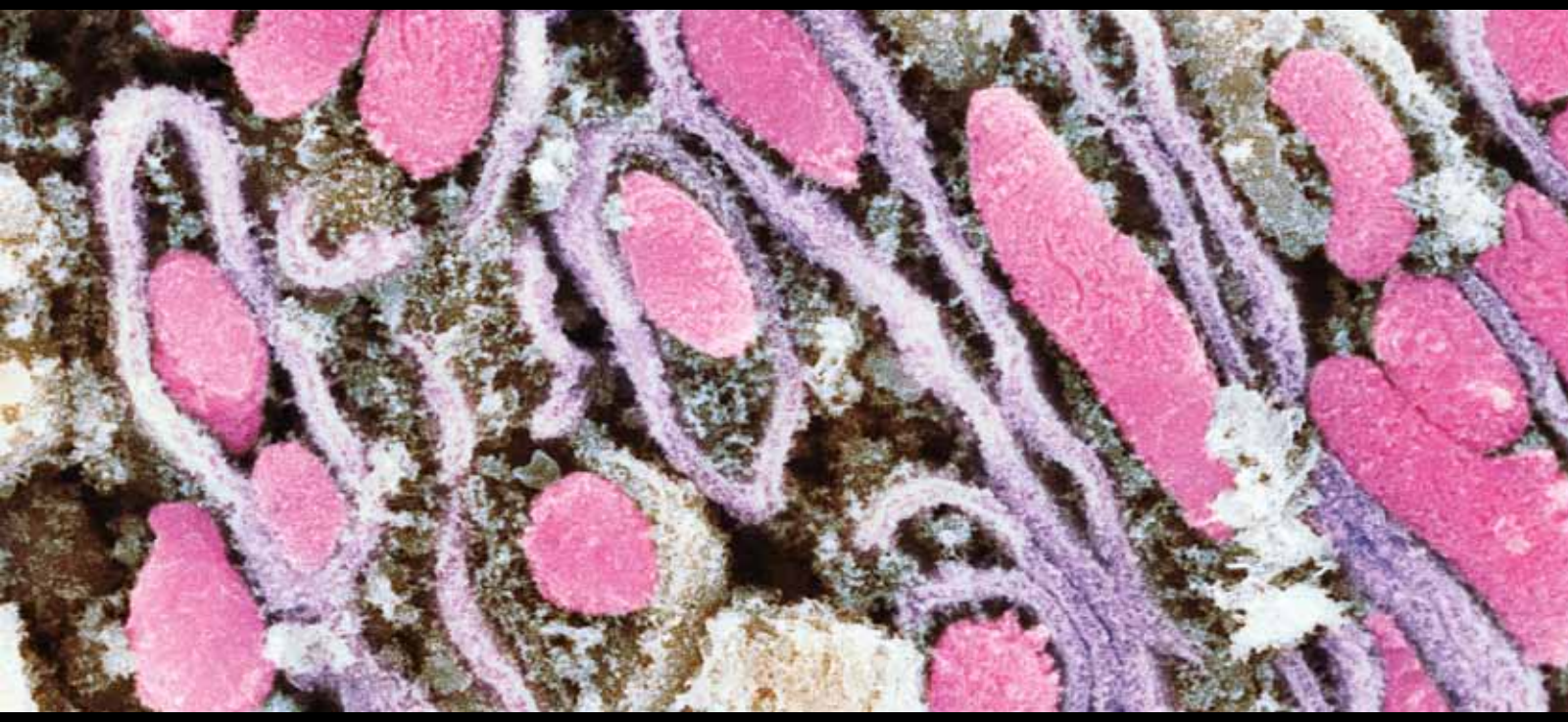
International Journal of Nephrology

The Cardiorenal Syndrome

Guest Editors: Mitchell H. Rosner, Anjay Rastogi, and Claudio Ronco



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International Journal of Nephrology
Volume 2011, Article ID 982092, 2 pages
doi:10.4061/2011/982092

Editorial

The Cardiorenal Syndrome

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Received 12 May 2011; Accepted 12 May 2011

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This special issue of the International Journal of Nephrology is the first nephrology journal edition devoted solely to the discussion of the cardiorenal syndrome and represents a landmark state-of-the-art discussion on such pathological entity. The cardiorenal syndrome (CRS) was first officially defined at a consensus conference of the Acute Dialysis Quality Initiative in 2009 [1]. This definition was made in the attempt to characterize and classify the various connections between acute and chronic heart and kidney disease. Although well known, heart and kidney interactions had not been clearly defined in the past nor were they completely elucidated and classified. The consensus conference defined 5 forms of heart-kidney interaction that would lay the foundation for both a common language in describing patients suffering from these syndromes as well as forming a schema for further research. The consensus conference recognized that communication between the heart and kidneys occurs through a variety of pathways that in the healthy state modulate cardiac output, vascular tone, maintenance of volume state, and excretion of waste products. However, a change in the performance of one of these organs elicits a cascade of mediators that affects the other and leads to a spiral of mutual organ dysfunction.

The five forms of the CRS include (1) type I CRS where acute heart failure is directly associated with acute kidney injury (AKI); (2) type II CRS in which chronic heart failure is associated with chronic kidney disease (CKD); (3) type III CRS where AKI is associated with acute heart failure; (4) type 4 CRS in which the driving factor of CKD is associated with chronic heart failure; (5) type 5 CRS where there is concomitant development of both kidney and heart failure. The importance of having such a classification scheme is due to the fact that both cardiovascular disease (CVD) and CKD are highly prevalent and overlapping conditions. For instance, it is estimated that 1 in 3 adults in the United States (US) (>100 million persons) has a diagnosis of some form of CVD (hypertension, coronary heart disease, heart failure (HF), stroke, or congenital heart disease), and nearly 13% of the US population has been estimated to have some form of CKD [2, 3]. Much of this disease burden occurs in the same patient as acute, and chronic abnormalities in cardiac function are associated with an increased risk for kidney injury, and patients with both AKI and CKD have a large burden of CVD [2–6]. For example, in the ADHERE study database of hospital admission for acute decompensated heart failure (ADHF), 27.4%, 43.5%, and 13.1% of all patient admissions were found to have mild, moderate, or severe kidney dysfunction, respectively [6]. It is thought that the overlap between CVD and kidney dysfunction represents common pathophysiological processes that interact in deleterious ways to promote a cycle of organ dysfunction. These critical, dynamic, and bidirectional interactions include varied pathophysiological pathways that are discussed in this special edition. These pathways range from hemodynamic interactions to widespread inflammation that affects multiple organ systems. As with any newly described syndrome, the questions outnumber the answers and papers in this edition attempt to offer both hypothesis for how organ crosstalk may occur between the heart and kidney, as well as describe important diagnostic aids for CRS, and potential therapies that may improve cardiac and kidney function and define questions that will require further elucidation.

Given both the prevalence and the impact of the CRS, it is clear that there is a mandate for more research in this evolving area. This journal edition represents a beginning on the road to answers.

Mitchell H. Rosner
Anjay Rastogi
Claudio Ronco

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SAGE-Hindawi Access to Research
International Journal of Nephrology
Volume 2011, Article ID 283137, 10 pages
doi:10.4061/2011/283137

Review Article

The Cardiorenal Syndrome: Making the Connection

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Received 18 August 2010; Accepted 17 September 2010

Academic Editor: Mitchell H. Rosner

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The heart and the kidneys share responsibility for maintaining hemodynamic stability and end-organ perfusion. Connections between these organs ensure that subtle physiologic changes in one system are tempered by compensation in the other through a variety of pathways and mediators. In the setting of underlying heart disease or chronic kidney disease, the capacity of each organ to respond to perturbation caused by the other may become compromised. This has recently led to the characterization of the cardiorenal syndrome (CRS). This review will primarily focus on CRS type 1 where acute decompensated heart failure (ADHF) results in activation of hemodynamic and neurohormonal factors leading to an acute drop in the glomerular filtration rate and the development of acute kidney injury. We will examine the scope and impact of this problem, the pathophysiology associated with this relationship, including underperfuson and venous congestion, diagnostic tools for earlier detection, and therapeutic interventions to prevent and treat this complication.

1. Introduction

The heart and the kidneys share responsibility for maintaining hemodynamic stability and end-organ perfusion through a tight-knit relationship that controls cardiac output, volume status, and vascular tone. Connections between these organs ensure that subtle physiologic changes in one system are tempered by compensation in the other. As such, hemodynamic control remains stable through a wide range of physiologic conditions.

Communication between the heart and kidneys occurs through a variety of pathways. These include perfusion pressure, filling pressure, and neurohormonal activity. In particular, some of the key mediators include the sympathetic nervous system, the renin-angiotensin-aldosterone axis, and atrial natriuretic peptide. These agents have receptors in the heart, the kidneys, and the vasculature that affect volume status, vascular tone, cardiac output, and inotropy. A change in the performance of one of these organs elicits a cascade of mediators that affects the other.

In the setting of underlying heart disease or chronic kidney disease, the capacity of each organ to respond to perturbation caused by the other may become compromised. Acute or chronic heart failure may push the kidneys beyond their ability to maintain glomerular filtration, regulate fluid and electrolytes, and clear metabolic waste. Similarly, acute kidney injury or chronic kidney disease affects cardiac performance through electrolyte dysequilibration, volume overload, and negative inotropy. Clinical, cardiac, and renal parameters associated with dysfunction in the other organ are identified in Table 1.

This special relationship and the interdependence of the kidneys and the heart is well recognized. The manner in which dysfunction of one organ affects the other has recently led to the characterization of the cardiorenal syndrome (CRS). At a consensus conference of the Acute Dialysis Quality Initiative (ADQI), the cardiorenal syndrome was subclassified into 5 types [2] based upon the organ that initiated the insult as well as the acuity or chronicity of the precipitating event. The classification system for the CRS is outlined in Table 2.

This review will primarily focus on CRS type 1, where acute cardiac decompensation results in activation of hemodynamic and neurohormonal factors that lead to an acute drop in GFR and the development of AKI. We will examine the scope and impact of this problem, the pathophysiology

Table 1: Risk factors for the cardiorenal syndrome [1].

Clinical
(i) Older age
(ii) Comorbid conditions (diabetes mellitus, uncontrolled hypertension, and anemia
(iii) Drugs
(a) Antiinflammatory agents
(b) Diuretics (thiazides, loop diuretics)
(c) Angiotensin converting enzyme inhibitors/angiotensin receptor blockers
(d) Aldosterone receptor antagonists
Heart
(i) History of heart failure or impaired left ventricular ejection fraction
(ii) Prior myocardial infection
(iii) New York Hear Association functional class
(iv) Elevated cardiac troponin
Kidney
(i) Chronic kidney disease (reduced eGFR, elevated BUN, creatinine, or cystatin)

Table 2: ADQI classification system of the cardiorenal syndrome [2].

	Inciting event	Secondary disturbance
CRS type 1	Acute decompensated heart failure	Acute kidney injury
CRS type 2	Chronic heart failure	Chronic kidney disease
CRS type 3	Acute kidney injury	Acute heart failure
CRS type 4	Chronic kidney disease	Chronic heart failure
CRS type 5	Codevelopment of heart failure and chronic kidney disease	

associated with this relationship, diagnostic clues for earlier detection, and therapeutic interventions to prevent and treat this complication.

2. Epidemiology

Heart failure is a common chronic condition affecting 2% of the adult population [3] and resulting in over 1 million annual admissions [4], making it the leading cause of hospitalization in the United States among adults over the age of 65. Health expenditures for heart failure in 2008 exceeded $35 billion dollars [5]. Acute kidney injury may complicate one-third of these admissions, resulting in a three fold increase in length of stay, a greater likelihood for hospital readmission, and a 22% higher mortality rate [6–9]. This reduction in outcomes occurs with increases in serum creatinine of as little as 0.33 mg/dl, regardless of its presence at admission or its development during the course of heart failure treatment [10, 11]

In addition, approximately 25% of patients with chronic heart failure have been found to have reduced GFR [12], independent of their level of left ventricular function [13]. A prospective cohort of 754 patients with chronic heart failure found only 17% of patients had an eGFR > 90 ml/min [14]. In the large Acute Decompensated Heart Failure National Registry (ADHERE), reduced GFR affected 30% of the 107,362 individuals [15]. Furthermore, 21% of patients had serum creatinine concentrations > 2 mg/dl, and 9% had serum creatinine concentrations > 3 mg/dl [16]. This reduction in kidney function has significant impact on both morbidity and mortality [17, 18]. In a meta-analysis of 80,098 hospitalized and nonhospitalized patients, an eGFR < 53 ml/min was associated with a 51% 1-year mortality compared to a 38% 1-year mortality for an eGFR < 90 ml/min. Preserved kidney function with an eGFR > 90 ml/min was associated with a 24% 1-year mortality [19].

3. Physiology of the Cardiorenal Axis

The heart, by way of regulating the systemic circulation, and the kidneys, through their effect on extracellular fluid volume, share responsibility for the hemodynamic balance in the body. The kidneys produce a glomerular filtrate that is dependent upon perfusion pressure and afferent and efferent arteriolar tone. The arteriolar resistance is under intrinsic myogenic control, and responsive to several neurohormonal systems. The renin-angiotensin-aldosterone system (RAAS), the sympathetic nervous system (SNS), and local vasodilators such as nitric oxide (NO), adenosine, and prostaglandins contribute to maintaining the glomerular filtration rate (GFR) through conditions of increased or decreased perfusion pressure. When renal perfusion pressure decreases, angiotensin II (AII) preferentially increases the efferent arteriolar resistance to preserve intraglomerular hydrostatic pressure and maintain GFR. Simultaneously, the afferent arteriole, under control of tubuloglomerular feedback and prostaglandins, dilates to increase the transmission of perfusion pressure into the glomerulus. An elegant system

senses decreased glomerular perfusion from hypovolemia or decreased cardiac output at the macula densa and the juxtaglomerular apparatus, then activates the RAAS, nitric oxide, adenosine, and prostaglandin production to prevent dramatic changes in kidney function.

We will now explore some of the mechanisms that effect kidney function during decompensated heart failure.

3.1. Underperfusion. Acute decompensated heart failure (ADHF) results in reduced effective arterial filling volume (EAFV) [20]. This decreased EAFV diminishes renal blood flow and subsequently renal perfusion pressure. Decreased tubular sodium and chloride delivery is sensed by the macula densa and the juxtaglomerular apparatus, activating the RAAS. RAAS enhances sodium and water retention to increase EAFV and stroke volume, but comes at the detrimental cost of volume overload. Furthermore, norepinephrine is released in response to systemic hypoperfusion sensed by baroreceptors. Whereas angiotensin causes efferent arteriole constriction, norepinephrine induces both afferent and efferent arteriole constriction and increases renal vascular resistance. In a setting of low cardiac output, both angiotensin and norepinephrine cause decreased renal blood flow (RBF), diverting blood to the coronary and cerebral circulations. When the normal compensatory mechanisms such as NO, bradykinin, adenosine, and prostaglandins are unable to maintain GFR in the setting of decreased RBF, the groundwork for renal ischemia is laid. It appears, therefore, that the cardiovascular effects on hemodynamics and the renal effects on extracellular fluid volume are in constant flux.

An imbalance in this relationship results in the CRS. In the setting of heart failure where low cardiac output and an overactive neurohormonal system push the compensatory limits, a simple insult such as NSAIDS or aggressive diuresis can precipitate acute kidney injury [21]. NSAIDs inhibit the protective effect of prostaglandins to dilate the afferent arteriole, while over diuresis might lead to further decreased EAFV. Diuretics are effective when properly dosed to allow reequilibration of fluid from the interstitial compartment into the intravascular compartment. If the rate of diuresis exceeds this shift, then kidney dysfunction occurs. Other observations have suggested that RBF is the most important determinant of GFR in patients with CHF [22].

3.2. Venous Congestion. While it is true that decreased forward flow as a result of decreased cardiac output in ADHF can cause acute deterioration in kidney function, there are several reasons why this mechanism fails to completely explain the development of the CRS. First, altered hemodynamics alone are inadequate to explain the mechanism of kidney injury in ADHF as redundant feedback mechanisms exist to prevent it. Second, the CRS has been observed in patients with diastolic dysfunction who have normal left ventricular systolic function [14]. In the ADHERE registry, acute kidney injury occurred at similar rates in patients with both systolic and diastolic dysfunction [23]. And finally, subgroup analysis of the ESCAPE trial showed evidence that poor forward flow alone was insufficient to explain worsening kidney function. In this trial, an improved cardiac index was not associated with improved renal outcomes, but increased CVP and atrial pressures were associated with decreased kidney function [24].

Observations dating back to the 1930s have suggested that renal venous congestion could also contribute to decreased glomerular filtration. Experiments conducted on canine models revealed that increased venous pressure in the kidneys caused changes in urinary sodium, chloride, and urea excretion similar to decreased arterial pressure. Urine flow decreased when renal venous pressures were increased to 20 mmHg. This also led to a drop in glomerular perfusion pressure, and a reduction in GFR [25]. It is hypothesized that increased venous pressure distends the venules surrounding the distal nephron. This leads to compression of the tubule, increased tubular fluid pressure, and backleak of filtrate into the interstitium. An increased interstitial pressure then results in venous congestion and interstitial hypoxia [26]. Furthermore, as hydrostatic pressure within the Bowman's capsule increases, GFR fails and the RAAS is activated and the SNS is triggered [27]. The sequence of events is shown in Figure 1.

Studies in human subjects have also demonstrated that increased central venous and right atrial pressure are associated with worsening kidney function as well as increased mortality [29, 30]. Damman and colleagues have demonstrated that increased venous pressure is an independent determinant of glomerular filtration in patients with heart failure [28]. In this study the lowest glomerular filtration rate was observed in patients with lowest renal blood flow and highest right atrial pressures.

3.3. Intra-Abdominal Hypertension. Intraabdominal hypertension might be yet another mechanism contributing to the CRS. Elevated intraabdominal pressure from ascites and abdominal wall edema is also prevalent in patients with ADHF, and associated with worsening kidney function [31]. Several studies have suggested that the deterioration in the kidney function is not due to direct parenchymal pressure on the kidneys, but rather due to elevated central venous pressure, arterial underfilling, and renal venous congestion [32, 33]. The decline in kidney function from increased intraabdominal pressure is mechanistically related to the venous congestion described above.

4. Mediators of the Cardiorenal Syndrome

There are a variety of neurohormonal mediators associated with the deterioration of kidney function in ADHF. Understanding these-mediators and effectors yields insight into the diagnosis and therapy of CRS.

4.1. Renin-Angiotensin-Aldosterone System. The CRS occurs with both hypoperfusion associated with decreased cardiac output as well as venous congestion. The actions of the RAAS, beyond its role to maintain hemodynamics, may explain this cardiorenal connection.

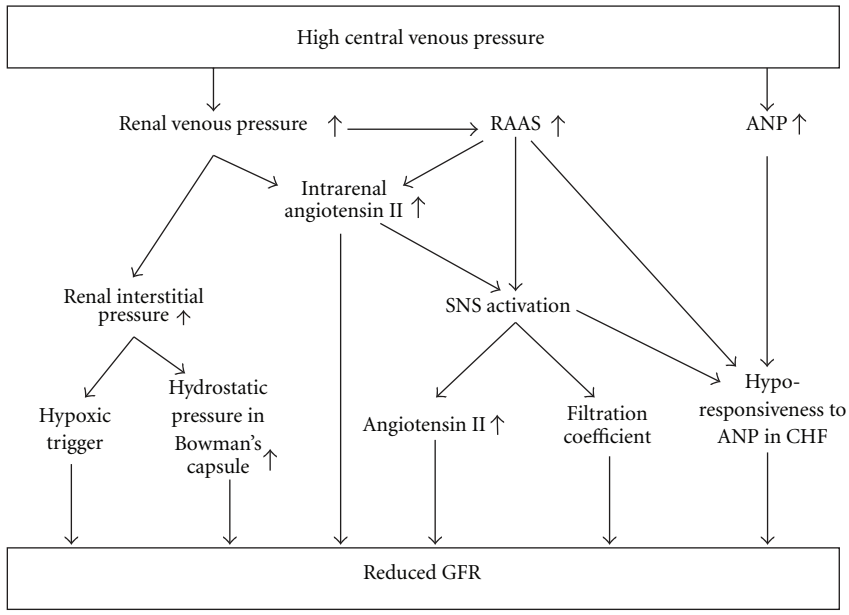

Figure 1: Pathophysiology of the relation between venous congestion and reduced glomerular filtration rate (GFR). Reprinted with modification from Damman et al. [28].

Activation of RAAS by hypoperfusion activates the sympathetic nervous system (SNS) [34], and mediates the release of reactive oxygen species (ROS) and mediators of vascular inflammation [35]. Angiotensin II activates both NADH-oxidase and NADPH-oxidase [36], which then generates reactive oxygen species. Studies have demonstrated this activity in vascular smooth muscle cells, cardiac myocytes, and both renal tubular cells [37] and glomeruli in the kidneys. ROS, specifically superoxides, have been implicated in organ injury and inflammation. The ensuing oxidative stress results in a proinflammatory state activating chemokines such as IL-1, IL-6, and TNF alpha, and attracting leucocytes. Furthermore, studies have shown that the effect of NADPH-oxidase mediated ROS release can be attenuated by angiotensin converting enzyme (ACE) inhibition.

Angiotensin II also has a role in chemokine regulation and monocyte recruitment. Angiotensin II increases Monocyte Chemoattractant Protein-1 (MCP-1) in mesangial and mononuclear cells by a mechanism dependent on nuclear factor-κB (NF-κB) activation [38]. These monocytes and chemokines play a major role in the propagation of kidney injury [39]. Angiotensin II also activates the sympathetic nervous system through its effect on the vasomotor center in the brain. This was established by showing increased muscle sympathetic nerve activity (MSNA) in patients with kidney failure [40]. Studies using ACE inhibitors and angiotensin receptor blockers (ARB) have shown decreased MSNA and decreased sympathetic activity [41, 42]. Thus AII seems to play a direct role in renal injury [43] and direct damage to the glomerular filtration barrier [44, 45].

4.2. Nitric oxide and Reactive Oxygen Species Disequilibrium. Nitric oxide, an endothelium-derived relaxing factor, is a vasodilator that acts to regulate vascular tone, blood pressure, and smooth muscle hypertrophy through downregulation of ACE and the AII type 1 receptor. NO therefore represents a physiologic antagonist of AII at both the glomerular and tubular levels [46, 47]. It also plays a role in tubuloglomerular feedback through dilation of the afferent arteriole [48]. In decompensated heart failure, RAAS activation causes angiotensin mediated hypertension through increased systemic vascular resistance, greater renal perfusion pressure through preferential efferent arteriolar vasoconstriction, and renal oxidative stress through enhanced NADPH-oxidase activity in rats [49]. Reduced activity of superoxide dismutase (SOD) is thought to be involved in increased ROS generation. Subsequently, there is a shift in the NO/ROS system to the ROS side. Several factors contribute to this shift. In heart failure, asymmetric dimethyl arginine (ADMA) levels are increased. ADMA is a novel cardiovascular risk factor that decreases NO levels [50]. Even mild heart failure is associated with decreased renal perfusion by way of NO inhibition. Also, Endothelin I (ET 1) is implicated in vasoconstriction, causing mesangial cell contraction and mesangial cell mitogenesis [51]. Whereas AII stimulates the release of ET 1, NO inhibits ET 1 release from endothelial cells. An imbalance in favor of more ET 1 production causes endothelial dysfunction as well as glomerular and interstitial damage [52].

4.3. Other Mediators. Atrial natriuretic peptide (ANP) and brain natriuretic peptide (BNP) are released in response to stretch of the cardiac chambers, and play a role in regulation of ECFV by inducing sodium and water loss. They are elevated in both heart failure and reduced kidney function. Although they are an ideal therapeutic target, their role in the pathophysiology of CRS is not known.

Erythropoietin is purported to decrease apoptosis in renal cells and cardiac myocytes by decreasing oxidative stress [53]. Small trials have revealed that heart failure patients who received erythropoietin had improved kidney function [54], but their place in the treatment of CRS cannot be confirmed without long-term studies.

Antidiuretic hormone (ADH) levels are elevated in HF due to nonosmotic stimuli from baroreceptor stimulation [55]. Antagonism of ADH would seem to have a role in the CRS, but studies of vasopressin receptor 2 antagonists did not result in improvement in kidney function [56].

There is direct evidence to demonstrate that HF is associated with tubulointerstitial damage. A recent study by Damman and colleagues showed that congestive heart failure is associated with increased markers of tubulointerstitial damage such as N-acetyl-beta-D-glucosaminidase (NAG), kidney injury molecule 1 (KIM-1), and neutrophil gelatinase associated lipocalin (NGAL) [57]. Other studies have also demonstrated renal tubular and interstitial damage as well [58].

In summary, it appears that regardless of whether decreased perfusion occurs as a result of hypoperfusion or venous congestion, the consequent processes resulting in kidney injury are the same. RAAS activation results in increased AII which stimulates NADH and NADPH-oxidases. The resulting NADPH/NADH suppresses superoxide dismutase, and increases reactive oxygen species. This results in the well known cascade of hypoxic ischemic injury, inflammation, apoptosis and cell death as shown in Figure 2.

5. Diagnosis

One of the cornerstones of CRS therapy is the early identification of worsening kidney function. This can be accomplished with the use of biomarkers that become detectable before the traditional tests for kidney function, including glomerular filtration rate or serum creatinine (Figure 3). Biomarkers such as NGAL, NAG, and KIM-1 have been implicated in tubulointerstitial damage and have been used to identify acute kidney injury [61–63]. Serum cystatin C is elevated earlier than creatinine. Furthermore, while cystatin C in the serum is a marker of reduced glomerular filtration, urinary cystatin C is a marker of tubular dysfunction [64]. Other biomarkers that have proven useful include BNP, IL-18, and Fatty Acid Binding Protein (FABP). Thus detection of these biomarkers might be used to diagnose CRS at an earlier time point, facilitate targeted therapy for CRS by modifying pharmacologic therapy, and monitor progression of disease. Nevertheless, a higher index of suspicion for identifying patients at CRS is needed as testing for biomarkers at this time is expensive.

Tests for volume status and end-organ perfusion are also useful in the diagnosis of CRS. Bioimpedence vector analysis is effective at assessing hydration status and BNP measurement provides an assessment of cardiac filling, although it is often elevated in patients with AKI without overt fluid overload. Urine sediment examination should be performed in differentiating CRS from other causes of AKI by excluding pathologic cells, casts, or crystals. Hyponatremia, when present, may indicate excess ADH and portend an overall poor prognosis. Although patients with ADHF have a poor prognosis to begin with, ensuing AKI that accompanies the CRS confers an even more dire condition.

6. Therapies for the Cardiorenal Syndrome

In patients with ADHF who present with worsening kidney function, management is challenging and effective therapies are lacking [66]. This is in large part due to the exclusion of patients with kidney dysfunction in many of the trials analyzing treatment for heart failure. A rational approach would be multi-modal, focusing on the underlying pathophysiology of CRS with the goal of disrupting the cardiorenal connections. Ideally, therapy for CRS would prevent the fulminant decompensation that jeopardizes kidney function. This requires use of biomarkers in appropriate settings to detect early changes in kidney function, and represents an opportunity for initiation of immediate treatment.

6.1. Diuretics. Although diuretics have a major role in the symptomatic treatment of heart failure, their effectiveness is limited due to diuretic resistance in CRS. Although renal hypoperfusion may require a reduction in the dose of diuretics, venous congestion may necessitate additional diuresis. Thus, delicate fluid management may involve monitoring urine flow, central venous pressures, and possible cardiac output to optimize renal physiology. Nevertheless, CVP monitoring is cumbersome and costly. A forthcoming trial, "Determining Optimal Dose and Duration of Diuretic Treatment in People With Acute Heart Failure (DOSE-AHF) study," is designed to answer these questions with regard to the role of diuretics in CRS [67].

6.2. Natriuretic Peptides. Several studies have explored the pharmacologic properties of natriuretic peptides in the treatment of heart failure. Nesiritide, a recombinant natriuretic peptide, decreases preload, after load, and pulmonary vascular resistance, while inducing diuresis. Because of its natriuretic and aquaretic properties, these agents seem to be an ideal candidate to relieve the venous congestion in CRS. Nevertheless, no studies have shown benefit on kidney function. In fact, a meta-analysis demonstrated poorer renal outcomes with nesiritide [68]. In one study, nesiritide when compared to placebo had no effect on glomerular filtration rate, renal plasma flow, urine output, and sodium excretion in patients with CRS [69]. To address these controversies, the "Acute Study of Clinical Effectiveness of Nesiritide in Decompensated Heart Failure Trial (ASCEND)" is underway [70].

6.3. Vasopressin Antagonists. By making use of their aquaretic properties, vasopressin (V2 receptor) antagonists have been used in severe heart failure. However, clinical trials such as the "Efficacy of Vasopressin Antagonism in Heart Failure Outcome Study With Tolvaptan (EVEREST)" trial showed

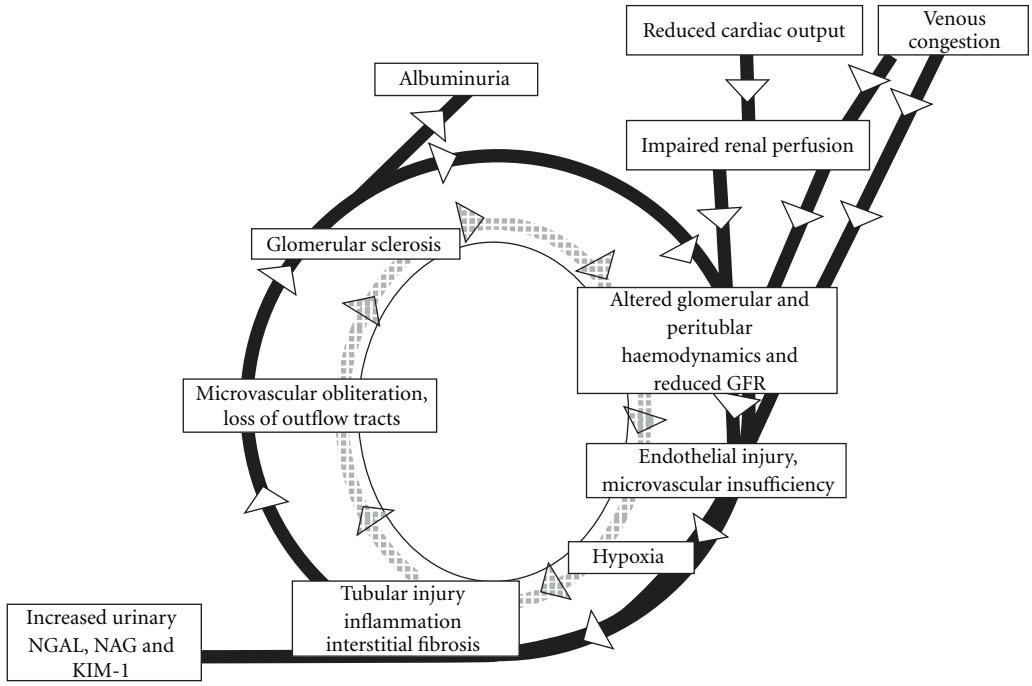

Figure 2: Hypothetical vicious circle of decreased glomerular function, endothelial injury, and tubular damage in heart failure. GFR: glomerular filtration rate. NGAL: neutrophil gelatinase associated lipocalin. NAG: N-acetyl-beta-D-glucosaminidase. KIM-1: kidney injury molecule 1. Adapted and reprinted with permission from Norman and Fine [59] and Damman et al. [60].

no benefit of tolvaptan, a vasopressin antagonist, on all-cause mortality or the combined end point of cardiovascular mortality or hospitalization for ADHF [56]. Kidney function remained stable throughout this trial, and the use of vasopressin antagonists in the CRS conundrum may be limited to those patients complicated by hyponatremia. Although other studies showed there was some renal benefit [71], the cost of these medications would prohibit them from being used routinely.

6.4. Adenosine Antagonist. Adenosine is generated locally in the macula densa in response to diuretics that block sodium and chloride absorption, resulting in afferent arteriolar constriction and decreased GFR. Antagonizing adenosine might have a role in preserving kidney function in CRS. To this extent, KW-3902, an adenosine A1-receptor antagonist, was found to improve kidney function and decrease diuretic resistance in patients with ADHF and CRS [72].

6.5. Ultrafiltration. Ultrafiltration is usually reserved for diuretic resistance in patients with ADHF. However, in CRS it might have an early role by rapidly reducing venous pressure. In two trials of ultrafiltration in patients with ADHF, the "Relief for Acutely Fluid-Overloaded Patients With Decompensated Congestive Heart Failure (RAPID-CHF)" and "Ultrafiltration Versus Intravenous Diuretics for Patients Hospitalized for Acute Decompensated Congestive Heart Failure (UNLOAD)," there was marked weight loss and relief of heart failure symptoms [73, 74], but no improvement of kidney function. Nevertheless, published case reports have shown improved kidney function with ultrafiltration [75]. A final verdict might come with the much awaited "Cardiorenal Rescue Study in Acute Decompensated Heart Failure (CARRESS-HF)" study which will assess the effectiveness of ultrafiltration in ADHF and CRS [76].

6.6. Inotropes. Although the use of inotropes in systolic heart failure may improve the EAFV and cardiac output, the inherent adverse effects of these agents, including arrhythmias and myocardial ischemia, have limited their utility. In fact, the "Outcomes of a Prospective Trial of Intravenous Milrinone for Exacerbations of Chronic Heart Failure (OPTIME-CHF)" trial revealed increased mortality and poorer outcomes in the milrinone arm [77].

Levosimendan, a phosphodiesterase inhibitor, has been studied in CRS. In one study, levosimendan resulted in improved GFR when compared to dobutamine [78]. However, another study of levosimendan and dobutamine did not show any benefit [79]. At this time, the role of inotropic agents in CRS remains unknown.

6.7. Neurohormonal Blockade. The role of RAAS blockade with ACE inhibitors, ARB, direct renin inhibitors, or aldosterone antagonists in CRS is also unclear. While most of these

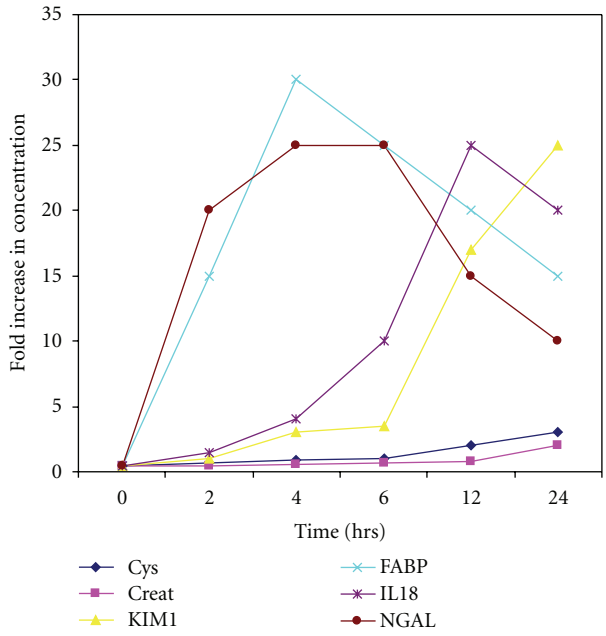

Figure 3: Urinary biomarker profiles in subjects who develop AKI after cardiopulmonary bypass (CPB) surgery. Abbreviations: AKI: acute kidney injury, defined as a 50% increase in serum creatinine from baseline; NGAL: neutrophil gelatinase associated lipocalin; IL-18: interleukin 18; KIM-1: kidney injury molecule 1; L-FABP: liver-type fatty acid binding protein; Cys: cystatin c; creat: creatinine. Adapted and modified with permission from Devarajan [65].

medications cause an acute drop in GFR through the dilatory effect on the efferent arteriole, they have long-term reno- and cardioprotective effects. Therefore, patients who are prone to develop CRS yet able to tolerate a small reduction in GFR, up to 30% from the baseline, may benefit from these agents. As RAAS has been implicated in oxidative damage, its interruption though ACE inhibition or angiotensin blockade may prevent the development of CRS.

Similar to RAAS blockade, beta blockers through their effect on the SNS may have a role in the long-term prevention of adverse cardiac events and in remodeling. However in CRS, their role is limited by the altered hemodynamics. Unless the underlying etiology of ADHF is myocardial infarction, beta blockers are often held until the patients are hemodynamically stable.

7. Summary

Cardiorenal syndrome represents a disruption of the robust relationship between the kidneys and the heart to preserve hemodynamics and maintain organ function. Despite the ability to adjust filling pressures, afterload, inotropy, cardiac output, and volume status in order to compensate for a wide range of perturbations, dysfunction in either of these organs creates a susceptibility to dysfunction in the other. The mechanisms for worsening kidney function in ADHF are likely due to underperfusion from reduced cardiac output, venous congestion impairing tubular function and glomerular filtration, and activation of neurohormonal mediators that effect renal blood flow and glomerular autoregulation. The RAAS, SNS, and NO pathways are instrumental in preserving kidney function in compensated HF, but play an aggravating role once HF acutely worsens.

Measures to reverse kidney dysfunction in ADHF require the early recognition and immediate treatment of CRS. Agents that target the physiologic mechanisms of CRS may be effective in restoring kidney function. These include diuretics, natriuretic peptides, or ultrafiltration to reduce venous congestion, inotropes to augment cardiac output, and RAAS and SNS blockade. Despite these interventions, CRS identifies patients at the limits of hemodynamic compensation and most susceptible to increased morbidity and mortality.

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SAGE-Hindawi Access to Research
International Journal of Nephrology
Volume 2011, Article ID 913029, 6 pages
doi:10.4061/2011/913029

Review Article

Cardiorenal Syndrome: An Unsolved Clinical Problem

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Received 20 August 2010; Revised 28 January 2011; Accepted 28 March 2011

Academic Editor: Anjay Rastogi

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The clinical relevance of the bidirectional cross-talk between heart and kidney is increasingly recognized. However, the optimal approach to the management of kidney dysfunction in heart failure remains unclear. The purpose of this article is to outline the most plausible pathophysiologic theories that attempt to explain the renal impairment in acute and chronic heart failure, and to review the current treatment strategies for these situations.

1. Introduction

Heart and kidney are inextricably linked to maintain homeostasis. Communication between these two organs occurs at multiple levels including the sympathetic nervous system (SNS), the renin-angiotensin-aldosterone system (RAAS), the antidiuretic hormone, endothelin, or the natriuretic peptides. The dysfunction of one of them contributes to the dysfunction of the other; renal dysfunction impairs cardiac performance, which again leads to further impairment of renal function. The term "cardiorenal syndrome" (CRS) was coined to define this situation, but a consensus of the diagnostic criteria has not been reached yet. Initially, it was characterized as a state in which therapy to relieve congestive heart failure (HF) symptoms was limited by further worsening renal function [1]. Although this definition does not accurately describe the complexity of its nature, it portrays a common situation in daily clinical practise. A broader definition of the CRS was developed by the Acute Dialysis Quality Initiative [2].

The CRS was classified into five categories, according to the underlying etiologies and the nature of concomitant cardiac and renal dysfunction (Table 1). Heart failure seems to be the primary failing organ in two of the five described features. CRS type 1 occurs when acute decompensated heart failure (ADHF) leads to acute kidney injury. CRS type 2 refers to the development of a progressive worsening of renal function (WRF) in the setting of chronic heart failure (CHF). Both, acute and progressive development of renal dysfunction in patients with heart failure, have been associated with independently worse outcomes compared with preserved renal function [3–13]. Therefore, a precise understanding of the pathophysiology of this syndrome is needed to provide the rationale for management strategies.

2. Pathophysiology

The pathophysiology of the cardiorenal syndrome remains unclear but can be attributed to three main factors: low-cardiac output, elevation of both intra-abdominal and central venous pressures, and neurohormonal and inflammatory activation [14, 15]. The terms "backward failure" and "forward failure" have been historically used to classify HF syndrome. Although not commonly used nowadays, this classification allows an intuitive approach to understand the underlying mechanisms of these forms of CRS. Forward failure implies arterial underfilling, which leads to a low-flow state. This appears to be one of the cornerstones in the development of CRS, but not the only one. Improvement in cardiac index did not always result in improved renal function. Multiple studies support this conclusion: The Evaluation Study of Congestive Heart Failure and Pulmonary Catheterization Effectiveness (ESCAPE) trial associated

baseline kidney dysfunction (estimated glomerular filtration rate, -GFR-, <60 mL/min) at admission and at discharge with an increased risk of death and rehospitalization [16]. Patients randomized to the group, in which therapy was guided by clinical assessment and a pulmonary artery catheter (PAC), presented significantly less deterioration of kidney function, compared with a therapy based on clinical assessment alone, but this did not imply an improvement in clinical outcomes in patients with baseline CKD. Incidence of WRF during hospitalization (serum creatinine > 0.3 mg/dL) was similar in both arms, and was not associated to increased outcomes of death or rehospitalization. Among hemodynamic parameters measured in the PAC arm, only right atrial pressure correlated weakly with baseline serum creatinine ($r = 0.165$, $P = .03$). Similar results were obtained by Mullens et al. [17]. They studied 145 patients admitted with ADHF and treated with intensive medical therapy guided by pulmonary artery catheter. Patients who developed WRF did not have a lower cardiac index on admission or at discharge when compared with those without WRF. The mean baseline cardiac index was significantly greater in subjects who developed WRF versus those who did not (2.00 ± 0.8 l/min/m^2 versus 1.8 ± 0.4 l/min/m^2, $P = .008$). At follow-up, the mean cardiac index and the central venous pressure remained superior (2.7 ± 0.7 l/min/m^2 versus 2.4 ± 0.5 l/min/m^2, $P = .01$ and 11 ± 8 mm Hg versus 8 ± 5 mm Hg, $P = .04$, resp.) in subjects who developed WRF.

These findings support the hypothesis that there must be another mechanism that contributes to renal impairment in heart failure. Rising renal venous pressure limits urine formation and renal flow. Several mechanisms have been proposed to explain this situation. Backward failure implies that systemic venous congestion also affects renal venous pressure and function (congestive kidney failure), by direct hypoxic damage or through RAAS/SNS stimulation way.

A substudy of the Studies of Left Ventricular Dysfunction (SOLVD) established the prognostic implication of jugular venous pressure on patients with CHF [18]. Patients with increased venous pressure had a significantly higher serum creatinine level (115 ± 27 versus 106 ± 27 μmol/L). Interestingly, Mullens et al. also described that patients who developed WRF had greater central venous pressure on admission (18 ± 7 mm Hg versus 12 ± 6 mm Hg, $P = .001$) and after intensive medical therapy (11 ± 8 mm Hg versus 8 ± 5 mm Hg, $P = .04$) [17]. The development of WRF occurred less frequently in patients who achieved a central venous pressure <8 mm Hg. Damman et al. evaluated right atrial pressure and cardiac index by right heart catheterisation, in 51 patients with cardiac dysfunction, secondary to pulmonary hypertension [19]. In a multivariate analysis, low renal blood flow and high right atrial pressure were independently associated with lower GFR.

Intra-abdominal pressure has been considered an alternative pathway to explain how decompensated HF may lead to WRF. Increased abdominal pressure may lead to renal impairment by a "compressing effect" in renal parenchyma. Hence, elevated intra-abdominal pressure (defined as >8 mm Hg) has been associated with significantly lower GFR compared with those with normal IAP in patients with advanced decompensated HF (mean LVEF 19%) [20]. These authors also studied the effect of mechanical fluid removal to reduce IAP in patients with ADHF, showing a strong correlation ($r = 0.77$, $P < .001$) was observed between improved renal function in patients reduction in IAP and with baseline elevated IAP [21].

In any case, hemodynamic changes do not fully explain the whole cardiorenal connection. Interventions focused on the interactions of the networks which link both systems (RAAS, imbalance between reactive oxygen species and nitric oxide, sympathetic nervous system and inflammation processes) might help to control the progression of the CRS [22].

Table 1: Cardiorenal syndrome: classification.

CRS type 1	Development of acute kidney injury in the setting of a sudden deterioration of heart function
CRS type 2	Progressive renal dysfunction in the setting of chronic cardiac dysfunction
CRS type 3	Abrupt and primary worsening of renal function leads to acute heart failure
CRS type 4	Primary chronic kidney disease contributes to the progressive development of chronic heart failure
CRS type 5	Combined cardiac and renal dysfunction caused by a systemic illness

Table 2: Summary of recommendations for clinical practice.

(i) Search for reversible causes: concomitant medications, hypovolemia, hypotension, and urinary tract obstruction
(ii) Loop diuretics are useful to alleviate congestive symptoms but should be used with caution: check renal function and serum electrolytes closely
(iii) ACEI, ARA II, and aldosterone antagonists should be add, in case of heart failure and systolic dysfunction: check renal function and serum electrolytes closely
(iv) Ultrafiltration may be considered refractory to diuretics in symptomatic patients
(v) Correcting anemia should be considered in cardiorenal syndrome type 2

3. Management of Worsening Renal Function in the Setting of Acute Decompensated Heart Failure

Despite its common pathophysiology, each CRS's type embraces a broad spectrum of clinical features. Therefore, therapies should be adapted to each single patient's own situation (Table 2).

Loop diuretics are first-line agents to alleviate congestive symptoms [23]. Although their use is widespread, there is little evidence of their influence in managing CRS. Their use may be associated with electrolyte abnormalities, further neurohormonal activation and worsening renal function. In addition, they may increase the risk to develop adverse effects of concomitant medications, such as angiotensin converting enzyme inhibitors (ACEI), angiotensin II receptor blockers

(ARB), or spironolactone. Hence, the first problem to deal with is to strike a balance between removing volume to relieve congestion without stimulating adverse effects.

There is lack of evidence in the literature about this topic, not only in AHF, but also in CKD patients, as they are systematically excluded from randomized trials. High-dose administration of intravenous loop diuretics has been associated with worse outcomes in HF patients [24, 25]. Results of the Dose Optimization Strategy Evaluation (DOSE) trial, recently presented at the American College of Cardiology (ACC) 2010 Scientific Sessions, may highlight this matter [26]. It included acute heart-failure patients with a prior diagnosis of chronic heart failure (CHF) and daily outpatient use of oral loop diuretics (80 mg to 240 mg) for at least one month. Patients with serum creatinine >3 mg/dL were excluded. Patients were randomized to either high dose (2.5 × their daily chronic oral furosemide dose given iv) or low dose (their daily chronic oral furosemide dose given iv) and were also randomized to dosing via intravenous bolus or continuous infusion. Median baseline creatinine was 1.5 mg/dL. The primary endpoints were symptom resolution and change in serum creatinine from admission to 72 hours. There were no significant differences among the different dosing strategies for any of the two endpoints. The high-dose strategy showed greater symptom improvement, ($P = .06$), but was also associated with mild increases in creatinine levels, defined as $a > 0.3$ mg/dL rise in creatinine. There were no differences among groups for death or rehospitalization outcomes. Results of this trial suggest that, apparently, an overaggressive use of loop diuretic is as safe as a conservative treatment. If the response to loop diuretics is inadequate, a thiazide should be added in a dose determined according to the patient's renal function. A synergistic response can result in profound diuresis. These patients should, therefore, be followed closely to prevent volume, magnesium, and potassium depletion. Again, this empirical management, which results to be effective in daily practise, has not been tested.

Vasodilators, such as intravenous nitroglycerin, are recommended at an early stage for AHF patients without hypotension or serious obstructive valvular disease [23]. The reduction in venous pressure may improve transrenal blood flow while protecting renal function, but doses that decrease blood pressure may cause a decline in renal perfusion and further activation of the RAAS. Although it has been published that isosorbide dinitrate should have a beneficial effect in patients with AHF [27], no randomized controlled studies have been carried out to evaluate its role neither in cardiorenal syndrome nor even in AHF. Nesiritide is a recombinant analogue of human brain natriuretic peptide for exogenous administration. The ASCEND trial (A Study testing the Effectiveness of Nesiritide in Patients with Acute Decompensated Heart Failure) enrolled 7,141 patients with severe HF, to determine whether nesiritide was superior to placebo in reducing the HF related hospitalization rate or all cause mortality at 30-days and improvement in dyspnea at six or 24 hours. Patients were randomly assigned to continuous intravenous nesiritide or placebo plus standard treatment for 30 days. Compared with placebo, nesiritide was not associated with a reduction in 30 day death or HF rehospitalization (10.1% versus 9.4%; $P = .31$). Data from ASCEND-HF showed no association between nesiritide and reduced renal function [28]. Vasopressin antagonists selectively inhibit the V2 receptor of renal distal tubules and collecting duct, increasing aquaresis and serum sodium in those who are hyponatremic. Safety and efficacy of these agents have been tested in several trials in patients with AHF during the acute phase. Although they have not proven long-term benefit on clinical outcomes, they could have a favorable effect on renal hemodynamics [29].

Adenosine A1 receptor antagonists improve renal blood flow and increase sodium excretion, by enhancing natriuresis, with preserving GFR, in combination with furosemide. An ongoing trial (A Study of the Selective A1 Adenosine Receptor Antagonist KW-3902 for Patients Hospitalized With Acute HF and Volume Overload to Assess Treatment Effect on Congestion and Renal Function, PROTECT-2 study) is evaluating its application in ADHF patients.

Ultrafiltration helps to remove the volume overload in symptomatic patients refractory to diuretics. The Ultrafiltration versus Intravenous Diuretics for Patients Hospitalized for Acute Decompensated Congestive Heart Failure (UNLOAD) trial demonstrated a greater weight loss in ultrafiltration group, as well as lower rehospitalization rates and emergency department visits, compared to a diuretic-based strategy [30].

Inotropic agents should be considered in patients with low-output states in the presence of signs of hypoperfusion or congestion despite the use of vasodilators and/or diuretics [23]. Dobutamine has been associated to an increase in renal blood flow, proportional to the increase in cardiac index. Low-dose dopamine has also been associated with a theoretical effect on renal blood flow. Although it has been proposed that an improvement in cardiac output might lead to preserving renal function, this widespread empirical therapy has not been tested in randomized trials. Only milrinone and levosimendan have been evaluated in this situation, and none of them have demonstrated an improvement in renal function [15, 31].

4. Management of Renal Dysfunction in Chronic Heart Failure

Mechanisms which lead to a progressive renal impairment in patients with CHF are still unclear. Several factors may contribute to this situation, including hemodynamic changes, diuretic's side effects, or a microvascular damage secondary to a concomitant illness (such as hypertension or diabetes).

Although many pharmacological and no pharmacological therapies have proven to be an advantage on survival in HF, their prescription is often limited by the fear to develop complications attributable to WRF. The results of the Registry to Improve the Use of Evidence-Based Heart Failure Therapies in the Outpatient Setting (IMPROVE HF) have been recently published [32]. The aim of this prospective study was to evaluate the adherence

to AHA/ACC guidelines recommendations in the management of chro-nic heart failure (ACEIs/ARB, β-blockers, aldoste-rone antagonists, cardiac resynchronization therapy, implantable cardioverter defibrillator, anticoagulation if atrial fibrillation/flutter, and patient education) and to determine the influence of renal dysfunction in applying these therapies. It included 13,164 nonhospitalized patients with severe systolic dysfunction (LVEF < 35%). Patients were classified into four groups, according to their CKD stage. Mean LVEF was around 25% in all groups. About 52% of the patients had a GFR <60 mL/min/1.73 m^2. The use of ACEI/ARB (87.4% in patients with GFR >90 mL/min/1.73 m^2 versus 57.9% in patients with GFR <29 mL/min/1.73 m^2, $P < .001$), β-blockers (90.4% in patients with GFR >90 mL/min/1.73 m^2 versus 86.2% in patients with GFR <29 mL/min/1.73m^2), and aldosterone antagonists was significantly lower in patients with a higher stage of CKD. Multivariate analysis showed that the severity of CKD was an independent predictor of adherence to ACEI/ARB (HR 0.94; CI 95% 0.88–0.99; $P = .018$), but not in the other recommended interventions.

Treatment with ACEI improves ventricular function (as evidenced by an increased ejection fraction and decreased ventricular size) and patient well-being, reduces hospital admission for worsening HF, and increases survival. This therapy should be used in all patients with symptomatic HF and a LVEF < 40% [23]. As it is common to observe a significant increase in the serum creatinine concentration (>0.3 mg/dL) within the initiation of treatment with ACEI, renal function should be closely monitored. ESC Guidelines of management of HF accept a 50% increase in creatinine serum level from baseline or an absolute concentration of 3 mg/dL, whichever is lower. If creatinine rises between 3–3.5 mg/dL, ESC guidelines recommend to halve dose of ACEI. Treatment with ACEI must be interrupted if creatinine serum concentration rises above 3.5 mg/dL. ARB may be considered as an alternative in patients who do not tolerate ACEI. The influence on cardiorenal protection of RAAS dual blockade, when an ARB is used in conjunction with an ACEI, has also been analyzed in several trials. Among patients with HF, combination therapy was associated with further impairment in kidney function [33]. An aldosterone antagonist should be added to treatment in symptomatic patients with HF and an LVEF < 35% [23]. Similar to ACEI, renal function should be closely monitored. If creatinine rises above 2.5 mg/dL (or potassium > 5.5 mmol/L), ESC guidelines suggest to halve the spironolactone or eplerenone doses. When serum creatinine is >3 mg/dL (or potassium > 6 mmol/L), treatment with aldosterone antagonists must be discontinued.

The Canadian Cardiovascular Society includes among its recommendations some options of management for these patients. Thus, renal function must be checked daily in patients with heart failure and increasing serum creatinine more than 30% from baseline, and ACEI, ARB, and aldosterone dose should be reduced until renal function stabilizes. In oliguric HF patients treatment with diuretics, ACEI, ARB, or aldosterone should be reviewed daily. Routine use of ACE inhibitors, ARBs or spironolactone in the setting of severe renal dysfunction (serum creatinine levels greater than 250 μmol/L or an increase of more than 50% from baseline) is not routinely recommended [34].

Despite these recommendations, it is important to emphasize that serum creatinine concentration is not an accurate measure of GFR. Creatinine serum levels vary according to gender, person's size, and muscle mass, and this must be taken into account. The most common formula for calculating the GFR has not been validated in acute renal failure, but there is on increasing interest in new renal biomarkers for the diagnosis and classification of CRS, such as cystatin C or the neutrophil gelatinase-associated lipocalin [35].

Anemia is a frequent and multifactorial finding in both CKD and CHF. Its prevalence is similar among patients with preserved and depressed LVEF. Neither ACC/AHA nor ESC guidelines establish the correction of anemia as a systematic target in patients with HF, although it has been associated with poor clinical outcomes. Even though there is actually no definitive evidence to the optimum approach for the management of anemia in patients with CHF which develop a progressive renal dysfunction (cardiorenal syndrome type 2), a pragmatical strategy for anemia correction, based on CKD guidelines and HF trials, has been proposed [36]. Because of the adverse cardiovascular effects of higher hematocrit in CKD trials, authors suggest a target hemoglobin of 10–12 g/dL at clinical practise. If Hb drops below 10 g/dL, iron deficiency should be excluded before starting therapy with erythropoiesis stimulating agents. Nonetheless, patients with HF might benefit from more aggressive anemia correction in view of the results of several cardiology trials [36–39].

5. Conclusion

Cardiorenal syndrome implies several interrelated mechanisms in patients with heart failure. The appropriate strategy to take care of these patients remains unclear, both in acute and chronic clinical situations. In accordance with the most plausible underlying pathophysiological mechanisms, treatment targets should be oriented toward an adequate intravascular volume management and to ensure a proper renal perfusion. Although there are encouraging advances around this unsolved clinical problem, further investigation should consider the progressive inclusion of patients with advanced renal impairment to allow a better understanding of cardiorenal syndrome.

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SAGE-Hindawi Access to Research
International Journal of Nephrology
Volume 2011, Article ID 762590, 10 pages
doi:10.4061/2011/762590

Review Article

Cardiorenal Syndromes: Pathophysiology to Prevention

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Received 21 August 2010; Accepted 30 September 2010

Academic Editor: Mitchell H. Rosner

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There is a strong association between both acute and chronic dysfunction of the heart and kidneys with respect to morbidity and mortality. The complex interrelationships of longitudinal changes in both organ systems have been difficult to describe and fully understand due to a lack of categorization of the common clinical scenarios where these phenomena are encountered. Thus, cardiorenal syndromes (CRSs) have been subdivided into five syndromes which represent clinical vignettes in which both the heart and the kidney are involved in bidirectional injury and dysfunction via a final common pathway of cell-to-cell death and accelerated apoptosis mediated by oxidative stress. Types 1 and 2 involve acute and chronic cardiovascular disease (CVD) scenarios leading to acute kidney injury (AKI) or accelerated chronic kidney disease (CKD). Types 3 and 4 describe AKI and CKD, respectively, leading primarily to heart failure, although it is possible that acute coronary syndromes, stroke, and arrhythmias could be CVD outcomes in these forms of CRS. Finally, CRSs type 5 describe a systemic insult to both heart and the kidneys, such as sepsis, where both organs are injured simultaneously in persons with previously normal heart and kidney function at baseline. Both blood and urine biomarkers, including the assessment of catalytic iron, a critical element to the generation of oxygen-free radicals and oxidative stress, are reviewed in this paper.

1. Introduction

The worldwide pandemic of excess adiposity is the "common soil" for mutual risk factors leading to cardiovascular disease (CVD) and chronic kidney disease (CKD) including the metabolic syndrome, diabetes, hypertension, dyslipidemia, neurohormonal activation, and systemic inflammation. Both cardiac and renal diseases commonly present in the same patient and have been associated with increased cost of care, complications, and mortality [1, 2]. There is an immediate and present need to categorize the complex relationships between acute and chronic organ injury and dysfunction that exist with respect to the heart and kidneys. The cardiorenal syndromes (CRSs) describe the dynamic interrelationship between heart and kidney malfunction and have been clarified in a recent consensus effort led by the Acute Dialysis Quality Initiative (ADQI) [3]. Five distinct CRSs have been proposed. This paper will review this new classification scheme and giving vignettes of each syndrome discuss available information on recognition and management. In addition, a targeted review of promising biomarkers will be presented. It is expected that these biomarkers will considerably enhance the current body of literature concerning CRSs which is largely based on single blood biomarker—serum creatinine and its derivative, the estimated glomerular filtration rate (eGFR).

2. Five Cardiorenal Syndromes

The plural term CRSs suggests several subtypes denoted by the principal organ dysfunction by temporal sequence (cardiac versus renal or simultaneous) as well as the relative acuity of each illness. Both organs must have or develop evidence of pathological changes to fulfill the criteria for definition. The umbrella term "*cardiorenal syndromes*" was defined as **"Disorders of the heart and kidneys whereby acute or chronic dysfunction in one organ may induce acute or chronic dysfunction of the other"** [3]. Figure 1 displays an array of possible pathophysiologic mechanisms for each

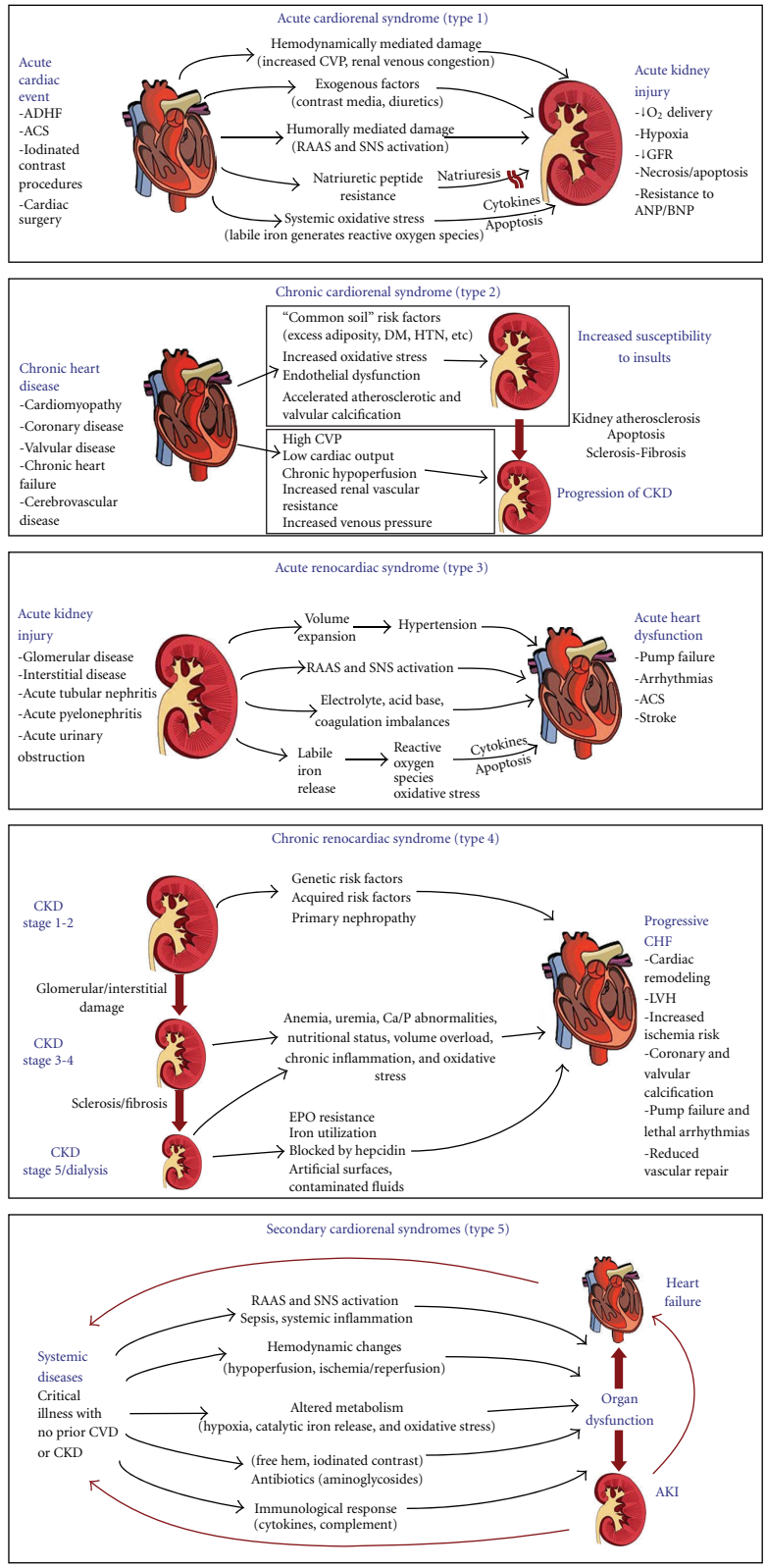

Figure 1: Pathophysiology and definitions of the five subtypes of cardiorenal syndromes.

syndrome. As shown, it has been recently understood that the process of oxidative stress resulting in cell dysfunction, accelerated apoptosis, and death is reliant on the cytosolic and extracellular presence of labile or catalytic iron. There are several steps in generation of reactive oxygen species (ROS). Oxygen may be reduced forming superoxide anion, which can undergo reduction by superoxide dismutase to form hydrogen peroxide which itself can then be reduced through several pathways. The net reaction is slow and in the presence of reduced transition metals such as ferric iron (Fe^{+3}), a Haber-Weiss reaction results in the rapid formation of the highly damaging hydroxyl radical from the superoxide anion. Likewise, in the presence of ferrous iron (Fe^{+2}), a Fenton-type reaction converts hydrogen peroxide to the hydroxyl radical. Thus, the presence of labile iron, in excess both in the cytosol and in the extracellular space, could result in the generation of the hydroxyl radical which further causes destruction of cellular organelles and membranes. Further reduction of hydroxyl radical finally ends in the formation of water. It has been theorized that a common element to all forms of oxidative stress to the heart and kidneys involves the periodic availability of unbound or poorly liganded iron [4]. There is a complex management system for iron metabolism keeping it bound in transport proteins, heme, and cellular organelles for normal functioning [5, 6]. If small amounts of iron are released from adjacent injured cells and not immediately bound, this poorly liganded (labile or catalytic) iron in either the ferric or ferrous states facilitates the rapid generation of oxygen-free radicals and the propagation of oxidative stress and injury across regions of vascular tissue [7]. Therefore, a putative final common pathway for common sources of organ injury resulting in CRSs including ischemia, neurohormonal activation, chemotoxicity, and sepsis involves the loss of control over normal iron management and the transient tissue and organ system exposure to catalytic iron.

2.1. Acute Cardiorenal Syndrome (Type 1): Acute Cardiac Event Precipitating AKI. This is a syndrome of worsening renal function that frequently complicates acute decompensated heart failure (ADHF) and acute coronary syndrome (ACS). Seven observational studies have reported on the frequency and outcomes of CRSs Type 1 in the setting of ADHF and five in ACS [8]. Approximately one-third of patients hospitalized for ADHF develop acute kidney injury (AKI) as defined by an increase in serum creatinine of $\geq$0.3 mg/dl [8, 9]. Baseline CKD, diabetes, prior HF, and initial presentation with hypertension are established risk predictors for CRSs Type 1 [10]. Complicated hospital courses with hemodynamic decompensation, longer inpatient stays, and higher mortality have all been consistently described with CRSs Type 1. However, part of this relationship can be attributed to confounding by temporal association as observed by the Prospective Outcomes Study in Heart Failure (POSH) study, where only ADHF cases with a rise in serum creatinine ($\geq$0.3 mg/dl) who concurrently developed hemodynamic compromise, cardiac arrest, infection, or acute coronary ischemia were observed to have a higher six-month mortality [11]. Conversely, those with a similar rise in serum creatinine but no other complications did not incur higher death rates in the hospital, at 30 or 180 days compared to those without such a rise in creatinine. Because CRSs Type 1 in patients with heart failure rarely occurs in the prehospital phase and more commonly develops after treatment is started in hospital, iatrogenic factors have been implicated. The use of loop diuretics, probably by further activating the renin-angiotensin system and possibly worsening intrarenal hemodynamics, has been identified as one of the modifiable in-hospital determinants of CRSs Type 1 [12]. In the Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterization Effectiveness (ESCAPE) trial, the use of higher doses of loop diuretics, causing hemoconcentration, resulted in a 5-fold increased rate of worsening renal function [13]. However, it should be noted despite these observations that aggressive diuresis was associated with a 69% reduction in death at 180 days. The presence of an elevated central venous pressure and inferred renal venous congestion, as opposed to hypotension or poor cardiac output, has been associated with the development of CRSs Type 1. The relative balance of arterial and venous pressure, volume, and flow resulting in congestion of the kidney appear to be important in the drop in renal filtration that occurs during acute treatment of AHDF [14].

Another scenario where CRSs Type 1 has been described is in the setting of coronary revascularization procedures. Acute contrast-induced and cardiopulmonary bypass surgery-associated AKI has been reported in approximately 15 and 30% of patients, respectively [15, 16]. Iodinated contrast causes transient renal vasoconstriction, and medullary hypoxia and is directly chemotoxic to renal tubular cells. Its use is the primary cause of AKI in the setting of ACS and elective coronary catheter-based procedures. In addition, contrast-induced acute kidney injury (CI-AKI) is an important pre-existing factor in the prior days before cardiac surgery rendering patients at risk for further renal injury with cardiopulmonary bypass. Cardiac surgery exposes the kidneys to hypothermic, pulseless reduced perfusion for 30–90 minutes and results in reduced renal perfusion in the setting of a proinflammatory state [17]. The extracorporeal circuit used in cardiopulmonary bypass surgery activates systemic factors and may release catalytic iron from heme, which works to induce AKI in the setting of reduced temperature and flow to the kidneys [18]. Reducing exposure to the perfusion circuit has not resulted in reduced rates of AKI but has attenuated its severity [19]. Contrast-induced AKI and cardiac surgery-associated AKI are in a temporal pathophysiologic sequence since almost every cardiac surgery patient operated upon in the urgent setting undergoes coronary angiography in the hours to days before surgery [20]. Similar to ADHF, patients undergoing revascularization with complications, CRSs Type 1 appears to be independently associated with a 3- to 4-fold increase in mortality irrespective of the use of renal replacement therapy [21, 22]. In all forms of CRSs Type 1, there is a risk of advancing to higher stages of CKD and end-stage renal disease (ESRD) [23]. The incremental and cumulative risk of these renal outcomes in patients undergoing multiple

coronary revascularization procedures over a lifetime is not known. Salient features of CRSs Type 1 described in the literature to date include (1) higher mortality risk can be attributed to nonrenal complications (shock, infection, and arrhythmias) occurring during the hospitalization and not the rise in creatinine itself, (2) intravascular iodinated contrast alone, and in conjunction with cardiopulmonary bypass, initiates AKI via a transient reduction in renal blood flow and medullary hypoxia followed by direct chemotoxicity to renal tubular cells, and (3) during ADHF hospitalization, the use of iodinated contrast or other cardiac procedures is associated with longer lengths of stay and higher mortality which is possibly in part attributable to CRSs Type 1 [24–26].

Preventive Approaches. It is beyond the scope of this paper to review the body of clinical trials that have attempted to reduce contrast-induced and cardiac surgery-associated AKI. The basic principles include avoidance of volume depletion, removal of superimposed renal toxic agents (nonsteroidal anti-inflammatory agents, aminoglycosides), minimization of the toxic exposure (iodinated contrast, time on cardiopulmonary bypass), and possibly the use of antioxidant agents such as N-acetylcysteine (for contrast exposure) and B-type natriuretic peptide in the perioperative period after cardiac surgery [27, 28]. More broadly across all forms of CRSs Type 1, consideration should be given for forms of continuous renal replacement therapy (CRRT) in the period of time surrounding the renal insult. Conceptually, the use of CRRT provides three important protective mechanisms that cannot be achieved pharmacologically as follows: (1) it ensures euvolemia and avoids hypo- or hypervolemia, (2) it provides sodium and solute (nitrogenous waste products) removal, and (3) by both mechanisms above, it may work to avoid both passive renal congestion and a toxic environment for the kidneys and allow their optimal function during a systemically vulnerable period [29]. Despite these advantages, there remains a lack of clinical trial data supporting CRRT over other forms of extracorporeal solute removal. Finally, for patients in whom anuria and serious renal failure have a high probability of occurring, the upstream use of CRRT removes the hazards around the critical period of initiation of dialysis including electrolyte imbalance, urgent catheter placement, and extreme volume overload.

2.2. Chronic Cardiorenal Syndrome (Type 2): Chronic CVD Leading to Progressive CKD. It is important to recognize that chronic CVD in some cases leads to the progression of CKD. Observational studies have suggested that CVD contributes to an excess risk of CKD and its progression (CRSs Type 2) [8]. The established risk factors for atherosclerosis, namely diabetes, hypertension, and smoking are independently associated with the development of CKD [30]. Left ventricular systolic and diastolic dysfunction can lead to alterations in neurohormonal activation, renal hemodynamics, and a variety of adverse cellular processes leading to apoptosis and renal fibrosis [31]. One-third of the prevalent pool of CVD has concurrent CKD and, when combined, leads to further disease progression [29]. In the National Kidney Foundation, Kidney Early Evaluation Program, CKD has been associated with premature CVD events including MI and stroke [32, 33]. Chronic kidney disease-associated bone and mineral disorder characterized by phosphate retention, relative vitamin D deficiency and calcium availability, and secondary hyperparathyroidism is pathophysiology linked to the accelerated calcific atherosclerosis observed in patients with CKD [34]. Hyperphosphatemia, due to phosphate retention, stimulates the conversion of vascular smooth muscle cells to osteoblastic-like cells which, via the Pit-1 receptor, are stimulated to produce extracellular calcium hydroxyapatite crystals in the vascular smooth muscle layer of atherosclerotic arteries [35, 36]. Thus, patients as a part of CRSs type 2 more commonly have vascular calcification, less vascular compliance, and a higher degree of chronic organ injury due to shear stress at the large, medium, and smaller vessel levels [37]. Despite these mechanisms specific to CRSs, CRSs Type 2 remains heavily confounded by the "common soil" of atherosclerosis and CKD. Excess adiposity and the cardiometabolic syndrome with activation of the sympathetic and renin-angiotensin systems as well as adipokine-stimulated systemic inflammation affect both organ systems; therefore, it is likely that for most patients with CRSs Type 2, concurrent organ injury is occurring based on these pathophysiologic mechanisms [38].

Approximately half of chronic HF patients have evidence of CKD defined as an estimated glomerular filtration rate (eGFR) <60 ml/min/1.73 m^2 [39]. The presence of CKD has been associated with more frequent hospitalizations and death from pump failure and arrhythmias [40, 41]. Sodium and water retention are the primary cardiac insults put forward as to how CKD worsens HF. It should also be mentioned that CKD is associated with diuretic resistance and higher rates of drug intolerance to inhibitors of the renin-angiotensin-aldosterone system. Patients with CKD and ESRD have greater risks of ventricular arrhythmias and higher defibrillation thresholds; thus, they may have higher failure rates of antiarrhythmic therapy and implantable cardiodefibrillators [42]. Greater left ventricular mass and cardiac fibrosis may be responsible electrophysiological findings in patients with CKD [43]. Finally, asymptomatic cerebral infarctions by magnetic resonance imaging have been associated with a rapid decline in renal function in approximately 30% of patients [44]. This suggests the possibility that systemic atherosclerosis contributes to more rapid progression of CKD. Future research on the systemic and direct effects of atherosclerosis on the kidney is needed.

Preventive Approaches. As a general axiom, pharmacologic therapies that have been beneficial for chronic CVD have been either neutral or favorable to the kidneys including use of renin angiotensin aldosterone system (RAAS) antagonists, beta-adrenergic blocking agents, and statins. Furthermore, other strategies which are modestly beneficial from a cardiac perspective have even a larger benefit on microvascular injury to the kidneys including glycemic control in diabetes and blood pressure control in those with hypertension [45]. Finally, there is some support from clinical trials that fibric acid derivatives may preferentially reduce rates of

microalbuminuria in patients with CKD. The long-term clinical implications of these observations are unknown [46].

2.3. Acute Cardiorenal Syndrome (Type 3): Acute Worsening of Renal Function Leading to Cardiac Events. A well-described vignette for CRSs Type 3 is the development of AKI resulting in volume overload, sodium retention, neurohormonal activation, and ADHF with the cardinal features fatigue, breathlessness, and peripheral edema. In children, isolated volume overload has been shown to induce myocardial dysfunction and CRSs Type 3 [47]. The picture is not so clear in adults, when acute on chronic disease is a frequent paradigm. It is conceivable that CRSs Type 3 could precipitate ACS, stroke, or other acute cardiac event; however, the epidemiological evidence and pathophysiological basis are yet to be described. In summary, CRSs Type 3 is not well defined for individual CVD events such as ACS, stroke, cardiac rehospitalization, arrhythmias, pump failure, and cardiac death and thus is a future research topic in terms of describing the epidemiology and pathogenesis of this syndrome [8].

Preventive Approaches. The major management principle concerning this syndrome is intra- and extravascular volume control with either use of diuretics and forms of extracorporeal volume and solute removal (CRRT, ultrafiltration, hemodialysis). In the setting of AKI, prevention of left ventricular volume overload is critical to maintain adequate cardiac output and systemic perfusion and avoid the viscous downward spiral in both cardiac and renal function.

2.4. Chronic Cardiorenal Syndrome (Type 4): CKD Leading to the Progression of CVD and Death. There is a graded and independent association between the severity of CKD, assessed by baseline eGFR, and incident as well as prevalent CVD [2]. A meta-analysis of 39 studies (1,371,990 participants) found a significant, independent relationship between the severity of CKD and the risk for all-cause death [48]. In this review, cardiovascular deaths constituted over 50% of fatalities. Thirteen studies have reported on the occurrence of CRSs Type 4 mainly in populations with ESRD on dialysis [8]. In this scenario, decreased renal function influences CVD outcomes in CRSs Type 4 by making conventional management of CAD or HF more difficult [49, 50]. Azotemia and hyperkalemia are known to limit the use of drugs that antagonize the renin-angiotensin aldosterone system; thus, fewer patients with CKD enjoy the cardiovascular benefits of angiotensin converting enzyme inhibitors, angiotensin II receptor antagonists, and aldosterone receptor blockers [51, 52]. The presence of CKD also increases the severity, worsens the response to treatment, and is associated with poor cardiac and renal outcomes in acute and chronic hypertension [53, 54]. Amongst clinicians, the perceived risks of AKI in patients with CKD generally produce more conservative management strategies which have been associated with poor outcomes in the setting of ACS and stable CVD [55].

Preventive Approaches. Optimal treatment of CKD with blood pressure and glycemic control, RAAS blockers, and disease-specific therapies, when indicated, are the best means of preventing this syndrome. Morbidities of CKD, including bone and mineral disorder and anemia, should be managed according to CKD guidelines; however, clinical trials have failed to demonstrate that treatment of these problems influences CVD outcomes [56, 57].

2.5. Secondary Cardiorenal Syndrome (Type 5): Systemic Illness Leading to Simultaneous Heart and Renal Failure. It is recognized that a systemic insult, particularly in a younger patient with no prior heart or kidney disease, can lead to simultaneous organ dysfunction. This is almost always in the setting of critical illness such as sepsis, multiple trauma, or burns and can be thought of being part of multiorgan system failure. There are limited data on the incidence and determinants of CRSs (Type 5) in part because confounders such as hypotension, respiratory failure, liver failure, and other organ injury beyond the cardiac and renal systems create a difficult human model for investigation. Sepsis as a precipitator of CRSs Type 5 is common, and its incidence is increasing, with a mortality estimated between 20% and 60% [58–60]. Approximately 11–64% of septic patients develop AKI that is associated with a higher morbidity and mortality [61]. Abnormalities in cardiac function are also common in sepsis including wall motion abnormalities and transient reductions in left ventricular ejection fraction [62]. Observational data have found approximately 30–80% of individuals with sepsis have measurable blood troponin I or T that elevates above the 99th detection limits [63]. These elevated cardiac biomarkers have been associated with reduced left ventricular function and higher mortality even in patients without known coronary disease [64, 65]. Importantly, volume overload as a result of aggressive fluid resuscitation appears to be a significant determinant of CRSs Type 5. Among the 3,147 patients enrolled in the Sepsis Occurrence in Acutely Ill Patients (SOAP), there was a 36% incidence of AKI, and volume overload was the strongest predictor of mortality [66]. Iatrogenic volume overload appears to play an important additional role, possibly along the lines described for CRSs Type 1 and passive venous congestion of the kidney, in the pathogenesis of AKI. At the same time, volume overload increases left ventricular wall tension and likely contributes to cardiac decompensation in those predisposed to both systolic and diastolic HF [67]. In summary for CRSs Type 5, both AKI and markers of cardiac injury followed by volume overload are common in sepsis, with each being associated with increased mortality. However, there is a current lack of integrative information on the incidence of bidirectional organ failure and its pathophysiological correlates in a variety of acute care settings.

Preventive Approaches. There are no proven methods to prevent or ameliorate this form of CRSs at this time. Randomized trials of early versus later intervention with CRRT have shown no differential benefit. Supportive care with a judicious intravenous fluid approach and the use of pressor agents as needed to avoid hypotension are reasonable but cannot be expected to avoid AKI or cardiac damage [68].

3. Biomarkers of Cardiorenal Syndromes

There is considerable interest in blood and urine biomarkers to detect CRSs. For decades, the rise in serum creatinine has been the only detectable sign of a reduction in glomerular filtration. Creatinine has had the disadvantages of being linked to creatine and the overall body muscle mass, hence, differing according to body size in addition to the rate of renal elimination [69]. Furthermore, the kidney both filters and secretes creatinine. Finally, the assays used to measure creatinine have not been standardized across laboratories; therefore, studies reporting values from multiple centers have inherent variation in values attributed to differences in measurement technique [70]. Hence, there is a clear need for better laboratory markers of renal filtration. An ideal marker would be independent of muscle mass, reflect actual renal filtration as the time it was measured, and be sensitive to changes in actual glomerular filtration rate (GFR) in order to signal clinicians to a meaningful change shortly after it occurs.

Unlike cardiac biomarkers indicating myocardial injury and overload (troponin, creatine kinase myocardial band, and natriuretic peptides), the field of nephrology has been devoid of approved blood or urine markers of AKI. Thus, the current paradigm is that when renal injury occurs, clinicians must wait to observe a reduction in GFR before AKI is inferred. The concept of measuring makers of the acute injury process is crucial to the early upstream identification of AKI before there is serious loss of organ function [71]. Below is a summary of relatively novel renal markers and what is known about them in acute cardiac and renal injury. Their use in the years to come will undoubtedly influence the epidemiology of CRSs. However, there are pitfalls to the widespread use of novel biomarkers including inappropriate conclusions along all lines of clinical decision making. Thus, considerable data are needed before any new marker enters the clinical arena.

3.1. Catalytic Iron. Iron is the most common metal element in the human body, and there are elaborate transport and management systems for its use in a variety of critical cellular systems including oxygen transport and cellular respiration. It has been known that poorly liganded iron is the critical basis for the generation of the hydroxyl radical, which is the most destructive of all reactive oxygen species. Using the bleomycin detectable assay, Lele and coworkers have recently demonstrated the release of catalytic iron into the blood in patients with acute coronary syndromes [72]. In this study, the appearance of catalytic iron preceded the rise in serum troponin and had an area under the receiver operating characteristic curve for the detection of acute myocardial infarction over 0.90. Labile iron is also believed to play an essential role in the oxidative organ damage of AKI as discussed above [73]. It is believed that local cellular and tissue availability of catalytic iron determines the degree and severity of organ injury in the setting of most hypoxic and other toxic insults [74]. Thus, catalytic iron may serve as both a diagnostic and therapeutic target by using iron chelators in the future for CRSs [75].

3.2. Neutrophil Gelatinase-Associated Lipocalin (NGAL). Siderocalin, or NGAL, was originally identified as a 25 kDa protein which is a natural siderophore which works to scavenge cellular and pericellular labile iron, and thus, reducing its availability for bacterial growth. By reducing the availability of poorly liganded Fe(II) and Fe(III), which are needed to catalyze the Haber-Weiss and Fenton equations in the generation of reactive oxygen species, NGAL appears to have an important role in limiting oxidative damage in both acute and chronic diseases. NGAL seems to be one of the earliest kidney markers of ischemic or nephrotoxic injury in animal models, and it may be detected in the blood and urine of humans soon after AKI. Several studies have confirmed these findings; in intensive care adult patients with AKI secondary to sepsis, ischemia, or nephrotoxins, NGAL is significantly increased in the plasma and urine when compared to normal controls [76].

3.3. Cystatin C. Cystatin C is a cysteine protease inhibitor that is synthesized and released into the blood at a relatively constant rate by all nucleated cells. It is freely filtered by the glomerulus, completely reabsorbed by the proximal tubule, and not secreted into urine. Its blood levels are not affected by age, gender, race, or muscle mass; thus, it appears to be a better predictor of glomerular function than serum creatinine in patients with CKD. In AKI, urinary excretion of cystatin C has been shown to predict the requirement for renal replacement therapy earlier than creatinine. Finally, cystatin C has consistently outperformed serum creatinine and eGFR in the risk prediction for events in patient with CVD [77].

3.4. Kidney Injury Molecule 1 (KIM-1). Kidney Injury Molecule 1 (KIM-1) is a transmembrane glycoprotein which is not normally detectable in urine [78]. KIM-1 is measurable in the urine after ischemic or nephrotoxic insults to proximal tubular cells [79]. Urinary KIM-1 seems to be highly specific for AKI due to systemic illnesses such as sepsis and not for prerenal azotemia or drug-induced renal injury. Importantly, KIM-1 may be elevated before there is histologic evidence of proximal tubular cell death [44].

3.5. N-Acetyl-β-(D)Glucosaminidase (NAG). Recognized over thirty years ago, NAG is a lysosomal brush border enzyme found in proximal tubular cells. It is a large protein (>130 kD) and is therefore not filtered through the glomerular membrane. NAG has been shown to function as a marker of AKI, reflecting particularly the degree of tubular damage. It is not only found in elevated urinary concentrations in AKI and CKD but also in diabetic patients, patients with essential hypertension and heart failure [80].

3.6. Interleukin-18 (IL-18). IL-18 is a proinflammatory cytokine detected in the urine after acute ischemic proximal tubular damage [81]. It displays sensitivity and specificity for ischemic AKI with an area under the receiver operating characteristic curve of >90% with increased levels 48 hours prior to increase of serum creatinine. It has been associated

with AKI mortality, but like other interleukins, it is not organ specific. IL-18 has also been theorized to participate in myocardial cell damage in the setting of ACS, and inhibitors of IL-18 expressed by stem cells have been shown to be protective in models of myocyte injury [82].

3.7. Liver Fatty Acid-Binding Protein (L-FABP). Liver fatty acid-binding protein (L-FABP) binds selectively to intracellular free unsaturated fatty acids and lipid peroxidation products during hypoxic tissue injury and is found in the urine of patients with AKI [83]. Urinary L-FABP is a potential biomarker for the detection and assessment of AKI and may be useful in predicting dialysis-free survival [84].

3.8. Tubular Enzymuria. Isoforms of a variety of enzymes released from proximal and renal tubular cells are measurable in the urine. These include gamma glutamyl transpeptidase (GGT), alkaline phosphatase, lactate dehydrogenase, and α and π glutathione S-transferase (GST) [85–87]. It is possible that a panel of these markers measure in the urine could give important internal validity to not only the presence of, but potentially the location of injury along the nephron [88].

4. Conclusions

This paper has summarized a newly proposed framework for CRSs in order to better understand five possible subtypes [3]. A description of possible heart-kidney interactions is critical to our understanding and will guide future investigations into pathophysiology, screening, diagnosis, prognosis, and management. Recent studies have identified and characterized several novel biomarkers for CRSs. It is anticipated that these biomarkers will help make an earlier diagnosis of CRSs as well as identify its specific type and potentially its pathophysiology. Of particular interest is the recognition that tiny amounts of poorly bound labile iron catalyze oxidative stress reactions and further propagate organ injury. This may be a final common mechanism for most CRSs variants, and thus a prime diagnostic and therapeutic target in future clinical study. It is hoped in the future that some of these new biomarkers including catalytic iron and the kidney's response, NGAL, will provide sufficient risk prediction and early diagnosis to allow for prevention and treatment CRSs. It remains to be seen whether or not effective prevention and treatment of CRSs will improve hard renal and cardiac outcomes including ESRD, hospitalizations, and death.

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SAGE-Hindawi Access to Research
International Journal of Nephrology
Volume 2011, Article ID 920195, 11 pages
doi:10.4061/2011/920195

Review Article

The Cardiorenal Syndrome: A Review

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Received 13 September 2010; Accepted 21 November 2010

Academic Editor: Mitchell H. Rosner

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Cardiorenal syndrome (CRS) is the umbrella term used to describe clinical conditions in which cardiac and renal dysfunctions coexist. Much has been written on this subject, but underlying pathophysiological mechanisms continue to be unravelled and implications for management continue to be debated. A classification system—incorporating five subtypes—has recently been proposed though it has yet to permeate into day-to-day clinical practice. CRS has garnered much attention from both the cardiological and nephrological communities since the condition is associated with significant morbidity and mortality. Renal dysfunction is highly prevalent amongst patients with heart failure and has been shown to be as powerful and independent a marker of adverse prognosis as ejection fraction. Similarly, patients with renal failure are considerably more likely to suffer cardiovascular disease than matched subjects from the general population. This paper begins by reviewing the epidemiology and classification of CRS before going on to consider the different pathological mechanisms underlying cardiorenal dysfunction. We then focus on management strategies and conclude by discussing future directions in the diagnosis and management of patients suffering with CRS.

1. Introduction

The heart is responsible for supplying the organs and tissues of the body with blood, and the kidneys, amongst other functions, play an integral role in fluid balance and salt homeostasis. It should therefore come as little surprise that renal dysfunction frequently accompanies cardiac failure and that cardiac dysfunction frequently accompanies renal failure. This interdependent relationship has come to be known as the "cardiorenal syndrome" [1]. This phrase has been in use since 2004 [2], but despite generating a plethora of papers in the literature and being discussed at length in dedicated conferences, CRS has until very recently lacked a universally accepted definition, and numerous key questions remain unanswered [3]. What is the true prevalence? What is the long-term prognosis? What is the exact underlying pathophysiology? We shall cover the epidemiology, pathophysiology, and current management of CRS in this paper, but we will begin with brief case histories which help demonstrate the heterogeneity of patients who fall under the umbrella term of CRS.

Case 1. A 63-year-old patient with known severe heart failure and chronic renal impairment (baseline creatinine 190 mmol/L, estimated glomerular filtration rate (eGFR) 23 mLs/min) was admitted with acute decompensated heart failure (ADHF). Creatinine on admission was similar to baseline, but over the next week renal function deteriorated significantly (urea 51.1 mmol/L, creatinine 503 mmol/L, eGFR 8) requiring inotropic support and then haemofiltration. Her inpatient stay lasted 7 weeks, of which over half was spent on high dependency or intensive care units. Unfortunately, she died from progressive pump failure several weeks after admission.

Case 2. A 31-year-old previously fit and well Indian man was admitted with a two-week history of malaise and a 2-day history of hemoptysis. Admission blood tests revealed urea level of 20 mmol/L and creatinine level of 1100 mmol/L. Bedside echocardiography revealed moderate global systolic dysfunction indicating probable uraemic cardiomyopathy. A renal biopsy confirmed the diagnosis of glomerulonephritis. After his first three sessions of

hemodialysis, echocardiography was repeated and revealed normal systolic function.

Case 3. A 32-year-old lady developed end-stage renal failure secondary to type 1 diabetes mellitus. She commenced hemodialysis in 2007, and just prior to this, transthoracic echocardiography revealed concentric ventricular hypertrophy and severely impaired systolic function. 6 months after she had been started on hemodialysis, repeat echocardiography revealed marked improvement in systolic function, with LV dysfunction now only mild rather than severe.

Case 4. A 28-year-old fit gentleman, with no past medical history, was admitted feeling unwell for the past 3 days. He was extremely ill when first seen: temperature 40°C, BP 70/35 mmHg, and pulse rate 130. Initial blood tests revealed marked leukocytosis (white cell count 41.5×10^9/L, neutrophil count 38.5×10^9/L) and acute renal failure (urea 6.2 mmol/L and creatinine 184 mmol/L). Transthoracic echocardiography revealed severely impaired systolic function. He was diagnosed with septic shock and treated with fluids and broad-spectrum intravenous antibiotics. In less than 72 hours, he was feeling significantly better and renal function had returned to normal. Numerous blood and urine cultures and throat swabs failed to yield a culpable organism. Repeat echocardiography one week later revealed normal systolic function.

All of these patients had coexistent cardiac and renal dysfunction but clearly with grossly different underlying pathology and, therefore, prognoses.

2. Epidemiology

Renal dysfunction is unfortunately extremely prevalent in patients with congestive cardiac failure (CCF), and the associated statistics make sombre reading. Data from the Acute Decompensated Heart Failure National Registry (ADHERE) of over 100,000 patients (admitted with ADHF) revealed that almost one third of patients have a history of renal dysfunction [4]. Another study found that, in a survey of outpatients with congestive cardiac failure, 39% patients in New York Heart Association (NYHA) class 4 and 31% of patients in NYHA class 3 had severely impaired renal function (creatinine clearance <30 mls/minute) [5]. Baseline renal function is as important an adverse prognostic marker as ejection fraction and NYHA functional class [6]. Elevated serum creatinine on admission to hospital with ADHF and worsening renal function during admission for ADHF have both been shown to predict prolonged hospitalisation, increased need for intensive care facilities, and increased mortality [7, 8].

Similarly, renal failure is clearly linked with increased adverse cardiovascular outcomes. Almost 44% of deaths in patients with end-stage renal failure (ESRF) are due to cardiovascular diseases [9], and a 2006 meta-analysis indicated that patients with ESRF are more likely to die from cardiovascular causes than from renal failure itself [10]. Death from cardiovascular causes is 10–20 times more common in patients with chronic renal failure than in matched segments of the general population [11]. Half of patients commencing hemodialysis will suffer a myocardial infarction within the following two years, and mortality in this patient population is high [12]. Increased myocardial mass (i.e., left ventricular hypertrophy)—which increases myocardial oxygen demand—is increased in mild-to-moderate as well as more advanced stages of renal failure [13].

On the other hand, treatment of renal dysfunction can improve cardiac function, although the majority of this evidence comes from ESRF patients receiving kidney transplants. A study of over 100 dialysis patients with known heart failure who underwent renal transplantation showed an improvement of ejection fraction from 32% to 52% and over two thirds of patients had complete normalisation of cardiac function [14]. There are a few other such reports, albeit, all in the transplant population [15–17].

3. Classification: Cardiorenal or Renocardiac?

CRS has, in the absence of a generally accepted definition, usually been perceived as renal dysfunction secondary to chronic cardiac dysfunction (i.e., heart failure). However, this clearly failed to address the numerous other instances in which cardiac and renal dysfunction coexist. Ronco et al. first proposed a five-part classification scheme for the cardiorenal syndromes in 2008 [18], and this has since been incorporated into the report from a consensus conference held in the same year [19]. The classification system is outlined in Table 1 but essentially recognises the multiple ways in which cardiorenal dysfunction occurs and defines the primary and secondary organ dysfunction in each case. This consensus group defined CRS as "disorders of the heart and kidneys whereby acute or chronic dysfunction in one organ may induce acute or chronic dysfunction of the other" [18]. This phraseology was chosen as it helps explain the bi-directional nature of the various syndromes. Bongartz and colleagues proposed the "cardiorenal connection" [20] as an addition to the haemodynamic framework (on the control of extracellular fluid volume (ECFV)) developed by the late physiologist Arthur Guyton and termed this the "severe cardiorenal syndrome" (SCRS). They stated that SCRS is a syndrome with "accelerated and extensive cardiovascular disease that has distinct properties not occurring in conditions that affect either organ alone" [20]. They proposed the renin-angiotensin-aldosterone system (RAAS), balance between nitric oxide (NO) and reactive oxygen species (ROS), inflammation, and sympathetic nervous system (SNS) as circuits within the cardiorenal connection. Derangement of any connector was thought to initiate a vicious downward spiral culminating in disturbance in the other connectors and culminating in cardiac and renal dysfunction via common final pathophysiological pathways. However, this terminology has not been widely adopted.

4. Pathophysiology

As our knowledge of CRS expands, it is becoming increasingly clear how complex the interaction between heart and

Table 1: Schematic of the classification system proposed by Ronco et al. [18] for subdivision of CRS into 5 subtypes based upon aetiology of dysfunction.

CRS type	Name	Description	Example
1	Acute cardiorenal	Acute cardiac dysfunction leading to acute kidney injury	Acute coronary syndrome causing acute heart failure and then renal dysfunction
2	Chronic cardiorenal	Chronic heart failure leading to renal dysfunction	Congestive cardiac failure
3	Acute renocardiac	Acute kidney injury leading to acute cardiac dysfunction	Uraemic cardiomyopathy secondary to acute renal failure
4	Chronic renocardiac	Chronic renal failure leading to cardiac dysfunction	Left ventricular hypertrophy and diastolic heart failure secondary to renal failure
5	Secondary	Systemic condition causing cardiac and renal dysfunction	Septic shock, vasculitis

kidneys is once one organ becomes diseased. We shall explore these mechanisms in greater detail in this section of the paper.

4.1. Old Paradigms Revisited: Beyond the Low-Flow Hypothesis. Conventional thinking for decades held that the progressive deterioration in renal function in heart failure patients was primarily as a result of reduced renal blood flow secondary to reduced cardiac output [21]. Inadequate renal afferent flow was said to activate the renin-angiotensin-aldosterone system (RAAS) leading to fluid retention, increased preload, and thus worsening pump failure. However, recent work suggests that, though correct, this is a very narrow and incomplete picture.

The Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterization Effectiveness (ESCAPE) trial [22] assessed pulmonary artery catheter-guided management of over 400 patients admitted with ADHF. It found no correlation between baseline renal function and cardiac index, and improvement of the latter did not result in improved renal function. Others have also found that improved cardiac index or reduced wedge pressure during pulmonary artery catheter-guided management failed to predict improvement in renal function [23, 24]. Additionally, worsening renal function has been demonstrated in ADHF patients despite normal systolic function (ejection fraction) [25], and thus, presumably, renal blood flow. In combination, these data suggest much more than simply reduced renal blood flow as an explanation for CRS.

4.2. The Renin-Angiotensin-Aldosterone System (RAAS): Friend Becomes Foe. Activation of the RAAS by reduced perfusion pressure is a protective mechanism against potentially dangerous conditions like haemorrhage. Unfortunately, when chronically stimulated—as in both heart and renal failure—the pathophysiological consequences are severe and deleteriously affect function of both organ systems. Renin is produced in the juxtaglomerular apparatus of the kidneys and catalyses the conversion of angiotensinogen I to angiotensinogen II, which is subsequently turned into angiotensin II (Ang II) by angiotensin-converting enzyme (ACE).

Ang II has numerous negative effects upon the cardiovascular system in heart failure patients, increasing both preload and afterload and thus myocardial oxygen demands. The main changes induced by Ang II are illustrated in Figure 1, but one of the most important recent advances has been recognition of the promotion of vascular inflammation [26]. Ang II activates the enzyme NADPH oxidase in endothelial cells, vascular smooth muscle cells [27], renal tubular cells [28], and cardiomyocytes [29]. This leads to the formation of ROS, mostly superoxide. A growing body of evidence suggests that ROS are responsible for the processes of aging, inflammation, and progressive organ dysfunction [30]. Nitric oxide (NO) is responsible for vasodilation and natriuresis and assists in renal control of ECFV. Superoxide antagonises these effects [31] but also reduces bioavailability of NO. Oxidative stress damages DNA [32], proteins [33], carbohydrates [34], and lipids [35] and also shifts cytokine production towards proinflammatory mediators such as interleukin-1, interleukin-6, and tumour necrosis factor alpha [36]. Interleukin-6 also stimulates fibroblasts leading to increased cardiac and renal fibrosis.

4.3. The Sympathetic Nervous System (SNS) in CRS. SNS activation is initially a protective mechanism in CCF patients, akin to RAAS activation. The aim is to maintain cardiac output by positive chronotropic and inotropic effects on the myocardium. Unfortunately, chronic SNS activation also results in numerous negative effects upon the cardiovascular system and kidneys. SNS overactivity leads to reduction in beta-adrenoceptor density within myocardium and also reduced adrenoceptor sensitivity in both renal [37] and cardiac failure [38]. Catecholamines are also thought to contribute to left ventricular hypertrophy seen in some patients [39]. SNS activation leads to increased cardiomyocyte apoptosis [40] and increases the release of the neurohormone Neuropeptide Y (NPY). NPY is a vascular growth promoter leading to neointimal formation (and thus atherosclerosis) [41], induces vasoconstriction, and also interferes with normal immune system function [42]. Renal sympathetic denervation in patients with resistant hypertension significantly improved renal function in one quarter of patients [43], and bilateral renal nerve ablation has been shown to reduce blood pressure at one-year followup

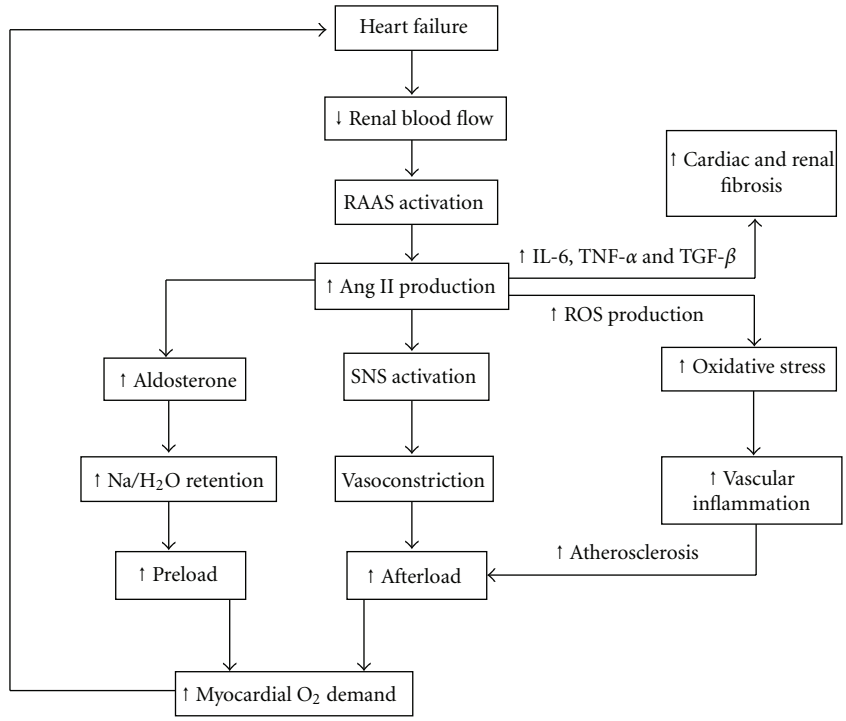

Figure 1: Illustration of the pathophysiological pathways activated by angiotensin II. Both preload and afterload are ultimately increased, leading to worsening cardiac and renal function (IL-6 = Interleukin 6; TNF-α = Tumour necrosis factor alpha; TGF-β = Transforming growth Factor beta; ROS = Reactive oxygen species).

[44]. However, these therapies have not been tested in the heart failure population and thus still requires further evaluation.

4.4. Intraabdominal Hypertension: Underrecognised or Overemphasised? Heart failure is marked by an elevation in central venous pressure which reduces the perfusion gradient across the renal capillary bed. Studies performed in the early part of the last century demonstrated that rising renal venous pressures could reduce or even abolish urine production [45], and rising renal venous pressure was more important than falling arterial (perfusion) pressure in this setting. Extrinsic compression of renal veins has also been shown to compromise renal function [46].

Intraabdominal pressure (IAP) is said to be elevated when >8 mmHg, and intraabdominal hypertension has been defined as a pressure >12 mmHg [47]. A study of 40 patients admitted with ADHF found that 24 had an IAP >8 mmHg though none had abdominal symptoms. The degree of reduction of IAP with diuretic treatment correlated with an improvement in renal function [48]. The ESCAPE trial found that baseline right atrial pressure, but not arterial blood flow, correlated with baseline serum creatinine [22].

Patients with baseline renal dysfunction or worsening renal function after admission have significantly elevated central venous pressure compared to those with less or no renal dysfunction [49]. Additionally, elevated jugular venous pressure on physical examination is associated with higher baseline serum creatinine and increased risk of hospitalisation due to ADHF and death due to pump failure [50].

4.5. The Cardiorenal Anaemia Syndrome (CRAS). CRAS was first described almost a decade ago by Silverberg et al. as "a vicious cycle of deterioration that leads to poor outcomes, including faster progression to ESRF and further progression of congestive heart failure" [51]. Their simple model suggested anaemia as a condition induced by dysfunction of either organ but also exacerbating dysfunction of either organ. Anaemia is present in over one-third of CRS patients [52]. The Candesartan in Heart Failure: Assessment of Reduction in Morbidity and Mortality (CHARM) study suggested that anaemia was an independent adverse prognostic factor in CCF patients [53]. There has, however, like for CRS, been a lack of consensus over the true definition, significance, and management strategy for patients with CRAS (if even such a "syndrome" exists). This has mainly stemmed from a lack of large-scale randomised controlled trials to guide management.

Anaemia is widely thought to have a multifactorial aetiology in patients with CKD or CCF, but iron deficiency is thought to play a prominent role in both [54, 55]. Some evidence does suggest benefit from treatment of iron deficiency in such patients. The Ferinject Assessment in patients with Iron deficiency and chronic Heart Failure (FAIR-HF) study assessed intravenous (IV) iron therapy in 459 symptomatic CCF patients with iron deficiency. It demonstrated that the treatment group had a significant

improvement in heart failure symptoms, exercise capacity, and quality of life *irrespective* of whether they actually had underlying anaemia or not [56]. Long-term safety data on the newer dextrans-free IV preparations are still awaited, but IV iron does appear to be emerging as an important therapy in patients with CRAS. However, current European guidelines for the management of heart failure (published before results of trials such as FAIR-HF were available) describe correction of anaemia in CCF patients as "unproven" and "not established as routine therapy" [57].

The role of erythropoietin stimulating agents (ESAs) is also controversial due to conflicting evidence. Erythropoietin is a cytokine produced in the kidneys that is essential for red blood cell production. Erythropoietin levels are reduced in renal failure but frequently elevated in heart failure. Scientific studies have shown that erythropoietin protects cardiomyocytes from apoptosis [58, 59] and that the mechanism appears to be upregulation of endothelial nitric oxide synthase [60]. A study of 26 heart failure patients with anaemia who received ESA found significantly improved exercise capacity which appeared to be principally due to increased oxygen delivery due to higher haemoglobin concentration [61]. However, studies have shown that patients with CCF have elevated endogenous erythropoietin levels and that this is associated with poorer survival independent of haemoglobin level [62, 63]. An additional study showed that an erythropoietin level higher than expected was an independent predictor of increased mortality even after adjustment for possible confounding variables [64]. Although initial small studies suggested benefit in correcting anaemia due to CKD with ESAs, three large multicentre phase III trials all had negative outcomes and put a severe question mark over the future of these agents. The Cardiovascular Risk Reduction by Early Anaemia Treatment with Epoetin Beta (CREATE) trial found that correcting anaemia early in patients with renal failure does not reduce their risk of cardiovascular complications [65]. The Trial to Reduce Cardiovascular Events with Aranesp Therapy (TREAT) study found that diabetic patients with renal failure and moderate anaemia had no benefit from receiving ESA and in fact had a statistically higher risk of stroke [66]. Finally, the Correction of Hemoglobin and Outcomes in Renal Insufficiency (CHOIR) trial found that aiming for a higher haemoglobin level in CKD patients with anaemia was associated with a higher risk of adverse outcome including death, hospitalisation for heart failure, or myocardial infarction [67]. A randomised trial of two dosing regimens of the ESA darbepoetin alfa in patients with heart failure and anaemia showed no improvement in NYHA class, LV ejection fraction, or Minnesota Living with Heart Failure questionnaire score [68]. Consequently, the routine use of ESA therapy to increase haemoglobin levels in anaemic CCF patients does not have a sound evidence base.

5. Management of CRS

Medical management of patients with concomitant cardiac and renal dysfunction remains tremendously challenging, and this is exacerbated by the fact that the vast majority of trials providing evidence for treatments in heart failure excluded patients with significant renal impairment [69]. The heterogeneous nature of patients with CRS also poses unique challenges with no single success-guaranteed therapy.

5.1. Diuretics: Not as Safe as Commonly Perceived? There is limited trial data proving mortality benefit for diuretics in CRS, but they have long been deemed an essential management strategy in these patients. Data from the ADHERE registry suggests that 81% of patients were using chronic diuretic therapy at the time of admission with ADHF [4]. Studies have shown, however, that furosemide decreases GFR in many patients [70], and higher doses of diuretics are *independently* associated with sudden cardiac death or death from pump failure [71, 72]. Furosemide also stimulates the RAAS and can thus increase fibrosis [30]. A systematic review and meta-analysis on the use of loop diuretics in management of patients with acute kidney injury found no mortality benefit, though there was a shorter required duration of renal replacement therapy [73]. A large observational cohort study—examining the use of diuretics in intensive care patients with acute renal failure—found a significantly increased risk of death or nonrecovery of baseline renal function in the patients receiving diuretics [74]. However, the two papers mentioned above looked at all mechanisms of renal dysfunction, not just the heart failure population. There is unfortunately a dearth of high-quality randomised controlled evidence to support or refute the use of diuretics in patients with cardiac and renal dysfunction. Therefore, in the absence of definitive data proving harm in heart failure population, diuretics should not be withheld from volume-overloaded patients.

Diuretic resistance is frequently used as a surrogate marker of poor prognosis in CCF patients. The most probable culpable mechanisms are inadequate diuretic dose, excessive sodium intake, delayed intestinal absorption due to gut mucosal oedema, decreased diuretic excretion into urine, and increased sodium reabsorption from other parts of the nephron not blocked by loop diuretics (e.g., distal convoluted tubule) [75, 76]. Concomitant use of nonsteroidal anti-inflammatory drugs can also contribute to diuretic resistance by diminishing synthesis of vasodilator and natriuretic prostaglandins [77].

In such patients there are several management options. Firstly, one should bear in mind that furosemide does not have a smooth dose-response curve, meaning that no natriuresis would occur until a threshold rate of drug excretion is reached [78]. Consequently, a patient not responding to 40 mg furosemide should have the dose doubled to 80 mg rather than the frequency doubled to twice daily. Secondly, patients should be instructed to restrict their salt intake to help achieve net fluid loss. Thirdly, the patient may require IV diuretic therapy to avoid the poor bioavailability frequently encountered due to reduced gastrointestinal blood flow, reduced intestinal peristalsis, and intestinal mucosal oedema. A Cochrane review [79] has confirmed that continuous IV furosemide infusion achieves a greater diuresis than bolus

IV doses and this is associated with reduced mortality and shorter hospital stay. Other treatment options include adding in a thiazide diuretic to block distal sodium reabsorption, a potassium-sparing diuretic such as spironolactone, or adding salt-poor albumin. Salt-poor albumin is thought to enhance delivery of furosemide to the kidney, and one small study suggested adding salt-poor albumin to a furosemide infusion significantly increased sodium excretion [80].

5.2. Angiotensin-Converting Enzyme (ACE) Inhibitors. ACE inhibitors are known to reduce mortality in patients with heart failure [81], though the majority of these studies excluded patients with significant renal impairment. The Cooperative North Scandinavian Enalapril Survival (CONSENSUS) study revealed that patients with the most severe CCF had a substantial increase in creatinine on initiation of an ACE inhibitor irrespective of baseline creatinine [82]. However, it is comforting to note that in the CONSENSUS trial the outcomes were better in the treatment arm even though mean creatinine increased. Indeed, some have proposed that the rise in creatinine after initiation of an ACE inhibitor actually may identify the subgroup of patients who derive the most benefit [83].

ACE inhibitors should be used with caution in patients with CRS and renal functional monitored closely during initiation and uptitration. This caution should not, however, be used to avoid ACE inhibitor therapy. Studies have shown that patients with first presentation of pulmonary oedema are frequently discharged without initiation of ACE inhibitor therapy for fear of worsening renal function [84]. However, as mentioned above, patients who derive prognostic benefit over the longer term from these drugs may experience slight deterioration of renal function in the short term. A concomitant reduction in diuretic dosage may be required (especially once the patient is euvolemic) to facilitate safe uptitration of the ACE inhibitor. The chances of deterioration of renal function after starting ACE inhibitor therapy can also be minimised by avoiding simultaneous use of NSAIDs and ensuring the patient is not hypovolemic at onset of treatment.

5.3. Inotropic Support: The Controversy Continues. Patients with CRS are often hypotensive, and admissions due to ADHF frequently result in severe hypotensive episodes or frank cardiogenic shock. This may be accompanied by oligoanuria, and inotropes are frequently used in this setting with the aim of improving cardiac output and thus renal blood flow. "Renal" or low-dose dopamine is known to increase renal blood flow [85] though there is conflicting evidence regarding its effect upon GFR [85, 86]. One study of 13 patients suggested that dopamine reduces renovascular resistance [87], though the baseline renal function of these patients is not stated. However, another larger study—in which 75% had acute renal failure—showed an increase in renovascular resistance in these patients with a fall in resistance in those with normal renal function [88]. Most importantly, no clinical trial to date has demonstrated a mortality benefit [89].

Trials of dobutamine and milrinone have shown improvement of cardiac index and, in proportion, renal blood flow—however, this has not translated into mortality benefit. The Outcomes of a Prospective Trial of Intravenous Milrinone for Exacerbations of a Chronic Heart Failure (OPTIME-HF) trial clearly rejected the hypothesis that milrinone would improve renal function and overall survival in ADHF patients [90].

The patient population who requires inotropic support for ADHF or cardiogenic shock is inherently complex, and thus designing adequately powered and well-conducted randomised trials poses clear challenges. However, it seems likely that short-term inotropic support for such patients in a low-output state is likely to continue. Current ESC heart failure guidelines state the evidence for using dobutamine as class IIa level B, dopamine class IIa level C, milrinone class IIb level B, and levosimendan class IIa level B (i.e., none has a class I or level of evidence A recommendation) [57].

5.4. Nesiritide: Hope Turns to Hype? Certain pharmacological agents—which held much promise during development—have failed to make the expected impact following results of phase III clinical trials. Nesiritide is an analogue of brain natriuretic peptide (BNP) and known to induce vasodilation and reduce filling pressures as well as augment cardiac output. The first large randomised trial of nesiritide in patients with CRS demonstrated no difference in GFR, renal plasma flow, urine output, sodium excretion, or mortality between treatment and placebo groups [91]. A meta-analysis of seven large randomised trials of nesiritide also showed a lack of mortality benefit at 30-day and 180-day followup [92]. A pooled analysis of three trials showed a strong trend (P value .057) towards increased early mortality with nesiritide [93]. The results of the Acute Study of Clinical Effectiveness of Nesiritide in Decompensated Heart Failure Trial (ASCEND) [94] are currently awaited and may help clarify if this agent has a future in the management of CRS (type 2) patients.

6. Future Directions in CRS

The ability to make a diagnosis of CRS early in a patient's assessment may allow early introduction of management strategies which would hopefully prevent further clinical and biochemical deterioration. Therefore, the development of novel biomarkers of acute kidney injury is a promising step. Neutrophil gelatinase-associated lipocalin [95], cystatin C [96], kidney injury molecule-1 [97], N-acetyl-β-(D)glucosaminidase [98], and interleukin-18 [99] have all been shown to act as markers of renal injury in a variety of different clinical scenarios, and further work is ongoing to help define their role in diagnosis and management.

Patients resistant to diuretic therapy may benefit from ultrafiltration (UF) or aquapheresis. This extracorporeal treatment permits removal of large fluid volumes more

speedily than diuretics and without inducing profound hypotension. The UNLOAD trial showed that, 48 hours after treatment, UF safely produced greater weight and net fluid loss than conventional IV diuretic therapy and at 90 days the UF group had fewer repeat admissions to hospital for fluid reaccumulation [100]. However, another trial demonstrated that UF did not improve renal haemodynamics (as judged by urine output, eGFR, and renal plasma flow) [101].

Arginine vasopressin (AVP) is released from the posterior pituitary gland and mediates water retention via the V_2receptor in the renal collecting ducts. AVP levels are elevated in heart failure patients and AVP antagonists (the "vaptans") have thus been developed. Tolvaptan was initially shown to reduce body weight and help normalize serum sodium in ADHF patients without adverse effect on blood pressure, heart rate, or renal function [102]. Later studies also demonstrated that tolvaptan, when compared to placebo, significantly reduced pulmonary arterial pressure, pulmonary capillary wedge pressure, and right atrial pressure as well as increasing urine output without adverse effect on renal function [103]. The multicentre international phase III Efficacy of Vasopressin Antagonism in Heart Failure Outcome Study with Tolvaptan (EVEREST) trial [104] randomised patients admitted with ADHF within 48 hours to receive either tolvaptan 30 mg once daily or placebo for a minimum time duration of 60 days. Tolvaptan was associated with more weight loss and less dyspnoea on days 1 and 7 and without adverse effect on renal function. However, the key end points of all-cause mortality, cardiovascular mortality, cardiovascular death, or hospitalization, and worsening heart failure were not different between the two groups [104].

Adenosine-A1 receptors are found in the kidney and thought to mediate urine output. Adenosine levels are increased in heart failure [105] and thus adenosine-A1 receptor antagonists were conceived; unfortunately, again, the vital randomised trial failed to show any benefit in ADHF patients [106].

CCF patients characteristically have an expanded extracellular fluid volume and contracted arterial blood volume with resultant regional perfusion abnormalities. This results in a series of complex neurohormonal changes leading to peripheral and central congestion and reduced renal blood flow [107]. Hypertonic saline solution (HSS) has been proposed as a useful adjunct to IV furosemide in ADHF patients with CRS with several postulated mechanisms of action: mobilisation of fluid from the extravascular space to the intravascular compartment by the osmotic effects of HSS and an increase in renal blood flow which can thus help overcome diuretic resistance [108]. Small studies have demonstrated the ability of HSS to augment renal blood flow and a larger trial—which randomised NYHA class 4 patients to IV furosemide plus HSS or IV furosemide bolus alone—revealed a greater degree of diuresis and natriuresis, lower rehospitalisation rate, and lower mortality rate in the HSS group versus placebo group [109]. However, routine use of HSS in ADHF patients remains rare, and its role in this patient population is yet to be defined.

7. Conclusion

As our review has hopefully demonstrated, CRS is an ominent development in many patients. However, prognosis is not uniform across all five subtypes and highly dependent upon the nature of the underlying disease process(es). The worst prognoses are in those with chronic dysfunction of both organ systems. CRS has generally been used so far to describe patients with renal dysfunction secondary to chronic heart failure; this group of patients have a particularly high morbidity and mortality. Difficulties remain regarding diagnostic pathways and appropriate management strategies. Fortunately, however, cardiologists and nephrologists are now acutely aware of the scale of the problem posed by CRS, and this "awakening" will hopefully translate into greater research into this fascinating yet challenging clinical conundrum.

Conflict of Interests

The authors declare no conflict of interests.

Abbreviations

ACE: Angiotensin-converting enzyme
ADHF: Acute decompensated heart failure
AVP: Arginine vasopressin
BNP: Brain natriuretic peptide
CCF: Congestive cardiac failure
CKD: Chronic kidney disease
CRAS: Cardiorenal anaemia syndrome
CRS: Cardiorenal syndrome
ECFV: Extracellular fluid volume
ESC: European Society of Cardiology
ESRF: End-stage renal failure
GFR: Glomerular filtration rate
HSS: Hypertonic saline solution
IAP: Intraabdominal pressure
IV: Intravenous
LV: Left ventricle
NO: Nitric oxide
NPY: Neuropeptide Y
NSAID: Nonsteroidal anti-inflammatory drug
RAAS: Renin-angiotensin-aldosterone-system
ROS: Reactive oxygen species
SNS: Sympathetic nervous system
UF: Ultrafiltration.

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SAGE-Hindawi Access to Research
International Journal of Nephrology
Volume 2011, Article ID 351291, 11 pages
doi:10.4061/2011/351291

Review Article

Heart-Kidney Interaction: Epidemiology of Cardiorenal Syndromes

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Received 27 August 2010; Accepted 26 November 2010

Academic Editor: Mitchell H. Rosner

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Cardiac and kidney diseases are common, increasingly encountered, and often coexist. Recently, the Acute Dialysis Quality Initiative (ADQI) Working Group convened a consensus conference to develop a classification scheme for the CRS and for five discrete subtypes. These CRS subtypes likely share pathophysiologic mechanisms, however, also have distinguishing clinical features, in terms of precipitating events, risk identification, natural history, and outcomes. Knowledge of the epidemiology of heart-kidney interaction stratified by the proposed CRS subtypes is increasingly important for understanding the overall burden of disease for each CRS subtype, along with associated morbidity, mortality, and health resource utilization. Likewise, an understanding of the epidemiology of CRS is necessary for characterizing whether there exists important knowledge gaps and to aid in the design of clinical studies. This paper will provide a summary of the epidemiology of the cardiorenal syndrome and its subtypes.

1. Introduction

On a global scale, evolving changes in demographics have lead to an aging population along with increasing rates of obesity, diabetes mellitus (DM), and hypertension. These emerging pandemics have also focused considerable attention on the public health importance and the broad implications of increasing rates of heart disease, kidney disease, and the concomitant occurrence of both heart and kidney disease.

An estimated 1 in 3 adults in the United States of America (USA) (or greater than 80 million persons) has a diagnosis of cardiovascular disease (CVD) (i.e., hypertension, coronary heart disease (CHD), heart failure (HF), stroke, or congenital heart disease) [1]. In the USA, the prevalence of any stage CKD has been recently estimated at 13% representing close to 30 million adults [2]. CKD has also emerged as an important and potentially modifiable predictor of CVD, including CHD, left ventricular hypertrophy, and HF [3]. Increasingly, there is recognition of the considerable clinical overlap and complex pathophysiology between CKD and CVD [4]. Cardiovascular disease may account for greater than 50% of all deaths in patients with CKD, occurring at rates 10- to 20-fold higher than an age-matched non-CKD population [5, 6]. This epidemic of CKD has potential far-reaching economic implications, as patients with CKD are more likely to be hospitalized, consume greater health resources, and have higher costs of care, both of which are increased further after progression to ESKD [7].

A description of the epidemiology of heart-kidney interactions is critical to understanding not only to overall burden of disease for each of the proposed CRS subtypes, but also their natural history, risk factors, associated morbidity and mortality, and potential health resource implications [8]. Likewise, an appreciation for the existing literature on the epidemiology and outcomes of CRS is necessary for recognizing whether there are important knowledge gaps and for the design of future observational studies and clinical trials. This paper will summarize the epidemiology and clinical outcomes associated with the CRS stratified by its subtypes.

2. Type 1 Cardiorenal Syndrome: Acute Cardiorenal Syndrome

The Acute Cardiorenal Syndrome (Type 1 CRS) is characterized by acute worsening of heart function leading to acute kidney injury (AKI) and/or dysfunction. Acute cardiac events that may contribute to AKI include acute decompensated heart failure (ADHF), acute coronary syndrome (ACS), cardiogenic shock, and cardiac surgery-associated low cardiac output syndrome.

Mostly commonly, observational studies have evaluated the development of AKI in association with ADHF and ACS (Tables 1 and 2). Many of these studies are limited in scope due to being performed retrospectively or being secondary and/or post hoc analyses from large databases [9–13] or secondary or analyses of clinical trials of drug therapy [8, 14, 15].

Most of these studies also use the term "worsening renal failure (WRF)" to describe the acute and/or subacute changes in kidney function that occurs following ADHF or ACS. For example, WRF has been defined as increases in serum creatinine (SCr) ≥26.5 μmol/L (0.3 mg/dL) [10, 13–16, 25–27], ≥44.2 μmol/L (0.5 mg/dL) [9, 10, 12, 13, 27, 28], ≥25% relative to SCr at the time of hospital admission, ≥50% at the time of hospital admission, and as the combined increase of ≥26.5 μmol/L (0.3 mg/dL) and ≥25% increase [17]. Stud-ies have also evaluated WRF as even smaller increments of rise in SCr (≥8.8 μmol/L (0.1 mg/dL)) [10, 12, 27] or as rate of decline in estimated GFR (eGFR) [29]. Aronson et al. evaluated WRF defined by a 50% increase in blood urea nitrogen above admission values [30]. Incidence estimates of WRF associated with ADHF and ACS have ranged between 24%–45% and 9%–19%, respectively. A small single center study found that AKI occurred in 48% of pediatric patients admitted for ADHF [31]. This wide range in incidence is attributed to differences in the definitions used for WRF, in the observed time-at-risk after hospitalization, and due to heterogeneity of the study populations.

Studies have used variable durations of observed time-at-risk for ascertainment of WRF. For example, in a cohort admitted with ADHF, Gottlieb et al. showed that 47% had WRF within three days of hospitalization [10]. Cowie et al. found that 50% occurred within four days [25]. Whereas, two observational studies found that 70%–90% of all WRF had occurred within the first week of hospitalization [11, 25]. Still, other studies have observed for WRF for 2 weeks [14] and up to 6 months [32]. These variations in ascertainment for WRF have the potential to introduce bias and misclassification. The most common definition for WRF has been any time within hospital admission [10, 11]. However, data have shown that the vast majority of WRF occurs early after hospital admission. Moreover, it is important to recognize that the pathophysiology of WRF/AKI likely varies at different time points. For example, WRF at presentation may be due to congestion and low cardiac output; however, investigations (i.e., cardiac catheterization and contrast media exposure) or interventions (i.e., furosemide, angiotensin converting enzyme [ACE] inhibitors) may impact kidney function and contribute, in part, to late WRF. These potential influences have not been well described in terms of time of onset of WRF.

The pathophysiologic mechanisms leading to WRF in ADHF are numerous and complex, but likely include alterations to cardiac output and systemic hemodynamics compromising kidney perfusion [33, 34] and pathologic compensatory neurohormonal activation [35]. An important risk factor also includes baseline kidney function and presence of CKD [19, 36]. Aronson et al. recently showed that persistent WRF after admission for ADHF was more likely in those with worse baseline kidney function [18]. Few studies have investigated the time course of WRF and whether there are observed differences in clinical outcome associated with transient WRF or persistent stepwise declines in kidney function after hospitalization for ADHF. Recently, Aronson et al. investigated this issue in a cohort of 467 patients admitted with ADHF [18]. WRF was defined as an absolute increase in SCr ≥ 44.2 μmol/L, whereas transient was defined as return to baseline within 30 days and persistent WRF as a sustained increase in SCr ≥ 44.2 μmol/L beyond 30 days. Of those developing WRF (33.9%), transient and persistent WRF occurred in 7.9% and 14.3%, respectively. At 6 months, mortality was 17.3%, 20.5%, and 46.1% in those with neither, transient and persistent WRF ($P < .0001$ for persistent versus no WRF), strongly suggesting a worse prognosis for those with persistent declines in kidney function.

Two studies have recently evaluated the association of novel biomarkers for predicting AKI/WRF in patients with AHDF [37, 38]. In a small cohort of 91 ADHF patients, serum neutrophil gelatinase-associated lipocalin (NGAL) was measured at the time of admission [37]. In total 35 patients (38%) developed WRF defined as an increase in SCr ≥ 26.5 μmol/L. In patients developing WRF, serum NGAL was significantly higher (194 ng/mL versus 128 ng/mL, $P = .004$). Those with an admission serum NGAL ≥ 140 ng/mL had a 7.4-fold increased risk of developing WRF. In another small cohort of 125 heart failure patients, Pfister et al. found elevated baseline NT-pro-BNP predicted subsequent AKI [38].

In both ADHF and ACS, AKI has consistently shown association with higher morbidity and mortality [11, 20, 45]. In ADHF, AKI is associated with increased risk for both short- and long-term all-cause and cardiovascular mortality [10, 11, 15–17, 19, 20, 25, 45]. In addition, data suggest that there is a biological gradient between AKI severity and mortality [27]. Several studies have shown development of AKI in association with ADHF prolonged stay in hospital [10, 11, 15–17, 19, 20, 25, 45]. Selected studies have also found that AKI in ADHF was associated with increased readmission rates [16, 17, 19, 45]. Recently, in a retrospective study of 20,063 Medicare beneficiaries hospitalized for ADHF, Kociol et al. found that 17.8% developed AKI (defined as an increase in SCr ≥ 27 μmol/L), with 64.5% readmitted and 35.4% dying within 1 year [20]. After adjustment for covariates, AKI was independently associated with long-term mortality (HR 1.12, 95% CI, 1.04–1.20).

AKI associated with ACS increases the risk of poor outcome [9, 12–14, 22–24, 28]. Even small acute changes

Table 1: Summary of studies fulfilling criteria for Acute Cardiorenal Syndrome (CRS Type 1) with a presenting diagnosis of acute decompensated heart failure.

Study	Population	Study type (data source)	AKI (WRF) definition	Incidence AKI (%)	Cardiac disease	Outcome
Nohria et al., 2008 [15]	$n = 433$ Mean Age 56 yrs Male % DM 34% HTN 47%	Retrospective (ESCAPE Trial)	SCr > 26.5 μmol/L	29.5	Hospitalized ADHF	All-cause death (6 m) (HR) increased for SCr > 106.1 AKI (>26.5 μmol/L) not associated with death/readmission
Logeart et al., 2008 [16]	$n = 416$ Age 71 yrs Male 59% DM 23% HTN 42%	Prospective	SCr > 26.5 μmol/L	37	Hospitalized ADHF Prevalence: LVEF 0.35 LVEF $\leq$ 0.45 70% Prior HF 45% Prior MI 55%	All-cause death (6 m) or Readmission (adj-HR) 1.74 Increased LOS 3 d Risk persisted whether AKI transient or not
Metra et al., 2008 [17]	$n = 318$ Mean Age 68 yrs Male 60% DM 34% HTN 53%	Prospective	SCr > 26.5 μmol/L & $\geq$ 25%	34	Hospitalized ADHF Prevalence: Prior MI 51% Prior HF 58%	CV death or readmission (adj-HR) 1.47 Increased LOS 7 d
Aronson and Burger [18]	$n = 467$	Prospective	SCr > 44.2 μmol/L	33.9 Transient 7.9 Persistent 14.3	Hospitalized ADHF	All-cause death (6 m) 17.3%, 20.5%, and 46.1% for no WRF, transient WRF, persistent WRF Adj-HR for persistent WRF 3.2 (95% CI, 2,1–5.0)
Belziti et al., 2010 [19]	$n = 200$	Retrospective	SCr > 26.5 μmol/L & $\geq$ 25%	23	Hospitalized ADHF	Higher mortality at 1-year ($P < .01$) Rehospitalization for WRF (HR 1.65, $P = .003$) Longer median LOS for WRF (9 versus 4 days, $P < .05$)
Kociol et al., 2010 [20]	$n = 20{,}063$	Retrospective	SCr > 26.5 μmol/L	17.8	Hospitalized ADHF	1-year mortality 35.4% (HR 1.12, 95% CI, 1.4–1.20) Rehospitalization 64.5%

SCr: serum creatinine; m: months; d: days; CV: cardiovascular; LOS: length of stay.

in serum creatinine modify the risk of death [14]. Among those developing AKIs, greater risk of cardiovascular events such as CHF, recurrent ACS, and stroke and need for rehospitalization have been shown [14, 23, 24]. Newsome et al. reported a greater likelihood of progression to ESKD in those with ACS complicated by AKI [12]. Recently, Goldberg et al. found increasing severity of and persistent AKI were associated with higher risk of death in patients surviving ST-elevation myocardial infarction (STEMI) [21]. This would imply, similar to studies with ADHF, that there is a biological gradient between AKI severity and duration and mortality.

These data would suggest that AKI in association with ADHF or ACS may further exacerbate cardiac injury and/or function and also contribute to exaggerated declines in kidney function. In a small cohort of 141 patients with reperfused anterior STEMI, those developing AKI were found to have higher plasma norepinephrine, BNP, interleukin-6 levels in the 2 weeks after reperfusion [23]. Moreover, those developing AKI have higher risk of in-hospital death ($P = .004$), major adverse cardiac events ($P = .02$), that correlated with greater observed left ventricular (LV) remodelling. This would imply that the observed heart-kidney interface in Type 1 CRS may synergistically act to further accelerate injury and/or dysfunction.

3. Type 2 Cardiorenal Syndrome: Chronic Cardiorenal Syndrome

This syndrome is characterized by chronic abnormalities in cardiac function leading to kidney injury or dysfunction. The term "chronic cardiac abnormalities" encompasses a number of different conditions and may include chronic LV dysfunction, atrial fibrillation, congenital heart disease, constrictive pericarditis, and chronic ischemic heart disease (Table 3).

Observational data clearly show that chronic heart and kidney disease commonly coexist, but such studies are unable to determine which of the two disease processes was primary versus secondary [46]. This therefore presents challenges when appraising the literature and attempting to classify patients into the CRS subtype definitions; it has been

Table 2: Summary of studies fulfilling criteria for Acute Cardiorenal Syndrome (CRS Type 1) with a presenting diagnosis of acute coronary syndrome.

Study	Population (n)	Study type (data source)	AKI (WRF) definition	Incidence AKI (%)	Cardiac disease	Outcome
Newsome et al., 2008 [12]	n = 87,094 Mean Age 77 yrs Male 50% DM 28%–37%	Retrospective (CCP)	Variable	Any 43.2 △SCr Quartiles: Q1: △0.1, 13.1; Q2:△0.2, 9.3; Q3: △0.3–0.5, 12.3; Q4: △0.6–3.0, 8.4	AMI Prevalence: Prior MI 31%–35% Prior HF 21%–35%	All-cause (death (1000 p-y)/HR): Q1 146/1.1; Q2 157/1.2; Q3 194/1.3; Q4 275/1.4 ESKD (incidence (1000 p-y)/HR): Q1 2.3/1.5; Q2 3.6/2.0; Q3 6.3/2.4; Q4 20/3.3
Parikh et al., 2008 [13]	n = 147,007 Age 76–78 yrs Male 49%-50% DM 29%–41%	Retrospective (CCP)	△SCr (μmol/L): Mild (26.5–35.4); Mod (44.2–88.4); Severe (≥88.4)	Any 19.4, Mild 7.1, Mod 7.1, Severe 5.2	AMI Prevalence: Prior AMI 30%–36% Prior HF 19%–35%	All-cause (10 yr) (death (crude%)/adj-HR): None 68/1.00; Mild 79/1.15; Mod 88/1.23 Severe >90/1.33
Goldberg et al., 2009 [21]	n = 1957 Age 59–70 yrs Male 79.4% DM 26.2%	Retrospective	△SCr (μmol/L): Mild (26.5–44.2), Mod-Severe (>44.2)	Mild 8.0 Mod-Severe 7.1	Prior AMI 20.9%	Adj-HR mortality: Mild transient 1.2; Mild persistent 1.8; Mod-severe transient 1.7; Mod-severe persistent 2.4
Mielniczuk et al., 2009 [22]	n = 3795	Retrospective	SCr > 25% over 1-month	5	—	Adj-HR 1.6 (95% CI, 1.1–2.3) for composite CV death, recurrent ACS, HF or stroke
Anzai et al., 2010 [23]	n = 141 Age 63 yrs Male 87% DM 36%	Prospective	SCr > 26.5 μmol/L within 48 hrs	22	Anterior STEMI	Higher in-hospital death (P = .004) and major adverse cardiac events (P = .02)
Marenzi et al., 2010 [24]	n = 97 Age 63–69 yrs Male 69% DM 18.6%	Prospective	SCr > 25%	55	STEMI + IABP	In-hospital death (RR 12.3, 95% CI, 1.8–84.9, P < .001). AKI associated with age > 75 yrs, LVEF < 40%, mechanical ventilation.

WRF: worsening renal function; SCr: serum creatinine; wks: weeks; m: months; CKD: chronic kidney disease; ESKD: end-stage kidney disease.

suggested to use the term Type 2/4 in these situations [8]. Large database studies often describe patient populations based on the existence of one disease process (i.e., HF) and subsequently estimate the occurrence of the other (CKD).

In the ADHERE study, a large dataset of 118,465 individual hospitalizations for ADHF, 27.4%, 43.5%, and 13.1% of patients were found to have mild, moderate, and severe kidney dysfunction at hospital admission [39]. Greater severity of kidney dysfunction correlated with worse clinical outcomes, including need for ICU admission, need for mechanical ventilation, longer hospitalization, and higher mortality. In the Digitalis Investigation Group trial, preexisting CKD was found in 45% of chronic HF patients and was associated with higher rate of hospitalization and death [39]. There was also evidence of a biologic gradient between CKD severity and outcome.

The Atherosclerosis Risk in Communities (ARIC) and Cardiovascular Health (CHS) studies recently provided some additional insight on the epidemiology of Type 2 CRS [40]. Patients with baseline CVD comprised 12.9% of the study cohort. At study entry, these patients had a mean SCr 79.6 μmol/L and estimated GFR 86.2 ml/min/1.73 m^2. After an average follow-up of 9.3 years, 7.2% of CVD patients had declines in kidney function when defined as an increase in SCr ≥ 35.4 μmol/L and 34% when defined as a decline in eGFR ≥ 15 ml/min/1.73 m^2. During follow-up, 5.6% developed new CKD. By multivariable analysis, baseline CVD was independently associated with both decline in kidney function and development of new CKD. These data strongly suggest that CVD is an important risk for measurable declines in kidney function (OR 1.70, 95% CI 1.36–2.31) and CKD (OR 1.75, 95% CI 1.32–2.32) and empirical proof of the concept of Type 2 CRS.

One clear example of CRS Type 2 is congenital heart disease, in which the heart disease temporally precedes any kidney disease. "Cyanotic nephropathy" (CN) has long been

Table 3: Summary of studies fulfilling criteria for Chronic Cardiorenal Syndrome (CRS Type 2).

Study	Population (n)	Study type (data source)	Cardiac disease	CKD	Cardiac-specific outcomes	Outcomes (%)
Heywood et al., 2007 [39]	N = 118,465 Mean Age 61.7–76.3 yrs Male 42%–57%	ADHERE registry	ADHF	eGFR 60–89: 27.4%; eGFR 30–59: 43.5%; eGFR 15–29: 13.1%; eGFR < 15: 7%	Use of cardioprotective meds (ACE-I and ARB) decreased with increasing degree of CKD	OR for in-hospital mortality: eGFR ≥ 90: 1.0; eGFR 60–89: 2.3; eGFR 30–59: 3.9; eGFR 15–29: 7.6; eGFR < 15: 6.5
Elsayed et al., 2007 [40]	N = 13826 Mean Age 58 yrs Male 56%	Prospective (ARIC and CHS)	Baseline CVD in 12.9%	eGFR decrease of at least 15 ml/min/1.73 m^2 to a final level < 60 ml/min/1.73 m^2 was seen in 34% of patients with baseline CVD	NA	OR for development of kidney disease 1.54 (CVD versus non-CVD)
Ahmed et al., 2007 [41]	N total = 7788 Mean Age 59.9–65.4 yrs Male 76%–81%	Retrospective (DIG trial); Propensity-matched study	Ambulatory patients with CHF	eGFR < 60 in 45%	A graded association was found between CKD-related deaths and LVEF	Matched HR: (CKD versus non-CKD) All-cause death 1.71
Campbell et al., 2009 [42]	N total = 7788 Mean Age 59.9–65.4 yrs Male 76%–81%	Retrospective (DIG trial); Propensity-matched study	Ambulatory patients with CHF	eGFR < 60 in 45%	Matched HR: (CKD versus non-CKD) CV hospitalization 1.17 HF hospitalization 1.08 CV death 1.24 HF death 1.42	Matched HR: (CKD versus non-CKD) All-cause hospitalization 1.18
Dimopoulos et al., 2008 [43]	N = 1102 Mean Age 36 yrs Male 48.5%	Retrospective (single center)	Adult congenital heart disease	eGFR 60%–89 41% eGFR < 60 9%	NA	All-cause death (HR) eGFR ≥ 90 1.0; eGFR < 60 3.25
Hillege et al., 2003 [44]	N = 298 Mean Age 51–67 yrs Male 70% DM 16%–27% HTN 6%–14%	Retrospective (CATS trial)	1st anterior wall MI	Change in GFRc Placebo: −5.5 ml/min/yr Captopril: −0.5 ml/min/yr	New CHF (RR) GFRc > 103: 1.0 GFRc 81–103: 1.23 GFRc < 81: 1.55	All-Cause death: 1-yr 8%

ARIC: atherosclerosis risk in communities study; ADHF: acute decompensated heart failure: GFRc: GFR estimated by Cockroft Gault; CATS: captopril and thrombolysis study; CVD: cardiovascular disease; CVS: cardiovascular health study; DIG: digoxin investigator group.

recognized as a potential complication of cyanotic congenital heart disease [47, 48]. Infants born with congenital heart defect, in the majority of circumstances, have normal kidneys. Dimopoulos et al. studied 1102 patients (mean age 36 yrs) surviving into adulthood with congenital heart disease [43]. Amongst this cohort, >50% had evidence of kidney dysfunction that was considered mild (eGFR 60 to 89 ml/min per 1.73 m^2) in 41% and moderate-severe (eGFR < 60 ml/min per 1.73 m^2) in 9%. Patients with Eisenmenger physiology had the lowest eGFR and the highest prevalence of moderate or severe reduced GFR (18%). Similarly, there was a trend towards greater kidney dysfunction in patients with more complex anatomy. However, kidney dysfunction was detected even among patients characterized as having "simple" defects. Importantly, kidney dysfunction had a substantial impact on mortality (propensity score-weighted HR 3.25, $P = .002$ for impaired versus normal GFR).

4. Acute Reno-Cardiac Syndrome (Type 3 CRS)

The Acute Reno-Cardiac Syndrome (Type 3 CRS) is characterized by acute worsening of kidney function that leads to acute cardiac injury and/or dysfunction, such as acute myocardial infarction, congestive heart failure, or arrhythmia. Conditions that may contribute to this syndrome include cardiac surgery-associated AKI, AKI after major noncardiac surgery, contrast-induced AKI (CI-AKI), other drug-induced nephropathies, and rhabdomyolysis.

The association of AKI and acute cardiac dysfunction with these conditions likely shares similar predisposing pathophysiologic mechanisms and risk factors for development (i.e., volume overload, systemic hypertension, retention of uremic solutes, hyperkalemia). However, the pathophysiologic mechanisms contributing to Type 3 CRS are likely to extend beyond simply retention of uremic solutes and/or volume overload. Defining the epidemiology of Type 3 CRS is challenging for several reasons. First, there is considerable heterogeneity in predisposing conditions causing AKI. Second, AKI has been variably defined across studies. Third, there is likely variable baseline risk for acute cardiac dysfunction across populations, such as increased susceptibility in selected individuals with subclinical cardiovascular disease. Finally, few clinical studies focused on AKI have reported on the event rates of acute cardiac dysfunction. Therefore, estimates of incidence and associated outcomes of acute cardiac dysfunction associated with AKI are largely context- and disease-specific.

For example, contrast media administration is a leading cause of iatrogenic AKI following diagnostic and interventional procedures and is associated with major adverse effects, progression of CKD, and consumption of health resources [49]. While AKI is most often attributable to the administration of contrast media, additional confounding factors, such as atheroembolic disease, renal hypoperfusion, concomitant nephrotoxins, may also be contributory. The reported incidence is highly variable depending on the population-at-risk being evaluated (i.e., age, CKD, DM, HF) and the type of procedure performed (i.e., emergent, intravascular, type, and volume of contrast media). Incidence estimates have been reported in the range of 1%–40% [49–51]. The natural history of CI-AKI in many patients may follow an asymptomatic rise in serum creatinine with early return to baseline, and these patients would not be expected to fulfill the criteria for Acute Reno-Cardiac Syndrome (Type 3 CRS). However, in an estimated 0.2%–1.1%, AKI progresses to require the initiation of renal replacement therapy (RRT) [49, 50, 52]. In these patients, AKI may be associated with volume overload, retention of uremic solutes, pulmonary edema, and cardiac arrhythmias. Importantly, those at-risk for developing CI-AKI requiring RRT may be identifiable *a priori*. However, the difficulty in evaluating the epidemiology of Acute Reno-Cardiac Syndrome (Type 3 CRS) attributable to CI-AKI is that few studies have specifically reported the temporal occurrence of cardiovascular events following contrast media exposure [53].

5. Chronic Reno-Cardiac Syndrome (Type 4 CRS)

The Chronic Reno-Cardiac Syndrome (Type 4 CRS) is a condition where primary CKD contributes a reduction in cardiac function, such as cardiac remodelling, left ventricular diastolic dysfunction or hypertrophy, and/or an increased risk for cardiovascular events, such as myocardial infarction, heart failure, or stroke. This CRS subtype refers to cardiac dysfunction and/or disease primarily occurring in response to CKD (Table 4).

Observational data have evaluated the cardiovascular event rates and outcomes in selected CKD-specific populations [54, 56, 57, 59–63]. Most have been retrospective and/or secondary post hoc analyses from large clinical registries or randomized trials. As mentioned above, this type of data cannot establish whether the primary process is the kidney disease (CRS Type 4) or the heart disease (CRS Type 2). Furthermore, defining the epidemiology of Type 4 CRS is challenging, and estimates are variable due to differences in (1) the populations-at-risk, (2) the clinical outcomes evaluated, (3) duration of time for ascertainment of study endpoints, and (4) the operational definitions used for defining CKD, cardiac disease, and/or mortality (i.e., all-cause or CVD-specific).

For example, the populations-at-risk in these studies, based on the presence and severity of CKD, ranged from near normal kidney function to ESKD. In a secondary analysis of the Hemodialysis (HEMO) Study, Cheung et al. found that 80% of ESKD patients had cardiac disease at enrollment [60]. Older patients, diabetics, and those having received a longer duration of maintenance hemodialysis (>3.7 years) had higher prevalence of pre-existing cardiac disease. During follow-up, 39.8% were admitted to hospital for cardiac-related diagnoses. Of these, 42.7% were attributable to ischemic CHD. Of the 39.4% of cardiac deaths, 61.5% were attributable to ischemic CHD. Baseline cardiac disease was significantly predictive of cardiac-specific death during follow-up (Relative Risk 2.57). Moreover, recent data have suggested that chronic maintenance hemodialysis induces repetitive myocardial injury and can accelerate declines in myocardial performance [64].

In CKD patients not receiving maintenance RRT, the prevalence of CVD varies considerably with CKD severity and the overall time-at-risk (i.e., duration of time with diagnosis of CKD) [58, 59, 62]. The risk of CVD events and death is also likely further modified by older age, comorbid illness, and presence of concomitant HF [54, 59, 62, 65]. In data from the NHANES II study, Muntner et al. found CVD prevalence of 4.5%, 7.9%, and 12.9% for patients with eGFR $\geq$ 90, 70–89, and $<$ 70 mL/min/cm^2, respectively [55]. Likewise, in a large population-based cohort, Go et al. found similar graded increases in CVD prevalence and HF, along with higher risk of subsequent cardiac events during follow-up associated with degree of decline in eGFR $<$ 60 mL/min/1.73 cm^2 [56]. This dose-response gradient in CVD prevalence by severity of CKD was also associated with higher trends in cardiac-specific and all-cause mortality [55–58]. Observational data have also shown that CKD accelerates the risk for and development of CVD [3, 59, 62]. This accelerated risk for cardiovascular events and disease in CKD may be the consequence of the unique pathophysiology that exists in these patients including hyper-homocysteinemia, elevated lipoprotein (a), oxidative stress, endothelial dysfunction, chronic inflammation (i.e., elevated C-reactive protein, interleukin-6), vascular remodelling (i.e., increased myocardial arteriolar wall thickness, reduced myocardial

Table 4: Summary of selected studies fulfilling criteria for Chronic Reno-Cardiac Syndrome (Type 4).

Study	Population (n)	Study type (data source)	CKD stage	Cardiac outcomes (%)	Outcomes (%)
Herzog et al., 1998 [54]	n = 34,189 Age ≥ 65 yrs 55% Male 56%	Retrospective (USRDS)	ESKD	Cardiac-Death: 1-yr 41%; 2-yr 52%; 5-yr 70.2%; 10-yr 83%	All-cause: 1-yr 59%; 2-yr 73%; 5-yr 90%; 10-yr 97%
Muntner et al., 2002 [55]	n = 6,534 Age 48–63 yrs Male 51%–61%	Retrospective (NHANES II)	eGFR < 70 75.9%	CV-Death (rate per 1000 p-y): eGFR ≥ 90: 4.1; eGFR 70–89: 8.6; eGFR < 70: 20.5	All-cause death (HR): eGFR ≥ 90: 1.00 eGFR 70–89: 1.64; eGFR < 70: 2.00
Go et al., 2004 [56]	n = 1.1 million Mean Age 52 yrs Male 45%	Retrospective (Kaiser Permanente)	≥ CKD stage III or eGFR < 60	CV Event (rate per 100 p-y/HR): eGFR 45–59: 3.65/1.4; eGFR 30–44: 11.3/2.0; eGFR 15–29: 21.8/2.8; eGFR < 15: 36.6/3.4	All-cause mortality (per 100 p-y/HR): eGFR 45–59: 1.1/1.2; eGFR 30–44: 4.8/1.8; eGFR 15–29: 11.4/3.2; eGFR < 15: 14.1/5.9
Foley et al., 2005 [3]	n = 1,091,201 Age ≥ 75 yrs 56.1 Male 39%	Retrospective (Medicare/USRDS)	CKD 3.8% (diagnostic coding)	CV Event Incidence: AMI 4–7 per 100 p-y; CHF 31–52 per 100 p-y; (HR 1.28–1.79)	All-cause death: HR 1.38–1.56
HIllege et al., 2006 [57]	n = 2,680 Mean Age 65 yrs Male 67%	Retrospective (CHARM)	eGFR < 60 36%	CV Death/Hosp. (HR) eGFR ≥ 90: 1.0; eGFR 75–89: 1.17; eGFR 60–74: 1.24; eGFR 45–59: 1.54 eGFR < 45: 1.86	All-cause death (HR) eGFR ≥ 90: 1.0; eGFR 75–89: 1.13; eGFR 60–74: 1.14; eGFR 45–59: 1.50 eGFR < 45: 1.91
McCullough et al., 2007 [58]	n = 37,153 Mean Age 53 yrs Male 31%	Retrospective (KEEP)	eGFR< 60 14.8%	Prevalence CVD (OR): eGFR ≥ 90 1.0; eGFR 60–89 1.1; eGFR 30–59 1.4; eGFR < 30 1.3	All-cause death (HR): CKD only 1.98; CVD only 3.02 CKD + CVD 3.80
McCullough et al., 2008 [59]	n = 31,417 Mean Age 45 yrs Male 24.5%	Retrospective (KEEP)	eGFR< 60 or ACR ≥ 30: 20.6%	Risk CVD/death (OR): CKD 1.44 No CKD 1.0	Worst survival for combined CKD and CVD at time of screening

ESKD: end-stage kidney disease; CKD: chronic kidney disease; DM: diabetes mellitus; HTN: hypertension; CHF: congestive heart failure; CVD: cerebrovascular disease; MA: microalbuminuria: CHD: coronary heart disease; LVH: left ventricular hypertrophy; CV: cardiovascular; eGFR: estimated glomerular filtration rate; ADHF: acute decompensated heart failure.

capillary density, increased cardiac interstitium [66]), alterations in platelet aggregation, neurohormonal activation, volume overload, reduced parenchymal mass, and deficiency in various hormones (i.e., vitamin D, erythropoietin) [67]. Another important consideration is that patients with CKD have often been excluded from clinical trials of interventions in CVD [4] and may receive less or suboptimal risk modifying and/or cardioprotective therapies, and perhaps as a consequence, receive less or suboptimal risk modifying and cardioprotective therapies such as aspirin, beta-blockers, and angiotensin-converting inhibitors despite evidence to suggest that CKD patients may similarly benefit [46, 68–70]. Finally, the genuine concern for treatment toxicities, intolerance, and/or risks in CKD patients or AKI may be such that therapy is not offered due to an unfounded perception of a less favourable risk-benefit ratio. These factors, in part, may provide explanation for the excess of CVD and associated poor outcomes for CKD patients.

Analogous to congenital heart disease being a prototype condition for CRS Type 2, genetic renal diseases can also be a similar example for CRS Type 4, in that the renal disease temporally precedes the cardiac disease. Autosomal dominant polycystic kidney disease (ADPKD) is one of the most common genetic renal diseases worldwide and is the fourth leading cause of ESRD in the United States of America [71]. Cardiovascular complications are the leading cause of death in ADPKD, and multiple cardiac conditions have been described in these patients. As with CKD in general, the prevalence of left ventricular hypertrophy (LVH) is higher in ADPKD compared to a control population, and the frequency increases progressively as GFR decreases. However, several studies have also shown increased LV mass indices, LV diastolic dysfunction, and endothelial dysfunction in young otherwise normotensive ADPKD subjects with well-preserved renal function [72].

6. Secondary Cardiorenal Syndromes (Type 5 CRS)

The Type 5 CRS is characterized by an acute or chronic systemic illness that concurrently induces cardiac and kidney

Table 5: Summary of potential etiologies for acute and chronic Secondary Cardiorenal Syndromes (Type 5).

(a) Acute Systemic Illness
Severe sepsis/septic shock
Specific infections
HIV
Malaria
Leptospirosis
Hepatitis C virus
Drug toxicity
Cocaine
Heroine
Calcium-channel blockers
Cancer chemotherapy
Connective tissue diseases
Systemic lupus erythematosus
Scleroderma
Antiphospholipid antibody syndrome
Microangiopathy
TTP/HUS
Pregnancy
Malignant hypertension
Hemorrhagic shock
Vasculitis
Malignancy (i.e., lymphoma/leukemia)
(b) Chronic Systemic Illness
Hypertension
Diabetes Mellitus
Primary/Secondary Amyloidosis
Multiple Myeloma/Paraproteinemias
Sarcoidosis
Liver Cirrhosis
Primary/Secondary Pulmonary Hypertension

injury and/or dysfunction. Limited data is available on the epidemiology of Secondary Cardiorenal Syndromes due largely to vast number of contributing acute and/or chronic systemic conditions that may predispose to it. Accordingly, estimates of incidence, risk identification, and outcomes for Type 5 CRS are considered largely disease, and/or context-specific and may be time-varying. Importantly, there is currently an incomplete understanding of the pathophysiologic mechanisms of secondary cardiac-kidney interaction. Specifically, whether concomitant cardiac and kidney dysfunction in systemic illness is merely coexisting or whether there is genuine bidirectional interaction that may directly contribute to aggravated dysfunction in either organ system remains unclear (see Table 5).

Sepsis represents a prototypical condition that may cause an acute form of Type 5 CRS. Approximately 11%–64% of septic patients develop AKI [73], and 46%–58% have sepsis as a major contributing factor to development of AKI [74]. Observational data have shown higher morbidity and mortality for those with septic AKI when compared to either sepsis or AKI alone [74, 75]. Similarly, abnormalities in cardiac function are common in septic patients [76]. The incidence of cardiac dysfunction in sepsis is conditional on the population-at-risk being studied, the definition used for detection of cardiac dysfunction (i.e., troponin, B-type natriuretic peptide, pulmonary artery catheter, echocardiography), severity of illness, resuscitation, and duration of illness prior to evaluation. However, observational data have found that approximately 30%–80% have elevated cardiac-specific troponins that often correlate with reduced cardiac function [77]. Accordingly, coexisting acute kidney and myocardial dysfunction is common in sepsis; however, there is a lack of integrative and epidemiologic studies that have specifically evaluated the pathophysiology, incidence, risk identification, and associated outcomes for septic patients with concomitant AKI and myocardial depression who fulfill criteria for Type 5 CRS.

7. Conclusions

Considerable data from observational studies and clinical trials have accumulated to show that acute or chronic cardiac disease can directly contribute to acute or chronic worsening kidney function and vice versa. The Cardiorenal Syndrome subtypes are characterized by important heart-kidney interactions that share some similarities in pathophysiology, however, appear to have important discriminating features, in terms of predisposing or precipitating events, risk identification, natural history, and outcomes. The Type 1 CRS is common, with incidence estimates of AKI in ADHF or ACS between 24%–45% and 9%–19%, respectively. Type 1 CRS clearly translates into higher morbidity and worse clinical outcome. Chronic heart disease and CKD are increasingly prevalent and frequently coexist. Accordingly, this presents challenges for applying the proposed definitions for Type 2 and 4 CRS "retrospectively" to the existing literature when the primary versus secondary process cannot be clearly distinguished. The rate of progression of preexisting CKD in patients with established cardiovascular disease deserves further study, as well as the effect of cardioprotective therapies on these renal endpoints. Prospective research incorporating novel biomarkers of kidney-heart interaction is needed for better understanding of both Types 2 and 4 CRS, along with studies of CKD-specific interventions in Type 4 CRS. Due to heterogeneity, the incidence and outcome estimates associated Type 3 CRS are largely context- and disease-specific. Limited data is available on the pathophysiology or epidemiology of secondary Type 5 CRS. Accordingly, the epidemiology of Type 5 CRS is also largely disease- and context-specific. In summary, there is a clear need for additional prospective studies to characterize the epidemiology of heart-kidney interactions across the CRS subtypes, not only for a better understanding of the overall burden of disease, but also for risk identification and design of potential targets for intervention.

Disclosures

None to declare.

Acknowledgments

Dr. S. M. Bagshaw is supported by a Clinical Investigator Award from the Alberta Heritage Foundation for Medical Research Clinical Fellowship. Dr. D. N. Cruz is supported by a fellowship from the International Society of Nephrology.

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SAGE-Hindawi Access to Research
International Journal of Nephrology
Volume 2011, Article ID 975782, 8 pages
doi:10.4061/2011/975782

Review Article

Cardiovascular and Renal Links along the Cardiorenal Continuum

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Received 17 August 2010; Accepted 7 February 2011

Academic Editor: C. Ronco

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The cardiorenal syndrome includes the widely known relationship between kidney function and cardiovascular disease. A large number of patients have various degrees of heart and kidney dysfunction worldwide, both in developed and developing countries. Disorders affecting one of them mostly involve the other. Such interactions represent the pathogenesis for a clinical condition called cardiorenal syndrome. Renal and cardiovascular disease shares similar etiologic risk factors. The majority of vascular events are caused by accelerated atherosclerosis. Moreover, cardiovascular events rarely occur in patients without underlying disease; rather, they typically take place as the final stage of a pathophysiological process that results in progressive vascular damage, including vital organ damage, specifically the kidney and the heart if these factors are uncontrolled. Chronic kidney disease is a novel risk factor included at this stage that accelerates both vascular and cardiac damage.

1. Introduction

The interaction between renal and cardiac function is very important for regulatory functions and hemodynamic control. The kidney plays the central role for body fluid volume homeostasis, electrolyte balance, and blood pressure regulation [1]. The relationship between heart and kidney occurs at multiple levels, including the rennin-angiotensin-aldosterone system (RAAS), the sympathetic nervous system (SNS), natriuretic peptides, endothelin, and antidiuretic hormones [2]. Therefore, understanding these two important systems is crucial to improve the management of patients with cardiorenal disease. An aging population and increasing incidence of hypertension, type 2 diabetes mellitus, obesity, and other cardiovascular (CV) risk factors are associated with an increasing incidence of cardiorenal disorders. Hence, it is not surprising that the prevalence of heart failure and chronic kidney disease (CKD) continues to increase. Furthermore, it has been shown that even mild-to-moderate deterioration of kidney function correlates with higher morbidity and mortality in patients with heart failure and acute coronary syndrome [3]. The strong relationship between CKD and accelerated CV disease morbidity and mortality has been shown in several epidemiologic data and clinical studies [4]. Moreover, whereas death rates from coronary artery disease have fallen by 35% in the last decade as a consequence of control of CV risk factors and optimal therapeutic management, patients with CKD have not accomplished that trend during that period. A significant number of patients with CKD die of CV complications before they progress to end-stage renal disease (ESRD), and renal dysfunction in patients with primary cardiac disease portends a significantly enhanced risk of morbidity and mortality from CVD [5]. Thus, with the aging of the population and control of CV risk factors, especially arterial hypertension, understanding the mechanisms of renal dysfunction as a pathogenic factor for cardiovascular (CV) disease is imperative.

2. Pathophysiological Mechanisms Underlying the Cardiorenal Disease

CVDs are a leading cause of death and serious morbidity or disabilities worldwide, and CV events rarely occur in patients without underlying disease; rather, they typically take place as the final stage of a pathophysiological process that results

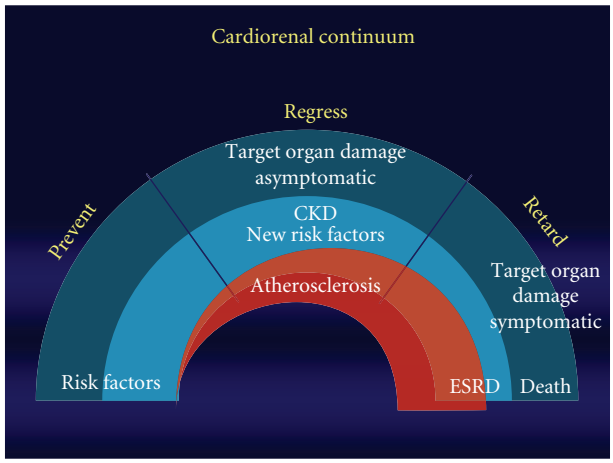

Figure 1: Graphic representation of the cardiorenal continuum.

in progressive vascular damage. This stage is called the cardiorenal continuum [6]. Figure 1 displays an overview of the cardiorenal continuum, illustrating a simplified version of the sequential occurrence of the atherosclerotic process from the first stage, in which CVD risk factors are detected and can be prevented if the conditions are appropriately controlled by implementing the optimal therapeutic approaches. A consensus conference has recently presented a classification of cardiorenal disease, including a division of five subtypes of cardiorenal syndromes, according to their pathophysiological mechanisms [7].

Renal and CV diseases share the same etiopathogenic risk factors, including hypertension, dyslipidemia, glucose metabolism disturbances, cigarette smoking, obesity, and physical inactivity. If these factors are controlled, then atherosclerotic process evolution and further target-organ damage (TOD) or CV events can be prevented. Therefore, prevention can be carried out not just at the first stage but along the whole continuum. As the cardiorenal process advances, atherosclerotic vascular damage progresses, and subclinical organ damage can be detected. This is an intermediate stage in the continuum of vascular disease and a determinant of overall CVD risk. CKD is included at this stage, and a number of conditions associated with renal-function decline, such as anemia, secondary hyperparathyroidism, or accumulation of atherogenic substances, become new CVD risk factors and accelerate vascular disease. Therapeutic approaches at this point can regress CV damage, as shown in the Losartan Intervention for Endpoint Reduction in Hypertension (LIFE) study, in which reduced urinary albumin/creatinine ratio (UACR) and regression of left ventricular hypertrophy (LVH) were associated with lower incidence of CV events. Therefore, strict objectives regarding CVD risk factors must be set up. A large body of evidence is now available concerning the crucial role of TOD in determining the CVD risk of individuals with and without hypertension. If regression of CV damage is not achieved, the process advances to the development of CV events and progression of CKD to overt nephropathy and CVD. Although prevention strategies must be present along the continuum, interventions at this point should only retard the occurrence of CV and renal events [8]. This last stage represents the situation of further progression of vascular disease, leading to the appearance of symptomatic TOD (myocardial infarction, angina, stroke, transient ischemic attack, advanced chronic renal failure, and peripheral artery disease), which eventually will lead to end-stage renal disease (ESRD) or death. At this stage, the best we can do is to retard the likelihood of such events.

3. Cardiovascular Disease Associated with Renal Disease

Underlying the cardiorenal continuum is the pathophysiological continuum, which describes the progressive processes at molecular and cellular levels that manifest as clinical disease. A vast amount of research over the last two decades has provided considerably more knowledge regarding the therapeutic interventions that are able to intervene along the continuum.

Therefore, as CVD risk factors can be evaluated, the process begins. At this first stage of cardiorenal disease, preventative approaches are the most relevant strategies to disrupt disease progression [9]. In this sense, some data have demonstrated that high-risk patients without evidence of renal damage may benefit from early therapeutic intervention. The multicenter, double-blind, randomized Bergamo Nephrologic Diabetes Complications Trial (BENEDICT) assessed whether pharmacological intervention could prevent microalbuminuria in high-risk patients with no evidence of organ damage. The main results showed that intervention decreased the incidence of microalbuminuria [10]. Evidence from other ongoing trials will shed light on this issue, as will the Randomised Olmesartan and Diabetes Microalbuminuria Prevention (ROADMAP) study—a placebo-controlled, multicenter, double-blind, parallel group study investigating the effect of the angiotensin receptor blocker (ARB) olmesartan medoxomil on the incidence of microalbuminuria in hypertensive people with type 2 diabetes and an objective of blood pressure <130/80 mmHg. In addition, ROADMAP will also analyze effects of olmesartan medoxomil on retinopathy and other microvascular circulations [11]. The results of the Diabetic Retinopathy Candesartan Trials (DIRECTs) are designed to examine primary (incidence) and secondary (progression) prevention of diabetic retinopathy when blocking angiotensin II type 1 receptors with the ARB candesartan in patients with normoalbuminuric, normotensive type 1 diabetes, and secondary prevention only in patients with normoalbuminuric, normotensive, or treated hypertensive type 2 diabetes. This trial series will also support prevention strategies to block advancement of the atherosclerotic process that leads to development of CV damage [12].

Optimal management in people with several risk factors is crucial, especially when hypertension is associated with other conditions. Awareness that several antihypertensive agents may exert undesirable metabolic effects has antihypertensive treatment trials to investigate the incidence of

new-onset diabetes. Almost all such trials with new-onset diabetes as an endpoint have shown a significantly greater incidence in patients treated with diuretics and/or beta-blockers compared with angiotensin-converting enzyme inhibitors (ACEIs), ARBs, or calcium antagonists [13–16]. Angiotensin receptor antagonists [17] and ACEIs [13] have been shown to be associated with significantly fewer new diabetes cases than were calcium antagonists. The Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial (ONTARGET) is comparing telmisartan, ramipril, and their combination for preventing CVD morbidity and mortality in high-risk patients [18]. Telmisartan was the ARB selected for the ONTARGET because it provides sustained antihypertensive activity over the 24 h between doses [19]. The comparator, the ACEI ramipril, was selected because in the Heart Outcomes Prevention Evaluation (HOPE) trial, ramipril was proved to reduce the incidence of CV events in a similar patient population [20]. Patients enrolled in ONTARGET have vascular disease (coronary artery disease, peripheral arterial occlusive disease, stroke) or diabetes with TOD. The primary outcome is a composite endpoint of CVD, death, stroke, acute myocardial infarction, and hospitalization for congestive heart failure. A variety of renal endpoints have also been included. The Telmisartan Randomized Assessment Study in ACE-I-Intolerant Subjects with CV Disease (TRANSCEND) is a parallel study within the ONTARGET that is comparing the CV protective effect of telmisartan with placebo in patients intolerant of ACEIs [18]. The first results of this trial have been published and emphasize that the telmisartan was equivalent to ramipril in treating patients with vascular disease or high-risk diabetes and was better tolerated [21]. The combination of these two drugs was associated with more adverse events without an increased benefit. More evidence about prevention along the cardiorenal continuum is expected from this trial, including more than 150,000 patient-years of data. The Trial of Preventing Hypertension (TROPHY) hypothesized that early treatment with candesartan might prevent or delay hypertension onset. The main results showed that candesartan was better in preventing development of hypertension versus placebo [22]. The Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT) evaluated the benefits associated specifically with the use of statins among patients with hypertension [23]. Atorvastatin, which was added to the treatment therapy in more than 10,000 patients with hypertension and additional CVD risk factors and a serum total cholesterol <6.5 mmol/L, reduced serum total cholesterol by 19.9% compared with placebo. This was accompanied by substantial benefits both with regard to total CV and renal events (36% reduction) and stroke (27% reduction). The Avoiding Cardiovascular Events through Combination Therapy in Patients Living with Systolic Hypertension (ACCOMPLISH) trial was recently terminated prematurely because the predefined efficacy outcome was achieved and an interim analysis reported. The trial recruited more than 11,400 patients who received either amlodipine in combination with benazepril or hydrochlorothiazide in combination with benazepril. A primary composite endpoint of CVD morbidity or mortality was defined as death from CV causes, fatal or nonfatal myocardial infarction or fatal or nonfatal stroke, revascularization, or unstable angina requiring hospitalization. Treatment with amlodipine/benazepril significantly reduced CVD morbidity and mortality compared with hydrochlorothiazide/benazepril (relative risk (RR) 0.80; 95% confidence interval (CI) 0.71–0.90) [24]. Mechanical and chemical damages resulting from these interrelated CVD risk factors promote general progression of vascular damage that begins with endothelial dysfunction and atherosclerosis. This leads to end-organ damage, such as LVH, subclinical atherosclerotic vascular damage, and kidney injury that can be detected by microalbuminuria and renal function derangement (estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m^2 or a slight increase in serum creatinine). At this second stage, vascular damage processes may be regressed, and inhibition of the rennin-angiotensin system (RAS) has been shown to be the most efficient pharmacological intervention along with strict control of CVD risk factors.

International guidelines devoted to arterial hypertension recognize microalbuminuria, elevated serum creatinine values, and reduced eGFR as major CVD risk factors that contribute to increased risk afforded by other coexisting factors [25–27]. The diagnosis of hypertension-induced renal damage in a hypertensive patient is usually based on reduced renal function and/or elevated urinary excretion of albumin. Renal function decline is classified in accordance with eGFR calculated by the abbreviated Modification of Diet in Renal Disease (MDRD) formula that assesses age, gender, race, and serum creatinine [28]. Values of eGFR <60 mL/min/1.73 m^2 indicate CKD stage 3, whereas values <30 and 15 mL/min/1.73 m^2 indicate CKD stages 4 and 5, respectively [29]. The Cockcroft-Gault formula estimates creatinine clearance (CrCl) and is based on age, gender, body weight, and serum creatinine [30]. This formula is applicable in the range >60 mL/min, but it overestimates CrCl in CKD stages 3–5 [31]. Both procedures help to detect mildly impaired renal function in the face of serum creatinine values that are still in the normal range.

Reduction in GFR and increase in CVD risk may also be inferred from increased serum levels of cystatin C [32]. Whereas elevated serum creatinine concentration or low eGFR (or CrCl) points to reduced rate of plasma filtered at the glomerular level, increased urinary albumin or protein excretion points to derangement in the glomerular filtration barrier, which allows increased albumin passage. Microalbuminuria has been shown to predict the development of overt diabetic nephropathy in those with either type 1 or type 2 diabetes [33]. However, only about 40% of those with type 2 diabetes will develop microalbuminuria, and, of those, approximately 50% will develop microalbuminuria in the following 10 years [34]. In contrast, in both diabetic and nondiabetic hypertensive patients, microalbuminuria, even below the threshold values currently considered [35], has been shown to predict CV events. Several studies report a continuous relationship between CVD—as well as non-CVD—mortality and urinary protein/creatinine ratios >3.9 mg/g in men and 7.5 mg/g in women [36]. Thus, the term "microalbuminuria" may be misleading (because it

falsely suggests a minor injury as well) and should, in theory, be replaced by the term "low-grade albuminuria" [37]. Microalbuminuria can be determined in spot urine samples (24 h or night-time urine samples are discouraged due to inaccuracy of urinary sampling) by indexing the urinary albumin concentration to the urinary creatinine concentration. Initial evidence concluding that microalbuminuria increases CVD risk came from observations involving high-risk patients [38]. Data from the HOPE study [39] confirmed the predictive value of microalbuminuria, which attained a predictive capacity similar to that of previous coronary artery disease and was equal for patients with and without accompanying diabetes. The relevance of urinary albumin excretion (UAE) as a CVD risk factor in patients with hypertension without diabetes and in the general population has also been demonstrated [40]. Some of these studies indicate that the relationship between urinary albumin and CVD risk is a continuum that starts below the established cutoff point indicated earlier. Definitely, both UAE and reduced GFR are independently associated with increased CVD risk, which is particularly elevated when both alterations coexist [41]. In fact, the prevalence of albuminuria, either micro or macro, increases as eGFR falls <60 mL/min/1.73 m^2 [42].

Patients developing ESRD are a minority in the group developing different forms of CKD. They could be considered survivors because CVD accounts for the majority of deaths of patients with CKD before the development of ESRD [43]. In turn, advanced CVD facilitates the development of CKD, and so the relationship between CKD and CVD becomes a vicious circle. That CKD and CVD are so closely related has resulted in increased interest in investigating the evolution of renal function in trials involving patients with hypertension, as well as those with heart failure and postmyocardial infarction. This interest is fully justified, as, in all these situations, renal function alterations are predictive for the development of CV events or death.

Even from the early stages, CKD adds to CVD risk in any patient with hypertension and in any patient presenting with established forms of CVD [44]. Reduction of CV events in the CKD population requires the implementation of effective integral therapeutic interventions that protect both the kidney and the CV system. These interventions have to be implemented in the very initial stages of CKD, and strict blood pressure control is imperative in any patient with an elevated global CVD risk and high blood pressure. In the absence of other CVD risk factors, elevated blood pressure levels are required in order to consider patients as having high-added CVD risks. In contrast, only high-normal blood pressure levels or even lower values are required for the same evaluation when patients present with three or more associated CVD risk factors, TOD, diabetes, or associated clinical conditions. Accordingly, patients with hypertension and a high-added level of CVD risk can be found in any of the three stages of the CV and renal disease continuum. As soon as renal function exhibits minor derangements, CVD risk continues to increase until ESRD develops.

As renal function declines, TOD appears and CKD adds several clinical characteristics that raise the possibility of a CV event as atherosclerotic disease progresses. CKD-induced anemia and secondary hyperparathyroidism globally worsen outcomes in patients with and without myocardiopathies, and correction of these conditions is crucial to reduce absolute CVD risk [45, 46]. Among patients who referred to the authors' hypertension unit, 7.6% had a decreased renal function according to serum creatinine levels, and 25% had a decreased CrCl [47]. Community-based longitudinal studies demonstrated that CKD is an independent risk factor for the composite study outcome, including myocardial infarction, fatal congestive heart failure, stroke, and death [48]. In patients with essential hypertension and normal renal function (defined as eGFR >90 mL/min/1.73 m^2), those who developed CKD during 13 years of followup had a CV event rate 2.5 times higher than did those with preserved renal function [49]. As widely evidenced in the hypertensive population, the higher the CVD risk, the higher the CKD prevalence [50].

Evidence for the relationship between renal dysfunction and adverse CV events was initially documented in the ESRD population in whom the incidence of CVD death is elevated. Around 50% of individuals with ESRD die from a CVD—a CVD mortality rate much higher than the age-adjusted CVD mortality rate in the general population. This discrepancy is present across all ages, but it is most marked in the younger age group, in which the CVD mortality rate is >300-fold in ESRD patients compared with age-matched controls with normal renal function [51]. By the time ESRD occurs, 40% of patients have evidence of CHF, and 85% of those patients have abnormal LV structure and function

The relationship between renal disease and CVD mortality has also been shown to extend to patients with more moderate degrees of renal impairment. Indeed, the majority of patients with eGFR <60 mL/min/1.73 m^2 die from CVD-related causes rather than progressing to ESRD. In addition, evidence of structural and functional cardiac abnormalities has been demonstrated. Data about cardiac structure in the renal insufficiency population has been described with echocardiographic techniques and comparable criteria for diagnosing LVH, detecting an LVH prevalence of 16% in patients with CrCl of >30 mL/min and 38% in those with CrCl <30 mL/min [52]. Therefore, LVH is common in patients with renal insufficiency even before they progress to dialysis, and so prevalence of LVH correlates with the degree of renal functional deterioration. Many reports have shown that the relationship between renal impairment and increased CVD mortality rate extends across the spectrum of renal dysfunction to cover the mildest degree of renal disease. Furthermore, this relationship appears to be maintained through populations with broadly diverse degrees of baseline CV health. LVH is an independent predictor of unfavorable prognosis in the hypertensive population, and, in the LIFE study, its relationship with albumin excretion was reported as being independent of age, blood pressure, diabetes mellitus, race, serum creatinine level, or smoking [53]. The prevalence of microalbuminuria was approximately twofold higher in patients with hypertension and eccentric or concentric LVH and minimally elevated in the group with concentric LV remodelling compared with patients with normal LV

geometry. Although the clinical significance of impaired renal function and LVH in patients with hypertension is not yet fully understood, numerous reports link renal albumin leakage with morbidity and mortality.

The LIFE study also showed that the simple measurement of UACR further refines risk stratification by LV geometry and that patients with LVH have an increased risk of also having albuminuria, a situation that should be further investigated to improve treatment and counselling. The risk for CVD endpoints increases in a stepwise trend with higher values for UACR in patients with diabetes. Data indicate that albuminuria at a lower level than that usually used as a cut point in patients with diabetes defines patients at increased risk of CVD morbidity and mortality. UACR did not predict the risk of myocardial infarction. Perhaps diabetes itself is a strong predictor for CVD morbidity and mortality, partly overlapping the influence of albuminuria as a risk factor in the population with rather low levels of albuminuria. Other studies suggest that albuminuria at levels below established values is a risk factor for CHF in patients with and without diabetes, signifying that the relationship between albuminuria and CVD risk from other populations cannot be directly applied to nondiabetic hypertensive patients [54].

Global (all risk factors) (AU: global, meaning worldwide, or treating all risk factors in the individual patient?) and strict control of the sum of CVD risk factors and therapeutic action in order to regress already established vascular damage must be the cornerstone of the medical strategy, because, if not stopped, the cardiorenal continuum progresses to CKD (proteinuria, eGFR $<30\,\text{mL/min/1.73}\,\text{m}^2$), overt CVD, and stroke. Interventions at this point are focused on delayed development of CV and renal events [27]. CV events and consequent death are dramatically reduced when UACR is decreased and GFR decline is avoided. If renal decline progresses to the final stage, proteinuria will occur. In type 2 diabetes, data from the Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan (RENAAL) trial showed that changes in albuminuria in the first 6 months of therapy were approximately linearly related to the degree of long-term renal protection: every 50% reduction in albuminuria in the first 6 months was associated with a 45% reduction in the risk for ESRD during later followup [55]. Furthermore, a secondary analysis of the Irbesartan in Diabetic Nephropathy Trial (IDNT) demonstrated that the risk for renal failure was reduced during the first year of the study when there were increases in proteinuria [56]. Subsequently, these two studies (IDNT and RENAAL) demonstrated that an ARB (irbesartan or losartan) was more effective than conventional therapy or a calcium channel blocker in slowing progression of nephropathy, regardless of blood pressure control. Moreover, secondary analyses of these two large trials demonstrated that there was some interaction between the effect of the ARB and the levels of blood pressure that were achieved. It can also be concluded that optimal levels of blood pressure tended to magnify the renoprotective effects of ARB in both trials. In the large cohort of patients with hypertension, microalbuminuria, and type 2 diabetes who participated in the Microalbuminuria, Cardiovascular, and Renal Outcomes–Heart Outcomes Prevention Evaluation (MICRO-HOPE), the ACEI compared with other treatments was more effective in reducing the incidence of overt nephropathy [57]. Furthermore, the Irbesartan in Patients with Type 2 Diabetes and Microalbuminuria (IRMA-2) study showed that treatment with the ARB irbesartan was much more effective than conventional therapy at both preventing the development of clinical proteinuria and favoring regression to normoalbuminuria in patients with microalbuminuria and type 2 diabetes, despite similar blood pressure control [58].

4. Global Therapeutic Approach Focused on Renal Outcomes

CKD progression, that is, reduced GFR, occurs at a variable rate, with a faster rate of decline generally noted among patients with diabetic nephropathy due to the presence of proteinuria. Several therapeutic options have been shown to be efficient in slowing the rate of renal function decline. Among these therapeutic treatments are blood-pressure-reducing drugs—preferably ACEIs and/or angiotensin II antagonists—low-salt and low-protein diets, and lipid-lowering drugs [59]. Unfortunately, for such treatments to be most efficacious and in agreement with the European Society of Hypertension/European Society of Cardiology guidelines, it is necessary to identify patients in an early stage of disease before significant loss of renal function has occurred. Such identification is simplified by estimating GFR and measuring microalbuminuria in any patient with hypertension. UACR levels of approximately $>2\,\text{mg/g}$ or an estimated excretion rate of 2 mg/day are significantly associated with death from CVD, myocardial infarction, stroke, and elevated blood pressure. As a result, reductions in albuminuria levels during treatment translate to regression of a number of vascular abnormalities in hypertension and thus a decrease in risk in general. In patients with type 2 diabetes and diabetic nephropathy, and also in patients with nondiabetic renal disease, data indicate that the extent of decreases in albuminuria during renin-angiotensin-aldosterone system intervention is associated with the degree of renal protection and also the degree of reduced CVD risk [60]. Reductions in both systolic and diastolic blood pressure are important in reducing albuminuria levels. Despite the firm relationship between blood pressure values and albuminuria, ACEIs and ARBs exhibit a more marked capacity to reduce microalbuminuria in patients with hypertension compared with a number of different therapeutic interventions, such as calcium antagonists, beta-blockers, or diuretics [61].

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SAGE-Hindawi Access to Research
International Journal of Nephrology
Volume 2011, Article ID 938651, 8 pages
doi:10.4061/2011/938651

Review Article

Cardiorenal Syndrome Type 4—Cardiovascular Disease in Patients with Chronic Kidney Disease: Epidemiology, Pathogenesis, and Management

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Received 30 August 2010; Accepted 3 January 2011

Academic Editor: Claudio Ronco

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The term cardiorenal syndrome refers to the interaction between the heart and the kidney in disease and encompasses five distinct types according to the initial site affected and the acute or chronic nature of the injury. Type 4, or chronic renocardiac syndrome, involves the features of chronic renal disease (CKD) leading to cardiovascular injury. There is sufficient epidemiologic evidence linking CKD with increased cardiovascular morbidity and mortality. The underlying pathophysiology goes beyond the highly prevalent traditional cardiovascular risk burden affecting renal patients. It involves CKD-related factors, which lead to cardiac and vascular pathology, mainly left ventricular hypertrophy, myocardial fibrosis, and vascular calcification. Risk management should consider both traditional and CKD-related factors, while therapeutic interventions, apart from appearing underutilized, still await further confirmation from large trials.

1. Introduction

The term cardiorenal syndrome has been introduced recently in an attempt to emphasize the tight interaction between the cardiovascular and renal systems in acute or chronic disease settings and to expand our knowledge regarding its pathogenesis, prevention, and potential treatment [1].

The definition encompasses different syndromes, all involving the heart and the kidney, "whereby acute or chronic dysfunction of one organ may induce an acute or chronic dysfunction of the other" [2]. According to the site of the initial injury and the acute or chronic nature of the process five distinct syndromes (types) are defined. In acute cardio-renal syndrome (Type 1), acute worsening of heart function leads to acute renal dysfunction. In chronic cardiorenal syndrome (Type 2), chronic cardiac dysfunction leads to chronic renal dysfunction. In acute renocardiac syndrome (Type 3), acute renal dysfunction causes cardiac dysfunction, and in chronic renocardiac syndrome (Type 4), chronic renal dysfunction leads to cardiovascular disease and increased cardiovascular mortality [1]. Finally, type 5, or secondary cardiorenal syndrome, involves systemic conditions such as diabetes mellitus, amyloidosis, systemic lupus erythematosus, or sepsis, which simultaneously affect both the heart and the kidney [2].

This paper will focus on cardiorenal syndrome type 4 (chronic renocardiac syndrome) presenting epidemiologic evidence of excess cardiovascular morbidity and mortality in patients with chronic kidney disease (CKD) as well as current knowledge on the pathogenesis and management of this syndrome.

2. Epidemiologic Evidence Linking CKD and Cardiovascular Disease (CVD)

CKD is defined as either a reduction in the glomerular filtration rate (GFR) to values below 60 ml/min/1.73 m^2, or the presence of kidney damage as reflected in an abnormal urine sediment (proteinuria, hematuria, and casts) or

abnormalities in renal architecture (e.g., polycystic kidney disease) even if the GFR is preserved within normal levels. GFR may be directly measured by renal clearance of specific substances (e.g., creatinine, inulin) and radioactive markers (e.g., 99mTc-DTPA) or it may be estimated (estimated GFR-eGFR), by the application of formulas incorporating serum creatinine and demographic parameters (Cockcroft-Gault, MDRD) [3].

Both proteinuria and the reduction of GFR have been associated with increased cardiovascular morbidity and mortality [4]. This association is so strong and clinically relevant that according to current guidelines the diagnosis of CKD places a patient into the highest cardiovascular risk level, irrespective of stratification according to traditional cardiovascular risk factors [3, 4]. Compared to the general population, CKD patients are still plagued by a frustratingly high mortality, which is mainly attributed to cardiovascular events, with death being far more probable than advancing into the final CKD stages and the need of renal replacement therapy (RRT) [5]. The high mortality afflicting patients on renal RRT, which for the ages between 25 and 35 may rise up to 375-fold compared to the general population [6], is derived almost by half of cardiovascular causes [7].

2.1. Proteinuria/Albuminuria and CVD. The abnormal quantities of protein in the urine (proteinuria) consist mainly of albumin (albuminuria) and can be semiquantitatively identified by urine dipstick testing, estimated by the urine protein-to-creatinine ratio (UPCR) or albumin-to-creatinine ratio (UACR) in a spot urine sample, or directly measured in a timed (usually 24 h) urine collection [3, 8]. The diagnosis of microalbuminuria (30–300 mg/day) and albuminuria (>300 mg/day) is mainly utilized in the evaluation of diabetic nephropathy, while proteinuria (>300 mg/day or UPCR >200 mg/g) is mostly used for nondiabetic CKD [8].

Whether considered a marker of systemic endothelial dysfunction or a result of renal damage [9], proteinuria has been associated with increased cardiovascular mortality in the general population, even at levels regarded as normal [10]. In repeated studies, the presence of micro- and macroalbuminuria and eGFR reduction were independent predictors of increased overall and cardiovascular mortality in diabetic [11] and nondiabetic individuals [12]. In a recently published large community-based study involving nearly one million adult subjects, the presence of proteinuria was assessed by urine dipstick or UACR. Higher levels of proteinuria were independently associated with an increased risk of myocardial infarction and all-cause mortality, as were decreased levels of eGFR. The severity of proteinuria was actually a stronger predictor of worse clinical outcomes than was eGFR reduction, a fact suggesting that levels of proteinuria may have a role in risk stratification of CKD patients, who are currently staged only according to their level of GFR [13].

2.2. GFR and CVD. Irrespective of the presence of proteinuria, GFR decline has been repeatedly associated with increased cardiovascular morbidity and mortality. In a large community study involving more than one million adults, an independent and graded association was observed between eGFR reduction and increased risk of death and cardiovascular events including hospitalization for coronary artery disease, heart failure, stroke, and peripheral vascular disease [14]. In middle-aged adults participating in the Atherosclerosis Risk in Community (ARIC) study, a baseline eGFR of less than 60 ml/min/1.73 m^2 was independently associated with an increased risk of developing peripheral arterial disease [15] or heart failure, irrespective of prevalent coronary artery disease [16]. According to United States Renal Data System 2007 annual report regarding incident dialysis patients, comorbidities included congestive heart failure in 34%, atherosclerotic heart disease in 22.5%, cerebrovascular disease in 10%, and peripheral vascular disease in 15% of cases [17].

2.3. Cardiovascular Outcomes in CKD. In patients with already established cardiovascular disease, renal impairment markedly worsens outcomes. An inverse relationship between eGFR and the extent of coronary stenotic lesions was shown [18], as well as increased probability of having three-vessel coronary artery disease with decreasing eGFR [19]. In a study of almost 15.000 patients, who had suffered myocardial infarction, even mild eGFR reduction at baseline was independently associated with increased overall mortality or a composite end point of death from cardiovascular causes, reinfarction, congestive heart failure, stroke, or resuscitation after cardiac arrest [20]. In patients undergoing coronary artery bypass grafting, a reduced baseline eGFR has also been associated with increased 30-day and long-term mortality [21]. Furthermore, in patients with advanced congestive heart failure, impaired renal function seems to be a stronger predictor of mortality than impaired cardiac function (left ventricular ejection fraction and New York Heart Association class) [22]. Finally, in a recent study also involving patients with heart failure, the presence of albuminuria significantly aggravated prognosis by exhibiting a strong and independent association with increased all-cause and cardiovascular mortality [23].

3. Cardiovascular Injury in CKD

Due to the vital importance for the rapidly growing population of CKD patients, the pathogenetic mechanisms leading to cardiovascular damage in renal disease are under constant investigation. More than a dozen of pathways have been identified including hyperactivity of the renin-angiotensin-aldosterone system, osmotic sodium retention, volume overload, endothelial dysfunction, dyslipidemia, coagulopathy, inflammation, and anemia [24], all leading to histomorphological alterations of the heart and vessels.

In addition, some key emerging topics in this field include sympathetic hyperactivity, cardiotonic steroids, nonosmotic sodium retention, and catalytic or labile iron. Sympathetic activation by the failing kidney leading to both renal disease progression and cardiovascular morbidity

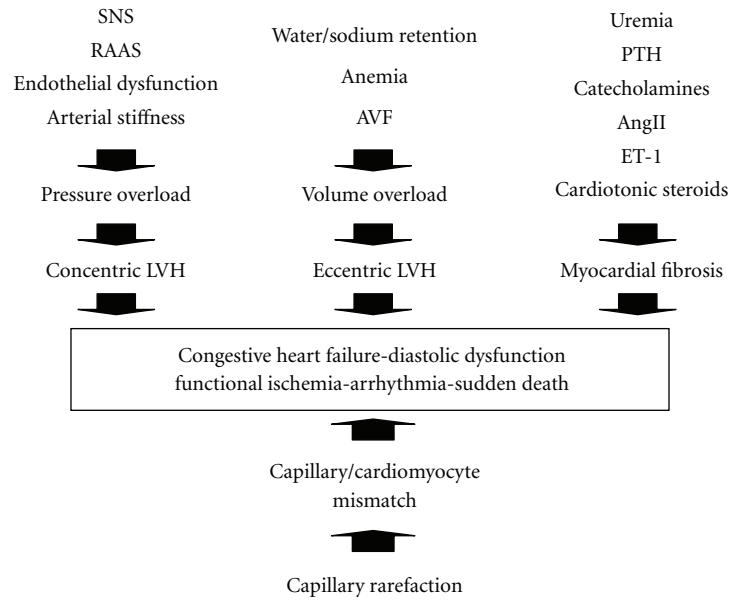

Figure 1: Heart alterations and their consequences in CKD. AVF: arteriovenous fistula, AngII: angiotensin II, ET-1: endothelin-1, LVH: left ventricular hypertrophy, PTH: parathormone, RAAS: renin-angiotensin-aldosterone system, SNS: sympathetic nervous system.

and mortality may provide a new target for therapeutic intervention [25]. Cardiotonic steroids are elevated in renal failure and have been linked to hypertension and to the development of uremic cardiomyopathy in animal models [26]. Nonosmotic sodium stores in the form of water-free Na+ accumulation in the skin have been proposed to contribute to the development of hypertension and thus might be associated to CKD progression and cardiovascular complications [27]. Finally, labile/catalytic iron is associated with oxidative stress in situations such as acute kidney injury after cardiac revascularisation and in diseases such as diabetes and may result in both kidney disease progression and cardiovascular complications [28]. However, an extensive analysis of all the above mechanisms lies outside the scopus of the present paper, and readers are referred to some excellent recent reviews [25–28].

3.1. The Heart in CKD. The mechanisms leading to cardiac alterations in CKD are depicted in Figure 1. Cardiac workload is increased in CKD. This increase is the result of two separate pathways both leading to left ventricular hypertrophy (LVH): pressure overload and volume overload. Pressure overload mainly derives from increased peripheral resistance and reduced arterial compliance due to sympathetic and renin-angiotensin system hyperactivity, hypertension, endothelial dysfunction, and vascular calcification/stiffening. It causes thickening of cardiac myofibres by parallel addition of sarcomeres, thus leading to concentric LVH. Volume overload is attributed to sodium and water retention, anemia, and the presence of an arteriovenous fistula in patients with end-stage renal disease (eGFR <15 ml/min/1.73 m^2 anticipating or on chronic dialysis). It results in lengthening of the cardiac myofibers by serial addition of sarcomeres thus causing eccentric LVH (left ventricular dilatation) [29, 30]. LVH in renal disease is a pathologic process and, unlike physiologic adaptations to increased workload (e.g., "athletes heart"), is accompanied by fibrosis, which is also attributed to conditions related to the uremic milieu, including increased levels of parathyroid hormone, endothelin, aldosterone, catecholamines, and cardiotonic steroids [26, 30, 31]. In a study involving 432 ESRD patients, only 16% had a normal echocardiogram at initiation of dialysis, the rest exhibiting mainly features of concentric LVH (41%) and left ventricular dilatation (28%), both associated with increased risk of heart failure and death [32]. A more recent study demonstrated progression of concentric LVH in 576 new dialysis patients followed up by echocardiography [33].

In addition to fibrosis and cardiomyocyte hypertrophy, histological changes of the heart in uremia also include myocyte apoptosis/necrosis resulting in myocyte number reduction, and microvascular abnormalities such as arteriolar wall thickening and capillary rarefaction, the latter being specific to uremia [29, 34].

The functional consequences of all the aforementioned structural changes include diastolic dysfunction [35], increased oxygen demand and impaired, myocardial oxygenation unrelated to coronary obstruction [34, 36]. This may explain the angiographic finding of patent coronaries in 30%–40% of uremic patients with ischemic heart disease/angina pectoris [34], as well as their predisposition to arrhythmias, both atrial and ventricular, and sudden death, which account for more than half of the cardiovascular mortality of patients on RRT [37, 38]. Susceptibility to arrhythmias and sudden death may be further increased by coronary artery disease/myocardial infarction, left ventricular hypertrophy, congestive heart failure, electrolyte abnormalities, chronic fluid overload, anemia, autonomic imbalance, and inflammation [38].

3.2. Vascular Changes in CKD. Ever since early reports of aortic thickening in uremic patients by Richard Bright in 1827, renal disease has been associated with vascular pathology [39]. Pathologic features include reduced elasticity/compliance of large arteries, as reflected in an increase of the arterial pulse wave velocity (PWV) [40, 41], thickening of the arterial wall, leading to an increased intima-media thickness (IMT) [42], and, mainly, vascular calcification [43, 44].

Vascular calcification has recently been the focus of attention mainly because of its established association with cardiovascular mortality in CKD patients [45]. Moreover, in the last decade, research has shown that it is not simply the result of passive mineral precipitation but rather an active and highly regulated process, closely resembling osteogenesis [43, 46], and is orchestrated by the arterial smooth muscle cell after its genotypic transformation to an osteoblast-like cell [43]. Ossification of the arterial wall is favoured by conditions like ageing, diabetes, inflammation, and especially CKD. In renal disease, vascular calcification is linked to hyperphosphatemia, lack of calcification inhibitors (i.e., fetuin-A, matrix GLa protein, osteopontin, or pyrophosphate) and derangements in regulators of mineral metabolism (i.e., vitamin D, parathormone, osteoprotegerin, and bone morphogenetic proteins) [43], and abnormalities in bone turnover such as secondary hyperparathyroidism and adynamic bone disease [46–48].

In addition, recent studies implied a role for the phosphatonin Fibroblast Growth Factor-23 (FGF-23) in the pathophysiology of chronic kidney disease—mineral bone disorder (CKD-CMD) and in vascular calcification. FGF-23 levels are elevated in CKD patients both on dialysis and on conservative treatment and have been associated with increased mortality and left ventricular hypertrophy. Moreover, FGF-23 has been linked to increased arterial stiffness, endothelial dysfunction, and vascular calcification. However, a causative relation and its value as a marker of cardiovascular status and/or phosphate-related toxicity, as well as its potential role as a target for intervention, still await further clarification [49].

Calcium deposits may surround atheromatous plaques in the arterial intima (atherosclerosis) or involve the medial layer of the arteries (arteriosclerosis—Moenckeberg's sclerosis) [50]. They can be visualised in plain X-ray films [51, 52] and quantified by more sophisticated and more expensive techniques like electron beam computed tomography (EBCT) [53, 54], the latter regarding mainly coronary artery calcification (CAC).

Whether vascular intima and media calcification are really distinct entities still remains controversial. Because of the results from experimental models as well as their difference in histopathologic features, location in the arterial tree, and pathophysiologic consequences, they tend to be regarded as distinct [50] although this view has recently been challenged [55, 56]. Both types of vascular calcification appear early in CKD, run an accelerated course, especially after RRT initiation [53, 54], and lead to high cardiovascular morbidity and mortality [45]. More importantly, a recent metareview on treatments for vascular calcification in CKD has demonstrated that no therapy to date, including statins and sevelamer, appears to influence their rate of progression [57].

In CKD patients, CAC score measurement as a tool for cardiovascular risk stratification may be affected by the unique presence of medial coronary calcification [58, 59] unrelated to obstructive coronary atherosclerosis, thus not necessarily leading to ischemia. Nevertheless, a high CAC score has been associated with increased mortality in CKD patients both before [60] and after the initiation of dialysis [61]. Apart from medial calcification, another feature characteristic of coronary artery disease (CAD) affecting CKD patients is the location of culprit atherosclerotic lesions. In renal patients with acute myocardial infarction, they were found to be located more proximal to the coronary ostia, which may account for the observed increased mortality [62].

Because CAD is highly prevalent in CKD patients, non-invasive screening tools for the prediction of asymptomatic coronary obstruction are needed. In recent studies, cardiac Troponin T (cTnT) has emerged as a powerful predictor of multiple-vessel CAD in asymptomatic hemodialysis patients [63, 64]. In addition, the acute kidney injury biomarker neutrophil gelatinase-associated lipocalin (NGAL) has recently been associated with both chronic renal impairment and cardiovascular complications and might potentially prove its worth as a cardiovascular risk predictor in CKD [65].

Aortic calcification assessed by lateral abdominal X-ray has also been associated with all-cause and cardiovascular mortality in dialysis patients and has been proposed as a simple tool for cardiovascular risk assessment and treatment guidance [52, 66].

4. Cardiovascular Risk Modification in CKD

Because of the heavy CVD burden affecting CKD patients, risk modification is vital in an effort to improve outcomes. Still CKD patients are usually excluded from large interventional trials [67] because of their expected adverse outcomes, thus hindering the evaluation of therapeutic interventions. Furthermore, interventions for traditional cardiovascular risk reduction already established in the general population have proved less effective in patients with CKD [24, 68, 69]. This seems to result into a kind of "therapeutic nihilism" [24], by denying treatment despite the presence of sound indications, for example, the underutilisation of antiplatelets, statins, β blockers, and ACE inhibitors in CKD patients with known CAD [70]. Furthermore, CKD patients are less likely to undergo coronary angiography, percutaneous coronary intervention, or bypass grafting, or to receive adjuvant treatments, such as GpIIb/IIIa inhibitors [67].

Strategies to reduce cardiovascular risk in CKD patients should target both traditional and non-traditional, that is, CKD-related factors. Traditional risk factors include hypertension, dyslipidemia, diabetes, obesity, physical activity, and smoking habit, while CKD-related factors refer to CKD progression, proteinuria, anemia, inflammation, mineral and bone disorder, LVH, oxidative stress, coagulopathy,

hyperactivity of the renin-angiotensin and the sympathetic nervous system, and dialysis dose and quality [67] (Table 1).

Setting of specific treatment targets is complicated, especially in patients on RRT, by findings of reverse epidemiology with a U-shaped curve associating mortality with blood pressure, BMI, cholesterol, and phosphate [71], possibly a result of the Malnutrition-Inflammation-Atherosclerosis (MIA) syndrome frequently encountered in this patient population [72, 73]. Further controversies also derive from recent results of increased morbidity and mortality in CKD patients associated with higher hemoglobin levels [74], intensive blood pressure [75] and glucose control [76], dual angiotensin II blockade [77] and suppression of parathyroid function, and bone turnover [47, 48], which question the safety of overaggressive intervention on specific laboratory and clinical parameters in this patient group. Rather than meticulously pursuing generalised targets, recent opinions suggest a potential benefit from a more individualised perspective, that takes into account patient-specific trends and distinctive dynamic features of the actual clinical situation [66, 78, 79].

Eagerly awaited is the publication of results from large randomised studies evaluating therapeutic interventions to lower cardiovascular morbidity and mortality in CKD patients, such as the ongoing EVOLVE (EValuation Of Cinacalcet HCl Therapy to Lower CardioVascular Events) [80] and the concluded SHARP (Study in Heart And Renal Protection). The latter, a double blind placebo-controlled study involving almost 9500 CKD patients (a third of them on dialysis) in 18 countries, has been able to demonstrate a significant reduction in cardiovascular events, such as myocardial infarction, stroke, or need for coronary artery revascularization, with the use of a combination of ezetimibe plus simvastatin, according to most recent results presented during the American Society of Nephrology Renal Week 2010 [81].

Until further results are available, current recommendation for predialysis patients suggests regular exercise, where feasible, smoking cessation, blood pressure control to <130/80 mmHg with preference to angiotensin-II-targeted treatment, $HbA1_c$ levels of <7.0%, Hb levels of 10–12 g/dL, LDL cholesterol levels as for the general population with high cardiovascular risk, sodium intake <2.4 g/day, maintenance of a BMI <25 kg/m^2, treatment of proteinuria, and avoidance of nephrotoxicity, aiming, apart from cardiovascular protection, at renal function preservation and slowing of CKD progression [3, 67, 82–84].

For patients on dialysis, blood pressure of <140/90 mmHg before and <130/80 mmHg after dialysis is recommended. Optimal levels of HbA1c and LDL-C seem to be less clearly defined, since they may not accurately reflect glycemic status [85] and atherogenic potential [86], mainly because of the short erythrocyte lifespan [85] and the qualitative rather than quantitative lipid abnormalities in uremia [86]. Special consideration must be taken to mineral bone disorder aiming at normal phosphorus levels, avoiding hypercalcemia, and treating secondary hyperparathyroidism judiciously in order to maintain the mineral buffering ability of active bone turnover, in order to ameliorate vascular calcification [66]. The latter is portrayed in recent recommendations regarding vascular calcification screening, phosphate binder choice, and target levels of parathormone [66, 87, 88]. Also of importance are dialysis adequacy, quality, and hemodynamic stability, as well as the optimization of conditions regarding inflammation and dialysis-related infections [89, 90].

Table 1: Targets for cardiovascular risk modification in CKD.

Traditional	CKD related
Physical activity	Proteinuria
Smoking	CKD progression
Obesity	Sympathetic nervous system
Blood pressure	Renin-angiotensin system
Glycemia	Left ventricular hypertrophy
Lipids	Mineral bone disorder
	Anaemia
	Inflammation
	Oxidative stress
	Coagulopathy
	Dialysis dose and quality

The treatment and prevention of arrhythmias and sudden death remains a challenge. Apart from attention to electrolyte disorders and avoidance of low-potassium dialysate, whenever possible, the use of β blockers seems beneficial. ACE inhibitors and angiotensin II receptor blockers appear promising but have yet to prove their efficacy in prospective trials [38]. Implantation of cardiac defibrillators in dialysis patients is associated with increased risk for bleeding and infection. Compared to patients with normal renal function, their use for primary prevention in CKD patients confers a reduced survival benefit, possibly due to comorbid conditions or increased defibrillation thresholds. On the other hand, implantation for secondary prevention is underused in dialysis patients, despite a proven effect in reducing mortality [37, 38].

In summary, CKD patients carry a heavy cardiovascular burden leading to high morbidity and mortality. This can be attributed to the high prevalence of traditional risk factors, such as advanced age, diabetes, and hypertension but also derives from CKD-related morbidity, such as sympathetic and renin-angiotensin hyperactivity, sodium retention, fluid overload, anemia, dyslipidemia, mineral-bone disorder and inflammation, which lead to structural alterations of the heart and vessels (chronic renocardiac syndrome). Aggressive risk modification, high index of suspicion for cardiovascular morbidity, proper intervention, and secondary prevention are essential. Large high-quality trials involving CKD patients are urgently needed to provide results, which could support effective treatment strategies. Until such results are available, avoiding "therapeutic nihilism" and aiming at established treatment targets with an individualised patient-oriented approach appears sensible.

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SAGE-Hindawi Access to Research
International Journal of Nephrology
Volume 2011, Article ID 245241, 7 pages
doi:10.4061/2011/245241

Review Article

The Role of Imaging in the Management of Cardiorenal Syndrome

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Received 23 August 2010; Accepted 4 January 2011

Academic Editor: Claudio Ronco

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Imaging of the kidney and the heart can provide valuable information in the diagnosis and management of cardiorenal syndromes. Ultrasound- (US-) based imaging (echocardiogram and renal US) is an essential component in the initial diagnostic workup of CRS. Echocardiography provides information on the structure and function of heart, and renal ultrasound is useful in differentiating between acute and chronic kidney disease and excluding certain causes of acute kidney injury such as obstructive uropathy. In this paper we overview the basic concepts of echocardiogram and renal ultrasound and will discuss the clinical utility of these imaging techniques in the management of cardiorenal syndromes. We will also discuss the role of other imaging modalities currently in clinical use such as computerized tomography and magnetic resonance imaging as well as novel techniques such as contrast-enhanced ultrasound imaging.

1. Introduction

The combination of cardiac and renal disease significantly increases the complexity and cost of health care [1]. The chronic kidney disease associated with heart failure has been recognized as an independent risk factor for morbidity and mortality [2–5]. The rate of cardiovascular mortality in the chronic kidney disease (CKD) population is 10–20 times that of those without CKD [6–8]. Recently, the Acute Dialysis Quality Initiative has published a document describing the definition and classification of cardiorenal syndrome (CRS) [1]. According to that document, the term cardiorenal syndrome refers to dysfunction of one organ system in presence of acute or chronic dysfunction of the other. According to the proposed classification, CRS is divided into 5 types. Types 1 and 2 include those with reduced kidney function due to either acute (type 1) or chronic cardiac dysfunction, and CRS 3 and 4 include worsening cardiac function in face of acute or chronic kidney disease, respectively. Secondary CRSs are grouped under type 5.

In this paper we will discuss the application of various imaging modalities in the diagnosis and management of CRS.

2. Ultrasonography

Imaging using ultrasound waves, ultrasonography, is a noninvasive, cost-effective, and widely available technology. The availability of new imaging modalities such as harmonic imaging, Doppler ultrasound for the study of blood flow, three-dimensional US and the advances in the technology and design of new transducers have significantly improved the quality of ultrasound (US) image. Currently, US imaging is the most widely used imaging modality in many fields, and indications for its use are expanding. US examination is considered the imaging modality of choice in the diagnosis and management of most cardiac and renal diseases. Therefore, the main focus of this paper would be on echocardiography and renal ultrasonography.

The US examination is based on interpretation of the character of the reflected sound waves from body tissues. The energy and the time lag at which these reflected US waves return and are picked up by the transducers determine the brightness and the depth of each tissue segment. The design and frequency of US transducers determine their utility in clinical imaging. In general, higher frequency probes generate images with higher resolution but because of limited

tissue penetration, high frequency transducers are used for imaging of superficial structures. Imaging of the heart and the kidneys requires frequencies in the range of 2–5 MHz (lower frequencies) to guarantee deeper penetration into the body. Imaging using ultrasound is limited in presence of gas and boney structures. High degree of reflection of US waves at the junction of soft tissue and gas or bone results in loss of signal from tissues beyond that point.

2.1. Echocardiography. Echocardiography is considered the preferred diagnostic method in cases suspicious of having heart failure [9]. It is a safe, noninvasive, and reproducible test applicable at bedside that provides valuable information on the anatomy and function of the heart. Using echocardiography, one can assess the structure of the myocardium and pericardium, global and regional LV function, and wall motion at rest and during pharmacologic stress. Two-dimensional (2D), gray-scale, or B (for brightness) mode echocardiography provides real-time images of heart structures and their motion. By imaging the heart in different planes, information on the dimensions, surface area, and volume of different chambers of the heart and valves can be obtained. M (for motion) mode echocardiography image is the graphic representation of the movement of cardiac structures based on the 2D image. Doppler echocardiography and color flow imaging provides information on the blood flow velocities and the pattern of blood flow within the heart. Pulsed and continuous wave Doppler US provide information on the velocity of blood flow in a specific location or the whole area within the path of ultrasound, respectively. Color flow Doppler provides information on velocity, turbulence, and direction of blood flow in the form of a colorful image superimposed on a 2D image.

Echocardiography provides useful information on left ventricular (LV) function. These include LV ejection fraction (LVEF), stroke volume, cardiac index, fractional shortening and regional wall motion analysis, among others. LVEF is the fraction of the left ventricular volume at the end of diastole that is ejected at the end of each contraction. Although there are objective ways to measure LVEF by plugging in accurate measurements of LV dimensions or volumes into a formula, in most cases, LVEF is a visual estimation of LV function and its accuracy depends on the experience of the interpreter. In one study of individuals with heart failure and reduced LVEF 6 months after a myocardial infarction [10], the overall accuracy of echocardiography in correctly assessing radionuclide ventriculography LVEF was 86%. In only one of 86 patients studied, there was a clinically significant difference between LVEFs estimated by the two methods (low LVEF by echocardiogram and normal LVEF by radionuclide technique) [10]. In another study, LVEF estimated by either echocardiography or electrocardiogram-gated single photon emission computed tomography (SPECT) were lower than those obtained by angiography. But they both did similarly well in accurately assessing LVEF of less than 40% or 35% in comparison to angiography [11]. Despite its limitations [12], determination of LVEF by 2-dimensional echocardiography is well accepted as the preferred measure of global LV function.

Certain echocardiographic parameters such as LV end-diastolic volume index, mitral deceleration time, and severity of mitral valve regurgitation are strong predictors of outcomes in individuals with advanced heart failure and reduced LVEF [13].

As many as 50% of all cases with clinical symptoms of heart failure have preserved LV function. Therefore, assessment of diastolic function in these cases is critical. Echocardiography is the noninvasive way of assessing diastolic function. Since almost 80% of LV filling during diastole (relaxation of the LV) occurs passively, abnormal relaxation of myocardium would result in impaired LV filling and diastolic dysfunction. M-mode, 2D, and Doppler echocardiogram are all useful in making the diagnosis of diastolic dysfunction and predicting outcomes [14]. Diastolic dysfunction can be graded based on the filling pressures and mitral inflow patterns obtained by echocardiography. Spectral tissue Doppler-derived index E/E′ appears to be a valuable tool in assessing left atrial pressure [15]. E and E′ represent peak early diastolic mitral flow and mitral annulus velocities, respectively. This index has shown a linear relationship with LV diastolic pressure irrespective of LVEF, heart rhythm, and rate [15]. The diagnostic accuracy of E/E′ is similar to that of B-type natriuretic peptide (BNP) in diagnosis of patients presenting with symptoms of heart failure with a wide range of LVEF [16].

Septal E/E′ at a cut-off value of 13 in patients presenting with acute dyspnea and preserved systolic function has a sensitivity of 76%–82% and specificity of 88%–91% for diagnosis of heart failure [17, 18].

2.2. Renal Ultrasonography. Kidney size and the echogenecity of the renal parenchyma provide useful information in the workup of kidney diseases. Normal kidney measures 9–13 cm in long axis. Length of the kidney correlates with height of the person while kidney volume correlates with weight, body surface area, and height [19]. Small kidney size is consistent with chronic kidney disease (CKD). However, not all CKD cases are associated with small kidneys. Normal or enlarged kidneys are seen in cases with HIV-associated nephropathy (HIVAN) [20], diabetic nephropathy, and monoclonal gammapathies.

Within the renal cortex the back scatter of the US waves occurs mainly from the glomeruli and blood. In general, normal renal cortex generates an US image that is less echogenic or darker than the adjacent liver tissue at the same depth. Increased echogenecity of renal cortex, that is, same or brighter than the liver, indicates renal disease. This finding on the gray-scale US has a specificity of 96% and positive predictive value of 67% for diagnosis of kidney disease [21].

Since glomeruli occupy only 8% of the cortical volume, isolated glomerular disease will not produce increased echogenecity [22]. Increased cortical echogenecity is usually indicative of CKD. However, echogenic kidneys can also be seen in cases with acute kidney injury (AKI). As an example, large and swollen kidneys with increased echogenecity are reported in cases with acute tubular necrosis (ATN) or lupus nephritis [23–25].

Ultrasound imaging of the kidneys is very useful in the diagnosis of obstructive uropathy. In fact, a negative kidney US exam for hydronephrosis rules out obstruction as the cause of AKI. When dilatation of calyces and proximal ureter is found, the diagnosis of urinary tract obstruction can be made. However, dilatation of renal calyces alone does not always indicate urinary tract obstruction. In fact, caliceal dilatation can be found during pregnancy and also in cases with diabetes insipidus [26, 27]. Dilatation of the distal ureter may provide clues for presence of obstruction at the level of bladder or urethra.

3. Role of Ultrasound in Management of CRS Patients

In patients suspicious of CRS, echocardiogram provides valuable information on cardiac structure and function and should be considered as one of the initial diagnostic studies. Around 27–40% of patients with acute decompensated heart failure (HF) develop acute kidney injury (AKI) [28]. At the same time, 45 to 63% of patients with chronic HF have CKD [29, 30]. Acute decompensated heart failure can occur in the setting of either systolic or diastolic dysfunction. Echocardiogram is the most useful diagnostic test in evaluating the cause of acute HF. In addition to providing information on systolic and diastolic function of the heart, echocardiogram is very useful in assessing regional wall motion abnormalities, condition and function of heart valves, and hemodynamics. Echocardiogram can also be used to rule out pericardial disease.

Systolic HF is defined as combination of symptoms of HF and LVEF less than 50%. Heart Failure with normal LVEF, also referred to as diastolic dysfunction, was not recognized as an entity by the cardiology community until about two decades ago. Patients with HF and normal LVEF usually have normal or reduced LV size, but enlarged left atria [31]. Although it is thought that LVH is the cause of HF with normal LVEF, the criteria for its diagnosis are only met in less than 50% of cases with HF and normal EF. Instead, these individuals have increased LV mass-to-volume ratio [32]. Doppler echocardiogram can provide valuable information on LV relaxation, filling pressures, and stiffness. However, this information needs to be interpreted carefully with special attention to clinical presentation (acute versus chronic, presence of symptoms, blood pressure readings, etc.). The 2007 consensus statement of the Heart Failure and Echocardiography Associations of the European Society of Cardiology suggested 3 essential criteria for the diagnosis of diastolic heart failure or heart failure with normal ejection fraction. They are presence of signs and symptoms of HF, normal or mildly abnormal LV size and systolic function (LVEF > 50% and an LV end-diastolic volume < 97 mL/m^2), and evidence of LV diastolic dysfunction via invasive or noninvasive methods.

Renal ultrasonography is valuable in differentiating between acute and chronic kidney disease and ruling out obstruction as a cause of worsening renal function. In cases suspicious of type 1 CRS, a normal renal ultrasound examination is expected. This is due to the acute nature of condition and the fact that reduced GFR is resulting from renal hypoperfusion. An exception would be cases in which acute HF results in acute worsening of GFR from an already low baseline level, or acute on chronic KD. In these cases, US features of CKD do not rule out the possibility of CRS type 1. Availability of previous kidney ultrasound images for comparison would be of great value in these cases. A few small single center studies suggest a role for Doppler ultrasound in the differential diagnosis of AKI. In one study, a normal (<0.71) resistive index [(peak systolic velocity − peak diastolic velocity)/peak diastolic velocity)] measured at the level of segmental renal arteries was seen in all individuals with a low fractional excretion of sodium (FENa), while individuals with high FENa had high resistive indices [33]. Among those with acute tubular necrosis and high FENa at baseline, there was a significant reduction in the RI after recovery from AKI episode [33].

4. Other Imaging Studies

4.1. Imaging of the Heart. Although echocardiogram is considered the imaging modality of choice in the workup of HF patients, in some cases more information on the structure and function of the heart might be necessary. In order to measure LVEF and volumes by echocardiography, a clear definition of endocardium is needed. This information is lacking in as many as 31% of cases [34]. Other imaging techniques might be needed to obtain more detailed information in these cases.

The most commonly used imaging in nuclear cardiology is single-photon emission computed tomography (SPECT) imaging of myocardial perfusion. After injection of the radiotracer, the isotope is extracted from the blood by viable myocytes and retained within the myocyte for some period of time. The photons are emitted from the myocardium which is in proportion to the magnitude of tracer uptake, and thus relates to perfusion. A gamma camera captures the photons and converts it into digital data which represents the magnitude of uptake and location of emission. Myocardial perfusion scanning using intravenous injection of technetium-99m- (^{99m}Tc-) labeled agents such as sestamibi ^{99m}Tc-labeled RBCs can be used for assessment of LVEF and regional wall motion abnormalities. Radionuclide imaging can be used to study the structure and function of the heart at rest and after exercise. LVEF, end-systolic, and end-diastolic volumes can be accurately measured by processing three dimensional images on gated SPECT using ^{99m}Tc agents [9].

Radionuclide ventriculography can be used to assess the left ventricular function. It can be performed either as first pass or equilibrium-gated techniques. Both techniques provide reliable means to asses the left and right ventricular function. The equilibrium technique is referred to as multiple-gated acquisition (MUGA) scanning. The RVG technique has advantages over echocardiography as there are no assumptions made about the ventricular geometry. Thus radionuclide imaging can provide accurate data about ventricular function [35].

While there is a high degree of correlation between measurements of ventricular end-systolic and end-diastolic volumes measured by gated SPECT and cardiac MR imaging, it appears that cardiac MR is superior in providing more accurate chamber volumes [36, 37].

Positron emission tomography (PET) is used to assess myocardial viability by assessing its metabolism using FDG or myocardial perfusion using rubidium (Rb) 82. PET imaging has several advantages over SPECT, including better spatial resolution, higher counting efficiencies, and excellent attenuation correction.

Computerized tomography (CT) techniques such as multi-slice CT and ultrafast electron beam tomography (EBT) are capable of providing images of the heart with high temporal and spatial resolutions. Multislice CT obtains images of the heart in many different imaging planes and is capable of providing information on cardiac volumes and dimensions. Fast imaging combined with electrocardiographic triggering reduces motion artifacts. EBT imaging occurs in milliseconds, which resolves the issue of cardiac motion during imaging. It has been shown to have comparable diagnostic accuracy in differentiating between ischemic and nonischemic cardiomyopathy compared to radionuclide stress testing in patients with HF [38]. However, EBT requires imaging using contrast for delineation of different chambers for determination of dimensions. This technique is also associated with high radiation exposure.

As a result of great advancements in the technology of magnetic resonance imaging, it can now be used for multiple purposes in evaluation of patients with cardiac diseases. Cardiac MR (CMR) is useful in assessing cardiac, great vessels and coronary anatomy and flow, ventricular function, myocardial viability, and perfusion. CMR provides the ability of imaging the heart in any desired plane in an unrestricted view, a clear advantage over echocardiography. Other advantages of CMR over echocardiography include the ease of studying the right ventricle due to its inherent three-dimensional nature and superior border detection between ventricular blood pool and the myocardium [34, 39–41]. Cardiac MR has very high accuracy and reproducibility for determination of ventricular volumes, stroke volume and ejection fraction [42, 43]. Using different MR sequences or techniques, it is possible to detect fibrosis, scarring, and inflammation of the myocardium. These advantages have resulted in making CMR the reference standard for ventricular volumetric assessment. In fact, in many institutions where this imaging modality is available, cardiac MR is considered the alternative diagnostic test to echocardiography in cases with poor ultrasound images or when myocarditis or infiltrative disease of the heart is suspected [44].

4.2. Imaging of the Kidney. Computerized tomography (CT) is the preferred imaging technique for the workup of kidney stones, renal masses, and renal arteries. Modern multidetector CT scanners are capable of acquiring thin slices of large areas of the body in one breath hold. Advancements in postprocessing techniques have also improved the diagnostic accuracy of CT scanning. Three-dimensional reconstruction of images is commonly used without compromising on the quality of the images. In fact, 3D reconstruction of CT angiograms has been rapidly omitting the need for catheter angiography [45, 46].

CT urography has almost completely replaced intravenous urograms in diagnosis of small stones and neoplasms of the kidney, ureters, and the urinary bladder. Filling defects within the collecting system might suggest a blood clot, stone, or a neoplasm. Unenhanced helical CT scan is the gold standard for diagnosing suspected renal colic secondary to kidney stones. Stones that are radiolucent on plain films are readily detectable by CT. In addition, CT scan provides valuable information on other signs of urinary tract obstruction such as hydronephrosis or hydroureter and streaking around these structures.

Contrast-enhanced CT is used to evaluate the arterial and venous supply of the kidney, renal parenchyma, and collecting system. Evaluation of the renal parenchyma occurs in the 3 phases, cortical phase, nephrographic, and excretory phase, after injection of the contrast. The detection of cortical or medullary lesions is best achieved during the nephrographic phase [47, 48]. CT imaging can also be used as a functional imaging modality for applications such as estimation of the GFR. Of course the risk of contrast-induced nephropathy is one of the main drawbacks of contrast-enhanced CT imaging, especially in individuals with acute or chronic kidney disease.

The preferred agent for radionuclide imaging of the kidneys is ^{99m}Tc. It provides good image quality with low radiation and has a short half-life. ^{99m}Tc can be bound to diethylenetriaminepentaacetic acid (DTPA) for measurement of GFR or mercaptoacetyltriglycine (MAG3) to measure renal blood flow. This imaging modality can be used in the differential diagnosis of AKI. Kidney uptake of ^{99m}Tc-MAG3 in the first 1-2 minutes after injection is reduced in cases with acute tubular necrosis, while it would be normal in individuals with prerenal AKI. Renal uptake of the tracer during the late phase (20 minutes after injection) is expected to be high in prerenal AKI as well as ATN but low in postrenal AKI [49].

The main utility of MR imaging in the study of the genitourinary tract is in staging of malignancies. Magnetic resonance angiography may be used to study renal arteries, but its use is limited because of the risk of nephrogenic systemic fibrosis in individuals with reduced renal function [50]. This risk is especially high (up to 20%) in individuals with AKI [51].

Sonographic imaging of kidneys with color Doppler and B mode has limited ability to evaluate the intrarenal arteries and arterioles. Imaging using ultrasound contrast agent can potentially overcome this limitation. The contrast agents used in renal US are gas-filled microbubbles that act similar to the red blood cells and remain in the intravascular space. In that regard, they are completely different from contrast-agents used in CT or MRI [52]. Contrast-enhanced echocardiography has been used in the clinical setting. A few US contrast agents are approved for the study of myocardial blood flow in humans. More recently, contrast enhanced ultrasonography (CEU) has been used in the study of changes in renal blood flow in response to physiologic and

pharmacologic stimuli in animal models and in human subjects with promising results [53–60]. In some studies CEU has been superior to color and power Doppler US examination in determining the cause of AKI [61]. While B mode US can provide information on structure of the kidneys, addition of ultrasound contrast agents has the potential of providing additional information on the pattern and quantity of regional and total RBF [61]. Once approved for clinical use in humans, CEU may be of great value in the work up of cases suspicious of CRS since altered renal hemodynamics are thought to be the cause of reduced GFR in these cases.

5. Conclusion

Ultrasound based imaging of the heart (echocardiography) and the kidney are the methods of choice in the work up of cases suspicious of CRS. US imaging is safe, noninvasive and widely available. It provides valuable information on the structure and function of the heart and the structure of the kidney. In clinical scenarios in which echocardiography is not helpful, cardiac MR and radionuclide scintigraphy can be used to assess LV function and structure. CT scan of the kidneys and the urinary tract is useful in the diagnosis of urinary tract obstruction and kidney stones. Contrast-based CT and MR studies are of limited use in CRS because of the potential complications. Contrast-enhanced ultrasound and other new investigational imaging modalities (MR) may prove to be useful in management of CRS cases.

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SAGE-Hindawi Access to Research
International Journal of Nephrology
Volume 2011, Article ID 630809, 8 pages
doi:10.4061/2011/630809

Review Article

Pharmacological Management of Cardiorenal Syndromes

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Received 10 August 2010; Accepted 28 March 2011

Academic Editor: Anjay Rastogi

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Cardiorenal syndromes are disorders of the heart and kidneys whereby acute or chronic dysfunction in one organ may induce acute or chronic dysfunction of the other. The pharmacological management of Cardiorenal syndromes may be complicated by unanticipated or unintended effects of agents targeting one organ on the other. Hence, a thorough understanding of the pathophysiology of these disorders is paramount. The treatment of cardiovascular diseases and risk factors may affect renal function and modify the progression of renal injury. Likewise, management of renal disease and associated complications can influence heart function or influence cardiovascular risk. In this paper, an overview of pharmacological management of acute and chronic Cardiorenal Syndromes is presented, and the need for high-quality future studies in this field is highlighted.

1. Introduction

Cardiorenal syndromes (CRS) affect a broad array of patients in both acute and chronic clinical situations, with significant ramifications in terms of morbidity and mortality. For instance, type 1 CRS, as seen in patients experiencing an abrupt increase in serum creatinine >0.3 mg/dL (>26 μmol/L) during hospitalization for acute decompensated heart failure (ADHF), is associated with increased length of stay, more complications, and higher mortality. In chronic heart failure, the coexistence of chronic kidney disease (CKD) with glomerular filtration rate (GFR) <60 mL/min/1.73 m^2 (type 2 CRS) significantly increases the risk for mortality. Acute kidney injury, for example, following contrast for radiological imaging, has been associated with subsequent adverse cardiovascular events, so-called type 3 CRS. Numerous studies have identified CKD as a graded and independent risk factor for cardiovascular events and outcomes, representing type 4 CRS. Systemic disorders that involve both the heart and kidneys (type 5 CRS) are a heterogeneous group, but when examining sepsis as an example, increasing numbers of organs involved dramatically increases mortality, particularly in those with evidence of septic cardiomyopathy [1] and acute kidney injury [2].

In this paper, we review briefly the pharmacological management of the various subtypes of CRS, highlighting the need for high-quality future studies. Table 1 presents a point-form summary of suggested management for these subtypes, along with pitfalls and questions for future research.

2. Management of Acute Cardiorenal Syndrome (Type 1)

Type 1 CRS appears in the setting of ADHF or cardiogenic shock for a number of reasons, with hemodynamic

Table 1

CRS subtype	General considerations and recommended therapies	Caveats/areas for future investigation
Acute cardio-renal (CRS 1)	Reduce congestion with diuretics, balance negative fluid balance with intravascular refilling	Infusion versus bolus; dose; electrolyte concerns
	Renin-angiotensin blockade may need to be reduced or even withheld with worsening renal function	
	With preserved or elevated blood pressure, empiric use of vasodilators	Limited data from uncontrolled trials; nitroprusside limited by toxicity
	Nesiritide may improve cardiac output and cause significant diuresis	Conflicting results of clinical trials; ongoing trials to determine safety, efficacy, and dose
	With low pressure, poor cardiac output, inotropes may be required as a bridge to recovery or transplantation	Intropes may provoke ischemia or arrhythmia; increased mortality in some studies; mechanical support (balloon pump, ventricular assist device, etc.) may be required
Chronic cardio-renal (CRS 2)	Renin-angiotensin blockade is of primary importance; may need to be reduced or withheld with significantly worsening renal function	Most studies have excluded patients with significant kidney disease; increase in creatinine >30% or potassium >5.0 mmol/L cause for concern
	Aldosterone antagonists may be cautiously considered	Creatinine >2.5 mg/dL (>220 μmol/L) or potassium >5.0 mmol/L were exclusions in clinical trials
	Beta-blockers are important adjuncts in congestive heart failure and/or ischemic heart disease	Some agents (atenolol, nadolol, sotalol) have altered pharmacokinetics; carvedilol may have an advantage over older drugs
	Concomitant anemia may worsen symptoms and outcomes	Unclear role of erythropoiesis-stimulating agents; parenteral iron encouraging in terms of symptoms as well as improved renal function
Acute reno-cardiac (CRS 3)	Contrast nephropathy is a common example of CRS 3; prevention is likely the best strategy	
	Numerous strategies tested; isotonic fluids and possibly N-acetylcysteine have the best evidence to date	Preexisting chronic kidney disease, age, diabetes, and volume contraction are amongst risks that predispose to contrast nephropathy
	Low osmolar, nonionic contrast may reduce risk of CRS 3	
Chronic reno-cardiac (CRS 4)	Multifaceted disorder with both traditional and non-traditional risk factors; graded risk based on degree of chronic kidney disease	Lifestyle modification (smoking, weight control, activity, and nutrition) of probable benefit but limited evidence
	Anemia closely related to poor outcomes; current guidelines recommend starting for sustained hemoglobin <10 g/dL (100 g/L) and targeting 10–12 g/dL (100–120 g/L)	Studies showed increased harm from higher targets; concerns have been raised about stroke risk, and risk in patients with cancer
	Management of chronic kidney disease-related mineral and bone disorders; phosphate binders, vitamin D analogs, controlling PTH	As yet, efficacy largely limited to putative surrogate endpoints; ongoing trials with hard cardiovascular endpoints awaited
	Lipid lowering with statins	Efficacy in dialysis-dependent patients is questioned; in lesser degrees of chronic kidney disease risk reduction is clearly established
Secondary cardio-renal (CRS 5)	Sepsis is a common example of CRS 5; management needs to focus on protecting/optimizing both cardiac and renal function	Other secondary causes of CRS 5 are a fruitful area for ongoing research
	Volume and pressor support to achieve a mean arterial pressure ≥65 mmHg and central venous pressure of 8 to 12 mmHg and adequate oxygen delivery	Early protocol-driven interventions lower risk of adverse renal outcomes and death due to cardiovascular collapse
	Norepinephrine preferred over dopamine in a randomized controlled trial (most patients had septic shock)	Higher incidence of cardiac arrhythmia and trend to increased need for dialysis with dopamine
	Addition of low-dose vasopressin in select patients	May decrease risk of adverse cardiac and renal outcomes

derangements ranging from acute pulmonary edema with hypertension through severe peripheral fluid overload to cardiogenic shock and hypotension [3–5]. Unfortunately, the management of type 1 CRS is largely empiric, as many of the traditional therapies to relieve congestive and/or ischemic symptoms (diuretics, vasodilators, and morphine) [5] have not been subjected to rigorous study. While hypotension and decreased cardiac output with neurohormonal activation have been the traditional explanations for worsening renal function in this setting, recent evidence has implicated high venous pressure and raised intra-abdominal pressure leading to renal venous congestion as important contributors to impairment of kidney function [6, 7], and indeed many patients with ADHF and type 1 CRS have preserved left ventricular ejection fraction and normal or high blood pressure. Hence, strategies to reduce congestion with diuretics and possibly ultrafiltration, and the use of vasodilators in select patients, are important steps in early management.

The goal of diuretic use should be to deplete the extracellular fluid volume at a rate that allows adequate time for intravascular refilling from the interstitium. To achieve adequate diuresis, infusions of loop diuretics have been demonstrated to have greater efficacy than intermittent dosing [8], and certainly loop diuretics are preferred to thiazides, whose actions are diminished in patients with impaired kidney function [9]. In a recent study, ADHF patients who developed hemoconcentration during diuresis (presumed to be diuresed in excess of refilling rate) did in fact have a greater risk of worsening renal function with an odds ratio of 5.3 ($P < .001$), however they also had lower 180-day mortality, with a hazard ratio of 0.31 ($P = .013$) [10]. Diuretics may hence need to be withheld or reduced to allow for plasma refilling. Finding the optimal balance between relief of ADHF symptoms while maintaining adequate kidney function will require further study, and the optimal dose and route of loop diuretic is being studied in the randomized trial DOSE-AHF [11].

If kidney function continues to worsen, blockade of the renin-angiotensin-aldosterone-system (RAAS) may be a contributing factor, necessitating withholding or delaying the introduction of angiotensin converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs) in order to maintain the GFR [12]. As a nonpharmacological strategy to more vigorously manage hypervolemia and circulatory congestion, ultrafiltration was demonstrated in the UNLOAD study to be superior to diuretics, in terms of greater weight loss, less requirement for vasoactive drugs, and fewer rehospitalizations and emergency room visits, with no difference in mortality [13]. The CARRESS-HF trial is currently being undertaken to further define the use of this therapy in patients with type 1 CRS [11].

For type 1 CRS patients with preserved or elevated blood pressure, vasodilators such as nitroglycerin and nitroprusside are often used to relieve symptoms and improve hemodynamics [14], though their efficacy has not been studied through randomized controlled trials, and their effect on reversing or preventing type 1 CRS is unknown. The use of nitroprusside in patients with impaired kidney function is potentially hazardous due to the accumulation of thiocyanate [15], however, in a nonrandomized trial which included patients with varying degrees of kidney function, its use was associated with improved outcomes and stable kidney function [16].

Nesiritide, a recombinant form of human B-type natriuretic peptide, quickly relieves dyspnea in acute heart failure states, through a combination of decreased preload, afterload and pulmonary vascular resistance, and increased cardiac output. It also causes a brisk diuresis due to direct renal effects including afferent arteriolar vasodilation and decreased sodium reabsorption [17]. However, a meta-analysis of trials in patients with ADHF found that nesiritide did not avert type 1 CRS and increased mortality [18]. Ongoing research will hopefully clarify its role in type 1 CRS [19].

When patients have low blood pressure and poor renal perfusion, positive inotropes such as dobutamine or phosphodiesterase inhibitors may be required [5]. However, the use of inotropes may actually accelerate some harmful processes such as ischemia or arrhythmia. Milrinone, for instance, was demonstrated to have a higher incidence of hypotension, more arrhythmias, and no benefit on mortality or hospitalization in ADHF patients [20]. Levosimendan, a phosphodiesterase inhibitor with calcium sensitizing activity, has shown mixed results in terms of the prevention and treatment of type 1 CRS [21, 22]. When patients with ADHF or cardiogenic shock and type 1 CRS are resistant to therapy, more invasive therapies such as intra-aortic balloon pulsation, ventricular assist devices, or artificial hearts may be required as a bridge to recovery of cardiac function or to transplantation.

Finally, a number of classes of agents targeting some of the vasoactive/neurohormonal effector pathways in type 1 CRS, specifically endothelin, adenosine, and vasopressin, have held promise in preclinical and early clinical trials. However, subsequent randomized trials have failed to show a benefit of antagonism of receptors for these targets [23–26].

3. Management of Chronic Cardiorenal Syndrome (Type 2)

Interruption of the RAAS is the primary goal in the management of type 2 CRS. However, RAAS blockade can lead to significant decrease in kidney function, and/or elevated potassium. Studies of RAAS blockade in heart failure have typically excluded CKD patients [27], but it is likely that these agents are renoprotective even in this population. The CONSENSUS trial, for example, included a number of subjects whose serum creatinine increased by 30% or greater with enalapril [28]. However, creatinine tended to stabilize and in many instances improved over the course of the study. Typically it is recommended that RAAS blockade may be carefully titrated provided the serum creatinine does not continue to rise beyond 30% and potassium is consistently below 5.0 mmol/L.

In terms of aldosterone blockade, drugs such as spironolactone and eplerenone are an important adjunct to therapy in patients with severe heart failure [29, 30]. However, the use of these agents in patients with CKD, and particularly in combination with other RAAS blockade, can dramatically

increase the risk of hospitalizations and mortality secondary to hyperkalemia [31]. Excluding patients with moderate CKD (creatinine level $\geq$2.5 mg/dL or 220 μmol/L) or hyperkalemia >5.0 mmol/L, which were exclusion criteria in the Randomized Aldactone Evaluation Study (RALES) [29], will minimize potential life-threatening complications [32].

Interruption of sympathetic tone through the use of beta-blockers is another important strategy for patients with congestive heart failure or ischemic heart disease. In general, these drugs should not adversely affect kidney function. Certain beta-blockers may be relatively contraindicated in CKD because of altered pharmacokinetics, such as atenolol, nadolol, or sotalol [33], and it is wise to consult a pharmacopoeia when prescribing beta-blockers to patients with CKD. Carvedilol, a beta-blocker with α_1 blocking effects, has been demonstrated to have favourable effects on kidney function in some CRS patients, hence may have a benefit over older beta-blockers [34].

Both congestive heart failure and CKD are associated with anemia, the latter of which is commonly treated with erythropoiesis-stimulating agents. Furthermore, the action of erythropoietin in the heart may reduce apoptosis, fibrosis, and inflammation [35, 36]. Hence, there has been intense interest in using erythropoiesis-stimulating agents in heart failure patients [37]. A small controlled trial suggested that administration of erythropoiesis-stimulating agents in patients with type 2 CRS and anemia led to improved cardiac function, reduction in left ventricular size, and lowering of BNP [38]. However, more recent work did not find significant improvement in a variety of important clinical parameters [39]. Ongoing clinical trials are required to establish if erythropoiesis-stimulating agents have a role to play in the management of congestive heart failure and type 2 CRS. Another approach to anemia management in type 2 CRS is parenteral iron. In the FAIR-HF study, patients were randomized to ferric carboxymaltose or placebo, and the active treatment group experienced an improvement in heart failure symptoms, Patient Global Assessment, 6-minute walk test and quality of life [40]. They also experienced a higher GFR at the study conclusion of 3.8 mL/min/1.73 m^2.

4. Management of Acute Reno-Cardiac Syndrome (Type 3)

In type 3 CRS, acute kidney injury occurs as a primary event (e.g., acute glomerulonephritis) or secondary event (e.g., radiocontrast, exogenous or endogenous nephrotoxins, postsurgical, etc.), and cardiac dysfunction is a common and often times fatal sequela [41]. A common example of type 3 CRS occurring in the hospital setting is contrast nephropathy, particularly in patients undergoing coronary and other angiographic procedures who have risk factors such as preexisting CKD, diabetes, older age or volume contraction. In these susceptible populations, prevention may provide the best opportunity to "treat" or avoid type 3 CRS. Many potential preventive strategies have been studied, including parenteral hydration (hypotonic or isotonic saline or bicarbonate), diuretics, mannitol, natriuretic peptides, dopamine, fenoldopam, theophylline, and N-acetylcysteine [42, 43]. To date, isotonic fluids have been the most successful intervention, with some controversy surrounding the effectiveness of N-acetylcysteine. Using a sensitive definition of acute kidney injury, Solomon and colleagues identified a possible role for the low-osmolar, nonionic monomer iopamidol in the prevention of contrast nephropathy [44]. In addition, they identified that the research subjects who experienced acute kidney injury were almost twice as likely to have major cardiovascular events (death, stroke, myocardial infarction, or dialysis) during the follow-up period, indicative of the seriousness of type 3 CRS.

Treatment of primary kidney diseases such as acute glomerulonephritis or kidney allograft rejection may potentially lessen the risk of type 3 CRS, but this has not been systematically studied. Furthermore, many immunosuppressive drugs used for such treatment have adverse effects on the cardiovascular system through their effects on blood pressure, lipids, and glucose metabolism. For instance, a recent meta-analysis comparing the calcineurin-inhibitors cyclosporine and tacrolimus found greater dyslipidemia in the cyclosporine group and higher risk of new onset diabetes in the tacrolimus group [45]. The drug sirolimus, working through the mammalian target of rapamycin (mTOR) pathway, leads to even greater perturbations in lipids and higher requirement for lipid-lowering therapy [46]. While direct and indirect influences of these agents may be potentially harmful to the heart, some investigators have implicated calcineurin in the development of left ventricular hypertrophy and heart failure in animal models [47]. The role of immunosuppression in the prevention or conversely the development of type 3 CRS needs further study.

5. Management of Chronic Reno-Cardiac Syndrome (Type 4)

The management of type 4 CRS is a multifaceted approach focusing on the reduction of cardiovascular risk factors and complications common to CKD patients. These include, but are not limited to, anemia, hypertension, altered bone, and mineral metabolism, dyslipidemia, smoking, albuminuria and malnutrition [48, 49]. Several therapies targeting such uremic complications as anemia, homocysteine, calcium-phosphate product and hyperparathyroidism are supported by observational studies demonstrating the association between adverse cardiovascular events and these conditions.

In observational studies, the treatment of anemia seems to lessen cardiovascular events, however this has not been borne out in randomized trials where higher hemoglobin targets have been associated with worse outcomes [50–53]. Hence, the use of erythropoiesis-stimulating agents to prevent type 4 CRS seems to be ineffective.

Elevated homocysteine has been associated with worsening cardiovascular outcomes in a number of observational studies [54], and has been a target of study in CKD. However, vitamin therapy to lower homocysteine has been unhelpful in patients with advanced CKD [55, 56] and harmful in patients with diabetes and more moderate CKD [57].

Observational studies have implicated elevated calcium-phosphate product, elevated phosphate, elevated parathyroid

hormone, and inadequate vitamin D receptor activation as potential risk factors for type 4 CRS [58–60]. Clinical trials to date have been generally disappointing. A meta-analysis of trials studying the use of the phosphate binder sevelamer indicated no significant benefit of therapy [61]. However, a subgroup analysis in older patients at higher cardiovascular risk suggests that phosphate binding may improve outcomes [62] and intensive lowering of calcium-phosphate product improves levels of C-reactive protein [63]. With respect to parathyroid hormone, high levels have been associated with adverse cardiovascular outcomes in CKD [59], and a systematic review revealed that cinacalcet, a drug used to lower parathyroid hormone, decreased hospitalizations related to cardiovascular disease [64]. A large randomized trial of cinacalcet is examining hard cardiovascular endpoints and mortality [65], and trials of phosphate binders and vitamin D analogs are ongoing.

The use of "statins" (3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors) is a cornerstone of risk factor modification in patients at risk for cardiac disease. Unfortunately, two high-profile negative trials in dialysis patients [66, 67] have cast a shadow of doubt over the use of statins to prevent type 4 CRS, at least in advanced CKD patients. The recently published Study of Heart and Renal Protection (SHARP) included 3,023 dialysis patients and 6,247 CKD patients not on dialysis, and preliminary results showed that a combination of simvastatin and ezetimibe lowered the risk of major atherosclerotic events, with a risk ratio of 0.83 (0.74–0.94, $P = .0022$) [68]. Of interest, the subgroup of patients on dialysis seemed to experience less of a benefit from the drug therapy, and all-cause mortality was unaffected. The full publication is eagerly awaited. In an earlier meta-analysis [69] Strippoli et al. demonstrated significant reductions in cardiovascular end points in CKD patients treated with statins, though again all-cause mortality was unchanged. Statins did not, however, cause adverse events in subjects with CKD compared to those with normal kidney function, and the SHARP study indicated that the combination of simvastatin and ezetimibe in this population was well tolerated with no hepatoxic or myopathic complications.

6. Management of Secondary Cardiorenal Syndrome (Type 5)

Examples of type 5 CRS include a heterogeneous group of disorders, such as sepsis, systemic lupus erythematosus, amyloidosis, and diabetes mellitus [70]. It is difficult to formulate a treatment strategy to encompass all of these disorders, but more important is the recognition that injury to one organ is likely to influence or injure the other organ, and *vice versa*. Therapies directed to the improvement in function of one organ need to consider the interaction with, and role of, the other.

As sepsis is one of the more common acute disorders that involves multiple organs, and often causes codysfunction of kidneys and heart, it provides a suitable example for the discussion of type 5 CRS and its management. The study of early goal-directed therapy by Rivers et al. demonstrated that early intervention significantly decreased in-hospital death due to cardiovascular collapse by approximately half (21.0 versus 10.3%; $P = .02$), and another study of protocol-driven targets in patients with septic shock [71] showed a significant reduction in the incidence of acute renal failure from 55.2% to 38.9% ($P = .015$). De Backer and colleagues compared dopamine with norepinephrine in the management of shock (the majority with septic shock) and found that the dopamine group had a higher incidence of cardiac arrhythmia, while displaying a trend towards greater dependence on renal replacement therapy [72]. Additionally, an important randomized study of conservative versus liberal fluid resuscitation in patients with acute lung injury [73] found that the more conservative strategy improved not only outcomes related to lung injury itself, such as oxygenation and ventilator days, but this strategy also led to less cardiovascular failure and a trend towards improved renal outcomes. Intriguingly, animal studies indicate that in spite of increased coronary and renal blood flow, these organs demonstrate diminished function in sepsis [74]. Another study indicated that low-dose vasopressin was effective in limiting cardiac and kidney injury in sepsis [75]. Recognition of type 5 CRS as an entity in sepsis and other systemic disorders will allow further research into the signalling and mechanisms of injury and allow for the development of rational and effective therapies.

7. Conclusions

The subtypes of CRS discussed in this paper present unique management challenges, but also opportunities for further research. Sadly, many pivotal heart failure trials of the past decades which have been instrumental in guiding therapy for millions of patients worldwide have systematically excluded patients with acute or chronic kidney disease, making it difficult to provide evidence-based treatment guidelines for type 1 and 2 CRS. The recognition of acute kidney injury as an important clinical outcome, coupled with more stringent and standardized diagnostic criteria, has led to a tremendous increase in research activity in recent years. The increased understanding of downstream consequences of acute kidney injury, and in particular its role in type 3 CRS, has only recently been appreciated. Clearly more high-quality research in this area is necessary. Finally, an astonishing number of cardioprotective trials in type 4 CRS have been negative [76]. This underscores the need to recognize CKD as a factor that not only heightens risk of cardiovascular disease, but also modifies (or even negates) the effect of treatments proven effective in other populations. Understanding the complex bidirectional interactions between the heart and the kidneys can only help foster future drug development and investigations into the prevention and management of all subtypes of CRS.

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SAGE-Hindawi Access to Research
International Journal of Nephrology
Volume 2011, Article ID 194910, 10 pages
doi:10.4061/2011/194910

Review Article

Therapeutic Options for the Management of the Cardiorenal Syndrome

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Received 17 August 2010; Accepted 11 October 2010

Academic Editor: Mitchell H. Rosner

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Patients with heart failure often present with impaired renal function, which is a predictor of poor outcome. The cardiorenal syndrome is the worsening of renal function, which is accelerated by worsening of heart failure or acute decompensated heart failure. Although it is a frequent clinical entity due to the improved survival of heart failure patients, still its pathophysiology is not well understood, and thus its therapeutic approach remains controversial and sometimes ineffective. Established therapeutic strategies, such as diuretics and inotropes, are often associated with resistance and limited clinical success. That leads to an increasing concern about novel options, such as the use of vasopressin antagonists, adenosine A1 receptor antagonists, and renal-protective dopamine. Initial clinical trials have shown quite encouraging results in some heart failure subpopulations but have failed to demonstrate a clear beneficial role of these agents. On the other hand, ultrafiltration appears to be a more promising therapeutic procedure that will improve volume regulation, while preserving renal and cardiac function. Further clinical studies are required in order to determine their net effect on renal function and potential cardiovascular outcomes. Until then, management of the cardiorenal syndrome remains quite empirical.

1. Introduction

Renal dysfunction is one of the most important comorbidities in heart failure. Decreased estimated glomerular filtration rate (GFR) seems to be a potent predictor of cardiovascular complications and mortality [1]. In addition, worsening heart failure or acute decompensated heart failure (ADHF) can accelerate worsening of renal function, that is what we call cardiorenal syndrome (CRS). The most common underlying risk factors that account for renal dysfunction in the setting of heart failure or cardiac dysfunction include hypertension, diabetes mellitus, severe atherosclerotic disease, elderly age, and a prior history of renal insufficiency or heart failure [2].

As patients with heart failure are surviving much longer and dying less frequently from primary arrhythmia, we suppose that the CRS will become more common in the near future. However, there is no a single definition that appropriately describes this entity. It is well accepted that cardiovascular morbidity and mortality and diminished renal function are closely correlated. This relationship exists regardless of whether the initial event is a parenchymal disease of the kidney or a cardiac disease. In SOLVD (Studies of Left Ventricular Dysfunction) trial, patients with a GFR less than 60 ml/minute/1.73 m^2 had a 40% higher risk of death [3, 4]. In addition, in the ADHERE (Acute Decompensated Heart Failure National Registry) population, mortality risk for the hospitalized patients could be estimated using three variables: systolic blood pressure, blood urea nitrogen (BUN), and serum creatinine levels. Two of the above three most important predictors of in-hospital survival are related to kidney function [5]. Similarly, Gottlieb et al. showed that in hospitalized patients, worsening renal function predicts a prolonged hospitalization or an increased risk of death [6].

The current proposed definition divides CRS into five subtypes: type I, acute CRS (20–25%), which reflects an abrupt worsening of cardiac function (e.g., acute cardiogenic shock or acutely decompensated congestive heart failure) leading to acute kidney injury; type II, chronic CRS (30–45%), in which chronic abnormalities in cardiac function

(e.g., chronic congestive heart failure) cause progressive and potentially permanent chronic kidney disease; type III, acute renocardiac syndrome (30–35%), which reflects an abrupt worsening of renal function (e.g., acute kidney ischaemia or glomerulonephritis) leading to acute cardiac disorder (e.g., heart failure, arrhythmia, or ischemia); type IV, chronic renocardiac syndrome (45–50%), in which chronic kidney disease (e.g., chronic glomerular or interstitial disease) contributes to decreased cardiac function, cardiac hypertrophy, and/or increased risk of adverse cardiovascular events; and type V, secondary CRS, meaning systemic diseases such as diabetes mellitus, sepsis, and amyloidosis that deteriorate simultaneously cardiac and renal function [7, 8].

2. Pathophysiology of the CRS

Heart and kidney performance are closely interrelated physiologically and pathophysiologically, both in health and in disease. Although there is a growing recognition of the frequent presentation of the CRS, its underlying pathophysiology is not yet well understood, and no consensus regarding its appropriate management has been achieved.

A decreased cardiac output in CHF resulting in reduced renal perfusion could be an easy explanation for the worsening renal function. But worsening renal function has also been demonstrated among patients with ADHF with preserved left ventricular ejection fraction. This deterioration in renal performance, despite a presumed preservation of blood flow to the kidneys, has led to the search of other pathophysiological mechanisms [9]. Although the pathophysiology varies according to the specific clinical circumstances, the general processes include neurohormonal factors and hemodynamic factors, such as intrarenal hemodynamics and transrenal perfusion pressure.

Transrenal perfusion pressure is estimated as mean arterial pressure minus central venous pressure. For the patient with heart failure and volume overload, the combination of high pulmonary artery or central venous pressure with low systemic pressure may cause a severe compromise of the net renal perfusion pressure. Therefore, when there is an opportunity to decrease central venous pressure through vasodilatation, improved oxygenation, or volume reduction, this can lead to significant improvements in renal blood flow and urine output [2].

Moreover, a very important contributor is the neurohormonal activation, which is mediated by activation of arterial baroreceptors and intrarenal sensors (Figure 1). That leads to exaggerated abnormalities in the activation of the renin-angiotensin-aldosterone system (RAAS), activation of the sympathetic nervous system (SNS), and also activation of the arginine-vasopressin system. The latter is an intrinsic self-defense system that maintains blood pressure and intravascular volume within normal range. Besides vasoconstriction and sodium retention that lead to increased preload and afterload, one of the most deleterious actions of the RAAS in CRS is the activation of NADPH-oxidase by angiotensin II. This results in the formation of reactive oxygen species (ROS). In CRS, there is no balance between NO and ROS because of the increased production of the latter. A major initiator of an inflammatory response is oxidative stress through the production and activation of proinflammatory cytokines, especially interleukin-1, interleukin-6, C-reactive protein, and tumor necrosis factor-a. It is well known that these cytokines play a crucial role in the pathophysiology of atherosclerosis. Moreover, they have negative inotropic effects, assist in cardiac remodeling, and cause thrombotic complications. Therefore, a vicious cycle sets in, promoting structural and functional damage to the heart and to the kidneys [10, 11].

The production of endothelin has also some adverse effects because it causes vasoconstriction and enhances hypertrophy of cardiac myocytes. Moreover, it stimulates noradrenaline, angiotensin II, and aldosterone [12].

Arginine vasopressin (AVP) has also detrimental effects on CRS progression by fluid retention and enhancement of angiotensin II and noradrenaline actions. In addition it simulates myocardial hypertrophy [13].

Adenosine and the related tubuloglomerular feedback is a recently identified contributing factor. Adenosine is locally released in the kidney under stress. It binds to receptors on the afferent arterioles and promotes vasoconstriction, thereby reducing renal blood flow. Activation of the receptor also enhances sodium reabsorption in the tubules, leading to further water and sodium retention. Acute delivery of sodium to the distal tubules due to diuretic therapy in ADHF will in turn stimulate further adenosine release and further reduction in the GFR. This pathway might be very attractive as a contemporary therapeutic target in CRS [14].

In heart failure, the SNS is initially activated by the baroflex to provide inotropic support and preserve cardiac output. However, excessive sympathetic activity can enhance cardiomyocyte apoptosis and focal myocardial necrosis, while the direct actions of catecholamines can lead to hypertrophy [11]. Finally, the aggressive use of diuretic agents may cause further neurohormonal activation and aggravate systemic and renal vasoconstriction, leading to additional impairment in renal performance. The consequent decline in blood flow and filtration contribute actively to the clinical entity of diuretic resistance [2].

3. Treatment of Patients with CRS

The heterogeneous and complex pathophysiology of CRS makes patient management a clinical challenge for the physicians. To date there is not a single success-guaranteed treatment for CRS because of two main reasons. The first one is that each patient has his own unique medical history, risk profile, and combination of comorbidities. The second one is that we have no evidence from clinical heart failure trials on which we can base our therapy for patients with significant renal dysfunction since most studies predominantly recruited populations with relatively preserved renal function [15]. Another serious point in the therapeutic approach of patients with CRS is the development of resistance to many standard therapies, such as diuretics and inotropes, which leads to an increasing concern about novel strategies (e.g., use of AVP antagonists, adenosine A1

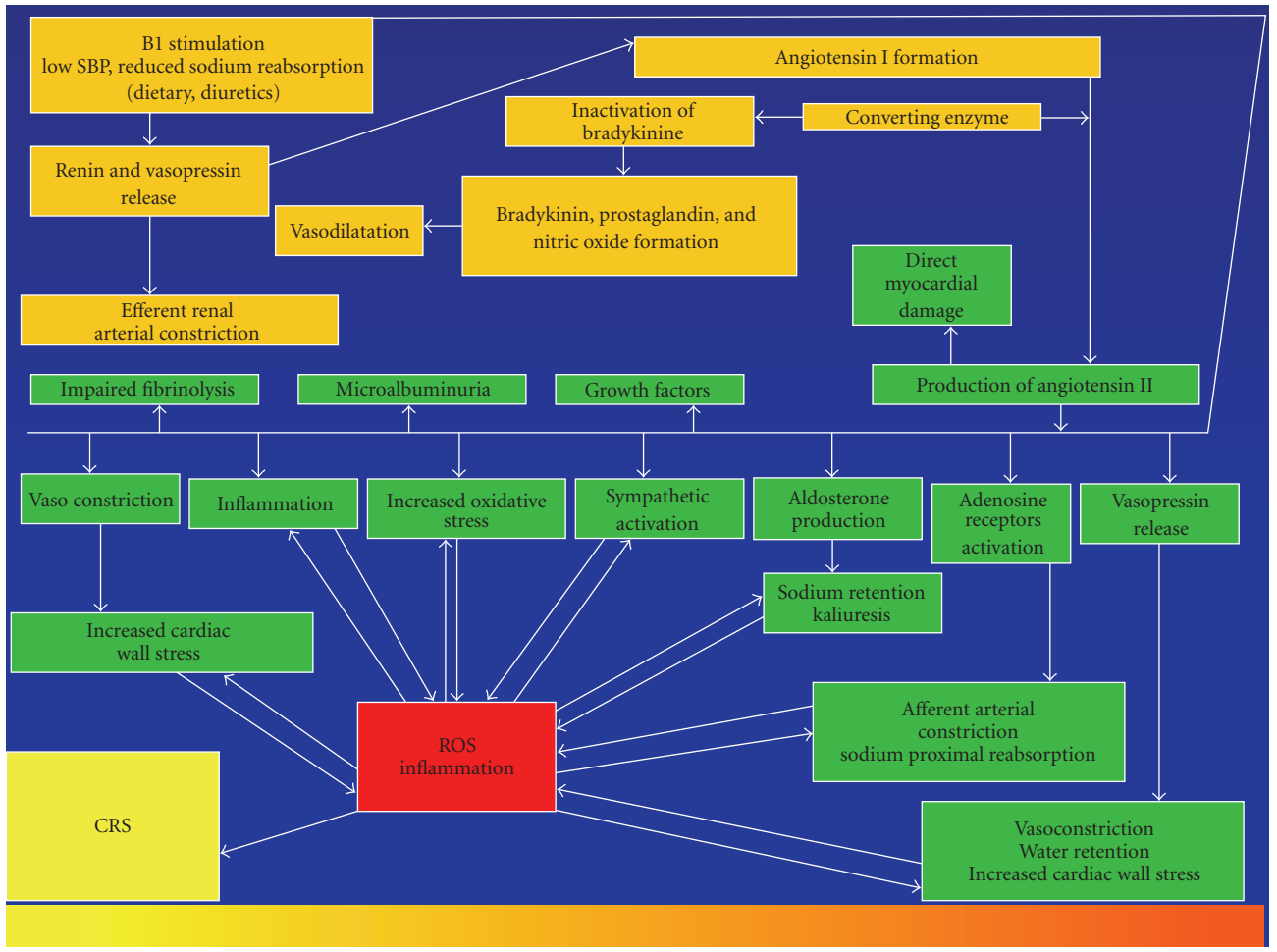

Figure 1: Pathophysiology of the cardiorenal syndrome. SBP: Systolic Blood Pressure; ROS: Reactive Oxygen Species; CRS: Cardiorenal Syndrome.

receptor antagonists, and ultrafiltration). As a result of the above, treatment of CRS patients is still quite empirical.

Generally, managing the patient with acute CRS often involves making therapeutic choices that are mutually contradictory. Because one is attempting to treat volume overload and congestion, the aggressive use of diuretics and volume depletion directly impairs renal function. Inhibitors of the RAAS (Angiotensin-converting enzyme inhibitors or angiotensin receptor blockers), although they are cardiorenal protective, can lead to temporary worsening of renal function. On the other hand, in order to preserve renal function, it is preferable to replace intravascular volume and provide a salt load, but these measures directly deteriorate cardiac congestion. Not surprisingly, many patients are discharged from hospital either still volume loaded or markedly worse in terms of renal function. That leads to a high readmission rate for patients recently discharged from hospital with heart or renal failure [2].

The management of the patient with ADHF and symptomatic congestion usually focuses on symptomatic relief and rapid removal of fluid. However, no therapies focused mainly on symptomatic relief or fluid removal have demonstrated any benefit on improving survival or attenuating the progression of the disease. This emphasizes the importance of instituting or optimizing disease-modifying therapy as soon as possible. These include, wherever they are appropriate, optimal doses of beta-blockers, angiotensin modulators, and aldosterone antagonists. All of these therapies, when used cautiously, will help to improve survival and reduce hospitalization rate. However, their effect on renal function and the hemodynamic status during acute decompensation will need close monitoring [2]. Table 1 summarizes some practical recommendations for the management of ADHF patients with type 1 CRS.

Body weight of the patient is the single most important indicator while managing the CRS. The patient needs continuous hemodynamic monitoring, especially if he has low blood pressure and uncertain filling pressure. Moderate restriction of daily salt intake ≤ 2 gr is recommended. It is also better to restrict the dietary fluid intake to 1000 ml–1500 ml or less than 1000 ml per 24 hours if the patient is hyponatremic. A few cases with low filling pressure and low

Table 1: Managing cardiorenal syndrome: Practical recommendations.

(1) Restrict fluid and sodium intake
(2) Increase furosemide dose
(3) Use continuous intravenous furosemide
(4) Add thiazides or metolazone
(5) Add renoprotective dopamine at 2–3 mcg/kg/min
(6) Add inotrope or vasodilator (according to systolic blood pressure)
(7) Start ultrafiltration
(8) Insert intra-aortic balloon pump
(9) Insert another device

blood pressure may need volume expansion [16]. Drugs that impair kidney function should be avoided (e.g., NSAIDs), or their dosage should be adjusted according to the existing GFR (e.g., antibiotics).

3.1. Diuretics. Diuretic agents have long been considered to be an initial and essential part of the management of the CRS patients. However, limited clinical trial data suggest their beneficial role. The importance of diuretic agents is illustrated by data from the ADHFNR (Acute Decompensated Heart Failure National Registry), which revealed that 80.8% of patients enrolled in the registry were on chronic diuretic therapy at the time of admission while 88% were treated acutely with an intravenous diuretic during their admission for ADHF [9].

Loop, thiazide, and potassium-sparing diuretic agents cause diuresis and natriuresis in about 20 minutes after administration, and therefore they provide effective short-term symptomatic relief. Nevertheless, they are not free from drawbacks, causing long-term detrimental cardiovascular effects. More specifically, they lead to activation of the neurohormonal system, indirectly deteriorate the function of the left ventricle, and increase systemic vascular resistance, plasma renin, aldosterone activity and plasma levels of neurohormones such as norepinephrine and arginine vasopressin. Through the above mechanisms, they result in promoting renal dysfunction, thus increasing the risk of mortality [17, 18].

In the absence of definitive data, patients with volume overload and nonhypotension should receive loop diuretics (slow high intravenous doses to minimize ototoxicity) or thiazides to alleviate symptoms. Despite the judicious use of loop diuretics, we should be very careful, because in the setting of ADHF and polypharmacy, such as the concomitant use of vasodilators, diuretics can cause hypotension in patients with systolic dysfunction and decreased cardiac preload.

A major problem the physicians have to face while treating patients with CRS is diuretic resistance, which is an indicator of poor prognosis in patients with CHF. It is described as a clinical state in which the diuretic response is diminished or lost before the therapeutic goal of relief from congestion has been reached. Many factors may be responsible for diuretic resistance, such as delayed intestinal absorption of oral drugs due to mucosal edema, decreased renal perfusion, decreased diuretic excretion into the urine, inadequate drug dosing, the concomitant use of NSAIDs, which inhibit the synthesis of vasodilator and natriuretic prostaglandins, and finally dietary noncompliance (e.g., excess salt intake) [3, 16, 19].

Diuretic resistance is a common entity in the managing of patients with CRS. The braking phenomenon or short-term tolerance means that the response to the diuretic is diminished after the first dose has been administered. This effect is treated by a continuous infusion of furosemide, rather than bolus doses, starting at 5 mg/dl to 10 mg/dl, following an intravenous thiazide diuretic (the combination of loop diuretic and thiazide diuretic can cause sequential nephron blockade of sodium reabsorption). However, combination therapy requires careful monitoring, as it may lead to excessive sodium and potassium loss [20]. The continuous intravenous infusion in contrast to bolus injections of loop diuretics in diuretic-refractory patients seems to maintain a more optimal and effective rate of drug delivery to the renal tubules and in turn inhibits sodium reabsorption more consistently. A Cochrane review examined eight trials comparing continuous infusion of a loop diuretic with bolus injections in 254 patients with CHF. The urine output was significantly greater in patients given continuous infusion, the incidence of ototoxicity was less, and the duration of hospitalization was significantly shortened [21].

Several factors should be taken into account when deciding the diuretic dose in patients with refractory edema. It is important to remember that diuretics do not have a smooth dose-response curve: no natriuresis occurs until a threshold rate of drug excretion is achieved. Therefore, a patient who does not respond to 20 mg of furosemide may not be exceeding this threshold, and the dose should be doubled rather than giving the same dose twice a day. In addition, the patient should cut down on his daily sodium intake, because high sodium can prevent net fluid loss even though adequate diuresis is being achieved. We should also consider the need for initial intravenous diuretic therapy in order to avoid the poor oral availability (only about 50% or less of oral furosemide is absorbed in edematous states) [3]. Table 2 summarizes some recommendations about the use of loop diuretics in heart failure patients according to the renal function [22].

It is also very important to mention that aggressive diuretic therapy at this stage could promote diuretic induced hypovolemia, exaggerating any pre-existing renal insufficiency as seen in acute CRS. Therefore a progressive and gradual diuresis as opposed to an aggressive and immediate one is recommended, especially in type 1 CRS [23].

Another approach to induce the efficacy of intravenous furosemide is to add salt-poor albumin in patients with low serum albumin levels. The furosemide-albumin complex is believed to deliver more diuretic to the kidney, primarily by staying in the vascular space. Studies have shown that adding salt-poor albumin substantially increased sodium excretion [24]. Finally, optimizing diuresis with the simultaneous use of hypertonic saline and diuretics has been studied and found

Table 2: Pharmacokinetics of loop diuretics according to the renal function in heart failure patients. IV: intravenous; CrCl: Creatinine Clearance.

	Moderate renal insufficiency	Severe renal insufficiency		Heart failure			
	Maximal intravenous dose (mg)			IV Loading dose (mg)	Infusion rate (mg/hr)		
Diuretic					CrCl <25 ml/min	CrCl 25–75 ml/min	CrCl >75 ml/min
Furosemide	80–160	160–200	40–80	40	20 then 40	10 then 20	10
Bumetanide	4–8	8–10	1–2	1	1 then 2	0.5 then 1	0.5
Torsemide	20–50	50–100	10–20	20	10 then 20	5 then 10	5

successful at relieving signs and symptoms of congestion [25].

3.2. ACE Inhibitors and Angiotensin Receptor Blockers (ARBs). Inhibitors of the RAAS are the key component in the management of patients with left ventricular systolic dysfunction. They improve survival in patients with heart failure and also prevent progressive renal insufficiency in diabetic nephropathy and other forms of chronic kidney disease. Nevertheless, in acute CRS these drugs should be used cautiously in patients with an underlying renal disease, because they may be associated with elevations in serum creatinine levels [26]. Although physicians frequently avoid or discontinue these drugs for fear of deteriorating renal function, the rise in serum creatinine levels after the initiation of an ACE inhibitor may identify a subgroup of patients who will achieve the greatest benefit from their use. Discontinuation of the ACEs because of renal dysfunction identified a patient group with heart failure who had an increased mortality risk [27].

Most trials that confirmed the benefits from the administration of ACE inhibitors, such as SOLVD [28], excluded patients with serum creatinine concentrations greater than 2 mg/dl. The Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS), in patients with severe heart failure, included patients with renal dysfunction, but only if their serum creatinine concentrations were no higher than 3.4 mg/dl. The subgroup of patients with creatinine levels higher than 2 mg/dl showed evidence of improved outcomes when treated with an ACE inhibitor. CONSENSUS also demonstrated that patients with the most severe heart failure had a substantial increase in creatinine levels (>30%), when an ACE inhibitor was added to their treatment, independent of their baseline renal function, while few patients needed to stop therapy [29]. To reduce the incidence of renal deterioration, patients should be started on the lowest dose of an ACE inhibitor, when the patient is considered not to be dehydrated, and concomitant use of NSAIDs should be avoided [15]. In addition, dosage up titration should be done very carefully. ACE inhibitor therapy in patients with baseline renal dysfunction is associated with significant long-term benefits and should be used in clinical routine, unless they are contraindicated (e.g., bilateral or high-grade renal artery stenosis and/or ACE/ARBs-induced hypotension) [30]. An effective approach is to continue these agents during hospitalization for DHF, despite an increase in creatinine levels, as long as renal dysfunction is not steadily impaired and severe hyperkalemia does not develop. ACE inhibitors are not usually related to worsening renal function in these patients. However, an expert physician should evaluate extreme clinical situations, such as cardiogenic shock or acute renal failure.

3.3. Low-Dose Dopamine. In clinical practice, low renal-protective doses of dopamine are commonly used in combination with diuretic therapy, although available data do not clearly support favorable effects on renal function. It is supposed that dopamine increases kidney blood flow, blunts the effects of norepinephrine and aldosterone, and, when given in low doses, promotes renal vasodilatation [31]. A prospective, double-blind, randomized, controlled study to investigate the effect of low-dose dopamine concluded that it can worsen renal perfusion in patients with acute renal failure, which adds to the trend to abandon the routine use of low-dose dopamine in critically ill patients [32].

A clinical trial (DAD-HF) by Triposkiadis et al. was announced in the Heart Failure Society of America Meeting 2009. It compared the effects of dopamine plus low-dose furosemide versus high-dose furosemide alone on kidney function and subjective perception of dyspnoea in ADHF. There were no differences in urine output or in dyspnoea score, but those patients who were treated with dopamine plus low-dose furosemide were less likely to have their renal function worsened at 24 hours or to develop hypokalemia. Although dopamine has been forgotten for a long time, it now seems that it may be undergoing a revival [33].

3.4. Inotropes. If the deteriorating renal function is thought to be related primarily to low cardiac output and subsequent reduced renal perfusion, positive inotropic agents (dobutamine, phosphodiesterase inhibitors, and levosimendan) may be used. These agents should be given only for low cardiac output states, for a short term and under close monitoring, as they may increase the risk of arrythmias. In both acute and chronic heart failure, inotropic drugs compared with placebo and vasodilators, have been related to an increased risk of mortality and other adverse cardiac events. Until more data are available, inotropic therapy

should be reserved for patients with clinical evidence of severe low cardiac output (candidates for bridging to more definite therapy), in which vasodilatory agents cannot be administrated due to low systemic pressure or low systemic vascular resistance [34, 35].

Levosimendan belongs to a promising new class of inotropic agents called "calcium sensitizers." A randomized trial showed a moderate or marked improvement in the patient's overall assessment of patients treated with levosimendan [36]. An experimental study by Zager et al. showed that levosimendan protects against ischemic acute renal failure due to severe renal vasoconstriction, in critical situations such as sepsis or acute heart failure [37].

3.5. Vasodilators and Natriuretic Peptide. Vasodilators such as intravenous nitroglycerin or nesiritide (recombinant human B-type atrial natriuretic peptide) have been shown to be much less deleterious to kidney function, especially when used at low doses that do not reduce blood pressure. Vasodilators can rapidly decrease ventricular filling pressures and central venous pressures and reduce myocardial oxygen consumption. Intravenous nitroglycerine is a vasodilator used to relieve pulmonary congestion in patients with ADHF. Frequent dose titration of intravenous nitroglycerine according to systemic blood pressure is necessary in order to achieve the desired hemodynamic effects and symptomatic relief. The decrease in venous pressure may be beneficial in reducing transrenal perfusion pressure. But still it is not clear whether intravenous nitroglycerine has long-term benefits on kidney function or survival [2].

B-type natriuretic peptide (BNP) is synthesized in the ventricular myocardium in response to overload and wall stress. BNP dilates arteries and veins, induces sodium excretion, and suppresses the RAAS. Nesiritide, a synthetic BNP, is an effective vasodilator with a mild diuretic action. Its administration results in venous, arterial, and coronary vasodilatation, decreasing the cardiac preload and afterload, which in turn increases cardiac output without direct inotropic effects. These hemodynamic effects are accompanied by natriuresis and diuresis, although the latter responses may be quantitatively smaller than those in normal subjects and seem to be blunted in patients with more severe heart failure. Nevertheless, creatinine clearance was not improved by nesiritide, even in patients who showed satisfactory natriuresis and diuresis [38, 39].

In the setting of CRS, renal effects of nesiritide were first described by Wang and colleagues. They designed and implemented a crossover clinical trial in which 15 participants received a 24-hour infusion of nesiritide according to the recommended bolus and infusion regimen and a 24-hour infusion of placebo on consecutive days, but in random order. They showed that nesiritide did not affect GFR, renal plasma flow, urine output, or sodium excretion [40]. The Vasodilatation in the Management of Acute Congestive Heart Failure (VMAC) trial assessed the impact of early nesiritide infusion on symptoms and pulmonary congestion in patients with DHF. A total of 489 patients with renal insufficiency received either nesiritide or nitroglycerin. At 24 hours, 83% of the patients with renal insufficiency and 91% of patients without renal insufficiency who were treated with nesiritide reported improvements in dyspnoea. Nesiritide might promote symptom improvement in heart failure patients with renal dysfunction but has no effect on kidney function [41]. A substudy of the Follow-Up Serial Infusions of Nesiritide trial (FUSION I) demonstrated that in heart failure patients who were at high risk for CRS, infusion of nesiritide at two doses (0.005 μg/kg/ml or 0.01 μg/kg/ml) was well tolerated with no deterioration of kidney function [42]. The serial infusion of nesiritide (FUSION II) trial was a study designed to look at intermittent infusion of nesiritide in patients with severe heart failure. Infusions were given either once or twice weekly over 12 weeks. This study demonstrated no significant effect on outcome or quality of life, but there was an effect on the kidney: an increasing serum creatinine level of more than 0.5 mg/dl was favorably affected by nesiritide [43].

Although first data show that low doses of nesiritide are potentially renal protective in the difficult clinical situation of treating patients with ADHF at risk for CRS, additional outcome information on the efficacy and safety of nesiritide is needed before it becomes an established therapy.

3.6. Ultrafiltration. The use of ultrafiltration is another potential therapeutic procedure in patients with diuretic resistance, which can alleviate volume overload. Ultrafiltration is a convective method for removing fluid and small-molecular-weight compounds from the circulatory system across a semipermeable membrane in response to a transmembrane pressure gradient. Conventional ultrafiltration requiring central venous access is more frequently used, especially if the patient is extremely edematous [44]. The hemodynamic changes produced by ultrafiltration are modest. The reduction in water is accompanied by decreases in right atrial pressure and wedge pressure. Cardiac output and stroke volume do not change or rise slightly [45]. Compared to loop diuretics, ultrafiltration is more efficient in removing sodium, while the neurohormonal activation is less for the same degree of volume reduction. An important point is that weight loss is sustained relatively to furosemide treatment. The typical volume of water removed per ultrafiltration session is 3 to 4 lt. Loop diuretics should be discontinued for the days the patient is receiving ultrafiltration in order to minimize electrocyte abnormalities and neurohormonal activation [46].

Several trials have evaluated the use and efficacy of ultrafiltration. Seven centers participated in a pilot randomized controlled study, RAPID CHF (Randomized Controlled Trial of Ultrafiltration for Decompensated Congestive Heart Failure: the Relief for Acutely Fluid-Overloaded Patients with Decompensated Congestive Heart Failure), which compared a single 8-hour ultrafiltration intervention to usual care of 40 patients hospitalized with DHF. Total fluid removal at 24 hours was greater with ultrafiltration than with the usual care, with a trend towards greater weight loss at 24 hours in the ultrafiltration group [47].

Ultrafiltration can potentially manage worsening renal function and decreased urine output despite escalating

doses of diuretics or diuretic resistance in severe heart failure. In the Ultrafiltration versus Intravenous Diuretics for patients Hospitalized for Acute Decompensated Heart Failure (UNLOAD) trial, patients with ADHF were randomly assigned to ultrafiltration with flows of up to 500 ml/h versus standard intravenous diuretics. The ultrafiltration group showed a greater weight loss and greater fluid removal at 48 hours, although the changes in dyspnoea score did not differ and both groups improved. The rates of re-hospitalization and the total days of hospitalization were significantly lower in the ultrafiltration group at a 3-month follow-up. However, preliminary data suggested that there was not a significant protective effect of ultrafiltration on kidney function. Surprisingly, there was no relationship between the amounts of fluid removal versus changes in serum creatinine levels, suggesting that other factors not associated with volume are responsible for the deterioration in renal function in CRS [48].

Overall, compared with the use of intravenous diuretics with or without combined vasoactive therapy, ultrafiltration provides a quick and predictable removal of fluid that is free of induced electrocytes abnormalities and associated consequences. On the other hand, ultrafiltration may be related to high daily cost as well as the need for large vein access and greater patient supervision [44].

3.7. Vasopressin Antagonists. Arginine vasopressin (AVP) or antidiuretic hormone is secreted by the posterior pituitary gland in response to hyperosmolality or volume depletion. Its actions are mediated by three types of receptors: V_{1A}, V_{1B}, and V_2. V_2 receptors are located in the distal tubules of the kidney and the collecting duct, and they provoke vasoconstriction and water reabsorption through aquaporin channels in the tubules. In heart failure, secretion of AVP may be enhanced due to low blood pressure or diminished arterial volume. Excess AVP can lead to hyponatremia. Selective V_2 antagonists (vaptans), such as tolvaptan and conivaptan, can effectively mobilize free water clearance and aquaresis and increase the serum sodium in those that are hyponatremic [48].

Some studies have reported a powerful aquaretic effect without renal impairment in patients with ADHF treated with tolvaptan. In the Acute and Chronic Therapeutic Impact of a Vasopressin Antagonist (ACTIV) trial, patients with acute heart failure showed a greater decrease in body weight, an increase in urine output and a slight increase in serum sodium at 24 hours receiving tolvaptan compared to those receiving placebo or standard therapy [49]. The much larger Efficacy of Vasopressin Antagonist in Heart Failure Outcome Study with Tolvaptan (EVEREST) confirmed the efficacy of early administration of vasopressin antagonists in decreasing mean body weight and improving dyspnoea. It comprised 4133 patients who were hospitalized for acute heart failure and then they were followed up during long-term treatment. Long-term outcomes of the patients did not differ between vasopressin antagonist and the placebo groups. This suggests that vaptans when used in the context of acute heart failure can modify kidney response to water retention. But still it does not favorably influence remodeling of heart and kidneys over the long term towards recovery [50, 51].

3.8. Adenosine Antagonists. Adenosine is generated by the breakdown of ATP and ADP in the renal tubules during the energy-requiring process of sodium excretion. As sodium excretion increases in conditions such as during diuretic therapy in sodium overload states (e.g., heart failure), extracellular adenosine concentrations rise and serve as a counterregulator trying to restore the balance between energy supply and demand. The elevated plasma adenosine levels observed in patients with heart failure can contribute to diuretic resistance and renal dysfunction. In the context of impaired tubular glomerular filtration, adenosine is released and binds to A_1 receptors to cause constriction of the afferent arterioles. This reduces renal blood flow and induces sodium reabsorption by the proximal tubules. A_1 adenosine receptor antagonists are novel agents that activate adenosine A_1 receptors and improve renal blood flow, promote diuresis, and increase sodium excretion.

The efficacy of an adenosine A_1 receptor antagonist in the treatment of patients with heart failure is still unsettled. Initial clinical studies seem to be quite controversial. Gottlieb et al. showed that the addition of BG9719 (A_1 adenoside antagonist) to furosemide in patients with heart failure and volume overload significantly increased diuresis and prevented a decline in kidney function [14]. On the other hand, the results of PROTECT (A Placebo-controlled Randomized Study of the Selective A_1 Adenosine Receptor Antagonist Rolofylline for Patients Hospitalized With Acute Decompensated Heart Failure and Volume Overload to Assess Treatment Effect on Congestion and Renal Function) clinical trial that were recently announced in the ESC 2009 showed that rolofylline did not meet neither the primary efficacy endpoints (dyspnoea improvement, treatment failure) nor the secondary efficacy end points (death, cardiovascular or renal rehospitalization, or persistent renal impairment), while the overall safety profiles of the placebo and rolofylline groups were similar (rolofylline was associated with higher incidence of seizure and a trend towards a higher incidence of stroke) [52]. In addition, the REACH UP trial, a multicenter, international, randomized, double-blind, placebo-controlled study did not demonstrate any clear benefit of rolofylline on clinical status or renal function in patients with ADHF and recent or acute worsening renal function. Although there were fewer deaths or rehospitalizations at 60 days in the rolofylline-treated patients, the numbers were small and did not reach statistical significance [53]. Thus, larger clinical trials are required in order to determine their net effect on renal function and potential cardiovascular outcomes.

3.9. Targeted Renal Delivery of Drugs. Targeted renal delivery of drugs has been proposed to increase local drug concentration in the hopes of inducing renal effects or providing a previously unattained effect. Direct intrarenal delivery (to both renal arteries simultaneously) will eliminate renal first pass, resulting in less systemic exposure and reduction of serious side effects. Intrarenal delivery of fenoldopam (dopamine D_1 agonist) was associated with a lower incidence

of hypotension than intravenous fenoldopam. This is also true for intrarenal versus intravenous administration of nesiritide because BNP has high first-pass renal metabolism [54].

3.10. Anemia and Erythropoietin. Although the prevalence of anemia in the heart failure population has been subject to very wide variations, it is a long recognized, common, and well-studied complication of chronic kidney disease (CKD). Furthermore, cardiorenal anemia syndrome refers to the simultaneous presence of anemia, heart failure, and CKD that forms a pathologic triad with an adverse impact on morbidity and mortality [55]. Several studies have shown that when anemia is corrected with subcutaneous erythropoietin, the cardiac function improves, as assessed by measurement of the ventricular ejection fraction and oxygen utilization during maximal exercise [56]. However, anemia should not be aggressively corrected in the renal failure population [57]. Recently, we have shown that darbepoetin alpha attenuates deleterious effects of oxidative and nitrosative stress into the cardiovascular system of anemic patients with CHF, counteracts neurohormonal activation, and also improves cardiac function and exercise capacity [58, 59]. The results of the Reduction of Events with Darbepoetin alpha in Heart Failure Trial (RED-HF trial) will determine the role and efficacy of treatment of anemia with darbepoetin alpha on the mortality and morbidity in heart failure subjects with symptomatic left ventricular systolic dysfunction and anemia [60].

3.11. Cardiac Transplantation/Cardiac Assist Devices. Patients with CRS are rarely candidates for advanced heart failure therapy, such as cardiac transplantation or implantation of a left ventricular assist device, because of their high surgical risk and poor prognosis. Still, there are devices such as the intraaortic balloon pump, which are used in low cardiac output states and contribute to the hemodynamic stabilization of the patients and therefore preserve renal function.

4. Conclusion

The challenges in the management of acute CRS will worsen before they get better due to our success in improving survival in heart failure patients. In addition, growing numbers of patients will survive to reach the true end-stage of heart failure. The previous focus on symptomatic treatment with increasing doses of diuretics and vasodilators, which met resistance, is now fading. The new focus should be to recognize the cardiorenal syndrome, recognize it early and treat the whole patient for long term. The optimization of heart failure therapy also preserves kidney function. Novel therapeutic options may offer additional opportunities to improve volume regulation, while preserving cardiac and renal function. A close cooperation of cardiologists, nephrologists, and internists is required, as well as a deeper understanding of the pathophysiology of the CRS, in order to establish an effective means of therapy in the future.

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SAGE-Hindawi Access to Research
International Journal of Nephrology
Volume 2011, Article ID 190230, 6 pages
doi:10.4061/2011/190230

Review Article

The Role of Ultrafiltration in Patients with Decompensated Heart Failure

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Received 15 August 2010; Accepted 1 September 2010

Academic Editor: Mitchell H. Rosner

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Congestion, due in large part to hypervolemia, is the primary driver of heart failure (HF) admissions. Relief of congestion has been traditionally achieved through the use of loop diuretics, but there is increasing concern that these agents, particularly at high doses, may be deleterious in the inpatient setting. In addition, patients with HF and the cardiorenal syndrome (CRS) have diminished response to loop diuretics, making these agents less effective at relieving congestion. Ultrafiltration, a mechanical volume removal strategy, has demonstrated promise in achieving safe and effective volume removal in patients with cardiorenal syndrome and diuretic refractoriness. This paper outlines the rationale for ultrafiltration in CRS and the available evidence regarding its use in patients with HF. At present, the utility of ultrafiltration is restricted to selected populations, but a greater understanding of how this technology impacts HF and CRS may expand its use.

1. Introduction

Despite significant advances in therapy and understanding of the disease, heart failure (HF) continues to remain a very morbid, mortal, and resource-consuming chronic illness. The total estimated direct and indirect cost of HF in the United States for 2010 is $39.2 billion [1]. Of particular concern are patients admitted to the hospital with congestion, as these patients are at greater risk of morbidity and mortality than those with stable heart failure [2]. Mean 30-day mortality in these patients is slightly above 10%, and the mean 30-day readmission rate is around 30% [3]. Dyspnea, a symptom of congestion and volume overload, is present in almost 90% of patients admitted to the hospital with heart failure [4]. Therapy aimed at relieving congestion and volume overload is therefore essential; prevention of recurrent volume accumulation is critical to disease stabilization. For over 50 years, the use of loop diuretics has been the main way to achieve fluid loss and decongestion. As heart failure progresses, patients may develop a declining renal function and a diuretic unresponsiveness, a condition termed the cardiorenal syndrome (CRS), which may make volume removal with diuretics difficult. It is in this setting that alternative means of fluid removal require consideration. This paper focuses on a mechanical method of fluid removal known as ultrafiltration.

2. Loop Diuretics: The Mainstay of Therapy for Volume Overload

As mentioned above, the predominant reason that HF patients present to the hospital is due to symptoms of congestion. These symptoms are usually associated with venous congestion and volume overload. In addition, signs of elevated venous congestion, namely a third heart sound and jugular venous distention, portend a poor prognosis in HF patients [5]. It is critically important, therefore, to reduce venous congestion prior to the development of symptoms and also to quickly relieve symptoms of congestion once present. This has been accomplished almost exclusively via the use of loop diuretics since about 1965. Loop diuretics block the sodium-potassium-chloride transporter in the ascending limb of the Loop of Henle. In order to act, they must be secreted into the tubular lumen. The pharmacokinetics and pharmacodynamics of these agents can vary considerably from patient to patient, and therefore these agents must be titrated to effective doses while minimizing toxicity [6]. With over 40 years of clinical experience in

using these agents, loop diuretics have been given a level A recommendation to restore and maintain normal volume status in HF patients in the Heart Failure Society of America practice guidelines [7], despite the availability of large-scale randomized trials which would be required to garner such a recommendation for a novel agent. There are problems with loop diuretics that have caused many to question their use, especially in the setting of decompensation.

3. Diuretic Resistance

Diuretic resistance, simply defined, is the progressive lack of efficacy of a given dose of diuretic to achieve an adequate urinary response. This necessitates the use of higher doses and combinations of loop and nonloop diuretics to achieve sodium and fluid loss, often at the expense of worsening renal function. Many factors contribute to the development of diuretic resistance. Worsening renal insufficiency leads to less secretion of diuretic into the tubular fluid, requiring a greater overall dose of diuretic in order for an effective amount of diuretic to reach its site of action [6]. Increased activation of the renin-angiotensin-aldosterone system, induced by diuretic use, results in increased sodium and water reabsorption through a variety of mechanisms. Hypertrophy of distal tubule epithelial cells results in greater sodium absorption distal to the Loop of Henle, the site of action of loop diuretics [8]. In patients with decompensated heart failure, venous pressure is also elevated, leading to decreased absorption of oral agents and decreased renal blood flow and renal sodium excretion [9]. Diuretic resistance is often found to coexist with renal insufficiency in patients with HF and, when present, defines the cardiorenal syndrome.

4. Loop Diuretics May Be Harmful

In addition to having diminished efficacy in patients with CRS, loop diuretics themselves, particularly when administered in high doses in an inpatient setting, may be harmful. Retrospective analyses of large multicenter trials of patients with HF have shown a consistent trend that nonpotassium sparing diuretics (NPSDs), of which loop diuretics are the primary agents used, are associated with worsened outcomes. An analysis of the Studies of Left Ventricular Dysfunction (SOLVD), a seminal randomized trial demonstrating the benefit of ACE inhibition in the progression of HF, demonstrated a higher all-cause and cardiovascular mortality in subjects on NPSDs versus those who were not [10]. These differences were not significant after multivariable adjustment, but a higher risk of arrhythmic death in patients on NPSDs persisted. An analysis of the Digitalis Investigation Group (DIG) trial, conducted to evaluate the influence of digoxin in mild-to-moderate chronic HF, also showed an increased risk of death, cardiovascular death, progressive HF death, sudden cardiac death, and HF hospitalizations in subjects on NPSDs [11, 12]. A subsequent study of over 1300 patients with advanced heart failure at a single center demonstrated a linear decrease in survival with increasing outpatient dose of loop diuretic [13]. This association persisted in multivariable analysis.

The Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterization Effectiveness (ESCAPE) trial, conducted to evaluate the use of pulmonary artery catheter in subjects admitted to the hospital with advanced heart failure, found a similar dose-response relationship between inpatient loop diuretic dose and adjusted 6-month mortality [14]. Using the Acute Decompensated Heart Failure (ADHERE) national registry, a large nationwide database of patients admitted to the hospital with heart failure, investigators were able to demonstrate that subjects receiving an inpatient intravenous dose of less than 160 mg of furosemide equivalents had lower in-hospital mortality, fewer episodes of worsening renal function, and shorter length of stay than subjects treated with >160 mg of furosemide equivalents per day, after propensity adjustment [15]. These association studies do not prove causation, and it is certainly possible that the need for a loop diuretic or a higher dose of loop diuretic is simply reflective of a greater HF disease severity and not an increased risk attributable to the loop diuretic itself. Small clinical trials have demonstrated short-term adverse clinical outcomes with higher doses of intravenous loop diuretics [16, 17]. One mechanism through which loop diuretics may exert a negative prognostic influence is hypokalemia, which may lead to ventricular arrhythmias. Activation of the renin-angiotensin-alsoterone system and sympathetic nervous system [18–20], known to influence HF progression, has been postulated as another potential mechanism. In a porcine model of pacing-induced HF, furosemide administration shortened time to left ventricular dysfunction, and serum aldosterone levels were significantly higher in the furosemide-treated animals [21].

The recently presented NIH-sponsored Diuretic Optimization Strategies Evaluation (DOSE) study was the first randomized trial of diuretic therapy in heart failure. It randomized patients admitted with decompensated HF and high outpatient diuretic dose (between 80 mg and 240 mg of furosemide daily) to high doses (2.5 times oral dose) and low doses (equivalent oral dose) of furosemide as well as continuous infusion versus intermittent therapy in a 2×2 factorial design. The change in creatinine from baseline to 72 hours was low and not different among groups. In the high dose group, there was a higher rate of creatinine elevation >3 mg/dL, but this did not translate into any difference in 60-day outcomes. Sixty day rate of death, rehospitalization, or ED visit was not different among groups and approached 45–50%. The study does provide some short-term data regarding the safety of intravenous loop diuretics in the inpatient setting. Lower dose diuretic therapy may be preferred as an initial approach, provided that the dose is escalated if there is suboptimal response at 48 hours.

5. What Is Ultrafiltration and How Does It Differ from Hemodialysis?

For nonnephrologists, it is useful to briefly review the underlying concepts of ultrafiltration (UF). UF involves a convective transfer of water and solutes (Figure 1). Plasma water is forced across a semipermeable membrane that allows movement of water and solutes (small molecules less

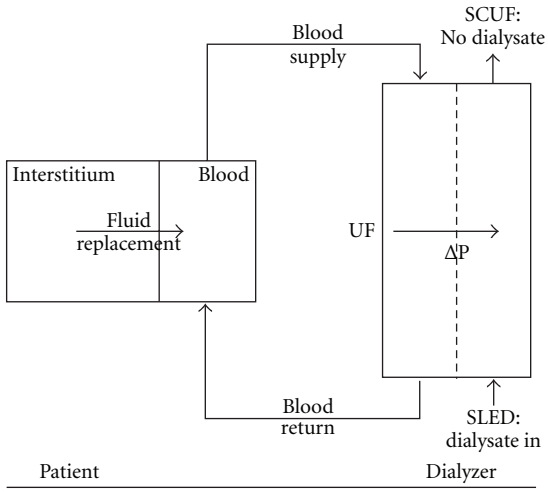

Figure 1: Dialytic techniques used in decompensated heart failure. Slow continuous ultrafiltration (SCUF) uses a hydrostatic pressure difference (ΔP) between the blood and nonblood sides of the membrane (dotted line within the dialyzer) to remove water and solutes from the plasma by ultrafiltration. Sustained low-efficiency dialysis (SLED) has the additional feature of dialysis fluid passed through the nonblood compartment in a countercurrent direction to the blood flow. Fluid removed from the blood must be replaced by transfer from the interstitial compartment. Failure of this fluid recovery will result in hemodynamic instability.

than 20 kDa) across the filter based on the transmembrane pressure difference (ΔP) between the blood and filtrate sides of the filter. Solute particles that are smaller than the filter pores can be "dragged" across into the ultrafiltrate with plasma water and are in the same concentration in the ultrafiltrate as they are in the prefilter plasma; thus the ultrafiltrate, or volume removed, is isotonic to plasma. The magnitude of water and solute clearance is proportional to the amount of ultrafiltrate formed and can be manipulated by changing the ΔP (i.e., by increasing the blood flow or by applying suction to the filtrate side). In slow continuous UF, the approach favored in HF patients, the amount of ultrafiltrate created is small (generally 2–4 mL/minute) and does not require replacement fluid infusion. The higher the rate of ultrafiltrate formed, the greater the chance of causing hemoconcentration and intravascular volume depletion. The goal is to remove volume at the same rate it can be recovered from the extravascular space. UF is generally used when loss of plasma water (and not solute clearance) is the main goal of therapy [22]. As most patients with HF have no need for solute exchange, this is the preferred and most studied method for mechanical volume removal in HF patients. The development of lower flow UF systems not requiring conventional dialysis catheters but rather large bore IV catheters has also led to potential implementation by nonrenal physicians and staff, also making this technology more broadly applied.

Conversely, the primary purpose of hemodialysis (HD) is solute exchange, not volume removal. In HD, solute transport occurs by passive diffusion and generally favors clearance of small molecules less than ~300 Da in size. The patient's blood and dialysate are separated by a semipermeable membrane with relatively small pores. Electrolytes and other solute particles small enough to pass through membrane pores diffuse freely down their concentration gradients, leading theoretically to equal concentrations on either side of the membrane. A process known as hemodiafiltration combines HD and UF by running dialysate countercurrent to blood flow and applying a pressure gradient across the membrane, yielding both diffusive and convective clearance. The large amount of ultrafiltrate created necessitates replacement fluid infusion.

6. Clinical Trials of UF in Patients with HF

Marenzi et al. studied the effects of UF in 24 patients with refractory CHF admitted to the cardiac intensive care unit for treatment of heart failure [23]. All had signs of volume overload. All patients were treated with UF via a conventional CRRT machine; access was via a double lumen y-shaped catheter in a femoral vein. UF resulted in an average of 4.9 L of fluid removal over a 9-hour period. Symptoms improved, and the response to subsequent diuretic therapy was enhanced, with a reduction in mean dose of diuretic following UF therapy. All patients had continuous hemodynamic data available via a Swann-Ganz catheter as well as invasive arterial pressure via an arterial line. No changes in heart rate, mean blood pressure, or systemic vascular resistance were observed, while mean right atrial pressure, pulmonary capillary wedge pressure, and mean pulmonary artery pressure were reduced. Intravascular volume, as estimated by hematocrit values, remained stable throughout the entire time of treatment despite the large amount of fluid removed overall. A fall in filling pressures with stable hematocit during UF indicated that a proportional volume of fluid was refilling the vasculature from the congested interstitium. This and other uncontrolled studies of UF in HF [24–26] showed that UF could be performed safely and could result in significant volume removal and symptom relief. These studies were performed using conventional renal dialysis equipment, but they led to the development of proprietary systems that were less cumbersome, lacked the need for central venous access, and required less specialized expertise to operate. In order to gain FDA approval for such equipment, randomized trials were required, which led to more robust data regarding the safety and efficacy of UF in patients with HF.

Costanzo et al. examined the utility of UF at a single center in 20 patients admitted with HF, volume overload, and renal insufficiency or diuretic resistance, defined as serum creatinine ≥1.5 mg/dL or furosemide >80 mg/day. Patients must not have had more than one diuretic dose prior to enrollment and must have been enrolled within 12 hours of admission. Major exlusion criteria were hematocrit >40%, systolic BP <85 mmHg, IV vasoactive therapy. Improvement in volume overload after ultrafiltration persisted at 30 and 90 days post discharge and no changes in renal function, electrolytes, or systolic BP were observed at hospital discharge, 30 days, or 90 days post discharge. Symptom scores improved by hospital discharge and these improvements were sustained

at 30 and 90 days. Notably, in the 3 months preceding ultrafiltration, 10 hospitalizations occurred in 9 patients. After ultrafiltration, one patient was admitted within 30 days and two more were admitted between 30 and 90 days for unrelated causes (not complications of UF and not CHF); medications did not change significantly for the 20 patients [27]. This study showed promising durability of the fluid removal by UF in addition to the short-term gains seen in prior studies but was limited by the lack of a control group.

The Relief for Acutely fluid-overloaded Patients with decompensated CHF (RAPID-CHF) trial was the first clinical trial to test the use of a less invasive UF device (System 100, CHF Solutions, Brooklyn Park, MN) that used a single 16-g intravenous catheter in the antecubital fossa rather than central venous access like most conventional devices capable of UF. This study was unblinded. A total of 40 patients were enrolled at 6 sites and randomized 1 : 1 to usual care or UF plus usual care. Inclusion criteria were inpatient admission with primary diagnosis of CHF, 2+ lower extremity edema, and one other sign of increased congestion. Major exclusion criteria included severe stenotic valvular disease, acute coronary syndrome, systolic BP < 90 mmHg at time of consent, hematocrit > 40%, poor peripheral venous access, and severe concomitant disease. All patients in the UF plus usual care group received a single 8-hour course of UF with fluid removal rates determined by the attending physician (up to 500 cc/hr). Diuretics were held during UF; thereafter, diuretics were administered at the discretion of the attending physician. Additional UF courses were allowed at the discretion of the treating physician. The primary endpoint was weight loss assessed at 24 hours after consent was obtained. In this intention-to-treat analysis, 2 patients in the UF group did not receive UF: one due to unsuccessful IV access and one due to inability to withdraw blood from the catheter. There was greater volume removal at 24 hours, but weight loss at 24 hours was not different between the two groups. Heart rate, systolic blood pressure, and electrolytes were not different between the two groups at 24 hours. Global dyspnea and CHF scores were improved in the UF group. UF was well tolerated without clinically significant bleeding or hypotension. There was one catheter site infection requiring a 4-week course of IV antibiotics [28].

The ultrafiltration versus intravenous diuretics for patients hospitalized for acute decompensated heart failure (UNLOAD) trial [29] enrolled a total of 200 patients at 28 centers. Patients were eligible if admitted to the hospital and enrolled within 24 hours with a primary diagnosis of heart failure and with 2 signs of hypervolemia. Exclusions were similar to RAPID-CHF, except that hematocrit had to be less than 45% and serum creatinine had to be at or below 3.0 mg/dL. Study participants were randomized to usual care or usual care plus UF with the System 100 device (CHF Solutions, Brooklyn Park, MN). Total extracorporeal blood volume of this device is 33 mL. All patients received 2 g sodium diet and 2000 mL fluid restriction. Subjects in the usual care group received a minimum intravenous diuretic of twice the before-hospitalization oral daily dose of diuretic. Subjects in the UF group received UF at up to 500 mL/hr with duration and rate left to discretion of treating physician.

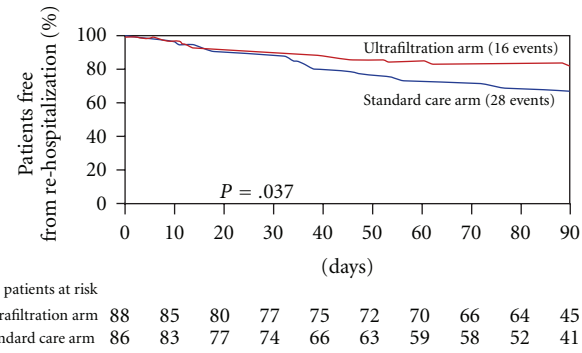

Figure 2: UNLOAD trial, freedom from rehospitalization. Kaplan-Meier estimate for freedom from rehospitalization for heart failure within 90 days of discharge in the ultrafiltration (red line) and usual care (blue line) groups.

Mean serum creatinine was 1.5 mg/dL in both groups; mean BNP was around 1300 pg/mL; mean daily oral dose of loop diuretic (furosemide equivalents) prior to admission was 120 mg. Patients were followed for 90 days or until death. Twenty patients (10%) died by 90 days, 9 in the UF group and 11 in the usual care goup; the study was not powered to detect differences in mortality. The trial met one of its primary efficacy endpoints of improved weight loss at 48 hours, but there was no difference in dyspnea score at 48 hours, the other primary efficacy endpoint. Dyspnea scores did not correlate with other HF-related outcomes. Fewer patients in the UF group required IV vasoactive therapies at 48 hours. With regard to safety, significant elevations in creatinine were similar in both groups; no correlation was found between fluid removed and changes in serum creatinine in either group. Hypotension during the 48hr period following randomization was similarly low in both groups. Fewer bleeding events occurred in the UF group than in the usual care group. Hypokalemia (K < 3.5 mEq/L) was less frequent in the UF group. With regard to secondary endpoints, lengths of stay were similar despite greater fluid loss in the UF group. Oral furosemide doses at discharge were lower in the UF group. Perhaps the most important observation in this study was the decrease in HF hospitalizations, HF rehospitalizations, rehospitalization days per patient, and unscheduled and emergency department visits for HF in the UF group (Figure 2). A subsequent analysis [30] demonstrated that this benefit was consistent relative to those treated with bolus or continuous infusion of intravenous diuretic.

Interestingly, there was a similar net fluid loss between subjects who received continuous infusion and those treated with UF, yet hospitalization rate was still lower in the UF group.

Liang et al. conducted a retrospective review of the experience at the Mayo Clinic using the System 100 device [31]. Patients in this small series had more advanced HF than in RAPID CHF and UNLOAD. A protocol had been developed prospectively in order to identify potential candidates for UF therapy. Ultrafiltration was attempted after failure of diuretic and/or IV vasoactive therapies. The case series included 11 patients with volume overload, systolic BP > 90 mmHg,

and diuretic refractoriness (as per the discretion of treating physician). Three patients had constriction/restriction as the etiology of heart failure, 2 had ischemic cardiomyopathy, and none had nonischemic dilated cardiomypathy. Average serum creatinine was 2.2 mg/dL and average BUN was 69 mg/dL. There were a total of 32 UF treatments that each lasted 8 hours in duration. Of the total UF runs, 75% removed more than 2500 mL of fluid, and 41% removed >3500 mL. There were no serious bleeding complications. Notably, 5 out of 11 patients required dialysis on the same or subsequent admission and 6-month mortality was 55%.

7. Costs

A recently published analysis using data derived from the UNLOAD study indicated that UF was associated with increased cost to society and the hospital versus IV diuretics, but decreased cost to Medicare via a decrease in hospitalizations for HF. The largest costs associated with UF were that of single-use disposable filters required for the proprietary UF system and hospital length of stay [32]. This analysis uses assumptions that tend to increase UF costs above that which might be seen in the real world, such as the use of multiple filters per patient and the use of UF (with similar length of stay and filter use) in a patient readmitted with HF who received UF during their index admission. Some have argued that using a conventional HD machine, which most hospitals already own, would reduce capital expenditure. Filter costs are also significantly lower for these machines. Currently, the disadvantages of such an approach, such as the need for central venous access and trained personnel and the lack of efficacy data supporting the use of conventional dialysis equipment in this manner, outweigh the potential savings [33, 34]. Future maneuvers by Medicare to incentivize hospitals to reduce readmission rates for HF may create a more favorable financial perspective for this technology from a hospital standpoint.

8. Future Directions

At this time, the reason for the increased efficacy of UF relative to diuretics is not clear. It does not appear to be entirely due to the amount of volume removed. Some have postulated that UF reduces levels of inflammatory cytokines, but this has not been proven; UF should not be able to clear such heavy molecules [35]. It is possible that relief of congestion, however it is achieved, will allow greater efficacy of loop diuretics and that UF is simply a more direct way to achieve this; the efficacy of UF is not dependent on renal function. Perhaps the removal of isotonic fluid with UF rather than hypotonic fluid with loop diuretics (i.e., total body sodium removal) is important [36]. Determining the mechanisms by which UF benefits HF patients, particularly those with CRS, may allow us to further elucidate the pathogenesis of CRS itself.

9. Conclusion

Congestion is the primary driver of admissions to the hospital due to HF. Relief of congestion has been traditionally achieved through the use of loop diuretics, but there is concern that these agents, particularly at high dose, may be deleterious in the inpatient setting. In addition, patients with advanced heart failure and the cardiorenal syndrome have diminished response to loop diuretics, making these agents less effective at relieving congestion. Preliminary data using UF, including a fairly large randomized trial, demonstrate no major safety concerns, improved volume removal versus diuretics alone, and decreased hospitalizations for HF at 90 days in selected patients. Major drawbacks are the increased cost of this technology and the invasiveness of the approach. Theoretical concerns, namely a predisposition to infectious and bleeding complications, especially due to the need for systemic heparinization during the procedure, have not been borne out in clinical trials. At the present time based on the available data, UF should be an inpatient therapeutic modality reserved as a second-line approach in diuretic-refractory patients (well above 80 mg/day of oral furosemide as outpatient and poor initial response to high-dose IV diuretics inpatient) with adequate blood pressure.

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SAGE-Hindawi Access to Research
International Journal of Nephrology
Volume 2011, Article ID 168461, 6 pages
doi:10.4061/2011/168461

Review Article

Cardiac Resynchronization Therapy in the Cardiorenal Syndrome

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Received 14 September 2010; Accepted 21 March 2011

Academic Editor: Anjay Rastogi

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The cardiorenal syndrome (CRS) is a complex clinical syndrome in which dysfunction of either the heart or the kidneys affects the functioning of the other organ system. Many therapies used in heart failure have further detrimental effects on renal function. Cardiac resynchronization therapy (CRT) is a relatively new form of device therapy that reduces morbidity and mortality in patients with heart failure. This review will discuss the effects of CRT on renal function in patients with CRS, the impact of baseline renal function on response to CRT, and potential risks associated with CRT in this unique population.

1. Introduction

It has long been recognized that heart failure and renal impairment frequently coexist and that functional decline in one organ system is often associated with a parallel decline in the other. In the past decade, the term "cardiorenal syndrome" (CRS) has been used to describe this complex process. Although initially described as a state in which "therapy to relieve congestive symptoms of heart failure is limited by further decline in renal function," [1] newer definitions and classification schemes have tried to capture the bidirectional feedback processes and complex pathophysiological interactions which exist between the heart and the kidneys. The CRS is not simply renal dysfunction as a result of a low-flow state induced by depressed cardiac function but rather a complex clinical syndrome in which hemodynamic abnormalities, neurohormonal activation, inflammation and oxidative stress cause dysfunction of both organ systems through symbiotic pathways [2]. In recognition of these complex interactions, Ronco and colleagues recently presented a classification system for CRS (Table 1) [3]. It is well recognized that an individual can simultaneously exhibit the pathophysiological characteristics of multiple types of CRS and that this classification scheme is not meant to discretely categorize patients into subgroups.

As our understanding of the underlying mechanisms of CRS has progressed, so has our recognition of the magnitude of the problem and of its prognostic significance. In ADHERE, a national registry of more than 100 000 nonselected patients admitted to hospital with acute decompensated heart failure, 31% of patients had chronic renal insufficiency, 20% had serum creatinine levels >2.0 mg/dL, and 5% were receiving dialysis [4]. Furthermore, even moderate renal insufficiency is associated with increased mortality in patients with symptomatic or asymptomatic LV dysfunction [5] or heart failure with preserved systolic function [6]; creatinine clearance predicts mortality independent of ejection fraction or functional capacity [7]. In the Studies of Left Ventricular Dysfunction (SOLVD) trials, decline in GFR was independently associated with increased risk of mortality in patients with heart failure, regardless of baseline renal function [8]. In patients admitted to hospital with heart failure, worsening renal function during admission predicts in-hospital mortality, complications, and longer duration of hospitalization [9]. On the other hand, cardiovascular disease including heart failure is common in patients with renal failure, and cardiovascular death is the leading cause of mortality among renal cohorts [10]. The risk of cardiovascular events increases rapidly with declining GFR [10].

Table 1: Classification system of cardiorenal syndrome (CRS).

	Description	Examples of inciting events	Examples of consequences
Type 1 CRS	Acute HF leads to AKI	(i) ADHF (ii) Cardiogenic shock (iii) Hypertensive pulmonary edema	(i) AKI (ii) Diuretic resistance
Type 2 CRS	Chronic HF leads to progressive CKD	(i) Chronic systolic HF (ii) Chronic HF with preserved systolic function	(i) Progressive CKD
Type 3 CRS	Acute renal dysfunction leads to acute cardiac dysfunction	(i) AKI (ii) Glomerulonephritis	(i) ADHF (ii) Acute HF (iii) Ischemia (iv) Arrhythmia (v) Decreased CO
Type 4 CRS	CKD leads to chronic cardiac dysfunction and/or increased risk of CV events	(i) CKD	(i) Systolic dysfunction (ii) LVH (iii) Diastolic dysfunction (iv) Coronary calcification (v) Decreased coronary perfusion
Type 5 CRS	Systemic disorder leads to cardiac and renal dysfunction	(i) Sepsis (ii) Vasculitis (iii) Diabetes (iv) Amyloidosis	(i) Acute HF (ii) Chronic HF (iii) AKI (iv) CKD

Adapted from [3]. ADHF: acutely decompensated heart failure; AKI: acute kidney injury; CKD: chronic kidney disease; CO: cardiac output; CV: cardiovascular; HF: heart failure; LVH: left ventricular hypertrophy.

Pharmacologic therapies for heart failure are often limited by adverse effects on renal function. Although angiotensin converting enzyme inhibitors (ACEIs), angiotensin II receptor blockers (ARBs), and aldosterone antagonists all prolong survival in heart failure patients [11–16], they are relatively contraindicated in patients with unstable renal function and may cause acute declines in glomerular filtration rate (GFR). Furthermore, most trials evaluating the efficacy of these therapies in heart failure excluded patients with evidence of significant renal dysfunction. Similarly, loop diuretics, which have never been demonstrated to improve outcomes in heart failure, are the mainstay of symptomatic treatment for volume overload and are frequently associated with a decline in renal function. Moreover, there is emerging data to suggest an increase in mortality with the use of these agents [17].

Pharmacological therapy centered on neurohormonal blockade remains first-line therapy for the majority of patients with systolic left ventricular dysfunction [18–20]. However, for those with advanced functional symptoms and depressed LV function, despite optimization of evidence-based HF therapies, cardiac resynchronization therapy may provide additional morbidity and mortality benefits.

In up to 30% of patients with heart failure, intraventricular conduction delay produces mechanical dyssynchrony, resulting in inefficient ventricular contraction and negative remodeling. Biventricular pacing may restore synchronous contraction of the interventricular septum and LV free wall with resultant improvement in LV geometry and function. Cardiac resynchronization therapy (CRT) improves symptoms, functional classification, echo parameters (including left ventricular ejection fraction and end-systolic volume, mitral regurgitation severity, and interventricular mechanical delay) and prolongs survival in patients with intraventricular conduction delay (QRS complex width >120 ms), LVEF ≤35%, and New York Heart Association (NYHA) class III-IV symptoms [21–24]. As such, each of the major societies' guidelines recommends CRT in this patient population [18–20].

2. Effect of Cardiac Resynchronization Therapy on Renal Function

Our understanding of the impact of CRT on renal function in patients with CRS has been limited by the exclusion of patients with renal failure from many randomized, clinical trials. The MIRACLE trial was a double-blinded, randomized and placebo-controlled trial in which patients with NYHA class III or IV symptoms, QRS duration ≥130 ms, LVEF ≤35%, and LV end-diastolic diameter ≥55 mm underwent implantation of a CRT device and were randomized to device on (treatment group) or device off (control group) [23]. Patients were excluded from the trial if their serum creatinine was >3.0 mg/dL. In a retrospective analysis of the MIRACLE trial [25], Boerrigter and colleagues assessed the effect of CRT on estimated GFR (eGFR) in patients falling into three categories: normal or increased eGFR (≥90 mL/min/1.73 m^2), mildly reduced eGFR (60 ≤ eGFR

< 90 mL/min/1.73 m^2), and moderately reduced eGFR (30 ≤ eGFR ≤ 60 mL/min/1.73 m^2). CRT significantly improved eGFR compared to control in patients with moderately reduced eGFR, but it had no effect in patients with normal, increased or mildly decreased eGFR. In patients with a baseline eGFR ≤ 60 mL/min/1.73 m^2, there were fewer patients in the treatment group than in the control group who experienced worsening renal function.

Similar observations have been made in nonrandomized studies. Adelstein and colleagues demonstrated that compared to standard defibrillator (SD) therapy, CRT-defibrillator (CRT-D) implantation was associated with improved renal function, as well as improved survival and improved LV systolic function on echocardiogram, in patients with baseline GFR 30–59 mL/min/1.73 m^2 [26]. Patients with GFR ≤30 mL/min/1.73 m^2 showed improved renal function but not improved survival after CRT-D implantation, while renal function deteriorated in those with GFR ≥ 60 mL/min/1.73 m^2. Although the authors did not specifically address the reason for the decline in this latter group, they did hypothesize that preserved renal function may be a surrogate for relatively compensated heart failure. The decline in GFR in this group could reflect the risks associated with device implantation (see below) or simply the natural progression of the cardiorenal syndrome, superimposed on minimal hemodynamic benefit of CRT at the level of the kidney. In another study, patients who were "responders" to CRT (those who demonstrated any improvement in LVEF after CRT implantation) showed mild improvement in GFR, while those who were "nonresponders" showed a decline in renal function [27]. As in other studies, this effect was even more pronounced in patients with baseline eGFR < 60 mL/min. Perhaps as a result of this, prescription of ACEI and ARB therapy increased in "responders", while it decreased in "nonresponders". ACEI and ARB therapies have a well-established survival benefit in HF patients, regardless of GFR [28], and the ability to offer them to patients may contribute to the overall benefit of CRT. In a similar study by Fung and colleagues, patients with a 10% reduction in LV end-systolic volume (LVESV) after CRT implantation maintained stable renal function, while those who failed to show improvement in LVESV had a significant decline in GFR [29]. From the limited data available, it appears that CRT-implantation, particularly when associated with improved LV function, is associated with improved renal function in patients with baseline renal impairment.

The proposed mechanisms by which CRT may improve renal function are based on our current understanding of the pathophysiology of renal failure in the broader context of the cardiorenal syndrome. Historically, it was believed that renal failure was a result of renal hypoperfusion, in turn, due to reduced cardiac output and diuretic-induced intravascular volume depletion [30]. More recently, it has been recognized that elevated central venous pressure may play an equally or even more important role in the progression of renal failure among HF patients. Increased right-sided filling pressures ultimately lead to renal congestion, reduced renal perfusion pressure, and direct ischemic injury as a result of increased interstitial pressure in the renal medulla [31, 32]. CRT may mitigate these processes, in part due to improved cardiac output [24, 33] and increased mean arterial pressure [22, 34]. It also leads to reductions in central venous pressure [34], and therefore, may improve renal perfusion by improving both "forward" and "backward" cardiac failure.

Neurohormonal activation may also play a role in the pathogenesis of the cardiorenal syndrome. Heart failure is clearly associated with activation of the sympathetic nervous system (SNS), the renin-angiotensin-aldosterone system (RAAS) and cardiac natriuretic peptides. Although the specific roles of these messenger pathways at the level of the kidney are still being elucidated, there is indirect evidence to suggest that interruption of both renal sympathetic innervation and of RAAS activation may produce beneficial renal effects [2]. Although catecholamine levels are not reduced with CRT [25], sympathetic nerve activity is diminished [35, 36], suggesting decreased adrenergic tone with CRT. In addition, long-term CRT is associated with reduced RAAS activity and stabilization of NT-proBNP levels in patients who demonstrate reverse LV remodeling but not in those who do not reverse remodel [37]. Taken together, these findings suggest that in addition to the benefits achieved through direct hemodynamic effects, CRT may positively impact renal function by interrupting deleterious neurohormonal pathways that are hypothesized to be culprit in the pathophysiology of heart failure.

3. Effect of Renal Dysfunction on Response to Cardiac Resynchronization Therapy

Baseline renal function may predict response to CRT both in terms of mortality and other clinically important endpoints. Shalaby and colleagues retrospectively studied 330 patients receiving CRT and found that those in the highest tertile of serum creatinine (1.4–3.0 mg/dL) had the highest mortality rate (28.7% versus 14.0% in other tertiles, $P = .008$) as well as the highest rate of the combined endpoint of mortality and heart failure hospitalization (41.6% versus 21.5%, $P = .001$) [38]. When studied as a continuous variable, each 0.1 mg/dL increase in creatinine was associated with an 11% increase in mortality and a 7% increase in the combined endpoint. Several other studies have similarly demonstrated that renal function is an independent predictor of survival [39, 40] and survival-free from heart transplantation or ventricular assist device (VAD) [41, 42] in patients receiving CRT and that the mortality benefit achieved with CRT-D over standard defibrillator therapy may be attenuated or lost at low eGFR [26]. The change in GFR following CRT implantation may also predict long-term outcomes. Fung and colleagues were able to demonstrate that patients whose renal function remained stable at 3 months after CRT implantation had lower all-cause mortality and lower combined mortality and HF hospitalization than those whose renal function declined [29].

Interestingly, in the same study [29], the group of patients who responded to CRT as characterized by LV reverse remodeling had worse renal function at baseline than the group who did not respond. Other investigators have

shown that LV mass may decrease and 6-minute walk distance may increase after CRT implantation in patients with eGFR $< 60\,\text{mL/min/1.73 m}^2$ to a greater extent than in patients with eGFR $\geq 60\,\text{mL/min/1.73 m}^2$ [25]. These findings may reflect the fact that while renal insufficiency is associated with a poor overall prognosis that cannot be completely reversed with current therapies, patients with reduced GFR have the most to gain from reversal of the neurohormonal and hemodynamic disturbances associated with heart failure.

4. Adverse Renal Consequences of Cardiac Resynchronization Therapy: Contrast-Induced Nephropathy

While there are many potential benefits to CRT in patients with the CRS, no procedure is entirely without risks. Implantation of the left ventricular lead typically requires contrast administration in order to locate the ostium of the coronary sinus and to define coronary venous anatomy. Contrast-induced nephropathy (CIN), typically defined as an elevation in serum creatinine of ≥25% following intravenous contrast administration, is frequently reported after other procedures such as coronary angiography and is associated with adverse outcomes including mortality [43]. Major risk factors for CIN include preexisting renal dysfunction, diabetes mellitus, congestive heart failure, volume of contrast used, female sex, and mean arterial pressure <100 mmHg [43–45]. In one study, CIN occurred in 10 of 68 patients (14%) undergoing CRT implantation; three of these patients required hemofiltration, and one died [46]. The incidence of CIN was higher (63%) in patients with baseline creatinine ≥200 umol/L, and CIN was associated with longer duration of hospital stay (19 versus 4 days, $P < .01$). Epicardial LV lead placement, via an open surgical procedure, has been proposed as an alternative in patients with renal insufficiency [47]. Although this approach is more invasive than catheter-based transvenous lead placement and is associated with longer ICU stay, it avoids the use of intravenous contrast dye and may be equally effective [48].

5. Conclusions

CRS is an important clinical syndrome affecting a large proportion of patients with primary heart failure, primary kidney disease, or both and is associated with a poor prognosis. Many pharmacologic therapies used in the management of heart failure have the potential to worsen renal function, particularly in patients who already have baseline renal insufficiency. Cardiac resynchronization therapy is an additional tool which can be used to manage this complex patient population; CRT may have the added benefit of specifically targeting many of the underlying pathophysiological mechanisms which are felt to be central to the propagation of CRS and data suggest that it may also be an effective means of treating heart failure while improving renal function in this population. CRS patients are at particularly high risk of mortality and other adverse events and they may remain at higher risk than isolated HF patients when treated with CRT, but the limited amount of available data suggests that they are still able to obtain some benefit from this therapy. More studies of CRT in this specific population, and in the individual subtypes of CRS, as well as the inclusion of CRS patients in large clinical trials, will allow a greater understanding of its impact on this important disease.

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SAGE-Hindawi Access to Research
International Journal of Nephrology
Volume 2011, Article ID 652967, 8 pages
doi:10.4061/2011/652967

Review Article

Cardiorenal Syndromes and Sepsis

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Received 13 September 2010; Revised 25 January 2011; Accepted 28 January 2011

Academic Editor: C. Ronco

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The cardiorenal syndrome is a clinical and pathophysiological entity defined as the concomitant presence of renal and cardiovascular dysfunction. In patients with severe sepsis and septic shock, acute cardiovascular, and renal derangements are common, that is, the septic cardiorenal syndrome. The aim of this paper is to describe the pathophysiology and clinical features of septic cardiorenal syndrome in light of the actual clinical and experimental evidence. In particular, the importance of systemic and intrarenal endothelial dysfunction, alterations of kidney perfusion, and myocardial function, organ "crosstalk" and ubiquitous inflammatory injury have been extensively reviewed in light of their role in cardiorenal syndrome etiology. Treatment includes early and targeted optimization of hemodynamics to reverse systemic hypotension and restore urinary output. In case of persistent renal impairment, renal replacement therapy may be used to remove cytokines and restore renal function.

1. Introduction and Definitions

The cardiorenal syndromes (CRSs) are relatively new clinical and pathophysiological entities which have been defined as the concomitant presence of renal and cardiovascular dysfunction [1]. According to Ronco and colleagues, five subtypes of the syndrome exist [2]. Type 1 CRS is defined as acute renal failure secondary to an abrupt worsening of cardiac function, for example, cardiogenic shock or acute congestive heart failure. Type 2 CRS describes a progressive and permanent chronic kidney dysfunction which is caused by chronic worsening in cardiac function, for example, chronic congestive heart failure. Type 3 CRS consists of an acute cardiac dysfunction (e.g., heart failure, arrhythmia, and ischemia) secondary to an abrupt worsening of renal function (e.g., acute kidney ischemia or glomerulonephritis). Type 4 CRS describes a state of chronic kidney disease (e.g., chronic glomerular disease) causing a decreased cardiac function, cardiac hypertrophy, and/or increased risk of adverse cardiovascular events. Type 5 CRS reflects concomitant cardiac and renal dysfunctions in the setting of a systemic condition which primarily affect both organs (e.g., diabetes mellitus and sepsis) [2].

The simultaneous presence of acute cardiovascular and renal alterations in septic patients is defined as septic cardiorenal syndrome. Cardiac and renal dysfunctions are often part of the clinical picture of severe sepsis and septic shock [3]. Following classification of Ronco, sepsis may represent an acute cause of Type 5 cardiorenal syndrome [2].

Renal dysfunction can be observed during severe sepsis and is part of the clinical picture of septic shock and multiple organ failure [1]. Acute renal failure is defined as an acute worsening of renal function based on increasing levels of serum creatinine or reduced urinary output [4]. Following RIFLE criteria, acute kidney injury (AKI) ranges from minor alterations in renal function to indication for renal replacement therapy [5]. AKI is common among critically ill patients, and sepsis and septic shock account for more than 50% of cases [6–8]. As suggested by Bellomo et al., sepsis-induced inflammatory injury of microvessels, hypotension and hypoperfusion during septic shock may play a causative role on development of AKI [2].

Moreover, a high proportion of septic patients develop left ventricular systolic impairment, either with or without involvement of other organs [9]. Cardiac dysfunction in sepsis is characterized by decreased contractility, impaired ventricular response to fluid therapy, and, in some patients, progressive ventricular dilatation. Current data support a complex underlying pathophysiology with a host of potential pathways leading to myocardial depression [10]. This is

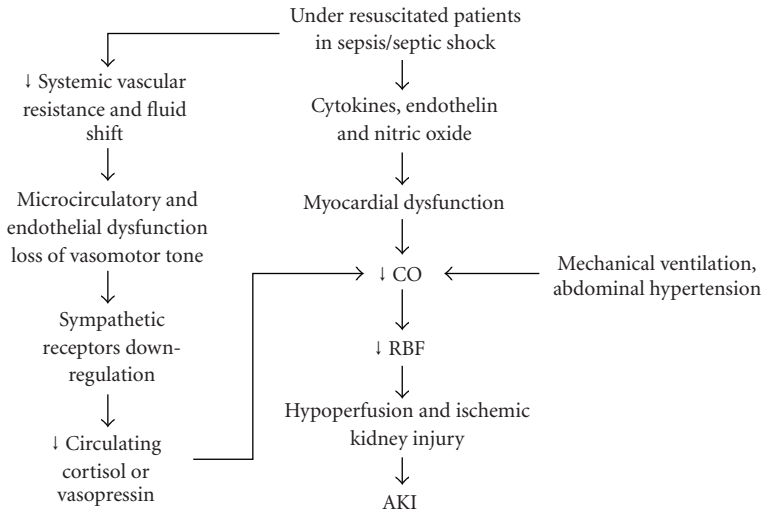

Figure 1: Hemodynamic alteration in underresuscitated sepsis patients (see text for details).

a well-described but poorly understood phenomenon in which microvascular alterations, autonomic dysregulation, metabolic changes and inflammatory signalling have all previously been hypothesized as potential mechanism for cardiac dysfunction [11].

Despite several studies investigate the incidence of AKI in sepsis or pathophysiology of septic cardiomyopathy, data are lacking about concomitant renal and cardiac injury in severe sepsis or septic shock. The purpose of this paper is to review pathophysiology and clinical aspects of septic cardiorenal syndrome in light of the actual clinical and experimental evidence.

2. Epidemiology

Incidence of sepsis in Europe is 350 new cases on 100.000 inhabitants per year [12] and its prevalence is high among all hospitalised patients (one–third) and, mostly, among those admitted to ICUs. Indeed, 10%–15% of all patients admitted to ICUs develop septic shock [13].

Moreover, numerous studies have shown septic AKI to be highly common among the critically ill, ranging from 16% to 41% [14, 15] of patients with severe sepsis and septic shock [16]. Patients with septic AKI are often older, have a higher prevalence of comorbidity and are more severely ill than those with nonseptic AKI [17].

On the other side, myocardial dysfunction may occur in up to 20% of patients with septic shock. Patients with myocardial dysfunction have significantly higher mortality (70%) compared to septic patients without cardiovascular impairment (20%) [18]. Biomarkers such as cardiac troponin T and I have been studied in sepsis. Elevations in cardiac troponin T and I correlate with the presence of left ventricular systolic dysfunction [19–21] and 30–80% of patients with severe sepsis and septic shock show NSTEMI on ECG with serum troponin values above the normal range. Furthermore, levels of cardiac troponin also correlate with duration of hypotension and intensity of vasopressor support in patients with septic shock [22, 23]. The potential role of B-type natriuretic peptide (BNP) as a biomarker has also been evaluated in septic patients. Recent studies have shown increased levels of BNP in patients with severe sepsis and septic shock [24]. Levels of BNP correlate with the degree of myocardial dysfunction and mortality [10]. More recently, echocardiography has been utilized to define heart dysfunction in severe sepsis and septic shock. In a longitudinal study with transthoracic echocardiography in septic shock patients, left ventricular ejection fraction was significantly depressed in all patients [25], resulting in severe reductions in left ventricular stroke volume. Of interest, these abnormalities were more pronounced in survivors than in nonsurvivors.

3. Hemodynamic Alterations

Type 1 cardiorenal syndrome is defined as an acute cardiac dysfunction which leads to acute renal failure, that is, acute cardiorenal syndrome [1]. Traditionally, septic AKI has been seen as the consequence of renal hypoperfusion and reduced renal blood flow, that is, an ischemic kidney injury, which occurs during severe sepsis, septic shock or multiple organ failure [26]. During early phases of septic shock, and in underresuscitated patients, systemic vasodilation and fluid shift reduce cardiac preload, thus reducing cardiac output. This may decrease renal blood flow (RBF) [27] and reduce glomerular filtration rate, leading to prerenal azotemia [26]. If renal hypoperfusion continues, ischemic injury to kidneys occurs, and AKI develops (see Figure 1).

Sepsis and septic shock are also characterized by a variable degree of myocardial dysfunction, which is linked to multiple factors. Experimental studies on laboratory animals show the role of mediators such as cytokines, endothelin [28], and nitric oxide [29] on myocardial cells and mitochondrial dysfunction [30] as possible mechanisms involved in this phenomenon [10]. Moreover, ventilation with positive end-expiratory pressure required by patients with severe

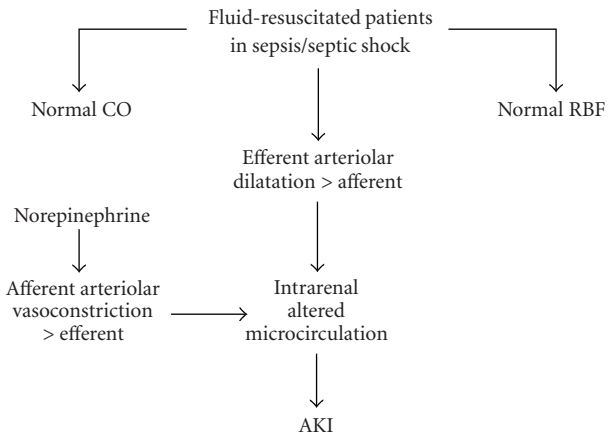

Figure 2: Hemodynamic alteration in fluid-resuscitated sepsis patients (see text for details).

sepsis or septic shock may contribute to intrarenal hemodynamic alterations. In a prospective experimental study on humans, Jacob et al. [31] evaluated the effects of increasing intrathoracic pressure with positive end-expiratory pressure on renal blood flow. High values of PEEP were associated to decreased mean arterial pressures, cardiac output and urinary output. PEEP-induced decrease in urinary output was correlated to renal perfusion pressure decrease. Furthermore, as demonstrated by Peng et al. [32] in bacteremic dogs, the presence of intrabdominal hypertension can adversely affect cardiac output and contribute to renal hypoperfusion (see Figure 1).

As a consequence of all these alterations, renal blood flow, and oxygen delivery decrease [33]. There is evidence that early goal directed hemodynamic optimization has positive effects on survival of septic patients, and restoring and maintaining good organ perfusion and oxygenation may account for this effect [34]. To preserve or restore renal function, a judicious, targeted use of fluids and vasopressors is recommended [35]. Recovery of renal function and diuresis herald a general improvement in systemic oxygen delivery and consumption which is of good prognostic value [26].

4. Microvascular Alterations

Sepsis-induced alterations of microcirculation are ubiquitous and are linked to both cardiovascular and renal failure [36]. Several studies [37–39] suggest that systemic vasodilation leads to reduced tissue oxygen delivery (DO_2), with progressive mitochondrial dysfunction/disruption and cytopathic hypoxia, which can cause organ failure [40]. In early phases of severe sepsis/septic shock, reduction in renal blood flow is associated to arterial hypotension, fluid shift, hypovolemia, and low cardiac output, that is, ischemic AKI (see above). Old experimental studies showed that renal blood flow was reduced in endotoxemic rats [41]. However, in fluid-resuscitated septic patients with AKI, cardiac output is normal or high and glomerular filtration rate can be low despite normal or high renal blood flow [26] (see Figure 2). This is because glomerular filtration rate is related to glomerular filtration pressure, which relies on the balance between afferent and efferent arteriolar tone. During sepsis glomerular efferent arteriola dilates more than afferent, thus reducing glomerular filtration pressure [42] (see Figure 2). Vasopressors, such norepinephrine, are employed to treat arterial hypotension during septic shock [3]. Besides increasing renal blood flow through a restored renal perfusion pressure, norepinephrine increases glomerular filtration rate acting on the afferent-efferent arteriolar tone, with a more intense vasoconstrictive effect on efferent arteriola [43]. In experimental models of septic shock in ewes, Langenberg at al. suggest that recovery from AKI has been associated to an increase in renal vascular resistance [44]. While a judicious use of vasopressors may contribute to restore glomerular filtration pressure and renal function, overzealous use of norepinephrine may also lead to afferent arteriolar vasoconstriction which reduces glomerular blood flow and filtration pressure. Moreover, the increased circulating level of catecholamines, which is part of the neurohormonal stress response to sepsis, results in sustained angiotensin II release, which can adversely affect renal perfusion [45]. All these effects contribute to cause and maintain renal dysfunction.

5. Organ "Crosstalk"

Type 3 cardiorenal syndrome is defined as AKI leading to acute cardiac dysfunction, that is, acute renocardiac syndrome [1]. Indeed, a marked left ventricular dilatation has been shown in experimental models of bilateral renal ischemia in mouse [46]. Three mechanisms may be involved, that is, fluid overload, myocardial inflammation, and reduced cytokines clearance.

During sepsis, renal hypoperfusion brings to progressive worsening fluid accumulation which can adversely impact on myocardial function, further decreasing cardiac output and renal blood flow, and initiating a vicious cycle between renal and cardiovascular dysfunction. Cardiac filling pressures increase, as does myocardial work load and oxygen consumption [27]. Sympathetic burden on cardiovascular system can be already high due to neurohormonal response to stress and use of vasopressors. Thus, acute cardiac dysfunction can precipitate, with further reduction in renal blood flow (see Figure 3).

The ischemic injury to kidneys may contribute to "long distance" organ damage in sepsis [47]. During ischemic renal injury in mouse, Kelly demonstrated increased myocardial levels of mRNA for TNF-alpha, IL-1, and ICAM-1, resulting in increased leukocyte infiltration and activation [46]. The same inflammatory damage could occur during sepsis-induced ischemic renal injury and lead to myocardial cells apoptosis and fibrosis [46], with progressive myocardial dysfunction. Indeed, sepsis-associated myocardial dysfunction can be prevented by anti-TNF-alpha antibodies or receptor antagonists [46] and cytokines removal by the mean of high volume hemofiltration has shown beneficial effects on cardiac function and hemodynamics in septic patients [48]. Knotek et al. showed the effect of TNF neutralization on renal function by a TNF-soluble receptor in the endotoxemic mice,

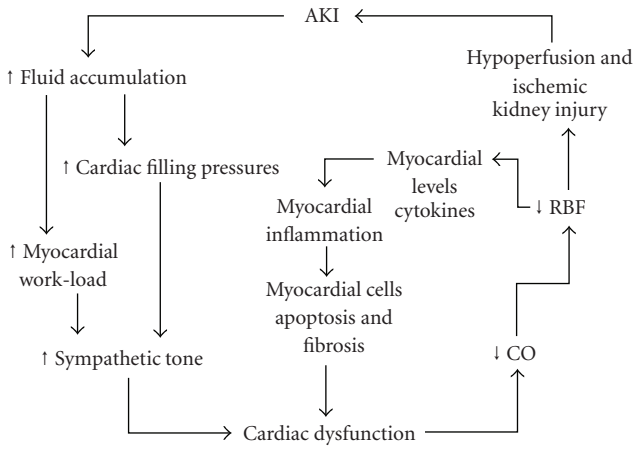

Figure 3: Organ "crosstalk" (see text for details).

demonstrating the role of TNF in the early renal dysfunction (16 h) [49].

Finally, AKI itself can result in reduced clearance of systemic, circulating cytokines, which can worsen myocardial inflammatory injury. Expressions of cytokines and leukocyte adhesion molecules, and expression of membrane ion and water-channel protein in distant organs, including the cardiovascular systems, are altered during AKI [50].

6. Organ Inflammation

Type 5 cardiorenal syndrome is defined as a systemic insult which leads to concomitant renal and cardiac dysfunction [1]. An inflammatory pathogenesis can be a common key feature for both the kidneys and cardiovascular system during sepsis, leading to cell ultrastructural alterations and organ dysfunction [47, 51]. In a prospective observational study on 1836 hospitalized patients with community-acquired pneumonia, Murugan at al. demonstrated that renal injury and AKI associated to pneumonia recognize an inflammatory pathogenesis [52]. In this paper, outcome of renal injured patients was strictly related to IL-6 plasma concentration [52]. Endotoxin mediated release of TNF-α may affect simultaneously kidneys and cardiovascular system [53]. In the endotoxemic mice, Knotek et al. suggested that TNF-alpha can be also released by glomerular mesangial cells in response to Gram-negative endotoxin and act promoting leukocyte migration and activation in renal tissue, thus inducing septic AKI [49]. In an experimental model of cultured human proximal tubular cells, Jo et al. demonstrated that endotoxin, TNF-α and other pro-inflammatory cytokines induced apoptosis of renal tubular cells [54].

Inflammation has a well-defined role in inducing hypotension in septic patients [55]. Proinflammatory cytokines, such as TNF-α, IL-1 and IL-6, may also induce myocardial inhibition [28–30]. Sepsis-induced release of nitric oxide and increased production of peroxynitrite also depress myocardial function. Tavernier et al. studied contractile function of cardiac myocytes isolated 12 h after induction of endotoxemia in rats. Authors demonstrated that cardiomyocytes from LPS-injected rats had depressed twitch shortening compared with control cells and that contractile depression was unaffected by inhibitors of nitric oxide synthase [56]. Moreover, in a retrospective analysis of human autoptic specimens, Kooy et al. demonstrated the formation of peroxynitrite within the myocardium during sepsis, suggesting a role for peroxynitrite in inflammation-associated myocardial dysfunction [57]. On the other hand, renal hypoperfusion during sepsis-induced low cardiac output state leads to myocardial inflammation, apoptosis, and fibrosis (see above) [46].

7. Changes in Microvascular Permeability

Sepsis induced inflammatory response causes diffuse alteration in microcirculation [58]. Microcirculatory dysfunction contributes to altered tissue perfusion and oxygen delivery/consumption, thus contributing to septic shock and renal failure, that is, type 5 CRS [2]. Enhanced endothelial expression of leukocyte adhesion molecules and alteration of endothelial cells contacts can increase microvascular permeability, thus leading to extravascular fluid shift, fluid overload, hypovolemia, reduced venous return, and low cardiac output. Interstitial edema further reduces oxygen delivery to tissues, and fluid overload is an independent risk factor for mortality among septic patients with AKI [59]. At renal level, increased expression of adhesion molecules is associated to enhanced leukocytes migration, which may lead to endothelial cells injury and detachment, as shown by Paller during experimental renal ischemic injury in rats [60]. Altered glomerular permeability results in microalbuminuria [61].

Glycocalix is a thin (0.5–1.2 μm) molecular structure which lies beneath capillary endothelial cells and regulates capillary flow, leukocytes adhesion and migration, platelets adhesion and coagulation [62]. It is important in regulating capillary permeability. Several studies suggest that glycocalix disruption may contribute to increased permeability, both in systemic and renal microcirculation [63, 64], increasing leukostasis, microthrombosis, fluid shift, and interstitial edema. This leads to reduced oxygen delivery to tissues and organ failure [65].

8. Clinical Features

Septic cardiorenal syndrome is a clinical diagnosis. Its definition implies concomitant presence of acute hemodynamic and renal dysfunction in a patient with sepsis. Sepsis is defined by two or more signs among tachycardia, tachypnea, leukocitosis/leukopenia, and fever/hypothermia [3]. In severe sepsis one acute organ dysfunction is present, usually cardiovascular or renal. Arterial hypotension, an arterial systolic pressure below 95 mmHg, or 40 mmHg below the usual in previously hypertensive patients, is typically observed when hemodynamic dysfunction becomes manifest [3]. Myocardial dysfunction may be present as well, with reduced myocardial contractility and left ventricular ejection fraction [66]. Serum cardiac troponins and B-type natriuretic peptide may be elevated as they are sensitive and specific biomarkers of myocardial damage [67]. As suggested by Ammann et al.,

in septic, critically ill patients, serum troponin I levels may increase in absence of coronary artery disease, as a marker of myocardial dysfunction, and its levels correlate with mortality rates [68, 69]. However, when AKI is present, serum troponin may be elevated due to underlying renal dysfunction [70], as demonstrated by Musso and Colleagues in patients with chronic renal failure [71].

Typically, reduced urine output and increased serum creatinine are considered as clinical signs of acute renal failure in clinical practice [72], and they were included in RIFLE criteria [6, 7]. However, serum creatinine lacks of sensitivity since its plasma levels rise only after half of the renal function is lost [73]. Alternative biomarkers for AKI include serum interleukin-18 and urinary kidney injury molecule-1, cystatin-C, and beta-2 microglobulin [74]. In an observational cohort study, Soni et al. demonstrated that neutrophil gelatinase associated lipocallin (NGAL) acted as a sensitive biomarker for AKI, particularly for septic AKI [72]. In a series of 143 critically ill children, serum NGAL was a sensitive marker for AKI during systemic inflammatory response syndrome (SIRS) and septic shock [75]. Its plasma level correlated with severity of the syndrome and showed some specificity for septic shock [75]. Recently, Bagshaw et al., in a prospective observational study, demonstrated that patients with septic AKI had higher levels of plasma and urine NGAL compared to those with nonseptic AKI [76]. Interestingly, NGAL, with interleukin-1 receptor antagonist and protein C, was recently included among plasma biomarkers which could allow an early diagnosis of septic shock and multiple organ failure in patients admitted to emergency department with suspected sepsis [77].

9. Treatment

Removal of infective source, antibiotic therapy and supportive care are all indicated in presence of sepsis-associated cardiovascular and renal dysfunction [3]. Early hemodynamic optimization was efficacious in reducing mortality among critically ill septic patients [34]. Fluids are administered to restore intravenous volume and vasopressors or inotropic drugs are infused to revert systemic vasodilation and myocardial depression. Their use should be targeted to specific and clinical end points, such as mean arterial pressure or central venous oxygen saturation [78]. Increased venous return and increased myocardial contractility lead to increased cardiac output. This may contribute to improved renal blood perfusion and glomerular filtration, thus restoring urinary output [79]. Loop diuretics, such furosemide, are often used to increase and/or maintain urinary output during septic AKI, but their efficacy has been questioned and their use may be detrimental on renal function [76]. If oliguria is present, fluid administration should be judicious as volume overload and tissue edema may develop, contributing to impaired lung function and tissue oxygenation [79]. Once systemic cardiovascular optimization has been obtained, a shift towards more restrictive fluid administration strategies has been advocated to reduce AKI associated complications [76]. When renal function is persistently reduced despite hemodynamic optimization, continuous renal replacement therapy (CRRT) is indicated [80]. Worsening serum creatinine levels, volume overload, metabolic acidosis, and electrolytic alterations usually mandate CRRT. CRRT, and particularly high volume venovenous hemofiltration, may also modulate inflammatory response during sepsis, acting through cytokine removal or adsorption, even though the exact mechanism is still debated [81]. However, definite evidence of CRRT for nonrenal indications is still lacking, venovenous hemofiltration can improve hemodynamics and revert sepsis-associated hypotension [82]. Thus, in patients with septic cardiorenal syndrome, CRRT may not be only supportive, but also contribute to reverse common causative factors.

10. Conclusions

Cardiorenal syndrome is common among patients with severe sepsis and septic shock. Pathogenesis is related to multiple factors affecting both the heart and kidneys, including shock related renal hypoperfusion, systemic and intrarenal vasodilation, ubiquitous inflammatory injury to tissues, endothelial dysfunction, and altered capillary permeability. Injured kidneys can further impair myocardial function, thus contributing to maintain shock and organ hypoperfusion. Early and targeted optimization of hemodynamics is indicated to reverse systemic hypotension and to restore urinary output. In case of persistent renal impairment, venovenous hemofiltration may be used to remove cytokines and restore renal function.

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SAGE-Hindawi Access to Research
International Journal of Nephrology
Volume 2011, Article ID 634903, 7 pages
doi:10.4061/2011/634903

Review Article

Cardiorenal Syndrome Caused by Heart Failure with Preserved Ejection Fraction

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Received 25 August 2010; Accepted 3 January 2011

Academic Editor: Claudio Ronco

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Since cardiorenal dysfunction is usually secondary to multiple factors acting in concert (and not only reduced cardiac output) in the present paper we are going to focus on the interrelationship between heart failure with normal ejection fraction and the development of cardiorenal syndrome. The coexistence of renal impairment in heart failure with preserved ejection fraction (CRS type 2 and 4) is common especially in older females with hypertension and/or diabetes. It can be hypothesized that the incidence of this disease association is growing, while clinical trials enrolling these patients are still lacking. The main mechanisms thought to be involved in the pathophysiology of this condition are represented by the increase of intra-abdominal and central venous pressure and the activation of the renin-angiotensin system. Differently from CRS in heart failure with reduced ejection fraction, the involvement of the kidney may be under-diagnosed in patients with heart failure and preserved ejection fraction and the optimal therapeutic strategy in this condition, though challenging, is far to be completely elucidated. Further studies are needed to assess the best therapeutic regimen in patients with renal dysfunction (and worsening) and heart failure and preserved ejection fraction.

1. Introduction

The cardiorenal syndrome (CRS) is a complex disease in which heart and kidney are simultaneously affected and their deleterious effects are reinforced in a feedback cycle, with accelerated progression of renal and myocardial damage [1–3].

The incidence of heart failure in the United States approaches 10 per 1000 in those older than 65 years and accounts for 1 million hospitalizations and 3 million office visits annually [4]. During the natural history of cardiac dysfunction, the critical importance of the cardiorenal interaction is emphasized by the fact that decreased renal function predicts cardiovascular mortality and complicates heart failure [5]. Baseline glomerular filtration rate (GFR) appears to be a stronger predictor of mortality in patients with HF than left ventricular ejection fraction or NYHA functional class [6]. In the Candesartan in Heart Failure: Assessment of Reduction in Mortality and Morbidity (CHARM), it was observed that impaired renal function was independently associated with heightened risk for death, cardiovascular death, and hospitalization for heart failure in patients with heart failure with both preserved as well as reduced LVEF [7]. Patients with chronic renal insufficiency are at strikingly higher risk for myocardial infarction, HF with systolic dysfunction, HF with preserved left ventricular ejection fraction, and death resulting from cardiac causes compared with individuals with normal GFR [8]. Conversely, reversal of renal dysfunction can improve cardiac function [9]. Hypertensive heart disease and HF with a normal ejection fraction are common among individuals with advanced and end-stage renal disease [10]. Renal disease patients with left ventricular hypertrophy have accelerated rates of coronary events and markers of uremia compared with those with normal left ventricular mass, and a high proportion of these individuals develop clinical HF [11]. It has recently been observed [12] that the 50% of patients with preclinical diastolic dysfunction had renal insufficiency that was defined by calculated creation clearance of <60 mL/min. In these patients, proposed mechanisms for the progression of

diastolic dysfunction include not only left ventricle stiffness, but also vascular stiffening (systemic and pulmonary) and volume expansion.

A more comprehensive characterization of the cardiorenal syndrome implicates the pathophysiologic disequilibrium between the heart and the kidney, in which malfunction of one organ consequently promotes the impairment of the other. Risk factors for its development include diabetes mellitus, hypertension, and a history of congestive heart failure or chronic renal failure.

Since cardiorenal dysfunction is usually secondary to multiple factors acting in concert (and not only reduced cardiac output) in the present paper we are going to focus on the interrelationship between heart failure with normal ejection fraction and the development of cardiorenal syndrome.

Firstly, we are going to summarize the recent evidence on heart failure with normal ejection fraction and on the cardiorenal syndromes. Then the main pathophysiologic mechanisms characterizing the cardiorenal syndrome developing in patients with heart failure and preserved ejection fraction (HFPEF) are hypothesized and the challenges in diagnosis and management of patients with cardiorenal syndrome and HFPEF are discussed.

2. The Cardiorenal Syndrome

The term *cardiorenal syndrome (CRS)* has been variably defined in the last decades without a well-accepted definition. Some investigators have suggested that this term should be used to describe patients with coexisting severe cardiac and renal dysfunction [13], while, more recently, a working group of the US National Heart, Lung, and Blood Institute used this term to describe the state in which advanced congestive heart failure (CHF) becomes complicated by acute impairment of kidney function [1–3]. According to these investigators, renal responses are thought largely to be the result of primary changes in cardiac function and CRS could be therefore defined as "a state in which therapy to relieve CHF symptoms is limited by further worsening renal function."

On the other hand, and from a broader point of view, taking into account the dynamic and close interplay between heart and kidney, the CRS has been recently viewed as "a pathophysiologic disorder of the heart and kidneys whereby acute or chronic dysfunction in one organ may induce acute or chronic dysfunction in the other organ" [1–3, 14, 15].

As recently reported in the consensus conference of the Acute Dialysis Quality Initiative [3], the cardiorenal syndromes (CRS) were defined as "*disorders of the heart and kidney whereby acute or chronic dysfunction in one organ may induce acute or chronic dysfunction of the other*" and five different types of cardiorenal syndrome are described [1–3].

According to this classification, the worsening of renal function occurring in patients with heart failure and preserved ejection fraction may belong to CRS type 2. In this syndrome, chronic heart disease and CKD frequently coexist and it can be hardly distinguished which disease came first. In other words, most often CRS type 2 cannot be distinguished from CRS type 4, in which, among chronic heart disease the following conditions should be considered: cardiomyopathy, LV remodelling and dysfunction, diabetic cardiomyopathy [16] congenital heart disease, but also diastolic dysfunction.

3. Heart Failure with Preserved Ejection Fraction

The incidence of heart failure with preserved ejection fraction (HFPEF) is reported to include about 50% of the general heart failure population [17], while the prevalence of HFPEF is still increasing over the last years when compared to the prevalence of heart failure with reduced ejection fraction (HFREF) [18]. Its prevalence is higher in the elderly [19, 20] (especially in females); in a recent study of HFPEF, all patients were aged >80 yrs, with a mean age of 87 [21].

Older age, hypertension, diabetes, obesity, and coronary artery disease are risk factors for both HFPEF and HFREF. [22]. In HFNEF, hypertension is a more common risk factor. While in HFREF ischemic heart disease is the most common etiology. In decompensated heart failure, 63% of patients with systolic and 54% of patients with diastolic heart failure have coronary artery disease [23].

As a result of modern evidence-based heart failure (HF) therapy, the prognosis of patients with heart failure with reduced left ventricular ejection fraction (HFREF) improved progressively over the past 3 decades. Conversely, despite frequent use of similar pharmacological agents, the prognosis of patients with heart failure with normal left ventricular ejection fraction (HFPEF) remained unaltered over the same time period [24–27].

It has been reported that the risk of sudden cardiac death is better correlated to left ventricular mass than to the ejection fraction [28]. The left ventricular mass is increased considerably in both HFPEF and HFREF; thus, the risk assessment for sudden cardiac death based on ejection fraction alone may not be appropriate [29].

Impaired left ventricular relaxation and increased passive stiffness is the principal functional derangement in HFPEF [30]. The pressure-volume relation during diastole shifts upward and to the left; as a result there is a disproportionately greater increase in diastolic pressure for any increase in volume. In HFPEF, because of the disproportionate increase in left ventricular diastolic pressure, there is an increase in left atrial and pulmonary venous pressure that is associated with symptoms and signs of pulmonary venous congestion [31]. Postcapillary pulmonary hypertension resulting from increased pulmonary venous pressure may precipitate right heart failure. Left ventricular stroke volume and cardiac output may also decline because of decreased end-diastolic volume (preload dependent). Currently, left diastolic but also nondiastolic abnormalities are discussed as possible reasons for HFPEF. Nondiastolic abnormalities may include an impairment of ventricular-vascular coupling [32], systolic left ventricular (LV) dyssynchrony, systolic and diastolic ventricular interactions (e.g., due to pericardial diseases, pulmonary hypertension), or chronotropic incompetence [33]

as possible contributors to the heart failure symptomatology of these patients, while pathologies inducing changes in chamber compliance lead to diastolic abnormalities of the left ventricle [32].

3.1. Main Mechanisms for the Pathophysiology of CRS Type 2 Associated with Heart Failure and Normal Ejection Fraction (Table 1)

3.1.1. Intra-Abdominal and Central Venous Pressure Elevation. The Poiseuille law summarizes the relationship between blood pressure, cardiac output, and systemic vascular resistance. Cardiac flow is dependent on a sufficient pressure gradient across the body's capillary networks. HF (and HF with preserved left ejection fraction) is marked by an elevation in central venous pressure, which attenuates the gradient across the glomerular capillary network. Indeed, there is increasing evidence to support roles for elevated renal venous pressure and intraabdominal pressure (IAP) in the development of progressive renal dysfunction in patients with HF. In one early experiment, Winton [34] reported that urine formation by isolated canine kidney was markedly reduced at renal venous pressures of 20 mmHg and abolished at pressures >25 mmHg. Renal blood flow was also diminished in proportion to the decrease in pressure gradient across the afferent and efferent renal circulations, probably caused by the increased efferent arterial pressure. Rising renal venous pressure limited urine formation and renal blood flow more than a reduction in arterial pressure. Bradley and Bradley showed that abdominal compression to produce IAP of 20 mmHg in normal individuals markedly reduced GFR and renal plasma flow. These relationships are supported by modern in vivo animal models [35]. In a broad spectrum of patients with cardiovascular disease, increased central venous pressure was associated with impaired renal function and independently associated with all-cause mortality. Interestingly the slope between CVP and impaired eGFR was steeper with relatively preserved cardiac function [36].

In patients who underwent elective cardiac surgery, preoperative presence of high CVP was a strong predictor of the occurrence of acute renal injury, independent of the presence of low cardiac output [37].

In the recent years, there has also been increasing recognition that oliguric acute renal dysfunction frequently accompanies abdominal compartment syndrome in surgical and trauma patients [38]. These changes are promptly reversed by abdominal decompression and may be associated with subsequent polyuria.

The concept that venous congestion, not arterial blood flow, is an important mediator of cardiorenal failure is supported by the findings of the Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterization Effectiveness trial, in which only baseline right atrial pressure, not arterial blood flow, correlated with baseline serum creatinine [39].

Several mechanisms by which abdominal pressure might contribute to CRS have been explored. Elevation of renal parenchymal pressure does not appear to have significant effects on GFR or renal blood flow. This was shown in studies of isolated porcine kidneys subjected to increasing amounts of extrinsic pressure [35]. Conversely, elevated central and renal venous pressures offer a stronger explanation for the relationship between elevated IAP and renal dysfunction. Elevating renal venous pressure by 30 mmHg for 2 hours in intact porcine kidneys resulted in a substantial reduction in renal blood flow and GFR [35]. Furthermore, patients with HF with impaired renal function at baseline or worsening renal function during hospitalization have significantly elevated central venous pressure relative to those with less renal impairment [40]. In one study of intensive medical therapy directed at volume reduction, hemodynamic profiles were monitored in all patients with pulmonary artery catheters, and only elevated central venous pressure correlated with worsening versus preserved renal function [41]. The role of elevated central and renal venous pressures is further supported by the association of elevated jugular venous pulsations on physical examination with higher baseline serum creatinine and increased risk for hospitalization and death caused by pump failure [42]. Finally, the association of tricuspid regurgitation with renal dysfunction was recently examined in 196 consecutive patients with HF. The authors found that patients with at least moderate tricuspid regurgitation by transthoracic echocardiography had lower estimated GFR and that a linear relationship existed between severity of tricuspid regurgitation and degree of GFR impairment.

Table 1: Mechanisms thought to be involved in the pathogenesis of the cardiorenal syndrome in HFPEF patients.

Main mechanisms
(i) Intra-abdominal and central venous pressure elevation.
(ii) Activations of the renin-angiotensin systematic.
Other mechanisms
(i) Sympathetic overactivity.
(ii) Oxidative injury and endothelial dysfunction.
Precipitating factors
Disease conditions that is, Infections.
Drugs, that is, nonsteroidal inflammatory agents.

3.1.2. Renin-Angiotensin-Aldosterone Axis and Renal Dysfunction. The extreme sodium avidity and ventricular remodelling conferred by RAAS elaboration in HF are a maladaptive response to altered hemodynamics, sympathetic signaling, and progressive renal dysfunction.

On a therapeutic point of view, drugs that block the renin-angiotensin system reduce the progression of both heart and CKD. The optimal approach is the combination of ACE-I and beta-blocker, the titration of dosage. The addition of either an ARB or aldosterone antagonist is depending on clinical conditions and patients characteristics. Therapy of CHF and coexisting renal impairment is still not evidence-based, since these patients are often excluded from clinical trials. Since these patients are typically hypervolemic,

more intensive diuretic therapy is needed. ACE-I and ARB initiation may cause deterioration in renal function, which is frequently transient and reversible. Anemia is often present in patients with CRS type 2 and correction of anemia may improve symptoms with no increase in survival [43].

Since the higher incidence of HF in the elderly, it should be remembered that these patients show increased susceptibility to renal dysfunction, impairment of sodium and water excretion, and postural hypotension, and aggravation of hypotension with the treatments (e.g., ACE-inhibitors, b-blockers, nitrates, and hydralazine). Therapy has to be individualized and consider aging-specific changes in physiology, drug metabolism, drug pharmacokinetics and tolerance, comorbidities, polypharmacy, and drug-drug interactions.

3.1.3. Other Mechanisms

Sympathetic Overactivity. The adverse consequences of sympathetic nervous system activity to the heart are well known. Less well appreciated are the systemic effects of renal sympathetic stimulation. There are now good data to suggest that the renal sympathetic activation leads to direct vascular effects. A recent pilot study of catheter-based renal sympathetic denervation in patients with resistant hypertension found significant improvements in GFR in 24% of patients undergoing the procedure [43]. In an HF population, denervation could possibly affect renal function and halt renal sympathetic nerve-mediated progression of cardiac failure related to elaboration of catecholamines and the RAAS. Further investigation into this exciting concept is needed to determine whether it is clinically relevant.

3.1.4. Oxidative Injury and Endothelial Dysfunction. Neurohormones are strong precipitants and mediators of an oxidative injury cascade that leads to widespread endothelial dysfunction, inflammation, and cell death in the CRS. In this setting, AT-II seems to be particularly important, exerting many deleterious effects through the activation of NADPH oxidase and NADH oxidase. AT-II activates these 2 enzymes within vascular smooth muscle cells, cardiac myocytes, and renal tubular epithelial cells, generating superoxide, a reactive oxygen species [44–46]. Reactive oxygen species have many unfavourable effects in living tissues and likely contribute to the processes of aging, inflammation, and progressive organ dysfunction. Growing evidence supports oxidative injury as a common link between progressive cardiac and renal dysfunction. Because both primary cardiac failure and primary renal failure lead to elaboration of the RAAS, activation of oxidases by AT-II in one organ has the potential to lead to progressive dysfunction in the secondary organ through reactive oxygen species generation.

In summary, it can be hypothesized that, in patients with HFPEF and cardiorenal syndrome, congestion [40, 41] leading to a reduction in the arteriovenous pressure gradient across the kidney, as well as decrements in mean arterial pressure and renal perfusion pressure, tends to reduce glomerular filtration rate. Concomitantly, there is the pathophysiologic activation of the renin-angiotensin-aldosterone system (RAAS) and the sympathetic nervous system (SNS) and the release of antidiuretic hormone, endothelin, cytokines, and various other inflammatory and vasoactive mediators that promote marked sodium and water retention, volume overload and adverse cardiovascular and renal remodeling. Under these conditions, another important mechanism contributing to cardiorenal dysfunction during the progression of heart failure is the deficiency in the production of compensatory natriuretic peptides and/or resistance to its renal actions [47, 48].

3.2. Diagnostic and Therapeutic Interventions for Cardiorenal Syndrome in HFPEF. So far there are no specific data on the diagnostic interventions in patients with cardiorenal syndrome and HFPEF.

Identifying the onset or progression of cardiorenal syndrome is paramount to proper management and can result in disease attenuation and prolonged survival both in patients with preserved EF and in those with reduced EF [49]. Though current research has been focusing on identifying markers that would permit an earlier or more accurate diagnosis of cardiorenal syndrome, no factor is specific for patients with HFPEF and CRS.

Neutrophil gelatinase-associated lipocalin (NGAL), a recently discovered acute kidney injury biomarker, indicating the accumulation of nephrotoxins and renal ischemia, typically precedes an elevation of creatinine by 48–72 h. Cystatin C, another acute kidney injury biomarker, has been suggested to be a better and earlier predictor of glomerular function than serum creatinine, as it is not affected by age, sex, race, or muscle mass.

B-type natriuretic peptide (BNP) or N-terminal pro-BNP (NT-pro-BNP) levels [50], which are general markers of HF, can be evaluated when HF diagnosis is not certain. Plasma levels of BNP or Ntpro- BNP increase with left ventricular mass, wall stress, and filling pressures. To date, baseline levels of NT-pro-BNP of 339 and 409 pg/mL have been reported in patients with HF-PEF, higher than in normal subjects but less elevated than usually observed in decompensated HF with low EF. However the relationship between BNP, renal function, and the severity of heart failure is less clear [3], not only for diagnostic purposes, but also for the management of therapy [51].

In regard to the potential diagnostic role(s) of imaging techniques, there is no specific data for patients with CRS and HFNEF. In the future, non-invasive techniques (such renal vein blood flow assessment by Doppler technique) should be refined to quantify renal blood flow. These data could be then correlated with cardiac and renal biomarkers and to guide ongoing therapy.

Despite the importance of HFNEF, the treatment of this phenotype remains poorly understood [52]. Pharmacologic treatment of HFNEF patients is aimed to decrease blood pressure, promote regression of LV hypertrophy, prevent tachycardia, treat symptoms of congestion, and maintain atrial contraction as recommended by the ACC and the AHA joint guidelines [53]. Optimizing hemodynamics is primarily

achieved through reduction of cardiac preload and afterload. ACE inhibitors and ARBs directly affect myocardial relaxation and compliance by blocking angiotensin II receptors, thereby reducing interstitial collagen deposition and fibrosis [54].

In many large, randomized, controlled clinical trials, researchers have assessed the beneficial effects of ACE inhibitors, b-block , and ARBs in HFREF patients, but these effects have not been established in HFNEF patients. Treatment recommendations are derived mainly from the large evidence-based trials that existed for management of HFREF [55] [Class I] or are based largely on the results of small, nonrandomized studies, clinical experience, and pathophysiologic reasoning [56] [Class III]. Recently, two large-scale HFNEF trials have reported their disappointing results: in the CHARMPreserved trial, the ARB candesartan produced a modest reduction in hospitalizations for HF but had no effect on mortality [57]; in PEP-CHF, the ACE-inhibitor perindopril had similar effects.

No data are so far available specifically for patients with CRS and HFPEF. It has been recently observed that decreased eGFR was associated with an increased risk of early postmyocardial infarction (MI) HF, the association being strongest in patients with preserved ejection fraction, in whom it was an important independent predictor of HF. Though renin-angiotensin-aldosterone blockade is well documented to reduce rates of late post-MI HF, particularly in patients with depressed EF, it is not known if intensive reninangiotensin-aldosterone blockade during the acute phase of MI affects rates of early post-MI HF in patients with preserved EF and impaired renal function [58].

It can be speculated that the therapeutic targets in patients with CRS and HFPEF are represented mainly by the reduction of cardiac filling pressure while maintaining adequate volume status.

Restriction of sodium intake and the administration of diuretics may be beneficial through reduction of LV ventricular filling pressures. They are also useful in treating hypertension, which is a common trigger for worsening HFNEF. In the Hong Kong Diastolic Heart Failure, diuretics alone appeared to be effective in reducing symptoms and improving quality of life in HFNEF patients [59].

Diuretics should therefore be initiated at low dose and uptitrated gradually to achieve adequate urine output. Once volume status is normalized, maintenance often requires chronic oral diuretic therapy with active fluid restriction to forestall the tendency to volume overload created by sustained neurohormonal activation and enhanced thirst. Clinicians should bear in mind that if aggressive therapy is employed, diuretic-induced hypovolemia can result in severe renal injury or exacerbate any preexisting renal insufficiency.

Whenever diuretic resistance develops in these patients, treatment does not differ from that of patients with CRS and HFREF, including ultrafiltration, when needed [3, 5].

All the conditions able to aggravate renal injury (i.e., anemia and infections) should be timely identified and properly treated and, similarly medications able to adversely influence renal function (such as nonsteroidal inflammatory agents) should be interrupted.

4. Conclusion

The coexistence of renal impairment in heart failure with preserved ejection fraction (CRS type 2 and 4) is common especially in older females with hypertension and/or diabetes. It can be hypothesized that the incidence of this disease association is growing, while clinical trials enrolling these patients are still lacking. Differently from CRS in heart failure with reduced ejection fraction, the involvement of the kidney may be under-diagnosed in patients with heart failure and preserved ejection fraction and the optimal therapeutic strategy in this condition, though challenging, is far to be completely elucidated. Further studies are needed to assess the best therapeutic regimen in patients with renal dysfunction (and worsening) and heart failure and preserved ejection fraction.

> "The people who bind themselves to systems are those who are unable to encompass the whole truth and try to catch it by the tail; a system is like the tail of truth, but the truth is like a lizard; it leaves its tail in your fingers and runs away knowing full well that it will grow a new one in a twinkling." (*Ivan Turgenev to Leo Tolstoy*)

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SAGE-Hindawi Access to Research
International Journal of Nephrology
Volume 2011, Article ID 785974, 5 pages
doi:10.4061/2011/785974

Clinical Study

Worsening Renal Function in Patients Hospitalized with Acute Heart Failure: Risk Factors and Prognostic Significances

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Received 2 August 2010; Accepted 31 August 2010

Academic Editor: Mitchell H. Rosner

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Objectives. To determine the prevalence, the clinical predictors, and the prognostic significances of Worsening Renal Function (WRF) in hospitalized patients with Acute Heart Failure (AHF). *Methods*. 394 consecutively hospitalized patients with AHF were evaluated. WRF was defined as an increase in serum creatinine of ≥0.3 mg/dL from baseline to discharge. *Results*. Nearly 11% of patients developed WRF. The independent predictors of WRF analyzed with a multivariable logistic regression were history of chronic kidney disease ($P = .047$), age >75 years ($P = .049$), and admission heart rates ≥100 bpm ($P = .004$). Mortality or rehospitalization rates at 1 month, 6 months, and 1year were not significantly different between patients with WRF and those without WRF. *Conclusion*. Different clinical predictors at hospital admission can be used to identify patients at increased risk for developing WRF. Patients with WRF compared with those without WRF experienced no significant differences in hospital length of stay, mortality, or rehospitalization rates.

1. Introduction

In the setting of heart failure, baseline renal insufficiency is a common and well-established independent marker of poor prognosis [1–6]. Worsening Renal Function (WRF) during the hospitalization for Acute Heart Failure (AHF) occurs frequently and may also have a prognostic significance. Indeed, several studies have reported that even small changes in renal function are associated with longer length of hospital stay, increased in-hospital costs, higher in-hospital mortality, higher mortality, and rehospitalization rates at short and long term [7–12]. However, not all the published information agree that WRF is associated with a worse clinical outcomes [13, 14]. Moreover, not all the studies have adopted the same definition of WRF [7, 8, 10, 11, 13–15] and in most of them only short-term followup (in-hospital complications and 6-months follow-up) was carried on [9–11]. Lastly, the major part of the results is derived from retrospective analyses, and in several studies a multivariate analysis was not performed to identify the independent prognostic value of WRF [7, 10, 11, 15]. Therefore, the role that WRF plays in general HF population is still to be better validated.

The goal of this study is to determine the prevalence, the clinical predictors, and the prognostic significance of WRF in a consecutive series of hospitalized patients for AHF.

2. Materials and Methods

2.1. Study Population. We enrolled patients consecutively admitted for AHF at our Institute from October 2002 to May 2008. Criteria for inclusion were exacerbation of previously documented Heart Failure (HF) or new onset of AHF using standard Framingham criteria [16]. The only criterion for exclusion was the presence of terminal noncardiac illness that could influence short-term prognosis.

2.2. Study Protocol. The study was approved by the local Ethics Committee, and all patients gave informed consent to participate.

All patients underwent a complete clinical and laboratory examination at the time of hospital admission and at hospital discharge. Estimated glomerular filtration rate (eGFR) was calculated using Modification of Diet in Renal Disease (MDRD) equation. This has been shown to be the best

method for the indirect assessment of renal function in HF population [17–19]. WRF was defined as an increase in serum creatinine of ≥0.3 mg/dL from baseline to discharge (WRF(CRE)). This value was chosen because it has previously been demonstrated to have the maximum sensitivity and specificity to predict the prognosis [11].

In order to verify the prognostic value of WRF, the hazard ratios for death and rehospitalization were also assessed for a decline in eGFR ≥20% from baseline to discharge (WRF(GFR)) [20].

Followup was performed by clinical visits and/or telephone calls at 1 month, 6 months, and 1 year. The main endpoints were hospital length of stay, death, and rehospitalization risks.

2.3. Statistical Analysis. Continuous variables were expressed as the arithmetic mean and the standard deviation (SD). Discrete variables were presented as a percentage. Associations between WRF and continuous variables were analyzed using Student's *t*-test for normal data and Wilcoxon test for not normally distributed variables. Discrete Variables were compared with the use of Chi-square analysis. A forward stepwise multivariable logistic regression analysis was performed to identify the independent variables predictive of WRF. All the variables which were significantly different ($P < .1$) between patients with and without WRF at univariable analysis were taken into multivariable analysis, but only retained at an exit significance value of $P < .05$. Associations of the development of WRF with the prognostic outcomes (hospital length of stay, hospitalization, and mortality risks) were assessed with a Cox proportional hazards analysis. Survival probability curves were constructed according to the Kaplan-Meier method.

3. Results

3.1. Baseline Characteristics and Prevalence of WRF. Patients' characteristics are presented in Table 1. We initially enrolled in the study 402 consecutive patients. Eight of them were lost to follow-up and were excluded from the analysis. No one of the lost to follow-up patients had developed the WRF during the index hospitalization. Therefore, the study population consists of 394 consecutive patients. The mean age of the cohort was 77.9 (SD 10.1) years, with nearly 70% of the patients over 75 years. The majority of the patients were male (67.5%). Almost 60% of the total population had a history of prior hypertension (58.4%), heart failure (61.7%), and acute coronary syndrome (57.4%). Relatively high percentages of diabetes (33%) and anemia (42.4%) were present in the population. The mean ejection fraction was 39.6% (SD 12.2) with 241 patients (61.2%) having EF < 45%. On admission, 159 (40.3%) patients were in NYHA class IV, 194 (49.2%) patients were in NYHA class III, and only 41 (10.4%) patients were in NYHA class II. At time of the admission, more than half of the patients were on diuretics (72.3%) and on ACE inhibitors (54.7%) treatments; 109 (27.7%) patients were receiving beta-blockers. The mean serum creatinine was 1.5 (SD 0.8) mg/dL with 111(28.2%) of the patients having values >1.5 mg/dL. WRF(CRE) and WRF(GFR) occurred, respectively, in 10.9% and in 11.6% of the population.

3.2. Predictors of WRF. In the univariable analysis, patients who experienced WRF(CRE) compared with those without WRF(CRE) were more likely to be older than 75 years, to have a history of preexisting Chronic Renal Failure (CRF), and to have higher heart rate (atrial or sinus arrhythmia with a heart rate >100 bpm). Higher serum creatinine (Scr) level and lower eGFR value at admission were also found to be significantly associated with the development of WRF. Moreover, patients with WRF(CRE) were more likely to be on calcium channel blockers and less likely to be on digoxin treatment. There were no significant differences in the other considered variables.

When a multivariable analysis was conducted (results listed in Table 2), preexisting CRF, admission heart rate (≥100 bpm), and age (>75 years) remained independent risk factors for the development of WRF(CRE) (resp., $P = .047$; .004; .049). Conversely, digoxin treatment resulted to have a protective effect against WRF(CRE) ($P = .024$).

3.3. WRF and Prognosis. The mean hospital length of stay during the index hospitalization was 8.8 ± 4.8 days [median: 7 days; interquartile range(iqr): 6–10] for the whole group. Patients who develop WRF(CRE) and patients without WRF(CRE) were similar in mean and median hospital length of stay (resp., mean: 8.5 ± 4.3 days; median: 7 days; iqr: 6–10; Versus mean: 8.9 ± 4.9 days; median: 7 days; iqr: 6–10; $P = .64$). Patients with and patients without WRF(GFR) experienced no significant differences in hospital length of stay (resp., mean: 8.0 ± 3.6 days; median: 7 days; iqr: 5–10; Versus mean: 8.9 ± 5 days; median: 7 days; iqr: 6–10; $P = .29$).

There were no statistically significant differences in rehospitalization risk between patients with WRF(CRE) and patients without WRF(CRE) at either 1 month, 6 months, or 12 months (results shown in Table 3). Patients with WRF(CRE) experienced no significantly higher risk of death at 1-, 6-, and 12-month followup (Table 3).

Similar results were observed when the WRF(GFR) definition was adopted (results shown in Table 4).

The combined endpoint death/rehospitalization was considered for the construction of Kaplan-Meier survival-free curves of patients with and without WRF(CRE). As it is possible to observe in Figure 1, the two curves were almost similar (log-rank test: $P = .947$).

4. Discussion

Several previous studies have reported a relatively high prevalence of WRF (around 25%) among patients hospitalized with acute heart failure [10, 12, 14, 21]. In our study, the prevalence of WRF is lower (11%). This is probably due to the fact that in our study patients with a transitory increase in Scr or decrease in eGFR, which did not persist at the moment of discharge, were not considered as WRF-patients.

Table 1: Characteristics at admission of the whole population and of patients with and without WRF (CRE).

	Total (n = 394)	WRF absent (n = 351)	WRF present (n = 43)	P-value
Demographics				
Age (mean, SD)	77.9 (10.1)	77.8 (10.3)	79.2 (8.4)	.380
Age > 75 years	274 (69.5)	239 (68.1)	35 (81.4)	.074
Males	266 (67.5)	236 (67.2)	30 (69.8)	.738
Medical history				
Prior heart failure	243 (61.7)	218 (62.1)	25 (58.1)	.613
Diabetes	130 (33.0)	108 (30.8)	12 (27.9)	.700
Valvular disease	108 (27.4)	99 (28.2)	9 (20.9)	.313
COPD	122 (30.9)	111 (31.6)	11 (25.6)	.418
Hypertension	230 (58.4)	201 (57.3)	29 (67.4)	.201
Peripheral vascular disease (PVD)	74 (18.8)	67 (19.1)	7 (16.3)	.656
Previus acute coronary syndrome	226 (57.4)	204 (58.1)	22 (51.2)	.384
Prior renal failure	95 (24.1)	76 (21.6)	19 (44.2)	.001
Clinical and laboratory parameters				
Systolic blood pressure, mm Hg (mean, SD)	132 (25.5)	131 (25.1)	137 (29.1)	.138
Systolic blood pressure >160 mm Hg	43 (10.9)	36 (10.3)	7 (16.3)	.230
Serum creatinine, mg/dL (mean, SD)	1.5 (0.8)	1.47 (0.8)	1.71 (0.9)	.066
Creatinine > 1, 5 mg/dL	111 (28.2)	92 (26.2)	19 (44.2)	.013
GFR, mL/min (mean, SD)	54 (23.5)	55 (22.8)	51 (28.4)	.070
GFR < 60 mL/min	239 (60.7)	207 (59.0)	32 (74.4)	.055
Sodium, mEq/L (mean, SD)	140 (4.4)	140 (4.5)	140 (3.5)	.854
Potassium, mEq/L (mean, SD)	4.0 (0.6)	4.0 (0.6)	3.9 (0.6)	.219
Glycemia, mg/dL (mean, SD)	76 (73.0)	78 (74.6)	58 (56.6)	.114
Haemoglobin, gr/dL (mean, SD)	12.6 (6.5)	12.7 (1.8)	12.1 (6.9)	.387
Anaemia (hemoglobin <12 gr/dL)	167 (42.4)	147 (41.9)	20 (46.5)	.562
Haematocrit (mean, SD)	38 (6.1)	39 (6.2)	38 (5.2)	.502
Azotemia, mg/dL (mean, SD)	46 (50.0)	45.5 (49.1)	50.2 (60.5)	.561
NYHA class (mean, SD)	3.3 (0.7)	3.3 (0.6)	3.3 (0.7)	.778
NYHA class III-IV	353 (89.6)	316 (90.0)	37 (86.0)	.420
KILLIP (mean, SD)	2.4 (0.6)	2.3 (0.6)	2.4 (0.6)	.363
Doppler echocardiography				
Ejection fraction (mean, SD)	39.6 (12.2)	39.5 (12.2)	39.7 (12.4)	.942
Ejection fraction <45%	241 (61.2)	215 (61.3)	26 (60.5)	.869
Left atrial size, mm (mean, SD)	46.3 (7.3)	46.4 (7.5)	45.2 (6.0)	.343
Left ventricular size, mm (mean, SD)	58.5 (9.5)	58.4 (10.0)	58.1 (6.7)	.982
Left atrial dilatation	232 (58.9)	211 (60.1)	21 (48.8)	.279
Left ventricular dilatation	265 (67.3)	237 (67.5)	28 (65.1)	.880
Elettrocardiogram				
LBBB	45 (11.4)	40 (11.4)	5 (11.6)	.960
Heart rate, bpm (mean, SD)	85.3 (17.0)	85 (17.0)	88 (16.3)	.276
Heart rate ≥ 100 bpm	80 (20.3)	64 (18.2)	16 (37.2)	.003
Atrial fibrillation	164 (41.6)	149 (42.4)	15 (34.9)	.342
Medical treatments				
Aldosterone antagonists	88 (22.3)	76 (21.6)	12 (27.9)	.352
Diuretics	285 (72.3)	255 (72.5)	30 (69.8)	.690
Beta-blockers	109 (27.7)	98 (27.9)	11 (25.6)	.746
Calcium channell blockers	60 (15.3)	49 (14.0)	11 (25.6)	.045
ACE inhibitors	215 (54.7)	190 (54.1)	25 (58.1)	.618
ARBs	37 (9.4)	30 (8.5)	7 (16.3)	.101
Statins	46 (11.7)	40 (11.4)	6 (14.0)	.865
ASA	163 (41.4)	143 (40.7)	20 (46.5)	.468
Warfarin	101 (25.6)	91 (25.9)	10 (23.3)	.705
Nitrates	144 (36.5)	133 (37.9)	11 (25.6)	.114
Digoxin	99 (25.1)	95 (27.1)	4 (9.3)	.006

ACE: angiotensin-converting enzyme; ARBs: angiotensin receptor blockers; ASA: acetylsalycilic acid; LBBB: left bundle branch block; COPD: chronic obstructive pulmunary disease; NYHA: New York Health Association.

Table 2: Predictors of WRF (CRE): multivariable analysis.

Predictors	Odds ratio	95% CI	*P*-value
Age > 75 years	2.34	1.00–5.46	.049
Calcium channel blockers	1.53	0.68–3.44	.300
Creatinine > 1, 5 mg/dL	0.90	0.33–2.50	.840
Digoxin	0.29	0.10–0.85	.024
Prior renal failure	2.80	1.01–7.79	.047
Heart rate ≥ 100 bpm	2.89	1.40–5.94	.004

CI: Confidence Interval.

Table 3: Association of WRF (CRE) with mortality and rehospitalizations risks.

	HR	95% CI	*P*-value
Mortality			
1 month	1.01	0.13–8.07	.99
6 months	0.80	0.32–1.99	.63
12 months	1.03	0.49–2.15	.94
Rehospitalization			
1 month	1.32	0.51–3.38	.56
6 months	1.00	0.59–1.70	.99
12 months	1.02	0.63–1.63	.95

CI: Confidence Interval.

Table 4: Association of WRF (GFR) with mortality and rehospitalizations risks.

	HR	95%	*P*-value
Mortality			
1 month	0.93	0.12–7.43	.94
6 months	0.89	0.38–2.08	.79
12 months	1.09	0.54–2.12	.81
Rehospitalization			
1 month	1.21	0.47–3.01	.69
6 months	0.82	0.47–1.43	.48
12 months	0.89	0.55–1.43	.63

CI: Confidence Interval.

The mechanisms which may cause WRF in patients with HF are multiple and are not completely understood [22]. Several predictors of WRF have been reported in the literature. One of the most acknowledged predictors is renal dysfunction either as a preexisting renal disease or as admission renal failure [8, 9, 13]. In a retrospective study carried on by Forman et al [10] on more 1000 patients, history of prior chronic heart failure, diabetes, systolic blood pressure >160 mmHg, and serum creatinine >1.5 mg/dL were identified as the most important predictors of WRF and used to elaborate a score to stratify the risk of developing WRF. Other reported important risk factors of WRF were: advanced age [7, 21], high systolic blood pressure [10, 14], diabetes [8, 10, 14], pulmonary edema [13], NYHA class [8], ejection fraction [8], use of high doses of furosemide [8, 9], and use of calcium channel blockers [9].

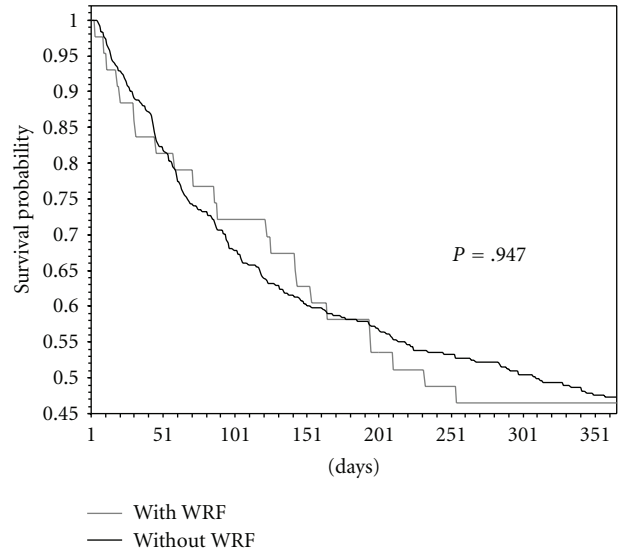

Figure 1: Kaplan-Meire hospitalization and morality free survival curves for patients with and without WRF.

In our study, we report that the history of preexisting renal failure is one of the strongest independent predictors of WRF. The age was found to be another independent predictor of WRF. Patients who are >75 years old were more likely to develop WRF.

In the univariable analysis, baseline serum creatinine and baseline eGFR were associated with WRF; however these links disappeared when the multivariable analysis were conducted. Although the results of some studies [10, 13] are not consistent with these findings, in the ESCAPE study baseline renal insufficiency was not predictive of WRF even in the univariable analysis [14], and similar results were observed in the prospective study of Metra et al. [8].

In our investigation, digoxin use was shown to have a protective effect against WRF. This result has not been reported previously. The effect does not disappear on multivariable analysis. Since the small number of patients on digoxin use, this observation is likely to be due only to chance.

Heart rate >100 bpm was another independent risk factor of WRF that was not previously reported. This finding may be due to an underlying more severe cardiac disease or to an underuse of medications in these patients.

Worsening renal function during the hospitalization for acute heart failure has been shown to be associated with lengthier hospitalization. However, in our study, the patients with WRF had almost equal mean hospital length of stay to those who did not develop WRF.

Similar short- and long-term rehospitalization and mortality rates were found in patients with and without WRF. Similar findings were observed adopting both definitions of WRF (WRF(CRE) and WRF(GFR)) to assess the prognostic significance of WRF. These data are in agreement with the results reported in a European multicenter prospective study (POSH study) [13] and in the ESCAPE study [14]. On the other hand, several studies have reported that even

small changes in serum creatinine during the hospitalization for acute heart failure are associated with higher rehospitalization risk and mortality rate. These conflicting results highlight the need of a better comprehension of the prognostic significances of WRF in patients with AHF. The fear of WRF may have important clinical consequences, since the physicians could tend to reduce diuretics dosages and to underuse important life-prolonging drugs such as aldosterone antagonists and ACE inhibitors.

Further prospective studies are needed to elucidate whether WRF, in the setting of AHF, is a justified fear or just a marker of intrinsic renal disease that is inevitable in patients with several risk factors.

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SAGE-Hindawi Access to Research
International Journal of Nephrology
Volume 2011, Article ID 490795, 12 pages
doi:10.4061/2011/490795

Review Article

ADPKD: Prototype of Cardiorenal Syndrome Type 4

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Received 23 August 2010; Accepted 26 October 2010

Academic Editor: Mitchell H. Rosner

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The cardiorenal syndrome type 4 (Chronic Renocardiac Syndrome) is characterized by a condition of primary chronic kidney disease (CKD) that leads to an impairment of the cardiac function, ventricular hypertrophy, diastolic dysfunction, and/or increased risk of adverse cardiovascular events. Clinically, it is very difficult to distinguish between CRS type 2 (Chronic Cardiorenal Syndrome) and CRS type 4 (Chronic Renocardiac Syndrome) because often it is not clear whether the primary cause of the syndrome depends on the heart or the kidney. Autosomal dominant polycystic kidney disease (ADPKD), a genetic disease that causes CKD, could be viewed as an ideal prototype of CRS type 4 because it is certain that the primary cause of cardiorenal syndrome is the kidney disease. In this paper, we will briefly review the epidemiology of ADPKD, conventional and novel biomarkers which may be useful in following the disease process, and prevention and treatment strategies.

1. Introduction

Heart performance and kidney function are closely interconnected, both in healthy and in disease conditions. It is also clear that there is a strong connection between renal and cardiovascular diseases. This bidirectional relationship between heart and kidney is physical, chemical, and biological. Primary disorders of one of these two organs often result in secondary dysfunction or injury to the other [1].

In this paper, we discuss about the ADPKD and its relation with cardiorenal syndrome. "Cardiorenal syndrome" (CRS) was defined as the pathophysiological disorder of the heart and kidney in which acute or chronic dysfunction in one organ may induce acute or chronic dysfunction in the other organ [2]. A large number of direct and indirect effects of each organ dysfunction can initiate and perpetuate the combined disorder of the two organs through a complex combination of neurohumoral feedback mechanisms [3]. For this reason, it was necessary to classify and divide the cardiorenal syndrome into different subtypes to provide a more concise and logically correct approach to this condition (see Table 1) [2].

Patients with CKD are at higher risk for cardiovascular events [4], and they have a 10- to 20-fold increased risk of cardiac death compared with age-gender-matched control subjects without CKD [5]. Part of this problem may be related to the fact that such individuals are also less likely to receive risk-modifying interventions compared to their non-CKD counterparts [6]. The association between reduced renal function and cardiovascular risk appears to consistently occur at estimated GFR levels below 60 ml/min/1.73 m^2 [7]. Clinically, it is very difficult to distinguish between CRS type 2 (Chronic Cardiorenal Syndrome) and CRS type 4 (Chronic Renocardiac Syndrome) because often it is not clear whether the primary cause of the syndrome depends on the heart or the kidney.

Autosomal dominant polycystic kidney disease, a genetic disease that causes CKD, could be viewed as an ideal prototype of CRS type 4 because it is certain that the kidney disease is the primary process. In this paper, we will briefly

Table 1: Classification of cardiorenal syndorme (CRS).

Acute cardiorenal syndrome	CRS type 1	Abrupt worsening of cardiac function leading to acute kidney injury (AKI)
Chronic cardiorenal syndrome	CRS type 2	Chronic abnormalities in cardiac function causing progressive chronic kidney disease (CKD)
Acute renocardiac syndrome	CRS type 3	Sudden worsening of renal function causing acute cardiac dysfunction
Chronic renocardiac syndrome	CRS type 4	Condition of primary CKD leading to an impairment of the cardiac function (ventricular hypertrophy, diastolic dysfunction) and/or increased risk of adverse cardiovascular events.
Secondary cardiorenal syndrome	CRS type 5	Systemic disorders (e.g., sepsis) causing both cardiac and renal dysfunction

review the epidemiology of ADPKD, conventional and novel biomarkers which may be useful in following the disease process, and prevention and treatment strategies.

2. Definition, Classification, and Epidemiology

ADPKD occurs worldwide and in all races and ethnic groups [8]. It accounts for ~10% of patients on renal replacement therapy representing an important cause of end-stage renal disease (ESRD) worldwide [9]. Prevalence of the disease is higher than that of Huntington disease, hemophilia, sickle cell disease, cystic fibrosis, myotonic dystrophy, and Down syndrome combined, and it occurs in approximately 1 of every 400 to 1000 live births [10]. Epidemiological data on the prevalence of ADPKD have been extensively reported, mainly in the United States and Europe. ADPKD is the fourth leading cause of CKD in the United States accounting for approximately 3% of cases [11]. In Europe, ADPKD as etiology of CKD Stage V has been reported as 7.8 and 6.0 per million for men and women, respectively [12]. With the advent of renal replacement therapy, cardiovascular complications have emerged as the major cause of death in ADPKD [13].

ADPKD is a genetically heterogeneous disease identified by two phenotypically similar forms associated with several mutations in two genes: the PKD1 gene located on chromosome 16 (16p13.3) and the PKD2 gene mapped to chromosome 4 (4q13–q23) [14]. A variety of genetic defects have been described in ADPKD patients, including deletions, frameshift, and missense mutations. Mutations of PKD1 gene, encoding the polycystin-1 protein, result in ADPKD type I (ADPKD1) which is responsible for approximately 85% of ADPKD cases. Gene PKD2 mutations, encoding the polycystin-2 protein, result in ADPKD type II (ADPKD2), corresponding to 15% of ADPKD cases [15].

Polycystin-1 is a large integral membrane protein with a domain architecture suggesting a function in cell-cell or cell-matrix interaction [16]. Polycystin-2 is a member of the calcium-permeable subfamily of transient receptor potential channels and forms a complex with polycystin-1 [17]. Polycystins are expressed in vascular smooth muscle and endothelia; it suggests a direct role of these proteins in the vascular manifestations of ADPKD [18, 19]. Both polycystin-1 and polycystin-2 are present in the primary cilium of tubular epithelial cells [20]. Mutations in these genes lead to abnormalities in cell proliferation, apoptosis, tubular basement membranes, and tubular fluid secretion, ultimately resulting in slowly expanding renal cysts [21].

The precise processes leading to cyst formation and loss of renal function remain incompletely understood. Several mechanisms contributing to the cyst formation have been identified, including a imbalance between epithelial cell proliferation and apoptosis, secretor defects, altered cell–matrix interactions, cell polarity, ciliary dysfunction, and altered intracellular signaling [22].

2.1. Clinical Presentation. Clinically, ADPKD is an adult-onset disease characterized by progressive, bilateral renal cyst development and expansion of the kidneys [23]. Many patients with ADPKD are completely asymptomatic and often are diagnosed because of their positive family history or the development of hypertension (HP) [21]. Whether ADPKD2 patients are compared to ADPKD1, they seem to have a milder clinical presentation. Cysts and kidney failure occur at an earlier age in ADPKD1; the average age of CKD stage V is approximately 57 years in type I versus 69 years in type II [24]. ADPKD is a disease with a variable clinical course not only among families with different mutations, but within families with a defined mutation as well; it can be explained to the large extent by its genetic heterogeneity and modifier genes. Cysts may also develop in other organs. Liver cysts develop in more than 80% of patients, and the cysts are usually larger in women than in men [25]. Usually, cysts do not affect liver function. About 10% of patients have cysts in the pancreas, but these are functionally insignificant. Other locations of cysts include the spleen, arachnoid membranes, and seminal vesicles in men [26].

Hypertension is probably the most remediable and serious complication of ADPKD [10]. The new onset of HP in a patient at risk for polycystic kidney disease should prompt aggressive treatment and diagnostic studies. These patients during the course of ADPKD have early and more severe left ventricular hypertrophy (LVH). ADPKD may also occur with abdominal, back, and flank pain. Hematuria may be present secondary to cysts rupture. Urinary tract infections are also common.

A number of noncystic manifestations such as cardiovascular deficits, cardiac valve abnormalities, diverticular disease, and intracranial aneurysms are also associated with

ADPKD; in fact, cardiovascular complications are the major cause of morbidity and mortality in patients with ADPKD [13].

2.2. Cardiovascular Complications. Mitral valve prolapsed (MVP) occurs in about 26% of affected adults compared with 2% of control subjects [27, 28]. Aortic valve insufficiency can occur in association with the aortic root. Although these lesions may progress with time, they rarely need valve replacement. Screening echocardiography is not indicated unless a murmur is detected on examination [12]. Pericardial effusion may occur with an increased frequency in patients with ADPKD (35% versus 9% in a control group of patients with another chronic nephropathy), possibly as a result of increased compliance (or as a collagen protein dysfunction) of the parietal pericardium. Nevertheless, these effusions are generally well tolerated and clinically inconsequential. It is known that the kidney disease is strongly associated with a greater carotid Intima-Media Thickness (IMT). Subjects with ADPKD, even with preserved renal function, have a greater carotid IMT compared with healthy controls; carotid IMT is higher in hypertensive ADPKD patients [29].

It is challenging to clearly segregate those cardiovascular features due to the genetic disorder versus the secondary cardiovascular consequences of declining kidney function per se. However, recent improvement and expansion of genetically modified ADPKD animal models which mimic the human form are providing additional insights into the molecular mechanisms governing these disease processes as well as the development of cardiovascular complications. Several studies have provided convincing evidence that these vascular abnormalities are caused by alterations in the arterial wall linked to mutations in PKD1 or PKD2 [30].

Heterozygous mutant PKD1 or PKD2 mice appear normal but develop single cysts in the kidney or liver late in life and have a reduced overall lifespan [23, 31]. Homozygous null mutant mice are embryonically lethal and die in utero or perinatally because of systemic defects with massively enlarged cystic kidneys, pancreatic ductal cysts, and pulmonary hypoplasia and often exhibit edema, vascular leaks, and rupture of blood vessels. It suggests the role of polycystins for the structural integrity of blood vessels [23, 31, 32].

In addition, most of the homozygous knockout embryos display multiple cardiac abnormalities including cardiac septation defects, double outlet right ventricle, and pericardial effusions [31, 33].

Moreover, Kurbegovic et al. engineered and described a Pkd1 transgenic mice (Pkd1(TAG) mice) that, in addition to the cystic phenotype, developed cardiac anomalies with severe left ventricular hypertrophy, marked aortic arch distention, and/or valvular stenosis and calcification [34].

Therefore, the cardiovascular complications seen in ADPKD patients begin to be recognized not only as a consequence of declining kidney function, but also as a defect due to the loss of polycystin-1 and/or polycystin-2 function in cardiovascular organs [31].

2.3. Hypertension and Left Ventricular Hypertrophy. As previously mentioned, hypertension and its consequent left ventricular hypertrophy are common in ADPKD patients, even in young adults, compared with unaffected controls [28]. Moreover, HP and LVH are associated with a faster progression to ESRD and an increased cardiovascular mortality [35, 36]. It is well known that HP and LVH are associated with an accelerated rate of renal functional deterioration [37]. Both HP and LVH are important risk factors for cardiovascular death, the most frequent cause of mortality in ADPKD patients [13]; thus left ventricular hypertrophy may be considered a powerful indicator of mortality [38].

Hypertension in ADPKD occurs before the loss of kidney function in 60% of affected individuals and increases to almost 100% in patients with CKD stage IV-V [39, 40]. The average age of onset of hypertension is 30–34 years [41], with men more commonly affected than women [42]. In added, its occurrence is earlier and more common in ADPKD1 than ADPKD2 patients [43]. The mechanisms leading to hypertension in ADPKD are not well understood.

However, it is now well known that increased activity of the intrarenal rather than the systemic renin-angiotensin system (RAS) is responsible for many forms of hypertension. Persistent elevation of intrarenal angiotensin II (ANG II) production with the inability to reduce ANG II in response to a high sodium intake will result in resetting the pressure-natriuresis relationship towards higher blood pressures leading to hypertension [44, 45].

Hypertension is associated with larger kidney size, reflecting a larger number of cysts and with the severity of kidney disease. Hypertensive ADPKD patients with normal kidney function show greater kidney volumes versus age-matched normotensive ADPKD men and women [41] increased proteinuria [46] and decreased renal blood flow [47]. Renal blood flow is reduced in hypertensive ADPKD patients versus matched essential hypertensive patients [47], and the renal resistive indices are also increased in hypertensive ADPKD subjects and are correlated with a loss of kidney function [43].

Renal structural changes play an important role in the pathogenesis of the HP, and renal arteriograms from end-stage ADPKD-nephrectomized specimens demonstrate marked attenuation of the vasculature due to the extrinsic compression by the presence of the cysts and their replacement by the latter [48]. Renal angiographic images of hypertensive ADPKD patients (from mild to advanced renal failure) show a large amount of a vascular renal substance peripheral to the outermost branches of the arterial tree [48].

Hypertensive ADPKD adults with normal kidney function show a greater frequency of LVH versus normotensive ADPKD men (50% versus 30%) and women (52% versus 22%) as well as with healthy controls [49]. They also show greater left ventricular mass index (LVMI) in comparison to matched essential hypertensive population [43, 50]. The prevalence of LVH is increased even in the early stages of CKD, and the frequency increases progressively as renal function decreases [51]. Several studies have shown increased LVMI, left ventricular diastolic dysfunction, endothelial dysfunction, and increased carotid IMT in young

normotensive patients with ADPKD with well-preserved renal function. These findings suggest the cardiovascular involvement in the early stages during the course of ADPKD [26]. In experimental studies, hypertrophy was found not only in the left, but also in the right ventricle; these findings exclude that simple hemodynamic factors (increased preload and afterload) are the only explanation [51]. It is quite important to appreciate that hypertrophic remodeling comprises not only cardiomyocyte hypertrophy, but also interstitial fibrosis and microvessel disease [38].

2.4. Intracranial Aneurysms. A major complication of ADPKD includes the intracranial aneurysms (ICAs); the prevalence of ICA in patients with ADPKD ranges from 4 to 12%, compared to a prevalence of 1% for the general population [52]. A familial clustering of ICA is found, with a 5 times greater chance of detecting an ICA in a subject with a relative with a ruptured ICA [52, 53]; it suggests that genetic factors may be associated with the development of this complication [23]. This family clustering is in agreement with the finding that patients with mutations in the 5′ region of PKD1 are more likely to have ICA than patients with 3′ mutations, especially in those with ICA rupture before 40 years old and in families with multiple cases of ICA or other vascular events [19].

Computed tomography, magnetic resonance angiography, and classical angiography are screening tests for detection of intracranial aneurysms in ADPKD subjects at high risk. The routine screening for asymptomatic ICA in all ADPKD individuals is not indicated, but in families with a proven case of ICA, a screening analysis is recommend in consultation with a neurosurgeon.

3. Biomarkers

In general, biomarkers can be divided into 3 subtypes based on the technical procedures used. Biomarkers measured by laboratory tests are defined as "laboratory or molecular biomarkers"; those related to signaling, imaging, and functional tests are defined as "functional biomarkers"; those related to genetic polymorphisms and other genomic tests are defined as "genetic biomarkers."

3.1. Laboratory and Molecular Biomarkers

3.1.1. Renal Biomarkers. In patients with ADPKD, a limited number of biomarkers have been investigated.

In a recent study, Meijer et al. investigated urinary biomarkers for different segments of the nephron in patients with ADPKD versus healthy controls. They choose urinary Immunoglobulin G (IgG) as a marker of glomerular damage; urinary β_2-microglobulin (B2M), urinary kidney injury molecule 1 (KIM-1), N-acetyl-β-D-glucosammide (NAG), and neutrophil gelatinase-associated lipocalin (NGAL) as markers for damage of the proximal tubule; urinary heart-type fatty acid binding protein (HFABP) as a marker for damage of the distal tubule. Urinary macrophage migration inhibitory factor (MIF) and monocyte chemotatic protein 1 (MCP-1) were chosen as markers of inflammation.

The most important finding of this study is that excretion of all urinary biomarkers from all segments of the nephron was increased in patients with ADPKD compared with control subjects.

Furthermore, NGAL excretion was associated with renal blood flow and total renal volume independent of albuminuria. In addition, B2M and H-FABP were associated inversely with measured GFR and effective renal blood flow independent of albuminuria; KIM-1, NGAL, and MCP-1 were associated positively with total renal volume independent of albuminuria [54].

In a recent paper, Bolignano et al. investigated and reported urinary and serum NGAL levels in a sample of 26 ADPKD patients. They found that urinary and serum NGAL levels were higher in ADPKD patients than in control subjects. They found a strong correlation with the glomerular filtration rate. In addiction, they divided patients into two groups according to the cystic development and kidney dimensions; subjects with higher cystic growth presented higher urinary and serum NGAL values with respect to others. They concluded that higher levels of NGAL are correlated to higher cystic growth and suggested that this protein could be also involved in the process of cystogenesis [55].

In 92 patients with ADPKD, Casal et al. reported a comparative study for three biomarker tests of early kidney damage such as urinary albumin and total β-N-acetylhexosaminidase (Hex) and its isoenzymes (Hex A, Hex B), as well as serum glutathione peroxidase, which has been considered as a marker of renal proximal tubular function. They found a frequent elevation of the urinary Hex and an alteration of its isoenzymatic profile, with 31% of the normotensive ADPKD subjects with normoalbuminuria already presenting an increased proportion of Hex B isoenzyme. Furthermore, keeping age constant, they reported a partial significant correlation between the ultrasound score (kidney size and number of cysts) and the proportion of Hex B, but not with albuminuria or cystatin C. This confirms the hypothesis that tubular damage plays a role in the pathogenesis and progression of ADPDK [56].

Wong et al. valued measure GFR and serum cystatin C (Cys C) levels in 18 children with ADPKD versus 41 children with minor renal pathological states.

Serum creatinine levels did not differ between the ADPKD and control group, but GFR was significantly greater in the ADPKD group than in controls. Cys C level for the ADPKD group was significantly lower than that of controls.

This study corroborates the increase of GFR in children and adolescents with ADPKD and the superior diagnostic performance of Cys C [57]. In fact, in patients with CKD, Cys C was proposed to perform better as a marker of GFR than serum creatinine [58].

Apart from being a good marker for renal function, Cys C appears to be also a marker of cardiovascular risk in CRS types 2 and 4 and offers complementary prognostic information to other cardiac biomarkers like troponin T and NT-proBNP [58, 59]. High concentrations of circulating Cys C have shown to be consistently and strongly associated with the cardiovascular outcomes [60].

Another index of ADPKD progression is microalbuminuria; in fact, there are numerous reports that have established that microalbuminuria is a frequent sign of kidney impairment in the disease, associated with a major cardiovascular risk. Microalbuminuria is present in patients with chronic heart failure (CHF) and progressive renal failure [46, 61]. In ADPKD patients, microalbuminuria is associated with an increase in arterial pressure [61, 62] and progression to renal failure [62], as well as with a more severe cystic involvement [61]. Martinez-Vea et al. examined the prevalence of microalbuminuria in a normotensive ADPKD population. The study showed a high prevalence of microalbuminuria in this group and a tendency of these patients towards a greater systolic blood pressure, plasma renin activity, and left ventricular mass [61]. There are few information about renal alterations and vascular remodeling in ADPKD patients with normal or minimally increased levels of urine albumin excretion.

3.1.2. Cardiac Biomarkers. The natriuretic peptides (NPs) are a well-described family of hormones with a major role in sodium and body volume homeostasis [63]. BNP (brain natriuretic peptide), and NT-proBNP are correlated with the severity of heart failure (HF) and left ventricular (LV) function and are useful markers for diagnosis, management, and prognosis in patients with normal renal function. Recent studies indicated that both BNP and troponin T have a diagnostic power in patients with CKD to predict cardiovascular disease [63, 64]. The NPs have shown prognostic utility in patients with various stages of renal insufficiency [65], demonstrating potential applications in CRS types 2 and 4. It is well established that patients with CKD have higher levels of both BNP and NT-proBNP than age- and gender-matched subjects without reduced renal function, even in the absence of clinical HF [66]. Thus, the relationship between BNP, renal function, and the severity of heart failure is less clear, and the association between NPs levels and renal function remains complex.

Cardiac troponin T (cTnT) is a specific marker for myocardial damage and a myocardial infarction. In hemodialysis patients, three large observational studies concordant with cTnT levels are associated strongly with the risk of incident for cardiovascular events [67–69]. Thus, increased cTnT levels represent a strong and independent predictor of global cardiovascular mortality in clinically stable hemodialysis patients. However, there are few studies describing the significance and the prognostic value of elevated serum cTnT levels in stable patients with moderate CKD [70].

At this time, the relationship between renal function and serum cTnT remains still unclear, and the significance of an increased cTnT concentration in patients with renal dysfunction remains controversial [71].

Unfortunately, there are currently no published data about specific cardiac biomarkers in ADPKD population.

3.2. Functional Biomarkers: Imaging Techniques (Table 2). Imaging techniques may enhance, extend, and refine our ability to diagnose and follow up cardiac and renal diseases.

3.2.1. Imaging Techniques for ADPKD Diagnosis. The main structural change seen for ADPKD is the formation of renal cysts; thus, it is evident that any enlargement of the cysts and the decrease in the volume of the renal parenchyma are the key factors in the progress of this disease [41]. Different imaging modalities such as Ultrasonography (US), Computed Tomography (CT), and Magnetic Resonance Imaging (MRI) have been used to quantify the size of the kidney in ADPKD. The consortium for radiologic imaging studies of polycystic kidney disease (CRISP) was created to develop innovative imaging techniques and analyses to follow disease progression or to evaluate treatments for ADPKD.

Ultrasonography was the earliest method used to measure kidney volume in vivo and has the advantage of being widely available and easily performed with modest cost in comparison with CT scan and MRI. Unfortunately, US cannot provide separate, reliable measurements of both the renal cyst volume and the renal parenchymal volume [72]. Individuals who are at risk for ADPKD are often screened by ultrasound using age-graded diagnostic criteria derived from individuals with mutations in PKD1 [73].

In families of unknown genotype, the presence of three or more (unilateral or bilateral) renal cysts is sufficient for establishing the diagnosis in individuals aged 15 to 39 years; two or more cysts in each kidney are sufficient for individuals aged 40 to 59 years, and four or more cysts in each kidney are required for older individuals aged 60 years. Conversely, less than two renal cysts in at-risk individuals aged $\geq$40 years are sufficient to exclude the disease. US imaging does not provide a sufficiently certain diagnosis in at-risk individuals younger than 30 years of age; so the utility of this technique for disease exclusion is limited in younger subjects.

Families with mutations in PKD2 typically have less severe disease; in ADPKD2, the mild renal cystic involvement has an adverse impact on the sensitivity of US criteria that apply to diagnose the disease. As a result of reduced test sensitivity, the diagnostic criteria in use have a suboptimal performance for individuals with mutations in PKD2 [73].

For younger individuals in whom US might yield equivocal or indeterminate results, a negative CT scan or MRI may provide further assurance that they are unaffected. CT scan and MRI have greater sensitivity so that smaller cysts ($\sim$2 mm compared with $\sim$10 mm for ultrasonography) can be detected [74]. Both CT and MRI avoid the potential pitfalls of US, that is, any operator-dependent techniques or the need for multiple image acquisitions of large kidneys. Contrast media-enhanced CT or electron beam CT techniques can provide accurate measurements not only of the total kidney volume, but also of the renal cyst volumes in ADPKD patients [75]. However, CT has two significant limitations: the radiation exposure and the requirement for administering intravenous contrast media. The contrast media may be associated with a small chance of serious allergic reactions and nephrotoxicity in patients with renal insufficiency.

MRI has increasingly been used because it provides high-resolution 3D images with excellent tissue contrast without exposure to ionizing radiation or iodinated contrast medium

Table 2: Imaging techniques.

ADPKD diagnosis	Ultrasonography (US)	Easy, available, and cheap method Limited utility for disease exclusion in younger subjects and suboptimal performance for individuals with ADPKD type II
	Computed tomography (CT) scan	Detect small cysts (~2 mm) Exposure to radiation and administration of intravenous contrast media
	Magnetic resonance imaging (MRI)	Provide high-resolution 3D images No exposure to radiation, no administration of intravenous contrast media
Diagnosis of cardiovascular complications	Echocardiography	Determine LV/RV size and function, LV wall motion abnormalities, valvular function and abnormalities, diastolic function, and presence or absence of pericardial abnormalities or intracardiac masses
	Transmitral pulsed doppler	Noninvasive method to evaluate the diastolic dysfunction Influenced the loading condition of the left atria and heart rate.
	Tissue doppler imaging (TDI)	Permit an assessment of myocardial motion, a sensitive index of ventricular relaxation
	Cardiovascular magnetic resonance imaging (cMRI)	Noninvasive test Gold standard for the assessment of ventricular dimensions.

[76]. While MRI is a reliable and precise method to measure renal volume, little information and data are available in the medical literature about the validity and accuracy of MRI-based kidney volume measurements in ADPKD patients [41, 76]. Initial preliminary reports from the CRISP indicate that MRI is as least as accurate as CT scan for determining the rate of increase in kidney volume [41]. At the present time, MRI appears not appropriate for routine application. Some of the limitations of MRI include relatively long image-acquisition times and variability in the quality of images that can be produced from different MR scanners [76].

3.2.2. Imaging Techniques for Diagnosis of Cardiovascular Complications. Echocardiography determines left/right ventricular size and function, left ventricular wall motion abnormalities, valvular function and abnormalities, diastolic function, and presence or absence of pericardial abnormalities or intracardiac masses; it also evaluates intracardiac filling pressures.

Transmitral pulsed doppler is the classical noninvasive method of evaluation of diastolic dysfunction; it is influenced by a variety of factors such as the loading condition of the left atria and heart rate. Tissue doppler imaging (TDI) is a new technique that permits an assessment of myocardial motion, a sensitive index of ventricular relaxation, which is more independent of the hemodynamic condition and, therefore, a more reliable diastolic function index [77]. Unlike transmitral pulsed doppler, TDI directly measures the mechanical wall function by calculating the velocity of myocardial movement and has been shown to better monitoring diastolic function of the myocardium.

Starting as a research method little more than a decade ago, cardiovascular magnetic resonance imaging (cMRI) has rapidly evolved to become a powerful diagnostic tool used in routine clinical cardiology. CMRI provides a relatively novel method for accurate definition of cardiac dimensions and is accepted as the "gold standard" for the assessment of ventricular dimensions. Benefits of cMRI include the ability to obtain a great deal of information with one noninvasive test. CMRI is used for the assessment of regional and global ventricular function and to answer questions regarding anatomy. CMRI is able to assess ischemic versus nonischemic disease, infiltrative disease, valvular and congenital disorders, and hypertrophic disease, and determine viability. Unfortunately, there are currently no published data using cMRI in ADPKD patients.

3.3. Genetic Biomarkers. Genetic tests are the "gold standard" to screen individuals for ADPKD. Molecular genetic tests are helpful when imaging results are equivocal and/or when a definite diagnosis is required in a younger adult. There are 2 methods for ADPKD DNA testing: linkage analysis and direct mutation screening.

Presymptomatic testing is possible in larger families by linkage analysis using highly informative microsatellite markers flanking the PKD1 and PKD2 genes. A significant limit of linkage analysis is the need for a relatively large number of affected family members in order to establish the gene involved in the disease. In linkage analysis, the segregation of chromosomal markers is examined and compared within a family in whom the clinical status (affected or unaffected) of each individual is known. By

examining several markers, a "haplotype" (a pattern of alleles on the same chromosome that are inherited together) that segregates with the disease can be determined [78]. There are several limitations to linkage testing; the most important is that no information can be obtained from testing the proband alone. Furthermore, linkage analysis cannot be used if a family is small, if family members refuse to participate, or if the proband is suspected to have a *de novo* mutation.

A direct mutation analysis is another method for molecular diagnosis in ADPKD. As ADPKD displays a high level of allelic heterogeneity, the complete screening of both genes is required. Most mutations are private (unique to a single family) and scattered throughout these genes with no clear "hot spots." Therefore, exon-by-exon screening of these genes is required to ensure a high sensitivity in detecting disease-causing mutations, thus screening approaches are expensive. Screening of individuals with ADPKD detects mutations in up to 91% of cases. However, only approximately 65% of patients have definite mutations with approximately 26% having nondefinite changes that require further evaluation [74]. ADPKD database (*Autosomal Dominant Polycystic Kidney Disease: Mutation Database*) collects every known variants on PKD1 and PKD2 to improve the diagnostic value of molecular screening.

Furthermore, the recent availability of clinical molecular genetic testing means such testing may be applied to asymptomatic at-risk relatives of subjects with ADPKD. As with most renal diseases, early diagnosis with implementation of effective interventions has important implications and the best chance for preventing or slowing renal progression and cardiac complications in patients with the ADPKD [79].

For example, the early intervention of diagnosing and aggressively treating blood pressure in these patients, particularly blockade of the renin-angiotensin system, has the potential of preventing LVH, cardiovascular complications, and mortality [79].

In that regard, Schrier et al. have reported that the age of ESRD in both men and women with ADPKD has increased in recent years and speculate that this effect has been associated with better blood pressure control and increased therapy with ACE inhibitors [80].

Other relevant indications for early identification of ADPKD include the provision of more detailed and specific information regarding prognosis and risk for complications, the ability to make more informed reproductive choices, motivation for enhanced compliance and medical followup, and the evaluation of living donors form affected families [81]. Screening is also important in clearing prospective living kidney donors from affected families [81]. Screening children under 18 years old is not strongly recommended because of the potential emotional and social impact of a positive diagnosis in these younger subjects. Before screening, counselling from experienced staff must be performed, in order to facilitate appropriate life-style decisions.

4. Prevention, Management, and Trials

The core of the prevention is that the reduction in the rate of progression of CKD may lead to a reduction of the incidence of chronic renocardiac syndrome. Many novel therapies have been evaluated in the cardiorenal syndrome setting, including agents that may block key local factors (e.g., adenosine A(I) receptor antagonists), improve diuresis, aquaresis, and natriuresis, and augment natural vasodilator mechanisms to improve renal perfusion [82].

There are no disease-specific therapies for any form of ADPKD, and no evidence-based guidelines on the management of ADPKD have been reported perhaps due to the very slow rate of disease progression. Interventions should be capable to slow down, stop, or reverse structural progression of the disease and should be able to prevent the decline of renal function improving clinical outcome. In ADPKD, only blood pressure control has been shown to have a favorable impact on disease progression and cardiovascular complication rate [83]. Rigorous control of blood pressure may prevent progression of renal disease and decreases the risk of cardiovascular morbidity that characterizes all patients with CKD. The KDOQI Clinical Practice guidelines on hypertension indicate that goal blood pressure should be less than 130/80 mmHg [84]. If there are no contraindications, an angiotensin-converting enzyme (ACE) inhibitor should be the initial antihypertensive agent. Increased renin-angiotensin system activity and extracellular volume expansion play an important role in the pathogenesis of HP in patients with ADPKD, thus patients generally respond well to these agents [85]. ACE inhibitors or angiotensin receptor blockers (ARBs) may have renoprotective properties increasing renal blood flow which correlates with progression of ADPKD and contributes to cyst growth [12, 47, 86]. In a meta-analysis of 11 randomized controlled trials, Jafar et al. found that ACE inhibitors were more effective in lowering urine protein excretion in patients with ADPKD compared to regimes without ACE inhibitors, and it was more evident in patients with higher levels of proteinuria. However, the benefit of ACE inhibitors on ADPKD progression remains inconclusive [86].

Whether salt restriction and ACE inhibitors and ARBs therapy fail to lower blood pressure sufficiently, it may be necessary to add a diuretic (thiazides initially, with a switch to loop diuretics if thiazides are not effective) [25]. Additional agents may then be added to gain an appropriate blood pressure control and ameliorate other clinical advantages, such as angina using a β-blockers or calcium channel blockers. Addition of β-blockers to ACE inhibitor/ARB therapy is a very attractive choice, with documented cardiovascular protective characteristics. Several studies have shown better preservation of renal function or reduction in proteinuria and LVH with ACE inhibitors or ARBs compared to diuretics or calcium channel blockers [87, 88].

A controlled trial, the Halt Progression of Polycystic Kidney Disease study (NCT00283686), funded by the National Institutes of Health, is under way to determine whether treatment with ACE inhibitors and ARBs, administered singly or in combination, will reduce the rate of increase in kidney volume and slow the decline in GFR [25]. Significant advances in terms to understand the genetics of ADPKD and molecular mechanisms responsible for cyst initiation have revealed likely targets for therapeutic intervention.

Table 3: Clinical trials for ADPKD.

	Start-finish date	Intervention	Action	Design
HALT-ADPKD STUDY (NCT00283686)	2006–2013	ACE inhibitors and ARBs (singly or in combination)	Reduce the rate of increase in kidney volume and slow the decline in GFR	Multicenter, randomized, placebo controlled
NCT00428948	2007–2011	V2 receptor antagonist (Tolvaptan)	Reduce the concentrations of cAMP and slow the progression of renal enlargement	Multicenter, double blind, placebo controlled
NCT00309283	2006–2010	Long-acting somatostatin (octreotide)	Inhibit the growth of the polycystic kidneys and liver	Randomized Single Center, Single blind, Placebo controlled
NCT00426153	2007–2010 (open-label extention)	Long-acting somatostatin (octreotide)	Inhibit the growth of the polycystic kidneys and liver	Double blind, Randomized, Placebo controlled, Crossover
NCT00565097	2007–2009 (open-label extention)	Long-acting somatostatin (lanreotide)	Inhibit the growth of the polycystic kidneys and liver	Double blind, Randomized, Placebo controlled
Trials with target mTOR	—	mTOR inhibitors (sirolimus, everolimus)	Modulate disease progression and development of renal cysts	—

At the present time, there are no therapies proving a cyst progression delay and their complications, and there is no proven antihypertensive drug of choice neither in ADPKD patients nor in ADPKD patients on dialysis. An effective control of HP remains one of the few modifiable factors by medical intervention and may delay the development of LVH, which is strongly related with diastolic dysfunction [21]. A better understanding of the pathophysiology and the availability of animal models has enabled the development of preclinical trials and the identification of promising candidate drugs for clinical trials [12].

An hopeful therapeutic strategy, to inhibit cyst development in ADPKD, is modulating cyclic AMP (cAMP) levels. Arginine vasopressin (AVP) is a potent activator of renal adenyl cyclase [25]. The effect of AVP, via V2 Receptors, on cAMP levels in the collecting duct and distal nephron and the role of cAMP in cystogenesis provided the rationale for preclinical trials of vasopressin V2 receptor (VPV2R) antagonists [89]. In particular, one of these drugs, OPC-31260, reduces the concentrations of cAMP and inhibits cyst development in animal models of ADPKD [90]. An antagonist with high potency and selectivity for the human VPV2R (tolvaptan) has also been shown to be an effective treatment in PKD2 mouse model of autosomal dominant polycystic kidney disease [91]. The usefulness of AVP-V2 inhibitors in slowing the progression of renal enlargement and insufficiency in patients with ADPKD is currently evaluating in a placebo-controlled trial (NCT00428948) [25]. Small clinical trials (NCT00309283, NCT00426153, and NCT00565097) have shown that the administration of octreotide or lanreotide for a period of 6 to 12 months inhibits the growth of polycystic kidneys and livers [92–94].

Another promising therapeutic strategy might involve inhibitors of mTOR. The absence of polycystin permits excessive kinase activity in the mammalian which is the target of rapamycin (mTOR) pathway and the development of renal cysts [26]. The mTOR system can be blocked by rapamycin (sirolimus, everolimus), so it may be another possible strategy to modulate disease progression in ADPKD patients. Wahl et al. [95] found that inhibition of mTOR with rapamycin slows ADPKD progression and kidney enlargement in rats. In a prospective study in humans, rapamycin reduced polycystic liver volumes in ADPKD renal transplant recipients [96]. Larger studies of longer duration are needed to confirm the safety and to sustain efficacy of these novel treatments.

Experimental and clinical studies have suggested that statins may slow the progression of chronic kidney disease in general and ADPKD specifically [97]. Statins are widely used to lower cholesterol, and they have anti-inflammatory and antiproliferative qualities. However, there are some reported animal studies in Han:SPRD rats, an ADPKD model with many of the characteristics of the disease in humans, that demonstrate that statins reduce cyst formation and improve renal function [98].

Moreover, Namli et al. have shown in patients with ADPKD that statins have a beneficial effect in the reversal of endothelial dysfunction, an early manifestation of vascular injury. Six months of simvastatin therapy resulted in a significant improvement of endothelial dysfunction in patients with ADPKD. This finding may be in part related to the pleiotropic effects of simvastatin [99].

A clinical trail is currently in progress at the University of Colorado regarding ADPKD and pravastatin

(NCT00456365) [100]. This study is designed to determine if the treatment with pravastatin can slow the progression of kidney and heart disease when initiated early in life in patients with ADPKD. This trial is expected to complete enrollment in 2011. The endpoints of interest in this three-year study include total kidney volume and LVH index as measured MRI; urinary albumin excretion and endothelial-dependent vasodilation as assessed by brachial ultrasound [100] (Table 3).

In conclusion, recent studies using different animal models of renal cystic diseases have suggested that various pharmacological interventions may modify disease progression. This clearly demonstrates that a better comprehension of the molecular and cellular defects underlying cystogenesis may lead to design novel therapeutic agents or a better use of existing ones. It is therefore likely that trials in human ADPKD will be carried out in the near future, especially as methods for assessing disease progression in the short term are now available [41, 101]. Other important thing is that genetic counseling to discuss genetic risk, screening, and prenatal and predictive testing should be offered to all individuals with or at risk of inheriting ADPKD.

5. Conflict of Interest

No authors have reported a conflict of interest.

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SAGE-Hindawi Access to Research
International Journal of Nephrology
Volume 2011, Article ID 351672, 11 pages
doi:10.4061/2011/351672

Review Article

Improving Prognosis Estimation in Patients with Heart Failure and the Cardiorenal Syndrome

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Received 22 September 2010; Accepted 17 February 2011

Academic Editor: Mitchell H. Rosner

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The coexistence of heart failure and renal dysfunction constitutes the "cardiorenal syndrome" which is increasingly recognized as a marker of poor prognosis. Patients with cardiorenal dysfunction constitute a large and heterogeneous group where individuals can have markedly different outcomes and disease courses. Thus, the determination of prognosis in this high risk group of patients may pose challenges for clinicians and for researchers alike. In this paper, we discuss the cardiorenal syndrome as it pertains to the patient with heart failure and considerations for further refining prognosis and outcomes in patients with heart failure and renal dysfunction. Conventional assessments of left ventricular function, renal clearance, and functional status can be complemented with identification of coexistent comorbidities, medication needs, microalbuminuria, anemia, biomarker levels, and pulmonary pressures to derive additional prognostic data that can aid management and provide future research directions for this challenging patient group.

1. Introduction: The Scope of the Cardiorenal Syndrome

Cardiac and renal dysfunctions often coexist. Approximately 70% of patients from community-based studies of heart failure (HF) have renal impairment, and 29% have moderate to severe renal dysfunction [1]. Furthermore, a published series from the Mayo Clinic reported that the serum creatinine levels of HF patients have increased steadily from 1987 to 2002 [2]. An analysis of the Candesartan in Heart Failure: Assessment of Reduction in Mortality and Morbidity (CHARM) trials demonstrated that the prevalence of renal dysfunction was similar among patients with preserved ejection fraction and those with systolic dysfunction [3]. Moreover, a comparison of patients with ischemic HF and idiopathic dilated cardiomyopathy revealed that renal dysfunction was common in both patient groups [4]. This suggests that renal dysfunction in HF does not simply reflect the degree of left ventricular dysfunction or systemic atherosclerosis. While a universal, simple definition of the cardiorenal syndrome (CRS) remains elusive, a classification scheme based on the underlying precipitant of the CRS has been proposed [5] (see Table 1).

Renal function is one of the strongest prognostic factors among patients with HF. In a meta-analysis of approximately 78,000 patients with HF, Smith et al. [1] showed that renal impairment portended an increased risk of death, with an adjusted hazard ratio (HR) of 1.56 (95% CI: 1.53–1.60, $P < .001$). Hillege et al. [3] demonstrated that this risk was observed across the range of eGFRs below 60 mL/min/1.73 m^2. The negative prognosis associated with a 10 mL/min/1.73 m^2 decline in eGFR was comparable to that of a 5% decline in left ventricular ejection fraction (LVEF). Moreover, the prognostic value of eGFR was not significantly different among patients with reduced or preserved left ventricular ejection fraction. However, it has been

Table 1: Classification scheme of the different types of the cardiorenal syndrome.

Type	Name	Description
1	Acute CRS	Acute worsening of heart function leading to kidney injury and/or dysfunction
2	Chronic CRS	Chronic abnormalities in heart function leading to kidney injury and/or dysfunction
3	Acute renocardiac syndrome	Acute worsening of kidney function leading to heart injury and/or dysfunction
4	Chronic renocardiac syndrome	Chronic kidney disease leading to heart injury, disease, and/or dysfunction
5	Secondary CRS	Systemic conditions leading to simultaneous injury and/or dysfunction of heart and kidney

suggested that renal dysfunction might be associated with worse outcomes in patients with idiopathic cardiomyopathy, compared to those with an ischemic HF etiology [4].

Accordingly, patients with combined cardiac and renal dysfunction constitute a high risk group that is also large and heterogeneous, supporting the need for additional parameters to further delineate their risk of death and/or disease progression. The strongest prognostic information for these patients will continue to be derived from LVEF, estimates of renal function and New York Heart Association (NYHA) functional status. However, other clinical variables may play an increasingly important role in risk stratifying this large patient group with the ultimate aim of targeted interventions to improve outcomes.

2. Measurement of Renal Dysfunction in Heart Failure

Renal function can be estimated in several ways, yielding different estimates of eGFR. This becomes especially prominent among CHF patients whose body compositions might be markedly different than the chronic kidney disease (CKD) populations in whom these formulas were derived. Smilde et al. prospectively validated the accuracy and prognostic value of the Cockcroft-Gault (CG), Modification of Diet in Renal Disease (MDRD), and simplified MDRD (sMDRD) equations among patients with HF by comparison with the gold standard of ^{125}I-iothalamate clearance [6]. All three formulas overestimated GFR in the lower ranges (<35 mL/min/1.73 m^2), underestimated it in the upper ranges (>65 mL/min/1.73 m^2), and functioned best in patients with NYHA classes III and IV. The MDRD was the most precise formula, while the CG was marginally more accurate. In comparison with directly measured GFR, the best prognostic value for cardiovascular outcomes came from creatinine clearance measurements using 24-hour urines and the MDRD equation, while the CG equation provided the least prognostic value. It has been reported that serum urea levels can also provide valuable prognostic information in CRS [7].

Accordingly, 24-hour urine collections should be periodically considered for determination of creatinine and urea clearance in HF patients with eGFR <35 mL/min/1.73 m^2, especially if heart transplantation or renal replacement therapy are being considered. Since creatinine is actively excreted into urine while urea is actively reabsorbed, measured creatinine clearance can significantly overestimate GFR in advanced CKD while urea clearances underestimate it. Thus, one method to estimate the GFR is to average both the creatinine and urea clearances, although this will require further study. There may be other potentially useful approaches to determine cardiorenal prognosis for HF patients including CG adjusted for body surface area [8], cystatin-C [9–14], and the Mayo eGFR formula [7].

3. Identifying Patients at Risk for Worsening Renal Function Based on Comorbid Conditions

A careful history of coexistent medical conditions can identify features that may increase the risk of subsequent renal compromise. Forman et al. examined risk factors for worsening renal function (WRF; defined as rise in serum creatinine of >0.3 mg/dL) among 1,004 consecutive patients admitted for a primary diagnosis of HF [15]. The highest risk of WRF was associated with elevated creatinine at admission. However, the presence of diabetes (adjusted hazard ratio [HR] 1.40) and a systolic blood pressure >160 mmHg (adjusted HR 1.37) were associated with a comparable risk of WRF to that of a history of prior HF (adjusted HR 1.31). A score derived from the regression model was useful in stratifying patient risk of WRF as shown in Table 2.

Other reported risk factors for WRF that can be identified at the time of admission for HF include

(i) rales/pulmonary edema [16, 17],

(ii) tachycardia [16],

(iii) female gender [16],

(iv) atrial fibrillation [17],

(v) peripheral arterial disease [17].

4. Cardiorenal Syndrome and Medications

The medications used by a patient can also provide insight into the stability of their cardiorenal axis. Furosemide is the one of most commonly prescribed medications among patients with HF, being used in over in 85% of outpatients at the time of hospital discharge [18]. Furosemide doses also frequently change among outpatients with HF [18]. In a study of 4,406 elderly patients discharged from an HF hospitalization, the prescription of higher furosemide doses (≥120 mg/day) was more common among patients with higher creatinine levels, preadmission furosemide use, ischemic or valvular HF etiology, diabetes, atrial fibrillation, and COPD. Patients who were prescribed higher furosemide

Table 2: Risk score developed by Forman et al. to predict worsening renal function [15].

Risk factor			Points	
History of HF			1	
Diabetes			1	
Systolic blood pressure >160 mmHg at admission			1	
Creatinine levels ≥1.5 and <2.5 mg/dL			2	
Creatinine levels ≥2.5 mg/dL			3	
Score	*n*	% of patients with score	% of Patients with worsening renal function	Relative risk
0	123	12.3	9.8	Referent
1	257	25.6	18.7	1.9
2	251	25	20.3	2.1
3	155	15.4	30.3	3.1
4+	218	21.7	52.8	5.4

doses were also more likely to exhibit hypotension, cardiomegaly, hyponatremia, and lower haemoglobin levels.

After extensive adjustment for covariates, exposure to higher furosemide dose was found to be predictive of death, hospitalization and renal dysfunction over five years of followup. Compared with the low-dose group (≤59 mg/day of furosemide), medium dose exposure (60–119 mg/day) was associated with increased mortality with an adjusted hazard ratio of 1.96 (95% CI: 1.79–2.15) while high dose exposure conferred an even greater mortality risk with a hazard ratio of 3.00 (95% CI: 2.72–3.31; both $P < .001$). There was a comparable increase in the risk of death both in and out of hospital, raising the possibility of an increased risk of both pump failure and sudden death. These potential mechanisms of death were supported by the observation of a higher risk of arrhythmias with increasing furosemide doses. Moreover, there was a dose-dependent increase in hospitalization risk that was strongest for HF events, suggesting that the adverse outcomes are most specifically related to HF progression. Similarly, the risk of renal dysfunction rose with increasing furosemide exposure, such that medium dose and high dose furosemide were associated with adjusted hazard ratios of 1.56 (95% CI: 1.38–1.76) and 2.16 (95% CI: 1.88–2.49) compared to the low dose group [18]. These findings were concordant with prior observations [19–22], suggesting that furosemide dose may represent a valuable "pharmamarker" of cardiorenal dysfunction, whose utility is enhanced by its ubiquitous use and dynamic nature that may indicate changes in HF control over time.

Treatment with angiotensin converting enzyme (ACE) inhibitors or angiotensin-receptor blockers (ARBs) was associated with improved prognosis in this study of furosemide use. As a reflection of their heightened risk, the high-dose furosemide group was less likely to be treated with ACE inhibitors [18]. This mirrors the results of a retrospective analysis of the Minnesota Heart Survey where ACE inhibitor or ARB use was compared among 2,169 patients hospitalized with HF. There was progressively lower utilization of ACE inhibitors with declining eGFR. However, the in-hospital use of ACE inhibitors or ARBs was independently associated with significantly reduced 30-day mortality with an adjusted odds ratio of 0.45 (95% CI: 0.28–0.59). Moreover, the discharge prescription of an ACE inhibitor or ARB was associated with a significant reduction in adjusted 1-year mortality with odds ratio of 0.72 (95% CI: 0.58–0.91) [23]. However, there appears to be no mortality benefit associated with ACE inhibitor or ARB use among dialysis patients [23].

The most common concerns with ACE inhibitors and ARBs include worsening renal function and/or hyperkalemia [24]. However, patient subgroups with perceived contraindications to ACE inhibitors, including those with renal dysfunction, may tolerate high-dose ACE inhibitors well [25]. In a review of 12 randomized clinical trials of ACE inhibitors in patients with renal dysfunction (serum creatinine >1.4 mg/dL), acute increases in serum creatinine of up to 30% that stabilize within the first two months of ACE inhibitor therapy were strongly predictive of long-term preservation of renal function. This prompted the authors to recommend that ACE inhibitors should only be withheld when the creatinine rise exceeds 30% above baseline within the first 2 months of initiation or if hyperkalemia develops [26]. Moreover, an analysis from the Digitalis Investigation Group trial showed that among patients with perceived contraindications to ACE inhibitors (most commonly renal insufficiency), use of ACE inhibitors was associated with significant survival benefit at four-year followup [24].

5. (Micro)albuminuria

Albuminuria is a convergence point for several physiological derangements common in HF and CKD such as volume overload, hypertension, diabetes, and inflammation [27–29]. The presence of proteinuria can serve as a marker of structural kidney damage [30–32] that can precede overt declines in renal function [33, 34]. Indeed, the presence of dipstick proteinuria with nearly normal renal function portends a higher risk of reaching end-stage renal disease than stage 4 CKD in the absence of a positive dipstick test [33, 34]. HF can also lead to albuminuria even in the absence of overt kidney dysfunction [35]. Nevertheless, albuminuria is more prevalent in HF patients with lower eGFR [35–37]. In the Valsartan in HF Trial, 5.6% of patients without CKD

(i.e., those with eGFR ≥60 mL/min/1.73 m^2) had dipstick-positive proteinuria compared to 10% of those with renal dysfunction [35]. In the Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto miocardico (GISSI-HF) trial, impaired renal function (eGFR <60 mL/min/1.73 m^2) was present in 30.1% of patients with normal urinary albumin excretion, 45.0% of those with microalbuminuria, and 53.0% of those with albuminuria [37]. It has been well reported that albuminuria is associated with worse outcomes in apparently healthy subjects as well as patients with cardiovascular disease, diabetes, and CKD [33, 34, 38–44].

The urinary albumin to creatinine ratio may further refine risk in patients with HF. In an analysis of 2,310 patients from the CHARM program [36], those with an elevated urinary albumin to creatinine ratio were older, had worse renal function, and had higher diabetes prevalence. They were also more likely to have been admitted for HF, and a higher proportion had NYHA functional class III or IV symptoms at randomization. The presence of microalbuminuria independently predicted a higher rate of adverse events, with hazard ratios for death of 1.62 (95% CI: 1.32–1.99) for microalbuminuria and 1.76 (95% CI: 1.32–2.35) for macroalbuminuria compared to normoalbuminuria (both comparisons $P < .001$) [36]. Similar observations were reported in two subsequent studies [35, 37], one of which demonstrated a progressive increase in the risk of death throughout the range of UACR's [37]. The proposed mechanisms of the increased risk associated with proteinuria are beyond the scope of this paper but have been reported elsewhere [45].

6. Anemia

Anemia is a common condition in both HF and CKD. Its estimated prevalence in patients with HF varies between 12–50% based on the cutoffs used [46–51]. In a meta-analysis of 153,180 HF patients from 34 studies, 37.2% were anemic [49]. The prevalence of anemia appears to be similar in patients with preserved and reduced left ventricular systolic function [51–53]. It is also a well-established feature of CKD, with anemia prevalence of 27% when eGFR is ≥60 mL/min/1.73 m^2 to 75.5% in the presence of end-stage renal disease [54]. While the etiology in advanced kidney disease is believed to be mostly related to decreased erythropoietin production [55, 56], the anemia of HF is marked by elevated erythropoietin levels, although the elevation is often lower than expected for the degree of anemia [57, 58]. This may be a consequence of the heightened inflammatory state that marks the HF syndrome [48, 57–59]. These factors may explain the inconsistent responses to erythropoietin stimulating agents in HF. Positive responses were observed in early, small trials but were not consistently replicated in larger trials with hard endpoints [60–63], including the TREAT trial which showed a higher stroke risk with darbepoetin alfa among patients with CKD and type 2 diabetes, approximately 1/3 of which had HF [61].

HF and CKD also share other elements that could contribute to anemia such as iron deficiency, B12, folate and other nutritional deficiencies, and hemodilution [55–57, 60, 64–67]. In addition, both disease states commonly require the use of ACE inhibitors which decrease erythropoietin levels [68] and impair the breakdown of hematopoeisis inhibitors [58]. In a study of 59,772 adults with HF, the prevalence of anemia was 37% in patients with eGFR >60 mL/min/1.73 m^2 compared to 82% in those with stage 5 CKD [69]. Thus, HF and CKD may act synergistically to increase the prevalence of anemia. Additionally, anemic HF patients are more likely to be older with comorbid diabetes, lower blood pressure, higher diuretic use, higher NYHA functional class, reduced exercise capacity, worse quality of life, and increased neurohormonal activity [46–48, 50, 51, 57, 60, 62, 65]. The presence of anemia is also linked to a greater risk of death and hospitalization among patients with HF [48, 49, 53, 69]. In the meta-analysis by Groenveld et al., 46.8% of anemic patients died compared with 29.5% of non-anemic patients among 153,180 patients followed for a minimum of 6 months [49]. Anemia was also associated with a hazard ratio of 1.43 for HF hospitalizations among 3,029 patients with NYHA class II to IV functional status and left ventricular ejection fraction <35% [53].

The mortality risk associated with anemia appears to be similar among patients with preserved or reduced ejection fraction [52]. However, the mortality risk is nonlinear so that it is disproportionately weighted towards patients with more severe anemia [48, 53, 69]. Some reports have suggested that the relationship is better approximated by a J-shaped curve such that the risk of death may also be increased in patients with supranormal hemoglobin levels [53, 69]. Among patients with CKD, anemia is also predictive of development of end-stage renal disease [70], cardiovascular events [71], and death [70, 71]. The contribution of anemia to mortality risk is dependent on the degree of renal dysfunction, likely reflecting the dominant effect of renal dysfunction on mortality risk in the CRS. For example, in the study by Go et al., the presence of hemoglobin <9.0 g/dL was associated with a hazard ratio for death of 5.91 in patients with eGFR >60 mL/min/1.73 m^2, while the hazard ratio was 1.99 in patients with eGFR <30 mL/min/1.73 m^2 [69].

7. Biomarkers

The introduction of cardiac troponin assays revolutionized the management of acute coronary syndromes (ACS) by providing a powerful diagnostic and prognostic tool. With widespread use came the recognition that cardiac troponins can also serve as strong prognostic markers in HF and CKD outside the ACS setting. Serum troponin levels are elevated in 6–50% of patients with acute HF and have been linked to an increased risk of death and cardiovascular events among hospitalized and ambulatory patients with HF throughout the spectrum of the disease [72–76] in a dose-response relationship [74]. In the setting of CKD, troponin measurements are frequently elevated in the absence of overt cardiac pathology [77–84], partly due to decreased renal clearance [85]. This CKD-associated elevation is more prominent for troponin T relative to troponin I [77, 78, 83].

Troponin elevation in CKD reflects ongoing myocardial damage and necrosis and is strongly associated with diabetes,

left ventricular dilatation, and impaired left ventricular systolic and diastolic function, without necessarily indicating the presence of severe coronary artery disease [86]. Elevations in troponin T have been more consistently linked to a poor prognosis in patients with CKD [77–84, 87–89], while studies conducted using troponin I have provided conflicting results [77, 78, 83]. In a meta-analysis of 3,931 patients from 28 studies, elevated troponin T (>0.1 ng/mL) was associated with increased all-cause mortality with a relative risk of 2.64 (95% CI: 2.17 to 3.20) in the setting of end-stage renal disease [78]. An important caveat is that blood measurements of troponin should be obtained just before dialysis [90].

B-type (brain) natriuretic peptide (BNP) and N-terminal pro-BNP (NT-pro-BNP) have also emerged as valuable markers of HF severity [91]. Since they have different clearance kinetics, their levels are not interchangeable, although they often correlate with each other. In particular, the clearance of NT-proBNP appears to be more affected by renal dysfunction than that of BNP [92]. However, both natriuretic peptides are elevated in patients with advanced CKD, suggesting that the elevation is multifactorial and not simply a result of decreased clearance [93–96]. Elevated levels of either natriuretic peptide are predictive of adverse outcomes among patients with HF. In a meta-analysis of 19 studies, each 100 pg/mL increase in BNP was associated with a 35% increase in the relative risk of death [97]. There is less data on the prognostic value of NT-proBNP in unselected patients with HF but it appears to confer similar information to BNP [98]. Natriuretic peptides are also predictive of outcomes in patients with preserved systolic function, where the severity of diastolic dysfunction has been found to correlate with increased levels of both BNP and NT-proBNP [99, 100]. The negative prognosis associated with natriuretic peptide elevation in CKD has been demonstrated in several studies [92].

The prognostic effects of these biomarkers are maintained in those with combined HF and renal disease. Their levels are still well correlated with left ventricular wall stress [101] and prognosis, although a higher NT-proBNP cutoff value is needed to separate patients with poor and intermediate prognosis. Bruch et al. compared the prognostic value of NT-proBNP in 183 ambulatory HF patients with CKD and 153 with eGFR >60 mL/min/1.73 m^2 and concluded that a cutoff value of 1,474 pg/mL best separated patients with poor and intermediate prognosis. Among patients with HF and CKD, cardiac event-free survival was 48% in patients above this cut-off compared with 93% in patients below it [102]. Anwarrudin et al. performed a similar analysis in patients presenting to the emergency department with HF, reaching the conclusion that NT-proBNP elevation was the strongest overall independent risk factor for 60-day mortality among those with eGFR <60 mL/min/1.73 m^2 with hazard ratio of 1.61 (95% CI: 1.14–2.26). NT-proBNP also independently predicted HF hospitalization with a hazard ratio of 1.26 [103].

The use of natriuretic peptides as prognostic variables requires attention to a few caveats. Firstly, natriuretic peptide levels are lower in obese patients, although they do maintain good diagnostic and prognostic value when used with appropriately lowered cut-offs [104]. Natriuretic peptides are also less useful in evaluating HF due to causes other than left ventricular dysfunction such as mitral stenosis or pericardial disease [91, 105, 106]. Ideally, natriuretic peptide levels should be used as a continuous variable that takes into account the patient's baseline levels if available [91].

The use of biomarkers in this setting will undoubtedly continue to grow. Neutrophil gelatinase-associated lipocalin (NGAL) is an early marker of acute kidney injury with improved kinetics in comparison to traditional markers of renal clearance [107, 108], which may independently predict prognosis in CRS [109–113]. Similarly, Cystatin C is a small serine protease inhibitor which is also being touted as a more accurate and earlier marker of renal dysfunction [10–14] and has already been shown to be a potent predictor of cardiovascular events and all-cause mortality in patients with and without overt cardiac or renal dysfunction [114–120]. The increasing utility of such biomarkers has sparked growing interest in "multimarker" approaches to assess disease severity and prognosis in the setting of the CRS [121–127]. However, it should be emphasized that biomarkers should be used as an adjunct to rather than a replacement for a full clinical assessment [128].

8. Pulmonary Hypertension

Pulmonary hypertension is a well-recognized consequence of HF, which constitutes Group 2 within the World Health Organization's classification of pulmonary hypertension [129]. Patients with CKD often have cardiac disease and pulmonary comorbidities such as sleep apnea that can lead to the development of pulmonary hypertension via increased left atrial pressure or chronic hypoxia in the absence of pulmonary arterial pathology [130–133]. The disproportionate prevalence of pulmonary hypertension in the absence of these causes within the CKD population is much less appreciated. In one study of patients with end-stage renal disease who did not have overt cardiac dysfunction or pulmonary disease, Doppler 2D echocardiography was used to estimate right ventricular systolic pressure 1-hour postdialysis, while at their dry weight. Of the study cohort, 39.7% had an estimated right ventricular systolic pressure >35 mmHg, while 13.8% had values >45 mmHg [130]. This high prevalence of pulmonary hypertension was replicated in two other studies from different continents [134, 135]. It is controversial whether pulmonary hypertension relates to the presence of end-stage renal disease itself or whether it is a consequence of dialysis, particularly via an arteriovenous fistula [130]. However, with reported prevalence of pulmonary hypertension as high as 39.1% in patients awaiting dialysis, and the improvement (and possible normalization) of right ventricular pressures among patients with end-stage renal disease after renal transplantation, evidence of an association is strengthened [130, 136].

The development of pulmonary hypertension in the presence of advanced CKD may be a harbinger of poor outcomes. In a study of 127 hemodialysis patients, 17 patients had pulmonary hypertension at dialysis outset, and 20 more developed elevated right-sided pressures after its

initiation. After multivariate adjustment, the presence of pulmonary hypertension prior to dialysis was associated with a hazard ratio of 3.6 for death (95% CI: 1.8–7.0) compared to patients without the condition at baseline. The development of new pulmonary hypertension after initiation of dialysis was associated with an adjusted hazard ratio for death of 2.1 (95% CI: 1.1–4.3) [133]. It remains unclear why the presence of pulmonary hypertension increases risk of death so prominently in the end-stage renal disease population that already has a high rate of events. The presence of pulmonary hypertension may be associated with higher risk of adverse outcomes because it may reflect (a) advanced cardiac or respiratory disease, (b) greater severity of kidney disease-associated endothelial dysfunction secondary to nitric oxide and endothelin-1 derangements [136–139], (c) greater derangement of calcium metabolism with greater subsequent vascular calcification [135], (d) a state of high cardiac output in patients with arteriovenous fistulas [130, 135, 136, 140, 141] which can induce high output HF, and (e) undiagnosed diastolic dysfunction, chronic volume overload, chronic hypoxia, or recurrent pulmonary embolic events [134, 135, 142].

9. Conclusion

The development of the CRS is linked to a marked increase in the rates of death and morbidity compared to patients with either HF or CKD in isolation. However, there are multiple widely available noninvasive factors that can help the clinician estimate prognosis more accurately within this large and heterogeneous patient group. An assessment of left ventricular ejection fraction, renal function, and functional status remain paramount. The identification of co-existent diagnoses may indicate a high risk of worsening renal failure during HF hospitalization. The use of high furosemide doses or nonuse of ACE inhibitors or ARBs may identify patients with a tenuous cardiorenal axis or possibly suboptimal medical management. The presence of concomitant microalbuminuria or anemia may also provide clues to greater severity of cardiorenal compromise. The use of biomarkers such as BNP, troponin, NGAL, and cystatin-C can provide additional information in monitoring this patient group. Finally, surveillance for pulmonary hypertension in patients with end-stage renal disease might allow for further refinement of prognosis in this patient group with its exceedingly high risk of death or morbidity.

Conflict of Interests

The authors have no conflicts of interest to declare.

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SAGE-Hindawi Access to Research
International Journal of Nephrology
Volume 2011, Article ID 413760, 5 pages
doi:10.4061/2011/413760

Research Article

Volume Assessment in Mechanically Ventilated Critical Care Patients Using Bioimpedance Vectorial Analysis, Brain Natriuretic Peptide, and Central Venous Pressure

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Received 6 July 2010; Accepted 28 September 2010

Academic Editor: Mitchell H. Rosner

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Purpose. Strategies for volume assessment of critically ill patients are limited, yet early goal-directed therapy improves outcomes. Central venous pressure (CVP), Bioimpedance Vectorial Analysis (BIVA), and brain natriuretic peptide (BNP) are potentially useful tools. We studied the utility of these measures, alone and in combination, to predict changing oxygenation. *Methods*. Thirty-four mechanically ventilated patients, 26 of whom had data beyond the first study day, were studied. Relationships were assessed between CVP, BIVA, BNP, and oxygenation index (O_2I) in a cross-sectional (baseline) and longitudinal fashion using both univariate and multivariable modeling. *Results*. At baseline, CVP and O_2I were positively correlated ($R = 0.39$; $P = .021$), while CVP and BIVA were weakly correlated ($R = -0.38$; $P = .025$). The association between slopes of variables over time was negligible, with the exception of BNP, whose slope was correlated with O_2I ($R = 0.40$; $P = .044$). Comparing tertiles of CVP, BIVA, and BNP slopes with the slope of O_2I revealed only modest agreement between BNP and O_2I (kappa = 0.25; $P = .067$). In a regression model, only BNP was significantly associated with O_2I; however, this was strengthened by including CVP in the model. *Conclusions*. BNP seems to be a valuable noninvasive measure of volume status in critical care and should be assessed in a prospective manner.

1. Purpose

Volume assessment and management in critically ill patients remains challenging [1]. Issues of timing, choice, amount of fluids, and type of volume assessments to guide therapy continue to be investigated. While early volume resuscitation and goal-directed therapy have been shown to improve mortality and morbidity [2, 3] and lessen the risk of acute kidney injury [3], management of patients with established acute lung injury reveals that a more conservative or "dry" strategy is more appropriate than a liberal or "wet" one [4]. Studies of the assessment of fluid status have shown that simple central venous pressure (CVP) monitoring is as effective, and safer, than more invasive means such as pulmonary artery occlusion pressure [5]. It is clear, however, that CVP does not tell the entire story, as patients with high right sided pressures may have reduced, normal, or increased effective circulating volume.

Bioimpedance vectorial analysis (BIVA) allows determination of extracellular fluid volume and total body water from measurements of resistivity of tissues to single or multifrequency emitted signals. BIVA has been used to

manage volume in hemodialysis patients for several decades. However, the use of BIVA in critically ill patients has not been extensively studied, and the data used to determine volume status have been derived from hemodynamically stable patients [6, 7].

Brain natriuretic peptide (BNP) is a biomarker used to identify patients with fluid overload and congestive heart failure [8]. In critical care, it has been shown to correlate with mortality and morbidity, though it has not been used to guide therapy [9, 10].

We conducted a pilot study to examine the relationships between CVP, BIVA, and BNP in order to determine which measure, or combination of measures, relate to volume status in critically ill, ventilated patients.

2. Methods

This study was approved by the Institutional Review Board of the San Bortolo Hospital, Vicenza, Italy, and conducted in the Intensive Care Unit (ICU). Any adult patient requiring mechanical ventilation was eligible. Because of the technical requirements for BIVA, patients with any upper or lower limb amputation, severe rhabdomyolysis, or erysipelas of both upper or lower limb were excluded. As the study required serial measurements over time, any patient not expected to survive 72–96 hours was excluded. Any patient with recent cardiac surgery was also excluded, as BNP and CVP may be grossly skewed. Likewise, patients with decompensated heart failure or acute coronary syndrome were excluded. As published, BIVA vectors were derived in Caucasians [6], we excluded non-Caucasians. A sample size of 30–40 patients was enrolled without formal sample-size calculations.

Within 48–72 hours of initiating mechanical ventilation, baseline assessment was undertaken including CVP, BIVA, and blood sample for BNP, hematocrit, and creatinine. BNP was determined using Triage MeterPro (Biosite Inc., San Diego, CA). CVP and BIVA were recorded in a blinded fashion by separate trained observers. CVP was obtained through a central venous catheter connected to a calibrated transducer using the level of the right atrium as a reference point. BIVA was performed using a plethysmograph emitting 800-μA and 50-kHz alternating sinusoidal current (EFG Electrofluidgraph, Akern s.r.l., Pontassieve, Florence, Italy) and previously published methods [11]. Clinical data were recorded, including primary illness, systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial pressure (MAP), heart rate (HR), weight, urine output, pressor doses, PO_2, FiO_2, and mean airway pressure. Additional measurements were made at 24 and 48 hour intervals to minimize diurnal variation in BNP. The fluid balance in the intervening period was calculated.

CVP was categorized as "low" (<4 cm H_2O), "high" ($\geq$14 cm H_2O), or "normal" (4–14 cm H_2O) [4]. For the BIVA, three patterns were considered according to published references for resistance/height (R/H) based on normals, adjusted for age, sex, and weight [7]: long vectors outside the 75% tolerance ellipse (upper pole of the target) were categorized as "dehydrated" and short vectors outside the 75% tolerance ellipse (lower pole of the target) as "hyperhydrated", while the remainder were "normohydrated". BNP was considered as a continuous variable and also divided into tertiles. Oxygenation index (O_2I) was calculated as the mean airway pressure divided by the ratio of PO_2/FiO_2 and multiplied by 100 [4], and the result was then divided into tertiles.

Using least-squares regression, measures of CVP over time were used to estimate slope, and ΔCVP was categorized as "falling" (<$-$2 cm/24h), "rising" (>2 cm/24 h), or "stable" (ΔCVP from -2 to 2 cm/24 h). BIVA change over time was estimated as the slope of R/H by time, and >30 ohm/m/day was categorized as "falling ECF"; <$-$30 ohm/m/day was "rising ECF", and values within $\pm$30 ohm/m/day were considered "stable ECF". Absolute values of BNP were used to estimate slope of BNP, and these slopes were divided into tertiles. Slope of O_2I was grouped into tertiles. In the event that a patient was extubated, the last available mean airway pressure was carried forward, and the most recent arterial blood gas values were used to estimate the O_2I for the purpose of calculating the slope.

The agreement between slopes of CVP, BIVA, and BNP against O_2I were estimated using Kappa statistics. Univariate correlations were assessed at baseline for O_2I, CVP, BIVA, and BNP. Slopes of change were also assessed between these variables and hemodynamic parameters, fluid balance, and other clinical parameters such as hematocrit and creatinine. Multiple linear regression was performed with O_2I and ΔO_2I as continuous dependent variables.

3. Results

Thirty-four patients were enrolled in the study, 22 (64.7%) were male, and the most common admitting diagnosis was trauma, in 12 (35.3%). Remaining baseline characteristics are presented in Table 1. The majority of patients were not on pressors or inotropes at baseline, and the mean noradrenaline dose was 0.007 ± 0.004 μcg/kg/min; dopamine was 1.6 ± 0.5 μcg/kg/min. In cross-sectional analysis at baseline, there was no relationship between tertiles of CVP, BIVA or BNP with O_2I; however, a weak correlation could be demonstrated between the continuous variables of CVP and O_2I ($R = 0.39$; $P = .021$) (see Figure 1) and a weak negative correlation between CVP and BIVA ($R = -0.38$; $P = .025$).

Twenty-six subjects had data available beyond the first study day to allow estimation of slopes of change of CVP, BIVA, BNP, and O_2I. For these subjects, mean slope of change of CVP was 0.03 mmHg/day, slope of BIVA was -6.1 ohm/m/day, slope of BNP was 60.3 pg/mL/day and slope of O_2I was 0.12 per day.

Comparing tertiles of CVP, BIVA, and BNP slopes with the slope of O_2I revealed modest agreement between BNP and O_2I (kappa = 0.25; $P = .067$) and no agreement between the other variables. The relationship between tertiles of BNP and O_2I slope is depicted in Figure 2. Similarly, using Spearman correlation, the slope of BNP was weakly correlated with O_2I ($R = 0.40$; $P = .044$) as shown in Figure 3. In a regression model examining all of the baseline variables and slopes of CVP, BIVA, and BNP as potential

Table 1: Baseline characteristics ($N = 34$).

Clinical variable	Mean	Standard error
Age (years)	59.2	3.6
SOFA[a] score day 1	7.1	0.4
CVP (cm H_2O)	10.4	0.6
Resistance by height (ohm/m)	262.3	14.4
BNP (pg/mL)	451.1	119.3
Hematocrit	0.32	0.01
Creatinine (mg/dL)	1.36	0.22
Systolic BP (mmHg)	132.8	4.5
Diastolic BP (mmHg)	58.1	2.0
Heart Rate (beats per minute)	82.3	3.5
Mean Arterial Pressure (mmHg)	89.9	2.8
PEEP (mmHg)	9.3	0.5
Mean Airway Pressure (mmHg)	14.4	0.6
P/F ratio	288.4	18.8
Oxygenation index	5.8	0.5

[a]Sequential Organ Failure Assessment score.

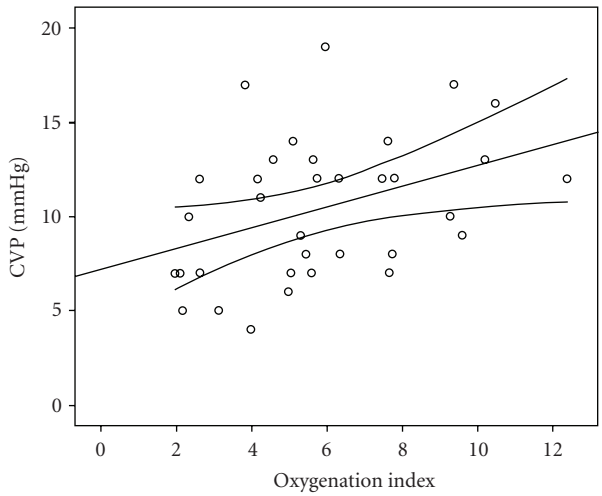

Figure 1: Correlation (with 95% confidence intervals) between baseline CVP and Oxygenation Index ($R = 0.39$; $P = .021$).

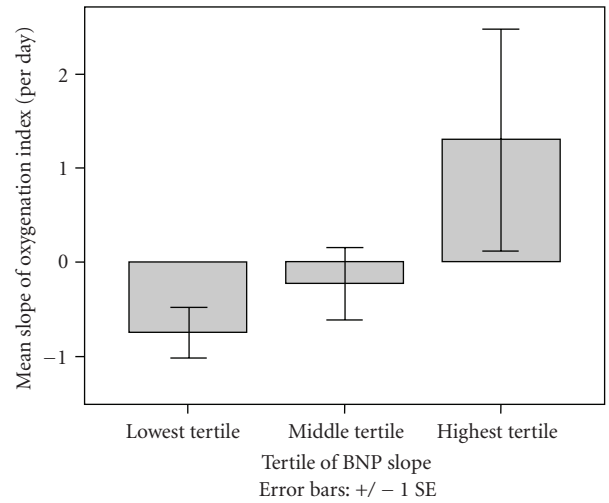

Figure 2: Mean slope of change of Oxygenation Index is shown categorized according to tertile of slope of change of BNP. Absolute difference between highest and lowest tertile 2.05 ± 1.04, $P = .067$ (ANOVA).

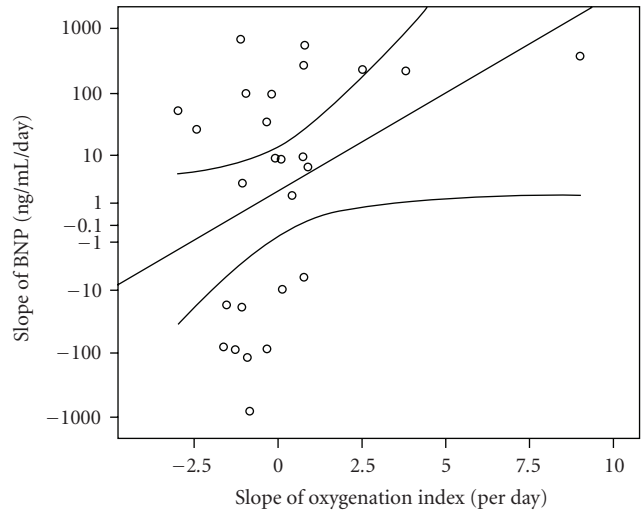

Figure 3: Correlation (with 95% confidence intervals) between slope of BNP and slope of Oxygenation Index ($R = 0.40$; $P = .044$).

variables, only BNP was significantly associated with O_2I, and this was strengthened by including CVP in the model. For each tertile increase in the slope of BNP, O_2I increased by 1.29 (95% CI 0.18–2.41; $P = .025$).

4. Conclusions

This is the first study attempting to find the most appropriate combination of minimally invasive bedside tools for volume assessment in critically ill patients requiring mechanical ventilation. While none of the markers at baseline, individually or in combination, were helpful in predicting those subjects whose oxygenation would improve or worsen, we identified that changes in BNP over time were correlated with important changes in O_2I. Furthermore, there was some indication that combining CVP and BNP in multivariable modeling further strengthened the latter variable's association with change in O_2I.

It is intuitive to think that measures of volume, be they measures of intravascular or extravascular (interstitial) volume, would be related to lung function and oxygenation. For instance, animal studies have shown that fluid balance can influence both the onset and resolution of severe "high-permeability" pulmonary edema [12, 13]. Excess extravascular lung water is a feature of all types of pulmonary edema

[14], and lower extravascular lung water correlates with fluid balance, decreased ventilator days, and ICU length of stay [15]. We chose CVP since local practice was such that most mechanically ventilated patients had central venous access appropriate for measurement of CVP. Furthermore, studies indicate a high level of agreement between clinical measures such as the external jugular pressure and the CVP [16]; hence, a ready estimate of CVP would be available in all subjects. We chose BIVA for its ease of use and noninvasive nature and its ability to provide an estimate of extravascular water. BNP was chosen for its ability to respond to myocardial stretch [17] and its utility in previous studies as a predictor of outcome [9, 10].

We did not find the addition of measures of BIVA to help in the fluid assessment of our cohort of patients. Previously, Piccoli and colleagues [6] demonstrated a modest degree of inverse correlation between CVP and impedance vector components, though this was stronger in the group that had significantly elevated CVP and weaker in the group with lower CVP. These authors suggested that the combination of CVP and BIVA might be useful in the volume assessment and management of critically ill patients. We were unable to demonstrate any correlation between BIVA and CVP, nor was the combination predictive of oxygenation. The principle difference between our study and that of Piccoli is that the minority of patients in the latter study were receiving mechanical ventilation, while this was a requirement for eligibility in our study. This may have played a role since mechanical ventilation with positive end-expiratory pressure (PEEP) likely and systematically elevated the CVP and possibly weakened any potential relationship between CVP and BIVA. Moreover, all the patients in our study had relatively high values of PEEP (8–10 cmH_2O).

We were able to demonstrate that change in BNP was associated with change in O_2I, and this relationship was strengthened modestly in multivariable regression by including slope of change of CVP. The choice of O_2I as an outcome may be justly criticized as a surrogate, but the study population was not large enough for us to predict more clinically important outcomes such as lung injury scores, length of ICU stay, or days of mechanical ventilation, for example. However, O_2I has been shown to be strongly associated with these more important outcomes in the Acute Respiratory Distress Syndrome (ARDS) clinical trials network study [4]. Another limitation of the study is that the methods used to assess volume were not compared against other methods such as echocardiography, ultrasound of the inferior vena cava, pulse pressure variation, or strove volume variation. This is a fair criticism; however, the study presented is the first in a series of pilot endeavours, the intent of which is to examine varying combinations of volume assessment. Additional studies utilizing the FloTrac Sensor and Vigileo Monitor (Edwards Lifesciences, S.A., Saint-Prex Switzerland) to measure stroke volume variation in critically ill patients in our institution are underway.

A larger study would have allowed us to explore more extreme values with greater confidence. For instance, inspection of the figures reveals greater variability at the extremes, and a larger sample size would have allowed a more sophisticated analysis of the relationships to see if nonlinear modeling would have provided a tighter fit with the data.

An additional limitation is the patient population, in whom the predominant admitting diagnosis was trauma (approximately one third). While the remainder had a variety of conditions including respiratory failure, decreased level of consciousness, sepsis, and intracranial hemorrhage or stroke; generalizability to the critical care population as a whole is difficult. Another potential limitation relates to our choice of waiting for 48–72 hours to enroll patients, during which time they could have stabilized to a point that may have dampened the strength of the relationships we observed.

Our results are consistent with the recent work of Levitt and colleagues [18], who carried out a similar prospective cohort study of critically ill patients and compared various measures of volume status. As in their study, we found no relationship between CVP and BNP over time. However, our study differs in that we examined the combination of these parameters in multivariable modeling and found them to provide complementary information in predicting improvements in oxygenation.

In summary, bedside measures of volume status, CVP and BIVA, were unhelpful alone in predicting favorable changes in O_2I, while changes in BNP over time did correlate with changes in O_2I. There was some indication that combining CVP and BNP improved the ability to predict change in O_2I. Whether or not interventions to optimize both CVP and BNP will result in improved outcomes in ventilated, critically ill patients will require further prospective study.

Acknowledgments

The authors are deeply grateful to the physicians and nurses of the San Bortolo Hospital Intensive Care Unit for their assistance in identifying eligible subjects for the study, and for capturing the important hemodynamic and clinical parameters necessary for the analysis.

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SAGE-Hindawi Access to Research
International Journal of Nephrology
Volume 2011, Article ID 365301, 8 pages
doi:10.4061/2011/365301

Review Article

Correction of Iron Deficiency in the Cardiorenal Syndrome

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Received 9 July 2010; Accepted 23 February 2011

Academic Editor: Anjay Rastogi

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Impaired energy metabolism is a feature of Congestive Heart Failure (CHF). Iron deficiency has been shown to reduce energy production in the cell in animals and humans. Iron deficiency is common in both Chronic Kidney Disease (CKD) and in CHF. Recent studies suggest that iron deficiency is an independent risk factor for mortality in CHF. Studies of correction of the anemia with intravenous (IV) iron in both CKD and CHF have shown an improvement in the anemia and, in some cases, in the renal function as well. Some CHF studies of correction of the iron deficiency have shown an improvement in cardiac function and structure as well as in exercise capacity and quality of life. This occurred independent of whether or not they had anemia, suggesting that the iron deficiency itself may be independently contributing to the worsening of the CHF and CKD. If future long-term studies confirm the safety and efficacy of IV iron in the treatment of iron deficiency in CKD and CHF, this will become a new addition to the therapeutic armamentarium of the cardiorenal syndrome, and parameters of iron deficiency will become part of the routine measurements performed in both CKD and CHF whether or not the patient is anemic.

1. Introduction

Impaired energy metabolism is a feature of the Congestive Heart Failure (CHF) syndrome [1]. The failing heart is an energy-starved heart, and energy-sparing treatments such as beta blockers, ACE inhibitors, or Angiotensin II blockers improve the prognosis [1]. Iron metabolism is crucial in all aspects of energy production in the body [2–4] and is particularly important for cells that are characterized by high energy demands such as skeletal myocytes and cardiomyocytes [2–4]. Iron has the ability to shuttle between two oxidative states, (ferric and ferrous iron) which makes it an efficient cofactor for several enzymes and the catalyst of numerous biochemical reactions [2–4]. The ferrous form Fe II can donate electrons while the Fe III form can accept electrons. Iron plays a crucial role in oxygen transport (as a component of hemoglobin (Hb)), oxygen storage (as a component of myoglobin), and oxidative metabolism (as a component of oxidative enzymes and respiratory chain processes).

It is also involved in the synthesis and degradation of lipids, carbohydrates, DNA, and RNA and in the metabolism of collagen, tyrosine, and catecholamines [2–4].

Therefore, iron deficiency can impair oxidative metabolism, cellular energetics, and cellular immune mechanisms. Iron deficiency in experimental models causes a major disruption in energy production and can lead to cardiac damage and dysfunction [5, 6]. Even in otherwise normal people, iron deficiency can reduce endurance and optimal energetics of skeletal muscle even if no anemia is present initially [7–10].

There is growing evidence that iron deficiency is common in CHF and may contribute to the increased mortality in this condition and that correction of the iron deficiency with IV iron can improve both cardiac and renal function, symptoms of CHF, exercise endurance, inflammation, and quality of life and may reduce hospitalization. However, more studies are needed to confirm this. Thus, correction of iron deficiency could become an important new addition to the treatment of the cardiorenal syndrome.

2. Prevalence of Iron Deficiency in CHF with and without Anemia and Its Prognostic Significance

The prevalence of iron deficiency in CHF depends on how iron deficiency is defined. If merely defined as a % Transferrin Saturation (%TSat) of <16, it was found in one preliminary study in 78% of anemic and 61% of nonanemic CHF patients, whereas if it was defined as a %TSat of <16 and a serum ferritin of 30–100 ug/L, it was found in only 15% of anemic and 20% of nonanemic CHF patients [11]. In one study of CHF patients, a low serum iron was found in 31% of anemics and 7% of nonanemics, a low serum ferritin in 21% of anemics and 7% of nonanemics, and at least one of the two in 43% of anemics and 15% of nonanemics [12]. In a study of CHF patients undergoing coronary stenting, 31% had iron deficiency as judged by a low serum iron and increased Total Iron Binding Capacity. Iron deficiency anemia strongly predicted cardiac mortality [13]. In another study of anemia in CHF, about half the patients had serum iron levels below normal, and the great majority of anemic patients also had an elevated soluble transferrin receptor (a quite dependable measure of iron deficiency) [14]. In a study of anemia in severe CHF, markedly reduced iron stores in the bone marrow were found in 73% of the cases [15] even though the great majority had a normal serum ferritin level.

In the largest observational study done to date [16], a prospective observational study, 546 patients with stable systolic mild to severe CHF were followed for a mean of 731 ± 350 days. Patients with severe renal disease were excluded and indeed the mean calculated glomerular filtration rate (GFR) was 80.5 mL/min/1.73 sq m. Iron deficiency was defined as a serum ferritin <100 ug/L or 100–300 ug/L with %TSat <20%. The prevalence of iron deficiency was 37 ± 4% for the entire population and was 32 ± 4% in the nonanemics and 57 ± 10% in the anemics (anemia was defined as a Hb < 12 g/dL in women and <13 g/dL in men). Even in those with mild heart failure as judged by NYHA I and II, the frequency of iron deficiency did not drop below 30%. The prevalence of iron deficiency was related to the female sex, the severity of the CHF as judged by the New York Heart Association class (NYHA) and by the Beta Natriuretic Peptide (BNP), and the severity of the inflammatory process as judged by C Reactive Protein (CRP). In univariate models, the 3-year survival rate was 59% in the iron deficiency group and 71% in the noniron deficiency group ($P = .0006$). In multivariable analysis, iron deficiency was considered an independent predictor of all-cause mortality after adjustment for confounders including anemia and severity of the CHF. The effect was seen as early as 6 months. The inclusion of anemia in the multivariable models did not change significantly the significance suggesting that iron deficiency may be a stronger prognostic indicator of survival than anemia. Thus, iron deficiency, independent of anemia and cardiac function, is related to a poor outcome in CHF.

Therefore absolute iron deficiency (defined as a serum ferritin < 100 ug/L and %TSat < 20%) or functional iron deficiency (defined as a serum ferritin > 100 ug/L and %TSAT < 20%) are commonly seen in CHF patients with anemia or even without anemia and are associated with an increased mortality.

3. Does Correction of the Anemia with Erythropoiesis Stimulating Agents (ESA) in Patients with CHF Improve the CHF?

Several metaanalyses which included nonplacebo controlled studies, and placebo-controlled studies of ESA along with oral or IV iron have shown improvement in many aspects of CHF without causing undesirable side effects [17–21]. But all of these studies have been small and/or short term and a total of about only 700 patients in all have been studied. On the other hand, in a larger metaanalysis of ESA treatment in CHF that included the CHF patients in the TREAT study, the Reduce Cardiovascular Events with Aranesp (TREAT) study in diabetics with renal insufficiency, pooled data from 9 placebo-controlled studies enrolling a total of 2,039 anemic CHF patients treated with ESA was associated with a neutral effect on both mortality and nonfatal heart failure events [22]. Therefore, the value of ESA in the anemia of CHF is still uncertain.

4. Growing Concern about the Safety of ESA

There is growing concern about the safety of ESA because of the hypertension, increased thrombotic events, and other cardiovascular complications and possible increased cancer risk seen with its use in CKD [23–25] so that there is growing interest in the use of IV iron alone or at least as the first step in the treatment of the anemia of CKD and CHF before an ESA is started.

5. Does Correction of Iron Deficiency in Patients with CHF Improve the CHF?

Six studies where intravenous (IV) iron has been used in iron-deficient CHF patients have been performed, but only two were placebo-controlled double blind studies [26, 27].

In one of these two studies [26], a single center study, 40 patients received either IV iron as iron sucrose (Venofer, Vifor Int Zurich) 200 mg a week for 5 weeks or a placebo infusion. Their Hb was <12.5 d/gL for men and <11.5 g/dL for women. Their initial serum ferritin was < 100 ng/mL and/or %TSat ≤20%. At 6-month followup there was a significant improvement in the Hb levels, NYHA, Left Ventricular Ejection Fraction (LVEF), 6 minute walk test (6MWT), hospitalization rate, Minnesota Living with Heart Failure Questionnaire Quality of Life (MLHFQ) scale, creatinine clearance, C-Reactive protein, and NT pro BNP, a slowing of the heart rate, and lower diuretic requirements in the treated compared to the control group.

In the other double blind placebo-controlled study, this one a multicenter study (The FAIR-HF study [27]), the patients were randomly assigned to IV ferric carboxylase 200 mg (Vifor Int Zurich) versus matching control in a 2 : 1 ratio. A total of 459 subjects with chronic left ventricular systolic dysfunction were studied. Their initial serum ferritin was <100 ug/L or 100–299 ug/L if %TSat was <20%. The mean initial Hb was between 9.5 and 13.0 g/dL. The exclusion criteria were uncontrolled hypertension, other significant heart disease, or impaired liver or renal function. They were given enough iron to maintain the %TSat at 25–45% and serum ferritin at 400–800 ng/mL. The primary end points were patient self assessment and investigator-assessed NYHA at 6 months. Secondary end points were 6-minute walk and quality of life (QOL) as assessed by the Kansas City Cardiomyopathy questionnaire and the European EQ 5D QOL visual analogue scale. Safety outcomes included hospitalizations and death. The initial Hb level was 11.9 g/dL, mean serum ferritin 50–60 ug/mL, and mean transferrin saturation 17%. At week 24 in the IV iron group the serum ferritin had increased to 313 ± 13 versus 74 ± 8 ng/mL. %TSat to 29 ± 1 versus 19 ± 1% and Hb to 13.0 ± 0.1 versus 12.5 ± 0.1 g/dL. All these were significant differences from placebo. The use of IV iron was associated with significant improvements in NYHA functional class, 6-minute walk distance (mean study effect 35.8 m) EQ5 patient global assessment scale, and Kansas City QOL scale. Renal function improved significantly only in the treated group. At 4 weeks the difference in GFR between the active treatment and placebo was 2.5 ± 1.5 mL/min/1.73 sqm, at 12 weeks it was 3.0 ± 1.3, and at 24 weeks it was 4.0 ± 1.7 mL/min/1.73 sqm. The magnitude of all the treatment effects did not differ in subjects with or without anemia (defined as a Hb ≤ 12 g/dL). The treatment effects were also not related to the initial age, presence of diabetes, initial severity of the CHF, renal function, or ferritin levels. Although there was no difference in first hospitalization for cardiovascular causes or death in the treated and nontreated, there was a trend to improvement in the two. There was no evidence of any adverse effects of the IV treatment compared to placebo. The improvements compared to controls were seen quite rapidly, even within the first month. The fact that the improvement was similar in the treated group unrelated to the initial Hb suggests that part of the effect of the IV iron might have been due to its direct effect on body tissues.

In the Ferric Iron Sucrose in Heart Failure study (FERRIC-HF) [28], a randomized open label observer blind study lasting 4 months in 35 patients with CHF who were either anemic (Hb < 12.5 g/dL) or non-anemic (Hb 12.5–14.5 g/dL) but all of whom were iron deficient, patients were assigned in a 2 : 1 ratio to receive 16 weeks of IV iron sucrose (Venofer) or to a control group. Unlike the previous 2 studies, treatment did not result in a significant improvement in Hb levels. Nevertheless there was a trend toward an improvement in exercise tolerance as judged by peak VO2 and a significant increase in peak VO2/kg in the treated group but not in the control group. There was also a trend toward an increase in absolute exercise duration and percentage change in exercise duration in the iron group but not in the control group. There were significant improvements in NYHA, patient global assessment, MLHFQ quality of life scale, and fatigue score in the iron group. All the changes were more pronounced in the anemic group than the nonanemic group. The heart rate fell in the anemic group only. The changes in peak VO2 were related to changes in %TSat but not to Hb in anemic patients suggesting therefore, as did the previous paper, that the improvement in CHF was due at least partially to the correction of the iron deficiency and not to an increase in Hb.

Bolger et al. [29] treated 16 CHF patients with intravenous iron sucrose (Venofer-Zurich) in an uncontrolled open label study. The Hb was <12 g/dL and the serum ferritin <400 ug/L. Patients were treated for 12–17 days and followed for 92 ± 6 days. Treatment was associated with an increase in the Hb level (11.2 ± 0.7 to 12.6 ± 1.2 g/dL) and a significant improvement in the NYHA class, MLHFQ score, and 6-min walk distance (6MWD). There was a trend toward improved renal function.

Usmanov et al. [30] treated 32 moderate to severe (NYHA III and IV) CHF patients and moderate renal failure (mean serum creatinine 2.3 mg/dL) with IV iron (Venofer) in an uncontrolled study for 26 weeks. The inclusion Hb was <11 g/dL. Iron sucrose was given in a dose of 100 mg 3 times a week for 3 weeks and then once weekly for 23 weeks (total dose 3200 mg of iron). The mean Hb increased from 10.7 ± 0.4 to 13.7 ± 0.4 in NYHA III and from 9.4 ± 0.6 to 12.7 ± 0.08 in NYHA IV. The mean serum iron, %TSat, ferritin were all lower than normal before treatment and increased to normal after treatment. There was a significant improvement in NYHA in the NYHA III group but not in the NYHA IV group. Initially there was evidence of severe cardiac hypertrophy and dilation and reduced LVEF, and these improved after 6 months of IV treatment, but more so in NYHA III than in NYHA IV. There was no change in renal function.

In a sixth study [31] which examined the effect of IV iron in bone marrow-confirmed iron deficiency anemia in severe CHF with anemia, 8 patients were randomly assigned to treatment with IV iron 300 mg once weekly for 6 weeks (total 1800 mg) and 8 others to the same treatment along with 50 ug darbepoetin once weekly for six weeks. Over the entire 3 months of treatment and followup, the Hb increased by 2.4 g/dL in the IV iron alone group and by 2.8 g/dL in the group with both agents. This small study suggests that the IV iron is a major contributor to the anemia. This study and that of Usmanov et al. [30] mentioned above also point out that higher doses of IV iron lead to greater Hb responses than lower doses, that is, there is a dose response relationship. This has been seen in CKD as well [32].

These studies suggest that the anemia of many CHF patients can be improved by IV iron alone. On the other hand, in several studies of anemia treatment in CHF [33, 34], the use of oral iron in anemic CHF patients for one year was not associated with any increase in Hb or improvement in any CHF parameters.

6. What Are the Causes of Iron Deficiency in CHF?

6.1. Chronic Kidney Disease (CKD). CKD is associated with reduced production of Erythropoietin (EPO) in the kidney. The renal damage seen in CHF is probably mainly due to reduced renal blood flow caused by the reduced cardiac output causing hypoxic renal damage [21, 35].

Iron deficiency is also common in CKD [36–39]. About half the cases of iron deficiency are absolute iron deficiency with low %TSat and low serum ferritin (usually associated with decreased iron stores), and about half are relative iron deficiency with low %TSat and normal or elevated serum ferritin (often associated with normal or increased iron stores). The iron deficiency is frequently associated with reduced iron deposits in the bone marrow [39, 40]. Because CKD is an inflammatory condition, increased cytokines may also contribute to the anemia and to the iron deficiency (see below). The use of Erythropoiesis Stimulating Agents (ESAs) in CKD will also rapidly reduce iron stores. The gastrointestinal causes of anemia in CKD are discussed below.

6.2. Elevated Cytokines Causing Abnormalities in EPO and Iron Metabolism. These cytokines are elaborated in CHF and CKD, especially Tumour Necrosis Factor alpha (TNF α) and interleukin-6 (IL-6). They can cause four haematological abnormalities [41, 42]:

(a) reduced EPO production in the kidney leading to inappropriately low levels in the blood for the degree of anemia present,

(b) reduced erythropoietic response of the bone marrow to ESA,

(c) hepcidin-induced failure of iron absorption from the gut, and

(d) hepcidin-induced trapping of iron in iron stores in the macrophages and hepatocytes.

Hepcidin [29, 30] is a protein released from the liver by IL-6. It inhibits the protein ferroportin which is found in the gastrointestinal tract and in macrophages and hepatocytes and is responsible for the release of iron from these three types of cells into the blood. Therefore if ferroportin is inhibited, gastrointestinal iron absorption is diminished, and iron is also not released from its storage in macrophages and hepatocytes. This results in a low serum iron leading to decreased delivery of iron to the bone marrow and therefore iron deficiency anemia, even in the presence of adequate total iron stores, the so-called functional iron deficiency. Since hepcidin is filtered and removed in the kidney, its levels increase in CKD, which can also partly explain the iron deficiency in CKD [43] and in CHF in whom about half the patients have renal insufficiency as judged by a creatinine clearance of <60 mL/min/1.73 sqm [44].

6.3. Gastrointestinal Problems. There are many other causes of iron deficiency in CKD including reduced iron intake due to low protein diets and anorexia, gastrointestinal blood loss due to uremia causing platelet dysfunction, as well as esophagitis, gastritis, tumors, platelet inhibitors and anticoagulants [45], and phosphate binders which can also bind iron. It has also been found that proton pump inhibitors such as omeprazole, which are extremely widely used, reduce iron absorption [46]. In addition, CHF itself can cause intestinal cell dysfunction due to bowel edema and other causes [47]. Frequent removal of blood for blood tests may also contribute to the anemia.

Also, as mentioned earlier, both CKD and CHF are inflammatory conditions with increased cytokines which can cause hepcidin-induced iron deficiency.

7. The Cellular Effects of Iron Deficiency

Iron is indispensable for life, serving as a metal cofactor for many enzymes, either nonheme iron-containing proteins or hemoproteins. Hemoproteins are involved in many crucial biologic functions including oxygen binding (hemoglobins), oxygen metabolism (oxidases, peroxidase, catalases, etc.), and electron transfer (cytochromes). Many nonheme iron-containing proteins catalyze key reactions involved in energy metabolism and DNA and RNA synthesis. In addition, iron-containing proteins are required for the metabolism of collagen, tyrosine, and catecholamines [2–4].

Experimental studies in animals have shown that severe iron deficiency can cause diastolic dysfunction and heart failure with pulmonary congestion, left ventricular hypertrophy and dilation, cardiac fibrosis, a reduction in the erythropoietin levels and a worsening of the molecular signaling pathways (as measured by cardiac STAT 3 phosphorylation), an increase in the inflammatory cytokine TNFα, and proteinuria [5]. This defect in the molecular signaling pathway in iron deficiency may be critical for the transition from adaptive cardiac hypertrophy to cardiac dysfunction in long-term iron deficiency. In addition, iron deficiency in rat hearts causes mitochondrial ultrastructural aberrations, irregular sarcomere organisation, and release of cytochrome C [6].

Iron may have anti-inflammatory effects. Compared to haemodialysis patients taking EPO alone, those taking EPO and IV iron had lower proinflammatory TNFα levels and higher anti-inflammatory cytokine IL-4 levels as well as lower levels of total peroxide (a marker of free radical concentration) [48].

8. Oral versus IV Iron in CKD

As mentioned earlier, in patients with CKD who are anemic, iron deficiency has been found in at least half the patients using either blood tests [36–39] or bone marrow biopsies [39, 40], and IV iron alone may increase the Hb significantly [39, 40, 49–51]. In most studies comparing oral to IV iron in CKD, IV iron has been found to produce a greater Hb response than oral iron with less side effects [32, 50, 51], and many patients can reach a target Hb of 11.0 to 12 g/dL with this therapy alone and therefore avoid the use of ESA altogether [32, 40, 49–51]. Although there has been concern

about IV iron causing renal disease [52], this has not been confirmed by other studies [32, 39, 40, 49–51]. Indeed, in one study renal function in CKD improved in the IV iron group but not in the oral iron group [50]. In most studies comparing oral to IV iron in CKD, IV iron has been found to produce a greater Hb response with less side effects [51]. As mentioned above, in several studies of anemia treatment in CHF [33, 34], the use of oral iron in anemic CHF patients for one year was not associated with any increase in Hb or improvement in any CHF parameters.

9. Iron Deficiency and Thrombocytosis

The incidence of venous thromboembolism is greatly increased in CHF [53], and indeed CHF is considered to be a hypercoagulable state [54]. Could iron deficiency in these CHF patients be one cause of this? Iron deficiency can cause thrombocytosis [55] which can lead to increased thrombosis, atherosclerosis, and increased mortality [56, 57]. Correction of the iron deficiency with IV iron in EPO-treated dialysis patients reduced the platelet count significantly [58]. This may be important, since thrombocytosis may be one of the missing links in causing the increased incidence of cardiovascular effects of EPO in CKD [56, 57] and in cancer [59, 60]. High doses of EPO in CKD are associated with more iron deficiency, more severe thrombocytosis, and increased mortality [56, 57]. Iron deficiency also increases oxidative stress [61].

10. The Administration of Iron in Anemic and Nonanemic People

Beutler showed over fifty years ago that iron deficiency can negatively affect enzymes throughout the body with or even without actual anemia being present [7]. He also showed in a randomised double-blind placebo-controlled crossover study that oral iron can improve fatigue in anemic and also in nonanemic iron deficient women [7], and this has been subsequently confirmed by others [8–10]. All these studies suggest that iron has a specific effect on the cells in addition to its ability to make hemoglobin.

11. What Assays Predict the Response to IV Iron?

The two commonly used tests to detect iron deficiency are a low % Transferrin Saturation (%TSat) and a low serum ferritin. But though they are low in absolute iron deficiency where iron stores are low, the %TSat may become low but the serum ferritin high in the presence of inflammation and therefore may not reflect iron status accurately. This is the so-called anemia of chronic disease. In fact, iron stores may be elevated in inflammation in the face of a low %TSat, and the serum ferritin may be elevated in the presence of depleted iron stores. There is no test that can predict with great accuracy the degree of response to IV iron in patients taking ESA in CKD [39, 62, 63]. However, generally in CKD the %TSat is a better predictor than ferritin, and the reticulocyte Hb is better than %TSat [62, 63], but the differences are probably not large enough to be clinically useful.

12. Concerns about the Safety of Iron

There is some evidence in hemodialysis patients that IV iron treatment is associated with a lower mortality [64–66]. Recently, in CKD patients not on dialysis, it was found that the lower the %TSat the higher the mortality, again raising the possibility that iron deficiency may be a common and reversible cause of severe cardiovascular disease [67]. However, IV iron can cause oxidative stress [68], and therefore long-term controlled studies of IV iron are needed to evaluate the effects of IV iron in CKD, as in CHF. Although there has been concern about increased iron stores being associated with increased risk of coronary heart disease [69] this has not been confirmed by others [70, 71], and the issue is still controversial. But the implications of the presence of iron deficiency in CHF are enormous since, as mentioned above, a high percentage of patients with CHF, whether anemic or not anemic, have true or functional iron deficiency. If correction of this iron deficiency proves both safe and effective, this could be a new and useful addition to the treatment of CHF.

13. How Does Anemia Cause or Worsen CHF?

It appears that anemia can exacerbate heart failure through a vicious circle in which tissue hypoxia and release of nitric oxide causes peripheral vasodilation which leads to decreased blood pressure which then causes increased sympathetic activation, renal vasoconstriction, reduced renal function, and activation of the renin-angiotensin aldosterone system [21, 35]. This in turn leads to fluid retention, left ventricular hypertrophy and dilatation, worsening heart failure, release of BNP arising from stress on the myocardium, and, to complete the vicious circle, further anemia.

14. The Cardiorenal Anemia Syndrome

About 10 years ago, we described the Cardio Renal Anemia syndrome (CRA syndrome) [72]. Our hypothesis was that there is a vicious circle operating between Congestive Heart Failure (CHF), Chronic Renal Failure, and anemia where each might cause or worsen the other. The correction of anemia was a major part of this vicious circle in the reduction of the severity of the CHF. In view of the possible independent association of iron deficiency and cardiac failure, renal failure, and anemia we now suggest renaming the syndrome the CRAID syndrome, the Cardio Renal Anemia Iron Deficiency Syndrome.

15. Conclusion

It is daunting to consider that the use of something as simple as IV iron in CHF patients with absolute or functional iron deficiency may have an important role to play in the treatment of a large percentage of CHF patients, both anemic

and nonanemic and with or without CKD. Clearly, long-term adequately-powered placebo-controlled studies of IV iron in CHF with hard endpoints are needed. In the meantime, in the assessment of patients with CKD and/or CHF, the laboratory markers of iron deficiency should be routinely measured. Faced with a patient with absolute or functional iron deficiency with or without anemia who has CHF with or without CKD, it is the authors' opinion that a trial of IV iron might reduce significantly the severity of these conditions and should be administered before an ESA is started.

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International Journal of Nephrology
Volume 2011, Article ID 951629, 6 pages
doi:10.4061/2011/951629

Research Article

B-Type Natriuretic Peptide in the Critically Ill with Acute Kidney Injury

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Received 20 July 2010; Revised 12 January 2011; Accepted 25 April 2011

Academic Editor: Anjay Rastogi

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Introduction. Acute kidney injury (AKI) is common in the intensive care unit (ICU) and associated with poor outcome. Plasma B-type natriuretic peptide (BNP) is a biomarker related to myocardial overload, and is elevated in some ICU patients. There is a high prevalence of both cardiac and renal dysfunction in ICU patients. *Aims*. To investigate whether plasma BNP levels in the first 48 hours were associated with AKI in ICU patients. *Methods*. We studied a cohort of 34 consecutive ICU patients. Primary outcome was presence of AKI on presentation, or during ICU stay. *Results*. For patients with AKI on presentation, BNP was statistically higher at 24 and 48 hours than No-AKI patients (865 versus 148 pg/mL; 1380 versus 131 pg/mL). For patients developing AKI during 48 hours, BNP was statistically higher at 0, 24 and 48 hours than No-AKI patients (510 versus 197 pg/mL; 552 versus 124 pg/mL; 949 versus 104 pg/mL). *Conclusion*. Critically ill patients with AKI on presentation or during ICU stay have higher levels of the cardiac biomarker BNP relative to No-AKI patients. Elevated levels of plasma BNP may help identify patients with elevated risk of AKI in the ICU setting. The mechanism for this cardiorenal connection requires further investigation.

1. Introduction

Acute kidney injury (AKI) is a common clinical problem in intensive care unit (ICU) patients and independently predicts poor outcome [1–4]. In the ICU setting, the overall incidence of AKI is approximately 36% [5, 6], and an increasing trend has been reported [7, 8]. Cardiac dysfunction is also common in patients with AKI in the ICU, and increasing interest exists in how the interaction of these two systems affects clinical outcomes in this group of patients.

B-type or brain natriuretic peptide (BNP) is a neurohormone secreted from ventricular myocardium in response to myocardial stretching and volume overload [9]. BNP has diagnostic and prognostic utility in patients with acute decompensated heart failure [10–13], and BNP is an independent predictor for cardiovascular events and overall mortality in various patient groups including those with chronic kidney disease [14–20].

However, it remains unclear whether plasma levels of BNP are useful in predicting AKI in critically ill patients. Therefore, our study aimed to investigate whether BNP levels in the first 48 hours may be useful in diagnosis of established AKI.

2. Methods

2.1. Patients and Study Protocol. We studied a cohort of 34 consecutive patients admitted to the ICU of "San Bortolo" Hospital, Vicenza, Italy, between December 2007 and April

2008. Patients requiring mechanical ventilation and admitted on any day from Monday to Wednesday were included, and we excluded patients with acute coronary syndrome or acute myocardial infarction. The study was approved by the Institutional Review Board. The primary outcome was presence of AKI during admission or development of AKI during ICU stay. Patients were classified as having AKI if any time during the first 48 hours after enrollment they had

(1) an increment of serum creatinine (SCr) of 0.3 mg/dL or more or an increase of at least 50% from baseline and/or,

(2) an episode of urine output less than 0.5 mL/kg/hr for more than six hours despite fluid challenge of 500 mL or more.

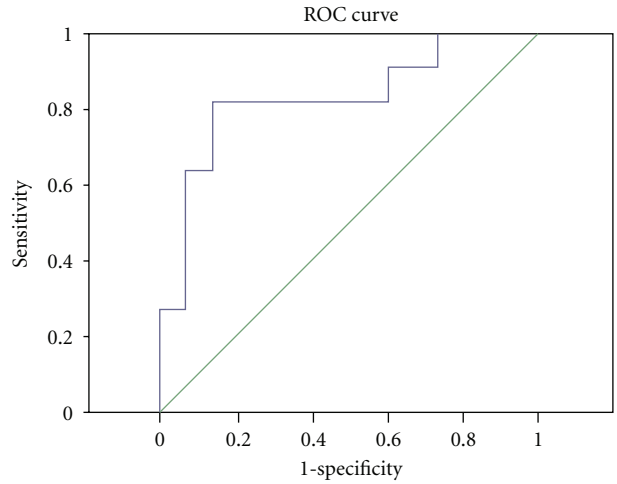
AKI was classified according to the RIFLE (Risk, Injury, Failure, Loss, and End-stage kidney disease) criteria [21]. The Sequential Organ Failure Assessment (SOFA) scores were calculated using standard methods [22]. Blood samples for plasma BNP and renal function were taken within 6 hours from admission and 24 and 48 hours later, to investigate association of BNP levels with clinical and laboratory parameters and SOFA score.

2.2. BNP Measurement. Plasma samples for BNP were stored at minus 80 degrees Celsius. Plasma BNP was measured with fluorescence-based immunoassay with the Triage point-of-care analyzer (Biosite Inc., San Diego, Calif., USA), which is a rapid quantitative measurement of BNP concentration in EDTA-anticoagulated whole blood or plasma. The method used single-use plastic cartridge with immobilized BNP antigen and BNP-specific monoclonal antibodies conjugated to fluorescent nanoparticles.

2.3. Statistical Analysis. Categorical variables are expressed as percentage and were compared with Fisher's Exact Test. Normally or near normally distributed variables were presented as means ± standard deviations (SD); non-normally distributed continuous data were presented as medians and interquartile ranges (IQR). Differences between groups were analyzed using Student's t and Mann-Whitney tests as appropriate. Differences between repeated measures within a group were analyzed using Friedman test. Statistical analysis was performed using the SPSS 15.0 (SPSS Inc, Chicago, Ill, USA). A P value < .05 was considered significant.

3. Results

During the study, a total of 34 patients were admitted to the ICU, and, of these, 26 met the inclusion criteria and had sufficient data for analysis. Furthermore, 9 (34.6%) fulfilled criteria for AKI, 5 (19.2%) had AKI on admission, and 4 (15.4%) more developed AKI during 48 hours. Characteristics of the patients are shown in Tables 1 and 2. Given the differences between SCr, age, and BNP at baseline, we did examine for correlations between these variables. While baseline SCr and BNP were not significantly correlated ($r = 0.27$, $P = .19$), there was a weak correlation between age and SCr ($r = 0.39$, $P = .048$) and a stronger correlation between age and baseline BNP ($r = .46$, $P = .02$).



ROC receiver operating characteristic
AUC area under the curve
BNP B-type or brain natriuretic peptide
AKI acute kidney injury
ICU intensive care unit

Figure 1: The ROC-AUC for BNP related to the presence of AKI on admission or development of AKI during ICU stay is 0.830.

In patients with AKI on admission, we found a higher SOFA score (10.0 ± 2.4 versus 6.1 ± 2.1; $P = .002$) and, as expected, higher SCr levels (1.85, IQR 1.76-1.94, versus 0.82, IQR 0.69-1.00 mg/dL; $P = .001$) compared to no-AKI patients. Moreover, AKI patients tended to have higher BNP values on admission compared to no-AKI patients (510, IQR 370–544, versus 197, IQR 57–393 pg/mL; $P = .06$) (Table 1). Plasma BNP levels were also statistically significantly higher for AKI patients at 24 and 48 hours after admission compared to no-AKI patients (Table 3). In addition, the increase in BNP of AKI patients during 48 hours (from 510 to 1380 pg/mL) was significant ($P = .012$) (Table 3 and Figure 2).

An additional 4 patients developed AKI after admission. These patients had on admission higher SCr (1.14 versus 0.82 mg/dL) and BNP (338 versus 197 pg/mL) levels compared to no-AKI patients.

We also analyzed levels of SCr and BNP in all patients developing AKI at any point during 48 hours ($n = 9$). For these patients, the difference in BNP versus no-AKI patients at admission was even more pronounced (510, IQR 232–832, versus 197, IQR 36–353 pg/mL; $P = .038$). Also, for the 9 patients developing AKI at any time during ICU stay, SCr and BNP levels at baseline and at 24 and 48 hours were significantly higher compared to no-AKI patients (Table 4).

4. Discussion

A large proportion of patients admitted to hospital, especially in the critical care setting, have various degrees of heart and kidney dysfunction [23]. Primary disorders of one of

Table 1: Characteristics of AKI and no-AKI patients at ICU admission.

	All (26)	AKI (5)	No-AKI (21)	*P* value
Male	57.7%	60.0%	57.1%	.91
Age, years	59.7 ± 21.7	77.6 ± 7.3	55.4 ± 21.9	.037
Weight, kg	77.4 ± 13.4	74.5 ± 8.8	78.1 ± 14.3	.36
SOFA score	6.9 ± 2.7	10.0 ± 2.4	6.1 ± 2.1	.002
Serum creatinine, mg/dL*	0.89 (0.64 to 1.28)	1.85 (1.76 to 1.94)	0.82 (0.69 to 1.00)	.001
Plasma BNP, pg/mL*	228 (67.5 to 544)	510 (370 to 544)	197 (57 to 393)	.06
Diagnosis on ICU admission				
Trauma	30.8%	0%	38.1%	.28
Pulmonary	26.9%	60%	19.0%	.10
Neurologic	26.9%	0%	33.3%	.28
Other	15.4%	40.0%	9.5%	.16

AKI: Acute kidney injury.
ICU: Intensive care unit.
SOFA: Sequential organ failure assessment.
BNP: B-type or brain natriuretic peptide.
*median and interquartile range.

Table 2: Median of creatinine and BNP of all patients during 48 hours.

	Baseline	24 hours	48 hours	*P* value
Serum creatinine, mg/dL	0.89 (0.64 to 1.28)	0.86 (0.65 to 1.50)	0.80 (0.71 to 0.89)	.86
Plasma BNP, pg/mL	228 (67.5 to 544)	282.5 (55.1 to 474)	220 (78.4 to 565)	.92

BNP: B-type or brain natriuretic peptide.

Table 3: Median of creatinine and BNP during 48 hours of ICU stay for patients with or without AKI on admission to ICU. The increase in BNP of AKI patients is significant ($P = .012$).

		AKI (5)	No-AKI (21)	*P* value
Serum creatinine, mg/dL	Baseline	1.85 (1.70 to 3.85)	0.82 (0.68 to 1.01)	.001
	24 hours	2.49 (1.60 to 4.53)	0.79 (0.64 to 0.97)	.001
	48 hours	2.14 (1.47 to 5.24)	0.78 (0.63 to 0.89)	.004
Plasma BNP, pg/mL	Baseline	510 (369 to 690)	197 (42 to 485)	.06
	24 hours	865 (344 to 948)	148 (47 to 447)	.047
	48 hours	1380 (985 to 1625)	131 (43 to 297)	<.001

BNP: B-type or brain natriuretic peptide.
ICU: Intensive care unit.
AKI: Acute kidney injury.

Table 4: Median of creatinine and BNP during 48 hours for patients developing AKI or not any time during their ICU stay.

		AKI (9)	No-AKI (17)	*P* value
Serum creatinine, mg/dL	Baseline	1.76 (1.01 to 1.90)	0.81 (0.68 to 0.89)	.002
	24 hours	1.70 (1.07 to 2.53)	0.70 (0.63 to 0.89)	.001
	48 hours	1.56 (0.98 to 2.47)	0.74 (0.62 to 0.82)	.001
Plasma BNP, pg/mL	Baseline	510 (232 to 832)	197 (36 to 353)	.038
	24 hours	552 (344 to 948)	124 (47 to 407)	.019
	48 hours	949 (297 to 1435)	104 (29 to 236)	.002

BNP: B-type or brain natriuretic peptide.
AKI: Acute kidney injury.
ICU: Intensive care unit.

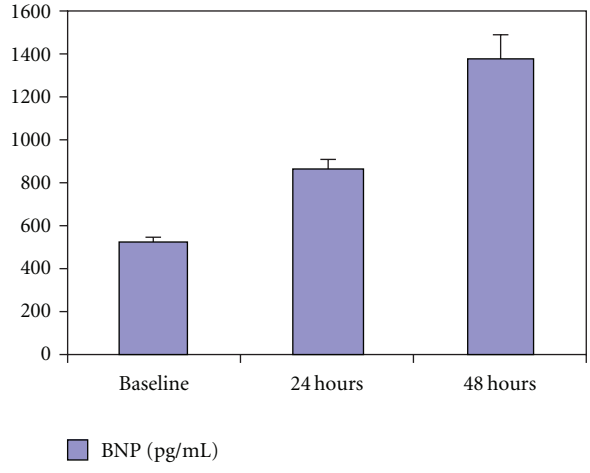


Figure 2: Increase in median of BNP of patients with AKI on admission to ICU ($P = .012$).

these two organs often result in secondary dysfunction or injury to the other [24]. Such pathophysiological interactions represent the basis for a clinical entity often referred to as the cardiorenal syndrome (CRS) [25]. Limited data are available regarding the diagnostic and prognostic utility of BNP in patients with AKI in intensive care unit. In a recent study, Park et al. [26] demonstrated that BNP levels have the diagnostic and prognostic capability for CRS type 4 in ICU patients, according to the novel classification of CRS [27, 28]. In our study, BNP was able to predict the presence of AKI on admission or development of AKI during ICU stay with a ROC-AUC 0.830 (Figure 1). No previous studies have focused on the significance of BNP in patients with AKI admitted to the ICU.

In ICU setting, emerging cardiac and renal impairment are strongly connected on neurohormonal basis via renin-angiotensin-aldosterone system BNP and nitric oxide, the sympathetic nervous system and other pathways such as coagulation and inflammation.

Burchill et al. have shown in experimental animal models that the acute effects of AKI on the heart occur as early as few hours after kidney injury, and that changes in cardiac structure are associated with increased cardiac BNP [29].

It could also be speculated that the changes in BNP observed in our study may partly reflect the pathophysiology between kidney and heart in AKI, the so-called CRS type 3 or acute renocardiac syndrome. In this category, AKI is believed to be the primary inciting factor, and cardiac failure is a common and in often times a fatal complication of AKI [27].

In our study, we demonstrate a dynamic interaction between AKI and plasma BNP levels in a cohort of mechanically ventilated ICU patients who were admitted primarily for noncardiac diagnosis. This calls attention to the possible utility of this marker in detecting AKI. Further, the results support the need for additional study of the potential value of plasma BNP levels in discrimination between AKI and no-AKI in critically ill patients.

To our knowledge, this is the first investigation of the association between plasma BNP levels and AKI in critically ill patients. We acknowledge some limitations in this study. Extensive information regarding patient comorbidities was not available and could not be added to our analysis. Plasma BNP levels can be affected by other variables such as age, and in our study AKI patients were significantly older than no-AKI patients, and age was correlated with baseline BNP, hence some of the association between BNP and AKI may have reflected the risk of AKI related to age. Additionally, while patients with acute myocardial infarction and acute coronary syndromes were excluded, massive information about previous or current cardiac dysfunction was not collected and could have influenced plasma BNP levels.

Furthermore, we did not perform objective assessment of cardiac function to document that increased BNP in this setting would be due to myocardial dysfunction. Finally, this study was not designed to look at the prognostic value of plasma BNP levels in critically ill patients with AKI. We hope that these preliminary results will encourage further study of these important questions.

5. Conclusion

In this pilot study, we have demonstrated for the first time an association between plasma BNP levels and AKI in critically ill patients. Patients with AKI have higher levels of BNP compared to no-AKI patients, and in AKI patients BNP levels continue to increase during the subsequent 48 hours. Our results suggest that plasma BNP may distinguish the occurrence of AKI. Additional studies are necessary to confirm our findings and to further shed light on the pathophysiologic interaction between kidney and heart during AKI.

Acknowledgment

The authors are grateful for the assistance of staff in Hospital Intensive Care Unit, San Bortolo in carrying out this study.

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SAGE-Hindawi Access to Research
International Journal of Nephrology
Volume 2011, Article ID 283475, 4 pages
doi:10.4061/2011/283475

Clinical Study

Pulmonary Hypertension in Dialysis Patients: A Cross-Sectional Italian Study

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Received 31 July 2010; Accepted 26 August 2010

Academic Editor: Mitchell H. Rosner

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Introduction. Pulmonary hypertension (PHT) is an independent predictor of mortality. The aim of this study was to relate pulmonary arterial pressure (PAP) to the cardiovascular status of dialysis patients. *Methods*. 27 peritoneal dialysis (PD) and 29 haemodialysis (HD) patients (60 ± 13 years, 37 males, dialysis vintage was 40 ± 48 months) had PAP measured by echocardiography. Clinical and laboratory data of the patients were recorded. *Results*. PHT (PAP > 35 mmHg) was detected in 22 patients (39%; PAP 42 ± 6 mmHg) and was diagnosed in 18.5% of PD patients and 58.6% of HD patients ($P = .0021$). The group of subjects with PH had higher dialysis vintage (63 ± 60 versus 27 ± 32 months, $P = .016$), interdialytic weight gain (2.1 ± 1 versus 1.3 ± 0.9 Kg, $P = .016$), lower diastolic blood pressure (73 ± 12 versus 80 ± 8 mmHg, $P = .01$) and ejection fraction (54 ± 13 versus 60 ± 7%, $P = .021$) than the patients with normal PAP. PAP was correlated positively with diastolic left ventricular volume ($r = 0.32$, $P = .013$) and negatively with ejection fraction ($r = -0.54$, $P < .0001$). PHT was independently associated with dialysis vintage (OR 1.022, 95% CI 1.002–1.041, $P = .029$) and diastolic blood pressure (OR 0.861, 95% CI 0.766–0.967, $P = .011$). *Conclusions*. PHT is frequent in dialysis patients, it appears to be a late complication of HD treatment, mainly related to cardiac performance and cardiovascular disease history.

1. Introduction

Pulmonary hypertension (PHT) is a progressive disorder complicating heart, lung, or systemic diseases, with increased morbidity and mortality regardless of its etiology [1]. Recently it has been found that PHT is a strong independent predictor of mortality in haemodialysis (HD) patients [2]. In patients with end-stage renal disease (ESRD), PHT has been recognized to be a frequent condition and it appears to be independent from cardiovascular disease prevalence [2]. In a recent review, the prevalence of PHT in ESRD patients was reported to be around 40%–50% [3]. Its frequency has been reported to be higher in HD patients than in peritoneal dialysis (PD) ones due to the presence of arteriovenous fistula (AVF) [4, 5]. Clinical features associated with PHT in ESRD are still a matter of debate, therefore, we evaluated clinical characteristics associated with high pulmonary arterial pressure (PAP) measured by echocardiography in a group of Italian dialysis patients.

2. Subjects and Methods

Between January 2007 and June 2007, 56 dialysis patients underwent PAP measurement by echocardiography (age 60 ± 13 years, dialysis vintage 40 ± 48 months). They were selected from a population of 127 subjects dialysing in a single centre because they accepted to undergo echocardiography. Twenty nine were on HD treatment via surgically created native AVF and 27 were on PD therapy. Glomerulonephritis was the commonest cause of uraemia ($n = 23$), ischaemic renal disease, cystic disease and interstitial nephritis were the renal diagnosis in 8 cases, respectively, 6 patients had diabetic nephropathy whereas 3 had undetermined renal diagnosis. Patients with chronic obstructive lung disease, chest wall or parenchymal lung disease, previous pulmonary embolism, collagen vascular disease, systemic lupus erythematosus were excluded.

The following demographic and clinical data were derived from clinical records: age, duration of dialysis

treatment, smoking and diabetes history. The increase in weight during the interdialytic time (interdialytic weight gain), systolic and diastolic blood pressure (BP) were averaged from values recorded at the beginning of dialysis sessions during the month preceding the date of echocardiography. BP measurements were performed according to guidelines [6]. Mean dry weight of each subject was averaged from the values recorded at the end of the dialysis sessions during the same period. Average levels of calcium, phosphate, parathyroid hormone (PTH, measured as intact molecule by radioimmunoassay), haemoglobin, haematocrit measured at least twice in the study period were calculated. Weekly dose of erythropoietin and calcium-phosphate product were also calculated. Ischaemic heart disease was defined either from history of myocardial infarction and/or angina associated to ischaemic changes on electrocardiogram, or by positive results at either electrocardiographic ergometry, dipyradamole scintigraphy, or dobutamine echocardiography. History of previous TIA or stroke defined cerebrovascular disease. History of claudication, amputation or presence of ischaemic lesions of lower limb extremities defined peripheral vascular disease. History of parathyroidectomy was also recorded.

Echocardiography was performed the day after a dialysis session when the patient had reached the "dry weight" prescribed by nephrologists on the clinical examination, in order to avoid clincal evident fluid overload. One experienced cardiologist performed all examinations using an Acuson Sequoia, 512 (Mountain View, CA, USA) ultrasound machine.

Every patient underwent a complete two-dimensional and Doppler echocardiography study.

Systolic pulmonary artery (PAP) pressure was calculated using the modified Bernoulli equation given by: PAP = 4 × (tricuspid systolic jet)^2 + 10 mm Hg (estimated right atrial pressure) [7]. According to Yigla et al. [2] PHT was defined as a systolic PAP > 35 mm Hg. Diastolic left ventricular volume, ejection fraction, mitral and aortic valve stenosis or incompetence were also derived from echocardiographic studies. Local ethics committee approved this observational study. The study was conducted according to the Declaration of Helsinky.

3. Statistical Analysis

Data are expressed as mean ± standard deviation and as percentage when the parameter was categorical. Patients were investigated dividing PD and HD subjects with and without PHT. Difference between groups were compared with Student's *t*-test for parametric continuous variables, Mann-Witney-U test for nonparametric continuous variables. Chi-square test was applied for estimating the occurrence of categorical variables. Pearson's correlation coefficient was used to test the relationship between PAP and echocardiographic parameters. Multiple logistic regression analysis was performed considering presence/absence of PHT as dependent variable, whilst all the variables that resulted statistically different in the univariate analysis, were considered as independent ones. A P value <.05 was used as the thresholds of statistical significance. All analyses were performed using StatView for windows.

Table 1: Data describing the 56 patients in whom pulmonary artery pressure was evaluated.

Age (year)	60 ± 13
Dialysis vintage (months)	40 ± 48
Dry weight (kg)	68,5 ± 15
Interdialytic weight gain (kg)	1,6 ± 1
Systolic blood pressure (mmHg)	132 ± 20
Diastolic blood pressure (mmHg)	77 ± 11
Calcium (mg/dl)	9 ± 1
Phosphate (mg/dl)	5 ± 1
Calcium-phosphate product (mg^2/dl^2)	48 ± 15
PTH (pg/ml)	344 ± 340
Haemoglobin (gr/dl)	11,3 ± 1,4
Haematocrit (%)	35 ± 5
Erythropoietin (IU/week)	7243 ± 8752
Left ventricular Diastolic Volume (ml)	116 ± 33
Ejection Fraction (%)	58 ± 10
PAP (mmHg)	33 ± 8

4. Results

Characteristics of the 56 patients investigated are summarized in Table 1, 22 of them had PHT (39%), their mean age was 66 ± 13 years and 37 were males.

Five (18.5%) in the PD group and 17 (58.6%) in the HD one had PAP > 35 mmHg (P = .0021). Clinical and biochemical data of the 22 patients with PHT (PAP 42 ± 6 mmHg) compared with the 34 patients without PH (28 ± 3 mmHg) are shown in Tables 2 and 3. The mean duration of dialysis therapy was significantly longer (63 ± 60 versus 27 ± 32 months, P = .0105) and interdialytic weight gain was higher (2.0 ± 1 versus 1.3 ± 0.9 Kg, P = .0168) in the PHT group than in group with normal PAP. On the contrary diastolic blood pressure (73 ± 12 versus 80 ± 8 mmHg, P = .01) and ejection fraction (54 ± 13 versus 60 ± 7%, P = .021) were lower in PHT patients than in subjects with normal PAP. In the same group we found higher prevalence of diabetes (18 versus 3%, P = .05) and mitral incompetence (100 versus 79%, P = .02).

PD patients with PHT had higher prevalence of diabetes (40 versus 0% P = .0021), aortic incompetence (100 versus 45%, P = .0267), higher systolic blood pressure (154 ± 29 versus 129 ± 13 mmHg, P = .0074) and lower ejection fraction (45 ± 15 versus 62 ± 5%, P = .0003) than those without PHT. HD patients with PHT had higher prevalence of smoking history (76 versus 41%, P = .0571) and lower diastolic blood pressure (69 ± 11 versus 79 ± 8 mmHg, P = .0196) than those without PHT.

PAP was correlated positively with diastolic left ventricular volume (r = 0.32, P = .013) negatively with ejection fraction (r = −0.54, P < .0001).

Table 2: Clinical and laboratory data of patients with and without pulmonary hypertension.

	PAP ≤ 35 ($n = 34$)	PAP > 35 ($n = 22$)	P
Age (year)	59 ± 14	61 ± 12	ns
Male/Female (n (%))	22/12	15/7	ns
Diabetes (n (%))	1 (3%)	4 (18%)	0.05
Smoking history (n (%))	19 (56%)	17 (77%)	ns
Dialysis vintage (months)	27 ± 32	63 ± 60	0.0105
Dry weight (kg)	70 ± 16	65 ± 13	ns
Interdialytic weight gain (kg)	1,3 ± 0,9	2,0 ± 1.0	0.0168
Systolic blood pressure (mmHg)	132 ± 15	132 ± 27	ns
Diastolic blood pressure (mmHg)	80 ± 8	73 ± 12	0.0102
Calcium (mg/dl)	8,9 ± 1	9 ± 1	ns
Phosphate (mg/dl)	5,2 ± 1,7	5,2 ± 0,9	ns
Calcium-phosphate product (mg^2/dl^2)	48 ± 18	48 ± 10	ns
PTH (pg/ml)	316 ± 313	388 ± 381	ns
Haemoglobin (gr/dl)	11,4 ± 1,5	11 ± 1,4	ns
Haematocrit (%)	36 ± 5	34 ± 5	ns
Erythropoietin (IU/week)	5980 ± 7664	9272 ± 10015	ns

Table 3: Cardiovascular condition of patients with and without pulmonary hypertension.

	PAP ≤ 35 ($n = 34$)	PAP > 35 ($n = 22$)	P
Hypertension history (n (%))	29 (85%)	17 (77%)	ns
Ischaemic heart disease (n (%))	11 (32%)	10 (45%)	ns
Cerebrovascular disease (n (%))	8 (24%)	5 (23%)	ns
Peripheral vascular disease (n (%))	11 (32%)	6 (27%)	ns
Parathyroidectomy history (n (%))	4 (12%)	0 (0%)	ns
Left ventricular hypertrophy (n (%))	25 (74%)	15 (68%)	ns
Left ventricular Diastolic Volume (ml)	110 ± 32	124 ± 33	ns
Ejection Fraction (%)	60 ± 7	54 ± 13	0.0216
Mitral stenosis (n (%))	1 (3%)	1 (5%)	ns
Mitral incompetence (n (%))	27 (79%)	22 (100%)	0.02
Aortic stenosis (n (%))	1 (3%)	3 (14%)	ns
Aortic incompetence (n (%))	17 (50%)	15 (68%)	ns

In the whole population multiple logistic regression analysis showed an independent association between PHT and dialysis vintage (Odds Ratio 1.022 (95% CI 1.002–1.041) ($P = .0297$)) and diastolic blood pressure (Odds Ratio 0.861 (95% CI 0.766–0.967) ($P = .0116$); $R2 = 0.328$).

5. Discussion

This is a cross-sectional study investigating a small number of dialysis patients dealing with a underconsidered clinical problem. Yigla et al. [2] demonstrated that patients with PHT evaluated by echocardiography at the beginning of HD treatment, and with PHT developing soon after HD initiation, had shorter survival than their counterparts without PHT. The mechanisms involved in PHT development are still under investigation, but it has been reported that HD patients with PHT show a significantly higher cardiac output than HD patients with normal PAP [3, 4]. It has been suggested that some factors, such as the size or the location of AVF, are involved in the mechanism that increases PAP. On the contrary Tarrass et al. [8] did not find any difference in cardiac output between patients with and without PHT, and the effect of AVF location was not statistically significant. Beigi et al. [9] reported a positive correlation between mean fistula flow and PAP and, as well as in our study, an inverse correlation between PAP and ejection fraction. Unfortunately we did not measured fistula flow, therefore we could not add anything regarding this relationship. However we confirm the strong reverse relationship between PAP and ejection fraction. It has been reported that PHT improved after successful kidney transplantation, as well as after short AVF compression, indicating that both ESRD and AVF contribute to its pathogenesis [5]. In our patients those treated with HD had higher frequency of PHT than those on PD. Moreover factors associated to PHT in subjects treated with HD and PD seems to be different, probably reflecting a different degree of damage of the cardiovascular system during the history of the renal replacement treatment. To the best of our knowledge this is the first study suggesting that PHT interpretation needs to be individualized based on renal replacement therapy, suggestion reinforced by the higher interdialytic weight gain in patients with PHT than in those with normal PAP and the positive relationship between PAP and diastolic left ventricular volume. In agreement with our finding Issa el al. [10] reported that time on dialysis was the strongest correlate of an elevated right ventricular systolic pressure. The same authors stated that right ventricular systolic pressure greater than 50 mmHg was associated with significant reduced posttransplant survival [10]. On the other hand Nakhoul et al. [5] demonstrated that reduced nitric oxide production could increase PAP, PHT among HD patients who underwent successful kidney transplantation reversed, even if their AVF remained patent.

Other risk factors for PHT have been identified. Harp et al. [11] in a retrospective study suggested that age was the only risk factor, since each year of age increased the odds of having PHT by 3%. Hyperparathyroidism, by causing precipitation of calcium in many tissues, could play a role in the development of PHT secondary to pulmonary artery calcifications. This notion is supported by an experimental study in a dog model of ESRD [12]: animals with increased PTH activity and lung calcium content had higher PAP values than the dogs which underwent parathyroidectomy, thus suggesting a link between PAP and hyperparathyroidism. On the contrary Amin et al. [13] did not confirm these findings in a group of ESRD on regular HD. In our patients age, calcium, phosphate, PTH concentrations and history of parathyroidectomy revealed no difference between those with and without PHT. In a recent study Havlucu et al. [14] evaluated 23 predialysis and 25 HD patients,

those with elevated PAP had increased PTH levels, cardiac output values and chronic renal failure duration; AVF flow and duration were positively and residual urine volume negatively correlated with PAP.

Kumbar et al. [15] reported, in 36 PD patients, that those with PHT had lower ejection fraction, higher prevalence of global hypokinesia and dilated left ventricular chamber than patients without PHT. In the same way our findings indicate that low cardiac performance is related to PHT in PD subjects. Moreover in agreement with Yigla et al. [2] we found a higher prevalence of valvular damage in subjects with PHT, however the difference was statistically significant only for aortic incompetence in the PD group.

The relationship between PHT and diastolic BP should be interpreted in the same way, considering low diastolic BP as an indirect index of arterial stiffness. PHT was more frequent in HD than in PD, however this could be a bias due to the fact that in the patients referred to our hospital, PD subjects are usually healthier subjects than HD ones. The latter are older than the former, and the presence of AVF in HD but not in PD patients was bound to determine different (and worse) hemodynamic conditions.

In conclusion our-cross-sectional and retrospective study confirms that PHT is a frequent condition in the uraemic population, especially in aged patients with poor cardiovascular conditions. Hence, PHT could complicate the clinical picture of dialysis patients. On the other hand, our findings indicate that PAP evaluation could be an useful parameter for cardiovascular risk stratification of uraemic patients that needs to be interpreted based on patient history.

Competing Interests

The authors declare that they have no competing interests. The authors did not get any financial support. The study has been conducted according to the Declaration of Helsinky.

Authors' Contributions

Fabio Fabbian, Stefano Cantelli, Christian Molino, Marco Pala, Carlo Longhini, Francesco Portaluppi, performed the clinical work, acquired, analyzed and interpreted the data. Fabio Fabbian and Francesco Portaluppi drafted the manuscript Christian Molino and Carlo Longhini performed the investigations Stefano Cantelli and Marco Pala collected the data. Every author reviewed and approved the manuscript that it is not under consideration for publication elsewhere in a similar form, in any language.

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SAGE-Hindawi Access to Research
International Journal of Nephrology
Volume 2011, Article ID 732746, 7 pages
doi:10.4061/2011/732746

Review Article

Hyponatremia and Congestive Heart Failure: A Marker of Increased Mortality and a Target for Therapy

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Received 2 August 2010; Accepted 23 February 2011

Academic Editor: Anjay Rastogi

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Heart failure is one of the most common chronic medical conditions in the developed world. It is characterized by neurohormonal activation of multiple systems that can lead to clinical deterioration and significant morbidity and mortality. In this regard, hyponatremia is due to inappropriate and continued vasopressin activity despite hypoosmolality and volume overload. Hyponatremia is also due to diuretic use in an attempt to manage volume overload. When hyponatremia occurs, it is a marker of heart failure severity and identifies patients with increased mortality. The recent introduction of specific vasopressin-receptor antagonists offers a targeted pharmacological approach to these pathophysiological derangements. Thus far, clinical trials with vasopressin-receptor antagonists have demonstrated an increase in free-water excretion, improvement in serum sodium, modest improvements in dyspnea but no improvement in mortality. Continued clinical trials with these agents are needed to determine their specific role in the treatment of both chronic and decompensated heart failure.

1. Introduction

Heart failure (HF) is an increasingly common condition, with recent American data revealing a 1 in 5 lifetime risk for both sexes, and over 5 million currently affected patients [1]. In addition to being common, morbidity and mortality attributable to HF continue to rise with over 1.1 million hospital discharges and 1 in 8 death certificates mentioning heart failure in 2006 [1]. HF has an annual mortality of 20% per year after diagnosis, and its estimated economic burden in the United Sates in 2009 was $37.2 billion [1].

Although HF manifests primarily with cardiopulmonary symptoms, hyponatremia is very common in this patient population. In fact, hyponatremia (variably defined as serum sodium <1342–136 mmol/L) is present in over 20% of patients admitted to hospital with HF [2, 3]. Not only is it a common occurrence, but it has repeatedly been shown to be a marker of increased mortality in the HF population [3, 4].

As will be discussed in this paper, both the maladaptive neurohormonal and renal changes as well as diuretic treatment of HF contribute to the development of hyponatremia [2–4]. In particular, the posterior pituitary hormone vasopressin leads to renal water retention and hyponatremia. As such, the recently developed vasopressin antagonists present an attractive target for the management of hyponatremia in HF [5].

2. Physiology of Water Handling

To appreciate the pathophysiology of hyponatremia in HF, it is important to understand the basic physiology of renal salt and water handling. With the exception of psychogenic polydipsia and low dietary solute intake, essentially all cases of true hyponatremia represent a failure to excrete maximally dilute urine. In the presence of normal renal function, this

failure is most often related to the action of vasopressin (AVP).

AVP is a hormone synthesized in the supraoptic (SON) and paraventricular nuclei of the hypothalamus and is released from the posterior pituitary [6]. Its effects are multiple and related to the affected receptor (Table 1). Binding to the V_{1a} receptor leads to vascular smooth muscle contraction [7] while V_2 receptor activation in the renal medulla leads to free water reabsorption by the collecting duct. Binding to V_2 receptors, located on the basolateral membrane of the cortical collecting duct cells, leads to increased aquaporin 2 (aqp-2) mRNA levels and translocation of aqp-2 to the apical membranes [6]. This increases tubular water permeability and allows water to move from the tubule to the medullary interstitium (down a concentration gradient), resulting in net reabsorption of free water. This movement of water is passive and relies upon a hypertonic renal medulla, the generation of which is partly dependant on the activity of the NKCC (sodium-potassium-2 chloride) channels in the ascending loop of henle [8]. Absence of AVP activity (such as in diabetes insipidus) leads to loss of high volume dilute urine.

AVP release is mediated by both osmotic as well as cardiac output and intravascular volume stimuli. Osmoreceptors present in the SON are exceedingly sensitive to changes in serum osmolality demonstrating alterations in AVP release in response to a 1% fluctuation in serum osmolality [9]. This sensitivity serves to keep serum osmolality tightly controlled with a threshold for AVP release of approximately 280 mOsm/Kg [9]. The nonosmotic stimuli for AVP release consist of reductions in cardiac output, intravascular blood volume, or blood pressure [9]. These stimuli, mediated through high (aortic arch and carotid sinus) and low (left atrial) pressure baroreceptors [10], enhance the secretion of AVP for any given osmotic stimulus [9, 10]. In effect, AVP will be released at a lower plasma osmolality when decreased intravascular volume, cardiac output or blood pressure are detected.

Recently, AVP has been shown to be a potent and independent regulator of the thiazide-sensitive Na(+)-Cl(−) cotransporter (NCC) [11, 12]. This action is mediated through the V_2-receptor and its clinical effects are, as yet, not clear but implicate AVP in the handling of sodium as well as water.

3. Pathophysiology of Hyponatremia in Heart Failure

In the normal physiologic state, alterations in serum osmolality serve as the primary control for AVP release. However, in conditions that lead to nonosmotic stimulation of AVP release, these stimuli may take precedence resulting in the acceptance of a lower serum osmolality [9]. Such is the case in HF where a decrease in cardiac output leads to a continued release AVP despite a reduction in osmolality, thus leading to hyponatremia. Multiple studies have demonstrated increased levels of AVP in HF leading accompanied by inadequate inhibition when exposed to a decrease in serum osmolality [13, 14]. Indeed, data in the Studies of Left Ventricular Dysfunction (SOLVD) show a progressive incremental increase in AVP levels with worsening HF symptoms [15]. It has also been shown that the density of AVP positive neurons in the SON is increased by as much as 30% in patients with HF [16].

A number of other neurohormonal abnormalities contribute to abnormalities in renal sodium (Na) and water handling. Arterial underfilling (from decreased cardiac output) detected by baroreceptors in the aortic arch, carotid sinus and afferent renal arterioles leads to activation of the sympathetic nervous system (SNS) and the renin-angiotensin-aldosterone system (RAAS) [2]. While the activation of these systems acts to preserve systemic perfusion pressure in patients with HF, it is a long-term maladaptive response that leads to avid Na and water retention in multiple nephron segments. This overload of Na and water may worsen cardiac function thus perpetuating the cycle of Na and water retention. In addition, angiotensin II is a potent inhibitor of thirst, which may lead to increased free water intake and exacerbation of hyponatremia [17].

Reductions in glomerular filtration rate are common in patients with HF and can eventually lead to a reduced capacity for water and Na excretion. It has been shown that the filtered load of Na decreases in parallel with declining GFR in patients receiving diuretics [18]. While salt intake in these patients exacerbates volume overload and HF, they are also at risk of worsening hyponatremia with increased free water intake.

Although a mainstay in the therapy of HF, diuretics can also cause hyponatremia. These drugs increase Na and water excretion thereby alleviating congestive symptoms and theoretically helping to optimize cardiac contractility. It is interesting to note that despite their widespread use, diuretics have not been shown to improve survival in HF patients [19]. Diuretics are prescribed in 85–100% of symptomatic and 16–35% asymptomatic patients with reduced left ventricular function [20–22]. Loop diuretics are the most commonly utilized diuretics and exert their salt wasting effects by inhibiting the NKCC channel in the thick ascending loop of Henle. Other diuretics used frequently in HF include thiazide diuretics and spironolactone. Thiazides inhibit the Na-Cl cotransporter in the distal convoluted tubule while spironolactone prevents activation of the mineralocorticoid receptor on the principal cells of the cortical collecting duct. Of these 3 classes, loop diuretics offer the most potent increase in Na and water excretion and thus are important agents in the treatment of states of volume overload.

In the general population, diuretic-induced hyponatremia is very common, with thiazides accounting for the 63% of the cases of severe hyponatremia, loop diuretics for 6%, and spironolactone for 1% [23]. The incidence of hyponatremia with thiazide diuretics may be as high as 11% in the elderly [24]. Several features may contribute to hyponatremia: (1) stimulation of AVP release secondary to diuretic-induced volume contraction, (2) decrease in GFR from intravascular volume contraction, (3) inhibition of urinary dilution capacity due to interference with Na absorption in the distal segments, and (4) hypokalemia induced intracellular shift of Na [24]. The thiazide effect in the distal

Table 1: The actions of vasopressin and its receptors.

Receptor	Location	Action
V_{1a}	Vascular smooth muscle	Vasoconstriction
		Myocardial hypertrophy
	Platelets	Aggregation
	Myometrium	Uterine contraction
V_{1b}	Anterior pituitary	Adrenocorticotropin hormone release
V_2	Renal collecting tubule	Induction of aquaporin-2
		Free water absorption
	Vascular endothelium	Release of von Willebrand factor
		Release of factor VIII

nephron accounts for its association with hyponatremia. Conversely, loop diuretics may be spared from causing hyponatremia by their effect on the NKCC co-transporter, which helps maintain the hypertonic medullary interstitium. A reduction in the tonicity in this area decreases the gradient for free water movement out of the tubules via aqp-2 channels and may therefore lessen the risk of hyponatremia as compared to thiazides.

Owing to their disruption of the medullary concentration gradient, loop diuretics may actually lead to an increase in Na in hyponatremic patients [25]. If, however, there is incomplete amelioration of the concentration gradient, administration of loop diuretics can still cause hyponatremia. This likely relates to further stimulation of the RAAS due to increased distal Na delivery thereby increasing angiotensin II, a well-known stimulant of AVP secretion [26].

4. Epidemiology of Hyponatremia in Heart Failure

Given the number of neurohormonal changes in patients with HF, it is not surprising that hyponatremia is very common in this population. With Na and water retention and decreased GFR from activation of the RAAS and SNS in the context of increased AVP levels, continued intake of hypotonic fluids may lead to hyponatremia. Of all patients admitted to hospital with a diagnosis of HF, 18–27% will have hyponatremia (Na < 135 mmol/L) on admission [27, 28].

Not only is hyponatremia common, it is also a strong marker of increased morbidity and mortality in HF patients. Lee and Packer [29] analyzed 30 clinical, hemodynamic, and biochemical variables and their association with survival in 203 consecutive patients with severe HF. The most powerful predictor of cardiovascular mortality was pretreatment serum Na, with hyponatremic patients having a substantially shorter median survival than patients with a normal serum Na (164 versus 373 days, $P = .006$). Similarly, in the Outcomes of a Prospective Trial of Intravenous Milrinone for Exacerbations of Chronic Heart Failure (OPTIME-CHF) study, both in hospital and 60-day mortality rates were highest for patients with the lowest admission serum Na [27]. In the Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients with Heart Failure (OPTIMIZE-HF) registry, patients with hyponatremia had significantly higher in-hospital and follow-up mortality rates and longer hospital stays [30]. In this study, for each 3 mmol/L decrease in serum Na below 140 mmol/L at admission, the risk of in-hospital mortality and follow-up mortality increased by 19.5% and 10%, respectively. More recently, the importance of persistent hyponatremia in HF patients was described in a cohort of patients enrolled in the Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterization Effectivenes (ESCAPE) [31]. Hyponatremia in this study was associated with higher 6-month mortality after covariate adjustment (hazard ratio(HR), for each 3 mmol/L decrease in serum Na, 1.23; 95% confidence interval (CI), 1.05–1.43; $P = .01$). After controlling for baseline variables and clinical response, patients with persistent hyponatremia had an increased risk of all-cause mortality (31% versus 16%; HR, 1.82; $P = .04$), HF rehospitalization (62% versus 43%; HR, 1.52; $P = .03$), and death or rehospitalization (73% versus 50%; HR, 1.54; $P = .01$) compared with normonatremic patients.

It is unclear whether this increased mortality directly related to hyponatremia or if the sodium abnormality is a marker of a more severe underlying illness. It is likely that it reflects a greater activation of the RAAS and SNS with higher levels of AVP leading to increased mortality. It has in fact been shown that patients with hyponatremia have higher circulating levels of catecholamines, renin, angiotensin, aldosterone, and AVP [32]. It is also feasible that the presence of hyponatremia limits options in terms of diuretic management and could potentially alter HF therapy leading to differences in mortality. Moreover, hyponatremia associated with diuretic use may be accompanied by multiple other metabolic abnormalities such as hypokalemia and hypomagnesemia that could increase mortality. In addition, severe hyponatremia and its correction can respectively lead to cerebral edema and the osmotic demyelination syndrome, both of which are associated with high morbidity and mortality.

5. Management of Hyponatremia in Heart Failure

Management of hyponatremia in heart failure demands a multifaceted approach including optimization of cardiac function (including prevention of volume overload and neurohormonal blockade), preservation of renal function,

and maintenance of appropriate fluid intake. In addition, the relatively newly developed vasopressin antagonists potentially offer an attractive therapeutic strategy for dealing with hyponatremia in HF. Of utmost importance in any patient with hyponatremia is to ensure adequate monitoring of serum Na levels, as rapid changes in either direction can have dire consequences.

5.1. Optimization of Cardiac Function. Perhaps a simplistic view of managing hyponatremia in HF is to ensure adequate cardiac output. Ideally, this would reduce the stimulation of baroreceptors and lessen the activation of the SNS and RAAS resulting in less renal avidity for Na and water and lower levels of AVP.

While detailed management of HF is beyond the scope of this paper, inhibition of the SNS and RAAS with β-blockers (BB) and angiotensin converting enzyme inhibitors (ACEi) or angiotensin receptor blockers (ARB) remain the cornerstone of chronic HF management [33]. These agents break the maladaptive cycle of neurohormonal activation and via multiple mechanisms lead to improved preservation of cardiac function [33]. They also lead to a reduction in left ventricular afterload facilitating an improvement in cardiac output. In addition, blockade of the aldosterone action with spironolactone or eplerenone decreases hospitalizations and mortality in patients with New York Heart Association (NYHA) class III and IV HF [34, 35]. In patients with acute exacerbations of HF, afterload reduction with ACEi and nitrates and utilization of positive inotropic agents may be used to improve cardiac output [36] thus increasing Na levels in hyponatremic patients.

As previously discussed, diuretics remain a mainstay of HF treatment and have complex effects on serum Na levels. Increasing Na and water loss can ease congestive symptoms and, especially in combination with afterload reduction and increased inotropy, can improve cardiac output in the volume-overloaded patient [36]. This is usually accomplished with loop diuretics, or a combination of loop and thiazide diuretics, and can lead to increased Na levels in the hyponatremic patient. It is important to note, however, that excessive diuresis leads to hypovolemia, activation of the SNS and RAAS, and decreased renal function. This effect can worsen cardiac function and lead to impaired renal Na and water handling resulting in hyponatremia from increased AVP release. In addition, a single bolus of furosemide has been associated with an increase in plasma renin activity, norepinephrine, and AVP leading to increased left ventricular filling pressure and decreased stroke volume [37]. This response to furosemide is potentially detrimental to the HF patient.

Diuretic use has been associated with increased mortality in both chronic and acute exacerbations of HF [38, 39]. It is difficult, however, to delineate a cause and effect relationship, and despite a lack of evidence for their effectiveness, diuretics will likely remain an important component of HF management for the foreseeable future. Due to the complex physiology of HF, the effect of loop diuretics on serum Na can be difficult to accurately predict thus making frequent monitoring of serum Na very important. In addition, nonpotassium sparing diuretics may lead to significant hypokalemia, hypomagnesemia, and decreased renal function. It is therefore prudent to ensure adequate monitoring of these parameters when using these agents.

5.2. Preservation of Renal Function. Patients with impaired renal function have a decreased capacity for Na and water excretion thus placing them at an increased risk of developing hyponatremia. Efforts to maintain normal renal function including blood pressure control, limiting use of nephrotoxic medications and contrast dye, and avoiding excessive diuresis may help to limit the risk of hyponatremia. In patients whose renal function is sufficiently poor to maintain appropriate Na and water balance, renal replacement therapy (hemodialysis or peritoneal dialysis) can remove excessive Na and water and maintain normal sodium levels.

5.3. Maintenance of Appropriate Fluid Intake. With high levels of circulating AVP, HF patients will have a limited capacity to excrete excess dietary free water. It thus follows that HF patients with hyponatremia should limit dietary water intake. The degree of limitation necessary will be patient specific and dictated by the degree of neurohormonal activation in each patient. Again, frequent monitoring will help ensure an appropriate rise in serum Na in response to the intervention.

5.4. Vasopressin Antagonists. Given the primary role of AVP in free water retention and the development of hyponatremia, antagonism of AVP action would seem like a rational therapeutic option in hyponatremic HF patients. As vasopressin also leads to vasoconstriction and cardiomyocyte hypertrophy [7], blocking its actions may have further beneficial effects in HF.

A number of such drugs have been developed and target either V_2 receptors selectively or a combination of V_2 or V_{1a} receptors. These agents lead to a selective loss in renal free water losses termed *aquaresis*. To date, no studies have shown a reduction in mortality with use of the vasopressor antagonists in HF.

Preclinical studies in animals and humans showed that administration of a V_2 receptor antagonist leads to an increase in free water excretion with little increased Na loss and no compensatory activation of the RAAS [40–42]. These positive results have led to a number of clinical trials of these agents in HF patients.

Georghiade et al. compared tolvaptan to placebo in 254 NYHA class III or IV outpatients who continued to receive standard HF therapy [43]. Patients received either 1 of 3 oral doses of tolvaptan (30, 45, or 60 mg/day) or placebo for a total of 25 days. Although all patients treated with tolvaptan had an increase in serum Na, the 28% who had baseline had hyponatremia the greatest rise. 80% of tolvaptan-treated patients with hyponatremia had normalization of serum Na on day 1 compared to 40% of those receiving placebo. These patients also had significant reductions in body weight with an improvement in HF symptoms. A similar study in 319 patients randomized patients to 1 of 3 tolvaptan doses (30, 60, or 90 mg) or placebo, in addition to standard HF

treatment for 60 days [28]. Patients in the tolvaptan group had small increases in serum Na; the greatest rise in Na was seen in the 21.3% of patients with baseline hyponatremia. Tolvaptan-treated patients also had a significant decrease in body weight at 24 hours (median 2.05 Kg in the highest dose group) with no changes in heart rate, blood pressure, renal function, or development of hypokalemia.

A larger study of 4133 patients assessed both- short and long-term outcomes in patients admitted with acutely decompensated HF [44, 45]. Patients were randomized to receive Tolvaptan 30 mg/day or placebo in addition to standard HF care. Short-term outcomes at 7 days revealed no difference in the primary outcome of global clinical status. Similar to the previous studies, however, the tolvaptan group did have a significant decrease in body weight and dyspnea. Of note, treatment with tolvaptan also led to significant increases in thirst, polyuria, and hypernatremia (1.4% versus 0%). The long-term follow-up trial over a mean of 9.9 months, found no difference in all-cause mortality, cardiovascular death, or HF hospitalizations between the groups. Improvements in dyspnea and serum Na were maintained throughout followup with similar side effects to those seen in the short-term trial. A subgroup analysis of the 8% of the patients with baseline hyponatremia found serum Na to be increased by 5.5 mmol/L and 1.8 mmol/L in the tolvaptan and placebo groups, respectively.

Similar short-term outcomes of increased urine output and serum sodium were found in patients with stable HF receiving lixivaptan, another V_2-receptor antagonist [46]. Ascending single doses of the drug were used and produced a dose-dependent increase in urine output but no long-term outcomes with this agent have been published.

Antagonism of the V_{1a} receptors in addition to the V_2 receptors has the added theoretical benefit of decreasing afterload by inhibiting AVP-mediated smooth muscle contraction. Conivaptan is one such agent with FDA approval for treatment of hypervolemic hyponatremia. In a randomized, double-blind, placebo-controlled, multicenter study, 84 patients with hyponatremia were randomized to receive 1 of 2 doses of conivaptan (20 mg bolus followed by 96 hour infusion of either 40 or 80 mg/day) or placebo, in addition to standard HF treatments [47]. Both doses of conivaptan were associated with significant increases in serum Na. Na levels increased by 6 mmol/L or were normalized in 69% of the 40 mg/day dose and 88.5% of the 80 mg/day dose by day 4, whereas only 20.7% of the placebo group achieved this goal.

Several studies of conivaptan in HF patients have yielded similar results to those with V_2-receptor antagonists [48–50]. Recipients of conivaptan had increases in urine output with decrease in left- and right-sided filling pressures and had minimal side effects. When compared with furosemide alone, a combination of furosemide and conivaptan produced a dose-dependent increase in urine output [50]. In addition, combination with higher doses of conivaptan (80 or 120 mg/day) led to small but significant increases in serum Na.

The precise role of vasopressin antagonists in the management of hyponatremic HF patients remains unclear. While no effects on mortality have been seen in clinical trials, there are clear improvements in symptoms in the majority of studies. To date, there have been no studies directly comparing the effects of V_2 and combined V_2/V_{1a}-recpetor antagonists which remains an interesting clinical question. It is important to note that in all of the aforementioned studies, vasopressin antagonists have been used in conjunction with usual HF treatment (including diuretics), and have not been studied as a replacement for loop diuretics.

6. Conclusion

Hyponatremia in HF is a frequent occurrence related to the activation of a multitude of neurohormonal pathways including the SNS, RAAS, and particularly the increased release of AVP. In addition to being common, hyponatremia is associated with increased mortality in the HF population. The treatment has traditionally consisted of RAAS and SNS blockade in combination with loop and thiazide diuretics and dietary water restriction. While this approach can be effective, diuretics have several detrimental metabolic side effects and may potentially worsen hyponatremia and cardiac function. Vasopressin antagonism represents a logical goal in the management of hyponatremia in the HF population. These agents have been shown to increase serum Na and free water clearance and improve HF symptoms, but have not yet been found to reduce long-term mortality. More trials are necessary to define an exact role for the vasopressin antagonists in HF patients.

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SAGE-Hindawi Access to Research
International Journal of Nephrology
Volume 2011, Article ID 412495, 6 pages
doi:10.4061/2011/412495

Research Article

Acute Childhood Cardiorenal Syndrome and Impact of Cardiovascular Morbidity on Survival

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Received 15 August 2010; Accepted 21 March 2011

Academic Editor: Anjay Rastogi

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Cardiorenal syndrome (CRS) clinical types, prevalence, aetiology, and acute cardiovascular morbidity impact on the outcome of acute kidney function perturbation were determined. Forty-seven of 101 (46.53%) patients with perturbed kidney function had CRS. Types 3 and 5 CRS were found in 10 and 37 patients, respectively. Type 3 CRS was due to acute glomerulonephritis (AGN; $n = 7$), captopril ($n = 1$), frusemide ($n = 1$), and hypovolaemia ($n = 1$). Malaria-associated haemoglobinuria ($n = 20$), septicaemia ($n = 11$), lupus nephritis ($n = 3$), tumour lysis syndrome ($n = 2$), and acute lymphoblastic leukaemia ($n = 1$) caused Type 5 CRS. The cumulative mortality in hypertensive CRS was similar to nonhypertensive CRS (51.4% versus 40.9%; $P = .119$). Mortality in CRS and non-CRS was similar (45.7% versus 24.5%; $P = .053$). Type 5 survived better than type 3 CRS (66.7% versus 12.5%; $P = .001$). Risk factors for mortality were Type 3 CRS ($P = .001$), AGN-associated CRS ($P = .023$), dialysis requiring CRS ($P = .008$), and heart failure due to causes other than anaemia ($P = .003$). All-cause-mortality was 34.2%. Preventive measures aimed at the preventable CRS aetiologies might be critical to reducing its prevalence.

1. Introduction

The cardiorenal syndrome (CRS) is a disorder of the heart and kidneys whereby acute or chronic dysfunction in one organ may induce acute or chronic dysfunction of the other [1, 2]; it is a recognized morbidity and mortality multiplier in critically ill children [3]. While heart failure (HF) is a clinical syndrome in which heart disease reduces cardiac output, increases venous pressures, and is accompanied by molecular abnormalities that cause progressive deterioration of the failing heart and premature myocardial cell death [4], acute kidney injury (AKI) is an abrupt clinical and/or laboratory manifestation of kidney dysfunction usually within 48 hours of bilateral kidney insult of any kind. Failure of both organs commonly coexists in critically ill children [5–7]. Congestive HF is a highly prevalent AKI comorbidity and a major indication for acute dialysis in children [5]. Recently, the 7th Acute Dialysis Quality Initiative (ADQI) workgroup classified CRS into five distinct clinical types, [1, 2] namely: acute CRS (Type 1)—acute worsening of heart function leading to kidney injury and/or dysfunction; chronic CRS (Type 2)—chronic abnormalities in heart function leading to kidney injury and/or dysfunction; acute renocardiac syndrome (Type 3)—acute worsening of kidney function (AKI) leading to heart injury and/or dysfunction; chronic renocardiac syndrome (Type 4)—chronic kidney disease leading to heart injury, disease, and/or dysfunction, and secondary CRS (Type 5)—systemic conditions leading to simultaneous injury and/or dysfunction of heart and kidney. While a lot of data have been published on chronic kidney disease as risk factor for cardiovascular morbidity and mortality in both children and adults (reviewed in [1–3]), there is paucity of specific data on acute cardiac dysfunction leading to AKI and vice versa in children especially [8]; in this study, an attempt was made to determine the prevalence, aetiology, clinical types of CRS, and impact of acute cardiovascular morbidity on the outcome of childhood acute kidney injury.

2. Patients and Methods

Clinical charts of patients managed for AKI-associated HF and acute glomerulonephritis (AGN)—associated HF in our

paediatric nephrology and hypertension unit were reviewed. It was a retrospective case-control study; patients who had either AKI or AGN without HF served as control (non-CRS). The objectives were to determine the prevalence, aetiology, clinical types of CRS, and impact of acute cardiovascular morbidity on the outcome of childhood AKI. The study period ranged between January 2005 and December 2009. Our hospital's Ethics and Research Committee approved the research protocol. The study conformed to the provisions of the revised Declaration of Helsinki, Edinburg, 2000.

Analyzed data were age, gender, anthropometry, vital signs, admission diagnosis, time of onset of HF and AKI, final AKI stage, hospitalization period, follow-up duration, urine output, and management outcome. Relevant laboratory investigations including serum creatinine (Scr) both at baseline and at followup were reviewed.

2.1. Definitions. AKI was diagnosed based on the acute kidney injury network (AKIN) criteria [9] as an absolute increase in serum creatinine (Scr) level within 48 hours of bilateral kidney insult by ≥0.3 mg/dL (≥26.4 μmol/L) or a 50% (1.5-fold) increase or more in Scr from the baseline. AKI was staged using the creatinine criteria of the AKIN workgroup [9]—Stage 1 AKI (AKI-1): rise in Scr by ≥0.3 mg/dL (26.4 μmol/L) or an increase of >150–200% (1.5- to 2-fold increase) from the baseline; Stage 2 AKI (AKI-2): rise in Scr by >200–300% (>2- to 3-fold increase) from baseline; Stage 3 AKI (AKI-3): rise in Scr by >300% (>3-fold) from the baseline or Scr ≥ 4.0 mg/dL (≥354 μmol/L) with an acute rise of at least 0.5 mg/dL (44 μmol/L). Nonoliguric AKI was defined as urine output that was persistently >0.5 mL/kg/hour in the setting of an abnormal Scr level. Anuric AKI was defined as the urine output that was <0.039 mL/kg/hr for 12 hr or more in the absence of an obstructive uropathy. AKI was staged based on the peak Scr (pScr) level. pScr was the highest Scr level reached in any patient either before death or before gradual return to normal. Those who were initially diagnosed AKI-1 or AKI-2 but later required dialyses were upgraded to AKI-3 as recommended [9]. The predictive eGFR equation with corrections for age, gender, and race derived by the Modification of Diet in Renal Disease (MDRD) [10] study group was used to determine the baseline Scr for patients who do not have baseline Scr as recommended by the 2nd ADQI workgroup [11]. For such patients, the 2nd ADQI recommended that normal estimated glomerular filtration rate (eGFR) ranging from 75 to 100 mL/min per 1.73 m^2 should be used. In this study, all AKI patients without baseline measure of renal function were assumed to have eGFR value of 100 mL/min/1.73 m^2. By the MDRD equation, $\text{eGFR} = 186 \times ([\text{Scr}]^{-1.154} \times \text{Age}^{-0.203} \times 0.742$ (if female) $\times$ 1.210 (if black)) [10].

Heart failure was diagnosed based on a combination of dyspnoea, tachycardia (heart rate >160, >150, >140, >120, and >100 beats/min for infants, children aged 1–3, 4–5, 6–12, and above 12 years, resp.), tachypnoea (respiratory rate >60, >40, >34, >30, and >20 breathes/min for infants, children aged 1–3, 4–5, 6–12, and above 12 years, resp.), tender hepatomegaly, and feeding difficulty with or without chest X-ray evidence of cardiomegaly (abnormal cardiothoracic ratio >60% in under fives and >55% in older children). HF severity was assessed and classified according to the modified Ross heart failure classification for children [12]—Class I heart failure: asymptomatic; Class II heart failure: mild tachypnoea or diaphoresis with feeding in infants or dyspnoea on exertion in older children; Class III heart failure: marked tachypnoea or diaphoresis with feeding in infants, marked dyspnoea on exertion, and prolonged feeding times with growth failure; Class IV heart failure: symptoms such as tachypnoea, retractions, grunting, or diaphoresis at rest. Hypertension was diagnosed based on the update of the 1987 Task Force Report on High Blood Pressure in Children and Adolescents [13]. CRS was classified based on the 7th ADQI consensus conference report [2].

The inclusion criteria were patients with acute perturbation of kidney function (AKI or AGN or both) with or without HF. Patients with chronic renal failure or acute-on-chronic renal failure were excluded. To determine the impact of HF on survival, mortality was compared between CRS (AKI + HF and AGN + HF) and non-CRS patients. The cumulative all-cause-mortality and CRS-specific mortality rates were determined.

2.2. Statistical Analysis. Descriptive statistics used comprised mean, standard deviation, median, percentages, and proportions. The comparative statistics were Student's *t*-test, Chi-square test, Cox regression analysis for hazard ratio (HR), Wilcoxon statistics, Kaplan-Meier survival analysis, and Mantel-Cox pairwise comparisons (Log-rank test) using the SPSS 15.0 for Windows evaluation version (2006, SPSS Inc.). A P-value <.05 was regarded as statistically significant.

3. Results

A total of 101 patients with acute perturbation of kidney function, namely, AKI and AGN were reviewed. There were 7 and 94 acute glomerulonephritis (AGN) and AKI patients, respectively. Forty seven of 101 (46.53%) patients with abnormal kidney function had HF-cardiorenal syndrome. HF was of the severest class (Class IV) in all the CRS patients. Age, gender, and blood pressure data are summarized in Table 1. Median age of 5.0 years (0.06–15.0) for controls was similar to that for CRS, $P = .689$. Types 3 and 5 CRS were found in 10 (21.3%) and 37 (78.7%) patients, respectively. Table 2 shows the relationship between the two CRS types in this study and their aetiologies. Two of 7 patients whose CRS was due to AGN had no associated AKI (AGN–AKI) while the remaining 5 had associated AKI. The pScr was 6.11 ± 4.0 (0.95–17.32) mg/dL. AKI-1, AKI-2, and AKI-3 accounted for 4 (8.50%), 5 (10.60%), and 36 (76.60%) CRS cases, respectively, while AGN-AKI accounted for the rest. Twenty-two (46.80%) of the CRS patients had oliguric AKI while nonoliguric and anuric AKI were seen in 11 (23.40%) and 14 (29.80%) patients, respectively. Oliguria duration in both CRS and controls was 6.9 ± 5.54 days and 7.5 ± 4.75 days, respectively ($P = .654$).

Anaemia was present in 43 of 47 CRS patients (91.5%). The haematocrit ranged from 4.0 to 32.0% with the 5th,

Table 1: Demographic and clinical characteristics of the cardiorenal syndrome patients ($n = 47$).

Demographic and baseline clinical characteristics	Results (%)
Age < 6 years	33 (70.21)
Age ≥ 6 years	14 (29.79)
Median age (range), years	4.0 (.3–14.5)
Gender	
Male	26 (55.32)
Female	21 (44.68)
Male to female ratio	1.24 : 1
Number with normal blood pressure (BP)[a]	26 (57.8)
Systolic BP range, mmHg	60–110
5th, 50th, and 95th percentiles in mmHg	63.5, 90, and 110
Diastolic BP range, mmHg	30–70
5th, 50th, and 95th percentiles in mmHg	33.5, 50, and 70
Mean arterial pressure range, mmHg	43.3–83.3
5th, 50th, and 95th percentiles in mmHg	44.49, 66.7, and 82.85
Number with hypertension	19 (42.2)
Systolic BP range, mmHg	90–190
5th, 50th, and 95th percentiles in mmHg	90, 120, and 190
Diastolic BP range, mmHg	60–130
5th, 50th, and 95th percentiles in mmHg	60, 80, and 130
Mean arterial pressure range, mmHg	73.3–150
5th, 50th, and 95th percentiles in mmHg	73.3, 93.3, and 150

[a]Blood pressure data available in 45 of 47 patients.

Table 2: Relation between cardiorenal syndrome types and their aetiologies.

Cardiorenal syndrome type and aetiology	Proportion of patients (%)
Type 3	
Acute glomerulonephritis	7.0 (70.0)
Captopril	1.0 (10.0)
Frusemide	1.0 (10.0)
Hypovolaemic shock due to gastroenteritis	1.0 (10.0)
Type 5	
Malaria-associated haemoglobinuria	20.0 (54.05)
Septicaemia	11.0 (29.73)
Lupus nephritis	3.0 (8.11)
Tumour lysis syndrome in Burkitt's lymphoma patients	2.0 (5.41)
Acute lymphoblastic leukaemia	1.0 (2.70)

50th, and the 95th haematocrit percentiles for the anemic CRS being 5.2%, 15.0%, and 27.6%, respectively. Severe, moderate, and mild anaemia occurred in 38 (88.37%), 2 (4.65%), and 3 (6.98%) patients, respectively, ($P = .000$). Malaria-associated haemoglobinuria (MAH), septicaemia, AGN, lupus nephritis and tumour lysis syndrome accounted

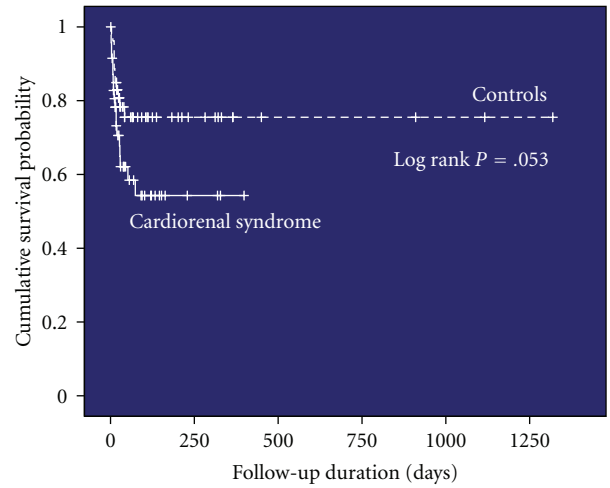

Figure 1: Kaplan-Meier survival curves showing that survival was not significantly higher in controls than in cardiorenal syndrome (75.5% versus 54.3%). Similarly, the survival times were not significantly different.

for 20 (46.51%), 10 (23.25%), 4 (9.30%), 3 (6.97%), and 2 (4.65%) anaemia cases, respectively. Hypovolaemia due to gastroenteritis, acute lymphoblastic leukaemia, captopril, and frusemide accounted for one (2.33%) case each, ($P = .000$). Anaemia was absent in 1 septicaemia and 3 AGN cases.

3.1. Followup and Outcome. The mean CRS hospitalization period was 21.90 ± 16.42 days (controls: 25.1 ± 19.7; $P = .361$). Both the CRS and non-CRS patients were, respectively, followed for 67.2 ± 90.97 (1.0 − 398.0) days and 128.96 ± 240.61 (1.0–1319.0; $P = .106$) days. Survival in CRS patients who were <6 years old was similar to older patients (14 versus 10 survivors; HR:.483, 95% CI: .157–1.488; $P = .205$). Cumulative mortality was higher in hypertensive (51.4%) than nonhypertensive (40.9%) CRS, but the difference did not reach statistical significance (HR:.476, 95% CI: .183–1.240; $P = .129$). Survival comparison between non-CRS (controls) and CRS patients revealed no statistically significant difference (HR:.496, 95% CI: .239–1.031; Figure 1). Figure 2 shows that patients with Type 5 CRS survived better than Type 3 CRS (HR:.479, 95% CI: .299–.768). The cumulative survival for MAH, septicaemia, and acute glomerulonephritis was 81.4%, 39.8%, and 21.4%, respectively; none of the patients with AKI due to hypovolaemia, frusemide, captopril, and leukaemia survived. CRS due to aetiologies other than AGN was significantly less associated with mortality compared with CRS due to AGN (40.4% versus 78.6%; HR: .544; 95% CI: .322–.919; $P = .023$). A pairwise comparison statistics (Wilcoxon) revealed that MAH survived significantly better than other CRS causes ($P = .014$). No death occurred in AKI-1, but there were 2 and 15 deaths in AKI-2 and AKI-3, respectively; AGN-AKI had one death. Mortality was similar in all AKI stages (HR: 1.872, 95% CI: .761–4.603) as well as in all the three AKI types (HR: 1.385, 95% CI: .799–2.400) of CRS. Survival comparisons among the AKI types in both CRS and non-CRS revealed no significant differences

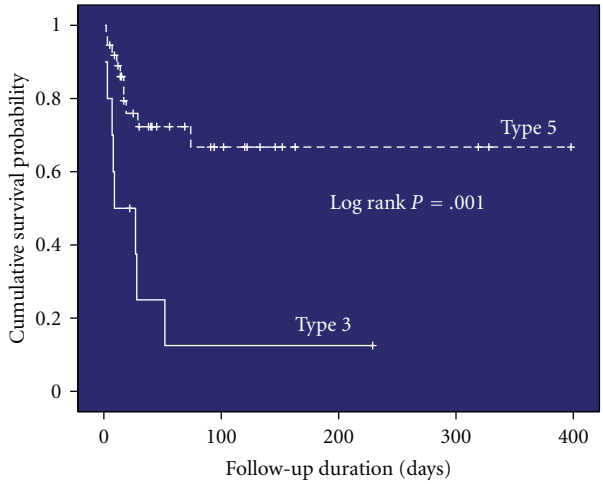

Figure 2: Kaplan-Meier survival curves showing significantly better survival in Type 5 compared to Type 3 cardiorenal syndrome (72.3% versus 12.5%).

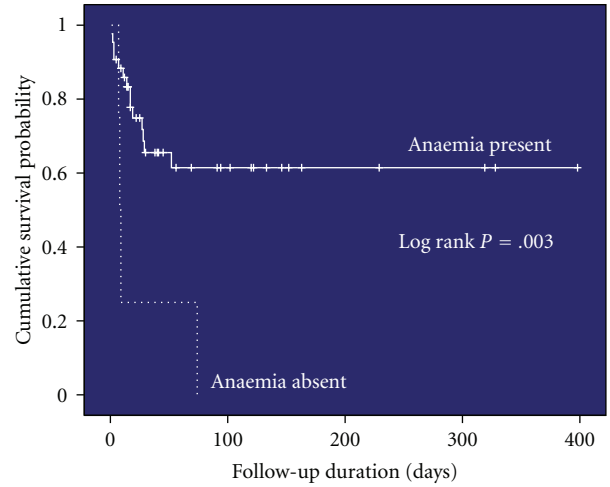

Figure 4: Kaplan-Meier survival curves comparing survival in cardiorenal syndrome patients with anaemia and those without anaemia. Patients with anaemia had significantly higher survival rate compared to nonanaemic patients (61.4% versus 25.0%).

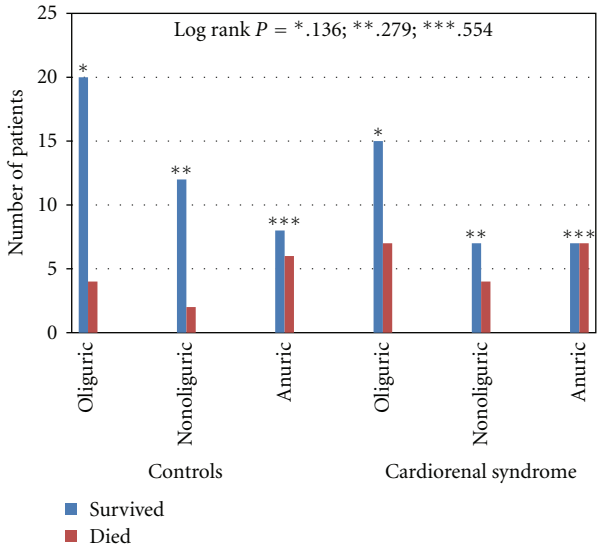

Figure 3: Comparisons between controls and patients with cardiorenal syndrome with regard to survival in the acute kidney injury (AKI) types. The number of patients surviving in oliguric, nonoliguric, and anuric AKI was similar in both groups of patients.

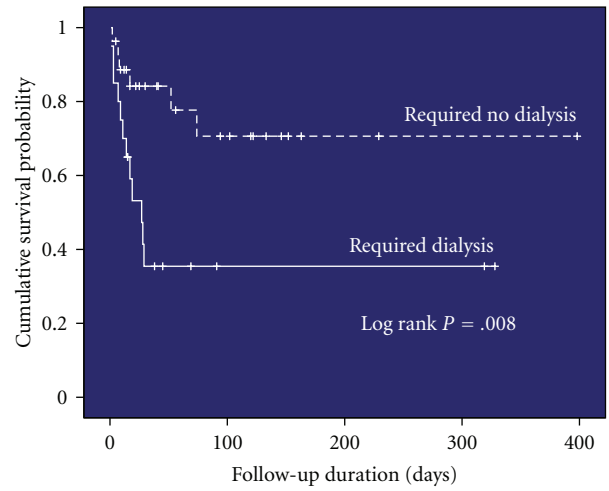

Figure 5: Kaplan-Meier survival curves for dialysis-requiring and non-dialysis requiring cardiorenal syndrome patients. Dialysis-requiring-cardiorenal syndrome had significantly lower survival rate compared to those who required no dialysis (35.5% versus 70.6%).

(Figure 3). Figure 4 shows that mortality in nonanaemic CRS patients was significantly higher compared to anaemic CRS (HR: 4.637, 95% CI: 1.496–14.370). The outcome was significantly better among CRS patients who required no dialysis than those who required dialysis (HR: .284, 95% CI:.106–.765; Figure 5). A stratification to CRS type showed that dialysis-requiring Type 3 CRS had significantly higher cumulative mortality rate than dialysis-requiring Type 5 CRS (100% versus 51.1%; Log rank $P = .049$). This was similarly so for those not requiring dialysis (Type 3 CRS: 70.0% versus Type 5 CRS: 19.1% mortality; Log rank $P = .039$). Further stratification for aetiology showed poorer survival with regards to Type 3 CRS compared to Type 5 as all Type 3 patients who required dialysis died ($n = 5$); all had AGN that was associated with poorer outcome compared to either MAH or septicaemia (Wilcoxon, $P = .001$). Eighteen CRS patients died at the end of 398 follow-up days, while 28 survived, and one took voluntary discharge. The cumulative CRS-specific mortality was 45.7%. Thirty

patients died overall (both CRS and controls) thus bringing the cumulative all-cause-mortality to 34.2%.

4. Discussion

This study revealed CRS as a highly prevalent clinical event in acute perturbation of kidney function with hypertension as a common cardiovascular comorbidity. Given the spectrum of CRS aetiology in this study, hypertension was probably the result of intravascular congestion brought about by oliguria seen in 76.6% of the patients on one hand, and activation of the renin-angiotensin-aldosterone-system following renal hypoperfusion secondary to acute proliferative changes of AGN on the other hand. Interestingly, hypertension was found not to be a significant risk factor for mortality in this study (HR: 0.476, 95% CI: 0.183–1.240).

The acute nature of the CRS and the accompanying hypertension, as well as, prompt response to antihypertensive treatment, and vascular decongestion following diuretic phase onset could be responsible for this. Left ventricular hypertrophy and congestive HF are common in childhood AGN and CKD with high mortality rate [7, 14–16]. In this study, HF was highly prevalent and mortality rate from CRS was equally high but was not significantly different from controls; this is not withstanding the fact that the HF was of the severest class (Class IV). Anaemia is a highly prevalent comorbidity in both AKI [5, 6, 17] and CKD [18]; it has been associated with increased severity of congestive HF, increased hospitalization, worse cardiac function and functional class, the need for higher doses of diuretics, progressive worsening of renal function, and reduced quality of life [19]. Anaemia occurred in 91.5% of our patients with anaemia-specific mortality rate of 38.6%. Nonanaemic CRS patients were, however, 4.6 times more likely to die than their anaemic counterparts (95% CI: 1.496–14.370). This is because the majority of the anaemic cases were due to malaria that responded rapidly to treatment; the acute nature of the accompanying congestive anaemic HF that responded promptly to blood transfusion also contributed to better survival in the anaemic CRS compared to nonanaemic CRS that was largely due to poor outcome septicaemia and AGN. While AKI stage and type did not influence the outcome in this study, Type 5 CRS was found to protect against mortality. The positive impact of Type 5 CRS on survival was due to the fact that the majority of the patients in this class had MAH that was significantly associated with the highest survival rate compared to Type 3 CRS in which majority of the patients had AGN that was significantly associated with very low survival rate. The fact that CRS patients who required no dialysis survived better than those who required dialysis (HR: 0.28; 95% CI: 0.106–0.765) could mean more severe structural kidney pathology and dysfunction in those needing dialysis. This was particularly more evident when CRS was stratified for CRS types and outcome.

It is concluded that CRS was a very common clinical event with high mortality rate in critically ill children. Compared to controls, CRS mortality rate was not significantly higher; risk factors for mortality in CRS were CRS Type 3, AGN-associated CRS, dialysis-requiring CRS, and heart failure not associated with anaemia. Preventive measures aimed at some of the preventable aetiologies of CRS might be critical to reducing its prevalence.

Conflict of Interests

The authors declare that there is no conflict of interests.

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SAGE-Hindawi Access to Research
International Journal of Nephrology
Volume 2011, Article ID 425923, 8 pages
doi:10.4061/2011/425923

Research Article

Heart-Kidney Biomarkers in Patients Undergoing Cardiac Stress Testing

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Received 15 August 2010; Accepted 24 September 2010

Academic Editor: Mitchell H. Rosner

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We examined association of inducible myocardial perfusion defects with cardiorenal biomarkers, and of diminished left ventricular ejection fraction (LVEF) with kidney injury marker plasma neutrophil gelatinase-associated lipocalin (NGAL). Patients undergoing nuclear myocardial perfusion stress imaging were divided into 2 groups. Biomarkers were analyzed pre- and poststress testing. Compared to the patients in the low ischemia group ($n = 16$), the patients in the high ischemia group ($n = 18$) demonstrated a significantly greater rise in cardiac biomarkers plasma BNP, NT-proBNP and cTnI. Subjects were also categorized based on pre- or poststress test detectable plasma NGAL. With stress, the group with no detectable NGAL had a segmental defect score 4.2 compared to 8.2 ($P = .06$) in the detectable NGAL group, and 0.9 vs. 3.8 ($P = .03$) at rest. BNP rose with stress to a greater degree in patients with detectable NGAL (10.2 vs. 3.5 pg/mL, $P = .03$). LVEF at rest and with stress was significantly lower in the detectable NGAL group; 55.8 versus 65.0 ($P = .03$) and 55.1 vs. 63.8 ($P = .04$), respectively. Myocardial perfusion defects associate with biomarkers of cardiac stress, and detectable plasma NGAL with significantly lower LVEF, suggesting a specific heart-kidney link.

1. Introduction

Bidirectional signaling between the heart and the kidneys is being increasingly recognized as an important determinant of progression of disease states in both organs. This interorgan relationship, called the cardiorenal syndromes, has been defined with a novel classification [1] and described in detail at a recent consensus conference [2]. The accurate characterization of the types of signaling and their consequences is paramount to the understanding of cardiorenal and renocardiac syndromes [1].

Both in coronary artery disease (CAD) and congestive heart failure (CHF) the levels of plasma B-type natriuretic peptides (BNPs) have been shown to be elevated compared to healthy controls [3, 4]. Furthermore, BNPs have established their role in diagnosing acute heart failure [5, 6] and have been shown to be strong prognostic markers for mortality in CAD [7, 8] and CHF patients [9], with and without renal insufficiency [10–13].

Neutrophil gelatinase-associated lipocalin (NGAL) is a novel biomarker reflecting damage to renal tubular cells, with elevated levels in urine and plasma from two hours onwards after acute insult to the kidneys [14]. Moreover, the rise of NGAL is detectable substantially faster than the possible rise in plasma creatinine thus allowing diagnosis of acute kidney injury earlier, and with better sensitivity [15]. NGAL

has been shown to be elevated also in patients with CHF, suggesting an association between cardiac and renal damage [16, 17].

During cardiac stress testing, a number of studies have indicated that BNPs may be higher at baseline or increase to a greater extent in those whose tests indicated the presence of ischemia [18, 19]. No published data exist on whether inducible myocardial ischemia during cardiac stress testing can cause injurious signaling to the kidneys measured by increase in plasma NGAL.

We designed this study in patients undergoing nuclear myocardial perfusion stress imaging to examine the relationship between baseline and poststress changes in the number of myocardial perfusion defects (as a surrogate for cardiac ischemia), with levels of several cardiac biomarkers (BNP, N-terminal-proBNP and cardiac troponin I), markers of oxidative stress (advanced oxidation protein products), pre- and poststress cardiac chamber size and left ventricular ejection fraction (LVEF). We also examined for an association between cardiac ischemia and diminished LVEF, and kidney injury through measurement of the biomarker plasma NGAL.

We hypothesized that subjects demonstrating higher levels of perfusion defects would have increased poststress levels of cardiac biomarkers, altered cardiac chamber dimensions, lower LVEF and increased levels of plasma NGAL.

2. Patients and Methods

2.1. Patients and Study Protocol. The study was performed and the blood samples collected and analyzed in San Bortolo Hospital, Vicenza, Italy, between December 2007 and February 2008. Consecutive adult patients undergoing elective nuclear stress perfusion imaging fulfilling inclusion criteria were invited to participate. Any outpatient planned to go to perfusion test was eligible for participation, regardless of the indication for the test, with the exclusion of patients with prior heart or kidney transplant. A convenience sample of 34 patients consented to the study. Nuclear stress test was performed according to hospital's normal procedure, and informed consent was obtained from all patients who participated in the study. The study was approved by the Institutional Review Board.

Subjects underwent perfusion stress imaging performed on a Tuesday of the week of enrollment, and blood samples were drawn approximately 10 minutes before, and two hours after the stress test, prior to discharge from the Nuclear Medicine department. A subsequent imaging study at rest was performed on the Friday of the same week to provide baseline perfusion images, during which no additional blood was drawn. The stress test was performed using bicycle ergometer exercise (16 patients), or pharmacologically using dipyridamole (0.56 mg/kg intravenously in 4 minutes) followed by aminophylline 120 mg intravenously (240 mg if any symptoms of side effects of dipyridamole were present). The scintigraphy was performed according to EANM/ESC guidelines [20], using 99mTc-sestamibi as tracer and a two-day gated SPECT protocol. The perfusion scan results were interpreted by two experts as per standardized guidelines for reporting [21, 22], blinded to the experimental laboratory results.

The recorded variables included date of birth, sex, age, type of perfusion study and stress (i.e., exercise or pharmacologic), cardiac risk factors, and previous known myocardial infarction or coronary artery disease. Medications that may influence BNP were recorded (nitrates, calcium antagonists, and beta blockers). The adequacy of the stress test was assessed by peak heart rate and blood pressure. Segmental myocardial perfusion defects at rest and with stress were reported per standardized guidelines as well as cardiac left ventricular end diastolic volume, end systolic volume, and ejection fraction. Changes with stress were calculated for all relevant variables. Ejection fraction and related measurements were compared between the rest and stress study results to calculate the changes (deltas).

Plasma creatinine was measured at baseline to determine the presence or absence of kidney dysfunction. Blood samples were taken pre- and postperfusion testing and analyzed for blood hemoglobin, plasma albumin, creatinine, BNP, N-terminal-proBNP (NT-proBNP), cardiac troponin I (cTnI), NGAL, and advanced oxidation protein products (AOPP). Changes in hematocrit and albumin with stress indicated acute shifts in plasma volume as previously described in [23], hence poststress values for all relevant analytes were adjusted based on delta albumin.

2.2. Specific Laboratory Techniques. Plasma BNP and cTnI were analyzed using immunochemiluminescence immunoassay and ADVIA Centaur analyzer (Siemens Healthcare Diagnostics Inc., Deerfield, IL) and plasma NT-proBNP with electrochemiluminescence immunoassay and Elecsys 2010 analyzer (Roche Diagnostics AG, Rotkreuz, Switzerland). Plasma samples for NGAL were quickly stored in minus 80 degrees Celcius for later analysis. Plasma NGAL was measured with fluorescence-based immunoassay with the Triage point-of-care analyzer (Biosite Inc., San Diego, CA, USA), which is a rapid quantitative measurement of NGAL concentration in EDTA-anticoagulated whole blood or plasma (single-use plastic cartridges with immobilized NGAL antigen and containing NGAL-specific monoclonal antibodies conjugated to fluorescent nanoparticles). The detection limits for this NGAL analysis are 60–1300 ng/mL. AOPP were measured by spectrophotometry and concentrations were expressed as micromoles per liter of chloramine-T equivalents.

2.3. Statistical Methods. According to the median value for inducible perfusion defects, which defined two groups (low and high inducible ischemia), study parameters were compared between-groups using unpaired t-tests (Mann-Whitney U test for skewed variables) or Fisher's exact test for categorical variables. Within-group changes (pre- and poststress) were analyzed using paired t-tests (or Wilcoxon signed rank test). Many NGAL levels were below the level of detection, and accurate pre- and postdeltas could not be calculated, hence comparisons could not be made between the low and high inducible ischemia groups. Therefore, subjects were categorized based on any level of detectable

NGAL (≥60 ng/mL) either before or after stress imaging, and the study parameters (cardiac biomarkers, cardiac chamber sizes, segmental defect scores) were compared between those with ($n = 23$) and without ($n = 11$) evidence of detectable NGAL. Analyses were conducted using SPSS version 16.0 (SPSS Inc., Chicago, Illinois) and $P < .05$ was required for statistical significance. Unless otherwise specified, values are expressed as mean ± standard deviation.

3. Results

There were 16 and 18 subjects in the low and high inducible ischemia groups, respectively. The groups were similar for all baseline demographic, laboratory, and cardiovascular parameters, with the exception of prior history of coronary angioplasty, which was more prevalent in the high inducible ischemia group (Table 1). Plasma albumin and hemoglobin fell significantly two hours after stress testing ($P < .001$).

Changes in cardiac biomarkers, oxidative stress, and various cardiovascular imaging parameters compared between the high and low inducible ischemia groups are presented in Table 2. Patients in the high ischemia group demonstrated a consistent rise in cardiac biomarkers with stress. For example, the rise in BNP following stress was 8.0 pg/mL greater in the high ischemia than the low ischemia group (delta-BNP 11.8 pg/mL versus 3.8 pg/mL, 95% confidence interval 1.2–14.7; $P = .02$). A similar pattern was seen with NT-proBNP, which increased more in the high ischemia group compared to the low ischemia group (delta NT-proBNP 59.1 pg/mL versus 5.0 pg/mL, 95% confidence interval 4.9–103.3; $P = .03$). Likewise, the poststress cTnI rose to 0.016 μg/L in the high ischemia group and to 0.008 μg/L in the low ischemia group ($P = .05$). A trend was seen with respect to change in end-diastolic volume, which increased in the high ischemia group by 6.5 mL versus 0.1 mL in the low ischemia group ($P = .07$). There also was a weaker trend towards higher oxidative stress in the high ischemia group, with AOPP of 121.2 μmol/L in the high ischemia versus 77.0 μmol/L in the low ischemia group ($P = .15$).

Plasma NGAL levels were below the limits of detection in many instances, both before and after stress, hence pre- and postcomparisons could not be made between groups based on their level of inducible ischemia. However, when the subjects were divided into two groups based on the presence or absence of detectable NGAL levels (≥60 ng/mL), before or after stress imaging, some clear differences emerged as presented in Table 3. Both plasma BNP and NT-proBNP rose with stress to a greater degree in the detectable NGAL group, and this was statistically significant in the former case, with BNP rising by 6.7 pg/mL more in the NGAL group (95% confidence interval 1.0–14.4 pg/mL; $P = .03$). Levels of cTnI at baseline, prior to stress imaging, were higher in the detectable NGAL group, at 0.010 versus 0.006 μg/L ($P = .05$). The subjects with detectable NGAL also had a significantly higher segmental defect score at rest, and higher end-diastolic and end-systolic volumes at rest and with stress. Ejection fraction was significantly lower both at rest and with stress in patients with detectable NGAL (all $P < .05$, Table 2).

4. Discussion

We designed this study to examine for evidence of cardiorenal signaling in patients with varying degrees of inducible cardiac ischemia and diminished systolic function. We clearly identified that those subjects with higher degrees of inducible ischemia had a consistent increase in a biomarker of cardiac injury (cTnI) and biomarkers of cardiac distress (BNP and NT-proBNP). Furthermore, the patients with lower LVEF had detectable plasma NGAL, that is, an increase in a biomarker of kidney injury.

Biomarkers are biological substances of human physiology, reflecting change in function or appearance of injury in certain organ or system of organs. The ideal biomarker is easily measured, specific for the organ under inspection, appears early after injury, shows the amount of injury, and correlates with prognosis [24]. In the discipline of cardiology, the cardiac troponins have been shown to possess these properties. In nephrology, early biomarkers indicating kidney injury have long been longed for and have only recently become available for clinical use [25].

In addition to cardiac troponins, B-type natriuretic peptides have gained success as diagnostic and prognostic biomarkers, especially among CHF patients [26]. BNPs are secreted by the cardiac ventricles in response to excessive stretching of myocytes, in heart failure and volume overload, and ischemic injury to myocardium [27]. Importantly, in earlier studies elevated levels of BNPs have been shown to be independent predictors of cardiovascular morbidity and mortality, both in patients with normal and impaired renal function, thus emphasizing the value of BNPs in assessment of cardiorenal syndrome [1, 10]. In our study, the levels of both BNP and NT-proBNP were significantly higher in patients with more myocardial ischemic perfusion defects.

Neutrophil gelatinase-associated lipocalin (NGAL) has emerged as a novel biomarker of acute kidney injury (AKI) [15]. NGAL is a 25-kDa protein widely spread within human body (kidney, prostate, uterus, salivary gland, epithelia of respiratory, and alimentary tracts) and shown to possess various biological properties, for instance kidney-protecting and nephron-inducing activity and bacteriostatic capability [15]. Although normally expressed at very low levels, it has been shown to rise in AKI, in human kidney cortical tubules, urine, and plasma and has therefore become a novel biomarker of acute renal damage [28]. Furthermore, the rise of NGAL takes place faster than a possible increase in plasma creatinine allowing detection of AKI earlier than with creatinine-based criteria and with good sensitivity and excellent specificity [29]. NGAL has been shown to increase in various settings of cardiac procedures and in critically ill patients with sepsis, renal ischemia and contrast media-induced nephropathy [30]. The acute rise of NGAL in most reported studies has taken place during two to six hours after an event compromising renal function and causing renal damage [15].

Interestingly, NGAL has been shown to be elevated in patients with CHF, possibly demonstrating a link between cardiac dysfunction and renal injury [16, 17]. This is in line with the results of our study, in which the patients with

Table 1: Baseline demographic, laboratory, and cardiovascular parameters according to the amount of myocardial ischemia (number of inducible myocardial perfusion defects).

Baseline variable	High inducible ischemia ($n = 18$)	Low inducible ischemia ($n = 16$)	P value
Demographic			
Age (years)	70.4 ± 6.7	67.6 ± 7.5	.25
Sex (% male)	77.8	75.0	.85
Weight (kg)	80.5 ± 12.1	78.1 ± 8.0	.66
Past history (%)			
Hypertension	38.9	43.8	.77
Current smoking	0.0	18.8	.09
Dyslipidemia	66.7	56.3	.53
Diabetes mellitus	22.2	12.5	.46
Myocardial infarction	77.8	43.8	.08
Coronary angioplasty	88.9	50.0	**.02**
Coronary bypass graft	5.6	12.5	.48
Medications (%)			
Nitrates	16.7	18.8	.87
Calcium antagonists	33.3	12.5	.23
Beta blockers	27.8	31.3	.82
Laboratory			
Creatinine (μmol/L)	86.0 ± 27.2	75.6 ± 16.6	.19
Albumin (g/L)	45.3 ± 2.3	44.6 ± 2.4	.39
Hemoglobin (g/L)	140.7 ± 13.4	147.0 ± 13.5	.18
Glucose (mmol/L)	6.4 ± 1.0	5.9 ± 0.7	.15
BNP (pg/mL)	80.3 ± 60.6	52.9 ± 43.9	.15
cTnI (μg/L)	0.010 ± 0.009	0.008 ± 0.007	.45
NT-proBNP (pg/mL)	580.4 ± 712.9	289.9 ± 215.8	.13
AOPP (μmol/L)	121.2 ± 116.3	77.0 ± 28.5	.15
NGAL (ng/mL)[†]	67.5 (60.0–115.5)	67.0 (60.0–90.8)	.60
Cardiovascular parameters (at rest)			
End diastolic volume (mL)	101.3 ± 29.7	105.2 ± 27.9	.70
End systolic volume (mL)	46.5 ± 24.5	43.8 ± 19.1	.73
Ejection fraction (%)	56.7 ± 10.6	61.1 ± 12.1	.27

[†]Data presented as median (IQR).

BNP: B-type natriuretic peptide, cTnI: cardiac troponin I, NT-proBNP: N-terminal-pro-B-type natriuretic peptide, AOPP: advanced oxidation protein products, NGAL: neutrophil gelatinase-associated lipocalin.

lower LVEF both at rest and with stress had detectable plasma NGAL, thus suggesting similar association between chronic heart failure and continuous kidney damage. The level of NGAL has also been shown to correlate with severity and progression of chronic kidney disease [31], which further increases the prognostic importance of elevated NGAL. Whether or not the damaged heart can be said to be "signaling" the kidneys through mechanisms independent of hemodynamic factors is the subject of ongoing study. Future work may reveal if NGAL is a useful biomarker in the evaluation of patients presenting with cardiorenal syndromes.

While our experimental model demonstrated a measurable cardiorenal signal in the context of cardiac ischemia and diminished LVEF with higher levels of BNPs, a secondary aim was to identify evidence that the relationship between cardiac ischemia and the kidneys was injurious to the kidneys (type 1 or 2 cardiorenal syndrome). To this end, we measured plasma NGAL as a marker of kidney injury. Subjects with detectable levels of NGAL in the plasma demonstrated greater incremental changes in natriuretic peptides in response to stress, had more segmental perfusion defects, higher end-diastolic and end-systolic volumes and lower LVEF with stress, and had higher baseline levels of the cardiac injury biomarker cTnI. Serum creatinine levels did not differ significantly between the groups before or after stress. While these observations are associations and do not speak specifically to mechanism, one plausible conclusion is that myocardial ischemia was contributing to a mild, subclinical level of kidney injury. In addition, diminished LVEF could be an injurious factor to renal tubular cells causing continuous, prolonged kidney injury. An alternative

Table 2: Changes in cardiac biomarkers, oxidative stress, and various cardiovascular imaging parameters compared between the high and low ischemia (number of inducible myocardial perfusion defects) groups.

Study variable	High inducible ischemia ($n = 18$)	Low inducible ischemia ($n = 16$)	P value
Laboratory			
Creatinine (μmol/L)—at rest	86.0 ± 27.2	75.6 ± 16.6	.19
Creatinine (μmol/L)—with stress	88.2 ± 28.6	78.5 ± 18.0	.25
ΔCreatinine (μmol/L)	2.2 ± 7.3	2.9 ± 8.0	.80
BNP (pg/mL)—at rest	80.3 ± 60.6	52.9 ± 43.9	.15
BNP (pg/mL)—with stress	92.1 ± 68.8	56.8 ± 40.3	.08
ΔBNP (pg/mL)	11.8 ± 11.8	3.8 ± 7.2	.02
cTnI (μg/L)—at rest	0.010 ± 0.009	0.008 ± 0.007	.45
cTnI (μg/L)—with stress	0.016 ± 0.014	0.008 ± 0.007	.05
ΔcTnI (μg/L)	0.007 ± 0.013	0.002 ± 0.004	.16
NT-proBNP (pg/mL)—at rest	580.4 ± 712.9	289.9 ± 215.8	.13
NT-proBNP (pg/mL)—with stress	639.5 ± 754.1	294.9 ± 204.3	.08
ΔNT-proBNP (pg/mL)	59.1 ± 84.9	5.0 ± 48.8	.03
AOPP (μmol/L)—at rest	121.2 ± 116.3	77.0 ± 28.5	.15
AOPP (μmol/L)—with stress	95.0 ± 102.2	65.2 ± 18.6	.26
ΔAOPP (μmol/L)	−26.1 ± 49.4	−11.8 ± 26.2	.29
Cardiovascular parameters			
Segmental perfusion defects—at rest	3.8 ± 5.5	1.8 ± 3.5	.22
Segmental perfusion defects—with stress	10.7 ± 7.1	2.6 ± 4.0	**<.001**
ΔSegmental perfusion defects	6.6 ± 3.0	0.8 ± 0.8	**<.001**
End diastolic volume (mL)—at rest	101.3 ± 29.7	105.2 ± 27.9	.70
End diastolic volume (mL)—with stress	107.8 ± 36.7	102.2 ± 27.4	.63
ΔEnd diastolic volume (mL)	6.5 ± 10.9	0.1 ± 8.8	.07
End systolic volume (mL)—at rest	46.5 ± 24.5	43.8 ± 19.1	.73
End systolic volume (mL)—with stress	51.1 ± 30.4	42.3 ± 19.7	.34
ΔEnd systolic volume (mL)	4.6 ± 8.7	0.4 ± 8.6	.19
Ejection fraction (%)—at rest	56.7 ± 10.6	61.1 ± 12.1	.27
Ejection fraction (%)—with stress	55.6 ± 11.6	60.6 ± 11.0	.21
ΔEjection fraction (%)	−1.1 ± 3.9	−0.5 ± 6.1	.74

Δ: delta (change from pre-stress to poststress test).
BNP: B-type natriuretic peptide, cTnI: cardiac troponin I, NT-proBNP: N-terminal-pro-B-type natriuretic peptide, AOPP: advanced oxidation protein products, NGAL: neutrophil gelatinase-associated lipocalin.

explanation is that subjects with evidence of kidney injury were predisposed to cardiac ischemia and/or decreased systolic function (renocardiac syndrome).

There are a few limitations in our study that merit discussion. Firstly, plasma NGAL was below the limits of detection in many instances, and hence lacked sensitivity to detect subtle degrees of AKI following myocardial stress and ischemia. Plasma and urinary NGAL have been shown to be sensitive and specific indicators and predictive biomarkers of acute kidney injury, in for instance, adult intensive care unit patients with sepsis, children undergoing cardiopulmonary bypass, adults with cardiac surgery, and in patients with contrast-induced nephropathy [32]. NGAL has performed especially well in relatively uncomplicated patient populations with AKI, with excellent receiver-operating characteristics [14, 32]. However, plasma NGAL measurement may be influenced by several confounding factors, such as systemic infections and inflammatory and malignant processes [32], for which our study population was not examined. It is also possible that in our study not enough time had elapsed following stress for NGAL to rise, as most studies examining the kinetics of plasma NGAL seem to indicate that a significant increase takes places more than two hours following the index event [15]. Future studies should consider using a panel of plasma and urinary biomarkers for AKI and follow subjects for a longer period of time. Secondly, the possible influence of dipyridamole on biomarkers such as NGAL and markers of oxidative stress should be taken into consideration. As a substance with antioxidative and antiapoptotic properties [33, 34], some of our results may have suffered interference by this agent. However, the low and high ischemia groups were well balanced in terms of their

Table 3: Results between groups based on existence of detectable plasma neutrophil gelatinase-associated lipocalin (NGAL).

Study variable	Detectable NGAL ($n = 23$)	No detectable NGAL ($n = 11$)	P value
Laboratory			
Creatinine (μmol/L)—at rest	84.0 ± 25.2	75.1 ± 17.5	.24
Creatinine (μmol/L)—with stress	87.4 ± 26.0	75.9 ± 19.4	.16
ΔCreatinine (μmol/L)	3.3 ± 8.1	0.8 ± 6.1	.32
BNP (pg/mL)—at rest	73.8 ± 57.6	53.9 ± 46.7	.29
BNP (pg/mL)—with stress	84.0 ± 64.3	57.5 ± 44.0	.17
ΔBNP (pg/mL)	10.2 ± 11.9	3.5 ± 4.8	**.03**
cTnI (μg/L)—at rest	0.010 ± 0.009	0.006 ± 0.003	**.05**
cTnI (μg/L)—with stress	0.013 ± 0.010	0.012 ± 0.016	.86
ΔcTnI (μg/L)	0.003 ± 0.007	0.007 ± 0.015	.39
NT-proBNP (pg/mL)—at rest	511.0 ± 642.0	303.1 ± 258.0	.19
NT-proBNP (pg/mL)—with stress	556.3 ± 685.6	312.1 ± 226.5	.13
ΔNT-proBNP (pg/mL)	45.4 ± 83.2	9.0 ± 46.0	.11
AOPP (μmol/L)—at rest	105.7 ± 102.0	89.3 ± 52.8	.54
AOPP (μmol/L)—with stress	85.8 ± 91.1	71.1 ± 24.7	.48
ΔAOPP (μmol/L)	−19.9 ± 41.9	−18.2 ± 38.6	.91
Cardiovascular parameters			
Segmental perfusion defects—at rest	3.8 ± 5.3	0.9 ± 2.1	**.03**
Segmental perfusion defects—with stress	8.2 ± 8.0	4.2 ± 3.7	.06
ΔSegmental perfusion defects	4.1 ± 3.8	3.3 ± 3.3	.51
End diastolic volume (mL)—at rest	108.4 ± 25.9	90.8 ± 31.7	.14
End diastolic volume (mL)—with stress	112.8 ± 32.5	90.2 ± 27.9	**.05**
ΔEnd diastolic volume (mL)	4.8 ± 11.2	0.8 ± 8.0	.25
End systolic volume (mL)—at rest	49.9 ± 21.5	34.7 ± 20.1	.07
End systolic volume (mL)—with stress	53.5 ± 27.5	34.4 ± 18.0	**.02**
ΔEnd systolic volume (mL)	3.6 ± 9.4	1.1 ± 7.4	.44
Ejection fraction (%)—at rest	55.8 ± 10.6	65.0 ± 10.7	**.03**
Ejection fraction (%)—with stress	55.1 ± 11.0	63.8 ± 10.3	**.04**
ΔEjection fraction (%)	−0.7 ± 5.1	−1.2 ± 4.9	.78

Δ: delta (change from prestress to poststress test).
BNP: B-type natriuretic peptide, cTnI: cardiac troponin I, NT-proBNP: N-terminal-pro-B-type natriuretic peptide, AOPP: advanced oxidation protein products, NGAL: neutrophil gelatinase-associated lipocalin.

exposure to dipyridamole, hence exposure should not have led to spurious findings in one group over another. Likewise, the administration of aminophylline (a nonselective adenosine receptor antagonist) as part of the stress imaging protocol may have indirectly interfered with our results. Adenosine can affect renal function through its effects on renal blood flow and tubuloglomerular feedback [35, 36], however the likelihood of exposure to aminophylline was similar in both high and low ischemia groups. Thirdly, the observations made in this study do not clearly provide a mechanism by which the ischemic heart is signaling the kidneys (or vice versa). While the endocrine effects of natriuretic peptides as signaling agents are not in dispute, one would not expect these to invoke kidney injury *per se*. Having identified that there does seem to be a relationship between the ischemic heart, and the heart with diminished systolic function, with a biomarker of kidney injury, further studies examining the role of cytokines, neurohormones, mediators of apoptosis, and other injurious pathways are planned. Additional limitations of our study are the rather low number of patients, and the number of measurements of plasma NGAL during the timecourse of the stress testing. Using multiple measurements, increasing the sample size and extending duration of posttest followup might have presented with a more distinct and positive rise in NGAL levels. Furthermore, the changes in the levels of cardiac biomarkers, while rather low in a clinical sense, were nonetheless statistically significant. We believe this represents a weak yet discernible signal as evidence for heart-kidney interactions.

To conclude, to our knowledge our study is novel in demonstrating the association between the amount of inducible myocardial ischemia with cardiorenal signaling and biomarker of kidney injury. Furthermore, we present the novel finding of the association between lower LVEF and detectable NGAL in patients undergoing cardiac stress

testing. Our results display intriguing, yet at present only suggestive insights into the signaling between the heart and the kidneys. Further studies to elucidate mechanisms at play in the complex bidirectional cardiorenal syndrome are ongoing.

Abbreviations

AKI:	Acute kidney injury
AOPP:	Advanced oxidation protein products
BNP:	Brain or B-type natriuretic peptide
CAD:	Coronary artery disease
CHF:	Congestive heart failure
cTnI:	Cardiac troponin I
LVEF:	Left ventricular ejection fraction
NGAL:	Neutrophil gelatinase-associated lipocalin
NT-proBNP:	N-terminal-pro-B-type natriuretic peptide.

Acknowledgment

The authors are grateful for the assistance of staff in St. Bortolo Hospital Nuclear Medicine Department in carrying out this study. Biosite Inc. (San Diego, CA, USA) provided the NGAL kits, as they were not commercially available at the time of the study.

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SAGE-Hindawi Access to Research
International Journal of Nephrology
Volume 2011, Article ID 809378, 10 pages
doi:10.4061/2011/809378

Research Article

Integrative Bioinformatics Analysis of Proteins Associated with the Cardiorenal Syndrome

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Received 19 August 2010; Accepted 17 September 2010

Academic Editor: Mitchell H. Rosner

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The cardiorenal syndrome refers to the coexistence of kidney and cardiovascular disease, where cardiovascular events are the most common cause of death in patients with chronic kidney disease. Both, cardiovascular as well as kidney diseases have been extensively analyzed on a molecular level, resulting in molecular features and associated processes indicating a cross-talk of the two disease etiologies on a pathophysiological level. In order to gain a comprehensive picture of molecular factors contributing to the bidirectional interplay between kidney and cardiovascular system, we mined the scientific literature for molecular features reported as associated with the cardiorenal syndrome, resulting in 280 unique genes/proteins. These features were then analyzed on the level of molecular processes and pathways utilizing various types of protein interaction networks. Next to well established molecular features associated with the renin-angiotensin system numerous proteins involved in signal transduction and cell communication were found, involving specific molecular functions covering receptor binding with natriuretic peptide receptor and ligands as well known example. An integrated analysis of identified features pinpointed a protein interaction network involving mediators of hemodynamic change and an accumulation of features associated with the endothelin and VEGF signaling pathway. Some of these features may function as novel therapeutic targets.

1. Introduction

The risk of developing cardiovascular disease (CVD) is dramatically increased in patients with chronic kidney diseases (CKDs). Mortality as a consequence of cardiovascular events is 10 to 30 times higher in patients on dialysis treatment than in the general population [1]. Due to this recognition of CVD as the leading cause of morbidity and mortality in patients with reduced kidney function, a growing body of literature has become available regarding this link of CKD and CVD, termed as cardiorenal syndrome (CRS).

CRS can be classified into five subtypes depending on the origin of damage (either the cardiovascular system or the kidney) and the course of disease (either acute or chronic) [2, 3]. Major mechanisms leading to CRS1 and CRS2 (acute and chronic cardiorenal syndrome) include hemodynamically mediated damage, hormonal factors, immune-mediated damage, low cardiac output, endothelial dysfunction, and chronic hypoperfusion. Hallmarks of kidney dysfunction leading to CRS3 and CRS4 (acute and chronic renocardiac syndrome) on the other hand are volume expansion, drop of the glomerular filtration rate, humoral signaling, anemia, uremic toxins, and inflammation. The fifth subtype of the cardiorenal syndrome (CRS5) describes the secondary cardiorenal syndrome which refers to systemic diseases such as diabetes that ultimately lead to simultaneous cardiovascular and kidney dysfunction.

The multitude of cardiac risk factors in patients with chronic kidney disease is complex and increases with age, the stage of kidney disease, and the level of proteinuria.

Another powerful risk factor is hypertension which goes along with sodium retention, and activation of the renin-angiotensin system. Atherosclerosis results from an impairment of endothelial function which, in turn, is associated with albuminuria. Changes in blood-lipid composition and oxidative stress as a consequence of inflammation due to renal dysfunction also contribute to endothelial dysfunction and subsequent CVD [4].

Management and therapy of the CRS is challenging since drugs in use for the treatment of cardiovascular diseases may go along with impairment of kidney function and vice versa. Examples include diuretics, ionotropes, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, or natriuretic peptides but treatment decision must be based on a combination of individual patient information and understanding of individual treatment options [5].

Biomarkers of relevance in the context of the CRS mainly hold proteins known either in the field of nephrology or cardiology, for the latter including, for example, the family of natriuretic peptides and troponins, whereas frequently reported renal-specific markers include neutrophil gelatinase-associated lipocalin (NGAL), kidney injury molecule 1 (KIM1), Cystatin C, interleukin 18 (IL18), and N-acetyl-β-D-glucosaminidase [6]. Levels of circulating fibroblast growth factor 23 (FGF-23) for example have been shown to be independently associated with left ventricular mass index and left ventricular hypertrophy in patients with CKD [7]. Chung and colleagues described the relationship between activation of matrix metalloproteinase 2 (MMP2) and elastic fiber degeneration, stiffening, medial calcification, and vasomotor dysfunction in macroarterial vasculature of dialyzed CKD patients [8]. Next to these proteins, a multitude of other molecular features is mentioned in the literature in the context of the cardiorenal syndrome. Perco et al. reported a list of 31 CVD biomarkers that were extracted from the literature and characterized with respect to biological function, gene expression in CKD, and known protein-protein interactions [9].

Literature mining approaches have the potential to reveal such biomarkers, thus providing a more global picture on genes, proteins, and metabolites associated with a specific disease. The biomedical literature can be seen as the condensed result of the combined effort of the scientific community, and as such represents the primary resource upon which further investigations may be based on. As such, it represents the primary resource upon which further investigations may be based on. PubMed, for instance, presently holds close to 20 million abstracts. Thus, computational literature mining tools assisting researchers in keeping pace with this ever-growing amount of fast changing information became indispensable [10, 11].

In the context of drug discovery, the most prevailing approach is based on concept cooccurrence [12, 13]. Here, a disease profile consisting of the concepts (e.g., drugs, genes, etc.) which are frequently mentioned together with the disease under analysis can be derived via text mining. Likewise, literature-based profiles for drugs or genes can be generated. Next to conveniently reaching an overview on biomarkers this information base may additionally be used to gain hints about yet undiscovered dependencies between diseases, drugs, and potential drug targets.

To further enhance text mining efforts, several "controlled vocabularies" ("ontologies") have been developed to allow a precise definition of the employed concepts [14]. The most popular ones are maintained by the U.S. Library of Medicine, namely, the Unified Medical Language System (UMLS) and the Medical Subject Headings (MeSH). Given that the majority of PubMed articles are indexed with MeSH, a fast and accurate extraction of biomedical concepts has become feasible [13, 15]. With the advent of literature mining approaches also in combination with high-throughput Omics experiments, a number of bioinformatics tools and ontologies have been developed for the analysis of resulting large sets of genes or proteins. Analyzing extended sets of biomarker candidates on the level of molecular pathways and processes, represented as protein interaction networks, adds another layer of information for the interpretation of molecular feature (biomarker) sets.

A recent review by Lusis and colleagues summarized studies dealing with network analyses in cardiovascular disease [16]. Networks based on prior knowledge, such as existing pathway sources, literature cocitations, or other correlation measures as coexpression and sequence similarity were outlined by Ashley et al. [17], who mapped genes being differentially regulated between patients suffering from de-novo atherosclerosis and in-stent restenosis on a cocitation network obtained by literature mining of Medline abstracts. Similar concepts can be followed by utilizing networks derived from physical protein interactions, or networks generated from measuring the response to experimental perturbations. Further approaches include system genetics and detailed analyses at the level of dynamic systems such as flux balance analyses which are often used to characterize enzymatic reactions in dynamic models of metabolism. Some of these approaches, especially highly abstracted network models on the level of phenotypes, managed to predict comorbidity patterns for myocardial infarction using a "human disease network" thus closing the gap to clinical applications [18].

Diez et al. presented another application of the network paradigm to reveal the mechanisms of cardiovascular disease, identifying a set of differentially expressed genes separating asymptomatic from symptomatic carotid stenosis patients [19]. Based on these transcriptomics data, a correlation network was generated. Furthermore, an association network of the differentially regulated genes was derived by mining the literature for gene associations thus resulting in an interaction network combining Omics data and associated features extracted from the literature. Subnetworks were identified, characterized by enriched lipid-, immune-, and atherogenesis-related pathways and gene ontology terms. On this level of representation, the interplay of APOC1 (a gene that is linked to coronary heart disease) became evident. Weiss et al. investigated networks on cardiovascular metabolism pointing out aspects of network structure, namely, differences between designed networks in engineering and networks having undergone an evolutionary process [20]. Based on the level of abstraction, three types of

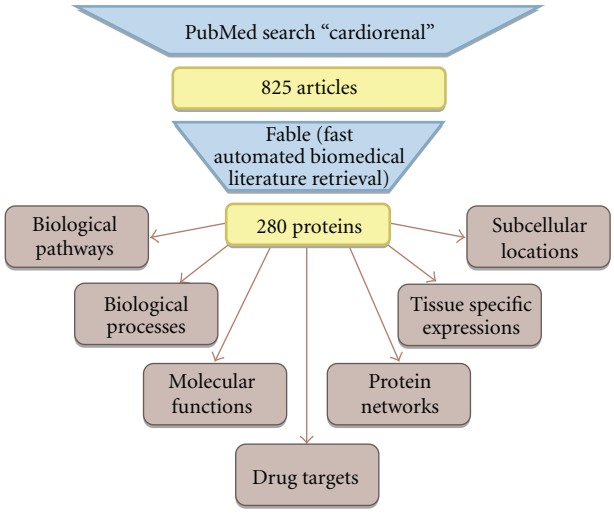

Figure 1: Overview scheme on the analysis workflow: Literature mining was applied for identifying unique proteins associated with CRS. Bioinformatics included feature characterization as well as network analysis.

network on cardiovascular metabolism were proposed: first, on the very abstract level of nodes and edges, metabolite networks described by using topological characteristics [21, 22], second physical, spatially compartmentalized networks including the description of energy fluxes in the network [23, 24], and on a third level dynamic networks [25–27].

The present knowledge regarding mechanisms leading to the formation of the CRS suggests a critical role for hemodynamic changes, originating either from the kidney or the cardiovascular system. In the following analysis, we used a literature mining approach to extract genes and proteins reported in the context of the cardiorenal syndrome, and analyzed these features on the level of protein interaction networks. Specific focus was laid on secreted proteins being specifically expressed in either renal or vascular tissue with the aim to identify molecular mediators potentially contributing to the cross-talk between the kidney and the cardiovascular system for allowing identification of novel therapeutic targets addressing both systems.

2. Materials and Methods

The general analysis strategy applied in this work is outlined in Figure 1. Major components include feature extraction via literature mining, followed by a range of bioinformatics analysis procedures for deciphering characteristics of individual features as well as joint interpretation on the level of protein interaction networks.

2.1. Literature Mining. The strength but also the challenge of biomedical text mining relies on the fact that the scientific literature embraces a variety of concepts (genes, drugs, diseases, etc.) which in turn are interrelated in a variety of ways. Thus, carefully designed text mining methods are needed to extract "meaningful" information and reduce the amount of noise present in the final results.

In general, text mining consists of two steps: Information Retrieval (IR) and Information Extraction (IE) [10]. The first consists in identifying documents which are of relevance for a certain research objective (e.g., a PubMed query for "cardiorenal"), whereas the later is used to extract facts from these documents. Named Entity Recognition (NER) can be seen as the most prevalent type of IE used in real world applications, aiming at the identification of biological entities like genes, cell types, or drugs.

Even though the concept of NER might appear almost trivial at a first glance, it actually represents a challenging computational problem as the existence of over fifty available tools demonstrates [28]. The key obstacle that needs to be addressed when extracting genes or proteins from free text relies in the term ambiguity present at multiple levels. Some genes are spelled like normal English words (e.g., "WAS" with the NCBI GeneID: 7454) and even a gene with the official Gene Symbol "T" exists (NCBI GeneID: 6862). The same gene may additionally be referred to in various ways due to different naming conventions.

Ultimately, this ambiguities lead to two different types of errors which all methods are confronted with: erratically assuming that a certain gene was mentioned in a paper (false positive) or erratically assuming that it was not mentioned, even though it actually was given (false negative) [29]. Based on the trade-off between these two types of errors, the precision of a method (i.e., how much of the predicted genes were actually mentioned in the document) and its recall (i.e., how much of all actually mentioned genes were also identified as such) are determined.

We chose a method favoring precision over recall for mining genes/proteins in Medline/PubMed abstracts. The Fast Automated Biomedical Literature Extraction (FABLE) tool available at http://fable.chop.edu/ was used in order to fulfill this task. The algorithm basically consists of two steps: first, a statistical classifier was used to train a probabilistic model, which served as basis for gene tagging, that is, to identify possible occurrences of a gene, taking the textual context into account. Given that such an occurrence exhibits a sufficient likelihood of actually representing a gene, this occurrence was normalized in a second step to the official Gene Symbol. This normalization step was based on gene synonym lists, which were compared to the predicted occurrence using both exact and relaxed pattern matching procedures. It has been shown that this approach is competitive to alternative methods such as standard information extraction techniques and direct pattern matching both in terms of precision and recall [30, 31]. We applied this procedures for all papers retrieved from PubMed associated with "cardiorenal" (PubMed status as of March 2010).

2.2. Functional Annotation of Identified Genes/Proteins. The list of genes and proteins identified on the basis of the literature mining approach was in a first step annotated using the Stanford Source tool [32]. The set of genes was

assigned to biological processes, pathways, and molecular functions using the PANTHER (Protein Analysis through Evolutionary Relationships) Classification System [33, 34]. Significantly enriched categories were identified using the whole human genome as a reference dataset. Biological processes, pathways, and molecular functions showing *P*-values below .0001 were considered as statistically significant in terms of feature enrichment.

The subcellular location of proteins was determined using experimental data provided by SwissProt [35]. For proteins not covered in SwissProt, *in-silico* predictions using WoLF PSORT were done [36]. WoLF PSORT computes probabilities based on the protein sequence of a given protein for ten subcellular locations. Subcellular location tags from SwissProt were mapped to the ten locations defined by WoLF PSORT. Only assignments that were either reported in SwissProt or showed a probability value of 1 according to WoLF PSORT were considered for subcellular location enrichment analysis. Based on a reference dataset of 45,008 proteins assigned to one of the WoLF PSORT categories, the significance of enrichment was calculated using the Fisher's exact test. *P*-values below .01 were considered as statistically significant.

Information on tissue-specific expression patterns was extracted from NCBI UniGene EST profiles. EST counts of in total 45 tissues were extracted for each gene. Tissue-specific expression patterns for each single tissue for each single gene were calculated based on the normalized transcripts per million counts as provided by UniGene [37].

2.3. Network Analysis Framework. For network analysis, we used an extended version of the protein dependency network "omicsNET" as described in Bernthaler et al. [38]. The network is comprised of information from protein-protein interactions, tissue-specific reference coexpression, shared pathway information, gene ontology distance, and subcellular colocalization, and was extended by networks generated from shared transcription factor binding sites and shared miRNA target sites. In omicsNET, these sources were consolidated into a single human protein reference interaction network, where edges represent pairwise dependencies between proteins.

Protein-protein dependencies were calculated between proteins in the list resulting from the literature mining approach. Furthermore, highly connected subgraphs were identified and functionally annotated. We only considered dependencies with high confidence in the network construction process and focused on genes reported at least twice in the scientific literature in the context of the cardiorenal syndrome in order to reduce the number of false positive assignments.

2.4. Identification of Drug Targets. Drug targets were identified in our set of 280 literature-derived proteins using information from DrugBank [39, 40]. DrugBank combines information on drugs and their molecular targets and currently contains around 4800 drug entities with more than 1350 FDA-approved small molecule drugs and more than 2500 protein drug targets.

3. Results and Discussion

3.1. Literature Mining. 825 papers associated with the term "cardiorenal" were identified in PubMed. In this set of 825 papers, 280 genes could be extracted utilizing FABLE, with 132 genes being reported at least twice. The top ranked gene, mentioned in 156 articles, was the aspartyl protease renin (REN), followed by the natriuretic peptide precurser A (NPPA), and angiotensinogen (AGT), with 122 and 64 reports, respectively.

The list of 54 genes mentioned in at least 5 articles along with the term cardiorenal is provided in Table 1 (see supplementary Table 1 for the total list of 280 genes in Supplementary Material available online at doi:10.4061/2011/809378). Next to the number of articles, the relative expression levels in the four tissues blood, heart, vascular, and kidney are provided based on data from the UniGene expressed sequence tag counts.

The top ranked feature in the list of 280 literature derived genes is renin (REN) which is secreted by cells of the juxtaglomerular apparatus of the kidney and plays a key role in the blood pressure and water balance-regulating renin-angiotensin system (RAS). The connection between CRS and an increased activity of this hormone system was first reported in 1971 [41] and its consequences like renal hypoxia, vasoconstriction, intraglomerular hypertension, glomerulosclerosis, tubulointerstitial fibrosis, and proteinuria continue to be demonstrated in clinical practice. Conservative therapy for blocking the RAS activity is the administration of angiotensin-converting enzyme inhibitors and angiotensin receptor blockers, but recent studies demonstrate the benefit of a combination with direct renin inhibitors [42].

Further genes frequently reported in association with CRS are the components of the natriuretic peptide system (NPS) NPPA and NPPB, as well as their receptors NPR1, NPR2, and NPR3. Functions of the NPS include the counter-regulation of RAS, and it is suggested that its activation provides organ protection in cardiorenal disease, especially in diabetic patients [43].

3.2. Functional Annotation. According to the PANTHER Classification System, the biological processes of "signal transduction" and "cell communication" were identified as most significantly enriched, with 135 and 136 genes assigned to these categories, respectively. In total, 28 processes showed a *P*-value > .0001 in terms of enrichment, including "blood circulation", "regulation of vasoconstriction", and "angiogenesis". The most significantly enriched molecular functions are "receptor binding" and "protein binding" (Table 2).

The two enriched categories "receptor binding" and "receptor activity" indicate that numerous receptors and ligands are involved in the cardiorenal syndrome. These receptors form the first line of molecules in a number of signaling cascades, which as such is another category

Table 1: List of identified genes/proteins, number of articles identified for cardiorenal, and relative expression levels based on UniGene EST counts for blood, heart, vascular, and kidney, and tissue showing maximum expression of a specific feature.

Symbol	Articles	Expression in blood (%)	Expression in heart (%)	Expression in vascular (%)	Expression in kidney (%)	Max. expression (%)	
REN	156	0	0	0	**19,27**	39,58	intestine
NPPA	122	**88,04**	0	0	0	88,04	heart
AGT	64	1,79	**18,54**	0	5,71	29,74	liver
ADM	55	0,95	1,38	1,09	3,11	15,3	adipose tissue
ACE	39	0,86	2,37	4,09	4,53	15,63	parathyroid
EDN1	39	0	4,12	**15,82**	2,77	32,68	umbilical cord
NPPB	31	**85,93**	0	0	1,2	85,93	heart
RAPGEF5	28	0	0	0	0,76	76,62	parathyroid
NOS3	27	3,92	2,69	2,33	2,2	20,32	spleen
EPO	22	0	0	0	0	58,82	prostate
CNP	21	0,85	1,74	3,58	5,4	18,03	brain
TGFB1	20	8,67	0,99	0	1,79	17,67	salivary gland
MME	19	0,26	3,59	0	**11,63**	12,06	lymph node
PTGS2	19	**16,39**	0	**29,1**	0,59	29,1	vascular
INS	18	0	0	0	0	100	pancreas
NPR1	17	0	1,32	2,29	2,83	23,69	mammary gland
NOS2	13	4,23	0	0	0	25,4	pharynx
DDR1	13	0	0,94	0	0,46	20,12	trachea
KNG1	10	0	0	0	**33,18**	57,18	liver
PLEK	10	**11,02**	0,34	1,77	0,87	16,81	lymph
NCF1	10	**10,88**	0	0	0,76	32,38	lymph node
HESX1	10	0	0	0	0	43,18	ovary
FOS	9	**19,04**	2,09	4,31	0,77	19,04	blood
CALCA	9	0	0	0	0	100	prostate
S100A6	9	1,2	0,87	5,16	1,18	20,08	umbilical cord
NOS1	8	0	0	0	1,68	65,97	muscle
AVP	8	0	0	0	**80**	80	kidney
RHOA	7	2,5	1,57	2,02	1,72	5,28	cervix
CYBB	7	**19,44**	0	2,55	3,15	27,68	lymph node
MAPK1	7	1,84	1,35	2,36	1,44	10,94	mouth
AKT1	7	1,14	1,57	0,45	1,51	13,52	salivary gland
ICAM1	7	3,19	0,55	2,39	1,62	15,19	spleen
CALCRL	7	0	2,55	**14,85**	1,39	25,06	trachea
SERPINE1	7	0,17	0,12	**14,5**	0,69	27,77	umbilical cord
EDNRA	7	0	6,4	2,21	1,63	10,94	uterus
SHBG	7	0	0	0	0	36,84	eye
RAMP2	7	5,09	0	0	1,85	28,7	thyroid
UTS2	7	0	0	0	3,88	35,92	spleen
OLR1	6	1,23	0	0	2,15	81,05	esophagus
AGTR1	6	0	5,19	0	3,3	19,1	larynx
NFKB1	6	4,69	0,76	0,66	1,62	8,69	nerve
UTS2R	6	0	0	0	0	100	ovary
NR3C2	6	0	0	6,41	7,08	20,74	stomach
EPHB2	6	6,73	0	0	2,85	14,78	umbilical cord

Table 1: Continued.

Symbol	Articles	Expression in blood (%)	Expression in heart (%)	Expression in vascular (%)	Expression in kidney (%)	Max. expression (%)	
ISYNA1	6	1,49	0,43	0,52	3,31	17,72	umbilical cord
GPR182	5	0	0	0	0	38,67	adrenal gland
COX8A	5	0,77	**11,02**	1,48	0,98	11,02	heart
CPOX	5	9,24	3,63	0	5,28	11,06	liver
EGFR	5	0	2,2	1,69	2,49	14,89	mouth
COX5A	5	0	0	0	0	100	muscle
CCL2	5	0	0	0	0	100	placenta
PPARG	5	0	1,46	2,52	3,72	12,08	placenta
CYBA	5	2,25	6,82	1,67	3,43	15,46	tonsil
RAMP3	5	7,76	0	0	2,54	21,44	adipose tissue

Table 2: List of enriched biological processes and molecular functions. Given are the total number of genes assigned to a process/function, the number of genes assigned as derived from literature mining, the number of genes expected from a statistical perspective, and the significance level of enrichment.

Biological process	No. genes total	No. genes CRS	No. genes CRS expected	*P*-value
Signal transduction	4191	135	57,67	4.55E-25
Cell communication	4365	136	60,07	6.84E-24
Cell surface receptor linked signal transduction	2235	91	30,76	3.80E-22
Immune system process	2628	97	36,16	9.70E-21
Blood circulation	210	28	2,89	5.11E-19
Regulation of biological process	59	18	0,81	1.01E-18
Regulation of vasoconstriction	59	18	0,81	1.01E-18
Molecular function	No. genes total	No. genes CRS	No. genes CRS expected	*P*-value
Receptor binding	1233	64	16,97	2.46E-20
Protein binding	3157	103	43,44	2.71E-18
Catalytic activity	5336	128	73,43	1.44E-12
Oxidoreductase activity	703	33	9,67	1.21E-09
Binding	6751	140	92,9	3.65E-09
Kinase activity	695	28	9,56	5.18E-07

enriched in genes associated with the cardiorenal syndrome. We therefore took a closer look at receptor-ligand interactions. We searched for receptors mainly expressed in the cardiovascular system having ligands predominantly secreted by the renal tissue, and vice versa.

The natriuretic peptide receptor NPR3 showed high expression in kidney tissue, whereas the ligands NPPA and NPPB were found to be almost exclusively expressed in the heart. Thus, a deregulation of blood pressure maintenance and extracellular fluid volume by heart-derived ligands of the natriuretic peptide system directly affect the kidney and may contribute to the formation of CRS.

Enrichment of the process "regulation of vasoconstriction" reflects the consequences of impaired heart function including a decreased cardiac output, and thus the hypoperfusion of organs. Since glomerular filtration is controlled by blood pressure, hypoperfusion of the kidney leads to the activation of the RAS and subsequent vasoconstriction, which, in turn, causes systemic hypertension and an increased heart preload [2].

22 PANTHER pathways could be identified as significantly enriched in the list of 280 literature-derived genes. 28 genes could be assigned to "angiogenesis", 21 genes to "endothelin mediated signaling", and 15 genes to the "VEGF signaling pathway" (Table 3).

The connection between angiogenic processes and cardiovascular disorders is well understood, since decreased cardiac output goes along with decreased organ perfusion, and vascularization is the natural response to diminution of blood supply. Apart from negative effects on organ function due to hypoperfusion, microvascularization is extensively performed at sites of inflammation which explains the role of angiogenesis in diseased kidney tissue. On the other hand, decreased vascularization and loss of capillaries lead to kidney fibrosis. However, deregulation of angiogenesis seems to be crucial for kidney function and a key regulatory mechanism of angiogenic processes is the VEGF signaling pathway [44–46]. A third enriched pathway is the "endothelin signaling pathway" which is known to regulate the renin-angiotensin system thus being a further player in

Table 3: List of enriched biological pathways. Given are the total number of genes assigned to a process/function, the number of genes assigned as derived from literature mining for CRS, the number of genes expected from a statistical perspective, and the significance level of enrichment.

Pathway	No. genes total	No. genes CRS	No. genes CRS expected	*P*-value
Angiogenesis	191	28	2,63	4.51E-20
Endothelin signaling pathway	91	21	1,25	3.33E-19
VEGF signaling pathway	75	15	1,03	3.33E-13
Inflammation mediated by chemokine and cytokine signaling pathway	283	24	3,89	2.76E-12
PDGF signaling pathway	159	18	2,19	1.68E-11
T cell activation	102	14	1,4	2.72E-10
Apoptosis signaling pathway	123	15	1,69	3.10E-10

the hemodynamic cross-talk between the kidney and the cardiovascular system.

Following the rationale that features secreted from kidney cells may lead to damage in vessels and vice versa, literature-derived proteins were classified in terms of subcellular location. The most significantly enriched compartment was "extracellular, including cell wall" with 81 genes being assigned to this category, whereas "nuclear" was significantly depleted with 48 genes as indicated in Figure 2 .

The list of 81 secreted genes included components of the renin-angiotensin system (REN, AGT, ACE) and the natriuretic peptide system (NPPA, NPPB), as well as some other regulators of vasoconstriction. Kininogen 1 (KNG1) for example is essential for the assembly of the blood pressure regulating kallikrein-kinin system. Another molecule serving as a vasodilator is the peptide hormone calcitonin-related polypeptide alpha (CALCA).

3.3. Network Analysis. A subset of 40 proteins out of the list of 132 proteins mentioned in at least two publications in the context of the cardiorenal syndrome formed a highly connected protein interaction network as given in Figure 3 . The main components of this protein network are mediators of hemodynamic change. An accumulation of features involved in previously described signaling pathways like the endothelin signaling pathway or the VEGF signaling pathway is evident. Next to these two pathways, a number of members of the blood pressure regulating kallikrein-kinin system and the renin-angiotensin system are part of this network.

Another highly connected cluster holds genes associated with leukocyte transendothelial migration. The process of leukocyte migration from blood into tissues is vital for inflammation, and it is known that inflammation is an important cardiorenal connector and a hallmark of kidney and heart diseases [5].

3.4. Identification of Drug Targets. 116 out of the 280 proteins associated with the CRS were listed as drug target for at least one drug in DrugBank (see supplementary Table 1). The proteins with the most number of drugs were PTGS1, PTGS2, and NOS3 with 49, 43, and 41 drugs associated. The drug with the most drug targets in our list of 280 proteins was NADH.

Standard therapeutic regimes in the context of cardiovascular and kidney disease included aliskiren, irbesartan, or ramipril. Another drug candidate is nesiritide, a recombinant B-type natriuretic peptide that counter-regulates the RAS, as used in the treatment of acute decompensated heart failure (ADHF). However, on the basis of a prospective, randomized, double-blinded, placebo-controlled clinical trial, Witteles et al. concluded that nesiritide therapy does not impact renal function in patients with ADHF and preexisting renal dysfunction [47].

It is known that reducing blood pressure has beneficial effects on renal function and there is a multitude of antihypertensive agents acting on the RAS. Administration of angiotensin receptor antagonists in combination with angiotensin-converting enzyme inhibitors showed a significant reduction of urine albumin creatinine ratio in patients with hypertension and microalbuminuria and thus, a reduction of the risk for myocardial infarction [48].

Further potential targets for regulation of hemodynamics are members of the endothelin signaling pathway. Endothelin receptor antagonists are used in the treatment of a variety of cardiovascular conditions but less is known about the effects on combined kidney dysfunction. Ding et al. showed in animal models that chronic endothelin receptor blockade with endothelin receptor antagonists is beneficial in the treatment of progressive renal dysfunction and sodium retention associated with chronic heart failure [49]. Studies in humans are required to fully elucidate the effects and risks of endothelin receptor antagonist treatment in patients with CRS.

4. Conclusions

In this work, we provide a comprehensive list of genes/proteins associated with the cardiorenal syndrome identified on the basis of a literature mining approach. On the basis of 825 articles identified in the context of CRS, 280 unique genes could be identified and were further characterized with respect to molecular function, biological processes, cellular pathways, subcellular location, tissue-specific expression, as well as on the level of protein interaction networks.

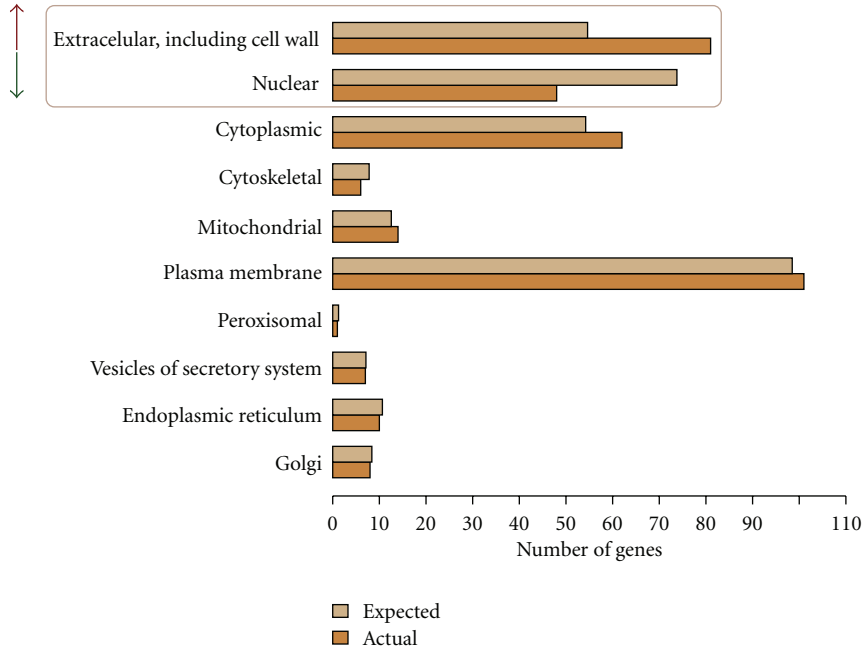

Figure 2: Subcellular location of literature-derived proteins. Presented are categories of subcellular location, the expected number of proteins in a particular category using the total set of human proteins, and the actual number of proteins found as being associated with CRS.

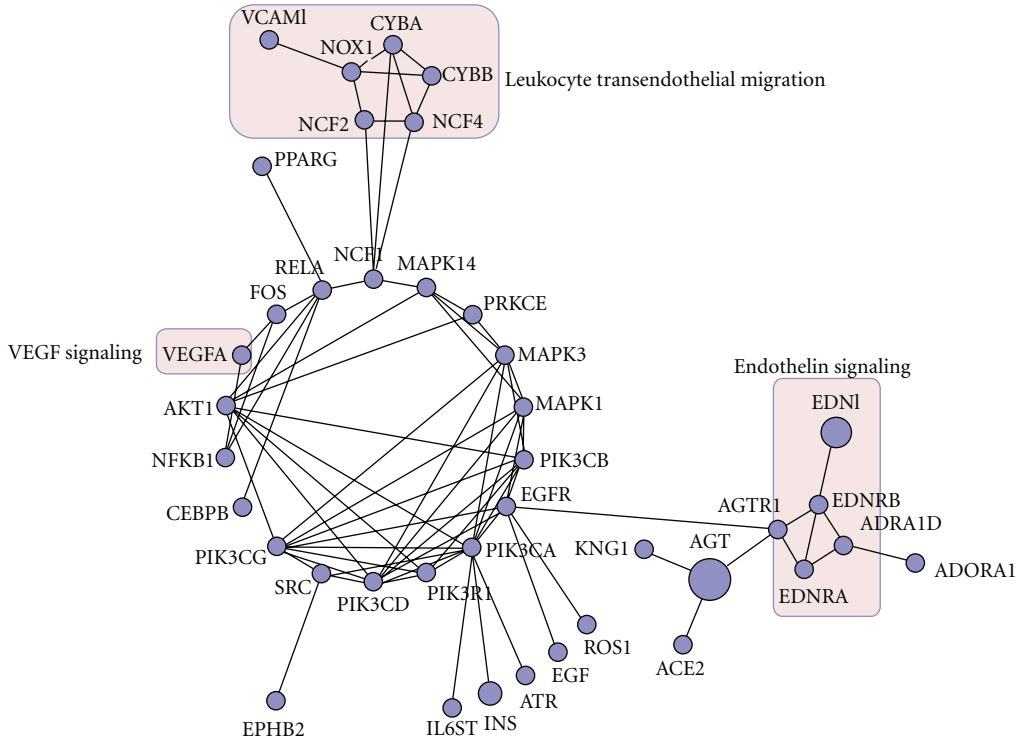

Figure 3: Protein interaction network of highly connected proteins associated with the cardiorenal syndrome. Nodes represent genes (gene symbols); edges indicate functional associations. Highlighted nodes represent proteins that are specific for either the VEGF signaling, the leukocyte transendothelial migration, or the endothelin signaling pathway.

The most frequently reported genes are involved in blood pressure regulating systems, particularly in the renin-angiotensin system (REN, AGT, ACE), as well as in the antagonistic natriuretic peptide system (NPPA, NPPB). Enriched molecular functions include "receptor binding" and "receptor activity". Of special note in this context are again players of the natriuretic peptide system, namely, the two ligands NPPA and NPPB and its receptor NPR3. Tissue-specific expression patterns of these molecules showed that NPPA and NPPB are mainly expressed in the heart, whereas their receptor NPR3 is highly expressed in kidney tissue, suggesting that this regulatory system is part of the cross-talk between the kidney and the cardiovascular system.

Therapy of the CRS is largely focused on natriuretic peptides or the renin-angiotensin system with a number of other molecular targets like the endothelin signaling pathway holding promise for future therapeutic strategies.

Altogether, the results of the present study strongly indicate the critical role of hemodynamic changes, blood pressure regulating hormone systems, and inflammatory processes in the formation of the CRS. Our analyses led to a comprehensive picture of molecular features involved in the functional interplay between the kidney and the cardiovascular system. One limitation of this automated literature mining approach is that we do not have experimental data on the expression levels of the reported molecules in the process of disease development. An obvious next step would therefore be to integrate the findings of this work with Omics datasets on kidney disease as well as vascular diseases. Such a combined approach has the potential to identify deregulated features for potentially identifying novel players for diagnostic or therapeutic approaches in the field of kidney and cardiovascular diseases.

Acknowledgment

This research was supported by Fresenius Medical Care Austria GmbH.

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International Journal of Nephrology
Volume 2011, Article ID 957164, 9 pages
doi:10.4061/2011/957164

Review Article

Proximal Tubule Cell Hypothesis for Cardiorenal Syndrome in Diabetes

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Received 6 September 2010; Accepted 5 November 2010

Academic Editor: Mitchell H. Rosner

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Incidence of cardiovascular disease (CVD) is remarkably high among patients with chronic kidney disease (CKD), even in the early microalbuminuric stages with normal glomerular filtration rates. Proximal tubule cells (PTCs) mediate metabolism and urinary excretion of vasculotoxic substances via apical and basolateral receptors and transporters. These cells also retrieve vasculoprotective substances from circulation or synthesize them for release into the circulation. PTCs are also involved in the uptake of sodium and phosphate, which are critical for hemodynamic regulation and maintaining the mineral balance, respectively. Dysregulation of PTC functions in CKD is likely to be associated with the development of CVD and is linked to the progression to end-stage renal disease. In particular, PTC dysfunction occurs early in diabetic nephropathy, a leading cause of CKD. It is therefore important to elucidate the mechanisms of PTC dysfunction to develop therapeutic strategies for treating cardiorenal syndrome in diabetes.

1. Introduction

Chronic kidney disease (CKD) is a worldwide public health problem, and the incidence of end-stage renal disease (ESRD) with poor outcomes and associated high costs is increasing. Patients with CKD are also at high risk of developing cardiovascular disease (CVD). It is therefore important to elucidate the pathogenesis of CKD and the mechanisms underlying its role in the development of CVD.

Albuminuria/proteinuria is a distinctive clinical sign in patients with CKD. Although a decrease in glomerular filtration rate (GFR) correlates with an increase in incidence of CVD, patients showing normal GFR with even mild albuminuria/proteinuria are also at risk of developing CVD [1, 2]. The link between albuminuria/proteinuria and CVD has generally been attributed to vascular endothelial injury associated with the development of atherosclerosis. However, endothelial injury may not only be a cause of CKD, but also a consequence of the disease. In addition, the vascular pathology of CKD is characterized by medial layer calcification that may be mediated by calcium-phosphate dysregulation [3]. Therefore, to clarify the mechanisms of CVD in patients with CKD, it is important to investigate the renal factors that cause albuminuria/proteinuria and those that are involved in the induction of vascular endothelial injury and calcification.

The aim of this paper is to hypothesize and verify on the basis of the available evidence that proximal tubule cell (PTC) dysfunction explains well the link between the development of albuminuria/proteinuria and cardiovascular risk, especially in diabetic nephropathy which is a leading cause of CKD and is highly associated with the development of CVD.

2. Overall Functions of PTCs

The various functions of PTCs include (1) reabsorption and intracellular processing of glomerular-filtered substances such as proteins, peptides, glucose, amino acids, uric acid, sodium, potassium, phosphate, and water via apical membrane receptors, transporters, and channels; (2) uptake of substances such as protein-bound compounds via basolateral membrane transporters followed by metabolism or secretion

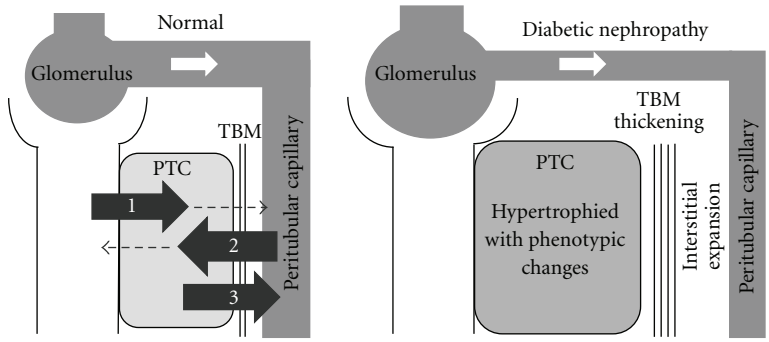

Figure 1: Normal functions of proximal tubule cells (PTCs) and structural changes around the cells in the early stages of diabetic nephropathy. Normal functions of PTCs include (1) reabsorption and intracellular processing of glomerular-filtered substances via apical membrane receptors, transporters, and channels; (2) uptake of substances via basolateral membrane transporters followed by metabolism or secretion into the urinary space; (3) synthesis of bioactive substances that are released to peritubular capillaries. These functions are impaired in diabetic nephropathy even at the early stages in which PTCs are hypertrophied with increased metabolic demands and are phenotypically altered. In addition, tubular basement membranes (TBMs) are thickened, and interstitial spaces are expanded with fibrosis, alienating PTCs from interacting with peritubular capillaries.

to the urinary space; (3) synthesis of substances that are released to the peritubular capillaries (Figure 1). Impairment of these diverse functions is likely to affect systemic hemodynamic and metabolic homeostasis and may mediate the development of CVD as discussed below.

3. Dysfunction of PTCs in Diabetic Nephropathy

In the early stages of diabetic nephropathy, PTCs are hypertrophied because of increased metabolic demands and phenotypically changed to express cytokines or chemokines [4]. Tubular basement membranes are thickened and interstitial spaces are expanded with fibrosis, isolating the PTCs from interaction with peritubular capillaries (Figure 1). Such structural changes and increased metabolic demands on PTCs are likely to cause ischemia in the cells. At more advanced stages, interstitial fibrosis is increased, peritubular capillaries become dispersed, and PTCs undergo atrophy, which further diminishes interaction between the cells and surrounding capillaries. Similar phenotypic changes of PTCs are also observed in patients with obesity or metabolic syndrome. In other glomerular diseases, tubulointerstitial damage also follows as a final common pathway for progression to ESRD [5].

4. Megalin and Cubilin: Two Endocytic Receptors in Apical PTC Membranes

Glomerular-filtered substances are reabsorbed by megalin and cubilin, two endocytic receptors expressed in apical PTC membranes (Figure 2). Megalin is a large (~600 kDa) glycoprotein member of the low-density lipoprotein receptor family [6, 7] that is primarily expressed in clathrin-coated pits [8]. Megalin-ligand complexes are internalized by invagination of clathrin-coated pits mediated by multiple adaptor proteins and motor molecules, forming endosomal vesicles. Acidification of the intravesicular lumen dissociates the ligands from megalin, and they are transported to lysosomes for degradation or storage, or secreted into the cytosol for further processing or transport. Megalin is recycled to the apical membranes through a recycling compartment. Megalin thus plays a critical role in reabsorption and metabolism of glomerular-filtered substances including albumin and low molecular weight proteins. Megalin knockout mice display low molecular weight proteinuria and albuminuria [9]. Furthermore, patients with Donnai-Barrow and facio-oculo-acoustico-renal syndromes, caused by mutations in the megalin gene, show increased urinary excretion of albumin and low molecular weight proteins [10].

Cubilin is a 460 kDa peripheral glycoprotein that lacks transmembrane and intracellular segments but is anchored to apical membranes in PTCs. It was originally identified as the receptor for intrinsic factor-vitamin B_{12} complex [11, 12]. Cubilin gene defects are the cause of hereditary megaloblastic anaemia 1 or Imerslund-Gräsbeck syndrome, known as selective vitamin B_{12} malabsorption with proteinuria [13]. Cubilin is also involved in the absorption of various protein ligands present in glomerular filtrates, including albumin, transferrin, and vitamin D-binding protein (DBP) [8]. Cubilin requires interaction with megalin to regulate its endocytic functions [14, 15]; however, it is bound more firmly by a protein called amnionless, forming a complex named CUBAM [16, 17] (Figure 2). Amnionless, a 38–50 kDa membrane protein with a single-transmembrane domain, was initially identified as a component required for normal development of the trunk mesoderm derived from the middle streak [18]. In addition, defects of the amnionless gene cause hereditary megaloblastic anaemia [19].

5. Impaired Reabsorption of Glomerular-Filtered Substances via Megalin and Cubilin in Diabetic Nephropathy

Decreased megalin expression in PTCs has been found in the early diabetic stages of experimental animals [20, 21].

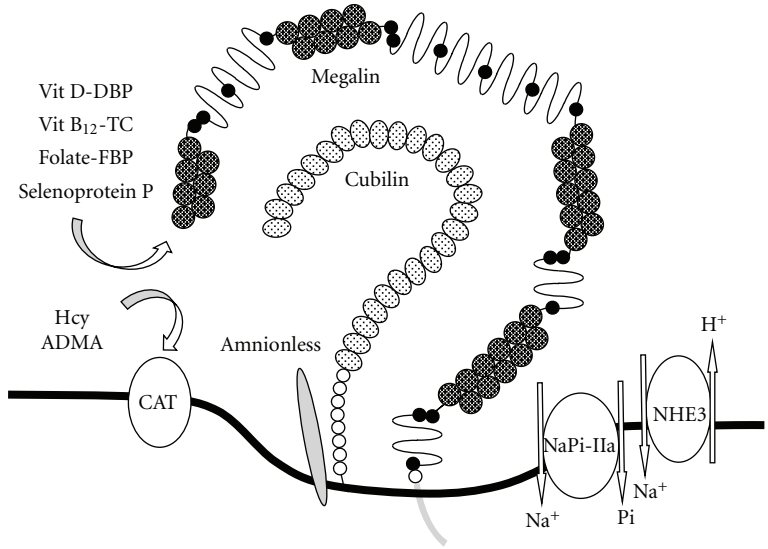

Figure 2: Endocytic receptors and transporters involved in the uptake of substances at the apical membranes of proximal tubule cells (PTCs). At apical membranes of PTCs, megalin and the cubilin-amnionless complex are involved in endcytosis of protein ligands. Megalin facilitates uptake of various ligands including vitamin D/vitamin D-binding protein (DBP), vitamin B_{12}/transcobalamin (TC), folate/folate-binding protein (FBP) complexes, and selenoprotein P. Similarly, cubilin facilitates uptake of the vitamin D/DBP complex. Type IIa Na/Pi cotransporter (NaPi-IIa) and Na^+/H^+ exchanger isoform 3 (NHE3) are primarily involved in the uptake of phosphate and sodium, respectively. Homocysteine (Hcy) and asymmetric dimethylarginine (ADMA) may be taken up by cationic amino acid transporters (CATs) and metabolized in PTCs. Dysregulation of the uptake or metabolism of these substances in PTCs in patients with CKD, especially with diabetic nephropathy, is likely to be involved in the mechanism that promotes the development of CVD.

It has also been suggested that the functions of megalin are impaired in patients during the early stages of diabetic nephropathy, since low molecular weight proteinuria is frequently observed in patients at these stages [22, 23]. Therefore, the altered regulation of megalin expression and its functions must be responsible for the early development of proteinuria/albuminuria in diabetic patients. The functions of cubilin, a direct receptor for albumin, may also be impaired in the early stages of diabetic nephropathy as urinary excretion of transferrin, another endocytic ligand of cubilin, is significantly increased in patients at the early stages [24]. The functions of both megalin and cubilin are likely to be further affected as tubulointerstitial injury in CKD progresses.

Cellular expression of megalin was found to be downregulated by TGF-ß [21]. We also found that megalin expression in cultured PTCs is upregulated following treatment with insulin or high-concentration glucose. Conversely, it is downregulated by angiotensin II [25]. Furthermore, we demonstrated that there is competitive crosstalk between angiotensin II type 1 receptor- and insulin-mediated signaling pathways in the regulation of megalin expression in the cells [25]. Anigotensin II may be a major factor in suppressing megalin expression in the early stages of diabetic nephropathy since intrarenal RAS is activated in the disease [26].

Decreased expression or functioning of megalin and/or cubilin results in reduced reabsorption of their glomerular-filtered ligands. Impaired reabsorption of some ligands of these receptors may be associated with the development of CVD, as described next.

6. Megalin- or Cubilin-Mediated Endocytic Ligands That May Promote Development of CVD When Depleted

6.1. Vitamin D. Megalin and cubilin take up the $25(OH)D_3$/DBP complex from glomerular filtrates [27, 28] (Figure 2). In PTCs, $25(OH)D_3$ is dissociated from DBP and converted by 1α-hydroxylase to $1,25(OH)_2D_3$, a biologically active form, which is released to the peritubular capillaries. Therefore, dysfunction of these endocytic receptors is an important cause of deficiency of both $25(OH)D_3$ and $1,25(OH)_2D_3$ in CKD in addition to other factors such as decreased 1α-hydroxylase activity. Vitamin D deficiency develops very early in the course of CKD, especially in diabetic nephropathy, and is associated with the development of CVD or mortality in patients at predialysis stages [29, 30]. Treatment with the activated vitamin D analogue calcitriol was significantly associated with improved survival of patients with CKD [31, 32]. In addition, vitamin D deficiency may also be associated with an increased risk of CVD in the general population [33], although the effects of vitamin D supplementation on the CVD-related mortality in the population remain controversial.

Many studies have investigated vitamin D deficiency-associated mechanisms of vascular calcification and cardiac dysfunction. Vitamin D acts on vascular smooth muscle cells

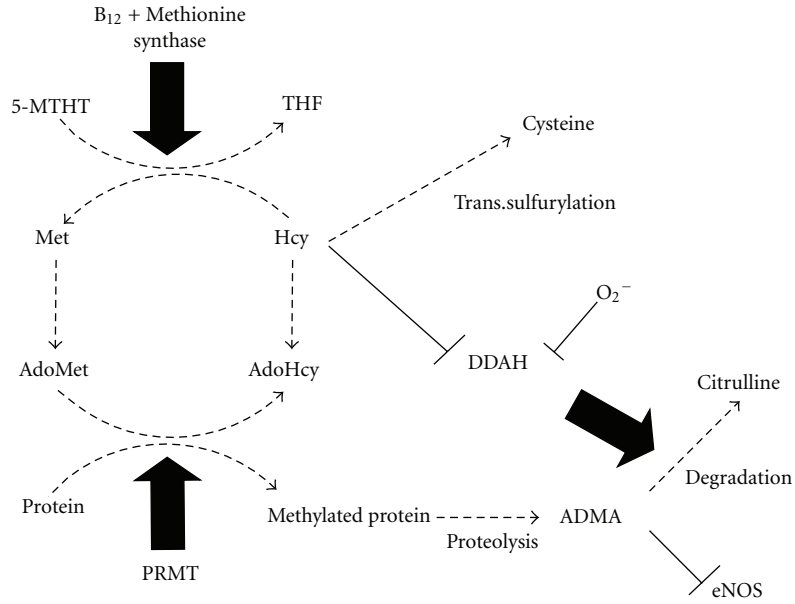

Figure 3: Intracellular synthesis and metabolism of homocysteine (Hcy) and asymmetric dimethylarginine (ADMA) and their biochemical link. Vitamin B_{12} serves as a cofactor for the formation of methionine (Met) from homocysteine (Hcy) by methionine synthase using 5-methyl-tetrahydrofolate (5-MTHF), the dominant folate form in serum. S-adenosylmethionine (AdoMet) is the intermediate in this reaction and serves as the methyl donor to form S-adenosylhomocysteine (AdoHcy). Hcy is either remethylated to Met or transsulfurated to cysteine. Asymmetric dimethylarginine (ADMA) is an endogenous competitive inhibitor of endothelial nitric oxide synthase (eNOS). ADMA is formed by methylation of arginine residues in proteins with protein methyltransferase (PRMT) and released after proteolysis. Metabolism of ADMA is mediated by dimethylarginine dimethylaminohydrolases (DDAHs), which are downregulated by reactive oxygen species and Hcy.

to inhibit activators of vascular calcification, such as core binding factor-1 (Cbfa1), bone morphogenic protein-2, type I collagen, interleukin-1b, interleukin-6, and transforming growth factor-ß, and to stimulate inhibitors of vascular calcification, such as matrix Gla protein and osteopontin [30]. Furthermore, decreased vitamin D-receptor activity increases circulating renin levels and blood pressure which results in left ventricular and myocyte hypertrophy [34].

6.2. Vitamin B_{12} and Folate. Vitamin B_{12} is a cofactor involved in the formation of methionine (Met) from homocysteine (Hcy) by cytoplasmic methionine synthase using 5-methyl-tetrahydrofolate (5-MTHF), the dominant folate form in serum, as a one-carbon donor [35] (Figure 3). Therefore, vitamin B_{12} and/or folate deficiency results in the accumulation of Hcy that is associated with the development of CVD. Following absorption from the intestine with intrinsic factor, vitamin B_{12} is bound in the serum with transcobalamin, a 45 kDa serum protein, for transport to target tissues. The transcobalamin-vitamin B_{12} complex is filtered by glomeruli and reabsorbed by megalin in PTCs [36] (Figure 2), which explains why vitamin B_{12} deficiency can be induced by decreased megalin function.

Folate binds to a carrier protein termed folate-binding protein and also to other proteins including albumin. Alternatively, it exists in free form in serum. After being filtered by glomeruli, protein-bound folate is reabsorbed by PTCs through megalin-mediated endocytosis while the free form is likely taken up by folate receptors [37] (Figure 2). Dysfunction of PTCs therefore results in decreased renal retrieval of folate, which subsequently leads to its deficiency.

6.3. Selenoprotein P. Megalin is also involved in the reabsorption of selenoprotein P, a selenium-carrier protein from glomerular filtrates [38, 39] (Figure 2). Selenium is released from selenoprotein P and used in PTCs to synthesize glutathione peroxidase 3 (GPx3), a major plasma antioxidant enzyme [40]. GPx3 is involved in maintaining the vascular bioavailability of nitric oxide, a major vasorelaxant, as well as inhibiting platelet function [41]. Therefore, reduced uptake of selenoprotein P in PTCs due to impaired megalin function may result in decreased GPx3 synthesis which may be associated with the development of vascular diseases. Notably, a recent proteome analysis revealed that serum GPx3 levels are significantly decreased in patients at the microalbuminuric stage of type 2 diabetes and even further at the progressive stages [42]. In fact, familial GPx3 deficiency has been associated with an increased risk of childhood stroke [43, 44]. Also, there have been reports that demonstrate decreased GPx 3 activity among patients with coronary artery disease, supporting a broader effect of this defect in the vascular system [45–47].

7. Increased Phosphate Reabsorption in PTCs

Hyperphosphatemia is significantly associated with the development of CVD and high mortality in patients with CKD, independent of estimated creatinine clearance [48].

Inorganic phosphate appears to act directly on cultured vascular smooth muscle cells to express the osteogenic markers Cbfa1 and osteocalcin, with subsequent mineralization of the extracellular matrix [49]. Serum phosphate concentration is regulated by intestinal absorption from dietary phosphate intake, but more importantly, by glomerular filtration and reabsorption of phosphate via type II Na/Pi cotransporters (NaPi-IIa and NaPi-IIc) in the apical membranes of PTCs. In particular, NaPi-IIa plays a central role in phosphate reabsorption in the kidney (Figure 2). The presence of hyperphosphatemic patients with CKD whose GFR is normal is well explained by a hypothesis that Na/Pi cotransporters in PTCs may be inappropriately upregulated. The functions of NaPi-IIa are regulated by various hormones and hormone-like substances, such as parathyroid hormone, fibroblast growth factor 23, and Klotho that all downregulate NaPi-IIa and induce phosphaturia. Regulation of NaPi-IIa is almost exclusively mediated via receptor-mediated endocytosis and lysosomal degradation of NaPi-IIa [50]. Because megalin mediates the endocytic pathway for degradation of NaPi-IIa [51], decreased megalin function may result in hypophosphaturia or hyperphosphatemia even in cases with normal GFR.

8. Increased Sodium Reabsorption in PTCs

Proximal tubular uptake of sodium is increased in patients with diabetic nephropathy [52–54] and metabolic syndrome [55, 56] and is associated with the development of hypertension, another potent factor for CVD [57]. Na^+/H^+ exchanger isoform 3 (NHE3) is the main NHE isoform in PTCs and mediates isotonic reabsorption of approximately two-thirds of filtered NaCl and water, reabsorption of bicarbonate, and secretion of ammonium ions [58] (Figure 2). Enhanced NHE3 activity is assumed to play a leading role in increased sodium reabsorption in diabetes while intrarenal RAS activation is also thought to be involved in the process [26]. Increased action of sodium glucose cotransporter SGLT2 is yet another factor promoting increased sodium uptake in PTCs in diabetes [59].

9. Impaired Metabolism of Vasculotoxic Substances Taken up via Apical Transporters/Receptors in PTCs

9.1. Homocysteine (Hcy). Hcy is a sulfhydryl amino acid formed by demethylation of Met (Figure 3). S-adenosylmethionine (AdoMet) is the intermediate in this reaction and serves as the methyl donor to form S-adenosylhomocysteine (AdoHcy). Hcy is either remethylated to Met or transsulfurated to cysteine. Approximately 75% of total plasma Hcy is bound to protein, primarily albumin, via a disulfide bond (bound Hcy), while the remaining 25% exists in a free-form unbound state (free Hcy) in humans.

When patients with extreme hyperhomocysteinemia due to genetic enzyme defects were found to suffer from premature atherosclerosis and venous thrombosis, Hcy was hypothesized to be a direct vasculotoxic agent [60]. Subsequently, it was shown that plasma Hcy is strongly associated with renal function, and that 85%–100% of ESRD patients have elevated Hcy levels [61]. Hyperhomocysteinemia is recognized as a risk marker for CVD in patients with ESRD unless their conditions are complicated with malnutrition or inflammation that induces hypoalbuminemia and apparent low plasma Hct levels [62, 63].

The kidney probably plays an important role in Hcy clearance and metabolism. It is highly likely that free Hcy is filtered by glomeruli and taken up via cationic amino acid transporters in the apical membranes of PTCs [64, 65] (Figure 2). However, renal uptake of Hcy derived from bound Hcy may be mediated by basolateral tubular transporters. It is therefore assumed that impaired uptake and/or metabolism of Hcy in PTCs are associated with hyperhomocysteinemia in patients with CKD or ESRD and the development of CVD.

Hyperhomocysteinemia is also associated with an increase in AdoHcy, which is considered another predictor of cardiovascular events. AdoHcy is a powerful competitive inhibitor of protein as well as DNA methyltransferases. Increased intracellular AdoHcy can be expected to result in hypomethylation of proteins and genes, which will in turn induce protein dysfunction and epigenetic dysregulation, respectively [66, 67].

9.2. Asymmetric Dimethylarginine (ADMA). ADMA, a naturally occurring L-arginine analogue, is an endogenous competitive inhibitor of nitric oxide synthase and an important inducer of endothelial dysfunction. ADMA is formed by the methylation of arginine residues in peptides with protein methyltransferase (PRMT) and their release after proteolysis. In this reaction, AdoMet is the methyl donor, and AdoHcy is the demethylated product. Formations of ADMA and Hcy are therefore biochemically linked (Figure 3).

An increased plasma concentration of ADMA is associated with the development of CVD [68]. In patients with nondiabetic CKD, blood concentrations of ADMA are markedly increased at an early stage, even when GFR is still within the normal range [69]. Increased plasma ADMA levels are also closely associated with the development and progression of nephropathy in patients with type 2 diabetes [70].

The kidney is an important organ for clearance of ADMA [71, 72], which is eliminated from circulation by both renal excretion and metabolic degradation. Renal uptake of ADMA is very likely mediated by cationic amino acid transporters that are predominantly expressed in the apical membranes of PTCs [73]. ADMA metabolism is mediated by dimethylarginine dimethylaminohydrolases (DDAHs), which are posttranscriptionally downregulated by reactive oxygen species and Hcy [74, 75]. Two isoforms of DDAH exist and are differentially localized and regulated. In the kidney, DDAH I is abundantly expressed in PTCs, while DDAH II is located in glomeruli, afferent arterioles, macula densa, and distal nephrons [76]. Recent studies have indicated that DDAH I is mainly involved in the regulation of plasma ADMA levels [77]. In addition, ADMA is formed by the activity of PRMT that is highly expressed in PTCs. In subtotally nephrectomized rats showing increased plasma ADMA

levels, DDAH protein levels were decreased while expression of PRMT was increased in the kidney [78]. Such effects are likely to mediate the mechanism of increasing plasma ADMA levels. Streptozotocin-induced rat diabetic kidneys also showed decreased DDAH I expression, which was reversed by telmisartan, an angiotensin II-receptor blocker [76].

9.3. Advanced Glycation End Products (AGEs) and Free Adduct Glycation, Oxidation, and Nitration Products. Megalin mediates proximal tubular uptake of AGEs, a potent factor of vascular injury [79]. It remains unclear how effectively AGEs are metabolized in PTCs, but this metabolic process may be affected in damaged PTCs. AGE precursors which include glycation, oxidation, and nitration free adducts are also excreted or metabolized in the kidney [80]. Methylglyoxal, one such dicarbonyl adduct, is a potent glycating agent associated with oxidative stress and vascular injury [81] and is increased in the serum of patients with CKD or uremia, probably because of reduced renal metabolism [80]. Methylglyoxal is metabolized by glyoxalase I that is usually expressed in PTCs but is downregulated in the rat model of renal injury [82]. This suggests that decreased enzymatic activities in PTCs may be a cause of increased serum methylglyoxal in CKD.

10. Impaired Uptake, Metabolism, or Urinary Excretion of Vasculotoxic Substances via Basolateral PTC Transporters in PTCs

10.1. Indoxyl Sulfate and Other Protein-Bound Uremic Toxins. Indoxyl sulfate is a protein-bound uremic toxin that results from the metabolism of dietary tryptophan. Increase of serum indoxyl sulfate in patients with CKD is associated with both the development of CVD and mortality [83]. Indoxyl sulfate is excreted in urine via the organic anion transporters OAT1 and OAT3 that are predominantly expressed in the basolateral membranes of PTCs [84]. These transporters are important as they are also involved in urinary excretion of other protein-bound uremic toxins such as 3-carboxy-4-methyl-5-propyl-2-furanpropionate, indoleacetate, and hippurate, which may also be associated with the development of CVD in patients with CKD [85].

10.2. Guanidino Succinate, Transaconitate, and ADMA. SLCO4C1 is a human kidney-specific organic anion transporting polypeptide that was first identified as a digoxin transporter [86]. In renal failure, basolateral SLCO4C1 expression in PTCs is decreased; however, the expression level of multidrug resistance protein 1 that mediates the tubular secretion of digoxin in the apical membranes of PTCs is not changed [86]. A kidney-specific transgenic rat line overexpressing human SLCO4C1 in PTCs was shown to significantly eliminate the uremic toxins guanidino succinate and *trans*-aconitate as well as ADMA from circulation, even when renal failure was induced by 5/6 nephrectomy [87]. In this study, pravastatin was also found to upregulate the expression of SLCO4C1 and facilitate the removal of circulating ADMA.

11. Decreased Synthesis of Vasculoprotective Substances by PTCs

As mentioned earlier, vasculoprotective substances such as $1,25(OH)_2D_3$ and GPx3 are synthesized by PTCs and secreted into circulation. In addition, renalase, a circulating monoamine oxidase, is a similar substance that is synthesized by the PTCs and regulates various cardiac functions and blood pressure [88]. Plasma concentrations of these factors are reduced in patients with CKD most likely because of decreased synthesis in the PTCs.

12. Therapeutic Strategies for Targeting PTC Dysfunction

Given the diverse and complex functions of PTCs, it is important to establish comprehensive therapeutic strategies to preserve PTC viability and maintain their broad range of functions in diabetic nephropathy and other disorders related to CKD. Therefore, it may not be sufficient to compensate only for specific functions of the cells; in fact, such an approach may explain why the outcomes of recent supplemental trials that used vitamin B_{12} and folate to target Hcy levels were controversial [89, 90]. In addition, vitamin B_{12} and folate deficiencies due to decreased PTC uptake may be masked by reduced GFR in advanced stages of CKD. Therefore, supplementation with these vitamins could lead to overdose and adverse side effects. Inhibitors of the renin-angiotensin II system and statins may effectively alleviate PTC dysfunction; however, the mechanisms of these agents acting on PTCs remain to be elucidated as the phenotypes or pharmacological responsiveness of PTCs may change according to pathogenic stages. Therefore, it is also necessary to develop effective biomarkers to evaluate and monitor the stages of PTC dysfunction.

13. Conclusions

Dysregulation of PTC functions is likely to mediate the multifactorial mechanisms of the development of CVD as well as progression to ESRD and therefore plays a role in cardiorenal syndrome. In particular, PTC dysfunction occurs at the early stages of diabetic nephropathy, a leading cause of CKD. It is important to elucidate the mechanisms of PTC dysfunction and establish therapeutic strategies that protect against PTC dysregulation.

Acknowledgment

This work was supported by a Grant-in-Aid for Scientific Research from the Ministry of Education, Science, and Culture of Japan (no. 21591023).

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