Review Article

The Cardiorenal Syndrome: A Review

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

1. Introduction

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

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

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

hemodialysis, echocardiography was repeated and revealed normal systolic function.

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

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

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

2. Epidemiology

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

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

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

3. Classification: Cardiorenal or Renocardiac?

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

4. Pathophysiology

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

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

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

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

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

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

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

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

4.3. The Sympathetic Nervous System (SNS) in CRS. SNS activation is initially a protective mechanism in CCF patients, akin to RAAS activation. The aim is to maintain cardiac output by positive chronotropic and inotropic effects on the myocardium. Unfortunately, chronic SNS activation also results in numerous negative effects upon the cardiovascular system and kidneys. SNS overactivity leads to reduction in beta-adrenoceptor density within myocardium and also reduced adrenoceptor sensitivity in both renal [37] and cardiac failure [38]. Catecholamines are also thought to contribute to left ventricular hypertrophy seen in some patients [39]. SNS activation leads to increased cardiomyocyte apoptosis [40] and increases the release of the neurohormone Neuropeptide Y (NPY). NPY is a vascular growth promoter leading to neointimal formation (and thus atherosclerosis) [41], induces vasoconstriction, and also interferes with normal immune system function [42]. Renal sympathetic denervation in patients with resistant hypertension significantly improved renal function in one quarter of patients [43], and bilateral renal nerve ablation has been shown to reduce blood pressure at one-year followup
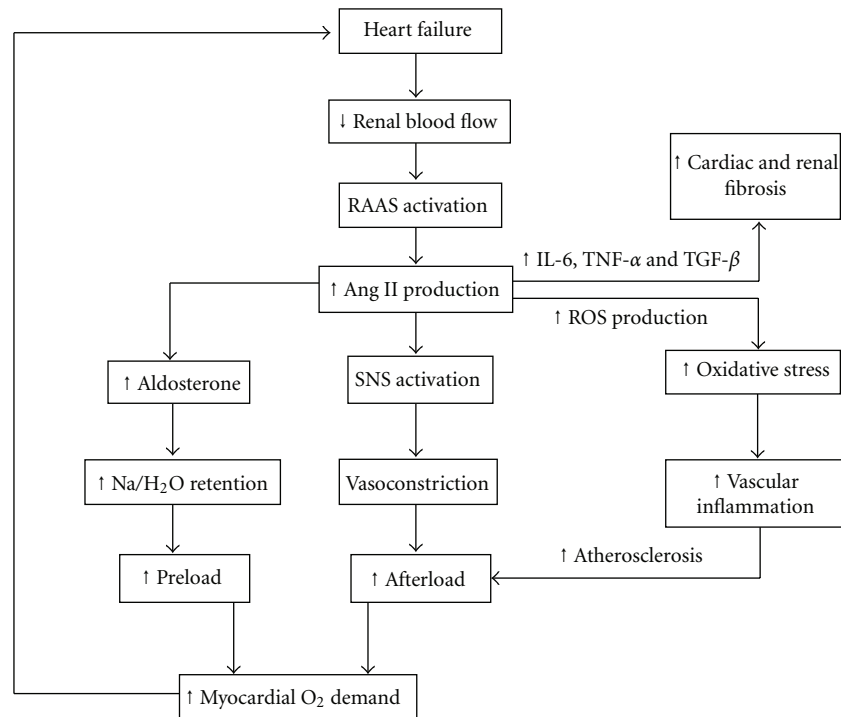
Figure 1: Illustration of the pathophysiological pathways activated by angiotensin II. Both preload and afterload are ultimately increased, leading to worsening cardiac and renal function (IL-6 = Interleukin 6; TNF-α = Tumour necrosis factor alpha; TGF-β = Transforming growth Factor beta; ROS = Reactive oxygen species).

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

4.4. Intraabdominal Hypertension: Underrecognised or Overemphasised?

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

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

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

hospitalisation due to ADHF and death due to pump failure [50].

4.5. The Cardiorenal Anaemia Syndrome (CRAS).

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

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

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

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

5. Management of CRS

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

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

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

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

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

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

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

5.3. Inotropic Support: The Controversy Continues. Patients with CRS are often hypotensive, and admissions due to ADHF frequently result in severe hypotensive episodes or frank cardiogenic shock. This may be accompanied by oligo-anuria, and inotropes are frequently used in this setting with the aim of improving cardiac output and thus renal blood flow. "Renal" or low-dose dopamine is known to increase renal blood flow [85] though there is conflicting evidence regarding its effect upon GFR [85, 86]. One study of 13 patients suggested that dopamine reduces renovascular resistance [87], though the baseline renal function of these patients is not stated. However, another larger study—in which 75% had acute renal failure—showed an increase in renovascular resistance in these patients with a fall in resistance in those with normal renal function [88]. Most

importantly, no clinical trial to date has demonstrated a mortality benefit [89].

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

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

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

6. Future Directions in CRS

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

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

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

Arginine vasopressin (AVP) is released from the posterior pituitary gland and mediates water retention via the V_2 receptor in the renal collecting ducts. AVP levels are elevated in heart failure patients and AVP antagonists (the "vaptans") have thus been developed. Tolvaptan was initially shown to reduce body weight and help normalize serum sodium in ADHF patients without adverse effect on blood pressure, heart rate, or renal function [102]. Later studies also demonstrated that tolvaptan, when compared to placebo, significantly reduced pulmonary arterial pressure, pulmonary capillary wedge pressure, and right atrial pressure as well as increasing urine output without adverse effect on renal function [103]. The multicentre international phase III Efficacy of Vasopressin Antagonism in Heart Failure Outcome Study with Tolvaptan (EVEREST) trial [104] randomised patients admitted with ADHF within 48 hours to receive either tolvaptan 30 mg once daily or placebo for a minimum time duration of 60 days. Tolvaptan was associated with more weight loss and less dyspnoea on days 1 and 7 and without adverse effect on renal function. However, the key end points of all-cause mortality, cardiovascular mortality, cardiovascular death, or hospitalization, and worsening heart failure were not different between the two groups [104].

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

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

7. Conclusion

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

Conflict of Interests

The authors declare no conflict of interests.

Abbreviations

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

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