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REVIEW ARTICLE

Chronic Heart Failure and Comorbid Renal Dysfunction - A Focus on Type 2 Cardiorenal Syndrome

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Abstract: The most important advancements in the Cardiorenal syndrome (CRS) are its definition and subsequent classifications. When the predominant pathology and pathophysiology is the heart, i.e. chronic heart failure (CHF), and where any renal impairment (RI) subsequent to this is secondary, the classification is type 2 CRS. There are unique differences in the pathophysiology and progression of individual subclasses. It is important to understand the evolution of CHF and consequences of subsequent RI as they are becoming increasingly prevalent, aggravate morbidity and mortality and limit many therapeutic options. In this paper we discuss the significance of the type 2 CRS patients in the context of the thematic series.

Keywords: Congestive Heart Failure, Cardiorenal Syndrome, Indigenous Australians, Renal Failure, Treatment, Type 2 Cardiorenal Syndrome.

INTRODUCTION

The cardiorenal syndrome (CRS) and many aspects in the understanding of this disease have been advanced enormously over the last decade. The association between renal failure and accelerated atherosclerosis was described by, Lindner et al, in 1974 [1]. In the latter years it was noticed that the umbrella term CRS was not sufficient to explain all the pathophysiological findings, the pathology in the organs, diagnosis and even management [2]. The combined group efforts and international consensus have consolidated CRS into five accepted sub-classes [3, 4]. Much of the future impetus will be to understand each of the individual subclasses better. The type 2 CRS is perhaps the most established for much of the early interest. Chronic Heart Failure (CHF) eventually causes renal impairment (RI) in nearly all cases, however, there are many other factors that can also contribute. These factors are critical in the sub classifications which are based on 2 principles: firstly, the organ predominately involved, thus the direction of the interaction; secondly, the chronology, predominately acute or chronic. The severity of involvement has not been factored.

CHF in isolation can inflict tremendous cost to health systems, approximately 2% where 60% of the cost is for hospitalizations [5-7]. It is also the most common cause of hospitalization over 65 years in the US and 5% of internal medical admissions in Europe. Readmissions are high between a third to one half in 6 months. Mortality is around 13% within 12 weeks of discharge in European cohorts [8-10]. In hospital mortality is between 4-7% and 5 year mortality approaching 60% [8, 11]. The incidence of 0.2-0.3% rises greatly with age to as high as 10 fold in those over 80 years of age [12]. Prevalence, from Rotterdam study, similarly shows rises from less than 1% between 55 and 64 years to 13% between 75 and 84 years [13]. With rapid aging, the temporal trend shows a steep increase in the developed world. This will also affect the quality of life of patients and their families [3]. Without factoring cardiac diseases, renal diseases also contribute to excess morbidity and mortality [14]. Similarly, cardiorenal interactions are worse than the individual organ pathologies. Here the severity of disease in either organ will naturally contribute to greater overall risks [15]. This review is focused on exploring the role of the kidney in CHF, particularly in the real world setting, or outside the controls of the randomized control trials. As there have been numerous publications on specifics and variants of CRS, we aim to maintain a context of the editorial theme [2, 3, 16]. We discuss the interaction between CHF and RI, now commonly known as the type 2 CRS.

DEFINING THE PROBLEMS IN TYPE 2 CRS

Definition

The precise definition of type 2 CRS, from the Acute Dialysis Quality Initiative (ADQI) consensus, *"...is charac-*

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terized by chronic abnormalities in cardiac function leading to kidney injury or dysfunction". The authors attempt to clarify *"…As such, the temporal relationship between the heart and kidney disease is an important aspect of the definition…observational data clearly show that chronic heart and kidney disease commonly coexist…however, such studies are unable to determine which of the two disease processes was primary or secondary. In these situations, it has been suggested to use the term CRS 'type 2/4'… In view of the above, the mere coexistence of cardiovascular disease and CKD is not sufficient to make a diagnosis of true CRS-2. In the specific setting of stable CHF, we propose the following two prerequisites to make a diagnosis of CRS2; first, that CHF and CKD coexist in the patient, and second, CHF causally underlies the occurrence or progression of CKD. The latter should be supported by both temporal association, i.e. documented or presumed onset of congestive HF temporally precedes the occurrence or progression of CKD, and by pathophysiological plausibility, that is, the manifestation and degree of kidney disease is plausibly explained by the underlying heart condition"* [4].

Epidemiology

There are sufficient studies from which results have been pooled to get an overview of the CRS. We know similarly that in isolation, CHF averages a 50% 5-year mortality and End Stage Renal Failure (ESRF) similarly [17, 18]. Similarly, RI is a risk factor for CHF [19, 20]. We are now subclassifying the intermediate grades, where as CHF becomes more severe and the risk of renal impairment also becomes greater. As we can see from the above definition, the working group made clarifications to better understand broader possibilities. There are very few studies, however that have looked at this longitudinally.

The most significant has been the ADHERE database of acute decompensated heart failure (ADHF). At the point of admission, in 118,465 cases, 9.0% had normal renal function (GFR > or = 90 mL x min x 1.73 m2), 27.4% had mild renal dysfunction (GFR 60-89 ml/min/1.73 m2), 43.5% had moderate renal dysfunction (GFR 30-59 mL/min/1.73 m2), 13.1% had severe renal dysfunction (GFR 15-29 ml/min/1.73 m2), and 7.0% had kidney failure (GFR < 15 ml/min/1.73 m2 or chronic dialysis). However, previously, only 33.4% of men and 27.3% of women were diagnosed with RI. In-hospital mortality was noted as 1.9% with normal renal function to 7.6% and 6.5% when patients suffer from severe dysfunction and ESRF. Worsening renal function (WRF) can also occur during inpatient stay or discharge. Prognostic medication use is decreased in both acute and chronic cases [15, 21, 22]. Thus, the picture is quite black and white, suggesting that CHF independently has a bad prognosis, in many cases there is already concomitant RI which is under diagnosed, and finally under treated. The data show that RI is the greatest independent risk factor for CHF outcomes, even greater than the ejection fraction [15].

Pathophysiology

The leading cause of CHF, excluding RI, includes ischemic heart diseases and myocardial infarction, diabetes mellitus (DM), the metabolic syndrome and hypertension. Hypercholesterolemia, cigarette smoking, family history and race similarly predispose or cause CHF through secondary means [23]. CHF evolves due a single hit, such as myocardial infarction or a cumulative process of multiple minor effects. Often one confounding entity is poorly controlled and causes significant system stress. When there are common processes, the reason for one organ being affected earlier or greater is unknown, and could perhaps relate to the greater stress on the myocardial cell compared to the others e.g. nephron. Thus, it would be fair to assume, that in theory, that the kidneys are unlikely to be normal to start with. In addition to the identical chronological association between myocyte, nephron and causative comorbidity, there is immediate stress on the kidney through pathophysiological connections when CHF develops. The connectivity of the vascular bed, and its regulation by the sympathetic nervous system (SNS) and renin-angiotension-aldosternone system (RAAS), continues the stress on the nephron. The long-term process results in scarring and fibrosis to both organs [2, 24].

In vivo, CHF as a syndrome occurs due to the over expression of biologically active molecules that are capable of deleterious effects (Fig. **1**). The cells such as the myocardial myocytes, are capable of producing these potentially toxic effectors within close vicinity of the injury with the capacity for ongoing autocrine and paracrine activity. The spill over of this toxic milieu reaches the kidney, which has to regulate salt and water retention to compensate for loss of cardiac output. The degree of ongoing chronic renal autoregulation following acute or chronic HF insults is unclear and is the scope of future works in the type 2 CRS [25, 26]. Finally, an important source of renal stress is increased cardiac preload. Increased venous pressures reduce transglomerular pressures and eGFR. Thus, it is important to ensure that attempts to maintain blood pressure by reducing diuresis can similarly impair renal function. This balance is a fine one and is among the important causes for under treatment.

The kidneys receive 25% of blood flow, where the majority goes to the cortex, which also has the greatest neural innervations to regulate changes acutely. The medulla receives only 10% of the blood supply. The renal microvascular bed however is continuous throughout. Thus, disease in any glomeruli could have implications when placed under supraphysiological stress from SNS or RAAS and matched with early disease in vascular endothelium and nitric oxide systems. Thus, when considering the total glomerular filtration rate (GFR), it is the sum of the contribution of single-nephron GFR (SNGFR). RBF and regulators of transglomerular pressures are among the most important contributors for GFR.

$SNGFR = kf\_x\ \Delta P.$

(kf = coefficient of filtration ΔP = pressure gradient)

Compensation to ensure adequate GFR includes increased renal blood flow (afferent arteriolar vasodilatation), filtration pressure (via efferentarteriolar vasoconstriction) and glomerular hypertrophy, and hyperfiltration (leads to scarring). CHF effects on the kidney become a problem when single nephron filtration fraction (SNFF) and SNGFR are functioning at reasonable capacity [24].

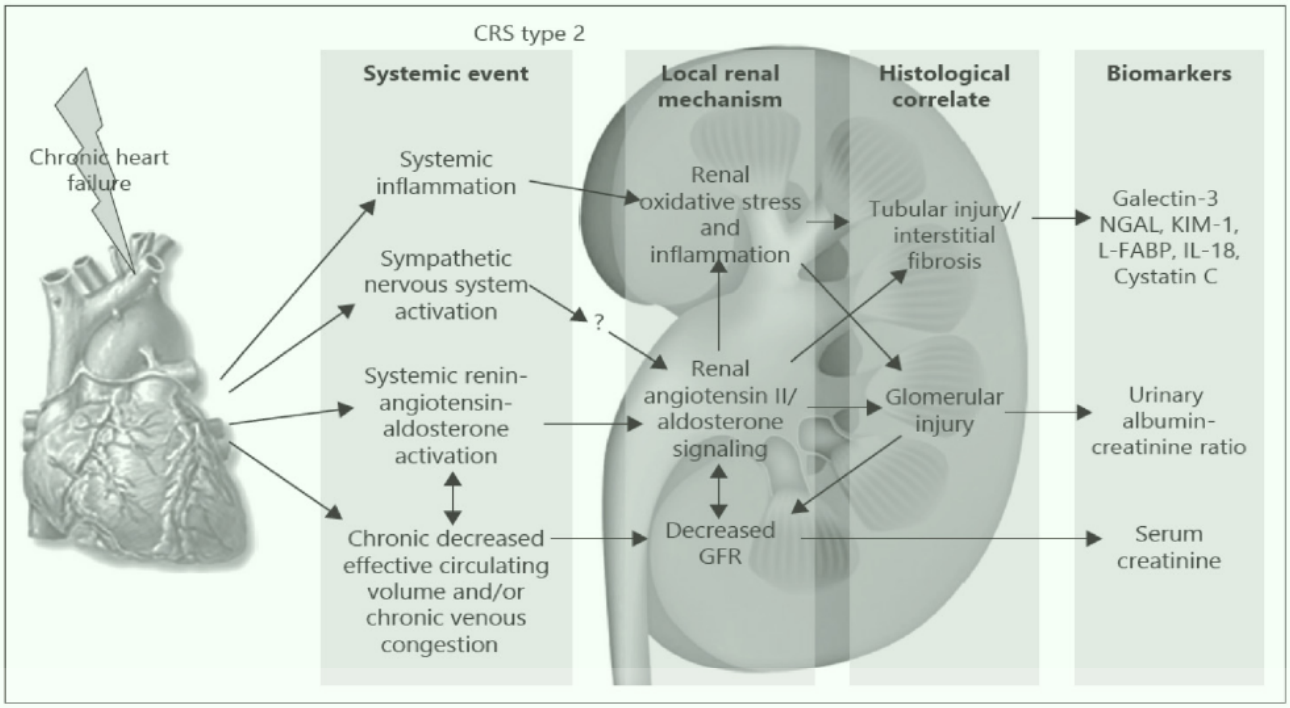

Fig. (1). CHF pathophysiology.

Vasodilator	Significance	Vasoconstrictor	Significance
Angiotensin II	++ T	Adrenomedullin	+ t
Aldosterone	++ T	Bradykinin	+ t
Arginine vasopressin	++ t	Catecholamines – central effects	++ T
Catecholamines – peripheral effects	++ T	Dopamine	++ t
Endothelin	++ t	Natriuretic peptides	++ t
Thromboxane	+ t	Nitric oxide	++ n
		Vasodilator prostaglandins	++ t

Abbreviations; + = minor effect; ++ major effect; n – no specific treatment; T – treatment provides symptom and prognosis benefits; t – treatment provides symptom relief only, specific agent available Modified from ref [24, 54].

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

DIAGNOSTICS

The ability to identify cardiovascular decompensation and subsequent renal injury early and accurately are the most important diagnostic tools. Unfortunately, we have still not identified which of these tools will answer the call with accuracy, consistency and cost effectiveness. A glance of the area and promising tools are discussed.

Cardiovascular Diagnostics

Accurate cardiovascular diagnostics has never been an issue since the advent of advanced tissue imaging and invasive coronary catheterization. For clients in more remote parts availability can be a factor. There are also more novel techniques utilizing Doppler, speckle tracking and cardiac MRI to provide information that correlates to earlier changes in the myocardium. While this is a more preventive aspect for CHF, it is nonetheless a beneficial advancement in the area that will spill over for the CRS. What has been more difficult however is determining precisely when patients are at greatest risk of decompensation, impairing renal blood flow and aggravating RF. Invasive device-based diagnostics, from implantable cardioverter defibrillators (ICDs) are available, however, with many technical issues when applied for daily clinical use [27].

NT-proBNP has been revolutionary for chronic HF and ADHF diagnosis. Confounders such as age, ethnicity, body mass index, sex and RF, for levels are being resolved, as

there are substantial bodies of evidence now. Natriuretic hormones independently predict hospitalization and all-cause mortality. For ADHF, higher admission levels and discharge levels predict worsen morbidity, mortality and readmissions [28, 29]. The role of NT-pro BNP and the kidneys has been less well studied. In the mild to moderate kidney disease study, 227 non diabetic patients were followed for nearly 7 years, plasma levels of NT-proBNP were significantly and independently higher among those who progressed sufficiently to the endpoint from those who did not (65 vs. 112 patients), highlighting a prognostic biomarker potential for an increased risk for accelerated progression of ESRD [30]. In 80 patients, with dyspnea and diagnosed with CHF, there was a significant inverse relationship between increased NT-proBNP and decreased GFR ($p<0.0001$) [31]. In a larger study of 599 patients with dyspnea, NT-pro BNP and GFR were inversely associated ($p < 0.001$) and even in those with GFR <60 ml/min/1.73 m2 was the strongest independent predictor for 60-day mortality (hazard ratio 1.61; 95% confidence interval 1.14 to 2.26; $p = 0.006$) [32]. At this point it will be difficult to tease out causation between NT-proBNP levels with WRF [33]. BNP is produced and secreted within ventricular myocytes in response to ventricular stretch [34]. Renal contribution to ventricular stress can be detected when BNP is used as an adjunct in a biomarker panel.

Renal Diagnostics

We published a review on the diagnostics in the CRS in 2012, and since that time there have been some important changes. Conventional biomarkers such as urea, and serum creatinine (SCr) remain the main stay. In all cases blood would be analyzed and an estimated GFR (eGFR) is provided. The limitations and consequences with various permutations in the CRS have been previously discussed [24]. The main gap is its failure to provide temporal information for injury or function in two critical situations, firstly, with the commencement of neprotoxic pharmacotherapy, and secondly, the inability of SCr to provide an accurate assessment of function in the acute settings. Cystatin-C (Cys-c), a low molecular weight (13-kDa), an endogenous proteinase inhibitor has a number of features as a reliable marker for injury, RI and eGFR. It originates from any nucleated cell, thus its production and release is constant regardless of age, race, sex, body mass, critical illness. Its levels rise before SCr and it is freely filtered by the glomerulus and completely reabsorbed by the proximal tubule [15]. In 823 CHF patients undergoing coronary angiography, Cys-C based eGFR improved major adverse cardiovascular event prediction independently to SCr and BNP, especially with eGFR $\geq$60 mL/min per 1.73 m^2 ($P<0.01$) [35]. In ADHF, 483 patients across multiple centres were followed for 12 months where all cause mortality was 25.4%. Cys-C levels above median (1.30 mg/L) showed the highest adjusted hazard ratio, 3.2 (95% CI 2.0-5.3), $P < 0.0001$, which increased significantly with each tertile. When SCr was normal elevated Cys-c provided additional risk stratification where 12-month mortality was 40.4% vs. 12.6% when both markers were within the normal range, $P < 0.0001$. Combining data from Cys-C and NT-proBNP improved risk stratification [36]. Many more observations for Cys –C and cardiovascular diseases are being made with Cyc-c with hypothetical links including RI, inflammation, atherosclerosis, myocardial remodeling, genetics and other [37]. Thus, Cys-C could provide renal specific information on injury, impairment and additional information in a biomarker panel.

Among the renal injury biomarkers we had previously raised Interluekin-18 (IL-18), Kidney Injury Molecule-1 (KIM-1), Liver-Type Fatty Acid-Binding Protein (L-FABP) and Neutrophil Gelatinase-Associated Lipocalin (NGAL) potential biomarkers individually or in a panel. The discriminatory capacity of IL-18 stands out as the major concern. KIM-1 is the closest biomarker for a 'troponin of the kidney'. Its discriminatory capacity is high as it is a highly expressed transmembrane protein in the proximal tubule. Its relative commercial in availability is a concern. Similarly, L-FABP neither has the specificity or commercial availability to warrant current consideration. NGAL is a 25-kDa protein bound to neutrophil granules that is up regulated greater than 10-fold in post ischemic renal injury. It is produced and secreted by renal tubular cells, hepatocytes and immune cells to a host of ischemic and inflammatory states [15]. The GALLANT [NGAL EvaLuation Along with B-type NaTriuretic Peptide (BNP) in acutely Decompensated Heart Failure] multicentre study assessed NGAL and BNP in 186 ADHF admissions for events; 29 ADHF and all cause mortality (16%) occurred at 30 days and patients with events had higher levels of NGAL than those without (134 vs. 84 ng/mL, $P < 0.001$). In multivariate analysis, NGAL predicted events ($P= 0.001$) are greater than SCr and BNP. Adding discharged NGAL improved stratification by more than 10% and 19% in those with and without events. The highest risk occurred in those with both elevation of NGAL and BNP (hazard ratio (HR) = 16.85, $P= 0.006$) [38]. Among 562 CHF patients, those who were in the New York Heart Association (NYHA) functional class II/III, were followed for several years, and the outcomes were correlated with NGAL, Cys-c and eGFR. Higher levels of NGAL independently correlated all cause mortality regardless of SCr or Cys-c levels. In ADHF admissions, patients who developed WRF had higher levels compared to those without (272 ± 205 versus 136 ± 127 ng/ml; $P = 0.0001$). Baseline NGAL levels were affected by prior RI. Levels around > 130 ng/ml overall seemed to predict adverse events [39, 40]. Critical care experiences have highlighted heterogeneity of results, where elevated NGAL does not actually predict acute kidney injury, when examining patients individually. The extra renal origins can explain some of this [41]. Whether urinary NGAL can resolve this issue is among the questions need to be explored. NGAL also appears to play in wider role in CHF and CVD, where our understanding is still evolving [42, 43].

Diagnostics Panels, Costs and Clinical Use

It is a simultaneously tricky, difficult and exciting time for physicians and researchers who care for patients with the CRS. Biomarkers must fulfill three criteria: firstly, provide repeated accurate measurement with reasonable cost and turnaround times; provide additional information; and finally provide measured levels that can be used to make clinical decisions [44, 45]. When we compare the traditional markers it can equally be questioned whether some of them like SCr are now meeting clinical needs for type 2 CRS. These new phases of biomarkers are potentially powerful predictors of

risk. There are gaps in specificity when used used individually in patients with comorbid pathologies that add confounders. There remain gaps in understanding baseline values with heterogeneous clinical scenarios and also how information can be used in combination as part of a panel. An important commercial tool is the point of care devices, which have combined BNP, Cys-c, D-dimer, hs-CRP, NGAL and Troponin [46]. Bellomo et al commented on the cost of $10 per test and 10 minutes labor in their intensive care (ICU). This equates to $20,000 per year on materials alone for new admissions to (ICU). The author felt that it is not cost effective to measure urine and blood levels routinely for clinical application in their intensive care unit [47]. There are clear constellations of clinical factors that point to increased risk. For example, Testani *et al*. studied the role of just BUN, SCr and BNP in 908 patients discharged with CHF diagnosis, the combined use of these biomarkers could risk stratify patients with RI into lower and higher risks [48]. There will be research opportunities in the future to better understand how to cost-effectively use these biomarkers, whom to target and when to target such patients. As for clinical use, it is feasible that these biomarkers are among the important non-invasive tools that contribute to the new paradigm once we learn how to use them better, and lower the costs.

THERAPEUTICS

CRS is undertreated at all levels including preventive and definitive treatments [15, 22]. Some recent publications have covered details for acute therapies, chronic therapies and management of comorbidities, and we refer readers to those [48-55]. In this study, we focused on therapeutic principles.

Optimizing CHF Care and Therapeutics

If we are going to focus entirely on delivering novel therapies in established type 2 CRS, we have invariably shifted the risk profile upward. It will be a debate as to when actual type 2 CRS develops, particularly in those with comorbidities that affect multiple organs, thus graying the boundaries on what is truly a prevention. It may also seem unclear as to what additional treatments need to be provided when the pathophysiological principles for treatment including RAAS and SNS blockade in conjunction with good control of comorbidity and risk factors are the same throughout. However, this is not exactly the case. Firstly, the Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients with Heart Failure (OPTIMIZE-HF) study data from 48, 612 patients provided two hundred fifty-nine patients participating in US hospitals with process-of-care improvement tools, which included evidence-based best-practice algorithms and customizable admission and discharge sets. Participation in the study was associated with increase in evidence based prescribtion, shorter hospitalizations and in hospital mortality, and use of process-of-care improvement tools and preprinted admission order sets further improved benefits [56]. Ensuring other factors like staffing and consistency in the distribution of services can also impact outcomes by ensuring that management for patients is always optimal [57]. The importance of OPTIMIZE-HF for the type 2 CRS was highlighted by Ezekovitz *et al*. who followed 6247 patients with CHF with angiographically proven coronary artery disease for 12 months. RI is common, greater in those with more advanced coronary disease, less likely to be prescribed prognostic therapies but achieve better outcomes when they are. Prognostic therapies seem to be prescribed contarary to CRS severity. In 7,487 patients in SOLVD, 6-17.5% were undertreated due to perceived contraindications where only 11 (0.15%) had azotemia and the average increase in SCr was 0.02 mg/dl [58]. In the HOPE study, hyperkalaemia (< 6.5mmol/l) did not increase cardiac risk but hypokalaemia (<3.5) did [59]. This study and others have raised the issues of inadequate therapies, with subtherapeutic dosing particularly due to few randomized control trial guides to follow and the fear of aggravating RI [15]. This problem can be particularly severe for the elderly where CHF (both systolic and diastolic) and, RI are more prevalent, the severity of both diseases seems to be parallel, and are among the most likely diseases to be undertreated [60, 61].

Optimizing Preventive Strategies

Prevention ought to occur in two stages: diagnostic, or finding risk parameters timely to be able to assess risk; and therapy, or instating treatments prior to disease onset or at the very earliest stages. In renal diagnostics we have sufficient tools such as urinary albumin creatinine ratios (UACR), which has now a long track record. Numerous studies have now confirmed that UACR can be used to diagnose and monitor the effects of treatments such as the RAAS blockers [62]. This test may still be underutilized by cardiologists in context of Type 2 CRS. There are still no adequate CHF guidelines for this. Several important cardiac surrogates are BNP and left ventricular hypertrophy. In this context, to obtain this information in asymptomatic individuals can be costly because it requires time, laboratory resources and equipment. However, in higher risk communities without CHF, McGrady *et al*., recruited 3550 patients, 664 patients were with the highest NT-proBNP quantile as compared to the lowest quantile who were older, and more likely to have left ventricular dysfunction, coronary disease and RI [63]. Left ventricular hypertrophy (LVH) similarly portends a poorer prognosis. Similarly, BNP provides a retrospective physiological profile of pressure and stress in the circulatory systems, which is similarly shared by the kidneys. When screening at a population level, data from the Framingham study suggest it to be an early surrogate for a number of cardiac specific diseases and comorbidites [64, 65]. LVH itself predates LVF and often with ongoing stress and perhaps an additional stress like RI [66, 67]. It thus becomes clearer that type 2 CRS, is a part of a larger cardiorenometabolic axis [66] that is interconnected throughout, where primary organ involved is perhaps the greatest differentiating factor. To be able to optimize prevention and ensure timely institution of therapies, we also need to understand how to best use the established and novel biomarkers.

Variations in Pathophysiology and Inherited Factors

There are several important areas including wider therapeutic options that factor inherited variations in pathophysiology. The guidelines are gradually factoring in these points [68], however, it is not enough. All CHF RCT

involving prognostic pharmacotherapy had a cut off which exclude more severe grades of RF ranging from SCr >151 to >300 μmol/l. Cruz et al. explored the correlation of prognostic therapies and CHF and observed that only four studies on RAAS blockers have been published from which conclusions can be derived [54]. Moreover, newer RAAS agents, which have extra class benefits, including Telmisartan, have strong evidence in for cardiovascular prevention, hypertension and diabetic renal disease treatment with modulation of glucose control through PPAR-γ [69, 70]. It is also perhaps one of the few RAAS agents with robust evidence in Type 2-4 CRS [71]. Among beta-blockers (ββ), vasodilatory agents, such as carvedilol and nebivolol have been shown to better control but not associated with weight gain, diabetes mellitus (DM), and atherogenic dyslipidemia. Vasodilating properties are due to alpha-1 blockade and nitric oxide potentiation, respectively [72]. These extra benefits also warrant further consideration. Finally, the SHARP study showed that a low dose of simvastatin combined with ezetemibe can reduce renal contribution to cardiovascular atherosclerotic risk [73]. This study was unique in many ways, as all previous studies on cholesterol lowering in ESRD were found to be ineffective. Recent data from large numbers of patients have shown associations with higher doses of statins with renal and diabetic and risks [74, 75]. This is a significant consideration for all patients requiring statin treatment in HF and any stage of RI. Most importantly, the CHF guidelines have not factored these variables.

Neproprotection requires consideration for inherent risks to the kidney both acquired and inherited. The most important example of variations in CHF pathophysiology between groups was highlighted by the A/V-HEFT studies. Prior to this, there have been observations for variations in therapies in RAAS blockers, ββ and therapies for hypertensive disorders. In addition, large prospective population data also observed the phenotypic differences in African American participants. When the vasodilating combinations of a nitrate and hydralazine were prescribed in NYHA class III/IV, 1050 black patients showed significantly improved survival (43 percent reduction in the rate of death from any cause [hazard ratio, 0.57; P=0.01). These findings were not reproduced with prazosin and in other races [76]. On the contrary, the Australian Aboriginal population suffers from very high risks of CHF and renal impairment. Although there have been limited studies, correlations have been observed between chronic hyperfiltration, metabolic, oxidative and other stressors on reduction in the number of nephron for which Indigenous Australians who could start with 404,000 fewer nephrons than non-Indigenous Australians, are at significantly greater risk from baseline. This issue again highlights why the protection of a comorbid condition, such as in the Type 2 CRS is very difficult. Essentially, the playing field is not equal at the start and our current understanding only allows for one strategy.

Assisted Therapeutics

Management in the CRS is a collaborative endeavor where the aim is to ensure that the therapy is delivered timely and adequately. Regarding to personnel, it is a combination of medical, surgical, critical care and allied health. The reasons for this are that there are a range of basic and complex treatments that can be delivered. As this syndrome exists as spectrum from mild to end stage from both the cardiac and renal perspectives, all teams are responsible for greater care. It is however vital that all members should be well informed. The commencement of hemodialysis is an example. More complex treatments commencement of neprotoxic agents require close supervision with biomarker monitoring. Limiting iatrogenic causes for WRF are understated, in an attempt to achieve good doses. This can only occur within a team structure. Team discussions allow consensus of therapies on off label use or borderline indication in the guidelines. Two important examples are biventricular-pacing support and temporary institution of left ventricular assist devices, while pharmacotherapy is instated [77-80]. The ensuring improvement in LVF leads to positive effect on RF.

CONCLUSION

The classification of secondary RI following established CHF as the type 2 CRS is a much welcomed recent advancement. It is now very clear that there are established cardiorenal links, which requires greater accountability from those only treating the heart. It is also likely that this may evolve into a larger cardiorenalmetabolic axis question. It is, however unfortunate, that many other aspects of the science are not available. There are gaps in: a) epidemiological understanding of the temporal causality; b) pathophysiological understanding of differentials in risk and therapeutic benefits, greater specifics on hemodynamic and cardiac neurohormal factors on nephron filtration, compensation, feedback and risk of fibrosis, and the reverse when RI has developed; c) diagnostics to better predict risk either individually or as a panel which will complement clinical practice with cost-effectiveness; and d) a better and broader understanding of how to safely institute mainstay therapies, when to consider a wider therapeutic paradigm and when to utilize invasive therapeutics, which can be factored into generic CHF guidelines. How we factor research studies to answer these questions are going to be equally challenging. The platform for clinical trials may require a large cohort, but may not receive Industry funding, to answer these questions. What advancement in CRS and the Type 2 CRS is teaching us is that we have the capacity to understand risk better, but are lacking in the tools to routinely diagnose it and execute management better. It also calls for a newer approach to clinical trials that is more inclusive in recruitment and broader in the questions it can answer.

ABBREVIATIONS

ADQI	=	acute dialysis quality initiative
ADHF	=	acute decompendated heart failure
ββ	=	beta-blockers
CHF	=	chronic heart failure
CRF	=	chronic renal failure
Cys-c	=	cystatin-C
DM	=	diabetes mellitus
eGFR	=	estimated glomerular filtration rate

ESRF	=	end stage renal failure
GFR	=	glomerular filtration rate
IL-18	=	Interluekin-18
KIM-1	=	Kidney Injury Molecule-1
L-FABP	=	Liver-Type Fatty Acid-Binding Protein
LVH	=	left ventricular hypertrophy
NYHA	=	New York Heart Association
OPTIMIZE-HF	=	Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients with Heart Failure
RAAS	=	renin-angiotension-aldosternone system
RF	=	renal function
RI	=	renal impairment
SCr	=	serum creatinine
SNS	=	sympathetic nervous system
UACR	=	urinary albumin creatinine ratios
WRF	=	worsening renal function

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CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

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