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W H Wilson Tang,1 Wilfried Mullens2

ABSTRACT
Worsening renal function during treatment of acute decompensated heart failure (ADHF) often complicates the treatment course of heart failure. Furthermore, the development of worsening renal function is a strong independent predictor of long-term adverse outcomes. Sometimes referred to as ‘cardiorenal syndrome,’ the definition varies widely, and the overall understanding of pathogenesis is limited. This is probably owing to the lack of precision and characterisation of renal compromise during treatment of heart failure. Traditionally, the predominant cause has been attributed to impairment of cardiac output and relative underfilling of arterial perfusion. Emerging data have led to a resurgence of interest in the importance of venous congestion and elevated intra-abdominal pressure rather than confining it to impaired forward cardiac output as the primary driver of renal impairment. These revived concepts may support the role of novel renal-sparing approaches to salt and water removal and renal preservation, but better ways to distinguish haemodynamic versus other nephrotoxic aetiologies are needed.

INTRODUCTION
The complex interactions between the failing heart and the kidneys in regulating salt and water balance still puzzle cardiologists and nephrologists alike. This is in part owing to the imprecise nomenclature, but clearly the ability to sustain the filtration and tubular functions of the kidneys by therapeutic interventions is vital to successful alleviation of congestion. In the setting of decompensated heart failure, coexisting renal insufficiency often complicates the treatment course. This paper describes the contemporary pathophysiological insights of the so-called ‘cardiorenal syndrome’ and worsening renal function in congested patients receiving treatment, with specific discussions about present and future strategies aiming to achieve renal preservation in the acute decompensated heart failure (ADHF) setting.

DEFINITION AND EPIDEMIOLOGY
The conceptual term ‘cardiorenal syndrome’ has been used to describe a wide variety of clinical settings involving concomitant impairment of cardiac and renal function. However, the strict definition describes the condition whereby treatment to relieve congestive symptoms of heart failure is limited by further decline in renal function (box 1).1 Some investigators have even proposed classification schemes2 5 despite the fact that there is no universally accepted definition. The epidemiology and definition of the cardiorenal syndrome are also not well defined. However, we recognised that a subset of patients admitted with ADHF may fulfill a more concrete and quantitative description of the cardiorenal syndrome characterised as an 0.5–0.5 mg/dl rise in serum creatinine or a decrease in glomerular filtration rate (GFR) of 9–15 ml/min during ADHF admission.4 5 This is often referred to as ‘worsening renal function,’ and has been used in most outcomes research studies.

The ability to recognize and treat patients with cardiorenal syndrome is very important in improving our current therapeutic strategies, since acute worsening of renal function during treatment of ADHF is a strong and consistent independent predictor of adverse outcomes.5–8 Furthermore, those with worsening renal function often require a longer length of hospital stay.5 It is clear that patients with pre-existing renal dysfunction are vulnerable to developing worsening renal function upon diuretic administration.5 8 Risk factors for developing cardiorenal syndrome are illustrated in box 2. In particular, the presence of underlying intrinsic kidney disease is one of the strongest risk factors, as it determines the ‘reserve’ available for the kidneys to respond to the insult posed by ADHF and the aggressive diuresis and natriuresis needed during treatment of ADHF. In the Acute Decompensated Heart Failure National Registry (ADHERE), baseline moderate and severe renal insufficiency were common on presentation with ADHF, and powerful markers for risk prediction.10

DIAGNOSIS AND BIOMARKERS
The gold standard for measuring renal function is to examine the effectiveness of glomerular filtration (ie, GFR, either by direct measurement or by biomarker-based estimations). However, methodologies used to measure GFR often require quantification of a measurable filtrate within a given time period. Formulae to estimate GFR are often derived in the stable, ambulatory setting for quantifying severity of intrinsic renal diseases and never during large-volume diuresis in the decompensated states. Instead, changes in serum creatinine have been used as an easily measurable surrogate for status of renal function. However, it is important to emphasise that serum creatinine and GFR have an exponential relationship. Small rises in serum creatinine in the near-normal range can reflect large reductions in GFR. Especially in the elderly with low muscle mass (source of creatinine), patients may have seemingly low serum creatinine levels but reduced GFR. This may result in the under-recognition of underlying renal impairment.11 In our experience, up to two-thirds of patients with heart failure admitted with ADHF at our institution have at least moderately reduced estimated GFR (<60 ml/min per 1.73 m²), despite many of them having levels of serum creatinine in the ‘normal range.’

There are reasons to expand our vantage point beyond assessing glomerular filtration. In fact,
impaired tubular function due to a wide variety of reasons may be far more detrimental to the ability of the kidney to maintain adequate fluid and salt balance. Traditionally, blood urea nitrogen (BUN) has not played a major diagnostic role in cardiorenal syndrome because of the dependency of BUN levels on extrarenal factors such as protein intake, catabolism and tubular reabsorption efficiency. An increased ratio of BUN-to-creatinine is often suggestive of pre-renal azotaemia, which may warrant adjustment of diuretic regimens. Recent data from the ADHERE Registry suggested admission BUN as one of the strongest predictors of in-hospital mortality, and post hoc analysis of several clinical trials and cohort databases also indicate the importance of linking BUN (baseline or rise during treatment) to poor short- and long-term outcomes. Refractory hyponatraemia despite diuretic treatment is another important indicator for the kidney’s inability to compensate for the volume expansion regardless of cardiac output, and can be a potential indication of underlying diuretic resistance.

Many of these adverse effects have been attributed to overzealous intravascular volume depletion leading to activation of neurohormonal systems. However, direct proof is lacking as most mechanistic demonstrations predated the use of neurohormonal antagonists. Only resolution of fluid retention has been associated with reduction in neurohormonal levels in patients with advanced heart failure. Other renal abnormalities affected by heart failure or its diuretic treatment include the development of secondary hyperaldosteronism, micronutrient deficiency and electrolyte abnormalities—all may lead to progressive clinical deterioration.

**PATHOPHYSIOLOGY**

The exact pathophysiological mechanism(s) responsible for cardiorenal syndrome and worsening renal function are multifactorial and not well defined. An overall imbalance in interactions between the failing heart, neurohormonal system and inflammatory responses has been implicated. All of which, in a vicious cycle, have been postulated to cause structural and functional damage to the kidneys and the heart. Several haemodynamic factors influencing the development of cardiorenal syndrome and worsening renal function during ADHF include: (a) the adequacy of arterial filling and renal perfusion; (b) degree of venous congestion; (c) presence of raised intra-abdominal pressure.

**Arterial filling and renal perfusion**

Clinically, worsening renal function typically occurs within days of hospitalisation, suggesting a direct causative effect of the haemodynamic derangement seen while initiating treatment for ADHF. Traditionally, worsening renal function has been attributed to hypoperfusion of the kidney due to low-output failure or hypotension (leading to pre-renal hypoperfusion or impaired renal ‘preload’). The reduced cardiac output together with redistribution of diminished cardiac output to mainly brain and heart will lead to diminished renal perfusion and a ‘vasomotor nephropathy’ (figure 1). In addition, redistribution of blood from the arterial to the venous circulation leads to an effective reduction in renal blood flow. These signals will then lead to enhanced sodium and water absorption via stimulation of the sympathetic nervous system, renin–angiotensin–aldosterone system, and vasopressin secretion, all in order to try to preserve renal perfusion and renal filtration fraction. Persistent hypoperfusion may even lead to renal parenchymal/cortical ischaemia or infarction. However, such elegant concepts are often difficult to measure in individual patients at the bedside, and different patients may have different responses to the same clinical setting based on their underlying pathologies, treatment and comorbidities. There are even suggestions that a circulating ‘myocardial depressant factor’ may in return contribute to low cardiac output leading to a vicious cycle.

We now recognise that the presence of low cardiac output in ADHF can only explain part of the pathophysiology. Recent data from large registries argue against diminished forward flow to renal arteries as the sole culprit for the pathogenesis of cardiorenal syndrome. Clinically, the proportion of patients presenting with heart failure caused by diminished filling of the renal vasculature as a result of low cardiac output is relatively small. In most cases, the reduced renal blood flow caused by circulatory impairment promptly leads to compensatory increase in filtration fraction, which preserves the GFR and also more than offsets any reduction in renal blood flow. It is only in more severe heart failure with extremely high renal vascular resistance (caused by the activation of the neurohormonal axis) and markedly diminished renal blood flow, that GFR falls markedly without further increase in filtration fraction. Two recent observations from ADHERE may also support this
Figure 1  Pathophysiology of cardiorenal syndrome. AVP, arginine vasopressin; RAAS, renin—angiotensin—aldosterone system; RV, right ventricle, SNS, sympathetic nervous system.

notion: (a) the incidence of worsening renal function was similar among patients with ADHF and reduced versus preserved systolic function (the latter often presents with increased left ventricular impedance rather than impaired cardiac output); (b) most patients with ADHF present with elevated, rather than low systemic blood pressure. It is important to re-emphasise that diminished renal blood flow may still contribute to worsening renal function, as patients with progressive pump failure or cardiogenic shock often develop progressive renal impairment that is reversible with advanced support or even renal replacement treatments.

Venous congestion
The concept that elevated venous pressure is transmitted back to the renal veins and kidneys leading to renal dysfunction is supported by a substantial amount of (and largely forgotten) older literature. Several authors, as early as 1931 by Professor Frank Watkins, described in an experimental model that iatrogenically induced hypervolaemia and an increase in renal vein pressure lead to renal insufficiency independent of cardiac output or renal blood flow. This seemed to be, to a certain extent, a reversible phenomenon as lowering of renal vein pressure immediately improved urine output and GFR. Other studies have also indicated that temporary renal vein compression results in reduced sodium excretion, increased renal interstitial pressure and reduced GFR.

In larger and more contemporary clinical experience, increased central venous pressure (CVP) had the strongest association with reduced GFR in patients with pulmonary hypertension as well as in those with cardiovascular diseases, particularly in those with evidence of low renal blood flow. With the kidney being an encapsulated organ, it was thought that increased venous pressure might distend the venules surrounding the distal ends of the tubules so that the lumen of the tubule could be obliterated until the pressure of the fluid within it exceeded that in the vein. Others simply postulated that increased CVP could be transmitted backwards to the renal veins and cause an increase in renal interstitial pressure. This may lead to a hypoxic state (ischaemia) of the renal parenchyma similar to the mechanism by which hepatic congestion leads to liver failure in heart failure. Furthermore, intrarenal but also systemic angiotensin II concentrations may increase with increasing renal venous pressure. This will lead to a further fall in GFR and will increase sympathetic system activity. Finally, counter-regulatory mechanisms to decrease sensitivity of the tubuloglomerular feedback may be blunted in heart failure, thereby compromising the maintenance of GFR. The combination of such haemodynamic and neurohormonal alterations induced by venous congestion will ultimately lead to a downward spiralling of renal function.

Raised intra-abdominal pressure
Patients with progressive cardiorenal compromise may complain of ‘fullness around the abdomen’ and have increased abdominal girth. Interestingly, frank ascites can be found only in a small subset of cases, and the others have been attributed to the presence of visceral (tissue) oedema as a result of progressive whole-body fluid accumulation. Extensive surgical literature has highlighted the contribution of raised intra-abdominal pressure (IAP, often up to 15–20 mm Hg, normal range 5–7 mm Hg) as part of the ‘abdominal compartment syndrome’ towards progressive renal compromise in surgical catastrophes. It has been recognised over the past century that elevated IAP can directly lead to renal compromise in the setting of abdominal compartment syndrome or other surgical conditions involving ascites or visceral/interstitial oedema. Elevated IAP may indirectly increase CVP as well as directly ‘compressing’ the kidneys, both leading to reduction in renal perfusion. The prevalence of raised IAP in patients with advanced heart failure admitted with haemodynamic derangements may be as high as 60% despite the lack of abdominal complaints. In particular, elevated IAP was associated with more impaired renal function at baseline. Also, improvement in renal function after intensive medical treatment was associated with a reduction of IAP in most patients, while a subset of patients who were unable to normalise IAP were associated with worsening renal function regardless of central haemodynamic measures. In the latter group, prompt reduction in IAP has been observed with the use of mechanical fluid removal, either by paracentesis (in the presence of ascites) or ultrafiltration.

IMPLICATIONS FOR THERAPEUTIC STRATEGIES
Three major therapeutic goals have evolved in the contemporary and future management of cardiorenal syndrome during admission for ADHF: (a) to avoid causing short-term harm with existing ADHF treatments; (b) to augment surveillance of (and to identify those at risk for) cardiorenal dysfunction; (c) to develop...
renal-preserving treatments. We will elaborate on these specific goals.

Avoid short-term harm with existing ADHF treatments
During intensive medical treatment with intravenous loop diuretics, GFR is often reduced owing to alterations of the delicate balance between intra- and extrarenal haemodynamics. Compartmentalisation of fluid retention must therefore play a role when the primary task of loop diuretics is to deplete sodium (and subsequent fluid) while relying on the refilling from extravascular sources. Therefore, treatments that fail to reduce the kidney congestion will probably aggravate or induce progressive renal dysfunction. Aggressive intravenous loop diuretic infusion tailored to decrease venous congestion and maximise urine flow and effective volume loss results in improved haemodynamics and heart failure symptoms and normalises renal function in most cases.20 Also, the Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterization Effectiveness (ESCAPE) trial has shown that renal function did not worsen when treatment was directed at lowering invasively measured CVP and pulmonary capillary wedge pressure, while it did worsen in the treatment arm guided by clinical assessment alone.43–44 A delicate balance of facilitating the consistent refill of intravascular volume removed by loop diuretic treatment from extravascular compartments is necessary to maintain renal perfusion and filtration.

Augment surveillance of cardiorenal dysfunction
The degree of creatinine rise has a highly variable effect on mortality that is dependent on the population studied.5 45 Newer biomarkers may indicate earlier or more cardiac-specific compromise with the combination of biomarkers like natriuretic peptides,46–47 cystatin C,48 or neutrophil gelatinase-associated lipocalin (NGAL).49 For example, if natriuretic peptide levels remained low, mortality rates were similar among patients with versus those without creatinine rise, which clearly indicates the importance of the cardiac substrate for such pathology.47 Haemodynamic monitoring devices can allow doctors to observe haemodynamic alterations in ambulatory patients with advanced heart failure (even remotely through the phone or internet). Their ability to provide haemodynamic guidance to the management of congestion is currently undergoing investigation.50

Develop renal-preserving treatments
Several treatment strategies are currently under investigation with the aim of renal preservation, although in most cases this hypothesis has yet to be proved (table 1). Selected patients with ADHF might benefit from certain device-based treatments. Catheter-based targeted delivery of drugs into the renal arteries is not a remote possibility. Direct intrarenal delivery will lead to decreased kidney congestion and maximise urine flow and effective volume loss than with intravenous diuretics alone, and were associated with a reduction in 90-day resource utilisation for heart failure.54 However, there are clear barriers to the broad adoption of clinical ultrafiltration, including its invasiveness and cost.

Most attention has focused on the potentially ‘renal-sparing’ role of synthetic natriuretic peptides or other drug classes in the treatment of ADHF. Clinical trials have demonstrated the efficacy of nesiritide in improving haemodynamic parameters and symptoms.55–56 Although there might be a modest natriuretic and diuretic effect with the drug, nesiritide treatment does not obviate the need for concurrent diuretic treatment.56 There have been concerns about renal insufficiency and even mortality at the expense of short-term symptomatic relief, although broader clinical experience has attributed such risks to avoidable hypotension associated with overzealous treatment. New-generation compounds like the adenosine A1 receptor blockers not only inhibit sodium reabsorption but also reverse the afferent arteriole vasoconstriction and underfilling, leading to improved natriuresis and diuresis.57–59 Novel devices that directly deliver drugs to the renal arteries or ameliorate excessive renal sympathetic drive are also promising in early clinical investigations. Understanding the role of all these new, promising, but expensive treatments will require greater insight into the pathophysiology underlying the cardiorenal interactions.

Table 1  Major ongoing clinical trials of renal-sparing treatment strategies

<table>
<thead>
<tr>
<th>Drug</th>
<th>Trial acronym</th>
<th>Phase</th>
<th>Sample size</th>
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<tr>
<td>Natriuretic peptides</td>
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<tr>
<td>Adenosine A1 receptor antagonists</td>
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<tr>
<td>Roleoflump</td>
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<td>BG-9928</td>
<td>POSEIDON/TRIDENT</td>
<td>II/III</td>
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<td>Ultrafiltration</td>
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CONCLUSION
Therapeutic strategies used to treat ADHF have been largely unchanged over the past few decades especially in relation to preserving cardiorenal interactions. Recognising that worsening renal function is an important and prevalent adverse outcome in...
ADHF with a complex pathophysiology, careful re-evaluation of important contributing factors and technological advances to characterise, as well as deliver, appropriate interventions may lead to safer and more effective ways to relieve congestion and improve haemodynamics.

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REFERENCES


