Cardiorenal Syndrome Type 4: Insights on Clinical Presentation and Pathophysiology from the Eleventh Consensus Conference of the Acute Dialysis Quality Initiative (ADQI)

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Abstract

In developed countries, the continuing rise in the prevalence of hypertension, hyperlipidemia and diabetes has contributed to an overall increase in the incidence of both cardiovascular disease (CVD) and chronic kidney disease (CKD). The observation that even modest reductions in renal function correlate with increased CVD morbidity and mortality has led to the recognition that CKD is an independent risk factor for CVD. Conversely, there is a growing recognition that many pathologic conditions that contribute to CVD, including coronary artery disease, left ventricular hypertrophy and diastolic dysfunction, can accelerate the decline in renal function. In addition, physiologic mechanisms designed to compensate for reduced glomerular filtration rate including activation of the

ADQI 11 Workgroup members are listed in Appendix 2.

renin-angiotensin-aldosterone axis, the release of fibroblastic growth factor 23 and other mechanisms for calcium-phosphate homeostasis as well as and the pathophysiologic effects of uremic toxins can also directly contribute to CVD. The end result of the interaction between changes in pressure and volume overload and the physiologic compensation for the loss of function in both the heart and the kidney leads to accelerated decline in both organ systems. This complex physiologic and pathophysiologic interplay between the cardiovascular and renal systems is collectively referred to as the cardiorenal syndrome. The discussion which follows is aimed at outlining the pathophysiologic mechanisms linking advanced CKD (4 and 5) to the development of cardiac abnormalities which occur with unique frequency and severity in patients with severe impairment of renal function.

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Epidemiology of Cardiovascular Disease in Chronic Kidney Disease

The rising prevalence of chronic kidney disease (CKD) and end-stage renal disease (ESRD) is a global medical and epidemiological problem [1]. In the United States it is estimated that up to 13% of the population (30 million people) have CKD. A growing body of evidence shows that declining renal function is an independent risk for cardiovascular disease (CVD). Patients with CKD are at higher risk for death following myocardial infarction and patients experiencing even transient renal dysfunction have increased long-term risk for CVD [1, 2].

While the mechanisms leading to increased risks for cardiovascular complications among CKD patients are not fully known, there is a growing awareness of the interdependence between these two organ systems. The renal response to impaired glomerular filtration rate (GFR) can lead to activation of multiple compensatory pathways including upregulation of the renin-angiotensin-aldosterone axis (RAAS) and sympathetic nervous system as well as activation of the calcium-parathyroid axis. These physiologic responses can be due to underlying diseases such as hypertension or diabetes or can be a response to the functional decline of either the heart or the kidney. The loss of renal mass leads to the accumulation of total body sodium and water with the subsequent stimulation of angiotensin and aldosterone production. The resulting hypertension coupled with direct effects of angiotensin and aldosterone on cardiac myocytes accelerates left ventricular hypertrophy (LVH) and cardiac fibrosis. The cardiorenal syndrome collectively describes the complex interactions between the physiologic and pathophysiologic consequences of declining function in both the heart and the kidney. The ADQI group has created separate classifications for the cardiorenal syndrome in an attempt to isolate some of the unique pathophysiologic mechanisms of this disorder with the intent to devise new strategies of treatment [3].

Coronary Atherosclerotic Heart Disease and Chronic Kidney Disease

Numerous epidemiologic and clinical studies have documented the association between even modest reductions in renal function and the increased risk for cardiovascular death. While there is a clear inverse association between reduced GFR and cardiovascular morbidity, the mechanisms that lead to an increased incidence of CVD following the onset of CKD are poorly understood. Patients with CKD have increased rates of atherosclerotic coronary artery disease (CAD), myocardial infarctions, LVH, and have an increased risk for sudden death. Longitudinal studies demonstrate that the risk for cardiovascular complications increases with progressive loss of renal function. The risks for cardiovascular complications for patients with eGFRs <30 ml/min/1.73 m² are up to 10-fold higher than those with eGFRs >60 ml/min/1.73 m² [4]. This startling prevalence of CVD complications exceeds the risk expected from typical cardiovascular risk factors (hypertension, hyperlipidemia, etc.) and suggests that the loss of renal function may directly contribute to the development of cardiovascular complications [5–7]. Small limited studies suggest that patients with early as well as late stage CKD have a higher prevalence of angiographically significant CAD. For example, Joki et al. [8] performed coronary angiography in 24 pre-dialysis ESRD patients in order to determine the prevalence and severity of coronary disease. When clinically significant coronary disease was defined as greater than 75% of one or more coronary vessels, Joki et al. found that 73% of symptomatic and 54% of asymptomatic CKD stage V patients had significant CAD. Moreover, these patients were more likely to have multivessel disease and ECG evidence of prior of ischemia. The high prevalence of CAD among asymptomatic CKD patients has been noted by other investigators. Ohtake et al. [9] performed coronary angiograms in 30 asymptomatic and 39 symptomatic CKD patients and found that 53% of asymptomatic patients had significant CAD. Of these patients, 10 (62.5%) had single-vessel disease, 4 (25%) had two-vessel disease, and 2 (12.5%) had triple-vessel disease. Moreover, 31% of these patients had greater than 90% luminal narrowing. It is also interesting to note that when stress nuclear cardiac scintigraphy was performed in these patients only 40% were found to have significant perfusion defects. This finding raised the question of whether stress nuclear cardiac scintigraphy is the appropriate method for CAD screening within the CKD population [9, 10]. A recent analysis from the Cochrane investigators demonstrated that the best accuracy for non-invasive screening for CAD in renal transplant candidates is achieved with dobutamine stress echocardiography [11]. To determine whether increased rates of CAD are also present in patients with less advanced CKD, Chonchol et al. [12] reviewed the cardiac catheterization studies in 261 patients with eGFR between 30 and 90

ml/min. Despite having relative preserved renal function, 51% of patients with eGFR >90 ml/min had a 70% stenosis in at least one coronary artery. In contrast, more than 84% patients with advanced renal disease (eGFR <30) were found to have significant CAD. Moreover, patients with advanced CKD were more likely to have significant left main and multivessel disease. These observations were supported by Charytan et al. [13] who also noted that compared to normal controls, patients with CKD and acute coronary syndrome were more likely to have atherosclerotic obstructions in the proximal portion of the coronary arteries [14].

Accelerated Coronary Calcification, Myocardial Calcification, and Reduced Aortic Compliance in CKD

The prevalence of atherosclerotic heart disease among CKD/ESRD patients is not sufficient to explain the observed rates of sudden cardiac death and cardiovascular complications [15]. While the mechanism(s) linking CKD to the occurrence of CVD events are not fully understood, osteoblastic transformation of vascular smooth muscle cells appears to be a critical component of the pathogenesis of vascular calcification in patients with CKD. There is a growing recognition that altered calcium-phosphate metabolism, impaired vitamin D production and secondary hyperparathyroidism can directly contribute to vascular calcification as a result of their effects on these osteoblastic-like cells. Hydroxyapatite is the principal structural component of bone and is produced by osteoblastic cells in both endothelial atheromata and the vascular media. These pathophysiologic mechanisms are hallmarks of the uremic condition and help to explain the prevalence of vascular calcification among CKD/ESRD patients [16]. The presence of coronary artery calcification is a potent predictor of cardiac events and may contribute to reduced coronary flow reserve observed in CKD/ESRD patients [17, 18]. The risk for developing coronary calcification increases with advancing renal disease. In a study of 119 pre-dialysis CKD patients, Garland et al. [19] quantified coronary calcification using high-resolution, multislice computed tomography and demonstrated that calcification of coronary vessels was detectable as early as CKD stage III. Of the patients studied, 83% had some degree of coronary calcification with a full 32% exhibiting severe disease. Interestingly, the severity and prevalence of calcification did not correlate with the stage of CKD. The development of vascular calcifications is not limited to coronary vessels but has also been detected in peripheral arteries. This observation may explain the higher rates of lower extremity amputations among CKD/ESRD patients [20]. In contrast to non-CKD patients, the quantity

and density of calcium deposits is greater among CKD patients. Recent studies using electron beam scanning and high-resolution computed tomography scans consistently found calcium deposits of several millimeters in depth raising the question of whether calcium deposits are not limited to the intima, but also extend into the vessel media. To investigate this question, Moe et al. [21] examined the inferior epigastric arteries in 41 ESRD patients undergoing renal transplantation and confirmed that arterial calcification was common in the medial layer of the vessel wall. In addition, immunostaining of calcified areas demonstrated the presence of bone matrix proteins including osteopontin, type I collagen and bone sialoprotein. In an autopsy study, Gross et al. [17] compared the distribution of coronary calcification in uremic and non-uremic patients and demonstrated that medial calcification was present in 16% of uremic patients but only 3% of those without renal dysfunction. Interestingly, medial calcification was associated with the presence of bone matrix proteins including osteocalcin as well as markers of chronic inflammation including transforming growth factor- β (TGF- β) and components of activated complement [22].

Increased calcium content of the myocardium has been demonstrated in ESRD patients and may contribute to reduced left ventricular (LV) compliance. It is also possible that disordered movement of calcium and potentially other electrolytes managed by myocytes and conducting tissue is responsible for the variety and prevalence of arrhythmias in CKD and ESRD. Aortic calcification is associated with reduced compliance as demonstrated on multiple studies [23, 24]. Thus, the shear stresses with each systole are greater in patients with CKD and ESRD, and in theory, have greater degrees of end-organ injury due to hypertension compared to those with more compliant vessels [24]. Moreover, even in the absence of epicardial coronary disease, reduced aortic compliance reduces coronary artery perfusion. While the mechanism is not fully understood, a generally accepted mechanistic view is that with falling aortic compliance reflected pulse waves in late systole raise central pressure which induces subendocardial ischemia through reduced diastolic filling [25].

Left Ventricular Hypertrophy and Chronic Kidney Disease

Both LVH and reduced LV function have long been recognized as complications of advanced renal disease. Moreover, the prevalence of LVH increases with declining renal function. Traditional risk factors including hypertension, diabetes mellitus, and volume overload contribute to the development of LVH in CKD populations. The observation that hyperparathyroidism, malnutrition, retained products of uremia and even the delivery of dialysis can contribute to

LVH has raised the question of whether CKD/ESRD populations are uniquely predisposed to the development of CVD. For example, the prevalence of LVH varies from 16 to 31% in individuals with GFR >30 ml/min, increasing to 60–75% prior to starting renal replacement therapy, and up to 90% of patients after the initiation of dialysis [23]. In a prospective study of 433 ESRD patients, Foley et al. [26] noted that 74% of patients had echocardiographic evidence of LVH with over 30% having concurrent LV failure. In a subsequent study, Foley et al. [27] prospectively followed 596 incident hemodialysis patients with no prior history of cardiac disease and determined whether the incidence of LVH correlates with duration of dialysis. Using serial echocardiograms to measure left ventricular mass index (LVMI), Foley et al. demonstrated that after 18 months of dialysis, LVMI increased in 62% patients with 49% developing overt LV failure. These observations raise the question of whether the very process of dialysis facilitates the development of LVH in ESRD patients. However, the more comprehensive and detailed IDEAL study failed to demonstrate that the initiation of dialysis in stage V CKD patients worsened existing LVH, suggesting that dialysis alone does not contribute to LVH nor is it able to reverse long-standing hypertrophic changes [13, 28]. The mechanisms which contribute to the ‘cardiomyopathy of advanced CKD’ are unknown, but a growing body of evidence indicates that retained products of uremia can directly alter cardiac structure. Because many uremic toxins are non-polar and highly protein-bound, their clearance by conventional dialyzers is very limited. These observations suggest that while dialysis itself may not directly contribute to the LVH associated with CKD, its inability to clear specific uremic toxins could indirectly contribute to cardiac remodeling. This is not to say that dialysis cannot alter cardiac function. For example, the elegant work of McIntyre et al. [29] has shown that conventional hemodialysis in children and adults may cause regional myocardial stunning through a mechanism that does not correspond to coronary artery vascular territories. This observation suggests that the wall motion abnormalities observed during dialysis are a form of myocardial stunning and should be considered as a form of non-Takosubo-type stress cardiomyopathy.

The clinical conditions that contribute to the development of LVH in CKD are similar to those occurring in other patient cohorts and include hypertension, pressure overload, and activation of the RAAS. Arteriosclerosis and hypertension promote myocyte hypertrophy which results in an increased LV mass through myocyte hypertrophy, an increased wall thickness and ultimately reduced ventricular compliance. Pathologic adaptations to increasing wall thickness contribute to a loss of capillary density, secondary myocardial fibrosis and further compensatory hypertrophy [30]. Clinical conditions that contribute to

Fig. 1. Declining GFR is associated with multiple stressors upon the CV system including volume/pressure overload, oxidative stress, and activation of the RAAS and neurohumoral pathways. Prior to the initiation of renal replacement therapy, the heart undergoes maladaptive responses including reduced diastolic compliance, LVH, reduction in myocardial capillary density and uremia-induced myocardial fibrosis. Following the initiation of renal replacement therapy, ‘non-physiologic’ fluid removal worsens myocardial ischemia leading to progressive heart failure and sudden cardiac death.

LVH in the general population such a reduced aortic compliance are often more common and severe in CKD patients. For example, arteriosclerotic changes that reduce aortic compliance in the general population are also present in CKD patients, but other variables including hyperphosphatemia and secondary vascular calcifications can further affect aortic compliance [31]. Moreover, the progressive loss of nephron mass inherent to CKD leads to accumulation of salt and water which secondarily contributes to hypertension and pressure and volume overload. These same conditions contribute to LVH through upregulation of RAAS subsequent release of pro-fibrotic factors such as galectin-3, TGF- β and endogenous cardiac steroids [32]. The unique relationship between CKD and the development of cardiovascular complications is supported by the beneficial effects of renal transplantation on cardiac structure and remodeling (fig. 1, 2).

Fig. 2. Modifiable and non-modifiable variables contribute to the link between CKD and major adverse cardiovascular events. Age and gender are non-modifiable variables, hypertension, correction of dyslipidemia, activation of RAAS and improved clearance of uremic toxins could be modified over time and reduce the prevalence of CRS-4.

For example, Wali et al. [33] studied 138 patients being evaluated for renal transplantation with established LV dysfunction defined as LVEF $\leq 40\%$ that was not correctable by revascularization. Interestingly, 69% of patients demonstrated a post-transplant increase in LVEF from a mean of 32 to 47% at 6 months and 57% 1 year after transplantation. These cardiovascular improvements were also shown to translate into improved patient survival. Patients whose post-transplant LVEF improved to greater than 50% were found to have an all-cause mortality that was 8-fold lower than patients whose LVEF failed to normalize.

Cardiac Myocyte-Capillary Mismatch

A complication of hypertrophic cardiomyopathies is that as cardiac myocytes enlarge, the density of capillaries needed to accommodate the increased oxygen demand is progressively reduced over time. To determine whether this effect is

exacerbated by uremic conditions, Amann et al. [34] compared myocardial capillary density in normal controls with dialysis patients and those with hypertensive cardiomyopathies. While hypertensive patients demonstrated a reduction in capillary density, this decrease was even more pronounced in ESRD patients and nearly 2-fold lower than normal controls. Moreover, myocyte diameter and volume of the interstitial space were significantly increased in uremic patients compared to the other groups. Amann et al. [34] observed that the collagen content of the myocardial interstitium rose to 25% – a value that is observed in patients with severe aortic stenosis and other conditions of pressure overload. Prolonged periods of hemodynamic stress can induce cardiac remodeling which includes the increased expression of interstitial myofibroblasts – a cell type that is not present in normal myocardium and is characterized by its fibrogenic potential. The observation that ESRD patients develop clinically significant reductions in myocardial capillary density raises the question of whether this observed histopathology is unique to the uremic condition [34]. On a clinical level, a reduction in the capillary density of the uremic myocardium may explain in part the exaggerated intolerance of ESRD patients to ischemia as well as the higher prevalence of diastolic dysfunction [35]. The combination of intolerance to myocardial ischemia, LVH, and myocardial fibrosis, coupled with non-physiologic alterations in volume and electrolytes (particularly in CKD-5 hemodialysis patients), renders ESRD patients particularly vulnerable to sudden cardiac death.

Uremia and Cardiac Fibrosis

In addition to hypertrophic changes in the heart, a growing body of evidence suggests that patients with advanced CKD develop a unique form of cardiac and fibrosis [36, 37]. For example, early post-mortem studies by Mall et al. [37] describe a unique form of cardiac and renal fibrosis that was observed in over 90% of CKD patients, but absent in non-uremic controls. Both ESRD patients and those with pre-dialysis CKD demonstrated a uniform pattern of intermyocardial fibrosis which differs from the endocardial to epicardial perivascular fibrosis pattern that is typical of hypertensive and ischemic cardiomyopathies. By light microscopy, trichrome staining and light microscopy consistently demonstrated diffuse interstitial fibrosis, while electron microscopy showed the presence of collagen but an absence of P2-M amyloid protein [37]. Figure 3a is representative of normal myocardium without interstitial fibrosis and a typical myocyte to capillary ratio. Figure 3b is representative of a patient with hypertensive cardiomyopathy. While individual myocytes are hypertrophied, myocar-

Fig. 3. **a** Myocardial biopsy of control patient. Size of myocytes estimated between vessels (red). $\times 200$. **b** Myocardium of hypertensive patient: increased myocyte cross-sectional area; reduced number capillaries per unit area; increased myocardial interstitial tissue. $\times 200$. **c** Myocardium of CKD patient: myocardial cross section markedly increased. Further reduction in myocardial capillary density. Reproduced with permission from [37].

dial fibrosis and capillary density are normal. This is contrasted by cardiac tissue obtained from a patient with CKD (fig. 3c). Of note, there is increased deposition of collagen and other extracellular matrix proteins with an associated reduction in the capillary/myocyte ratio [34]. The mechanisms leading to CKD/ESRD cardiac fibrosis are poorly understood, but recent studies suggest that substances in the plasma of uremic patients' components of uremia plasma including indoxyl sulfate and *p*-cresol can directly contribute to cardiac fibrosis. Indoxyl sulfate and other non-polar uremic toxins are highly protein-bound and thus exhibit very poor clearance by dialysis. While indoxyl sulfate concentrations in healthy subjects range between 1 and 2.9 mM, they can exceed 500 mM in patients with advanced CKD [28]. At these concentrations, indoxyl sulfate directly contributes to the generation of cardiac fibrosis through the synthesis of TGF- β , tissue inhibitor of metalloproteinase-1 (TIMP-1) and $\alpha 1$ collagen. Moreover, protein-bound uremic toxins have been shown to stimulate cardiac remodeling through activation of the p38 MAPK, p42/44 MAPK, and NF- κ B

pathways. These observations underscore the need to identify the clinical consequences of the cardiorenal syndrome and to define the unique physiologic and pathophysiologic interdependence between the two organs [38–40].

Galectin-3 and Cardiac Remodeling

There is an increasing recognition that diastolic dysfunction and other manifestations of decompensated heart failure are associated with myocardial infiltration by macrophages and monocytes. While a number of candidate mediators for these changes have been investigated, recent studies have consistently demonstrated a marked upregulation of galectin-3 [41]. Galectin-3 is a member of the β -galactoside-binding lectin family that is synthesized by macrophages and known to interact with specific extracellular matrix proteins including laminin, synexin and integrins. Pre-clinical studies find that galectin-3 can also bind directly to cardiac fibroblasts and reduced LV function through an increase in collagen production [42]. In a recent study of 232 patients with NYHA class III or IV heart failure, Lok et al. [43] used NT-proBNP and eGFR to adjust for severity of heart disease and degree of renal dysfunction and demonstrated that serum galectin-3 levels were independent predictors of cardiovascular mortality. Moreover, Lin et al. [44] followed 106 patients with NYHA class II heart failure and found a direct correlation between serum galectin-3 levels and markers of chronic inflammation. The observation that galectin-3 levels correlate with type III amino-terminal propeptide of procollagen (PIIINP), MMP-2, and TIMP-1 suggests that myocardial macrophage infiltration enhances turnover of extracellular matrix proteins in patients with established heart failure. Despite the role of infiltrating macrophages in the synthesis of galectin-3, studies have failed to show a correlation between the severity of heart failure and plasma galectin-3 levels. Gopal et al. [45] studied 119 patients with varying degrees of heart failure and failed to correlate galectin-3 levels with LV ejection fraction or level of cardiac function. In contrast, plasma galectin-3 levels are significantly affected by changes in renal clearance. Gopal et al. noted that for patients with an eGFR <30 ml/min, plasma galectin-3 levels can be 2-fold higher than normal controls.

Fibroblast Growth Factor 23

The link between compensation for falling GFR and the subsequent downstream effects of cardiovascular structure and function is a central component of the cardiorenal syndrome (fig. 4). Recent pre-clinical and clinical studies

Fig. 4. In the kidney and parathyroid glands, FGF23 signaling requires FGFR and the co-receptor klotho. FGF23-klotho binding to FGFR stimulates autophosphorylation of the receptor tyrosine kinase and induces signaling through three major pathways: Ras-MAPK, PI3K-Akt, and PLC-PKC. FGF23 regulates phosphorus balance by altering expression of genes involved in parathyroid, vitamin D, and phosphorus metabolism. In cardiomyocytes, FGF2 signaling requires FGFR and heparan sulfate proteoglycans (HSP) as co-receptor and signals primarily through the Ras-MAPK pathway. Binding of FGF23 to FGFR on cardiomyocytes stimulates autophosphorylation of the receptor tyrosine kinase independent of klotho, which is not expressed in cardiomyocytes, and signals primarily through the PLC-calcineurin pathway. Whether HSP acts as co-receptor remains to be determined. Reproduced with permission from [46].

have shown an association between the family of fibroblast growth factors (FGF) and the development of a pathologic and load-independent form of LVH. The FGFs are a family of peptides with broad biologic functions that include the regulation of growth and differentiation of cardiac myocytes. In contrast to other members of the FGF family, FGF23 has evolved unique paracrine functions in the kidney which facilitate phosphate excretion by blocking the synthesis of vitamin D₃ and inhibition of phosphate resorption in the proximal nephron [46]. The loss of nephron mass and subsequent accumulation of phosphate leads to a compensatory rise in FGF23 levels. While this physiologic com-

pensation serves to maintain calcium-phosphate metabolism, prolonged elevations of FGF23 can contribute to LVH and cardiac remodeling. Recent studies have shown that even modest reductions in GFR can stimulate FGF23 production. Gutiérrez et al. [47] noted that for patients with CKD stage II, FGF23 levels can be 2–5 times above normal values, while levels in ESRD patient are often a 1,000-fold higher than normal controls [48]. In an early attempt to link FGF23 levels development of LVH, Gutiérrez et al. [47] used echocardiography to determine LVMI and coronary artery calcification in 162 patients with CKD. Using multivariable-adjusted regression analysis, the authors noted a 5% rise in LVMI for every log increase in FGF23 levels. Moreover, patients in the highest tertile of FGF23 were found to have a 2.4-fold higher risk for coronary artery calcifications. While the data from this study and others like it were suggestive of a causal role for FGF23 in CVD of CKD patients, the studies were limited by small sample size and cross-sectional design [49]. More recently, Faul et al. [46] utilized a large multicenter prospective study cohort to examine the potential causal relationship between FGF23 and the development of LVH in CKD patients with GFR between 20 and 70 ml/min. In the highest quartile of FGF23, the prevalence of concentric LVH was 49% while evidence of cardiac remodeling was seen in 20% of patients.

Conclusions

The complexity of cardiorenal syndrome (CRS) along with its associated comorbidities poses a significant challenge for the cardiology and nephrology communities. The ADQI group believes that prior to the creation of meaningful options for the prevention and treatment of this disorder, it will be necessary to identify subgroups of CRS patients that are defined by their underlying pathophysiology. We have defined the CRS-4 patients by focusing upon both the primary and compensatory physiologic responses to declining organ function that contributes to clinical phenotype of CRS-4. We highlighted specific clinical characteristics of CRS-4 that are critical to patient diagnosis and clinical management including accelerated coronary disease, cardiac hypertrophy/fibrosis and the direct role of dialysis in cardiovascular outcomes. We propose that CRS-4 is a unique subgroup of the CRS and that by defining this specific group of patients, it will enable the creation of disease-specific therapies.

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