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Review

Cardiorenal Syndrome and Heart Failure—Challenges and Opportunities

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ABSTRACT

Cardiorenal syndromes (CRS) describe concomitant bidirectional dysfunction of the heart and kidneys in which 1 organ initiates, perpetuates, and/or accelerates decline of the other. CRS are common in heart failure and universally portend worsened prognosis. Despite this heavy disease burden, the appropriate diagnosis and classification of CRS remains problematic. In addition to the hemodynamic drivers of decreased renal perfusion and increased renal vein pressure, induction of the renin-angiotensin-aldosterone system, stimulation of the sympathetic nervous system, disruption of balance between nitric oxide and reactive oxygen species, and inflammation are implicated in the pathogenesis of CRS. Medical therapy of heart failure including renin-angiotensin-aldosterone system inhibition and β-adrenergic blockade can blunt these deleterious processes. Renovascular disease can accelerate the progression of CRS. Volume overload and diuretic resistance are common and complicate the management of CRS. In heart failure and CRS being treated with diuretics, worsening creatinine is not associated with worsened outcome if clinical decongestion is achieved. Adjunctive therapy is often required in the management of volume overload in CRS, but evidence for these therapies is limited.

RÉSUMÉ

Le syndrome cardiorénal (SCR) est caractérisé par une dysfonction bidirectionnelle et concomitante du cœur et des reins dans laquelle l'un de ces deux organes déclenche, perpétue et/ou accélère le déclin de l'autre. Le SCR est fréquent dans l'insuffisance cardiaque et, dans tous les cas, laisse présager un pronostic plus défavorable. Malgré le lourd fardeau du SCR, son diagnostic et sa classification demeurent difficiles. Outre les causes hémodynamiques comme la diminution de l'irrigation rénale et l'augmentation de la pression dans la veine rénale, d'autres facteurs comme l'induction du système rénine-angiotensine-aldostérone, la stimulation du système nerveux sympathique, la perturbation de l'équilibre entre l'oxyde nitrique et le dérivé réactif de l'oxygène et l'inflammation jouent également un rôle dans la pathogenèse du SCR. Le traitement médical de l'insuffisance cardiaque, y compris par l'inhibition du système rénine-angiotensine-aldostérone et le blocage des récepteurs bêta-adrénergiques, peut atténuer ces processus délétères. La maladie rénovasculaire peut accélérer la progression du SCR. La surcharge volémique et la résistance diurétique sont fréquentes et compliquent la prise en charge du SCR. Lorsque l'insuffisance cardiaque et le SCR sont traités par des

Cardiorenal syndromes (CRS) is an all-encompassing term that describes the complex interplay between concomitant cardiac and renal dysfunction in which disease of 1 organ initiates, perpetuates, and/or accelerates decline in the other. In the setting of heart failure, CRS comprise one-quarter to one-third of presentations and universally portend worse clinical outcomes.[1-7] Accordingly, there is considerable interest in the appropriate classification, diagnosis, and management of CRS in heart failure.[7,8] In this review, we describe challenges related to the classification of CRS, pathophysiological mechanisms leading to CRS, and clinical considerations in the management of patients with heart failure and concomitant renal dysfunction.

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Diagnosis of CRS

A widely published classification scheme separates CRS into 4 categories on the basis of the primary organ driving bidirectional dysfunction and the acuity of decline, as well as a fifth category describing CRS occurring in the presence of

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Anemia and iron deficiency are importantly associated with CRS and might amplify decline of cardiac and renal function. End-stage cardiac and/or renal disease represents an especially poor prognosis with limited therapeutic options. Overall, worsening renal function is associated with significantly increased mortality. Despite progress in the area of CRS, there are still multiple pathophysiological and clinical aspects of CRS that need further research to eventually develop effective therapeutic options.

diurétiques, l'élévation du taux de créatinine n'est pas associée à une aggravation du problème si une décongestion clinique peut être obtenue. Un traitement d'appoint est souvent nécessaire pour contrer la surcharge volémique dans le SCR, mais les données probantes sur l'efficacité d'un tel traitement sont rares. L'anémie et la carence en fer sont associées de façon importante au SCR et pourraient amplifier le déclin des fonctions cardiaque et rénale. L'insuffisance cardiaque et l'insuffisance rénale terminales ont un pronostic particulièrement défavorable et leurs options thérapeutiques sont très limitées. Dans l'ensemble, la détérioration de la fonction rénale est associée à une augmentation significative de la mortalité. Malgré les progrès réalisés dans le traitement du SCR, il subsiste de multiples facettes de cette affection, tant physiopathologiques que cliniques, qui devraient faire l'objet de recherches dans le but de trouver des options thérapeutiques efficaces.

systemic disease (Table 1).[9,10] However, this classification scheme has not resulted in a change in clinical practice or research directions[11] and there are several noteworthy shortcomings that limit its utility.[12] Primarily, heterogenous characterizations of renal and cardiac dysfunction are ubiquitous. Three commonly cited classification systems, the Kidney Disease: Improving Global Outcomes Clinical Practice Guideline for Acute Kidney Injury,[13] Acute Dialysis Quality Initiative Risk, Injury, Failure, Loss, and End-stage renal disease criteria,[14] and the Acute Kidney Injury Network classification[15] have been used to define acute kidney injury (AKI) in the nephrology literature. Further complicating assessment of renal injury, absolute and percentage increases in creatinine have been used to define renal impairment or worsening renal function in numerous heart failure studies.[16] Although unifying criteria have been proposed, widespread acceptance remains elusive to date.[3] A failure of this classification scheme to highlight the mechanisms of action further restricts its utility. Although the same organ might be affected by an insult, pathophysiological drivers, and thus response to therapy, can widely differ between precipitants of CRS. Moreover, in acute presentations it can be difficult to ascertain temporal relationships between cardiac and renal dysfunction.[4] Finally, the classification does not exclude patients with criteria that would obfuscate the clinical picture, such as patients with severe gastrointestinal bleeding.

These challenges have led researchers to identify biomarkers that might have utility in the diagnosis of CRS. In the Neutrophil **G**elatinase-**A**ssociated **L**ipcalin (NGAL) Eva**l**uation **A**long With B-type **Na**triuretic Peptide in Acutely Decompensated Heart Failure (GALLANT; ClinicalTrials.gov identifier: NCT00693745) trial the utility of plasma neutrophil gelatinase-associated lipocalin (NGAL; a measure of AKI), was evaluated in acute heart failure (AHF).[17] Plasma NGAL was a strong prognostic biomarker for rehospitalization for heart failure within 30 days.[17] On a short-term basis (ie, 48-72 hours after presentation), NGAL was independently associated with worsening renal function in patients with AHF.[18] However, the utility of plasma NGAL above creatinine was called into question in a subsequent trial.[19] In chronic heart failure, increased levels of urinary kidney injury molecule-1 (KIM-1), N-acetyl-β-D-glucosaminidase (NAG), and NGAL are associated with worsening renal function, which portends poor prognosis.[20] Interestingly, KIM-1 and NAG can be elevated in heart failure patients with normal kidney function on the basis of creatinine, suggesting that some patients might be developing renal injury, particularly tubular damage, in the context of heart failure without a decline in glomerular filtration rate (GFR).[21] Indeed, elevated excretion of NAG and KIM-1 was associated with progression of chronic kidney disease (CKD) in heart failure patients.[22] Further research is needed to establish whether these biomarkers might be useful in establishing the chronicity of declining renal function, differentiating tubular injury from a rise in creatinine without true injury, and identifying patients who have tubular injury in chronic heart failure despite normal kidney function.

Pathophysiology of CRS

The interaction between the heart and kidneys in CRS has been the subject of considerable interest but mechanistic pathways have yet to be fully elucidated.[12] Hemodynamic factors, previously thought to be sole contributors to the CRS, cannot fully explain observed clinical consequences.[12] Indeed, outpatients with heart failure without significant hemodynamic derangements suffer from a greater rate of estimated GFR (eGFR) decline than would be expected from aging alone.[23] The other major pathophysiological mechanisms linking the heart and the kidneys have been denoted as cardiorenal connectors. These include activation of the renin-angiotensin-aldosterone system (RAAS), stimulation of the sympathetic nervous system (SNS), inflammation, and dysregulation of the balance between nitric oxide (NO) and reactive oxygen species (ROS; Fig. 1).[8] There is significant interplay between these cardiorenal connectors, allowing them to potentiate each other and further disrupt cardiac and renal function. Fibrosis, a common result of inflammation and oxidative stress, is also a marker of more severe irreversible heart failure and CKD, which has led some authors to label it as a key driver in the pathophysiology of CRS.[11]

Table 1. Classification of CRS

Classification	Timing	Primary organ affected	Description	Examples of disease states
CRS type 1 (acute cardiorenal)	Acute	Heart	Acute heart failure causing acute kidney injury	• Acute decompensation of chronic heart failure • Acute heart failure secondary to ischemia, valvulopathy, or dysrhythmia • Isolated right heart failure
CRS type 2 (chronic cardiorenal)	Chronic	Heart	Chronic heart failure causing chronic kidney disease	• Chronic heart failure
CRS type 3 (acute renocardiac)	Acute	Kidneys	Acute kidney injury leading to acute heart failure	• Urinary tract obstruction • Acute renal failure (eg, glomerulonephritis) • Renal transplantation • Bilateral renal artery stenosis
CRS type 4 (chronic renocardiac)	Chronic	Kidneys	Chronic kidney disease leading to chronic heart failure	• Chronic kidney disease
CRS type 5 (systemic disease)	Acute or chronic	Heart and kidneys	Systemic disease causing concomitant heart failure and kidney disease (acute or chronic)	• Sepsis • Diabetes mellitus • Cirrhosis • Infiltrative disease • Vasculitis

CRS, cardiorenal syndrome.
Data from Ronco et al.[10]

Hemodynamic Factors

Classically, inadequate renal perfusion due to decreased cardiac output was thought to be primary precipitant of worsening renal function in CRS.[24] However, it is now recognized that decreased cardiac output and venous congestion are hemodynamic contributors to CRS.[25] In situations such as severe sepsis, decreased renal perfusion due to excessive vasodilatation is an important precipitant of CRS. In contrast, most patients with heart failure maintain adequate renal perfusion yet are still susceptible to worsening renal function and CRS. On the basis of this observation and a wealth of data, venous congestion is now recognized as a primary hemodynamic precipitant of worsening renal function.[26] Increasing right atrial pressure results in altered flow patterns in renal veins.[27] Clinically, elevated central venous pressure is associated with decreased renal function and worsening prognosis in heart failure.[26,28] Specifically, increased renal vein pressure increases interstitial and tubular hydrostatic pressure and induces strong renal vasoconstriction, leading to decreased renal blood flow and glomerular filtration.[29,30] Worsening renal function precipitates further volume overload, which can, in turn, lead to increased central venous pressure and increased renal venous pressure. Importantly, merely the presence of altered intrarenal venous flow patterns, independent of right atrial pressure, also correlate with clinical outcomes in heart failure.[31] Altogether the association between systemic congestion with increased renal vein pressure as a consequence and worsening renal function is now well established. It remains to be elucidated, however, how increased renal vein pressure leads to renal vasoconstriction. An extended discussion regarding diuresis to control volume overload is presented later in this review.

RAAS

Activation of the RAAS is a feature of heart failure and CKD.[8,32] Decreased renal perfusion is sensed by the juxtaglomerular apparatus, resulting in secretion of renin into the circulation via the juxtaglomerular cells. Subsequently, angiotensin II is produced, which, in turn, stimulates the adrenal cortex to release aldosterone. Activation of the RAAS has numerous physiologic consequences in the human body, including peripheral vasoconstriction, increased sodium and water retention, and activation of the SNS.[8] In addition, increased RAAS activity has been observed after experimentally increased renal vein pressure.[33] In heart failure, activation of the RAAS can decrease cardiac energy supply and cardiac efficiency.[34] Chronically elevated aldosterone levels are implicated in myocardial and renal fibrosis.[35]

Importantly, the RAAS has a significant effect on other cardiorenal connectors. RAAS activation results in increased activity of the SNS through central stimulation to increase sympathetic outflow, adrenally-mediated effects, and local activation at sympathetic nerve endings.[36] Increased levels of inflammatory biomarker tumour necrosis factor in patients with chronic heart failure are associated with activation of the RAAS.[37] Furthermore, mineralocorticoid excess is associated with activation of the inflammatory cascade, which ultimately leads to cardiac and renal fibrosis.[38] Chronic activation of RAAS impairs mitochondrial function and increases oxidative stress.[39] Activation of the RAAS increases myocardial nicotinamide adenine dinucleotide phosphate (NADPH) oxidase activity, disrupting the balance between NO and ROS in the myocardium, resulting in heart failure.[40,41]

RAAS blockade, in the form of angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers, or mineralocorticoid receptor antagonists, is an integral component in the management of heart failure and CKD.[24] In heart failure, RAAS blockade prevents excessive sodium reabsorption and adverse cardiac remodelling.[42] In patients with renal failure, RAAS blockade reduces sympathetic hyperactivity, further supporting the previously described interplay between cardiorenal connectors.[43,44] Although adverse effects of RAAS blockade such as hypotension and hyperkalemia can complicate management of patients, a clear mortality benefit of RAAS blockade in heart failure has been shown in numerous

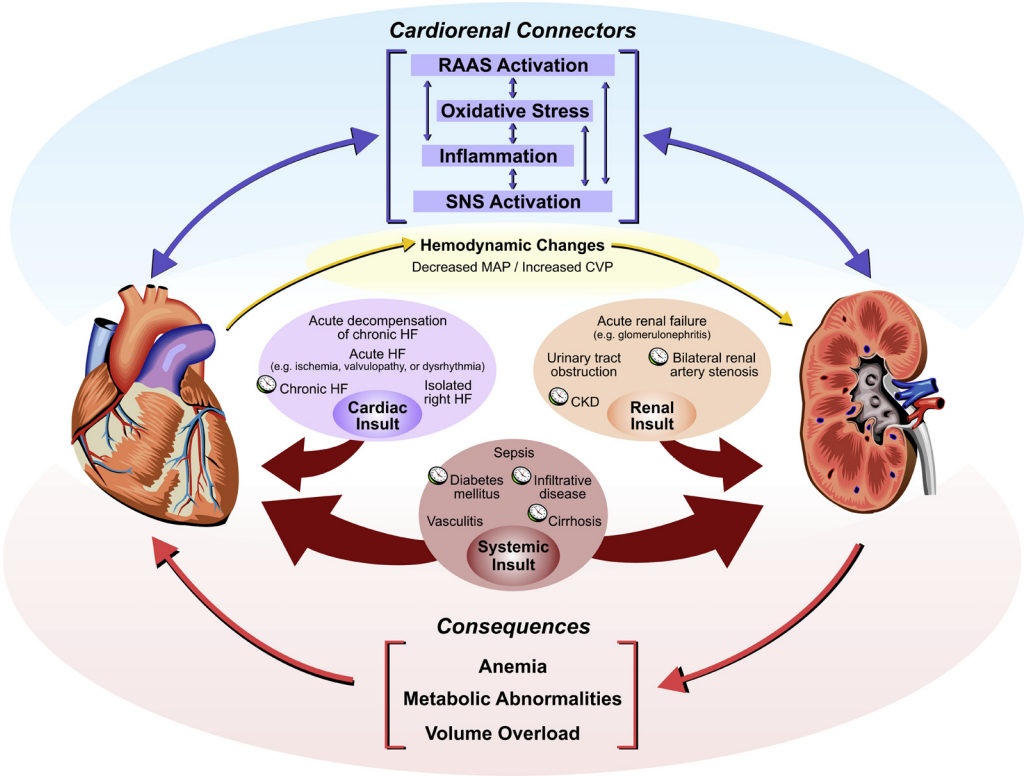

Figure 1. A schematic depiction of the cardiorenal syndrome. Cardiac, renal, or systemic insults result in dysfunction of the heart and/or kidneys. Clocks are used to denote conditions that typically present chronically. The cardiorenal connectors mediate cross-talk between the heart and the kidneys, causing concomitant organ dysfunction. Cardiac dysfunction results in hemodynamic changes, which results in renal dysfunction. The consequences of cardiorenal syndrome include anemia, metabolic abnormalities, and volume overload. CKD, chronic kidney disease; CVP, central venous pressure; HF, heart failure; MAP, mean arterial pressure; RAAS, renin-angiotensin-aldosterone system; SNS, sympathetic nervous system.

clinical trials.[6] In CKD, RAAS inhibition results in lower proteinuria and a decreased rate of GFR decline in a wide range of patients.[45] Despite these benefits in isolated heart or renal failure, there is a surprising dearth of studies in well defined cardiorenal patients on the effect of initiation, maintenance, or cessation of RAAS blockade on renal function, diuresis, and other clinical outcomes. The ACE 2/angiotensin 1-7 axis has emerged as the protective arm of the RAAS and is protective in the cardiovascular and renal systems suggesting that clinical trials with these agents are warranted.[46,47]

SNS

Overactivation of the SNS is a feature common to heart failure and CKD.[48,49] In chronic heart failure, the SNS is activated by suppression of inhibitory cardiovascular reflexes including the arterial baroreceptor reflex, augmentation of the excitatory cardiovascular reflexes such as the arterial chemoreceptor reflex, and alterations in the central nervous system response to these aforementioned reflexes; these changes result in the induction of apoptosis, oxidative damage, and chronic adverse cardiac remodelling.[48] Heart failure itself is associated with increased renal norepinephrine spillover.[50] In the kidney, excess sympathetic drive is also precipitated by renal ischemia, chemoreflex activation, and/or NO imbalance, which results in sodium retention, decreased renal blood flow, and increased plasma renin.[49,51] In CKD, the heart becomes desensitized to the action of β-adrenergic stimulation.[52] Overall, increased renal sympathetic activity is associated with decreased GFR and left ventricular (LV) ejection fraction.[53] SNS hyperactivity can potentiate other cardiorenal connectors by inducing inflammation via increased cytokine production in the liver and heart, increasing ROS production, and directly stimulating the RAAS via renin release.[8] Inappropriate activation of the RAAS in CKD is considered a primary driving force for activation of the SNS, resulting in a vicious circle of deleterious RAAS and SNS activation.

Numerous trials in heart failure have shown the significant benefit of blunting SNS overactivation by β-blockade, and, accordingly, β-blockers remain an integral component of the medical management of heart failure.[6] With regard to other non-β-blocker agents, the **Mox**onidine **Con**gestive Heart Failure (MOXCON; unlisted on ClinicalTrials.gov) trial examined the use of the sympatholytic drug moxonidine in heart failure patients.[54] The trial was prematurely terminated because of increased morbidity and mortality, suggesting that central sympathetic inhibition in heart failure might be deleterious.[54] In contrast, renal denervation might improve left ventricular LV hypertrophy and diastolic dysfunction in hypertensive patients independent of an antihypertensive effect.[55] Emerging data suggest that renal denervation improves symptoms and LV function in heart failure with reduced

ejection fraction patients, whereas improvements in surrogate end points might be expected in heart failure with preserved ejection fraction patients.[56] However, the failure of renal denervation to improve outcomes in resistant hypertension has dampened enthusiasm for this potential therapy.[57] Of note, vagal nerve stimulation and baroreceptor activation trials have shown equivocal results thus far.[58] Similar benefits of SNS inhibition appear to be present in the kidney, but strong clinical data are lacking. Independent of blood pressure, β-blockade reduced the progression of glomerulosclerosis in rats.[59] In humans, studies involving β-blockers and CKD have shown benefit only when used as an antihypertensive agent, and was inferior to RAAS blockade.[60] Otherwise, there is weak evidence that renal denervation and the aforementioned sympatholytic drug moxonidine could be renoprotective in patients with CKD.[61,62] Unfortunately, there are no trials regarding SNS inhibition in well defined cardiorenal patients; further research is needed to explore the therapeutic potential of interrupting nervous system traffic in the various CRS.

Inflammation

CKD, especially end-stage renal disease, and chronic heart failure are associated with elevation of proinflammatory cytokines, which portends worse outcomes.[37,63-66] Indeed, worsening heart failure correlates with increased levels of proinflammatory cytokines.[67] Traditional sources of proinflammatory cytokines include production by circulating cells, particularly monocytes, and locally by the heart and kidneys in response.[63] More recently, it has been shown that venous congestion and/or intestinal ischemia can lead to endotoxin absorption from the bowel and subsequent systemic inflammation.[68] Protein-bound uremic toxins induce inflammation in endothelial cells through multiple mechanisms.[69] Regardless of the source, inflammation is at the basis of progression of endothelial dysfunction and vascular disease.[70] Inflammation causes local oxidative stress at the endothelium, disrupting the endothelial barrier and causing tissue injury.[70] Worsening inflammation is associated with progression of cardiovascular and renal disease.[64,68] In heart failure, worsening inflammation causes cardiomyocyte apoptosis.[71] Elevated C-reactive protein concentrations are associated with increased all-cause and cardiovascular mortality in uremic patients.[72] An evolving paradigm implicates inflammation in the pathogenesis of heart failure with preserved ejection fraction,[73] as well as concomitant renal dysfunction.[74,75]

Inflammation can potentiate the other cardiorenal connectors. Inflammation can cause the release of renin, activating the RAAS.[8] Cytokine production activates the SNS by increasing serum norepinephrine concentrations.[8] Finally, inflammation causes release of ROS from leukocytes.[76] However, directed anti-inflammatory therapies have yet to improve outcomes in cardiovascular and renal disease. The **A**nti-**T**NF **T**herapy **A**gainst **C**ongestive **H**eart Failure (ATTACH; unlisted on ClinicalTrials.gov) trial examined the effect of the anti-tumour necrosis factor drug infliximab in patients with heart failure and showed no benefit and potential harm with higher doses of the drug.[77] A similar trial has not been conducted to date in CKD. Because of the heterogeneous effects of cytokines and potential adverse events, it is understandable that anti-inflammatory therapies in CRS are limited; further studies are needed to identify potential therapeutic targets to decrease inflammation in patients with combined heart and kidney failure.

Oxidative Stress, NO, and Antioxidant Capacity

Another crucial mechanism involved in combined heart and kidney failure is the balance between oxidative stress, NO, and antioxidant forces. Increased ROS production results in increased NADPH oxidase and xanthine oxidase activity, as well as NO synthase uncoupling.[8] Heightened NADPH oxidase activity is correlated with myocardial oxidative stress.[41] Increased endothelium-bound xanthine-oxidase activity results in vascular oxidative stress and endothelial dysfunction in patients with heart failure.[78] Diminished antioxidant capacity is also a major component of CKD,[79] and, in conjunction with inflammation, can contribute to cardiovascular complications.[80] Uremic solutes such as β-2 microglobulin, cysteine, homocysteine, and advanced glycosylated end products cause oxidative injury, whereas malnutrition and loss via dialysis can diminish levels of antioxidants.[8] Overall, oxidative stress is implicated in the pathogenesis of heart failure,[41] promotes endothelial dysfunction,[24] and induces cardiomyocyte apoptosis.[71]

NO-ROS imbalance also potentiates other cardiorenal connectors. Oxidative stress can activate the SNS, increasing heart rate and blood pressure.[8] Importantly, oxidative stress damages proteins, carbohydrates, and lipids and initiates an inflammatory response by increasing production and activation of proinflammatory cytokines, causing endothelial dysfunction.[8,81] Finally, oxidative damage to renal tubular or interstitial cells might impair feedback mechanisms, causing increased RAAS activity.[82] Animal studies have shown that NO reduction causes permanent cardiac and renal dysfunction in CKD.[83] Conversely, an NO donor was shown to ameliorate the cardiac dysfunction in an animal model of CRS.[84] Although therapies to diminish oxidative stress and improve cardiac and renal dysfunction have been evaluated in trials, there is no solid evidence in the setting of combined heart and kidney failure. The association of xanthine oxidase activity with endothelial dysfunction has led to the evaluation of this therapeutic option in heart failure patients,[85] and might represent a potential target in CRS. As with the other cardiorenal connectors, more research is needed to identify new therapeutic options to limit oxidative stress in patients with CRS.

Renal Artery Stenosis

Atherosclerotic renal artery stenosis is a common cause of CKD, secondary hypertension, and heart failure and represents a prototypical potentiator of CRS.[86,87] Situations in which renal artery stenosis should be considered and diagnosis is reviewed elsewhere.[88] Bilateral renal artery stenosis can present with flash pulmonary edema, also known as Pickering syndrome, and hypertensive heart failure, and is independently associated with decreased survival.[89-91] Bilateral renal artery stenosis leads to decreased renal perfusion and subsequent activation of the RAAS and SNS, which eventually result in sodium retention, resistant hypertension, renal injury, and, ultimately, heart failure.[92] Approximately 75% of

patients with atherosclerotic renal artery stenosis have diastolic dysfunction and only 5% have normal cardiac structure and function.[93] Revascularization procedures in patients with bilateral renal artery stenosis failed to improved outcomes over medical therapy in several trials.[94-96] However, these trials were underpowered to discriminate whether there could be benefit in patients with flash pulmonary edema, resistant hypertension, or progressive renal decline. Accordingly, Canadian guidelines reserve revascularization for patients for these specific indications.[88]

Management of Consequences of CRS: Volume Overload

Volume overload is a consequence of CRS. Because worsening volume overload results in increasing central venous pressure and renal vein pressure, management of volume overload is an important therapeutic goal in the management of heart failure with CRS. Loop diuretics are first-line therapy for relieving symptoms of congestion and improving venous hemodynamics[97] but can be complicated by diuretic resistance, especially in the presence of CRS.[98] Although new treatment pathways involving relative blood volume measurement, bioimpedance vector analysis, and other monitoring devices are emerging, the optimal diuretic strategy in CRS has yet to be elucidated.[7] Specifically, the evidence to guide choice of diuretic, mode of administration, use of adjunctive medications such as ACE inhibitors, and role of device therapy is lacking.

Universal measures for patients with CRS and volume overload include nonpharmacologic therapies and medication review. Dietary sodium and fluid restriction have been considered a cornerstone of therapy for AHF, especially in the setting of chronic renal disease, and has been extrapolated to patients with CRS. Despite a potential physiological basis for this recommendations, the benefit of these interventions is inconclusive[99]; Canadian heart failure guidelines make weak recommendations regarding dietary sodium and fluid intake.[6] Definitive studies are required to guide the management of patients with CRS. In presentations complicated by hypotension, discontinuation of antihypertensive medications is warranted, along with potential initiation of vasoactive medications. Nonsteroidal anti-inflammatory drugs and other medications known to increase the risk of heart failure should be discontinued.[100]

Although preservation of renal function has been classically described as a target in management of AHF,[101] there is increasing evidence that holding or decreasing diuretics in the face of apparent worsening renal function to prevent further renal decline via optimization of the Frank-Starling curve to maintain cardiac output might be deleterious.[102] As described previously, it is in fact renal venous congestion that is the primary driver of AKI in heart failure, rather than decreased effective circulating volume.[26] Indeed, multiple studies in AHF have shown that rising creatinine level alone is not independently associated with worsening clinical outcomes; it is only deleterious when there is persistent evidence of congestion.[103,104] Patients with good diuretic response have improved clinical outcomes, but, interestingly, worsening renal function was noted in patients with the best and worst response to diuretics.[105] This paradigm shift has led some authors to suggest new terminology such as pseudo-AKI or pseudo-worsening renal function to denote situations in which creatinine level rises and GFR declines without true renal injury (Table 2).[3] In patients with CRS, clinical signs of congestion should supersede rising creatinine level.[97]

In AHF with CRS, there are currently no trials available that have examined the effect of loop diuretics on the cardiorenal interaction. Therefore, diuresis in heart failure with CRS has defaulted to extrapolating data from heart failure with or without concomitant renal dysfunction. In the **D**iuretic **O**ptimization **S**trategies **E**valuation (DOSE; ClinicalTrials.gov identifier: NCT00577135) trial continuous infusion of loop diuretics vs intermittent boluses were compared; at 72 hours, continuous infusion made no significant difference in global assessment of symptoms or mean change in creatinine level, relative to intermittent boluses.[106] Further studies specifically in patients with CRS are needed to examine if loop diuretics and the achievement of euvolemia can modify the cardiorenal interaction.

Diuretic resistance in patients with AHF is associated with hypotension, worsening renal function, decreased urine output, increased risk of rehospitalization, and increased risk of death.[97,105,107,108] Major mechanisms of diuretic resistance include compensatory distal reabsorption of sodium[109] and activation of the RAAS and the SNS.[110,111] Although diuretic resistance remains a major problem, there are limited clinical trial data on the efficacy of adjuncts to loop diuretic therapy. Classically, thiazide-like diuretics (eg, metolazone), which act at the distal convoluted tubule, were used in addition in cases of resistant heart failure.[112] However, some data suggest that uptitration of loop diuretics is initially preferred over the additional use of thiazide-like diuretics because of an increased prevalence of hypokalemia, hyponatremia, worsening renal function, and increased mortality after propensity adjustment with the latter strategy.[113] Several classes of medications that precipitate diuresis have been trialed in the management of diuretic-resistant AHF. Mineralocorticoid receptor antagonists, vasopressin antagonists, dopamine, and natriuretic peptides have all been evaluated in heart failure with poor results, but not specifically in CRS.[114-116] Vasopressin antagonists in particular, such as tolvaptan, have been used in patients with severe hyponatremia,[97] but otherwise do not improve morbidity or mortality in AHF.[115] Although poorly studied in patients with heart failure and CRS, increased intra-abdominal pressure might contribute to diuretic resistance and is correlated with renal dysfunction in patients with heart failure, presumably via diminished capacitance of splanchnic vasculature.[117] Clearly, further study is needed to determine whether increased abdominal pressure is an important consideration in CRS and whether compartment volume removal is beneficial in these patients.

Extracorporeal therapy is a potentially useful adjunct to diuretic therapy in patients with heart failure, particularly in patients with advanced renal dysfunction with significant resistance to diuretic therapy. Various trials of ultrafiltration in heart failure alone have shown limited benefit.[118-120] Nevertheless, some authors have argued that the failure of ultrafiltration to clearly show superiority in these previous trials is attributable to infrequent hemodynamic measurement and suboptimal tailoring of ultrafiltration therapy.[121] European guidelines suggest that a high score ($\geq$ 12) during objective

Table 2. Suggested definitions of worsening renal function and acute kidney injury

Term and setting	Measure	Temporality	sCr or eGFR	Other criteria
AKI (acute HF)	Relative sCr	Within 1-7 days before or during hospitalization	• Increase 1.5-1.9 times baseline sCr within 1-7 days before or during hospitalization	Deterioration in heart failure status or failure to improve or requirement of inotropic support, UF, or RRT
	Absolute sCr	Within 48 hours	• $\geq$ 26.5 mmol/L increase in sCr	Deterioration in heart failure status or failure to improve or requirement of inotropic support, UF, or RRT
	Urine output	Over 6-12 hours	• Urine output $<$ 0.5 mL/kg/h	Deterioration in heart failure status or failure to improve or requirement of inotropic support, UF, or RRT
Pseudo-AKI (acute HF)	Multiple	Within 1-7 days before or during hospitalization	Not meeting AKI criteria*	
WRF (Chronic HF)	Absolute and relative sCr	Over 1-26 weeks	• $\geq$ 26.5 mmol/L and $\geq$ 25% increase in sCr	Deterioration in HF status but not leading to hospitalization
	eGFR	Over 1-26 weeks	• $\geq$ 20% decrease in eGFR	Deterioration in HF status but not leading to hospitalization
Pseudo-WRF	Multiple	Over 1-26 weeks	Not meeting WRF criteria*	

AKI definitions do not include eGFR because eGFR calculations assume steady-state renal function.

AKI, acute kidney injury; eGFR, estimated glomerular filtration rate; HF, heart failure; RRT, renal replacement therapy; sCr, serum creatinine; UF, ultrafiltration; WRF, worsening renal function.

* Damman et al.[3] suggest that doubling or a $>$ 88.4 μmol/L rise in serum creatinine should trigger further investigation even if falling into the pseudo-AKI or pseudo-WRF categories.

Modified from Damman et al.[3] with permission from Oxford University Press.

assessment of congestion during diuretic therapy and decreased urine output ($<$ 1000 mL in 24 hours) is indicative of diuretic resistance and an indication for ultrafiltration.[122] Further research regarding ultrafiltration in the management of heart failure and CRS, especially in context of diuretic resistance, is warranted.

Essentially, there is distinct lack of evidence to help guide the management of volume overload in CRS. Further trials on choice of diuretic, diuretic regimen, adjunct medications (eg, RAAS inhibition), and the use of ultrafiltration in well defined cardiorenal patients would perhaps shed light on this clinically challenging area.

Anemia, Erythropoietin, and Iron Deficiency

Anemia, along with erythropoietin deficiency and resistance, in CKD represents a potential cardiorenal connector.[123] Indeed, some authors have proposed the existence of a cardiorenal anemia syndrome on the basis of worsening mortality in heart failure patients with coexisting renal dysfunction and anemia.[124] Erythropoietin receptors are present in the heart, kidney, and vascular system, and, accordingly, erythropoietin has notable effects outside of its role in erythropoiesis. Erythropoietin has several effects on the aforementioned cardiorenal connecters: it can modulate NO release, diminish ROS, dampen inflammation, and might diminish RAAS activation.[123]

The prevalence of anemia in the setting of chronic heart failure is difficult to estimate because of varying definitions but is likely close to 50%,[125-127] and is even more common in patients with acute decompensated heart failure.[128] Anemia is associated with increased mortality in chronic heart and renal failure patients.[126,129,130] There are many mechanisms implicated in the anemia observed in heart failure and its associated deleterious outcomes but little is known about iron handling in these patients. Conflicting evidence shows the potential benefit for parenteral iron therapy for patients with heart failure.[131-134] With regard to erythropoietin, although hematocrit levels are associated with improved cardiovascular and renal outcomes, targeting higher levels using erythropoietin does not appear to confer any benefit and is associated with potential harm, likely related to increased blood viscosity.[135] In patients with systolic heart failure, 2 randomized controlled trials showed no significant clinical benefits to erythropoietin supplementation.[136,137] Because there are no specific trials regarding anemia and erythropoietin deficiency in cardiorenal patients, more studies are warranted.

End-Stage Disease

In patients with end-stage renal disease and secondary heart failure, renal transplantation is a viable therapeutic option. After renal transplantation, LV hypertrophy is reversed and improved LV function, via speckle-tracking echocardiography, is observed.[138] Unsurprisingly, renal transplantation in patients with end-stage renal disease and heart failure with reduced ejection fraction results in an increase in LV ejection fraction, New York Heart Association functional class, and improves survival.[139] Current Canadian guidelines endorse the use of renal transplantation for this purpose.[140] Of note, persistent CRS despite renal transplantation has been attributed to persistence of a high-flow arteriovenous fistula, leading to high-output heart failure.[141,142]

There is debate regarding cardiac transplantation in patients with end-stage heart failure and concomitant renal dysfunction.[143] Current international guidelines suggest that irreversible renal dysfunction with an eGFR $<$ 30 mL/min/1.73 m^2 is a relative contraindication for heart transplantation.[143] However, it can be difficult to ascertain the proportion of renal dysfunction attributable to underlying heart disease that would be expected to reverse after transplantation.[143] Early guideline-directed management of heart failure aimed at preservation of renal function is important to prevent irreversible progression of renal dysfunction.[144] Renal dysfunction secondary to calcineurin inhibitor use is an

important post-transplantation consideration. In patients with a combined irreversible CRS, simultaneous heart and kidney transplantation is a rare but possible option.[145] Similar outcomes data for LV assist devices (LVADs) are lacking, but these devices are being implanted more in patients with CRS.[146] Registry data suggest that preimplantation renal dysfunction predicts higher mortality in patients who receive an LVAD, and therefore early LVAD implantation should be considered before the CRS becomes severe.[147]

Prognosis

Although renal dysfunction is recognized as a marker of worsened clinical outcomes, data regarding prognosis of patients with CRS are lacking, in large part because of the aforementioned problems related to diagnosis and classification of CRS. Nevertheless, data regarding concomitant heart failure and renal dysfunction might be cautiously extrapolated to patients with CRS. A meta-analysis of heart failure patients with renal impairment showed increased mortality with any renal impairment (defined as a creatinine of $>$ 88.4 μmol/L and/or an eGFR of $<$ 90 mL/min/1.73 m^2; hazard ratio $=$ 1.56) and moderate-to-severe impairment (defined as a creatinine of $>$ 132.6 μmol/L and/or an eGFR of $<$ 53 mL/min/1.73 m^2; hazard ratio, 2.31), corresponding to 7% increased risk for every 10 mL/min/1.73 m^2 decrease in eGFR.[148] A prospective cohort study reported a 1% increase in mortality for each 1 mL/min decrease in creatinine clearance after adjustment for all other prognostic factors, which was significantly attenuated by ACE inhibition (odds ratio, 0.46) and β-blockade (odds ratio, 0.40) in those with creatinine clearance $<$ 60 mL/min.[149] Studies pertaining to prognosis in patients with well defined CRS are needed.

Conclusions

CRS describes concomitant bidirectional dysfunction of the heart and kidneys in which 1 organ initiates, perpetuates, and/or accelerates decline of the other, resulting in worsened prognosis. Despite its high prevalence and effect on clinical outcomes, the diagnosis and management of CRS is fraught with difficulty. Further research is needed to better understand the pathogenesis of CRS, enable appropriate diagnosis and classification, optimize existing therapies, and discover potential new avenues of treatment in CRS.

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