of AF recurrence after an index pulmonary vein isolation procedure for AF.

**Methods and Results:** Seventy-eight patients (48 men, mean age 60 ± 1.1 years) with paroxysmal or persistent AF underwent an index pulmonary vein isolation procedure between 2010 and 2014 using either radiofrequency (n=64) or cryoballoon (n=14). Over a 6-month follow-up period, 35 patients had recurrence (44.9%) when monitored using Holter monitoring and in-office ECGs. The modified HATCH score was associated on univariate testing with AF recurrence. In multivariate logistic regression analyses including factors known to be associated with AF recurrence, the modified HATCH score (p: 0.03) was independently associated with AF recurrence and showed superior test characteristics using ROC curve analysis (C statistic = 0.64 for modified HATCH vs. 0.55 for CHADS2). The difference between the modified HATCH and the CHADS2 scores in predicting recurrence was not statistically significant (p = 0.8).

**Conclusions:** AF recurred in 44% of patients over a 6-month follow-up. A modified HATCH including OSA successfully identified individuals at risk for 6-month recurrence. Further research is needed including larger cohorts of patients undergoing ablation and followed for more extended periods to further validate the performance of the modified HATCH score.
USE OF VASCULAR COLLAGEN SEALING DEVICE TO CLOSE VASCULAR ACCESS IN PATIENTS UNDERGOING ELECTROPHYSIOLOGICAL PROCEDURES

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Background: The Angio-seal STS plus device (St. Jude Medical, St. Paul, MN, USA) is a vascular collagen device (VCD), used for sealing the arteriotomy sites mechanically. While the device is widely used for femoral arterial puncture sites, its use in patients undergoing electrophysiology (EP) procedures employing multiple venous accesses is not well studied. We conducted a retrospective analysis of outcomes related to VCD use in patients undergoing EP procedures (including ablation).

Method: 26 consecutive patients who underwent EP procedure in recent past were analyzed (16 males, age 57±15 years, weight 96±21 kg). They required a total of 76 VCDs following EP procedures using multiple sheaths (6F to 10F). All patients were on full anticoagulation (heparin or warfarin) during procedure. 73 VCDs were used in femoral veins (right or left) and 3 in femoral arteries. Given only two available sizes, 6F VCD was used to close venotomy size up to 7F while 8F VCD was used for size up to 10F. Patients were allowed to ambulate 2 hours after the procedure. Following complications were assessed during and 1 week after the procedure: ecchymosis, hematoma, infection and a clinical evidence of deep vein thrombosis, arterio-venous fistula or pseudoaneurysm.

Result: Mean number of VCDs per patient was 3 (range, 2-4). Initial success in deployment of VCD was seen in 25 out of 26 cases. The deployment failure was due to loss of vascular access. This case of non-deployment was managed with prolonged manual pressure. All patients could ambulate after 2 hours. No complications were noted other than 1 patient having ecchymoses of both groins diagnosed during follow-up.

Conclusion: Use of VCD is feasible and safe in patients undergoing EP procedures requiring multiple vascular accesses and periprocedural anticoagulation. VCDs (Angio-seal 6F and 8F) could be safely used for up to 2F larger venotomy sizes. Early ambulation allowed by VCD use may improve patient satisfaction.
TRENDS AND OUTCOMES IN CATHETER ABLATION OF VENTRICULAR TACHYCARDIA IN ISCHEMIC CARDIOMYOPATHY

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Background: Catheter ablation has been used to treat incessant ventricular tachycardia (VT) and also to prevent or reduce the frequency of episodes of VT in patients with ischemic cardiomyopathy. However, there are limited data regarding the complications and in-hospital mortality after catheter ablation for ischemic VT.

Methods: We used the 2002-2011 Nationwide Inpatient Sample (NIS) databases to identify all patients aged ≥18 years with a primary diagnosis of VT (ICD-9-CM code 427.1) and who also had a secondary diagnosis of prior history of myocardial infarction (ICD-9-CM 412). Patients with supraventricular arrhythmias were excluded. Patients who underwent catheter ablation were identified using ICD-9-CM procedure code 37.34. Mantel-Haenszel χ² test of linear association was used to examine trends in catheter ablation, its in-hospital complications, and in-hospital mortality.

Results: From 2002 to 2011, among 81,539 patients admitted with ischemic VT, 4,653 (5.7%) underwent catheter ablation. The proportion of patients with ischemic VT who underwent catheter ablation increased significantly from 2.8% in 2002 to 10.8% in 2011 (p_trend <0.001). The overall rate of any in-hospital complication was 11.2% (523/4,653) with vascular complications (6.9%) being the most common. Other complications included cardiac (4.3%) and neurological (0.5%). In-hospital mortality associated with catheter ablation for ischemic VT was 1.6% (75/4,653). From 2002 to 2011, there was no significant change in the overall complication rate (8.4% to 10.2%, p_trend = 0.101; adjusted OR 0.97, 95% CI 0.56-1.66) and in-hospital mortality (1.3% to 1.8%, p_trend = 0.266; adjusted OR 0.45, 95% CI 0.11-1.80) following catheter ablation for ischemic VT.

Conclusions: Catheter ablation utilization rates in patients with ischemic VT have increased over the past 10 years. In-hospital complication rates and in-hospital mortality following the procedure have not changed significantly.
PROCEDURAL TIME IMPROVES WITH OPERATOR EXPERIENCE IN PULMONARY VEIN ISOLATION USING THE CRYOBALLOON

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Objective: To determine the degree to which experience affects procedural times in pulmonary vein isolation using the Arctic Front Cryoballoon (Medtronic, Inc.)

Background: Early studies with the Cryoballoon catheter report procedural times which are comparable to historically reported times with radiofrequency catheter ablation. Of note, however, procedural times were likely influenced by the novelty of the procedure.

Methods: Procedure times of 60 patients undergoing pulmonary vein isolation using the Arctic Front Cryoballoon catheter for treatment of atrial fibrillation from October 2011 through July 2013 were examined. All patients had paroxysmal atrial fibrillation and were undergoing initial pulmonary vein isolation. All procedures were performed with a single trans-septal puncture. Procedural time was defined as the time from administration of local anesthetic prior to obtaining venous access to the withdrawal of catheters to the right atrium. Procedural times of the first 30 procedures (10/19/11-6/5/12) were compared to the most recent 30 procedures (12/21/12-7/26/13).

Results: Patient characteristics were comparable between the two groups. Mean procedural time for the first 30 procedures performed was 155.83 +/- 36.53 minutes as compared with 104.53 +/- 18.7 minutes (p< 0.0001). Procedural time improved by 51.3 minutes over a period of two years. This improvement was primarily in left atrial dwell time. Dwell time for the first 30 procedures was 121.1 +/- 36.6 minutes as compared to 72.5 +/- 12.9 minutes in the recent procedures (p< 0.0001). There was no statistically significant difference in the time to the trans-septal puncture. There was no significant difference in the immediate success rate or the incidence of complications.

Conclusions: Procedural time for pulmonary vein isolation using the Cryoballoon catheter is significantly shortened with experience. The bulk of improvement in procedure derives from a decrease in left atrial dwell time. In addition, variability in procedure time was reduced by 50%.
EFFECT OF LEFT ATRIAL SIZE AND PRESSURE ON ABLATION TIME AND CLINICAL OUTCOMES WITH CRYOABLATION USING NEW GENERATION ARCTIC FRONT ADVANCE BALLOON IN PATIENTS WITH PAROXYSMAL ATRIAL FIBRILLATION

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**Background** - Cryoablation of atrial fibrillation (AF) with the Arctic Front Advance balloon (AFACA) is a treatment modality available in patients with paroxysmal atrial fibrillation (PAF). The effect of left atrial (LA) size and its pressure hemodynamics on ablation time and recurrence rate with this new generation balloon have not been studied previously in detail.

**Methods** - We retrospectively studied 118 consecutive patients with PAF who underwent AFACA from 7/12 – 5/13. LA pressures were available in 60 patients. The hemodynamics in terms of left atrial pressure was studied at the entry of LA through the inter-atrial septum before the start of the cryoablation. The mean LA pressures were recorded and were compared to the LA sizes obtained during echocardiography prior to the procedure. The average ablation time and the recurrence rate of the AF between 3 to 6 months post procedure were also calculated.

**Results** - The average age of the patients was 60.8±11.0 (mean±SD) with 37 (61.7%) males. The correlation among cryoablation variables was calculated using ANOVA test as shown in table 1.

**Conclusions** - LA size and mean LA pressure have no significant effect on average cryoablation time and ablation outcomes at 3 to 6 months in patients with PAF.

<table>
<thead>
<tr>
<th>LA size</th>
<th>Normal</th>
<th>Mildly dilated</th>
<th>Moderately dilated</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients, n(%)</td>
<td>23(38%)</td>
<td>26(43%)</td>
<td>10(16.7%)</td>
<td>N/A</td>
</tr>
<tr>
<td>Mean LA pressure(mmHg)</td>
<td>10.4±5.2</td>
<td>10.8±4.7</td>
<td>11.1±5.1</td>
<td>0.92</td>
</tr>
<tr>
<td>Average ablation time(min)</td>
<td>37.9±9.4</td>
<td>34.0±5.6</td>
<td>34.3±9.1</td>
<td>0.20</td>
</tr>
<tr>
<td>Recurrence rate during 3 to 6 months, n (%)</td>
<td>5(21.7)</td>
<td>7(26.9)</td>
<td>3(30)</td>
<td>0.86</td>
</tr>
</tbody>
</table>
FOOD IN THE BRAIN: A RARE COMPLICATION OF LEFT-ATRIAL ABLATION

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Case: A 77-year-old female presented with the complaint of persistent fever, chills and mild dysphagia for three days. Her history was significant for paroxysmal atrial fibrillation for which she underwent cryotherapy ablation 17 days prior to admission. Blood cultures were negative. She was treated with appropriate antibiotics. For evaluation of her dysphagia, esophageal x-ray with gastrografin was done and showed a possible sinus tract extending from the thoracic esophagus. On the same day, she developed weakness in left upper extremity and bilateral lower extremities. CT of the head revealed multifocal emboli. A Trans-thoracic echo did not show any clot in the atra. Subsequently thoracic CT confirmed our suspicion of a left atrio-esophageal fistula (AEF), which was thought to be the culprit for stroke secondary to possible postprandial food emboli. Patient was then taken to the operating room for surgical repair of AEF. Despite all efforts she expired 3 days after surgery.

Discussion: Although AEF post left atrial ablation (LAAB) is a very rare occurrence, it is essential for clinicians to be aware of this life threatening complication. An AEF should be suspected if there is a history of recent LAAB with subsequent fever, dysphagia, postprandial transient ischemic attack or stroke, seizures or altered mental status. The latency for occurrence is between days to five weeks after the intervention. Once AEF is suspected, oral intake should be avoided to prevent postprandial food embolism. Furthermore, any diagnostic work up such as transesophageal echocardiogram, which could manipulate or enlarge the fistula must be avoided.

Conclusion: AEF is a rare but deadly complication of left atrial ablation which requires high level of suspicion for timely and accurate diagnosis and treatment.
Background - Carotid sinus syndrome (CSS) is an extreme reflex response to carotid sinus stimulation manifesting as recurrent syncope and pre-syncope. Permanent pacemaker (PPM) placement is ideally suited for the cardio-inhibitory subtype of CSS. Data on the contemporary PPM utilization rates in CSS are limited.

Objectives - To analyze the baseline demographic and clinical characteristics, PPM utilization rates and pacing mode type in elderly patients with syncope and CSS.

Methods - We analyzed the 2009-2010 Nationwide Inpatient Sample databases to identify all patients aged ≥65 years with the principal diagnosis of syncope (ICD-9-CM code 780.2). Patients with CSS were then identified using ICD-9-CM code 337.01. Data on demographics, comorbidities, PPM utilization and pacing mode type were extracted and analyzed.

Results - Of 337,195 patients with syncope, 240 (0.07%) had a concomitant diagnosis of CSS. Patients with CSS had a mean age of 79.5 ± 7.3 years; and were more likely to be caucasian and male. None of the patients with CSS had a diagnosis of high-degree atrioventricular, bifascicular or trifascicular block, or ventricular fibrillation. None of the patients in the CSS group died during hospitalization. In patients with CSS, 35% (84/240) underwent PPM implantation (mean age 77.5 ± 8.6 years). PPM utilization rate was higher in females (49.4%) than in males (27.3%), and in whites (41.8%) than in non-whites (20.8%). 11.9% of patients with CSS who underwent PPM placement had a concomitant diagnosis of sick sinus syndrome. Dual chamber atrioventricular sequential pacing (DDD mode) was used in all patients with CSS undergoing PPM implantation. The average length of stay was longer in CSS patients undergoing PPM placement (2.9 versus 2.6 days, p=0.003).

Conclusions - Approximately one-third of elderly patients with syncope and CSS underwent PPM placement. DDD mode was used in these elderly patients with syncope and CSS.
ORAL ANTICOAGULATION AND DEVELOPMENT OF POCKET HEMATOMAS FOLLOWING CARDIAC DEVICE IMPLANTATION

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2. University of Kansas Hospital, Kansas City, KS, USA

Objective: To examine the frequency of pocket hematoma formation and the impact of uninterrupted oral anticoagulation (OAC) among patients undergoing cardiac device implantation.

Background: Implantation of permanent pacemakers (PPM) or implantable cardiac defibrillators (ICD) may be complicated by the development of pocket hematomas. Many patients receiving cardiac implants also have indications for chronic OAC which may further increase the risk of hematoma.

Methods: This was a retrospective cohort study of adult patients undergoing cardiac device implantation between January 1, 2011 and December 31, 2012 at an academic teaching hospital. The patient cohort was identified using the HERON (Healthcare Enterprise Repository for Ontological Narration) repository, a searchable clinical database. Medical records were reviewed for demographics, comorbidities, medications, and development of pocket hematomas within 30 days of device implantation. Demographic variables were assessed using descriptive statistics. Chi-square was used to compare hematoma formation between patients who were and were not therapeutically anticoagulated.

Results: The final cohort included 380 patients. Of these 261 received a PPM and 119 received an ICD. The median age was 68.4 years and 56.6% were male. Cardiovascular comorbidities were common. The incidence of hematomas for the entire cohort was 9.7%. Hematoma formation was more common among those receiving ICD than PPM (18.5% vs 5.7% respectively, p<0.001). The average time from implant to hematoma was 5.7 days. Eighty patients (21.1%) were receiving uninterrupted OAC. The majority (71.3%) were taking warfarin, 11.2% rivaroxaban and 17.5% dabigatran. Pocket hematomas developed in 21.3% of those on OAC vs 6.7% of those not on OAC (p<0.001).

Conclusions: In this cohort of patients undergoing implantation of a cardiac device, the incidence of pocket hematoma was increased by the use of uninterrupted OAC. Patients should be monitored closely for signs of bleeding and hematoma formation particularly during the first 5-7 days.
CEPHALIC VEIN CUTDOWN FOR LEFT VENTRICULAR LEAD PLACEMENT IN BIVENTRICULAR DEVICE UPGRADES

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Cephalic vein (CV) cutdown is an effective technique for right atrial and ventricular lead placement in patients receiving pacemakers and ICD’s. However, bleeding complication has limited its use. The purpose of our study is to evaluate the feasibility of CV cutdown for addition of LV lead in patients requiring upgrade of pre-existing devices to biventricular devices.

Methods: We performed a retrospective analysis of implanted devices at the Zablocki VA Medical Center between 09/2003 and 01/2008. Patient population included those receiving upgrades of pre-existing devices (initially implanted using subclavian vein) to biventricular devices via the CV cutdown.

Results: Ten patients met the above stated criteria and the CV was easily identified in all during the procedure. In 8 of the 10 patients (80%), CV was utilized for successful LV lead placement. In the other 2 patients, a venogram revealed occlusion of the CV; therefore access was obtained via the innominate vein in one, and the axillary vein in the other. Of the 8 successful CV upgrades, 4 underwent upgrade of dual chamber ICD to biventricular ICD, 2 had upgrade of dual chamber pacemaker to biventricular pacemaker, and 2 with upgrade of single chamber ICD to atrioventricular ICD. The right atrial lead was placed via the same CV in the latter two. No patients were noted to have more than minimal blood loss, significant hematoma requiring evacuation or pneumothorax.

Conclusions: The CV cutdown approach is feasible and can be safely utilized in LV lead placement in patients requiring addition of one or even two leads for upgrade of pre-existing devices. There were no procedural complications, especially excessive blood loss, which prohibits its use in the initial LV lead implant procedures. This is likely to be due to pre-existing leads preventing back-bleeding.
SUBCUTANEOUS IMPLANTABLE CARDIOVERTER DEFIBRILLATOR IMPLANTATION IN PATIENTS WITH CHRONIC KIDNEY DISEASE

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Objective: We analyzed the safety and efficacy of subcutaneous implantable cardioverter defibrillator (S-ICD) (Cameron Health/Boston Scientific) implantation in patients with advanced chronic kidney disease (CKD).

Background: S-ICD has been approved to provide defibrillation therapy for life threatening ventricular tachyarrhythmias. The safety of S-ICD implantation in patients with advanced CKD is unknown. These patients have significantly increased risk of cardiovascular morbidity and mortality. Also, CKD patients often have vascular access issues and are more prone to bloodstream infections. S-ICD does not require any vascular access. We report our single center experience of S-ICD implantation in these patients.

Methods: We evaluated the patients implanted with S-ICD at our center between November 2012 and February 2014 with glomerular filtration rate (GFR) ≤40ml/min. GFR was determined using the Modification of Diet in Renal Disease (MDRD) Study equation. Patient information was collected from inpatient and outpatient records.

Results: Of the 43 patients implanted with S-ICD at our center, 11 patients had a GFR ≤40ml/min. Eight patients were already on hemodialysis. Six were female, eight had ischemic cardiomyopathy and nine were African-American. The average age was 56 ±16 years and mean ejection fraction was 26.5%. Seven patients underwent successful defibrillation threshold testing. There were no peri-procedural complications. During a mean follow up of four months, two patients died- one from ischemic bowel and other from PEA arrest. There were no infectious complications and no mortality from ventricular tachyarrhythmias.

Conclusions: S-ICD can be safely implanted in patients with advanced CKD, including patients on hemodialysis. Long-term follow-up is needed to determine the efficacy of S-ICD in patients with chronic kidney disease.
PERICARDITIS INDUCED HYPONATREMIA FOLLOWING PERMANENT PACEMAKER IMPLANTATION

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Introduction: Pericardial effusion along with pleural effusion is one of the rare complications of permanent pacemaker placement. Although extremely uncommon, it is more prevalent in elderly patients and may be complicated with hyponatremia.

Case Histories: We observed development of hyponatremia in association with pericardial effusion and pleural effusion, within one month after pacemaker placement in two women with BMI of < 20.

Case 1: An 87-year-old woman, who underwent a transvenous AV sequential pacemaker, because of severe bradycardia and complete heart block. Three weeks later, she complained of progressive left sided rib cage pain and poor oral intake. Her chest x-ray showed bilateral pleural effusion. Echocardiography showed moderately large amount of pericardial effusion, but no evidence for tamponade. Analysis of pleural fluid was consistent with an exudative effusion. She also had hyponatremia (Na=119 mEq/dl). Extensive work up suggested hyponatremia presumably due to SIADH, caused by pericardial/plural effusion. She was treated with colchicine and repeat echocardiogram showed complete resolution of pericardial effusion and electrolyte abnormalities.

Case 2: An 83 year old woman with history of severe sick sinus syndrome required a transvenous AV sequential pacemaker 3 weeks ago. She now presents with generalized weakness, fatigue and poor oral intake of over one week. Her chest x ray showed moderate pleural effusion (right > left ). There was a small-moderate pericardial effusion echocardiographically, and her serum sodium was 116 mEq/dl. She was treated with colchicine with resolution of her pericardial effusion and electrolyte abnormalities.

Discussion: Although extremely uncommon, pericarditis can develop following transvenous pacemaker insertion, which may result in hyponatremia likely due to SIADH. Common scenario may be seen in an elderly petite woman with low BMI (<20), usually after using a helical screw/active fixation pacing leads, several weeks post implant. Early recognition and therapy can significantly improve outcome and morbidity.
AN IMPLANTABLE CARDIAC DEVICE LEAD AND ANTIPHOSPHOLIPID SYNDROME CAUSING A RARE COMPLICATION - SUPERIOR VENA CAVA SYNDROME

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Introduction: Superior vena cava syndrome is due to an obstruction or stenosis of the central venous system. Since its first description, the etiology of superior vena cava syndrome has greatly evolved, mostly due to the development of new invasive intravascular techniques. Currently, more cases are attributed to thrombosis secondary to cardiac implantable devices.

Case Report: A 71-year-old man with a history of antiphospholipid antibody syndrome had severe ischemic cardiomyopathy and malignant ventricular tachycardias requiring an ICD implantation about 9 years ago. He presented to the hospital with episodes of severe rectal bleeding necessitating treatment with fresh frozen plasma and transient withholding of warfarin. Subsequently, he developed acute facial swelling along with flushing of his face complicating with catastrophic antiphospholipid syndrome despite therapy with argatroban and arixtra. CT scan of the brain did not show any evidence for acute bleeding. There was a concern for superior vena cava syndrome, thus a venogram was obtained, which showed near complete obstruction of the left superior vena cava near the cavoatrial junction. There were numerous venous collaterals draining retrograde through the azygos vein into the inferior vena cava suggesting acute with superimposed chronic obstruction near the existing ICD leads in the superior vena cava. His symptoms improved with anticoagulation, angioplasty and later removal of the ICD.

Discussion: Superior vena cava syndrome has mostly been associated with infections and malignancies. More cases have been reported recently in association with pacemakers and ICD leads. Of the 25% reported, only 1–3% become symptomatic, the remaining benefitting from good collaterals development. In this case, the main mechanism underlying the development of superior vena cava syndrome is de novo thrombosis caused by the antiphospholipid syndrome over the pre-existing fibrous tissue stenosis due to repeated trauma from the ICD leads.
OXIDATIVE AND HYPOXIC STRESS IN SUSTAINED INFLATION RESUSCITATION IN A SWINE MODEL OF NEONATAL HYPOXIA

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Background: We recently reported that chest compression (CC) superimposed by sustained inflation (SI) improved survival and return of spontaneous circulation compared to coordinated 3:1 C:V in a swine model of neonatal asphyxia (Schmolzer et al, Circulation 2013).

Objective: To determine differences in oxidative stress and hypoxic injury markers of heart and lung in piglets resuscitated with SI with CC compared to coordinated 3:1 C:V.

Method: This is a secondary analysis of our previous report using a swine model of neonatal asphyxia. Organ tissue samples of the heart and lung (n=3-7 per group) were snap-frozen and stored at -80°C after autopsy following a 4-hour recovery period after asphyxia. The left ventricle and lower lobe of the right lung were ground and homogenized in appropriate buffer solutions and subsequently analyzed for glutathione (GSSG/GSH ratio), lactate and protein levels. In addition, the cumulative alveolar oxygen exposure in the lung was estimated based on the duration of using of 21% and 100% oxygen and blood gases during the resuscitation protocol.

Results: There were no significant differences among groups for heart and lung tissue lactate levels at 4 hours after asphyxia. GSSG/GSH ratio differences were significant in the lung samples (0.05±0.01 vs. 0.14±0.03, respectively, p=0.047). The cumulative oxygen exposure positively correlated with tissue GSSG/GSH ratio in the lung but not the heart (r=0.52, p=0.04 and r=-0.34, p=0.2, respectively). We noted a modest but insignificant correlation between alveolar oxygen exposure and tissue total and oxidized glutathione content (r=0.61 and r=0.56; p=0.06 and p=0.09, respectively) but not between glutathione ratio and tissue lactate, in the lungs of asphyxiated piglets.

Conclusion: The novel resuscitation method may further reduce (alveolar) oxygen exposure and lung tissue oxidative stress in asphyxiated neonates, in addition to the faster return of spontaneous circulation and improved hemodynamics.
CONGENITAL HEART DISEASE IN THE NEWBORNS OF IRANIAN DIABETIC MOTHERS
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2. Shahid Sadoughi University of Medical Sciences, Yazd, Iran
3. Iranian Nurses Association, Tehran, Iran

Introduction: Despite the discovery of insulin and current improvement in diabetics care, congenital malformations in diabetics are still more frequent than in the general population. The aim of this study was to identify congenital heart diseases (CHD) in the newborns of diabetic mothers (IDMS).

Methods: In our prospective study, color doppler echocardiography was performed in 75 consecutive full term newborns of diabetic mothers by GE Vivid3 echocardiographic device. Newborns were classified into two subgroups according to the type of the mothers’ diabetes: pregestational and gestational. They were also those were classified into three subgroups according to their birth weight: appropriate, large and small for gestational age. Data analysis was made by Fisher exact test and Chi-Square test.

Results: Forty nine (65%) and thirty six (35%) of subjects were infants of gestational (IGDM) and pregestational diabetic mothers (IPDM), respectively. Fifty five Newborns (73%) were appropriate, fourteen (19%) were large and six (8%) were small for gestational age. The most common echocardiographic findings included: patent ductus arteriosus (PDA: 54.7%), hypertrophic cardiomyopathy (HCMP: 24%), ventricular septal defect (VSD: 4%), atrial septal defect (ASD: 2.7%), transposition of great arteries (TGA: 1.3%) and coarctation of the Aorta (COA: 1.3%). Overall incidence of congenital heart diseases was 9.3 after exclusion of PDA and HCMP cases. The incidence of congenital heart diseases was higher in macrosomic than nonmacrosomic infants of diabetic mothers (P<0.001). Congenital heart diseases were more common in infants of pregestational than gestational diabetic mothers (P=0.004).

Conclusion: Our results showed that diabetic mothers are at increased risk of giving birth to a newborn with congenital heart disease, and transthoracic echocardiography is recommended for all infants of diabetic mothers.
OPTICAL COHERENCE TOMOGRAPHY IMAGING OF THE PATENT DUCTUS ARTERIOSUS: FIRST KNOWN USES IN CONGENITAL HEART DISEASE

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**Background:** Angiography is used to assess ductal morphology and caliber during interventional closure of the ductus arteriosus. We are evaluating the use of optical coherence tomography (OCT) to evaluate ductal anatomy given the potential benefit of superior resolution and lower radiation.

**Methods:** Standard angiograms were performed on two patients with patent ductus arteriosus prior to device occlusion. OCT was then used to obtain high-resolution three-dimensional vessel reconstructions. Devices were chosen based on angiographic measurements.

**Results:** OCT resulted in excellent three-dimensional anatomic definition, with minimal lumenal measurements of 2.2 x 3.1 mm and 1.6 x 2.3 mm, respectively, compared to angiographic measurements of 2.6 mm and 1.4 mm.

**Conclusion:** To our knowledge, this is the first reported use of OCT use in patients with congenital heart disease. We found OCT imaging of the PDA to be feasible, and only used a small amount of additional radiation and contrast. The three-dimensional OCT reconstructions provided additional anatomic information that could potentially improve device selection, as in both of our cases would have led to choosing larger devices than what was chosen based on angiography. In addition, once the technique is perfected, little or no angiography or fluoroscopy will be required to perform imaging runs, and only a small injection of contrast appears to be sufficient for vessel imaging. More work needs to be done to comprehensively evaluate this modality, but if OCT is shown to be comparable or superior, it may potentially replace standard angiography by improving accuracy and decreasing overall radiation use in selected interventional procedures such as this one.
HEART: HELPING EMERGING ADULTS WITH CONGENITAL HEART DISEASE RECONCILE TRANSITION

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While the number of adults living with congenital heart disease (CHD) has now surpassed that of children, there is little guidance for patients and caregivers on how to make the transition from pediatric to adult centers. Our objective is to identify the developmental stages reached by young adults with CHD. Emerging adulthood is considered to be a distinct developmental period during which individuals aged 18 to 29 reach adult milestones, and is the stage during which adults with CHD make the transition from pediatric to adult cardiology care, usually solely based on age. Fifty-six participants (age 18-40, mean 29) with CHD completed the Markers of Adulthood questionnaire of their perception of adulthood and achievement of traditional adult developmental milestones. By the Bethesda classification of severity of CHD, 14 patients had simple lesions, 25 moderate, and 13 complex; the latter group had significantly more cardiac surgeries and more clinic visits, but similar functional class. 30% of patients overall and 56% of emerging adults felt they had not reached adulthood (mean 24.3 years [18-35]). Bethesda classification was not significantly different between patients who felt they had or had not reached adulthood. Compared to published data of other emerging adults, patients with CHD considered accepting responsibility for their actions and having a relationship with their parents as equal adults more important markers of having reached adulthood than the traditional milestones of completing education, independence in their finances and living situation.

In conclusion, patients across the spectrum of disease severity had similar perceptions of adulthood and reached similar milestones. 30% of CHD patients between the ages of 18 and 40 did not consider they had reached adulthood, and had different views of adulthood than published data on healthy volunteers. This study offers insight in ways to support the development of emerging adults with CHD.
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TRANSCATHETER CLOSURE OF PATENT DUCTUS ARTERIOSUS IN CHILDREN WEIGHING LESS THAN 6 KG

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Patent ductus arteriosus is inversely proportional to gestational age, and the hemodynamic outcome is due to a left-to-right shunt. Therapeutic options are described as pharmacological management, and, when this fails or is contraindicated, open surgical or endovascular closure it is necessary.

Percutaneous closure findings are described below using Amplatzer duct occluder in children with persistent ductus arteriosus weighing less than 6 kg, in whom difficulties are described by percutaneous closure in the literature.

Methods: We reviewed, the medical records of patients who had an indication for surgical closure in patent ductus arteriosus weighing less than 6 kg in whom endovascular closure was performed.

Results and conclusions: Twenty patients with average weight of 2,061 grams, from this, 11 of them had less than 2,000 g. All patients had heart murmur and 11 clinical manifestations of heart failure; 17 patients had radiological test with isolated cardiomegaly were or combined pulmonary overcirculation.

The average diameter of the angiographic measure of patent ductus arteriosus was 3 mm, with a QP / Qs average of 2.1. Ductus’ type was A in 16 patients and, the remaining four was C. In all patients, general anesthesia was used. The artery and vein access in 10 patients, 6 with arterial access and 4 with vein access. Children with weight less than 1500 g with venous access.

No mortality occurred, and just in one of them the echocardiography monitoring showed a residual shunt without hemodynamic repercussions.

The case series review presented with transcatheter closure of patent ductus arteriosus in children weighing less than 6 kg using Amplatzer devices shows findings of successful closure in all patients.
VECTORCARDIOGRAPHIC VERSUS 12-LEAD CHANGES IN KAWASAKI DISEASE

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Introduction: Kawasaki disease (KD) is a vasculitis that causes inflammation in children. Traditional 12-lead criteria, the spatial QRS-T angle, and principle T-wave component were used to identify KD patients as well as to differentiate between those with and without coronary involvement.

Methods: Traditional electrocardiograms (ECG), spatial QRS-T angles, and principle T-wave component vectors from a total of 100 patients were assessed. 50 KD patients were compared to 50 age-matched control patients blindly and retrospectively. KD patients were subdivided into 27 with and 23 without coronary artery abnormalities (CAA). CAA was considered mild (Boston z-score >2.5<3), moderate (z-score >3<8), and severe (z-score >8). Student T-test was used to compare KD patients and controls and between KD patients with and without CAA. Analysis of variance (ANOVA) of the EKG parameters was used to compare patients with mild, moderate, and severe CAA. The odds ratio and relative risk were calculated for significant differences.

Results: Significant differences were found in the principle T-wave component between KD patients and controls (mean 0.39±0.19 versus 0.62±0.34mV, p<0.01). An odds ratio was 26.2 (confidence interval (CI) 1.49 to 460.5) and the relative risk was 1.25 (CI 1.08 to 1.43). There were no significant difference in traditional ECG or other vectorcardiographic criteria between KD and control patients, nor between those the groups of KD patients with mild, moderate, and severe CAA.

Conclusion: Differences exist between KD patients and controls in the principle T-wave vector component suggesting repolarization abnormalities exist in KD, likely secondary to cardiac edema and inflammation from this vasculitis. Traditional EKG findings are not sensitive enough to differentiate between KD patients with or without CAA or from normal patients, but vectorcardiographic parameters show promise and may one day be used to help guide treatment, however studies are needed to validate this method.
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ACCURATE MURMUR RECOGNITION IN CARDIOLOGISTS - PREMATURE REQUIEM OR PHOENIX RISING?
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Objectives: In the current era of echocardiography there is less reliance on physical examination. Historically the accuracy of cardiac auscultation by cardiologists to detect various heart sounds had been high (> 80%). This study was designed 1) To access the current accuracy of cardiac auscultation in cardiologists since auscultation will now be tested on the ABIM cardiology boards and 2) To access the impact of a brief intervention on their proficiency.

Methods: Cardiologists attending a national meeting from 2011 to 2013 were assessed on their ability to recognize basic murmurs e.g. aortic stenosis and mitral regurgitation; intermediate murmurs e.g. mitral valve prolapse and hypertrophic obstructive cardiomyopathy and advanced murmurs e.g. combined mitral stenosis and mitral regurgitation. A pretest evaluated the participant’s ability to recognize heart sounds prior to the learning module. Each of these learning modules consisted of 200 repetitions of each heart sound with phonocardiograms and echocardiographic images lasting 30 minutes. The heart sounds were retested in a post-test immediately afterwards.

Results: 3404 tests were performed by 1244 participating cardiologists. The average pre-test mean scores for the basic group was 43% that improved to 82% in the post test, for the intermediate group was 61% in the pre-test that improved to 94% in the post test and was 74% in advanced group that improved to 93% in the post test. The learning module made a statistically significant improvement in the detection of the heart sounds across all basic, intermediate and advanced heart sound categories (P value < 0.001 by paired T-test)

Conclusion: Proficiency of cardiac auscultation in cardiologists is currently not optimal. However, our study showed that a brief 30 minute intervention can significantly improve the accuracy of cardiac auscultation.
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TRANSFUSIONS ASSOCIATED WITH LEFT HEART CATHETERIZATION IN PATIENTS WITH CIRRHOSIS AND THROMBOCYTOPENIA

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Background: More patients with cirrhosis are undergoing left cardiac catheterization (LHC) as part of preoperative liver transplant evaluation. Such patients with thrombocytopenia are more susceptible to requiring blood product transfusions. Objective: We aimed to examine transfusion patterns associated with transradial (TR) and transfemoral (TF) approach in this group of patients.

Methods: A retrospective analysis was conducted in consecutive adult patients with the diagnosis of cirrhosis and thrombocytopenia who underwent LHC between January 2008 and August 2013 at a single center. Statistical analysis was performed using tools such as Fisher’s exact test and t-test.

Results: A total of 154 patients who underwent LHC were enrolled in the study. The mean age was 64 and 70% were males. A total of 132 patients underwent TF LHC and 22 patients underwent TR LHC. In the TF group, 24 of the patients received a blood product transfusion in relation to the LHC whereas in the TR group, none of the patients received a blood product transfusion (p=0.026). There was no major statistical difference between the two groups (Table 1). The mean platelet count in the transfemoral group was 100,401 and in the transradial group was 101,409 (p=0.890).

Conclusion: Cirrhotic patients with thrombocytopenia who undergo transradial LHC when compared to transfemoral LHC are associated with significantly less blood product transfusions. Additional study of safety and complications of LHC in patients with cirrhosis is warranted.
Background: The degree of pre-HSCT cardiac abnormalities may impact the risk of morbidity after HSCT. However, there is no detailed data in regard of cardiac functional and anatomical status in patients with multiple myeloma (MM) pre-HSCT.

Objective: We aimed to describe the prevalence of the cardiovascular abnormalities detected in pretransplant evaluation of a single center.

Methods: Eight consecutive patients with MM who underwent HSCT were evaluated retrospectively. All clinical, electrocardiographic, and transthoracic echocardiographic (TTE) data are recorded. The cardiac functions and the frequency of cardiac abnormalities detected in pre-HSCT patients were investigated. We analyzed the impact of different pre-transplantation chemotherapy (CT) regimen on cardiological parameters.

Results: A total of 88 patients (30F/50M, 57.9±6.1617;7.4 years) with MM were recruited to the study. 37.5% of patients had radiotherapy history before HSCT. We observed increased left atrial diameter in 22.7%, decreased EF in 10.4%, aortic regurgitation 29.3%, pulmonary artery hypertension in 5.3%, mitral regurgitation in 60%, tricuspid regurgitation in 50%, LV hypertrophy in 40%, diastolic dysfunction in 76.9%, and pericardial effusion in 5.3%. We detected low voltage criteria in precordial leads (23.6%) and extremity leads (8.3%), poor R wave progression (16.7%), pseudo-infarct pattern (15.3%), and arrhythmia (27.8%). P wave dispersion was 40.07±6.1617;14.4. PR dispersion was more than healthy controls. Thalidomide-dexamethasone CT related with significant low voltage on extremity derivations (p=0.028). On ECG of patients receiving bortezomib-dexamethasone CT we observed more QT-dispersion and pseudo infarct pattern (p=0.036). Bortezomib-dexamethasone-cyclophosphamide CT was related with less EF (p=0.015) and diastolic dysfunction (p=0.029). We observed more pseudo infarct pattern in patients receiving bortezomib-dexamethasone (p=0.05). There was no relationship between CT regimen used and PR dispersion.

Conclusion: In myeloma patients who are HSCT candidates cardiac functional and anatomical abnormalities are frequently detected by TTE and ECG. PR dispersion was increased independent of any CT regimen.
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PROGRESSION OF CAROTID ARTERIOSCLEROSIS MAY NOT BE ASSOCIATED WITH CEREBRAL INFARCTION
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Cerebral infarction has not been shown to be associated with carotid arteriosclerosis in details. Then, we compared carotid plaque with cerebral infarction by magnetic resonance imaging (MRI).

Methods We evaluated 128 patients who underwent head MRI and carotid ultrasonography. Age ranged between 49 and 85 (male 69.2 ± 8, Female 66.9 ± 9.0: mean ± SD). Plaque score (PS) was calculated by US, and MRI findings were classified as follow CI scores: 0: WNL, 1: leukoaraiosis 2: lacunar infarction, 3: cerebral infarction. Cardio Ankle Vasculat Index (CAVI) was calculated as arterial stiffness.

Results: CI or lacunar infarction was observed in 4 (2.7%) out of 15 cases without plaque, 15 (39.4%) out of 38 cases with PS of less than 5 (mild), 16 (44.4%) out of 36 cases with PS between 5 and 10 (moderate), and in 12 (63.2%) out of 19 cases with PS of more than 10 (marked). Incidence of CI or lacunar infarct was greater in cases with PS than in those without. CI score was 1.29 ± 1.2 in cases without plaque, 1.59 ± 1.32 in mild, 1.5 ± 1.32 in moderate, and 2.27 ± 1.16 in marked (P = 0.34 vs cases without plaque). CAVI was 10.91 ± 1.39 in cases with CI or lacunar infarct and 8.72 ± 1.14 in those without (P < 0.001). Out of 14 cases with CI, no plaque was observed in 3, and plaque was observed at contralateral internal carotid artery in 3, and at ipsilateral in 8.

Conclusions: In general, carotid arteriosclerosis is associated with degree of cerebral ischemia and aortic stiffness, however, cerebral infarction may occur in patients with none or mild carotid arteriosclerosis.
Chronobiology is a branch of biomedical sciences devoted to the study of biological rhythms, that according to cycle length, are classified into: circadian (period of around 24 hours), ultradian (less than 24 hours), and infradian (more than 24 hours, e.g., days, weeks, months), and their interactions with bodily functions. The cardiovascular system is a suggestive example of such organization, since arterial blood pressure, heart rate, vascular tone, coagulation/fibrinolysis, exhibit rhythmic changes. Chronoepidemiology deals with the interaction between biological rhythms and onset of different diseases, and many studies have yielded rhythmic variations in the occurrence of myocardial infarction, stroke, and pulmonary embolism. Acute aortic rupture or dissection (AARD) represent life-threatening conditions characterized by high mortality, and many studies have explored the possible existence of rhythmic patterns as well. A recent meta-analysis from our group on the available literature, showed an evident and significant preference for occurrence of AARD during Winter months (particularly in December), on Monday, and during morning hours (6am – noon). These results, strengthened by their uniformity in different countries, provide further confirmation that the temporal variation in acute aortic diseases does not simply reflect a random phenomenon. Many different pathogenetic mechanisms may explain the existence of a temporal variation in the onset of acute cardiovascular diseases. On one hand, a constellation of unfavourable factors, each of them probably not so harmful if taken alone, but reinforced by their contemporary presence, could trigger overt disease. On the other hand, the potential negative role of external or internal disruption of circadian clocks located in the peripheral organs, including cardiomyocytes, vascular smooth muscle cells and endothelial cells, could also play a role.
Endovascular aortic aneurysm repair (EVAR) is now widely accepted as the preferred method of mitigating the risk of rupture in patients with documented abdominal aneurysms. Beginning in higher volume centers, the procedure is now performed in smaller community hospitals. This report highlights the rapid introduction and success of an EVAR program in a very small (100-bed) medical center in a small community in Northern Arizona. Since the arrival of a Board-certified vascular surgeon in late 2006 and the development of an EVAR program, the demographic, outcome and follow-up data on all 65 abdominal aneurysm interventions performed at Verde Valley Medical Center have been collected. Procedural success has been 100%, with no conversions to open repair. The median LOS has been 1.0+/-.9 days with 2 pts readmitted within a week for short stays (1 COPD, 1 CHF). The 1 perioperative death was in a pt with an 11.5 cm ruptured AAA. During follow-up, there has been 1 type II endoleak which sealed spontaneously at 9 months, 2 pts with Type I endoleaks required repeat EVAR at 1 year, a 3rd pt had an open repair & 1 pt had occlusion of the left limb, treated with a stent graft. Three patients have died from unrelated causes in the follow up period. This report describes an ongoing successful EVAR program at a very small community hospital. Despite its size the hospital has also had a successful primary and elective coronary interventional program without onsite cardiothoracic surgical support for over 10 years with over 2500 coronary interventions performed without the need for emergency surgical intervention. While higher volume surgical centers may be associated with lower complication rates and better survival, experienced operators and well-trained support staff can also favorably impact outcomes.
Regulator T cells (Tregs) are anti-inflammatory CD4+CD25+Foxp3+ T cells that are impaired in both numbers and activities in human and experimental coronary heart diseases. Abdominal aortic aneurysm (AAA) is an aortic disease that its pathogenesis involves extensive infiltration of pro-inflammatory cells that release pro-inflammatory cytokines to activate vascular cells and other inflammatory cells, thereby leading to arterial wall remodeling, expansion, and rupture. Using immunostaining of human AAA lesions, we found that the numbers of CD4+Foxp3+ Tregs were also reduced in these lesions. ELISA of Treg protein Foxp3 demonstrated significantly lower Foxp3 proteins in plasma cell lysate preparations from patients with AAAs (n=485) than those from age and gender-matched AAA-free controls (n=204) (121.43±46.63 vs. 190.61±39.02 ng/mL, P<0.00001). Pearson’s correlation test (r = –0.147, P=0.007) and multivariate linear regression test (B= –0.013±0.005, P=0.006) demonstrated significant and negative association between plasma cell Foxp3 protein with human AAA annual growth rate. In angiotensin II (Ang-II)-induced AAAs, lesion Foxp3+ Treg numbers were correlated negatively and significantly with the concentrations of Ang-II that was used to infuse apolipoprotein E-deficient (Apoe–/–) mice (r= –0.883, P<0.0001). Increased abdominal aortic diameterd in Ang-II infusion-induced AAAs in Apoe–/– mice can be significantly suppressed if mice received adoptive transfer of in vitro prepared Tregs from wild-type (WT) mice before Ang-II infusion. In contrast, when Tregs from interleukin-10-deficient (Il10–/–) mice were used, these Tregs failed to suppress Ang-II infusion-induced AAAs in Apoe–/– mice, although Foxp3 immunostaining demonstrated similar numbers of Tregs in AAA lesions from Apoe–/– mice between recipient mice received Tregs from WT mice or Il10–/– mice. These observations suggest that Tregs suppress AAA growth by releasing IL10.
Recent studies have confirmed a close association between various medical conditions (intracranial aneurysm, abdominal aortic aneurysm, temporal arteritis, autoimmune disorder, renal cysts), certain aortic anatomic variants (bovine aortic arch, direct origin of left vertebral artery from aortic arch, bicuspid aortic valve), and a family history of aneurysm disease with thoracic aortic aneurysm and dissection. This presentation reviews these associations. We propose to capitalize on these associations as powerful and expanding opportunities to diagnose the virulent but silent disease of thoracic aortic aneurysm. This can be accomplished by recognition of this “guilt by association”. Thus, patients with associated diseases and anatomic variants should be investigated for silent aortic aneurysms. Such a paradigm holds substantial potential for reducing death from the silent killer represented by thoracic aortic aneurysm disease.
PATHOGENESIS, DIAGNOSIS AND TREATMENT OF AORTIC ANEURYSM AND PERIPHERAL ARTERY DISEASE

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CONTRADICTORY EFFECTS OF HYPERLIPIDEMIA AND DIABETES MELLITUS ON PROGRESSION OF ABDOMINAL AORTIC ANEURYSM: PATHOBIOLGICAL MECHANISMS

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Diabetes Mellitus (DM) and Hypercholesterolemia are well-established risk factors for atherosclerotic occlusive disease. However, only the latter has been shown to be a risk factor for abdominal aortic aneurysm (AAA). We recently developed a novel, robust, swine model of AAA based on laparoscopically-delivered, periarterial application of calcium chloride with angiotensin-II infusion and hyperlipidemic diet that closely resembles the pathobiology of human AAA. In this presentation we report that this three-part regimen results in deposition of calcium within the elastic fibers of the media and intima followed by a robust inflammatory response at these sites, disruption and fragmentation of the elastica, damage to medial smooth muscle cells, reactive fibromuscular hyperplasia, intramural hemorrhage, and markedly increased external aortic diameter. However, expansion of the aortic lumen (>50% over baseline) occurred only in the pigs that were fed the hyperlipidemic diet but not in controls with normal diet. In this talk we will discuss the role of hypercholesterolemia in luminal expansion, and will point out the pathobiological differences from that which occurs in DM where increased glycation is thought to facilitate cross-linking during collagen formation resulting in stiffening of the extracellular matrix rendering it less prone to proteolysis thereby reducing the likelihood of aneurysmal expansion and rupture. Further studies using streptozotocin to induce experimental DM, with and without hypercholesterolemia, would be expected to greatly strengthen the relevance of this model to the human clinical situation and further support its reliability as a mechanism-based platform for testing novel treatments and technologies for AAA prevention.
During their natural history, blood vessels undergo enduring, and sometimes irreversible structural changes in size and composition, a process commonly referred to as vascular remodeling. Many of these changes are initiated as a physiological response allowing adaptation and repair of the vessel wall, however inappropriate remodeling underlies the pathogenesis of major cardiovascular conditions, such as atherosclerosis, hypertension, or aneurysmal disease. We had hypothesized that degradation of the extracellular matrix scaffold of blood vessels was needed in order to allow for their reshaping, and we pioneered investigations into the role of enzymes called matrix metalloproteinases (MMPs). These can degrade all the extracellular matrix components, as well as control the biological activity of other molecules involved in tissue remodeling. We demonstrated that MMPs were released by vascular and inflammatory cells in vitro and within the arterial wall under the influence of major drivers of vascular remodeling including hemodynamics, injury, inflammation, and oxidative stress. Using a variety of experimental and clinical observations we also demonstrated that MMP activity was associated with, and indeed was needed, for pathological arterial wall remodeling. Based on these results we proposed that MMPs are major effectors of vascular remodeling in general, and that they can specifically weaken atherosclerotic plaque shoulders ("vulnerable shoulders"). Interest in MMPs and other vascular proteases in relation to physiological and pathological vascular remodeling continues to grow. Accumulated evidence points to potential therapeutic interventions that might prevent or limit the effects of a number of clinical events, such as plaque or arterial wall disruptions. The continued lack of specific synthetic inhibitors restrict the ability to therapeutically control vascular remodeling, suggesting as a potential alternative the manipulation of intrinsic drivers of remodeling, either via risk factors, biological processes, or natural inhibitors, including those that drive and control MMP expression and enzymatic activity.
In polyvascular disease, carotid arteriosclerosis may be associated with progression of coronary and/or peripheral artery lesions. We evaluated association between carotid plaque score (PS) and obstructed lesion in 106 patients with peripheral artery disease (PAD). We studied 68 PAD patients (82 obstructed lesions) with anterior tibial artery and/or posterior tibial artery (group A), 22 PAD patients (29 lesions) with femoral or iliac obstructive disease (group B). PS was 11.0±4.76 in group B, and 12.1±5.83 in group A. Number of risk factor (NRF) was 2.93±0.73 in group B and 2.27±1.15 in group A. Carotid arteriosclerosis or NRF in tibial disease is similar to that in iliofemoral disease. We also studied in the patients with coronary artery disease (CAD). In 18 cases without plaque, there were only 1 case (5.6%) with 3-vessel disease (VD) and the mean number of diseased vessel (MNDV) was 1.34±0.60. The mean NRF was 2.19. In 51 cases with mild carotid arteriosclerosis (CA) (0<PS<5), MNDV was 1.42. MNRF was 2.14. In 37 cases with moderate CA (5≤PS<10), MNDV was 2.0±0.81. MNRF was 2.22±1.01. In 17 cases with marked CA (10≤PS), MNDV was 2.18±0.88 and MNRF was 1.84±0.73. PS was significantly associated with number of DV in CAD patients. Influence of lesion characteristics was evaluated in the patients who underwent percutaneous transluminal angioplasty (PTA) for PAD. The 53 superficial femoral artery (SFA) lesions, and 24 IA lesions were evaluated. No significant difference in restenosis rate was observed between cases with calcified lesion and those without calcified lesions. In conclusion, evaluation of carotid arteriosclerosis is more important to predict presence or severity of polyvascular disease than NRF.
USE OF FRACTION FLOW RESERVE TO PREDICT CHANGES OVER TIME IN MANAGEMENT OF SUPERFICIAL FEMORAL ARTERY

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Background: Peripheral arterial disease (PAD) is a condition characterized by progressive narrowing of the arteries in the peripheral vascular bed which affect patient quality of life. The purposes of this study were to 1) establish the feasibility of performing peripheral FFR (pFFR) in the peripheral vascular circulation, 2) correlate post intervention pFFR with future restenosis, and 3) demonstrate an association between pFFR and peak systolic velocity measured by duplex ultrasound.

Method: The first 20 patients who met the criteria and consented were enrolled in the study from December 2007 to April 2009. The enrolled patients underwent baseline ankle brachial index, Doppler ultrasound of the extremity, renal function studies and Edinburgh claudication questionnaire. The patients were followed with three ABI recordings and Doppler ultrasound, using the General Electric (GE) Vivid 7 ultrasound machine, of the intervened extremity during the one year follow up period.

Results: The mean baseline pre intervention pFFR prior to adenosine was 0.79 ± 8 and post adenosine pre intervention pFFR was 0.71 ± 13. There was a correlation between pre intervention hyperemic pFFR and baseline PSV values. In patients with post-procedure FFR less than 0.95 there was a significant rise of PSV levels over time.

Conclusion: This is the first study to demonstrate that the peripheral vascular bed does respond to vasodilatation thereby supporting the use of FFR for this procedure. In our study, post-intervention FFR less than 0.95 predicts increased PSV over time which is a reasonably accepted surrogate for restenosis.
PERIPHERAL BLOOD- BUT NOT BONE MARROW-DERIVED ENDOTHELIAL PROGENITOR CELL THERAPY LIMITS EXPERIMENTAL ABDOMINAL AORTIC ANEURYSM DEVELOPMENT

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Background – Abdominal aortic aneurysms (AAAs) are characterized by the loss of the endothelial cell (EC) monolayer and its replacement by an intraluminal thrombus. We have previously shown that the restoration of the EC lining by cell therapy, using mature ECs or circulating endothelial progenitor cells (EPCs) limits AAA expansion in rats. The low levels of EPCs in the adult circulation led us to test another source of EPCs. Our goal was to compare the healing properties between peripheral blood-derived EPCs (PB-EPCs) and bone marrow-derived EPCs (BM-EPCs) on AAA dynamic in rats.

Methods and results – EPCs were collected by in vitro culture of mononuclear cells derived from rat peripheral blood or bone marrow. For cell therapy, 3.10^6 PB-EPCs (n=16) or BM-EPCs (n=16), or serum-free medium (controls; n=18) were seeded endovascularly immediately after surgery in the rat xenograft model. Expanded rat PB-EPCs and BM-EPCs displayed typical endothelial cell markers and angiogenic potential in vitro. While PB-EPCs were negative for the monocytic CD14 marker, BM-EPCs were CD14-positive. In vivo, the local transplantation of PB-EPCs reduced AAA formation in rats at 28 days (D28), while BM-EPC failed to display any stabilizing properties. Furthermore, cell therapy using PB-EPCs but not BM-EPCs was associated with the reestablishment of the endothelial lining, the reconstruction of a smooth muscle cell-rich new wall, the preservation of medial elastin content and a decreased aortic macrophage infiltration. Cultured PB-EPCs exhibited significantly higher expression levels of leukemia inducible factor, and lower levels of proinflammatory mediators, such as Metalloprotease-2, Cyclophilin A and Insulin Growthfactor-1.

Conclusion – Autologous PB-EPCs outperform BM-EPCs in stabilizing experimental AAAs and appear more clinically suitable for controlling AAA dynamics.
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RAPAMYCIN INHIBITS THORACIC AORTIC ANEURYSM FORMATION THROUGH SUPPRESSION OF PRO-INFLAMMATORY MEDIATORS

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Although infiltration of inflammatory cells in the aortic wall was frequently observed in thoracic aortic aneurysm (TAA) formation, the precise inflammatory pathways involved have not been clearly defined. In this study, we utilized the calcium chloride (CaCl2)-induced rat TAA model [Geng L. et al, Exp Mol Pathol. 89(1):72-81] to explore the potential role of mammalian target of rapamycin (mTOR) signaling pathway in the disease development. Male Sprague-Dawley rats (250-300 g) underwent periarterial exposure of thoracic aorta to either 0.5M CaCl2 (n = 20) or normal saline (0.90% NaCl, n = 20); and a subgroup of CaCl2-treated rats received nasal administration of rapamycin or PBS one day before the surgery. Without pre-administration of rapamycin, western blot and immunohistochemistry assays performed at 2 days post treatment revealed significantly enhanced phosphorylation of mTOR and expression of pro-inflammatory cytokines [i.e. tumor necrosis factor alpha (TNF-α), Interleukin 6 (IL-6) and Interleukin 1 beta (IL-1β)] in the CaCl2-treated aortic segments compared to the NaCl-treated segments. At 2 weeks post treatment, H&E and Verhoeff-Van Gieson (VVG) stainings showed aneurysmal alteration and disappearance of normal wavy elastic structures in the aortic segments exposed to CaCl2. In contrast, pre-administration of rapamycin on CaCl2-treated rats attenuated mTOR phosphorylation and down regulated the pro-inflammatory mediators [i.e. TNF-α, IL-6, IL-1β, matrix metallopeptidases 2 and 9 (MMP2 and MMP9)] to the control level. Most significantly, the CaCl2-induced TAA formation has been inhibited. Further in vitro cell culture experiments using smooth muscle cell (SMC) line A7r5 suggested that inhibition of the mTOR signaling pathway by rapamycin could promote differentiation of SMCs as reflected by reduced expression of S100A4 and osteopontin (OPN).
IS CILOSTAZOL A GOOD CHOICE TO REDUCE RESTENOSIS AFTER PERIPHERAL VASCULAR DISEASE STENTING? A META-ANALYSIS

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Background: Cilostazol has an important role for the medical management of peripheral vascular disease (PAD). It remains unclear whether cilostazol, which has been shown to improve the clinical outcomes of endovascular therapy for femoropopliteal lesions, also reduces angiographic restenosis. We aim to analyze those studies that have compared cilostazol to any other anti-thrombotic regimen in order to prevent stent restenosis (SR).

Methods: We systematically searched Pub Med, Embase and Cochrane up to January 2014. Subjects of analysis were stent restenosis and lesion patency up to 12 months follow-up. We used Fixed or Random Effect analysis using the Cochrane Handbook of Systematic Reviews. We stratified the comparison as cilostazol and aspirin compared ticlopidine and aspirin (Analysis 1), and cilostazol and aspirin compared to aspirin alone (Analysis 2).

Results: Out of 205 articles, 4 clinical studies were included in the two analyses. The pooled data provided a total of 110 patients, 51 of which received cilostazol and aspirin. When compared to ticlopidine and aspirin, the cilostazol group significantly reduced () the incidence of restenosis (OR 0.24; CI 0.10-0.54; p < 0.01), lead to increase lesion patency (Figure 1). Analysis 2 presented only one randomized trial that also demonstrated significant decrease of SR.

Conclusion: Our analysis suggests that cilostazol when compared to the other available anti-thrombotic regimens might lead to decreased SR and increase the patency of the lesion. Randomized clinical trials are urged to confirm this.
Endothelial nitric oxide synthase (eNOS) is a major source of endothelium-derived nitric oxide (NO) production which could protect against cerebro- and cardiovascular disorders. Rho-associated kinase (ROCK) is well-known to downregulate eNOS expression via destabilization of eNOS mRNA. Although its precise mechanism still remains unclear, we recently identified eukaryotic elongation factor 1-A1 (eEF1A1) as a downstream target of ROCK. Indeed, eEF1A1 shortened eNOS mRNA stability by its binding to 3' untranslated region (3'-UTR) of eNOS mRNA. We hypothesized that eNOS mRNA stability could be regulated by ROCK1 and/or ROCK2-mediated eEF1A1 activation. In addition, we sought to elucidate whether ROCK-mediated changes in eNOS expression could contribute to neuroprotection following acute cerebral injury. Interestingly, we found that eEF1A1 was strongly phosphorylated by constitutively active ROCK2, but weakly by constitutively active ROCK1. Also, RNA electrophoretic mobility shift assay showed that eEF1A1 binding affinity with 3'-UTR of eNOS mRNA was enhanced by ROCK2-mediated eEF1A1 phosphorylation. In human umbilical vein endothelial cells, a ROCK inhibitor, fasudil, decreased eEF1A1 phosphorylation, while total eEF1A1 expression was not altered. Consistently, eNOS expression and eNOS mRNA stability were increased in primary cultured endothelial cells isolated from haploinsufficient Rock2+/- mice compared to WT and Rock1+/- . Similarly, the infarct volume and neurological damage following transient cerebral ischemia and reperfusion were also reduced in Rock2+/- mice and these reductions were dependent on eNOS expression verified by the additional findings on transient cerebral ischemia of double mutant mice, namely eNOS−/−Rock1+/- and eNOS−/−Rock2+/- mice. These findings indicate that ROCK2 regulates eNOS mRNA stability by enhancing eEF1A binding affinity to 3'-UTR of eNOS mRNA following eEF1A1 phosphorylation and that inhibition of ROCK2 contributes to the primary benefits of ROCK inhibitors on stroke protection, suggesting that ROCK2 could be a promising therapeutic target on cerebral ischemic stroke.
The main objective of this study was to determine whether or not monocyte infiltration occurs in the pre-diabetic (PD) cardiomyopathy hearts and the role of monocytes in the pathogenesis of diabetic cardiomyopathy. We hypothesize that the PD cardiomyopathy heart is significantly populated with monocytes and that BMP-7, a novel mediator of monocyte polarization, activates infiltrated monocytes into anti-inflammatory M2 macrophages, thereby inhibiting apoptosis and fibrosis and improving cardiac function. Animals were divided into three groups: control, PD, or PD+BMP-7 groups. PD and PD+BMP-7 groups were administered STZ (50 mg/kg) whereas control animals received sodium citrate buffer. Afterwards, the PD+BMP-7 group were administered BMP-7 (200 µg/ kg) for three days. Our data show significantly increased infiltrated monocytes and associated pro-inflammatory cytokines, adverse cardiac remodeling, and heart dysfunction in the PD group (p<0.05). Interestingly, M2 macrophage polarization and associated anti-inflammatory cytokines were enhanced, reduced adverse cardiac remodeling, and improved cardiac function in the PD+BMP-7 group (p<0.05). In conclusion, our data suggest, that diabetic cardiomyopathy is associated with increased monocyte infiltration, released of pro-inflammatory cytokines, which contributes to adverse cardiac remodeling, and cardiac dysfunction. Moreover, we report that BMP-7 possesses novel therapeutic potential in its ability to polarize monocytes into M2 macrophages and confer cardiac protection in the PD heart.
PRIMING THE PROTEASOME BY PKG: A NOVEL CARDIOPROTECTIVE MECHANISM OF SILDENAFIL

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Protein quality control (PQC) functions to minimize the amount and toxicity of misfolded proteins in the cell. PQC is performed by intricate collaboration between molecular chaperones and targeted protein degradation. The latter is primarily carried out by the ubiquitin-proteasome system and autophagy. Data from both experimental studies and human failing hearts suggest that cardiac PQC inadequacy, especially proteasome functional insufficiency, plays a pathogenic role in the development of congestive heart failure (CHF) resulting from a large subset of heart diseases. Hence, improving cardiac proteasomal function may conceivably become a novel therapeutic strategy to block the progression of these forms of heart disease to CHF. We previously demonstrated that overexpression of proteasome activator 28 (PA28) enhances cardiac proteasome function in vitro and in vivo. A small-molecule compound (a USP14 inhibitor) was shown by others to enhance proteasome proteolytic function in cultured non-cardiac cells. Until very recently, no agent has been demonstrated to increase proteasome function in the heart. To better understand how proteasome function is regulated, we have recently discovered that protein kinase G (PKG) positively regulates proteasomal degradation of misfolded proteins in both cultured cardiomyocytes and the heart of intact mice. Likely through phosphorylating specific proteasome subunits and thereby priming the proteasome, PKG activation induced by either pharmacological or genetic means facilitated the degradation of a surrogate and a bona fide misfolded protein in cultured cardiomyocytes. PKG enhancement by sildenafil significantly increased proteasomal peptidase activities and reduced the protein level, but not mRNA level, of a surrogate proteasome substrate in the heart. Furthermore, long-term administration of sildenafil significantly reduced the accumulation of ubiquitinated proteins and protein aggregation in cardiomyocytes and delayed cardiac malfunction in a well-documented mouse model of cardiac proteinopathy. Our findings indicate that stimulating PKG can improve cardiac proteasomes, representing a novel protective mechanism of sildenafil.
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THE PIVOTAL ROLE OF L-ARGININE IN THE ISCHEMIC HEART PRECONDITIONING - A NANOMEDICAL APPROACH

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Ischemic preconditioning with a short coronary artery occlusion has been shown to protect the heart against a subsequent myocardial infarction. Although several endogenous molecules have been implicated in the heart adaptation to an ischemic event, its mechanism is not well understood. A nanomedical approach was used to study, in vivo and ex vivo, the concentration changes of small molecules in the heart during preconditioning. Catheter-protected nanosensors, with a diameter of 300nM, were implanted into the left ventricular wall of the heart of New Zealand white rabbits, in order to measure the concentration of nitric oxide (NO), peroxynitrite (ONOO-), superoxide (O2-), and carbon monoxide (CO), as well as, tetrahydrobiopterin and L-arginine. Ischemia triggered fast release of NO level, which peaked at 1.2±0.2 micromol/L, after 5 minutes. The release of NO was accompanied by the generation of superoxide, which reached maximum concentration after 7±1 minutes, and peroxynitrite which peaked after 17±2 minutes. At 15 minutes of ischemia, equal concentrations (0.8± micromole/L) of NO, O2-, and ONOO- were measured. After 19 minutes, the cytoprotective NO significantly decreased and the cytotoxic ONOO- increased. Therefore, the ratio of NO/ONOO- decreased to 0.05±0.03 from the preischemic ratio of 7:1. Ischemic preconditioning was achieved by an episode of 4-7 minutes of occlusion, followed by 15-60 minutes of reperfusion prior to the 60 minute occlusion. L-arginine content in the heart was measured during different stages of ischemic preconditioning, reperfusion and ischemia. The content of L-arginine increased significantly, from 14 nmol/L per mg protein by 10-50%, after preconditioning. The increase in L-arginine content after preconditioning correlated directly with the decrease of infarct size (25±6%) when compared to the control (48±5%). These results support the hypothesis that the cardioprotective effect of ischemic preconditioning is dependent on L-arginine availability.
Cell therapy, therapeutic angiogenesis and other regenerative therapies are an attractive option for patients with several coronary heart disease not amenable to surgery or percutaneous intervention. However, despite very robust efficacy in preclinical studies, nearly all clinical trials have been negative or nearly so. We have investigated the effects of both type 1 and type 2 diabetes on collateral vessel formation in the heart and associated signaling, using porcine models in the setting of chronic myocardial ischemia. Type 1 and type 2 diabetes were induced in male miniswine using the pancreatic beta-cell specific toxin alloxan, or in swine fed a high fat diet, respectively. Age-matched swine served as controls. Eight weeks following induction, chronic ischemia was induced by ameroid constrictor placement around the circumflex artery. Marked glucose intolerance was documented. Myocardial perfusion, function and microvascular endothelial function and associated signaling pathways were evaluated. Both type 1 and type 2 diabetic animals exhibited significant endothelial dysfunction and a marked reduction in ischemia induced collateral vessel formation. In addition, in both models, collateral dependent perfusion and the angiogenic response to exogenous VEGF and other angiogenic growth factors were impaired compared to the response observed in otherwise normal pigs. Expression of VEGF, Ang-1 and Tie-2 was reduced, while anti-angiogenic proteins, angiostatin and endostatin were significantly elevated in the diabetic myocardium, and this was also observed in patients with diabetes. In conclusion, both type 1 and type 2 diabetes results in a profound impairment in the myocardial angiogenic response to chronic ischemia in porcine models. These models may allow us to better understand the pathophysiology of diabetes with regard to vascular formation, and understand why regenerative strategies in patients have shown little benefit to date. They may offer optimism for the future due to a better understanding of mechanisms involved.
Background and Objectives: Bendavia is a small water soluble molecule that freely crosses cell membranes and localizes to the inner mitochondrial membrane where it associates with cardiolipin and reduces intracellular reactive oxygen species (ROS) production. Our objective was to determine Bendavia’s effect on myocardial infarction. Methods and Results: In isolated guinea pig hearts exposed to 20 minutes of global ischemia and 2 hours of reperfusion, Bendavia, administered either throughout ischemia/reperfusion or given only at reperfusion, reduced myocardial infarct size by approximately 40%. In an in-vitro model Bendavia primarily reduced myocyte death that occurred with ROS burst at the time of reoxygenation, even though it is not a ROS scavenger. In an in-vivo rabbit model, there was a trend for Bendavia to reduce infarct size (by 18%) in rabbits with risk zones of greater than 20% (p=0.09); while for any given risk zone, the extent of no-reflow was reduced by Bendavia (p=0.0085). When administration of Bendavia was delayed by 10 minutes after reperfusion, it did not demonstrate a beneficial effect. 6-week administration of Bendavia starting 2 hours after permanent coronary artery occlusion in the rat model decreased scar circumference to 40% LV versus vehicle (47%; p=0.024), and reduced LV volumes. Bendavia improved ejection fraction by an absolute 6% (p=0.005) and fractional shortening by 21% (p=0.047). Bendavia preserved expression of mitochondrial function related genes in the non-infarcted border zone adjacent to the infarct and preserved expression of the SERCA 2a gene at the infarct border zone. Conclusion: The mitochondria targeting peptide, Bendavia demonstrated a reduction in reperfusion injury when administered acutely in myocardial ischemia/reperfusion models. When administered chronically in a permanent coronary artery occlusion model, Bendavia improved post myocardial infarction remodeling and left ventricular dysfunction.
TICAGRELOR LIMITS MYOCARDIAL INFARCT SIZE- AN ADENOSINE AND COX2 DEPENDENT EFFECT

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Background: In a phase III clinical trial (PLATO) Ticagrelor (TIC) showed better clinical outcomes than Clopidogrel (CLOP) in patients with acute coronary syndromes. In addition to P2Y12 receptor antagonism, TIC prevents cell uptake of adenosine and thus, may augment adenosine effects. Adenosine protects the heart against ischemia-reperfusion injury. We compared the effects of CLOP and TIC on myocardial infarct size (IS).

Methods: Rats received oral TIC (0, 75, 150 or 300 mg/kg/d) or CLOP (30 or 90 mg/kg/d) for 7d and underwent 30min coronary artery ligation and 24h reperfusion. Area at risk (AR) was assessed by blue dye and IS by TTC. We assessed whether adenosine receptor inhibition (CGS15943, an A2A/A1 antagonist) or COX inhibition by either aspirin (5, 10, or 25 mg/kg) or specific COX1 (SC560) or COX2 (SC5815) inhibitors could reduce the IS-limiting effects of TIC. COX2 enzyme activity was assessed by ELISA and expression by rt-PCR.

Results: TIC, dose-dependently, reduced IS (IS in the control group was 53.2±2.4% of the AR and 42.2±1.6%, 34.7±1.3% and 22.3±1.3% in the TIC 75, 150 and 300 mg/kg/d, respectively), whereas CLOP had no effect (50.2±1.1% and 50.5±2.0%, respectively). Adenosine receptor antagonism blocked the TIC effect. COX2 inhibition by SC5815 or high-dose (10 and 25 mg/kg/d) aspirin attenuated the IS-limiting effect of TIC, whereas COX1 inhibition or low-dose aspirin (5 mg/kg/d) had no effect. TIC, but not CLOP, upregulated COX2 expression and activity. This effect was blocked by adenosine receptor antagonism. TIC, but not CLOP increased Akt and eNOS phosphorylation.

Conclusions: TIC, but not CLP reduces myocardial IS. The protective effect of TIC was dependent on adenosine receptor activation with downstream upregulation of eNOS and COX2 activity. Blocking COX2 with either specific COX2 inhibitor or high-dose of aspirin abrogated the IS-limiting effects of TIC.
MicroRNAs (miRNAs) have emerged as a novel class of endogenous, small, non-coding RNAs that negatively regulate gene expression via degradation or translational inhibition of their target mRNAs. In the heart, miRNAs have been involved in several clinical scenarios including ischemia/reperfusion and preconditioning suggesting that regulation of their function could be used as a novel cardioprotective strategy. In particular, miRNA-1, miRNA-21, miRNA-24, miRNA-29, miRNA-92a, miRNA-126, miRNA-133, miRNA-320, miRNA-199a, miRNA-208 and miRNA-195 have been shown to be regulated after myocardial infarction. Following ischemic preconditioning (IPC), we observed significant increase in miRNA-1, miRNA-21 and miRNA-24 in the heart. Treatment with the miRNAs derived from the hearts subjected to IPC protected the hearts against ischemia/reperfusion injury, as shown by a reduction of infarct size as compared with saline or non-IPC miRNA-treated control. This protective effect was abolished by treatment with the miRNA-21 inhibitor. In addition, one of the powerful pharmacological preconditioning agent, sildenafil (Viagra) also resulted in upregulation of miRNA-21 in the heart. Pretreatment of hearts with adenoviral vector encoding miR-21eraser prior to sildenafil preconditioning abolished the infarct limiting effect of sildenafil. These results suggest that miRNA-21 is one of important mediator of cardioprotection induced by IPC and sildenafil.
Minocycline is a semisynthetic second-generation tetracycline with proven safety, which is used in humans for the treatment of acne and urethritis. The drug is also considered for the treatment of severe chronic inflammatory diseases, such as rheumatoid arthritis, as it exerts anti-inflammatory effects that are completely separate and distinct from its antimicrobial action. It has been shown that minocycline protects the brain in rodent models of global and focal cerebral ischaemia as well as in patients with acute stroke. The significant neuroprotection was attributed to decreased expression of caspase-1 and cyclooxygenase 2 (COX-2), as well as inhibition of the inducible form of nitric oxide synthase (iNOS). Minocycline was also shown to inhibit mitochondrial leakage of cytochrome c and delay progression of amyotrophic lateral sclerosis in a transgenic mouse model of the disease. Protective effects of minocycline during ischemia/reperfusion (I/R) injury to a new target organ, the heart, have also been recently documented. Minocycline significantly reduced the post-ischemic occurrence of necrotic and apoptotic cell death, with normalization of developed and diastolic pressure. In regard to its antiapoptotic mechanism of action, minocycline reduced the expression level of initiator caspases, increased the ratio of XIAP to Smac/DIABLO at both the mRNA and protein level, and prevented the mitochondria-mediated release of cytochrome c and Smac/DIABLO. These synergetic actions dramatically prevented the post-ischemic induction of caspase activity associated with cardiac I/R injury. Owing to its safety record and multiple novel mechanisms of action, minocycline may be clinically useful not only to supply neuroprotection, but as cardioprotective agent, to ameliorate the cardiac dysfunction and cell loss associated with I/R injury.
Hypoxia-inducible factor (HIF)-prolyl hydroxylases (PHD1, PHD2 and PHD3) are oxygen sensors that regulate the stability of the HIFs in an oxygen-dependent manner thus mediating cellular adaptive responses to changes in oxygen supply. Suppression of PHD enzymes leads to stabilization of HIFs and offers a potential treatment option for many ischemic disorders such as peripheral artery occlusive disease, myocardial infarction, and stroke. The HIF is a key player as it activates a broad range of genes protecting cells against hypoxia. Its content is determined by its degradation rate by intracellular oxygen sensors, PHDs. Small molecule PHD inhibitors improve hypoxic injury in experimental animals. We studied cardioprotection and the extent of perfusion during Hind limb ischemia (HLI) in genetic models by disrupting individual PHDs (PHD-1-/- and PHD-3-/-). PHD-2 inhibition was found to be embryonically lethal. In our study both inhibition of PHD-1 and PHD-3 stimulated various protective mechanisms, induced angiogenesis in both the models. The molecular mechanism behind the PHD-1 mediated cardioprotection is probably HIF-1alpha expression followed by regulation of its target genes, including beta-catenin, eNOS, NF-kappa B, and Bcl-2. Whereas PHD-3 inhibition enhanced angiogenesis and reduced oxidative stress in the ischemic myocardium (MI) and HLI. Inhibition of PHD-3 domain enhances VEGF and Bcl-2 expression and improved ischemia-induced neovascularization and increased blood flow in a mouse model offering a potential, new therapeutic approach in the treatment of CAD and PAD. Collectively, our novel and unique approach to understand the molecular mechanism of inhibition of PHDs and its effect could prove to be a strategic therapeutic modality to treat ischemia related cardiac failure or peripheral arterial diseases and may ultimately improve quality of life and mitigate disease progression in affected subjects.
A NEW CARDIAC MARKER DURING FIRST TRIMESTER SCREENING?
DETECTION OF FETAL PULMONARY VEINS BY DOPPLER B MODE AND X FLOW BETWEEN 12-15 WEEKS OF GESTATION

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Background: Changes in venous system might reflect variations in cardiac performance (1). Scant data exist about the analysis of the pulmonary veins before 17 weeks of gestation (2,3,4). The aim of the study was to determine: (a) the feasibility of pulmonary venous Doppler flow velocity wave (FVW) detection using either ultrasound Mode B or X flow in normal fetuses during first trimester of gestation, and (b) if reversal of the A wave in the pulmonary vein (PV) is a marker of major cardiac defects.

Methods: 211 pregnant women underwent congenital heart disease screening during the first trimester in our center (Centro de Estudios Ultrasonograficos Perinatales, Venezuela). The screening comprised: fetal heart rate monitoring, and fetal echocardiography: four chamber, and outflow tracts views; with Doppler velocity of: (a) PV, (b) ductus venosus, (c) tricuspid, and (d) mitral flows. The upper right PV was used to record the FVW using four-chamber view by either B mode (158 fetuses) and/or X flow (70 fetuses). Cases were re-evaluated by late pregnancy echocardiography. Statistical analysis was performed using Chi-square with Yates correction.

Results: The PV’s FVW was detected between 12-15 weeks of gestation in 86.7% and 90% of cases by Mode-B and X-flow respectively. There was no statistical significant difference between the two methods (p-value 0.63). Five out of Six cases of PV reversal had confirmed major cardiac defects (AV-canal, functional cardiomyopathy, type-B interrupted aortic arch, VSD, and hypoplastic left-heart). The sixth case was lost during follow up, but early echocardiography suggested aortic coarctation.

Conclusion: The FVW of PV can be obtained either by ultrasound 2D or by X flow with a similar rate of success between 12-15 weeks of gestation. The presence of pulmonary A vein reversal may suggest cardiac anomaly.
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THE IMPACT OF CAROTID ARTERY ATHEROSCLEROSIS ON THE RISK OF ADVERSE CARDIAC EVENTS IS DEPENDENT ON THE PRESENCE OF PRE-EXISTENT CORONARY ARTERY DISEASE
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Objective: We sought to examine the differential impact of carotid atherosclerosis (CA) on the risk of major adverse coronary and cerebrovascular events (MACCE) in patients with vs. without coronary artery disease (CAD) diagnosed angiographically.

Background: CA is reportedly a strong predictor of imminent cardiac events, even in the absence of established CAD. Previous outcome reports have varied greatly in CAD and carotid artery stenosis (CAS) definitions so the prognostic interplay between CA and future MACCE remains unclear.

Methods: We conducted a follow-up survey of 1,391 patients who underwent clinically-driven coronary angiography and a same-day carotid Doppler study. Follow-up time was defined as the time to either death or MACCE.

Results: Of the 1,391 patients included in the study, angiographic CAD was present in 1,105 patients (79%). The mean follow-up was 1,574 days. Rates of the composite MACCE endpoint were higher among patients with CAD compared to those without CAD (48% vs. 20%, HR=2.1, p<0.001), whereas the rates of all-cause mortality (10% vs. 9%, HR=0.94, p=0.81) and stroke (7% vs. 5%, HR=0.67, p=0.3) did not differ significantly between both groups. By multivariate analysis, the presence of clinically significant CAS (≥50% stenosis) was independently predictive of all-cause mortality (HR=3.08, 95% CI 1.03-9.1, p=0.04) and trended toward an independent association with the composite MACCE endpoint (HR=2.13, 95%CI 0.9-4.9, p=0.08) among patients without CAD. CAS was not independently associated with either outcome among patients with CAD.

Conclusions: The prognostic implications of CAS are predominantly imparted in the absence of preexistent CAD verified by angiography.
CARDIOVASCULAR IMAGING MODALITIES FOR EVALUATION OF CORONARY CIRCULATION, CARDIAC STRUCTURE AND FUNCTION

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CARDIAC MRI AS A SENSITIVE SCREENING TOOL IN MYOTONIC DYSTROPHY
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Background: Myotonic dystrophy (DM) is a multisystem disorder with progressive skeletal myopathy, cardiac conduction disease and cardiomyopathy. Electrocardiography (ECG) poorly predicts the need for pacemaker therapy, which helps avert sudden death that affects nearly 1/3 of patients. Autopsy evidence of cardiac fibrosis in DM has prompted in vivo studies using cardiac magnetic resonance (CMR); however, traditional late gadolinium enhancement (LGE) CMR may be insensitive to diffuse interstitial fibrosis. We investigated T1 mapping to measure myocardial extracellular volume (ECV) vs. LGE as markers of substrate for conduction system disease and adverse events in DM.

Methods: Over six years, 42 DM patients underwent screening ECG and CMR examination, a subset of which included pre- and post-contrast T1 mapping and measurement of hematocrit. Invasive electrophysiological (EP) testing was performed per clinical discretion, typically in instances of abnormal ECG or LGE-CMR. The presence of conduction disease was defined as a PR interval >200ms and/or QRS >100ms on ECG, H-V interval >70ms by EP testing, or documented episode of ventricular tachycardia or other sustained arrhythmia.

Results: 27 (64%) DM patients were found to have conduction disease. A higher proportion of patients with vs. those without conduction disease demonstrated baseline LGE-positivity (65% vs. 35%, p=0.10). While ECV did not differ between these groups (24±5 vs. 23±3%, p=NS), those with significant PR prolongation had higher myocardial ECV values compared to those with normal PR intervals (29±3 vs. 23±4%, p=0.03).

Conclusions: Increased myocardial extracellular volume correlates with atrioventricular conduction delay in patients with DM1, who also carry a high risk of heart block and sudden cardiac death. This noninvasive imaging biomarker warrants further evaluation in optimizing primary prevention device placement to reduce adverse outcomes due to conduction system disease in patients with high genetic risk. LGE-CMR may offer prognostic value in identifying DM patients at high risk of cardiac events.
VALUE OF THORACIC AORTIC CALCIUM IN PREDICTION OF OBSTRUCTIVE CORONARY ARTERY DISEASE

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Background. Gated, non-contrast computed tomography (CT) scans used for assessment of coronary calcium score (CAC) also identify thoracic aortic calcium (TAC). TAC is associated with age, coronary risk factors and CAC. It is unclear if TAC can provide incremental value over CAC for prediction of obstructive coronary artery disease (CAD).

Methods. Multi (64)-detector CT was performed in 153 adults [age 51±12 years, 55% women, body mass index 32±7 kg/m², 55% hypertensive, 11% diabetic, 30% smoker, 48% hypercholesterolemic, Framingham risk score 5±6] for evaluation of suspected CAD. Thoracic aortic (from pulmonary bifurcation to cardiac apex in each 2.5 mm slice) calcium was graded on the basis of total number of calcific plaques at least 2.5 mm in length (0=absent to 3+ ≥3 plaques). Obstructive CAD was defined as ≥1 major coronary artery stenosis (≥50%) on CT angiogram.

Results. TAC was present in 50 (33%) patients. Compared to those without (n=103), patients with TAC were older (63±9-vs-46±10), more often hypertensive (74%-vs-46%) or hypercholesterolemic (68%-vs-39%), had higher median (25th, 75th percentiles) CAC scores [153 (9,378) –vs-0 (0,3)] and more often had a CAC score > 100 (52%-vs-13%) or >400 (25%-vs-6%) [All p<0.01]. TAC provided no incremental value for prediction of obstructive CAD in patients with CAC>100 [OR 0.3 (95% CI 0.0, 8.3), p=0.5]. However, in those with CAC score ≤100, any TAC was associated with significantly higher prevalence of CAD [OR 4.7 (95% CI 1.7, 12.6), p=0.002]. This association was stronger for those with CAC ≤100 and 3+ TAC [OR 6.0 (95% CI 1.6, 23.4), p=0.009] [Figure].

Conclusion. Presence of TAC on CT in patients with low CAC scores (≤100) identifies those at higher likelihood of having obstructive CAD on CT coronary angiography.
REAL TIME THREE DIMENSIONAL ECHOCARDIOGRAPHY IN VALVULAR PULMONARY STENOSIS AMONG PEDIATRIC AGE GROUP

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Background: Two Dimensional transthoracic echocardiography (2D–TTE) has been the standard diagnostic imaging technique in patients with pulmonary valve stenosis (PVS). One of the most important advances in echocardiography has been the development of real time three dimensional transthoracic echocardiography (RT 3D-TTE) matrix-array transducers allowing real-time volume rendering images and off-line volumetric quantification techniques from three-dimensional data set obtained from a single heart beat. Right ventricular outflow tract and pulmonary valve was not studied before by RT 3-D TTE among children.

Objective: To determine the feasibility of RT 3D-TTE in the evaluation of PVS and measurement of pulmonary valve annulus (PVA), to assess its reliability, reproducibility and to test the concordance of this new method when compared with the standard 2D-TTE and invasive transcatheter angiography measurement.

Methods: Prospective clinical study included 30 pediatric patients with mean age 2.76 years diagnosed with moderate to severe pulmonary valve stenosis were assessed by 2D-TTE, 3D-TTE and transcatheter angiography.

Results: Transcatheter angiography sizing of (PVA) diameter had higher Pearson's correlation coefficient with RT 3-D TTE measurements (r = 0.909 & 0.812 respectively) than for 2-D TTE (r = 0.752). Measurements of PVA by the three techniques were compared with the reference standard by means of a Bland–Altman plot. The smallest mean absolute difference was obtained between (PVA) measurement transcatheter angiography (0.01(-0.07) cm) and RT 3D TTE diameter (0.01(-0.09) cm) rather than 2D TTE (0.11 (-0.06)cm). Interobserver reproducibility was calculated by means of intraclass correlation coefficient (ICC) of 2D-TEE was 0.983 (CI 95% 0.969 - 0.991; P < 0.001). Similarly, the value obtained with 3D-TTE was 0.981 (CI 95% 0.965–0.990; P < 0.001).

Conclusion: RT 3D-TTE assessment of PVA is a novel feasible, reliable and reproducible imaging technique among pediatric age group with PVS.
A MULTIMODAL APPROACH TO IMAGE INFLAMMATORY LIPID-RICH ATEROMATA USING AN INTEGRATED HIGH-SPEED INTRAVASCULAR OCT/NIRF CATHETER WITH A FDA-APPROVED INDOCYANINE GREEN

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Backgrounds: Atherosclerotic plaque rupture, the most important cause of acute cardiovascular events, has been strongly related with lipid-rich inflamed coronary plaques. The purpose of this study was to estimate lipid-rich inflamed plaques in vivo using a fully integrated high-speed optical coherence tomography (OCT)/near-infrared fluorescence (NIRF) molecular imaging with a FDA-approved indocyanine green (ICG).

Methods and Results: An integrated high-speed intravascular OCT/NIRF imaging catheter and a dual-modal OCT/NIRF system were constructed based on a clinical OCT platform. For imaging lipid-rich inflamed plaques, the FDA approved NIRF emitting ICG (2.25 mg/kg) or saline was injected intravenously into atherosclerotic rabbit models induced by balloon injury and 12- to 14-weeks of high-cholesterol diets. Twenty minutes after injection, in vivo OCT/NIRF imaging of infrarenal aorta and iliac arteries were performed only under contrast flushing through catheter (pullback speed up to 20 mm/sec). High-resolution OCT images of the vessel wall were acquired and strong NIRF signals were simultaneously detected in the OCT-visualized atheroma of the ICG injected rabbits. The in vivo NIRF target-to-background ratio (TBR) was nearly 4.3 times greater in the ICG-injected rabbits than in the saline-injected controls (6.63 ± 1.03 vs. 1.54 ± 0.17; p < 0.05). Ex vivo peak plaque TBRs was more than 3.2 times greater in ICG injected rabbits than in controls (7.34 ± 0.86 vs. 2.31 ± 0.17; p < 0.05) on fluorescence reflectance imaging (FRI), which correlated well with the in vivo TBRs (p < 0.05, R² = 0.53 without significant bias (-0.37). Cellular ICG uptake, correlative fluorescence microscopy, and histopathology also corroborate the in vivo imaging findings.

Conclusions: Integrated OCT/NIRF structural/molecular imaging with a clinically available NIRF emitting ICG precisely demonstrated lipid-rich inflamed atheroma in coronary sized vessels. This highly translatable dual-modal imaging approach could offer a new avenue for accurate estimation of high-risk coronary plaques.
TISSUE DOPPLER IMAGING AND LATE-ONSET ANTHRACYCLINE-INDUCED SUB-CLINICAL CARDIOVASCULAR DISEASE IN LONG TERM SURVIVORS OF CHILDHOOD CANCER

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\textbf{Background}: There is concern that conventional echocardiography (echo) may not detect early deterioration in cardiac function, especially diastolic dysfunction, in long term survivors of childhood cancer, who received anthracyclines. Tissue Doppler Imaging (TDI) allows the direct measurement of myocardial motion velocity, thus allowing reliable evaluation of systolic and diastolic function. There are limited data on the use of TDI in assessing cardiotoxicity from anthracyclines, a common chemotherapy administered to children.

\textbf{Methods}: This was a single institution, prospective, comparative study of 11 long-term survivors who had been treated with anthracyclines and 22 age-matched controls. The study group and the control group underwent conventional echo and TDI; operators were blind to study group.

\textbf{Results}: Conventional echo measurements were similar in both groups. Using TDI, cases had a lower mean E' velocity (9.7 ± 1.7 cm/s vs. 11.4 ± 1.3 cm/s, \textit{p}=0.004) and a lower E'/A' (1.8 ± 0.5 vs. 2.2 ± 0.4, \textit{p}=0.022) at the mid-interventricular septum than controls. Fifty four percent of the study group subjects had E' septum velocity < 10 cm/s compared to 9.1% of the controls (\textit{p}=0.004). The heart rate was significantly higher among the cases with E' < 10 cm/s compared to cases with E' > 10 cm/s. All patients who received chemotherapy and radiation therapy (RT) had lower septal E' septum velocity and E'/A' ratio compared to others in the study group, although it did not reach significance. We did not find any additional associations between TDI parameters and other disease variables.

\textbf{Conclusions}: In long-term survivors of childhood cancer that received anthracyclines, diastolic dysfunction can be detected earlier by using TDI before the presence of overt systolic dysfunction as detected by conventional echocardiogram. TDI measurements in conjunction with conventional echo maybe warranted in pediatric anthracycline-recipients to detect subclinical cardiovascular disease.
Objective: We hypothesize that in a healthy population left ventricular outflow tract (LVOT) velocity time integral (VTI) is higher than VTI of descending thoracic aorta (DTA) and this relationship may be exploited clinically to validate the former.

Background: Measurement of LVOT VTI, stroke distance, by pulse wave (PWD) Doppler is technician, instrument and reader dependent. Variability may be decreased by increased number of observations, readers and technicians. However, this approach is not practicable due to time constrains.

Methods: We compared the LVOT VTI obtained by PWD against the VTI measured from DTA, abdominal aorta (AA) and pulmonary artery among 109 subjects that underwent routine transthoracic echocardiogram prior to initiation of chemotherapy for malignancies. These subjects had normal cardiac function by echocardiography and were free of cardiac symptoms.

Results: The ratio of LVOT VTI (n=80) to DTA VTI (n=74) was 1.27. There was a difference of 19.6% between LVOT VTI and DTA VTI (LVOT VTI-DTA VTI/LVOT VTI) x 100, with the former being higher. This percentage decrease in VTI from LVOT VTI to AA VTI was directly proportional to the LVOT VTI. Similarly, there was a difference of 23.4% (DTA VTI-AA VTI x 100) in the VTI values obtained from DTA and AA. Moreover, there was a decrease of 40.4% (LVOT VTI-AA VTI/LVOT VTI x 100) when LVOT VTI was compared against AAVTI. The ratio of aortic VTI to pulmonary VTI was 1.24.

Conclusion: Our hypothesis is supported that VTI values decrease in a linear fashion from the LVOT to descending thoracic aorta in subjects with normal cardiac structure and function. This change is likely a function of decreased circulating volume reaching the DTA. Clinically, any deviation from this relationship should be treated as abnormal and prompt further investigation. Our findings support measurement of DTA VTI in clinical practice.
CORONARY ARTERY DISEASE IN ASYMPTOMATIC MALE ATHLETES AGED 45 YEARS OR OLDER WITH A LOW ESC SCORE RISK: THE EMERGING ROLE OF CORONARY CT ANGIOGRAPHY

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². Meander Medical Center, Amersfoort, Netherlands
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Background Over 90 percent of exercise related cardiac arrests occur in men aged 45 years or older, in whom coronary artery disease is the main cause. The current cardiovascular evaluation of middle aged recreational athletes essentially consists of a medical history, physical examination, resting and exercise electrocardiography. Multi detector computer tomography coronary angiography provides a minimally invasive, low radiation dose opportunity to image the coronary arteries. We aim to assess the feasibility and added value of CT coronary angiography in asymptomatic male athletes aged over 45 years who underwent a sports medical evaluation.

Methods A total of 320 participants underwent prospective ECG triggered MDCT coronary angiography using a 256 slice CT scanner. After exclusion of 44 participants with diabetes, receiving drugs for hypertension, or an ESC risk score over 4 percent a group of 276 men with a low ESC SCORE risk 0 to 4 percent remained in whom the presence of coronary artery disease was defined as a Coronary Artery Calcium Score above 100 Agatston Units or more than 50 percent luminal stenosis.

Results In 41, 15 percent of 276, (95 percent CI 10.8 to 19.1) participants with a low ESC SCORE risk 0-4 percent and good exercise tolerance on bicycle testing, relevant coronary artery disease, CACS over 100 or luminal stenosis over 50 percent was found. The number needed to screen was 6.7.

Conclusion Minimally invasive MDCT coronary angiography is feasible and detects relevant coronary artery disease in 15 percent of asymptomatic male athletes over 45 years with a low ESC SCORE risk with normal exercise testing.
ECHOCARDIOGRAPHIC PREDICTORS OF ATRIAL FIBRILLATION PREVALENCE IN PATIENTS ON HEMODIALYSIS

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2. Mercy Catholic Medical Center; An affiliate of Drexel University, Darby, PA, USA

Introduction: Hemodialysis (HD) is associated with cardiovascular structural modifications. Left atrial (LA) size is an independent predictor of increased risk of cardiovascular morbidity due to atrial fibrillation (AF) in general population. We investigated the association of LA size, as a risk factor, with the prevalence of AF in HD patients.

Method: All patients who were admitted to hospital during July 2010 to June 2011 with the diagnosis of end stage renal disease on HD with or without AF and had transthoracic echocardiography (TTE) done, were included in this study. Data on TTE, demographic and clinical features of the study population was collected.

Results: In 122 unique patients, AF prevalence was 21% with average LA diameter of 42.2±6.9mm. Using upper normal limit of LA size (38mm) as cutoff, the odds ratio of having AF was 3.4 times greater in those with an average increase of 4mm in LA diameter from the cutoff (p<0.01). Odds of having AF doubles up in hemodialysis patients with age more than 60 years. Multivariate logistic regression analysis showed that LA size was independently associated with AF prevalence but hypertension, coronary artery disease, diabetes mellitus and left ventricular ejection fraction <40% were not.

Conclusion: In hemodialysis patients, LA dilatation is significantly associated with atrial fibrillation. AF adds to morbidity and mortality in HD patients, therefore strategies should be directed towards early detection, monitoring and possible management of the high risk HD patients.
ASSOCIATION OF VITAMIN D LEVELS TO SHORT AND LONG TERM MAJOR ADVERSE CARDIAC EVENTS AMONG ACS AND NON-ACS PATIENTS

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2. Intermountain Medical Center, Murray, UT

Background: There is abundant evidence that 25(OH)VitD deficiency is associated with various CV complications, but it remains uncertain whether this association is causal. An alternative explanation is that the systemic stress, such as during acute coronary syndrome (ACS) event, may cause a transient, possibly artifactual, reduction in the measured blood levels of 25 (OH)VitD.

Methods: Pts (N=4,140) undergoing coronary angiography and having 25[OH]VitD levels were studied. 25(OH)VitD was stratified into 3 categories (ng/mL): ≥30 (n=582), 20-29 (n=2484), and <20 (n=1062). Multivariable Cox hazard regression was used to evaluate the association of 25(OH)VitD and ACS to major CV.

Results: 2241 (54.1%) pts presented with ACS. Age was similar between ACS and non-ACS (63.8±12.0 vs. 64.0±12.0, p=0.54); more men presented with ACS (68.5% vs. 63.8%, p=0.002). Only 14.1% of patients had a 25(OH)VitD ≥30 (ACS: 12.8% vs. non-ACS: 15.6%, p=0.01). It appears that the association of 25(OH)VitD to MACE is increased among those presenting with ACS (Table). However, with increased time after the ACS event, the modification is attenuated.

Conclusion: Levels of 25(OH)VitD among ACS patients appears to be more predictive of MACE than among non-ACS pts. Whether the acute event of ACS affects 25(OH)VitD requires further study in studies of serial sampling.

Table. Multivariable hazard ratios (HR) for the association ACS and 25(OH) vitamin D categories to MACE (referent: Non-ACS, vitamin D ≥30).

<table>
<thead>
<tr>
<th></th>
<th>30 day MACE</th>
<th>6 month MACE</th>
<th>1 year MACE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-ACS, vitamin D 20-29</td>
<td>HR=1.234, p=0.783</td>
<td>HR=0.993, p=0.984</td>
<td>HR=1.379, p=0.326</td>
</tr>
<tr>
<td>Non-ACS, vitamin D &lt;20</td>
<td>HR=1.561, p=0.576</td>
<td>HR=0.797, p=0.565</td>
<td>HR=1.327, p=0.427</td>
</tr>
<tr>
<td>ACS, vitamin D ≥30</td>
<td>HR=2.940, p=0.193</td>
<td>HR=1.508, p=0.329</td>
<td>HR=1.769, p=0.145</td>
</tr>
<tr>
<td>ACS, vitamin D 20-29</td>
<td>HR=1.789, p=0.442</td>
<td>HR=0.906, p=0.783</td>
<td>HR=1.141, p=0.694</td>
</tr>
<tr>
<td>ACS, vitamin D &lt;20</td>
<td>HR=3.644, p=0.091</td>
<td>HR=1.400, p=0.365</td>
<td>HR=1.768, p=0.102</td>
</tr>
</tbody>
</table>
THE PROGNOSTIC SIGNIFICANCE OF ELEVATED TROPONINS IN PATIENTS WITH SEPSIS: A META-ANALYSIS

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Objective: To investigate the relationship between elevated troponins in patients with sepsis and mortality.

Background: Troponin elevation is common in sepsis and reflects myocardial injury, but the role of cardiac troponins in risk stratification of patients with sepsis is still debated.

Methods: Observational studies from Pubmed, Medline and those manually searched up to December 2013 were reviewed. Studies in which a 2 x 2 table could be constructed between troponin and mortality were selected for meta-analysis. We pooled odds ratios and risk ratios using the Mantel Haenszel calculations with fixed effect. Heterogeneity was considered present at $I^2 > 50\%$.

Results: Fourteen studies encompassing 1,568 patients were included. The prevalence of elevated troponin was 63.3 %. Death occurred in 36.8% of septic patients with elevated troponin compared with 19.3% of septic patients without troponin elevation. Elevated troponin was found to be significantly associated with mortality (risk ratio 2.03; 95% CI 1.70–2.43; p < 0.00001), with low heterogeneity across studies ($I^2=0\%$, see Table 1)

Conclusion: Troponin elevation in patients with sepsis predicts a higher risk of mortality. Further studies are needed to determine if selection of this subset of patients for more aggressive therapy leads to a reduction in mortality.

Table 1: Relationship between elevated troponin in sepsis and mortality

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Positive Troponin</th>
<th>Negative Troponin</th>
<th>Risk Ratio M-H, Random 95% CI</th>
<th>Risk Ratio M-H, Random 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aminani et al, 2003</td>
<td>12</td>
<td>32</td>
<td>2.67 (1.64, 4.39)</td>
<td></td>
</tr>
<tr>
<td>Burchardt et al, 2000</td>
<td>6</td>
<td>17</td>
<td>0.59 (0.15, 2.2)</td>
<td></td>
</tr>
<tr>
<td>Celli et al, 2008</td>
<td>17</td>
<td>11</td>
<td>2.00 (1.58, 2.54)</td>
<td></td>
</tr>
<tr>
<td>Chetcuti et al, 2009</td>
<td>3</td>
<td>17</td>
<td>4.00 (1.97, 8.19)</td>
<td></td>
</tr>
<tr>
<td>John et al, 2007</td>
<td>26</td>
<td>17</td>
<td>1.76 (1.68, 2.85)</td>
<td></td>
</tr>
<tr>
<td>John et al, 2010</td>
<td>145</td>
<td>20</td>
<td>2.38 (1.54, 3.63)</td>
<td></td>
</tr>
<tr>
<td>Kellia et al, 2013</td>
<td>10</td>
<td>16</td>
<td>4.00 (1.97, 8.19)</td>
<td></td>
</tr>
<tr>
<td>Ranzi et al, 2011</td>
<td>31</td>
<td>124</td>
<td>1.30 (0.76, 2.22)</td>
<td></td>
</tr>
<tr>
<td>Stock et al, 2008</td>
<td>12</td>
<td>42</td>
<td>1.37 (1.05, 1.74)</td>
<td></td>
</tr>
<tr>
<td>Sales et al, 1988</td>
<td>15</td>
<td>18</td>
<td>2.22 (0.83, 6.57)</td>
<td></td>
</tr>
<tr>
<td>Tzempelis et al, 2012</td>
<td>35</td>
<td>165</td>
<td>2.86 (1.69, 4.10)</td>
<td></td>
</tr>
<tr>
<td>Turner et al, 1989</td>
<td>14</td>
<td>23</td>
<td>2.00 (0.59, 4.93)</td>
<td></td>
</tr>
</tbody>
</table>

Total (95% CI) 575 100.0% 2.03 (1.70, 2.43)

Heterogeneity Test: $\chi^2 = 7.42, df = 12 (P = 0.60); I^2 = 0\%$

Test for overall effect: $Z = 7.01 (P < 0.00001)$
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CLINICAL SIGNIFICANCE OF CORONARY ARTERY ANATOMY IN STRESS INDUCED CARDIOMYOPATHY
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Medical College of Wisconsin, Milwaukee, WI, USA

Background: Stress induced cardiomyopathy (SIC) is characterized by left ventricular apical ballooning and manifests as acute coronary syndrome in patients with normal or minimal epicardial coronary artery disease during a stressful event. Our aim is to correlate coronary anatomy and other risk factors in SIC.

Methods: We investigated 36 SIC patients (28F, 8M) who had a cardiac catheterization and divided them into two groups by absence or presence of coronary artery disease (CAD) and examined the risk factor profiles. The location of coronary artery stenosis, extent of disease, and whether the LAD coronary artery had wrapped around the apex of the heart, was examined.

Results: 14 patients showed no CAD (0% stenosis) while 22 patients showed CAD (mean 35.2±15.0% stenosis), with CAD of the LAD (37.3±19.0%), LCX (32.0±17.8%), and RCA (35.7±12.7%). The non-CAD patients were more likely to have a wrap-around LAD (11/14) than the patients with CAD (8/22) (P = 0.0134). 14 patients without CAD, with mean age of 49±9.7 years, were younger than 22 patients with CAD, with mean age of 64±14 years (p= 0.0015), and were less likely to have HTN (4/14 vs. 16/22) (P: 0.0073). TG of 169±165mg/dL vs. 136±70.2mg/dL, HDL of 39±18mg/dL vs. 48±17mg/dL, and LDL of 81±35mg/dL vs. 86±37mg/dL were not different between the two groups (P:NS).

Conclusions: More than half of patients with SIC had coronary artery disease, albeit hemodynamically insignificant, suggesting many patients with SIC have ongoing atherosclerosis, associated with more HTN in the CAD group, and a younger age in the non-CAD group. More wrap around LAD in non-CAD group suggests this unique anatomy may play a role in developing SIC in patients without CAD.
DOES SYNTAX SCORE PREDICT THE DEGREE OF PEAK TROPONIN ELEVATION IN PATIENTS WITH ACUTE CORONARY SYNDROMES?

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¹Lutheran Medical Center, Brooklyn, NY, USA

Background: Both syntax score and peak troponins have been associated with higher long-term mortality rates and major adverse cardiac events in patients with coronary artery disease. We investigated if the syntax score could predict the degree of troponin release in patients with acute coronary syndromes (ACS).

Methods: Electronic medical records of 697 patients undergoing cardiac catheterization (CC) from 2010-2012 were reviewed retrospectively to collect the data on CC indications, patient demographics, cardiovascular risk factors, syntax score and angiographic findings. A total of 165 patients with ACS including those who underwent percutaneous coronary intervention (PCI), as well as those who did not undergo PCI were included. Mean peak troponin levels during hospitalization were calculated. Univariate, multivariate linear regression and pearson correlation analyses were done.

Results: Table 1 shows the significant findings of univariate analysis. Syntax score was independently associated (p = 0.002, Beta 1.15) with peak troponin levels on linear regression. Pearson correlation showed a positive correlation (r = 0.257, p = 0.001) between syntax score and peak troponin levels.

Conclusion: Our study suggests an association between coronary lesion complexity and peak troponins elevation. We found a correlation between higher syntax score and elevated peak troponin levels in patients with ACS, which warrants further investigation.

Table 1:

<table>
<thead>
<tr>
<th>Syntax Score (n)</th>
<th>Peak Troponin (ng/ml) Mean ± Std Dev.</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>1–6 (n = 46)</td>
<td>9.57 ± 27.40</td>
<td>0.001</td>
</tr>
<tr>
<td>7–14 (n = 47)</td>
<td>27.70 ± 53.65</td>
<td></td>
</tr>
<tr>
<td>&gt;14 (n = 72)</td>
<td>49.99 ± 67.01</td>
<td></td>
</tr>
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</table>
Patients with chest pain account for approximately 8 million visits to emergency departments annually. A detailed history with emphasis on location, quality of pain, exacerbating and alleviating factors is important to the proper triage and management of these patients as the majority do not have a cardiac cause of their symptoms. The goal of this study was to assess inter-rater agreement between emergency department (ED) physicians and trained abstractors at evaluating chest pain. Prospective evaluation of the Diamond score in ED observation unit patients presenting with chest pain (PADS-EDOU Study) is ongoing at Hershey Medical Center with a projected enrollment of 500 patients. Exercise physiologists trained in evaluation of chest pain, interview patients prior to undergoing stress echocardiography, using a standardized questionnaire to assess chest pain characteristics. We compared prospectively collected data to that collected by ED physicians based on retrospective review of the ED note. Variables of interest were: chest pain location, pain axis (axis I included crushing, pressing, heaviness, burning, or tightness; axis II included sticking, sharp, stabbing, worse with breathing, or pinprick sensation), exacerbating and alleviating factors. Cohen’s kappa was used to assess inter-rater reliability. Inter-rater agreement on location of chest pain and pain axis was found to be ‘good’ (k = 0.710 and k = 0.674). However, agreement on alleviating factors was only moderate (k = 0.488) and exacerbating factors was ‘fair’ (k = 0.33). Inter-rater agreement on Diamond criteria (typical, atypical, non-anginal) was also ‘fair’ (k = 0.24). Chest pain in the ED is a common presenting symptom. Appropriate evaluation requires a careful history and this study demonstrates there may be considerable room for improvement. Standardized assessment tools, such as the questionnaire used by trained abstractors in the PADS-EDOU Study could be used to improve history taking and reduce unnecessary testing in this patient cohort.
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INDUCTION OF AUTOLOGOUS BONE MARROW STEM CELLS BY LOW-LEVEL LASER THERAPY HAS BENEFICIAL EFFECTS ON THE INFARCTED PORCINE HEART FOLLOWING ACUTE MYOCARDIAL INFARCTION

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2. Assaf Harofeh Medical Center, Zerifin, Israel

Background: Low level laser therapy (LLLT) has been found to modulate various biological processes including enhancement of regeneration.

Aims: Demonstrate that LLLT application to the stem cells in the bone marrow can induce and cause recruitment of mesenchymal stem cells (MSCs) to the infarcted porcine heart and affect scarring following myocardial infarction (MI).

Methods: The experiment was performed in the R&D unit of Assaf Harofeh Medical Center, on farm pigs (3-4 month old, 35-40 Kg). MI was induced by balloon catheterization placed in the coronary artery (LAD) and inflated for 90 min. Laser was applied (infrared, 400mw power output) to the tibia and iliac bones (non-invasive to the bone) 30 min, 2 and 7 days post-induction of MI for a duration of 100 sec. Control (non-laser-treated) pigs were treated as above but the laser was not turned on. Pigs were sacrificed 90 days post-MI. The extent of scarring (infarct size) was analyzed by MRI and TTC staining and further histological sections.

Results: Mortality after MI occurred in 43% of the non-laser-treated pigs, as compared to 0% mortality in the laser-treated ones (Fisher's exact test p =0.14). The infarct size (% of scarring out of the LV volume) in the 4 laser-treated pigs was 5.3± 2.2% which was 68% significantly (p<0.05) lower than the infarct size (16.6±3.7%) of the control, non-laser-treated pigs. At 24 hrs post-MI the level of Toponin-I in the blood of the laser treated pigs was significantly (p<0.002) 44% lower in the laser-treated pigs relative to non–treated ones. The MRI findings are pending. The mean density of small blood vessels was 6.5-fold significantly (p<0.025) higher in the laser-treated vs. control.

Conclusions: LLLT application to BM in pigs cause a marked reduction in scarring post MI and enhanced angiogenesis.
ACUTE CORONARY SYNDROMES: DETECTION, PREVENTION AND TREATMENT

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DESCRIPTION OF IN-HOSPITAL MANAGEMENT OF ACUTE CORONARY SYNDROME IN VENEZUELA AND LATIN AMERICA (EPICOR STUDY)

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1Ascardio, Barquisimeto, Venezuela; 2Hospital Universitario de Caracas, Caracas, Venezuela
3Centro Policlínico La Viña, Valencia, Venezuela; 4Hospital Universitario Dr. Angel Larralde, Valencia, Venezuela; 5Departamento Médico de AstraZeneca, Caracas, Venezuela

Objective: To describe management of Acute Coronary Syndrome (ACS) in Venezuela (VZ) and the total Latin American (LatAm) population (Mexico, Brazil, Argentina and Venezuela) of a multinational study.

Background: Overall mortality rates due to ACS are numerically higher in LatAm than in other regions. The large, multinational EPICOR (Long-term follow up of antithrombotic therapy in Acute Coronary Syndrome patients) study (NCT01171404) provides current information on ACS management.

Methods: Patients from 127 hospitals of various types in LatAm, including 33 in VZ, were recruited following an index event (hospitalization for ACS) and stratified by STEMI and unstable angina (UA) + NSTEMI status. This analysis of patients who survived to discharge, reports status on arrival and management in hospital.

Results: A total of 2069 patients from LatAm survived to discharge, including 515 from VZ. Details of patient status and management are shown in the Table. Antiplatelet and anticoagulant treatments were extensively used.

Conclusions: Duration of hospitalization was similar in VZ to LatAm as a whole. This result in VZ was achieved with numerically lower rates of cardiac catheterization, shorter times to first PCI in UA/NSTEMI patients, and slightly greater use of prophylactic anticoagulants than in the total LatAm population.

<table>
<thead>
<tr>
<th></th>
<th>STEMI VZ</th>
<th>STEMI LatAm</th>
<th>UA / NSTEMI VZ</th>
<th>UA / NSTEMI LatAm</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients, n (% male)</td>
<td>241 (74)</td>
<td>1066 (79)</td>
<td>274 (66)</td>
<td>1003 (66)</td>
</tr>
<tr>
<td>Age, years (median, range)</td>
<td>58 (28-98)</td>
<td>58 (23-98)</td>
<td>62 (33-89)</td>
<td>63 (28-97)</td>
</tr>
<tr>
<td>Previous CVD, %</td>
<td>22</td>
<td>23</td>
<td>46</td>
<td>50</td>
</tr>
<tr>
<td>Symptom onset to ECG time, h, median (range)</td>
<td>4 (0.1-250)</td>
<td>3 (0.771)</td>
<td>4 (0.1-82)</td>
<td>4 (0.1-717)</td>
</tr>
</tbody>
</table>

Interventions

| Cardiac catheterization, % | 41 | 67 | 32 | 60 |
| Thrombolysis, %            | 37 | 33 | 1.1 | 1.2 |
| Stent insertion, %         | 73 | 69 | 46 | 52 |
| Time to first PCI, h, median (range) | 16 (0-362) | 16 (0-774) | 28 (0-144) | 48 (0-910) |

In-hospital medication

| Antiplatelets, % | 100 | 100 | 100 | 100 |
| Anticoagulants (prophylactic), % | 75 | 70 | 77 | 71 |
| Thrombolytics, % | 34 | 31 | 0.7 | 1.0 |
| Days in hospital, median (range) | 6 (1-98) | 8 (1-157) | 5 (2-62) | 6 (1-62) |
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INFLUENCE OF METEOROLOGICAL FACTORS ON IN-HOSPITAL MORTALITY IN PATIENTS ADMITTED WITH ST-ELEVATION MYOCARDIAL INFARCTION IN NORTHEASTERN PENNSYLVANIA
I. Ahmed, S.J. Voyce, I. Pallekonda, J. Snedeker
1. The Wright Center of Graduate Medical Education, Scranton, PA, USA
2. The Commonwealth Medical College, Scranton, PA, USA

Background: The impact of seasonal variation on the mortality of acute myocardial infarction patients has been reported. However, there is no data on the impact of seasonal pattern on the outcome of patients with ST-elevation myocardial infarction.

Methods: Retrospective analysis of 399 patients from 06/2010 to 03/2012 presenting with STEMI who underwent primary percutaneous coronary intervention in a community medical center were included in the study. Weather variables including temperature, wind speed, barometric pressure, humidity and dew point were recorded from wundergorund.com. We analyzed if particular weather variables had significant influence on in-hospital mortality. We have compared STEMI clustered during fall and winter to spring and summer.

Results: We found no difference in the rate of admission during fall and winter (49%) as compared to summer and spring (52%) (P=0.08). Seasonal admission does not predict in hospital mortality (fall and winter versus summer and spring; 6.2% vs 3.6%, P=0.36). Average temperature was 6-degree lower on the day of admission (P=0.006) and 4-degree lower the day prior the admission (P=0.09) during winter and spring. There were no difference in the humidity, wind speed, dew point, barometric pressure on the day of admission and the day prior to the admission during fall and winter as compared to summer and spring (P>0.05). Weather variables did not predict mortality (P>0.05). Door-to-balloon time was longer during fall and winter (63±34 minutes) as compared to summer and spring (57±28 minutes) (P=0.04). In our study, longer DTB predicts mortality (P=0.001). Arrival to the emergency room via ambulance was higher during spring and summer as compared to fall and winter (P=0.003).

Conclusion: Seasonality did not predict STEMI admissions or in-hospital mortality in patients undergoing primary PCI. Door-to-balloon time was longer during fall and winter.
Background: Blood transfusion in case of severe anemia is very useful. It will increase blood oxygen-carrying capacity, thus presumably alleviating myocardial ischemia. On the other hand, it may also result in volume overload and induce hypercoagulability. However, the impact of blood transfusion to overcome bleeding in acute myocardial infarction is still controversial.

Methods: All patients who admitted to our hospital with diagnosis of acute ST Elevation myocardial infarction (STEMI) since January 2011 to December 2013 were enrolled. All clinical and laboratory variables were recorded. Transfusion was performed if hemoglobin level was less than 8 g/dl. All cause of death occurring within 30 days of admission to an acute care was defined as in-hospital mortality.

Results: A total of 571 patients was included with the mean age 55.8 ± 9.5 years. There were 90 patients (15.8%) developed bleeding during in-hospital treatment. In-hospital mortality was occurred in 11 patients (1.9%). From all the patient who developed bleeding, 21 patients (26.9%) was given red blood transfusion. We found that in-hospital mortality was significantly higher in patients who was given blood transfusion compared to no transfusion (71.4% vs 28.6%, p value 0.014). Multivariate analysis using logistic regression analysis also revealed that blood transfusion was associated with in-hospital mortality in patients with bleeding during STEMI.

Conclusions: Blood transfusion due to bleeding in patients with STEMI was significantly associated with higher in-hospital mortality.
THE EFFECT OF SHORTENING FMC-DEVICE TIME (<90 MINUTES) IN ST-ELEVATION MYOCARDIAL INFARCTION (STEMI) PATIENTS TRANSFERRED FROM NON-PCI CAPABLE HOSPITALS FOR PRIMARY PCI

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Introduction: In STEMI patients early reperfusion is an important consideration in improving outcomes. Patient presented to non-PCI (percutaneous coronary intervention) capable hospitals should have a first medical contact to device time (FMC-device) of < 120 minutes for primary PCI. Our study examined the effect of reducing the FMC-device time to ≤ 90 mins on length of stay and in-hospital mortality in STEMI patients who were transferred from a non-PCI capable hospital to our centre for primary PCI.

Methods: It is a retrospective observational chart review. We examined 637 consecutive STEMI patients who were transferred to our institution from non-PCI capable hospitals with acute STEMI and underwent PCI. The FMC-device time was calculated and patients were divided into two groups those with FMC-device time of ≤ 90 mins (earlier group) and >90 mins (latter group). Of the 637 patients 221 (34.7%) had a FMC-Device time ≤ 90 mins and 416 (65.3%) had a FMC-device time of > 90mins. In-hospital mortality and length of hospital stay was compared between the two groups.

Results: The mean age was 61.8±13.4 and was not significantly different between the groups. The earlier group had 72.9% male compared to 64.9% in the latter group (p=0.04). Median Length of hospital stay was 3 days compared to 4 days in the latter group (p=0.356). There were 7 (3.2%) deaths in the earlier group compared to 23(5.5%) in the latter group (p=0.181).

Conclusion: Our study showed that there is a trend towards lower mortality and decreased length of hospital stay in patients with FMC-device time ≤ 90 minutes that is not statistically significant. A larger study is needed to further examine the effect of reducing FMC-device time in STEMI patients.
The field of complex congenital heart disease (CHD) has evolved greatly, allowing for more patients to survive into adulthood. Emerging is a new era of changing demographics that must be matched with services and infrastructures commensurate with its growth. Healthcare issues are multi-faceted, requiring a multi-disciplinary approach led by qualified adult congenital heart disease specialists. According to the World Health Organization (WHO), a well-functioning healthcare system requires reliable information on which to base decisions and policies. Access to healthcare, however, is largely influenced by social and economic conditions as well as the healthcare policies in place. To deliver a better understanding of the changing epidemiology of CHD as well as the impact of changing demographics of CHD on health services utilization and the impact of changing demographics of CHD policy and quality of heart disease care will be the goal of this lecture. Knowledge on the prevalence of adult congenital heart disease can inform the need for specialised services. Future planning and resource allocation for manpower and infrastructure development, based on accurate demographic data, is critical to confront the growing challenge of an increased adult CHD population.
Next generation sequencing analysis of families with congenital heart disease

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Few specific causes of congenital heart defects (CHDs) are well characterized, and most cases are due to the effects of multiple genetic and environmental factors and their interactions. A genetic predisposition has been suggested, based on familial clusters reported for nearly all cardiac malformations, and the increased recurrence risk after a first affected baby or with an affected parent. Despite multiple genome-wide association studies of large cohorts and numerous candidate gene studies, only a few genes are known for CHD malformations. We are undertaking next generation DNA sequencing analysis of samples from patients with CHD.

In families with highly penetrant phenotypes (multiple affected individuals) we are identifying novel deleterious variants that segregate with disease. These have been identified in novel genes, often affecting new pathways, supporting the presumed heterogeneity of defects that can cause CHD.

In small families and sporadic cases we are identifying a large number of novel or rare deleterious variants in genes or pathways previously associated with CHD, such as cardiac transcription factors or histone associated proteins.

Interestingly in many cases we are detecting multiple variants in genes encoding related proteins (such as interacting proteins or protein in the same pathway), in several cases inherited from different parents.

These data support the hypothesis that sporadic cases of CHD arise from patients having inheriting multiple moderate risk variants that together create a genetic milieu that leads to the developmental abnormalities.
Objectives: To discuss the spectrum of anomalies which require cardiac surgery in the adult congenital heart disease (ACHD) patient.

Background: There are >1,000,000 ACHD patients in North America. Cardiac surgery in those is divided into three categories:

1. Great complexity: cyanotic lesions, single ventricle, double-outlet ventricle
2. Moderate complexity: anomalous pulmonary venous drainage, atrophicventricular septal defects, coarctation, Ebstein’s, right ventricular (RV) or left ventricular (LV) outflow tract obstruction, non-secundum atrial septal defect (ASD), pulmonary regurgitation (PR) or stenosis, tetralogy of Fallot, complicated ventricular septal defect (VSD)
3. Simple complexity: isolated congenital valve stenosis or insufficiency, simple VSD, secundum ASD

Results: Treatment decisions should be individualized:

- ASD: should undergo closure if RV volume overload exists, irrespective of symptoms, with concomitant maze procedures for atrial fibrillation.
- VSD: should undergo surgical closure if pulmonary-to-systemic blood flow ratio is >1.5 and pulmonary vascular resistance is <2/3 systemic.
- Valve repair/replacement: Worsening CHD valvar stenosis or regurgitation should undergo valve therapy as in patients with non-congenital valve disease. Most are reoperative.
- Subaortic stenosis: Should undergo resection if peak LV outflow tract gradients exceed 50mmHg
- RV outflow tract obstruction: Severe valvar obstruction requires surgery if percutaneous therapy is contraindicated. Subvalvar stenosis, supravalvar stenosis and double-chambered RV require surgery.
- Anomalous aortic origin of coronary arteries (AAOCA): Surgery for patients with left AAOCA irrespective of symptoms, and with right AAOCA with ischemia.
- Pulmonary valve replacement: For severe PR with symptoms, RV dysfunction/enlargement, arrhythmias, or significant tricuspid insufficiency.
- Ebstein’s: Surgery if symptoms, cyanosis, embolism or progressive RV dilatation/dysfunction.
- Single ventricle: Some will present in adulthood; they should undergo staged palliation if otherwise suitable.

Conclusions: Cardiac surgery for ACHD patients involves a wide spectrum of lesions with established indications and reasonable morbidity and mortality. As more CHD patients survive into adulthood, the variety of cardiac surgical repairs will increase in complexity.
AORTIC REGURGITATION: IMPACT OF PREOPERATIVE SYMPTOMS FOR POST-VALVE REPLACEMENT SURVIVAL ON PROGNOSTICATION FROM MYOCARDIAL CONTRACTILITY

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Background: Both preoperative symptoms and severe preoperative myocardial contractility deficit predict survival among patients (pts) undergoing aortic valve replacement (AVR) for aortic regurgitation (AR). The interactive effects of these predictors are unknown.

Methods: Among 66 consecutively studied pts with severe AR and AVR (age 49±15 yrs at AVR, 86% male), we determined pre-AVR symptom status as New York Heart Association Functional Class (FC). We also calculated contractility as pre-AVR change [Δ] in LVEF from rest to exercise [ex] adjusted for Δ in end-systolic wall stress [ESS] from rest to ex [ΔEF-ΔESS] using combined echocardiographic and radionuclide cineangiographic data. We related previously published severe contractility deficit (ΔEF-ΔESS≥17) and FC 2-4 symptoms to late post-AVR survival.

Results: During 15 yr follow up, 22 pts died (15 of cardiovascular cause). Cox model analysis revealed a relation between both pre-AVR ΔEF-ΔESS and symptoms on post AVR death (p=.001[all causes], p=.029 [cardiovascular]). Log rank test comparisons, among FC-2-4 pts, ΔEF-ΔESS deficit ≥17 (severe) conferred a ~3-fold increase in avg annual mortality risk vs. pts without this deficit.

Conclusions: The prognostic importance of preoperative symptoms is modulated by the concomitant presence of a severe contractility deficit. Pts with both characteristics are at high risk for late postoperative death and should be closely monitored after AVR.
According to the most recent American College of Cardiology/American Heart Association guidelines, peak velocity greater than 4 m/sec, a mean gradient of more than 40 mmHg and a valve area of less than 1.0 cm² is considered severe aortic stenosis (AS). Aortic valve surgery should be done promptly in symptomatic patients or patients with reduced left ventricular ejection fraction (EF) with severe AS because of a dismal prognosis without operation. However, diagnosis of severe AS is difficult in some due to mismatch between transvalvular mean gradient and aortic valve area. Specifically, some patients present with low trans-valvular gradient and yet have a calculated valve area of less than 1.0 cm². This scenario can occur due to low stroke volume in patients with reduced left ventricular EF, termed “low-flow, low-gradient, severe AS.” More recently, it has been recognized that some patients, often women with hypertension and concentric hypertrophy, have preserved left ventricular EF and yet have severe AS with low gradient due to low stroke volume (SVI <35 ml/m²), termed “paradoxical low-flow, low-gradient severe AS”. Diagnosis of these two entities can be challenging given that mild aortic valve stenosis may also result in similar hemodynamic variables due to lack of aortic valve excursion from poor stroke volume. When the left ventricular EF and stroke volume are reduced, one can use Dobutamine challenge to augment the stroke volume to differentiate patients with true severe AS from “pseudo” stenosis (mild stenosis). In the scenario of patients with normal left ventricular EF and reduced stroke volume, one may need to consider an alternative method of AS severity assessment such as multi-slice computed tomography to measure the aortic valve calcium score and/or Dobutamine challenge to confirm the diagnosis of severe AS before subjecting the patient to aortic valve intervention.
ATORVASTATIN ATTENUATES ATHEROSCLEROSIS IN THE VALVES AND FEMURS FROM HYPERCHOLESTEROLEMIC LDLR-/- MICE AS=OP

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Atherosclerosis and osteoporosis are the leading causes of morbidity and mortality in the aging population in the United States. Evidence indicates that hyperlipidemia plays a paradoxical role in these disease processes. However, the hyperlipidemic mechanisms of atherosclerotic calcification and decrease bone mass are under investigation. This study proposes to test in an experimental hypercholesterolemia model if atherosclerosis develops in the valve and osteoporosis develops in the femurs, and to determine if statins play a protective role. LDLR-/- mice (n=60) were treated with Group I (n=20) normal diet, Group II (n=20) 1.25% chol diet (w/w), and Group III (n=20) 1.25% (w/w) chol diet+atorv to determine the development of calcification in the hearts and osteoporosis in the bones. The aortic valve and aortas (AVA) was examined for myofibroblast cell proliferation, calcification, and bone matrix markers by immunohistochemistry and RTPCR. Bone formation was assessed by microComputed Tomography (microCT), calcein injection, osteocalcin, cbfa-1 and osteopontin expression. The cholesterol diet induced complex bone formations by microCT in the calcified AVA with an increase in cellular proliferation, osteopontin, osteocalcin and cbfa-1 expression. Atorvastatin reduced bone formation, cellular proliferation and cbfa-1 levels and calcification in the AVA. Ex vivo analysis of calcein label demonstrated an increase in calcein label (4+) in the hypercholesterolemia AVA and the periosteal femoral bone surface with attenuation of the calcein label (1+) with atorvastatin therapy in the AVA and the femoral bones. (Calcein Scale =1-4, 4+=severe label, 1+=minimal label). Hypercholesterolemic AV calcification and bone turnover is attenuated by atorvastatin and is mediated in part by an osteoblast pathway. This model may have future implications in the treatment of cardiovascular calcification and osteoporosis with statin therapy.
A TALE OF TWO HEARTS: ANY NEW ECHOCARDIOGRAPHY TRICKS IN VALVULAR HEART DISEASE?

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One of the most challenging tasks dilemma in valvular heart disease is choosing the appropriate timing for surgical intervention. Current clinical measures of left ventricular function (ejection fraction and ventricular dimensions) are not sensitive enough to detect early myocardial dysfunction. This is outlined in the clinical cases presented. More sensitive methods for detecting early subclinical LV dysfunction are critically needed in valvular heart disease. Emerging methods are reviewed.
A relatively large proportion of our population manifests valvular abnormalities. A smaller though still substantial portion has valvular heart disease (VHD) that is hemodynamically moderate to severe and that can be expected to progress to heart failure or, occasionally, sudden death. To obtain data for our region, we conducted a longitudinal study of 2.7 million inpatient records obtained between 1983-2012 from the New York State (NYS) Department of Health’s Statewide Planning and Research Cooperative System (SPARCS), including primary or secondary diagnoses of aortic, mitral, tricuspid and/or pulmonic VHD. Analysis showed that while the number of total hospitalizations in NYS declined by approximately half a million patients over the 30-year period of observation, the number of patients hospitalized with clinically recognized VHD and the number of valve replacements or repairs performed among these patients increased linearly over time through 2007 and remained at these elevated levels through 2012; these data generally mirrored changes in the aging of the inpatient population. The incidence of hospitalizations including a diagnosis of VHD increased from 34,395 cases/year in 1983 to 122,375 cases/year, an overall rate of increase of approximately 8.5 percent/year. Also noted was a linear increase in the number of invasive therapeutic valve procedures (primarily replacements) performed during this interval (2,582 procedures/year performed in 1983 vs. 7,787 procedures/year performed in 2012, an increase of 6.7 percent/year). Based on these estimates, we conclude that the VHD inpatient population in NYS has grown significantly over the past 30 years. Increasingly, health care resources must be targeted to dealing with this continued public health problem.
Myocardial hypertrophy has a prominent role in valvular heart disease. The evaluation of hypertrophy is invaluable when determining the hemodynamic significance of a valve lesion, as the myocardium responds to increased load from regurgitant or stenotic valve lesions with growth in predictable patterns. Cardiac hypertrophy is initially adaptive to the pathologically increased load, but with time the hypertrophic response may itself contribute to the development of heart failure in severe valve disease. Better understanding of this progression could allow pharmacological targeting of responsible molecular pathways. It is increasingly clear that a number of interconnected intra-cellular signaling pathways are involved in the development of physiological and pathological cardiac hypertrophy. Known triggers for hypertrophy include mechanical stretch sensed at the level of the extra-cellular matrix, the cell membrane, or the sarcomere, and receptor activation. The mechanical signal sensed by the myocardium differs in important ways between pressure and volume overload. Most work has been done in pressure overload models displaying concentric hypertrophy, where activation of a number of pathways is associated with a phenotype similar to that of human aortic stenosis. Characteristics for these models are myocardial fibrosis and an activation pattern dissimilar to that of physiologic hypertrophy. Volume overload models are less used, and have typically been fistula-type models. Recently, we and others have used a closed-chest rat model of aortic regurgitation to evaluate the development of left-sided eccentric hypertrophy. In contrast to the findings in pressure overload, volume overload hearts display much less fibrosis, and a different pattern of hypertrophic pathway activation is seen – in several ways similar to that seen in physiologic hypertrophy.
DEVICE CLOSURE OF COMPLEX ATRIAL SEPTAL DEFECT IN ADULTS- ISSUES AND SOLUTIONS

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A complex ASD is defined as presence of a large- \( \geq 20\text{mm} \) (stretched diameter \( \geq 26\text{ mm} \)) ASD associated with a deficient (\( \leq 4\text{ mm} \)) rim located at the anterior, inferior, or posterior portion of the atrial septum, two separate ASDs within the atrial septum (distant or close to each other); and multi-fenestrated septum, defects associated with a floppy, redundant, and hyper mobile atrial septum (excursion \( \geq 10\text{ mm} \)), considered to be aneurysmal, irrespective of their size.

The logic of a rim is to be understood as for a circular or an oval orifice it may be not be logical to have a fixed number of rims. Ideally the entire circumference must have rims and need to be interrogated. The complex anatomy of IAS does not allow this interrogation. It is important to know as what is an adequate rim- 5mm is considered as sufficient. But is it true for all the rims and what about superior rim (6-7mm is considered borderline) and is the length only issue? What about thin and/or floppy margins? It is important to know as which ones are suitable for device closure, for example a deficient aortic rim. Which ones increase the likelihood of complications and which ones to avoid completely. Similarly which ones cannot be closed like any large ASDs \( >38\text{mm} \) diameter and those with absent or truly deficient IVC rim, SVC rim, superior rim (PVs rim), inferior (AV valves) rim, those with absent rims in >2 areas and where device is too large to fit in the atria.

The ones which increase likelihood of complications include deficient aortic and posterior rims, deficient superior rim, floppy rims, small child with a large ASD and an unusually placed ASD? Balloon sizing is very useful to understand tissue characteristics and size in large defects with floppy margins and deficient rim and an unusually placed- If there is a waist there is a way! Balloon assisted technique seems to be a solution to all difficult and complex ASDs.

In conclusion large ASDs can be closed but in addition to size- rims and stability of the septum define limits. Use of an “adequate” size device that safely fits is ideal. If IVC rim is completely absent or >2 rims are significantly deficient it may be better NOT to do it. Always ask you- I can do it but shall I do it?
Prevention of thromboembolic events using oral anticoagulant drugs (OAC) is mandatory in several patients with atrial fibrillation. Therefore, OAC have been developed and used since decades. However, efficacy of these must be well balanced with the risk of inherent bleeding complications. Dicumarine (DC-D) derivates are useful but need monitoring and show several food and drug interactions, which may be critical. Therefore, novel OAC (NOAC) have been developed. These new drugs interact with two different targets (factor IIa or factor Xa of the coagulation cascade). Actually, the clinical results of four NOACS (dabigatran (DAB), rivaroxaban (RIV), apixaban (API), edoxaban (EDO)) have been presented in four major trials (RELY, ROCKET-AF, ARISTOTLE, ENGAGE-AF) of stroke prevention in atrial fibrillation in comparison with warfarin. Pharmacokinetics and pharmacodynamics of the four NOACS are different. Thus, DAB and API are given twice/daily whereas RIV and EDO have been tested in once daily approach. In addition, renal clearance ranges from 25% with API to 80% with DAB (33% with RIV and 35% with EDO). Furthermore, bioavailability, hours to maximal concentration, CYP metabolism, transporters, protein binding and half-life also differ between NOACS. Thus, plasma levels of NOACs may influence and also be influenced by some drugs, which are often used (e.g. diltiazem, amiodarone, etc.). Therefore, physicians need to know the main results of the four major clinical trials, those of important sub-studies and also the major differences between the four NOACS in order to manage properly the stroke preventive strategies of patients with atrial fibrillation. In addition, since NOACs have been used in different dosages during the trials, physicians should know which populations do benefit of low or high dosages of the NOACs and how to manage complications. In resume, NOACs demonstrate several advantages over DC-D but physicians need to know how to implement treatment with these new drugs and which are the main results and characteristics of all of them.
ATRIAL ARRHYTHMIAS: TREATMENT AND SEQUELAE

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LEFT ATRIAL SIZE AND FUNCTION: ROLE IN PROGNOSIS

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The principal role of the left atrium (LA) is to modulate LV filling and cardiovascular performance by functioning as a reservoir for pulmonary venous return during systole, a conduit for pulmonary venous return during early diastole, and a booster pump that augments ventricular filling during late diastole. Interplay exists between these atrial functions and ventricular performance throughout the cardiac cycle. The resurgence of interest in atrial size and function has enhanced our understanding of the atrial contributions to cardiovascular performance in health and disease. The reasons responsible for this renaissance are multifactorial and include the use of atrial size as a biomarker that integrates the magnitude and duration of diastolic LV function, the development of sophisticated, non-invasive indices of LA size and function, and the increasingly recognized importance of LA size and function in determining cardiovascular risk and prognosis. While atrial size and function can be assessed with echocardiography, cardiac tomography and cardiac magnetic resonance, echocardiography is best suited for these tasks because of its availability, safety, versatility, and ability to image in real-time with high temporal and spatial resolution. LA function is most often assessed echocardiographically using volumetric analysis, spectral Doppler of transmitral, pulmonary venous, and left atrial appendage flow, and tissue Doppler and deformation analysis (strain and strain rate imaging) of the left atrial body. Indices of LA size and function are markers of cardiovascular risk in the general population, and in patients with atrial fibrillation, cardiomyopathy, ischemic heart disease, and valvular heart disease. However, despite considerable data, risk stratification and decision-making strategies incorporating these parameters are not currently exploited in clinical practice; needed are robust confirmatory, prospective clinical outcome data, standardization of equipment and analytic techniques, and studies to determine the impact of therapies that reverse remodel the LA and improve LA function on clinical outcomes.
Silent cerebral events (SCE) have been identified on magnetic resonance imaging (MRI) in asymptomatic patients after atrial fibrillation (AF) ablation. Comparative analysis using a consistent MRI definition is missing and factors influencing the risk of SCE are poorly understood. The incidence of SCE may be related to the thromboembolic potential of a procedure or/and technology and therefore reduction may lead to lower symptomatic complication rates.

Methods: Patients undergoing AF ablation underwent post-ablation cerebral MRI. SCE were identified based on a sensitive definition using a 1.5Tesla MRI including DWI and ADC-map (but not including FLAIR). AF ablation was performed either using different ablation techniques including single-tip radiofrequency ablation, balloon-based and procedures with multipolar ablation catheters. Differences in regard to SCL rates and potential predictors were analyzed.

Results: The incidence of SCE in regard to the ablation device used differed in between 20 to 37%. There was a significantly higher incidence of SCE in patients with compared to without exchanges of catheters over a single transseptal sheath and in patients with left atrial dilation. No other parameters like procedural cardioversion or minimum ACT during the procedure were related to SCE.

Documentation of left atrial low voltage areas correlated with a higher incidence of SCE.

In a subgroup analysis incidence of SCE was lower when patients were ablated under continued oral anticoagulation compared to novel oral anticoagulants or without continuous appropriate anticoagulation bridged with low-molecular weight heparin.

Conclusions: When using a sensitive MRI definition of SCL incidences are relevantly higher compared to using the “old” definition including the FLAIR-sequence. Patient baseline characteristics, technology-associated and procedural characteristics associated with a higher risk of SCL have been identified. Modification of procedural steps of the AF ablation procedure may further reduce the risk of SCE.
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ALDOSTERONE, COPEPTIN AND OTHER NEUROENDOCRINE MARKERS IN PATIENTS WITH STROKE

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In comparison to coronary heart disease, the pathogenic mechanisms in stroke are very heterogeneous and reliable biomarkers to predict stroke severity and outcome are not available yet. The activation of neuroendocrine functions, particularly those involved in the stress response, represent important aspects of stroke pathophysiology. One of the first responses to cerebral ischemia is the activation of the hypothalamic-pituitary-adrenocortical axis. Increased concentrations of plasma cortisol after stroke were associated with high mortality and poor functional outcome. Moreover, elevated concentrations of circulating aldosterone and mineralocorticoid receptor activation contribute to the development of cerebrovascular pathology and to the incidence and outcome of stroke. Recently, a predictive value of copeptin, a peptide derived from the same precursor as cardiovascular hormone vasopressin, has been demonstrated. The present study was undertaken to determine the value of a battery of neuroendocrine factors with respect to predicting functional outcome of acute stroke within 7 days and 3 months. The sample consisted of 101 patients (46 men, 55 women). The results confirmed the prognostic value of plasma copeptin, in particular the correlation of copeptin concentrations measured on the first day of acute stroke with the clinical state defined by the National Institute of Health Stroke Scale (NIHSS) on day 7. High concentrations of plasma cortisol on day 1 predicted more severe clinical state not only on day 7 but also on day 90. Interestingly, a rapid decrease in cortisol levels during the acute phase of stroke was associated with more detrimental functional outcome (modified Rankin scale). Moreover, poor functional outcome evaluated on day 90 was associated with a pronounced rise of aldosterone concentrations within the first week following stroke. Evaluation of a battery of neuroendocrine factors rather than only one potential biomarker may be a useful approach in stroke outcome prediction. Supported by APVV-0028-10.
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THROMBO-EMBOLISM OR ATERHO-THROMBO-EMBOLISM IN ATRIAL FIBRILLATION?
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Atrial fibrillation (AF) is the most common cardiac arrhythmia that is associated with a high risk of cardiovascular events and increased morbidity and mortality. Even if cardiovascular events are prevalently localized in the cerebral circulation there is a growing body of evidence that AF patients may experience not only ischemic stroke of thrombo-embolic origin but also athero-thrombotic complication. Thus, patients with AF are typically associated with different risk factors of athero-thrombosis including, overall, hypertension which may be detected in about 70-80% of the population; other risk factors are diabetes and dyslipidemia. This accounts for instrumental evidence of systemic atherosclerosis associated to AF. Thus, signs of atherosclerosis have been detected in the thoracic aorta, as represented by aortic plaque assessed by trans-esophageal echocardiography; patients with complex aortic plaque had fourfold increased rate of stroke compared to plaque-free patients. Peripheral artery disease is an established marker of systemic atherosclerosis, which depicts patients at higher risk of myocardial infarction and stroke. The prevalence of PAD in AF is greatly variable ranging from 4% to 16%. Recent data form the Italian registry ARA PACIS demonstrated that as high as 20% of AF patients have low ankle/brachial index, indicating that a large number of AF suffers from systemic atherosclerosis. The association between systemic signs of atherosclerosis and AF is important to explain the complex clinical picture complicating the course of AF patients. Thus, atherosclerosis of coronary tree with ensuing development of acute coronary syndromes such as myocardial infarction (MI) is a typical feature of AF clinical history. In recent clinical trials with the new oral anticoagulants the rate of annual MI was about 1%, which was less than the rate of stroke. In an analysis of trials in which the rate of MI was registered, the occurrence of MI was, however, relatively close to stroke particularly in AF patients older than 70 with an event rate sometimes even higher. In conclusion experimental and clinical data suggest that in AF athero-thrombosis and thromboembolism coexist and that athero-thromboembolism better defines the pathophysiology and clinical complications of this disease. Inflammation, oxidative stress and a pro-thrombotic state along with functional and structural changes of atria concur to create a unique disease which ultimately leads to stroke of different origin (atherosclerotic and embolic) and MI. Preventive modulation of these phenomena may help to reduce the tremendously negative social impact of AF.
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THE MOST COST EFFICIENT WAY TO CARDIOVERT A NEWBORN IN ATRIAL FLUTTER
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Introduction: Newborn atrial flutter (AFL) can be treated by direct current cardioversion (DCC), transesophageal pacing or medications. To date, no study has evaluated the cost effectiveness of these approaches.

Objective: The purpose is to compare the cost effectiveness of DCC, transesophageal pacing and digoxin as the treatment method of AFL in neonates.

Materials and Methods: A meta-analysis of published studies regarding success rates of cardioversion of neonatal AFL (age < 2 months) was imputed into a decision tree model comparing the efficacy and cost of DCC, transesophageal pacing and digoxin. The assumed conversion rates were DCC 82.5%, transesophageal pacing 60% and digoxin 50%. Patients that failed initial attempt at cardioversion progressed to the next methodology until successful. Data was analyzed to assess the cost effectiveness of these methods of cardioversion based upon 2013 medicaid reimbursement rates for hospital, physician, medications and equipment. Assumptions made: all required IV access, all that underwent DCC or transesophageal pacing were sedated and intubated, and NICU stay of 3 days for DCC or transesophageal pacing and 4 days for digoxin, each failed conversion added one additional day.

Results: The cost analysis for cardioversion of AFL found the most efficient method was DCC at a cost of $9,918. Transesophageal pacing was next at a cost of $10,304 per attempt and the least cost effective was digoxin alone at a cost of $14,016. A majority of additional cost, regardless of method, comes from prolonged stay and failure rate. Conclusion: The most cost efficient method of cardioverting a neonate with AFL is DCC. It has the highest success rates, shorter length of stay and results in a cost saving ranging from $386 to $4,098.
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MANAGEMENT OF ATRIAL FLUTTER
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Atrial flutter affects nearly 1 million people in the United States, particularly the older age group and men. It is frequently seen in patients with heart failure, hypertension, diabetes mellitus, COPD and in postoperative states.

Atrial flutter entails an annual stroke rate of approximately 3%. Like, atrial fibrillation, atrial flutter can be managed by rate control versus rhythm control along with anticoagulation depending on the risk profile.

Acute management of atrial flutter consists of:

1. Direct current cardioversion
2. Chemical cardioversion with Ibutilide
3. Radiofrequency catheter ablation
4. Antitachycardia pacing

Unlike atrial fibrillation, catheter ablation of typical atrial flutter is a technically simpler procedure with efficacy close to 95% and complication rates less than 1%. Termination of atrial flutter along with bidirectional block in the tricuspid valve annulus-inferior vena cava isthmus has emerged as a standard endpoint for the ablation procedure.

Atypical incisional atrial flutter after congenital heart surgery is a challenging problem. Recently, atypical left atrial flutter after atrial fibrillation ablation has emerged as another important subset. According to the ACC/AHA and HRS guidelines, even though DC cardioversion is a Class I indication for acute management of atrial flutter; due to high recurrence rates, catheter ablation is the most effective treatment for long term management.
Atrial fibrillation (A Fib) is the most common arrhythmia seen in the elderly. A Fib has been shown to be associated with cognitive decline and dementia. However, there are only few studies which assessed the relationship of A Fib with Mild Cognitive Impairment (MCI).

**Aim:** To investigate the association of A Fib with MCI in the elderly.

**Methods:** In this retrospective cross-sectional study, charts between 2010-2011 were reviewed in the outpatient Senior’s Clinic at the University of Alberta Hospital. Subjects with brain CT were included in the study. Subjects with incomplete information, intracranial hemorrhage, stroke, cerebral edema, and/or normal pressure hydrocephalus on the CT were excluded. WMD was quantified on CT using Wahlund’s scoring protocol. History of A Fib was obtained from the chart. MCI was diagnosed by doing cognitive assessment. Logistic regression analysis was done to determine the association of A Fib with MCI after controlling for confounding vascular risk factors.

**Results:** Of the 505 subjects who were included in the study, 68(14%) had a history of A Fib. The mean age was 79.8 years (SD= 7.04). The prevalence of A Fib in MCI was 20%. With the logistic regression analysis, there was a significant association between A Fib and MCI, unadjusted Odds Ratio(OR)=1.95 (95% CI 1.16-3.26), p=0.01, which remained significant even after correcting for age, sex, h/o stroke and other vascular risk factors, adjusted OR=1.93(95% CI, 1.10-3.38), p=0.02

**Conclusion:** There was a significant association between A Fib and MCI. This study raises the possible mechanisms of hypoperfusion and ischemic damage to the brain in causing MCI due to A fib.
DISCOVERY OF A NEW INDEX OF DUAL PATHWAY ATRIOVENTRICULAR NODE CONDUCTION

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Dual pathway atrioventricular (AV) node electrophysiology is the basis of AV nodal reentrant tachycardia (AVNRT). Current clinical criterion for dual pathway conduction is a discontinuity or “jump” in the AV conduction curve. Although it is intuitive that a “jump” in the AV conduction curve indicates a switch from fast pathway to slow pathway conduction, this is only speculation. In addition, the criterion cannot be used to monitor dual pathway conduction on a beat by beat basis. Over the years, we have discovered and validated in rabbit hearts that dual pathway AV conduction results in a new phenomenon, originally termed His electrogram alternans (recently renamed Zhang’s phenomenon). It is found that His electrogram recorded from the superior His bundle domain (superior His electrogram) is high-in-amplitude at basic beats and long coupling intervals (i.e., fast pathway conduction) and low-amplitude at short prematurities (i.e., slow pathway conduction). In contrast, His electrogram recorded from the inferior His bundle domain (inferior His electrogram) is always from low-amplitude during fast pathway conduction to high-amplitude during slow pathway conduction. This novel index permits monitoring AV conduction pattern (through the fast or slow pathway) on a beat by beat basis in various conditions, either at a single premature beat, during fast regular rates or even during atrial fibrillation. We have demonstrated recently that dual pathway conduction produces functional dissociation in the distal node, resulting in superior-fast and inferior-slow dual inputs into the His bundle, which is the electrophysiological basis for the formation of this new phenomenon during dual pathway conduction. The phenomenon has been replicated by other investigators in rabbit hearts as well as in isolated human hearts. However, clinical feasibility studies to record this phenomenon remain needed before this novel index can be applied in patients during cardiac electrophysiology studies.
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RESIDUAL RISK FROM ELEVATED LIPOPROTEIN A BUT NOT APOLIPOPROTEIN B OR NON-HDL CHOLESTEROL AT HEART CENTERS FOR WOMEN

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Introduction: Studies show improved prediction of cardiovascular (CV) events by using non-traditional markers of risk such as lipoprotein a (Lpa), non-HDL cholesterol (NHDL), and apolipoprotein B (apoB). Discordance of LDL cholesterol (LDL) with NHDL and apoB was recently shown to be predictive of CV events.

Objective: To determine the residual risk after accounting for traditional risk markers in women seen in heart centers for women (HCW).

Methods: Patients (pts) from Chicago and Atlanta HCW with apoB and Lpa were identified. NHDL was calculated (total cholesterol minus HDL cholesterol). Residual risk was analyzed by identifying discordance between LDL and: NHDL, apoB and Lpa.

Results: We evaluated 1089 pts, ages 18-83, from 2009 to 2014. LDL vs NHDL and apoB had minimal discordance with good correlation. LDL and Lpa showed significant discordance with weak correlation. See figure 1.

Conclusion: A significant proportion of women seen at HCW had residual risk identified by elevated Lpa but not apoB and NHDL. Multiple studies have shown that elevated Lpa is associated with increased risk of CV events. Current lipid lowering drugs do not mitigate the risk of elevated Lpa. New drugs that lower both LDL and Lpa may reduce CV risk in these women.
Background. Cardiovascular diseases are the second most common cause of non-AIDS related mortality in an aging HIV population. Objectives of this study were to examine incidence rate and clinical correlates of cardio-cerebrovascular (CVD) events in a cohort of HIV-infected individuals as compared to a matched group of non-HIV-infected individuals.

Methods. Combined cardiovascular events in a matched cohort of HIV-infected and non-HIV-infected adults, 18 years and older, served through the South Carolina (SC) Medicaid program during 1994-2011 were examined using time-dependent proportional hazards regression and marginal structural models.

Results. 13,632 study cohort adults contributed 88,359 person-years of follow-up. The median age of the study cohort was 39 years (interquartile range [IQR]: 31-46 years) and the majority were men (57 percent) and African American (71 percent). Incidence rate of CVD events in the HIV-infected group as compared to matched non-HIV-infected group (22 vs. 20 per 1000 person years.) The adjusted relative risk (aRR) of incident CVD was higher among HIV-infected individuals exposed to combination antiretroviral therapy (cART) compared to the non-HIV infected group (aRR 1.15; 95 percent CI 1.04-1.27), but did not differ from the cART-naïve HIV-infected adults. Marginal structural modeling suggested a higher risk of incident CVD events in HIV-infected individuals with exposure to protease inhibitors (PIs) (aRR 1.99; CI 1.53-2.60) and non-nucleoside reverse transcriptase inhibitors (NNRTIs) (aRR 2.19; CI 1.58-3.05) compared to no exposure. Declining CD4 T-cell counts and Hepatitis C co-infection were associated with a higher risk of incident CVD events.

Conclusion. Even after adjusting for traditional risk factors and sociodemographic characteristics, exposure to PIs and NNRTIs was associated with increased risk of CVD events in our population. Frequent screening of clinical risks factors and use of cART regimens with safer cardiometabolic profiles may potentially mitigate long-term risk of potentially fatal CVD events in this population.
CERTAIN CARDIOVASCULAR RISK FACTORS ARE SIGNIFICANT DETERMINANTS OF LONGEVITY IN INITIALLY HEALTHY WOMEN

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Background. The ways by which some individuals attain a long and healthy lifespan remain unclear. We tested the hypothesis that cardiovascular disease (CVD) risk factors are associated with the ability to achieve longevity, and in particular longevity free of developing CVD or cancer.

Methods. We assessed the relationship between baseline CVD risk factors and ability to achieve longevity (age at least 80 years) in 4804 participants of the Women’s Health Study who had the chance to reach age 80 years by the last follow up (median 17 years). Longevity achievers were grouped by longevity profiles: 1) Survivors developed chronic disease before age 70; 2) Delayers developed chronic disease at or after age 70; and, 3) Escapers never developed chronic disease.

Results. In total, 3,536 women achieved longevity, and most did so without ever developing CVD or cancer. In multivariable-adjusted logistic regression models, overall longevity and longevity free of CVD were associated positively with household income at least 40,000 dollars (OR 1.25, CI 1.07-1.46), and inversely with diabetes (0.53, 0.41-0.81) and active smoking (0.37, 0.29-0.47). Longevity free of CVD was additionally associated positively with HDL-cholesterol (1.14, 1.00-1.29) and vigorous exercise at least 4 times/week (1.29, 1.02-1.64), and inversely with hypertension (0.75, 0.65-0.86). Longevity free of cancer was associated positively with vigorous exercise (1.25, 1.03-1.52), and inversely with diabetes (0.71, 0.53-0.94), active smoking (0.46, 0.37-0.56), and consuming at least 1 alcoholic drink/day (0.82, 0.68-0.99). A simple composite score based on being a non-diabetic, non-smoker, and frequent vigorous exerciser differentiated between the survivors, delayers, and escapers (Figure at www.silkview.com/iacfigure).

Conclusion. Certain CVD risk factors, in particular being a non-diabetic, non-smoker, and frequent vigorous exerciser, are associated with the ability of initially healthy women to achieve overall longevity as well as longevity free of ever developing CVD or cancer.
Treatment recommendations to reduce cardiovascular (CV) complications in patients with renal disease may benefit from noninvasive vascular testing and risk evaluations. We have studied noninvasively: common carotid intima media thickness (CIMT), plaque, stenosis and brachial artery flow mediated dilatation in chronic kidney disease and end stage renal disease (ESRD) patients. After one year we evaluated the value of CV risk factors for predicting end point events (EP) with a neural networks artificial intelligence model (NN). After five years we have “retrained” its network system, optimizing the architecture, and tested its mortality prediction performance. Doppler tests were performed on 93 subjects: 67 renal disease patients and 26 healthy matched subjects. The original (NN) used for EP prediction was created in MATLAB. This used 93 subjects' data as input. The computational experiments for the five years mortality data have utilized 24 CV risk factors including traditional and noninvasive markers (P1), experiment 1, and repeated without carotid plaque/stenosis features (P2), experiment 2. Principal component analysis retraining process only uses elements contributing more than 0.01%. Five years mortality events, present on about 50% from the ESRD patients with carotid stenosis, plaque, or CIMT over 75 percentile, were computed into the NN thru adapting learning. The artificial architectures were 72:54:6:12 and 21:18:1:2 for the experiment 1 and 72:57:6:9 and 21:15:1:5 for the experiment 2. Success mortality rate prediction was significantly higher utilizing carotid structural markers: P1=0.8571, versus P2=0.5714. Extrapolating only for the renal disease: P’1= 0.833, versus P’2= 0.666. We conclude that the noninvasive carotid markers greatly increase our NN performance to CV mortality prediction in renal disease. This model has the ability to learn from the past data and retrain with new information. Its larger scale optimization may help medical decision making toward risk stratification and cardiovascular protective and renal replacement therapy choices.
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CHANGES IN TOTAL CHOLESTEROL LEVELS IN THE ICELANDIC POPULATION ARE NOT RELATED TO STATIN, BUT RATHER DIETARY FACTORS

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Background: Total cholesterol (TC) levels have decreased in Western populations over the last decades. The drop in population TC has been very great from the early 1990s in Iceland and many other countries, coinciding with the introduction of lipid lowering medication and frequently attributed to statin use. However, few studies have been able to address this directly due to lack of information on statin use in the same individuals as TC has been measured in at the population level.

Methods & results: We address this in the population based studies of the Icelandic Heart Association, carried out over the last 45 years. TC was measured in fasting blood in 8 different cross sectional samples between 1967 and 2008 of 34,237 men and women of age 25-74 with information on lipid medication. Statin use has been increasing mainly after 1990 and today statin use is about 16% among men and about 7% in women. In 1993 TC was 5.91 mmol/L on average in men and women and had dropped to 5.18 mmol/L in men not taking statins and 5.10 mmol/L in those taking statins. The decline in population level of TC has the same characteristic for those not taking lipid lowering drugs as for those on statins. Similar picture was seen for women.

Conclusion: It can be stated that the rapid decline in TC of the Icelandic population over the last 20 years or so is not explained by the introduction of lipid lowering medication. This can largely been attributed to dietary changes, mainly reduced intake of saturated fat. The drop in TC explains 32% of the 80% drop in coronary artery disease mortality in Iceland between 1981-2006. It is likely that the same applies to other populations where similar trend is seen and lipid lowering medication is similar or even less.
NIASPIRIN: COMBINATIONS OF NIACIN WITH ASPIRIN TO REDUCE NIACIN INDUCED FLUSH

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Background: High-dose niacin has been shown to have great cardiovascular benefits, especially on increasing high-density lipoprotein and decreasing triglycerides and low-density lipoprotein. However, niacin induced cutaneous flush, with a reported incidence of 82-100%, has been identified as the primary reason for its strikingly poor compliance. Conventional therapy has consisted of ingesting aspirin thirty minutes prior to niacin.

Objectives: To determine whether simultaneous ingestion of niacin with various regimens of aspirin (chewed, swallowed) will reduce flush response over niacin plus placebo.

Methods: Prospective, single-blinded, placebo-controlled crossover design study of eighteen healthy adults was conducted in which 1000mg niacin was ingested concurrently with chewed aspirin 162mg, swallowed aspirin 162mg, or chewed aspirin 81mg/swallowed aspirin 81mg. Flushing response was self-rated using the validated Global Flushing Severity Score (GFSS) scale. Primary outcome was peak flush intensity; secondary outcomes were total flush score, number of significant flushing events, and length of flush.

Results: All regimens showed statistically significant benefit over placebo in all four outcomes. The swallowed aspirin group showed the greatest absolute decrease in peak flush, with average -1.89 +/- 1.94 point change (p = 0.001), and the greatest average decrease in total flush score (-8.78 points +/- 11.02, p = 0.002). Chewed aspirin exhibited greatest improvement in number of significant flushing events (-1.28 +/- 1.41, p = 0.001) and length of flush (-38.33 +/- 42.18, p = 0.001).

Conclusion: Our data suggests that any simultaneous aspirin administration (chewed, swallowed, or combination) decreases overall flush response. Swallowed aspirin showed the greatest benefit in reducing flush intensity and chewed aspirin the greatest benefit in reducing length of flush. We speculate that a niacin and aspirin combination pill would make for a more tolerable regimen and ultimately improve compliance.
OMENTIN SIGNIFICANTLY PREDICTS CARDIOVASCULAR EVENTS INDEPENDENTLY FROM BASELINE CORONARY ARTERY DISEASE

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Background and Objectives: Some recent small cross-sectional studies have described associations of the new adipocytokine omentin with atherosclerosis. However, the power of omentin to predict cardiovascular events has not yet been investigated and is therefore addressed in the present study.

Methods and Results: We measured plasma omentin in a series of 295 patients undergoing coronary angiography for the evaluation of established or suspected stable CAD; cardiovascular events were recorded over a mean follow-up period of 3.3 years. During the follow-up period, 17.6\% of our patients suffered cardiovascular events, corresponding to an annual event rate of 5.3\%. Plasma omentin significantly predicted cardiovascular events both univariately (standardized adjusted HR = 1.409 [95\%CI 1.173-1.694], p=2.52e-4), after adjustment for age, gender, BMI, diabetes, hypertension, LDL cholesterol, HDL cholesterol and smoking 1.410 [95\%CI 1.157-1.718], p=6.51 e-4), and after additional adjustment for the presence of angiographically determined significant CAD at the baseline angiography (HR = 1.515 [95\%CI 1.234-1.862], p=7.50 e-5).

Conclusions: From this first prospective evaluation of the cardiovascular risk associated with plasma omentin we conclude that elevated omentin is a strong predictor of cardiovascular events independently from conventional cardiovascular risk factors and from the presence and extent of baseline CAD.
Background: Asians in the United States (US) are a mixed population, yet are grouped when assessing risk of coronary artery disease (CAD). South Asians (SAs) from the Indian subcontinent have a higher risk of premature CAD (pCAD) in their country of origin and in the US. We conducted a literature search to explain the increased risk of CAD in SAs.

Methods: A review of literature in PubMed was done using “SAs, Asian Indians, CVD risk, lipoprotein a (Lpa) and CAD”.

Results: We reviewed 57 papers which showed that traditional risk factors (RF), while important in predicting CAD risk, do not explain the higher risk in SAs. We found that: 1) Lpa was shown to accentuate the risk associated with nearly all conventional and novel RFs and Lpa was a better risk predictor in women. 2) Genetically determined elevations in Lpa by the apo gene play an integral role in promoting and potentiating the risk and severity of pCAD in SAs versus other ethnic groups. 3) The risk of pCAD from Lpa excess is higher in postmenopausal women than menopausal women. 4) In younger women with pCAD, a synergistic effect of Lpa with traditional RFs exists, especially with smoking and family history. 5) SA women in the US have one of the highest CAD mortality rates among other ethnic groups (30% higher than white women and over 300% higher than Chinese women. 6) Standard risk scores in the US significantly underestimate risk in SAs by greater than 100%. 7) No randomized clinical trials have been done to assess benefits of CAD treatment in SAs.

Conclusion: An emphasis on emerging RFs such as elevated Lpa and genetic testing may better assess the risk of CAD in SAs. Randomized clinical trials with outcomes are desperately needed to test whether initiation of aggressive CAD prevention can reduce CAD risk in SAs.
Objective: To study the influence of job stress on risk (HR) of myocardial infarction (MI) and stroke in female population aged of 25-64 years in Russia over 16 years of follow-up.

Methods: Under the third screening of the WHO "MONICA-psychosocial" program (MOPSY) random representative sample of women aged 25-64 years (n=870) were surveyed in Novosibirsk. Questionnaire based on Karasek's job demands-control model proposed by MOPSY protocol was used to estimate levels of job stress. From 1995 to 2010 women were followed for the incidence of MI and stroke with using with using “Acute Myocardial Infarction Registry” data (an ongoing WHO program), medical records. Cox regression model was used for HR of MI and stroke.

Results: The prevalence of high job stress level in women aged 25-64 years was 31.6%. Over 16-th years of study MI developed in 2.7% of women, stroke in 6.3% women. HR of MI over 16 years of follow-up in women with high job stress was 3.22-fold higher (95.0% CI:1.15-9.04, p<0.05), HR of stroke was 1.96-fold higher (95.0% CI:1.01-3.79, p<0.05) compared to those with lower levels of stress. There were increasing of MI and stroke rates in married women experienced stress at work. With regard to occupational class there were an increasing MI rates in “engineers”, but it was more likely in “physical workers” with stress at work for stroke.

Conclusions: Prevalence of stress at work in female population aged 25-64 years is 31.6%. Women with high job stress have significantly higher risk of stroke and MI over 16-th years of follow-up. Rates of MI and stroke development were more likely in married women with high job stress in professional class “engineers” and “physical workers”.
Objectives: To study the effects of high density lipoprotein cholesterol (HDL-C) and co-morbidities on long-term mortality in revascularized patients with stable ischemic heart disease (SIHD). Background: Recent randomized trials (AIM-HIGH, HPS2-THRIVE) failed to show mortality benefit associated with increased HDL-C in SIHD patients. However, effects of HDL-C on mortality specifically in percutaneously revascularized SIHD patients on optimal medical therapy (OMT) are not well studied.

Methods: Demographic and clinical data were collected on 329 consecutive SIHD percutaneously revascularized patients (mean age: 63±12 years, females: 31%, hypertension: 73%, diabetes: 26%, current smoking: 22%) on OMT, which included: beta-blockers: 96%, ACEI or ARB: 72%, aspirin ± clopidogrel: 97%, and statins: 76% at the time of PCI. The primary outcome measure was long-term (70±1 months) mortality.

Results: Diabetes was associated with significantly reduced mean survival (64±3 vs. 70±1 months, P<0.002) and increased risk of mortality (hazard ratio [HR]: 2.5, 95% CI 1.3-4.7, P=0.004), when compared to patients without diabetes. When adjusted for baseline characteristics, diabetes (HR: 2.6, 95% CI 1.3-5.3, P=0.007) and older age (HR: 2.2 per decade, 95% CI 1.5-3, P<0.001) were predictive of increased mortality. Baseline HDL-C levels were similar in patients with (32±9 mg/dL) or without diabetes (34±11 mg/dL, P=0.132). Increased HDL-C levels were associated with decreased long-term mortality (HR: 0.8 per 5 mg/dL, 95% CI 0.6-0.9, P=0.015). Protective effects of HDL-C persisted in patients stratified by statin therapy. LDL-C had no effects on long-term outcomes despite lower average baseline levels in patients with diabetes (82±33 mg/dL vs. 94±39 mg/dL in patients without diabetes, P=0.012).

Conclusions: In SIHD patients on OMT undergoing elective PCI, diabetes remains a strong predictor of reduced survival while protective effects of HDL-C persist on the background of statin therapy. Therefore, HDL-C remains an attractive potential therapeutic target in this high-risk population with diabetes.
THE EFFECT OF SIROLIMUS ON CHOLESTEROL CRYSTAL VOLUME EXPANSION: IMPLICATIONS FOR PLAQUE STABILIZATION

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Background: Sirolimus has been used as a stent coating to reduce the incidence of re-stenosis in implanted coronary artery stents. Cholesterol has been shown to expand in volume upon crystallization leading to rupture of atherosclerotic plaques during myocardial infarction and stroke. We tested the effect of sirolimus on volume expansion during cholesterol crystallization.

Methods: Cholesterol powder (3g) was mixed with sirolimus (1 to 4.5mg) and melted to a liquid state in volumetric cylinders. The volume was recorded at the meniscus and the liquid allowed to crystalize at room temperature. Volume expansion was measured from the liquid meniscus line to the peak height expansion of crystals. Crystallography of samples was performed to determine percent decrease in crystallization.

Results: There was a consistent and significant dose-related attenuation of cholesterol crystal volume expansion with sirolimus. Complete inhibition of volume expansion occurred at 4.5mg of sirolimus (Figure). Also, crystallography demonstrated a 7% reduction in cholesterol crystallization.

Conclusions: These findings suggest that sirolimus coating of stents may contribute to plaque stabilization following angioplasty procedures by inhibiting further volume expansion of cholesterol. This may also contribute to their beneficial effects on recurrent cardiovascular events at treated sites.
Background: High heart rate is independently associated with higher cardiovascular mortality and usually occurs in sedentary persons. Inactivity can also lead to obesity. The purpose of this study was to evaluate any association between body size as an independent marker of higher heart rate.

Method: We used a data base that was generated during screening echocardiography for prevention of sudden death. Using a questionnaire, the occurrence of physical symptoms were documented and correlated with obesity, gender, race, heart rate and blood pressures with documented heart rate during screening. We found 2,779 subjects with documented heart rate (HR) and body mass index between the ages 4-79 years with a mean age of 23 year. We correlated the presence of high heart rate of > 90 beats per minutes (BPM) with different body mass index (BMI) categories.

Results: High heart rate of > 90 was considerably associated with higher BMI categories (for BMI >30, OR 1.518, CI: 1.009-1.625). Using multivariate analysis, high heart rate remained independently associated with high BMI > 30, (p <0.005).

Conclusion: Higher heart rate is independently and strongly associated with larger body size in. This suggests that obesity has negative effect on cardiovascular system.
THE NOVEL SMALL LEUCINE-RICH REPEAT PROTEIN PODOCAN INHIBITS SMOOTH MUSCLE CELL ACTIVATION AND NEOINTIMA FORMATION VIA MODULATION OF THE CANONICAL WNT-PATHWAY AND IS DIFFERENTLY EXPRESSED IN HUMAN PRIMARY VERSUS RESTENOTIC CORONARY LESIONS

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Background: Smooth muscle cell (SMC) migration and proliferation critically influence the clinical course of vascular disease. We tested the effect of the novel small leucine-rich repeat protein podocan on SMC migration and proliferation using a podocan deficient mouse in combination with a model of arterial injury and aortic explant SMC culture. In addition, we examined the effect of overexpression of the human form of podocan on human SMCs and tested for podocan expression in human atherosclerosis. In all these conditions, we concomitantly evaluated the Wnt-TCF (T-cell factor) pathway.

Methods and Results: Podocan was strongly and selectively expressed in arteries of wild-type mice after injury. Podocan deficient mice showed increased arterial lesion formation compared with wild-type littermates in response to injury (P<0.05). Also, SMC proliferation was increased in arteries of podocan-deficient mice compared with wild type (P<0.05). In vitro, migration and proliferation were increased in podocan-deficient SMCs and were normalized by transfection with the wild-type podocan gene (P<0.05). In addition, upregulation of the Wnt-TCF pathway was found in SMCs of podocan deficient mice both in vitro and in vivo. On the other hand, podocan overexpression in human SMCs significantly reduced SMC migration and proliferation, inhibiting the Wnt-TCF pathway. Podocan and a Wnt-TCF pathway marker were differently expressed in human coronary restenotic versus primary lesions.

Conclusions: Podocan appears to be a potent negative regulator of the migration and proliferation of both murine and human SMCs. The lack of podocan results in excessive arterial repair and prolonged SMC proliferation, which likely is mediated by the Wnt-TCF pathway.
Objectives: The aim of this study was to characterize the role that the miR-146a-Plk2 network plays in regulating lin-BMCs apoptosis, senescence and self renewal in angiogenesis and cardiac repair.

Background: Lineage negative bone marrow cells (lin-BMCs) mediate vascular repair. Aging-associated apoptosis and senescence result in reduced number and functionality of lin-BMCs impairing their pro-repair capacity. The molecular mechanisms underlying lin-BMCs apoptosis and senescence are poorly understood. MicroRNAs (miRNAs) regulate many important biological processes. The identification of miRNA-mRNA networks that modulate the health and functionality of lin-BMCs is a critical step in understanding the process of vascular repair.

Methods: Lin- BMCs were isolated from young (3-week-old) wild type (WT), young apoE-/-, aged WT (29-month-old) and aged apoE-/- (12 month-old) C57BL/6 mice. Global miRNA and gene expression profiling were analyzed.

Results: Transcriptome analysis in lin- BMCs isolated from young and aged wild type (wt) and apoE-/- mice showed a significant aging-associated increase in miR-146a expression. Plk2 is predicted to be a miR-146a target and Plk2 expression is inversely correlated with miR-146a levels. Luciferase reporter assays confirmed Plk2 as a direct target of miR-146a. MiR-146a overexpression in young lin-BMCs inhibited Plk2 expression resulting in increased senescence and apoptosis in vitro, as well as, impaired angiogenic capacity in vitro and in vivo. Conversely, suppression of miR-146a in aged lin-BMCs increased Plk2 expression, rejuvenated lin-BMCs, resulting in decreased senescence and apoptosis, leading to improved angiogenesis in vitro and in vivo.

Conclusions: 1) miR-146a regulates lin-BMCs apoptosis and senescence by suppressing Plk2 expression; and 2) modulation of miR-146a or its target Plk2 may represent a potential therapeutic intervention to improve lin-BMCs-mediated angiogenesis and vascular repair.
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CD137 SIGNALING INCLUDING FACTORS FROM T CELLS AND MACROPHAGES ACCELERATE UNSTABLE ATHEROSCLEROTIC PLAQUE
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Mature atherosclerotic plaque advances to a vulnerable plaque, being more prone to rupture, which leads to atherothrombotic vascular disease. CD137, a member of tumor necrosis factor receptor superfamily (TNFRSF), has been reported to be expressed in atherosclerotic plaques, and to promote lesion formation. However, the role of CD137 in atherosclerotic plaque stability and its possible molecular and cellular mechanisms are poorly understood. Here, we show that CD137 induced unstable plaque which was characterized by increased plaque necrosis decreased collagen and vascular smooth muscle cells (VSMCs) content, and increased macrophage infiltration. CD137 also increased infiltration of effector T (Teff) cells into plaque lesion sites resulting in increase of IFN-gamma expression. Interestingly, Teff cell derived IFN-gamma inhibits collagen synthesis in VSMCs. Furthermore, CD137 activation increased the apoptosis of VSMC possibly due to a decrease of anti-apoptotic regulator, such as Bcl-2, followed by up-regulation of cleaved caspase-3. In macrophages, activation of CD137 signaling boosted oxidized LDL (oxLDL) induced matrix metalloproteinase-9 (MMP-9) expression via p38 mitogen-activated protein kinase (MAPK) and extracellular signal-regulated kinase1/2 (ERK1/2) signaling pathways. Our observations indicate that activation of CD137 signaling decreased plaque stability in advanced atherosclerotic plaque via the combined effects on Teff cells, VSMCs, and macrophages. Thus, inhibition of CD137 signaling appears to be a promising therapeutic strategy for enhancing plaque stability.
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MODULATION OF CYSTEINE-RICH PROTEIN 2 EXPRESSION IN VASCULAR INJURY AND ATHEROSCLEROSIS
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Vascular smooth muscle cells (VSMCs) of the arterial wall normally display a differentiated and contractile phenotype. In response to arterial injury, VSMCs switch to a synthetic phenotype, contributing to vascular remodeling. Cysteine-rich protein 2 (CRP2) is a cytoskeletal protein expressed in VSMCs and blunts VSMC migration in part by sequestering the scaffolding protein p130Cas at focal adhesions. CRP2 deficiency in mice increases neointima formation following arterial injury. The goal of this study was to use Csrp2 promoter-lacZ transgenic mice to analyze CRP2 expression during VSMC phenotypic modulation. In a neointima formation model after carotid artery cessation of blood flow, lacZ reporter activity and smooth muscle (SM) alpha-actin expression in the media were rapidly downregulated 4 days after carotid ligation. Fourteen days after ligation, there was a high level expression of both Csrp2 promoter activity and SM alpha-actin protein expression in neointimal cells. In mice fed with an atherogenic diet, Csrp2 promoter activity was detected within complex atherosclerotic lesions. Interestingly, Csrp2 promoter activity was also present in the fibrous caps of complicated atherosclerotic lesions, indicating that CRP2 might contribute to plaque stability. These findings support the concept that CRP2 contributes to the phenotypic modulation of VSMCs during vascular disease. Modulating transcription to increase CRP2 expression during vascular injury might attenuate vascular remodeling. Alternatively, increased CRP2 expression at the fibrous caps of advanced lesion might also serve to protect atherosclerotic plaques from rupture.
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LINCRNA-P21 REGULATES NEOINTIMA FORMATION AND ATHEROSCLEROSIS BY ENHANCING P53 ACTIVITY
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Background: Long non-coding RNAs (lncRNAs) recently have been implicated in many biological processes and diseases. Atherosclerosis is a major risk factor for cardiovascular disease. However, the functional role of lncRNAs in atherosclerosis is largely unknown.

Methods and Results: We identified lincRNA-p21 as a key regulator of atherosclerosis. The expression of lincRNA-p21 was dramatically down-regulated in atherosclerotic plaques of mice, an animal model for atherosclerosis. Through loss- and gain-of function approaches, we showed that lincRNA-p21 represses cell proliferation and induces apoptosis in vascular smooth muscle cells (VSMCs) in vitro. Moreover, we found that inhibition of lincRNA-p21 results in neointimal hyperplasia in vivo in a carotid artery injury model. Mechanistically, we revealed that lincRNA-p21, which is a transcriptional target of p53, feeds back to enhance p53 transcriptional activity via binding to mouse double minute 2 (MDM2), an E3 ubiquitin-protein ligase. The association of lincRNA-p21 and MDM2 releases MDM2 repression of p53, enabling p53 to interact with p300 to regulate apoptosis, cell proliferation and suppress neointima formation. Finally, we show that lincRNA-p21 expression is decreased in coronary artery disease patients.

Conclusions: Our studies identified lincRNA-p21 as a novel regulator of cell proliferation and apoptosis and suggest that this lncRNA could serve as a therapeutic target to treat atherosclerosis.
PRO-ATHEROGENIC ACTIONS OF INTERFERON-GAMMA ON MACROPHAGES IN ATHEROSCLEROSIS

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\textbf{Objectives:} To investigate the pro-atherogenic actions of interferon-gamma (IFN-gamma) on human macrophages during atherosclerosis.

\textbf{Background:} Atherosclerosis is an inflammatory disorder of the vasculature regulated by cytokines. Interferon-gamma is a key pro-atherogenic cytokine that is involved in all stages of this disease, including foam cell formation, amplification of the inflammatory response and the regulation of plaque stability. The purpose of this study was to investigate the molecular mechanisms underlying the pro-atherogenic actions of interferon-gamma on macrophages during atherosclerosis.

\textbf{Methods:} The studies used a combination of mouse model systems, human THP-1 cell line and primary cultures of human monocyte-derived macrophages. Molecular mechanisms were delineated using real-time quantitative PCR, western blot analysis, promoter analysis, biochemical assays and RNA interference assays.

\textbf{Results:} IFN-gamma promoted macrophage foam cell formation, induced the expression of a range of pro-inflammatory genes and regulated the expression of several microRNAs. Extracellular signal-regulated kinase (ERK) was integral to the IFN-gamma-mediated uptake of modified lipoproteins by macrophages and the expression of key genes implicated in atherosclerosis. The action of ERK was mediated through the regulation of phosphorylation of signal transducer and activator of transcription-1 (STAT1) on serine 727. We are currently investigating the role of the ERK-1:STAT1 axis in atherosclerosis in vivo.

\textbf{Conclusions:} The studies provide key insights into the pro-atherogenic actions of interferon-gamma.

\textbf{Funding:} British Heart Foundation
HISTOMORPHOMETRIC CHANGES IN THE AORTA OF MICE WITH CHRONIC CHAGAS DISEASE UNDERGOING MILD EXERCISE

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Changes related to vascular dysfunction, such as micro vascular spasm associated with infection, reduced blood flow, platelet aggregation and increased myocardial inflammation and fibrosis have been described as causes of arterial compliance due to Chagas cardiomyopathy.Moreover, aerobic exercises are widely indicated for the treatment of various disorders of the cardiovascular system.

Purpose: To evaluate using morphometric and stereological methods the aspect of extracellular matrix of the tunica media from ascending aorta of mice Balb-C chronic Chagas disease undergoing mild exercise extra-cellular matrix.

Materials and Methods: 20 male mice at four months of age were used for experiments. The animals were divided into 4 groups (n=5): SC (sedentary control), TC (trained control), SI (sedentary infected) and TI (trained infected). 1000 forms of Trypanosoma cruzi (Y strain) were inoculated in animals in groups IS and IT, after 40 days was reported chronic phase of the disease.

Physical exercise (swimming) consisted of daily half-hour, 5 times a week for 8 consecutive weeks in bath temperature of 30° C. After the trial period, euthanasia was done and withdrawal of the ascending aorta, which was prepared by histological staining procedures with Hematoxylin-Eosin and Verhoeff. The number density of the elastic lamellae (Nv [lam]), the aortas, inside diameter (ID) and outer (OD) and relative tunica medium/light (Rm/light) were analyzed. The analysis was performed under light microscopy using an image program (Axio Vision Plus).

Results: The analysis revealed a significant increase in Nv [lam], the ID and OD and a decrease in Rm/light in the aortas of the animals SI group compared with the SC group. The training promoted a recovery of these parameters in the IT group.

Conclusions: Light exercise can be used as an adjuvant to non-medication improves vascular compliance of chronic chagasic mice.
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URIC ACID PROMOTES CHEMOKINES AND ADHESION MOLECULES PRODUCTION IN VASCULAR ENDOTHELIAL CELLS AND INCREASES THE MIGRATION AND ADHESION CAPACITIES VIA NUCLEAR FACTOR-KAPPA B SIGNALING PATHWAY


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Background and aims: Previous studies have revealed that hyperuricaemia was an important risk factor for atherosclerosis. However, the potential mechanisms are not well understood. The migration and adhesion of leukocytes to endothelial cells play a key role in the initiation and development of atherosclerosis, so in this study we investigated the monocyte-endothelial cell interactions and the potential signaling pathways involved under uric acid (UA)-stimulated condition.

Methods and results: Primary human umbilical vein endothelial cells (HUVECs) were cultured and exposed to different concentrations of UA for various periods, and then we evaluated the expression and release of chemoattractant protein-1 (MCP-1), interleukin 8 (IL-8), vascular cell adhesion molecule-1 (VCAM-1) and intercellular adhesion molecule-1 (ICAM-1). Monocyte-endothelial cell interactions were elucidated by chemotaxis and adhesion assays, and nuclear factor-kappa B (NF-kB) activity was explored by electrophoretic mobility shift assay (EMSA). The results showed that viability of HUVECs was impaired after prolonged exposure to higher concentration of UA. The expression of MCP-1, IL-8, VCAM-1 and ICAM-1 in HUVECs were elevated by UA in a dose- and time-dependent manner, the migration and adhesion of THP-1 cells to HUVECs were also promoted and the activated NF-kB was significantly increased in HUVECs. UA-induced responses were ameliorated by the organic anion transporter inhibitor probenecid and the NF-kB inhibitor BAY 11-7082. Besides, we found that human endothelial cells express urate transporter-1 (URAT1), which was not regulated by UA.

Conclusion: UA stimulates the production of chemokines and adhesion molecules in endothelial cells and dramatically increases the migration and adhesion of monocytes to endothelial cells via NF-kB signaling pathway, the process of which requires intracellular uptake of UA. The promotion of monocyte-endothelial cell interactions may accelerate atherosclerosis in hyperuricaemia patients.
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CRIF1 DEFICIENCY INDUCES P66SHC-MEDIATED OXIDATIVE STRESS AND ENDOTHELIAL ACTIVATION
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Mitochondrial dysfunction has been implicated in the pathophysiology of various cardiovascular diseases. CRIF1 is a protein present in the mitochondria associated with large mitoribosomal subunits, and CRIF1 knockdown induces mitochondrial dysfunction and promotes ROS production. p66shc is a redox enzyme implicated in mitochondrial ROS generation and translation of oxidative signals and, therefore, is a key factor for oxidative stress in endothelial cells. In this study, we investigated whether mitochondrial dysfunction induced by CRIF1 knockdown induces p66shc stimulation and plays any role in mitochondrial dysfunction-induced endothelial activation. Knockdown of CRIF1 decreased the expression of mitochondrial oxidative phosphorylation (OXPHOS) complexes I, III and IV, leading to increased mitochondrial ROS (mtROS) and hyperpolarization of the mitochondrial membrane potential. Knockdown of CRIF1 also stimulated phosphorylation of p66shc and increased cytosolic ROS in endothelial cells. Furthermore, the expression of vascular cell adhesion molecule-1 and endoplasmic reticulum stress proteins were increased upon CRIF1 knockdown in endothelial cells. However, p66shc knockdown blunted the alteration in mitochondrial dynamics and ROS production in CRIF1 knockdown endothelial cells. In addition, p66shc knockdown reduced the CRIF1 knockdown-induced increases in adhesion between monocytes and endothelial cells. Taken together, these results suggest that CRIF1 knockdown partially induces endothelial activation via increased ROS production and phosphorylation of p66shc.
PHARMACOLOGICAL MODULATION OF VASCULAR-ENDOTHELIAL FUNCTION

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EFFECTS OF CHRONIC CARDIOVASCULAR PHARMACOLOGY ON LONG-TERM SURVIVAL IN STROKE PATIENTS
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Objectives: We aimed to investigate effects of the background and post-stroke cardiovascular medications on long-term survival in stroke patients.

Background: Stroke patients typically have multiple cardiovascular morbidities requiring chronic “background” pharmacotherapy. The prognostic effects of these medications on long-term survival of stroke patients need to be further studied.

Methods: Univariate and multivariate logistic regression modeling and survival analysis based on demographic and clinical data was performed in 380 consecutive non-hemorrhagic stroke subjects. Effects of pre- and post-stroke cardiovascular medical therapy on survival were compared.

Results: Pre- or post-stroke therapy with aspirin, clopidogrel, ACE inhibitors-ARB, or statin did not affect long-term outcomes. However, increased long-term mortality was noted in patients on pre-stroke beta-blocker (HR=1.7 95%CI 1.2-2.7%, p=0.031) or coumadin therapy (HR=2.3 95%CI 1.2-4.5, p=0.031). Increased long-term mortality was noted in patients on post-stroke beta-blocker (HR=2 95%CI 1.3-3.2, p=0.003), but not on coumadin therapy. When compared to the rest of the cohort, patients on pre-stroke beta-blocker therapy were older (71+/−13 vs. 64+/−16 years, p<0.001), with history of CAD (47 vs. 12%, p<0.001), hypertension (93 vs. 62%, p<0.001), diabetes (34 vs. 24%, p=0.023), dyslipidemia (70 vs. 47%, p<0.001), and hemodialysis (8 vs. 3%, p=0.035). When adjusted for co-morbidities, pre-stroke beta-blocker therapy was not predictive of decreased long-term mortality. Similarly, when compared to the rest of the cohort, patients on post-stroke beta-blocker therapy were older (70+/−14 vs. 62+/−16 years, p<0.001), with history of CAD (33 vs. 12%, p<0.001), hypertension (84 vs. 59%, p<0.001), diabetes (34 vs. 21%, p=0.023), and dyslipidemia (60 vs. 48%, p<0.001). When adjusted for co-morbidities, post-stroke beta-blocker therapy was not predictive of decreased long-term mortality.

Conclusions: In non-hemorrhagic stroke patients, chronic use of cardiovascular medications does not directly predict long-term outcomes. Rather, it is indicative of multiple co-morbidities common in this high risk patient population.
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ANTI-INFLAMMATORY EFFECT OF RESVERATROL IN HUMAN CORONARY ARTERIAL ENDOTHELIAL CELLS VIA AUTOPHAGY: IMPLICATION FOR THE TREATMENT OF KAWASAKI DISEASE

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Kawasaki disease (KD) is an acute febrile vasculitis of childhood and is the leading cause of acquired heart disease in children in the developed world. If untreated, KD can result in coronary aneurysms in 25% of patients, who are at risk of myocardial infarction, sudden death, and congestive heart failure. Despite the success, 10-20% of children will have persistent or recrudescent fever after their first infusion of IVIG. These patients are at increased risk of developing coronary artery abnormalities. Additional therapies should be explored to decrease the incidence of coronary arteritis complication and improve the prognosis in Kawasaki disease. Induced autophagy with resveratrol confers cardioprotection during ischemia and reperfusion in rats.

KD is associated with elevated production of inflammatory cytokines, causing damage to the coronary arteries. Serum TNF-alpha levels are elevated in KD, which was supposed to activate the endothelial cells. As a result, adhesion molecules such as intercellular adhesion molecule-1 (ICAM-1) and vascular cellular adhesion molecule-1 (VCAM-1) are expressed in the endothelial cells, and leucocytes adhere firmly to endothelial cells. The leucocytes then damage the endothelial cells and smooth muscle cells and cause vasculitis.

In this study, we examined the anti-inflammatory effects of resveratrol on TNF-alpha-induced adhesion molecule expression (VCAM-1 and ICAM-1) and cytokine production (interleukin (IL)-1beta, IL-6 and IL-8) in HCAECs. Pretreatment with resveratrol significantly inhibited TNF-alpha-induced adhesion molecules and cytokines production in HCAECs via the activation of autophagy. Our results suggest that adjunctive resveratrol therapy may modulate the inflammatory response during KD vasculitis and explore the role of autophagy in the pathogenesis of the complication and the promising therapy.
Differential Role of Osteopontin and Tenascin-C in Advanced Coronary Atherosclerosis: Coronary Rotational Atherectomy Study

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Objective: Osteopontin (OPN) and tenascin-C (TNC) are extracellular matrix proteins and play a role in atherosclerotic plaque development. However, little in vivo evidence is available about their potential relations with vascular inflammation. To examine the hypothesis that OPN and TNC are regulated by inflammatory process, we measured peripheral levels of OPN, TNC, and pentaxin 3 (PTX3) before and after rotational coronary atherectomy (RA), which ablates coronary atheroma into blood stream.

Methods and Results: We enrolled consecutive 81 patients (mean age: 69 years, M/F=46/35) treated successfully with RA. OPN levels (mean±SD, ng/ml) significantly (p<0.0001) increased immediately after RA (from 743±451 to 886±483), further increased to 1277±721 3 hours later, and returned to 889±563 at the time of 24 hours after procedure. TNC levels increased behind the changes of OPN and reached the peak at 24 hours after procedure (from 66±60 to 80±61 ng/ml). PTX3 levels significantly (p<0.0001) increased immediately after RA (from 4.7±3.7 to 5.6±4.2 ng/ml), further increased to 8.2±5.3 3 hours later, and returned to 7.2±6.5 24 hours after procedure. Preprocedural levels of OPN showed significant and positive association with those of TNC (r=0.446, p<0.0001). Furthermore, both OPN and TNC levels were positively associated with log-transformed hsCRP (r=0.526, p<0.0001 and r=0.449, p<0.0001) and with log-transformed PTX3 (r=0.416, p=0.0001 and r=0.286, p=0.0097). Both increases of OPN and TNC after RA showed significant and positive associations with log-transformed increase of PTX3 (r=0.464, p<0.0001 and r=0.498, p<0.0001, respectively).

Conclusions: These results suggest that both OPN and TNC levels are associated with vascular inflammation, and that OPN and TNC may play a differential role in a response to vascular injury caused by RA procedure.
TREATMENT OF CORONARY IN-STENT RESTENOSIS WITH PACLITAXEL-COATED BALLOON CATHETER: 36- MONTH CLINICAL RESULTS

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Background and Objectives: Paclitaxel-coated balloons (PCB) have been proven to be effective for the treatment of coronary in-stent restenosis (ISR) after bare-metal stent (BMS) or drug-eluting stent (DES) implantation. This study aims to evaluate the long-term safety and efficacy of the second-generation SeQuent Please PCB in coronary ISR. Methods: Between May 2009 and February 2011, all consecutive patients with ISR lesions treated with the SeQuent Please PCB at our institution were prospectively included. Patients were followed up for 36 months by clinical observation. The primary endpoint was the clinically driven target lesion revascularization (TLR) rate at 36 months. The secondary endpoint was the rate of major adverse cardiac events (MACE: defined as a composite of cardiac death, myocardial infarction, and TLR) at 36 months. Results: 63 patients with 73 ISR lesions (39 BMS, 34 DES) were included. Mean age was 67.4±11.7 years and 55.6% were diabetics. The majority of patients presented with stable angina (61.9%). The target lesion was mainly located in the right coronary artery (42.5%). The mean reference vessel diameter was 3.0±0.5 mm and the mean target lesion length was 19.7±6.6 mm. Procedural success was 100%. The TLR rate was 4.8% after 36 months. Cumulative MACE at 36 months was 11.1%, with 4.8% cardiac death and 3.2% myocardial infarction. No vessel thrombosis was documented. The TLR rate did not differ for PCB angioplasty for BMS-ISR compared with DES-ISR (2.9% vs. 7.1%, p=0.58). Baseline lesion characteristics and procedural data did not differ except for a longer lesion length for BMS-ISR compared with DES-ISR (21.7±6.0 mm vs. 17.3±6.5 mm, p=0.004).

Conclusions: Treatment of coronary ISR with the SeQuent Please PCB provides good clinical outcomes demonstrated by the low TLR rate and low MACE rates at long-term follow-up.
DIFFERENT AND SAME PROGNOSTIC IMPLICATION OF LOW PREPROCEDURAL TIMI FLOW BETWEEN STEMI AND NON-STEMI IN THE PATIENTS UNDERGOING PERCUTANEOUS CORONARY INTERVENTION

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Reduced pre-procedural Thrombolysis in Myocardial Infarction (TIMI) flow in patients with ST-segment elevation myocardial infarction (STEMI) has been associated with mortality. However, clinical implication of low pre-procedural TIMI flow in patients with non-ST segment elevation myocardial infarction (NSTEMI) has not been clear. The aim of the study was to compare the clinical prognosis of low pre-procedural TIMI flow between patients with STEMI and NSTEMI undergoing percutaneous coronary intervention (PCI). We evaluated 7336 patients with low pre-procedural TIMI flow (TIMI 0/1) presenting STEMI and NSTEMI who had undergone PCI in a nationwide Korea Acute Myocardial Infarction Registry (KAMIR). The patients were divided into STEMI group (n=4852) and NSTEMI group (n=2484). The 12-month major adverse cardiac event (MACE) was compared between the 2 groups. After adjustment using propensity score stratification, NSTEMI group had lower MACE (7.58% vs 9.69%; HR 0.78; 95% CI 0.63 to 0.96; p=0.020) than STEMI group, which may be attributable to repeat revascularization at 12 months (3.83% vs. 5.06%; HR 0.75; 95% CI 0.56 to 1.0; p=0.053). However cardiac death occurred in 1.37% of NSTEMI and 1.61% of STEMI (p=0.527). In logistic regression, there was no difference of non-fetal myocardial infarction, CABG, non-cardiac death between 2 groups during 12-month clinical follow up. In conclusion, low pre-procedural TIMI flow (TIMI0/1) in NSTEMI was associated with lower MACE rather than STEMI. However, clinical implication of low pre-procedural TIMI flow (TIMI0/1) in patients with non-STEMI may not be distinctive of cardiac death in comparison to STEMI.
INFLUENCE OF ACCESS AND ANTICOAGULANT ON THE HOSPITAL LENGTH OF STAY IN DOING PRIMARY PERCUTANEOUS CORONARY INTERVENTION: US ACADEMIC CENTER EXPERIENCE

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Background: Trans-radial intervention (TRI) for primary percutaneous coronary intervention (PPCI) is associated with fewer bleeding complications and shorter length of stay. Compared with UFH, use of bivalirudin in the treatment of patients who undergo PPCI appears to be cost-saving in routine practice settings because of reduced lengths of stay. But there were no studies done on the hospital length of stay combining both radial access and bivalirudin.

Methods: We did a retrospective analysis of 117 patients with ST-segment elevation myocardial infarction (STEMI) who had PPCI in our academic center from January 2010 till May 2013. We excluded patients with cardiac arrest, cardiogenic shock and who had staged procedures during the index admission. Major bleeding was defined using CathPCI registry.

Results: Baseline and procedural characteristics shown in the table. The mean length of stay in patients with bleeding complications was 4.61 days and without was 3.25 days (P<0.0001). It was 2.85 days in radial group and 4.06 days in femoral group (P<0.0001). The same with Bivalirudin was 3.81 days and Heparin was 3.74 days (P=0.73). The mean length of stay among the four subgroups were 2.56 vs. 3 vs. 3.97 vs. 4.4 days each in the four groups shown on the table (P<0.0001).

Conclusions: In this single center retrospective observational analysis of PPCI patients, the combination of bivalirudin and radial approach showed significant trend in lessening the length of stay in the hospital compared to other combinations.
INCIDENCE AND PREDICTORS OF STENT THROMBOSIS AFTER PERCUTANEOUS CORONARY INTERVENTION IN ACUTE MYOCARDIAL INFARCTION

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Background: Stent thrombosis has not been solved and catastrophic problem in patients underwent percutaneous coronary intervention (PCI). However, there was a paucity of data about the incidence, predictors and prognosis of stent thrombosis (ST) in acute myocardial infarction (AMI) after PCI.

Methods: We consecutively enrolled 4,748 AMI patients who underwent PCI in the COREA-AMI (Convergent Registry of Catholic and Chonnam University for AMI) from January 2004 to December 2009. We analyzed the incidence, prognosis, and predictors definite or probable ST by Academic Research Consortium.

Results: Median follow up duration was 41.9 months (interquatile range 27.4 to 58.9 months). Bare-metal stents (BMS) and drug-eluting stents (DES) were implanted in 451 (9.6%) and 4,269 (90.4%) patients, respectively. Definite or probable ST during follow up occurred in 136 patients (3.7%), including 44 early (1.0%), 38 late (0.9%), and 54 very late (2.0%). And annual incidence of ST after 1 year from index PCI was from 0.5% to 0.6%. There was no difference of the rate of ST between BMS and DES (4.4% and 3.7%, p=0.23) and between Non-ST-segment elevation MI and ST-segment elevation MI (3.0% and 4.1%, p=0.24). The independent predictors of ST were no reflow phenomenon (hazard ratio (HR) 2.03, 95% confidence interval (CI) 1.31-3.12), decreased left ventricular ejection fraction (LV EF) (HR 0.97, 95% CI 0.95-0.99), anemia (HR 1.50, 95% CI 1.06-2.13) and mean stent diameter <3.0 mm (HR 1.50, 95% CI 1.01-2.22)

Conclusion: Stent thrombosis is not uncommon in patient with AMI underwent PCI irrespective of stent type or clinical presentation. And no reflow phenomenon, decreased LV EF, anemia and mean stent diameter <3.0 mm are independent predictors of ST.
DOES THE SEVERITY OF CORONARY ARTERY DISEASE PREDICT THE USE OF CONTRAST VOLUME DURING CARDIAC CATHETERIZATION?

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\textbf{Background:} The volume of contrast used during cardiac catheterization (CC) is correlated with risk of contrast induced nephropathy (CIN). We sought to determine if contrast volume use was related to the severity of coronary artery disease.

\textbf{Methods:} Electronic medical records of 708 patients undergoing CC from 2010-2012 were reviewed retrospectively to collect data on contrast volume, cardiovascular risk factors and angiographic findings. Mean contrast volumes were calculated for the variables. Univariate, multivariate logistic and linear regression analyses were done.

\textbf{Results:} Table 1 shows significant findings of univariate analysis. The number of vessels with obstructive lesions (>50\%) (p=0.01; Beta -14.17) and the presence of lesions with >70\% stenosis in major epicardial vessels (p=0.019; Beta 24.39) were determined to be independent on regression analysis.

\textbf{Discussion:} There appears to be elevated contrast use in patients with single, double vessel disease or lesions >70\% stenosis in major epicardial vessels likely due to the requirement of more angiographic images to determine the revascularization approaches. Patients with triple vessel disease required a lesser amount of contrast likely due to the need for bypass surgery as opposed to interventional strategies. This study shows that increasing disease severity leads to increase in contrast volume use and therefore may potentially increase risk of CIN.

\textbf{Table 1: Univariate Analysis}

<table>
<thead>
<tr>
<th>Number of Coronary Vessels with Obstructive Lesions</th>
<th>Number of Patients (n)</th>
<th>Contrast Volume (ml) Mean ±SD</th>
<th>95% Confidence Interval for Mean</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>249</td>
<td>68.6 ± 52.5</td>
<td>62.0 - 75.1</td>
<td>0.001</td>
</tr>
<tr>
<td>1</td>
<td>163</td>
<td>126.7 ± 63.7</td>
<td>116.8 - 136.5</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>160</td>
<td>132.7 ± 71.1</td>
<td>121.6 – 143.8</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>136</td>
<td>107.8 ± 67.2</td>
<td>96.4 – 119.2</td>
<td></td>
</tr>
<tr>
<td>Lesions with &gt;70% Stenosis in Major Epicardial Vessels*</td>
<td>Present (337)</td>
<td>129.2 ± 71.2</td>
<td>(-56.6) – (-37.6)</td>
<td>0.001</td>
</tr>
<tr>
<td></td>
<td>Absent (363)</td>
<td>82.1 ± 55.9</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Epicardial vessels include left main, left circumflex, left anterior descending, posterior descending and right main coronary arteries.
SAFETY AND EFFICACY OF POLYMER FREE VS. BASED DRUG-ELUTING STENTS. A META-ANALYSIS OF RANDOMIZED TRIALS

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Objectives: The aim of this study was to perform a meta-analysis of randomized controlled trials (RCTs) comparing the safety and efficacy profile of Polymer free drug-eluting stents (PF-DES) vs. polymer based-DES (PB-DES).

Background: PF-DES have recently been developed to improve the delayed healing and hypersensitive reaction in the vessel. However, uncertainty exists regarding the relative performance of PF-DES versus PB-DES in percutaneous coronary intervention.

Methods PubMed, Embase, and Cochrane Central Register of Controlled Trials (CENTRAL) were searched for RCTs that compared PF-DES and PB-DES, enrolling at least 100 patients. Efficacy endpoints were target-lesion revascularization (TLR) and in-stent late loss (ISLL). Safety endpoints were cardiac death, death, myocardial infarction (MI), composite of definite and probable stent thrombosis (ST).

Results: The meta-analysis included 8 RCTs (n=6,182) with a median follow-up of 28.5 months clinical outcomes and 7 RCTs (n=4,741) with ISLL results. The results showed that there was no difference between PF-DES and PB-DES with regard to cardiac death, death, ST, MI, ISLL or TLR.

Conclusions: PF-DES are comparable as PB-DES with regard to cardiac death, death, ST, MI, ISLL and TLR. Although avoidance of permanent polymer is interesting with presumed long-term implications, safety and efficacy advantage remain subject to future investigation.
INTERVENTIONAL CARDIOLOGY

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CALCIFIED LESION DOES NOT INFLUENCE OUTCOME AFTER PERCUTANEOUS ANGIOPLASTY WITH STENTING
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We evaluated influence of lesion characteristics in the patients who underwent percutaneous transluminal angioplasty (PTA) for peripheral artery disease (PAD). Methods: Ultrasonography (US) and computed tomography angiography (CTA) were used in 75 patients with PAD (mean 65.3 years old). We had 43 cases with superficial femoral artery (SFA), 14 cases with iliac artery (IA), 10 cases with both SFA and IA, and 8 cases with tibial disease. Cardiovascular risk factors including diabetes mellitus (DM), hypertension, smoking history, dyslipidemia and chronic kidney disease.

Results: In all patients with IA and/or SFA lesion, stenting was performed. However, only balloononing was done in tibial lesions. At 1 year follow-up, restenosis occurred in 5 cases (17.9%) out of 28 SFA cases and 1 (7.1%) out of 14 IA cases with calcified lesions. On the other hand, restenosis occurred in 3 (12%) out of 25 SFA cases and 0 out of 10 IA cases without calcification. No significant difference in restenosis rate was observed between cases with calcified lesion and those without calcified lesions. In iliac or femoral lesions, there was no difference in number of risk factor between the patients without restenosis and those with restenosis (2.39±0.89 vs 2.45±0.90) mean ± standard deviation). Percentage of DM was not different between the patients with restenosis (7/9, 77.5%) and the patients without (7/12, 67.2%). Cigarette smoking was observed in 6 (66.7%) patients with restenosis, and 48 (71.6%) patients without. In tibial disease, restenosis occurred in 4 out of 11 lesions. There was no difference in age, number of risk factor and carotid PS between patients with restenosis and those without.

Conclusions: US is as useful as CTA for evaluation of PTA. If stenosed lesion is successfully dilated with stenting, calcification in the lesion or number of risk factor may not affect outcome. However, restenosis rate is still high in patients with tibial disease.
THE COMPLEX CORONARY ANGIOPLASTY TRANSRADIAL

J.M. Telayna, C.S. Garcia, R.A. Costantini
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Introduction: The transradial coronary angioplasty (TPCI) has between his attractions minor complications and more comfort and short stay hospital. On the other hand, this route has been related to major exposition to radiation and major technical difficulty with major trend to failure of procedure that makes counter balance the initial attraction. In the context of clinical situations time dependent like the acute myocardial infarct or challenging technically as occlusions chronic total or bifurcations, the TPCI can turn out to be a "complex" coronary angioplasty.

Objective: To determine the clinical results and of the procedure in complex coronary angioplasty radial route vs. femoral route.

Material and methods: From January, 2006 to October, 2013 were realized 362 interventions defined as "complex" being the group A (radial group) n= 112 patients and the group B (transfemoral group) n= 250 patients. The basal characteristics, group A and B respectively - n(%): average age 57,2±9 vs 60,2±12 years (p=0,01); diabetics 17(15) vs 58(23); ventricular left function minor 50% 25(22) vs 50(20); previous revascularization 20(18) vs 66(26); chronic stable angina 10(9) vs 33(13); SCANoST and unstable angina 35(31) vs 37(15) p=0,0004; SCAST 65(58) vs 179(72) p=0,01; other clinical status 2(2) vs 1(0,4); disease of multiple coronary vessels 54(48) vs 139(56); treatment of multiple coronary vessels 33(29) vs 68(27); bifurcations 44(39) vs 45(18) p=0,00002; occlusions chronic total 9(8) vs 3(8); more than 2 guide catheters 7(6) vs 15(6); maneuvers of active support 6(5) vs 6(2).Results: Time of room 90±34min vs 88±40 min; radioscopy time 19±11 vs 19±15min p=0,01; dye material 231±17 ml vs 256±99 ml p=0,01; technical success 112 (100) vs 242 (97) p=0,06; myocardial infarct 3 (2,6) vs 5 (2); major bruise 1 (0,8) vs 3 (1,2); cardiac death 1 (0,8) vs 9 (3,6).

Conclusions: The complex coronary angioplasty for access radial presented favorable variables of the procedure without impact in adverse major cardiovascular events in opposite of femoral route.
INTERVENTIONAL CARDIOLOGY

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TISULAR IMPACT IN THE CORONARY COMPLETE REVASCULARIZATION IN PATIENTS WITH ACUTE MYOCARDIAL INFARCT AND CARDIAC FAILURE

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Objective: To evaluate outcomes to six months in patients with acute myocardial infarct with elevation segment ST (AMIST) and moderate cardiac failure; according to the revascularization has been complete or not and analyze the relation of the biochemical outcomes of injuries myocardial and of tisular perfusion in this scene.

Material and methods: There were included patients (p.) with AMIST and cardiac failure (K&K 2-3) underwent primary coronary angioplasty (PCI) and multivessels coronary disease. The groups: GA (PCI only of the culprit vessel) and GB (PCI multivessel in the same session) completed follow-up to 6 months and were evaluated troponin, CPK, lactic acid and the nadir of venous central saturation (SVO2).

Results: Of 342 procedures of PCI realized, 53 they presented criteria of inclusion. Basal characteristics: GA(n=32) and GB(n=21) respectively: age 61,6±11,2 vs 59±14,5; diabetes 28% vs. 28%; prior myocardial infarct 21% vs 19%; ventricular function 40,6±16 vs 46,5±22; anterior infarct 31% vs 42%; compromise anterior descending artery 53% vs 90% p=0.006; millimeters of stent implanted 46±32 vs 71,5±32 p=0,007. Differences were not observed in the intrahospitalary mortality GA 25% vs GB 9%, reinfarct GA 0% vs GB 9.5%, cardiac mortality to 6 months GA 26% vs GB 9%, reinfarct to 6 months GA 3% vs GB 4%. The final primary point combined to 6 months was in 56% GA vs 23% GB (p=0,04).There were not differences in troponin GA 2.00 ug/dl vs GB 4,77 p=0,27, total CPK GA 1951 U/l vs GB 1870 U/l, p=0.63, peak of lactic GA 3.4 mmol/dl vs GB 3.4, p=0.48. The nadir of SVO2 was lower in GA 55.6±7.7 vs 66.2±8.3%, p=0.002.

Conclusions: The complete coronary revascularization in the same session in the IAMSST and moderate cardiac failure presented fewer clinical events combined and minor suffering tisular systemic.
IN-STENT ANCHORING FACILITATES BALLOON DELIVERY FOR FINAL KISSING

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Background: Kissing balloon (KB) inflation has been developed for percutaneous bifurcation interventions to improve outcomes and reduced angiographic (re)stenosis. However, this procedure is sometimes technically challenging due to inability to deliver side branch (SB) balloon cross the structure of main vessel (MV) stent(s).

Purpose: To develop an improved technique for SB balloon delivery.

Methods: Patients (n equal to fifteen) with chest pain and an angiographically significant (more than seventy-five percent) SB lesion after MV stent, were included. In-stent anchoring technique was performed: First, the size-matched non-compliant balloon is accurate positioned in the anchored zone ± of MV stent (between the ostium of SB and the distal edge of the stent). Second, the in-stent balloon is inflated usually at high pressure and operator pulls the balloon and both wires as an anchor and at the same time, pushes the SB balloon through the MV stent structures.

Results: The primary kissing balloon success rate was one hundred percent. There was no angiographic vessel complication, in particular dissection, thrombus and acute occlusion, until hospital discharge.

Conclusion: In-stent anchoring is a safe and effective balloon delivery technique for final kissing. However, more cases are needed to provide further verification and evaluation.
HYPERTENSION: BASIC, CLINICAL AND EPIDEMIOLOGICAL

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AUTOMATED PRECLINICAL ENCOUNTER BLOOD PRESSURES VERSUS MANUAL PHYSICIAN BLOOD PRESSURES IN CARDIOVASCULAR CLINIC
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Objective: Assess accuracy of medical assistant automated blood pressure (MABP) prior to ambulatory visit versus manual readings obtained by cardiology fellow (CBP).

Introduction: Accurate BP is important to guiding medical therapy and risk reduction. Significant morbidity and costs is added to patients’ care if data is inaccurate. We performed this analysis to determine potential risks or errors in management based on BP.

Method: A prospective quality analysis was performed from November 1st, 2013 to January 31st, 2014. Patients had initial MABP performed using GE Healthcare Dash 2500 and Dash 3000 automated sphygmomanometer. A follow up CBP was performed before discharge. The primary endpoint was the difference between the systolic BP and diastolic BP readings during both encounters. An additional endpoint was the change in JNC7 hypertension classification.

Results: A total of 147 patients met inclusion criteria. The mean systolic MABP was 152.9 mmHg, whereas the mean systolic CBP was 138.4 mmHg with a mean difference of 14.5 mmHg (95% CI 11.72 - 17.19, P = < 0.001). The mean diastolic MABP was 74.95 mmHg compared to CBP diastolic of 75.63 mmHg, a mean difference of -0.69 mmHg (95% CI -2.22 - 0.848, P = 0.38). Compared to the MABP, the CBP led to a significant reclassification with 38% lower hypertension class, 58% unchanged, and the remainder at a higher classification (P<0.001).

Conclusions: MABP were much higher than CBP. Forty-two percent of patients assessed changed classification with 38% percent being lowered. Failure to repeat MABP may lead to misdiagnosis or misclassification, and result in adverse outcomes. MABP is often falsely elevated and should not be the only documented BP. Training of technicians, nursing and physicians is critical for accurate diagnosis. Falsely elevated BP may adversely affect care, pay for performance measures, and increase morbidity.
HAS OBESITY IN HYPERTENSIVE PATIENTS AN IMPACT ON CARDIOVASCULAR AND CATECHOLAMINE RESPONSES DURING MENTAL STRESS?

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Background: The mechanisms underlying the association between obesity and arterial hypertension, and in particular the role played in this context by the sympathetic nervous system, are still a matter of considerable debate. Objectives: The present study was aimed to investigate sympathoadrenal responses to a mental stress test in young patients with incipient hypertension with and without obesity. The main hypothesis to be verified was that the presence of obesity in patients with diagnosed hypertension has an additive effect on cardiovascular and catecholamine responses to a mental stress task.

Methods: The participants were young male subjects, 8 with hypertension grade I, with BMI less than 25kg/m² (HT), 10 with hypertension grade I, with BMI more than 30kg/m² (HT OB), 13 healthy controls with BMI less than 25kg/m² (C), 14 healthy controls with BMI more than 30kg/m² (OB). The Stroop word-color test was used as the stress model. ECG was recorded continuously to evaluate heart rate variability. Blood pressure (BP) and catecholamine concentrations were measured at baseline, at the end of mental stress test and 15 min thereafter.

Results: Patients with HT demonstrated increased adrenaline concentrations at baseline and during the mental stress test as well as enhanced stress-induced noradrenaline release compared to that in healthy controls. A higher baseline systolic BP was observed in the group of obese otherwise healthy subjects than in lean controls. Obese subjects exhibited a lower stress-induced increase of systolic BP compared to lean individuals. The changes in systolic BP negatively correlated with BMI.

Conclusions: The present data demonstrate higher sympathoadrenal activity manifested by augmented noradrenaline response to mental stress in early-stage hypertension. In discrepancy with the prevailing opinion we have demonstrated a reduced response of systolic BP during mental-stress task. Combination of obesity and hypertension does not produce additional increase in baseline sympathetic activity.

Supported by APVV-0028-10.
Hypertension has been associated with Parkinson’s disease (PD), but data on antihypertensive drugs and PD are inconclusive. We aim to evaluate different classes of antihypertensive drugs for an association with PD in patients with hypertension. Hypertensive patients who were free of PD, dementia and stroke were recruited from 2005-2006 using the Taiwan National Health Insurance Database. We examined the association between the use of calcium channel blockers (CCBs), angiotensin converting enzyme inhibitors (ACEIs), angiotensin receptor blockers (ARBs) and the incidence of PD using beta-blockers as the reference group. Cox regression model with time-varying medication use was applied. Among 65,001 hypertensive patients with a mean follow-up period of 4.6 years, the use of dihydropyridine CCBs, but not non-dihydropyridine CCBs, was associated with a reduced risk of PD (adjusted hazard ratio [aHR], 0.71; 95% CI, 0.57-0.90). Further decreased association was observed for higher cumulative doses of felodipine (aHR, 0.54; 95% CI, 0.36-0.80) and amlodipine (aHR, 0.60; 95% CI, 0.45-0.79). There was no association between the use of ACEIs (aHR, 0.80; 95% CI, 0.64-1.00) or ARBs (aHR, 0.86; 95% CI, 0.69-1.08) with PD. A potentially decreased association was only found for higher cumulative use of ACEIs (HR, 0.52; 95% CI, 0.34-0.80) and ARBs (HR, 0.52; 95% CI, 0.33-0.80). Our study suggests centrally-acting dihydropyridine CCB use and high cumulative doses of ACEIs and ARBs may associate with a decreased incidence of PD in hypertensive patients. Further long-term follow-up studies are needed to confirm the potential beneficial effects of antihypertensive agents in PD.
Objectives: Numerous studies have consistently shown an association between blunted sleep-time relative BP decline (non-dipping) and increased cardiovascular (CVD) risk. It remains a point of discussion, however, whether the non-dipper BP pattern or just elevated BP is an independent predictor of future CVD events. Accordingly, we investigated the role of dipping status and ambulatory BP (ABPM) level as contributing factors for CVD morbidity and mortality.

Methods: This study involved 11255 subjects, 6028 men/5227 women, 58.9+/-14.5 years of age, with baseline ambulatory BP ranging from normotension to hypertension, prospectively evaluated throughout a 4.0-year mean follow-up. BP was measured for 48h. The CVD outcome was defined as the composite of CVD death, myocardial infarction, coronary revascularization, heart failure, and stroke. Subjects were divided into four categories on the basis of dipping status and ambulatory BP: (i) dipper vs. non-dipper, and (ii) normal ambulatory BP if the awake systolic (SBP)/diastolic BP (DBP) means were <135/85 mmHg and the asleep SBP/DBP means were <120/70 mmHg, and elevated ambulatory BP otherwise.

Results: Cox survival analyses, adjusted for the significant influential characteristics of age, sex, diabetes, chronic kidney disease, cigarette smoking, waist perimeter, and previous CVD event, documented non-dipper subjects had significantly higher CVD risk than dippers, whether they had normal (P<0.001) or elevated ambulatory BP (P<0.001). Non-dippers with normal BP had similar hazard ratio of CVD events (1.77 [95%CI: 1.36-2.31]) than dippers with elevated ambulatory BP (1.47 [1.13-1.89]; P=0.108 between groups).

Conclusions: The elevated CVD risk in “normotensive” individuals with a non-dipper BP profile represents a clear paradox, as those persons do not have “normal BP” or low CVD risk. Our findings also indicate the need to redefine the concepts of normotension/hypertension, so far established on the unique basis of BP level, mainly if not exclusively measured at the clinic, independently of circadian BP patterning.
Background: The absence or blunting of the normal ambulatory recorded nighttime pressure dip in hypertensives is well recognized as a significant risk for subsequent cardiovascular events. White coat hypertension studies also demonstrate blunted dipping imparting on the entity the concept of “intermediate risk factor” for hypertension. However extensive recording for ambulatory blood pressure studies over the years has established that white coat hypertension is not a definable disease entity but an episodic occurrence. It maybe super imposed on normal pressure individuals and increasingly in older age on essential hypertensives. We review our ambulatory blood pressure data to further define this concept.

Method: Participants: N=157 patients (> 18 years) on hypertensive medications. Procedure: Ambulatory blood pressure data were reviewed. Patients fell into one of three cohorts; 1) with uncontrolled essential hypertension (EH), 2) white coat episodic hypertension (WCH), and 3) controlled hypertension (CH).

Analytic strategy: Groups were compared across sociodemographic and medical characteristics using ANOVA with post hoc comparisons or Chi square analyses as appropriate.

Results: There were no significant group differences across relevant sociodemographic variables (e.g., age). As expected, there were significant differences across groups in regard to a wide range of blood pressure variables (e.g., average 24 hour pressures, rate of rise of systolic blood pressure in the early morning, all ps < .05). WCH and CH groups were not significantly different across diastolic blood pressures in the day, night and early morning. Notable, there was no significant difference in the incidence of blunted nighttime dipping across the three groups. There were no significant differences between the percentage of nighttime dippers and blunted dippers across the three groups.

Conclusion: In medicated patients nighttime dipping and blunted dipping is not a valid indicator for future cardiovascular events.
ARRHYTHMIAS: DIAGNOSIS AND TREATMENT

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EFFECT OF CPAP THERAPY ON CARDIAC REPOLARIZATION IN PATIENT POPULATION WITH OBSTRUCTIVE SLEEP APNEA
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2. Mercy Catholic Medical Center; an affiliate of Drexel University, Darby, PA, USA

Background: Delayed cardiac re-polarization leading to prolongation of the corrected QT (QTc) interval is a well-characterized precursor of arrhythmia. Obstructive Sleep Apnea (OSA) causes increase in QTc and can be a precursor of cardiac arrhythmia. We investigated the effect of Continuous Positive Airway Pressure (CPAP) therapy on QTc in the patient population of OSA.

Methods: The patients who underwent sleep study during the time period of September-December 2012 were selected. Demographic, detailed medical, electrocardiographic (EKG), Apnea-Hypopnea index (AHI), and CPAP’s smart card data was obtained from pulmonary outpatient clinic records. Patients with missing or unavailable EKG’s were excluded. Eighty-four selected patients were divided into Treatment (31 patients; age 61±11; positive sleep study with compliance to CPAP >70% on smart card), No Treatment (43 patient; age 55±10; positive sleep study but noncompliant to CPAP <70% on smart card) and Control (10 patient; 51±10; negative sleep study) groups respectively. QTc data prior and after two months of Treatment or No treatment was evaluated.

Results: There was no correlation found between AHI and QTc among the study groups. CPAP therapy decreased QTc by 14±2 milliseconds in OSA patients in treatment group (448±27; 436±18) compared to No Treatment group (446±31; 448±27) which is statistically significant (p-value <0.01, CI >95%). In control group, change in QTc is statistically insignificant (432±27; 433±17; p-value 0.08).

Conclusions: QTc decreased in patients with OSA who were compliant to CPAP treatment compared to the ones without treatment. QTc time did not change significantly in patients without the diagnosis of OSA.
ARRHYTHMIAS: DIAGNOSIS AND TREATMENT

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OPTIMAL DURATION OF HOLTER RECORDINGS: IS THERE ADDITIONAL YIELD FROM 48 VERSUS 24 HOURS?
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The duration of Holter recordings is either 24 or 48 hours based on physician preference. Little research exists regarding the ideal recording duration.

Purpose: Using 48-hour recordings, we investigated whether the yield of the first 24-hours (Day#1) was different from the second 24-hours (Day#2).

Methods: We analyzed data from 60 randomly selected patients who had 48-hour Holters performed from 2012-2013. Variables included heart rate, ectopy, arrhythmias, and QTc. Statistical differences were calculated using paired two-sample t-tests.

Results: Mean age=53 (range=18–88) yrs; Males=28/60 (47%). Indications for Holter recordings included: palpitations (n=42), presyncope (4), monitoring for atrial arrhythmia (3), AV block (2), AF rate control (3), ventricular arrhythmia detection (3), sick sinus syndrome (2), and prolonged QT (1). Statistical analysis revealed no significant difference (all P>0.05) between data from Day 1 and Day 2 for all variables except for minimum QTc (441 versus 446, p=0.04) and AF duration (22.5 min versus 23.4 min, p=0.01) (Table).

Conclusion: There were no statistically significant or clinically meaningful differences in Holter data between the first and second day. The increased recording duration had no added clinical yield but incurred doubled costs, since all 48-hour Holters were billed as two 24-hour Holters.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Day 1</th>
<th>Day 2</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean HR (beats/min)</td>
<td>76.93</td>
<td>77.56</td>
<td>0.47</td>
</tr>
<tr>
<td>Min HR (beats/min)</td>
<td>49.92</td>
<td>50.42</td>
<td>0.21</td>
</tr>
<tr>
<td>Max HR (beats/min)</td>
<td>127.23</td>
<td>129.55</td>
<td>0.12</td>
</tr>
<tr>
<td>Number of PACs</td>
<td>457.10</td>
<td>369.88</td>
<td>0.38</td>
</tr>
<tr>
<td>Number of SVT Runs</td>
<td>2.23</td>
<td>1.86</td>
<td>0.49</td>
</tr>
<tr>
<td>Longest SVT Run (beats)</td>
<td>5.41</td>
<td>6.73</td>
<td>0.48</td>
</tr>
<tr>
<td>AF duration (minutes)</td>
<td>22.50</td>
<td>23.40</td>
<td>0.01</td>
</tr>
<tr>
<td>AF beats</td>
<td>99696.60</td>
<td>103793.20</td>
<td>0.30</td>
</tr>
<tr>
<td>Number of PVCs</td>
<td>242.30</td>
<td>216.15</td>
<td>0.24</td>
</tr>
<tr>
<td>Number of Couplets</td>
<td>18.43</td>
<td>22.28</td>
<td>0.16</td>
</tr>
<tr>
<td>Number of Triplets</td>
<td>1.63</td>
<td>2.37</td>
<td>0.31</td>
</tr>
<tr>
<td>Number of VT Runs</td>
<td>5.75</td>
<td>6.50</td>
<td>0.32</td>
</tr>
<tr>
<td>Longest VT Run (beats)</td>
<td>2.50</td>
<td>5.50</td>
<td>0.32</td>
</tr>
<tr>
<td>Avg QTc (ms)</td>
<td>444.18</td>
<td>447.53</td>
<td>0.11</td>
</tr>
<tr>
<td>Min QTc (ms)</td>
<td>348.65</td>
<td>366.07</td>
<td>0.01</td>
</tr>
<tr>
<td>Max QTc (ms)</td>
<td>609.43</td>
<td>604.97</td>
<td>0.66</td>
</tr>
</tbody>
</table>
ARRHYTHMIAS: DIAGNOSIS AND TREATMENT

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ACCURACY OF TACHYARRHYTHMIA DIAGNOSIS ON SURFACE ELECTROCARDIOGRAMS (ECG)
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2. MetroWest Medical Center, Framingham, MA, USA

Objectives: To study how precisely physicians can identify the underlying rhythm of tachyarrhythmia from surface ECGs.

Background: Tachyarrhythmia is a common clinical problem. Surface ECGs are the first diagnostic tool that will direct initial management.

Method: Seventy surface ECGs during tachyarrhythmia were obtained. The definite diagnosis were determined by electrophysiology (EP) study. Participants from a tertiary-care teaching hospital were asked to interpret the same set of ECGs, blinded to the actual diagnosis. The accuracy of tachyarrhythmia interpretation was evaluated. Comparisons were carried out using chi-square with Bonferroni correction if necessary.

Results: There was trend toward higher accuracy in higher levels of training. However, this was only significant when comparing medical students with fellows or attendings (p<0.001). EP attendings also have higher accuracy than residents (p=0.001). This difference is mainly due to misdiagnosis in: sinus tachycardia, atrial flutter, atrial fibrillation, atrioventricular nodal reentrant tachycardia (AVNRT) and ventricular tachycardia (VT). Overall, atrial tachycardia, atrioventricular reciprocating tachycardia (AVRT), and junctional tachycardia were most commonly misdiagnosed (79%, 68%, 85% respectively).

Conclusions: Although there are algorithms to help identify mechanism of tachyarrhythmia on surface ECGs, the accuracy of diagnosis is still imperfect. Even high-risk arrhythmia, such as VT, are commonly incorrectly diagnosed.

Table 1 Accurate diagnosis of each tachyarrhythmia, sorted by levels of training.

<table>
<thead>
<tr>
<th></th>
<th>Medical Student (n=5)</th>
<th>Medical Resident (n=4)</th>
<th>Cardiology Fellow (n=3)</th>
<th>EP Fellow (n=3)</th>
<th>Cardiology attending (n=2)</th>
<th>EP attending (n=3)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sinus tachycardia</td>
<td>19(54%)</td>
<td>22(79%)</td>
<td>18(86%)</td>
<td>18(86%)</td>
<td>12(86%)</td>
<td>20(95%)</td>
<td>0.005</td>
</tr>
<tr>
<td>Atrial tachycardia</td>
<td>5(20%)</td>
<td>2(10%)</td>
<td>3(20%)</td>
<td>2(13%)</td>
<td>3(30%)</td>
<td>6(40%)</td>
<td>0.330</td>
</tr>
<tr>
<td>MAT</td>
<td>3(60%)</td>
<td>2(50%)</td>
<td>3(100%)</td>
<td>2(67%)</td>
<td>2(100%)</td>
<td>1(33%)</td>
<td>0.484</td>
</tr>
<tr>
<td>Atrial flutter</td>
<td>21(28%)</td>
<td>18(30%)</td>
<td>25(56%)</td>
<td>25(56%)</td>
<td>20(67%)</td>
<td>25(56%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>20(50%)</td>
<td>22(69%)</td>
<td>20(83%)</td>
<td>17(71%)</td>
<td>10(63%)</td>
<td>21(88%)</td>
<td>0.022</td>
</tr>
<tr>
<td>AVNRT</td>
<td>24(34%)</td>
<td>32(57%)</td>
<td>22(52%)</td>
<td>29(69%)</td>
<td>20(71%)</td>
<td>34(81%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>AVRT</td>
<td>13(26%)</td>
<td>13(35%)</td>
<td>7(23%)</td>
<td>13(43%)</td>
<td>7(35%)</td>
<td>11(37%)</td>
<td>0.532</td>
</tr>
<tr>
<td>Junctional tachycardia</td>
<td>1(20%)</td>
<td>1(25%)</td>
<td>1(33%)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0.759</td>
</tr>
<tr>
<td>Ventricular tachycardia</td>
<td>38(84%)</td>
<td>28(78%)</td>
<td>18(67%)</td>
<td>20(74%)</td>
<td>11(61%)</td>
<td>26(96%)</td>
<td>0.039</td>
</tr>
<tr>
<td>Total</td>
<td>144(41%)</td>
<td>141(50%)</td>
<td>117(56%)</td>
<td>126(60%)</td>
<td>85(61%)</td>
<td>144(69%)</td>
<td>&lt;0.001</td>
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INFLAMMATORY MARKERS IN PATIENTS WITH IMPAIRED LEFT VENTRICULAR FUNCTION WITH AND WITHOUT ISCHEMIC HEART DISEASE UNDERGOING CARDIOVERTER DEFIBRILLATOR IMPLANTATION FOR LIFE THREATENING VENTRICULAR ARRHYTHMIAS
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Introduction-Aim: Patients with impaired left ventricular (LV) function are at an increased risk for sudden cardiac death due to serious ventricular arrhythmias. Main causes of impaired LV function are ischemic heart disease (IHD) (ischemic cardiomyopathy) and dilated cardiomyopathy. One therapeutic option for ventricular arrhythmias is the implantation of cardioverter defibrillators (ICD). There are still scarce data regarding the role of certain risk factors, such as inflammation markers, on the incidence of such arrhythmias. The aim of our study was to investigate the role of inflammation in patients with life threatening ventricular arrhythmias and reduced LV function due to either ischemic or dilated cardiomyopathy.

Patients and Methods: Our study included 28 male patients (mean age=64±9.3 yrs) undergoing ICD implantation for life threatening ventricular arrhythmias; 12 patients had impaired LV function without IHD, 10 patients had impaired LV with IHD and 6 patients had preserved LV function and no IHD (control group). Samples were drawn from the subclavian vein and analyzed for IL-1beta, IL-6, IFN-gamma, TNF-alpha and hsCRP.

Results: In 78% of the patients IL-1beta, IL-6, IFN-gamma, TNF-alpha and hsCRP levels were within normal values. No significant differences among the levels of all markers in all three groups were observed with the exception of IL-1â, which was significantly higher in patients with impaired LV and no IHD compared with the control group.

Conclusions:
- Our results do not support a relationship between inflammation and life threatening ventricular arrhythmias in the studied patient groups
- However, higher IL-1â levels were found in patients with impaired LV and no IHD, compared with controls, a finding that may suggest enhanced inflammatory activity in those patients.
ARRHYTHMIAS: DIAGNOSIS AND TREATMENT

DEADLY GOLYTELY

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Objectives/Background: Ventricular tachycardia (VT) and ventricular fibrillation (VF) are the underlying rhythm in most cases of sudden cardiac death in the United States. Determination of the underlying etiology is important to optimize management. We describe a case involving VT due to a reversible cause: hypokalemia.

Description: An 83-year-old man with ischemic cardiomyopathy and VT, status post implantable cardioverter defibrillator (ICD) placement was admitted to an outside hospital for evaluation of lower gastrointestinal bleeding. An oral bowel prep of polyethylene glycol plus electrolyte solution (GoLytely), was administered. He then had cardiac arrest due to pulseless monomorphic VT and was successfully resuscitated with ACLS protocol which included chest compressions, defibrillation and amiodarone. The provider team reported his ICD did not fire despite VT. Labs demonstrated hypokalemia (2.9 mEq/L) so he was given potassium supplementation. Upon transfer to our institution, interrogation of his ICD revealed it was set to treat VT at rate more than 140 bpm so it was changed to 130 bpm. He was treated with mexiletine, his home metoprolol, amiodarone, and potassium supplementation without further episodes of VT.

Results/Discussion: Reversible causes of VT, such as electrolyte imbalances (i.e. hypokalemia, hypomagnesemia) should be corrected immediately. VT is diagnosed by demonstration of specific findings on a rhythm strip or ECG which include wide complex tachycardia, ventriculoatrial dissociation, and fusion and capture beats. Management of VT depends on several different factors including hemodynamic stability and VT morphology. While hemodynamically stable VT may be managed initially with antiarrhythmic medications, unstable VT should be treated with immediate cardioversion/defibrillation. Long term treatment for clinically stable patients with VT includes various antiarrhythmics, ICD placement or ablation.

Conclusion: Determination of the underlying cause of VT is vital in optimal management. While rarely reported, hypokalemia secondary to polyethylene glycol bowel prep may cause or exacerbate VT.
NEW INSIGHTS INTO PATHOGENESIS AND MANAGEMENT OF HEART FAILURE

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CARDIOPROTECTIVE EFFECT OF METFORMINE IN DIABETIC PATIENTS TREATED WITH ANTHRACYCLINES

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Objective: The aim of this study is to assess the effect of metformin against heart failure development in Hispanic and Black female patients with breast cancer treated with doxorubicin.

Background: Doxorubicin (DOX) is well known for causing cardiotoxicity. Recent studies established that metformin (MET), an oral anti-diabetic drug, has antioxidant activity. Rat models of DOX-induced cardiotoxicity, co-treatment with MET, significantly decreased DOX-induced biochemical, histopathological, and ultrastructural changes.

Method: We reviewed medical charts of Hispanic and Black female patients from the chemotherapy infusion center between 2006 and 2012. We included active oncologic patients with type 2 diabetes mellitus, and normal left ventricular ejection fraction assessed by nuclear cardiac scan, who received doxorubicin-based treatment for breast cancer. We defined new onset heart failure (HF) as left ventricular ejection fraction <45% that was assessed at the end of the treatment. We compared new onset HF in patients with and without metformin. Metformin treatment was the independent variable; new onset HF was the outcome. Statistical analyses were performed by Pearson’s chi-square test.

Results: 199 charts of female diabetic patients who were treated with doxorubicin due to breast cancer were analyzed; mean age [SD] 55.5 [9.7] years; 52% Hispanic, 48% Black. After treatment, HF developed in 25/199 (12.6%). The metformin group included 129 subjects, 70 of which were controls. New onset HF was found in 14/70 (20%) of controls and 11/129 (8.5%) within the metformin group, OR 0.37 (95% CI 0.16 – 0.87) p=0.019.

Conclusion: These findings suggest that MET might prevent DOX-induced cardiotoxicity in this specific population.
NEW INSIGHTS INTO PATHOGENESIS AND MANAGEMENT OF HEART FAILURE

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IMPROVING CLINICAL OUTCOMES AND RECOVERY OF PERIPARTUM CARDIOMYOPATHY PATIENTS USING BROMOCRIPTINE: A SYSTEMATIC REVIEW

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Background: Peripartum cardiomyopathy is a rare and distinct entity of dilated cardiomyopathy that occurs in women between one month antepartum and five months postpartum. Though uncommon, it has serious consequences for the mother and child. In the Philippines, there are very few studies regarding this disease, mostly reporting its prevalence and outcomes in specific hospital settings. The risk factors and cause explaining its pathogenesis have not been defined. Recently, increased proteolytic cathepsin D activity in cardiomyocytes, resulting in production of 16-kDa prolactin fragments with anti-angiogenic and apoptotic properties have been implicated to contribute to PPCM. With this concept, bromocriptine, an ergoline derivative and dopamine agonist, with its prolactin-blocking properties, is the new and causal option for treating PPCM.

Objective: To illustrate over-all effectiveness of bromocriptine in improving clinical outcomes and recovery in PPCM.

Methods: A systematic search was done on Google Scholar, PUBMED, The Cochrane Central Register of Controlled Trials, EBSCO, U.S. National Library of Medicine, CINAHL and ClinicalTrials.gov, from inception to December 2013 to identify RCTs, reports, reviews, and commentaries on bromocriptine in PPCM. Studies regarding its side-effects were also taken into account and reviewed. The main outcomes identified and described included recovery, length of hospital stay, status on follow-up; and echocardiographic LV parameters.

Results: Nine case reports, one proof-of-concept pilot study, and on-going RCT (Phase 2) were identified, the rest are observational studies, reviews, and commentaries. According to studies, bromocriptine, administered with standard management for decompensated heart failure, led to improved clinical outcomes and shortened hospital stays. However, side-effects such as myocardial infarction, central retinal vein occlusion, CVA, marked hypertension, and post-partum psychosis should not be undermined.

Conclusion: Though very promising, caution should be observed in use of bromocriptine among PPCM patients. More comprehensive trials will also be needed to further prove its efficacy and safety for use.
NEW INSIGHTS INTO PATHOGENESIS AND MANAGEMENT OF HEART FAILURE

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CARVEDILOL AS SINGLE AGENT TREATMENT FOR TRASTUZUMAB CARDIOTOXICITY USING GLOBAL LONGITUDINAL PEAK STRAIN CHANGES
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Objectives: Use of trastuzumab (TCH) in HER2-positive breast cancer has been shown to improve disease-free survival when used alone or with anthracyclines. However, in patients receiving these drugs, a relative reduction in left ventricular ejection fraction (LVEF) has been reported. Carvedilol therapy is a possible way to halt LVEF decline. Decreases in global longitudinal peak strain (GLPS), by echocardiography, precede decline in LVEF by 3 months or more in patients receiving TCH for HER2-positive breast cancer. This study shows Carvedilol therapy is an effective treatment for HER2-positive breast cancer patients with GLPS is an accurate measurement for dosing.

Background: A 52 year old woman with HER2-positive breast cancer was treated with trastuzumab (TCH). After 3 months of therapy, GLPS worsened. She started carvedilol for cardioprotection and TCH therapy continued. Follow-up echocardiograms showed improvement in LVEF and GLPS.

Methods: In patients receiving TCH, baseline and 3 month echos were performed to assess LVEF. If LVEF dropped below 50%, TCH therapy was typically stopped until LVEF improved, or therapy was discontinued. To prevent this interruption, GLPS was used to predict patients at risk for cardiotoxicity and intervene with Carvedilol therapy. Carvedilol therapy was initiated for a change in GLPS by 2 percent or more and below -18%. Serial echocardiograms were used to demonstrate improvement in LVEF and GLPS during continued TCH therapy.

Results: The baseline echocardiogram showed 2D LVEF 56%, 4D LVEF 55%, GLPS -20.4%. Following TCH for 3 months, repeat echocardiogram demonstrated 2D LVEF 54%, 4D LVEF 49%, GLPS -17%. Carvedilol was titrated to maximal dose of 12.5 mg BID. Four weeks post carvedilol, echo showed improvement with 2D LVEF 61%, 4D LVEF 54%, GLPS -19.9%.

Conclusions: Showing 2.9% improvement in GLPS, this case suggests the use of carvedilol in conjunction with TCH therapy can restore normal left ventricular compliance.
QUALITY AND PHYSICIAN PREFERENCE OF PORTABLE ELECTROCARDIOGRAPHIC DEVICE RHYTHM STRIPS

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Ambulatory electrocardiographic (ECG) monitoring devices are widely used in the evaluation of patients (pts) with palpitations. With the emergence of portable ECG (pECG) devices, pts have increasing options for self-monitoring. We evaluated overall pECG data quality and physician preference of commercially available pECG monitoring devices. Four different pECG devices were selected, chosen based on ease of accessibility for pt purchase, differences in cost, and differences in device operability. Twenty hospitalized pts on cardiac telemetry consented to the study and were asked to record their heart rhythm for 30 seconds using the pECG devices (Device 1 - Shenzhen Creative Industry, Easy ECG Monitor PC-80A, $149; Device 2 - Beijing Choice Electronic Technology Handheld ECG Monitor MD100B, $160; Device 3 - AliveCor, Heart Monitor, $199; and Device 4 - Omron, Portable ECG Monitor HCG-801, $290). Device 4 required being held to the chest wall, while other devices were handheld. Rhythm strips were assessed by 5 physician readers for quality by analysis of baseline sway and artifact by number scale (0 for none, 1 for minimal, 2 for moderate and 3 for maximal sway and artifact). pECG strips were also compared to hospital telemetry strips for physician preference and interpretability. Based on analysis, the device with least baseline sway was device 4 (mean 0.76 ±0.73) and most baseline sway was device 1 (mean 1.08 ± 0.71). The device with the most artifact was device 1 (mean 1.98 ± 0.39) and the least was device 4 (mean 1.07 ±0.65). For pECG rhythm strips compared to telemetry by readers, the pECG was preferred 5/20 (25%) as compared to telemetry for device 1. For device 2, the pECG was preferred 2/20 (10%), for device 3, pECG was preferred 6/20 (30%) and for device 4, pECG was preferred 9/20 (45%).
ADVERSE LEFT VENTRICULAR REMODELING, INCIDENT HEART FAILURE, AND VENTRICULAR ARRHYTHMIAS

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Objective: To examine the association of adverse left ventricular (LV) remodeling with the eventual development of 1) heart failure and 2) ventricular arrhythmias.

Methods: The patterns of structural remodeling used herein were based on those originally described by Linzbach (AJC. 1960; 5:370) and later expanded by Gaasch and Zile (JACC. 2011; 58:1733). LV chamber enlargement is described as eccentric geometry with or without LV hypertrophy (LVH); normal chamber size is described as concentric geometry with or without LVH; relative wall thickness (RWT) was also examined

Results: Baseline echocardiographic data from 3181 participants (age>65) in the Cardiovascular Health Study were examined and outcome data were obtained 13 years later. In eccentric geometry with increased LV mass (eccentric LVH, n=191) incident heart failure (IHF) was more common (37 vs 29%, p=0.02) than in eccentric geometry without LVH (n= 286). In concentric geometry and LVH (concentric LVH, n=223), IHF was more common (32 vs 16%, p=0.001) than in those without LVH (n=2481). In concentric geometry without LVH, IHF was more common in those with RWT>0.42 (concentric remodeling) than in those with RWT<0.42 (21vs15%, p=0.01). When LV enlargement and/or LVH was present, RWT did not affect IHF rate. In a separate study of 129 patients with a low LV ejection fraction (EF<0.45) and an implantable cardiac defibrillator, the occurrence of ventricular tachycardia/fibrillation (VT/VF, device interrogation) was 43% in patients with eccentric LVH, 30% in concentric LVH/remodeling, and 12% in normal geometry (p<0.02). Duration of follow up was 3.5-4 years. The EF was similar in these three groups (29,30,31% respectively, p=ns) with distinctly different patterns of structural remodeling

Conclusion: Different patterns of LV remodeling defined by measurement of LV chamber size and wall mass are associated with significant differences in IHF and VT/VF. Adverse structural remodeling appears to have more prognostic value than functional abnormalities.
AGING AND HEART FAILURE: UPDATE 2014

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The aging population with heart failure (HF) is increasing worldwide. Morbidity and mortality from hypertension (HTN) and myocardial infarction (MI), the leading causes of HF and health care costs are increasing in the elderly (age ≥ 65 years). Aging is progressive and results in cardiovascular changes that impact disease expression and response to therapy. Aging is associated with increased risk for HTN, MI and HF. Aging-related changes contribute to adverse cardiac remodeling and an accelerated march to HF. The remodeling involves changes in cardiovascular structure, cellular and subcellular, physiological/pathophysiological pathways, and responses to stress/injury. While optimal healing is critical for survival with favorable outcome, defective post-MI healing with aging contributes to adverse remodeling leading to poor outcomes. While better post-MI therapies have improved survival, therapy for optimizing post-MI healing is lacking. While early reperfusion therapy may reduce MI size and accelerate healing, delayed reperfusion of large infarcts may result in reperfusion damage, impaired healing and adverse remodeling in the elderly. Progressive left ventricular remodeling and progression to HF are persistent problems in older patients. Aging-related changes have important therapeutic implications. Therapy for the young may not be optimal for the old. Several recommended post-MI therapies can impact early and late phases of healing in positive or negative directions. Preclinical studies suggest that pathways during early and late phases can be targeted for optimizing post-infarct healing and the march to HF. Better post-MI therapies have improved survival but therapy for optimizing healing is lacking. Progressive remodeling and progression to HF with preserved ejection fraction (HFPEF) or reduced EF (HFREF) are persistent problems in older patients and have important therapeutic implications. Studies suggest that in the elderly, pathways can be targeted for optimizing post-MI healing in HFREF, and therapy of HFPEF post-HTN.
CARDIAC STRUCTURE AND FUNCTION IN FAILING AND NON-FAILING HEARTS

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HFPEF (HEART FAILURE WITH PRESERVED EJECTION FRACTION)
PATHOPHYSIOLOGY: IMPLICATIONS FOR THERAPEUTIC TARGETS
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In contrast to well-developed algorithms for the evaluation and treatment of patients with heart failure in the setting of reduced ejection fraction (HFREF), the diagnosis and management of patients with preserved EF heart failure (HFPEF) remains challenging. Pathophysiologically, impaired diastolic reserve characterizes heart failure with preserved ejection fraction (HFPEF) and in many cases detailed phenotypic characterization is only possible with detailed hemodynamic evaluation. In particular, examination of the pulmonary artery and left ventricular filling pressure response to exercise during invasive hemodynamic assessment provides key diagnostic information. From a mechanistic standpoint, although the presence of excess extracellular matrix has been presumed to be the fundamental mechanism underpinning HFPEF physiology, recent data suggest a potential contribution by other mechanisms affecting active and passive components of diastolic function including inflammatory, microvascular and energetic pathways. In addition, the failure of antagonists of the angiotensin and aldosterone systems in clinical trials underscores the need to investigate other potential targets. In addition to pharmacologic approaches for HFPEF, device based approaches for the modification of intra-cardiac pressures have also been developed providing an alternative therapeutic approach for HFPEF patients.
Left ventricular (LV) hypertrophy and fibrosis are important determinants of morbidity and mortality in hypertrophic cardiomyopathy (HCM). Regression of hypertrophy remote from the interventricular septum is observed after septal reduction therapy with myectomy or alcohol ablation. A number of drug classes have been put forward as potential modifiers of the natural history of HCM. Animal and human studies have suggested that angiotensin II receptor blockers (ARBs) attenuate progression of hypertrophy and fibrosis in HCM. In a mouse model of HCM, the ARB losartan reversed cardiac interstitial fibrosis. In double-blind fashion, we randomly assigned patients (3 women; age 51±13 years) with HCM to receive placebo (n=9) or losartan 50 mg twice a day (n=11) for 1 year. Patients with LV outflow tract gradient > 30 mmHg at rest or with Valsalva maneuver were excluded. CMR was performed at baseline and at 1 year to measure LV mass and extent of fibrosis as assessed by late gadolinium enhancement (LGE). There was a trend towards a significant difference in the percent change in LV mass (median [interquartile range], +5 [-4, +21] % on placebo vs. -5 [-11, -0.9] % on losartan; p=0.06). There was a significant difference in the percent change in extent of LGE (mean ± standard deviation, +31±26 % on placebo vs. -23±45 % on losartan; p=0.03). Our study demonstrated attenuation of progression of myocardial fibrosis by losartan in patients with nonobstructive HCM. A similarly designed study by another group showed no demonstrable effect of spironolactone. Verification of our results in a larger trial is required to confirm a place for ARBs in the management of HCM. We are currently participating in a multicenter trial of the ARB valsartan in genotype positive patients with overt or latent HCM.
Heart failure with preserved ejection fraction (HFpEF) refers to a broad clinical syndrome categorized by signs and symptoms of heart failure and with normal or near normal ejection fraction. HFpEF is associated with high morbidity and enormous economic burden to society. Despite considerable progress in treatment of heart failure with reduced ejection fraction (HFrEF), treatment of patients with HFpEF remains symptom based, and to date no therapy has been proven effective in this disorder. Several clinical outcomes trials in HFpEF have been unsuccessful in proving the benefit of a therapy, including trials that have tested several inhibitors of the renin-angiotensin-aldosterone system. A number of factors have influenced the likelihood of success of these studies, including limited understanding of the pathophysiologic basis of the disorder, difficulty with diagnosis, use of endpoints that don’t reflect the burden of disease, and various issues of trial execution. Diastolic dysfunction has been thought to be the primary pathophysiologic abnormality in HFpEF. However, diastolic dysfunction is highly prevalent in the elderly population without heart failure. Moreover, abnormalities of systolic function appear to be prevalent in patients with HFpEF and also appear to be prognostically important. Patients enrolled in trials need to have objective evidence of heart failure and biomarkers such as BNP or evidence of structural heart disease appear to identify patients at highest risk of events, the enrollment of whom is essential to a successful outcomes trial. Traditional time to first event analyses may be insensitive in a syndrome like HFpEF where multiple hospitalizations are commonplace. Recurrent event analyses may provide more power in a HFpEF trial. Finally, problems with trial execution, including drop-ins, drop-outs, can reduce the likelihood of a clinical trials success. HFpEF remains a heterogeneous syndrome, and better phenotyping of HFpEF patients may allow us to more effectively target specific therapies to specific etiologies.
Constrictive pericarditis and restrictive cardiomyopathy are 2 forms of diastolic heart failure that might have similar clinical presentations. The differentiation of these 2 disorders is crucial because constrictive pericarditis can potentially be cured by pericardiectomy, whereas restrictive cardiomyopathy is usually treated symptomatically. Spectral Doppler echocardiography is a useful tool for diagnosing constrictive pericarditis and differentiating it from restrictive cardiomyopathy. Although both conditions can show any of the different phases of restriction on conventional Doppler measurement of the mitral inflow, respiratory changes of mitral inflow are quite different in these 2 conditions. Because the myocardium is isolated from the intrathoracic respiratory pressure changes in constrictive pericarditis, there are significant flow changes over the mitral and tricuspid valves during inspiration and expiration. During inspiration, the pulmonary capillary pressure drops, whereas the intracardiac pressure is not affected; therefore, the inflow to the left ventricle over the mitral valve is reduced in constrictive pericarditis. On the other hand, the flow over the tricuspid valve increases during inspiration. All these can be visualized by Doppler echocardiography over the mitral and tricuspid valve with simultaneous graphic recording of the phases of respiration. The interventricular septum will also show a leftward shift during early diastole under inspiration, due to ventricular interdependence resulting from encasement of the heart in the rigid pericardium shell. These techniques have been found to be reasonably sensitive and specific for the diagnosis of constrictive cardiomyopathy. Tissue Doppler and color M-mode echocardiography are also highly sensitive and specific in the differential diagnosis of these two entities. In restrictive cardiomyopathy, mitral E’velocity is reduced, whereas it is normal or elevated in constrictive pericarditis. Also color M-mode echocardiography has a high diagnostic accuracy for the diagnosis of constrictive cardiomyopathy and differentiating it from restrictive cardiomyopathy.
HFpEF (HF preserved Ejection Fraction, also known as diastolic HF) accounts for up to 50% of all HF presentations, but there remains no evidence-based clinical therapies. Importantly, the incidence of HFpEF continues to increase and a greater percentage of HF patients being hospitalized have HFpEF. The latest disappointing HFpEF clinical trial was TOPCAT and it follows in the trails of several other negative HFpEF trials. HFpEF patients are usually older women with a history of hypertension. However, obesity, coronary artery disease (CAD), diabetes mellitus, atrial fibrillation, and hyperlipidemia are also highly prevalent in HFpEF. However, hypertension remains the most important cause of HFpEF, with a prevalence of 60-89% from HF trials, studies and registries. Despite these facts, we propose a different approach should be undertaken and that is to understand pathogenic mechanism of HFpEF—in order to design new therapies for higher prevalent disease.

Human endomyocardial biopsy samples from HFpEF patients demonstrate greater myofibrillar density and collagen volume fraction than HF reduced EF (HFrEF). Similarly, an experimental mouse model of HFpEF from our lab had marked myocardial fibrosis and elevated myocardial matrix metalloproteinase (MMP) protein expression. Therapeutic use of both hydralazine and nitrates in this HFpEF model did not decrease MMP expression, fibrosis or left ventricular hypertrophy (LVH); but improved diastolic dysfunction parameters and exercise tolerance. This was likely due to interactions of vasculature and ventricular stiffness. HFpEF was induced in mice deficient in adiponectin—an adipocyte-derived cytokine that may modulate obesity-linked complications such as insulin resistance, CAD and hypertension. Here lack of adiponectin in HFpEF exacerbated LVH, diastolic dysfunction and HF. This was accompanied by increased myocardial MMP-2, TNF-a and interferon expression. Our study suggested that in HFpEF, aldosterone and RAAS negatively regulated adiponectin produced by adipose tissue, thereby providing evidence of inter-tissue communication between adipose tissue and the heart.
Dynamic left ventricular outflow tract obstruction (LVOTO) is well recognized and many consider this a component of hypertrophic cardiomyopathy (HCM). In clinical practice, we encounter LVOTO in various settings without HCM. LVOTO can manifest as chest discomfort, dyspnea, palpitation or syncope. ECG ST depression, T wave inversions and hypotension simulate acute coronary syndrome. Symptoms and the characteristic late peaking ejection systolic murmur may be transient and requires tailored echocardiography and Doppler interrogation to correlate hemodynamic significance. Typically, older women with smaller hearts and pre-existing left ventricular hypertrophy from long-standing hypertension manifest LVOTO with blood loss, dehydration or other causes for intravascular volume depletion. Except for modest concentric left ventricular hypertrophy, prior echocardiograms would be typically unrevealing and ‘normal’. Intensive care protocols that involve initiation of inotropic infusions for reduced mixed venous saturation place the crucial role in precipitating or aggravating this situation. House staff and nursing may not recognize that inotrope infusion is contributing to further decline in hemodynamics. Takotsubo stress cardiomyopathy and large anterior wall myocardial infarctions both result in basal segment compensatory hypercontractility and left ventricular outflow crowding. Dobutamine stress testing is another well recognized setting for development of transient dynamic LV outflow obstruction in the absence of significant structural heart disease. Case series have documented aggravation of LVOTO with intra-aortic balloon pump again due to reduced afterload. Over the last few years, we have encountered several ‘isolated LVOTO’ patients in the absence of any of the above recognized precipitating factors. Given the fact that the diagnostic Doppler echocardiographic finding of elevated late peaking outflow gradient could be transient, timely echocardiography becomes crucial in the evaluation of these patients. Intravenous volume replacement, rate reduction with beta-blockers and avoiding cardiac stimulant medications are key to LVOTO management.
LEFT VENTRICULAR FUNCTION IN PATIENTS WITH CHRONIC TOTAL OCCLUSION OF LAD: LONG-TERM FOLLOW UP

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Background: There is no agreement regarding the revascularization of patients with chronic total occlusions (CTO) of left descending artery (LAD) and signs of ischemia. One of the treatment goals is improvement of left ventricle (LV) function.

Methods: 32 patients with CTO of LAD were included. All patients had positive result of exercise stress echocardiography (SE) with the ischemia in LAD zone. 12 patients underwent CABG - LIMA to LAD, 9 patients had PCI of LAD and 11 patients did not get any revascularization. Mean follow-up period was 6 years. Diastolic diameter, diastolic volume, systolic volume and ejection fraction (EF) of LV were estimated. Exercise SE was performed and wall motion score index (WMSI) was evaluated before and after the stress.

Results: End-diastolic diameter, end-diastolic volume reduction and end-systolic volume reduction were observed among the patients with medical treatment (p<0.05). No significant changes of LV structure parameters were found in groups of patients after CABG or PCI. EV and WMSI did not change significantly in any group. ∆WMSI parameter significantly decreased in all three groups (p<0.05), especially in the PCI group (p<0.01).

Conclusion: In spite of absence of revascularization patients with isolated CTO of LAD demonstrate improvement of LV parameters and reduction of ischemia level.
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RIGHT VENTRICULAR FAILURE AFTER IMPLANTATION OF LEFT VENTRICULAR ASSIST DEVICES

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Despite (1) improved outcomes and lower rates of right ventricular failure (RVF) with continuous-flow left ventricular assist devices (LVADs) and (2) development of clinical prediction scores to facilitate preoperative identification of patients at risk for RVF after LVAD implantation, RVF still occurs in 13%-40% of continuous-flow device recipients. RVF can lead to systemic hypoperfusion, multi-organ failure, higher perioperative mortality, and reduced survival to transplantation, but also to prolonged or recurrent hospitalization and poor quality of life even in less extreme cases. However, clinical prediction models and echocardiographic parameters used in isolation have failed to consistently identify patients at increased risk for RVF. Beyond the inherent challenges in the assessment of RV function with cardiac imaging, risk stratification for RVF in LVAD candidates is also confounded by intra-operative events, concomitant surgical procedures, and post-operative changes in hemodynamics and device settings. Additional challenges include evolving mechanical circulatory support technology and shifts in target population. However, the full potential of contemporary imaging, especially echocardiography, has not been fully utilized in the preoperative assessment of LVAD candidates. In particular, a number of reports from different centers have now pointed to the potential value of RV mechanics for RVF risk stratification. Nevertheless, preoperative RV function is still assessed subjectively in many patients. Standardization of echocardiographic protocols before and after device implantation across LVAD centers, multi-center pilot studies with RV mechanics, and more objective definitions of RVF, potentially incorporating RV systolic function parameters, could help overcome the challenges associated with RVF risk assessment. Quantitative RV systolic function parameters can be used to track RV function over time postoperatively and potentially track the effect of afterload-reducing agents. Finally, because the entire field is moving fast, it would be important for research and clinical practice to converge by leveraging current data collection tools and regularly updating predictive models.
Molecular targeting is becoming increasingly recognized as a necessary means for drug development and the successful treatment of an individual’s disease onset and progression. Although multiple pathways can be responsible for cardiac or vascular disorders in patients, kinase pathways in the vascular system that involve phosphoinositide 3-kinase (PI 3-K), protein kinase B (Akt), and the mammalian target of rapamycin (mTOR) offer especially exciting prospects for developing strategies for disease in the cardiovascular system. PI 3-K, Akt, and mTOR pathways including the protein complexes mTORC1 and mTORC2 not only determine cellular survival during acute and chronic disorders, but also maintain a complex relationship over the control of cellular regenerative pathways that involve apoptosis and autophagy that can lead to a variety of clinical outcomes. These molecular pathways partner with novel signal transduction mechanisms, such as wingless and growth factors, to modulate endothelial and cardiomyocyte development and growth as well as the interaction of vascular cells with inflammatory processes. Our work identifies the kinase signaling pathways of PI 3-K, Akt, and mTOR with their molecular cellular partners as new prospects for the treatment of vascular disease. Further investigation and knowledge of these pathways can offer precision targeting for the development of novel strategies for patients suffering from disorders of the cardiovascular system.
NOVEL APPROACHES FOR VASCULAR THERAPIES

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SERPINS AS THERAPY – FROM VIRUS TO MAN
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Serpins have critical regulatory roles in coagulation, inflammatory, and apoptotic pathways. These ubiquitous regulators are present in organisms from viruses to horseshoe crabs to mammals, representing a large percentage of circulating proteins in the blood. The impact of serpins on normal physiological function and homeostasis is evident in patients with genetic mutations that case severe disorders such as deficiency in alpha1 antitrypsin and neuroserpin or acquired illness as for lethal sepsis with disseminated intravascular coagulation (DIC) where there is extensive serpin dysregulation. Modification of serpin activity is used for treating some clinical disorders, i.e. heparin is used to decrease clotting through activation of anti-thrombin (AT or SERPINC1) and alpha anti-trypsin replacement (SERPINA1 deficiency) which is given to patients with genetic deficiency and emphysema. Prior studies have also reported the use of N terminal serpin peptides for treatment in sepsis and HIV. Our research group has been examining virus-derived serpins as potential therapeutics. Prior work beginning with our original studies with the Myxomaviral serpin, Serp-1, have demonstrated significant reductions in vascular disease with Serp-1 treatment in models of arterial balloon angioplasty to aortic, renal and cardiac transplants. Serp-1 treatment improved mortality in lethal Mouse gamma herpes virus (MHV68) in interferon gamma receptor (IFNγR) knock out mice and mouse adapted Zaire Ebola infection where we detected marked reductions in pulmonary hemorrhage and congestion Serp-1 has also been tested in a phase 2A clinical trial after coronary stent implant for patients with unstable coronary syndromes and small heart attacks (NSTEMI or Non ST Elevation Myocardial Infarctions) with a demonstrated significant reduction in markers for myocardial damage. Related work using mammalian serpins as therapeutics such as neuroserpin (NSP or SERPINI1) have also demonstrated anti-inflammatory activity and even reduced tumor growth in animal models. In recent work we have assessed the capacity of Viral and mammalian serpin reactive center loop (RCL) peptides to expand serpin functions and to reduce inflammatory responses detecting reductions in plaque growth in an aortic transplant model. In conclusion, viral serpins have evolved over many millions of years to form highly efficient regulators of host central inflammatory pathways, identifying new therapeutic horizons and potential function as anti-inflammatory protein drugs.
Vascular endothelium damage occurs in acute situations such as following percutaneous coronary intervention or spontaneously plaque rupture. Tissue damages can also result from chronic conditions linked to cardiovascular risk factors such as diabetes, dyslipidemia and hypertension, which induce a sustained pro-inflammatory status and impair vascular endothelial cell functions. These alterations impact the antithrombotic properties, vascular tone control and permeability of the endothelium that releases pro-inflammatory mediators which coordinate tissue and cellular responses part of the vascular healing process. Platelet-neutrophil interactions and endothelial cells can modulate vascular healing. We have shown that vascular stents may lead to long term thrombo-inflammation and endothelial dysfunction. Furthermore, by inhibiting p-selectin and platelet-neutrophil interactions and by enhancing reendothelialisation, we demonstrated an improvement in vascular healing with a reduction in peri-procedural complications. The activation profile of endothelial cells can profoundly impact on the recruitment, firm adhesion and integration of leukocytes and bone marrow-derived progenitor cells including circulating endothelial progenitor cells. In previous studies we also showed that the 17beta-estradiol has beneficial effects on vascular cells by reducing pro-inflammatory molecule expression by endothelial cells and by modulating smooth muscle cells proliferation and migration. Drug-eluting stents reduce restenosis, however, long term vascular effects and late thrombo-inflammatory reactions could mitigate the initial clinical benefits. Resorbable vascular scaffolds offer a promising new approach to revascularisation combining drug elution to reduce restenosis and resorption with restoration of endothelial function. Conclusion: Platelet-neutrophil interactions and endothelial dysfunction can impact on vascular healing. While drug-eluting stents reduce restenosis, bioresorbable vascular scaffolds may offer a promising platform for revascularisation.
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CARDIOVASCULAR RISK FACTORS AND ENDOTHELIAL DYSFUNCTION

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Many cardiovascular risk factors, such as hyperlipidemia, diabetes, hypertension, and smoking, as well as obesity and metabolic syndrome, are associated with impaired endothelium dependent vasorelaxation, mainly due to the impairment of the endothelial nitric oxide synthase (eNOS) system. This impairment may involve reduced activity and expression of eNOS, decreased sensitivity to nitric oxide (NO) or increased degradation of NO by reaction with superoxide. However, the detailed molecular regulation pathways for these risk factors impairing the vascular system are multifactorial and not fully understood. Recently, we have studied the functional roles and molecular mechanisms of several emerging risk factors such as HIV infection, antiretroviral therapy, adipokines and CD40L in endothelial dysfunction. These mechanistic studies of these cardiovascular risk factors are clinically significant because they may lead towards new and effective strategies for the prevention and treatment of cardiovascular disease.
Enhanced external counterpulsation (EECP) is an outpatient therapy for the treatment of stable ischemic heart disease, angina and heart failure. Although a non-invasive therapy, EECP treatment produces a marked acute hemodynamic effect similar to that produced by the invasive intra-aortic balloon pump. The safety and efficacy of EECP therapy for angina and heart failure treatment have been well documented. Recently, investigators have studied the mechanisms of action of EECP therapy, including improvement in endothelial function caused by increased systemic blood flow velocity and beneficial vascular shear effects. Our group and others have demonstrated a reproducible global endothelial function improvement that is associated with an observed dose-dependent increase in the release of endothelial nitric oxide synthase (eNOs) and the vasodilator nitric oxide (NO), as well as reduction of the vasoconstrictor endothelin (ET-1). Others have shown that EECP therapy is associated with an increase in vascular endothelial growth factor levels and, together with the mechanical pressure gradient generated during EECP, may promote coronary collateral flow, improve coronary flow dynamics and increase microcirculatory density. We have also documented an association between EECP-derived improvements in endothelial function and decreased circulating levels of inflammatory cytokines and activated endothelial progenitor stem cells. In this way, EECP has been proposed as a modality to promote vascular homeostasis through replacement and repair of the endothelium, thereby enhancing endothelial function and modifying the atherosclerotic process and progression of cardiovascular disease.
The aim of this lecture is to discuss research involving the ligand of the aryl hydrocarbon receptor (AhR) and their role in cardio-renal syndrome. AhR is a ligand-activated nuclear receptor/transcription factor belonging to the basic helix-loop-helix/per-AhR nuclear translocator-Sim family of proteins. While activation of the AhR with ligands is well known to regulate drug metabolisms, cancer growth and development of organs in fetal life, more recently an interesting pathophysiological role of AhR has been reported indicating that AhR also controls vascular function. Accelerated senescence and inflammation with enhanced oxidative stress in cardiovascular system are observed in chronic kidney disease (CKD) patients and such correlation between CKD and cardiovascular disease (CVD) is recognized as cardio-renal syndrome. Indoxyl sulfate (IS), one of the protein-bound uremic toxins, is metabolized in the liver by using tryptophan-derived indole produced by tryptophanase in intestinal bacteria and normally excreted into urine, however, reduced renal clearance elevates serum level of IS, which in turn, enhances oxidative stress in CKD patients. Recently, we reported that IS functions as a ligand of AhR in endothelial cells, leading to enhanced ROS production via NADPH oxidase. Furthermore, we revealed that IS-induced activation of AhR causes vascular inflammation as well as premature senescence in endothelial cells, indicating IS influences endothelial function via AhR signaling pathway. These findings have opened new avenues of research on the possibility of targeting the AhR to treat cardio-renal syndrome. In the lecture, I will show our recent data indicating the importance of AhR signaling pathway in cardio-renal syndrome.
SYNERGISTIC REDUCTION OF ATHEROSCLEROSIS BY THE COMBINED LXR LIGAND AND ERK1/2 INHIBITOR---A MULTIPLE MECHANISMS DEPENDENT PATHWAY

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Objective: This study investigated if the combined LXR ligand and ERK1/2 inhibitor can synergistically reduce atherosclerosis without hypertriglyceridemia.

Background: Formation of macrophage/foam cells, endothelial injury and hypertriglyceridemia contribute to atherosclerosis. Macrophage ABCA1 and RCT inhibit atherosclerosis. LXR stimulates ABCA1 expression but induces hypertriglyceridemia. ERK1/2 inhibitors synergize LXR-induced ABCA1 expression.

Methods: U0126 and T0901317 were used as a combination therapy to treat apoE deficient mice followed by determination of atherosclerosis, hypertriglyceridemia, and the involved mechanisms.

Results: U0126 synergized T0901317-reduced atherosclerosis but totally blocked T0901317-induced hypertriglyceridemia. The combination therapy synergistically activated ABCA1 expression and RCT, and inhibited foam cell formation and macrophage accumulation in aortic root. It also induced miR-126 expression in endothelial and smooth muscle cells thereby decreasing RGS16 and VCAM-1 expression while increasing CXCL12 and CXCR4 expression in aortic root. U0126 or combined with T0901317 inhibited expression of genes for TG biosynthesis while stimulated expression of genes for TG hydrolysis and fatty acid oxidation thereby blocking hypertriglyceridemia.

Conclusions: By increasing macrophage cholesterol metabolism and endothelial repair while blocking hypertriglyceridemia, the combined ERK1/2 inhibitor and LXR ligand can function as a novel therapy to synergistically reduce atherosclerosis.
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RESCUE OF PHYSIOLOGIC VASCULAR REPAIR BY CASPASE-INHIBITION: A NOVEL APPROACH TO BETTER TREAT ADVANCED ATHEROSCLEROSIS

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Background: Apoptosis underlies the failure of important vascular defense mechanisms and is a hallmark of advanced atherosclerosis. In particular, cells undergoing apoptosis contribute to atherosclerosis progression via enhanced inflammation and impaired progenitor cell-mediated arterial repair. To test whether effective arterial repair can be restored by inhibiting apoptosis we studied the effect of caspase-inhibition (CI) in a mouse model of atherosclerosis.

Methods and Results: Apo-E-/- mice (n=42) were fed Western Diet for 6 months and, thereafter, were randomized into receiving caspase-inhibitor Q-VD-OPH at a daily dose of 10 mg/kg (n=10) or 30 mg/kg (n=10), or control peptide (n=12) for 21 days. Plasma cholesterol levels remained unchanged in all groups. Abdominal aortic plaque burden and aortic root atherosclerotic plaque area were both significantly and dose dependently reduced by CI (P<0.01). CI resulted in a strong reduction of macrophage content and a significant increase in both alpha-actin and c-kit positive cells in atherosclerotic lesions (P<0.01). Plaque cell apoptosis was nearly abrogated by CI (P<0.01). In addition, the systemic injection of GFP+ c-kit progenitor cells ex vivo treated with CI into ApoE-/- mice with established atherosclerosis yielded viable intimal GFP+ cells expressing alpha-actin and Tenascin at 48 hours whereas no intact GFP+ c-kit cells were found after ex vivo treatment with control peptide.

Conclusions: Effective suppression of apoptosis by CI transformed advanced lesions into a more stable phenotype without lowering serum lipid levels. This points to apoptosis as major rate limiting step in atherosclerotic plaque repair and as prime target for future therapeutic strategies.
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TRANSLATION OF GENOMIC DISCOVERIES FOR CAD: FUNCTIONAL STUDIES
OF ADAMTS7 AS AN EXAMPLE

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GWAS have identified almost 50 loci for coronary artery disease (CAD) e.g., we identified ADAMTS7 as locus for CAD and ABO as a locus for MI in patients with CAD. Intense work is underway to define the functional basis of CAD association for novel loci in order to advance mechanistic knowledge and therapeutic opportunity. As an example, data on the ADAMTS7 locus is presented. The ADAMTS7-association with CAD has not been validated in experimental models and whether loss of ADAMTS7 function is atheroprotective or atherogenic is not clear. An Adamts7 (Ats7) knockout mouse, with knock-in of a beta-galactosidase reporter gene, was bred onto both the LDLR and APOE KO hyperlipidemic mouse models and atherosclerosis studies were performed on Ats7/LDLR and Ats7/APOE double KO (dKO) mice. Mice were fed western diet for 16 weeks (LDLR) or 10 weeks (APOE), and aortas and aortic roots were harvested. No differences in plasma lipids were observed between experimental groups in either study. Ats7/LDLR dKO males (N=7) and females (N=13) displayed significant reductions in lesion formation in aortas by en face (58%, p<0.005 and 61%, p<0.0001 respectively) and in aortic roots (31%, p=0.04 and 22%, p=0.002 respectively) compared to control LDLR-/- male (N=6) and female (N=10) littermates. Ats7/APOE dKO males (N=16) and females (N=13) displayed significantly reduced lesion formation by en face (62%, p<0.0001 and 54%, p<0.0001 respectively) compared to control APOE-/- males (N=9) and females (N=10). Femoral wire injury experiments suggested reduced neointimal formation in Ats7 KO mice at 28 days post-injury. Aortic rings from Ats7/LDLR dKO mice embedded in collagen have reduced cell migration compared to control LDLR aortic rings. These data represent the first in vivo experimental validation of Adamts7 as an atherogenic gene. These data support the concept that pharmacological inhibition of ADAMTS7 should be atheroprotective in humans.
SMOKING STATUS AND SURVIVAL AFTER IN-HOSPITAL CARDIAC ARREST –
THE SMOKER’S PARADOX REVISITED

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Background – Each year, approximately 200,000 in-hospital cardiac arrests (IHCA) occur in the United States with overall survival rates of 18 to 20%. The effect of smoking on outcomes after IHCA has not been investigated.

Objectives – To assess the association between smoking and survival after cardiopulmonary resuscitation for IHCA.

Methods – Nationwide Inpatient Sample databases from 2003-2011 were analyzed for all patients ≥ 18 years of age who underwent cardiopulmonary resuscitation (defined by International Classification of Diseases, 9th Revision Clinical Modification codes 99.60 to 99.63) for IHCA to study the baseline demographic and clinical characteristics of smokers (current and former) and non-smokers. Survival to hospital discharge was compared between smokers and non-smokers using multivariate logistic regression (adjusted for baseline demographics, hospital characteristics, co-morbidities, primary diagnosis of acute myocardial infarction and cardiac arrest rhythm).

Results - Of the 838,464 patients with cardiopulmonary resuscitation for IHCA, 116,569 (13.9%) were smokers. Smokers were more likely to be younger, Caucasian and males (P<0.001). They were also more likely to have dyslipidemia, coronary artery disease, prior myocardial infarction, prior transient ischemic attack or stroke, prior cardiac arrest, chronic pulmonary disease, hypertension, obesity and peripheral vascular disease (P<0.001 for all). Atrial fibrillation, congestive heart failure, diabetes with complications and chronic renal failure were less prevalent in smokers (P<0.001 for all). They were also more likely to have a primary diagnosis of acute myocardial infarction (24.3 versus 20.5 %, P<0.001) and ventricular tachycardia/fibrillation as the cardiac arrest rhythm (14.8 % versus 9.1%, P< 0.001). Smokers had an improved survival to hospital discharge after IHCA than non-smokers (28.2% versus 24.1%, unadjusted OR 1.24, 95% CI 1.22-1.26, adjusted OR 1.06, 95% CI 1.05-1.08, P<0.001).

Conclusions – Smoking was independently associated with higher survival after IHCA – consistent with a smoker’s paradox.
A NOVEL APPROACH FOR BIVENTRICULAR PACING: UTILIZING TEMPORARY CORONARY SINUS CATHETER GUIDANCE VIA FEMORAL VEIN APPROACH

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Background: Left ventricular (LV) lead placement can be difficult due to anatomical variations as well as valves at the Coronary Sinus (CS) ostium. Cannulating the CS temporarily via the femoral vein (FV) as a roadmap prior to placing the LV lead can be a good alternative. The objective of this study was to assess the differences in fluoroscopy times (FT) and total procedure times (TPT) utilizing this approach compared to the standard technique.

Methods: A retrospective cohort study of 135 patients was performed at the Zablocki VA Hospital who had initial LV lead placement per standard indications. Two equally experienced operators were identified: one exclusively used the FV approach and another used the standard approach plus the FV approach for the more difficult right sided implants, only. TPT and FT were compared between the two groups.

Results: There were a total of 60 in the FV group (including one patient who crossed over from non-FV group) and 75 in the non-FV group. FT for the FV group averaged 44.4 +/- 28.8 minutes (m) and for the non-FV group was 39.7 +/- 32.76 m (p=0.1945). TPT for the FV group averaged 3.66 +/- 1.1 hours (h) (including the average 28 m required to cannulate the CS, chest preparation and operator scrub out and in times). Total procedure time for the non-CS group was 2.88 +/- 1.7 h (p=<0.001). The median difference is 1.1 h longer in the FV group with 95% median CI of (0.6, 1.5) h. Excluding the first 20 patients (to account for operator learning curve) this difference was not statistically significant. There were no procedural complications including those utilizing the FV approach.

Conclusion: Temporary CS catheter guidance via FV approach remains a unique alternative in patients with difficult or unusual anatomy and has comparable FT and TPT as compared to standard technique.
ARRHYTHMIA I: SUDDEN CARDIAC DEATH / ADVANCES IN IMPLANTABLE RHYTHM DEVICE THERAPY

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BASELINE PROLONGED T-PEAK TO T-END/QT INTERVAL MAY PREDICT MORTALITY BUT NOT SUDDEN CARDIAC DEATH IN HEMODIALYSIS PATIENTS

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Sudden cardiac death (SCD) is the leading cause of death among hemodialysis patients (HD pts). Traditional risk factors (e.g. EF <40% or CAD) are poor predictors for SCD in this population. Renal disease induces left ventricular hypertrophy and fibrosis, predisposing pts to SCD. The interval between the peak and the end of the T wave (TpTe) is prolonged by HD. Whether a prolonged TpTe (pTpTe) is associated with an increase in SCD or mortality in HD pts is unknown. We hypothesized that a pTpTe (>85 ms) or a prolonged TpTe/QT (> 0.25)(pTpTe/QT) is associated with an increase in SCD and mortality. In this single-site study of 402 pts new to HD, 207 (51%) met inclusion criteria. The major reason for exclusion was not having an ECG obtained within 18 months of initiation of HD. pTpTe and pTpTe/QT were present in 95 (46%) and 53 (26%) of pts respectively. At 4 years, 152 pts died; 25 (16%) from SCD. Incidence of SCD in pts with pTpTe vs. control was 8.4% and 15.2% respectively. Incidence of SCD among pts with pTpTe/QT vs. control was 7.5 % and 13.6% respectively. A trend towards increased all-cause mortality was seen in pts with pTpTe/QT (p = 0.06). However, there was no significant difference in rates of SCD or all-cause mortality between pts with a pTpTe vs. control. In conclusion, there was a trend for increased all-cause mortality in pts with pTpTe/QT, albeit not reaching statistical significance in this analysis. Larger studies will be needed to further establish the relationship between pTpTe and pTpTe/QT with mortality in ESRD.
SAFETY AND COST EFFECTIVENESS OF SYNCOPE EVALUATION UNIT

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Background: Few studies have demonstrated safety and cost effectiveness of syncope evaluation units (SEU). None of these studies have been conducted in the United States. Hence, they are not currently widely implemented. We propose to assess the safety and estimate the cost savings in a hypothetical SEU using an algorithm based upon the current European Society of Cardiology (ESC) guidelines for risk stratification of patients presenting with syncope.

Methods: We studied 600 patients admitted with transient loss of consciousness (TLOC) to our hospital from January 2011-December 2011. Patients were then risk stratified using an algorithm designed in concurrence with the ESC guidelines. High-risk patients were deemed appropriate for admission. Intermediate-risk patients were observed in SEU for 24 hours and were admitted if they developed high-risk features. Low-risk patients were discharged home after observation of maximum 6 hours. We calculated the cost difference between actual admissions versus a hypothetical SEU.

Results: A total of 132 (22 percent) patients had nonsyncopal TLOC. Seventy-seven (12.8 percent) were low-risk, 345 (57.5 percent) were intermediate-risk, and 46 (7.7 percent) were high-risk. Twenty-five (4.1 percent) patients among the intermediate-risk developed high-risk features. Actual length of stay (LOS) for non high-risk patients was 1517 days, whereas LOS for the same patients in SEU was 340 days. Total cost was estimated to be 4,738,990 dollars. The total cost savings in SEU was 1,738,683 dollars.

Conclusions: SEU using guidelines-based algorithm helps in easy, safe and reliable risk stratification of patients with syncope and will save millions of dollars for the hospitals in current economic crisis.
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ARRHYTHMIC OUTCOMES IN ARRHYTHMOGENIC CARDIOMYOPATHY WITH IMPLANTABLE CARDIOVERTER DEFIBRILATOR

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Objectives: To compare arrhythmic events in Arrhythmogenic Right (ARVC) versus Left Ventricular Cardiomyopathy (ALVC) after implantable cardioverter defibrillator (ICD) implantation.

Background: Despite left ventricular involvement in ARVC has been reported as a marker of high risk of ventricular arrhythmias and sudden death, we lack evidence on the arrhythmic burden in ALVC.

Methods and Results: 38 consecutive patients with: 20 (53%) ARVC, (80% males; median age 45 years old [32-50]) and 18 (47%) ALVC (56% males; median age 47 [35-54] years old; 12 DCM, 4 LVNC, 2 mixed phenotype). All had an ICD implanted, 23 (61%) for secondary prevention (13 (65%) of ARVC and 10 (56%) ALVC group). Median follow up was 41 [19-76] months. ICD readings were carefully reviewed. All sustained ventricular tachycardia (SVT) and ventricular fibrillation (VF) were analysed. 10 (26%) patients (5 ARVC and 5 ALVC) had at least one episode of sustained ventricular tachycardia or fibrillation (SVT/VF). Annual rate of SVT/VF was similar in both groups 7.3% [95%CI: 2.4-17.0] in ARVC versus 7.8% [95%CI: 3.0-16.0] for ALVC, p=0.8). 2 ALVC patients received appropriate therapy for VF. Annual rate of SVT/VF was similar in primary versus secondary prevention groups 11.7% [95%CI: 4.3-25.48] versus 12.1% [95%CI: 6.6-20.4], p=ns). Survival free from SVT/VF was similar in both groups (p=0.6). There was not significant difference between primary and secondary prevention groups in ARVC or ALVC (log rank p=0.4 and p=0.4 for ARVC and ALVC respectively). In 7 (15%) patients (4 ARVC, 3 ALVC) were VT triggered by exercise.

Conclusion: A high incidence of arrhythmic events is observed in ARVC and ALVC after ICD implantation with annual rates of 7%. Left predominant disease was not associated to a higher arrhythmic burden compared to classical ARVC. There was no difference in ventricular arrhythmias in primary versus secondary prevention in our series.
CIRCULATING MICRORNAs CHANGES IN CRT RESPONDERS

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MicroRNAs (miRNAs) play an important role in the pathogenesis of structural alterations of the failing heart through regulating negatively the expression levels of genes that govern the process of adaptive and maladaptive cardiac remodelling. We studied whether LV reverse remodelling after CRT was associated with changes of circulating miRNAs in patients with heart failure (HF) and dyssynchrony. A prospective, non-randomized self-control trial was performed in 81 patients with HF eligible for CRT. At baseline, to select the HF miRNA profile, we evaluated the expression of 84 miRNAs in three groups of patients: healthy subjects (healthy group, n = 15); patients with HF (HF group, n = 81); and patients without HF matched for age, sex, and concomitant disease with HF patients control group, n = 60). At 12 months, the selected miRNA profile was evaluated in plasma from responder (n = 55) and non-responder HF patients (n = 26) to CRT. In the test cohort, the HF patients were characterized by lower expression of 48 miRNAs (all P < 0.04) as compared with healthy subjects. In the validation cohort, the HF patients were characterized by lower expression of 24miRNAs (all P < 0.03) as compared with control patients. At 12 months, 55 patients (68%) were considered responders and 26 non-responders to CRT (32%). Responders showed an increase in expression of 19 miRNAs (all P < 0.03) compared with baseline expression, whereas in the non-responders we observed an increase of six miRNAs (all P < 0.05) compared with baseline expression. At follow-up, miRNAs were differentially expressed between responders and non-responders. The responders were characterized by higher expression of five miRNAs (miRNA-26b-5p, miRNA-145-5p, miRNA-92a-3p, miRNA-30e-5p, and miRNA-29a-3p; P < 0.01 for all) as compared with non-responders. In responders, reverse remodelling is associated with favourable changes in miRNAs that regulate cardiac fibrosis, apoptosis, and hypertrophy.
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THORACOSCOPIC PERICARDIAL PATCH INSULATION FOR INTRACTABLE PHRENIC NERVE STIMULATION FOLLOWING CARDIAC RESYNCHRONIZATION
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Cardiac Resynchronization Therapy (CRT) is an important modality in the treatment of Chronic Heart Failure, but can be complicated by phrenic nerve stimulation in one third of cases, with disabling symptoms in 1:20 patients. This occurs due to the proximity of the CRT electrodes in the coronary veins to the phrenic nerve outside the pericardium. Lead repositioning is sometimes not possible if the original placement was difficult. Electronic repositioning may be considered where programmable multipolar leads have been placed, but this can compromise the electrical vector and therefore efficacy of CRT. Epicardial lead placement is also possible, but requires open surgery and is associated with higher risks than transvenous placement.

We describe a technique of insulating the phrenic nerve using a video-assisted thoracoscopic surgical (VATS) approach in two patients including one who suffered from dextrocardia with situs inversus.

The patients are prepared for thoracoscopic surgery with a double-lumen endotracheal tube to allow deflation of the lung on the operated side. A short-acting muscle relaxant and subsequent facial nerve testing is required to ensure that the efficacy of the insulation can be tested intraoperatively. With the patient in the lateral position, the CRT should be activated to demonstrate the pre-insulation twitch. Using a standard three-port VATS technique, the pericardium posterior and parallel to the phrenic nerve can be opened and the a four-layer thickness of a non-absorbable material such as bovine pericardium used to insulate the nerve. Migration is prevented using a sealant spray such as Tisseel. The pericardium is left open and a single pleural drain sited prior to lung re-expansion.

Where patients are denied the benefits of CRT due to the disabling side-effects of phrenic nerve stimulation, thoracoscopic patch insulation may provide a low-risk option to improve symptoms until the widespread availability of programmable multipolar leads obviates this need.
MAGNETIC RESONANCE IMAGING CONDITIONAL PACEMAKER: TREND SETTING TECHNOLOGY – A SINGLE CENTER EXPERIENCE

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Introduction. Magnetic Resonance Imaging (MRI) provides essential diagnostic information in a variety of organ system diseases. The increasing number of cardiac implantable devices (pacemakers and defibrillators) has precluded MRI imaging in many patients. Advances in device technology, however, have led to the development of highly sophisticated MRI conditional (safe) devices and intracardiac leads. We describe our initial experience with two of such devices (Revo-Surescan and Advisa, Medtronic Inc.).

Methods. We retrospectively analyzed data of 92 patients (52% men; mean age 65±10 years; 28% diabetics; 68% hypertensives; 13% chronic kidney disease; 13% documented history of prior transient ischemic attacks and/or cerebrovascular accident) that underwent implantation of MRI conditional pacemakers during years 2011-2013. All demographic and clinical information were extracted from electronic hospital and outpatient medical records.

Results. The indications for device implantation included sinus nodal disease (SND, 43%), advanced atrioventricular nodal disease (AVND, 52%) or both SND and AVND (5%). The choice of MRI conditional device was made on the basis of the current and/or projected need for future MRI evaluation of syncope (29%), seizure disorder (3%), benign cystic neural lesions (1%), neurodegenerative diseases (2%) and malignant neural tumors (4%). The overall percentage of complications (both lead related and non-lead related) was 14%. These included 4 lead dislodgements (4%) and 1 pericarditis (1%). There were no lead perforations, lead failures or pericardial effusions. During the follow-up period, 12 (13%) underwent uneventful MRI imaging (Figure 1).

Conclusions. Our experience indicates that MRI conditional devices can be implanted safely and allow continued needed advanced imaging in patients with chronic neurologic diseases. The advantage of implanting MR conditional pacers especially in patients with pertinent neurological history was once again exemplified in our observational study with 12/92 (13%) of the included patients getting MR studies for multitude of indications.
Objective: We analyzed the safety of subcutaneous implantable cardioverter defibrillator (S-ICD) (Cameron Health/Boston Scientific) implantation after transvenous device extraction. 

Background: S-ICD is an appealing option for patients after transvenous defibrillator removal due to any cause, especially infection. These patients are at a higher risk for repeat infections and venous occlusion. We report our single-center experience of S-ICD implantation in patients with prior device extraction.

Methods: We evaluated the patients implanted with a S-ICD after previous transvenous device extraction at our center between October 2012 and February 2014. Patient information was collected from inpatient and outpatient records.

Results: Of the 43 pts implanted with S-ICD at our center, 8 patients had a previous device extraction. Seven were male and seven had ischemic cardiomyopathy. The average age was 60 ±17 years. Seven patients had a pocket or blood stream infection; and one had lead malfunction. Median duration between extraction and implantation of S-ICD was 75 days. Two devices were implanted during the same hospitalization; one of those was done on the same day. Successful defibrillation threshold (DFT) testing was performed in six pts. DFT testing was not performed due to inconsistent anticoagulation in setting of chronic atrial fibrillation in one patient and hypotension during the implantation in the other. There were no procedural complications. There were no infectious complications or inappropriate shocks during a mean follow up of 3 months.

Conclusions: Patients undergoing device extraction are at an increased risk for endovascular complications and repeat infections with reimplantation of a transvenous device. S-ICD is a safe and viable option for these patients. It can be safely implanted early after the extraction without any increased risk of complications.
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LOW-ENERGY DIETS: AN IMPORTANT CAUSE FOR ACQUIRED LONG QT SYNDROME AND UNEXPECTED SUDDEN DEATH
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Objective: To determine whether starvation diets influence cardiac repolarization, as indicated by electrocardiographic QT interval.

Background: Starvation diets might lead to QT interval prolongation, torsade de pointes and sudden death. Examination of weekly ECG of 29 patients on very-low caloric intake for weight loss demonstrated prolongation of the QTc interval in 20 patients during the seventh week at the end of the fast. The importance of these findings is illustrated by one patient reported in the Texas Heart Institute Journal (2003), with QTc lengthening after fasting who sustained cardiac arrest due to torsade de pointes, successfully resuscitated.

Methods: The electrocardiograms were assessed in 29 healthy obese (BMI>27 kg/m²) subjects on very-low caloric diets (800 kcal/d) for 7-weeks. Corrected QT intervals were measured along with serum albumin and electrolytes at the beginning, once weekly and the end of diet therapy. The QT interval was measured from the onset of the QRS complex to the end of the T wave in all leads, where the end of the T wave could be clearly defined. QT intervals were corrected for heart rate using the Bazett formula. The patients with atrial fibrillation, bundle branch block and pacemakers were excluded from the study.

Results: The QTc interval before the start of diet was 0.42*+/−0.025s by manual measurement and 0.41*+/−0.022s by automated measurement. 20 of the patients showed a QTc interval of greater than 0.43s, and 12 patients demonstrated moderate QT prolongation (>0.45s) at the end of the fast.

Conclusions: This study suggests that, a pre-diet ECG should be carefully assessed for QT interval prolongation before initiating of dieting, and QT prolongation drugs should be avoided in subjects on starvation diets. The fact that these patients are often young and otherwise healthy makes their ECG monitoring all the more critical.
NEW ORAL ANTICOAGULANTS IN PATIENTS WITH CANCER: CURRENT STATE OF EVIDENCE

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Objectives: In this meta-analysis, we evaluated the efficacy and safety of NOAC in patients with cancer.

Background: Effectiveness of new oral anticoagulants (NOAC) in patients with cancer is not clearly defined. There remain concerns of doubtful benefit and chances of potential harm with newer agents.

Methods: PubMed, Cochrane Library, EMBASE, Web of Science and CINAHL databases were searched from January 01, 2001 through February 28, 2013. Randomized controlled trials (RCTs) reporting efficacy and safety data of NOACs (rivaroxaban, dabigatran and apixaban) with control [low-molecular-weight heparin (LMWH)/vitamin K antagonists/placebo] for patients with cancer were included. Primary efficacy outcome was venous thromboembolism (VTE) or VTE-related death, and primary safety outcome was clinically relevant bleeding. We used random-effects models.

Results: Six trials randomized 19,832 patients, and 1,197 patients had cancer. Risk of VTE or VTE related death was not significantly different with NOAC vs control (odds ratio 0.80, 95% CI 0.39–1.65) in patients with cancer. Separate analysis for individual effects, showed similar results for rivaroxaban (OR 1.08, 95% CI 0.60–1.94) and dabigatran (OR 0.91, 95% CI 0.21–3.91). Clinically relevant bleeding was not higher with NOAC compared to control (OR 1.49, 95% CI 0.82–2.71); individual effect of rivaroxaban showed similar results. No statistically significant difference of efficacy and safety with NOAC was found between patients with and without cancer.

Conclusions: Rivaroxaban might be equally effective and safe as vitamin K antagonist in patients with cancer. Dabigatran is as effective as comparator; however, safety profile of dabigatran is unknown. Randomized trials of new anticoagulants specific to the cancer population are necessary, and NOAC also need to be evaluated against LMWH.

Figure: Efficacy of rivaroxaban, dabigatran in patients with cancer

| A. Efficacy of rivaroxaban in patients with cancer |
|---------------------------------|----------------|----------------|----------------|----------------|
| Study or Subgroup               | Rivaroxaban     | Control        | Odds Ratio     | Odds Ratio     |
|                                | Events          | Total           | Weight         | M-H, Random, 95% CI |
| ENSTEIN 2010                    | 218             | 593            | 19.1%          | 0.99 [0.16, 5.28] |
| ENSTEIN PE 2012                 | 218             | 593            | 20.9%          | 0.93 [0.18, 5.85] |
| MAGELLAN 2013                   | 207             | 202            | 15             | 73.4%          | 1.38 [0.88, 2.17] |
| Total (95% CI)                  | 434             | 491            | 90.0%          | 1.08 [0.90, 1.34] |
| Total events                    | 246             | 23             |
| Heterogeneity Test \( \chi^2 = 0.00 \), df = 1, \( P = 0.98 \)     |

| B. Efficacy of dabigatran in patients with cancer |
|-----------------------------------------------|----------------|----------------|----------------|
| Study or Subgroup                             | Dabigatran     | Control        | Odds Ratio     | Odds Ratio     |
|                                | Events          | Total           | Weight         | M-H, Random, 95% CI |
| RE-COVER 2010                                 | 57             | 53             | 53.9%          | 0.95 [0.98, 2.51] |
| RE-MEDY 2013                                  | 64             | 15             | 56.1%          | 2.63 [0.39, 22.87] |
| Total (95% CI)                                | 121             | 68            |
| Total events                                  | 4              | 7              |
| Heterogeneity Test \( \chi^2 = 0.00 \), df = 1, \( P = 0.94 \)   |

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THE IMPACT OF THE DISTANCE FROM THE INTERVENTIONAL CARDIOLOGIST’S HOME TO THE HOSPITAL DURING OFF HOURS. IS THERE A NEED FOR 24/7 IN HOSPITAL STEMI TEAM?

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Objectives and Background: The importance of door to balloon time (DTBT) is highlighted by its inclusion as a core quality measure by the center for Medicare and Medicaid services and Joint Commission on Accreditation of Healthcare organizations. The impact of the distance from the interventional cardiologist’s home to the hospital has not previously been evaluated. We investigated the effect of time of day on the DTBT in patients having primary percutaneous coronary intervention (pPCI). Furthermore, we evaluated the impact of distance of the on call interventional cardiologist from the hospital on the DTBT and major adverse cardiac events (MACE) in patients undergoing pPCI during the off hours.

Methods and Results: Patients enrolled in the study presented with ST elevation myocardial infarction (STEMI) either in the field or to the emergency department and underwent pPCI from October 2007 to July 2009. There were 10 interventional cardiologists performing pPCI during this time period of the study. Significant predictors of DTBT included a history of prior MI (p = 0.001), prior PCI (p=0.021), prior coronary artery bypass grafting (p<0.001), and history of diabetes (p=0.004). Congestive heart failure was marginally significant (p=0.07). The strongest predictor of DTBT was on versus off hours. Mean DTBT was 18.5 minutes (min) greater during off hours (72 minutes) compared to on-hours (53.5 minutes). The difference was 22 minutes after adjustment for the other significant factors in multiple regression analysis. Notably, distance from the cardiologist’s home to the hospital was not associated with DTBT on univariable (p= 0.24) or multivariable analysis (p=0.20) either individually or in interaction with the after-hours designation.

Conclusion: When pPCI is performed in a highly organized STEMI center with broad staff support and expertise in cardiac care, the distance of the interventionalist from the hospital during off hours was not associated with DTBT or MACE.
USING MAGNETIC STRUTS TO ALLEVIATE ADVERSE HAEMODYNAMIC FLOW EFFECTS AROUND DRUG-ELUTING STENTS

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Objective: To assess the feasibility of utilising magnetic stent struts in drug-eluting stents (DES) to alleviate the adverse effects of non-physiological shear stresses which may precipitate late-stent thrombosis (LST).

Background: Adverse haemodynamic flow effects may promote LST in arteries featuring DES by: 1) amplifying platelet-activating high wall shear stresses (WSS) along the top surfaces of the stent struts, and 2) increasing endothelial dysfunction due to regions of low WSS adjacent to the struts. By magnetising the stent struts, two major forces may be induced on the surrounding blood: 1) magnetisation forces which reorient red blood cells to align with the magnetic field, and 2) Lorentz forces which oppose the motion of the conducting fluid. This study investigates whether these forces can be used to locally alter blood flow in the vicinity of DES struts in a manner which alleviates the disturbances which precipitate LST.

Methods: Two-dimensional steady-state Computational Fluid Dynamics simulations were used to numerically model blood flow over a single DES strut with a square cross section. The magnetic flux density is varied at the strut to elucidate magnetic effects on the blood flow. Each model is compared in terms of the magnitude of WSS in the vicinity of the stent strut and the lengths of separated flow regions. Drug transport into the surrounding arterial tissue is also compared.

Results & Conclusions: Magnetising the stent struts is found to influence blood flow behaviour by: 1) reducing the magnitude of WSS along the top strut surface and 2) reducing the size of separated flow regions aft of the strut. These results convey that DES thrombogenicity can be reduced through the implementation of magnetic struts, and without significantly retarding drug transport into the arterial tissue. However, prohibitively strong magnetic fields may be required to achieve these results.
SAFETY AND EFFICACY OF DEGRADABLE VS. PERMANENT POLYMER DRUG-ELUTING STENTS. A META-ANALYSIS OF 18,395 PATIENTS FROM RANDOMIZED TRIALS

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Background—Degradable polymer drug-eluting stents (DP-DES) represents a promising strategy to improve the delayed healing and hypersensitive reaction in the vessel. However, the efficacy and safety of DP-DES vs. permanent polymer drug-eluting stents (PP-DES) are less well defined. The aim of this meta-analysis was to compare the total, short (<30 days), mid (30 days-1 year) and long (>1 year) term outcomes of DP-DES vs. PP-DES.

Methods—PubMed, Embase, and Cochrane Central Register of Controlled Trials (CENTRAL) were searched for randomized clinical trials to compare any of approved DP- and PP-DES. Efficacy endpoints were target-lesion revascularization (TLR) and in-stent late loss (ISLL). Safety endpoints were death, myocardial infarction (MI), definite and probable stent thrombosis (ST).

Results—The meta-analysis included 19 RCTs (n=18,395) with interest results. As compared with DES, there was a significantly reduced very late ST (OR [95% CI] = 0.42 [0.24-0.77], p=0.000) and ISLL (OR [95% CI] = -0.07 [-0.12-0.02], p=0.000) in DP-DES patients. However, there were no difference for other safety and efficiency outcomes between DP-DES and PP-DES, except that the stratified analysis showed a significant decreased TLR with DP-DES as compared to paclitaxel-eluting stent (OR [95% CI]=0.41[0.20-0.81], p=0.457).

Conclusions: DP-DES is more effective in reducing very late ST and ISLL, as well as comparable to PP-DES with regard to death, TLR and MI. Further large RCTs with long-term follow-up are warranted to better define the relative merits of DP-DES.
OUTCOMES OF PFTE COVERED STENTS IMPLANTED DURING PCI FOR MANAGEMENT OF ACUTE CORONARY PERFORATION

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Background: Coronary perforation is a rare complication of percutaneous coronary intervention (PCI). Perforation occurs in 0.1% to 3% of cases and results in cardiac tamponade in up to 60% of cases. Mortality rates are approximately 10%. The purpose of this study was to evaluate the outcomes of patients receiving PFTE covered stents for the management of acute coronary perforation.

Methods: Data was collected retrospectively on all patients receiving PCI from 1/1/2005–12/31/2011, who received PFTE covered stents to evaluate the incidence of major cardiac events. Major cardiac events were defined as: cardiac tamponade, death, emergent surgical drainage, myocardial infarction, or the need for emergent coronary artery bypass grafting.

Results: 6031 PCI’s were performed. Of those who underwent PCI, nine patients had coronary artery perforation (0.15%). Average hospital stay was 3.67 days. Five patients had left anterior descending artery perforations. Saphenous vein and left circumflex artery perforations were also seen. Three patients had PCI for non-ST elevation myocardial infarction/unstable angina, one for ST elevation myocardial infarction, and five underwent PCI for an abnormal stress test. All patients (100%) had resolution of previous perforation following PFTE placement without complications and mortality rates were zero percent at six and twelve months. Two patients had procedures independent of the perforation. One patient received PFTE placement after a known diagnosis of cardiac tamponade. Another patient had severe coronary disease and required coronary artery bypass grafting, which was independent of PFTE placement.

Conclusion: There was no evidence of major cardiac events following stent placement. Two complications were independent of the PFTE placement. In our cohort, PFTE placement for coronary artery perforation during PCI was beneficial acutely and up to 12 months following PFTE placement.
MID-TERM OUTCOMES OF HIGH RISK LEFT MAIN CORONARY ARTERY PERCUTANEOUS CORONARY INTERVENTION (PCI) IN AN ELDERLY POPULATION

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Objectives: To evaluate the outcomes of left main coronary artery (LMCA) percutaneous coronary intervention (PCI) in an elderly population.

Background: PCI has become an alternative to coronary artery bypass graft (CABG) surgery for high risk patients with LMCA stenosis. However, there is paucity of data evaluating LMCA PCI outcomes in patients >70 years of age.

Methods: High risk patients who underwent LMCA PCI between January 2009 and May 2013 were identified, and their clinical, procedural, and outcomes data were collected for analysis.

Results: The cohort consisted of 21 patients, 76% males, with a mean age of 75.3 ± 11.8 years. Comorbidities included hypertension (91%), diabetes mellitus (38%), chronic kidney disease (29%), prior CABG (14%), and prior PCI (28%). The most common indication for cardiac catheterization was unstable angina/NSTEMI (76%) and all had significant LMCA disease. 67% of the patients were deemed not candidates for CABG (mean STS mortality risk score of 7.8 ± 7.1), and 33% refused surgery (mean STS of 2.1 ± 1.6). In addition to the LMCA PCI, LAD and circumflex coronary artery PCI was performed in 52 and 48%, respectively. Unprotected LMCA PCI was performed in 86% and hemodynamic support was used in 14% of the cases. The median number of stents used was 2 (IQR 1-3), most of which were drug-eluting 76%. The median length of stay after PCI was 2 days (IQR 1-5). At 30 days post PCI, there was 1 bleeding requiring blood transfusion and 1 repeat revascularization (4.8% each), but there were no vascular complications, cerebrovascular accidents, myocardial infarctions, or deaths. The survival rate at a mean follow-up of 16 months was 91.5%.

Conclusions: Despite the significant comorbidities typically associated with the elderly, LMCA stenting is feasible and safe in this population, providing excellent short- and mid-term outcomes.
LONG-TERM OUTCOMES OF PERCUTANEOUS TREATMENT OF LEFT MAIN: DEDICATED STENT VERSUS USUAL TREATMENT WITH DES

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Background: Percutaneous treatment of left main (LM) often involves treating its bifurcation, which can be done by using one of the common techniques and ending with kissing or by using a dedicated stent (DS). The Bioss DS is a DES platform with two different diameters, proximal and distal to the bifurcation, to accommodate the different size of the vessels in this context.

Objectives: We present our series of LM treated with Bioss DS versus a control group treated with standard DES, evaluating the long-term clinical results.

Methods: Prospective observational study of patients with severe LM disease who were treated percutaneously with BiossDS or with standard DES between January 2012 and November 2013. MACE during follow-up were evaluated.

Results: We included 38 patients, 87% male, with severe LM disease treated percutaneously, of which 21 were treated by standard DES and 17 by BiossDS. The baseline characteristics of the patients showed: age 70.4 years in DES group vs 68.6 in BiossDS group (ns), diabetes 57% vs 64% (ns), current smoking 23% vs 12% (ns), hypertension 80% vs 58% (ns). The average size of the stents used was 3.17x18.38 mm vs 3x3.76x16.94 mm, respectively. During follow-up in the group treated with standard DES we found 3 cases of exitus, 1 case of MI and 2 cases of angina; and 71% of the patients were free of MACE during 11 months of median follow-up. In the group treated by BiossDS we found 1 case of MI associated with stent restenosis of the LM and 3 cases of angina, which we performed a coronary angiography, demonstrating a good result of the previous stent in LM; 77% of patients of this group were free of MACE during follow-up.

Conclusion: In our series we found a good outcome of patients with severe LM disease, with better clinical outcome and less MACE in the BiossDS group than the standard treatment with DES group.
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OUTCOMES OF PATIENTS TREATED WITH DRUG ELUTING STENTS WITH BIODEGRADABLE VERSUS BIOSTABLE POLYMER
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Background: Drug Eluting stents (DES) significantly reduce restenosis and target lesion revascularization. But it have introduced a new concept: late thrombosis (LST) because of the persistence of polymer in the arterial wall. It involves a prolonged dual antiplatelet therapy: problems of intolerance, bleeding, need to interrupt prior to interventions, higher cost. Preclinical trial 90 day results, using stents with biodegradable polymer (BDP), show complete stent endothelization.

Objectives: We assessed the hypothesis that DES with BDP release (Alex, Balton Ltd) could offer better results than DES with biostable polymer (BSP) (Promus, Boston Scientific, and Xience, Abbott) on a long-term follow-up.

Methods and Results: We studied 209 patients underwent a PCI with DES between may 2011 and october 2013. Average follow up was 20.6 months. The end points were: death, myocardial infarction, stroke, new target lesion revascularization and need of coronary artery bypass graft surgery. 97 patients were included in the BSP release arm and 112 patients in the BDP release arm. During the follow-up there was two LST in the BSP group and none in the other. Restenosis was found in 4 patients in the first group and in 7 patients in the second group (4.1% versus 6.3 %, respectively, NS). Progression of disease was observed in 5 patients of the first group and 2 in the other (5.2% versus 2.7 %, respectively, NS). Only one patient in BDP group underwent revascularization surgery. At the end, there were no incidents in 86 patients of the BSP release group and 102 patients BDP release group (88.7% versus 91.1%, respectively; NS).

Conclusions: Our clinical outcomes show that there weren’t LST in the BDP group during the follow up, with an equivalent profile of safety and efficacy that the BSP group. Stents with BDP might represent a solution to prevent late stent thrombosis.
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INTER-PROVIDER VARIATION IN DIAGNOSES AND CARDIAC CATHETERIZATION USE

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Objective: To understand variations in the diagnosis of acute coronary syndrome (ACS) and use of cardiac catheterization based on the attending provider.

Background: Significant variations in clinical care provided for most medical conditions are well described. Similar variations in use of various tests and interventions provided by cardiologists are also well described. We conducted this investigation to understand this variation in our local practice environment.

Methods: We gathered data from all patients with an elevated troponin level in a single Veterans Affairs (VA) medical center. One of several attending VA cardiologists prospectively evaluated each patient’s presentation and course of care. Statistical analysis included calculation of univariate odds ratios (OR) and multivariate logistic regression.

Results: We included data from 1017 patients evaluated between 2006 and 2007. 29.9% of patients with positive troponin were diagnosed with ACS and 22% of patients underwent catheterization. The rates of diagnosing ACS (p<0.001) differed between attending, ranging from 21.2% to 51.5%. Rate of catheterization (p<0.001) also differed, ranging from 15.0% to 69.7%. When comparing the patient cohorts for each attending, medical history elements and TIMI score > 2 were not different, however electrocardiogram (ECG) changes (p=0.028) and troponin value > 3 times normal (p=0.041) were. In multivariate regression, ECG changes (OR 5.46, p=0.022), TIMI score (OR 1.81, p<0.001), and level of troponin (OR 2.38, p<0.001) were independently associated with catheterization, as were two of the attendings (attending A, OR 30.93, p<0.001; attending D, OR 1.87, p=0.012).

Conclusion: The likelihood of a patient with a positive troponin being diagnosed with ACS and undergoing catheterization depends on their clinical presentation, however, significant variability can also be seen depending on the attending physician staffing the case.
The American College of Cardiology Foundation/American Heart Association 2011 expert consensus document on hypertension in the elderly recommended the blood pressure (BP) in patients with primary hypertension or in patients at high risk for cardiovascular events such as those with coronary heart disease, stroke, peripheral arterial disease, diabetes, chronic kidney disease, and heart failure be less than 140/90 mm Hg in adults with hypertension younger than 80 years and the systolic BP reduced to 140-145 mm Hg if tolerated in persons with hypertension aged 80 years and older. The European Society of Hypertension/European Society of Cardiology 2013 hypertension guidelines recommended that reducing BP to <130/80 mm Hg in patients at high risk for cardiovascular events was unsupported by prospective trial data and that the systolic BP should be reduced to <140 mm Hg in these patients with hypertension younger than 80 years and to between 140-150 mm Hg in patients aged 80 years and older. The Eighth Joint National Committee on hypertension 2014 guidelines recommended treating adults with primary hypertension or hypertension associated with diabetes or nondiabetic chronic kidney disease younger than 60 years to a BP goal of <140/90 mm Hg and in adults aged 60 years and older to a BP goal of <150/90 mm Hg. The ongoing Reasons for Geographic Differences in Stroke (REGARDS) study of 13,948 adults aged ≥55 years showed that the systolic BP should be reduced to <140 mm Hg for optimal reduction of cardiovascular events including in the 1,839 patients aged 75 years and older.
HYPERTENSION – RISK AND MANAGEMENT

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OPTIMAL BLOOD PRESSURE LEVELS IN THE ELDERLY? RESULTS OF REGARDS STUDY. SHOULD WE CORRECT THE GUIDELINES?
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The aim of the study was to identify the association of systolic blood pressure (SBP) levels with cardiovascular events, all-cause mortality, and falls among elderly persons taking antihypertensive medication. US adults ≥45 years of age taking antihypertensive medication enrolled in the Reasons for Geographic And Racial Differences in Stroke (REGARDS) study between January 1st, 2003 and October 31st, 2007 were categorized into 3 age groups: 55-64, 65-74 and ≥75 years old and baseline on-treatment SBP levels. Our primary analyses focused on incident cardiovascular disease (CVD) (n=9,787) and all-cause mortality (n=13,948). CVD was analyzed through December 31, 2009 (median follow-up 4.5 years) and all-cause mortality through March 31, 2012 (median follow-up 6 years). During follow-up, 530 (5.4%) participants had CVD events and 2095 (15%) participants died. After multivariable adjustment among participants ≥75, the incidence of CVD per 1,000 person-years (95% confidence interval) was 16.9 (11.1-25.7), 13.4 (9.2-19.7), 11.6 (7.6-17.7), 17.8 (11.2-27.5) and 36.7 (26.6-50.8) at SBP levels of <120, 120-129, 130-139, 140-149, and ≥150 mmHg, respectively. For the same SBP categories, the adjusted CVD incidence rates were 9.3 (7.2-12.0), 10.0 (8.1-12.3), 9.4 (7.5-11.8), 14.0 (11.0-17.8), and 16.4 (12.5-21.4), respectively, among participants 55-64 years, and 16.5 (13.6-21.5), 17.4 (14.8-20.6), 19.2 (16.4-22.5), 22.3 (18.6-26.9), and 27.6 (22.7-33.4), respectively, for participants 65-74 years. Among participants aged 55-64 and 65-74 years, a linear association was present between higher SBP categories and all-cause mortality risk (each p-trend<0.001). In contrast, for participants ≥75 years no association was present between SBP and all-cause mortality (p-trend=0.319). No association was present between on-treatment SBP and falls among participants <75 years of age but participants ≥75 with on-treatment SBP <120 mmHg had an increased risk of falls. Among adults aged ≥55 taking antihypertensive medication, SBP between 120-139 mmHg was significantly associated with a reduced risk for cardiovascular and all-cause mortality outcomes.
DUAL AT1 RECEPTOR/NEPRILYSIN INHIBITION (‘ARNI’) IN HYPERTENSION: AN IMPROVEMENT VERSUS AT1 RECEPTOR BLOCKADE?

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Neprilysin inhibitors (NEPi) prevent natriuretic peptide breakdown, thereby promoting vasodilation and natriuresis. On the other hand, they increase angiotensin and endothelin-1 (ET-1). The combined NEP/ACE inhibitor omapatrilat displayed potent effects in hypertension and heart failure, but these were accompanied by the occurrence of angioedema due to bradykinin accumulation. This should not occur when combining an ARB with a NEPi. This study evaluated the benefit of ARNI vs. ARB in renin-overexpressing hypertensive TGR(mREN2)27 rats. TGR(mREN2)27 rats were treated for three weeks with vehicle, the ARB irbesartan (IRB) or IRB + the NEPi thiorphan (0.1 and 1.0 mg per kg per day; TH0.1 and TH1.0). Hemodynamics were measured by telemetry. Vascular reactivity was determined in mesenteric arteries. Baseline MAP was 168±3 mmHg. All treatments lowered MAP by maximally 50 mmHg around day 4. After 7 days, MAP started to increase again in the IRB and IRB+TH1.0 groups, to 141±10 mmHg and 133±10 mmHg, respectively, on day 21. The MAP of rats treated with IRB+TH0.1 remained low at 104±5 mmHg on day 21. Heart-to-body weight ratio, cardiac ANP expression and myocyt size decreased only in the IRB+TH0.1 group. Urinary ET-1 increased by TH0.1 and TH1.0 versus IRB alone, indicating increased ET-1 production during ARNI treatment. Vasodilation to acetylcholine (endothelium-dependent) or the NO donor SNAP (endothelium-independent) were unaffected by all treatments. ET-1-induced constriction was diminished in the IRB+TH0.1 group, and studies with the ET-1 type B receptor (ETBR) antagonist BQ788 revealed that this was possibly due to an upregulation of ETBR. In conclusion, TH0.1 enhanced the blood pressure-lowering effects of irbesartan and diminished cardiac hypertrophy. Higher doses of thiorphan did not exert such effects, possibly because NEPi-induced ET-1 accumulation now counteracted its beneficial effects on natriuretic peptides. Upregulation of vasodilatory ETBR may have occurred to prevent the hypertensive effects of ET-1 accumulation.
GI PROTEINS, NATRIURETIC PEPTIDE RECEPTOR- C AND REGULATION OF BLOOD PRESSURE
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Objectives: C-ANP4-23, a ring deleted analog of atrial natriuretic peptide (ANP) that specifically interacts with natriuretic peptide receptor-C (NPR-C) has been shown to decrease the enhanced expression of Gialpha proteins, implicated in the pathogenesis of hypertension. In the present study, we investigated whether in vivo treatment of spontaneously hypertensive rats (SHR) with C-ANP4-23 could attenuate the development of high blood pressure (BP) and explore the underlying mechanism/s responsible for this response.

Methods and Results: The BP started increasing in SHR at 4 weeks and increased to about 190 mmHg at 8 weeks. However, intraperitoneal injection of C-ANP4-23 at the concentration of 2 or 10 nmole/kg body weight to prehypertensive SHR attenuated the development of high BP and at 8 weeks it was decreased by about 20 mmHg and 50 mmHg respectively but not in WKY rats. The C-ANP4-23 treatment also decreased the enhanced levels of Gialpha proteins in heart and aorta as determined by Western blotting. In addition, the enhanced levels of superoxide anion, peroxynitrite, NADPH oxidase activity and the enhanced expression of NOX-4, P47phox, nitrotyrosine and decreased levels of eNOS were attenuated by C-ANP4-23 treatment, however, the altered levels of NPR-A/NPR-C were not affected by this treatment.

Conclusions: These results indicate that NPR-C activation by C-ANP4-23 attenuates the development of high BP in SHR through the inhibition of enhanced levels of Gialpha proteins and nitrooxidative stress and not through eNOS /cGMP pathway and suggest that NPR-C ligand may be used as therapeutic agent in the treatment of cardiovascular complications including hypertension(Supported by CIHR).
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ANTIHYPERTENSIVE EFFECT OF FLAXSEED
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Secoisolariciresinol diglucoside, a phytoestrogen, has been isolated from flaxseed. Phytoestrogen has hypotensive activity.
The objective of this study was to investigate if SDG has hypotensive activity and if this effect is mediated through L-arginine-nitric oxide pathway. The effects of SDG on arterial pressures were conducted on anesthetized Sprague Dawley rats. Various doses (3, 5, 10, 15 and 20mg/kg) of SDG were given intravenously and the effect on the arterial pressures were measured for 4 hours. The SDG produced a maximal drop in the arterial pressures within 15 minutes after which the pressures began to recover slowly. The drop in the pressures were still significant even after 4 hours of SDG administration. The hypotensive effects were dose-dependent for 3, 5 and 10mg/kg. The SDG-induced hypotensive effect was blocked by Ng-monomethyl-L-arginine (L-NMMA), an inhibitor of nitric oxide synthase. However the effect was blocked by oxadiazolo quinoxalin, an inhibitor of guanylate cyclase. In conclusion, SDG a component of flaxseed is a long acting hypotensive agent and the hypotensive effect is mediated through guanylate cyclase enzyme. SDG may effective in the treatment of hypertension.
Resistant or difficult to treat hypertension is not uncommon and is a nightmare for both primary care physicians and specialists. It is defined as an uncontrolled hypertension with blood pressure consistently above 140/90mmHg despite adequate regimen with four or more antihypertensives, preferably with one that includes a diuretic. The short and long-term outcomes are worse in patients with resistant hypertension compared to those patients whose hypertension is controlled with lifestyle modification and medications. Pseudo resistance has to be ruled out in all cases of resistant hypertension before considering additional treatment strategies for this patient population. 

Catheter based renal denervation had shown promising results in their pivotal trials in Europe and Asia, and has been approved as a treatment strategy for patients with resistant hypertension in Europe. Modulation of neuro-hormonal control of blood pressure through denervation of sympathetic nerve fibers around the renal arteries has been shown to successfully reduce the blood pressure with minimal side effects in preclinical animal and human trials. However, the recent Simplicity HTN 3 trial, a more rigorously controlled study that enrolled patients in US, failed to show similar beneficial results. Baroreceptor Activation Therapy is another promising strategy that is being studied and has promising preliminary results. This mode of therapy has not gained rapid enthusiasm and acceptance due to more invasive nature of this surgical procedure, especially in the limelight of the promising initial results with renal denervation therapy. This therapy has not been tested in a large randomized trial, hence the external validity of beneficial preliminary results is still questionable. It is important to recognize the importance of lifestyle modification and adequate work up for identifying a secondary cause performed before selecting patients to advanced treatment modalities for treatment of resistant hypertension.
Background: Blood pressure control has been shown to reduce the risk of coronary heart disease (CHD) among diabetic patients, however, it is not known whether the lowest clinical blood pressure achieved ultimately results in the lowest risk of CHD in diabetic patients.

Objective: To examine the race-specific association between blood pressure and the risk of CHD among African American and white diabetic patients in the Louisiana State University Hospital-Based Longitudinal Study (LSUHLS).

Methods: We performed a prospective cohort study (2000-2009) on diabetic patients including 17,536 African American and 12,618 White. Cox proportional hazards regression models were used to estimate the association of blood pressure at baseline and during follow-up with CHD risk.

Results: During a mean follow up of 6.0 years, 7,260 CHD incident cases were identified. The multivariable-adjusted hazard ratios of CHD associated with different levels of systolic/diastolic blood pressure at baseline (<110/65, 110-119/65-69, 120-129/70-80, 130-139/80-90 [reference group], 140-159/90-100, and ≥160/100 mmHg) were 1.73 (95% CI 1.41-2.12), 1.16 (0.97-1.38), 1.04 (0.92-1.17), 1.00, 1.06 (0.97-1.18), and 1.11 (1.01-1.22) (P trend <0.001) for African Americans, and 1.60 (95% CI 1.34-1.91), 1.27 (1.10-1.47), 1.08 (0.96-1.20), 1.00, 0.95 (0.86-1.04), and 0.99 (0.80-1.10) (P trend<0.001) for whites, respectively. A U-shaped association of isolated systolic and diastolic blood pressure at baseline as well as blood pressure during follow-up with CHD risk was observed among both African American and White diabetic patients (all P trend<0.001).

Conclusions: Our study suggests that there is a U-shaped or inverse association between BP and the risk of CHD, and aggressive blood pressure control (blood pressure<120/70 mmHg) is associated with an increased risk of CHD among both African American and white patients with diabetes.
Diagnosis of hypertension and clinical decisions regarding its treatment are typically based upon clinic blood pressure (BP) measurements, occasionally supplemented by wake-time patient self-assessment. Yet, correlation between BP level and target organ damage, cardiovascular disease (CVD) risk, and long-term prognosis is greater for ambulatory BP monitoring (ABPM) than daytime in-clinic measurements. Additionally, consistent evidence of numerous studies substantiates the ABPM-determined asleep BP mean is an independent and stronger predictor of CVD risk than the awake or 24h means. Most importantly, when the asleep BP mean is adjusted by the awake mean, only the former is a significant independent predictor of CVD outcome. Hence, cost-effective adequate control of sleep-time BP is of marked clinical relevance. Endogenous circadian rhythms explain statistically and clinically significant ingestion-time differences in efficacy, duration of action, safety, and/or effects on the daily BP pattern of most hypertension medications and their combinations. For example, bedtime versus morning ingestion of angiotensin-converting enzyme inhibitors and angiotensin receptor blockers better controls the asleep BP mean, with additional benefit, independent of medication terminal half-life, of converting the 24h BP profile into more normal dipper patterning. The MAPEC Study, first prospective randomized treatment-time investigation testing the worthiness of bedtime chronotherapy with at least one conventional hypertension medications to specifically target attenuation of asleep BP, demonstrated, relative to conventional morning therapy, significantly better reduction of CVD risk. The MAPEC Study not only documents the asleep BP mean is the most significant prognostic marker of CVD and stroke morbidity and mortality, but it also substantiates attenuation of the asleep BP mean by a bedtime hypertension treatment strategy with the entire daily dose of >1 hypertension medications significantly reduces CVD risk, both in the general hypertension population and in patients of greater vulnerability and enhanced CVD risk, i.e., those diagnosed with chronic kidney disease, diabetes, and resistant hypertension.
HYPERTENSION – RISK AND MANAGEMENT

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PREVALENCE AND CLINICAL IMPLICATIONS OF SLEEP-TIME HYPERTENSION
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Numerous studies consistently document the sleep-time blood pressure (BP) mean derived from ambulatory BP monitoring (ABPM) is a stronger predictor of cardiovascular (CV) risk than clinic measurements and the awake or 24h means. A blunted sleep-time BP decline (non-dipper patterning) has also been associated with elevated risk of end-organ injury and CV events. A highly prevalent non-dipper pattern, or even sleep-time BP increase (riser patterning) is common in patients with chronic kidney disease (CKD), congestive heart failure, left ventricular hypertrophy, resistant hypertension, and diabetes, among several other medical conditions. We compared the features of the ambulatory BP pattern of 2954 hypertensive patients with diabetes and 9811 hypertensives without diabetes enrolled in the ongoing multicenter Hygia Project, designed to evaluate prospectively CV risk by ABPM in primary care centers of Northwest Spain. The prevalence of non-dipping was significantly higher in patients with than without diabetes (62.1 vs. 45.9%; P<0.001); however, the largest difference between groups was the prevalence of riser BP patterning (19.9 vs. 8.1%; P<0.001). Additionally, 89.2% of uncontrolled hypertensive patients with diabetes evidenced sleep-time hypertension. Interestingly, the prevalence of non-dipping was significantly higher when all hypertension medications were ingested upon awakening (68.6%) than when at least 1 (55.8%) or all of them (49.7%; P<0.001 between groups) were taken at bedtime. The latter treatment-group also showed significantly higher prevalence of properly controlled ambulatory BP (P<0.001), which was achieved by a significantly lesser number of hypertension medications (P<0.001). Further evaluation of the same cohort documents that the prevalence of non-dipper BP patterning was significantly higher in patients with (60.6%) than without CKD (43.2%; P<0.001 between groups). Most important, 90.7% of uncontrolled hypertensive participants with CKD evidenced sleep-time hypertension. These collective findings constitute the rationale for testing bedtime chronotherapeutic strategies to improve the management of high BP and to reduce CV risk.
Hemodynamic support has a limited but very specific and important role in the management of myocardial ischemia in the cardiac catheterization lab. Indications for its use include (1) cardiogenic shock, particularly in the setting of Acute Myocardial Infarction in which case the immediate support provides the time and hemodynamic stability to complete revascularization. Until recently, operators have relied heavily on the intra aortic balloon for hemodynamic support, but recent studies have raised questions regarding the effectiveness of the IABP in such cases thus further supporting this option. In addition, hemodynamic support is useful as an adjunct to (2) high anatomic risk PCI to provide “hemodynamic safety” and again, time to allow complete and high quality PCI. High anatomic risk is generally defined as LVEF of < 30% or 3 vessel disease and an LVEF of < 35%. The latter use has developed as the application of percutaneous revascularization for the treatment of severe, multi-vessel coronary artery disease has become more common, particularly in patients who are surgical “turndowns” because of multi-organ risk factors adversely impacting more usual surgical intervention.

Most commonly, hemodynamic support is provided by percutaneous insertion of an Impella catheter (Abiomed, Danvers, Ma.) with a potential cardiac output of up to 3.9 L/min using the newest catheter design. Data suggests better outcomes for patients treated early, before cardiogenic shock occurs or escalates. Defining patient populations most likely to benefit from percutaneous hemodynamic support in the absence of cardiogenic shock continues to evolve.

By case examples the above patient types will be illustrated emphasizing the value of hemodynamic support with data from pertinent studies documenting the benefit.

In summary, hemodynamic support for patients cardiogenic shock as early as possible as well as in conjunction with specific, risk PCI can improve outcomes.
Decision-making in treating a coronary chronic total occlusion (CTO) should align with guidelines and appropriate use criteria for management of the non-CTO lesion, utilizing the same criteria, i.e. the extent of symptoms and ischemia and the adequacy of medical therapy. The idea that collaterals adequately perfuse the myocardium in the CTO territory is a myth; in fact, that region may be considered a chronically ischemic zone. When matched with patients without a CTO for all coronary syndromes, prognosis is worse for the CTO patient. Additionally, a CTO in patients with left ventricular dysfunction and an ICD is the most potent predictor for ICD shocks and second most important parameter related to mortality. Available data have shown that revascularization with PCI of a CTO can improve symptoms, decrease the need for bypass surgery and improve ventricular function and suggest that survival is improved. The use of percutaneous coronary intervention (PCI) to recanalize the CTO has been limited by a relatively poor success rate of 60-70%. The use of newer techniques can improve may increase success rate to 85-90% and increase the poor of PCI candidate. They include the antegrade dissection-re-entry technique with dedicated tools for this purpose including the CrossBoss, Sting-Ray balloon, and dedicated re-entry wire. In addition, the use of retrograde techniques, both intra-luminal and dissection re-entry, increase the success rate to a range where patients with multivessel disease and a CTO may be completely revascularized by percutaneous methods. Currently no randomized trials have demonstrated that CTO PCI is more effective than medical therapy or bypass surgery but such trials are ongoing and should provide increased clarity in decision-making.
PCI VERSUS CABG IN MULTIPLE VESSEL CAD

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CAD is number one killer in the world. CABG and PCI are both safe and established invasive treatment modalities for CAD. However conflicting information exists when comparing their long term efficacy in multiple vessel disease (MVD). The introduction of DES for PCI and Off Pump and MIDCAB Byepass Surgery have tremendously improved both the techniques. For Single & DVD with normal LV function and in low risk cases with EF ≥50% with TVD perhaps results of both modalities are similar. The recent SYNTAX trial has shown CABG to be superior to PCI in high risk patients of MVD with 5year mortality 2.3 times higher in PCI as compared to CABG especially when PVD, tobacco use, DM and heart failure are associated. For LMCA plus SVD PCI was better and for LMCA with 2VD or 3VD, CABG was better. The recent FREEDOM trial has shown that CABG for MVD with DM was associated with reduction in risk of MI and all cause mortality while PCI was associated with lower risk of stroke but more revascularisations and surgery should be preferred to PCI in such cases. To conclude, for low risk patients of MVD the PCI results were almost similar to CABG while in high risk cases and complex MVD CABG is a better option especially with SYNTAX score ≥22. Refinements in PCI techniques including Fractional flow reserve guarded revascularization and improvement in stent technology are likely to strengthen the role of PCI in complex MVD.
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UPDATE ON CORONARY BIFURCATION CLASSIFICATION AND TECHNIQUES
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There are many classifications for coronary bifurcation lesions. This talk will focus on most comprehensive classification of bifurcation lesions that is simple, practical and inclusive of other important features of coronary bifurcation lesions that are not mentioned in other classifications. This classification is based on a system composed of a single prefix [prefix B (for Bifurcation lesion)] to which up to 3 main suffixes are added describing important anatomical features of a given bifurcation lesion. This classification addresses two important technical features of bifurcation lesions: the proximal segment size, and the bifurcation angle. It is known that if the proximal segment is too small, the kissing stenting technique cannot be utilized (small is defined as less than 2/3 of the sum of the diameters of both branch vessels, suffix S for small). Medina classification does not include this important anatomical feature in their classification and this review did not mention this important feature. The second suffix describes the involvement of the disease area of the bifurcation branches, i.e., if both ostia at the bifurcation site are involved, number 2 is used, if the main branch only is involved, 1m is used and if the side branch only is involved, 1s is used. B2 lesions in this classification are a true bifurcation lesion. An algorithmic approach to coronary intervention using this classification. A detailed algorithmic approach based on Movahed’s classification was recently published. Further more new data in regards to new technique and outcome of bifurcation lesions will be discussed such as lack of benefit in two stent technique vs one stent and use of jailed balloon technique in side branch during main branch stenting for side branch protection.
In patients who require coronary artery bypass grafting (CABG), the risk of perioperative stroke is close to 2%. Several studies reported that the risk of stroke associated with CABG is < 2% in patients with no significant carotid disease and 3% in patients with asymptomatic severe carotid stenosis. The risk increases to 5% in patients with bilateral carotid stenosis or a history of stroke or transient ischemic attack (TIA) and to 7% to 11% in patients with carotid occlusion. Combined carotid and cardiac surgical procedures are performed frequently in an effort to reduce the incidence of postoperative stroke. The timing and sequence of revascularization are controversial and influenced by the respective symptom severity of the coronary and carotid disease. Treatment options include combined CABG and carotid endarterectomy (CEA), staged CEA followed by CABG or CABG followed by CEA. Another emerging treatment plan include carotid angioplasty and stenting (CAS) with cerebral protection followed by CABG. In the absence of randomized trials comparing these treatment options or no revascularization before CABG, management needs to be individualized using the generally agreed upon concepts.
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BIOMARKERS OF CARDIAC ALLOGRAFT VASCULOPATHY

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Cardiac allograft vasculopathy (CAV) still remains a major cause of morbidity and mortality influencing long term outcomes in cardiac transplantation. CAV is characterized by diffuse intimal proliferation with sparing of the internal elastic lamina which differentiates it from native atherosclerosis. CAV is a manifestation of chronic rejection.

Immunological and other environmental factors have been implicated in this process. Endomyocardial biopsies continue to be the gold standard for detecting rejection while intravascular ultrasound and coronary angiography continue to be used to detect CAV. Biomarkers could serve as a substitute because of the cost and invasive nature of these techniques with potential for drastic complications such as perforation and tamponade. The pathway to biomarker discovery can rest on all or combinations of three major areas of modern day investigational tools such as genomics, proteomics and metabolomics. Biomarker discovery has been an ongoing process. This review helps to consolidate the existing literature on the various approaches in biomarker discovery with reference to acute and chronic rejection processes which lead to CAV. Molecular diagnostics at the cellular and subcellular levels as surveillance tests for acute rejection help control development and progression of CAV. At the genomic level cytokine gene profiling detects acute cellular rejection with excellent negative predictive value. A microarray derived panel of 5 genes recently identified has a high positive predictive value for acute rejection.

Proteomic profiling of CAV versus non-CAV patients provides a protein signature with a sensitivity and specificity of approximately 80% and 89% respectively. Small molecules such as ADMA (Asymmetric Dimethyl Arginine) and growth factors such as VEGF-C, VEGF-A and PF-4 have been associated with CAV. In conclusion biomarker panels may be the answer to non-invasive detection of CAV.
ASSOCIATION OF COAGULOPATHY AND IN-HOSPITAL MORTALITY AMONG HEART TRANSPLANT RECIPIENTS

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⁴ University of Alabama at Birmingham and VA Medical Center, Birmingham, AL, USA

Background: Pre-transplant coagulopathy trends and associated outcomes among heart transplant recipients have not been studied from a national database.

Methods: Using the Nationwide Inpatient Sample (NIS) databases 2003–2010 we assembled a weighted sample of 13,966 first-time heart transplant recipients, of which 3,804 (27%) had pre-transplant coagulopathy (defined as a comorbidity variable, based on ICD-9 and DRG codes). Propensity scores for coagulopathy were calculated for all patients and used to assemble a weighted matched cohort of 3,600 and 3,603 patients respectively with and without coagulopathy balanced in 32 baseline characteristics.

Results: Prevalence of pre-transplant coagulopathy among heart transplant recipients increased from 16% in 2003 to 41% in 2010 (Trend P<0.001). In-hospital mortality occurred in 10% and 4% of matched heart transplant recipients with and without coagulopathy, respectively (odds ratio {OR}, 2.49; 95% confidence interval {CI}, 2.04-3.04; P<0.001; Figure). Pre-transplant coagulopathy was associated with an increased length of hospital stay, higher total hospital charge and higher chance of receiving blood transfusion (Table).

Conclusion: In this national study of hospitalized patients receiving heart transplant, pre-transplant coagulopathy was common and steadily increased over last decade. Coagulopathy was independently associated with poor in-hospital outcomes. These findings may impact the selection of patients for heart transplantation.

<table>
<thead>
<tr>
<th>Table: In-hospital outcomes among propensity-matched weighted population of first time heart transplant recipients at NIS 2003-2010 (N=7203)</th>
</tr>
</thead>
<tbody>
<tr>
<td>In-hospital outcomes</td>
</tr>
<tr>
<td>----------------------</td>
</tr>
<tr>
<td>Mortality</td>
</tr>
<tr>
<td>No coagulopathy</td>
</tr>
<tr>
<td>Coagulopathy</td>
</tr>
<tr>
<td>Length of stay ≥ median 22 days</td>
</tr>
<tr>
<td>Total charge ≥ median $413,178</td>
</tr>
<tr>
<td>Blood transfusion</td>
</tr>
</tbody>
</table>

Figure: Kaplan-Meier plots of in-hospital mortality among propensity-matched weighted heart transplant recipients (N=1420) with and without pre-transplant coagulopathy.
SHOULD CILOSTAZOL BE INCLUDED INTO THE TREATMENT POST CAROTID STENTING? : A META-ANALYSIS

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Background: Optimal platelet inhibition is an important therapeutic adjunct in patients with carotid artery stenosis undergoing carotid artery stenting (CAS). Cilostazol use has been demonstrated to be very efficacious by leading stent patency in both coronary and infra-popliteal stenting. CAS is also at risk for in-stent re-stenosis (ISR) and therefore optimal anti-platelet therapy should be used. We aimed to evaluate if the use of cilostazol among patients who underwent CAS would lead to any benefit or no harm.

Methods: We searched Pub Med and Cochrane through January 2014 for all the clinical data that directly compared cilostazol to other anti-platelet regimen as such aspirin and thienopiridine after CAS. We evaluated the risk for ISR within one to two years post procedure. RevMan 5.2 was used for the analysis.

Results: Out of 72 articles, 5 clinical studies were included in the analysis. The pooled data provided a total of 1004 patients, 390 of which received cilostazol. When compared to other anti-platelet regimen, cilostazol significantly reduced the incidence of ISR (OR 0.15; CI 0.06-0.37; p < 0.0001) (Figure 1).

Conclusion: Our analysis suggests that cilostazol use after CAS might add the benefit by improving ISR. Still the clinical benefit is yet to be elucidated. Therefore large randomized trials are warranted.

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Cilostazol</th>
<th>Control</th>
<th>Odds Ratio M-H, Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Events</td>
<td>Total</td>
<td>Events</td>
<td>Total</td>
</tr>
<tr>
<td>Kato 2012</td>
<td>0</td>
<td>29</td>
<td>10</td>
</tr>
<tr>
<td>Takayama 2013</td>
<td>0</td>
<td>30</td>
<td>5</td>
</tr>
<tr>
<td>Takigawa 2010</td>
<td>0</td>
<td>27</td>
<td>11</td>
</tr>
<tr>
<td>Tsutsumi 2013</td>
<td>0</td>
<td>97</td>
<td>4</td>
</tr>
<tr>
<td>Yamagami 2012</td>
<td>3</td>
<td>207</td>
<td>22</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>390</td>
<td>614</td>
<td>100.0%</td>
</tr>
</tbody>
</table>

Total events 3 52

Heterogeneity: CH² = 0.76, df = 4 (P = 0.94); I² = 0%
Test for overall effect: Z = 4.08 (P < 0.0001)
DECREASED INCIDENCE OF ATRIAL FIBRILLATION FOLLOWING OPEN HEART SURGERY USING MODIFIED DEL NIDO CARDIOPLEGIA

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Background: Del Nido cardioplegia, a crystalloid based solution which includes lidocaine and is given as a single dose, has been used in congenital cardiac surgery. We retrospectively compared a modified del Nido solution—8 parts blood and 1 part cardioplegia with lidocaine—with our conventional whole blood cardioplegia to investigate the safety and efficacy in adult cardiac surgery.

Methods: From 6/1/13, we used a single dose of modified del Nido cardioplegia in 92 consecutive operations (Group I): 48 isolated Coronary Artery Bypass Graft (CABG), 31 isolated valve, 13 combined CABG and valve. We propensity matched 79 patients operated on by the same surgeon (Group II) and 88 patients operated on by other surgeons in the group (Group III) who received conventional whole blood cardioplegia.

Results: Group I was similar to Groups II and III in operative characteristics except perfusion time of 82 minutes(range 64-127) in Group I vs. 108 minutes(84-139) in Group III, p= 0.002, and cross-clamp time of 62 minutes(51–87) in Group I vs. 80 minutes(63–102) in Group III, p = 0.011. Post-operative outcomes were similar including inotrope requirements, ventilation time, length of stay (LOS, median 7 days, range 5-10) and operative mortality (3.8%, 2.5%, 3.4% for Groups I, II, III, respectively). Atrial fibrillation was significantly less frequent in Group I: 10% vs 25.3% (Group II, p = 0.021), vs 26.1% (Group III, p = 0.01). Median peak 24-hour CKMB levels were slightly higher in Group I vs Group II (22.3 ng/ml, range 15.6 -40.3 vs. 18.4 ng/ml, range 13.9–28.2, p = 0.04) and Group III(21.7 ng/ml, range 14.4-40.1 vs. 15.5 ng/ml, range 11.3-26.3, p = 0.003).

Conclusions: Modified del Nido cardioplegia is safe, effective, and associated with decreased post-operative atrial fibrillation compared with conventional whole blood cardioplegia. Higher CKMB levels did not translate into adverse clinical outcomes.
CHRONIC OBSTRUCTIVE PULMONARY DISEASE IS ASSOCIATED WITH WORSE SURVIVAL IN PATIENTS RECEIVING HEART TRANSPLANT: ANALYSIS FROM UNOS REGISTRY
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Objectives: To investigate whether the presence of COPD before OHT portends poorer post-orthotopic heart transplant (OHT) outcomes.

Methods: We searched the UNOS registry for all patients (age > 18) who received OHT for ischemic and non-ischemic dilated cardiomyopathy from 2000-2013. We excluded all patients who underwent heart-lung transplants. We used Kaplan-Meier method and Cox proportional hazards model for survival analysis.

Results: We identified 375 patients with COPD and 9998 patients without COPD. Compared with patients without COPD, patients with COPD were older (mean age 57.3 (7.8) vs 52.2 (11.7), p<0.001), have higher mean BMI (27.2 vs 26.6, p<0.05), higher percentage of cigarette use (81.1% vs 51.5%, p<0.001), hypertension (52.7% vs 41.0%, p<0.001), cerebrovascular disease (7.2% vs 3.8%, p<0.001), peripheral vascular disease (6.4% vs 3.4%, p<0.001), pulmonary embolism (2.5% vs 1.2%, p=0.05), angina (46.8% vs 36.0%, p<0.001), peptic ulcer disease (8.4% vs 5.1%, p<0.01), ischemic cardiomyopathy (58.9% vs 48.0%, p<0.001), diabetes (13.4% vs 8.3%, p<0.005), chronic steroid use (14.1% vs 10.1%, p<0.05), higher antiarrhythmic use (42.3% vs 36.5%, p<0.05). They also had higher cardiac output (4.76 vs 4.56, p<0.05). Mean patient survival after OHT was lower in COPD than in non-COPD groups (2979.7 days vs 3341.96 days, p<0.001). Mean cardiac allograft survival was also lower in COPD patients than those without COPD (2965.4 vs 3285.4 days, log-rank test p<0.001). After adjustment for age, baseline Creatinine, Diabetes status, BMI, PRA, and gender, COPD predicted worse graft survival (HR 0.68, CI: 0.57-0.82, p<0.001). COPD was associated with higher incidence of post-transplant infection (34.7% vs 23.7%, p<0.001) and more incidence of surgical procedures (21.9% vs 15.0%, p<0.001)

Conclusion: Patients with COPD have more comorbidities than those without and COPD is an independent predictor of worse patient and graft survival in patients who undergo OHT.
ASSOCIATION OF VITAMIN D DEFICIENCY WITH ATRIAL FIBRILLATION

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Background: A growing body of data suggests that low 25-hydroxyvitamin D (25[OH] Vit D) levels may adversely affect cardiovascular health. In atrial fibrillation (AF), atrial remodeling and fibrosis are often encountered. It is thought that the renin–angiotensin–aldosterone system (RAAS) plays a role in these pathophysiologic changes. Vitamin D deficiency activates the RAAS.

Objective: We aimed to investigate the association of Vitamin D deficiency with AF.

Methods: A retrospective analysis was conducted in consecutive adult patients who received 25[OH] Vit D measurements as part of their clinical care between January 1, 2007 to September 9, 2013 at Loyola University Medical Center (total n=42660). Patients were grouped into the following categories of 25[OH] Vit D during the study period (ng/mL): 0-10 (n=3590), 10-20 (n=11960), 20-30 (n=13259), 30-40 (n=8476), 40-100 (n=5315), and > 100 (n=60). Logistic regression analysis was used to evaluate 25[OH] Vit D categories, age, gender, race, HTN, CAD and CHF for incidence of AF (determined by ICD-9 codes).

Results: A total of 42660 patients (73% females) were studied. AF was diagnosed in 3886 patients (57% females). The mean 25[OH] Vit D level was significantly lower in patients with AF than without AF (25.1±13.2 v 26.6±13.7 ng/mL, p<0.001). There was a significant increased risk of incident AF, independent of age, gender, race, HTN, CAD, and CHF associated with 25[OH] Vit D of 0-10 ng/mL (odds ratio [OR], 1.19; 95% CI, 1.02 to 1.39) and 10-20 ng/mL (OR, 1.14; 95% CI, 1.01 to 1.27). The other 25[OH] Vit D categories did not confer a greater independent risk of incident AF. Females had a significant decreased risk of incident AF compared to males (OR, 0.63, 95% CI, 0.58 to 0.68).

Conclusion: In this patient population, severe 25[OH] Vit D deficiency is associated with a significant independent risk of incident AF.
ARRHYTHMIA II: DIAGNOSIS, DRUG THERAPY, ABLATION

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BRIEF EPISODES OF SILENT ATRIAL FIBRILLATION PREDICT CLINICAL VASCULAR BRAIN DISEASE IN TYPE 2 DIABETIC PATIENTS
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Objectives: This study evaluated whether subclinical episodes of atrial fibrillation (AF) were associated with an increased risk of silent cerebral infarct (SCI) and stroke in diabetic patients younger than 60 years who did not have other clinical evidence of AF and cerebrovascular disease at baseline.

Background: In type 2 diabetic patients, one-fourth of strokes are of unknown cause, and subclinical episodes of AF may be a common etiologic factor.

Methods: 464 type 2 diabetic patients younger than 60 years were included in a longitudinal observational study matched to patients without diabetes. Patients underwent 48-h electrocardiographic Holter monitoring quarterly to detect brief subclinical episodes of AF (duration of AF <48 h) and were followed up for 37 months. The outcomes were SCI, assessed by magnetic resonance imaging of the brain, and stroke events during the follow-up period.

Results: The prevalence of subclinical episodes of AF was significantly greater among patients with diabetes compared with matched healthy subjects (11% vs. 1.6%, p < 0.0001). During an average duration of 37 months, 43 stroke events occurred in the diabetic population, no events occurred in healthy subjects. Diabetic patients with silent episodes of AF (n = 176) had a higher baseline prevalence of SCI (61% vs. 29%; p < 0.01) and a higher number of stroke events (17.3% vs. 5.9%; p < 0.01) during the follow-up period than the other patients (n = 288). An episode of silent AF was an independent determinant of SCI (odds ratio: 4.441; p < 0.001; confidence interval: 2.42 to 8.16) and an independent predictor of the occurrence of stroke in diabetic patients (hazard ratio: 4.6; p < 0.01; confidence interval: 2.7 to 9.1).

Conclusions: Subclinical episodes of AF occurred frequently in type 2 diabetic patients and were associated with a significantly increased risk of SCI and stroke.
ADENOSINE A2A RECEPTORS FUNCTION IN VASOVAGAL SYCPOPE

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Adenosine is a nucleoside that comes from the dephosphorylation of ATP and which impacts the cardiovascular system. Adenosine acts via four receptors namely A1 R, A2A R, A2B R and A3 R depending on their pharmacological properties. Activation of A1 or A3 receptors leads to the inhibition of cAMP production while activation of A2A receptors leads to the production of cAMP by target cells (myocytes and sino atrial node). Activation of A1 R leads to bradycardia while activation of A2A R mostly induce vasodilation. Adenosine is likely implicated in vasovagal syncope (VVS), because high adenosine plasma levels have been found in VVS patients that increase more during head up tilt test, which is a useful test for the exploration of VVS. Furthermore, high expression of A2A R have been reported in VVS. However nothing is known about the function of these receptors. Using Adonis, a specific made antibody with A2A R agonist properties, we evaluate binding parameters (Dissociation constant KD and cAMP production (ie EC50) by peripheral blood mononuclear cells of 16 VVS patients and 8 healthy subjects. A2A R expression evaluated by western blot was higher in patients compared with controls 11.5 ±1.2 vs 7.7±0.8 AU ; p=0.04). KD values were higher in patients compared with controls (2.1±0.2 x10-7 vs 5±1 x10-8 µM ; p<0.05). In healthy subjects EC 50 was higher than KD (2.8±0.4x10-7 vs 5±1.7 x 10-8 p<0.01). In four patients EC 50 was near 10 folds lower than KD (EC50/KD = 9.6) suggesting the presence of A2A R of reserve(Spare receptors) in these patients. Spare receptors are suspected when the biological effects occurs while not all the receptors are occupied by the agonist. We conclude that the function of A2A R in VVS patients is preserved. The presence of spare receptors in VVS is discuss.
PREGNANCY IS ASSOCIATED WITH AN INCREASED DENSITY OF THE PACEMAKER CURRENT I-F IN MURINE SINOATRIAL NODE

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Background: Pregnancy is associated with numerous changes in the cardiovascular system, one of which is an elevated heart rate that may increase risk of cardiac arrhythmia. The basis for this increase in heart rate during pregnancy is poorly understood. Among the ion channels expressed in the sinoatrial node (SAN), the hyperpolarization-activated cyclic nucleotide-gated (HCN) channels coding for If are critical for cardiac pacemaker activity. Thus, the objective of this study was to examine the role of the pacemaker current and its underlying HCN channel isoforms in the increased heart rate in pregnancy.

Methods and Results: Consistent with human data, surface ECG recordings reveal that late pregnant mice (P, 18-19 gestation days) have faster heart rate (531±14 bpm) compared with nonpregnant (NP) mice (470±27 bpm; P<0.03). Results obtained with Langendorff-perfused hearts showed that this difference persisted in the absence of autonomic nervous tone (NP, 327±16 bpm; P, 385±18 bpm; P<0.02). Current-clamp and voltage-clamp recordings were obtained using spontaneously beating cells isolated from the SAN of pregnant and nonpregnant mice. The spontaneous action potential of SAN cells from pregnant mice displayed accelerated pacing rate (NP, 292±13 bpm; P, 330±12 bpm; P=0.047) and increased diastolic depolarization (NP, 0.20±0.03 V/s; P, 0.40±0.06 V/s; P=0.004). If current density was significantly higher in SAN cells isolated from pregnant (at -90 mV, -28.6±2.9 pA/pF) compared to nonpregnant (-15.2±1.0 pA/pF; P=0.0002) mice. The increased If density was explained by higher protein expression of HCN2 channel isoform with no change either in the protein expression of HCN4 or the voltage dependence of the If activation curve.

Conclusions: Together these results show that an increase in HCN2 channel expression upregulates If current density and contributes to the acceleration of sinoatrial node automaticity and explains, at least in part, how heart rate may be elevated in pregnancy.
ARRHYTHMIA II: DIAGNOSIS, DRUG THERAPY, ABLATION

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ADOPTION OF SMARTPHONES, TABLETS AND MOBILE APPLICATIONS AMONG PATIENTS WITH ATRIAL FIBRILLATION

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Health-Related applications (APPS) for smartphones and tablets are a potential new platform for ambulatory heart rhythm monitoring, preventing unnecessary emergency room (ER) visits and hospital admissions for atrial fibrillation (AF).

Methods: Surveyed AF patients in cardiology and primary care clinics regarding their use of mobile technology.

Results: 102 AF patients were included (49 female; age 18-44:13%, 45-64:31%, >65:56%). Patients had associated hypertension (51%), coronary artery disease (18%), heart failure (13%) and other form of heart disease (5%). 78% own a cell phone, 42% are smartphones. A personal computer, laptop, iPod or tablet is owned by 78% of patients. 40% report using APPS (in a smartphone 78%, tablet 61% and iPod 10%), only 9% use health related APPS, including fitness and weight management APPS. None use APPS to learn about AF, monitor heart rate, anticoagulation or cardiac rhythm. Among APPS users, 63% use them once a day or more, 10% less than once a month. 62% look up medical information online, 50% more than once a month. When asked about willingness to pay for health APPS, 44% are not willing to pay even if an ER visit is prevented. 21% are not willing to use the technology if provided free or covered by insurance. Hospital admission within the previous year made no difference in the willingness to pay or use the technology (P=NS).

Conclusions: Most AF patients surveyed have access to mobile technology and 40% use APPS on smartphones or tablets. Use of APPS for health purposes is limited and no patient reported using them for AF. Lack of outcomes-based research, structured programs for incorporation of this technology in patient care, cost, and lack of familiarity with APPS and devices may be limiting factors. A comprehensive strategy to develop, market and demonstrate benefits of this rapidly growing technology is urgently needed.
Objective: The purpose of this study is to evaluate pulmonary vein (PV) antum circular ablation plus longitudinal mapping ablation to the residual musculature fascicles (RMF) of the pulmonary veins on the immediate and longterm efficacy of paroxysmal atrial fibrillation (AF).

Methods: Patients satisfied following criteria were randomized into Group 1 (PV antum circular ablation) and group 2 (PV antum circular ablation plus longitudinal mapping ablation to RMF): 1. symptomatic AF lasted for more than 1 year and occurred more than 1 time per month. 2. without organic heart disease. 3. Refractory to antiarrhythmic agents including amiodarone. 4. Informed consent was obtained. In group 1, superior and inferior PVs were isolated as a whole circle at the antum by circular ablation. In group 2, except the procedure in group 1, RMF was mapped and ablated longitudinally in PV. The designed acute endpoint in both groups was PV complete isolation. Parameters of procedure time, fluoroscopy time, energy delivery time and PV isolation rate were compared between two groups. AF occurrence was followed up by Holter monitoring.

Results: Sixty-eight patients (M/F=42/26, age 57.32±11.56 years) were enrolled into the study. They were divided into group 1 (34, 56.71±9.83 years) and group 2 (34, 58.55±11.19 years). Parameters comparison between two groups was seen in the table. There were no differences in procedure time, fluoroscopy time and energy delivery time between two groups (P<0.05). The PV isolation rate of group 2 was significantly higher than that in group1 (92.65% vs 100%, P<0.05). During the follow-up of 15.36±3.47 months, the AF occurrence rate of group2 was significantly lower than that in group1 (17.65% vs 5.88%, P<0.01).

Conclusions: Additional longitudinal ablation to the residual musculature fascicle of the PV on the basis of PV antum circular ablation improves the immediate and long-term efficacy of paroxysmal atrial fibrillation.
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SCREENING FOR ATRIAL FIBRILLATION USING A BLOOD PRESSURE MONITOR: OMRON VS MICROLIFE
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Background: Screening for atrial fibrillation (AF) by assessing the pulse is recommended in high risk patients. Multiple clinical trials demonstrated that the Microlife blood pressure monitor (BPM) with AF detection is more accurate than pulse palpation. This led to a change in practice guidelines in the UK where AF screening with the Microlife device is recommended instead of pulse palpation.

Introduction: Many BPMs have irregular heart beat detection but they have not been shown to detect AF reliably. Recently, one study, in a highly select population, suggested that the Omron BPM with irregular heartbeat detection has a higher sensitivity for AF than the Microlife BPM. In order to verify these results we compared the Microlife and the Omron BPMs to EKG readings for AF detection in general cardiology patients.

Methods: The study inclusion criteria were age >50 without a pacemaker. A total of 199 subjects were enrolled, 30 with AF. Each subject had a 12-lead EKG, one Omron BPM reading and three Microlife BPM readings as per device instructions.

Results: The Omron BPM had a sensitivity of 30% and a specificity of 98%. In comparison, the individual Microlife BPM readings had a sensitivity of 93% and specificity of 88%.

Conclusion: The Microlife blood pressure monitor is superior to the Omron BPM for AF screening. The Omron BPM has too low a sensitivity to be useful for AF screening. Only BPMs with clinically validated AF detection should be used to screen for AF.
ARRHYTHMIA II: DIAGNOSIS, DRUG THERAPY, ABLATION

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IMPACT OF CATHETER ABLATION ON P-WAVE PARAMETERS ON 12- LEAD ELECTROCARDIOGRAM IN PATIENTS WITH ATRIAL FIBRILLATION

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Background: P-wave abnormalities have been described in the patients with Atrial Fibrillation (AF). There is paucity of data on the effect of catheter ablation (CA) on P-wave parameters. We describe the changes in P-wave parameters after CA in patients with AF.

Methods: We reviewed data on P-wave parameters (P-wave duration, amplitude and area) in leads V1 and aVF and changes in the P-terminal force (Ptf; product of duration and amplitude of terminal part of P-wave) in lead V1 from 12-lead electrocardiograms obtained prior to and after CA of a total of 46 (28 paroxysmal and 18 persistent) AF patients.

Results: The median age of patients in our study was 63 (range: 30-77) years. We noticed significant reduction in the P-wave duration (from 87.39 + 28.62 ms at baseline to 72.09 + 24.59 ms; p = 0.0072) and P-wave area in lead V1 (12.16 + 5.54 mV ms at baseline to 8.30 + 5.78 mV ms, p = 0.0015) after CA. There was also significant decrease in P-wave duration (from 92.57 + 19.67 ms at baseline to 76.48 + 16.32 ms after CA, p = 0.0001) and P-wave area in lead aVF (12.61 + 4.05 at baseline to 9.77 + 3.86 mV ms after CA, p = 0.0001). CA also led to a significant decrease in Ptf (from 4.56 + 1.88 at baseline to 2.85 + 1.42 mV ms, p < 0.0001).

Conclusion: Radiofrequency catheter ablation of AF leads to modification of P-wave parameters with substantial diminution in both the amplitude and duration of the P-wave in leads V1 and aVF. This likely represents reduction in electrically active atrial tissue after ablation, and may serve as a marker for the extent of ablated atrial tissue.
ARRHYTHMIA II: DIAGNOSIS, DRUG THERAPY, ABLATION

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TO DESCRIBE OUR EXPERIENCE WITH ARCTIC FRONT ADVANCE CRYOBALLOON ABLATION SYSTEM IN THE TREATMENT OF PAROXYSMAL ATRIAL FIBRILLATION AT A HIGH VOLUME CENTER IN THE U.S.

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Background: Cryoablation is increasingly being used for treatment of drug resistant symptomatic atrial fibrillation (AF). The Arctic Front Advance Cryoballoon ablation system (AFACA), a second-generation cryoballoon, was engineered to allow for more even cooling on the distal portion of the balloon. We analyzed our experience with AFACA in the treatment of paroxysmal AF in terms of procedural and ablation parameters with clinical success rates.

Methods: We retrospectively studied 118 consecutive patients with paroxysmal AF who underwent cryoablation with AFACA starting from July 2012 to May 2013. We studied procedural, cryoablation parameters and recurrences over 3 and 6 months. Success rate at 6 months was also calculated. The impact of these parameters on procedural success during cryoablation of paroxysmal AF with AFACA system was assessed.

Results: Among all patients, 75(63.6%) were male and the mean age of the study population was 60.4 ± 11.1 years. The total ablation time was 34.5 ± 7.9 min, ablation time per vein was 8.3 ± 2 and ablation time per lesion was 3.5 ± 0.6 min. The procedural time was 139.7 ± 45.9 minutes, fluoroscopy time was 24.7 ± 13.8 minutes and the contrast used was 61.6 ± 26.7 ml. The average lowest balloon temperature recorded was -54.1 ± 10.7 ºC. Complications both major and minor were seen in 26(22%) patients with minor pericarditis in 13(11%), transient phrenic nerve palsy in 6 (5.1%), transient ischemic attack in 3(2.5%), esophageal injury in 2(1.7%) patients, atrio-esophageal fistula in 1(0.8%) and mild pulmonary vein stenosis in 1(0.8%). The 6 months follow-up was available in 116(98.3%) patients. The recurrence of the PAF was seen in 30(25.8%) patients over 3 months and 22(19.0%) patients during 3 to 6 month period. The procedural success rate at 6 months without anti-arrhythmic drugs was 76.7%.

Conclusions: AFACA system is a safe treatment for paroxysmal AF with very low serious complication rate and optimum success rate.
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DOES TREATMENT STRATEGY FOR ATRIAL FIBRILLATION AFFECT MYOCARDIAL CONTRACTILITY?
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Aim: To estimate changes of myocardial contractility in patients with ischemic heart disease (IHD) and persistent atrial fibrillation (AF) treated with amiodarone 200 mg daily compared with bisoprolol 5 mg daily.

Material and methods: A total of 47 IHD patients with persistent AF were enrolled into the study. Sinus rhythm (SR) was restored during the first 24 hours of hospitalization in all the patients. After SR restoration, the patients were randomly allocated to two groups receiving either amiodarone 200 mg daily during 6 months for SR maintenance (group I) or bisoprolol 5 mg daily for ventricular rate (VR) control (group II). To estimate myocardial inotropic function all patients underwent planar radionuclide ventriculography (RVG) and echocardiography during the first 24 hours after SR restoration and 6 months later.

Results: We found changes in left ventricle (LV) diastolic function, reduction of left atrium (LA) contribution to LV filling, and increase in LA anteroposterior dimension during the first 24 hours after SR restoration in all patients. Six-month SR maintenance in the I group caused significant decrease in isovolumic relaxation time (IVRT) from 103.4±1.01 ms to 96.4±1.1 ms (p=0.02) and reduction of LA anteroposterior dimension to 36.1±3.8 mm (p=0.03). In patients from I group achieving the target VR improved LV diastolic function (IVRT reduced from 104.3±1.2 ms to 97.3±1.2 ms; P=0.03) but did not affect the LA size (44.1±3.1 mm and 43.5±3.0 mm, respectively). Atrial inotropic function only changed in the patients of group I.

Conclusion: Six-month SR maintenance on amiodarone in IHD patients with persistent AF resulted in reduction of LA size and improvement of LA contractility as well as LV diastolic parameters. Achieving the target VR after 6 months on bisoprolol improved LV diastolic function, but did not affect LA size and contractility.
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COMPARISON OF VARIOUS FATTY ACID ROLES ON THE RISK OF ATRIAL FIBRILLATION AMONG ADULT TAIWANESE FROM A COMMUNITY-BASED COHORT STUDY

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Background: Evidence for various fatty acids as the role in the risk of atrial fibrillation was scanty, especially from the population-based cohort data.
Objectives: To investigate extensively the effect of various fatty acids on the risk of atrial fibrillation and to compare the performance measures after adding specific fatty acid.
Methods: We conducted a community-based cohort based on 1291 participants (60.5 +/- 10.3 yrs, 45.7% women) who undertook electrocardiography, echocardiography and gas chromatography for fatty acid profile measurements. A total of 31 participants were ascertained as atrial fibrillation status.
Results: Compared with those without atrial fibrillation, participants with atrial fibrillation were more likely to have a lower eicosapentaenoic acid (EPA), docosahexaenoic acid (DHA), EPA/arachnoid acid ratio (AA), and highly unsaturated fatty acid (HUFA) concentration and a higher transfat concentration and n-6/n-3 fatty acid ratio. Various fatty acid concentrations were not related to echocardiographically measures, including left ventricular mass and ejection fraction. For EPA level, the multivariate odds ratio on the risk of atrial fibrillation was 0.31 (95% confidence interval [CI], 0.11-0.85) for second quartile, 0.16 (95% CI, 0.05-0.55) for third quartile and 0.27 (95% CI, 0.10-0.75) for fourth quartile (test for trend, P= 0.005). The area under receiver operating characteristic curve was 0.786 (95% CI, 0.707-0.866) for the risk model including EPA. In addition, the model adding EPA improved the prediction performance on the risk of atrial fibrillation (net reclassification improvement, 33.2%, P= 0.002, integrated discrimination improvement, 3.1%, P=0.001). Other fatty acids, including DHA, transfat and HUFA, had a modest effect on the risk, compared with EPA concentration.
Conclusion: Our findings suggested that n-3 fatty acids, especially EPA, were inversely associated with the risk of atrial fibrillation.
ELECTROPHYSIOLOGICAL STUDIES IN PATIENTS WITH PAROXYSMAL TACHYCARDIA WITHOUT ECG DOCUMENTATION: PREVALENCE OF INDUCIBLE ARRHYTHMIAS AND CLINICAL OUTCOME. A PROSPECTIVE REGISTRY

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Background: A significant proportion of patients presenting with paroxysmal tachycardia has no ECG documentation. In these patients an EP-Study (EPS) may be performed to facilitate the diagnosis.

Methods: In a prospective registry we compared the prevalence of inducible arrhythmias and the clinical outcome in 525 patients with and without ECG documentation.

Results: Compared to patients with a documented SVT a smaller but relevant proportion of patients (63.7%) without ECG documentation had inducible tachycardias. AVNRT was the most common type in both groups. Patients with an inducible SVT and no documentation were significantly younger, had a shorter episode duration and a lower hospitalization rate, which may be the cause for the lacking documentation. Similar to patients with documented SVTs most of these patients (90.0%) were asymptomatic or clinically improved after the EPS. Even 43% of patients without an inducible tachycardia improved clinically, probably due to the ensuring information that no tachycardia could be provoked. In particular, patients between 31 and 60 years of age or with symptoms for longer than 10 years seemed to benefit most from an EPS because they were more likely to have inducible SVTs, that could be cured by RF-ablation.

Conclusion: Our data support the view that a relevant proportion of patients with suspected paroxysmal tachycardia without an ECG documentation has inducible tachycardia which can be treated by RF-ablation and will therefore have a benefit from an EPS.
MOLECULAR / CELLULAR SURVIVAL AND REGENERATION IN CARDIAC DISEASE

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IVABRADINE INHIBITS APOPTOSIS AND NECROSIS IN PRIMARY AND CULTURED CARDIAC MYOCYTES EXPOSED TO HYPOXIA REOXYGENATION INSULT THROUGH ITS HCN CHANNEL BLOCKING ACTIVITY

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Introduction: The heart-rate lowering agent Ivabradine (Ivab) is used for cardiac ischaemia; its activity is mediated by inhibition of hyperpolarisation-activated and cyclic nucleotide-gated (HCN) channels in the sino-atrial node.
Aim: To demonstrate that pharmacologically concentrations of Ivab improves cardiac myocyte viability in vitro after hypoxia reoxygenation (HxR) insult.
Methods: Freshly isolated adult rat primary ventricular myocytes (PVM) and cultured H9c2 myocyte-like cells were treated with 1 or 3 microM Ivab, exposed to 1 or 2 h hypoxia (residual oxygen <2% of saturation) followed by re-culture for 24 h under normoxic conditions (reoxygenation). Cells were assessed for viability and mitochondrial function including ATP levels and the ATP/ADP ratio. In other studies cells were transfected with SiRNA to knockdown HCN-2 or HCN-4 expression before Ivab treatment and experimental HxR insult.
Results: Ivab dose-dependently decreased LDH release (~2- and 4-fold; 1 or 3 microM Ivab, respectively) and inhibited caspase activation (decreased 1.7- and 1.4-fold) in PVM and H9c2 cells. This enhancement of cell viability involved maintenance of mitochondrial function and sustained ATP production (as judged by assessing the ATP/ADP ratio, mitochondrial membrane potential and intracellular [ATP]). Addition of Ivab post-hypoxia, but before reoxygenation, decreased Ivab’s protective action. The involvement of cardiomyocyte HCN channels in Ivab’s cardioprotective action was demonstrated by using targeted SiRNA approaches to inhibit HCN-2 (decreased ~60% vs control) or HCN-4 (decreased ~75% vs control) mRNA expression. Targeted knockdown of HCN-2 or HCN-4 channels reversed the protective action of Ivab after HxR insult; loss of activity followed the order HCN-2 > HCN-4.
Conclusions: Ivabradine markedly improves cultured myocyte viability after experimental HxR injury. This activity is independent of heart rate-lowering but is a consequence of Ivab inhibiting HCN-2/4 channels.
RANOLAZINE ADMINISTERED AFTER DOXORUBICIN TREATMENT, PREVENTS CARDIOTOXICITY IN MICE

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Purpose: Anthracyclines are first line drugs against cancer, but produce a cardiomyopathy through multiple mechanisms, which include, Ca2+ overload due to reduced SERCA2a activity, inappropriate opening of the RyR2, and impaired myocardial energetics. Anthracyclines generate Reactive Oxigen and Nitrogen Species (ROS and RNS), posing the heart at increased demand for oxygen, thus setting the stage for a metabolic ischemia that also activates late INa, the target of Ranolazine (RAN). Here, we aim at assessing whether RAN, diminishing intracellular Ca2+ through its inhibition of late INa blunts anthracyclines cardiotoxicity.

Methods: To evaluate cardiac function in vivo, fractional shortening (FS) and ejection fraction (EF) were measured by M/B mode echocardiography and radial and longitudinal strain (RS and LS) were measured using 2D speckle-tracking echocardiography, in C57/B6 mice, 2-4 mo old, at day 0, and after 2 and 7 days of daily administration of Doxorubicin (Doxo, 2.17 mg/kg/day, ip). These measurements were repeated after 5 days of RAN treatment (750 mg/kg/day, a dose comparable to the one used in humans) initiated at the end of Doxo treatment.

Results: In our in vivo studies, after 7 days with Doxo, FS decreased to 50.5±8.4%, p<0.05 vs 61.5±1% (sham), EF to 82.2±8.1%, p<0.05 vs 91.3±0.5% (sham), RS to 14.3±4.7%, p<0.01 vs 40.5±4.8% (sham), and LS to -16.6±7.9%, p<0.01 vs 38.8±6% (sham). Interestingly, in mice treated with Ran after Doxo treatment, indices of cardiac function recovered: FS was 61.5±1.1%, EF was 91.25±1.1%, p<0.01 vs mice treated with Doxo for 7 days; RS was 29.5±3.4%, p<0.05 vs mice treated with Doxo for 7 days; however the alteration of LS persists after treatment with RAN (25.5±6.3%, p=0.16).

Conclusions: RAN post-treatment blunts cardiotoxic effects due to anthracyclines, as demonstrated by the normalization of the values of FS, EF and RS. It remains to explain the persistent abnormality of the LS.
REMOTE ISCHAEMIC PRECONDITIONING ATTENUATES EGR-1 EXPRESSION FOLLOWING MYOCARDIAL ISCHAEMIA REPERFUSION INJURY THROUGH ACTIVATION OF THE JAK-STAT PATHWAY, NITRIC OXIDE SIGNALLING AND SUPEROXIDE GENERATED BY NADPH OXIDASES

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Objectives: To determine the molecular pathways involved in the protective effect of remote ischaemic preconditioning (rIPC) on infarct size and the attenuation of Early Growth Response (EGR)-1 expression following myocardial ischaemia reperfusion (I/R) injury.

Methods: Male rats (250-350g) were subjected to transient (30 min) occlusion of the left anterior descending (LAD) coronary artery with or without prior (3 x 5 min) rIPC of the hind-limb muscle. Hearts were excised at various time-points following surgical intervention and the infarct size and expression of molecular markers of I/R injury were determined. Rat cardiac myoblast H9c2 cells were subjected to hypoxic preconditioning (HPC) coupled with hypoxia re-oxygenation (H/R) injury to determine the effects of HPC on cell viability, apoptosis and the transcription of inflammatory cytokines with flow cytometry and real-time PCR respectively. Intracellular signaling pathways regulated by rIPC were determined with the use of selective inhibitors and thereafter assessed with Western blot and real-time PCR.

Results: Rats subjected to rIPC prior to myocardial I/R injury exhibited a 40% reduction in infarct size with a concomitant reduction in cardiac EGR-1 transcription compared to rats not receiving rIPC. In vitro we showed that preconditioning exerts a protective effect on cell viability including a reduction in apoptosis and a concurrent attenuation in EGR-1 expression compared to cells exposed to H/R alone. Selective inhibition of intracellular signaling pathways confirmed that rIPC increased production of intracellular nitric oxide and NADPH oxidase generated superoxide via activation of the JAK-STAT pathway which inactivated ERK ½ and JNK signaling pathways ultimately leading to the suppression of EGR-1 expression.

Conclusions: rIPC reduces myocardial infarct size in vivo and is protective against H/R induced late stage apoptosis in vitro. Furthermore, in vitro we delineated that rIPC attenuates EGR-1 expression through increased nitric oxide and superoxide generation via JAK-STAT pathway activation.
ALPHA LINOLENIC ACID-RICH FLAXSEED REGULATES SURVIVAL IN CARDIOMYOCYTES
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Marin-derived omega n-3 fatty acids induce beneficial effects on the cardiovascular system, while indecisive findings have been so far obtained with alpha linolenic acid (ALA), a flaxseed-derived omega-3 fatty acid. Nevertheless, ALA could represent a valuable alternative to marine products. The present study has been carried out to investigate the potential flaxseed/ALA protective effects in in vivo and in vitro models of degenerative cardiac diseases and the mechanisms involved in the protective process. The in vivo models were the hereditary cardiomyopathic hamster, in which increased plasma and cardiac tissue tumor necrosis factor (TNF) concentrations associate with widespread myocardial apoptosis, and mice with myocardial damage induced by Isoproterenol (ISO) administration. Results have demonstrated that a flaxseed-enriched diet administered in hamsters from weaning to death preserved the heart structure and function significantly extending the animal longevity. In ISO-mice, the extension of the injured area was limited when the animals were fed with a flaxseed-enriched diet before the induction of the ischemic damage. In isolated neonatal murine cardiomyocytes exposed to TNF and ISO, ALA pre-treatment inhibited the onset of the apoptosis. In TNF-treated cells, ALA up-regulated the expression of anti-apoptotic protein Bcl-2 and Bcl-XL and enhanced caveolin-3 expression inhibiting the internalization of the caveolar TNF receptor determining the abortion of the apoptotic vs. survival cascade. This study unveiled a novel mechanism involving the TNF receptor and helped to explain the n-3 PUFA cardioprotective effects. Prospectively, it can be envisaged that a “membrane lipid therapy” can be set up to limit myocardial injuries caused by degenerative diseases.
BRANCHED-CHAIN AMINO ACIDS PREVENT HEART FAILURE IN RATS

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Introduction: Heart failure (HF) is associated with changes in energy metabolism of the heart, as well as in skeletal muscles. Branched-chain amino acids (BCAA) reportedly promote mitochondrial biogenesis in heart and skeletal muscles. Objective: We assessed the hypothesis that BCAA prevent HF.

Methods: Dahl salt-sensitive (DS) rats fed a high-salt (HS) diet were used as a model of HF. BCAA (1.5 mg/g body weight/day) were administered in drinking water from the phase of left ventricular hypertrophy. DS rats fed a low-salt (LS) diet only as a control (LS-C, n=8), DS rats fed a LS diet and BCAA (LS-BCAA, n=8), DS rats fed a HS diet only (HS-C, n=30), and DS rats fed a HS diet and BCAA (HS-BCAA, n=30) were used. Survival and cardiac function were monitored, and animals were sacrificed at the phase of HF and analyzed.

Results: BCAA improved the survival of rats with HF (p=0.03) and preserved the cardiac systolic function assessed on echocardiography (p=0.033). The body weight was decreased in HS-C compared with LS-C (p<0.001), and BCAA inhibited the body weight loss (p=0.037). Proliferator-activated receptor-gamma coactivator (PGC)-1alpha was decreased in heart tissue of HS-C compared with that of LS-C. PGC-1alpha expression was not changed in the heart of HS-BCAA compared with that of HS-C, but it was increased in the skeletal muscles of HS-BCAA compared with that of HS-C.

Conclusion: BCAA prolonged survival and preserved the body weight and the cardiac function in a rat model of HF.
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DECIPHERING THE SYSTEMS BIOLOGY OF MICRORNAS IN PULMONARY HYPERTENSION AND CARDIOVASCULAR DISEASE

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Over the past decade, the importance of non-coding RNAs such as microRNAs has been established in numerous processes that drive human pathogenesis. These crucial molecular regulators modulate networks of target gene transcripts that orchestrate cellular phenotypes such as cell survival, differentiation, proliferation, and metabolism among others and then affect cardiopulmonary vascular disease conditions. Many of these same pathophenotypes figure prominently in the complex pathogenesis of pulmonary hypertension (PH). Clinically, PH is defined by elevated pulmonary arterial pressures, affects the delivery of blood and oxygen to the body, and can progress to heart failure, multiple organ system failure, and death. It is an enigmatic vascular disorder characterized by a histological panvasculopathy and driven by disparate upstream triggers such as hypoxia, inflammation, and bone morphogenetic protein signaling. Yet, the importance of just a few microRNAs in PH has been recognized, and our understanding of the integrative functions of these molecules in this disease is limited. By harnessing the atlases of human molecular data that are now available, we have used computational "network-based" analyses to make predictions regarding the disease-specific actions of microRNAs that have not been possible to this point. We have validated these computational predictions in laboratory-based experimentation in mice and humans, thus defining crucial pathogenic actions of specific microRNAs in PH. Combining systems biology with traditional experimental approaches should not only further reveal the spectrum of molecular pathways that cause PH but also offer novel and much needed diagnostic and therapeutic strategies. Moreover, we envision that such a network-based discovery method could also be applied to a wide range of cardiovascular diseases in the future, where the complex molecular dynamics of disease susceptibility are still poorly defined.
PROTEIN TYROSINE PHOSPHATASES AS NOVEL THERAPEUTIC TARGET AGAINST ACUTE CARDIAC ISCHEMIA

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Background: Recent examples showed that disruption of protein tyrosine phosphate (PTP) function as an underlying cause of human diseases and recent studies had reported that PTP inhibition can improve peripheral endothelial dysfunction in animal models of chronic heart failure. However, the role of PTP in acute cardiac ischemia is unknown and no prior literature can be found.

Methods and Results: We have shown for the first time that phosphotyrosine (pTyr) signaling was perturbed concomitantly with increased activity of PTPs (assayed via biotinylated a-bromobenzyl phosphonate probe) in the left ventricle of ischemic mouse heart in early hours (2 hours post left anterior descending coronary artery ligation) as well as in cultured myocardial H9c2 cells exposed to hypoxia for 4 hours. Moreover, using modified cysteinyll-labeling assay for reversible oxidation, we demonstrated that hypoxia-driven reduction of the active-site Cys residue is the key to activate endogenous PTPs, in which resulted in diminished pTyr signaling associated with a loss of F-actin cytoskeletal integrity. We hypothesized that nitric oxide (NO) donors might prevent PTP activation via Cys s-nitrosylation, thus suppressing the ischemic or hypoxic injury to cardiomyocytes. This was proven in cell models that s-nitrosoglutathione (GSNO) attenuated pTyr signaling perturbation and cytoskeletal disruption in hypoxic H9c2 cells. In addition, ischemia-induced cardiac injury in mice was markedly attenuated by GSNO treatment through either intraperitoneal injection (GSNO, 5 mg/kg 10 minutes before cardiac infarction surgery) or intracardiac injection (GSNO, 1 mg/kg immediate injected near the infarction sites), with a significant rebound of pTyr signaling and a decrease in cardiac enzyme including CPK and LDH.

Conclusion: Together our data confirms a protective role of NO to the ischemic heart via s-nitrosylation and inactivation of PTPs. This study also revealing the potential for PTPs to represent a new class of therapeutic target in early stage of cardiac ischemia.
OPTICAL MOLECULAR IMAGING OF ATEROMA INFLAMMATION IN MURINE CAROTID PLAQUES WITH A NOVEL, MANNOSE RECEPTOR TARGETING NEAR-INFRARED FLUORESCENCE PROBE

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Background: Macrophage-rich atheromata is associated with the evolution and destabilization of plaques. The objective of this study was to image inflammatory macrophages in atherosclerotic plaques with a novel, mannose receptor (MR) targeting near-infrared fluorescence (NIRF) probe mice using an intravital fluorescence microscopy.

Methods and Results: A novel NIRF probe was fabricated by chemically conjugating glycol chitosan with mannose-PEG, cholesterol and NIRF dyes such as Cy5.5 (ext/emi 675/694 nm). In vitro, MR-Cy5.5 was strongly uptaken by RAW264.7 cells in time- and concentration dependent manner. In vivo plaque imaging was performed in apoE(-/-) mice using a high-speed multi-channel laser scanning microscope 48 hours after i.v. injection of MR-Cy5.5. NIRF signals were much more strongly enhanced in carotid plaques of MR-Cy5.5 injected apoE(-/-) mice compared to non-targeting Cy5.5 injected apoE(-/-) mice or MR-Cy5.5 injected CL57BL/6 control mice (p<0.05). Fluorescence microscopy and immunostaining corroborated the NIRF signals in vivo, which co-localized well with plaque macrophages. MR-Cy5.5 did not show any particular toxicity.

Conclusions: Optical molecular imaging with a MR-NIRF safely allows in vivo detection of the macrophages in murine atheromata. This translatable novel imaging technology may provide an additional avenue for high-risk plaque imaging.
MYOCARDITIS IS A MARKER OF ACTIVE DISEASE IN ARRYTHMOGENIC CARDIOMYOPATHY: ANALYSIS OF CLINICAL FEATURES AND OUTCOMES

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**Objectives:** We aimed to evaluate the clinical features of myocarditis in arrhythmogenic cardiomyopathy (ACM) patients and to see whether they are associated with poor prognosis and a high risk of ventricular arrhythmias.

**Background:** Not only is myocarditis known to be related to arrhythmogenic cardiomyopathy but myocarditis-like episodes seem to be part of its clinical spectrum.

**Methods and Results:** We analyzed two groups: affected ACM patients and their non-affected mutation-carrying relatives. 1. Classical arrhythmogenic right ventricular cardiomyopathy patients (81 patients, 65% males, median age 45±17 years) and left side ACM patients (30 patients, 49% males, median age 42±21 years old) defined by patients carrying a pathogenic mutation associated with ACM alongside a phenotype of dilated cardiomyopathy, a history of ventricular arrhythmias and/or a family history of sudden death. 2. Non affected mutation-carrying relatives (54 cases, 37% males, median age 40±23 years old; 24 from classical ARVC families and 30 from left side ACM). Six (3.6%) patients that presented with a clinical diagnosis of acute myocarditis over a median follow up of 34 months. It was the first clinical manifestation in four patients. Five (4.5%) myocarditis cases occurred in the group of affected ACM patients and one (1.8%) case in the group of non-affected mutation carriers. Blood tests carried out at the time of the episodes did not show an elevation in inflammatory markers. None of the patients before mentioned developed pericardial effusion.

**Conclusions:** Myocarditis may reflect an active phase in ACM and it may be the first clinical presentation. Changes in the phenotype are expected to occur during these phases, ranging from isolated ECG changes to worsening in the systolic dysfunction or ventricular arrhythmia. An active phase should be suspected in the event of myocarditis associated with a family history of ACM.
CYP2C19 GENETIC VARIATION AND INDIVIDUALIZED CLOPIDOGREL PRESCRIPTION IN A CARDIOLOGY CLINIC – A PERSPECTIVE STUDY

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Background: Genetic variation of CYP2C19 leads to altered enzymatic activity that will likely affect clinical efficacy of clopidogrel, which depends on CYP2C19 for activation. FDA recommended genotyping of CYP2C19 prior to initiation of clopidogrel.

Objectives: To evaluate CYP2C19 genetic variations and clinical outcomes of genetic information-guided medicating of clopidogrel.

Methods: DNA sequences of CYP2C19 are analyzed in 301 patients in our clinic; distributions of variant alleles, genotypes and phenotypes are analyzed. Individual clopidogrel recommendation and a follow up plan are made.

Results: The absolute numbers and frequencies of loss-of-function CYP2C19 alleles in the 301 patients are [expressed as: variant: number (frequency)]: *2: 106 (17.6%), *4: 3 (0.5%), *8: 3 (0.5%), and *10: 1 (0.16%). Those of gain-of-function allele are: *17: 119 (19.8%), and those of normal allele are: *1: 370 (61.5%). The phenotype distributions are [expressed as: phenotype (patient number): genotype (patient number)]: Poor-Metabolizer (12): *2/*2 (10), *2/*4 (1) and *2/*8 (1); Intermediate-Metabolizer (63): *1/*2 (59), *1/*4 (2), *1/*8 (1) and *1/*10 (1); Normal-Intermediate-Metabolizer (26): *2/*17 (25) and *8/*17 (1); Normal-Metabolizer (119): *1/*1 (119); Rapid-Metabolizer (69): *1/*17 (69) and UltraRapid-Metabolizer (12): *17/*17 (12). Clopidogrel was switched to prasugrel (less dependent on CYP2C19 for activation) in PM patients, and discontinued in RM and URM patients. For those who’re not on clopidogrel but carry abnormal allele(s), “clopidogrel caution” is documented. Patients are then followed up for one year with a primary endpoint of 1) any ACS-related ER visit/hospitalization, 2) cardiac death and 3) excessive bleeding.

Conclusions/Discussion: The relatively high frequencies of both gain-of-function (18.8%) and loss-of-function (19.8%) alleles in our patients makes genotyping CYP2C19 clinically relevant. The following predictions will be tested in the following year: 1) switching to prasugrel in PM genotype improves clinical outcome; 2) whereas discontinue or lowering clopidogrel doses in RM genotype decrease bleeding risk.
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GENETIC INFORMATION-GUIDED THROMBOEMBOLISM PRECAUTION AND TREATMENT IN A CARDIOLOGY CLINIC – A PERSPECTIVE STUDY
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Background: The G1691A factor V mutation is the most common genetic cause of enhanced risk of venous thrombosis. The G20210A variant of Factor II (Prothrombin) is the second most common genetic defect for inherited thrombosis. The C677T, and to a lesser extent, the A1298C variant of the gene encoding methylenetetrahydrofolate reductase (MTHFR), can lead to decreased enzymatic activities and hence hyperhomocysteinemia.

Objectives: To risk-stratify thromboembolism by evaluating factor-II, factor-V and MTHFR genetic variations and observe overall clinic outcome in our cardiology clinic.

Methods: DNA sequences of factor-II, factor-V and MTHFR are analyzed in 302 patients, and individual recommendation and follow up plan are made based on genotype.

Results: The G/A genotype (moderate risk of thrombosis) of factor V are seen in 4.97% of our population and no A/A genotype are seen. Mutant allele (A) frequency is 2.48%. Similarly, frequency of G/A genotype (moderate risk of thrombosis) of factor II is 2.32%. In contrast, both C677T and A1298C variations of MTHFR gene are common. Genotype of C/T(moderate risk of thrombosis) and T/T(severe risk of thrombosis) at 677 sites are seen in 44.7 and 10.93% of the population respectively. Similar mutation frequency is seen at the 1298 site. “Thromboembolism caution” is documented for patients carrying the above mutation(s). Individual recommendation is made for anti-thrombotic/anti-platelet if relevant. All patients are then followed up for two years with primary endpoints of 1) ACS, PE or DVT events, and 2) all cause death.

Conclusions/Discussion: Based on the known risk for thromboembolism in patient carrying mutations in factor II, factor V and MTHFR, genotype information should be analyzed and made available to facilitate the shared decision-making mechanism with patients in regarding anti-thrombotic / anti-platelet therapy by assisting to weigh the risk vs benefit (bleeding vs thromboembolism). Predicted clinical outcomes will be tested in the following two years.
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DISTRIBUTION OF CORONARY CALCIFICATIONS IN PATIENTS WITH SUSPECTED CORONARY HEART DISEASE
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Background: Coronary calcifications are a marker of coronary atherosclerosis. The role of coronary calcium scoring (CS) as part of the initial evaluation of patients with suspected coronary heart disease (CHD) is controversially discussed. The primary goal of this study was to characterize the coronary calcium distribution in this particular patient population. In a second step we aimed to establish a possible clinical implication utilizing CS for the diagnosis of CHD.

Methods: CS procedure was performed by either using a multidetector or a dual-source CT scanner. All patients underwent invasive coronary angiography (ICA) as the current gold standard for CHD detection. A total of 4,137 (2,780 men; mean age: 60.5±12.4 years) consecutive patients were included.

Results: Mean CS was 288±446 (range: 0-5252). Overall coronary artery calcifications significantly increased with patients’ age. In 2,048 patients (mean CS: 101±239; range: 0-5252) significant CHD (≥50% stenosis) was excluded by ICA (1,939 patients without calcifications). In remaining 2,089 patients (51%; mean CS: 607±821; range: 0-5252) significant CHD was documented leading to intervention in 732 patients. A threshold of zero calcifications (existence of calcified tissue) had the best overall sensitivity and negative predictive value (NPV) with 99%. Overall specificity with 34% and overall positive predictive value (PPV) with 24% were rather low.

Conclusion: Coronary calcium scoring is able to exclude significant CHD in patients with suspected CHD with a high NPV, and therefore possibly reduce the number of invasive diagnostic examinations. Due to the low specificity and PPV CS cannot be used to indicate ICA.
EPICARDIAL ADIPOSE TISSUE THICKNESS UNDERESTIMATE TOTAL CARDIAC FAT CONTENT: COMPARISON OF UNIDIMENSIONAL AND VOLUMETRIC METHODS

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Background. Epicardial adipose tissue (EAT), a form of visceral fat, is associated with coronary artery disease (CAD) risk factors, and directly implicated in pathogenesis of coronary atherosclerosis. Simple unidimensional echocardiographic measurement of EAT thickness overlying the right ventricle has been advocated for quantitative assessment of cardiac fat content (CFC). We aimed to determine the relation of unidimensional EAT thickness to CFC measured volumetrically by multi (64)-detector computed tomography (CT).

Methods. A total of 151 adults [age 26-83 (mean 51±12) years, 55% men, 10% diabetic, 55% hypertensive, 48% hyperlipidemic and 31% smokers] underwent CT coronary angiography for suspected CAD. EAT thickness was measured perpendicular to the right ventricular free wall in a transverse mid-ventricular slice and total CFC was measured by semi-automated densitometry.

Results. EAT thickness ranged from 0-10.8 (mean 2.3±1617;2.4) mm and correlated directly with CFC [25-274 (122±47) ml] (r=0.52, p<0.001) [Figure]. EAT thickness also correlated directly with coronary calcium score (r=0.19, p=0.03) and with age (r=0.24, p=0.003) but not with gender, total cholesterol, high-density cholesterol, presence of hypertension or diabetes or history of smoking. Despite statistical correlation of EAT thickness and CFC, a sizable proportion of the patients with up to 160 ml of cardiac adipose tissue showed no or minimal deposition of fat over the anterior epicardium [Figure].

Conclusion. Simple, unidimensional measurement of EAT thickness may underestimates CFC in many patients with moderate to large increases in cardiac adipose tissue.
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SHARED MEDICAL APPOINTMENT TO PRE-SCREEN CCTA PATIENTS - A NOVEL APPROACH IN ESTABLISHING CARDIAC CT PROGRAM

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Background: Coronary computed tomography angiography (CCTA) is increasingly used as an effective non-invasive method to optimally visualize coronary artery anatomy. However, CCTA is not an optimal option for patients with an uncontrolled heart rate and renal disease. Patients are often pre-medicated with beta blockers to control heart rate, as increased heart rate adversely effects image quality. Similarly, for better visualization sublingual nitroglycerin is used to vasodilate the coronary vessels. This requires phosphodiesterase type 5 inhibitors to be stopped 24-48 hours prior to the test. Similarly metformin is held, and pre-medication for contrast allergy is given if needed prior to the test. Without proper pre-screening, tests are usually delayed or cancelled or have non-diagnostic results. This has impact on hospital finances, scheduling and patient’s comfort.

Aim: We propose a novel and cost effective approach of using shared medical appointment (SMA) clinic to prescreen multiple CCTA patients, to avoid delays or cancellations.

Methods: Our cardiac CT program at phoenix VA was established in 2013. The percentage of non-diagnostic or cancelled studies due to improper screening was 25% in the year 2013. In 2014 we established SMA clinic, in which the patients are seen by a cardiology provider and a cardiac nurse, with 4-8 patients screened in 1-2 hours. Screening is done based on the established indications and contraindications of CCTA. We conducted a patient survey after the Cardiac CT was performed.

Results: We were able to demonstrate that patients pre-screened in SMA clinic had fewer rescheduled or cancelled appointments and only 5% (4/80) of patients had non-diagnostic studies. Patient’s survey demonstrated more confidence and the satisfaction in the test results.

Conclusion: SMA clinic improved utilization of available resources by reducing rescheduled CCTA appointments, improving the quality of studies and reducing adverse reactions. A structured CCTA program needs a good pre-screening program.
LIPIDS, LIPOPROTEIN DISORDERS AND CAD

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CLINICAL IMPLICATIONS OF THE EICOSAPENTAENOIC ACID TO ARACHIDONIC ACID RATIO IN PATIENTS WITH CORONARY ARTERY DISEASE

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Background: The ratio of eicosapentaenoic acid (EPA) to arachidonic acid (AA) (EPA/AA) has been reported to be lower in patients with coronary artery disease (CAD) than non-CAD population. However, it is unclear whether this parameter is related to clinical manifestations of CAD, acute coronary syndrome (ACS) or stable angina pectoris (SAP). The aim of this study was to assess the impact of EPA/AA ratio on the clinical manifestations of CAD.

Methods: The serum EPA/AA ratio was examined in 236 patients with CAD, 160 with ACS and 76 with SAP, who underwent percutaneous coronary intervention. The determinants of clinical manifestations were analyzed among the patient characteristics, coronary risk factors, and lipid profiles.

Results: Serum EPA level and EPA/AA ratio were significantly lower and low density lipoprotein-cholesterol (LDL-C) level was significantly higher in patients with ACS compared with SAP (49.7±34.0 vs. 60.6±30.8 μg/ml, 0.33±0.23 vs. 0.39±0.22 and 117.2±37.0 vs. 99.8±28.5 mg/dl p<0.05, respectively). Hypertension, dyslipidemia, angiotensin converting enzyme inhibitor/angiotensin receptor blockers (ACE-I/ARBs) use and statin use were more frequent in the SAP group and smoking was more common in the ACS group. Multiple logistic regression analysis revealed that less ACE-I/ARBs use, less statin use, and low EPA/AA ratio correlated independently with clinical manifestations of ACS.

Conclusions: Serum EPA/AA ratio was one of the important determinant factors for development of ACS in patients with CAD.
EFFICACY AND TOLERABILITY OF TWO DIFFERENT FORMULATIONS OF ATORVASTATIN IN PATIENTS WITH HYPERCHOLESTEROLEMIA; MULTICENTER, PROSPECTIVE, RANDOMIZED TRIAL

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Objective: Atorvastatin is widely used to decrease low density lipoprotein cholesterol (LDL-C) level and improve cardiovascular outcomes. We designed this study to compare the efficacy and tolerability of generic formulation and original reference formulation (Lipitor) of atorvastatin, both at 20 mg once daily in patients with primary hypercholesterolemia.

Methods: This study was a prospective double blind, randomized study. Hypercholesterolemic patients who did not achieve LDL cholesterol goal according to NCEP-ATP III guideline were randomized to generic formulation or reference formulation of atorvastatin 20 mg/day for 8 weeks. The primary endpoint was percent change of LDL-C level from baseline to week 8. Secondary endpoints included the percent change in total cholesterol, triglyceride, high density lipoprotein cholesterol (HDL-C) level, apolipoprotein B/A1 ratio, LDL/HDL ratio, LDL-C particle size, high-sensitivity C reactive protein (hs-CRP) from baseline to week 8 and achievement rate of LDL-C goal.

Results: 184 patients (92 per each group, 59.5±9 years) were included. LDL-C level was significantly decreased from baseline to week 8 in both groups and there was no significant difference of percent change of LDL-C level between groups (-38.3±13.3% in test group, -40.6±11.9% in reference group, P=0.49). The between-group differences in percent changes of total cholesterol and triglyceride level were not statistically significant. And there was no significant difference between two groups in percent changes of HDL-C, apolipoprotein B/A1, LDL-C/HDL-C, LDL-C particle size, hs-CRP and achievement rate of LDL-C goal. None of study group experienced treatment-related serious adverse events. Three patients (3.3%) of test formulation group and four patients (4.4%) of reference formulation group showed mild treatment related adverse events but there were no significant differences between two groups.

Conclusions: There were no significant differences in the efficacy and tolerability between the test and reference formulations of atorvastatin in patients with primary hypercholesterolemia.
LIPOPROTEIN FRACTIONS AND SUBFRACTIONS IN A MURINE MODEL OF EARLY ATHEROSCLEROSIS

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Objective: To evaluate the effect of repeated P-407 treatment on lipoprotein fractions and subfractions, as well as the onset of atherosclerosis, in a mouse model of early atherosclerosis.

Background: Early diagnosis and changes associated with atherosclerosis are important to clinical medicine. Chronic administration of poloxamer 407 (P-407) produces atherosclerosis in mice with significant dislipidemia and damage to heart vessels.

Methods: We induced early atherosclerosis in mice by using repeated P-407 administration (300 mg/kg, twice per week, 30 days) so as to produce a sustained atherogenic serum lipid profile. A small-angle X-ray scattering (SAXS) method was used for the determination of the fractional and subfractional composition of lipoprotein-cholesterol (LP-C) and lipoprotein-triglyceride (LP-TG) fractions and subfractions.

Results: Mice with early development of atherosclerosis revealed significant dyslipidemia, moderately elevated blood pressure, general lipidosis (lipid deposition in liver cells), and contractile-type changes in cardiomyocytes. The steady-state serum total cholesterol and TG were significantly greater for mice repeatedly treated with P-407 than corresponding values observed following a single dose of P-407 and, therefore, serum lipids returned to baseline values more slowly for mice chronically treated with P-407.

The onset of atherosclerosis was characterized by a steady increase in atherogenic subfractions typical of atherosclerosis observed in humans; namely, an increase in low-density LP (LDL), intermediate-density LP (IDL), and very-low-density LP (VLDL, subfractions VLDL3-5, VLDL1-2).

Conclusions: SAXS was useful in revealing the early changes in the LP-C and LP-TG subfractions during the onset of experimental atherosclerosis.
PSYCHIATRIC COMORBIDITY AFTER ACUTE MYOCARDIAL INFARCTION: A POPULATION-BASED COHORT STUDY

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Objectives: To explore the longitudinal course of psychiatric comorbidity after an acute myocardial infarction (MI) and to investigate whether risk factors for psychiatric comorbidity are associated with outcomes in the aftermath of MI.

Background: Acute MI is not only a life-threatening disease, but also a traumatic event for patients. Previous studies showed that pre-existing psychiatric disorders increase the risk of incident coronary heart disease, low quality of life, poor medication adherence and all-cause mortality among patients following an acute MI. It is unclear, however, whether this association between mental illness and the recurrence of MI is present after an MI.

Methods: A nationwide population-based study was conducted using the Taiwan National Health Insurance database from 1 million sampling cohort dataset. As MI cases, we selected all hospitalized patients due to a first MI in 2006. As controls, we selected individuals who had never been admitted to hospitals. Those who had been diagnosed with any psychiatric disorders were excluded.

Results: A total of 3,151 patients suffered from an acute MI and 6,736 controls. During 5-year follow-up, the incidence rates of any psychiatric disorders were 8.2% and 2.8% in the MI and control groups, respectively. MI patients with psychiatric comorbidity were younger than those with psychiatric disorders in the control group. In addition, the risk of psychiatric disorders was the highest during the first year following an acute MI (hazard ratio [HR], 1.28; 95% confidence interval [CI], 1.06-1.54) than the control group and so was the recurrence of MI (HR, 1.50; 95%CI, 1.07-2.08).

Conclusions: Acute MI is followed by an increased risk of psychiatric comorbidity and the recurrence of MI, suggesting the importance of early identifying patients with MI for a range of mental disorders to prevent patients from another heart attack, especially at a young age.
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PREVALENCE AND DETERMINANTS OF INSOMNIA FOLLOWING A MYOCARDIAL INFARCTION

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Objectives: Insomnia in the general population has been associated with significant daytime dysfunction including fatigue, depression, and poorer health-related quality of life (HRQoL). Sleep difficulties have been understudied in patients following a myocardial infarction (MI). The aim of this study was to examine the prevalence and factors associated with insomnia at 4-6 weeks following a MI.

Methods: 155 men (mean age 62.0, SD 11.3) and 58 women (mean age 66.0, SD 12.6) completed standardized self-report questionnaires regarding insomnia (Insomnia Severity Index-ISI) HRQoL, and various sociodemographic, clinical, behavioral and psychosocial variables at 4-6 weeks following a MI. Statistical analysis examined the relationship between insomnia severity and sociodemographic, clinical, behavioural and psychosocial factors.

Results: ISI scores suggestive of clinical insomnia (ISI were reported in 18.7% of the sample (17.9% men; 20.7% women), with another 26.3% reporting symptoms at a subthreshold level (24.5% men; 31% women). Patients experiencing insomnia reported poorer HRQoL across all 8 domains, including physical functioning, role limitations due to physical health problems, bodily pain, vitality, and social functioning). Multivariate linear regression analyses stratified by gender showed common and specific independent factors associated with insomnia in men and women following a MI. For men, greater dysfunctional sleep beliefs (p<.001) and elevated depressive symptoms (p=0.002) were associated with increased insomnia symptoms. In women, greater dysfunctional beliefs (p=0.035), alcohol intake (p=0.004) and younger age (p=0.043) was associated with insomnia severity.

Conclusion: Our data suggest that following a MI men and women have common and specific risk factors associated with insomnia. Identification and treatment targeting modifiable factors such as dysfunctional sleep related thoughts, depressed mood, and unhealthy lifestyle factors may form the basis of a gender-tailored intervention program for the reduction of insomnia in persons following a myocardial infarction.
HBA1C AMONG ANGIOGRAPHIED CORONARY PATIENTS MORE STRONGLY PREDICTS CARDIOVASCULAR RISK IN WOMEN THAN IN MEN

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Background and Objectives: The power of HbA1c to predict future cardiovascular events in the clinically important high-risk population of patients undergoing coronary angiography has not been investigated so far. In the present study we therefore addressed this issue and also tested the hypothesis that gender modulates the impact of HbA1c on cardiovascular event risk.

Methods and Results: We prospectively recorded cardiovascular events over a mean follow-up period of 4.4 years in a large consecutive series of 1449 patients, including 484 women and 965 men who did not have previously known diabetes and who underwent coronary angiography for the evaluation of stable coronary artery disease. During follow-up, the incidence of cardiovascular events was 19.5% in women and 25.6% in men, corresponding to annual event rates of 4.4% and 5.8%; p = 0.001. Among women, HbA1c strongly and significantly predicted cardiovascular events (adjusted OR for a 1% increase in HbA1c = 1.69 [1.16-2.45]; p = 0.006), whereas the association between HbA1c and cardiovascular events was weaker and statistically non-significant in men (OR = 1.15 [0.95-1.39]; p = 0.147. An interaction term gender x HbA1c was significant (p = 0.024), indicating that HbA1c was a significantly stronger predictor of cardiovascular events among women than among men.

Conclusions: We conclude that HbA1c is a significantly stronger predictor of cardiovascular event risk in women than in men among patients undergoing coronary angiography.
PROBNP STRONGLY PREDICTS VASCULAR EVENTS INDEPENDENTLY FROM THE ANGIOGRAPHICALLY DETERMINED CORONARY ARTERY STATE

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Background and Objectives: The power of pro-B-type natriuretic peptide (proBNP) to predict cardiovascular events is unclear, in particular in patients with type 2 diabetes (T2DM). We therefore aimed at investigating whether proBNP predicts major cardiovascular events in patients with T2DM as well as in subjects without diabetes in a large cohort of patients characterized by coronary angiography at baseline.

Methods and Results: We prospectively recorded major cardiovascular events in a cohort of 718 consecutive patients undergoing coronary angiography for the evaluation of established or suspected stable CAD over 3.2±1.2 years. Overall, the incidence of cardiovascular events was higher among patients with T2DM than among subjects who did not have diabetes. Cardiovascular risk increased significantly over tertiles of proBNP both among patients with diabetes (6.3%, 24.1%, and 32.4%; p = 0.004) and among non-diabetic subjects (11.5%, 11.4%, and 21.1%; p = 0.012). Also as a continuous variable, baseline proBNP proved strongly predictive of major cardiovascular events both among patients with T2DM and among non-diabetic subjects (standardized adjusted HRs = 1.40 [1.12 - 1.74], p = 0.003 and 1.19 [1.06 - 1.33], p = 0.003, respectively) after adjustment for age, gender, BMI, LDL cholesterol, HDL cholesterol, hypertension, and smoking. Additional adjustment for the angiographically determined baseline presence of CAD did not significantly attenuate these results.

Conclusions: We conclude that proBNP both among patients with type 2 diabetes and among non-diabetic subjects strongly predicts future macrovascular events independently from the baseline coronary artery disease state.
ASSOCIATION OF FRIESINGER SCORE AND ELEVATED SERUM TRANSAMINASE LEVELS IN OCTOGENARIANS

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Introduction: Studies have linked elevated serum aspartate transaminase (AST) and alanine transaminase (ALT) levels to acute ST-elevation myocardial infarction (STEMI). We examined association between elevated AST, ALT levels (>35 IU) and angiographic coronary artery disease (CAD) in absence of STEMI, in Octogenarians.

Methods: A retrospective analysis of Octogenarians who underwent elective coronary catheterization between 2008-2012 was done. 419 patients without acute STEMI, alcoholism or viral hepatitis were included. All had serum AST, ALT levels measured. Friesinger score (FS) was used to determine angiographic severity of CAD. A score ≥5 was considered as extensive CAD. The two cohorts, a) AST, ALT >35 IU and b) AST, ALT ≤ 35 IU were compared.

Results: Elevated AST, ALT levels were associated with a higher FS (5.15 vs. 4.13, p=0.004), greater prevalence of extensive CAD, (FS > 5) (48.9% vs. 36%, p=0.008), a higher mean vessel score (2.10 vs. 1.72, p=0.016) and a higher triple vessel CAD (45.0% vs 34.3%, p=0.026). On logistic regression, elevated AST, ALT levels were associated with an increased risk of having FS ≥5 (OR=1.70, p=0.008, 95%CI: 1.15-2.52), significant after adjusting for age, sex, BMI, diabetes, hypertension, dyslipidemia and smoking (OR=1.73, p=0.010, 95%CI: 1.14-2.64)

Conclusions: Elevated AST, ALT levels are a marker of more severe angiographic CAD in Octogenarians, as measured by Friesinger score, even in the absence of STEMI.

<table>
<thead>
<tr>
<th>Total patients (N)= 419</th>
<th>ALT,AST≤35 (n=239)</th>
<th>ALT or AST&gt;35 (n=180)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Baseline Characteristics</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>84.55±4.13</td>
<td>84.74±3.94</td>
<td>0.626 (t)</td>
</tr>
<tr>
<td>Women</td>
<td>117(48.95%)</td>
<td>93(51.66%)</td>
<td>0.582*</td>
</tr>
<tr>
<td>Race (Caucasian)</td>
<td>189(79.1%)</td>
<td>148(82.2%)</td>
<td>0.282*</td>
</tr>
<tr>
<td>BMI</td>
<td>27.92±0.39</td>
<td>27.82±0.65</td>
<td>0.894 (t)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>85(35.6%)</td>
<td>73(40.6%)</td>
<td>0.297*</td>
</tr>
<tr>
<td>Hypertension</td>
<td>213(89.1%)</td>
<td>161(89.4%)</td>
<td>0.916*</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>196(82.0%)</td>
<td>155(86.1%)</td>
<td>0.26*</td>
</tr>
<tr>
<td>Smoking :Never</td>
<td>111(46.4%)</td>
<td>83(46.1%)</td>
<td>0.552*</td>
</tr>
<tr>
<td>Current</td>
<td>8(3.3%)</td>
<td>3(1.7%)</td>
<td></td>
</tr>
<tr>
<td>Former</td>
<td>120(50.2%)</td>
<td>94(52.2%)</td>
<td></td>
</tr>
<tr>
<td><strong>Outcomes</strong></td>
<td></td>
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</tr>
<tr>
<td>Friesinger score (mean)</td>
<td>4.13±0.21</td>
<td>5.15±0.29</td>
<td>0.004 (t)</td>
</tr>
<tr>
<td>Friesinger score ≥5</td>
<td>86(36.0%)</td>
<td>88(48.9%)</td>
<td>0.008*</td>
</tr>
<tr>
<td>Triple Vessel CAD</td>
<td>82(34.3%)</td>
<td>81(45.0%)</td>
<td>0.026*</td>
</tr>
<tr>
<td>Mean Vessel Score</td>
<td>1.72±0.10</td>
<td>2.10±0.12</td>
<td>0.016 (t)</td>
</tr>
<tr>
<td>(t) unpaired t test</td>
<td>* Chi sq test</td>
<td>Expressed as mean±SEM</td>
<td></td>
</tr>
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</table>

(t) unpaired t test              * Chi sq test

Expressed as mean±SEM
Cigarette smoking is one of the major risk factors for cardiovascular disease while the association between smoking and coronary atherosclerosis is well established, the impact on left and especially right ventricular diastolic function has been unknown; in this study we assessed the result of acute and chronic smoking on left and right ventricular diastolic function.

Methods: 50 healthy smokers and 50 non smoker (control) (age<40 years, BMI<25 kg/m2) enrolled. Mitral inflow(Em, Am) and tricuspid inflow(E t,A t) as well as annulus velocity diastolic parameters with echocardiography were obtained before, 5 min and 30 min after smoking in case group and compared with control group.

Results: Late diastolic mitral inflow (Am) and late diastolic mitral annular velocity (ams) significantly increase. After 5 minutes, isovolumic relaxation time(IVRT) prolonged and (ams) increased that be regarding to impaired LV diastolic function. Et remained significantly decreased and ams and At increased. diastolic blood pressure (DBP) after 5 min increased and after 30 min, returned to baseline. pulmonary artery pressure before and after smoking was not changed.

Conclusion: LV diastolic function impaired after chronic smoking but RV diastolic function was not changed. acute smoking caused RV and LV diastolic dysfunction. the changes in mitral and tricuspid parameters remained unaltered even 30 min afterward, although DBP returned to normal. the mechanism behind this effect cannot be explained only by changing in DBP and PAP.
DETERMINANTS OF THE HEALTH-RELATED QUALITY OF LIFE IN MALE PATIENTS WITH CORONARY ARTERY DISEASE

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Background: Health-related quality of life (HRQoL) measures can help evaluate the physical, mental and emotional implications of cardiovascular disease (CVD) as well as the effects of medical interventions. HRQoL is a useful tool to clinicians in terms of evaluating the impact of CVD on patients and may improve decision-making and resource allocation.

Objectives: We sought to investigate the cardiovascular confounding factors for HRQoL in male patients with coronary artery disease (CAD) by using EQ-5D questionnaire.

Materials & Methods: A total of 63 male patients (59.3 ±11.8 years) with CAD were recruited to the study. All clinical, laboratory parameters, medications and abnormalities detected by echocardiography were recorded. Patients were screened for QoL by using EQ-5D questionnaire. The EQ visual analogue scale (EQ VAS) was used as a quantitative measure. Relation between the EQ-5D score and 5 dimensions of questionnaire with all clinical, echocardiographic and demographic parameters was investigated.

Results: The EQ VAS and EQ-5D scores were 71.97±19.25 and 0.72±0.21, respectively. Aging, BMI, DM, previous CABG, complete blood count and blood chemistry, remaining echocardiographic and clinical parameters and distribution of CAD did not cause any significant difference on EQ-5D and VAS scores. EQ-5D score was higher in patients with pulmonary arterial hypertension than those without (0.74±0.19 vs. 0.56±0.25, p=0.025). There was significant difference in the anxiety/depression score between groups categorized according to presence of the low EF or LV diastolic dysfunction (p<0.05). Regression analysis revealed that one point increment of heart rate yields to 0.03 point rise of EQ-5D score and one point increment of EF yields to 0.06 point rise of EQ-5D score.

Conclusion: Ventricular diameters and pulmonary artery pressure can affect the HRQoL, in addition heart rate and EF have strong impact on the HRQoL score index assessed by EQ-5D questionnaire in male patients with CAD.
HYPOMAGNESAEMIA IN MENOPAUSAL WOMEN; RELATIONSHIPS WITH ATHEROSCLEROSIS RISK FACTORS AND LOW LEVEL INFLAMMATORY SYNDROME IN PATIENTS WITH CARDIOVASCULAR DISEASE

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Objectives: To study relationships between hypomagnesaemia (HMg) and presence of "classical" cardiovascular risk factors and of inflammatory syndrome (C reactive protein -CRP-, serum fibrinogen -Fb-, divers cytokines, etc.).

Methods: Was studied 151 women admitted in hospital with mean age 67±9 years, in a mean interval from menopause beginning of 6.7 years. The data analysis was effectuated by comparison of the incidence of the coronary risk factors linked to HMg.

Results: Coronary disease was presented as: history of myocardial infarction (45%), angina pectoris (31%), ischemic cardiomyopathy (5%), stroke (5%), atrial fibrillation (27%). Mean serum cholesterol was 217±58mg%, smoking index 106±26, systolic arterial pressure 155±29mmHg, mean missing teeth 16±11, presence of high CRP level in 35.4%, Fb 448 ±94mg%, serum calcium 9,5±0.9mg%, serum magnesium 2.2±0. mg%. The comparison of the women with normal or reduced levels of serum Mg (Mg LT 1.8mg%, 51 patients), shown significant differences for: age 66±8 years in normal Mg group, versus 70±9 years in reduced Mg group (P LT 0.001); high CRP level in 26%, versus 44%, (P LT 0.04); body height of the women (LT 1.5 m) from normal Mg group in 25%, versus 43% in reduced Mg group (P LT 0.04). We found not a relationship between the Mg level and the other coronary risk factors as cholesterol, smoking, missing teeth, and so.

Conclusions: The HMg intervenes mainly by alteration of: membrane ions exchange, functionality of endothelium, insulin resistance, inflammation mechanism. In menopausal women with ischemic heart disease. Magnesium deficit may be important and is found in patients more aged, with reduced body height, and with increased serum level of CRP. These data may have some therapy consequences: correction of HMg, check of magnesium level regularly, especially in menopausal women with described characteristics.
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MACRONUTRIENT INTAKE IS NOT ASSOCIATED WITH CORONARY ARTERY CALCIFICATION IN HEALTHY KOREAN ADULTS
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Background: Macronutrients influence cardiovascular disease but there is little information supporting the relationships between coronary artery calcification (CAC) as a measure of pre-clinical atherosclerosis and macronutrients.
Objectives: The aim of this study was to identify whether macronutrient intake is related with CAC in healthy Korean adults.
Design: 10,793 subjects (9,429 men and 1,364 women) in a cohort who participated in a comprehensive health examination were enrolled. The CAC score, and anthropometric and biochemical markers were measured. Subjects were divided into two groups: CAC (CAC score >0) or non-CAC group (CAC score =0). Nutrient intake including energy, carbohydrate (CHO), protein and fat were obtained using food frequency questionnaire (FFQ) data. Macronutrient intake was expressed as the ratio of energy from each macronutrient to total energy. Subjects were classified into three groups by tertiles of intake for each macronutrient.
Results: In adjusted analysis, prevalence of CAC significantly differed among tertile groups of CHO and fat intake in men (p<0.001, p<0.01) and women (p<0.05, p<0.01). However, multiple logistic regression analysis revealed that the odds ratios (ORs) for CAC were not significantly different according to tertile groups of each macronutrient intake after adjustment in men (CHO; OR=0.961 [95% CI=0.824-1.122], protein; OR=1.016 [95% CI=0.870-1.186], fat; OR=1.213 [95% CI=0.895-1.643] and women (CHO; OR=1.160 [95% CI=0.552-2.440, protein; OR=1.261 [95% CI=0.629-2.528], fat; OR=0.627 [95% CI=0.288-1.365]). Highest energy intake group showed significantly lower ORs for CAC than lowest energy intake group in multivariate models only in men (OR=0.775 [95% CI=0.663-0.907], p<0.01). This significance was not observed in women.
Conclusions: The presence of CAC was not associated with energy intake or macronutrient intake.
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RISK OF STROKE AND MYOCARDIAL INFARCTION IN WOMEN WITH LOW SOCIAL SUPPORT IN RUSSIA OVER 16 YEARS: MONICA-PSYCHOSOCIAL EPIDEMIOLOGICAL STUDY

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Objective: To study the effect of social support (SS) on relative risk of stroke and myocardial infarction (MI) in female population of 25-64 years in Russia over 16 years of follow-up.

Methods: Under the third screening of the WHO "MONICA-psychosocial" program random representative sample of women aged 25-64 years (n=870) were surveyed in Novosibirsk. Berkman-Sym test was used to measure indices of close contacts (ICC) and social network (SNI). From 1995 to 2010 women were followed for the incidence of stroke and MI with using Myocardial Infarction Registry data. Cox regression model was used for relative risk assessment (HR) of stroke, MI.

Results: Low levels of ICC and SNI was revealed in 57.1% and 77.7% of women, respectively. Stroke was developed in 5.1% of women, MI – in 2.2%. HR of MI over 16 years of study were in 4.9-fold (95.0%CI:1.108-21.762; p<0.05) and 2.9-fold (95.0%CI:1.040-8.208; p<0.05) higher for low ICC and SNI, respectively compared to higher SS levels. HR of stroke was 4.1 (95.0%CI:1.193-14.055; p<0.05) and 2.7 (95.0%CI:1.094-6.763; p<0.05) for low ICC and SNI, respectively. Married and unmarried women with low ICC and hard physical workers with low ICC and SNI had higher rate of stroke development (p for all<0.05).

Conclusions: The prevalence of low SS in women aged 25-64 in Russia is high. Risk of stroke and MI over 16 years of study was significantly higher in women with low ICC and SNI, especially in married ones in manual labor class.
Background: Cardiovascular disease is the leading cause of death in the United States. In the last decades, preventive measures have achieved a remarkable reduction in cardiovascular mortality. However, cardiovascular disease prevention is difficult to implement in a low socioeconomic status (SES) population due to lack of access to medical care, greater patient mobility and cultural barriers. In this study, we examine the impact of a cardiovascular charity clinic on risk factor reduction of a low income, uninsured population over 20 years.

Methods: Medical records of 301 patients that visited the clinic between 1990 and 2010 were used to extract demographic and medical information related to their cardiovascular risk profile. These parameters included age, sex, blood pressure, lipid panel, fasting blood glucose and body mass index (BMI). The trends of each measurement and Framingham score were examined over time.

Results: We observed a significant improvement in multiple modifiable risk factors. Patients reduced their systolic (1.85 mmHg/year) and diastolic (1.38 mmHg/year) blood pressures, fasting glucose (5.48 mg/dL/year), total cholesterol (6.82 mg/dL/year), LDL (5.72 mg/dL/year), triglycerides (12.57 mg/dL/year) and increased HDL (1.02 mg/dL/year). This resulted in the overall reduction of Framingham score (0.28 points/year) in a high-risk group.

Conclusions: Provision of accessible medical care to a low SES population has achieved a reduction in cardiovascular risk factors, which translates into decreased cardiovascular morbidity and improved health of the community.
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CHRONIC HEART FAILURE PATIENTS WITH REDUCED VERSUS PRESERVED EJECTION FRACTION IN SAUDI ARABIAN COHORT

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Purpose: Patients with heart failure and preserved ejection fraction (HFpEF) have more or less different clinical profile than patients with heart failure and reduced ejection (HFrEF). We aimed to study this clinical profile differences and outcome in a cohort of heart failure patients followed in the heart failure clinic in a tertiary care center in Saudi Arabia.

Methods: We conducted a prospective study for high risk chronic heart failure patients (HRCHF) patients in a tertiary care center in Saudi Arabia between October 2009 and October 2011. We compared HRCHF patients with reduced ejection fraction (EF< 40%) versus those with preserved (EF > 40%).

Results: The study enrolled 436 patients with median age (IQR) of 58.2 (14) years; 69% men, 95% Saudis; and 74.1% had reduced EF. Patients with reduced EF were relatively younger (56.2% vs 63.2%), more likely to be males (71.5% vs 47%) and current/ex-smokers (37.2% vs 26.7%), and less likely to have history of diabetes mellitus (54.2% vs 68%) and hypertension (58% vs 75%). They were more likely to have ischemic heart disease (45.6% vs 38%) and idiopathic dilated cardiomyopathy (32.8% vs 4%) rather than hypertensive (5% vs 32%) or primary valvular (6.7% vs 11%) heart disease as the main etiologies. They were more likely to be treated with, beta-blockers (92.8% vs 77.2%), ACE-I/ARB (85% vs 73%), aldosterone inhibitor (43.3% vs 16.7%), digitalis (28.4% vs 16.2%), and ICD/CRT (22% vs 2%) (P-value was significant for all above comparisons). The overall 1 year mortality rate was 13% vs 12% and the 1 year re-admission rate 42% vs 38% with nonsignificant P value.

Conclusions: HRCHF patients in Saudi Arabia are younger in age, and predominantly have reduced EF compared with patients in the developed countries.
Background: Ventricular assist devices (VAD) have become an established therapy for patients with end-stage heart failure. The two main reasons for this development are the shortage of appropriate donor organs and the increasing number of patients waiting for heart transplantation (HTX). Furthermore, the enormous advances in the technical equipment and the rising clinical experience have improved the implantation technique, the durability and the long-term patient outcomes.

Methods: We reviewed all cases of left ventricular assist device (LVAD) implantation at our Erlangen Heart Center during January 2000 - July 2013. The main aim of this study was to analyze the underlying pathology from the cardiac apex removed during the implantation. From all patients, we created a follow-up, analyzed the pathological features with the clinical diagnoses and described the overall outcome.

Results: VAD implantation was performed in 266 cases at our center in the last 13 years. From these patients 223 underwent LVAD or biventricular (BVAD) implantation; the remaining received a right (RVAD) implantation. The most frequent underlying clinical diagnoses were dilated (n=84, 37.7%, DCM) or ischemic (n=61, 27.4%, ICM) cardiomyopathy. The pathological findings in the apex biopsy were generally non-specific and showed variable interstitial myocardial fibrosis with evidence of fibre loss, fatty degeneration and variable irregular atrophy of muscle fibres, consistent with dilated and ischemic cardiomyopathies as the most frequent causes of heart failure in these patients.

Conclusion: Pathological findings in cardiac apex removed during LAVD implantation are rather non-specific and they generally reflect the late stage or consequences of chronic myocardial damage in cases of dilated or ischemic cardiomyopathies. Variable patchy chronic inflammatory changes may be observed in cardiomyopathies as a non-specific reaction caused by myocardial fiber damage and should not lead to misinterpretation as evidence of myocarditis or revision of original diagnosis.
TRENDS IN INTRA-AORTIC BALLOON PUMP USE OVER TIME WITH INDICATION FOR USE

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Introduction: The Intra-Aortic Balloon Pump (IABP) was first used in 1968. Since its development clinicians have expanded its use from patients with Acute Myocardial Infarctions with Cardiogenic Shock (AMI w/ CS) to include pre-operative use before CABG, valve replacement surgery, and LVAD placement. Additional clinical studies have evaluated prophylactic IABP use prior to high-risk PCI and AMI w/o CS. The aim of this study was to review indication and early outcomes after IABP placement.

Methods: In this retrospective study we included all patients with an IABP placed in the cardiac catheterization suite between January 2008 and December 2013. The primary analysis was overall trends in IABP use over time by indications. Secondary analysis included 30 day all-cause mortality rate, 1 year hospital re-admission rate, and 1 year all-cause mortality rate. The main safety analysis was IABP complications including thrombocytopenia.

Results: There were a total of 610 patients included in this retrospective review. The most common indication for IABP placement was AMI w/ CS. The total number of IABPs placed per year varied from 83 up to 145, but there was no significant trend in total numbers placed. The overall 30 day mortality rate was 18% with the highest rate associated AMI w/ CS (32%). The 1 year re-admission rate was 47%, and the 1 year all-cause mortality rate was 26% with the highest rate associated with AMI w/ CS (37%). There were 25 complications associated with the IABP (4%) and 39 patients (6%) developed thrombocytopenia requiring HIT testing.

Conclusions: Overall, there was no significant change in the total number of IABPs placed per year; however there was a significant decrease in IABP use for High-risk PCI. Independent factors that portend a poor 30 day outcome included placement for AMI w/ CS, advanced age, specifically age >75, and elevated lactate.
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DEPRESSION AND DECREASED RISK OF IN-HOSPITAL MORTALITY AMONG HEART TRANSPLANT RECIPIENTS: FINDINGS FROM A US NATIONAL STUDY


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Background: Depression is a common problem among patients awaiting heart transplantation, but little is known about the impact of pre-transplant depression and its treatment on outcomes of heart transplantation.

Methods: Of 13,961 heart transplant recipients (ICD-9 procedure code 37.51) within the Nationwide Inpatient Sample (NIS) datasets 2003-2010, 1,199 (8.6%) had pre-transplant depression (defined as AHRQ comorbidity variable, based on ICD-9 and DRG codes). Multivariable logistic regression models were used to measure the association of depression and in-hospital outcomes among these patients.

Results: Prevalence of pre-transplant depression among heart transplant recipients increased from 5.7% in 2003 to 9.3% in 2010 (Trend P, <0.001). In-hospital mortality occurred in 2.5% and 5.5% of heart transplant recipients with and without depression, respectively (Adj. odds ratio {OR}, 0.60; 95% confidence interval {CI}, 0.41-0.88; P<0.001). Pre-transplant depression was not associated with a prolonged hospital stay and total hospital charge (Table).

Conclusion: Prevalence of pre-transplant depression among heart-transplant recipients was low but steadily increased over time and was associated with lower risk of in-hospital mortality. Whether this is the result of a true but paradoxical association, confounding, or an under-diagnosis phenomena needs further research.
A NEW CLASSIFICATION FOR CORONARY ARTERY BIFURCATION LESIONS

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Objectives, Background: Coronary lesions located on the bifurcations of coronary arteries, present a wide range of both angiographic and anatomical types. The simplest and most useful classification, so far, has been the one proposed by Medina and colleagues, in 2006. Despite the usefulness of the Medina classification, there is lack of description of important characteristics of bifurcation lesions.

We propose a modification of the Medina classification which is more detailed, adding some of the features, we consider important for an accurate description of a bifurcation lesion.

Methods: We call this classification, the PDS Medina classification, were P, stands for proximal main vessel, S for the side branch and D for the distal main branch. When the main proximal or distal vessel is less than 3mm, then we use the upper case letters P or D and when it is more than 3mm, we use lower case letters p or d, respectively. The same for the side branch, but the cutting point is 2mm. When the side branch is more than 2mm, we use the upper case S and when it is less than 2mm, we use the lower case letters.

In order to describe the side branch angulation, we propose to use more if the angle is more than 70 degrees and less, when it is less than 70 degrees. If there is a need to describe more futures upper case corresponding letters can be used, like C for calcification.

Results: As an example, I,0,I, PdS less, stands for main branch bigger than 3mm, distal branch smaller than 3mm and side branch bigger than 2mm. The side branch angulation is more than 70 degrees.

Conclusions: This classification without adding significant complexity in the description of a bifurcation lesion, gives important information about the characteristics of such a lesion.
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ARE AIRBAGS PROTECTIVE OR DETRIMENTAL TO THE HEART POST MOTOR VEHICLE ACCIDENTS?
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Background: Airbags have been shown to decrease morbidity and mortality associated with motor vehicle accidents (MVA) when used in conjunction with seat belts. Airbag deployment alone however, has recently been implicated as a cause of significant thoracic injuries to unrestrained drivers. This includes major cardiovascular and pulmonary complications. Airbags provide safety to occupants of cars and reduce mortality by 25-30%. When not used in accordance with international standards, however, they can cause serious injury.

Objectives: Physicians must maintain a high index of suspicion for injury when evaluating drivers who were not wearing seat belts when airbags deployed, regardless of the speed of the collision given that increased thoracic injury with airbags has also been described in the literature. Even new technology, specifically Side Air Bag (SAB), has been associated with a higher rate of thoracic injury. Given that regulations are a driving force for airbag technology, further research and scrutiny by medical teams is needed to study the effects of airbag technology advancements on morbidity and mortality rates of car accidents to help in making improvements in the future and to guide the lawmakers in implementing rules that can help protect the safety of occupants.

The major cardiovascular problems following airbag deployment described in the literature are: aortic transection, tricuspid valve injury delayed cardiac rupture (right atrial rupture), cardiac contusion (reversible cardiac injury), acute coronary occlusion and myocardial infarction, aortic valve avulsion, airbag trauma induced cutaneous fistulae in a heart transplant patient, delayed cardiac tamponade complicating airbag deployment, and hemopericardium. The first cases of airbag related cardiac traumas were reported in 1993. Airbag deployment has been reported to be the cause of the following thoracic injuries: rib fractures, chest wall burns, sternum fractures, and bilateral pneumothorax. Airbags have also been implicated in the following pulmonary conditions: exacerbation of asthma, reactive airway diseases, new onset asthma, and inhalational chemical pneumonitis.

Methods: We searched online databases from 1970 to January 2013 and included 17 retrospective studies, 12 systematic review articles, 18 case reports, 5 prospective studies, 1 lab study, 3 cohort studies and 1 meta-analysis. Outcomes included clinical/functional response, left ventricular (LV) remodeling, hospitalizations and mortality.

Conclusion: Airbags provide safety to occupants of cars and reduce mortality by 25-30%. Even new airbag technology, has been associated with a higher rate of thoracic injury including cardiovascular and pulmonary complications. Further investigation is needed to study the effects of airbag technology advancements on morbidity and mortality rates of car accidents to aid lawmakers in implementing rules that can help protect the safety of occupants.
STUDY THE EFFECT OF CORONARY ARTERY BYPASS GRAFT (CABG) WITH EXTRA CORPOREAL CIRCULATION (ECC) ON HEARING STATUS: ASSESSING A WIDE RANGE OF FREQUENCIES PRE-AND POST –OPERATIVELY

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Background: The purpose of present study was to evaluate the possible effect of coronary artery bypass graft (CABG) with extra corporeal circulation (ECC) on hearing status via assessing a wide range of frequencies pre-and post –operatively.

Materials and Methods: Twenty patients who underwent CABG operation were enrolled in the study. Pure tone audiometry (PTA) performed pre-and post -operatively. Patient's pre- and post-operative hearing status was compared. Baseline parameters were taken in account to assess potential risk factors for hearing loss and hearing threshold alternation following the surgery.

Results: For the right ear, differences between pre-and post –operative hearing thresholds were statistically significant at all frequencies except for 2000HZ, 8000HZ, 9000HZ and 16000HZ. For the left ear, differences between pre-and post –operative hearing thresholds were statistically significant at all frequencies except for 10000HZ and 16000 HZ. Pearson correlation and Mann-Whitney U-Test revealed that some baseline parameters could be served as risk factors or protective factors for hearing threshold alternation following CABG.

Conclusion: CABG can lead to significant post-operative changes in hearing levels at some frequencies. But these changes could be prevented via modifying some parameters before and during surgery.

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COMPLIANCE AND UTILIZATION OF REMOTE HOME MONITORING FOR FIRST TRANSMISSION IN PATIENTS GIVEN MONITORS AT TIME OF CARDIAC DEVICE IMPLANTATION

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Background: Although remote home monitoring (RHM) is becoming increasingly more popular in the care of the patients with cardiovascular implantable electronic devices (CIED), it is still underutilized. We hypothesized that if patients were enrolled in RHM and received the monitor on the day of their implant, utilization and compliance with this technology would improve.

Methods: We retrospectively studied consecutive patients discharged on the same day of an elective outpatient CIED from 1/2013-7/2013 who underwent either an initial device implant or device upgrade. Prior to discharge, all patients underwent device interrogation and were issued RHM with instructions on setup. These same day monitor (SDM) patients were instructed to send the first transmission the day following implant. The control group had patients who received new devices in 2010, but were enrolled in RHM at a subsequent device clinic appointment after few days post-implant. Compliance with home monitoring was compared between groups.

Results: The SDM population had 150 patients and the control group consisted of 439 patients. Only one SDM patient was lost to follow-up. In the SDM group, 62(41%) patients sent the first transmission within one day, 75(50%) patients within 3 days, and 90(60%) patients within one week. No patients in the control group transmitted within one week. The 1, 3 and 6 month first transmission rates for the SDM and control group were 109(73%) versus 36(8%; p<0.001), 122(82%) versus 135(31%; p<0.001) and 130(87%) versus 180(41%; p <0.001), respectively. The mean time to first transmission for the SDM group and control group was 16.7 versus 77.3 days, (p < 0.001).

Conclusions: Enrolling patients for RHM at the time of device implant leads to better utilization of the technology. At six months, twice as many patients had transmitted when they were given monitors at time of device implant.
SAFETY AND CLINICAL OUTCOMES OF SAME DAY DISCHARGE IN PATIENTS UNDERGOING ELECTIVE CARDIAC DEVICE IMPLANTATION

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Background: Although the practice of same day discharge (SDD) after cardiac implantable electronic device (CIED) implantation has been gaining popularity in some centers in the U.S., the safety of this approach has not been well demonstrated. We hypothesized that it is safe to send our patients home on the same day with a CIED implant by following a standardized algorithm-driven SDD strategy.

Methods: We retrospectively studied 150 consecutive patients discharged on the same day after elective outpatient CIED implantation from 1/2013-7/2013. The patients were eligible for SDD if they were not pacer dependent, had no procedural complications, had an adequate support system at home and lived within 75 miles of the hospital. All patients were issued Home Monitors with instructions to send the first transmission the next day. All patients were seen in device clinic visit within one month. Complications and re-admissions within 30 days were analyzed.

Results: The study population consisted of 150 patients, with mean age of 60.4±15.5 years; 63% male. The follow-up was available in 99.3%. Patients were discharged in 151.9± 50 min post-implant. Prior to discharge, the only complication of lead dislodgement was seen in 1(0.7%) patient. Complications that were found during device clinic follow-up included: lead dislodgement in 1 (0.7%), inappropriate shock in 1(0.7%), moderate hematoma in 2(1.4%) and wound dehiscence in 1(0.7%). None of the patients had pneumothorax, cardiac tamponade, lead fracture, diaphragmatic stimulation (that could not be resolved by reprogramming), device failure or death. No significant complications were identified with HM transmissions. The 30 day readmission rate was 2.7% (4 patients, n=149) for the following: inappropriate shocks in 1 (0.7%), lead dislodgement in 1 (0.7%) and suspected infection in 2(1.3%) patients.

Conclusions: Outpatients presenting for CIED implantation who fulfill specific selection criteria can safely be discharged the same day of their procedure.
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PROVIDING EQUITY IN CARE DELIVERY BY RACE, ETHNICITY AND LANGUAGE: TEXAS HEALTH RESOURCES’ INITIAL REVIEW

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Hypothesis: Race, ethnicity and language can influence health choices and behaviors, and may result in disparities in health care delivery systems.

Objective: To determine potential differences in inpatient (IP) core measures based on race, ethnicity and language at Texas Health Resources (THR), one of the largest faith-based, non-profit health systems in the United States.

Methods: A retrospective review was completed from a sample of clinical data (N=19,873 cases) derived from 13 wholly-owned facilities in regards to inpatient (IP) core measures in (%) cases; this data was collected spanning 15 months from 2012-2013. Core measures analyzed were Acute Myocardial Infarction (AMI) (13.6%), Congestive Heart Failure (CHF) (20.5%), Pneumonia (PN) (24.8%), and Surgical care (SCIP) (41.2%) by race (non-Hispanic White, non-Hispanic Black, Native American / Hawaiian / Pacific Islander, Asian and Other), ethnicity (Hispanic and non-Hispanic), and by preferred language (English and Spanish).

Results: IP core measures performance determined a (%) difference to reference point (non-Hispanic White) by race, ethnicity, and language in AMI (0.3-1.2%), CHF (0.7-3.0%), PN (0.5-3.7%), and SCIP (0-0.7%).

Conclusions: Our initial observations suggest that no major discrepancies of IP core measures exist analyzing race, ethnicity, and preferred language within the THR care delivery system.
**CARDIOVASCULAR QUALITY IMPROVEMENT AND OUTCOMES**

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**THE COST AND BENEFITS OF HELICOPTER EMERGENCY MEDICAL SERVICES INSTEAD OF THE GROUND UNIT IN CHEST TRAUMATIC PATIENTS: A COST-EFFECTIVENESS ANALYSIS**

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**Study objective:** Aero medical crews offer an advanced level of practice and rapid transport to definitive care; however, their efficacy remains unproven. Here we explore the impact of aero medical response in patients with moderate to severe traumatic chest injury.

**Methods:** This was a cross-sectional study using our county trauma registry. All patients with chest trauma injury, who referred to our emergency department by helicopter or car, were included. The impact of aeromedical response was determined using logistic regression, adjusting for age, sex, mechanism, preadmission Glasgow Coma Scale score and Injury Severity Score. Finally, the aeromedical patients undergoing field intubation were compared with ground patients undergoing emergency department (ED) intubation.

**Results:** A total of 243 patients meeting all inclusion and exclusion criteria and with complete data sets were identified. Overall mortality was 25% in the air- and ground-transported cohorts, but outcomes were not significantly better for the aeromedical patients when adjusted for age, sex, mechanism of injury, hypotension, Glasgow Coma Scale score, head Abbreviated Injury Score, and Injury Severity Score (adjusted odds ratio [OR] 1.90; 95% confidence interval [CI] 1.60 to 2.25; P: 0001). Good outcomes (discharge to home, jail, psychiatric facility, rehabilitation, or leaving against medical advice) were also higher in aeromedical patients (adjusted OR 1.36; 95% CI 1.18 to 1.58; P: 0001).

**Conclusion:** Here we analyze a large database of patients with moderate to severe traumatic chest injury. Aeromedical response appears to yield no significantly improved outcomes after adjustment for multiple influential factors in patients with moderate to severe traumatic chest injury.
SERIAL ECHOCARDIOGRAPHY FOR EARLY DIAGNOSIS OF CARDIOTOXICITY IN BREAST CANCER PATIENTS TREATED WITH TRASTUZUMAB

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Background: Trastuzumab (Herceptin) is a recombinant humanized monoclonal antibody used to treat HER2-positive breast cancer. Rarely, it can cause toxicity such as cardiomyopathy. Early diagnosis of adverse cardiac effects could prevent CHF. The role of echocardiography in early detection remains unclear. We aimed to determine if serial echocardiograms reveal any changes in systolic or diastolic variables that may lead to early diagnosis of cardiotoxicity due to trastuzumab.

Methods: A retrospective analysis was conducted in consecutive adult breast cancer patients who were started on adjuvant trastuzumab therapy between February 2008 and March 2010 at Loyola University Medical Center. Patients received an average dose of 240 mg/kg/year to 268 mg/kg/year over a 12-month period. Serial echocardiograms were performed in all patients at 3 to 6 month intervals beyond the therapy period. A comparison of systolic and diastolic function variables was performed using the student t-test with the Bonferroni correction.

Results: A total of 17 patients who received trastuzumab therapy were enrolled in the study. The median age was 49. The mean follow-up period for serial echocardiograms was 16 months during which each patient had a mean of 4.7 echocardiograms performed. There was no significant difference in left ventricular ejection fraction between the initial and subsequent studies (initial vs final: 60.9 ± 4.0 vs. 57.6 ± 12.8%, p=0.33). Also, there was no significant difference in any of the diastolic function variables between the initial and subsequent studies. Both the left ventricular and left atrial size measurements remained unchanged as well.

Conclusion: Trastuzumab at standard doses does not appear to have appreciable effects on resting myocardial systolic and diastolic function as determined by conventional echocardiographic and Doppler indices. Serial echocardiographic studies to detect sub-clinical changes in myocardial systolic and diastolic function which might presage impending cardiomyopathy do not appear warranted in asymptomatic patients.
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PREDICTORS OF MORTALITY IN HOSPITALIZED PATIENTS WITH HYPERKALEMIA
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Introduction: Hyperkalemia is a common electrolyte abnormality associated with increased all cause and in-hospital mortality. This study was done to determine the predictors of mortality in hospitalized patients with hyperkalemia.

Methods: All patients diagnosed with hyperkalemia from January 1, 2010 to December 31, 2011 either at the time of admission or during the course of hospitalization were included in the study. Patients with end stage renal disease and on dialysis were excluded. Hyperkalemia was defined as serum potassium > 5.1 mEq/l.

Results: Of 16,420 hospitalizations, 451 (2.74%) had hyperkalemia. After excluding readmissions, the final cohort included 408 patients. The mean age of patients with hyperkalemia was 64 ± 17 years. The mean serum potassium was 5.7 ± 0.59 mEq/L. Prolonged duration prior to hyperkalemia resolution (OR1.06, 95% CI 1.03-1.09, p < 0.001) was associated with increased in-hospital mortality. Multivariate analysis of factors associated with prolonged duration of hyperkalemia showed that, patients who had non-steroidal anti-inflammatory drugs induced hyperkalemia had a 59% higher chance of early hyperkalemia resolution (HR 1.59, 95% CI 1.03-2.45, p = 0.035). However, presence of metabolic acidosis (HR 0.77, 95% CI 0.62-0.96, p = 0.021), acute kidney injury (AKI) (HR 0.77, 95% CI 0.63-0.96, p = 0.018), and high peak serum potassium (HR 0.61, 95% CI 0.50-0.75, p < 0.001) predicted prolonged duration of hyperkalemia. Metabolic acidosis (p = 0.009), AKI (p = 0.03), and hyperkalemia secondary to potassium supplements (p = 0.008) were also independent predictors of increased in-hospital mortality. Interestingly, patients who received calcium gluconate for treatment of hyperkalemia had higher in-patient mortality (OR 4.62, 95% CI 1.60-13.35, p = 0.005).

Conclusion: Increased mortality with prolonged duration prior to hyperkalemia resolution shows the need for protocol based aggressive management of hyperkalemia.
A SINGLE-CENTER RETROSPECTIVE COMPARISON OF STRESS ECHOCARDIOGRAPHY UTILIZATION BETWEEN FAMILY MEDICINE PHYSICIANS AND INTERNISTS

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Background: In the US, total expenditures related to cardiovascular imaging are approaching $17 billion and comprise one-fifth to one-third of all imaging expenditures. The use of stress testing has increased significantly over the past decade, however the rate of positive studies has declined. Differences in physician expertise and training could have important effects on ordering practices. The objective of this study was to compare the pretest probability of patients undergoing outpatient stress echocardiography, using the Diamond-Forrester criteria, between providers in an academic medical center.

Methods: We performed a retrospective cohort study on 692 consecutive patients, aged 18 years and older, who underwent outpatient stress echocardiography (SE) ordered by Family and Community Medicine (FCM) and Internal Medicine (IM) providers between the period January 1 2012 and December 31 2012. Patients were assigned to very low (<5%), low (<25%), intermediate (25-75%), and high (>75%) pretest probability subgroups. Pretest probabilities as well as predictive accuracy of stress echocardiography were compared between the FCM and IM groups.

Results: FCM providers were more likely to order SE on very low risk patients (16% versus 3%; p = 0.007) whereas IM providers were more likely to order SE on intermediate risk patients (48% versus 30%; p = 0.007). FCM providers were also more likely to order SE on asymptomatic patients (13% versus 8%; p = 0.17). For FCM and IM providers the positive predictive value of stress echocardiography was 37% and 64% (p=0.17) respectively.

Conclusion: Important differences were found between FCM and IM providers in SE ordering which could be attributable to differences in training and level of expertise in cardiovascular medicine. This could have important implications for improving stress test ordering throughout the country.
IS THE DASH DIET THE OPTIMAL DIET FOR HEART FAILURE PATIENTS?

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Background: For symptomatic heart failure (HF) the major focus remains evidence based pharmacologics and devices. Little guideline evidence exists for nutritional support of HF patients beyond recommendations on limiting sodium excess. Endothelial dysfunction has been recognized as a pathophysiologic mechanism in the progression of HF. We sought to examine the effects of the DASH diet on HF outcomes.

Methods: Forty chronic Stage C, functional class I to III, HF patients were randomized to either be on a DASH diet regimen or follow the general HF dietary recommendations for 1 month. Age was 40 to 84 (mean 64) years; 22 were men. Mean ejection fraction was 42±15. Large and small arterial elasticity (LAE, SAE) at rest were obtained using the pressure pulse contour analysis technique. Data collected included exercise capacity as measured by 6-min walk test, weight and DASH diet index score for compliance.

Results: Average DASH diet index score was 6.8/11. The net change in LAE at 1 month was significantly improved in the DASH group when compared to the control group (p < 0.05). Additionally, patients in the DASH group had improved 6-minute walk distance at 1 month compared to their control counterparts (p < 0.05). There was also a trend towards weight loss (-2.5kg) in the DASH group, and weight gain (+0.8kg) in the control group at 1 month. (p <0.05).

Conclusion: Compared to dietary controls, patients who followed a DASH diet had improved large artery compliance and 6 minute walk times. The impact of other diet models on key surrogates of outcome in HF patients is unknown. The DASH diet may be an important adjunctive therapy for patients with symptomatic HF; it is time to focus interest on the potential impact dietary approaches may have on HF outcomes.
MEDITERRANEAN DIET AND SECONDARY PREVENTION OF CVD

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Adherence to a healthy dietary pattern, such as the Mediterranean diet, exerts a beneficial role regarding the development of coronary heart disease. In addition, several studies support the protective role of the Mediterranean diet as far as secondary prevention of CVD is concerned. This review, examining results from prospective cohort and cross-sectional studies, as well as clinical trials, aims to clarify whether the beneficial effect of the Mediterranean dietary pattern on secondary prevention of CVD is due to the impact of this diet on weight loss and obesity status or an independent effect. Although not all studies show a protective effect of the Mediterranean diet on body weight and obesity, the evidence suggests a possible mediating beneficial role of obesity regarding this dietary pattern on secondary CVD prevention.
LOOKING BACK ON THE LOOK AHEAD TRIAL

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Look AHEAD was the largest and longest randomized clinical trial designed to test whether improved lifestyle can prevent cardiovascular disease in adult patients with diabetes. Sixteen U.S. study centers randomly assigned 5145 overweight or obese patients to Intensive Lifestyle Intervention (ILI) or a Diabetes Support and Education (DSE) comparison group. ILI goals were: sustained weight loss of ≥ 7% of initial weight and increased physical activity to ≥ 175 minutes a week. All ILI and DSE participants were required to have an established relationship with a primary care provider (to reduce cost and mirror real clinical practice); no known cardiovascular disease; and to have BMI ≥25.0, glycated hemoglobin of 11% or less, systolic blood pressure <160 mm Hg, diastolic blood pressure <100 mm Hg, and triglycerides < 600 mg/dl. They had to successfully complete a maximal graded exercise tolerance test (GXT), “showing it would be safe to exercise.” By one year ILI participants showed greater improvement than DSE participants in weight loss, fitness, glycated hemoglobin, and in all cardiovascular risk factors, except LDL cholesterol. Smaller, still significant differences were observed by trial end. Look AHEAD was closed for futility after 10 years by the DSMB, when only 418 DSE patients and 403 ILI patients had a cardiovascular event, although most microvascular complications were significantly improved in the ILI group.

The design and protocol were based on novel design choices adopted to reduce costs and risks and promote retention. The eligibility criteria yielded unusually healthy patients with diabetes, thereby reducing CVD event rates. Alternatively, it is possible that macrovascular disease cannot be prevented or slowed by weight loss within 10 years in adults, particularly those who had diabetes for an average of 14 years at baseline.
SATURATED FAT INTAKE AND THE GENESIS OF CORONARY ARTERY DISEASE – WHERE’S THE EVIDENCE?
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Dietary saturated fat intake has long been blamed for causing coronary artery disease based on scant epidemiological data. However, little evidence supports the notion that reducing saturated fat intake would reduce coronary artery disease. In fact, growing research suggests that our obsession with reducing saturated fat intake has led to increased consumption of refined carbohydrates which has in turn led to an explosion of obesity and related illnesses. In this presentation, we explore the historical, epidemiological and randomized trial data linking saturated fat intake and coronary artery disease. We propose that modifying a single dietary ingredient would be unlikely to reduce the risk of CAD. Moreover, the undue focus on saturated fats has diverted our attention from the importance of overall quality of diet and a healthy lifestyle in promoting cardiovascular health. Our proposed concept of “lifestyle synergy” describes the influence of various factors (of which diet is one component) on the risk of cardiovascular disease. Our expensive and widespread efforts to curb saturated fat intake are misguided and should be abandoned in favor of promoting improving overall quality of diet and lifestyle.
INTEGRATING NUTRITION EDUCATION INTO THE CARDIOVASCULAR CURRICULUM CHANGES MEDICAL STUDENT EATING HABITS

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Background and Objective: Surveys of medical student curricula continue to demonstrate that nutrition education is not universally adequate. One measure of nutritional educational competence is a positive change in student eating habits. The objective of this study was to evaluate whether integrating nutrition education within the second year fall medical student cardiovascular course, while utilizing the “Rate Your Plate” questionnaire (RYP) (©2005 Brown University) coupled with knowledge of student personal 30 year risk of a cardiovascular event were useful in changing students’ eating behaviors.

Methods and Results: Thirty-two students completed an unpublished 24-item questionnaire (modified RYP) about their eating habits in the spring of their first year. The same students then completed the questionnaire in the spring of their second year. Mean scores at baseline and one year later were 57.19 and 58.97, respectively (Paired t-test: p <0.01). Pearson correlation coefficient between 30-year relative risk, adjusted for family history, and change in RYP score was -0.322 (ns) suggesting that risk knowledge did not play a role in changing eating habits. A separate control group of 33 second year students were exposed to the integrated nutrition education program before the RYP questionnaire was introduced into the curriculum. Their RYP score (56.35) was significantly lower than 38 second year students who were taught with RYP plus the integrated program (59.58, p=.041) when data for all participants were analyzed as separate groups by ANOVA and paired comparisons made by Tukey-Kramer test with p correction. This suggests that addition of the RYP questionnaire to the curriculum did contribute to improve eating.

Conclusion: While medical students were eating healthy at baseline, integration of nutrition education within the second year cardiovascular medical curriculum improved heart healthy eating habits. However, knowledge of personal 30-year cardiovascular event risk was not correlated with their change in eating habits.
DO VITAMIN AND MINERAL SUPPLEMENTS HAVE A ROLE IN CARDIOVASCULAR DISEASE PREVENTION?

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Basic research and clinical studies demonstrate several plausible mechanisms by which vitamins and minerals may prevent or slow the progression of atherosclerosis, while observational studies indicate that individuals with high intakes of these essential nutrients or fruit and vegetable intake may have a decreased risk of cardiovascular disease (CVD). In turn, researchers have actively sought to identify particular constituents of foods that underlie a potential effect. However, the inherent heterogeneity in study design, participant characteristics, potential confounding, interactions with other vitamin and food components, and other elements of epidemiologic studies makes any assertion of causality problematic and dependent upon randomized clinical trials (RCTs). Yet these findings have not been easily replicated in RCTs testing selected individual or combined vitamin and mineral supplements, leaving the precise mechanistic role of essential vitamins and minerals on CVD elusive. In addition, the Physicians’ Health Study II (PHS II) tested a multivitamin among 14,641 male US physicians aged 50+ years through 2011 with more than a decade of treatment and follow-up and found no overall effect on the primary endpoint of major cardiovascular events (nonfatal myocardial infarction, nonfatal stroke, fatal CVD). This has led many to question the role of vitamin and mineral supplements in CVD prevention, along with the necessity and potential limitations of RCTs. Notably, any potential inverse association for vitamin and mineral supplements should also extend to key risk factors leading to CVD, such as diabetes, hypertension, and hypercholesterolemia, which continue to increase in prevalence and public health importance in the United States and worldwide. These cardiovascular risk factors represent important targets for CVD prevention by vitamin and mineral supplements on their own, while providing important insights into more specific mechanisms through which these supplements may prevent CVD.
DIET, LIFESTYLE AND CVD PREVENTION – NEW ORIGINS

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ALTERNATE HEALTHY EATING INDEX, MEDITERRANEAN AND DASH DIETARY PATTERNS AND RISK OF DEATH IN THE PHYSICIAN’S HEALTH STUDY

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Background: While Mediterranean (MED) diet has been shown to lower total mortality, only limited data are available on the effects of MED diet on cause-specific mortality. Furthermore, it is unknown whether the MED diet is associated with lower risk of total and cause-specific mortality among physicians who may already have optimal risk profile as defined by the Framingham risk score.

Objective: To assess associations of MED and DASH diet score with total, cardiovascular, and cancer death in male physicians. We also sought to compare results from MED and DASH diets with findings from dietary patterns based on published recommendations (alternate healthy eating index-aHEI).

Methods: We prospectively analyzed data on 19,619 US male physicians who provided data on their dietary habits in 1997 using food frequency questionnaires. Mortality was adjudicated by an endpoint committee and Cox proportional hazard models were used to estimate odds ratios.

Results: For every doubling of MED score, multivariable adjusted hazard ratios were 0.81 (95% CI: 0.77-0.86) for total mortality; 0.83 (0.4-0.93) for CVD death; and 0.84 (0.76-0.94) for cancer death. Corresponding values were 0.81 (0.71-0.93); 0.90 (0.70-1.17); and 0.93 (0.74-1.18) and for DASH score and for 0.59 (0.52-0.68); 0.62 (0.48-0.80); and 0.68 (0.54-0.86) for aHEI score.

Conclusions: Our data are consistent with a lower risk of total mortality for all three diet scores whereas only DASH and aHEI scores were inversely associated with CVD- and cancer deaths.
RACIAL DIFFERENCES IN VITAMIN D/PARATHYROID HORMONE ENDOCRINE SYSTEM AND CARDIOVASCULAR DISEASE

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It is well-known that the vitamin D endocrine system acts synergistically with parathyroid hormone (PTH) to regulate calcium homeostasis and skeletal integrity. The bioavailability of vitamin D and its metabolites is largely regulated by vitamin D binding protein (VDBP). Recent observational studies have suggested a possible relationship between low circulating levels of 25-hydroxy vitamin D [25(OH)D], high levels of PTH, and increased risk of cardiovascular disease (CVD). VDBP could potentially be a predictor of CVD events or an effect modifier of the relation between 25(OH)D and/or PTH and CVD. There is evidence that blacks have lower 25(OH)D and higher PTH and experience a disproportionate burden of CVD compared with whites. Limited evidence from prospective studies found lowest 25(OH)D concentrations in blacks but a significant association between low 25(OH)D and an increased risk of CHD events in white adults but not in black adults. These data add important insights to the complex relationship among race/ethnicity, vitamin D metabolism, and CHD. Clearly, further research is needed to clarify whether differences in 25(OH)D and PTH levels and VDBP by race/ethnicity may partly contribute to racial/ethnic disparities in CVD event rates. This presentation provides a brief review of the current evidence linking biomarkers of vitamin D/PTH system and CVD from observational studies to intervention trials.
DIETARY FATTY ACIDS COMPOSITION AS A RISK FACTOR FOR CARDIOMETABOLIC DISORDERS

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The association between dietary fatty acids (FAs) and cardiovascular disease (CVD) has been investigated for decades. It is well accepted that diets low in saturated and trans FAs reduce risk of CVD, largely through lowering the level of LDL-cholesterol. The association of different FAs with risk of diabetes is less studied. In general, high intake of saturated FA (SFA) is associated with increased risk of impaired glucose tolerance, insulin resistance, and type 2 diabetes. The associations for monounsaturated FA (MUFA) and polyunsaturated FA (PUFA) are mixed. The study on dietary FAs in association with hypertension is more limited. Cross-sectional studies suggest a positive association for saturated fats and an inverse association for unsaturated fats with blood pressure (BP). Prospective studies are very few. These associations between dietary FAs and cardiometabolic disorders may be mediated by effects of FAs on obesity. Dietary fat is a major contributor to total energy intake. However, different FAs differ in metabolic rates, capacity to induce lipid synthesis and oxidation, and mobilization to various tissues. Animal studies show that high saturated fat diets led to greater body fat accumulation, while long-chain omega-3 FAs prevent the enhancement of fat mass. Only a few epidemiologic studies have examined the prospective association between dietary FAs and body weight change. We recently conducted analysis in the Women’s Health Study to examine the association of erythrocyte FAs, as biomarker of dietary FAs, with body weight change and risk of becoming overweight among initially normal-weight women. We found suggestive evidence that erythrocyte omega-6 PUFA was positively associated, and omega-3 PUFA inversely associated, with the risk of becoming overweight and weight gain. Future studies are needed to further investigate the interplay between subtypes of FAs and body weight and body fat as well as the biologic mechanisms underlying the associations.
DIET, LIFESTYLE AND CVD PREVENTION – NEW ORIGINS

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THE ROLE OF EXERCISE AND REHABILITATION FOR HEART FAILURE PATIENTS
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Regular exercise enhances muscular function and strength and promotes the body’s ability to consume and utilize oxygen; while it improves the capacity of blood vessels to dilate in response to exercise, left ventricular diastolic function and neurohormonal activation. Despite those facts, and the recent guidelines regarding the management of heart failure; the recommendation for exercise among heart failure patients has been poorly implemented in daily clinical practice. This has been attributed to the fact that several types of training protocols have been used in rehabilitation programs, with an ongoing debate regarding the intensity and type of exercise training that can provide optimal effects for chronic heart failure patients. Most studies of rehabilitation in heart failure patients were performed using moderate intensity continuous training (50%–70% of $\dot{V}O_2$peak) or repetitions of high-intensity intervals (80%–95% of $\dot{V}O_2$peak) of a relatively long duration (2–5 min), separated by moderately intense recovery periods. A recent meta-analysis suggested that combined (strength and intermittent) exercise training elicits larger benefits in peak VO$_2$ than intermittent exercise training alone, although intermittent exercise training elicits larger benefits in peak VO$_2$ and VE/VCO$_2$ than continuous exercise training in patients with moderate to severe heart failure. It seems that application of a combined high intensity interval exercise program in patients with systolic heart failure of ischemic or idiopathic origin seems to offer substantial beneficial effects on several hemodynamic and clinical factors and especially on markers of quality of life, improving the ability to perform daily activities, even in terminally ill patients. Furthermore, other programs of respiratory exercise and electric muscle functional electrical stimulation have shown beneficial effects on endothelium and functional status indices and quality of like even in advanced stage heart failure patients.
ADVANCES IN THE TREATMENT AND MANAGEMENT OF HEART FAILURE

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THE MANAGEMENT OF PATIENTS WITH ADVANCED HEART FAILURE
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Advanced heart failure (AHF) is growing in magnitude and represents a major public health problem. AHF patients are heterogeneous with varying clinical presentations. Left ventricular assist device (LVAD) support is an accepted treatment of patients with AHF. Success with LVADs as bridge-to-transplant therapy has led to their successful use as an alternate to a transplant (ie, as destination therapy [DT]). The REMATCH trial showed a 48% reduction in all-cause mortality in patients receiving LVAD therapy versus OMM (P = 0.001). One-year survival was 52% in the LVAD group and 25% in the OMM group, whereas 2-year survival was 23% and 8%, respectively. However, the number of AHF that qualify for these advanced treatments is relatively small. Despite evidence based medical and pharmacologic advances the management of AHF remains challenging, especially in the ambulatory setting. There is an urgent need to develop strategies to reduce hospitalizations and re-admission rates for heart failure in general. AHF carries a high burden of symptoms, suffering, and death. Palliative care can complement traditional care to improve symptom amelioration, patient-caregiver communication, emotional support, and medical decision making. Palliative therapies is still underused in AHF treatment. Planning for adverse events and the end of life, can be integrated into HF care early in illness. Discussions that acknowledge the uncertainty of HF course and length of life and incorporate patient and family goals and values facilitates this planning. Clear processes for weighing potential benefits and burdens of interventions and therapies should accompany decision-making.
Readmissions are common following an admission for heart failure occurring in 20-30% of patients within 30 days of discharge. Many payers including U.S. Medicare have estimated that a large fraction of these readmissions are preventable (up to 75%). Accordingly, the U.S. Medicare program has instituted financial penalties for hospitals with higher than average readmission rates. In response, hospitals are now keenly interested in interventions to reduce 30 day readmissions for patients with heart failure. The presentation will review published reports on the fraction of readmissions that are deemed preventable and randomized trial data of interventions designed to reduce readmissions. In addition the presentation will include a new analysis (unpublished) of US Veterans Affairs Hospital data on the readmission impact of the Hospital to Home (H2H) Initiative of the American College of Cardiology and Institute for Health Care Improvement. Our findings suggest that while interventions such as the Hospital to Home may be effective their impact is long-term and not easily measured at 30 days.
Heart failure with preserved ejection fraction (HFPEF) is an epidemic condition for which effective pharmacologic therapies are urgently needed. Several pharmacologic agents that provide substantial benefit in heart failure with reduced ejection fraction have failed to so in HFPEF. There is currently a need to better understand mechanisms that contribute to the pathophysiology of this condition. Whereas initial studies focused on left ventricular diastolic dysfunction and, subsequently, myocardial systolic abnormalities, increasing attention is being directed to peripheral organs, including the arterial tree, skeletal muscle, and the kidneys. The arterial tree affects the afterload of the left ventricle, which can induce myocardial remodeling and dysfunction. In addition, the arterial tree regulates flow distribution and thus overall peripheral oxygen extraction during exercise. Mitochondrial abnormalities in skeletal muscle and abnormalities in the cardio-renal axis have also been proposed.
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CARDIORENAL SYNDROME: NOT AS STRAIGHT FORWARD AS WE USED TO THINK

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Simultaneous dysfunction of the heart and the kidney represents a distinct spectrum of disease states composed of complex clinical scenarios with potentially adverse outcomes. Worsening renal function (WRF) in the setting of acute decompensated heart failure (ADHF) is one such clinical setup with not yet well-characterized underlying mechanisms. It is of paramount importance to characterize the pathways leading to WRF in ADHF in order to develop a mechanistically-relevant management strategy. There has been a shifting paradigm in our understanding of the cardiorenal interactions in patients with ADHF questioning some contemporary concepts such as the low forward flow theory or high backward pressure hypothesis. Besides, emerging data do not fully support our conventional thinking about other aspects of these interactions such as the independent adverse impact of WRF on the outcomes of patients with ADHF, pointing to congestion as a possibly overlooked factor. The findings of the recent studies also suggest that apparent improvement in renal function might be yet another risk factor for untoward outcomes in this patient population, further challenging our current understanding of the cardiorenal interactions. This talk will provide a brief overview of these emerging controversies in the field of cardiorenal syndrome with the goal of identifying the areas where clinical research can be most helpful to fill the gaps in our understanding.
CRT has evolved as an established treatment for advanced heart failure symptoms, impaired LV function and intraventricular conduction delay despite substantial improvement in technology and optimization techniques 30% - 40% of pts fail to gain significant clinical benefit. What are the clinical challenges? 1. Venous System Access (inability to cannulate, pass the LV lead in a CS branch) 2. Maintaining Lead Stability (dislocation rate 6-14 %). 3. Non-Optimal Pacing Site (unsatisfactory pacing parameters). 4. High Pacing Threshold. 5. Phrenic Nerve Stimulation (PNS; 37% PNS detected, 22% clinical relevant; posture dependent, detection of PNS at implantation poor sensitivity, occurs up to 22% at pacing sites most associated with reverse remodeling). New Technologies are needed to increase implantation success. One of the most advantages was the development of a quadripolar left ventricular lead. Quadripolar lead technology allows pacing options over 5 cm on the left ventricle, facilitates Quadripolar multisite LV and RV pacing. CRT with the Quartet™ LV Lead Improves Implant Efficiency (lead implant times were 28% faster, fluoroscopic exposure 55% lower, implantation success > 95%, low rates of dislocation and PNS (4.5% vs 26%). Therefore rehospitalization/reinterventions is reduced with lower rehospitalizations rates and reduced costs. Pacing site is crucial for improving ventricular mechanics. Basal or midventricular pacing site better than apical. Multipolar lead may facilitate targeting of more proximal CS branches (targeting more basal or mid ventricular pacing sites). May reduce nonresponder rate (more choice, avoiding scar tissue pacing). Avoid PNS. More choice of the best performing pacing configuration and by enhancing to achieve a stable lead position at good target position. More solutions to common problems faced by physicians during implantation and FU.
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419 COLCHICINE AND NEW MANAGEMENT STRATEGIES FOR ACUTE AND RECURRENT PERICARDITIS

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Background. Disease recurrence is the major and most common complication of pericarditis and its prevention may reduce morbidity and management costs. Colchicine has been intensively studied in the last decade for pericarditis prevention.

Methods. Controlled clinical studies were searched in several databases and were included provided they focused on the pharmacologic primary or secondary prevention of pericarditis. We performed a meta-analysis including studies primary outcome, adverse events, and drug withdrawal.

Results. From the initial sample of 175 citations, 7 controlled clinical trials were finally included (1275 patients): 5 studies were double-blind randomised controlled trials (RCT), and 2 studies were open-label RCTs. Trials followed patients for a mean of 19 months. Meta-analytic pooling showed that colchicine use was associated with a reduced risk of pericarditis during follow-up (OR=0.33 [0.25-0.44], p for effect< 0.001, p for heterogeneity=0.98, I2=0%) either for primary or secondary prevention without a significant higher risk of adverse events (OR=1.28 [0.84-1.93], p for effect= 0.25, p for heterogeneity=0.72, I2=0%), and drug withdrawals compared with placebo (OR=1.54 [0.98-2.41], p for effect=0.06, p for heterogeneity=0.54, I2=0%). Gastrointestinal intolerance is the most frequent side effect (mean incidence 8%), but no severe adverse events were recorded.

Conclusions. Colchicine is safe and efficacious for the primary and secondary prevention of pericarditis without a significant increase of the risk of side effects and drug withdrawals. At present colchicine is the only drug that has been proven efficacious and safe for pericarditis prevention in more than one clinical trial with a similar effect for primary or secondary prevention. On this basis, the drug should be considered as a first line agent for pericarditis prevention (Journal of Cardiovascular Medicine 2014; in press).
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SKELETAL MUSCLE HYPERTROPHY INDUCED BY NOVEL KAATSU REHABILITATION AND PREVENTION OF SARCOPENIA
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Sarcopenia, the loss of muscle mass, is an important problem in the older population. To prevent it, high-intensity exercise is usually required, but it can not be carried in the elderly. Low-intensity exercise under restriction of muscle blood flow (RMBF), named as KAATSU training, is a new strength rehabilitation method, which stimulates numerous muscle fibers and can produce increased muscle size and strength even with low-intensity loading. In this lecture, we introduce two recent our clinical and basic researches. (1) Effects of KAATSU training using low-intensity resistance exercise on muscle strength/mass and its safety in the elderly. (2) Acute effects of electrical stimulation (EMS) under RMBF on microvascular pO2, mammalian target of rapamycin (mTOR) signaling pathways, and transcripts associated with proteolysis in rat KAATSU model. (3) Chronic effects of EMS under RMBF on muscle hypertrophy and muscle signaling. Isometric contractions under RMBF significantly enhanced phosphorylation of mTOR signaling including ribosomal protein S6, compared with control EMS. And, this EMS stimulation under RMBF (3 times a week for 3 weeks) significantly enhanced muscle strength and muscle mass in rat KAATSU model. KAATSU training (twice a week for 3 months) significantly increased muscle strength and mass in older subjects without any side effects. We concluded that the KAATSU training may be a novel and effective rehabilitation method for preventing and improving sarcopenia.
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PERICARDIAL INVOLVEMENT FREQUENTLY COMPLICATING PULMONARY AND/OR SYSTEMIC SARCOID GRANULOMATOSIS. A LIFE-LONG, MULTI STAGE DISEASE, PERIODICAL STUDY IN 278 BIOPSY –PROVEN SARCOIDOSIS PATIENTS
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Introduction: Nearly 21% of pulmonary and/or systemic Sarcoidosis(S) patients (pts) appear developing pericardial involvement in their initial Hospital admission.
Purpose: Evaluation of the total, multi stage, pericardial effusion frequency (P.Ef), not so far, well established and reported in the literature.
Material: 178/278 biopsy-proven, pulmonary and/or systemic Sarcoidosis Pts, 56 males and 122 females, mean age 47,8 yrs, were free of cardiovascular pathology and investigated for the possible development of the multi-stage, symptomatic or latent, pericardial granulomatosis.
Methods: Pts underwent clinical examination, ECG, PFTs, blood tests, ABGs, periodical echocardiography and occasionally radionuclide myocardial scintigraphy by Technetium-99m-Pyrophosphate (Tc-99m-pyp).
Results: 1.Total, multi-stage, P.Ef. in 49% 2. Usually latent and small to moderate frequency of pericardial constriction 3. P.Ef. concomitant with abnormal radionuclide myocardial imaging in 42% 4. Asymmetric Septal Hypertrophy (ASH) coincident with abnormal myocardial scan in 21,5% 5. Confirmed Sudden Cardiac Death (SCD) cases by the present study only appeared in 1,3% Pts, undergoing corticosteroid therapy.
Conclusions: 1) P.Ef. in 49% totally, evaluated periodically, indicates an unexpectedly frequent percentage of pericardial involvement appearing in multi-various stage of life-long sarcoid granulomatosis, which has never been previously well established in the literature 2) P.Ef. coincident with abnormal myocardial scan could be compatible with the presence of myopericardial involvement in 42% 3) ASH, mimicking hypertrophic cardiomyopathy and co-existed with abnormal cardiac scintigraphy was presumably due to sarcoid cardiomyopathy in 21,5% 4. Latent pericardial constriction and/or LV diastolic Dysfunction should be differentiated and could be responsible for the unexplained dyspnea and chest tightness 5) Unlike the literature, the surprising low percentage of SCD cases(1,3%) confirmed by the present study, were possibly considered relating to long term corticosteroid treatment.
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422 IMATINIB: A NOVEL CANDIDATE FOR TREATMENT OF PERMEABILITY EDEMA
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Endothelial hyperpermeability and vascular leakage are significant pathogenic phenomena. Although contributing to life-threatening conditions like acute respiratory distress syndrome, they currently lack specific therapy. In a case-report we reported fast resolution of pulmonary edema upon treatment with the tyrosine kinase inhibitor imatinib. We tested the hypothesis that imatinib protects against endothelial barrier dysfunction and elucidated how imatinib attenuates edema formation. Imatinib inhibited the thrombin-induced macromolecule passage through human endothelial monolayers, and reduced the maximal drop in trans-endothelial electrical resistance upon thrombin and histamine stimulation. Moreover, imatinib attenuated the thrombin-induced loss of the adherens junction proteins VE-cadherin and beta-catenin. Small interfering RNA knock-downs of the imatinib-sensitive kinases revealed that imatinib attenuates endothelial barrier dysfunction via inhibition of Abl-related gene kinase (ARG/Abl2), a previously unknown mediator of endothelial hyperpermeability. Arg was activated by endothelial stimulation with thrombin, histamine, and vascular endothelial growth factor, as evidenced by a 2-3 fold increase in CrkL phosphorylation, the downstream target of ARG. The clinical relevance of ARG was confirmed by increased amounts of phosphorylated CrkL in the pulmonary endothelium of septic patients. To test the protective effects of imatinib in vivo, mice were pretreated with imatinib and PAR-1 agonist. Pulmonary vascular permeability was evaluated by measuring the Kfc of isolated perfused mouse lungs. Imatinib pretreated lungs showed a lower Kfc. ARG-deficient mice showed a significant reduction of VEGF-induced vascular leakage. ARG was activated upon endothelial activation in vitro. Finally, we describe treatment of a patient suffering from vascular leak with imatinib in a controlled setting. Thus, we demonstrated that the tyrosine kinase inhibitor imatinib protects against endothelial barrier dysfunction in vitro and in vivo. Imatinib exerts its protective effects via inhibition of ARG/Abl2. These data indicate imatinib may be a novel therapeutic strategy for treatment of endothelial hyperpermeability and lung edema.
THE RELEVANCE OF GENETICS IN PROVIDING UNDERSTANDING AND TREATMENT FOR CARDIOVASCULAR DISEASE

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PHARMACOGENETICS-GUIDED INDIVIDUAL WARFARIN DOSING IN A CARDIOLOGY CLINIC – A PERSPECTIVE OBSERVATORY STUDY

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Background: The VKORC1 is the major target of warfarin inhibition, and CYP2C9 is a key metabolizer of warfarin. Genetic variations of VKORC1 and CYP2C9 affect warfarin sensitivity, clearance and bleeding risk. Variations of the two genes explain about 40% of warfarin dosing variability.

Objectives: To evaluate CYP2C9 and VKORC1 genetic variations and their clinical values for warfarin dosing.

Methods: DNA sequences of CYP2C9 and VKORC1 are analyzed in 304 patients in our clinic. Phenotype-specific warfarin dosing is analyzed and individual dosing recommendation together with follow-up plan are formulated.

Results: Distributions of the three CYP2C9 phenotypes in our patients are: Extensive (normal)-Metabolism (EM):190, Intermediate-Metabolism (IM):104 and Slow-Metabolism (SM):10. Among those patients who are on warfarin (n=64, all have therapeutic INR), average dose (mg/week, mean±SE) in EM group (32.6 ± 2.7, n=37) is significantly higher than that in IM group (22.2±2.1, n=25), P=0.0078. Average dose in SM is 13.1±3.0, n=2. Distributions of VKORC1 phenotypes are: Low-Warfarin-Sensitivity (LWS):109, Intermediate-WS (IMWS):145 and High-WS (HWS):50. Average warfarin dose of each phenotype are: LWS, 34.3±4.3, n=20; IMWS, 25.5±2.0, n=36; and HWS, 23.0 ±3.8, n=8, respectively. Although not statistically significant (p=0.07), a trend towards higher dose in LWS is evident. “Coumadin caution” is taken for those who have high-risk phenotype: CYP2C9-IM/SM, VKORC1-HWS or high-risk combo: VKORC1-HWS+CYP2C9-IM (n=17) and VKORC1-HWS+CYP2C9-SM (n=1). The patients are then followed up for one year looking at 1) thrombotic event, 2) major bleeding event and 3) INR>5 event.

Conclusions/Discussion: Our data suggests that CYP2C9-IM phenotype need only 2/3 dose of warfarin as compared to EM. Similarly, VKORC1-HWS phenotype needs only 2/3 dose as compared to LWS patient. Testing for CYP2C9 and VKORC1 helps to estimate individual warfarin maintenance dosages, and to identify those who require low dose. This approach should help to lower bleeding events without compromising clinical efficacy.
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A MICRO-RNA-410 REGULATED LIPOPROTEIN LIPASE POLYMORPHISM IS ASSOCIATED WITH TRIGLYCERIDES AND STROKE INCIDENCE

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Objectives and Background: microRNAs (miRNAs), small noncoding RNAs, have emerged as important epigenetic regulators of many processes related to cardiovascular diseases (CVD). miRNAs act as inhibitors of gene expression by binding to miRNA recognition elements within the 3’ UTR of their target mRNAs. Single nucleotide polymorphisms (SNPs) can alter miRNA binding by either creating a new or destroying an existing target site. In a previous work we demonstrated that the minor allele of the rs13702 SNP (T>C) in the 3’ UTR of the lipoprotein lipase (LPL) gene disrupts a miRNA recognition element seed site for the miRNA-410, resulting in a gain-of-function. Our objective was to analyze the association of this SNP with triglycerides, HDL-C, oxidative stress parameters and incidence of CVD in a Mediterranean population.

Methods: We studied 7,187 participants in the PREDIMED with a median follow-up of 4.8 years. Triglycerides, HDL-C and oxidative stress parameters were determined at baseline. Incidence of major CVD was assessed. We estimated hazard ratios (HR) by Cox regression.

Results: We observed a strong inverse association between this miRNA target site SNP and triglycerides [B: -0.13 mmol/l (-11 mg/dl) per C-allele, 95%CI: -0.20, -0.05; P=3.4x10-13] and a direct association with higher HDL-C [B: 0.029 mmol/l per C-allele, 95%CI: 0.02, 0.04; P=1.1x10-5] in the whole population at baseline. We also detected an inverse association with the oxidative stress markers malondialdehyde and 8-oxo-7'-dihydro-2'-deoxyguanosine in nuclear DNA (in a sub-sample). Moreover, this miRNA-410 target site SNPs was associated with lower stroke incidence in the whole population, that remained significant after multivariable adjustment (HR: 0.74; 95%CI: 0.57, 0.97; P=0.029 per C-allele).
ATF3 PROTECT AGAINST PRESSURE OVERLOAD HEART FAILURE VIA BECLIN-1 PATHWAY

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Background: Activating transcription factor 3 (ATF3) is a member of the CREB/ATF family of transcription factors, which has been implicated in cardiovascular and inflammatory system and is rapidly induced by ischemic-reperfusion injuries. However, its effect on heart failure induced by pressure overloading is unclear.

Methods and Results: We performed transverse aortic banding (TAB) on both ATF3 gene deleted mice (ATF3-/-) and wild type (WT) mice. Our data demonstrated that decrease left ventricular contractility with loss of normal cardiac hypertrophic remodeling were observed by echocardiography in ATF3-/- mice as compared to the WT mice. The level of apoptosis, TUNEL-positive cells, and activated caspase-3 were also higher in ATF3-/- mice. Restoration of ATF3 expression in the heart of ATF3-/- mice by adenovirus-induced ATF3 treatment dramatically improved the cardiac contractility following TAB. Molecular and biochemical analysis, including chromatin immune-precipitation and in vitro/in vivo promoter assay demonstrated that binding of ATF3 on the ATF/CRE element of the beclin-1 promoter and observed that ATF3 can reduce autophagy via suppress beclin-1 dependent pathway. Furthermore, we demonstrated that infusion of tert-butylhydroquinone (tBHQ), a selective ATF3 inducer, can increase ATF3 expression via NRF2 transcriptional factor and inhibited TAB induced cardiac dilatation and increased left ventricular contractility thus rescue heart failure.

Conclusion: Our data reveal a novel epigenetic regulation mediated by the stress-inducible gene ATF3 on TAB-induced cardiac dysfunction. Therefore, we suggest that ATF3 activator tBHQ may have therapeutic potential for pressure overload heart failure induced by chronic hypertension or other pressure overload induced heart failure.
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RAPID UP-REGULATION AND CLEARANCE OF DISTINCT CIRCULATING MICRORNAS AFTER PROLONGED AEROBIC EXERCISE
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Objectives: To determine whether specific c-miRNAs are differentially up-regulated following prolonged aerobic exercise.

Background: MicroRNAs (miRNAs) are intracellular mediators of adaptive processes important in aerobic exercise. MiRNAs can be released into the bloodstream as “circulating” miRNAs (c-miRNAs). However, regulation of such release, especially during extended aerobic exercise, remains poorly defined.

Methods: We measured c-miRNA concentrations enriched in muscle (miR-1, miR-133a, miR-499-5p), cardiac tissue (miR-208a), the vascular endothelium (miR-126), as well as those important in inflammation (miR-146a) in healthy male marathon runners (N=21) at rest, immediately and 24 hours after a marathon (42 kilometer foot race). Reverse transcription-quantitative ‘real time’ polymerase chain reaction (RT-QPCR) was utilized to quantify levels of candidate c-miRNAs. We also compared c-miRNAs to conventional protein biomarkers reflective of skeletal muscle damage (creatine phosphokinase), cardiac stress and necrosis (cardiac troponin I, high-sensitivity cardiac troponin I, N-terminal prohormone of brain natriuretic peptide), and systemic inflammation (high-sensitivity C-reactive protein).

Results: Candidate c-miRNAs increased immediately after the marathon and significantly declined to near pre-race levels or lower by 24 hours after the race. For instance, c-miR-208a increased 71.6±26.9 fold (mean±SEM, p=0.005 vs. pre-run) immediately after the marathon but returned to near baseline (12.3±6.0 fold, p=0.596 vs. pre-run) 24 hours later. However, the magnitude of change for each c-miRNA differed, even when originating from the same tissue type. In contrast, traditional biomarkers of muscle, cardiac tissue and inflammation increased after exercise but either remained elevated or marginally declined at 24 hours post-exercise.

Conclusions: Candidate c-miRNAs respond differentially to prolonged exercise, suggesting the existence of specific mechanisms of c-miRNA release and clearance not fully explained by generalized cellular injury. Furthermore, c-miRNA expression patterns differ in a temporal fashion from corollary conventional tissue-specific biomarkers, emphasizing the potential of c-miRNAs as unique, real-time markers of exercise-induced tissue adaptation.
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RANOLAZINE PREVENTS TRASTUZUMAB-CARDIOTOXICITY IN EXPERIMENTAL MODELS

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Purpose. ErbB2 is overexpressed in about 25% of breast cancers. It modulates myocardial development and function in the heart. Trastuzumab (T), an anti-ErbB2 inhibitor, has improved the prognosis of patients with breast cancer, but is related to an increased risk of asymptomatic left ventricular (LV) dysfunction (3-34%) and heart failure (2-4%). The mechanisms of T cardiotoxicity are not entirely known and can include changes in Ca2+ regulation related to blockade of ErbB2. Here, we aim at assessing whether RAN, diminishing intracellular Ca2+ through its inhibition of late INa, blunts T cardiotoxicity in vivo.

Methods. To evaluate cardiac function in vivo, fractional shortening (FS) and ejection fraction (EF) were measured by echocardiography M-Mode in C57BL6 mice, 2-4 mo old, pretreated with RAN (750mg/kg/day, a dose comparable to the one used in humans) per os for 3 days. RAN was then administered for additional 7 days, alone and together with T (2.25 mg/kg/day ip), according to our well established protocol.

Results. In our in vivo studies, after 7 days with T, FS decreased to 49±1.5%, p<0.01 vs 60±0.5% (sham), and EF to 81+.2%, p<0.01 vs 91+.1% (sham). RAN alone did not change FS (59±2%) nor EF 89+.1%. Interestingly, in mice treated with RAN and T, the reduction in cardiac function was milder: FS was 58±1%, EF was 90+.1%, p=0.01 and p<0.01 respectively, vs T alone.

Conclusions. In our mouse model, T produces LV dysfunction and RAN blunts T cardiotoxic effects. We plan to test RAN as a cardioprotective agent with other antineoplastic cardiotoxic drugs in our experimental models and to define the mechanisms of cardioprotection.
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VARIATION IN THE MINICHROMOSOME MAINTENANCE COMPLEX COMPONENT 6 GENE, DAIRY INTAKE AND CARDIOVASCULAR RISK

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Objectives and Background: Single nucleotide polymorphisms (SNPs) in the minichromosome maintenance complex component 6 (MCM6) gene are associated with differential transcriptional activation of the promoter of the neighboring lactase (LCT) gene and, thereby, influence lactase persistence (LP) in adulthood. The rs4988235 SNP, located at -13910 bp upstream from the LCT gene (-13910C>T) within intron 13 of the MCM6 has been the most studied SNP in relation to LP, dairy intake and obesity-related diseases. However, other SNPs may be more relevant. Although currently there is an intense debate regarding the association between dairy intake and cardiovascular diseases (CVD), few studies have integrated the genetic variation in these analyses. Our objectives were to select the most relevant SNPs in the MCM6 gene and to study their association with dairy intake and CVD risk.

Methods: We carried out a bioinformatic analysis for the selection of the most relevant MCM6 SNPs (700K Illumina microarray) and studied their associations with dairy intake and CVD incidence in the PREDIMED study (n=7,187 participants with a median follow-up of 4.8 years).

Results: We selected the rs375468 (A>G) SNP within intron 15 of the MCM6 as the most relevant variant. It was strongly associated with total dairy intake: 359+/−210 g/d in lactase non persistent (LNP) AA subjects; 386+/−225 g/d in AG (LP) and 400+/−229 g/d in GG (LP); P=0.00000006. This association remained significant after adjustment for sex, age, field center, diabetes and total energy intake (P=0.00002). When we applied the Mendelian randomization approach, using the MCM6 genotype as a proxy for dairy intake to explore the association between the SNP and incidence of total CVD, no significant results were found in the population as a whole (P=0.357).

Conclusions: Despite the strong association between the rs375468 SNP and dairy intake, no such association with CVD incidence was observed.
Nonviral gene therapy is an attractive method for treating cardiovascular disease; however, achieving appropriate gene expression levels is often problematic. To enhance expression, we have developed a delivery approach using in vivo gene electro transfer (GET). Swine model was used to assess GET delivery of pVEGF and effect on level of coronary perfusion in the ischemic heart. Myocardial ischemia was induced by occluding the LAD. Animals received no treatment, injection of pVEGF or injection of pVEGF with electro transfer. Animals were maintained for up to seven weeks following delivery and at designated time points underwent injection site excision to determine expression levels or evaluated for level of perfusion in ischemic area. Electric pulses were synchronized with the QRS complex. Levels of expression could be maintained for 2-14 days and were dependent on pulse conditions. Area of ischemia was quantified using a SPY Intraoperative Perfusion Assessment System. Within two weeks, treated animals had increased fluorescent intensity in the ischemic area suggesting an increase in perfusion. Arteriograms before treatment and at various time points following treatment indicated angiogenesis had occurred. Cardiac enzymes increased in all hearts suggesting equivalent amounts of ischemia in all groups. Histological analysis revealed that infarct size was reduced in animals treated with pVEGF +GET (20 ms; 60 V) compared to controls. Cardiac output was significantly greater (p<0.03) 14 days post-infarct in GET treated animals compared to immediately after surgery. Left ventricular mechanical function was significantly greater in GET treated vs control groups. Based on these results, gene delivery to the heart can be successfully accomplished using GET and evidence suggests the potential for a therapeutic effect.
THE RELEVANCE OF GENETICS IN PROVIDING UNDERSTANDING AND TREATMENT FOR CARDIOVASCULAR DISEASE

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THE FAMILY HISTORY AND GENETIC RISK DISCONNECT IN WOMEN
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Introduction: Assessing a patient’s risk for coronary artery disease (CAD) is an evolving art. Family history of CAD (FHx) is a risk factor used to assess risk, however it is often difficult to assess the accuracy of FHx. The 9p21 genotype test and measurement of lipoprotein (a) (Lpa) may be helpful in determining heritable risk. We hypothesize that there is poor association between self-reported FHx, clinically relevant elevated Lpa, and high-risk variants of the 9p21 gene.

Methods: A retrospective review of women from 2 Heart Centers for Women from 2004-2014 was done to evaluate the relationships among patient reported FHx, Lpa, and 9p21 genetic testing for two single nucleotide polymorphisms on 9p21 (rs10757278 and rs1333049). Univariate analysis was done separately to assess association between FHx and Lpa greater than the 90th percentile (≤65.5mg/dL), elevated Lpa (>30mg/dL) and high-risk variants of the 9p21 gene. Association between FHx and either Lpa greater than 90th percentile or high-risk 9p21 genotype was also completed.

Results: There were 842 women (age range 21-80 years) who had data with FHx and Lpa. Of these, 159 had 9p21 genotype data. No association was found between FHx when analyzed with elevated Lpa (p=0.351), Lpa greater than the 90th percentile (p=0.123), high-risk 9p21 genotype (p=0.454), and either Lpa greater than the 90th percentile or high-risk 9p21 genotype (p=0.885). There was a trend toward more patients without FHx of CAD having elevated Lpa (>30mg/dL and ≥65.5 mg/dL) or high-risk 9p21 genotype (p=0.391).

Conclusions: Family history was not predictive of elevated Lpa or high-risk 9p21 variants. We believe that lack of standard FHx assessment should not discourage clinicians from assessing a patient’s high-risk traits such as elevated Lpa and 9p21.
Skeletal muscle is a plastic organ that adapts its mass to various stresses by affecting pathways that regulate protein and cellular turnover. KAATSU training, a new strength rehabilitation method, which stimulates numerous muscle fibers and can produce increased muscle size and strength even with low-intensity loading under the restriction of muscle blood flow (RMBF). We investigated the effects of repetitive application of RMBF on microvascular PO2 (Pmvo2), mammalian target of rapamycin (mTOR) signaling pathways, and transcripts associated with proteolysis in rat skeletal muscle. Eleven-week-old male Wistar rats under anesthesia were subjected to six repetitions of muscle blood flow restriction consisting of 100 mmHg restriction for 5 min applied to the proximal portion of the right thigh, each followed by 3 min rest. During RRMBF, Pmvo2 was measured by phosphorescence quenching techniques. The total RNA and protein of the tibialis anterior muscle were obtained from control, and rats with RRMBF immediately after the stimuli (0 h), 1 h, 3 h, and 6 h. The protein expression, and phosphorylation of signaling proteins were determined by western blotting. The total muscle weight was significantly increased in rats 0 h, but not in rats 1-6 h. During RRMBF, Pmvo2 significantly decreased, and gradually recovered at rest period. RRMBF significantly increased phosphorylation of p70 S6-kinase (p70S6k), a downstream target of mTOR, and ribosomal protein S6 1 h after the stimuli. The protein level of REDD1 and phosphorylation of AMPK did not change. The mRNA expression levels of FOXO3a, MuRF-1, and myostatin were not significantly altered. These results suggest that RRMBF enhances mTOR signaling pathways in skeletal muscle using a rat model, while it does not affect the ubiquitin/proteolysis pathway, REDD1, AMPK. RRMBF may be a novel method for preventing muscle loss in bed rest patients and patients with disuse syndrome.
CURRENT CONCEPTS AND FUTURE DIRECTIONS IN ISCHEMIC HEART DISEASE AND ACUTE CORONARY SYNDROME

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OLD AND EMERGING OPTIONS FOR TREATMENT OF REFRACTORY ANGINA: A CRITICAL APPRAISAL
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Patients with refractory angina are considered to be not suitable candidates for a revascularization procedure, and remain symptomatic despite good medical therapy. However, some patients with refractory angina, experience a marked symptomatic relief after adjustment of their antianginal drugs and lifestyle modifications, including regular exercise. External Enhanced Counter Pulsation (EECP) has also proved useful in these patients and improves CCS angina class in registry data. But randomized sham controlled studies are lacking with EECP. Percutaneous transmyocardial revascularization, initially thought to be effective, is not superior to a sham procedure. And surgical laser transmyocardial revascularization may be effective in selected patients, but is not subjected to a sham procedure, and is used infrequently at present. Spinal cord stimulation is used in European countries with good results in open label trials, but needs to be subjected to randomized studies. Newer antianginal agents (ranolazine, ivabradine and trimetazidine), and older medications (allopurinol and colchicine), look promising, but placebo controlled studies are lacking in this patient group. Patients considered to be poor candidates for a revascularization procedure, are now undergoing stenting of the total coronary occlusions and or of occluded venous graft, with good initial results. But randomized sham controlled studies are needed to establish their long term effectiveness. Gene based therapy, has produced conflicting results, and pilot studies using cell based therapy look promising. A recent report of coronary sinus occlusion devise to increase coronary venous pressure and thus coronary subendocardial blood flow is under active investigation. If all else fails heart transplant remains a last resort in selected patients.
CURRENT CONCEPTS AND FUTURE DIRECTIONS IN ISCHEMIC HEART DISEASE AND ACUTE CORONARY SYNDROME

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MANAGEMENT OF STABLE ISCHEMIC HEART DISEASE: OVERVIEW OF RECENT GUIDELINES

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Management guidelines regarding diagnosis and treatment of stable ischemic heart disease (SIHD) have evolved with time. In 2012, the ACCF/AHA/ACP SIHD Guidelines (Fihn, Gardin, et al. J Am Coll Cardiol. 2012;60:e44-e164.) emphasized important concepts, e.g., the following: (1) Most SIHD patients should have a trial of guideline-directed medical therapy (GDMT), including risk factor modification, before considering revascularization to improve symptoms. Deferring revascularization is generally not associated with worse outcomes: In the COURAGE Trial (Boden, et al. N Engl J Med. 2007;356:1503-16.), percutaneous coronary intervention (PCI) added to GDMT did not reduce the risk of death, MI, or other major CV events compared with GDMT alone. (2) Prior to revascularization to improve symptoms, coronary anatomy should be correlated with functional studies to ensure that lesions responsible for symptoms are targeted. In the FAME Study (Pijls, et al. J Am Coll Cardiol. 2010;56:177-84.), routine measurement of fractional flow reserve in patients with multi-vessel CAD undergoing PCI reduced mortality and MI compared with standard angiography-guided PCI (12.9% vs 8.4%, p=0.02). (3) Exercise and imaging studies should generally be repeated only for a change in clinical status—not annually. (4) A beta blocker is a first-line agent for treatment of angina; however, most patients require multiple medications with different mechanisms of action for symptom control. Angina may persist for many patients despite medical therapy and/or revascularization. The 2013 European Society of Cardiology guidelines on management of SIHD (Montalescot, et al. Eur Heart J. 2013;34:2949-3003.) also emphasize that in light of the results of the FREEDOM Trial (Farkouh, et al. N Engl J Med. 2012;367:2375-84.), coronary artery bypass graft surgery may be the preferred revascularization strategy in diabetic patients with multi-vessel disease. Guidelines have emphasized the importance of shared decision-making between patient and provider in making important diagnostic and therapeutic choices.
Atherosclerosis is a systemic disease with focal manifestations. Each coronary lesion progresses in an independent manner, indicating that local vascular factors play a major role responsible for the behavior of individual plaques. The endothelium is in a unique position to respond to the extremely dynamic forces acting on the vessel wall because of the complex 3D geometry associated with the natural curvature of the artery and the presence of upstream focal atherosclerotic obstructions. The natural history of individual plaques is very heterogeneous over time. Local low endothelial shear stress (ESS) leads to creation of an early plaque; the arterial wall remodeling response likely determines if that plaque will progress due to ongoing local low ESS, or will become quiescent. If the plaque remains in an area of local low ESS then it will likely develop phenotypic manifestations of more advanced atherosclerosis including more lipid accumulation and intense inflammation. Ongoing inflammation exacerbates plaque instability and increases the likelihood of plaque disruption leading to either an acute coronary syndrome or intraplaque hemorrhage leading to plaque enlargement and abrupt luminal encroachment. High ESS may also contribute to plaque disruption. In-vivo imaging methodologies now exist to characterize the local ESS patterns, the plaque morphology, and the arterial remodeling response. Only about 5% of high-risk plaques actually progress to cause a new cardiac event. Large plaque burden and local low ESS each have an independent positive predictive value (PPV) of 20% to predict new events, but the combination of both predictors has a PPV >40%. Detection of local inflammation or large lipid pool may further enhance prediction of high-risk plaques likely to cause a new event. Accurate identification of early stages of high-risk coronary lesions may allow for preemptive strategies to treat such high-risk plaques and prevent new cardiac events.
CURRENT CONCEPTS AND FUTURE DIRECTIONS IN ISCHEMIC HEART DISEASE AND ACUTE CORONARY SYNDROME

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FRACTIONAL FLOW RESERVE (FFR) AT 2014- WHERE ARE WE AND WHERE IS IT GOING
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New society guidelines support now the use of FFR over to assess intermediate stable native coronary lesions (now defined as 50-90% diameter stenosis when stress imaging is contraindicated, non-diagnostic, discordant or unavailable. In subjects with stable coronary artery disease (CAD) percutaneous coronary intervention (PCI) of lesions with FFR <0.80 improves symptom control and hospitalization for urgent revascularization however the predictive value for clinical events remains low (~20% in 2 years).

There is limited data regarding the role of FFR in guiding therapy acute coronary syndromes, left main disease, vein grafts and mammary lesions, peri-procedural PCI results, sidebranch intervention in bifurcation lesion stenting or non-coronary interventions.

In the past 5 years sub-optimal vasodilatation was observed with intracoronary or intravenous adenosine and new agents (regadenoson and nitroprusside) as well as instantaneous wave free ratio (iFR) were trialed. While newer agents are effective and safe iFR did not seem to yield similar resistance (2.5 fold higher) or results as FFR (iFR was 9% higher with precision limits of ±17%). Attempts to produce non-invasive CT angiography (CTA) based FFR map are encouraging but are still lacking the precision of FFR.

In the next 5 years we are hoping that the role of iFR and non-invasive CTA based FFR will be further clarified. The role of FFR in additional patient and lesion subsets should be refined in coronaries as well as other vascular beds. Algorithms and tools to determine the relative contribution of multiple sequential or parallel lesions may further facilitate the use of FFR in multi-vessel disease.
IS ISCHEMIA UNIVERSAL IN A CHRONIC TOTAL OCCLUSION?

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During routine coronary angiography 30% of patients are noted to have chronic total occlusions (CTO) of coronary arteries. Percutaneous revascularization is attempted much less frequently for CTO compared to non-CTO lesions. Even though CTO is a common reason for referral to coronary artery bypass surgery, percutaneous coronary intervention (PCI) for CTO has been criticized. The commonly cited reasons for this being development of large collaterals providing sufficient blood flow to the CTO myocardium, less likelihood of ischemia if CTO myocardium is hypokinetic or akinetic and lastly poor long-term outcomes following PCI for CTO. As per Appropriate Use Criteria for PCI revascularization, CTO PCI is consider appropriate with class III or IV angina in spite of maximal medical therapy. Fractional flow reserve (FFR) is an adjunctive tool utilized in the catheterization laboratory to determine ischemia in a non-CTO stenosis. FFR can also be used to determine presence of ischemia in CTO lesions. This ischemia in CTO lesions has also been related to worse clinical outcomes of patients with CTO such as increased risk of arrhythmias and poor tolerance of future acute coronary syndromes. Recent studies using FFR in symptomatic patients with CTO have demonstrated that ischemia is universal in these patients and PCI of these lesions can effectively improve symptoms. Also in patients with an intermediate stenosis of donor artery supplying collaterals to the CTO myocardium, the ischemia in the donor artery territory can be normalized by successful CTO recanalization by PCI.
CURRENT CONCEPTS AND FUTURE DIRECTIONS IN ISCHEMIC HEART DISEASE AND ACUTE CORONARY SYNDROME

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OPTIMAL DURATION OF DUAL ANTIPLATELET THERAPY AFTER DES IMPLANTATION: EXCELLENT TRIAL AND FUTURE PERSPECTIVES

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ACC/AHA guideline recommends the continuation of dual antiplatelet therapy (DAPT) at least for 12 months after DES implantation to reduce the risk of stent thrombosis. Prolonged DAPT may cause a higher risk of bleeding and also an inappropriate delay of urgent surgery or procedures. EXCELLENT trial was the first randomized controlled trial to determine the safety of 6-month vs. 12-month duration of DAPT. 12-month target vessel failure was similar between 6-month and 12-month group (HR=1.10 [95% CI 0.68-1.79], p=0.71, p for non-inferiority = 0.001). The composite of death, MI, stent thrombosis, cerebrovascular event, or TIMI major bleeding was also not significantly different (HR=1.15 [0.64-2.06], p=0.64). But, 6-month DAPT was associated with higher event in diabetic and first generation DES subgroups. This study was limited by the small sample size and soft endpoint. PRODIGY trial compared 6-month vs. 24-month DAPT. The composite of death, MI or cerebrovascular event was not significantly different between 2 group, but BARC 2,3,5 bleeding was significantly higher in 24-month group. RESET trial and OPTIMIZE trial proved the safety of 3-month DAPT duration after the implantation of zotarolimus-eluting Endeavor Sprint stent, which, however, is currently not available. We are expecting the result of DAPT and ISAR-SAFE trial. In this era of second generation DES, the optimal DAPT duration will be shorter than that recommended in current guidelines.

In the patients with acute coronary syndrome (ACS), DAPT for more than 12 month is strongly recommended. Currently SMART-DATE trial is going on to test the safety of 6-month duration of DAPT in ACS patients treated with second generation DES. In addition to shorter DAPT duration, replacing aspirin with clopidogrel or new antiplatelet agent will be the next target to study. The future antiplatelet therapy will be safer and more convenient, considering bleeding risk as well as ischemic risk.
In patients with suspected ischemia, the data derived from one type of imaging test may be insufficient to assess its significance. In 62 patients, two imaging techniques were utilized to assess the extent of ischemia and help determine clinical management. 130 dual studies consisting of both a myocardial perfusion test (MPT) and an exercise echocardiogram (EXE) were performed on the same 62 patients. The median patient age was 68, and ninety-one percent were male. The tests were conducted within two months of each other. Myocardial perfusion was evaluated by exercise SPECT, adenosine SPECT, or a PET scan. EXEs were performed by using a treadmill and BRUCE protocol and imaging before and immediately after exercise. Ischemia by perfusion not associated with exercise wall motion abnormalities was considered mild. If ischemia was seen with both techniques, it was considered significant and handled appropriately. Fifty-five percent of the MPTs and thirty-five percent of the EXEs were abnormal. In approximately twenty-three percent of the dual studies, a positive MPT was not associated with wall motion abnormalities in the EXE, thus leaving the diagnosis of ischemia open. In conclusion, dual imaging is a useful tool to determine the true extent of ischemia in a cardiology practice.
CURRENT CONCEPTS AND FUTURE DIRECTIONS IN ISCHEMIC HEART DISEASE AND ACUTE CORONARY SYNDROME

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ATYPICAL AND UNUSUAL CLINICAL PRESENTATIONS OF PATIENTS WITH ISCHEMIC HEART DISEASE
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Ischemic heart disease is the leading cause of death worldwide accounting for 7 million deaths annually. Chest pain is the cardinal symptom in patients with ischemic heart disease (IHD). This symptom also serves as a trigger for prompt investigation and treatment measures. However, up to 40 percent of patients with atypical symptoms seek medical attention and pose numerous missed opportunities for the best care. These atypical and unusual symptoms in IHD patients include fatigue, dyspnea, diaphoresis, nausea, vomiting, dizziness, vertigo, interscapular and epigastric pain. These atypical symptoms are more common in the elderly, diabetic and female patients. Myocardial infarction patients presenting with atypical symptoms may not receive prompt EKG and reperfusion treatment thereby leading to higher mortality and morbidity in this group of patients. These IHD patients with atypical presentation have not been studied adequately. One study has showed a 2 fold increase of in-hospital mortality in myocardial infarction patients with atypical symptoms. As people age, diabetes and hypertension becoming more prevalent, we would expect to see far greater number of IHD patients with atypical and unusual presentations. Therefore, a high index of suspicion for MI is essential in these patients presenting with unusual symptoms to avoid excess mortality and morbidity. There has been an ongoing research exploring newer techniques of detecting the pre-myocardial infarction state in high risk patients.
CURRENT CONCEPTS AND FUTURE DIRECTIONS IN ISCHEMIC HEART DISEASE AND ACUTE CORONARY SYNDROME

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STABLE ISCHEMIC HEART DISEASE: EVOLVING CONCEPTS AND THE ROLE OF ISCHEMIA

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The optimal strategy for the management of patients with stable ischemic heart disease (SIHD) has been a matter of considerable debate over the past two decades. During this time period, there have been notable technologic evolutions in catheter-based revascularization that include the advent of bare metal and drug-eluting stents, the genesis of more effective antiplatelet therapy, the continued refinement of stent delivery platforms, improving operator experience and quality improvement initiatives which have led to declining complication rates. As a result, the approach to the management of SIHD has shifted increasingly from an initial pharmacologic strategy to one that embraces an initial percutaneous coronary intervention (PCI) approach. However, such a management paradigm is not fully supported by robust outcomes data, which suggests the need for a critical reappraisal of contemporary clinical practice. In particular, clinical decision-making is now better informed because of the results of several important randomized control trials that have rigorously compared the hard clinical endpoints of death and myocardial infarction (MI) in patients with SIHD who have undergone PCI with contemporary, guideline-directed medical therapy combined with lifestyle intervention.
Purpose: While coronary computed tomography angiography (CCTA) has a high negative predictive value using invasive coronary angiography (ICA) as reference standard, current methods that rely on coronary artery morphology alone have lower specificity for predicting either anatomic or functional significance of coronary lesions. The purpose is to describe the use of CT contrast enhancement patterns and its relationship to blood flow in the coronary arteries. Metrics derived from these methods are currently in translation for use in conjunction with traditional CCTA interpretation.

Methods: CCTA contrast opacification is described with its relation to blood flow using a simple model that is derived from CT images. Differences between 320-detector row coronary CT images acquired with temporal uniformity and other methods are described. To date, two types of parameters have been developed to quantify the contrast opacification and test it as a tool to assess the hemodynamics of coronary artery lesion. Results: The two types of parameters, contrast opacification differences and contrast opacification gradients, have been studied by independent laboratories. The transluminal attenuation gradient (TAG) was described after the contrast opacification gradient and is nearly equivalent to the contrast opacification gradient. The gradient is defined as the linear regression coefficient of intracoronary contrast attenuation measured in Hounsfield units versus axial distance. A simplified theory of first-pass lumen blood flow in the aorta supports both of these strategies as a method to enhance the specificity of CCTA to detect a lesion that is hemodynamically significant. Data from different CT platforms will be reviewed for each of the parameters.

Conclusion: Coronary CT contrast opacification is related to coronary blood flow. At present, the gradient of the contrast opacification along the coronary artery can be used to extract this information, and future work will focus on enhancement to these methods to increase the specificity of CCTA.
SHOULD DUAL ANTI-PLATELET THERAPY FOR CORONARY ARTERY DISEASE BE MORE OR LESS THAN 12 MONTHS? : A META-ANALYSIS

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Background: Current ACC/AHA guidelines recommend dual anti-platelet therapy (DAT) for 12 months after coronary artery disease (CAD) treatment with drug eluting stent in order to prevent stent thrombosis. It is yet to be determined the ideal duration for DAT. We performed a meta-analysis of all clinical prospective studies to assess the impact of DAT duration.

Methods: We systematically searched PubMed, Embase and Cochrane up to January 2014 for randomized clinical trials comparing 3 to 6 months (short-term) of DAT to 12 months (standard) and prospective studies comparing 12 months to 24 months (prolonged-term) of DAT. Outcomes analyzed included all-cause death, myocardial infarction (MI), stroke, target vessel revascularization (TVR), cardiac death, and bleeding complications from 12-24 months follow-up.

Results: Total of 3 RCTs were included and provided 6679 patients; 3344 in the short-term group and 3335 in the standard. The majority of studies used the DES second generation. There was no difference among groups for death, MI, stroke, TVR and cardiac death. Standard group was significantly associated to increased risk of bleeding complications (Figure 1). Regarding the prolonged-term analysis, the two studies included did not disclose any difference among groups (Figure 2).

Conclusion: The short-term duration of DAT should be considered if not equal to standard duration at least to carry less complication rate as bleeding whereas prolongation of DAT might not add any additional benefit. The use of second generation DES might play a role on these findings. Further randomized trials that also include the new anti-platelets agents are warranted.
OBESITY, DIABETES AND CVD

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THE MACROPHAGE A2B ADENOSINE RECEPTOR REGULATES OBESITY-INDUCED TISSUE INSULIN SENSITIVITY
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High fat diet (HFD)-induced type 2 diabetes continues to be an epidemic with significant risk for various pathologies. In a previous study we identified the A2b adenosine receptor (A2bAR), an established regulator of inflammation, as a regulator of HFD-induced insulin resistance. In particular, HFD was associated with vast upregulation of liver A2bAR in control mice, while mice lacking this receptor showed augmented liver inflammation and tissue insulin resistance. Considering that the A2bAR is highly expressed in macrophages, here, we explored the contribution of macrophage expression of A2bAR to the control of insulin resistance. This inquiry was addressed in a two-fold approach, including a pharmacological approach, using gadolinium chloride to deplete hepatic resident macrophages, the Kupffer cells, and a transgenic mouse model expressing the A2bAR gene in macrophages on an otherwise A2bAR null background. Depletion of liver Kupffer cells significantly ameliorated tissue insulin signaling both in control and A2bAR null mice fed HFD, suggesting that A2bAR expression in other sites does not have an effect that overrides the essential role of Kupffer cells. Reinstatement of macrophage A2bAR expression in A2bAR null mice fed HFD restored insulin tolerance and tissue insulin signaling to the level of control mice. The mechanism for this effect involves A2bAR-medicated changes in cAMP in macrophages, reducing the expression and release of inflammatory cytokines, which reduce the level of insulin receptor-2. Thus, our results illustrate that macrophage A2bAR signaling is needed and sufficient for relaying the protective effect of the A2bAR against HFD-induced tissue inflammation and insulin resistance in mice.
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METABOLIC SYNDROME CRITERIA: CAUSE VERSUS EFFECT OF CARDIOMETABOLIC DISEASE

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Although metabolic syndrome (MetSyn)-criteria provide a convenient tool to recognize individuals at increased cardiometabolic disease-risk, they appear haphazard, mixing descriptors of body-phenotype with lab-tests and a vascular condition. Are MetSyn-criteria causes or effects? Can they explain MetSyn-pathophysiology and guide therapy?

Insulin resistance (IR) underlies MetSyn. IR arises in response to stressors. Inflammatory/oxidative stress-pathways underlie IR-mechanisms. IR is the metabolic expression of inflammation. IR terminates anabolic/vascular insulin-signaling in non-essential organs and engenders an insulin-resistant catabolic state to fuel essential immune cells. Concurrently, mitogenic insulin-signaling is enhanced by secondary hyperinsulinemia. Barring reversal of precipitating factors, IR begets further IR.

The acute survival-benefit of IR-pathways is lost when this acute fix becomes protracted. IR and underlying mechanisms erode intracellular/intramitochondrial biochemical pathways, eventually engendering cell senescence, cell drop-out, tissue dysfunction, physiologic aging, progressing to age-related chronic disease irrespective of chronological age, as reflected in MetSyn and comorbidities.

Causes and effects of IR can be dissected from MetSyn-criteria:

<table>
<thead>
<tr>
<th>MetSyn-Criterion</th>
<th>IR-Cause → versus Effect ←</th>
<th>Tissue</th>
</tr>
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<tbody>
<tr>
<td>Waist-circumference</td>
<td>→</td>
<td>Adipose</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>←</td>
<td>Liver</td>
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<tr>
<td>Hypertension</td>
<td>←</td>
<td>Vasculature</td>
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<tr>
<td>Hyperglycemia</td>
<td>←</td>
<td>Skeletal muscle, Heart, Pancreas</td>
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IR-related disease-pathways and target-tissues require a multifaceted approach, comprising antioxidant, anti-inflammatory, stress-relieving therapeutic-lifestyle-changes (TLCs) complemented by pharmacotherapies with broad-spectrum impact due to pleiotropic (antioxidant, anti-inflammatory, mitochondrioprotective, anticoagulant, vasculoprotective, antiproliferative, insulin-sensitizing) effects that comprehensively reverse IR and delay/prevent MetSyn-comorbidities.

<table>
<thead>
<tr>
<th>MetSyn-Criterion</th>
<th>Disease Pathway</th>
<th>Intervention</th>
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<tbody>
<tr>
<td>Waist-circumference</td>
<td>Inflammation, Oxidative stress, Mitochondrial dysfunction, FFAs, Hypoadiponecetinemia</td>
<td>TLC: Weight loss, Mediterranean diet, Rx chronic infections, Exercise, Restorative sleep, Stress relaxation, Smoking cessation, Bariatric surgery</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>Hepatic IR, NAFLD, TG/HDL</td>
<td>Pharmacotherapy: “Broad spectrum” statin, Metformin?</td>
</tr>
<tr>
<td>Hypertension</td>
<td>Endothelial dysfunction, Hypercoagulability, Vascular disease</td>
<td>Pharmacotherapy: RAAS antagonism, Vasodilating betablocker, Aspirin or other antiplatelet therapy</td>
</tr>
<tr>
<td>Hyperglycemia</td>
<td>Mitochondrial dysfunction, Energy deficit, Decreased aerobic capacity, Ectopic fat, Muscle, cardiac, pancreatic IR, Heart failure, Type 2 DM</td>
<td>TLC Metformin?</td>
</tr>
</tbody>
</table>

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MITOCHONDRIAL DYSFUNCTION AND DIABETIC HEART DISEASE
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Most diabetic patients die from heart disease or stroke, highlighting the importance of understanding and treating cardiovascular complications of diabetes. A large body of evidence indicates that mitochondrial dysfunction and increased generation of reactive oxygen species (ROS) are critical to diabetic heart damage. However, several clinical trials have failed to confirm the ability of antioxidant therapies to reduce heart failure in diabetic patients. This may reflect the fact that antioxidants can only scavenge existing ROS, but cannot curb continuous ROS generation from injured mitochondria, which are a major source and a target of intracellular ROS in diabetes. A healthy mitochondrial network is maintained through a number of quality control mechanisms including mitochondrial autophagy, also known as mitophagy, which degrades dysfunctional mitochondria that are segregated from the network by mitochondrial fission. Using distinct fluorescent reporters, we found that the general autophagy is inhibited while the selective mitophagy is enhanced in cardiomyocytes treated with high glucose, an independent risk factor for heart failure in diabetic patients. This result is associated with increased mitochondrial fragmentation, suggesting that autophagy, mitophagy and mitochondrial fission are coordinately but differentially regulated by high glucose. Intriguingly, using genetic gain- and loss-of-function approaches, we showed that autophagy inhibition, mitophagy activation or mitochondrial fragmentation each is an adaptive response that limits high glucose cardiotoxicity as measured by the levels of oxidative injury, mitochondrial damage, ROS generation and cardiomyocyte death. Consistently, autophagy is inhibited in type 1 diabetic mouse heart, which protects against diabetic cardiac injury. Using a novel mitophagy reporter mouse, we are assessing mitophagy and mitochondrial fragmentation in the diabetic heart and determining the functional significance of these two events in the pathogenesis of diabetic cardiomyopathy. This study will provide a basis for designing drugs that may reduce diabetic cardiac injury by enhancing mitochondria quality control mechanisms.
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BENEFITS AND RISKS OF ANTI-DIABETIC TREATMENT IN PATIENTS WITH CORONARY ARTERY DISEASE AND HEART FAILURE

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VIVIT Institute, Feldkirch, Austria

Diabetes mellitus is a paramount risk factor both for coronary artery disease (CAD) and heart failure, and the prevalence of diabetes among patients with CAD or heart failure is high. While better glucose control epidemiologically is associated with a lower incidence of cardiovascular events, lowering blood glucose failed to lower the incidence of macrovascular diabetes complications, i.e. of atherosclerotic cardiovascular disease in multiple trials, in particular among patients with established CAD. Aggressive glucose lowering even was associated with increased mortality in one landmark trial. Pathophysiologically, hypoglycemia poses patients with CAD or heart failure at an increased risk of cardiac arrhythmia. With regard to specific anti-diabetic agents, data from randomized trials point towards a favorable impact of pioglitazone and metformin on cardiovascular event risk. Because of signals that rosiglitazone confers an increase in cardiovascular event risk, the FDA required that new anti-diabetic drugs are tested for cardiovascular safety in adequately powered trials; for example the cardiovascular safety of the DPP-4 inhibitors alogliptin and saxagliptin has recently been demonstrated. Pioglitazone increases fluid retention and therefore is contraindicated in patients with heart failure. Even though metformin is formally contraindicated in patients with heart failure, the prognosis of heart failure patients on metformin in registries is better than of those on other anti-diabetic drugs. Importantly, the prevention of microvascular diabetes complications is important also in CAD or heart failure patients. Like for other patients, the American Diabetes Association therefore recommends an HbA1c goal of <7.0% in these patients.
OBESITY, DIABETES AND CVD

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SERENDIPITY IN MEDICINE; DOES CHANCE TRULY FAVOR THE PREPARED MIND?

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Serendipity means a "fortuitous happenstance" or "pleasant surprise". It was first coined by Horace Walpole in 1754. In a letter he wrote to a friend Walpole explained an unexpected discovery he had made by reference to a Persian fairy tale, The Three Princes of Serendip. The princes, he told his correspondent, were “always making discoveries, by accidents and sagacity, of things which they were not in quest of’. The notion of serendipity is a common occurrence throughout the history of scientific and medical innovation such as Alexander Fleming's accidental discovery of penicillin in 1928. One example of luck in science is when drugs under investigation become known for different, unexpected uses. This was the case for minoxidil, sildenafil and many other medications. Less obvious is the use of microwave technology that has found its way into medicinal practice. Discussion of these and other fascinating examples that interestingly, potentially undermine the role of the randomized clinical trial will ensue.
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HIGH CARDIOVASCULAR RISK IN NON-ALCOHOLIC FATTY LIVER DISEASE: A POSSIBLE ROLE FOR INCREASED OXIDATIVE STRESS?
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2. Department of Internal Medicine and Medical Specialties, Sapienza University, Rome, Italy

Background: Nonalcoholic fatty liver disease (NAFLD) is the most emerging form of chronic liver disease worldwide, which may progress into cirrhosis, and liver cancer. However, people with NAFLD have an increased chance of developing cardiovascular diseases, which represent the major causes of death in this setting. Several lines of evidence suggest that chronic oxidative stress is one of the key mechanisms responsible for liver damage and disease progression in NAFLD. At the same time, there is sound evidence that oxidative stress centrally contributes to atherothrombosis and is involved at all stages of atherosclerotic plaque evolution. The aim was to assess the relationship between two markers of systemic oxidative stress - urinary 8-iso-prostaglandin-alpha; (8-iso-alpha;) and serum soluble NOX2-derived peptide (NOX2-dp) and the severity of liver steatosis in subjects with NAFLD.

Methods: The study was performed in 264 consecutive patients referred for suspected metabolic disease. Steatosis was defined according to Hamachi ultrasonographic criteria. Oxidative stress was assessed by urinary 8-iso-alpha; and serum NOX2-dp levels.

Results: Patients with NAFLD had higher (p<0001) mean values of urinary 8-iso-PGF2-alpha; and of serum NOX2-dp, ALT, Cytokeratin-18 and homeostasis model of insulin resistance and lower values of serum adiponectin as compared to those without. Prevalence of metabolic syndrome was significantly higher in patients with NAFLD. In addition, the levels of urinary 8-iso-alpha; were independent predictors of non-alcoholic fatty liver and a strong association of urinary 8-iso-PGF2-alpha; and of serum NOX2-dp with the severity of steatosis at ultrasound was also observed.

Conclusions: We demonstrated an increased NOX2-generated oxidative stress in subjects with NAFLD. These findings may further contribute to a better understanding of the association between NAFLD and cardiovascular diseases.
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IMPACT OF METABOLIC SYNDROME ON SUBCLINICAL ATHEROSCLEROSIS IN ASYMPTOMATIC INDIVIDUALS

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2. Asan Medical Center, University of Ulsan College of Medicine, Seoul, Korea

Objectives: The purpose of this study was to investigate the clinical impact of metabolic syndrome (MetS) on the risk of subclinical atherosclerosis in asymptomatic individuals.

Background: Little is known about subclinical atherosclerosis on coronary computed tomographic angiography (CCTA) in asymptomatic individuals with MetS.

Methods and Results: We retrospectively enrolled 5,213 asymptomatic individuals who underwent CCTA. Cardiac events were defined as a composite of all-cause death, non-fatal myocardial infarction, acute coronary syndrome, or coronary revascularization. Of the study population, 2,042 (39.2%) had MetS. Individuals with MetS had more plaques, significant CAD (coronary artery disease), and significant CAD in the left main (LM) or proximal left anterior descending (LAD) artery than those without (p<0.001 for all). On multivariate analysis, MetS was an independent predictor of significant CAD in at least one coronary artery and significant CAD in the LM or proximal LAD. During the follow-up period (median 28.1 [interquartile range, 19.2–36.5] months), a total of 114 cardiac events occurred in 111 individuals. Individuals with MetS had more cardiac events than those without (2.8% versus 1.7%, p=0.007). In the group with MetS, those with significant CAD had the majority of cardiac events (19.9% versus 0.4%, p<0.001). Furthermore, in the MetS group with significant CAD, those with significant CAD in the LM or proximal LAD had more cardiac events (31.0% versus 14.0%, p=0.001).

Conclusions: MetS was associated with subclinical atherosclerosis on CCTA with subsequent high risk for cardiac events. These findings suggest the importance of reduction for unfavorable metabolic conditions in asymptomatic individuals.
DISEASE PATHWAYS AND NEW TREATMENT STRATEGIES IN HEART FAILURE AND CARDIOMYOPATHIES

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TREATING RAPID ATRIAL FIBRILLATION IN DECOMPENSATED HEART FAILURE: METOPROLOL IS SUPERIOR TO DILTIAZEM
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2. Barnes Jewish Hospital, St. Louis, Missouri, USA

Objective: We sought to determine the difference in efficacy and safety between beta and calcium channel blockade for the acute treatment of atrial fibrillation with rapid ventricular response (AF-RVR) in the setting of decompensated congestive heart failure (HF).

Background: Rate control is an acceptable treatment strategy for AF-RVR, yet common rate controlling agents such as metoprolol and diltiazem are cautioned in decompensated HF for fear of exacerbating HF symptoms. Studies directly comparing these two agents in this setting are lacking and treatment recommendations are primarily derived from subgroup analysis from larger HF or AF trials.

Methods: We performed a retrospective analysis of patients admitted with decompensated HF and AF-RVR who received either intravenous (IV) metoprolol or IV diltiazem from 3/2009 to 3/2013. The primary endpoint was a composite of achievement of rate control (<110 beats per minute) or conversion to sinus rhythm by 24 hours after start of drug.

Results: There were no baseline differences between the metoprolol (n=83) and diltiazem (n=90) cohorts. While there was no difference in the composite primary endpoint (87% vs. 84%, p=0.83), the metoprolol group had a higher rate of conversion to sinus rhythm (41% vs. 23%, p=0.014, see figure) by 24 hours. There were no differences in secondary endpoints of hypotension, bradycardia, DC cardioversion, or worsening heart failure (see table).

Conclusion: In patients with AF-RVR in the setting of decompensated HF, metoprolol and diltiazem have similar efficacy for rate control, but metoprolol is associated with higher conversion to sinus rhythm. Unlike previously thought, both agents were equally safe without a significant rate of adverse effects or worsening heart failure.

![Graph showing rate control following IV infusion over 24 hours](image-url)
DISEASE PATHWAYS AND NEW TREATMENT STRATEGIES IN HEART FAILURE AND CARDIOMYOPATHIES

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PREDICTORS OF HEART FAILURE WITH PRESERVED EJECTION FRACTION (HFpEF)

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2. Department of Cardiology, University of Texas Medical Branch
3. School of Nursing, University of Texas Medical Branch, Galveston, TX, USA

Background: Identifying the factors that lead to the development of HFpEF has become important as no treatment has shown to effect mortality in HFpEF.

Methods: In a retrospective study, we reviewed the medical records and echocardiographic characteristics of patients who presented to the echocardiographic lab in a tertiary care academic center between 2008 and 2011. Patients were said to have HFpEF if they had EF ≥ 50%, history of CHF according to Framingham criteria and were NYHA II or above for a period of three months. Using logistic regression analysis the impact of various clinical and demographic predictors on HFpEF was assessed after adjusting for potential confounders.

Results: HFpEF was found in 101(13.5%), 238(16.5%), & 81(30.9%) patients with Normal Diastolic Function (n=746), LVDD I (n=1435), & LVDD II/III (n=262), respectively. Patients with LVDDII/III, CKD stage4, OSA, COPD and Atrial Fibrillation were more likely to develop HFpEF(OR : 2.8, 2.6, 2.2, 2.7, 2.6 respectively, p < 0.01).Patient who did not have pulmonary hypertension by echo criteria(RVSP<40 mm Hg) were unlikely to develop HFpEF(OR:1.69, p < 0.01).

Conclusion: Severe stages of renal impairment and Left Ventricular Diastolic Dysfunction along with OSA, COPD and Atrial Fibrillation seem to be independent predictors of HFpEF.
### Figure I. Predictors of HFpEF

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Wald</th>
<th>Sig.</th>
<th>Exp(B)</th>
<th>95% C.I for EXP(B)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Lower</td>
<td>Upper</td>
</tr>
<tr>
<td>A.Fib (+)**</td>
<td>24.678</td>
<td>.000</td>
<td>2.634</td>
<td>1.798</td>
</tr>
<tr>
<td>LVDD I</td>
<td>.291</td>
<td>.589</td>
<td>1.094</td>
<td>.789</td>
</tr>
<tr>
<td>LVDD II/III**</td>
<td>14.343</td>
<td>.000</td>
<td>2.828</td>
<td>1.651</td>
</tr>
<tr>
<td>Pulm. HTN(-)*</td>
<td>7.295</td>
<td>.007</td>
<td>.589</td>
<td>.401</td>
</tr>
<tr>
<td>Pulm-HTN(+)</td>
<td>.259</td>
<td>.611</td>
<td>1.124</td>
<td>.717</td>
</tr>
<tr>
<td>CKD stage2</td>
<td>.242</td>
<td>.623</td>
<td>1.095</td>
<td>.763</td>
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<tr>
<td>CKD stage3</td>
<td>2.819</td>
<td>.093</td>
<td>1.443</td>
<td>.940</td>
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<tr>
<td>CKD stage4*</td>
<td>8.999</td>
<td>.003</td>
<td>2.632</td>
<td>1.399</td>
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<td>CKD stage5</td>
<td>.264</td>
<td>.608</td>
<td>.818</td>
<td>.381</td>
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<tr>
<td>BMI &lt;30</td>
<td>.713</td>
<td>.398</td>
<td>1.642</td>
<td>.520</td>
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<td>BMI ≥30</td>
<td>1.812</td>
<td>.178</td>
<td>2.180</td>
<td>.701</td>
</tr>
<tr>
<td>DM(+)</td>
<td>.004</td>
<td>.950</td>
<td>.990</td>
<td>.716</td>
</tr>
<tr>
<td>History of Smoking(+)</td>
<td>1.191</td>
<td>.275</td>
<td>1.193</td>
<td>.869</td>
</tr>
<tr>
<td>OSA(+)*</td>
<td>9.198</td>
<td>.002</td>
<td>2.224</td>
<td>1.327</td>
</tr>
<tr>
<td>Gender (M)</td>
<td>.245</td>
<td>.621</td>
<td>1.081</td>
<td>.794</td>
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<tr>
<td>CAD(+)</td>
<td>2.915</td>
<td>.088</td>
<td>1.329</td>
<td>.959</td>
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<tr>
<td>Age &lt; 60 yrs</td>
<td>.192</td>
<td>.662</td>
<td>.772</td>
<td>.242</td>
</tr>
<tr>
<td>Age ≥ 60 yrs</td>
<td>.393</td>
<td>.530</td>
<td>.694</td>
<td>.221</td>
</tr>
<tr>
<td>COPD(+)**</td>
<td>21.307</td>
<td>.000</td>
<td>2.723</td>
<td>1.780</td>
</tr>
</tbody>
</table>

(*+) Presence; (-) Absence; LVDD: Left Ventricular Diastolic Dysfunction Stage I; LVDD II/III: Left Ventricular Diastolic Dysfunction Stages II & III; Pulm HTN: Pulmonary Hypertension (RVSP ≥ 40 mm Hg); CKD: Chronic Kidney Disease; BMI: Body Mass Index; DM: Diabetes Mellitus; OSA: Obstructive Sleep Apnea; (M): Males; CAD: Coronary Artery Disease; COPD: Chronic Obstructive Pulmonary Disease; * Significant at p<0.01 ; ** Significant at p<0.001
OPTIMIZING HEART FAILURE OUTCOMES: WHICH HOSPITAL CARE MODEL CAN WE LEARN FROM?

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2. Heartland Cardiology Wichita, KS, USA

Background: Several studies have evaluated the utility of the hospitalist model in the management of heart failure patients. However data is lacking on the outcomes among patients admitted to teaching hospitalist services compared to other physician categories.

Methods: We conducted a retrospective cohort study of 1735 patients 18 years of age or older hospitalized for heart failure between January 2010 and December 2012 in 2 community hospitals in the United States. We compared the outcomes of care by 3 teaching hospitalist groups, non-teaching hospitalist groups, cardiologists, nephrologists and community primary care physicians. The primary outcome was the in-hospital mortality and the secondary outcomes were the 30-day readmission rates, hospital length of stay, rates of discharge to home, nursing facility or hospice.

Results: The teaching hospitalists had the lowest in-hospital all-cause mortality rate (0.94%; p<0.05), the lowest 30-day re-admission rates (3.4%; p<0.05). The average length of stay was significantly shorter with the teaching hospitalists and non-teaching hospitalists (5.2 and 5.3 days respectively) compared with the other physician categories (p<0.05). A higher proportion of patients were discharged home by the teaching hospitalists compared with the other physician categories, while there was no significant difference in the proportion of patients discharged with hospice.

Conclusions: Patients admitted by teaching hospitalists had the lowest mortality rates, shortest average length of stay, lowest 30-day readmission rates and were more likely to be discharged home compared to other physician groups. The difference in outcomes may be multifactorial and there’s need for further studies to determine patient profiles, differences in the care delivery process or any other factors that may explain differences in outcomes and may provide lessons on how to improve clinical outcomes of hospitalized heart failure patients.
COMPARATIVE EFFECTIVENESS OF TRANSITIONAL CARE SERVICES IN PATIENTS DISCHARGED FROM THE HOSPITAL WITH HEART FAILURE (HF): A META-ANALYSIS

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\textsuperscript{1}. Population Health Research Institute and McMaster University, Hamilton, Ontario, Canada
\textsuperscript{2}. University of Cambridge, Cambridge, United Kingdom
\textsuperscript{3}. Tokyo Bay Medical Center, Tokyo, Japan
\textsuperscript{4}. McMaster University, Hamilton, Ontario, Canada

\textit{Background:} Patients are at increased risk of readmission and death following hospitalization for Heart Failure (HF). Transitional care services can improve post-discharge outcomes, but the comparative effectiveness of different services is unclear.

\textit{Objective:} To evaluate the effectiveness of various transitional care services in decreasing all-cause readmissions and mortality following hospitalization for HF. \textit{Sources:} We searched Pubmed, Embase, CINAHL, and the Cochrane Clinical Trials Register for trials that evaluated the efficacy of transitional care services in patients discharged from the hospital with HF, limiting the search to articles published 2000-2011, inclusive.

\textit{Study Selection:} We selected randomized clinical trials (RCTs) that recruited hospitalized patients with a primary diagnosis of HF; offered a transitional care intervention; provided >1 month of post-discharge follow-up; and reported outcomes of all-cause readmission or mortality.

\textit{Data Extraction and synthesis} – >2 authors independently reviewed each study and extracted data. Disagreements were resolved by consensus.

\textit{Primary outcomes:} All-cause readmissions and mortality.

\textit{Results:} We included 34 RCTs that randomized 5938 HF patients to transitional care services or usual post-discharge care. Services included telephone calls, home nurse visits, case management, remote tele-monitoring, pharmacist interventions, and multidisciplinary HF clinics (HFC). Overall, transitional care services significantly decreased all-cause readmissions (RR 0.75, 95% CI 0.65-0.86) and mortality (RR 0.80, 95% CI 0.71-0.90) during follow-up. Among the transitional care services evaluated, case management (RR 0.68, 95% CI 0.53-0.88) and multidisciplinary HFCs (RR 0.77, 95% CI 0.66-0.99) significantly decreased all-cause readmissions. Home nurse visits (RR 0.84, 95% CI 0.72-0.99) and multidisciplinary HFCs (0.67, 95% CI 0.53-0.85) significantly decreased all-cause mortality. Pharmacist interventions, tele-monitoring, and telephone calls did not influence readmissions or mortality.

\textit{Conclusions:} Transitional care services improve clinical outcomes after hospitalization for HF. Among the various transitional care services evaluated, multidisciplinary HFCs were unique in decreasing both all-cause readmissions and all-cause mortality in patients discharged from the hospital with HF.
INFLUENCE OF PREHYPERTENSION AND STAGE-1 HYPERTENSION ON THE OUTCOME OF ADULTS WITH HYPERTROPHIC CARDIOMYOPATHY

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Background: Prehypertension (PreH) and stage-1 hypertension (SIH) are prevalent among adults (~35% and 15%, respectively) and are recognized risk factors for cardiovascular complications. Treatment of PreH and SIH improves outcomes. Hypertension is reported in ~1/3 of older patients with hypertrophic cardiomyopathy (HCM) and is associated with older age, higher left ventricular (LV) outflow tract gradients and higher prevalence of symptoms. Prevalence and significance of PreH and SIH in HCM is not studied.

Methodology: We identified 196 adults (age 68±17, 54% men) with HCM and characterized them based on blood pressure (BP) at presentation and during follow up (mean 4.8 years): normal (NBP, n=74), PreH (BP 120-139/80-89 mmHg, n=58) or SIH (BP 140-159/90-99 mmHg, n=64). HCM was defined as non-uniformly hypertrophied LV (>15mm) without systemic (other than mild-hypertension) or cardiac disease that could explain degree of hypertrophy.

Results: Patients with PreH and SIH had comparable demographics/clinical features and were older with higher prevalence of diabetes, coronary artery disease and clinical heart failure compared to NBP. All 3 groups had similar echocardiographic features including LV wall thickness, cavity size, and outflow tract obstruction, left atrial size as well as mitral regurgitation severity. However, heart failure and mortality during follow up was higher among PreH or SIH compared to NBP (Table).

Discussion and Conclusion: PreH is common among HCM adults, has comparable clinical profile to SIH, and markedly differs from NBP. Despite demographic and clinical differences, echocardiographic features of HCM are similar among HCM BP subgroups. PreH identifies HCM patients with similar adverse outcome to those with SIH.

<table>
<thead>
<tr>
<th>Findings at last visit</th>
<th>NBP (n=74)</th>
<th>PreH (n=58)</th>
<th>SIH (n=64)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exertional dyspnea</td>
<td>17 (23%)</td>
<td>20 (34%) *</td>
<td>27 (42%)*#</td>
</tr>
<tr>
<td>Atrial Fibrillation</td>
<td>7 (9%)</td>
<td>2 (3%)</td>
<td>2 (3%)</td>
</tr>
<tr>
<td>Clinical CHF (≥NYHA class II)</td>
<td>41 (56%)</td>
<td>48 (82%) *</td>
<td>52 (82%)*#</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Follow-up events</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>ICD placement</td>
<td>9 (12%)</td>
<td>2 (3%) *</td>
<td>2 (3%)*#</td>
</tr>
<tr>
<td>Pacemaker</td>
<td>9 (12%)</td>
<td>14 (24%)</td>
<td>8 (13%)</td>
</tr>
<tr>
<td>Stroke</td>
<td>3 (4%)</td>
<td>3 (5%)</td>
<td>3 (5%)</td>
</tr>
<tr>
<td>Death</td>
<td>14 (19%)</td>
<td>20 (34%) *</td>
<td>18 (28%)*#</td>
</tr>
</tbody>
</table>

* p<0.05 compared to NBP; # p=NS compared to PreH
ASSOCIATION OF HUMANIN A NOVEL MITOCHONDRIAL DERIVED PROTEIN 
AND HUMAN HEART FAILURE: RESULTS OF A PILOT INVESTIGATION

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2. USC Davis School of Gerontology, LA, CA, USA

Introduction: Humanin a novel mitochondrial derived protein mediates a number of “protective”
effect including amelioration of mitochondrial damage, antagonism of apoptotic signaling and
reduced inflammation. Heart failure, at the cellular level is a result of how constituent cells of the
recruit complex signaling networks mediating metabolism, growth and survival to response to
stress. Although mitochondria, as arbiters of metabolism and survival reside at the nexus of this
process, relatively little is known about mitochondrial derived peptides in heart failure.

Objective: To determine whether circulating levels of humanin, correlate with severity of heart
failure due to reduced systolic function.

Methods: A total of 20 adult patients were recruited. Eligible subjects had HFrEF with LVEF <
40, irrespective of etiology. Subjects with acute STEMI, severe or hepatic pulmonary disease or
recent CABG were excluded. Historic controls from the BVAIT trial (B-Vitamin Atherosclerosis
Intervention Trials) were used in some analyses.

Results: The population was predominately male mean age was 60 (SD 11.11, range 35 to 82).
Mean ejection fraction was 21.26 (SD, 7.639, 95% CI 17.34, 25.19). There was a statistically
significant correlation of humanin levels by NYHA class by two way ANOVA (p> 0.05, F value
7.715.) with humanin levels declining with worsening NYHA class. In an analysis of 10 study
subjects paired with age, gender and race matched historic controls a statistically significant
difference was observed between subjects with heart failure, regardless of severity and subjects
without ( 1646 vs. 1286 P<0.05, SE difference of the means 149.5).

Conclusion: In a small population, circulating humanin was seen to be decreased relative to
gender, age and race matched controls. Circulating levels of humanin were also noted to decrease
with severity of HF as measured by functional class. Humanin may have value as a complementary
biomarker with utility in risk stratification.
DECREASED RENAL FUNCTION IS ASSOCIATED WITH HEART FAILURE READMISSION

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KU School of Medicine, Wichita, Kansas, USA

Background: Heart Failure is the leading cause of morbidity and mortality, as well as hospitalization rates in the US. An impetus has been created to identify improved predictors to prevent hospital readmission. The aim of this study was to determine if renal function has an association with heart failure re-admissions.

Methods: A retrospective cohort study was performed utilizing data from three community hospitals in the United States. A total of 127 patients with heart failure were evaluated over one year comparing glomerular filtration rate (GFR) at admission and discharge and 30-day readmission status.

Results: There is a significant difference by readmission status in the change in Glomerular filtration rate from admission to discharge. The Glomerular filtration rate of patients readmitted in 30 days had an average decrease in Glomerular filtration rate by 2.46 mL/min/1.73 m² whereas patients not readmitted in 30 days had an average increase in Glomerular filtration rate by 1.92 mL/min/1.73 m². In the 28 readmitted patients, 13 (46%) had a decrease in Glomerular filtration rate, 6 (21%) had an increase, and 9 had no change (32%). In the 99 patients not readmitted, 33 (33%) had a decrease in Glomerular filtration rate, 48 (48%) had an increase, and 18 (18%) had no change.

Conclusion: A decline in renal function over hospitalization in patients with heart failure is associated with an increase in readmission for heart failure. Providers should be cognizant of the need to optimize renal function as well as cardiac function during hospitalization.
EDHFIC: INITIAL EXPERIENCE WITH A NOVEL MULTIDISCIPLINARY COLLABORATION TO DECREASE HEART FAILURE ADMISSIONS

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Objective: Heart failure (HF) accounts for 25\% of cardiovascular hospitalizations and 1-2\% of total health care expenditures, costing about $18,000 US per admission. Insurers, including Medicare, no longer reimburse for HF patients readmitted within 30 days of an index admission. Implementation of cross-departmental strategies to minimize admissions without compromising quality and safety are crucial. We describe a novel integration between ED staff and the HF/Infusion Center (IC) to lower HF admissions and readmissions.

Methods: Prospective pilot study at a 100,000 yearly census adult tertiary care ED. From 11/2011 – 3/2014, potential participants with NYHA Class II-IV HF were identified remotely using an EMR based screening tool. Patients excluded for new diagnosis HF, hemodynamic instability, inability to walk and/or abnormal cardiac biomarkers. For potential participants, a Heart Failure Cardiologist confirmed eligibility and facilitated either immediate transfer to IC for treatment or discharge with next day IC follow-up.

Results: 646 ED patients were screened over the study period. 52 (8\%) potential IC candidates were identified of which 20 (38\%) were enrolled. Among enrolled patients, 16 (80\%) patients were transferred to the IC and 4 (20\%) were discharged home with next day IC follow-up. Limited transportation and ability to follow-up in the infusion center were most common reasons for failure to enroll. There were no deaths and patients were effectively treated until symptoms subsided. The screening required 15-30 minutes per day and anecdotally patient satisfaction was high.

Conclusion: Fostering collaboration between ED and HF teams can significantly improve triage of heart failure patients avoiding not only selected inpatient admissions, but also potential future readmissions. HF patients presenting to the ED can be safely evaluated and transferred to a specialized IC for treatment. This strategy simultaneously maintains standard of care, exposes patients to Heart Failure specialists, and avoids nearly $18,000 per admission.
Introduction: Postpericardiotomy syndrome (PPS) is a potential inflammatory pleuropericardial complication after cardiac surgery. Symptomatic treatment is similar to acute pericarditis using NSAIDs, steroids and colchicine. Unfortunately, current recommendation for primary prevention is not yet available.

Objective: This study aims to determine the efficacy and safety of colchicine for the primary prevention of PPS.

Methods: Extensive search for RCTs focusing on the use of colchicine for primary prevention of PPS was done using several databases. Free text search for unpublished trials as well as search from the local research registry was likewise facilitated. Each article was appraised independently by two reviewers. The data were analyzed using RevMan 5.

Results: Three RCTs were included with a total of 591 patients. Results showed that colchicine decreased the incidence of PPS with a risk ratio of 0.43 (95% CI 0.27-0.67, p for effect 0.0002, p for heterogeneity 0.93, I²=0%). There was no observable publication bias. Majority of the patients complained of gastrointestinal symptoms and the reasons for drug withdrawal are mostly related to side effects. Nevertheless, both outcomes were statistically insignificant compared to placebo. No life threatening side effect was documented in the study population.

Conclusion: As an anti-inflammatory agent, colchicine is highly effective and appears to be safe in the primary prevention of PPS.
Objective: Cardio-toxicity from chemotherapy is known to have adverse effects on the heart. Cardio-protective therapy has been shown to be effective in preventing a decline in left ventricular function. Using serial echocardiograms including global longitudinal peak strain (GLPS) and left ventricular ejection fraction (LVEF), this case study demonstrates the negative effect of Trastuzumab (TCH) treatment without cardio-protective therapy on cardiac function.

Background: Recurrence of HER2-positive breast cancer is commonly treated with TCH to improve survival. However, a greater than 10% relative reduction in LVEF has been reported for patients treated with this therapy. Echocardiography can be utilized throughout therapy to monitor LVEF and GLPS. These measurements can predict cardiac decline in patients treated with TCH. The patient assessed in this case refused cardio-protective therapy during her TCH treatment.

Methods: This study incorporated the use of GLPS into the cardio-oncology echo protocol to predict risk for TCH cardio-toxicity. Baseline and serial echocardiograms (every three months) were performed during this patient’s therapy to assess LVEF and GLPS. It was decided that if LVEF dropped below 50%, TCH therapy was to be stopped until LVEF improved, or therapy was discontinued.

Results: Baseline echocardiogram showed two dimensional (2D) LVEF 72%. Seven weeks later, the second echo demonstrated 2D LVEF 64%. GLPS analysis was not available. Twelve weeks later, a third echocardiogram was performed and demonstrated 2D LVEF 54%, GLPS -13.7%. The LVEF remained above 50%, therefore TCH therapy was continued. A fourth echo, performed twelve weeks later, showed 2D LVEF 38%, GLPS -14.5%. TCH therapy was discontinued.

Conclusions: With the use of TCH therapy alone, the LVEF continued to decline and TCH was discontinued after six months of therapy. Serial echocardiograms utilizing GLPS and LVEF measurements proved to be excellent predictors of left ventricular function decline.
DISEASE PATHWAYS AND NEW TREATMENT STRATEGIES IN HEART FAILURE AND CARDIOMYOPATHIES

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PREDICTORS OF LEFT VENTRICULAR DYSFUNCTION AFTER ARTERIAL-VENOUS FISTULA PLACEMENT

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Background and Objectives: Arterial-venous (AV) fistula creates high-output state which may lead to left ventricular (LV) dilatation and/or systolic dysfunction. We investigated predictors of LV dilatation and systolic dysfunction after AV fistula placement.

Material and Methods: Charts and echocardiograms in 197 consecutive fistula recipients (57+/–16 years old, 40% females, 13% with CAD, 49% with diabetes, 85% with hypertension) were reviewed. ANOVA, chi-square, and logistic regression tests were employed.

Results: After AV fistula placement, 18% of patients had systolic dysfunction and 12% had LV dilatation. LV systolic dysfunction or dilatation was noted in 23%.

Age, gender, CAD, or diabetes were not predictive of LV dilatation. However, LV dilatation was less likely in history of hypertension (70 vs. 87% in normal LVEDD, p=0.042) with 0.343 (0.118-0.996, p=0.049) risk reduction of LV dilatation.

Gender, hypertension, or diabetes were not predictive of systolic dysfunction. Patients with systolic dysfunction were older (75+/–14 vs. 55+/–16 in normal EF, 63+/–15 in mild, and 62+/–14 years old in moderate dysfunction, p<0.002) and with increased prevalence of CAD (44 vs. 15% w/o CAD, p<0.001). CAD conferred 5.436 (1.771-16.690, p=0.003) risk of LV dysfunction, and age was associated with 2.862 (per decade, 1.385-5.914, p=0.004) risk of LV dysfunction.

Conclusions: LV systolic dysfunction and/or LV dilatation are common in patients after surgical AV fistula placement. Age and coronary artery disease are associated with increased risk of LV systolic dysfunction. Routine transthoracic echocardiography after AV fistula in younger patients without history of CAD has low diagnostic yield and probably not warranted.
ENHANCED INHIBITORY EFFECTS OF AMIODARONE ON HERG CHANNELS DUE TO A COMPOUND MUTATION L539/FS47-HERG LINKED TO LONG QT SYNDROME TYPE 2

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Objective: We aimed to clarify the effect of L539/fs-hERG on the response of hERG channels to amiodarone and the mechanisms underlying the amiodarone-induced long QT syndrome.

Background: Drug-induced long QT syndrome (LQTS) is a clinically highly relevant form of acquired LQTS. Mutations linked to inherited LQTS may underlie the increased risk of drug-induced LQTS. The mutant L539/fs-hERG is a compound mutation that generates truncated channel protein and suppresses wide type hERG (WT-hERG) channel function via a dominant-negative mechanism, resulting in decreased hERG currents.

Methods: The L539/fs-hERG plasmids were transfected into the HEK293 cells stably expressing WT-hERG channels to simulate heterozygous mutant (WT+L539/fs-hERG). Whole-cell patch clamp was used to evaluate electrophysiological consequences of the WT-hERG and WT+L539/fs-hERG channels in HEK 293 cells exposed to amiodarone. Additionally, we also used laser confocal scanning microscopy to evaluate the effect of amiodarone on the expression of hERG protein.

Results: Amiodarone inhibits currents obtained from HEK 293 cells expressing WT-hERG channels and WT+L539/fs-hERG. In comparison of WT-hERG channels exposed to amiodarone, however, WT+L539/fs-hERG channels showed significant decrease in the maximal density of tail currents. With respect to the gating properties of hERG channels, L539/fs-hERG alters the potential of amiodarone to influence the characteristics of activation, inactivation, recovery from inactivation and deactivation of hERG channels. Additionally, images of amiodarone-treated cells expressing WT+L539/fs-hERG showed a severe retention of hERG protein in the endoplasmic reticulum and significant reduction of mature hERG protein expression on the membrane of HEK293 cells, compared to the counterparts of WT-hERG.

Conclusion: L539/fs47-hERG enhances the inhibitory effect of amiodarone on hERG channels. This may explain, at least in part, the increased risk of drug-induced LQTS and its propensity to severe arrhythmias in affected individuals receiving amiodarone.
GAB1 IS ESSENTIAL FOR CARDIOPROTECTION AGAINST ISCHEMIC/REPERFUSION INJURY

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2. Third Hospital, Peking University and Key Laboratory of Cardiovascular Molecular Biology and Regulatory peptides Ministry of Health, Beijing, China
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Recently, we have shown that Grb-2-associated binder 1 (Gab1), an intracellular scaffolding adaptor, has a protective effect against limb ischemia via mediating angiogenic signaling pathways. However, the role of Gab1 in cardiac ischemia/reperfusion (I/R) injury remains unknown. In this study, we show that Gab1 is required for cardioprotection against I/R injury. I/R injury led to remarkable phosphorylation of Gab1 in cardiomyocyte. Compared with control mice, the mice with cardiomyocyte-specific deletion of Gab1 gene (CGKO mice) exhibited an increase in infarct size and decrease in cardiac function after I/R injury. Consistently, in hearts of CGKO mice subjected to I/R, the activation of caspase 3 and myocardial apoptosis were markedly enhanced whereas the activation of Akt and MAPK, which is critical for cardiomyocyte survival, was attenuated. As oxidative stress is regarded as a major contributor to myocardial I/R injury, we then examined the protective role of Gab1 in isolated adult cardiomyocytes under exposure to oxidant hydrogen peroxide. The effects of Gab1 against I/R injury were recapitulated in isolated adult cardiomyocytes following exposure to hydrogen peroxide. Furthermore, we found that Gab1-mediated oxidative signaling and cardioprotective effects were blocked by ErbB receptor and Src kinase inhibitors. In conclusion, our results suggest that Gab1 is essential for cardioprotection against I/R oxidative injury via mediating survival signaling.
PREVALENCE OF ANTIPLATELET DRUG RESISTANCE IN ASIAN COMMUNITY

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Clopidogrel, in combination with Aspirin, is currently the standard of care for patients undergoing PCI. Many clinical trials have shown that, in high-risk patients, prolonged dual antiplatelet treatment is more effective than Aspirin alone in preventing MACE. However, despite the use of such therapy, a considerable number of patients continue to have recurrent thrombotic events. Clopidogrel is the commonly used P2 Y12 receptor antagonist used in the treatment of ischemic heart disease and stroke. Poor metabolizers treated with Clopidogrel exhibit higher cardiovascular event rates. Asian population has been found to show higher resistance to Clopidogrel.

151 consecutive patients who underwent coronary angioplasty for acute coronary syndrome were selected for the study. All patients had 300 mg Aspirin and 600 mg for Clopidogrel as loading dose. 150 mg Aspirin and 75 mg twice daily of Clopidogrel were given as the maintenance dose. VerifyNow point of care platelet function study were done 5 days after starting of Clopidogrel. Aspirin resistance was defined as more 550 aspirin resistance units and Clopidogrel resistance is defined more than 213 platelets resistance units.

Result: 84.8% were male subjects 15.2% were women. 50.3% were diabetics. 27.2% patients were Aspirin resistant and 33.8% were resistant to Clopidogrel. 7% showed dual antiplatelet resistance. Clopidogrel resistance was more common in female (P value <0.001). Clopidogrel resistance was significantly more common than Aspirin resistance in diabetic subjects.

Conclusion: Aspirin and Clopidogrel resistance are common in Asian population. It is surprising that correlation between Aspirin / Clopidogrel resistance, genetic polymorphism, and clinical data do not correlate to explain the long term benefits of drug therapy.
We studied antioxidant effect of metabolic drug eltacin contained amino acids (glutamate, cysteine, glycine) in old patients with ischemic heart disease. The use of eltacin (220 mg x 3 times per day) in addition with traditional therapy (â-adrenoblockers, aspirin, Ca-antagonists, nitrates, diuretics) of aging patients (69 ± 2.7 years old) with ischemic heart disease, angina pectoris functional class II-III was estimated. Before and 21 days after the therapy ECG-monitoring, EchoCG data were examined. The use of eltacin in therapy of patients resulted in an increase of glutathione (GSH) maintenance and activity of GSH-related enzymes (glutathione peroxidase, glutathione transferase) as well as Cu,Zn-superoxide dismutase and catalase in erythrocytes up to control values depressed until the treatment. The increase of antioxidant state of erythrocytes was accompanied by the decrease of lipid peroxidation and depression of ROS production. Extent of the development of antioxidant response was time-related and correlated with reduction of extrasystoles number. In contrast to group of patients (29 patients) obtained only traditional addition of eltacin to the therapy of group of 30 patients (randomized groups) caused more effective decrease of extrasystoles number. Under the influence of traditional therapy number of extrasystoles decreased from 18.33 ± 3.5 to 8.33 ± 2.7 whereas under the use of eltacin in combination with traditional therapy number of extrasystoles reduced from 12.60± 4.3 to 4.40 ± 2.0 during 24 hours. It could be concluded that metabolic drug eltacin possesses antioxidant and antiarrhythmic effects.
ESSENTIAL ROLE OF UVRAG IN CARDIAC FUNCTION

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2. Institutes of Biomedical Sciences, Fudan University, Shanghai, China

UVRAG has been suggested to regulate autophagy and endocytic trafficking. However, the physiological function of UVRAG remains elusive. We sought to determine the role of UVRAG in cardiac function by using UVRAG knockout mice generated by piggyBac transposition. Young UVRAG knockout mice exhibited normal cardiac morphology and function. However, old UVRAG knockout mice developed age-related cardiomyopathy with compromised cardiac function. In addition, the heart from old UVRAG-deficient mice showed impaired autophagic flux, increased apoptosis and enhanced pro-inflammatory cytokine expression. We then determine the impact of UVRAG deficiency on doxorubicin-induced cardiotoxicity. The mice at 2 months of age were treated with doxorubicin to induce cardiomyopathy. UVRAG knockout mice were more susceptible to doxorubicin-induced lethality. Moreover, UVRAG knockout mice showed decreased myocardial function accompanied by enhanced collagen accumulation, impaired autophagic flux, increased apoptosis and reactive oxygen species (ROS) production in the heart compared with wild type controls following doxorubicin treatment. Taking together, these data demonstrate that UVRAG plays a vital role in cardiac function.
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HIGH-FAT DIET ENHANCED CTRP1 PROTEIN STIMULATES SIGNALING PATHWAY RELATED TO MUSCLE CONTRACTION IN C2C12 MYOCYTES
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Adiponectin, adipocyte specific secretary protein, is known to have metabolic function. The adiponectin is composed of N-terminal collagen domain which contributes formation of homotrimer and C-terminal complement and TNF-a related protein (CTRP) domain. Genbank database were searched to find proteins that have CTRP domain. We found 9 family member of CTRP domain containing protein. To find out function of these family proteins, tissue expression pattern of each CTRP was examined. CTRP1 is highly expressed in adipose tissues and adrenal glands. Interestingly CTRP1 expression is localized in zona glomerulosa in which aldosterone is synthesized and secreted. Thus CTRP1 could play a role in an obesity-related hypertension. To examine this possibility, C2C12 myocytes were treated with recombinant CTRP1 and then signaling pathway was analyzed. The recombinant CTRP1 stimulated phosphorylation of myosin light chain through ERK activation. The further study is undergoing to solve detailed molecular mechanism of CTRP1-mediated MLC activation.
IMPORTANT ETHNIC DIFFERENCES IN STROKE VOLUME (SV) – BODY SURFACE AREA (BSA) RELATIONS: ECHONORMAL META-ANALYSIS

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2. University of Auckland, Auckland, New Zealand
3. Unitec Institute of Technology, Auckland, New Zealand
4. National Heart and Lung Institute, Imperial College, London, UK

**Background:** Few data exist regarding relationship between SV and body size and gender among different ethnic groups—potentially important when determining a “low flow state,” e.g., in aortic stenosis patients.

**Objectives:** We investigated ethnic and gender differences in normative values for SV and its components—i.e., LV end-diastolic volume (LVEDV) and ejection fraction (LVEF)—and their relationship to BSA.

**Methods:** EchoNoRMAL included 2D LV echocardiography data in adults—5,500 Europeans (Euro), 948 East Asians (EA), and 607 South Asians (SA)—without cardiovascular disease (CVD) or CVD risk factors. We used ANOVA to assess inter-ethnic differences within gender and linear regression to model association between SV and BSA, tested for ethnic interaction.

**Results:** SV and LVEDV were smaller in SA than in Euro and EA men/women (Table). Inter-ethnic differences in LVEF were less than for LVEDV (p< 0.001, men and women). Furthermore, relationship between SV and BSA was significantly different for SA compared to Euro (regression interaction: p< 0.001, men, p=0.04, women) and to EA women (p=0.01).

**Conclusion:** Significant ethnic group differences in SV and LVEDV—with South Asians having lowest values, despite not having lowest BSAs—suggest that SV and “low flow” ranges should be ethnicity (and gender) based.

<table>
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<th>LVEF</th>
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*Substantial missing data; All comparisons for inter-ethnic differences within gender are p< 0.001, except for HR in men (p=0.07).
ECHOCARDIOGRAPHIC INDICES ASSOCIATED WITH THE PHENOTYPE OF FRAILTY

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Background: There are few studies describing the association between cardiac structure and function and the frailty phenotype in older adults.

Methods: We measured frailty in patients ≥65 years of age undergoing a clinically indicated transthoracic echocardiogram (TTE) at Mayo Clinic, Rochester, MN, from 6/2012 through 2/2013. Frailty was determined based on deficits of weight loss, exhaustion, physical activity, gait speed, and grip strength (3 features or greater = frail; 1-2 features = intermediate frailty; 0 features = not frail). Pearson correlation was used to examine bivariate associations between TTE variables and frailty deficits. A multivariable model was used to study TTE indices associated with frailty.

Results: Of 257 patients studied, 50 (19.5%) were frail, 167 (65.0%) had intermediate frailty, and 40 (15.5%) were not frail. TTE indices correlating with the frailty score included left atrial volume (r=0.14, p=0.03), stroke volume (r=-0.21; p<0.001), E/A ratio (r=0.26; p<0.001), and right ventricular systolic pressure (r=0.33; p<0.001). In multivariable analysis, after accounting for age, left atrial volume, stroke volume, and right ventricular systolic pressure were associated with frailty (Table).

Conclusions: Right ventricular systolic pressure, stroke volume, and left atrial volume had significant associations with the frailty phenotype.

<table>
<thead>
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<th>Variables</th>
<th>Beta Estimate</th>
<th>Adjusted OR (95% CI)</th>
<th>p value</th>
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<td>Stroke volume</td>
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<td>Right ventricular systolic pressure</td>
<td>0.034</td>
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ANALYSIS OF VALVAR AND LEFT VENTRICULAR PARAMETERS IN INFECTIVE AORTIC ENDOCARDITIS AS PREDICTORS OF OUTCOME: A COMBINED ASSESSMENT BY TRANSESOPHAGEAL AND STRAIN ECHOCARDIOGRAPHY

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Purpose. The timing of surgery is crucial for patients with aortic endocarditis in whom medical therapy fails. The aim of our study is to identify potential echocardiographic "markers" of adverse events in patients with aortic regurgitation from infective endocarditis.

Methods. Fifteen patients with aortic regurgitation (AR) from infective endocarditis were studied by transesophageal echocardiography (TEE) and transthoracic speckle tracking echocardiography (STE). Fifteen healthy subjects were selected as controls. Vegetation size was assessed by TEE. Standard transthoracic echocardiographic parameters were determined. Global left ventricular (LV) longitudinal strain (LS), radial and circumferential strain were measured by STE. Averaged LV rotation and rotational velocities from the base and apex were obtained and used for calculation of LV torsion (LVtor). Mitral annular velocities were also obtained by tissue Doppler imaging (TDI).

Results. Mean percentage intraobserver variability was 6% for LV-LS and 8% for LV-tor, and mean percentage interobserver variability was 11% for for LV-LS and 12% for LV-tor. Severe AR had decreased LS compared with control subjects. LVtor decreased significantly in severe AR compared to normals (p<.001) as a result of a predominant decrease in apical rotation. By multivariate analysis, LV-LS (p=0.03), LV-tor (p=0.008) and vegetation size (p=0.009) were predictive of adverse events. ROC curves suggested that thresholds offering an adequate compromise between sensitivity and specificity for adverse events detection were -18.4% for mean global LV-LS (AUC .76), 12mm for vegetation size (AUC .84), and 19.7 degrees for LVtor (AUC .89). The combination of vegetation size and LVtor had the highest diagnostic accuracy for identifying adverse outcome, superior to vegetation size (p=.008) or LVtor alone (p=.026).

Conclusions. The combined evaluation of the characteristics of vegetating masses and LV function strain parameters improve the sensitivity of echocardiographic indices in predicting cardiac morbidity and mortality of aortic regurgitation from infective endocarditis.
ENHANCEMENT OF PEAK AORTIC VELOCITY SIGNALS BY CONTRAST MICROBUBBLES
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Background: Aortic velocity signals obtained by continuous wave (CW) Doppler echocardiography and the resulting hemodynamics and pressure gradient across the aortic valve are critical determinants for aortic stenosis (AS) assessment. However, clinically, these diagnostically important measurements of velocity, pressure gradient, and estimated effective aortic orifice area are often mutually discordant. Suboptimal echocardiographic Doppler signals, various gain settings, and blooming effects from contrast enhanced ultrasound (CEUS) cause under- or overestimation of the severity of AS.

Methods: Using a mechanical left ventricular model that replicates valvular function, we compared transvalvular aortic peak velocity measurements acquired with CW Doppler ultrasound for various gain settings (-42, -30, -20, -10, 0 dB) to simulate suboptimal and optimal scans, with and without contrast. For contrast enhanced measurements, the peak velocity was tracked temporally following a bolus injection of Definity microbubbles.

Results: Each plot (data obtained at -10 dB gain, measured velocity without contrast is 2.53 m/s) presented a similar trend with 4 phases: (1) a temporary artificial increase in measured velocity from the blooming effect, (2) reduction of the blooming phase leading to (3) a phase of relative stability of the velocity measurement indicated by a decrease in the standard deviation (SD) and corresponding to a “true” velocity measured under optimal conditions without contrast, and (4) an increased variability in the measured velocity as the concentration of contrast agent progressively diminishes and the SD increases, especially in low-gain conditions.

Conclusion: The results suggest that a presence of a contrast agent does not artificially alter peak velocity measurements by Doppler ultrasound and, in fact, may contribute to their stability in phase 3. However, physicians and sonographers should be aware of the blooming effect (phase 1 and 2) or less-reliable measurements (phase 4). This may be avoided by recognizing and collecting data during the ‘steady state’ phase 3.
Background. The purpose of the present study was to analyze segmental atrial function by three-dimensional speckle-tracking echocardiography (3DSTE) in patients with patent foramen ovale six months after the implantation of occluder devices.

Methods. Patients with atrial septal devices (n = 65) were followed up for six months after device implantation and compared with a normal age-matched group (n = 35). A subgroup of 12 patients who developed paroxysmal atrial fibrillation (PAF) after device insertion were also studied. Atrial peak ventricular systolic longitudinal strain (LS), circumferential strain (CS), and area strain (AS) and peak pre–atrial contraction longitudinal strain, circumferential strain, and area strain were determined using 3D STE, and SDs of times to peaks of regional atrial strain were calculated as indices of dyssynchrony. 3DSTE was able to measure atrial strain in 62 of the 65 implanted patients and in all patients with PAF.

Results. The mean time for analysis with 3D STE was 20% shorter than with two-dimensional speckle-tracking echocardiography (p<0.05). Values of interobserver and intraobserver variability of atrial strain by 3DSTE were <11% and <13%, respectively. LS, CS, and AS were reduced in patients with atrial devices compared with controls, and further reductions of these parameters were observed in patients with PAF. By multivariate analysis, LS (p=0.002), AS (p<0.001), and CS (p<0.05) were independent predictors of PAF. Patients with PAF showed smaller peak pre–atrial contraction longitudinal strain and peak pre–atrial contraction area strain compared with controls.

Conclusions. Patients with atrial septal devices have significant global and segmental atrial dysfunction as assessed by 3DSTE. The localized regional dysfunction is likely due to the direct mechanical effect associated with occluder implantation. This may have implications for the evaluation of long term atrial function and selection of devices of appropriate sizes.
Background. Prolonged QRS duration and mechanic-electrical interaction are markers of increased sudden death risk in tetralogy of Fallot (TF). The combined effects of preoperative hypertrophy and hypoxia, possible intraoperative myocardial damage, type of reconstruction, and acquired postoperative lesions such as pulmonary regurgitation may result in impaired RV deformation. Recently speckle tracking echocardiography (STE) has been proposed to assess mechanical dyssynchrony in these patients but the role of electromechanical dysfunction is not completely clear.

Methods. Fifteen patients after TF repair (aged 17-51 years) with dilated right ventricle, right bundle branch block (QRS \( \geq 120 \text{ms} \)), and NYHA class I or greater were studied with two-dimensional and three-dimensional echocardiography (3DE) and STE. Right ventricular volumes and right ventricular ejection fractions (3D-RVEF) were obtained. Right intraventricular dyssynchrony was determined as the difference between the longest and shortest electromechanical coupling times in the basal septal and lateral RV segments. Interventricular dyssynchrony was determined as the difference between electromechanical coupling times in the basal lateral LV segment and the most delayed RV segment. Fifteen age-matched healthy subjects were selected as controls.

Results. Right intraventricular dyssynchrony (76.2±23.8ms vs 12.7±9.1ms) and interventricular dyssynchrony (75.2±24.3ms vs 11.3±8.2ms) were shown in patients compared to normal controls. Right intraventricular dyssynchrony correlated with RV longitudinal strain, 3D RV end-systolic volume, and QRS duration. Interventricular dyssynchrony correlated with RV longitudinal strain, RV systolic pressure, 3D-RVEF, and QRS duration. Reduced RV strain, 3D-RVEF and prolonged QRS duration were the main determinant factors predicting dyssynchrony by multivariate analysis. On ROC curves RV strain and 3D-RVEF had optimal predictive accuracy of the NYHA functional class and a larger area under the receiver operating characteristic curve than the QRS duration.

Conclusions. RV systolic dysfunction and dyssynchrony can be identified in patients with repaired TF by 3DE and STE. Dyssynchrony is associated with reduced 3D-RVEF and RV myocardial deformation.
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TWO-DIMENSIONAL AND THREE-DIMENSIONAL SPECKLE-TRACKING ECHOCARDIOGRAPHY IN THE ASSESSMENT OF LEFT AND RIGHT VENTRICULAR FUNCTION AFTER MITRACLIP IMPLANTATION IN FUNCTIONAL MITRAL REGURGITATION
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**Background.** Our purpose was to determine the changes of left (LV) and right (RV) ventricular function with two-dimensional (2DSTE) and three-dimensional speckle-tracking echocardiography (3DSTE) after percutaneous mitral valve repair with the MitraClip system (Abbott, Abbott Park, IL) in high-risk surgical patients with severe functional mitral regurgitation (MR).

**Methods.** Patients underwent 2D and 3D transthoracic echocardiography before MitraClip implantation and after 6 months of follow-up. Longitudinal, circumferential, radial strains, and global area strain (GAS) were calculated by 2DSTE and 3DSTE. Data analysis was performed offline.

**Results.** Fifteen patients with moderate-to-severe or severe MR undergoing MitraClip were prospectively included. Device success was achieved in 14 patients. New York Heart Association functional class improved acutely at discharge (from 3.2±0.6 to 2.7±0.5, p<0.005) and continued to improve progressively during follow-up (2.4±0.6, p<0.001). Echocardiography was performed at discharge and at six months. The primary efficacy end point (MR reduction of at least 1.0 grade or reduction of regurgitant orifice area by 0.1 cm² or LV end-diastolic volume by 10% compared with baseline) was obtained in 11 patients. A significant improvement was shown in 3D LV ejection fraction (27.3±7.2 vs 36.5±10.2%, p<0.005), 3D LV volumes (end-diastolic volume, 139.8±38.4 vs 108.4±39.6mL, p<0.001, end-systolic volume, 109.7±36.8 vs 71.9±38.1mL, p<0.001), 3D left atrial volume (107.4 to 86.5mL, p<0.005), 2D global longitudinal strain (-9.2±2.4 vs -13.8±4.6%, p<0.005), 3D global longitudinal strain (-8.5±2.8 vs -12.2±3.9%, p<0.001), and 3D GAS (-27.8±4.7 vs -31.3±5.2%, p<0.001). A significant improvement was also shown in 3D RV ejection fraction (from 42.2±8.1 to 53.1±7.6%, p<0.005) and 2D global free-wall RV strain (-18.1±4.5 vs -23.3±4.8%, p<0.001).

**Conclusions.** Our results indicate significant improvements of LV and RV function and deformation and clinical parameters 6 months after MitraClip. Compared with 2D LV strain imaging, 3D speckle-tracking echocardiography allowed significantly faster image acquisition and data analysis.
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CORRELATION OF LEFT ATRIAL APPENDAGE (LAA) INFLOW AND OUTFLOW VELOCITIES WITH THE CHADS2 AND CHA2DS2-VASC SCORES
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Objectives: The study was designed to assess if a relationship exists between LAA ejection velocities and CHADS scores and if CHADS2 and CHA2DS2-VASc scores differentially predict LAA ejection velocities.

Background: In patients with atrial fibrillation or flutter (AF/AFL) a left atrial appendage (LAA) ejection velocity measured via transesophageal echocardiography (TEE) of 40 cm/sec and greater has been shown to correlate with a reduced risk of developing LAA thrombus while velocities less than 40 cm/sec are at higher risk. The CHADS2 and CHA2DS2-VASc scores calculated from clinical variables have been developed to risk stratify patients with atrial fibrillation/flutter in regard to the need for anticoagulation. We seek to investigate whether LAA velocities above and below 40 cm/sec correlate with respective high and low risk CHADS scores.

Methods: A retrospective chart review was performed on all patients in the last 5 years who had a transesophageal echocardiogram (TEE) in which LAA velocity was measured. Once these patients were identified, relevant clinical information allowing for the calculation of the CHADS2 and CHA2DS2-VASc scores were also extracted from the patient record.

Results: Patient data from a total of 153 patients were included in the study. A statistically significant correlation between LAA velocity and CHADS2 score (r=-.02) or between LAA velocity and CHA2DS2-VASc scores (r=-.04) was not found.

Conclusions: We could not identify a relationship between either the CHADS2 or CHA2DS2-VASc scores and LAA velocities. This was true regardless of whether patients were in sinus rhythm or atrial fibrillation at the time of the TEE. While reduced LAA velocities increase the risk of LAA thrombus, stroke in patients with atrial fibrillation is likely secondary to a complex interplay of multiple clinical variables.
ROLE OF SIMULATION IN ECHOCARDIOGRAPHY TRAINING IN CARDIOLOGY FELLOWS: A PILOT STUDY

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Background: Cardiology fellows in training typically do an “apprenticeship” to develop the necessary practical skills in a clinical environment. The expectation after completion of the 3 year cardiology training is the ability to perform a transthoracic echocardiogram if technician is unavailable, untrained and for reproducibility. However, there can be significant limitations to the existing style of training in this environment, especially in the early stages of learning. We seek to investigate the current knowledge and expertise of cardiology fellows in transthoracic echocardiography and whether simulator assisted training improves performance.

Method: 15 cardiology fellows without prior certification in echocardiography were enrolled. After filling a questionnaire, all participants were given Vimedix “patient” (with one random pre-designated chest pain diagnosis). Performance was evaluated by:

a) Accuracy in diagnosis (correct/incorrect)
b) Anatomical Identification Score (+1 correct identification of a cardiac structure, -1 over-diagnosis)
c) Technical Score ( +1 each correct view, -1 incorrect technique)
d) Time to diagnoses. Participants were provided a training booklet and bedside demonstration. Same scanning exercise was repeated in 1-3 days.

Results: Significant improvement in anatomical (p<0.05), technical (p<0.05) and questionnaire (p<0.05) performance was seen. Significance was maintained in fellows who had <20 TTE hands-on and in those with >20 TTE hands-on experience. Scores of the first year fellows after training were significantly better than the second and third years before training (p<0.05). No significant difference in accuracy was observed. (p=NS).

Conclusions: Performance scores increased with minimal instruction. After training, fellows adopted a systematic approach and obtained more views in the same time duration. The 1 years with training outperformed 2 and 3 years without training suggesting that an extremely limited but focused training session may be more effective than years of passive observation. However, a more detailed training session and longer practice time may be required to improve accuracy.
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**A META-ANALYSIS OF ASSOCIATION BETWEEN EPICARDIAL ADIPOSE TISSUE AND DIASTOLIC DYSFUNCTION**

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**Background:** Epicardial adipose tissue (EAT) is a metabolically active fat depot located adjacent to the myocardium with no structure separating them. This leaves the myocardium highly exposed to EAT-derived adipokines, increasing the risk of developing myocardial dysfunction. The purpose of this study is to conduct a meta-analysis to evaluate the relationship between epicardial fat thickness (EFT) and left ventricular diastolic dysfunction (LVDD) and its predictors.

**Methods:** We searched all databases for studies reporting EFT in patients with LVDD and those with normal diastolic function. We included case-control, cohort and cross-sectional studies and calculated the weighted standardized mean difference (SMD) in EFT between both groups using the Dersimonian and Laird method and metaregression.

**Results:** Our search strategy yielded 40 articles of which only 3 cross-sectional studies met the eligibility criteria. The studies included 204 patients with LVDD and 206 with normal diastolic function who were matched by body mass index (BMI). The median EFT in those with LVDD was 5.1mm (2.3 – 7.9) compared to 2.8mm (1.7 – 6.3) in those with normal diastolic function. The SMD of EFT between both groups was 0.910 with 95% CI (0.705-1.115) (figure). Neither age, nor BMI or the prevalence of hypertension was associated with the higher SMD seen in those with LVDD (p>0.05).

**Conclusion:** Increased EFT thickness is associated with LVDD and this association was not explained by age, hypertension or BMI.
BICUSPID AORTIC VALVE AND AORTIC ROOT MORPHOLOGY IN HISPANIC PATIENTS

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Objectives: The aim of this study was to evaluate the aortic valve and the ascending aorta morphology in Hispanic patients with bicuspid aortic valve (BAV).

Background: BAV is amongst the most common congenital valve abnormalities and it has been associated with ascending aortopathy. Inter-racial differences have been described between Caucasian and African-American patients with BAV, which may have clinical and therapeutic implications. Whether Hispanic patients demonstrate similar associations has not been reported thus far.

Methods: We retrospectively reviewed all heart operations performed at our institution between April 2008 and June 2013, to identify patients who underwent aortic valve replacement for BAV. All echocardiograms were reviewed to compare cusp morphology, valvular lesions, and aortic dimensions between Hispanic and Non-Hispanic individuals.

Results: A total of 291 patients were identified (Hispanic = 159, Non-Hispanic = 132), with a mean age 62 ±13 years. There were no differences between the two groups in baseline characteristics that include hypertension, diabetes mellitus, dyslipidemia and left ventricular ejection fraction. In both Hispanics and Non-Hispanics, the most prevalent cusp morphology was fusion of right and left coronary cusps (83% for both), followed by right and non-coronary cusps fusion (16% vs. 15%), and left and non-coronary cusps fusion (0.5 vs. 1%) (p=0.76). The most common indication for surgery was severe aortic stenosis. Hispanic patients had a significantly larger aortic annulus diameter (2.6 ± 0.3 vs. 2.2 ± 0.23 cm, p=0.04), with a trend towards a larger dimension at the sinus of Valsalva (3.5 ± 0.5 vs. 3.0 ± 0.5, p=0.07).

Conclusions: Compared to other ethnic groups, Hispanics were observed to have larger aortic annular diameters, with similar morphologic cusp features. This is the first study to report phenotypic data on Hispanic patients with BAV, and may aid in the diagnosis and surgical management.
Changes in LV Systolic Function and Dimensions After AV Fistula Placement

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Background: Arterio-venous (AV) fistulas increase cardiac output which may lead to high-output heart failure. On the contrary, decreased afterload due to AV fistula may increase stroke volume and improve systolic function. We sought to evaluate effects of AV fistula on change in left ventricular (LV) dimensions and ejection fraction (EF) following AV fistula placement.

Material and Methods: Pre- and post-AV fistula transthoracic echocardiograms were reviewed and compared in 76 (57+/−16 years old, 38% females, 18% with history of coronary artery disease, 46% with diabetes, 92% with hypertension) consecutive AV fistula recipients. Chamber dimensions and systolic function quantification was performed according to the American Society of Echocardiography recommendations. ANOVA, chi-square, and logistic regression tests were employed.

Results: After AV fistula, LV end-diastolic dimensions (LVEDD) increased in 6% (4/67), decreased in 6% (4/67), and stayed unchanged in 88% (59/67). Gender, diabetes, coronary artery disease, or hypertension history were not predictive of changes in LVEDD after AV fistula placement. Pre-procedural LV dilatation was not predictive of post-AV fistula LVEDD increase. After AV fistula, LV ejection fraction (LVEF) improved in 13% (10/76), decreased in 13% (10/76), and stayed unchanged in 77% (56/76). In 63% (5/8) patients with moderate or severe LV systolic dysfunction at baseline, LV function improved after AV fistula placement (p<0.0001). Post-AV fistula increase in LVEDD was accompanied by worsening in LV ejection fraction (LVEF) in 3/4 patients (p<0.001). There was also a trend towards post-AV fistula worsening in LVEF in patients with increased post-procedure LVEDD (3/9, 33%) vs. normal LVEDD (6/63, 9.5%, p=0.130).

Conclusions: In patients with end-stage renal disease, LV enlargement and systolic dysfunction are relatively uncommon after AV fistula placement. When present, LV dilatation after AV fistula placement is frequently associated with LV systolic dysfunction. Routine transthoracic echocardiographic evaluation after AV fistula placement does not appear to be warranted.
ANOMALOUS ORIGIN OF THE LEFT CORONARY ARTERY FROM THE PULMONARY TRUNK IN ASYMPTOMATIC ADOLESCENT ATHLETE. CASE REPORT

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The first clinical description in conjunction with the autopsy findings of anomalous origin of the left coronary artery from the pulmonary trunk (English ALCAPA) were described by Bland and colleagues in 1933, so the anomaly is also called syndrome Bland-White-Garland, although it is a rare event in young and adult patients, the diagnostic and therapeutic implications remain a challenge for a 17-year-old asymptomatic athlete with this potentially lethal diagnosis.

ALCAPA syndrome (anomalous left coronary artery from the pulmonary artery) is the abnormal implantation of the left coronary artery in the main pulmonary artery, occurs in 1 in 300,000 live births (1, 2), and represents 0.25% -0.5% of all congenital heart defects (3). The consequence of failure is the reduction of irrigation in the left ventricle which predisposes to arrhythmias, cardiomegaly, heart failure or sudden death in the first year of life, however up to 15% of patients reach adulthood through the development of collateral circulation between the right and left coronary artery. Although a 90% mortality in affected during the first year of life, ALCAPA syndrome is not just a disease of children, therefore, the presence of electrocardiographic findings consistent hypertrophy or ischemia and major described, echocardiographic signs: increased systolic coronary flow in the presence of coronary collateral circulation, left to right shunt in the pulmonary trunk especially in the diastolic phase, dysfunction of the mitral valve and subvalvular apparatus dilated right coronary artery, you should think about this potentially lethal disease.

Figure 1: Color doppler echocardiography 2d long axis wherein dilated right coronary sclerosis papillary muscle collateral circulation is observed at the level of the septum

Figure 2: Echocardiogram 2 D short axis where diastolic flow is observed from the pulmonary trunk and the

Figure 3: Right coronary angiography where dilated right shows, great system of collaterals and retrograde filling of the left coronary artery, which rises in the pulmonary trunk

Figure 4: Functional magnetic resonance imaging in short axis can be observed sagittal great dilatation of the right coronary artery with collateral system, absence of the left coronary ostium, mild dilatation of the left ventricle.
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**3D TRANSESOPHAGEAL ECHOCARDIOGRAPHY IMPROVES LEFT ATRIAL APPENDAGE EVALUATION PRIOR TO CARDIOVERSION**

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**Background:** Transesophageal echocardiography (TEE) is the standard imaging modality to detect left atrial appendage (LAA) thrombus. It is indicated prior to direct current cardioversion (CV) in patients with atrial fibrillation (AF) who have not been efficiently anticoagulated for at least 3 weeks. When a thrombus is identified, CV is delayed for 3-4 weeks. Repeat TEE is frequently requested to confirm resolution of thrombus on effective anticoagulation.

**Methods:** We report a case where 3D TEE images demonstrated the absence of LAA thrombus despite repeated contrary findings on 2D TEE.

**Case description:** 59 year old man with history of hypertension, symptomatic persistent AF and tachycardia induced cardiomyopathy was referred for a third TEE prior to elective CV after 3 months of anticoagulation. The patient had prior CV two years before with TEE showing no LAA thrombus on dabigatran. Due to recurrence of symptomatic AF off anticoagulation, the patient was referred for TEE. Two 2D TEEs performed 6 weeks apart, despite anticoagulation with rivaroxaban, showed images compatible with LAA thrombus. The third TEE suggested persistent mobile LAA thrombus on 2D images but 3D TEE showed the echo-density in the LAA was consistent with artifact and absence of thrombus. The patient underwent CV without any complications upon 6 months of follow-up.

**Discussion:** Echocardiographic artifacts are known for false positive TEE in detection of LAA thrombus. Treatment for AF is usually delayed and repeat TEE is done to reassure patient and clinician. 3D TEE allowed simultaneous visualization of multiple planes improving the exploration of the LAA.

**Conclusions:** 3D TEE may improve the accuracy of TEE in establishing the presence of LAA thrombus. Routine use of 3D TEE may result in lower incidence of LAA thrombus, reduction of repeat diagnostic procedures and delayed CV. A systematic evaluation of this approach is being evaluated in our institution.
ATRIAL FIBRILLATION AND STROKE PREVENTION

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HOW IS THE QUALITY OF INR CONTROL FOR STROKE PREVENTION IN NON-VALVULAR ATRIAL FIBRILLATION IN CLINICAL PRAXIS?
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Objectives: To analyze how precise is INR control in patients of an urban area with previous stroke and atrial fibrillation treated with dicumarine derivates since in this very high-risk population it is mandatory prevent recurrence and to avoid bleeding.

Methods and Results: We analyzed 4590 INR level determinations of 131 patients (age 77±9 years, 63% male, 80% with arterial hypertension, 37% diabetic, 45% with dyslipemia) all with previous stroke and with atrial fibrillation during a follow-up of 25±21 months. The mean number of INR determinations per person was 35±26. A total of 2013 INR determinations (44%) showed an inappropriate level (<2 or >3). Thus, a mean of 15±11 determinations/person demonstrated a result not in therapeutic range and overall patients were during 8.2±8 months at risk of thromboembolic or bleeding events in relationship to INR out of therapeutic range. During follow-up, cardiovascular events (any ischemic or hemorrhagic) occurred in 52% (n=68) of patients. INR determinations obtained at time of cardiovascular events (n=54) showed an inappropriate level of anticoagulation in 38 patients (70%). Furthermore, cardiovascular and total mortality were of 26% (n=35) and 43% (n=57), respectively. A total 88 patients (67%) suffered any cardiovascular event or died during the follow-up period.

Conclusions: Appropriate INR control is mandatory for prevention of serious cardiovascular complications, especially in patients with previous stroke and atrial fibrillation. This population shows a very high risk of suffering cardiovascular events and mortality during the follow-up. In clinical praxis, management of oral anticoagulation with dicumarine derivates is far of being optimal, even in urban areas.
AGE AND GENDER COMPARISONS OF ATRIAL FIBRILLATION PREVALENCE IN PATIENTS WITH HYPERTENSION AND NORMAL BLOOD PRESSURE

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Background: Hypertension (HTN) and aging are recognized risk factors for atrial fibrillation (AF). We sought to compare the prevalence of AF in HTN patients to those with normal blood pressure (NBP).

Methods: Cross-sectional stratified comparison of adults with identified HTN (ICD-9 billing code) with NBP patients.

Results: Of 27,575 HTN patients, 49% were female, 90% were white and 77% had BP at goal (<140/90 mmHg) at their last clinic visit in 2009. The group included 10,267 (37%) elderly (65 – 79 years) and 4,446 (16%) very elderly (≥80 years). Of 86,711 patients with NBP, 55% were female, 86% were white, 99% had normal BP at last clinic visit, with 12479 (14%) elderly and 3056 (3.5%) very elderly. Compared to HTN patients, there was a lower overall prevalence of AF in the NBP patients (3.7% vs 8.7%, \( p < 0.001 \)). Prevalence rates were similar (11.6% vs 11.4%, \( p = 0.67 \)) in both NBP and HTN elderly patients (65-79 years), while in the very elderly, prevalence was higher in the NBP group than in the HTN group (22.6% vs 19.6%, \( p = 0.002 \)). In females, prevalence of AF was not significantly different in NBP and HTN groups in both the elderly (9.0% vs 8.7%, \( p = 0.62 \)) and the very elderly (16.9% vs 18.0%, \( p = 0.4 \)). Rates were also not significantly different in elderly NBP and HTN men (13.9% vs 14.1%, \( p = 0.74 \)), however AF was more frequent in very elderly men with NBP (26.6% vs 21.7%, \( p < 0.001 \)).

Conclusions: When compared to similarly aged patients with hypertension, our findings show that the prevalence of atrial fibrillation was greater among very elderly men with normal blood pressure.
ANTITHROMBOTIC THERAPY IN ELDERLY PATIENTS WITH ATRIAL FIBRILLATION: A SINGLE CENTER RETROSPECTIVE STUDY
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Abstract: Objective The aim of this study was to investigate antithrombotic therapy status in elderly patients with atrial fibrillation (AF) in our hospital.

Methods: Elderly AF patients (≥60 years), admission records were analyzed retrospectively from Jan. 2012 to Dec. 2013.

Results: A total of 1,000 patients were enrolled, 57.3% male, mean age of 75.3 ± 8.0 years old, 54.7% of the patients ≥75 years old, paroxysmal AF 39.4% and non-paroxysmal AF 60.6%. All patients, 29.1% were received anticoagulant therapy, including warfarin anticoagulation therapy of 27.8% and novel oral anticoagulant usage of 1.3%, antiplatelet therapy of 39.5% and untreated of 31.4%. The prevalence of ischemic stroke (IS) or a history of transient ischemic attack (TIA) was 31.9%, 28.8% of the patients received anticoagulant treatment. Among the patients of CHADS2 score ≥ 1, 70.1% were received antithrombotic therapy, anticoagulant therapy rate 29.8%. In the CHADS2 ≥ 2 cohort, anticoagulant therapy rate was 28.8%. Anticoagulation rate in IS high-risk patients ≥ 75 years was less than < 75 years patients (25.4% vs. 36.5%, P=0.002). With the increase of HAS-BLED score, IS high-risk patients receiving anticoagulant therapy was reduced. Anticoagulant therapy rate in IS high-risk patients with HAS-BLED score ≥ 2 was lower than patients with score < 2 (27.1% vs. 41.7%, P=0.006). Anticoagulation rate in IS high-risk patients with paroxysmal AF was lower than patients with non-paroxysmal AF (19.8% vs. 34.0%, P<0.001). Anticoagulant therapy rate in high risk of IS patients with coronary heart disease was lower than the IS high risk patients without coronary artery disease (23.4% vs. 34.1%, P=0.001).

Conclusions: The current anticoagulant therapy in elderly AF patients in our hospital is clearly insufficient, especially in patients with higher stroke risk. Antiplatelet therapy is still very common used as suboptimal alternative anticoagulant therapy.
ELEVATED SERUM URIC ACID LEVELS AND DIASTOLIC DYSFUNCTION IN PATIENTS WITH ATRIAL FIBRILLATION CONVERTED TO SINUS RHYTHM

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Background: Association between increased uric acid levels and atrial fibrillation has been reported recently. The purpose of this study is to assess whether serum uric acid, which is a marker of oxidative stress and inflammation, might correlate with left ventricular diastolic dysfunction in patients with atrial fibrillation (AF) converted to sinus rhythm.

Methods: A total of 195 patients were included in this study. Patients were underwent a comprehensive Doppler echocardiography examination one day after the AF ablation. We measured mitral E wave and mitral annular e wave velocities, E wave deceleration time (DtE), E/e ratio, and left ventricular ejection fraction. A restrictive mitral filling pattern (RMFP) was defined as either E/A ratio >2 or E/A >1 and DtE<140 milliseconds.

Results: Mean age was 58.4 ± 10.8 years (74% male). Uric acid levels correlated significantly with E/A ratio(r =0.18, P = 0.013), DtE (r =-0.22, P <0.002) which are parameters of diastolic dysfunction. However, patients with a RMFP had no significant differences in uric acid levels compared with patients without RMFP (5.35±1.35 mg/dL vs. 5.48±1.46mg/dL, respectively, P = 0.541). There was no correlation between uric acid and left ventricular ejection fraction. Interestingly, the ratio of the transmitral and myocardial peak early diastolic velocities (E/ e) showed inverse relationship with uric acid levels (r = -0.16, P =0.031).

Conclusions: Increased uric acid levels might be correlated with diastolic dysfunction in AF conversion to sinus rhythm. Xanthine oxydase inhibition in patients with AF who were converted to sinus rhythm might help improve of diastolic function.
Angioedema: An Uncommon But Potentially Life-Threatening Drug Reaction of Apixiban

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Case Description: A 92 year old male with atrial fibrillation and left atrial thrombus required anticoagulation prior to cardioversion. He has no history of any medication allergies or adverse drug reactions. He was prescribed Apixiban 2.5mg twice daily. After taking his initial dose, the next day the patient complained of severe neck pruritus and lip and tongue swelling. He denied any shortness of breath, voice changes, or skin rash. On physical examination, he demonstrated tachypnea and tachycardia. Inspection of the head and neck revealed symmetric periorbital edema and swelling of his tongue, sublingual soft tissues, buccal mucosa, and pharynx. Lung examination demonstrated diffuse wheezing and rales. The remainder of the physical exam was benign. Apixiban was abruptly discontinued. He was started on intravenous steroids and histamine blockers. His periorbital swelling and symptoms markedly improved the following day and he did not require any additional corticosteroids.

Discussion: Angioedema, characterized by immediate swelling of the skin, lips and tongue, is a potentially fatal condition if not promptly recognized and treated. It can be triggered by medications, food allergens, emotional stress, and local trauma. Apixiban is a Factor Xa inhibitor. The Apixaban for reduction in stroke and other ThromboemboLic events in atrial fibrillation (ARISTOTLE) trial demonstrated its superiority over warfarin in reducing risk of stroke and systemic embolism, major bleeding, and all-cause mortality for patients with non-valvular atrial fibrillation. Hypersensitivity reactions including skin rash, hives, angioedema, and syncope were reported in less than one percent of patients receiving Apixiban. According to Drugcite.com, only six cases of angioedema were reported to the Food and Drug Administration which comprises only 0.4% of reported side effects. Angioedema is rarely reported as a medication reaction.

Conclusion: Angioedema due to Apixiban is an uncommon but potentially life threatening reaction of which clinicians need to be made aware.
HEPATITIS C PATIENTS HAVE A HIGHER RISK OF ATRIAL FIBRILLATION

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Background: Hepatitis C (Hep C) and Atrial fibrillation (AF) pose huge health burdens. Chronic inflammatory conditions have been shown to increase the risk of AF. However, limited data on the causative role of chronic infections exists. The current study was done to study the risk of AF in patients with Hep C and to examine if Hep C is an independent risk factor for AF.

Methods: We conducted a retrospective database study at the University of Arkansas for Medical Sciences. Validated International classification of diseases (ICD 9) codes were used to identify patients with Hep C and AF. Age and sex matched controls without Hep C were identified for comparison. Statistical analysis was done using SPSS version 21.0.

Results: A total of 9,685 patients with Hep C and 12,799 without Hep C were identified. Hep C patients had a higher risk of AF when compared to controls (1.84% vs. 1.07%; OR 1.36, 95%CI= 1.09-1.69, p=0.05). Hep C patients also have a significantly higher incidence of hypertension, diabetes, COPD and obesity.

Conclusions: Patients with Hep C have a higher risk of AF due to increased incidence of traditional cardiac risk factors. However, chronic inflammation induced by Hep C could be a contributor. Further prospective studies examining this association may help differentiate association from causality.
ATRIAL FIBRILLATION AND STROKE PREVENTION

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OBSERVATIONAL STUDY OF THE CHARACTERISTICS AND MANAGEMENT OF PATIENTS ADMITTED WITH A PRIMARY DIAGNOSIS OF ATRIAL FIBRILLATION

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Background: The incidence of Atrial Fibrillation (AF) in patients over the age of 40 is ~25% and is an increasingly common cause of hospitalization. The cost of hospitalization for AF patients is a large portion of the annual cost of AF treatment in the US. This study adds to the insights of a previous study conducted at CAMC that looked at AF patients presenting to the Emergency Room.

Objective: Evaluate the following outcomes of patients admitted with a primary diagnosis of AF:
1. Method of conversion to normal sinus rhythm
2. Use of rhythm controlling medications
3. Time to conversion of normal sinus rhythm after admission

Methodology: Retrospective chart review of patients admitted at Charleston Area Medical Center with a primary diagnosis of AF between 2011 and 2012. Exclusion criteria included patients with AF admitted with a primary diagnosis other than AF. Results: A total of 226 charts were reviewed. Of patients admitted, 45% converted to normal sinus rhythm during their hospitalization and 20% converted prior to admission. Of those who converted, 14% had a cardioversion; the rest converted spontaneously. Greater than 90% of patients were placed on diltiazem and a beta blocker. Percentage of patients discharged on amiodarone was 16%, beta blocker was 62%, and diltiazem was 17%.

Conclusion: Of those patients who converted to normal sinus rhythm, only 14% had a cardioversion. This suggests an opportunity for more efficient care and reduction of economic burden to the healthcare system by early recognition of those needing cardioversion and those patients who can be discharged earlier with appropriate rhythm control medications.
SPONTANEOUS SUBDURAL HEMATOMA WHILE ON XARELTO (RIVAROXABAN)

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Introduction: Bleeding events are the most frequent adverse reactions associated with oral anticoagulants (OAC). The ROCKET AF (The Rivaroxaban-once daily, oral direct Factor Xa inhibition compared with vitamin K antagonism for prevention of stroke and embolism trial in Atrial Fibrillation) showed that rivaroxaban had 40% lower risk of intracranial and fatal bleeding compared to warfarin. Bleeding associated with rivaroxaban is usually secondary to trauma, fall or uncontrolled hypertension but we present a case of spontaneous subdural and extradural hemorrhage in a patient on rivaroxaban with no identifiable cause.

Case: A 77-year-old female patient with history of controlled hypertension was started on rivaroxaban after being diagnosed with atrial fibrillation. Five months later, she presented with painful swelling on her head but had no neurological symptoms. She denied head trauma, injury or fall. Creatinine and platelet counts were normal. A brain computerized tomography (CT) illustrated a large extradural hematoma and a right occipital subdural hematoma. Absence of neurological signs justified conservative management with close monitoring and withholding rivaroxaban. Repeat CT scan the following day showed improvement of the subdural hematoma with complete resolution on follow up imaging in 6 weeks.

Discussion: Intracranial bleeding can be divided into intracerebral, subdural/epidural, and subarachnoid hemorrhages. "Spontaneous" implies lack of observable injury, but many authors suspect that unrecognized trauma (i.e. minor trauma in sports, vomiting or coughing) may initiate bleeding. Although there was a recent case report of traumatic subdural hematoma in a patient on rivaroxaban treated with FEIBA (Factor Eight Inhibitor Bypassing Activity), currently there are no reports on spontaneous subdural hematomas associated with rivaroxaban. Our patient lacked provoking factors (trauma, renal dysfunction, or uncontrolled blood pressure), yet developed a spontaneous subdural hematoma, which is a serious complication. Awareness and early recognition of this grave complication and withdrawal of rivaroxaban can be lifesaving.
PREDICTED AND OBSERVED OUTCOMES OF MINIMALLY INVASIVE SURGERY FOR NATIVE AORTIC OR MITRAL VALVE INFECTIVE ENDOCARDITIS VIA A RIGHT MINI-THORACOTOMY APPROACH

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Objectives: Our study analyzed the feasibility of a right mini-thoracotomy approach to isolated valve surgery for native aortic or mitral valve infective endocarditis (IE).

Background: Despite improvements in the treatment of IE with concomitant medical and surgical therapy, morbidity remains high. A minimally invasive approach to aortic and mitral valve surgery has been associated with improved outcomes in high-risk populations.

Methods: All heart operations performed at our institution between January 2008 and December 2012 were retrospectively reviewed. The predicted outcomes, utilizing the Society of Thoracic Surgeons risk model, were compared with the observed outcomes in patients who underwent surgery via a right mini-thoracotomy for isolated native aortic or mitral valve IE.

Results: A total of 32 patients were identified, with a mean age of 62 ± 13 years. There were 6 (19%) females, and 3 (9%) patients had prior coronary artery bypass grafting. The mean preoperative creatinine was 1.5 ± 1.4 mg/dl and the mean left ventricular ejection fraction was 58 ± 10%. There were 11 aortic valve replacements, 9 mitral valve replacements, and 12 mitral valve repairs. The median cardiopulmonary bypass and aortic cross-clamp times were 119 (IQR 101-143) and 91 (IQR 73-109) minutes, respectively. The median intensive care unit and hospital length of stays were 41 (IQR 26-101) hours and 6 (IQR 5-10) days, respectively. Compared to the predicted outcomes, a minimally invasive approach was associated with a low rate of reoperation for any reason (0 versus 11%, p=0.02), and a higher incidence of short hospital length of stay (< 6 days and discharged alive) (50% versus 31%, p=0.02).

Conclusions: A minimally invasive right-mini thoracotomy approach for isolated native aortic or mitral valve IE is associated with low rates of any required reoperation and an enhanced postoperative recovery, and may be considered as an alternative to median sternotomy surgery.
HEART VALVE DISEASE – CAUSES, SYMPTOMS, DIAGNOSIS AND TREATMENT

TRANSCUTANEOUS AORTIC VALVE REPLACEMENT UNDER FLUOROSCOPIC GUIDANCE AND LOCAL ANESTHESIA ONLY

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Purpose: To assess the feasibility of transcatheter aortic valve implantation (TAVI) in local anesthesia and only mild analgesic medication under fluoroscopic guidance in a large monocentric patient collective including Medtronic CoreValve prostheses and Edwards Sapien XT prostheses.

Methods: 510 consecutive patients underwent TAVI in local anesthesia with lidocaine and mild analgesic medication with piritramide. To prevent nausea, all patients were treated with metoclopramide-hydrochloride and 62 mg dimenhydrinate. Extensive monitoring consisted of a 6-electrode, virtual 12-lead electrocardiogram, pulse oximetry, and invasive arterial pressure measurement from the sheath. There was no continuous surveillance by an anesthesiologist.

Results: A total of 510 patients underwent TAVI during the study period with 505 of 510 cases successfully performed without the use of general anesthesia. There was no need for conversion to general anesthesia except for 6 patients who required cardio-pulmonary resuscitation. Conscious sedation with intravenous administration of midazolam due to agitated patients or administration of inotropic medication due to prolonged hypotension was necessary in only 11 of the 510 patients. The combined safety endpoint according to VARC was reached in 13.4%.

Conclusion: Our results demonstrate that TAVI performed in local anesthesia with only mild analgesic medication and under fluoroscopic guidance is feasible with good results. This approach not only offers many potential advantages for the patients but could also result in a remarkable decrease in the need for staff, costs and length of in-hospital stay.
Effects of Gender on Transcatheter Aortic Valve Replacement Outcomes

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Background and hypothesis: Female gender is associated with smaller body surface area, decreased aortic dimensions, and lower glomerular filtration rate. Effects of gender on outcomes of transcatheter aortic valve replacement (TAVR) have not been investigated.

Methods: A retrospective chart review was conducted in 68 consecutive patients who underwent TAVR for aortic stenosis as they could not undergo surgery, 34 females (53%) treated at a single academic medical center. Outcomes were adjudicated according to the PARTNERS trial definitions (NEJM 2010; 363: 1597-1607). Analyses of variation, correlation, chi-square, and logistic regression were used. The study was approved by the institutional IRB.

Results: Female gender was associated with larger body mass index (29.9 +/- 7.2 vs. 28.5 +/- 5.3 kg/m² in males, p=0.405) but smaller body surface area (1.8 +/- 0.2 vs. 2 +/- 0.2 in males, p=0.002). Females had similar aortic valve gradient and area, but significantly better ejection fraction (53 +/- 10.9 vs. 47 +/- 11.4% in males, p=0.021). Chest wall deformities were more common in females (8.8 vs. 0% in males, p=0.096). Females were more likely to undergo transapical valve implantation (35 vs. 27% in males, p=0.457) and more likely to receive 23 mm prosthetic valve (94% vs. 7% in males, p<0.001). Despite the reported differences, female gender was not associated with increased rate of 1 year events, including death (p=0.27), stroke (p=0.61) myocardial infarction (p=0.29), repeat hospitalization (p=0.12), vascular complications (p=0.65), acute kidney injury (p=0.29), bleeding (p=0.72), atrial fibrillation (p=0.09), endocarditis (p=0.29), or need for pacemaker (p=0.56).

Conclusion: Despite significant gender-related differences, likely associated with smaller stature in women, TAVR outcomes are similar in men and women. Gender should not affect patient selection for TAVR. More studies of this important subject are needed.
HEART VALVE DISEASE – CAUSES, SYMPTOMS, DIAGNOSIS AND TREATMENT

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DO EDWARD SAPIENS AND COREVALVE TRANSCATHETER DEVICES HAVE DIFFERENT PROCEDURE COMPLICATIONS FOR AORTIC VALVE REPLACEMENT? A META-ANALYSIS

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Background: TAVR is a therapeutic alternative for high-surgical-risk patients with severe symptomatic aortic stenosis. There are currently available two different types of devices that can be clinically used in the USA: Edward Sapiens (ES) and CoreValve (CV). We aimed to analyze the difference in complications among those two devices.

Methods: We searched PubMed, EMBASE, and Cochrane databases up to January 2014. The studied outcomes were pacemaker implantation, acute kidney injury (AKI), major vascular complications, and conversion to open heart surgery and moderate to severe perivalvular aortic regurgitation. We used Fixed or Random Effect analysis using the Cochrane Handbook of Systematic Reviews.

Results: 5 studies provided a total of 5087 non-overlapping patients, 3170 received ES and 1917 CV device. As demonstrated in figure 1, ES valve presented fewer complications as such as pacemaker implantation, conversion to open heart surgery and significantly less major bleeding complications (4.2% ES vs. 6.3% CV; p<0.05). There was no difference in regards AKI or perivalvular leaking.

Conclusion: Our analysis has suggested that bleeding complications might be more common in the CV whereas some other complications might not differ among TAVR devices. Further randomized trials are warranted.
ASSOCIATION OF AORTIC VALVE CALCIFICATION AND EPICARDIAL FAT VOLUME

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Introduction: Epicardial adipose tissue (EAT) has emerged as an important factor of coronary artery atherosclerosis due to the endocrine potential of EAT including secretion of several proinflammatory mediators. The pathogenesis of aortic valve calcification (AVC) shares many similarities with atherosclerosis. Therefore, we hypothesized a potential association of AVC with epicardial fat volume (EFV).

Methods: A cross-sectional study in 139 patients (mean age 72 ± 8 years) with echocardiographically proven AVC was performed. For quantification of AVC and EFV, all patients underwent non-contrast-enhanced DSCT (Definition, Siemens, Germany). EFV of patients with AVC was compared to values obtained from a control population (n=30, age 54 ± 17 years) without relevant coronary or aortic valve calcification (mean Agatston AVC score 2 ± 5) as assessed by DSCT. For measurement of EFV non-contrast CT images were used and the total sum of the EAT volume from the pulmonary artery bifurcation to the cardiac apex using 3mm slice thickness was calculated. In addition, we stratified patients with AVC in a low calcification group and a high calcification group according to the median of AVC (1038).

Results: The mean AVC score in the study group was 1408 ± 1459. Patients with AVC showed significantly higher EFV (163 ± 65 cm³) as compared to a controls without relevant coronary or valvular calcification (94 ± 46 cm³, p<0.001). Epicardial fat volume in the low calcification group (n=70) were significantly smaller (151 ± 50 cm³) than EFV of patients in the high calcification group (175 ± 76 cm³, p=0.03; n=69).

Conclusions: Patients with AVC showed increased EFV compared to a reference population without relevant coronary or valvular calcification. Furthermore, our data demonstrated a moderate association between the severity of AVC and EFV indicating a possible role of epicardial adipose tissue in the valvular calcification process.
IMPACT OF POSTOPERATIVE COMPLICATIONS ON LONG-TERM SURVIVAL IN ISOLATED AORTIC VALVE REPLACEMENT

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Objective: To evaluate the impact of postoperative complications on long-term survival of isolated surgical aortic valve replacement during a 10-year period.

Methods: The long-term survival of 200 patients undergoing isolated aortic valve replacement between January 2004 and January 2006 was analyzed according to their preoperative symptoms and postoperative complications.

Results: Factors affecting long-term survival included age (p = 0.009), NYHA class (p = 0.005) and the postoperative acute renal failure (p= 0.0012). Evaluation of factors affecting 1, 3, 5, 10-year survival showed their variability. By contrast, sex (p=0.62), the presence of postoperative atrial fibrillation (p=0.79), prosthesis-patient mismatch (p=0.43) did not influence outcome in these patients. Actuarial survival at one, three, five and ten years was 94.1%, 90.4%, 87.5% and 73.9% respectively.

Conclusion: Postoperative acute renal failure is associated with increased rates of in-hospital adverse events and decreased 1,3,5,10 year survival after isolated AVR.
AGE ADJUSTED MORTALITY RATE FROM AORTIC VALVE SURGERY SHOWED PERSISTENT REDUCTION IN THE UNITED STATES WITH ELIMINATION OF GENDER GAP IN RECENT YEARS

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Background: Advancement in the surgical technique should translate into better outcome. The goal of this study was to evaluate mortality trend from aortic valve surgery in the United State using large inpatient database.

Method: The Nationwide Inpatient Sample (NIS) database was used to calculate the age-adjusted mortality rate from aortic valve surgery from 1988 to 2007 in the United State using ICD-9 coding for aortic valve surgery.

Results: We found that age adjusted mortality rate from aortic valve surgery gradually decreased from 1988 until end of study in 2007 to lowest level with elimination of gender gap that was seen in early years. (For men age adjusted mortality rate from aortic valve surgery in 1988 was 438 per 100,000 with steady reduction to the lowest level of 256 per 100,000 in 2007 For women, age adjusted mortality from aortic valve surgery was 620 per 100,000 in 1988 with steady reduction to the lowest level of 215 per 100,000 in the year 2007).

Conclusion: Age adjusted mortality from aortic valve surgery has been gradually decreased in the last decade suggesting improvement in surgical technics and post-surgical care has lead to better outcome.
OBESITY AND OUTCOMES IN NORTH-AMERICAN PATIENTS TREATED WITH TRANSCATHETER AORTIC-VALVE REPLACEMENT

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Background and hypothesis: French investigators reported improved trans-catheter aortic valve replacement (TAVR) outcomes in overweight patients (Am J Cardiol 2013; 112: 1932-7). Similar studies in US patients are lacking.

Methods: A retrospective chart review was conducted in 64 consecutive inoperable TAVR patients treated at a single US academic center. Outcomes were adjudicated and analyzed using PARTNERS trial definitions and results (NEJM 2010; 363: 1597-1607). Analyses of variation, correlation, chi-square, and logistic regression were used.

Results: Mean Body Mass Index (BMI) was 29.3+-6.4 kg/m2 and ranged from 17.7 to 55. Patients with increased BMI were younger (p=0.001) and more likely to have history of PCI (p=0.025). There was a trend towards increased aortic valve area, higher ejection fraction, and lower STS score in increased BMI. Majority (81%) of overweight patients were treated with trans-femoral approach vs. 47% of underweight or with normal weight patients (p=0.066). Otherwise, there were no significant differences related to BMI.

Our TAVR outcomes were comparable with published PARTNERS results. We have observed lower rate of bleeding at 30 days (2 vs 17% in PARTNERS, p=0.002) and 1 year (8 vs 22%, p=0.011), lower 30 day stroke rate (0 vs. 7%, p=0.039), and lower rate of any vascular complications at 30 days (16 vs 31%, p=0.022) and 1 year (19 vs 32%, p=0.044). TAVR outcomes were similar, regardless of the BMI. There was a trend towards fewer repeat hospitalization in higher BMI patients (HR 0.923, 95% CI 0.843-1.01, p=0.081) with decreased 1 year vascular complication (HR 0.913, 95%CI 0.28-1.006, p=0.065).

Conclusion: In a single institution North-American cohort study, increased BMI did not influence TAVR outcomes, which is different from a single European study reporting improved TAVR outcomes in increased BMI. Significantly increased or low BMI should not preclude TAVR consideration. More studies of this important subject are needed.
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OUR APPROACH TO SURGERY OF THE AORTIC ROOT ABSCESS: A 15-YEARS EXPERIENCE

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In this study, we present our surgical approach for aortic root abscess due to infective endocarditis.

**Methods:** Aortic root abscess is the most severe complication of infective endocarditis. 27 patients, consisting of 20 males (74%), with a mean age of 37±13 years have been studied. Of the patients, 21 (78%) had native valve, whereas 6 (22%) had prosthetic valve. Surgery consisted of radical resection of the abscess, reconstruction of the annulus with patches, and valve replacement. Root replacement was utilized in 5 patients. 6 patients, with prior valve surgery, were reoperated. The mean follow-up was 6.8±3.7 (range between 0.1-11.6) years.

**Results:** All patients underwent 29 different surgical procedures. Isolated AVR in 15 patients (56%) (mechanical valve in 13 and bioprosthetic valve in 2), replacement of both aortic and mitral valve in 4 patients, and root replacement in 5 patients were the most common procedures. Bentall procedure with flanged technique was performed in 3 patients who underwent aortic root replacement. In this technique, the flanged part of a handmade composite graft was used at the level of subannular area. Hospital mortality after emergency surgery was 11% (n=3). Atrioventricular block was occurred in 4 of 27 patients postoperatively, and 1 patient required permanent pacemaker implantation. The overall 1-,5- and 10-year survival rates were 70.3±5.8%, 62.9±6.4% and 59.2±7.2%, respectively.

**Conclusion:** The surgical management of aortic root pathology is complicated and difficult due to high risk of morbidity and mortality. After the complete resection of periannular abscess, replacement of aortic root can be implement for reconstruction of the root. We suggest to replace the aortic root with a composite graft containing a mechanical or bioprosthetic valve, because it represents the best anatomical fit for replacement with less bleeding.
HEART VALVE DISEASE – CAUSES, SYMPTOMS, DIAGNOSIS AND TREATMENT

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INCIDENCE AND PREDICTORS OF PERMANENT PACEMAKER IMPLANTATION AFTER VALVE SURGERY- A SINGLE CENTRE EXPERIENCE

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Introduction: Patients going for valve surgery have a higher incidence (3-8%) of permanent pacemaker implantation (PPMI) compared to those who undergo coronary artery bypass grafting (<1%). PPMI post cardiac surgery is associated with higher incidence of complications. This study was done to examine the incidence of PPMI post-valvular surgery and determine predictors that can identify high risk patients.

Methods: It was a retrospective chart review that included 197 consecutive patients who underwent valve surgery. Patients who underwent post-operative PPMI were identified as cases and those without PPMI served as controls. 72 different predictive variables were compared between the two groups. Mean follow up duration was 30 days.

Results: Baseline Demographics including age, sex, CAD, DM and HTN were similar between the two groups. Post-surgery 9.6% patients underwent PPMI. Incidence of PPMI for aortic, mitral and multivalvular surgery was 8.3%, 17.6% and 15.4% respectively. Mean surgery to PPMI duration was 5.4 days. Presence of preoperative right bundle branch block (RBBB) significantly increased the incidence of PPMI (P=.004). Indications for PPMI were complete heart block (26.3%), junctional rhythm (21.1%), sinus node dysfunction (31.6%) and atrial fibrillation with slow ventricular response (5.3%). Cardiac outcomes (peri-operative MI, death, and stroke) were not significantly different between the two groups. Being on rate control and anti-arrhythmic medications, other conduction abnormalities, leaflet calcification, endocarditis, surgery type and prior valve surgery did not significantly increase the incidence of PPMI.

Conclusion: Patient going for valve surgery are at significant risk for requiring post-operative PPMI. Incidence of PPMI was significantly higher in patients going for mitral or multivalve surgery and those who had pre-operative RBBB. A larger study is needed to determine significance for other variables.
HEART VALVE DISEASE – CAUSES, SYMPTOMS, DIAGNOSIS AND TREATMENT

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THE OPTIMAL CHOICE OF AVR PROSTHESIS AT AGE 60- WARFARIN OR REOPERATION
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There has been a monumental reshuffle toward the use of bioprosthetic valves. From the Society of Thoracic Surgeons (STS) database, use of mechanical valves in aortic position has decreased from 49.9% in 1997 to 20.5% in 2006, whereas bioprosthetic valve usage increased from 43.6% in 1997 to 78.4% regardless of age. Classic teaching recommended mechanical valve for younger patients due to its durability at the expense of life time anticoagulation. In contrast, bioprostheses will free patients from anticoagulation but exposes them to the risk of SVD which increases with time. As the trend grows toward increased use of bioprostheses, age limit for bioprosthetic valve use versus mechanical valve is intensely debated. In the most updated American College of Cardiology/American Heart Association (ACC/AHA) guideline from 2008, patient age is no longer the Class I recommendation for prosthetic choice in aortic valve replacements (AVR). The removal of cutoff age in ACC/AHA guideline is supported by some surgeons for the following reasons. (1)Current bioprostheses appear to have lower rates of structural valve deterioration than the first-generation bioprostheses. (2)The risks of reoperation have continued to decrease over time. (3)Young patients undergoing valve surgery are often reluctant to accept warfarin therapy and the activity constraints associated with anticoagulants. In addition, future application of transcatheter valve-in-valve replacement is highly anticipated. We reviewed the outcomes in patients under age 60, which showed that the survival between mechanical valve and bioprosthetic valves are similar and one does not have advantage over the other. The use of bioprostheses lowers the chance of major bleeding event. Due to low life expectancy after valve surgery, average patients do not outlive the durability of bioprostheses at the age of 60. It is critical for physicians to provide good information to aid the understanding of true risks and benefits.
NEW LBBB FOLLOWING TRANSCATHETER SAPIEN VALVE: INSIGHT INTO MECHANISMS

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Background: Left bundle branch block (LBBB) induced by trans-catheter aortic valve implantation (TAVI) affects clinical outcomes. The incidence of new LBBB is higher with Core-Valve than SAPIEN valve, likely due to longer prosthesis and deeper implantation. The mechanism of new LBBB caused by SAPIEN valve is unclear.

Methods: Thirty seven consecutive TAVI cases using SAPIEN valve (20 trans-femoral, 17 trans-apical) were included. All EKGs before and after procedure and on discharge were reviewed.

Results: Four patients with baseline LBBB were excluded. New LBBB occurred in 9 (27%) patients: 7 (21%) resolved within 24 hours, and 2 (6%) persisted on discharge. Coaxial mal-alignment in the left ventricular outflow tract (LVOT) was noted in the 2 patients with new persistent LBBB (figure). No mal-alignment was seen in the 7 cases with transient LBBB or cases without LBBB.

Conclusions: Transient TAVI-induced LBBB using SAPIEN valve is common, and may be related to transient compression or ischemia by balloon or valve prosthesis, or to rapid ventricular pacing. However, new persistent LBBB is relatively uncommon and may be related to SAPIEN valve prosthesis mal-alignment in the LVOT, therefore potentially avoidable.
Objective: Replacement procedures in patients with aortic root dilatation became more important with increasing information about the dynamic nature and physiology of the aortic root. In our study, we evaluated early and mid term results in patient with valve sparing aortic root reimplantation.

Methods: 32 patients with aortic root aneurysm were included to our study between April 2009 and February 2014. David V procedure was performed in 32 patients. Native aortic valve was kept in 22 patient because of normal structure and function. Aortic valve was repaired in 9 patients.

Results: There was no operative mortality. One patient died due to renal and respiratory failure and one patient died due to myocardial stunning in early term. Aortic valve function is normally in 29 (90,6%) patients (<=1°regurgitation) in the early postoperative period. 2nd degree of aortic regurgitation was detected in 3 (9,4%) patients.

There was no mortality postoperative late period.

Conclusions: Valve sparing aortic root reimplantation improves quality of life in patients. Patients are kept from complication of mechanical valve and anticoagulant therapy. If necessary to replace the aortic valve in elderly patient, the stentless biological aortic valve can be used in these patients.
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VALVULAR MIGRATION AFTER TRANSCATHETER AORTIC VALVE IMPLANTATION: A CASE SERIES

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Introduction: Transcatheter Aortic Valve Implantation (TAVI) is the recommended therapy for patients with severe aortic stenosis who are not suitable candidates for surgery. Prosthetic valve embolization is a rare but serious complication after deployment.

Case 1: An 85 y/o male underwent successful 26 mm SAPIEN prosthetic valve insertion via transfemoral approach. TEE showed that the prosthetic valve was positioned slightly low down the annulus, but with mild aortic insufficiency, patient was transferred to the floors. Postoperative course was complicated by hemodynamic instability requiring pacemaker insertion and vasopressor support. Fluoroscopy showed that the prosthetic valve had migrated into the left ventricle allowing for severe aortic insufficiency and cardiogenic shock. A “valve in valve” was placed 3 mm higher than the original position, achieving improved seal around the annulus. Hemodynamics improved instantly.

Case 2: An 83 y/o male underwent TAVI via transapical approach. During the deployment of the 26-mm SAPIEN prosthetic valve, it embolized into the ascending aortic arch. Attempt to inflate a valvuloplasty balloon from the groin and drag the stent into the descending aorta was unsuccessful due to severe peripheral vascular disease. A second 26 mm SAPIEN valve was deployed at the aortic annulus. Patient was discharged with a prosthetic valve in the aortic arch.

Discussion: It is now known that all 3 sinuses of the aorta must be perpendicular to the long axis of the valve plane prior to deployment. In relation to the aortic annulus, prosthetic valves can embolize into the aorta if positioned too high, or into the left ventricle if positioned too low. Embolization of the valve to the aorta is well tolerated as long as coaxial wire positioning is maintained, preventing the valve from flipping over to obstruct antegrade blood flow.
THE DRIER THE BETTER: DOES RISING CREATININE FOLLOWING ULTRAFILTRATION IN ACUTE DECOMPENSATED HEART FAILURE PREDICT READMISSION?

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Introduction: Hospitalizations for acute decompensated heart failure (ADHF) have been increasing and costs related to readmissions account for a majority of total cost of care. Ultrafiltration (UF) is now being considered for ADHF refractory to medical therapy. Purpose: To evaluate clinical outcomes in ADHF among patients treated with UF

Methods: A retrospective study was conducted at Banner Good Samaritan and Banner Heart Hospitals between 1/1/2006-11/01/2012 identifying patients with ADHF who received UF. Continuous data are reported as means and standard deviations. A Mann-Whitney U test was used to compare differences in continuous variables.

Results: There were a total of 67 patients, 68.7% of whom were male. More than half (55.2%) of the patients were classified as having severely reduced ejection fraction (EF). Of the 67 patients, 43 had chronic kidney disease (CKD) and 22 patients developed acute kidney injury (AKI) during treatment. 19 patients (28.4%) were placed on dobutamine; 14 of these had a severely reduced EF. Serum creatinine increased on average by 0.30 (0.62), mean BNP decreased by 1675 (2897), and mean weight decreased by 7.4 kg (9.6). For our study group, overall 30-day readmission rate was 23%. There were 6 in-hospital deaths. Of the 61 patients who survived their admission, the 30-day readmission rate was 6.2% for patients who developed AKI and 29% for those who did not (p=0.064). Also, of the 61 patients who survived, there was no significant difference in 30-day readmission rate between those with CKD (22.5%) and those without (23.8%). Interestingly, those who died during the index hospitalization had a greater increase in serum creatinine than those who survived.

Conclusion: An increase in serum creatinine for patients with ADHF treated with UF appears to be a predictor of in-hospital mortality, while a lesser increase seems to be predictive of 30-day readmission.
PREDICTORS AND MARKERS OF HEART FAILURE OUTCOME

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COMPARISON OF HOSPITAL READMISSION RATES IN HEART FAILURE PATIENTS WITH REDUCED VS. PRESERVED LEFT VENTRICULAR EJECTION FRACTION

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**Background:** Heart failure (HF) is a chronic disease characterized by recurrent decompensations and the need for repeat hospitalization. The federal government has recently implemented financial penalties which have resulted in an increased focus on reducing the rate of readmission of HF patients. Nationally, approximately 1 in 4 Medicare patients admitted with HF is readmitted within 30 days of discharge. We sought to compare the rate of 30 day readmission in patients with HF with reduced left ventricular ejection fraction (HFREF) to HF patients with preserved left ventricular ejection fraction (HFPEF).

**Methods:** We retrospectively analyzed all consecutive patients admitted for HF in 2012 at our community-based teaching hospital. HFREF was defined as LVEF<50% as assessed by transthoracic echocardiography. Readmission rate at 30 days from hospital discharge was compared in patients with HFREF to patients with HFPEF.

**Results:** There were 703 patients admitted with the primary diagnosis of HF; 248 (35.3%) with HFREF, 455 (64.7%) with HFPEF (demographic data is displayed in table). Patients with HFPEF were more likely to be female. The 30 day readmission rate for HFREF patients was 16.1% (40/248) vs. 10.9% (50/455) for HFPEF patients (p=0.02).

**Conclusion:** We found the rate of 30 day readmission to be higher amongst HF patients with HFREF as compared to HFPEF. In parallel with ongoing efforts to reduce the readmission rate of HF patients, it is important to better define the patient characteristics of those most likely to be readmitted.

<table>
<thead>
<tr>
<th>Demographic data</th>
<th>HFREF (LVEF&lt;50%) n=248</th>
<th>HFPEF (LVEF&gt;50%) n=455</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender (female)</td>
<td>53.4%</td>
<td>62.4%</td>
<td>0.01</td>
</tr>
<tr>
<td>Age (yrs)</td>
<td>81.2 +/- 9.7</td>
<td>82.2 +/- 8.9</td>
<td>0.11</td>
</tr>
<tr>
<td>LV ejection fraction</td>
<td>33.5% +/- 11.0</td>
<td>59.0% +/- 7.5</td>
<td>0.05</td>
</tr>
<tr>
<td>30 day readmission rate</td>
<td>16.1%</td>
<td>10.9%</td>
<td>0.02</td>
</tr>
</tbody>
</table>
PREDICTORS AND MARKERS OF HEART FAILURE OUTCOME

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A TEAM BASED STRATEGY TO MANAGE HIGH RISK HEART FAILURE PATIENTS IN A LARGE URBAN HEALTHCARE DELIVERY MODEL
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Background: Although Heart Failure (HF) mortality has improved, HF admissions contribute to over half of all HF related cost in the United States. Team based HF management demonstrated improved outcomes.

Purpose: Demonstrate the impact of a team based HF program at Cedars Sinai Healthcare Foundation, an ACO affiliated with Cedars Sinai Hospital, on HF admissions and 30-day readmissions.

Methods: Cardiologists identified high risk patients from an outpatient panel of 3,500 patients. The HF program includes cardiologists, a clinical pharmacist, nutritionist, home nurse practitioners, and a palliative care team. Services offered included education, medication reconciliation, medication safety monitoring and optimization based on clinical parameters and serum brain natriuretic peptide as directed by a CHF trained and cardiologist supervised clinical pharmacist. For patients presenting with severe volume overload, cardiologists utilized point of care ultrasound (GE Healthcare Vscan) to guide the need for in-office IV diuretics. A retrospective review of all patients referred to the HF Program over 14 months was conducted. Participants in the program for 12 months were included. Cedars Sinai Medical Center HF admissions, 30-day readmissions, 12 months pre and post-enrollment were included.

Results: Of 170 patients, 35 were excluded (No initial consult N = 7; HF resolved N = 2; Declined enrollment N = 8; Transfer of care N = 6; Lost to follow-up N = 2; Admitted to assisted living facility N = 1; Hospice N = 3; Deceased N = 6). Of the 135 patients included, 52 participated for at least 12 months. Eighty-five HF admissions and 14 30-day readmissions occurred in the patient cohort 12 months pre-enrollment. Thirty-one HF admissions and 2 30-day HF readmissions occurred in the patient cohort 12 months post-enrollment.

Conclusions: The HF program has demonstrated a reduction in HF hospital admissions and 30-day readmissions 12 months post-enrollment compared to 12 months pre-enrollment.
INCIDENCE, RISK FACTORS, AND OUTCOME OF ACUTE DECOMPENSATED HEART FAILURE (ADHF) SUPERIMPOSED ACUTE EXACERBATION OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE (AECOPD)

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Advocate Illinois Masonic Medical Center, Chicago, IL, USA

Background: COPD and cardiovascular disease share similar risk factors. Recognizing ADHF in the presence of AECOPD is complicated by similarities in symptoms and physical findings. BNP has been studied to be used as a detector for ADHF in AECOPD but it is still controversial because many conditions encountered in COPD i.e. pulmonary hypertension and right ventricular stress have been shown to contribute to the increase of BNP. We sought to examine other risk factors and effect of ADHF on AECOPD.

Methods: This study is a retrospective review of 136 patients hospitalized for AECOPD from January 1, 2011 to December 31, 2011. The demographic data, clinical manifestation, laboratory findings, and treatment were collected from medical record. The length of hospital stay (LOS) and all-cause mortality (MR) were compared between AECOPD group and ADHF superimposed AECOPD group.

Results: From 136 patients (mean 69.7±11.7 years old, 47.1 % male), 22 patients were diagnosed with coexistent AECOPD and ADHF (16.2%), whereas 114 patients were in AECOPD group. The factors that were found to be associated with coexistent ADHF and AECOPD were hypertension (95.5 % vs 73.7 %, p = 0.03), hyperlipidemia (63.6%vs33.3%,p=0.01), diabetes (59.1%vs32.5%,p=0.02), and coronary artery disease (59.1%vs32.7%,p<0.01), peripheral edema (50%vs13.2%,p<0.01), and BNP level (464vs122,p<0.01). In binary logistic regression analysis, elevated BNP (OR=10.7;95%CI:2.5-40.7,P<0.01) and peripheral edema (OR=6.4;95%CI:1.5-20.8,P=0.01) were independent variables associated with conexisting of ADHF in AECOPD. LOS was 4.6 days and 3.4 days (p=0.20) in coexistent AECOPD and ADHF group and AECOPD group respectively. The 1-year MR are 27.3% and 24.6% (p=0.78) between 2 groups.

Conclusions: Coexistence of ADHF and AECOPD is not uncommon. From our study, the incidence was 16.2%. The factors significantly associated with concomitant conditions are BNP level and peripheral edema. The outcomes, in term of LOS and MR, in both groups are comparable.
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EFFECT OF CARE TRANSITION INTERVENTIONS ON DIFFERENT HEART FAILURE PATIENT SUBGROUPS, DEFINED BY UNDERLYING ETIOLOGY: ARE THERE IDENTIFIABLE SUBGROUPS MORE LIKELY TO BENEFIT?
T. Kern¹, I. Kedan², A. Kimchi¹,²
1. David Geffen School of Medicine, UCLA, Los Angeles, CA, USA
2. Cedars-Sinai Heart Institute, Los Angeles, CA, USA

Background: The cause of heart failure syndrome is multifactorial and heterogeneous. Heart failure intervention trials may not always address the specific etiology of heart failure when evaluating and interpreting results. Despite the extensive resources directed towards heart failure care transition interventions, the success with regard to reducing readmissions and improving health outcomes has been limited while the expense remains staggering.

Objective: The purpose of this study was to determine if published randomized controlled heart failure care transition intervention trials performed subgroup analyses based on the different etiologies of heart failure. Additionally, we investigated whether specific patient subgroups, identified by heart failure etiology, received differential benefit.

Methods: We conducted a PubMed keyword search to identify randomized controlled trials evaluating the effect of different heart failure care transition interventions on health outcomes and hospital readmissions. We focused on the following interventions: education, nursing follow-up at home, nursing follow-up in clinic, nursing follow-up by telephone, exercise program, and telemonitoring. We also examined if subgroup analyses based on underlying heart failure etiology (ie coronary artery disease, ischemic, diabetes, hypertension, arrhythmia, valvular disease, and heart failure with preserved ejection fraction) was performed and if differences in response to the intervention existed between subgroups.

Results: Twenty-five heart failure intervention trials met the search criteria. Of these studies, five trials performed one or more subgroup analyses based on the etiology of heart failure. No study demonstrated a significant differential subgroup response to intervention (Table 1).

Conclusion: The majority of the reviewed studies was limited by small sample size and did not address the question of which subgroup of heart failure patients are more likely to benefit from care transition interventions. Further study is needed in order to identify those patients who are likely to benefit from these interventions.

<table>
<thead>
<tr>
<th>Year published</th>
<th>Author (Trial)</th>
<th>Number of subjects</th>
<th>Intervention</th>
<th>Did the trial perform subgroup analyses based on HF etiology?</th>
<th>If yes, was a significant difference in outcomes observed?</th>
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<tr>
<td>2012</td>
<td>Stewart (WHICH?)</td>
<td>280</td>
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<td>2012</td>
<td>Witham</td>
<td>107</td>
<td>Exercise</td>
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<td>2012</td>
<td>Boyne</td>
<td>382</td>
<td>Telemonitoring</td>
<td>No</td>
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<tr>
<td>2011</td>
<td>Koehler (TIM-HF)</td>
<td>710</td>
<td>Telemonitoring</td>
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<tr>
<td>Year published</td>
<td>Author (Trial)</td>
<td>Number of subjects</td>
<td>Intervention</td>
<td>Did the trial perform subgroup analyses based on HF etiology?</td>
<td>If yes, was a significant difference in outcomes observed?</td>
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<td>Stauffer</td>
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<td>2010</td>
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<td>Nursing follow-up (clinic) Education Exercise</td>
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<td>2009</td>
<td>O’Connor (HF-ACTION)</td>
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<td>Yes (ischemic vs. non-ischemic) (preserved vs. reduced EF)</td>
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<td>128</td>
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<tr>
<td>2008</td>
<td>Bocchi (REMADHE)</td>
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<td>Yes (ischemic vs. non-ischemic) (diabetes vs. no diabetes)</td>
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<td>DeWalt</td>
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<td>2006</td>
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<td>Nursing follow-up (home) Education</td>
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<td>2005</td>
<td>GESICA (DIAL)</td>
<td>1518</td>
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<td>2005</td>
<td>Cleland (TEN-HMS)</td>
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<td>2005</td>
<td>Dunagan</td>
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<td>2004</td>
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<td>2004</td>
<td>Koelling</td>
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<td>Education</td>
<td>Yes (CAD vs. no CAD)</td>
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<tr>
<td>2004</td>
<td>Kimmelstiel (SPAN-CHF)</td>
<td>200</td>
<td>Nursing follow-up (telephone) Education</td>
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<td>2004</td>
<td>Thompson</td>
<td>106</td>
<td>Nursing follow-up (home) Education</td>
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<td>2003</td>
<td>Goldberg (WHARF)</td>
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<td>Telemonitoring</td>
<td>No</td>
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<td>2003</td>
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<td>2002</td>
<td>Krumholz</td>
<td>88</td>
<td>Education</td>
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<td>2002</td>
<td>Doughty</td>
<td>197</td>
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</tbody>
</table>

Table 1: Summary of trials
IMPACT OF ECHO-GUIDED MEDICATION OPTIMIZATION IN PATIENTS WITH CHRONIC HEART FAILURE

F. Garcia Trobo, L. Pastori, B. Manduca, G. Pekler, F. Visco
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Objective: The aim of this study is to evaluate the possible benefits of using common echocardiographic parameters for medication optimization in patients with chronic heart failure (CHF).

Background: Multiple methods have been proposed to guide medical therapy in CHF patients. To date there is no clear consensus or gold standard in this regard. We need to improve our ability to evaluate these patients and establish guidelines for optimal patient care and improved quality of life so as to avoid unnecessary and/or prolonged hospital admissions.

Method: We followed up with 51 clinically compensate CHF patients from our Hospital Heart Failure Outpatient Program from January to April 2014. Medication was optimized in subsequent visits by using the following trans thoracic echocardiographic (TTE) parameters: tricuspid annular plane motion score (TAPSI) and inferior vena cava (IVC) distension. Our goals of treatment were to achieve an increase of at least 25% in the ejection fraction (EF) and a decrease in pro-bnp levels. These levels were measured in all patients on the first and in the last day of the study. The rate of hospital admissions of this group was also reviewed during this period of time.

Results: 23 patients (45%) presented an increase of the ejection fraction of at least 25% from the baseline, pro-bnp reduction levels were observed in 20 of the subjects (39.2%) and the hospital admission rate for decompensate CHF was 4% in 90 days. No statistical difference was noted between decreased pro-bnp levels and improvement of the EF.

Conclusion: These findings suggest that using echocardiography as reference for medication optimization in patients with chronic heart failure might improve ejection fraction, decrease pro-bnp levels, and reduce the rate of hospital admissions in 90 days.
FACTORS AFFECTING CARDIO-RENAL SYNDROME AND OUTCOMES IN ACUTE CONGESTIVE HEART FAILURE PATIENTS

The Wright Center for Graduate Medical Education, Scranton, PA, USA

Background: Identification of patients who are at risk for cardiorenal syndrome is important as these patients need aggressive therapy early on. Cardio-renal syndrome can have prognostic implications among acute heart failure patients. Several factors play a role in cardio-renal syndrome and these factors have not been investigated thoroughly. A retrospective analysis of these factors may help understand the syndrome better as well as predict the occurrence of this syndrome in a patient with acute heart failure.

Aim: To evaluate factors associated with worsening renal function in acute congestive heart failure as well investigate any relationship with length of stay and mortality.

Methods: We performed a retrospective-prospective observational study with a sample size of 185 patients. The entire project was compliant with HIPAA. We included all patients with acute and acute on chronic congestive heart failure patients. We excluded dialysis patients and those who developed acute congestive heart failure after hospitalization from other causes. Patients without acute kidney injury served as controls. We measured several variables like age, gender, underlying chronic diseases, sleep apnea, medications, laboratory values like hemoglobin, sodium levels, echo findings like ejection fraction and elevated right heart pressures.

Results: We used the statistical software Minitab employing logistic regression and T-Test to analyze the data. Underlying chronic kidney disease was found to be associated with acute kidney injury (p-value < 0.05). The association of other factors with AKI was not statistically significant. The length of stay among AKI patients was significantly higher than among patients without AKI. (6.36 days vs 4.8 days). There was no difference observed in mortality.