Biomarkers of Cardiovascular Damage

Paul O. Collinson David C. Gaze

Departments of Chemical Pathology, Cardiac Research and Cardiology, St George's Hospital and Medical School, London, UK

Key Words

Ischaemia • Acute coronary syndrome • Prognostic risk assessment • Chest pain • Myocardial infarction • Biomarkers • Ischaemia-modified albumin • Cardiac troponin T • Cardiac troponin I • N-terminal B-type natriuretic peptide

Abstract

Acute coronary syndromes (ACS) are due to the rupture or erosion of atheromatous plaques. This produces, depending on plaque size, vascular anatomy and degree of collateral circulation, progressive tissue ischaemia which may progress to cardiomyocyte necrosis. This may then result in cardiac remodelling. Serum biomarkers are available which can be used for diagnosis of all of these stages. Markers to detect myocardial ischaemia at the pre-infarction stage are potentially the most interesting but also the most challenging. An ischaemia marker offers the opportunity to intervene to prevent progression to infarction. The problems with potential ischaemia markers are specificity and the reference diagnostic standard against which they can be judged. To date, only one, ischaemia-modified albumin[®], has reached the point where clinical studies can be performed. The measurement of the cardiac troponins, cardiac troponin T and cardiac troponin I, have become recognised as the diagnostic reference standard for myocardial necrosis. The sensitive nature of these tests has also revealed that myocardial necrosis is also found in a range of other clinical situations, highlighting the

need to use all clinical information for diagnosis of acute myocardial infarction. The measurement of B-type natriuretic peptides can be shown to be diagnostic and prognostic in both ACS and detecting the sequelae of post-infarction myocardial insufficiency. The role of the B-type natriuretic peptides in detection of cardiac failure, both acute and chronic, is well defined but remains the subject of further studies, in ACS.

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The pathophysiology of acute coronary syndromes (ACS) is now accepted as the rupture or erosion of an atheromatous plaque [1]. This process may be self-limiting or progressive (fig. 1) and may occur rapidly (minutes to hours) or over a longer period (over several days).

The concept of rupture of a single plaque with all of the clinical effects due to occlusion of a single downstream vessel has been shown to be too simplistic. Intravascular ultrasound has shown that plaque rupture is often multiple and may affect arteries other than the one considered to be responsible for the location of the ischaemic area (the culprit artery) [2, 3]. The exposure of the plaque core activates the clotting cascade and results in thrombosis within the plaque. This then initiates platelet aggregation. There are three possible mechanisms by which damage to the myocardium may occur.

Fig. 1. Plaque rupture – the balance between thrombosis and thrombolysis.

Fig. 2. Plaque formation and progression.

- Intraluminal platelet aggregation may cause sufficient vascular occlusion for cardiomyocyte damage to occur. Occlusion does not have to be total to produce myonecrosis. Partial occlusion will produce a reduction in the rate of blood supply in the myocardium downstream. If there is already supply/demand mismatch in this area, the reduction in blood supply may be enough to render an area of myocardium non-viable. The tissue will then become sufficiently ischaemic for necrosis to occur. This is most likely to affect small

areas of myocardium at the watersheds of different branches of the vascular supply.

- The second mechanism is the release of platelet micro-aggregates. These will embolise small vessels causing ischaemia and localised infarction [4, 5].
- Finally, progression of white thrombus formation to activation of the clotting cascade will result in partial or total occlusion of the vessel. Partial occlusion will produce ischaemia and necrosis if it produces inadequate flow to maintain tissue viability downstream, as

Fig. 3. Progression of vascular occlusion to ischaemia and infarction. ED = Emergency department.

described above. Total occlusion will initially produce ischaemia. This will progress to necrosis if maintained and there is inadequate or no collateral blood supply. The final phase will be organisation of the thrombus and infarcted area with healing by fibrosis (fig. 2).

The consequences of plaque rupture and subsequent vascular occlusion can therefore be divided into three phases. There will be an initial phase of myocardial ischaemia. If prolonged, this will then result in cardiac necrosis. Finally, there will be a phase of repair and vascular remodelling. This is illustrated schematically in figure 3. There are serum cardiac biomarkers that can be utilised at each phase of the process. This article will provide an overview of current markers of myocardial ischaemia, necrosis and dysfunction and discuss the reasons why biomarker measurements are now incorporated within documents produced by the American College of Cardiology and European Cardiac Society for the diagnosis and management of suspected ACS and acute myocardial infarction (AMI).

Biomarkers of Myocardial Ischaemia

The detection of ischaemia prior to infarction represents a diagnostic and therapeutic challenge. In theory, if ischaemia can be detected prior to progression to necrosis, it may be possible to intervene earlier than at present to either limit or prevent myocardial damage. Three markers of ischaemia have been studied, choline, unbound free fatty acids (FFAu) and ischaemia-modified albumin (IMA®).

Choline

Choline is released by cleavage of membrane phospholipids by phospholipase D to yield plasma choline. It has been shown experimentally that phospholipase activation occurs in a number of processes thought to be involved in plaque destabilisation [6]. Macrophages in plaques produce phospholipase. Ischaemic membrane damage also produces phospholipid breakdown. Both of these processes could result in choline release into the

plasma. Plasma choline is subsequently taken up by erythrocytes via a choline transporter [7, 8]. Choline release is believed to occur very early during ischaemia.

Measurement of whole blood choline experimentally by proton magnetic resonance spectroscopy and subsequently by HPLC-mass spectrometry of whole blood samples first demonstrated increased whole blood choline in ACS. Measurement of whole blood choline on admission ($n = 357$) alone or in combination with troponin measurement was found to be a marker of major adverse cardiac events (MACE) at the 30-day follow-up [9]. Measurement of whole blood choline was not a good marker for a subsequent diagnosis of AMI but did distinguish between high- and low-risk patients without AMI (sensitivity 86.4%, specificity 86.2%). The limitation of this technique is the methodology. HPLC-mass spectrometry is not available as a routine diagnostic procedure. Until methods suitable for routine clinical use are developed, it will not be possible to evaluate the value of whole blood choline measurements.

Unbound Free Fatty Acids

Ischaemia is associated with the release of free fatty acids (FFA) from muscle tissue, especially cardiac muscle. The majority of FFA are bound to albumin but a small amount of FFAu are found in the serum [10]. FFAu can be measured using the fluorescent probe, acrylodan intestinal fatty acid-binding protein. Using angioplasty as a model of ischaemia, a significant rise in FFAu following balloon inflation was demonstrated in 22 patients when measurements were performed 5 min before and 30 min after procedure [11]. Accompanying ST segment changes in the electrocardiogram (ECG) occurred in only 11 of the patients but was associated with the highest FFAu values.

Early measurements of FFAu were studied in the thrombolysis in myocardial infarction II study. Diagnostic sensitivity of measurements for a final diagnosis of AMI was 91% on admission and 98% at 50 min after admission [6]. Unfortunately, this study enrolled patients with ST segment elevation myocardial infarction (STEMI), so studied a group where biochemical diagnosis is not required and where the prior probability of AMI is 100% [12]. The value of this marker must be considered unproven until studies are performed in representative populations. A recombinant form of acrylodan intestinal fatty acid binding protein has been developed. Fatty acid-binding results in displacement of the fluorescent tag and can be detected fluorimetrically. A point of care test incorporating this technology has been developed but as yet no clinical data has been presented [6].

Ischaemia-Modified Albumin

Myocardial ischaemia results in acidosis, generation of free radicals and release of free copper and zinc [13–15]. The N-terminus of albumin is known to bind not only transition metals such as cobalt II, nickel II and copper II ions [16] but also to be susceptible to biochemical degradation [17]. This has led to the observation that ischaemia resulted in a reduced ability of albumin to bind cobalt. This is the basis of the albumin cobalt binding test (ACB® test) for IMA [18, 19]. A measured amount of cobalt is added to the test sample and the amount of unbound cobalt is detected colourimetrically following addition of dithiothreitol. The amount of unbound cobalt is directly proportional to the amount of IMA.

It has been demonstrated that the N-terminus is the cobalt binding site and that modification of the N-terminus affects cobalt binding [20]. The postulated mechanism is therefore free radical generation with damage to the N-terminus to generate IMA. The N-terminal sequence analysis of the albumin in samples which tested positive for ischaemia by the ACB test did not show any sequence changes [21]. Ischaemia did not produce an alteration of the N-terminal sequence, although it did reduce the ability to bind cobalt. The mechanism of IMA generation therefore remains unexplained at this time.

Studies of the role of IMA have concentrated on its ability to predict a final diagnosis of AMI. Utilising the first-generation ACB test admission measurements of IMA have shown sensitivity of 39.1% ($n = 299$) [22] to 83% ($n = 256$) [23]. When a non-commercial test was used, the sensitivity was 94% ($n = 163$) for a final diagnosis of ischaemia, but the test had poor predictive power in discriminating between patients with or without AMI [21].

Studies using the second-generation of the assay have defined the kinetics of IMA release. Using balloon angioplasty as a model, a distinct rise and fall in IMA can be demonstrated following coronary artery occlusion with values peaking soon after ischaemia, decreasing by 6 h and returning to normal at 24 h from occlusion [24]. The magnitude of elevation is related to the degree of induced ischaemia, as there is correlation with duration and number of balloon inflations and the magnitude of collateral blood flow [25, 26]. In patients undergoing cardioversion, IMA elevation occurs and the magnitude of elevation correlates to ECG evidence of ischaemia [27].

The role of IMA measurement is in combination with other tests for rule in or rule out of AMI. The ACB test has been evaluated in patients presenting to the emergency department with chest pain suggesting ACS. Diag-

nostic sensitivity for a final diagnosis of AMI has been reported at 95% (n = 208) [28] and 100% (n = 538) [29] for the combination of ECG, cardiac troponin T (cTnT) and IMA on admission. A recently published meta-analysis of IMA as a rule out test showed a negative predictive value of 94.4–97.1% [30].

Two problems remain to be resolved with IMA. The first is the exact mechanism by which IMA is formed and its relationship to the underlying pathophysiology of ischaemia. The second is the assay format. Very low albumin levels [31] and co-incident lactic acidosis affect assay performance [32] and samples need to be analysed rapidly. IMA currently remains the only ischaemia assay to reach the clinical validation stage.

Interpreting clinical studies of ischaemia markers is challenging. There is the problem of the test population. This is a common feature in evaluation studies of cardiac biomarkers. The majority of published studies have utilised a clinical trial sample bank. The exclusion criteria for trial entry result in the elimination of patients with potentially confounding clinical conditions as well as raising the probability of pre-existing cardiac disease, often to 100%. A particular problem in studying myocardial ischaemia is the lack of a reference diagnostic test for myocardial ischaemia itself. An analogy is the initial evaluation of troponin testing where specificity was apparently poor. This was not due to the test itself but because the reference method for diagnosis of myocardial infarction, creatine kinase MB isoenzyme (CK-MB), was insufficiently sensitive [33]. The use of outcome measures as an independent reference standard is one way of solving this problem, as was shown for cardiac troponin. It is interesting to note that an elevated IMA appears to also be an outcome predictor.

Biomarkers of Necrosis

The measurement of cardiac troponin is now considered the 'gold standard' test for myocardial necrosis. Although there may be a role for measurement of cytosolic markers such as myoglobin and CK-MB, cTnT and cardiac troponin I (cTnI) measurement are the final arbiters for a diagnosis of AMI [34, 35]. The reason for the dominant position of troponin measurement is due to the sensitivity and specificity of the test and the evidence base for outcome prediction.

The sensitivity of any testing modality is dependent on the discrimination that can be achieved between the normal and abnormal state. This is determined by the background level of signal in the normal state, the back-

ground noise, and the change of level in the signal in the abnormal state. This is referred to as the signal to noise ratio. Currently with cardiac troponins, the background level in the circulation appears to be determined by the detection limit of the assay. Although there may be a background level of cardiac troponin in the circulation, this is undetectable in the majority of cases by the assays currently commercially available. The cardiac troponins are found only in cardiac tissue. Elevation occurs only where there is myocardial damage. The combination of low background with cardiospecificity means that although in absolute terms the amount of cardiac troponin released is less than the amount of CK-MB, the ability to detect it is much greater, the signal to noise ratio is much higher.

Clinical studies of cardiac troponin have consistently shown that elevations do not occur where there is pure skeletal muscle trauma [36, 37]. Initial reports suggested that cardiac troponin could be detected when there was skeletal muscle regeneration [38]. A series of studies subsequently demonstrated that there is no evidence for expression of cardiac isoforms either at the protein [39–41] or mRNA level [42]. The early reports represented methodological problems with the techniques used [43–45].

Cardiac troponins are detectable in the serum within 3–4 h of myocardial damage and remain detectable for up to 5 days for cTnI and 10 days for cTnT. Troponin biochemistry and measurement methodology has been reviewed in detail elsewhere [46]. Measurement technology for cTnT is supplied by only one manufacturer. Measurement of cTnI is available on a range of platforms from different manufacturers. These methods do not produce numerically similar results.

Clinical studies of troponin have concentrated on the diagnostic and prognostic utility of testing. Initial studies on cTnT showed that troponin could be detected in a significant proportion of patients who were classed as having unstable angina using the conventional WHO criteria for myocardial infarction. In these studies, both short-term and long-term follow-up showed that an elevated troponin was associated with an increased rate of MACE [47, 48]. Despite methodological differences between the cTnI methods, a similar series of studies for the different cTnI methods has also shown that cTnI elevation predicts MACE in patients with unstable angina [49–52]. It is notable that there has not been a single study in the acute ACS population that has failed to demonstrate that cTnT or cTnI elevation in patients with unstable angina predicts MACE. This has been confirmed in a series of meta-analyses [53–55].

Fig. 4. Relationship between WHO and European Society of Cardiology/American College of Cardiology definition of myocardial infarction.

The superiority of cTnT and cTnI measurement has led to their being proposed as the recommended 'gold standard' test for detection of myocardial infarction. The use of cTnT and cTnI results in approximately 33% of patients previously classified as unstable angina being reclassified as AMI. The relationship between the WHO and new classification is indicated schematically in figure 4.

The three mechanisms by which troponin release can occur in ACS were described above, necrosis from partial or total vascular occlusion and platelet emboli. Troponin released into the circulation appears to be stable, although there is loss of some N-terminal and C-terminal immunoreactivity [46]. It has been suggested that there may be intracellular degradation of troponin prior to release [56]. Intracellular degradation may occur during ischaemia, prior to infarction [57]. This question is currently unresolved. Whilst intracellular degradation does occur during infarction, the majority of troponin released following myocyte necrosis is as the intact troponin molecule.

The clinical role of cardiac troponin measurement can be divided into three clinical categories based on the presenting ECG and clinical assessment of the patient. These are: patients presenting with ST elevation on the ECG who have a presumed diagnosis of STEMI; patients with questionable ACS at high risk of non-ST elevation myocardial infarction (NSTEMI) and patients with questionable ACS at low risk of NSTEMI.

Patients Presenting with STEMI

In patients with a presumptive diagnosis of STEMI, management is aimed at establishing patency of the acutely occluded vessel by primary percutaneous intervention (PCI) or thrombolysis. There is no role for cardiac troponin measurement in the initial management of this group. Studies have shown that an elevated cardiac troponin at first presentation identifies a high-risk group [58, 59]. The role of cardiac troponin measurement in STEMI is to confirm the final diagnosis. ST elevation on the ECG is not 100% specific in routine clinical practice [60]. Troponin measurement will also provide quantification of damage [61, 62]. It can be shown that cardiac troponin measurements allow prediction of ejection fraction [63–66] and so quantification of infarct size [67].

Patients Presenting without ST Elevation Considered at High Risk of ACS

Patients presenting with high-risk questionable ACS require confirmation or exclusion of NSTEMI and risk stratification. Patients can be categorised into those who are troponin positive on admission, positive 12–24 h after admission or who are negative on admission and remain negative at 12–24 h from admission. The most important practical use of troponin measurement is for rule out. An undetectable cTnT or cTnI when measured 12–24 h from admission means that NSTEMI is excluded. The patient is at low risk and can be considered for hospital discharge. A negative troponin result does not rule out a flow limiting stenosis. Further investigation by either stress testing [68] or perfusion scanning is required [69, 70]. The combination of a negative exercise stress test plus a negative troponin has an excellent negative predictive value and identifies a very-low-risk population.

A number of studies in ACS populations have shown that the presence of detectable cTnT and cTnI can be used to identify high-risk patients who will benefit from interventions [71]. This includes response to low-molecular-weight heparins [72], glycoprotein IIb/IIIa antagonists [73] and revascularisation [74]. This has led to the incorporation of troponin measurement into management guidelines [75, 76].

Patients Presenting without ST Elevation Considered at Low Risk of ACS

In the low-risk chest pain population, the prior probability of disease is low and a strategy of earlier biomarker measurement can be used. The currently recommended strategy is to measure multiple biomarkers, usually a combination of CK-MB, myoglobin and cardiac troponin.

nin. Sensitivity can be further enhanced by using the rate of change of biomarkers in addition to the absolute value. Well-validated protocols using the combination of CK-MB and troponin testing over a 6-hour period following admission have been shown to be clinically safe and cost-effective [77, 78]. Alternative strategies have been proposed utilising shorter sampling intervals. Measurement of cTnI, CK-MB and myoglobin on admission and 90 min from admission has been studied [79]. This strategy, although demonstrated to be diagnostically accurate, is not backed up by any clinical trial evidence. The most usual protocol is to take a sample on admission and 6–9 h later. Patients who test negative for biomarkers should then be followed up by stress testing or perfusion imaging. Protocols based on troponin alone have been evaluated and are equally diagnostically efficient [80]. The advent of more sensitive troponin assays will accelerate this trend. Protocols based on troponin measurement alone can be expected to replace the use of myoglobin and CK-MB for the early rule out of myocardial infarction in the low-risk patient group.

Elevation of Cardiac Troponins without ACS

Cardiac troponins are sensitive and specific markers of myocardial damage. AMI is not the only cause of cardiac damage. Elevation of cardiac troponin occurs in a range of other conditions associated with non-ACS cardiac damage. These elevations carry prognostic significance. Three situations where there is troponin elevation deserve special comment, renal failure, PCI and drug-induced cardiotoxicity.

Renal Failure

Troponin elevation is common in patients with renal failure. This was originally described only for cTnT [81]. It was suggested that this represented an analytical false positive. Subsequent studies showed that both cTnT and cTnI are elevated in patients with renal failure [82]. A number of studies have confirmed that elevations of cTnT and cTnI are common in renal failure and that they are prognostic [83]. This has been confirmed by meta-analysis [84]. In a detailed study, 121 patients with end-stage renal disease selected for renal transplantation were investigated. All patients underwent coronary angiography as well as detailed biochemical assessment and dobutamine stress echocardiography. Elevated cTnT did not predict the presence of coronary artery disease but did predict survival. An abnormal dobutamine stress echo

indicative of global dysfunction was associated with increased cTnT and an adverse outcome [85]. In patients with end-stage renal failure undergoing haemodialysis, troponin elevation is prognostic and related not to coronary artery disease but to evidence of global cardiac damage [86].

Percutaneous Intervention

The release of biomarkers following PCI was first described in 1985 but has been the subject of continuing investigation. There have been reports from over 60 studies, with the incidence of elevated biomarkers ranging from 0 to 69% depending on biomarker and cut-off. For cTnT it is 7–69% and for cTnI 5–53% [87]. Cardiac magnetic resonance imaging has demonstrated that elevations of both CK-MB [88] and cTnI [89] can be directly related to evidence of myocardial necrosis. The relationship of this biomarker elevation to outcome thereafter is a matter of contention [90, 91].

There is an extensive literature on CK-MB elevation and a smaller literature on elevation of cTnT and cTnI [62–94]. The literature on CK-MB elevation is not consistent. There has been debate as to whether or not CK-MB elevation does predict an adverse outcome after PCI. A meta-analysis has shown incremental increase in risk of long-term mortality according to degree of CK-MB elevation [92]. A large study compared patients undergoing PCI with those having medical management alone. It was shown that an elevated CK-MB after PCI conveyed the same relative risk of death as spontaneous CK-MB elevation in the non-PCI group. However, the absolute risk of death was lower in the post-PCI group [86]. The data for cardiac troponin are even less certain. Even when CK-MB elevation has occurred, troponin elevation may not be predictive [93]. In a recent study of 2,352 patients undergoing angioplasty it was found that post-angioplasty elevation of cTnT was of prognostic significance only in patients with detectable cTnT before PCI was undertaken [94].

Elevations of cTnT and cTnI, like CK-MB, do occur after PCI but are not major predictors of adverse outcomes. It is likely that a range of other factors including reason for PCI (urgent vs. elective), lesion complexity, aspirin resistance and co-incident therapy are the major determinants of subsequent events [87]. Two patterns of myocardial damage associated with post-PCI troponin elevation have been described, type 1 and type 2. In type 1 pattern there is damage in proximity to the target lesion. This is probably due to side branch occlusion, although damage to small vessels in proximity to the site of

balloon inflation is possible. In type 2 pattern there is damage to the distal perfusion territory of the treated artery. This is due to microparticles, plaque debris and thrombus dislodged by the procedure causing micro-vascular plugging, platelet and neutrophil activation as well as the neurohormonal systemic effects of the procedure [87]. The type of damage is therefore not the same as that seen in AMI but represents a distinct type of secondary ischaemic cardiac injury, peri-procedural injury.

Drug-Induced Cardiotoxicity

The release of cardiac troponins following drug therapy is of considerable interest for diagnosis, monitoring and drug safety studies. The release of cardiac troponins following cocaine ingestion has been documented and could potentially be a cause of diagnostic confusion in patients presenting with chest pain [95, 96]. Non-invasive cardiac imaging demonstrates that this troponin release correlates with evidence of myocardial damage. Elevation is most extreme when associated with coronary artery disease probably due to the cocaine-induced coronary vasospasm [97]. Troponin release has been documented in response to a number of toxins and cytotoxic drugs [98]. This has been most extensively studied in respect of chemotherapy with anthracyclines. A number of studies have shown elevation of both cTnT [99] and cTnI [100]. These elevations have been shown to be of prognostic significance. It has been suggested that cytotoxic dosing should be modified if there is evidence of cardiac damage indicated by troponin release. Strategies to minimise troponin release following chemotherapy are currently being investigated. Measurement of natriuretic peptides may prove to be a better strategy in this group.

Summary

The redefinition of myocardial infarction requires a rise and fall in troponin in the presence of a clinical suspicion of coronary artery disease. The original document also proposed this in the context of PCI. There is a quantitative difference between the troponin release after PCI and that seen in the context of ACS. It is therefore reasonable to consider this as a different type of injury. Troponin release due to myocardial damage can be divided into three categories [101]. Troponin release occurs due to primary ischaemic cardiac injury when there

is troponin damage in the context of a ruptured plaque. Troponin release can also occur due to secondary ischaemic cardiac injury where ischaemia is the underlying cause but primary plaque rupture does not occur. Finally, there can be non-ischaemic cardiac injury where the cause is due to direct cardiac damage. The mechanism of troponin release in secondary ischaemic cardiac injury will be a combination of direct vascular occlusion and supply-demand mismatch, with the balance between the two components dependant on the underlying cause. The troponin elevations of non-ischaemic cardiac injury will arise in any condition where there is direct damage to the myocardial vasculature or the myocardium due to the underlying disease process. Examples are given in table 1.

Biomarkers of Cardiac Dysfunction

Four types of natriuretic peptide have been described: atrial, B-type, C-type and D-type. Atrial natriuretic peptide is produced by the atria of the heart in response to acute volume changes. B-type natriuretic peptide (BNP) is secreted predominantly by the ventricular wall myocytes in response to increased ventricular stretch. It is an unusual hormone, as it is not stored to any major extent but is under constant transcription and translation. Translation of mRNA produces a prohormone which is then cleaved by corin (fig. 5) to yield the active portion of the molecule, BNP and the N-terminal portion of the hormone, NTproBNP. C-type natriuretic peptide is produced by the endothelium. A D-type natriuretic peptide has been found in the venom of the green mamba (genus *Dendroaspis*), but whether there is a physiological equivalent in man remains to be definitively shown. Clinical studies have focused on the use of BNP and NTproBNP measurements.

The measurement of natriuretic peptides is not new, with demonstration of increased levels of BNP and NTproBNP reported over 10 years ago [102]. The difference is that assays are now available on high-throughput automated immunoassay platforms permitting their use in routine clinical practice [103–106]. The only major difference between measurement of BNP and NTproBNP is the superior sample stability of NTproBNP, which may make it a more suitable test for primary-care applications. Recommendations for the quality specifications of these assays have recently been produced [107].

Cardiac failure is an increasing public health problem with rising incidence and poor survival [108]. It has been

Table 1. Secondary ischaemic and non-ischaemic causes of cardiac injury

<i>Primary ischaemic cardiac injury</i>		
Thrombotic coronary artery occlusion due to platelets/fibrin	STEMI	
	NSTEMI (non-Q-wave MI plus cTn-positive unstable angina)	
<i>Secondary ischaemic cardiac injury</i>		
Coronary intervention	primary PTCA	distal embolisation from atheroma or debris
	elective PTCA	side branch occlusion
	CABG	distal embolisation or debris
		side branch occlusion
		global ischaemia from inadequate perfusion, myocardial cell production of anoxia
Sympathomimetics	cocaine abuse	
	catecholamine storm	head injury, stroke, intracerebral bleeding
Pulmonary embolus	presumed right heart strain or hypoxia	
Coronary artery spasm	in Japan – up to 10% of admissions for chest pain	
Coronary artery embolisation	clot	
	air	
	CABG	
Coronary artery inflammation with microvascular occlusion	vasculitides	
	connective tissue damage (e.g. Pompe's disease)	
	systemic lupus erythematosus	
End-stage renal failure	severer coronary artery disease, but 50% end-stage renal disease patients have normal coronaries	
Rhythm disorders	prolonged tachycardia or bradycardia with ischaemic heart disease	
Acute heart failure	only if due to ischaemic heart disease	
Direct coronary trauma		
Extreme endurance exercise	extreme marathons	wall motion abnormalities
	extreme training	cTn-positive deaths presumed due to extreme oxygen debt producing ischaemia
<i>Non-ischaemic cardiac injury</i>		
Known causes of myocarditis	infection	bacterial or viral
		rheumatic myocarditis
		septic shock
		acute pericarditis
	inflammation	
	autoimmune	polymyositis
		scleroderma
		sarcoidosis
	drug-induced	alcohol
		cocaine abuse
		chemotherapy
	toxins	snake, puffer fish envenomation
Cardiac trauma	direct	road traffic accident
		stabbing
	cardiac surgery	
Metabolic/toxic	renal failure	
	multiple organ failure	
PTCA = Percutaneous transluminal coronary angioplasty; CABG = coronary artery bypass grafting.

Fig. 5. Secretion of B-type natriuretic peptide.

estimated that the median survival from time of diagnosis may be as little as 3.2 years [109]. Measurements of NTproBNP and BNP can be used in a number of different clinical situations for the diagnosis of suspected cardiac failure.

Detection of Chronic Ventricular Dysfunction in Primary-Care Patients

The clinical detection of cardiac failure is known to be difficult. It has been estimated that between 30 and 60% of referrals from primary to secondary care with a diagnosis of presumed cardiac failure are incorrect. Anything which could be used to refine the initial assessment of the patient prior to referral to raise the probability of a correct diagnosis is therefore of interest. Studies have been undertaken to evaluate the potential of measurement of BNP/NTproBNP in primary care as an initial test to exclude a diagnosis of heart failure. The results of these studies evaluated test performance by receiver-operating characteristic (ROC) curve analysis. They reported areas under the ROC curve in the range 0.85–0.95 depending on the population studied [110–

116]. Negative predictive values of 95–100% were obtained. Outcome studies in primary care showed that an elevated BNP/NTproBNP predicts risk of admission with heart failure as well as risk of death [116]. In a study of 1,205 asymptomatic patients in primary care, measurement of NTproBNP allowed exclusion of a range of cardiac abnormalities including systolic and diastolic dysfunction [117]. It has been suggested that BNP/NTproBNP measurement should be used as the 'gold standard' test for ventricular dysfunction.

There is increasing evidence that BNP/NTproBNP has a role in selection and monitoring therapy in patients with heart failure. Studies have shown that, like cTnT and cTnI in ACS, BNP/NTproBNP measurement can be used to predict which patients will respond to beta blockers such as carvedilol [118]. In the large Valsartan Heart Failure Trial [119, 120], a prospective randomised controlled trial of valsartan versus placebo ($n = 4,284$ patients), measurement of BNP on trial enrolment and reduction of BNP during treatment predicted outcome. There has been one small randomised controlled trial ($n = 69$) comparing treatment based on BNP with treatment based on

Table 2. Role of current serum cardiac biomarkers

ECG change	ST elevation	No ST elevation	No ST elevation	No ST elevation
Probability of ischaemic heart disease	high	high	medium-low	very low
Ischaemia markers	clinical role currently unproven		possible rule out role, further studies awaited	
Cardiac troponin	audit of diagnosis infarct size	selection for intervention exclusion of AMI	exclusion of AMI alteration of treatment	exclusion of AMI
Natriuretic peptides	no acute role		evaluation of acute dyspnoea only	

clinical assessment. Those randomised to BNP-based management had significantly less cardiovascular events, heart failure or death [121]. Further trials are underway and are due to report.

Detection of Acute Heart Failure in the Emergency Department

Even for hospital physicians, the differential diagnosis of a patient presenting with acute shortness of breath remains challenging. The role of the type of natriuretic peptide for differential diagnosis in this group of patients has been studied. Measurement of BNP/NTproBNP in patients presenting to the emergency department has been shown to be diagnostically efficient compared to an adjudicated final diagnosis of cardiac failure. BNP measurement had an area under the ROC curve in ROC curve analysis of 0.91 (n = 1,586) [122] and a similar study with NTproBNP showed areas under the ROC curve from 0.86 to 0.99 (n = 1,256) depending on the age of the patient [123, 124]. In a prospective randomised trial of diagnosis based on BNP with conventional clinical diagnosis in 452 patients, the diagnostic pathway including BNP produced reduction in hospital stay, stay in intensive care and lower cost but equivalent mortality [125].

The role of BNP/NTproBNP in patients presenting with ACS remains more uncertain. Studies have shown that measurement of BNP/NTproBNP on admission in both selected and unselected ACS patients can be used to predict outcome. This can be using BNP/NTproBNP measurement alone or in combination with other markers [126–129]. BNP/NTproBNP measurements have been combined with other biomarkers including CRP and cardiac troponin [127] or cardiac troponin alone [128]. Measurements of NTproBNP/BNP provide additive information under these circumstances, with the worst prognosis

seen when the greatest number of biomarkers are elevated.

Caution must be exercised before advocating the routine measurement of BNP/NTproBNP in ACS patients. There is no data, observational or trial-based, that shows how knowledge of BNP/NTproBNP value can be used to alter management or outcome. In addition, in a large study of 6,809 patients enrolled in a large clinical trial (GUSTO IV), different biomarkers could be shown to predict different outcomes. Measurement of cTnT was an excellent predictor of subsequent AMI, whereas NTproBNP was not. Conversely, NTproBNP was the best outcome predictor for subsequent death [130]. Further studies are required to define the role of BNP/NTproBNP in ACS.

Conclusion: Current Role of Serum Cardiac Biomarkers in Routine Clinical Practice

The roles of cTnT and cTnI are well established in the diagnosis and management of patients with questionable ACS. The clinician needs to remember that although both sensitive and specific for cardiomyocyte damage, AMI remains a clinical diagnosis to which cTnT and cTnI measurements contribute but are not the only feature. Both cTnT and cTnI can be elevated in a number of other clinical conditions, with and without a background of underlying atheromatous disease. Ischaemia markers are promising but further work is required because of the problems of specificity and the reference diagnostic standard. Measurement of BNP/NTproBNP has a well-defined place in the detection of acute or chronic cardiac dysfunction, but the role in ACS remains to be clarified. The roles of all these markers are summarised in table 2.

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