Pathophysiology of Cardiorenal Syndrome Type 2 in Stable Chronic Heart Failure: Workgroup Statements from the Eleventh Consensus Conference of the Acute Dialysis Quality Initiative (ADQI)

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Abstract

In cardiorenal syndrome (CRS) type 2, chronic heart failure (HF) results in the onset or progression of chronic kidney disease (CKD). Examples of CRS type 2 (CRS2) include progressive CKD resulting from chronic HF in congenital or acquired heart disease or from repeated bouts of acute decompensated HF. Animal data and clinical studies indicate that extended periods of chronic HF result in altered renal hemodynamics followed by progressive renal pathology. Experimental and clinical data indicate that CRS2 is characterized by mild to moderate proteinuria, a progressive decline of glomerular filtration rate, and an elevated expression of renal injury biomarkers. Important pathophysiological triggers of renal disease progression include chronic increases in renal venous pressure, maladaptive activation of the renin-angiotensin-aldosterone axis and the sympathetic nervous system, as well as a chronic inflammatory state. Intrarenal oxidative stress and proinflammatory

ADQI 11 Workgroup members are listed in Appendix 2.

signaling precipitate structural injury, including glomerulosclerosis and tubulointerstitial fibrosis. Yet, clinical interventional trials that directly test the impact of renin-angiotensin system antagonists and β -blockers on the progression of CKD in CRS2 are lacking. Secondary analyses of trials designed to assess the impact of these agents on cardiovascular endpoints have failed to show a consistent benefit regarding renal functional parameters. In contrast, left ventricular assist device placement and cardiac resynchronization therapy in HF patients consistently improved renal function, suggesting a marked potential for reversibility in many cases of CRS2. Future research should be directed towards the evaluation of novel biomarkers to improve the diagnosis, severity grading as well as our understanding of the pathophysiology of CRS2. In addition, there is a need for interventional trials in HF patients to address long-term renal endpoints incorporating clinical information and measures of renal function as well as renal injury.

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Cardiorenal syndrome (CRS) is defined as a complex pathophysiological disorder of the heart and kidneys in which acute or chronic dysfunction in one organ may induce acute or chronic dysfunction in the other organ. All subtypes are associated with increased mortality and morbidity, with a significant impact on health resource utilization. An understanding of the specific pathophysiologic mechanisms underlying each subtype will have important implications for risk factor modification, management, and future clinical trials.

CRS type 2 (CRS2) is characterized by chronic abnormalities in cardiac function leading to kidney injury or dysfunction. As such, the temporal relationship between the heart and kidney disease is an important aspect of the definition. While observational data clearly show that chronic heart and kidney disease commonly coexist, large database studies often assemble the patient cohort based on the existence of one disease process (e.g. chronic heart failure (HF)) and subsequently describe the prevalence of the other (chronic kidney disease (CKD)) [1, 2]. For example, CKD has been observed in 26–63% of CHF patients [1–3]. However, such studies are unable to determine which of the two disease processes was primary versus secondary, presenting challenges when attempting to classify patients into the CRS subtype definitions. In these situations, it has been suggested to use the term CRS ‘type 2/4’ [4].

CRS2 in Stable Chronic Heart Failure

In view of the above, the mere coexistence of cardiovascular disease and CKD is not sufficient to make a diagnosis of true CRS2. In the specific setting of stable CHF, we propose the following two prerequisites to make a diagnosis of CRS2; first, that CHF and CKD coexist in the patient, and second, CHF causally underlies the occurrence or progression of CKD. The latter should be supported by both tempo-

Chronic HF	Leading to	EITHER: New onset of CKD
Definition		Definition
Symptoms typical of HF Signs typical of HF (HF-REF) Reduced LVEF OR: (HF-PEF) Normal or mildly reduced EF and LV not dilated, with relevant structural disease and/or diastolic dysfunction (according to ESC, ACC/AHA)		Albuminuria and/or GFR <60 ml/min/1.73m ² (according to KDIGO/KDOQI)
		OR: Progression of CKD
Sustained ↓ eGFR of >5 ml/min/1.73m ² /year, or >10 ml/min/1.73m ² /5 years* OR: sustained increase in albuminuria		
PLUS		
Temporal association: A documented or presumed onset of congestive heart failure precedes the occurrence or progression of CKD		
and		
Pathophysiological plausibility: The manifestation and degree of kidney disease is plausibly explained by the underlying heart condition.		

Fig. 1. Proposed definition of CRS2 in stable chronic HF. Reproduced with permission from ADQI [62].*National Collaborating Centre for Chronic Conditions. Chronic kidney disease: national clinical guideline for early identification and management in adults in primary and secondary care. London: Royal College of Physicians, September 2008.

ral association, i.e. documented or presumed onset of congestive HF temporally precedes the occurrence or progression of CKD, and by pathophysiological plausibility, that is, the manifestation and degree of kidney disease is plausibly explained by the underlying heart condition (fig. 1). One clear example of CRS2 would be congenital heart disease and ‘cyanotic nephropathy’, in which the heart disease temporally precedes any kidney disease. Another would be an acute cardiac event (e.g. acute myocardial infarction) resulting in chronic left ventricular (LV) dysfunction, then followed by the onset of CKD or progression of preexisting CKD.

Heterogeneity in the human HF population and aspects unique to cyanotic heart disease make it difficult to tease out specific mechanisms for CRS2 based on human studies. Therefore, animal studies provide important insight into the pathogenesis of CRS2 by mimicking human phenotypes (table 1). Although multiple and complex mechanisms have been proposed, the predominant mechanisms include neurohormonal activation, hemodynamic factors of renal hypoperfusion and venous congestion, inflammation and oxidative stress (fig. 2). Aside from specific mechanisms, we posit that multiple episodes of acute de-

Table 1. Animal models of heart failure and CRS2

Mechanism	Study	Model	Follow-up days	Biochemical outcomes	Histologic outcomes
RAAS activation	Onozato (2007)	Salt-sensitive Dahl rat HF model; eplerenone and/or trandolapril	126	ACEI or combination: lower creatinine, lower albuminuria Epl: lower albuminuria	ACEI: ↓ glomerular sclerosis, ↓ oxidative stress Epl or combination: ↓ glomerular sclerosis, ↓ oxidative stress and ↓ TGF-β
SNS activation	Rafiq (2012)	Rat aortic regurgitation; renal denervation, and/or olmesartan	180	Denervation lowers albuminuria, plasma norepinephrine, renal Ang2 ARBlowersBNP,renalAng2	Denervation lessens glomerular injury and oxidative stress Denervation and ARB lessen further
Inflammation, fibrosis	Lu (2012)	Mouse coronary ligation; knockout for LOX-1	21	LOX-1 knockout had preserved GFR compared with control	LOX-1 knockout had less renal expression of pro-IL-1b, TGF-β, VCAM, fewer PMNs, ↓collagen/fibrosis
	Lekawanvijit (2012)	Rat coronary ligation	112	HF rats had lower GFR and more albuminuria than control	HF rats had marked increases in phosphorylated Smad2, KIM-1, IL-6, TGF-β and CD68+ cells, with significant interstitial fibrosis
	Entin-Meer (2012)	Rat coronary ligation	30	HF rats had lower GFR and more albuminuria than control	HF rats had marked increases in KIM-1, NGAL, CD3 and CD68+ cells, with significant interstitial fibrosis

compensation of the heart or kidney may contribute to the progression of HF and CKD (fig. 3). This is suggested by data showing that the number of previous hospitalizations for HF was a strong predictor of mortality after controlling for other known risk factors for HF survival [5]. Although repeat hospitalizations may be considered a marker of disease severity, suboptimal care or poor patient compliance, repeated acute decompensation could potentially lead to modification of cardiac structure, increased fibrosis and LV modeling. Moreover, on long-term follow-up of 70 patients with dilated cardiomyopathy, frequency of HF admissions was independently associated with development of CKD (defined as estimated creatinine clearance <60 ml/min) [6]. Similarly, the detrimental effect of acute kidney injury episodes on the development and progression of CKD has been demonstrated in animal models and in epidemiologic studies [7].

Animal Models and Pathophysiological Insights into CRS2

In experimental HF, there is a reduction in glomerular plasma flow, but an elevated glomerular filtration fraction due to efferent arteriolar vasoconstriction. When these changes persist for extended time periods (3–6 months in the rat

Fig. 2. Predominant pathophysiologic mechanisms of CRS2 in stable chronic HF. Reproduced with permission from ADQI [62]

Fig. 3. Repeated acute events (HF decompensation and/or acute kidney injury) may contribute to the progression of chronic heart and kidney dysfunction. Reproduced with permission from ADQI [62].

model), there is increasing evidence of glomerular pathology as evidenced by albuminuria, podocyte injury and histological changes consistent with focal and segmental glomerulosclerosis. Variable decreases of glomerular filtration rate (GFR) have been reported in experimental chronic HF. Importantly, many of the changes appear to be related to systemic and local renal increases in sympathetic nervous system (SNS) and renin-angiotensin-aldosterone system (RAAS) activation.

One of the principle roles of a properly functioning cardiorenal axis is the maintenance of extracellular fluid volume homeostasis. A complex system of volume and pressure sensors, afferent and efferent feedback loops, local and distant vasoactive substances and neurohormonal systems with built-in redundancies serves to continuously monitor and adapt to changing extracellular fluid volume and blood pressure. When such systems are intact and working properly, they respond rapidly to ever-changing hemodynamics and volume status, and ensure adequate tissue perfusion and oxygen delivery. Some of the most important effector mechanisms include the SNS and RAAS.

In the setting of significant cardiac dysfunction, falling cardiac output and underfilling of the renal arterial tree results in activation of both SNS and RAAS [8]. It has long been recognized that the kidneys of patients with HF release substantial amounts of renin into the circulation [9], and this leads in turn to production of angiotensin II. Angiotensin II, working principally through the AT1 receptor, has broad-reaching effects. It is a powerful vasoconstrictor leading to increased systemic vascular resistance, venous tone and congestion, and has potent central nervous system effects on thirst, and activates the SNS. Angiotensin II also exerts significant effects on the kidneys stimulating tubular sodium reabsorption. Its powerful vasoconstrictive effects leads to preferential constriction of the efferent arteriole which in turn leads to increased glomerular filtration fraction, causing an increase in the oncotic pressure of the peritubular capillaries, enhancing the ability to return sodium and fluid to the circulation. The pivotal role of the RAAS system in this process has been demonstrated in animal models involving coronary artery ligation and subsequent infarction and HF [10] (table 1).

In support of clinical observational data implicating high venous pressure as an alternative and important cause of worsening GFR in HF, particularly with preserved ejection fraction and normal or high blood pressure, Kishimoto et al. [11] demonstrated in a dog model that renal venous hypertension, independent of changes in systemic arterial blood pressure, led not only to decreased renal blood flow and GFR, but also to increased renin release. This provides evidence for RAAS activation in the setting of HF characterized by venous hypertension and congestion, and not necessarily requiring decreased effective circulating volume as the stimulus.

In addition to the maladaptive worsening of pressure and volume overload, the chronic activation of the SNS and RAAS is thought to contribute to the progression of CKD characteristic of CRS2. In an elegant animal model of chronic volume overload, Rafiq et al. [12] surgically induced aortic regurgitation in uninephrectomized rats and examined intrarenal levels of norepinephrine and angiotensin II, as well as albuminuria, renal function and histologic evidence of podocyte injury and reactive oxygen species production. They found that chronic volume overload led to predictable changes in the structure and function of the heart, with corresponding increases in both intrarenal SNS and RAAS activity, and that progressive kidney injury could be prevented by renal denervation and angiotensin receptor blockade. The authors propose that activation of the SNS and local angiotensin II stimulates NADPH oxidase-dependent reactive oxygen species generation in the kidney, and these processes lead to podocyte injury and albuminuria.

Angiotensin II is also a potent stimulus for aldosterone release from the adrenal gland, leading to even further augmented sodium reabsorption in the distal nephron, contributing to pressure and volume overload. Moreover, aldosterone has been implicated in progression of CKD and renal fibrosis in a variety of clinical situations and through a number of mechanisms [13]. With an increased level of aldosterone in the kidney, pronounced oxidative stress occurs, via signaling from the paracrine glycoprotein galectin-3, pro-fibrotic cytokine transforming growth factor- β (TGF- β) is upregulated, followed by increases in fibronectin, leading to renal fibrosis and glomerulosclerosis. With respect to CRS2, Onozato et al. [14] examined Dahl salt-sensitive HF rats where increased aldosterone was felt to contribute to worsening kidney function through increased oxidant stress and production of TGF- β . In this experiment, untreated animals with HF developed subsequent proteinuria, elevated creatinine and glomerulosclerosis with increased expression of NADPH oxidase, TGF- β and fibronectin. They demonstrated that angiotensin-converting enzyme (ACE) inhibition and aldosterone blockade with eplerenone diminished oxidative stress, and TGF- β was more effectively suppressed by aldosterone blockade than by ACE inhibition. The combination was able to prevent histologic renal damage, and lowered both creatinine and proteinuria to control levels. It needs to be noted that this model did not separate the effects of hypertension from those of CHF on the progression of kidney disease. Yet, it suggests an interplay of hypertension-induced and HF-associated renal injury with a related and mutually perpetuating pathophysiology.

Inflammation is an additional non-hemodynamic mechanism postulated in the progression of CKD in the setting of CHF. Inflammatory responses are designed to provide protection and promote healing in disease states. Cardiac

myocytes, under the stress of mechanical stretch or ischemia, are capable of producing a broad array of inflammatory cytokines and invoking elements of the innate immune response [15]. Furthermore, venous congestion may increase gut absorption of endotoxin leading to additional inflammatory responses – while venous congestion itself is a stimulus for peripheral synthesis and release of inflammatory mediators [16]. Clinical evidence for this pro-inflammatory state comes from observations that patients with severe HF have markedly elevated levels of tumor necrosis factor (TNF)- α , upregulation of soluble receptors for TNF, and a number of interleukins (IL) including IL-1 β , IL-18 and IL-6, as well as several cellular adhesion molecules.

It is conceivable that these systemic responses to HF could contribute to distant organ damage in the kidneys, though direct evidence for this cardiorenal link is only now emerging. In an acute myocardial infarction model in mice, Lu et al. [17] induced significant suppression of LV function accompanied by a marked pro-oxidant and pro-inflammatory state. These animals demonstrated evidence of CRS type 1, with acute rise in creatinine, however kidney dysfunction did not return to baseline, and histologically the kidneys were found to express a variety of pro-inflammatory molecules, pro-interleukin-1b (IL-1b), vascular cell adhesion molecule-1 (VCAM-1), and TGF- β . Early changes included inflammatory cellular infiltrates, while animals sacrificed later in the course of study demonstrated perivascular, periglomerular and peritubular fibrosis with increased markers of collagen formation, consistent with the human phenotype of CRS2. Knockout mice with a deletion that prevents production of the pro-inflammatory molecule lectin-like oxidized low-density lipoprotein receptor-1 (LOX-1), demonstrated significant abrogation of these responses, with improved renal and cardiac function and morphology.

In a rat model of CRS2 [18], rats with underlying kidney dysfunction were subjected to left anterior descending coronary artery ligation, and further progression of advanced CKD ensued over 30 days of follow-up. HF rats demonstrated marked increases in biomarkers of renal injury neutrophil gelatinase-associated lipocalin (NGAL) and kidney injury molecule 1 (KIM-1), as well as patchy atrophic scarring with prominent clusters of CD3+ and CD68+ immune cells and significant interstitial fibrosis in renal tissue. In another rat model of CRS2, Lekawanvijit et al. [19] likewise performed left anterior descending coronary artery ligation to induce HF, and sacrificed animals after 16 weeks of chronic CHF. They also found increased expression of KIM-1 as well as the intracellular transcription factor phosphorylated Smad2, IL-6 and TGF- β in the HF animals. Associated with these inflammatory markers were infiltrates with CD68+ immune cells, and significant interstitial fibrosis. Similarly, in a rat model of right HF secondary to monocrotaline-induced pulmonary hypertension

and characterized by venous congestion, Angelini et al. [20, 21] demonstrated at the same time neurohormonal activation with increased levels of BNP, angiotensin II and inflammation. Pro-inflammatory cytokines (IL-1 α , β , IL-2, IL-4, IL-6, IL-10, TNF- α) were significantly increased and apoptosis was observed in the heart, lung, skeletal muscle, as well as in the vascular smooth muscle, tubular and glomerular cells of the kidney [Vescovo, pers. commun.]. In this model, NGAL detected by mRNA tissue extraction was also significantly increased in the HF rats compared to controls.

Clinical Studies and Pathophysiological Insights into CRS2

Data in humans provide support for these findings from animal studies. In a small autopsy study of 8 patients with CHF-related renal dysfunction, renal tissue also showed increased interstitial fibrosis, CD68+ immune cells and markers of oxidative stress (Rac1 expression and protein nitrosylation) [22]. Peritubular capillaries were dilated by 35%, believed to be indicative of increased venous pressure in the kidney. In other larger studies, increased central venous or right atrial pressures were associated with impaired renal function and independently related to all-cause mortality in a broad spectrum of patients with cardiovascular disease, including acute and chronic HF [23–25]. This relationship was more pronounced when reduced renal perfusion was also present [25]. As suggested by animal studies, the raised central venous pressure may be transmitted backwards to the renal veins raising renal interstitial pressure, and resulting in subsequent systemic and intra-renal activation of the RAAS and SNS.

Clinical trials in which specific pathophysiologic mechanisms were the therapeutic targets also serve as an important resource for understanding the mechanisms of CRS2. Unfortunately, large randomized clinical trials in CHF focus on cardiovascular mortality and adverse cardiac events, and renal outcomes are usually reported as safety endpoints, if at all. A limited number of studies reported on long-term changes in creatinine or GFR, micro- or macroalbuminuria or other aspects relevant to kidney damage such as markers of fibrosis or of inflammation, some as post hoc analyses (table 2).

Several studies have been carried out in chronic HF aimed to block the RAAS. These have been done both with ACE inhibitors (ACEIs) and angiotensin II receptor blockers (ARBs). The drugs most extensively studied have been enalapril and captopril for ACEIs and valsartan and candesartan for ARBs. In the SOLVD study of enalapril in CHF, the net deterioration of eGFR from baseline to 14 days was slightly greater in the enalapril group compared to

Table 2. Selected clinical trials on chronic heart failure and renal outcomes

Mechanism	Agent	Study	Study population	CKD patients excluded, yes/no
RAAS activation ACEIs/ ARBs	Enalapril	Capes, 2000 SOLVD trial	Clinically stable CHF (LVEF <35%) (n = 6,700)	no
		Testani, 2011, SOLVD		
	Captopril	Ljungman, 1992 CONSENSUS	Heart failure NYHA IV (n = 250)	no
		Hillege, 2003 CATS	Post-MI (n = 298)	no
	Valsartan	Anand, 2009 VALHEFT	Symptomatic heart failure EF <40% (n = 5,000)	yes Cr >2.5
	Candesartan	Jackson, 2009 CHARM-added	Heart failure NYHA II–IV EF <40% (n = 2,500)	no
SNS activation betablockers	Carvedilol	Wali, 2011 COPERNICUS CAPRICORN	Severe heart failure EF <25% (n = 4,200)	no
	Bisoprolol	Damman, 2011 Castagno, 2010 CIBIS II	CHF NYHA III–IV EF <35% (n = 2,660)	no, but substudy conducted in patients with Cr <3.4
	Nebivolol	Cohen-Solal, 2009 SENIORS	Symptomatic CHF Age >70 (n = 2,100)	yes, excluded if Cr >250 µmol/l
Aldoste- rone	Spirono- lactone	Pitt, 1999 Vardeny, 2012 RALES	CHF EF <35% (n = 1,600)	yes, excluded if Cr >2.5 mg/dl
		Zannad, 2001 RALES	Substudy on 261 patients	yes, excluded if Cr >2.5
	Eplerenone	Rossignol, 2012 EPHESUS	HF after MI EF <40% (n = 6,600)	no
		Zannad, 2011 EMPHASIS HF	HF NYHA II EF <35% (n = 2,700)	no
Renal hypoperfusion	Cardiac resynchro- nization	Boerrigter, 2008 MIRACLE	NYHA III–IV EF35% QRS >0.13 (n = 600)	no
	Left ventricle- assisted device	Sandner, 2009	Advanced CHF Bridge to Tx (n = 86)	no
Inflam- mation	Infliximab	Chung, 2003 ATTACH	CHF NYHA III–IV EF <35% (n = 150)	no
	Etanercept	Mann, 2004 RENEWAL	CHF NYHA III–IV EF <30% (n = 2,048)	no

Primary endpoint/ duration of follow-up	Renal outcomes Cr/eGFR	Albuminuria
Composite of CV death and re-admission for HF/48 months	Not stated 14 days decline GFR >20% exited in 20% increase mortality	Decreased proteinuria in diabetic patients, not in non-diabetics Not stated
Crude mortality 6 months	Average initial increase Cr 10–15%	Not stated
Echo ventricular remodeling 1 year	Decline GFR 5.5 in placebo and 0.5 in captopril	Not stated
Mortality + first morbid event 1,000 days	Slight decrease in GFR in valsartan (–3.9 vs. placebo)	Proteinuria associated with 28% increased mortality
CV death Hospital admission 41 months	Not stated	62% increased death in patients with microal- buminuria and 76% with macroalbuminuria. Candesartan did not prevent excessive excreti- on of urinary proteins
All-cause mortality and hospitalization 10 months	Transient increase in serum creatinine more common with carvedilol (4.6 vs. 1.8% in placebo, $p < 0.001$) among CKD patients	Not stated
All-cause mortality hospitalization 18 months	Not stated	Not stated
All-cause mortality hospitalization 30 months	No difference in Δ eGFR between nebivolol and placebo	Not stated
Death of any cause 36 months	WRF 17% in spironolactone vs. 7% placebo but risk of death maintained Cr increase 0.05 to 0.1 after 1 year follow-up	Not stated
Death of any cause 36 months	Not stated Other: markers of collagen synthesis (PINP PICP PIIINP) decreased with spironolactone	Not stated
All deaths hospitalization 24 months	Cr increase 0.06 after 1 year 4.6 after 2 years vs. placebo 2.7	Not stated
All deaths hospitalization 21 months	Cr increase 0.09 at trial cut-off	Not stated
Improved, unchanged, worsened symptom score 12 months	GFR increased 2.7 in patients with GFR 30–60	Not stated
Renal function 6 months	Renal function improves after LVAD implantation	Not stated
Improvement clinical status (NYHA). Death, hospitalization 28 weeks	Not stated	Not stated
Clinical status at 24 weeks. Death, hospitalization	Not stated	Not stated

placebo. While early worsening of renal function was associated with increased mortality in the placebo group, it was free from adverse prognostic significance in the enalapril group [26]. In the same study, diabetic patients showed a decreased proteinuria with enalapril treatment [27]. An additional multivariable analysis suggested that despite a higher incidence of early worsening renal function in the enalapril group, there was no risk of longer term deterioration of eGFR compared with placebo [28]. In the CONSENSUS trial, patients randomized to enalapril showed an average increase in creatinine of 10–15% [29]. Hillege et al. [30] in post-MI patients with HF, although they observed a general deterioration of renal function after the acute event, reported that captopril preserved GFR when compared to placebo. In the VALHEFT trial a slight decrease in GFR in valsartan patients was observed (–3.9 vs. placebo). The presence of dipstick proteinuria was associated with a 28% increase in mortality risk [31]. In the CHARM-Added trial with candesartan, a 62 and 76% increased risk of death was observed in patients with micro- and macroalbuminuria, respectively. Candesartan did not prevent proteinuria [32]. Together, the current state of published evidence remains inconclusive regarding the role of ACEIs or ARBs in the prevention of the progression of CRS2.

CHF treatment with direct inhibitors of aldosterone receptors brought about a significant improvement in terms of survival and hospitalizations. Available data on spironolactone in the RALES trial showed worsening renal function in 17% of treated patients versus 7% in the placebo group, but the benefits on mortality were present in spite of this. Creatinine increased by approximately 0.05–0.1 mg/dl after 1 year follow-up in the spironolactone group with no significant change in the placebo group [33]. In the EPHESUS trial with eplerenone in post-MI patients with CHF, a creatinine increase of 0.06 mg/dl was observed after 1 year and 4.6 mg/dl after 2 years, while the placebo group had only an increase of 2.7 mg/dl. In the EPHESUS trial, eplerenone produced a 0.09 mg/dl increase in creatinine at trial cut-off [34–36]. A decrease in surrogate markers of collagen synthesis (PINP, PICP, PIIINP) after spironolactone treatment suggests that fibrosis could be reduced after anti-aldosterone treatment [37].

It is important to note that a slight, expected, increase in creatinine, particularly in trials with inhibitors of RAAS, does not necessarily mean a progression of the CRS2. Data on survival, symptoms, exercise capacity, proteinuria or albuminuria are clearly visible with these drugs despite a small increase in serum creatinine. It is likely that serum creatinine, as a marker for GFR, is an inadequate biomarker for actual progression of disease given the difficulty in differentiating true progressive CKD from hemodynamic (and therefore potentially reversible) changes in GFR due to RAAS blockade and effects on filtration fraction.

β -Blockers have become first-line treatment for CHF after the publication of COPERNICUS, CAPRICORN and CIBIS trials. In a meta-analysis of the CAPRICORN and COPERNICUS studies, carvedilol was associated with an increased relative incidence in transient increase in serum creatinine without need for dialysis (4.6 vs. 1.8% in placebo, $p < 0.001$) among CKD patients [38]. In the CIBIS trial, GFR was shown to be lower in patients with congestion. Bisoprolol showed greater benefits in patients with CKD (GFR <45) compared to placebo [39] and in this trial β -blocker treatment did not show any increase in serum creatinine. In elderly patients, nebivolol treatment did not modify GFR [40]. Overall there is inconsistency in the data on impact of β -blockers on creatinine in these trials.

Inflammation has been shown to play an important role in the pathophysiology of HF both in terms of progression of cardiac damage and deterioration of the clinical status. Inflammation also plays an important role in the pathogenesis of kidney damage and progression of deterioration of renal function. This observation led several investigators to use TNF- α inhibitors in the treatment of HF. The results of several trials with infliximab or etanercept have been rather disappointing. Indeed either futility or excessive mortality have been shown with these drugs, despite an observed decrease in plasma levels of hsCRP and IL-6. This is corroborated by the results of the ATTACH, RECOVER and RENASSAINCE (RENEWAL) trials [41, 42]. However there are no reports in these trials of renal function.

Hypoperfusion in HF can be improved with cardiac resynchronization or left ventricular assist devices. In one study, cardiac resynchronization increased GFR by 2.7 ml/min in the subgroup of patients with GFR between 30 and 60 [43]. Sandner et al. [44] showed that renal function improves after left ventricular assist device implantation for bridging to cardiac transplantation. In an observational study on 10 children with cyanotic congenital heart disease, urinary excretion of albumin and markers of tubular injury, such as brush-border leucine-aminopeptidase and lysosomal N-acetyl- β -D-glucosaminidase (NAG) decreased significantly after palliative heart surgery. This was paralleled by an improvement in oxygen saturation levels and a decrease in hematocrit to near-normal levels [45].

Biomarkers of Renal Function

To date, assessment of renal dysfunction in clinical HF studies has been largely limited to traditional biomarkers such as creatinine (or its derivative, eGFR) and urine protein and albumin excretion. In CHF, both impaired renal func-

Table 3. Selected studies on novel renal biomarkers in chronic heart failure

Study	Study population	Specimen	Biomarker	HF vs. control subjects
Tang, 2008	Clinically stable CHF outpatients (n = 139)	Plasma	Cystatin C	No controls
Damman, 2008, 2010	Clinically stable CHF outpatients (n = 90)	Urine	NGAL NAG KIM-1	HF > controls HF > controls HF > controls
Jungbauer, 2011	CHF (n = 173)	Urine	NGAL	HF = controls
			NAG	HF = controls
			KIM-1	HF > controls
Poniatowski, 2009	CHF due to CAD (n = 150)	Serum	NGAL Cystatin C	No controls
		Urine	NGAL Cystatin C	
Bolignano, 2009	CHF (elderly, age >65 years) (n = 46)	Serum	NGAL	HF > controls
Yndestad, 2009	CHF (n = 150)	Serum	NGAL	HF > controls
Shrestha, 2011	CHF (LVEF ≤35%) (n = 130)	Plasma	NGAL	No controls

CAD = Coronary artery disease; CHF = chronic heart failure; Cr = creatinine; GFR = glomerular filtration rate; HF = heart failure; NS = not stated.

tion (as indicated by elevated creatinine or decreased eGFR) and increased urinary albumin excretion are powerful and independent predictors of prognosis [32, 46]. Both are associated with heightened risk for death, cardiovascular death, and hospitalization, in patients with both preserved as well as reduced LVEF. In CKD, the level of eGFR and albuminuria has been shown to be prognostic of long-term renal outcomes [47, 48]; this has not been demonstrated in CHF [49]. More recently, novel renal biomarkers, such as cystatin C (CysC), NGAL, KIM-1, and NAG have also been studied in CHF patients [50–57] (table 3). In many, but not all, studies, levels of these biomarkers are modestly elevated in CHF compared to control subjects, even among those with apparently normal renal function. While some of these biomarkers appear to have some prognostic properties with regard to adverse cardiovascular events, no study has looked at long-term change in renal function as an outcome.

Plasma CysC, believed to be a more sensitive marker of impaired GFR compared to creatinine, has been reported as an independent predictor of death,

Biomarker correlates with (in HF patients only)			Renal outcomes
renal function	clinical HF severity	natriuretic peptides	
Yes	Yes	Yes	NS
No	NS	No	NS
Yes	NS	Yes	NS
No	NS	Yes	NS
Yes, with albuminuria	No	No	No association with diuretic dose
No, with Cr/eGFR	Yes	Yes	Elevated in patients on higher (vs. lower) diuretic doses
Yes, with albuminuria	Yes	Yes	Elevated in patients on higher (vs. lower) diuretic doses
No, with Cr/eGFR			
Yes	Yes	NS	NS
Yes	NS	NS	NS
Yes	Yes	NS	NS
NS	NS	NS	NS
No	Yes	NS	NS
NS	Yes	Yes	NS
Yes	Yes	Yes	

cardiac transplantation and HF hospitalizations [52, 54]. CysC also correlated with NT-pro-BNP levels and measures of LV dysfunction [52]. Studies assessing urinary CysC levels in CHF populations are currently lacking.

Recently, a systematic review summarized studies on NGAL in a spectrum of cardiovascular diseases, including CHF [50]. Animal and human tissue studies demonstrated that NGAL is highly expressed in failing myocardium and myocarditis, and it is also expressed in atherosclerotic plaques. Data on NGAL in a CRS2 rat model have been also been discussed above [18]. In clinical studies, blood and urine NGAL levels generally correlate with creatinine or eGFR; they also correlate with clinical and biochemical markers (e.g. natriuretic peptides) of HF severity in some, but not all, studies [50]. Systemic NGAL levels have also been associated with increased mortality and HF hospitalization [50, 53, 55, 58, 59].

Analogous findings have also been reported for NAG and KIM-1. Urine levels of KIM-1, but not NAG or NGAL, are elevated in symptomatic HF compared to controls [60]. KIM-1 and NAG levels correlated with severity of

HF, and were also predictors of all-cause mortality and HF hospitalization on survival curve analysis. In 2,130 patients participating in the GISSI-HF trial, CHF patients who experienced a composite outcome of death or HF hospitalization had a significantly lower eGFR and a significantly higher urinary excretion of albumin, NAG, KIM-1, and NGAL [53]. On multivariable regression, the strongest association was seen with urinary NAG.

Although data on novel renal biomarkers in CHF is limited to date, they have great potential to enhance our understanding of CRS2 pathophysiology and should be evaluated in future large randomized controlled trials in HF. Indeed, the MinerAlocorticoid Receptor Antagonist Tolerability Study (ARTS) will examine the effects of the non-steroidal, mineralocorticoid receptor antagonist BAY 94-8862 on biomarkers of cardiac and renal function and injury, including the natriuretic peptides, KIM-1, NGAL, and CysC [61]. Results from this small study will undoubtedly inform future CRS2 trials.

Conclusion

In CRS2, the HF temporally precedes the occurrence or progression of CKD, and the manifestation and degree of kidney disease is plausibly explained by the underlying heart condition. Multiple and complex mechanisms have been proposed for CRS2; the most predominant being systemic and local renal increases in SNS and RAAS activation, hemodynamic factors of renal hypoperfusion and venous congestion, and inflammatory pathways. Animal models provide important insight into the pathogenesis of CRS2 by mimicking human phenotypes. Of the multitude of randomized controlled trials in CHF, relatively few reported long-term renal outcomes. While increased risk of kidney functional decline has been reported in some studies of RAAS inhibitors, most of the difference seen at the end of follow-up appeared to be attributable to the early treatment period. To date, renal outcomes have been largely limited to traditional biomarkers such as creatinine, eGFR, and urinary albumin excretion. Novel renal biomarkers appear to have some prognostic properties with regard to adverse cardiovascular events in CHF patients, but no study has looked at long-term change in renal function as an outcome. Ongoing and future interventional trials incorporating biomarkers of cardiac and renal function and injury among the endpoints will enhance our understanding of the pathophysiologic mechanisms behind CRS2.

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