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Cardiorenal Syndrome: Multi-organ Dysfunction Involving the Heart, Kidney and Vasculature

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Abstract

Cardiorenal syndrome (CRS) is a multi-organ disease, encompassing heart, kidney and vascular system dysfunction. CRS remains a worldwide problem, with high morbidity and mortality, and inflicts a significant burden on the healthcare system. The pathophysiology is complex, involving interactions between neurohormones, inflammatory processes, oxidative stress and metabolic derangements. Therapies remain inadequate, mainly comprising symptomatic care with minimal prospect of full recovery. Challenges include limiting the contradictory effects of multi-organ targeted drug prescriptions and continuous monitoring of volume overload. Novel strategies such as multi-organ transplantation and innovative dialysis modalities have been considered, but lack evidence in the CRS context. The adjunct use of pharmaceuticals targeting alternative pathways showing positive results in preclinical models also warrant further validation in the clinic. In recent years, studies have identified the involvement of gut dysbiosis, uremic toxin accumulation, sphingolipid imbalance and other unconventional contributors, which has encouraged a shift in the paradigm of CRS therapy.

Keywords: Cardiorenal syndrome, cardiac, renal, vascular, pathophysiology, uremic toxins, sphingolipids, diagnosis, management

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Abbreviations

AKI	acute kidney injury
ARNi	angiotensin receptor blockers and neprilysin inhibitor
Ang-II	angiotensin II
ANP	atrial natriuretic peptide
BNP	b-type natriuretic peptide
CKD	chronic kidney disease
CNP	type natriuretic peptide
CT	Computed Tomography
CV	cardiovascular
CVD	cardiovascular disease
Cer	ceramide
Des	dihydroceramide desaturase
dhCer	dihydroceramide
ESRD	end-stage renal disease
HF	heart failure
HKTx	heart and kidney transplantation
HTx	heart transplantation
KTx	kidney transplantation
LVAD	left ventricular assist device
LVH	left ventricular hypertrophy
MARCE	major adverse cardiovascular renal event
MI	myocardial infarction
miRNA	microRNA
NPS	natriuretic peptide system
PBUT	protein-bound uremic toxin
PET	Positron Emission tomography
RAAS	renin-angiotensin-aldosterone system
S1P	sphingosine 1 phosphate
SK	sphingosine kinase

SL	sphingolipid
SLGT2	sodium glucose transporter 2 inhibitor
SNS	sympathetic nervous system
sST2	soluble suppression of tumorigenicity 2
TIMPs	tissue inhibitors of MMPs

1. Introduction

The cardiovascular, renal and vasculo-endothelial systems work closely to maintain vascular tone, blood volume and hemodynamic stability, and are therefore inevitably interrelated in diseased states. The bidirectional relationship of the heart and the kidney, whereby the failure of one organ escalates or causes pathological changes in the other, is now widely known as 'cardiorenal syndrome' (CRS). It is indubitable that CRS must occur in the co-presence of vascular dysfunction, most notably due to the hypertensive milieu caused by volume overload and venous congestion. Currently, no evidence-based treatment guidelines exist for CRS, and thus treatment is largely pragmatic.

This review of CRS will discuss its definition, classifications, and pathophysiology. Challenges in current diagnostic and therapeutic management options as well as novel developments in recent years will also be outlined. Finally, uremic toxin accumulation and the role of the unconventional sphingolipids in the cardiorenal setting will be highlighted.

2. Overview of cardiorenal syndrome

2.1 Definition

The heart-kidney-vasculature crosstalk consists of complex biological processes, wherein these organs interact synergistically to maintain major physiological functions. CRS (also known as renocardiac syndrome) is the principal term involving either heart or kidney dysfunction that is detrimental to the other organ, ultimately leading to the failure of both. The deleterious impact of one organ on the other may be direct or indirect, and comprises an intricate feedback system involving regulatory hormones, inflammatory molecules and oxidative stress responses (Figure 1).

2.2 Classification

CV comorbid illnesses are the predominant cause of death among people with CKD in a large part of the world, including Australia, Asia, Europe and North America (Shiba & Shimokawa, 2011). Nearly 75% of end-stage renal disease (ESRD) patients have left ventricular hypertrophy (LVH), 40% of whom have coronary artery disease (Bongartz, Cramer, Doevendans, Joles & Braam, 2005). Around 20% of HF patients have moderate to severe renal dysfunction, and more than 60% at least have mild renal dysfunction (Liu, 2008). The incidence of chronic HF is also 15 times higher in chronic kidney disease (CKD) patients than healthy individuals (Silverberg, Wexler, Blum, Schwartz & Iaina, 2004). Furthermore, dialysis is associated with increased annual mortality rate of more than 20%, half of which is cardiovascular (CV)-related (Liu, Lekawanvijit, Kompa, Wang, Kelly & Krum, 2012).

Based on the Acute Dialysis Quality Initiative consensus, CRS can be classified into 5 types based on the primary organ which drives the disease crosstalk (cardiorenal or renocardiac), the disease onset, as well as presence of systemic disease (Table 1). Of note, this classification does not pertain a patient to a certain type of CRS throughout the disease course. Thus, there is a possibility to transition between different CRS types, which magnifies the complexity of the syndrome. It must also be highlighted that CRS epidemiological figures (e.g. incidence, prevalence) often stand with large number variations attributed to the different definitions used. For example, while nephrologists use the term acute kidney injury (AKI), cardiologists refer to the condition as worsening renal failure (Ronco et al., 2010). The concept of MARCE (major adverse cardiovascular renal event) is useful to help researchers further understand the prevalence of CRS, and its utilization as an endpoint in contemporary trial is highly encouraged. The definition of MARCE varies from study to study, but generally entails a combination of cardiovascular and renal parameters to assess cardiorenal endpoints.

2.3 Pathophysiology

The mechanisms involved in CRS progression are multifaceted. Key contributors of CRS progression encompass neurohormonal, hemodynamic, biochemical, immunological and inflammatory constituents, as well as non-traditional exogenous causes (Figure 1).

2.3.1 Neurohormonal and sympathetic nervous system pathway interaction

Reduced cardiac output leads to renal hypoperfusion. This in turn induces sodium retention to preserve plasma volume *via* the activation of the renin-angiotensin-aldosterone system (RAAS). Increased sodium levels cause the narrowing of glomerular arterioles, depleting glomerular filtration rate (GFR). In turn, to maintain GFR in a low-output state, vasoconstriction of the efferent arterioles is required to increase glomerular filtration pressure. However, vasoconstriction further decreases renal perfusion, and if prolonged, causes renal injury due to hypoxia. The production of aldosterone also instigates maladaptive sodium reabsorption in renal distal tubules, which leads to volume overload and expansion of extracellular fluid.

Angiotensin-II (Ang-II), a key neurohormone of the RAAS system, causes water and sodium retention by increasing the expression of sodium transporters in renal proximal tubule. Ang-II also influences aldosterone production, which acts on mineralocorticoid receptors in the renal distal tubules and collecting ducts to promote sodium retention. Additionally, both Ang-II and aldosterone stimulate cardiac fibrosis by stimulating fibroblast growth and collagen synthesis (See, Kompa, Martin, Lewis & Krum, 2005). Furthermore, cardiac myocytes undergo hypertrophy to compensate for hemodynamic impairment and elevated neurohormone levels (Buglioni & Burnett Jr, 2015).

Sympathetic nervous system (SNS) hyperactivity is a compensatory mechanism to maintain cardiac output and inotropic support. With progressing CKD, SNS is overactivated in response to renal ischemia, increased Ang-II levels and decreased nitric oxide, and results in hypertension, LVH and LV dilatation (Kumar, Bogle & Banerjee, 2014). At the molecular level, cardiac myocyte hypertrophy, apoptosis and necrosis linked to ROS production are observed as a direct action of catecholamines (Bongartz, Cramer, Doevendans, Joles & Braam, 2005). Persistent activation of the myocardial β1-adrenoceptor leads to impaired receptor-signal transduction (Hatamizadeh, Fonarow, Budoff, Darabian, Kovesdy & Kalantar-Zadeh, 2013). Increased SNS activity also induces vasoconstriction and reduces renal blood flow, which triggers the release of renin (Metra, Cotter, Gheorghiade, Dei Cas & Voors, 2012). Furthermore, sodium transport at the proximal tubules increases due to upregulation of apical Na+/H+ exchanger *via* β-adrenoceptor stimulation (Graziani, Pini, Oldani, Cucchiari, Podesta & Badalamenti, 2014). Antidiuretic hormone (or vasopressin), released *via* baroreceptor activation or indirectly through the SNS, is another vital hormone that leads to fluid retention (Ronco, Haapio, House, Anavekar & Bellomo, 2008). Antidiuretic hormone activates the V1α receptor on vascular smooth muscle cells to cause vasoconstriction, and *via* the V2 receptors in collecting distal tubules to promote water diffusion from tubular lumen into the interstitium (Graziani, Pini, Oldani, Cucchiari, Podesta & Badalamenti, 2014).

Increased salt/water retention due to RAAS/SNS activation also leads to increased intra-abdominal pressure and venous congestion. Venous congestion in the form of increased central venous pressure decreases the pressure gradient across capillary network, reducing perfusion (Kumar, Wettersten & Garimella, 2019). In the CRS context, this results in congestion, glomerular dysfunction and compromised natriuresis (Kumar, Wettersten & Garimella, 2019; Rangaswami et al., 2019). Elevated intra-abdominal pressure also diminishes renal function by reducing GFR and plasma flow (Kumar, Wettersten & Garimella, 2019).

Collectively with the RAAS and SNS, the natriuretic peptide system (NPS) is also recognized an important neurohumoral system that maintains cardiorenal homeostasis. Specifically, the NPS is comprised of 4 endogenous hormones, atrial NP (ANP) b-type NP (BNP), C-type NP (CNP) and urodilatin (Kuhn, 2016; Lee & Burnett, 2007; von Lueder et al., 2013). ANP and BNP are primarily produced in the heart with urodilatin synthesized in the kidney and these NPs activate the pGC-A receptor, while CNP is primarily synthesized in the

endothelium and kidney and activates the pGC-B receptor. Following pGC activation, the second messenger 3′, 5′ cyclic guanosine monophosphate is produced and elicits widespread beneficial cardiovascular and renal actions including vasodilation, natriuresis, diuresis, and inhibition of fibrosis and cardiomyocyte hypertrophy. The NPS, RAAS and SNS are highly integrated systems of which considerable crosstalk exists between them and the NPS is counter-regulatory to both the RAAS and SNS, who generally work in a cooperative manner. Indeed, the NPS has the ability to inhibit the RAAS and SNS and vice versa (Lee & Burnett, 2007). Thus, the pathophysiology of CRS has classically been viewed as a consequence of an imbalance between the RAAS and/or SNS and the NPS.

2.3.2 Inflammation

In CRS, volume overload and venous congestion are two major pathophysiological events leading to inflammation, wherein hyperactivation of RAAS and SNS (predominantly involving Ang-II and aldosterone) are the leading instigators. Tissue injury is also known to recruit inflammatory cells i.e. monocytes and increases cytokine production, most notably IL-1, IL-6 and TNF-α, to the damaged area. Physiologically, pro-inflammatory molecules are needed for the stabilization of an injury site, such as the generation of scar tissues in myocardial infarction (MI) to prevent ventricular rupture. However, long-term activation can result in pathological fibrosis (Liu et al., 2013) and endothelial impairment (Kumar, Bogle & Banerjee, 2014), aggravating renal vasoconstriction and worsening of heart failure (HF). Elevated IL-1β levels post-MI were correlated with SNS hyperactivity (Bongartz, Cramer, Doevendans, Joles & Braam, 2005). Increased renal TNF-α and IL-6 expression is linked to the activation of NF-κB signaling pathway, a major regulator of cellular inflammation.

2.3.3 Oxidative stress

Oxidative stress is a condition of excess oxidant production relative to the stabilizing antioxidants (nitric oxide) (Virzi et al., 2015). It is noteworthy that a low amount of ROS is required for cellular growth, differentiation, adhesion, senescence and apoptotic activities, and this is only possible because of the ROS-nitric oxide homeostasis. During ischemic events such as MI, oxygen depletion impedes mitochondrial function, causing generation of ROS during reperfusion but increased ROS may induce cellular apoptosis, resulting in compensatory ventricular hypertrophy and fibrosis (Rubattu et al., 2013). In the glomeruli, ROS is known to mediate cellular proliferation, and cause glomerular hypertrophy and scarring, disrupting renal function (Gelasco & Raymond, 2006). ROS is also linked to upregulation of chemokines and cytokines *via* NF-κB activation, and thereby inflammation (Virzi et al., 2015). Following MI, these mechanisms augment endothelial permeability, mediating kidney injury in the process. Indeed, type 1 CRS patients exhibit higher circulating levels of IL-6 and ROS compared to acute HF patients alone (Virzi et al., 2015).

2.3.4 Fibrosis

Fibrosis, in form of extracellular matrix deposition, functions to maintain integrity of an organ after tissue injury (Liu, Lekawanvijit, Kompa, Wang, Kelly & Krum, 2012; Rockey, Bell & Hill, 2015). However, prolonged extracellular matrix accumulation can disturb the mechanical function and electrical conductivity of the heart. Extracellular matrix buildup can also cause a progressive decline in renal function related to glomerular and tubular scarring. In addition, perivascular fibrosis is commonly observed in cardiac and renal fibrotic disease models and linked to vascular impairment. Therefore, fibrosis has been proposed to be a major contributor in the CRS context.

Mechanisms underlying fibrosis are well highlighted in the literature, but treatments addressing this pathophysiology remain an unmet clinical need. In general, collagen synthesis and degradation (and thereby extracellular matrix) regulation and dysregulation is fundamental in facilitating physiological and pathological

fibrosis. Collagen synthesis is promoted by pathophysiology and tissue injury, whilst its degradation is driven by MMPs and countered by tissue inhibitors of MMPs (TIMPs). An imbalance in the activity of MMPs and TIMPs results in pathological fibrosis. These events are also linked to vascular smooth muscle and endothelial cell trans-differentiation into to a pro-fibrotic phenotype (i.e. myofibroblasts), which is also well characterized in cardiac and renal fibroblasts (Fan, Takawale, Lee & Kassiri, 2012; Hewitson, 2012; See et al., 2013). Fibrosis is also mediated by an array of intracellular and extracellular growth factors and cytokines (Liu, Lekawanvijit, Kompa, Wang, Kelly & Krum, 2012; Yang et al., 2017). TGF-β1 is one of the most prominent growth factors involved in extracellular matrix production, proliferation and differentiation, as well as immune modulation (Hundae & McCullough, 2014). Ang-II exerts pro-fibrotic effects through TGF-β1 activation, and the Ang-II-TGF-β1 interplay is linked to chronic hypertension and myocardial fibrosis (See et al., 2013; Wang et al., 2015). Aldosterone is linked to cardiorenal TIMP-MMP dysregulation *via* NF-κB activation and TGF-β1 influence (Meng, Tang, Li & Lan, 2015). Recently, more novel fibrosis mediators have been identified, chief among those is soluble suppression of tumorigenicity 2 (sST2), a decoy of IL-33. In chronic conditions, local or neighboring cells release sST2, which blocks the physiological binding of IL-33 to ST2 receptor on the cell membrane and promotes pathological fibrosis and adverse cardiac remodeling (Bayes-Genis, Gonzalez & Lupon, 2018). In addition, uremic toxins, chronic inflammation and metabolic disorders such as dyslipidemia are also associated with cardiac, renal and vascular fibrosis (Lekawanvijit, Kompa, Wang, Kelly & Krum, 2012) with similar RAAS- and non-RAAS-related mechanisms, as well as deficiencies in NPs (Sangaralingham et al., 2011b), have been proposed to underlie the pathophysiology.

2.3.5 Vascular endothelial system dysfunction

Pressure overload in CKD instigates hypertrophy of the arterial wall and increased wall-to-lumen ratio. This is signified by increased wall thickness and arterial diameter, specifically due to thickening of the arterial intima and deposition of extracellular matrix (Georgianos, Sarafidis & Liakopoulos, 2015). These processes result in decreased arterial compliance, which compromises blood flow from the heart to various organ tissues. Diminished elasticity of the artery is the main contributing factor of LVH, myocardial hypoperfusion and eventually chronic HF (Georgianos, Sarafidis & Liakopoulos, 2015). There is also increased expression of endothelial adhesion molecules, such as vascular and intracellular cell adhesion molecule-1, which are involved in atherogenic proliferation of vascular smooth muscle cells, inflammation and plaque formation (Liu, Liu, Zhang, Cheng & Jiang, 2014). Atherosclerosis, in turn, increases the risk of hypertension, LVH and decreased coronary perfusion (Sarnak et al., 2003). Decreased coronary perfusion also leads to narrowing of the arterial lumen, which further impairs the myocardium due to hypoxia (Sarnak et al., 2003).

Activation of RAAS also instigates the release of endothelin-1 by endothelial cells, predominantly under the influence of Ang-II. Endothelin-1 promotes vascular remodeling by increasing inflammatory cell infiltration into the vasculature (Kohan, 2010). Pathological cardiac hypertrophy is also related to increased endothelin-1 and decreased nitric oxide levels (Cohn, Ferrari & Sharpe, 2000). These events incite cardiac fibroblast proliferation and collagen synthesis, resulting in maladaptive cardiac fibrosis (Cohn, Ferrari & Sharpe, 2000). In the kidney, endothelin-1 is synthesized due to increased expression of cytokines, chemokines, growth factors and ROS leading to renal fibrosis and inflammation (Kohan, 2010).

2.3.6 Anemia

Anemia is an independent predictor for mortality in the CRS setting, with the prevalence reported ranging from 5% to 55% (Rangaswami et al., 2019). Anemia in the CKD-HF setting is attributed to the defect in erythropoiesis and depletion of iron bioavailability due to reduced renal function. This leads to ischemia and peripheral vasodilation, and subsequently RAAS-SNS hyperactivation, volume overload and venous congestion. Additionally, reduction of antioxidant-containing red blood cells increases oxidative stress in organ tissues, further aggravating insults (Rangaswami et al., 2019). Pathologic outcomes include renal nephron loss and interstitial fibrosis, as well as LVH and ischemic and necrotic myocardium (Otaki et al., 2014).

2.3.7 Systemic disease

Systemic disease is the underlying cause of secondary CRS (Type 5). It is difficult to delineate a single pathway due to a plethora of mechanisms involved in the crosstalk of systemic disease and heart and kidney impairment. In general, any systemic or autoimmune disease will result in frequently observed CRS pathophysiology such as RAAS activation, inflammation and oxidative stress. Sepsis is the most commonly reviewed condition in relation to Type 5 CRS. CRS-relevant biochemical and clinical profiles of septic patients include increased renal vascular resistance and under-perfusion, early elevation of pro-inflammatory molecules, infection-induced cardiorenal toxicity and abnormal diastolic filling and arrhythmias due to dysfunction in autonomic nervous system (Kotecha, Vallabhajosyula, Coville & Kashani, 2018; Kumar, Wettersten & Garimella, 2019). Additionally, sepsis management such as intense fluid resuscitation efforts can exacerbate volume overload (McCullough & Ahmad, 2011), posing a clinical challenge.

3. Diagnosis, prognosis and treatment of cardiorenal syndrome

3.1 Diagnostic and prognostic measures

3.1.1 Cardiac, renal and vascular biomarkers – which to trust?

Biomarkers are essential in the diagnostic and prognostic aspects of disease management, as well as to monitor patient response to therapy. Traditional cardiac markers such as leukocytosis and C-reactive protein are non-specific myocardial markers. In the renal context, serum creatinine and eGFR are central in AKI and CKD diagnosis and staging. These markers are supported by clinical familiarity for interpretation and extensive availability, but lack accuracy in regard to injury site or disease type. Blood urea nitrogen is associated with HF outcomes in healthy populations (Matsue et al., 2017) and is another common marker in renal disease. However, blood urea nitrogen is affected by factors such as protein intake, use of steroids and catabolism process (Sheerin et al., 2014). Early identification of organ damage, such as in the setting of AKI, can help preserve function and prevent disease progression. Other biomarkers should supplement traditional biomarkers to guide diagnosis and treatment in CRS patients.

IL-18, sST2, kidney injury molecule, cystatin-C, neutrophil gelatinase-associated lipocalin and CNP are new, promising, and highly specialized biomarkers that are renal site- and/or time-specific and responsive (Ronco & Di Lullo, 2014). Cystatin-C also has prognostic value in HF mortality (Legrand, Mebazaa, Ronco & Januzzi, 2014). sST2 is released by cardiac myocytes and endothelial cells in inflammation or cardiac dysfunction, and is a good predictor of various cardiac function and sensitive to AKI prognosis in MI patients (Fan, Chang & Chen, 2018). Cardiac troponin is an excellent marker of myocardial injury and can predict CV and all-cause mortality in CKD and ESRD patients (Fu, Zhao, Ye & Luo, 2018). The cardiac stress peptide BNP is now a popular marker for ventricular impairment that predicts mortality in sepsis and renal replacement therapy (RRT) in AKI (Buglioni et al., 2015). More recently, urinary CNP has identified as potential biomarker of renal remodeling and injury in cardiorenal disease states such aging, HF and AKI (Chen et al., 2019a; Sangaralingham et al., 2011a; Zakeri, Sangaralingham, Sandberg, Heublein, Scott & Burnett, 2013) and has prognostic value with respect to all-cause mortality and a combined endpoint of HF hospitalization and death in acute decompensated HF patients (Zakeri, Sangaralingham, Sandberg, Heublein, Scott & Burnett, 2013). Angiopoietin 2, which influences vascular permeability, is also increased in acute coronary syndrome patients, and is a robust predictor of mortality in AKI patients requiring dialysis (Fan, Chang & Chen, 2018). Soluble thrombomodulin, an endothelial injury marker, can reliably predict AKI in MI patients together with angiopoietin 2 (Fan, Chang & Chen, 2018). MicroRNA (miRNA) is another potentially useful novel biomarker in the CRS setting, with unique site- and function-specific profiles in the heart, kidney and vasculature. However, clinical application of miRNA is hampered by a few factors, including the poorly defined use of single versus multi miRNA markers (signature miRNAs), difficulty

of reproducibility due to varying handling and processing methodologies, and complex analysis protocols and thus long turn-around times (Backes, Meese & Keller, 2016). Additionally, timing of miRNA dysregulation is poorly defined in cardiorenal and vascular diseases, with most studies (particularly cardiovascular disease (CVD)-related) indicating late stage compensation (Huang, Li, Wu, Han & Li, 2019). Therefore, breakthroughs of robust early-phase miRNAs for diagnostic and prognostic use in these settings are much awaited.

Overall, given the complex pathophysiology of CRS, a multi-marker approach is likely needed to gain a better diagnostic/prognostic profile. New biomarkers are limited by their low availability in the clinic and a lack of universal guidelines for cut-off values and proper use. Discovery and large clinical trial validations is needed to develop specific biomarkers for CRS diagnosis and prognosis.

3.1.2 Imaging modalities

Imaging modalities play an important role in CRS to assess organ structure and function for diagnostic purposes, as well as research. Ultrasonography is a safe, non-invasive tool to help detect congestive signs, such as increased central venous and pulmonary artery pressure in both CKD and CVD populations (Ronco & Di Lullo, 2014). Echocardiography is particularly useful to detect LVH, ischemic cardiomyopathy, valvular abnormalities and other cardiac structural pathologies. Renal ultrasound is useful to assess intrarenal hemodynamics, particularly the newly developed contrast-enhanced ultrasonography (George & Kalantarinia, 2011). In an imaging study, Breidthardt *et al* found that chronic renal parenchymal damage may be the underlying cause of renal impairment in HF, not renal hypoperfusion as widely postulated (Breidthardt et al., 2015). This is supported by Iida and colleagues which showed intrarenal venous flow, which depends highly on parenchymal integrity, was strongly correlated with right atrial pressure and clinical outcomes of HF patients (Iida et al., 2016). Altogether, these studies suggest progressive renal pathophysiology in HF begin with increased renal venous congestion, followed by reduced intrarenal parenchymal compliance and eventually parenchymal damage. These studies also highlight the merit of ultrasonography to advance our understanding of CRS.

MRI is useful to assess ventricular dimensions, function and fibrosis in the heart, and GFR, renal blood flow and oxygenation in the kidney. MRI is a reliable alternative to echocardiography in suspected myocarditis or infiltrative disease (George & Kalantarinia, 2011). The new, gadolinium-free BOLD MRI is advantageous to detect renal hypoxia and correlates well with renal biomarkers in the CVD setting, but currently lacks clinical application (Grande, Terlizzese & Iacoviello, 2017). Computed tomography (CT) is rarely used to evaluate renal function due to contrast-induced renal toxicity, though it is useful to detect cardio-embolic sources (Grande, Terlizzese & Iacoviello, 2017; Hur & Choi, 2017). Similarly, coronary angiography is associated with contrast-induced AKI (Meinel, De Cecco, Schoepf & Katzberg, 2014). Although, both CT and MRI allow extensive visualization of vessel lumen and wall (Tuna & Tatli, 2014). Nuclear imaging, such as Positron Emission Tomography (PET), provides additional structural information to CT and site-specific localization of disease (George & Kalantarinia, 2011; Grande, Terlizzese & Iacoviello, 2017). Though its utilization is wide in cardiorenal research, PET is not often used in the clinic (Grande, Terlizzese & Iacoviello, 2017).

3.1.3 External and implanted devices

Bioelectrical devices can help assess fluid status. A number of studies have demonstrated a relationship between reduced impedance values (i.e. volume overload) and adverse events, including rehospitalization and mortality (Ronco & Di Lullo, 2014). Bioimpedance devices jointly with BNP have shown promise in guiding discharge timing and the prevention of diuretic-induced AKI in HF patients and as hydration status indicator in hemodialysis patients (Yilmaz et al., 2014). Intra-abdominal pressure is another important clinical parameter in CRS, which is related to venous congestion. Intra-abdominal pressure measurements can be obtained *via* a transducer-equipped urinary bladder catheter (Ronco & Di Lullo, 2014).

Implantable devices to measure fluid status also exist, but such devices have yet to be evaluated in CRS setting. One study showed the use of OptiVol (Medtronic), an intrathoracic impedance monitor, to improve HF prognosis, but had little effect on hospital admissions and outpatient visits despite utilization of visit alerts (Vamos et al., 2018). Pulmonary artery catheterization is no longer used clinically as it had demonstrated no benefit on mortality and rehospitalization in acute HF (Binanay et al., 2005), but it might be useful to detect and treat subclinical congestion (Rangaswami et al., 2019). Although, cardiorenal hemodynamic measurements by invasive catheterization may be confounded by intra-abdominal pressure or ascites (Rangaswami et al., 2019), thus results must be interpreted with caution.

3.2 Management

3.2.1 Managing contradictory effect of multi-organ drug interactions

Decongestive measures are essential to modulate volume overload and increased intra-abdominal pressure as well as providing symptomatic relief. Diuretics remain the primary agent to correct volume overload, especially in CRS of cardiac origin (Rubinstein & Sanford, 2019). CRS patients may require a much higher dose due to diuretic resistance (short-term tolerance) (Koniari, Nikolaou, Paraskevaidis & Parissis, 2010), which is common especially in those with type 1 CRS (Cohen, 2014). High-dose diuretics certainly leads to a greater diuresis and decongestion effect, but may cause transient renal impairment (Krishnamoorthy & Felker, 2014).

Inotropics are useful to treat hypotension and low cardiac output. For patients showing congestive signs without severe cardiac output reduction, inotropics are potentially pro-arrhythmic and confer no survival benefit, and should be avoided as per American College of Cardiology/American Heart Association HF guidelines (Cowger & Radjef, 2018). Dobutamine and milrinone improve cardiac index in proportion with renal blood flow, though their effect on mortality or clinical outcomes is unclear (Kim, 2013; Klein et al., 2008). Low-dose dopamine-diuretic combination, as well as levosimendan (a phosphodiesterase inhibitor), have shown conflicting results in various trials in terms of renal functional improvement (Giamouzis et al., 2010; Kim, 2013; Mebazaa et al., 2007). β-blockers may be useful to improve forward flow. Adjunct use of β-blockers (metoprolol, bisoprolol and nebivolol in HF, and carvedilol in ESRD patients) is renoprotective, and associated with reduced hospitalization and mortality (Hart & Bakris, 2007; Rangaswami et al., 2019). Of note, β-blockers are contraindicated in decompensated HF due to potential side effects of hypotension and bradycardia. However, their withdrawal is associated with mortality (Prins, Neill, Tyler, Eckman & Duval, 2015), and should be continued if deemed possible.

RAAS inhibition is one of the primary pharmacological therapies in HF and CKD. Angiotensin receptor blockers and angiotensin converting enzyme inhibitors is known to cause transient and reversible worsening of renal function, thus patient monitoring is necessary. The use of RAAS inhibitors is recommended after volume depletion has been addressed, starting at the lowest dose, while avoiding nonsteroidal anti-inflammatory drugs (Takahama & Kitakaze, 2017). Of note, trials have shown reduced mortality rate by RAAS inhibition with higher dose only, and whether the same outcome can be expected with lower dosage is uncertain (Rubinstein & Sanford, 2019). RAAS inhibitors may also be limited by hyperkalemia, which can lead to detrimental arrhythmias (Clegg, Cody & Palmer, 2017). Recently, a superior dual-acting angiotensin receptor blockers and neprilysin inhibitor (ARNi), sacubitril-valsartan, was approved for use in HF with satisfactory renal tolerance (Damman et al., 2018). The addition of neprilysin inhibition provides modulatory effect on endogenous vasoactive peptides such as NPs and bradykinin, resulting in beneficial remodeling and vasodilation (D'Elia, Iacovoni, Vaduganathan, Lorini, Perlini & Senni, 2017). Given the therapeutic success of sacubitril-valsartan via NP augmentation, designer NP analogues such as MANP (also known as ZD100) (McKie, Cataliotti, Ichiki, Sangaralingham, Chen & Burnett, 2014), CRRL-269 (Chen et al., 2019a), NPA7 (Meems et al., 2019), C53 (Chen et al., 2019b) or cenderitide (also known as CD-NP) (Kawakami et al., 2018), may offer an alternative, yet complementary, therapeutic strategy for CRS and are currently under advanced preclinical and clinical development. Empagliflozin and canagliflozin, sodium-glucose cotransporter 2 (SGLT2) inhibitors,

demonstrated beneficial CV and all-cause mortality and hospitalization in diabetic patients with high CV risk (Zinman et al., 2015). More recently, another SGLT2 inhibitor dapagliflozin was shown to reduce HF hospitalization and CV death when added to standard care in HF patients with normal to mild impairment in renal function, regardless of diabetic status (McMurray et al., 2019). The suitability of these novel classes of drugs in the CRS setting is of high clinical interest.

3.2.2 Clinical devices to aid therapy

Volume expansion is a critical pathophysiology in CRS that needs constant monitoring. There are a number of commercial blood volume devices available. Unfortunately, these devices have not been investigated in the context of CRS. The CardioMEMS, an implantable hemodynamic sensor, demonstrated beneficial outcomes in HF patients with up to stage 2 CKD only (Givertz et al., 2017). Ultrafiltration, a mechanical fluid removal system, is linked with greater fluid removal and symptomatic relief (Marana, Marenzi & Kazory, 2014). However, ultafiltration is associated with reduced renal function with unknown effect on mortality and other hard endpoints (Marana, Marenzi & Kazory, 2014). Furthermore, ultafiltration systems for dialysis patients require highly trained staff to operate (Balter, Artemyev & Zabetakis, 2015). Portable, user-friendly ultafiltration devices are constantly being developed and may be of use for suitable patients in the future.

Dialysis remains the most common option for RRT in ESRD patients. A few small studies have been conducted in CRS patients and are worth noting. Hemodialysis appears beneficial in terms of reducing hospital readmission, length of hospital stay and survival when combined with ultafiltration for terminal Type 2 CRS patients (Leskovar, Furlan, Poznic, Potisek & Adamlje, 2017). Peritoneal dialysis appears to be safe and effective for fluid control in type 1 (Ponce, Goes, Oliveira & Balbi, 2017) and type 2 CRS patients (Shao et al., 2018), however its benefit on survival is unclear. Whether continuous or intermittent dialysis or RRT altogether is suitable may depend on disease onset. For instance, continuous RRT as a rescue therapy for Type 1 CRS was associated with poor prognosis and high in-hospital mortality (Prins, Wille, Tallaj & Tolwani, 2015), while intermittent RRT in chronic CRS was shown to be beneficial in terms of reducing readmission and deaths (Repasos et al., 2015). These studies are largely limited by the small number of participants in the study, highlighting the need for larger studies to confirm these observations. Studies in CRS of renal and systemic origin (Types 3-5) are also warranted.

A left ventricular assist device (LVAD) is an implantable mechanical pump to elevate cardiac output (Cowger & Radjef, 2018). Experts have suggested that LVAD may benefit those with Type 2 CRS (Ross et al., 2018). LVAD use in patients not eligible for heart transplantation improved 1-year survival and quality of life (Cowger & Radjef, 2018). In terms of kidney function, LVAD's long-term impact is concerning despite initial improvement in renal function, including in CKD patients (Kazory, 2013; Roehm, Vest & Weiner, 2018). Notably, AKI is observed in 15 to 45% of patients on LVADs (Roehm, Vest & Weiner, 2018; Ross et al., 2018). The Aortix (Procyrion), a percutaneous cardiac pumping device, has shown promising results in improving renal perfusion and cardiac output, and is in process for the next clinical trial phase (Cowger & Radjef, 2018). Drawbacks of implantable devices include the need of constant anticoagulation therapy, and risks of component dislodgement, AKI-induced hemolysis and extracorporeal complications (Cowger & Radjef, 2018). Moreover, device use in general lacks widely accepted guidelines, and is costly (Kazory, 2013). Perioperative complications are possible, however this can be minimized with good clinical practice as well as extensive risk assessment prior to decision for implantation.

3.2.3 Transplantation: heart, kidney or both?

Separate heart and kidney transplantations are options for end-stage patients. Dual transplantation involving both organs is much less considered. Renal function is an important contributor to heart transplantation (HTx) post-operative survival (Seoane-Pillado et al., 2017). Likewise, CV risk factor in kidney transplantation (KTx) is well correlated with higher post-transplantation mortality (Seoane-Pillado et al., 2017). Multiple studies have

shown combined heart and kidney transplantation (HKTx) to be a safe option in patients with concomitant heart and kidney failure (Reich et al., 2019; Wong, Chee, Healy, Egan, Sadlier & O'Meara, 2017). HKTx reduces rate of cardiac allograft vasculopathy and dysfunction than heart transplantation (HTx) alone (Karamlou et al., 2014; Sato et al., 2019). HKTx patients have the same rate of hospitalization lengths and long-term survival, with better immune modulation benefits (lower cellular and antibody-mediated rejection events) than HTx (Awad et al., 2017). Both dialysis-dependent and patients with reduced preoperative GFR benefit from HKTx in terms of long-term survival (Kilic et al., 2015). Furthermore, a recent analysis suggested similar safety and efficacy of HKTx in patients older and younger than 60 years, regardless of sensitization (panel-reactive antibody) levels (Awad et al., 2019).

Presently, no formal guidelines exist for HKTx, including in the CRS context. Limitations include lack of organ donors, especially a 'single' donor to source both heart and kidney. There are also concerns regarding the physiological aspect (differentiating patients needing the procedure) and ethical aspect (dissemination of a rare resource to a morbid population) of multi-organ transplantation such as the HKTx (Stites & Wiseman, 2016). Not surprisingly, the procedure also comes with high costs. Another tradeoff is the high peri- and post-operative mortality, primarily due to KTx surgery complications (Lopez-Sainz et al., 2015).

3.2.4 Other treatments

Unlike the other CRS types, management of underlying disease is key for secondary CRS. In sepsis, this includes early antibiotics and fluid resuscitation and vasopressor therapy for septic shock (Kotecha, Vallabhajosyula, Coville & Kashani, 2018). Therapeutic adjuncts including source control, mechanical ventilation and blood product transfusions may be warranted in some clinical scenarios (Kotecha, Vallabhajosyula, Coville & Kashani, 2018). Anemic conditions in CRS patients should also be addressed. Darbepoetin alfa, an erythropoiesis-stimulating agent, did not improve CV outcomes in the CKD cohort (Charytan, Fishbane, Malyszko, McCullough & Goldsmith, 2015). In fact, general consensus points to negative effect of erythropoiesis-stimulating agent use. However, iron supplementation is encouraged, and was shown to improve symptoms and hospitalization in HF patients (Charytan, Fishbane, Malyszko, McCullough & Goldsmith, 2015).

Palliative care should also be directed throughout the disease course. The goal of palliative care is to improve quality of life and reduce suffering among patients and families. Clinicians must discuss clearly goals of care and make appropriate referrals, and end-of life treatment and hospice care planned accordingly in line with patient preference. With progressing HF, use of medical devices such as pacemakers is not as useful compared to symptomatic, emotional and spiritual care (Diop, Rudolph, Zimmerman, Richter & Skarf, 2017). Dialytic and non-dialytic options must be outlined openly to all kidney disease patients. Of note, RRT may not benefit patients older than 75, especially those with multiple comorbidities (Combs & Davison, 2015). Additionally, chronic heart and kidney disease patients often have depleted psychosocial and spiritual drive due to significant fatigue, existential distress, depression and anxiety, among many others, which require integrated care (Figure 2).

4. Special considerations for cardiorenal syndrome

4.1 Role of uremic toxins

4.1.1 Gut dysbiosis

In the healthy human gut, the microbial community thrives symbiotically and aids in various metabolic functions, such as digestion and/or degradation of dietary nutrients and bile biotransformation. Gut dysbiosis refers to the quantitative and qualitative imbalance in intestinal microbial community, which negatively alters the overall composition and metabolic outcomes. Pathological changes seen in gut dysbiosis include

inflammatory cell infiltration into the lamina propria, villous height reduction and crypt elongation (Nallu, Sharma, Ramezani, Muralidharan & Raj, 2017). There is also reduction in tight junction proteins in the colonic mucosa (Nallu, Sharma, Ramezani, Muralidharan & Raj, 2017). This results in disrupted gut barrier function, allowing unfiltered translocation of uremic toxins into the circulation.

Gut dysbiosis has been observed in both HF and CKD patients. Pathophysiological processes in CKD and CVD may lead to hypoperfusion of intestinal villi, resulting in ischemia and disturbance of intestinal permeability (Nallu, Sharma, Ramezani, Muralidharan & Raj, 2017). Reduced intestinal integrity has been linked to atherosclerotic plaque and vascular fibrosis, as well as alteration of vascular tone (Ahmadmehrabi & Tang, 2017; Lau et al., 2017). CKD-induced gut dysbiosis is thought to be the result of alteration of nutrient bioavailability and an increase in luminal pH due to the elevation in ammonia (Evenepoel, Poesen & Meijers, 2017). Whether gut dysbiosis is a potential "cause" or a downstream effect of CRS is unclear. However, it is certain that the gut-heart-kidney axis exist and has a huge implication for CRS therapeutics as discussed further below. It is also likely that the effect of gut dysbiosis can exacerbate CRS pathophysiology and vice versa, although mechanisms remain largely unclear. One of the key contributors related to gut-dysbiosis in the CRS setting is uremic toxin accumulation. Uremic toxins are byproducts of microbial metabolism of dietary protein in the gut. Impaired renal excretory function leads to accumulation of these solutes, which has been shown to have cardiac, renal and vascular effects.

4.1.2 Protein-bound uremic toxins

Protein-bound uremic toxin (PBUT) is a subclass of uremic toxin with high protein binding capacity. Its unbound free form has a relatively low (and hence dialyzable) molecular weight, however is non-dialyzable in the large protein-toxin complex form (~500 kDa). PBUT equilibrium also cannot be restored during dialysis due to this extensive protein-binding characteristic and therefore remains in circulation to enter organ tissues and cause deleterious effects. Jansen et al have meticulously reviewed PBUT protein binding mechanisms (Jansen, Jankowski, Gajjala, Wetzels & Masereeuw, 2017). We have also comprehensively reviewed molecular mechanisms involved in PBUTs effect in the heart, kidney and vasculature based on preclinical findings (Savira et al., 2019).

Systemic accumulation of gut derived PBUTs has been recognized to be detrimental in both HF and CKD, largely based on observational studies. Indoxyl sulfate (IS) and *p*-cresol or its subjugate *p*-cresol sulfate (PCS) are the most widely studied PBUTs to date. IS and PCS are linked to increased progression and mortality in CKD patients and PCS to CV outcomes. In the CKD cohort, increased IS level is linked to elevated levels of adhesion molecules, plasma von Willebrand Factor and thrombomodulin, signifying a pro-thrombotic effect (Kaminski, Pawlak, Karbowska, Mysliwiec & Pawlak, 2017). IS level is also negatively correlated with the number of circulating endothelial progenitor cells (Wu et al., 2013), highlighting a potential anti-angiogenic characteristic. PCS is associated with infection-related hospitalization and septicemia (Banerjee et al., 2017), while IS is associated with the first HF event in the ESRD cohort (Cao et al., 2015). ROS-mediated cardiovascular and renal effects of PBUT are widely demonstrated in preclinical settings (Savira et al., 2019). Most importantly, GFR is a poor predictor of PBUT accumulation (Eloot et al., 2011). This suggests GFR does not reflect PBUT accumulation and the deleterious effects it might have. In addition, PBUT has potential applicability as diagnostic/prognostic marker in cardiac and renal disease. For instance, IS was shown to be beneficial for the detection and prediction of atherosclerosis (Yamazaki et al., 2015), and the progression of cardiac and renal dysfunction (Shimazu et al., 2013; Taki & Niwa, 2007).

4.1.3 Addressing microbiome imbalance and uremic toxin accumulation

There are several principles to manage circulating levels of uremic toxins, particularly non-dialyzable protein-bound solutes: 1) mitigation of internal production, 2) inhibition of mechanistic pathways, and 3) improvement in dialysis modalities (Figure 3).

To limit internal production of uremic solutes, a low protein diet was shown to reduce IS level in CKD patients (Black et al., 2018). However, the Modification of Diet in Renal Disease study showed that low protein diet did not delay CKD progression and instead increased the risk of death (Menon et al., 2009). There are also health concerns with long-term low protein consumption. Use of symbiotic therapy (prebiotic and probiotic) showed positive modification of stool microbiome and reduced circulating IS levels (Rossi et al., 2016), further evaluation in a larger trial is warranted. AST-120, a carbon adsorbent of indole (IS precursor), demonstrated a huge potential as a therapeutic strategy to counter PBUTs. Substantial evidence of cardiovascular and renal benefits in various preclinical and small to medium trials led to its approval in Japan, Taiwan, Korea and Philippines. However, AST-120 failed to achieve primary outcomes in two of its largest trials to date (EPPIC and CAP-KD) (Cha et al., 2016; Schulman et al., 2015). Use of AST-120 combined with a mild low protein diet has been suggested to be beneficial and warrants further investigation.

Theoretically, there will be circulating PBUTs that have already gained entry into cells and cause deleterious outcomes. The only approach to mitigate these effects is to inhibit signaling pathways activated by PBUTs at the molecular level. This has been tested mostly in preclinical scenarios, and clinical studies in the CRS context remain entirely non-existent to date. Some noteworthy PBUT-activated pathways include the pro-inflammatory NF-κB, and the MAPK family: the apoptosis signal-regulating kinase 1 and the downstream p38 MAPK, ERK1/2 and JNK. All these pathways are involved in PBUT-mediated heart, kidney and vascular dysfunction, and are activated in cellular stress or inflammatory responses (Savira et al., 2019). Aryl hydrocarbon receptor is another important PBUT-related intracellular target as it has been widely shown mediate IS's deleterious effects (Koizumi, Tatebe, Watanabe, Yamazaki, Ikeda & Morita, 2014). Further investigation may prove these and other potentially new pathways as therapeutic targets for CRS. In terms of drug development, key challenges to overcome include toxicity issues, sufficient compound optimization and the need for exhaustive testing both in laboratory-based setting and the clinic. Many inhibitors fail to progress further often due to toxicity issues in the early phase of trials.

Removal of PBUT is limited by conventional dialysis. However, daily short hemodialysis compared to standard hemodialysis has been shown to improve PBUT removal such as IS and p-cresol (precursor of PCS), as well as uric acid, creatinine and urea (Fagugli, De Smet, Buoncristiani, Lameire & Vanholder, 2002). Dialysis time extension also enhanced reduction ratio of PBUTs (Cornelis et al., 2015). Addition of nanoporous sorbents on the dialysis membrane was shown to increase PBUT removal in a laboratory-based study (Pavlenko et al., 2017). Reducing PBUT protein binding by increasing blood ionic strength and pH in blood-purification strategies may be viable options according to *in vitro* validations (Krieter et al., 2017; Shi, Tian, Wang, Shen, Zhu & Ding, 2019). Similarly, competitive binding *via* chemical displacers is another feasible avenue (Madero et al., 2019; Tao et al., 2016). Newer dialysis machines equipped with a 'medium cut-off membranes', such as the Theranova dialyzer, are capable of removing middle-sized molecules (García-Prieto et al., 2018), but studies assessing PBUT are limited. Importantly, most of these studies are preliminary in nature, and remain to be validated in further preclinical models and larger human cohorts.

4.2 Lipid imbalance

4.2.1 Role of low- and high-density lipids

Lipid metabolism is an integral part of cardiac function. LDL and HDL imbalance is an established process in mediating vascular dysfunction and atherosclerotic diseases. In both CVD and renal disease, lipid metabolism is impaired. The clinical profile of dyslipidemia in these settings comprises increased LDL and triglycerides and decreased LDL levels. LDL is critically involved in early atherosclerotic plaque formation due to its oxidization and structural modification. Oxidized LDL levels are markedly elevated in CKD patients, likely due to increased oxidative stress events. Conversely, HDL is vasculoprotective, showcasing anti-atherogenic, anti-inflammatory as well as antioxidant effects.

The principal lipid-lowering treatment is statin (HMG-CoA reductase inhibitor) administration. Statins exhibit a CV-protective effect, reducing and preventing CVD, and potentially kidney disease (Bianchi, Grimaldi & Bigazzi, 2011). However, statins are less efficacious in advanced renal impairment. Mortality benefit of statin has been challenged by large trials, though morbidity reduction is evident (Cleland, Hutchinson, Pellicori & Clark, 2014). HDL agonists, such as niacins and fibrates, are a promising strategy in lipid-lowering therapy. Fibrates are commonly prescribed for the triglyceride modulating effect, but clinical studies involving fibrates are far fewer than those of statins. Fibrates have beneficial CV-reducing risk in mild-moderate CKD, but the effect is unclear in advanced stages (Androulakis et al., 2017). Niacin is not cleared by the kidneys and may be safe in the CKD setting, but has poor tolerance (Androulakis et al., 2017). Statin and fibrate combinations are associated with increased PCSK9 level, an LDL receptor regulator, likely reducing lipid-lowering effects (Dincer, Dagel, Afsar, Covic, Ortiz & Kanbay, 2019). PCSK9 inhibitors has been shown to be more efficacious than statins in reducing LDL and CV events (Dincer, Dagel, Afsar, Covic, Ortiz & Kanbay, 2019), and adjunct inhibition with statin and fibrate combination therapy may be beneficial.

4.2.2 Role of sphingolipids

Sphingolipids (SLs) are traditionally recognized as a part of the cell membrane structure. However, studies have shown SLs involvement in various cellular function and dysfunction. The scope for SL discussion is vast, but notably, targeting enzymes and biomolecules involved in the *de novo* SL synthesis pathway for disease therapy has gained interest in recent years. This may be due to direct relevance with SL plasma level regulation (Magaye et al., 2018). The *de novo* pathway synthesis for SL production is best summarized into the non-reversible conversion of dihydroceramide (dhCer) into ceramide (Cer). This is mediated by the gatekeeper enzyme dihydroceramide desaturase 1 and 2 (Des-1 and 2) (Figure 4).

The implication of the dhCer and Cer imbalance remains largely unclear. However, higher Cer levels have been linked to chronic oxidative stress, lipid raft formation, cardiac and ischemic renal injury and mortality in HF patients (Reforgiato et al., 2016; Zager, Iwata, Conrad, Burkhart & Igarashi, 1997). Cer increments, but not dhCer, also cause smooth muscle cell apoptosis and instigate ROS-related pathways in endothelial cells (Magaye et al., 2018). RAAS-SL interaction is poorly defined, however aldosterone and Ang-II-mediated Cer production is associated with cellular apoptosis, vascular contraction and oxidative stress (Ueda, 2017). On the other hand, reduced dhCer level is linked to increased insulin resistance (Magaye et al., 2018). Interestingly, suppression of the enzyme sphingosine kinase (SK) 1 was demonstrated to exacerbate renal fibrosis in disease models (Ren et al., 2009), and conversely, its upregulation results in anti-fibrotic outcomes (Bajwa et al., 2010). This is albeit SK1's role in converting Cer-derived sphingosine into sphingosine 1 phosphate (S1P) (Figure 4). S1P itself is linked to fibrotic lesions (Pyne, Dubois & Pyne, 2013), however such effects may arrive from its extracellular action, with intracellular S1P instigating anti-fibrotic benefits (Schwalm, Pfeilschifter & Huwiler, 2014). It is also puzzling that increased SK1 level in humans and disease models are associated with deleterious effects, while other studies confirmed the protective role of its overexpression as previously discussed (Huwiler & Pfeilschifter, 2018). Furthermore, increased dhCer level is realized in atherosclerotic plaques and hypercholesterolemic rats (Magaye et al., 2018). Overall, current evidence suggests a more complicated physiological and

pathophysiological implication to the dhCer-Cer balance than naming either one a straightforward "good" or "bad" SL, as such may be the case for LDL and HDL. There appears to be some factors influencing the effect of various SLs, including bi-functionality, site of action, type of SL (identified by structural variations) and potentially disease onset. With better understanding of their actions, SLs could potentially become useful markers in cardiac, renal and vascular dysfunction.

Nevertheless, therapeutic implications of SLs are evolving. SL-based therapy is generally aimed to reduce synthesis of certain SL substrates. The current challenge is to avoid lethal implication of SL synthesis blockade, which largely depends on the magnitude (i.e. global and non-global blockade), the target within the pathway, and appropriate intracellular or extracellular inhibition as per the desired outcome (Schiffmann, 2015; Schwalm, Pfeilschifter & Huwiler, 2014). Partial inhibition is generally benign, as demonstrated in preclinical models (Schiffmann, 2015). Targeting Des-1 is largely contemplated to restore dhCer and Cer balance. However, the consequence of Des-1 inhibition in the cardiorenal context is hardly known. SKs and S1P receptors are also potential targets, with both inhibition and promotion of their expression being considered as therapeutic strategies. Further investigation detailing the behavior of various forms of SLs are necessary to understand the benefits for SL-targeted therapy in diseases including CRS.

5. Conclusion

Comprising a complex and multifactorial pathophysiology, CRS is a clinical challenge. Diagnostic, prognostic and therapeutic measures in the CRS setting are limited. Current pharmacological therapies are powerful, but insufficient to satisfactorily reverse or mitigate CRS progression, thus is a high priority area for drug discovery and novel therapeutic strategies. Treatment for patients with CRS needs to be integrative and continuous, addressing physical and psychosocial symptoms. Renewed initiatives and concerted efforts between nephrologists, cardiologists and scientists should be built to establish robust guidelines and promote translational research addressing this cohort of patients. Focus on potentially overlooked contributing factors, such as uremic toxin accumulation and sphingolipid imbalance, is also warranted.

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Conflict of Interest

Drs. Burnett and Sangaralingham are listed as co-inventors on issued or filed patents related to the use of urinary CNP as a biomarker and Mayo Clinic holds patent rights. Dr. Burnett is the co-inventor on issued or filed patents related to cenderitide and NPA7 and Mayo Clinic holds patent rights. Dr. Burnett is also listed as a co-inventor of MANP and Mayo Clinic has licensed MANP to Zumbro Discovery of which Dr. Burnett is a co-founder and holds equity. All other authors have no conflict of interest to declare.

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CRS category	***Disease onset and direction***	***Primary disease example***	***Secondary disease example***	***Epidemiology***
Type 1	*Acute, cardiorenal*	*Right ventricular failure, acute HF, acute coronary syndrome, cardiogenic shock*	*AKI, renal ischemia*	*50% of all CRS cases*
Type 2	*Chronic, cardiorenal*	*Chronic HF*	*CKD, ESRD*	*20% of all CRS cases*
Type 3	*Acute, renocardiac*	*AKI, renal ischemia*	*Arrhythmia, acute HF, cardiac ischemia*	*Poorly defined*
Type 4	*Chronic, renocardiac*	*CKD, ESRD*	*Chronic HF, diastolic dysfunction*	*Poorly defined*
Type 5	*Secondary CRS*	*Sepsis, cirrhosis, autoimmune diseases*	*CRS*	*Poorly defined*

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Table

Table 1. Cardiorenal syndrome overview

HF: heart failure, AKI: acute kidney injury, CRS: cardiorenal syndrome, HF: heart failure, ESRD: end-stage renal disease.

Figures

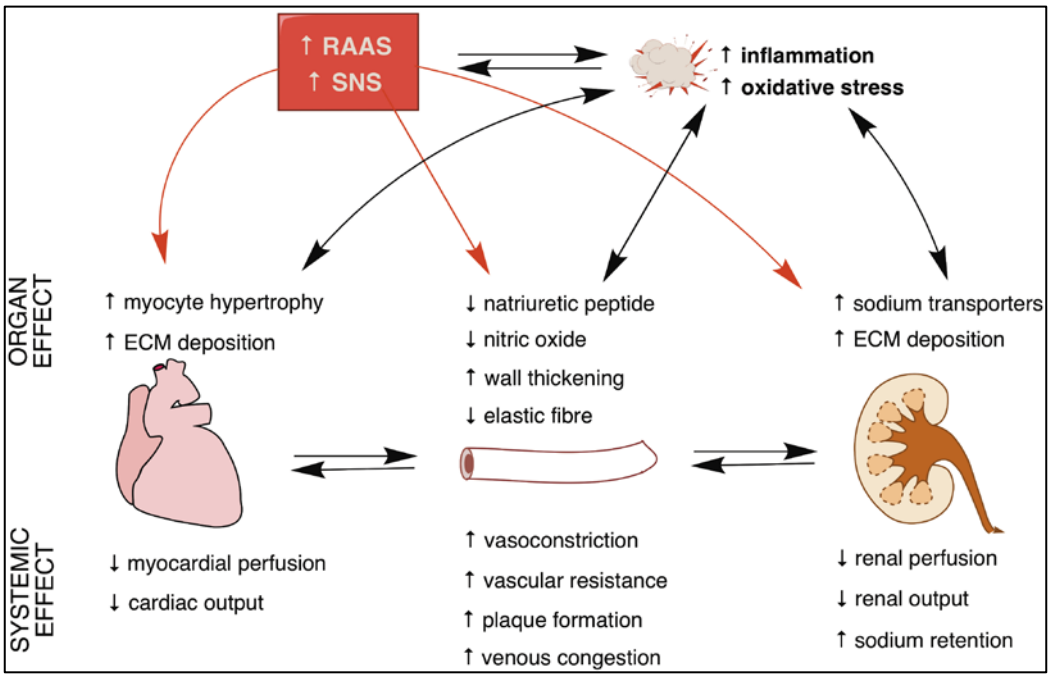


Figure 1. Organ crosstalk in cardiorenal syndrome pathophysiology

RAAS and SNS overactivation and NPS derangement initiates phenotypic and other molecular changes in the heart, kidney and vasculature. These changes cause organ dysfunction, leading to systemic implications which in turn affect other organs due to bidirectionality.

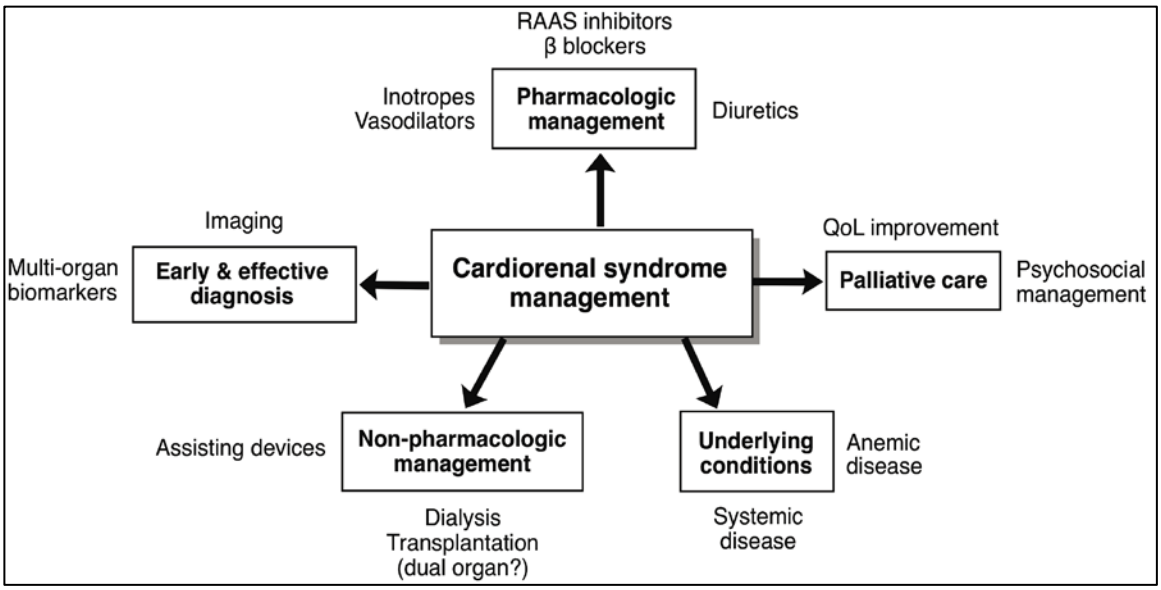


Figure 2. Principle of cardiorenal syndrome management

Management of CRS encompasses several important perspectives. Diagnostic measures should aid early and effective diagnosis to address underlying diseases, with special encouragement of multi-marker use. Treatments may involve pharmacologic or non-pharmacologic, or a combination of both as warranted by disease progression. Special care should be exercised in patients with systemic disease or other clinical conditions such as anemia, and the treatment should consider cardiorenal impacts. Palliative care is essential; physicians should not treat just the disease but psychosocial issues that come with having CRS and seek to improve patient quality of life.

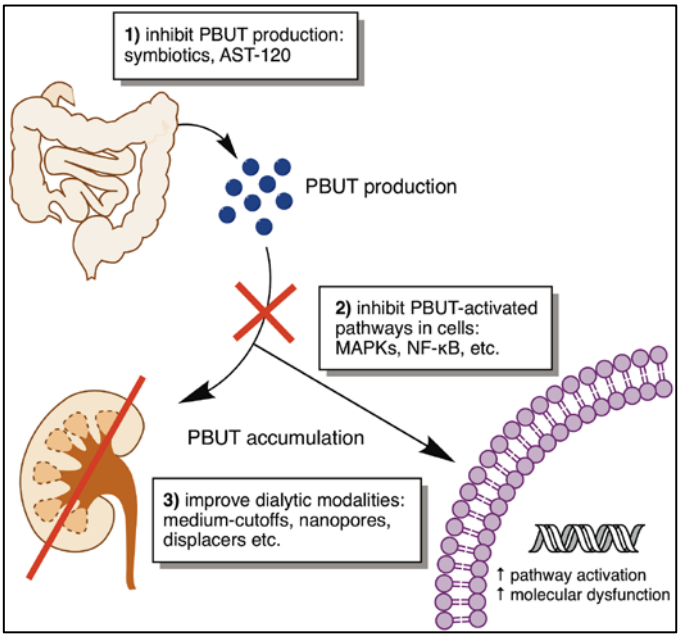


Figure 3. Therapeutic strategies for protein-bound uremic toxin accumulation

PBUTs are generated in the gut and normally cleared by the kidney. Renal impairment results in PBUT accumulation in the circulation, leading to deleterious effects. Strategies to mitigate the effects of PBUTs can therefore be summarized into: 1) inhibition of PBUT production in the gut; 2) inhibition of targeted pathways activated by PBUTs that have gained entry into cells; 3) improvement of dialytic modalities for PBUT removal.

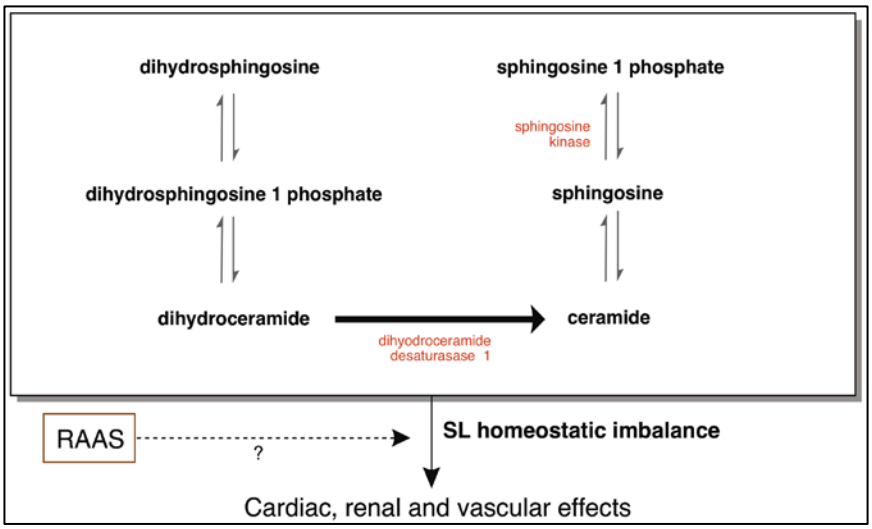
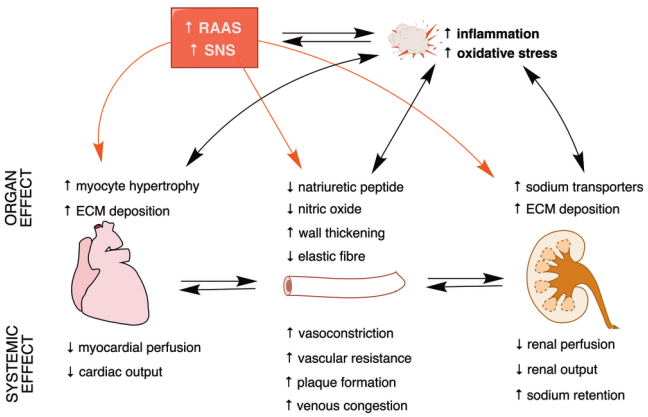


Figure 4. Sphingolipid imbalance and potential impacts on cardiorenal and vascular systems

Sphingolipid imbalance has potential negative cardiac, renal and vascular implications. Of particular interest is the non-reversible conversion of dhCer into Cer within the de novo synthesis pathway mediated by Des-1, conceivably making Des-1 an attractive target to restore SL imbalance. RAAS, particularly angiotensin-II, has been postulated to interact with SLs, though mechanisms remain obscure. N.B. the de novo SL synthesis pathway has been simplified for illustration purposes.



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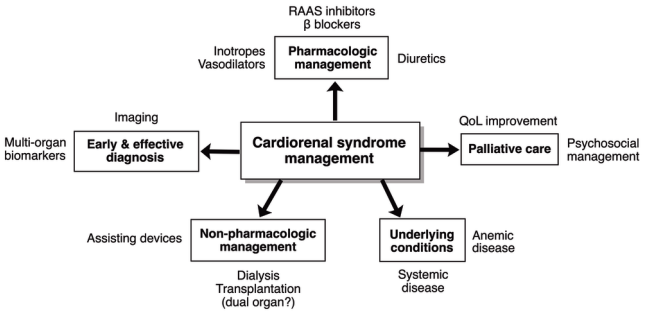

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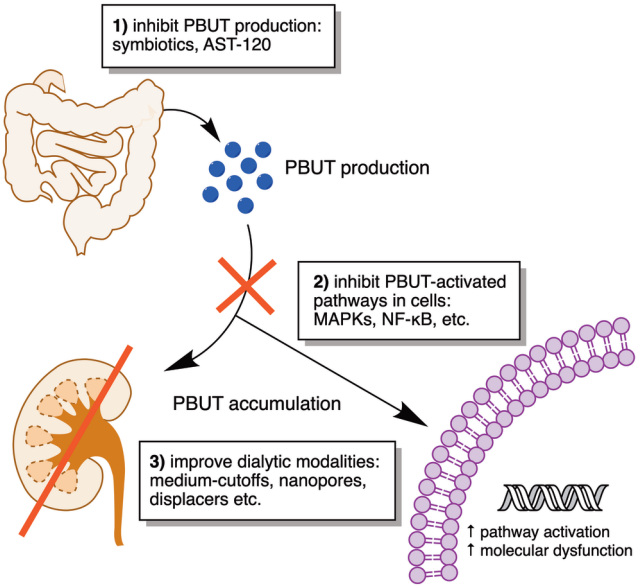

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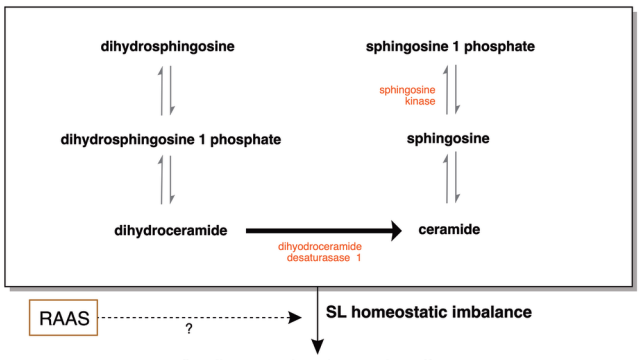

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