Our understanding of the cardiorenal syndrome continues to progress. Decades of research have led to a better definition of the clinical cardiorenal syndrome and have laid the groundwork for understanding its pathophysiology. Although improvements have been made, there are still knowledge gaps concerning the interactions of these two organ systems. In the present review, we examine those interactions in the setting of acute and chronic cardiac decompensation and the resulting impacts on renal dysfunction. Recognition and prevention of this syndrome may help to better serve a growing patient population.

Key words
Cardiorenal syndrome, chronic kidney disease, coronary artery disease, heart failure

Introduction
The clinical entity known as the cardiorenal syndrome is a growing conundrum. The term attempts to convey the relationship between the cardiovascular and renal organ systems, whose interconnection has actually been appreciated for quite some time. Several decades ago, Dr. Arthur Guyton described mechanisms of feedback through cardiac hemodynamics that lead to dysfunction of both organs.

This concept of worsening renal function secondary to poor left ventricular function has evolved to an understanding of other pathophysiologic mechanisms. Attempts to describe the interactions have led to a clinical classification system (Table I) based on the initial organ and the chronicity of dysfunction (1). Classification of a problem is helpful, but the continued morbidity and mortality reveal that understanding the pathophysiology and potential treatment options is paramount. In the present review, we focus on the implications of acute and chronic cardiac decompensation for renal dysfunction (cardiorenal syndrome types 1 and 2).

Discussion

The acutely decompensated heart: cardiorenal syndrome type 1
Renal dysfunction in the setting of an acutely decompensated heart has been shown to result in poor outcomes. The Acute Decompensated Heart Failure National Registry evaluated more than 100,000 patients admitted with a diagnosis of acute decompensated heart failure. The registry showed that more than 30% of patients hospitalized had a history of renal insufficiency and that 20% had serum creatinine levels in excess of 2.0 mg/dL (2). In a subsequent analysis of the registry, Fonarow et al. demonstrated that the best predictors of in-hospital mortality were a high level of blood urea nitrogen (>43 mg/dL) and serum creatinine [sCr (>2.75 mg/dL)] at admission (3).

Acute cardiac decompensation is most commonly caused by an ischemic event. The American Heart Association estimated that, in 2010, more than 1 million people in the United States had either a new or recurrent ischemic coronary event (4). In this setting of an acute coronary event, the potential complications of
contrast-induced nephropathy (CIN) and cardiogenic shock can lead to significant renal dysfunction.

Contrast-induced nephropathy is a potential complication of coronary angiograms performed in the setting of ischemic heart disease. Various studies have looked at whether changes in the available types of radiocontrast media over the past several decades have affected the incidence of CIN. One of those studies, performed by Rudnick et al., demonstrated that the incidence of increased sCr (defined as an increase greater than 1.0 mg/dL) was lower with a nonionic than with an ionic contrast medium (3.2% vs 7.1%).

A subgroup analysis (Table II) showed that CIN was higher in patients with both renal insufficiency and diabetes at baseline (5). The availability of various contrast media has led to differences in reported incidence rates, which range from 0% to as high as 50% in high-risk individuals (6). Regardless of the contrast medium used, the risk of CIN can potentially be reduced by identifying high-risk patients and by limiting the amount of contrast used.

Patients presenting with cardiogenic shock already experience significant mortality. When shock is associated with kidney injury, mortality rates are worse. Marenzi et al. published data on patients presenting with an ST-elevation myocardial infarction complicated by cardiogenic shock and showed that acute kidney injury (AKI) occurred in more than 50% of those patients. Patients whose course was complicated by AKI had a mortality rate of 50%, which was significantly higher than the 2.2% in patients without that complication (7). Koreny et al. showed similar results in a population of post-infarction patients in cardiogenic shock. The in-hospital mortality rates in their analysis were increased by more than 30% in the setting of acute renal failure compared with normal renal function (8). These two studies demonstrate that AKI is a serious complication that portends poor outcomes.

Kidney injury in the heart disease setting is likely a result of hypoperfusion secondary to poor cardiac output. In hypoperfused kidneys, the renin–angiotensin–aldosterone system (RAAS) is activated. The juxtaglomerular apparatus releases renin in this setting, starting a cascade in which angiotensinogen is eventually converted to angiotensin II (AngII), among other byproducts (9). The AngII leads to vasoconstriction, aldosterone secretion, and a high level of oxidative stress. Vasoconstriction of the renal arterioles is likely mediated by an increase of endothelin 1, a byproduct of increased AngII levels (10). Other end-products (such as aldosterone) result in water retention by reabsorption of sodium from the distal tubules. The net effect is an increase in pulmonary vascular congestion and worsening renal ischemia that perpetuates RAAS activation.

Early detection of AKI in this setting may potentially protect the kidneys through early institution of treatment. The commonly used biomarkers such as sCr and blood urea nitrogen may not identify subtle injury to the kidneys and may therefore delay diagnosis.

Recent research has focused on novel biomarkers for the detection of AKI. One such marker, neutrophil gelatinase–associated lipocalin (NGAL), is a protein that has been shown in mouse models to be released in early renal ischemia (11). In the setting of cardiac surgery patients, Mishra et al. demonstrated that NGAL concentrations were elevated several hours after surgery—compared with days when sCr alone is being measured (12). Recently, NGAL was also noted to be overexpressed in hypertensive patients and the walls of aortic aneurysms; it is also potentially linked to atherosclerosis (13). The pathophysiologic mechanism is secondary to NGAL mediation through the inflammatory cascade and is released by activated neutrophils. These other potential applications of NGAL are being further investigated.

### Chronic heart failure: cardiorenal syndrome type 2

In the setting of chronic heart failure, renal function predicts outcomes. In one study, glomerular filtration rate (GFR) was inversely proportional to the likelihood of hospitalization and cardiovascular death (14). As

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<th>Group</th>
<th>Condition</th>
<th>CIN incidence (%)</th>
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<tr>
<td></td>
<td>RI DM</td>
<td>Nonionic contrast</td>
</tr>
<tr>
<td>1</td>
<td>– –</td>
<td>0.0</td>
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<tr>
<td>2</td>
<td>– +</td>
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<tr>
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* From Rudnick et al. (5).

Renal insufficiency = serum creatinine ≥ 1.5 mg/dL; CIN = increase of serum creatinine by more than 1.0 mg/dL in 48 – 72 hours.
mentioned earlier, the background pathophysiology is thought to be poor cardiac output that leads to activation of RAAS and negative myocardial remodeling. Although this concept is the prevailing one, it may not be the only pathophysiologic mechanism leading to worsening renal function. The feed-forward mechanisms of AngII and increased inflammatory markers and reactive oxygen species (Figure 1) further exacerbate these abnormalities (15).

The Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterization Effectiveness (ESCAPE) trial assessed the effectiveness of therapy guided by a pulmonary artery catheterization (PAC) compared with that guided by clinical assessment alone in heart failure patients. The 433 patients enrolled into the study had a median baseline sCr of 1.5 mg/dL and a median GFR of 71.4 mL/min (16). In a post-hoc analysis of the 193 patients in the PAC arm, no correlations were observed for sCr or GFR with pulmonary capillary wedge pressure, cardiac index, or systemic vascular resistance. Patients in the PAC arm had a significantly improved cardiac index (to 2.4 L/min/m² from 1.9 L/min/m²), but that change did not affect renal function (17). These results suggest that mechanisms other than decreased perfusion secondary to reduced cardiac output are at work (Figure 1).

Although improvement in cardiac output did not improve renal function in the ESCAPE trial, a significant correlation was observed for right atrial pressure with baseline sCr and GFR. That finding has been validated in other studies. In 145 patients admitted with decompensated heart failure, Mullens et al. demonstrated that higher baseline central venous pressure was associated with a higher risk of worsening renal function. When a central venous pressure of less than 8 mmHg was achieved, the renal function worsened less often (18). As in the ESCAPE trial, cardiac index showed no correlation with worsening renal function, showing that other cardiorenal hemodynamic interactions such as systemic venous congestion can cause renal dysfunction. Increases in venous pressure can reduce the gradient across the glomerular capillary bed, affecting renal perfusion. Studies have also suggested that external compression of the renal veins leads to worsened renal function (19). In this setting of elevated right atrial pressure, it is interesting to note that the release of atrial natriuretic peptides has little effect in maintaining intravascular volume, a result that may in part be secondary to the effects of RAAS activation and resistance of the kidneys to atrial natriuretic peptides.

Another pathophysiologic mechanism that may explain worsening renal function in the setting of chronic heart failure is an increase in sympathetic activation. Catecholamine levels increase in an attempt to improve inotropic and chronotropic responses of the left ventricle, improving cardiac output. Although initially helpful, chronic sympathetic activation leads to downregulation of beta receptors and serves to diminish cardiac output. Other negative effects such as left ventricular hypertrophy can also worsen ventricular function. Vasoconstriction caused by catecholamines can lead to RAAS activation, perpetuating positive

![Figure 1 Schematic diagram of the potential mechanisms by which congestive heart failure may exacerbate renal dysfunction and feed forward to worsening heart failure. The vicious cycle of worsening heart failure that begets worsening renal function begetting worsening heart failure is perpetuated by inflammatory mediators and reactive oxygen species (ROS). RAAS = renin–angiotensin–aldosterone system; IL = interleukin; TNFa = tumor necrosis factor α; TGFβ = transforming growth factor β; AngII = angiotensin II; SNS = sympathetic nervous system. Adapted from Shah and Greaves (15).](image-url)
feedback mechanisms. Increased venous congestion and activation of the sympathetic nervous system may both serve to explain the results of the ESCAPE trial, demonstrating that renal dysfunction in chronic heart failure goes beyond just poor cardiac output.

Gaps in our understanding of cardiorenal syndrome types 1 and 2

Most of the knowledge about the pathophysiology of cardiorenal syndrome type 2 suggests that hemodynamically guided therapy should improve outcomes. However, the ESCAPE trial, a well-conducted trial that set out to test that hypothesis, showed no difference. Given those findings, a key remaining question is “Why does optimizing hemodynamics to increase cardiac index not improve renal function?”

Current understanding suggests that there must be a trigger for renal dysfunction at the initiation of these massive neurohormonal adjustments so common in chronic heart failure. Work conducted to understand this early trigger may prevent cardiorenal syndrome type 2. In addition, the current understanding of cardiorenal syndrome type 1 may be enhanced by the knowledge gained. In either scenario, substantial work at the basic pathophysiologic level must be undertaken to further knowledge so that these significant conditions can be treated and prevented.

Summary

The management of cardiorenal syndrome is an evolving challenge. Loop diuretics remain the standard therapy in exacerbated acute heart failure, although their overuse can cause hypovolemia and RAAS activation. Initial studies on other options, such as nesiritide and ultrafiltration, seem promising, and more definitive trials are still underway. Adenosine receptor antagonists are another area of current investigation, because blockade of adenosine receptors has been shown to affect the vascular tone of renal arterioles. The availability of these treatment options is expanding, but effective treatment begins with an understanding of the pathophysiology of the cardiorenal axis. Future studies of novel markers for prevention and potential treatments for reversal of renal dysfunction caused by heart failure will perhaps alleviate the impact of cardiorenal syndrome. Until then, this clinical entity will continue to be a complex challenge for all clinicians.

Disclosures

The authors have no financial conflicts of interest to declare.

References


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