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Type 4 Cardiorenal Syndrome: Myocardial Dysfunction, Fibrosis, and Heart Failure in Patients with Chronic Kidney Disease

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Abstract

Chronic kidney disease manifested by a reduction in glomerular filtration function, albuminuria, or markers of chronic renal injury have been consistently associated with the development of heart failure, heart failure hospitalizations, and cardiac mortality. The principal mechanisms by which the cardiac ventricles ultimately fail include pressure overload, volume overload, and cardiomyopathy. Chronic and acute kidney diseases contribute via these pathways to cardiomyopathic processes that can be visualized as adverse remodeling, systolic and diastolic dysfunction, and now with modern imaging and molecular techniques, myocardial fibrosis. It appears that both within the myocardium and the renal parenchyma, as there is loss of functional tissue, there is the deposition of collagen and other proteins resulting in fibrosis. Once this form of repair is initiated, it appears that it is progressively pathogenic itself leading to worsened cardiorenal syndrome type 4, a viscous cycle initiated by kidney disease and leading to heart failure hospitalizations and death. This paper will explore the complicated pathophysiologic processes involved in this syndrome with the aim of elucidating potential future diagnostic and therapeutic targets.

Keywords: Chronic kidney disease; Heart failure; Cardiac fibrosis; Remodeling; Cardiorenal syndrome; Natriuretic peptide; Galectin-3

Introduction

Chronic Kidney Disease (CKD) is characterized by a decrease in Glomerular Filtration Rate (GFR) due to a loss of functioning nephrons within the kidney and/or proteinuria secondary to break down of the glomerular filtration barrier and incomplete tubular reabsorption. World-wide the prevalence of both CKD and end stage kidney disease is dramatically increasing [1]. In the United States it is estimated that 13% of the population (or 30 million adults) are affected by CKD [2]. Often kidney disease is asymptomatic at first with a gradual or stepwise progression depending on the etiology of kidney injury. It is not until severe or end-stage disease is present are symptoms readily apparent. Therefore renal disease is often identified in its initial stages solely by abnormalities in laboratory testing.

Chronic kidney disease and myocardial dysfunction often occur concurrently. While kidney disease and Heart Failure (HF) share many common risk factors, it is clear that CKD itself places patients at higher risk for cardiovascular disease—most frequently HF [3]. Heart failure is the leading cause of death in patients with CKD [4]. Even mild chronic renal insufficiency has been shown to significantly increase cardiovascular morbidity and mortality [5]. The most common final pathways leading to death are cardiac pump failure or sudden fatal arrhythmias.

End Stage Renal Disease (ESRD) in particular is associated with a 500 fold increase in cardiovascular mortality when compared to matched controls with normal renal function [6]. Smith et al. identified a 7% increase risk of mortality for every 10 ml/min decrease of estimated GFR in patients with HF [7]. Among patients with ESRD approximately 15% have systolic dysfunction, 40% have HF, and 70% have Left Ventricular Hypertrophy (LVH) [8,9]. Chronic kidney disease often complicates the treatment of HF. The Acute Decompensated Heart Failure National Registry (ADHERE) is a database of 105,000 patients in the United States admitted to the hospital for treatment of acutely decompensated HF. Of patients entered into this registry about 1 in every 3 had evidence of renal impairment (21% had serum creatinine concentrations >2.0 mg/dL, 9% had serum creatinine >3.0 mg/dL) [10].

As the kidney begins to fail and the GFR continues to decrease the kidney becomes unable to perform basic physiologic functions. The many physiologic disturbances associated with CKD are, at this time, incompletely understood and likely vary from individual to individual [11]. There are however, several processes that are known to directly or indirectly damage the heart and lead to myocardial dysfunction [12]. In general these processes include hemodynamic derangements such as pressure and volume overload and nonhemodynamic factors that directly promote adverse remodeling. Pressure overload, manifest as initially masked and then measurable systemic hypertension (HTN), results from activation of several neurohormonal systems, various vasoactive substances, sodium retention, and arterial vascular stiffness. Volume overload results from impaired sodium excretion, chronic anemia, and as a consequence of certain vascular access strategies used during hemodialysis. Nonhemodynamic factors that directly induce hypertrophy and fibrosis include cell signaling proteins, neurohormones, and accumulation of a variety of altered structural proteins [13].

To aid in teaching and understanding, the human body is traditionally divided into twelve individual organ systems. In practice, however, all organ systems are intimately related in both structure and function. This is particularly true for the heart and kidney where

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dysfunction in one organ promotes and amplifies dysfunction in the other. It has been described elsewhere how HF leads to deterioration in renal function as type 1 and type 2 cardiorenal syndrome [13,14]. Here we describe the reverse scenario where both hemodynamic and nonhemodynamic factors associated with CKD lead to myocardial damage and worsening HF, termed type 4 cardiorenal syndrome or chronic renocardiac syndrome (Figure 1).

Hemodynamic Interactions

The kidney is the organ primarily responsible for regulating fluid and electrolyte homeostasis. As such the kidney holds a commanding role in determining volume status. Despite large day to day variation in salt and water intake the kidney is able to maintain both a constant total body water content and serum osmolality. Each component of the human kidney evolved to fulfill a specific function. An understanding of these functions allows one to appreciate the consequences of CKD. The glomeruli form as multiple bunches (tufts) of capillaries surrounded by podocytes, together they "filter" plasma by allowing selective permeability based on molecular size and ionic charge of various solutes. Proteins are relatively large and carry a net negative charge so in healthy kidneys few proteins are filtered. The proximal tubule is the main site for reabsorption of filtered solutes. The filtration barrier is a complex structure from the glomerular capillary lumen, charged glycocalyx, fenestrated endothelial cells, basement membrane, and podocytes which form the visceral layer of Bowman's capsule where filtered urine first appears [15]. Approximately 70% of filtered salt and water, 100% of filtered glucose, 60% of calcium and phosphate, and almost all the filtered amino acids are re-absorbed within the proximal tubule. The loop of Henle is responsible for establishing a medullary solute gradient that is utilized by more distal segments in order to concentrate urine and thus excrete urine more concentrated than blood. Active transport of sodium, potassium, and chloride (1Na, K, and 2Cl) ions in the ascending loop establish the osmotic gradient. The distal convoluted tubule contributes to sodium, potassium and therefore water reabsorption. Relatively dilute urine then passes into the collecting ducts which are formed by the confluence of multiple distal convoluted tubules. Collecting ducts have water channels regulated by Antidiuretic Hormone (ADH). ADH secretion increases water permeability of the collecting duct thereby allowing for reabsorption of water from hypotonic urine. By utilizing the medullary concentration gradient established by the loop of Henle, free water is absorbed and hypertonic urine can be formed [16,17].

Pressure Overload

Hypertension is the most common antecedent condition in both CKD and HF [18]. Almost all patients who reach end stage disease suffer are hypertensive; Agarwal et al. found a prevalence of 80% in the United States [19]. Many studies on essential HTN have implicated the kidney's ability to excrete sodium and maintain extracellular fluid volume as key elements in the pathogenesis of systemic HTN. In both rat [20] and human [21,22] models cross transplant of a kidney from a hypertensive donor to a normotensive host results in the development of HTN in the recipient thus implicating the kidney as the culprit [18]. Hypertension in CKD is associated with increased peripheral vascular resistance, major mechanisms responsible for this include activation of neurohormonal systems and increased arterial wall stiffness. These neurohormonal systems include the sympathetic nervous system, the renin-angiotensin-aldosterone system, arginine-vasopressin (or antidiuretic hormone), and endothelin. Elevated peripheral vascular resistance increases cardiac afterload which is the pressure the heart must generate in order to pump blood forward. The LaPlace relationship states that ventricular wall tension is directly proportional to the pressure exerted across the wall and the radius of the ventricle and inversely proportional to wall thickness [23]. Therefore increased pressure across the wall will result in a proportional increase in wall tension. In order to compensate for an increase in ventricular wall tension the wall thickness must increase. Clinically this is evident as ventricular hypertrophy. Like volume overload, chronic pressure overload puts additional stress on the heart, decreases cardiac output, and promotes cardiac remodeling. Chronic activation of neurohormonal systems also directly contributes to ventricular remodeling and hypertrophy.

Both plasma renin activity and angiotensin II concentrations are elevated in the setting of CKD [24]. Angiotensin II increases sodium retention, regulates GFR, potentiates the renal effects of sympathetic nervous system stimulation, and increases release of vasopressin from the posterior pituitary gland and aldosterone from the adrenal cortex. Vasopressin acts on the collecting duct to increase reabsorption of hypotonic water (discussed below). Aldosterone enhances reabsorption of sodium and water thereby expanding extracellular fluid volume. Angiotensin II and Aldosterone both causes systemic arterial vasoconstriction and directly promote cardiac remodeling. The net effect of Renin-Angiotensin-Aldosterone System (RAAS) activation is increased systemic blood pressure via both vasoconstriction and extracellular fluid expansion. Inhibition of the renin-angiotensin-aldosterone system results in blood pressure lowering in hypertensive patients and survival benefit in HF [25].

Renal failure is associated with increased sympathetic nervous system output and elevated circulating levels of catecholamines. Sympathetic overdrive has been demonstrated in both early and advanced stages of kidney disease, with levels that increase with worsening renal function [26]. Sympathetic stimulation results in several physiologic changes that under normal circumstances serve to maintain cardiac output and vascular integrity. In the setting of HF and/or renal failure these compensatory responses worsen cardiac performance. Stimulation of renal adrenergic receptors promotes release of renin from juxtaglomerular cells and reabsorption of sodium from tubular cells. Recent trials have demonstrated significant improvement in systemic HTN with renal autonomic denervation

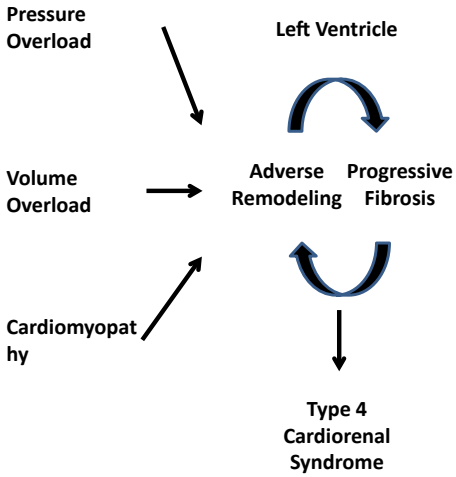

Figure 1: Pathophysiologic mechanisms for the development and progression of type 4 cardiorenal syndrome.

highlighting the importance of this neuroendocrine system at the level of the kidneys [27].

Arginine Vasopressin (AVP) is a peptide hormone produced in the hypothalamus and secreted from the posterior lobe of the pituitary gland. Release of AVP is regulated by osmoreceptors in the hypothalamus and baroreceptors located in the carotid arteries, aortic arch, and atria. It exerts its physiologic effects via interaction with two distinct receptors: the V_1 and V_2 receptors. The V_{1a} receptor is located on vascular smooth muscle cells. Activation of this receptor results in vasoconstriction. Intravenous infusion of AVP in HF patients results in increases in both systemic vascular resistance and pulmonary capillary wedge pressure [28]. The V_2 receptor is located on the basolateral membrane of collecting duct cells in the kidney. Activation of this receptor results in insertion of aquaporin-2 channels in the apical membrane. This directly results in reabsorption of free water by utilization of the medullary concentration gradient established by the loop of Henle. Clinically, administration of V_2 receptor antagonists in patients with mild HF results in a large increase in dilute urine production, lowers body weight, and improves signs of vascular congestion [29]. Patients with both CKD and chronic HF have elevated plasma levels of AVP. The release of AVP is mediated by activation of high-pressure baroreceptors (i.e. non-osmotic release). These patients are subject to both the elevated afterload secondary to increased systemic vascular resistance resulting from V_{1a} receptor mediated vasoconstriction and increased preload resulting from water retention secondary to V_2 receptor mediated antidiuretic effect. Additionally arginine vasopressin has direct effects in promoting myocardial hypertrophy and fibrosis. The Survival and Ventricular Enlargement (SOLVED) trial determined that high plasma levels of AVP were associated with increased 1 year cardiac mortality [30]. It appears that AVP plays a role in both the pathophysiology and progression of HF.

The endothelin family consists of three small peptide hormones. Endothelin-1 (ET-1) is the most prominent isoform found in humans. It is released from endothelial cells and exerts its main effect on the endothelial cells themselves and neighboring smooth muscle. Two types of endothelin receptors have been identified: ET-A and ET-B. In the cardiovascular system these receptors have been identified on endothelial, vascular smooth muscle, and myocardial cells, as well as on myocardial fibroblasts [31]. In the kidney ET receptors are found on mesangial, renal tubular, and medullary collecting duct cells and renal fibroblasts. Levels of plasma ET-1 are increased in both CKD [32] and HF [33]. In fact, in patients with diabetic nephropathy, plasma levels of ET-1 directly correlate with serum creatinine and degree of albuminuria [34]. Proteinuria alone stimulates production of ET-1 by proximal tubule cells [35] providing a direct link between worsening kidney functions and elevated ET-1. Several physiologic actions of ET contribute to the progression of both heart and kidney disease. Endothelin is the most powerful endogenous vasoconstrictor yet discovered, therefore elevated levels can have a profound effect on systemic HTN and afterload. Several studies using ET-1 receptor antagonists have demonstrated a significant decrease in blood pressure in patients with resistant HTN [36] and normal blood pressure [37]. Endothelin-1 also promotes vascular cell hypertrophy, smooth muscle proliferation, inflammatory cell infiltration and fibrosis leading to vascular remodeling which contributes to HTN [38]. Endothelin has direct effects on the myocardium that promote damage and diminish performance. Elevated levels promote myocyte hypertrophy and increase proliferation and activation of myocardial fibroblasts which leads to fibrosis. Under normal conditions ET-1 works to maintain volume homeostasis by inhibiting reabsorption of sodium from the medullary collecting duct high levels however, may lead to renal artery constriction (resulting in renal hypoperfusion) and sodium retention with concomitant volume overload. Endothelin-1 increases sympathetic outflow and plasma levels of angiotensin II and vasopressin. Plasma levels of ET-1 correlate with worsening Left Ventricular Ejection Fraction (LVEF) [39]. The role of endothelin in both HF and CKD is not completely understood; however, it is apparent that ET-1 modulates several systems involved in the progression of both diseases. While clinical trials to date have yielded disappointing results, drugs that modulate the actions of endothelin have the potential for large gains in the battle against HF (similar to antagonists of the RAAS and sympathetic systems).

Blood pressure can be defined using Ohm's law where arterial blood pressure is proportional to the flow through the arteries (cardiac output) and the resistance to flow (systemic vascular resistance). Arterial calcification results in increased vascular stiffness which increases systemic vascular resistance and therefore blood pressure, particularly in patients with CKD. Both subintimal and medial calcification are manifestations of atherosclerosis and contribute to loss of compliance of arteries and both processes are accelerated in CKD [40]. Ming-Cheng et al. demonstrated a graded relationship between stage of kidney disease and arterial stiffness (as assessed by aortic pulse wave velocity) [41]. Multiple potential mechanisms to account for accelerated vascular calcification in CKD have been described. Alterations in calcium metabolism with hyperphosphatemia and increased calcium-phosphate product results in systemic soft tissue calcification. There is evidence for damage of vascular smooth muscle cells resulting in cell death or phenotypic transformation to osteoblast-like cells [42]. Under normal conditions calcium and phosphate concentrations exceed their solubility product; therefore there must be inhibitors of calcification. It is possible that either the activity or concentration of these inhibitors is diminished in CKD [43]. Loss of arterial compliance secondary to calcification raises systemic vascular resistance which directly results in increased systemic blood pressure, afterload, and cardiac work.

Progressive pressure overload, manifest as resistant systemic HTN, is very common in patients with CKD. Increased systemic blood pressure increases cardiac afterload which increases workload and oxygen consumption of the myocardium. This leads directly to concentric LVH which is evident as increased LV wall thickness. Left ventricular hypertrophy causes impaired ventricular relaxation which results in diastolic dysfunction. Cardiac fibroblasts in tissue culture have been shown to increase collagen production within 24 hours of being exposed to cyclic mechanical strain [44]. Fibroblasts have multiple mechanisms to sense mechanical strain, including components of the cytoskeleton, integrins located in the cellular membrane, and stretch-activated membrane channels. With the use of scanning electron microscopy it has been demonstrated that the collagen weave is thickened in the pressure-overloaded, hypertrophied heart [45]. Long term strain induced collage production leads to frank myocardial fibrosis as discussed below.

Volume Overload

Patients with HF suffer from retention of sodium and water. This results in expansion of the extracellular fluid compartment which leads to volume overload. Fluid retention directly leads to increased ventricular filling pressures which results in many of the signs and symptoms associated with HF including dyspnea, jugular venous distension, hepatic congestion, orthopnea, and peripheral edema.

Elevated ventricular filling pressures (preload) increase cardiac workload and result in dilatation of the impaired ventricle. Additionally several conditions present in CKD contribute to volume overload by increasing overall demand for cardiac output. These include chronic anemia where the blood has a diminished oxygen carrying capacity and the presence of an arteriovenous fistula for hemodialysis access which diverts a percentage of cardiac output away from the systemic circulation [46].

Heart failure is defined as the inability of the heart to provide adequate blood flow to perfuse peripheral tissue resulting in the stasis of blood which accounts for the cardinal features of effort intolerance, dyspnea, and edema. The kidney, and other volume sensing organs, experience this "arterial underfilling" as a relative hypovolemia. In response multiple counter regulatory systems are activated that result in renal sodium and water retention despite an already expanded extracellular fluid compartment. There are two mechanisms responsible for arterial underfilling in HF. First reduced cardiac output results in decreased forward flow or "forward failure". Cardiac output is determined by the heart rate and the stroke volume. The failing heart is unable to generate an adequate stroke volume in order maintain cardiac output. Decreased cardiac output decreases perfusion to peripheral tissues which is experienced as arterial underfilling. The second mechanism involves right sided pump failure that results in increased central venous pressure or "backward failure". Central venous congestion is clinically evident as increased jugular venous pressure and peripheral edema. Increased central venous pressure is transmitted downstream to the capillary beds of other organ systems including the kidneys [47]. Thus, elevated central venous pressure has been not only linked to the development of acute cardiorenal syndromes, but is also associated with albuminuria due to chronic renal congestion in conjunction with activation of neurohormonal signals.

Arterial underfilling is manifest as decreased effective arterial volume. Decreased volume activates baroreceptors in the carotid sinus, aortic arch, left ventricle, and juxtaglomerular apparatus. These receptors, whose primary function is regulating intravascular volume, signal the kidney to retain sodium and water. There is also evidence for chemoreceptors located in the heart, liver, and pulmonary circulation that may augment renal sodium and water handling in response to various substances present in higher levels within the circulation in patients with HF. There appears to be receptors in the central venous system (especially in the atria) that are sensitive to distention and therefore respond to increases in central venous volume. These receptors promote natriuresis by stimulating the kidney to excrete more sodium and water. With HF this system may become dysfunctional and even have a reverse effect (promoting sodium and water retention). The end result is with pump failure and decreased cardiac output, vascular congestion and edema are worsened by a paradoxical renal response where sodium and water are retained in spite of expanded extracellular volume. This results in worsening symptoms of vascular congestion and edema [12].

In patients with a normal GFR approximately 100 times more sodium is filtered by the kidney than is absorbed through the GI tract [16]. Therefore small changes in GFR can drastically alter the sodium load delivered to the distal nephron. However diminished GFR alone does not appear to be the predominant factor effecting sodium retention. Many patients with mild to moderate HF retain sodium yet they have normal or near normal GFRs, in fact with high output HF the GFR can be increased above normal. It is not until ESRD that depressed GFR directly results in fluid retention. Decreases in GFR (along with increases in proximal tubule sodium reabsorption secondary to arterial underfilling) results in less fluid reaching the distal nephron. This impairs the kidney's ability to excrete free water.

Chronic kidney disease additionally effects the treatment of fluid overload [18]. Diuretics, especially loop diuretics, are commonly used to treat symptomatic fluid overload. Loop diuretics act on the sodium, potassium, 2 chloride channel located on the thick ascending loop of Henle. This transporter is responsible for the electrically neutral reabsorption of 4 ions from within the lumen resulting in the formation of hypotonic urine and the hypertonic medullary interstitium required for reabsorption of free water from the collecting ducts. Inhibition of this transporter results in a greater sodium load reaching the distal convoluted tubule and collecting ducts thereby increasing sodium and thus water excretion. Decreasing the hypertonicity of the medullary interstitium impairs the kidney's ability to reabsorb free water from the medullary collecting ducts. Worsening of renal function often complicates treatment of advanced HF using diuretics and is associated with diuretic resistance. Worsening renal function and diuretic resistance are associated with deterioration in cardiac function, more frequent and longer hospitalizations related to HF, and increased morbidity and mortality.

Chronic kidney disease leads to chronic anemia through a functional deficiency of erythropoietin. Al-Ahmad et al. found that deficiency of erythropoietin accelerates LVH and cardiac remodeling, even in patients with mild kidney disease [48]. Anemia is characterized as a decrease in the oxygen carrying capacity; therefore the heart must pump a larger volume of blood in order to provide the same amount of oxygen to the peripheral tissues. This can result in high output HF and Left Ventricular (LV) dilatation secondary to volume overload, especially when there is increased oxygen demand as seen with exercise or infection. Chronic anemia has also been shown to cause LVH [49]. It has been shown that treating anemia with exogenous erythropoietin and supplemental iron improves HF symptoms, exercise tolerance, and peak oxygen consumption while reducing hospitalizations [50].

Once CKD progresses to ESRD which requiring renal replacement therapy several options are available. Hemodialysis is currently the most common form of renal replacement therapy. Hemodialysis requires repetitive access to the blood stream; this is accomplished with the use of indwelling catheters, implantable grafts, and the creation of surgical Arteriovenous (AV) fistulas. Indwelling catheters are often used temporarily as they are prone to infection and do not reliably provide ideal flow for dialysis. Therefore the majority of patients receiving hemodialysis do so via an implanted graft or AV fistula. These are usually placed in the upper extremity, in the forearm they typically have flow rates of 400-800 ml/min in the brachial artery flow is typically 800-1500 ml/min [51]. The flow through the fistula is recirculated into the pulmonary circulation, thus in the presence of a fistula, a portion of cardiac output will be diverted away from the systemic circulation. The increased flow to the pulmonary circulation increases cardiac preload which the heart experiences as increased blood volume and subsequent volume overload. It has been shown that the overload secondary to fistula creation results in alterations in cardiac structure and function, particularly eccentric LVH [52]. Additionally, several studies have demonstrated reversal of LVH (particularly eccentric LVH, which implies improvement in volume overload) and improvement in cardiac function following closure of a fistula in both patients who received renal transplant [53] and in those who were converted to an indwelling catheter [54]. Patients with end stage kidney disease are at risk for volume overload secondary to diminished GFR alone (see above). The

presence of a fistula, while necessary to sustain life, can exacerbate this condition and lead to further remodeling manifested by myocardial hypertrophy, chamber dilatation, and increased stiffness.

Non-Hemodynamic Factors

Many factors associated with CKD have deleterious effects on cardiac structure and function independent from any hemodynamic change. These processes directly promote myocardial fibrosis and LVH. Chronic activation of the renin-angiotensin system, oxidative stress, chronic inflammation, and disturbances in phosphate metabolism has all been implicated in the development of myocardial dysfunction [55]. Further understanding of these processes holds the potential for the development of novel therapeutic interventions.

In addition to sodium and water retention (discussed above), increased activity of the renin-angiotensin-aldosterone system directly promotes cardiac remodeling and myocardial fibrosis (Figure 2). Chronic excess aldosterone has been shown to result in fibrosis in all chambers of the heart, the kidney, and other organs. This may be due to aldosterone induced increase in production of the profibrotic cytokine transforming growth factor beta [56]. Both Angiotensin II and aldosterone have been shown to stimulate cardiac myocytes to secrete connective tissue growth factor, which acts on cardiac fibroblasts to promote the production and accumulation of collagen which leads to fibrosis. Treatment with the angiotensin II receptor antagonist losartan has been shown to reduce myocardial collagen content and LV chamber stiffness [57]. Additionally spironolactone (an aldosterone receptor antagonist) has been shown to improve cardiac diastolic function and reverse myocardial fibrosis in humans [58]. Spironolactone has become standard therapy in patients with severe HF since the Randomized Aldactone Evaluation Study (RALES) demonstrated a 30% reduction in mortality when it was added to standard HF therapy [59]. There is evidence that aldosterone mediates remodeling by direct interaction with the tissues of the heart [60]. The survival benefit gained with the use of Angiotensin Converting Enzyme (ACE) inhibitors is derived from blockade of this pathway. Unfortunately ACE inhibitor use can contribute to decreased GFR and worsening renal function through prostaglandin mediated dilation of the glomerular efferent arteriole. Worsening renal function is often associated with metabolic acidosis and hyperkalemia. Aldosterone promotes potassium clearance therefore blockade of the RAAS system decreases potassium excretion by the kidney. Both worsening renal function and life threatening hyperkalemia can preclude use of ACE inhibitors in patients with renal failure, thus depriving this patient population from the associated benefits in disease progression, and survival.

Kidney disease is associated with a graded increase in markers of oxidative stress, even in early stages of disease. Oxidative stress results from an imbalance between the production of Reactive Oxygen Species (ROS) and the removal of ROS. There is the potential to form excess ROS whenever there is occurrence of oxidation/reduction reactions, which involve transfer of electrons primarily from catalytic or unbound iron (Fe^{2+}, Fe^{3+}) [61]. For example oxygen is reduced in the mitochondria of mammalian cells as electrons are passed through the electron transport chain during aerobic metabolism [62]. Other sources include the nicotinamide Dinucleotide Phosphate Oxidase Complex (NADPH), xanthine oxidase, lipoxygenases, and cyclooxygenases among others. Potential damaging ROS include superoxide anions, hydrogen peroxide, or the very damaging hydroxyl radical. Increased oxidative burden in CKD is evidenced by elevated levels of oxidized proteins, malonyladialdehyde, and oxidized LDL particles. Multiple studies have shown an inverse correlation between markers of oxidative stress and GFR [63,64]. It appears that increased production of ROS is responsible for this oxidative stress in early stages of kidney disease; it is not until end stage disease that plasma antioxidant capacity begins to decrease [65]. There is, however, evidence that intracellular antioxidant capability is diminished in early stages of CKD [66,67]. Reactive oxygen species have been shown to modulate the activity of matrix metalloproteinase and fibroblast collagen synthesis [68], thus affecting myocardial fibrosis as discussed below. One study, enrolling 134 patients, examined the effects of administration of the mild antioxidant N-Acetylcysteine (NAC; 600 mg twice daily) on the composite end point of myocardial infarction, cardiac death, coronary angioplasty or bypass grafting, ischemic stroke, and peripheral vascular disease. Over a 14 month follow up period 28% of the NAC treated patients versus 47% of the control patients reached one of the primary end points ($P<0.03$) [69]. There was, however, no significant difference in any individual end point between the two groups. It is possible that a larger sample size and longer follow up period would have sufficient power to detect these differences. In general, antioxidant therapies have failed in both acute and chronic renal disease for the following reasons: 1) most antioxidants including those that modulate glutathione and another counter regulatory pathways are relatively weak compared to the pro-oxidant reactions; 2) therapies may have been given at insufficient doses or durations for benefit and 3) the fundamental regulators of abnormal oxidative stress are not sufficiently addressed with available antioxidant therapies. The most promising approaches include therapeutic cooling, catalytic iron chelation, and alkalinization as these maneuvers all work to slow the final common Haber-Weiss and Fenton equations involved in generation of the dangerous hydroxyl radical in cells and tissues [61]. More research is needed to determine what role antioxidant therapy holds in preventing cardiovascular disease especially in the presence of CKD.

A major factor contributing to increased production of ROS in CKD is the presence of unbound liable iron molecules capable

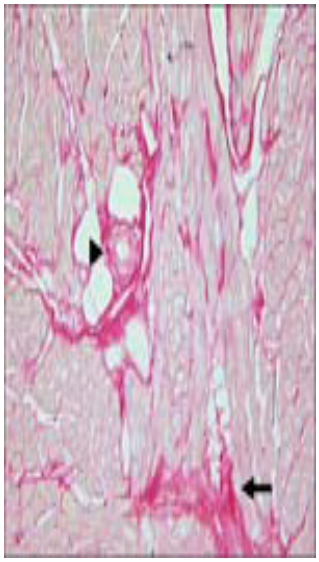

Figure 2: Myocardial fibrosis in chronic kidney disease. Microscopic image of the myocardium of a patient with stage 3 CKD, arterial hypertension and left ventricular hypertrophy showing interstitial (arrow) and perivascular (arrow head) deposition of collagen fibers stained with picrosirius red. (Original magnifications 20X) Reproduced with permission from Diez et al.

of catalyzing oxygen reduction reactions. Without the presence of catalytic iron the development of reactive oxygen species is relatively slow. Oxygen is reduced to form superoxide anions which can go through another reduction to form hydrogen peroxide which can be further reduced. There are multiple enzyme systems that intervene at various steps in order to prevent the development of damaging reactive oxygen species. Both ferric (Fe^{3+}) and ferrous (Fe^{2+}) iron are capable of catalyzing reactions that rapidly convert hydrogen peroxide into the highly damaging hydroxyl radical [70]. Normally almost all iron in the body is bound to proteins (including transfer proteins, heme, and intracellular proteins). Unbound iron, that is capable of participating as a catalyst in reduction reactions, is released from adjacent damaged cells. Patients with CKD often receive an additional iron load in the form of iron supplementation as part of the treatment of chronic anima, thus, are exposed to excess catalytic iron during infusions.

There is considerable enthusiasm for a commercially available diagnostic test measuring Neutrophil Gelatinase Associated Lipocalin (NGAL) or siderocalin. This protein binds natural siderophores and works to remove a catalytic iron from the renal parenchyma. It is produced in large quantities in the distal tubule and is measurable in blood and urine. Of note, it becomes moderately elevated in CKD and acutely can raise several-fold in response to acute kidney injury [71]. Siderocalin has been shown to be elevated in patients with ADHF predicting the need for renal replacement therapies and or death [72]. It is unknown at present whether or not NGAL could serve as a therapeutic target either via infusion of recombinant protein or molecular mimicry with the intent of reducing oxidative stress results in cell dysfunction, accelerated apoptosis, and cell death, and fibrosis [73]. One such molecular approach, using an NGAL-like agent to bind available tissue catalytic iron is with the mild iron chelator oral deferiprone, is an attractive therapeutic target from a conceptual standpoint.

It has been well documented that CKD is associated with chronic low grade inflammation. Patients with CKD have multiple markers for systemic inflammation including acute phase reactants (elevated levels of C-Reactive Protein (CRP), and fibrinogen, and low albumin), cytokines (IL-6, TNF-α, and CD 40 ligand), and adhesion molecules [74]. The exact mechanism leading to the development of chronic inflammation in CKD is currently unknown, but likely includes increased production and reduced excretion of proinflammatory molecules (acute phase reactants and cytokines), activation of the RAAS systems, and the presence comorbid inflammatory conditions [75]. Chronic inflammation promotes progression of atherosclerosis which leads to cardiac ischemia and worsening myocardial function. Inflammatory mediators promote the expression of adhesion molecules on vascular endothelial cells which bind to circulating immune cells resulting in migration into the vessel wall. Monocytes are activated, take up oxidized LDL particles, and become foam cells which initiate and promote progression of arterial plaques. Additionally certain inflammatory mediators, such as TNF-α and IL-6 may have a direct toxic effect on the heart. Rodent studies demonstrate that TNF has a negative inotropic effect on the myocardium and chronic exposure results in increased ventricular volume and depressed LVEF in a dose dependent manner [76]. There are a few potential mechanisms under investigation: through a neutral sphingomyelinase pathway (manifest immediately), through a Nitric Oxide (NO) mediated pathway (delayed manifestation), and indirectly via increased activity of IL-18 (which likely acts through a NO mediated pathway). Interleukin-6 also has a negative ionotropic effect that acts via a NO pathway. Chronic inflammatory mediators have various effects on ventricular remodeling and myocardial cell death. It has been shown that elevated levels of CRP, IL-6, and fibrinogen are independent predictors of adverse cardiovascular outcomes in both CKD and apparently healthy patients [77,78].

As kidney disease progresses patients begin to develop disturbances in calcium and phosphate metabolism. Phosphorus clearance is impaired once GFR falls below approximately 30 mL/min (stage IV disease). Impaired clearance leads to phosphate retention and hyperphosphatemia. Hyperphosphatemia is the principal cause of secondary hyperparathyroidism that develops in patients with CKD. Phosphate has a direct stimulatory effect on Parathyroid Hormone (PTH) production and worsens hypocalcemia by binding with calcium and precipitating in peripheral tissues. Thus as renal disease worsens patients experience worsening hyperparathyroidism, hyperphosphatemia, and hypocalcemia. Parathyroid hormone has direct hypertropic effects on myocardial cells as demonstrated in cultured rodent myocytes. Exposure to PTH induces protein synthesis and increases myocardial cell volume [79]. A population based study including 27,000 healthily subjects conducted in Norway found elevated levels of PTH to be positively associated with LVH [80]. Additionally, elevated PTH levels appear to have a permissive effect on myocardial fibrosis. The effect of PTH on hypertrophy and fibrosis (and therefore LVH) is independent of HTN [81]. Several studies have shown improvement in LVH and LV function following parathyroidectomy or renal transplantation, however, a recent prospective randomized trial of PTH suppression with paricalcitol, showed no impact on the progression of LVH in patients with CKD [82,83].

In an effort to maintain normal serum phosphate levels in the face of reduced renal phosphate clearance osteocytes in the bone releases Fibroblast Growth Factor-23 (FGF-23) and levels are markedly elevated in patients with CKD [84]. Levels begin to rise before hyperphosphatemia develops; therefore increased serum FGF-23 is one of the earliest indicators of impaired phosphate metabolism. FGF-23 acts on the renal tubules to increase the fractional excretion of phosphate. FGF-23 also acts on fibroblasts to increase collagen production. Patients with high levels of FGF-23 have an increased prevalence of LVH, particularly concentric hypertrophy [85]. It is possible that high circulating levels of FGF-23 activate other fibroblast growth hormone receptors (particularly the FGF-2 receptor) which are known to be linked to the development concentric LVH. More research is needed to establish the efficacy of initiating phosphate lowering treatments (dietary phosphate restriction and phosphate binders) in the setting of elevated FGF-23 in order to prevent progression of LVH.

Adverse Cardiac Remodeling

Cardiac remodeling is a frequently identified in patients with CKD. Remodeling can be defined as molecular, cellular, interstitial, and genome expression changes that manifest as myocyte hypertrophy, intramyocardial cell fibrosis, and decreased capillary density [86]. Clinically, remodeling is identified as changes in size, shape, and function of the heart. As described above, many damaging processes are initiated and/or accelerated in patients with CKD. There is a high rate of both eccentric (ventricular dilatation owing to volume overload) and concentric (increased ventricular wall thickness secondary to pressure overload) hypertrophy in patients with CKD. Additionally, in the setting of renal insufficiency there are many nonhemodynamic factors that promote both hypertrophy and fibrosis (Figure 3). Myocardial cell hypertrophy and fibrosis of the Extracellular Matrix (ECM) are key factors leading to myocardial dysfunction and symptomatic HF.

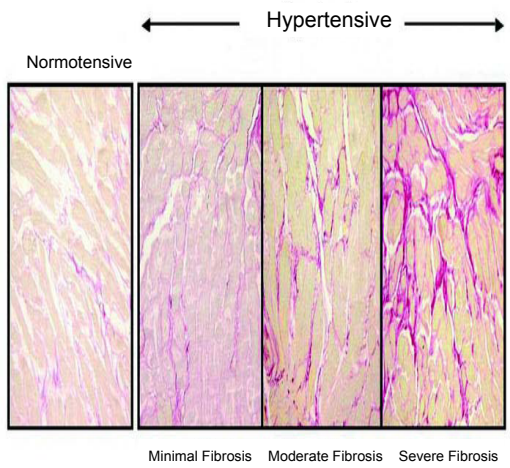

Figure 3: Collagen content in the hearts of a normotensive patient and 3 patients with hypertensive heart disease. Patients are classified according to the degree of myocardial fibrosis: minimum (left), moderate (center), and severe (right). Sections are stained with picrosirius red and collagen fibers appear red. Reproduced with permission from Diez et al.

Cardiac remodeling can be both adaptive and destructive. By definition myocardial infarction results in necrosis of the myocytes in the region of the heart that lost blood flow. Fibroblasts are recruited to the infarcted area and secrete collagen in order to from a scar [87]. Scar formation maintains integrity of the ventricular wall which would otherwise risk rupture. Remodeling is also seen in highly trained endurance athletes where the heart undergoes compensatory changes in geometry and function that allow the heart to support an increased cardiac output [88]. In the initial phases of volume or pressure overload remodeling also serves to maintain cardiac output. In these situations remodeling is an important physiologic response that acts to maintain circulatory integrity. Pathologic remodeling, on the other hand, develops in response to prolonged stress on the heart from chronic volume overload, pressure overload, and non-hemodynamic factors. This pathologic remodeling involves diffuse fibrosis and hypertrophy which leads to increased myocardial stiffness and impaired diastolic relaxation. Remodeling under these conditions is associated with HF progression and poor prognosis [89].

Left Ventricular Hypertrophy and Dilatation

Left ventricular hypertrophy is another component of the cardiac remodeling seen in patients with CKD. At the cellular level LVH is determined by an increase in size of the cardiac myocytes. The incidence of LVH is as high as 80% in patients with end stage kidney disease when starting dialysis [90]. Both eccentric and concentric hypertrophies are common. Altered hemodynamic loading conditions stretch the myocyte cell membrane which leads to activation of hypertrophy associated genes, synthesis of contractile proteins, and assembly of sarcomeres [91]. There is decreased phosphorylation of sarcomeric proteins, as well as changes in various structural proteins, such as titin which connects adjacent sarcomeres and participates in cell signaling. The importance of titin in myocardial structure and function has been demonstrated by a recent study that identified truncating mutations of titin in 25% of familial cases of dilated cardiomyopathy, 18% of sporadic cases, and only 3% in healthy controls [92]. Eccentric hypertrophy results from chronic volume overload (increased preload) which leads to myocardial cell dropout, lengthening of myocytes, and ultimately chamber dilatation. Concentric hypertrophy is the result of chronic pressure overload (i.e. HTN, or increased afterload) and is seen as myocardial cell thickening. Both preload and afterload related processes affect the heart simultaneously and likely affect both patterns of hypertrophy. There appears to be an additive or even synergistic effect in promoting LVH. Additionally many of the previously mentioned processes present in CKD have direct hypertrophic effects that are independent from their hemodynamic effects (e.g. RAAS activation, increase sympathetic output, oxidative stress, inflammation, increased endothelin activity, hyperparathyroidism, and FGF-23).

There are several ways to measure LV mass. Initially LV mass was determine by EKG criteria (voltage criteria), physical exam (palpation of the point of maximum impulse) and cardiomegaly on chest x-ray (increased cardiothoracic index on posterior-anterior views). These methods are easy and inexpensive but they have a low sensitivity for detecting LVH. Cardiac MRI is the gold standard as it can accurately assess LV mass, volume, geometry, and fibrosis [93]. Significant limitations to widespread use include cost, accessibility, and contraindications such as the presence of implanted devices. Therefore echocardiography has been established as the main tool for assessment of LV mass. However the accuracy of LV mass determination by echocardiography is dependent on operator technique, adequacy of acoustic windows, the index used for normalization of gathered data, and timing of study in relation to dialysis. Two- and three-dimensional echocardiography techniques increase accuracy and precision; with the accuracy of three-dimensional ultrasound approaching that of cardiac MRI [94].

Fibrosis

The primary structural component of the extracellular matrix is fibrillar collagen. There are 5 types of fibrillar collagen, type I and type III are the predominant isoforms in the heart, accounting for approximately 80% of the myocardial collagen [95]. Collagen forms a structural scaffold that provides both strength and elasticity. This scaffold is important in maintaining structural integrity of the myocardium and actively participates in force generation and transmission across the LV wall. Properties of the connective tissue matrix determine ventricular size and shape and provide resistance to myocardial deformation during diastolic filling. With nearly the tensile strength of steel type I collagen is very resistant to longitudinal stretch. Taken in whole, the extracellular matrix is the primary determinant of ventricular stiffness and passive relaxation during diastole.

Collagen is produced in and secreted from myocardial fibroblasts and myofibroblasts. By cell count fibroblasts are the most abundant cell type in the human heart [96]. Procollagen molecules are synthesized in the endoplasmic reticulum of fibroblasts. The pro-protein contains approximately 1000 amino acids arranged in 3 alpha helical chains. This long, stiff pro-protein is secreted into the interstitial space where it undergoes processing. Pro-collagen N- and C-proteinases cleave the N- and C-terminal sequences respectively. The resulting collagen molecules are less soluble; they self-assemble into collagen fibrils which aggregate to form collagen fibers. Cross links that form within and between collagen fibers provide added strength [97]. Collagen degradation is regulated by the action of proteolytic enzymes (Matrix Metalloproteinases [MMP]) and Tissue Inhibitors of Metalloproteinases (TIMP). The MMP/TIMP ratio regulates the rate of collagen degradation within the myocardium [98]. There are multiple enzymes in the ECM that intervene at various steps in this process that can either slow down or accelerate collagen deposition or turnover.

The collagen deposition/turnover balance can be approximated by measuring serum levels of byproducts of collagen synthesis and degradation. The C-terminal portion of the type I procollagen molecule (PICP) is cleaved and released in a 1:1 ratio, therefore PICP levels detected in the blood provide an estimate of type I collagen synthesis. Additionally elevated levels of PICP have correlated with worse outcomes in HF, myocardial infarction, and HTN [99]. When type I collagen is degraded the C-terminal telopeptide (CITP) is released into the blood and is an indicator of collagen turnover. Determination of the PICP to CITP ratio allows for estimation of the net collagen balance [100]. This ratio is elevated in hypertropic hearts, indicating that type I collagen synthesis is exceeding breakdown resulting in frank myocardial fibrosis. While attractive due to biologic simplicity and quick turnaround time, widespread clinical use is hampered as serum concentrations of PICP and CITP are effected by multiple variables, including renal insufficiency, hepatic impairment, bone disease, and thyroid disease [101].

In addition to collagen, the ECM exists as a complex dynamic structure containing laminin, elastin, fibronectin, proteoglycans, glycosaminoglycans, basement membrane, and bioactive signaling molecules (shown histopathologically in Figures 2 and 3). The extracellular matrix (ECM) of the heart undergoes constant turnover regulated by fibroblasts, myocytes, and infiltrating immune cells [102]. The ECM is highly adaptive, it responds to mechanical stress, neurohormonal activity, inflammation, and oxidative stress. Alterations in the cellular environment induce changes in the collagen composition and other matrix components as well as alterations in the expression and activity of MMPs and TIMPs. In response to prolonged stress myocardial fibroblasts are replaced with a more actively fibrogenic cell type known as myofibroblasts, which are not seen in the myocardium of healthy hearts. Myofibroblasts are identified by the presence of several smooth muscle proteins including alpha-actin, SMemb/nonmuscle myosin heavy chain-B, and tropomyosin [103]. Additionally there is a relative increase in the MMP to TIMP ratio in both coronary sinus and peripheral blood [104]. This sets the stage for increased ECM turnover with both an increase in production and degradation of ECM components.

An imbalance between collagen production by myofibroblasts and degradation by MMPs results in a net accumulation of fibrillar collagen and frank myocardial fibrosis. The various factors previously described that are associated with CKD appear to have an additive or even synergistic effect on promoting myocardial hypertrophy and fibrosis. Early on in the course of CKD hemodynamic overload, oxidative stress, inflammation, and excess hypertrophic growth factors are involved. As CKD progresses chronic anemia, hyperphosphatemia, and uremic toxins also play a role in promoting fibrosis. In a recent study, Martin et al. demonstrated early myocardial fibrosis with impaired diastolic function in an experimental model of mild renal insufficiency produced by unilateral nephrectomy [105]. Four weeks after nephrectomy rats in the investigational group showed a significant increase in myocardial fibrosis compared to controls. These findings were independent of any change in blood pressure, sodium retention, activation of aldosterone, GFR, proteinuria, or plasma B-type Natriuretic Peptide (BNP) level. At 16 weeks these changes progressed to more global remodeling and dysfunction with increases in LV mass, LV end diastolic diameter, and plasma BNP and modest decrease in LVEF.

The degree of myocardial fibrosis can be assessed by direct endomyocardial biopsy, magnetic resonance imaging, serum biomarkers, or by evaluating the functional consequences using 2D-echocardiography with tissue Doppler or strain rate imaging [106]. Multiple studies using the different modalities have demonstrated myocardial fibrosis to be more common in hypertensive patients with CKD than hypertensives with normal renal function [107,108]. Using 2D-echo with tissue Doppler the prevalence of diastolic dysfunction (estimated by calculation of E/E' ratio) was found to be as high as 62% in patients with stage 5 CKD [109]. Additionally the E/E' ratio was identified as an independent predictor of all cause mortality, with a median follow up of 4 years. The degree of myocardial fibrosis correlates with impairments in stroke volume, cardiac output, and functional class [110].

Over the last two decades, with the development of highly sensitive and cost effect assays, serum biomarkers have become integral tools in all phases of diagnosis, management, and prognosis of HF. Commonly used as a marker for acute coronary syndromes, cardiac troponin T and I are also useful in patients with chronic HF. In normal healthy myocytes, troponin regulates the interaction between actin and myosin [111] and is therefore intimately involved in myocardial contraction and force generation. When myocardial injury results in cell necrosis, troponins (I and T) are release into the circulation and are thus an indicator of myocardial cell death. Given this context, it is not surprising to learn that elevated levels of troponin I in both acute [112] and chronic [113] HF are predictive of adverse outcome. This likely represents on-going myocardial injury leading to myocyte necrosis. Kawahara et al. determined that patients with either ischemic or nonischemic cardiomyopathy who had a troponin I >0.03 ng/mL at baseline were at increased risk for cardiac death. Additionally, any increase in serum troponin concentrations over the 6 month study period was associated with increased risk of cardiac death with a hazard ratio of 3.59 [114]. With the introduction of highly sensitive assays for cardiac troponins, serum levels (both baseline and trends) are now useful, independent predictors of cardiac death in patients with HF.

B-type (or brain) natriuretic peptide is a 32-amino acid peptide hormone released into circulation from cardiac myocytes in response to mechanical stress. It is therefore a useful indicator of both acute and chronic ventricular overload [115]. B-type natriuretic peptide has several physiologic effects that act to relieve stress on the heart. It acts directly on smooth muscles cells in the walls of the large veins to induce venodilation which decreases cardiac preload. It dilates arteries which decreases systemic vascular resistance and therefore lowers afterload. In the kidney BNP increases GFR and the fractional excretion of sodium which induces natriuresis and diuresis. It is co-secreted along with a biologically inactive N-terminal fragment (NT-proBNP). Both substances can be measured in peripheral blood and are markers for ventricular overload. Serum levels of BNP and NT-proBNP are used to diagnose acute HF, monitor response to treatment, and in determining prognosis in chronic HF. B-type natriuretic peptide is particularly helpful in identifying patients with diastolic dysfunction or HF with preserved LVEF who would benefit from HF specific therapy. Several studies in asymptomatic patients found that even small rises in BNP to 80-100 pg/ml (still within the normal range) doubled the risk of death and cardiovascular events [116]. There is nearly a 35% increase the relative risk of death for every 100 pg/ml increase in BNP in patients with HF. B-type natriuretic peptide appears to be a better prognostic predictor then traditional clinical assessment, including functional class and possibly even LVEF assessed by 2D-echocardiography. Treatment with natriuretic peptide infusions have shown decreases in cardiac preload [117] and reduced cardiac fibrosis [118]. Nesiritide, a recombinant human BNP, has been approved by the U.S. Food and Drug Administration (USFDA) to treat acute decompensated HF,

however, has not been shown to improve clinical outcomes including rehospitalization or death. In order to obtain a more favorable hemodynamic profile several natriuretic peptide derivatives have been developed. The first chimeric natriuretic peptide (CD-NP) comprised the C-terminus of the dendroaspis peptide (derived from snake venom) and the peptide ring component of the cardiac-type natriuretic (CNP) [119]. CD-NP has been shown to have a potent natriuretic effect, antagonize the RAAS system, inhibit cardiac fibroblast proliferation and collagen synthesis, and importantly not cause significant systemic hypotension [120,121]. BNP and other natriuretic peptide derivatives are now utilized in the diagnosis of acute decompensated HF, chronic compensated HF (including HF with preserved LVEF), prognostication, and treatment.

Much attention has been paid to various serum biomarkers that are related to collagen metabolism. These biomarkers can potentially provide a reliable noninvasive way to quantify the collagen balance and therefore the degree of fibrosis. As outlined above, serum PICP concentration provides insight into collagen production, while CITP concentrations indicate collagen breakdown. Assays are available that quantify the serum concentration of enzymes that regulate collage degradation (including MMPs and TIMPs). The first USFDA cleared marker of fibrosis is galectin-3, a member of the beta-galactoside-binding lectin family [122]. It appears to have an important role in regulating fibrosis and remodeling [123]. Galectin-3 is present within the myocardium at sites of injury; it acts on fibroblasts to promote conversion into myofibroblasts and increased collagen production [124]. It also down-regulates levels of certain MMPs, thus decreasing collagen degradation. Infusion of galactin-3 into the pericardium of rats with normal hearts results in extensive myocardial fibrosis [125]. In animals, galactin-3 levels correlate with active fibrotic disease; levels are low in normal rats, peak with maximal fibrosis, and fall to almost zero with recovery [126]. Similar observations have been made in humans; with higher serum levels found in patients with acute exacerbations of HF. Lok et al. determined elevated serum level of galactin-3 is an independent predictor of mortality in patients with HF [127]. Many commonly used biomarkers are substances released upon damage to or stress on the myocardium (including troponin and BNP), these can be considered to be bystander biomarkers as they are not actively involved in promoting disease progression. Galactin-3 on the other hand, appears to play an active part in disease progression therefore, it can be thought of as a culprit molecule and as such offers the opportunity for interventions that disrupt the pathological process. Modified citrus pectin has been shown to reduce galectin-3 expression and disease severity in experimental acute kidney injury [128]. Identifying patients with elevated serum levels of galectin-3 offers the opportunity to provide targeted therapy (citrus pectin) and that alters the active disease process thereby limiting the extent of fibrosis.

Another biomarker that appears to be helpful in risk stratification of patients with HF, particularly after an acute myocardial infarction, is serum levels of soluble ST2 receptor (ST2r). This receptor is a member of the toll-like/interleukin-1 receptor family and exists in both a membrane bound and soluble form [129]. The soluble form appears to function as a decoy receptor by binding and neutralizing circulating interleukin-33 (IL-33). Interleukin-33 has been shown to have antifibrotic and antihypertrophic properties in cultured cardiomyocytes and in mice subjected to experimental pressure overload [130]. The protective effects of IL-33 are antagonized when soluble ST2r is added. Serum levels of soluble ST2r rise early after acute myocardial infarction [131] and are elevated in both acute [132] and chronic [133] HF. Transcription of soluble ST2r is induced in cultured cardiomyocytes and cardiac fibroblasts in response to the application of mechanical strain. The serum level of ST2r has been shown to correlate with both early and medium-term LV function and the degree of remodeling over time [134]. In an 1141 patient cohort, elevated baseline levels of serum ST2r carried a markedly increased risk of death or heart transplantation, establishing ST2r as a prognostic factor for long term adverse events [135]. More research is needed to determine what the exact role is for soluble ST2r and IL-33 in the development of fibrosis and remodeling.

Functional Consequences

Diastolic dysfunction is the predominate physiology seen in patients with CKD and is associated with a higher mortality rate then systolic dysfunction [136]. Both myocardial fibrosis and LVH cause ventricular stiffening and impaired relaxation which decreases ventricular compliance and leads to diastolic dysfunction. The LV becomes very sensitive to volume changes, thus the physiologic consequence of reduced ventricular compliance is that LV diastolic pressure can rise sharply with negligible increases in LV volume. The increased diastolic pressure is transmitted downstream from the LV to the left atrium and pulmonary circulation resulting in congestion. The converse is patients undergoing dialysis where removal of volume causes a sharp fall in LV diastolic pressure which leads to hypotension and hemodynamic instability during dialysis. The inability to increase ventricular volume means the heart has a relatively fixed stroke volume therefore cardiac output is very sensitive to changes in heart rate. Increasing heart rate will increase cardiac output to a point however increasing the rate decreases time available for ventricular filling. In stiff, fibrotic ventricles decreased time for diastolic filling decreases end diastolic volume and therefore stroke volume. This results in an overall impaired ability to increase cardiac output in response to physiologic demand, clinically evident as impaired exercise tolerance and exertional dyspnea.

In the absence of acute ischemic injury, it is now understood that CKD can lead to adverse cardiac remodeling and fibrosis, derangements of diastolic function, and ultimately LV dilatation and reduced LVEF HF. At this stage, the clinical syndrome is typically progression and is a common cause of hospitalization and cause specific death [137]. All of the features and complications of cardiorenal syndrome type 4 manifested by low LVEF HF have been described and found to be increased with progressively lower levels of GFR including increased symptoms, decreased exercise tolerance, reduced peak oxygen consumption, higher risks of arrhythmias, thromboembolism, device failure, and death [138-141].

Conclusion

Identification of the pathophysiological mechanisms underlying cardiorenal syndrome type 4 will allow for a better understanding of the clinical consequences of these diseases. Further research into the specific derangements will open the door for development of novel therapeutic targets aimed at treating the underlying disease etiology and thus prevent disease initiation and progression. Such interventions can be expected to impact mortality in the same fashion as antagonists of the renin-angiotensin-aldosterone and sympathetic nervous systems.

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