When Cardiac Failure, Kidney Dysfunction, and Kidney Injury Intersect in Acute Conditions: The Case of Cardiorenal Syndrome

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Objective: To review and describe diagnostic and prognostic value of biomarkers of renal function and renal injury in the cardiorenal syndrome complicating acutely decompensated heart failure.

Data Sources: PubMed search and review of relevant medical literature.

Study Selection: Two reviewers screened and selected studies in English with diagnostic or prognostic assessment of biomarkers of renal injury.

Data Extraction: Narrative review of the medical literature.

Data Synthesis: Cardiorenal syndrome has a complex pathophysiology and has a generally poor prognosis in patients with acutely decompensated heart failure. Among the methods to recognize risk for cardiorenal syndrome may be the use of circulating or urinary biomarkers, which may allow for more accurate early diagnosis and risk stratification; use of biomarkers may provide important pathophysiologic understanding beyond risk prediction. However, different phenotypes of patients with acute renal dysfunction may be present, which has ramifications with respect to response to treatment strategies. Addition of biomarkers of renal injury may provide additional prognostic value to biomarkers of renal or cardiac function, but more data are needed.

Conclusions: Biomarkers reflecting renal function and injury are likely to better phenotype subgroups of patients with cardiorenal syndrome and to provide unique prognostic information. Future studies are needed relative to strategies using such biomarkers to guide care of affected patients. (*Crit Care Med* 2014; 42:2109–2117)

Key Words: acute kidney injury; biomarkers; mortality; outcome; renal failure; treatment

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Acute renal failure due to acutely decompensated heart failure (ADHF) is so commonplace, and it has been called cardiorenal syndrome (CRS) (1). CRS has been associated with poor prognosis, with the occurrence of worsening renal function (WRF) strongly associated with mortality in this setting. Early recognition of CRS and better understanding of its pathophysiology are critical to guide therapy and hopefully improve outcome of affected patients. CRS is present in almost half of the patients admitted for ADHF without shock and in 71% in case of cardiogenic shock (2). Among the promising emerging methods to recognize risk for CRS may be the use of circulating or urinary biomarkers, possibly

for more accurate early diagnosis and risk stratification. Use of biomarkers has an advantage in that they provide important pathophysiologic understanding as well. In this review, we will summarize available data regarding biomarkers of renal function and renal injury and discuss their potential value in patients with ADHF.

CURRENT UNDERSTANDING OF THE PATHOPHYSIOLOGY OF CRS

The CRS has been classified into five subtypes (**Table 1**). Type 1 CRS, representing the renal consequences of acute heart conditions, will be our focus in the present review (3). ADHF represents the leading cause of the CRS; besides the intersection of medical factors leading to heart failure (HF) and renal disease, causes of CRS include systemic hemodynamic factors, deranged intrarenal hemodynamics, and activation of inflammation/immune pathways; therapy intervention in acute setting is a frequently neglected cause of WRF in this setting as well.

Role of Systemic Hemodynamics

The role of renal venous congestion has long been thought to be critical for the development of CRS. Winton (5) observed that an increase in renal venous pressure above 24 mm Hg diminished renal blood flow in an ex vivo study of dog kidneys. Later, other authors showed that increased venous pressure led to substantial change in renal structure and function, related in part to induction of renal hypoxia, increase interstitial pressure, increase in local oxidative stress, immune and inflammatory processes, and interstitial fibrosis (6). Interestingly, maintenance of renal perfusion pressure did not entirely protect the kidney (7), suggesting that increased venous pressure independently affects renal function and structure.

Convincing clinical data recently highlighted this association between elevated central venous pressure (CVP) and the risk of WRF (**Table 2**). A key point, however, is that isolated moderate increase of right atrial pressure or renal vein pressure is not sufficient to induce renal dysfunction, but in the context of complex pathophysiology, the risk for renal injury rises. Strategies to decrease elevated renal vein pressure in patients with CRS may be associated with an improvement of renal function (8); readers can refer to a recent extensive review on this subject (9).

Reduced renal blood flow in the context of ADHF (especially in case of low cardiac output or cardiogenic shock) may contribute to the development of CRS, although clinical data showing that increasing renal blood flow prevents or reverses CRS are scarce, and the true contribution of impaired cardiac output remains debated. Indeed, cardiac output and/or left ventricular ejection fraction poorly predicts the occurrence of WRF in ADHF (4), and short of cardiogenic shock, in most cases, cardiac output appears more than sufficient to maintain renal perfusion to an adequate level. Thus, other important factors must be considered, notably intrarenal congestion.

Role of Intrarenal Hemodynamics

Glomerular filtration is driven by the pressure gradient across the glomerular capillary walls, itself being determined by the opposing forces of the hydraulic and oncotic pressures gradients between the capillaries and the Bowman space. When renal plasma flow and/or renal perfusion pressure are compromised, autoregulation mechanisms respond to maintain glomerular filtration; this is achieved by modulating the vascular tone of the glomerular efferent and afferent arterioles (10). Although vasoconstriction of the efferent arteriole tends to maintain hydraulic capillary pressure and glomerular filtration rate (GFR), vasoconstriction of the afferent arteriole tends to decrease it. This process is regulated by tubuloglomerular feedback, which consists in an increase of the glomerular afferent arteriole vascular tone in response to a raise of solute concentration at the macula densa of the distal tubule. Patients with ADHF often have several factors known to impair renal autoregulation, including up-regulation of the renin-angiotensin-aldosterone system (RAAS), hypertension, diabetes, atherosclerosis, and treatment with angiotensin-converting enzyme (ACE) inhibitors; as well, acute kidney injury (AKI) itself may lead to impaired autoregulation (**Fig. 1**).

Role of Inflammation

The role of systemic inflammation and infiltration by immune cells appears to lay a major role in the development of ischemic or septic AKI (11). HF has furthermore also been associated with systemic inflammatory response and elevated concentrations of circulating cytokines (12). A role of inflammation and activation of immune cells has therefore been proposed to participate into the mechanism of renal damage and renal failure in

TABLE 1. Summary of Different Types of Cardiorenal Syndromes According to Ronco et al (3)

CRS Type	Condition	Definition
Type 1	Acute CRS	Rapid worsening of cardiac function leading to acute kidney injury
Type 2	Chronic CRS	Chronic abnormalities in cardiac function leading to progressive chronic kidney disease
Type 3	Acute renocardiac syndrome	Abrupt and primary worsening of kidney function causing acute cardiac dysfunction
Type 4	Chronic renocardiac syndrome	Primary chronic kidney disease causing decrease cardiac function, ventricular hypertrophy, diastolic dysfunction, and/or increased risk of adverse cardiovascular events
Type 5	Secondary CRS	Presence of combined cardiac and renal dysfunction due to acute or chronic systemic disorders

CRS = cardiorenal syndrome.

TABLE 2. Summarizing Clinical Studies of Association Between Hemodynamics Variables and Development of Cardiorenal Syndrome

Reference	Year	Variables Investigated	Patients	Population	Main Results
Legrand et al (36)	2013	CO, central venous oxygen saturation, mean arterial pressure, SAP, DAP, CVP	137	Patients with severe sepsis	Only CVP and DAP were associated with the development of AKI
Drazner et al (37)	2013	RAP	433	Patients hospitalized with HF randomized in PAC group or standard care	High RAP was associated with impaired renal function. No influence of PAC monitoring on WRF
Tanaka et al (38)	2011	Inferior vena cava diameter	20	Patients with dilated or hypertrophic HF and renal dysfunction	GFR was correlated to IVC diameter ($r = 0.5$, $p = 0.02$)
Guglin et al (39)	2011	CVP, RPP, CI, LVEF	178	Patients scheduled for right heart catheterization	GFR was correlated to CVP and RPP but not CI and LVEF
Damman et al (40)	2010	Clinical signs of congestion	2,647	Chronic patients with HF	Clinical signs of congestion were independently associated with alteration of GFR ($p = 0.012$)
Testani et al (41)	2010	Echocardiography (RV function, CO)	141	Patients with HF	RV dysfunction and lack of inspiratory inferior vena cava collapse at admission were associated with significant improvement of renal function after improved volume status. CO was similar between those with or without WRF
Mullens et al (42)	2009	CVP, CI, PAOP	145	Patient with ADHF admitted to ICU with pulmonary arterial catheter	CVP was the most important hemodynamic variable associated with WRF in ADHF. SAP and PAOP were not predictive for WRF
Damman et al (43)	2009	CVP, CI	2,557	Patients who underwent right heart cauterization	CVP was independently associated with GFR and mortality. CI was associated with eGFR ($r = 0.123$, $p < 0.0001$)
Damman et al (44)	2007	RAP, CI	51	Patients with pulmonary hypertension candidate for lung transplantation	Low RBF and high RAP were associated with WRF. CI was associated with WRF only in univariate analysis but not in multivariate analysis
Van Biesen et al (45)	2005	CVP	257	ICU patient with sepsis and AKI	Patients developing AKI had higher CVP

CO = cardiac output, SAP = systolic arterial pressure, DAP = diastolic arterial pressure, CVP = central venous pressure, AKI = acute kidney injury, RAP = right atrial pressure, HF = heart failure, GFR = glomerular filtration rate, RPP = renal perfusion pressure, CI = cardiac index, LVEF = left ventricular ejection fraction, PAOP = pulmonary artery occlusion pressure, ADHF = acutely decompensated heart failure, PAC = pulmonary artery catheter, IVC = inferior vena cava, RV = right ventricle, RBF = renal blood flow.

CRS. An interrelation between renal injury and cardiac inflammation was described with activation of inflammatory pathways in the heart after renal ischemia-reperfusion (13). On the other hand, venous congestion has been proposed to induce systemic and renal inflammation, partially due to endotoxin release from the gut and activation of the RAAS and sympathic system (14). Systemic inflammation has in turn been shown to activate intrarenal adhesion molecules monocyte chemoattractant protein-1 (MCP-1), intercellular adhesion molecule-1, and vascular cell adhesion molecule-1, which all recruit immune cells, thus promoting local inflammation. To what extent inflammation participates in the development of CRS and how these systems interact remains, however, largely unexplored. Although we are not aware of favorable outcome associated with specific treatments targeting the inflammatory response, part of the potential benefit of ACE inhibitors might be mediated through control of inflammation and oxidative stress activation of angiotensin II, which has been shown to lead to regional increase in numerous inflammatory substances (such as tumor necrosis factor, interleukin-6, MCP-1, nicotinamide adenine dinucleotide oxidase, and nicotinamide adenine dinucleotide phosphate oxidase), as well as up-regulation of nuclear factor κβ.

UNDERSTANDING THE PROGNOSTIC IMPACT ASSOCIATED WITH WRF

Clinically, the occurrence of acute WRF has long been recognized to be a strong determinant of poor outcome in patients

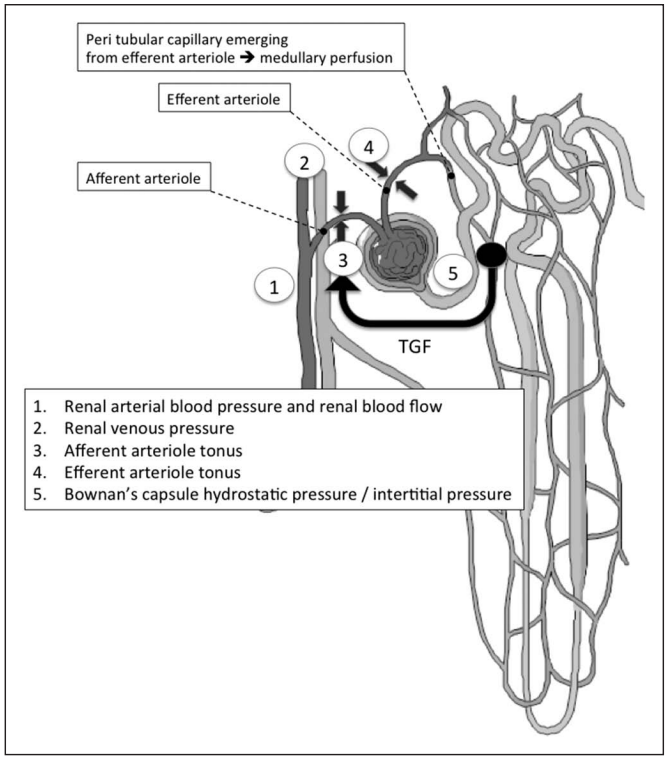

Figure 1. Intrarenal hemodynamic factors influencing both glomerular filtration (GFR) and renal blood flow and medullary perfusion. For instance, angiotensin-converting enzyme inhibitors can lead to uncoupling between GFR and renal perfusion; vasodilation of the efferent arteriole induces a decrease in glomerular capillary hydrostatic pressure, while increasing regional blood flow and medullary perfusion.
TGF = tubuloglomerular feedback.

with ADHF, with or without cardiogenic shock (15). This is indisputable. However, an important nuance to understanding CRS relates to the fact that not every rise in serum creatinine during treatment for ADHF is associated with the same poor prognosis. Testani et al (16, 17) have suggested that those patients treated with IV diuretics for ADHF that develop a slight decrease of GFR had a better survival compared with patients with stable GFR. The temporal relationship between renal impairment and choice and intensity of treatment is worthy of focus, in order to better understand the various "faces" of CRS.

Does Aggressive Care for ADHF "Uncouple" the Risk Associated With WRF?

In the current era, decongestion with loop diuretics remains the cornerstone of the treatment of ADHF, and although loop diuretics may themselves have toxic effects on renal function, good data suggest that aggressive removal of fluid is a necessary component of management of CRS; in this, the balance between renal dysfunction from therapy and that from CRS may be manageable, potentially "uncoupling" the risk of WRF in this setting. As an example, Testani et al (16, 17) observed in two large single-center cohort studies that patients with ADHF and CRS who received more aggressive fluid depletion and negative fluid balance throughout hospitalization may have had more exaggerated WRF but had better mid- and long-term outcome. Similar results were seen in a post hoc analysis of the PROTECT (Patients Hospitalized with Acute Decompensated Heart Failure and Volume Overload to Assess Treatment Effect on Congestion and Renal Function) trial (18). Similarly, in a separate prospective, double-blind, randomized trial, patients receiving high doses of furosemide (773 mg vs 358 mg over 72 hr) had more fluid loss and experienced more WRF (23% vs 14%, $p = 0.04$) (19). However, mortality was comparable between two groups while patients in the high-dose group had greater more relief from dyspnea. Similar results were seen in patients treated with aggressive unloading with either ultrafiltration or high-dose diuretic strategies (21); in this study, rise in creatinine consequent to more aggressive fluid removal was not obviously associated with a tax on short-term prognosis.

ACE inhibitor treatment may also influence the prognosis associated with WRF. Data indicate that those patients receiving ACE inhibitors were having better prognosis, particularly those with mild CRS (20). These results may indicate that WRF in these patients occurred due to change in glomerular hemodynamics but with no ongoing renal injury.

Besides diuretics, rapid removal of fluid via paracentesis or ultrafiltration may be associated with an improvement of renal function (8); however, studies comparing ultrafiltration to diuresis have returned mixed results relative to whether the former is better at mitigating CRS (21). Clearly, a better understanding of the phenotype of CRS is needed, to tailor therapy to the individual patient.

Importantly, it is worth mentioning that diuretic therapy or ultrafiltration was administered "blindly" in interventional studies but neither guided by physiology variables (CVP or other variables indicative of the fluid status) or biomarkers. This appears clearly a limitation to treatment best efficacy since not all patients are likely to respond "alike" to such treatments.

Are ADHF Patients With Improving Renal Function an Unrecognized Category of CRS?

Although being associated with higher mortality than normal renal function (22), improvement of renal function in patients with renal dysfunction at admission (defined as a 20% increase of estimated GFR during hospitalization) is associated with lower risk than persistent CRS (2). These results may arise from different causes. First, patients presenting with renal dysfunction at admission are likely to be patients with most severe forms of HF and chronic kidney disease, identifying a more vulnerable, fragile patient. Second, initial renal dysfunction may have led to discontinuation (or no introduction) of treatments known to positively affect outcome or to the introduction to inotropic agents with their well-described potentially negative impact on outcome.

Together, these data suggest that different subtypes of patients with abnormalities of renal function exist, yielding different risk profiles, and as a consequence, better delineation of the mechanism of renal dysfunction in ADHF is necessary. In this line, there is great expectation that biomarkers may better phenotype subgroups of patients with WRF.

RENAL FUNCTION VERSUS RENAL INJURY IN ADHF: THE POTENTIAL VALUE OF BIOMARKERS

In regard to the foregoing discussion, it is worthwhile to concede difficulty in accurately diagnosing CRS using clinical means. Indeed, the current definition of WRF lies on an identification of creatinine change (usually defined as a rise of 0.3 mg/L or > 50% of baseline) in the context of a clinical syndrome, such as ADHF. As a rise in creatinine is well recognized to lag well after AKI and changes in creatinine are agnostic to the mechanism of AKI this is an imperfect tool. As well, urine output is not included in most clinical studies of CRS.

To better refine the phenotypes of CRS, we have suggested that other biomarkers may provide a more mechanistically driven means by which CRS may be diagnosed (23). Such biomarkers may include those reflecting renal function and injury (**Fig. 2**).

Biomarkers of Renal Function in CRS

Alteration of baseline renal function has been reported in several studies both to increase the risk of CRS and to be associated with higher short- and long-term mortality rates. Although serum creatinine and estimation of GFR represent the two most widely used ways to assess renal function, as noted above, in the context of CRS, both are less trustworthy. Beyond the limitations noted above, formulae to estimate GFR have not been validated during acute changes in renal function (**Supplemental Table 1**, Supplemental Digital Content 1, http://links.lww.com/CCM/A974).

Blood Urea Nitrogen. Neurohormonal activation plays a critical role in the pathogenesis of both ADHF and CRS and is of substantial prognostic meaning in this population. In this regard, active plasma renin concentration has been shown to be associated with worse prognosis, particularly in patients with altered renal function (24). Because urea nitrogen reabsorption at the tubular level is under influence of the RAAS activation, blood urea nitrogen (BUN) has been proposed as a prognostic surrogate for neurohormonal activation in patients with ADHF (25). Indeed, several studies indicate BUN to be a stronger predictor of mortality than creatinine or estimated GFR (26).

Cystatin C. Cystatin C 13.3-kDa nonglycosylated cysteine protease inhibitor is produced by all nucleated cells of the body and released at a constant rate, freely filtered by the glomerulus, and then reabsorbed by the tubular epithelial cells where it is catabolized. Concentrations of cystatin C are not confounded by muscle mass or age, and the biomarker has been shown to be particularly superior to creatinine or estimation of GFR for identifying mild renal insufficiency. Although increase of plasma cystatin C is held as reflecting decrease of GFR, detection of cystatin C into the urine appears to be a biomarker of tubular injury and altered catabolism of the protein. Cystatin C is prognostic in patients with ADHF. For example, Manzano-Fernández et al (27) showed that cystatin C (and another peptide, β-trace protein [BTP], discussed below) was superior to serum creatinine, estimated GFR, and BUN in a population of patients with a median estimated GFR less than 60 mL/min. Lassus et al (28) observed that both a modest rise of serum creatinine (> 0.2 mg/L) and/or serum cystatin C were associated with mortality. Interestingly, among patients with slight increase of serum creatinine (> 0.2 mg/dL), only those with a concomitant rise in cystatin C more than 0.3 mg/L had higher risk of 90-day mortality. In cardiogenic shock, high cystatin C was also associated with mortality (29).

The role of cystatin C (either measured in blood or urine) for predicting onset or mechanism of WRF in patients with ADHF remains entirely unexplored and requires evaluation.

BTP. BTP is a low-molecular-weight glycoprotein (between 23 and 29 kDa), which has emerged as a promising novel marker of GFR. BTP is filtered and reabsorbed by tubular cells, so urinary BTP values may represent tubular dysfunction (30). Beyond its role for estimating

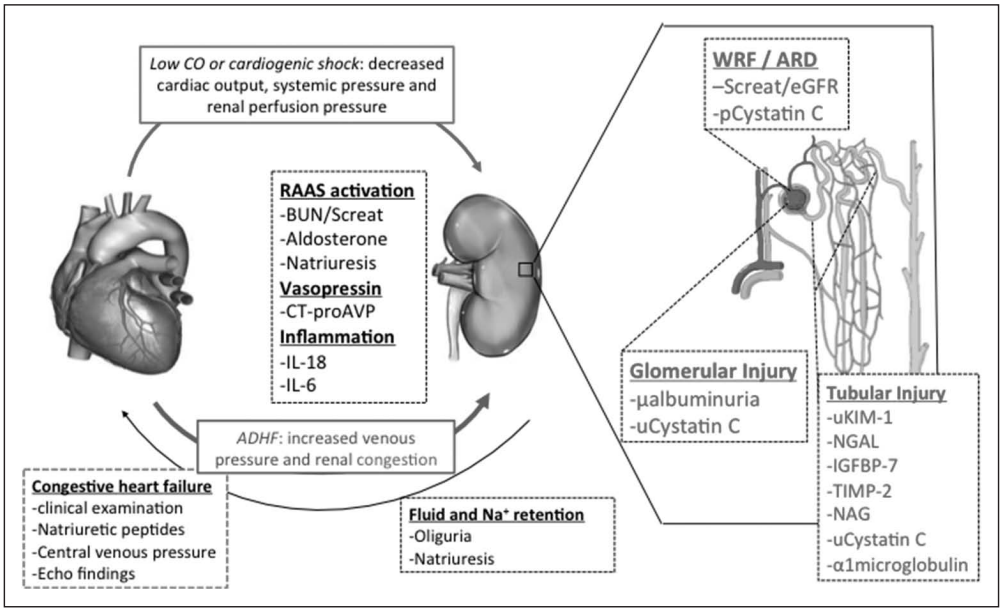

Figure 2. The potential role for biomarkers to assess different components of cardiorenal pathophysiology. Forward factors combined with backward factors (i.e., venous congestion) affect renal function and/or injury. In turn, renal injury can affect myocardial structure and function in inducing cardiac damage with a vicious circle leading to further deterioration of cardiorenal syndrome. CO = cardiac output, RAAS = rennin-angio tensin-aldosterone system, BUN = blood urea nitrogen, IL = interleukin, ADHF = acutely decompensated heart failure, WRF = worsening renal function, eGFR = estimated glomerular filtration rate, KIM-1 = kidney injury molecule-1, NGAL = neutrophil gelatinase–associated lipocalin, IGFBP-7 = insulin-like growth factor binding protein-7, TIMP-2 = tissue inhibitor of metalloproteinase 2, NAG = N-acetyl-β-D-glucosaminidase, CT-proAVP = C-terminal pro-arginine vasopressin, ARD = acute renal dysfunction.

renal function, BTP is also emerging as a novel biomarker in cardiovascular risk (27). Much like with cystatin C, the role of BTP to define phenotype and/or predict WRF remains unknown.

Biomarkers of Renal Injury

In analogy to the highly cardiac-specific troponins, substantial efforts have been made to identify specific biomarkers of renal injury. In theory, such biomarkers might be of value for predicting WRF. Although the characteristics and predictive value of several renal biomarkers have been extensively reviewed recently in different clinical settings, we review available data with respect specifically to patients with CRS (**Supplemental Table 2**, Supplemental Digital Content 2, http://links.lww.com/CCM/A975).

Neutrophil Gelatinase–Associated Lipocalin. Neutrophil gelatinase–associated lipocalin (NGAL) is a member of the lipocalin superfamily of proteins. It is a siderophore expressed in various types of cells including epithelial cells, freely filtered by the glomerulus and reabsorbed by proximal tubular cells (25). NGAL is also highly expressed in the ischemic kidney, mostly in the distal nephron segment, and has therefore been proposed as a highly sensitive biomarker of renal injury. Data regarding the value of NGAL to predict WRF in patients with HF have been conflicting, with most studies showing at best modest predictive value (Supplemental Table 2, Supplemental Digital Content 2, http://links.lww.com/CCM/A975). Part of the uncertainty about blood NGAL relates to its specificity: its expression has been shown to be under influence of various conditions, including chronic renal disease, atherosclerosis, inflammation, cancer, or myocardial damage (31). In this line, urine NGAL has been suggested more specific of renal injury than plasma NGAL. However, no study has so far supported this assumption in CRS.

Relative to prognosis, NGAL has been shown to identify patients at high risk for complications with ADHF. For example, in the NGAL evaLuation Along with B-type NaTriuretic peptide in acutely decompensated heart failure (GALLANT) trial, serum NGAL concentrations were additive to B-type natriuretic peptide (BNP) for prediction of death (32). In a multicenter study, Dupont el al (33) also found that urine NGAL was associated with death or rehospitalization at 180 days in a population of patients with ADHF.

Thus, much remains unknown about the role of NGAL in those with CRS, including the relative merits of blood versus urine measurement.

Kidney Injury Molecule-1. Kidney injury molecule (KIM)-1 is a type I transmembrane glycoprotein, undetectable in normal kidney tissue but highly expressed in postischemic kidneys, making it a potential marker for proximal tubular injury in CRS (34). In one pathophysiologic study, KIM-1 appeared to more specifically detect congestion-induced renal injury than NGAL (35). Increased urine concentrations of KIM-1 have also been associated with mortality in patients with HF. However, only one study has assessed the predictive value of KIM-1 in patients with ADHF and failed to show a difference between patients with and without AKI with respect to KIM-1 concentration (Supplemental Table 2, Supplemental Digital Content 2, http://links.lww.com/CCM/A975).

N-Acetyl-β-D-Glucosaminidase. N-acetyl-β-D-glucosaminidase (NAG) is a lysosomal brush border enzyme of the proximal tubule cells being released into the urine after renal injury (27). Interestingly, NAG (as well as KIM-1) does not appear correlated to biomarkers of renal function. Although patients with increased NAG levels have higher risk of death or hospitalization independent of GFR in chronic HF patients, no study has so far assessed the predictive value of NAG for WRF in ADHF patients (Supplemental Table 2, Supplemental Digital Content 2, http://links.lww.com/CCM/A975) (46–59).

How Biomarkers Could Redefine CRSs?

Considering that CRS is focused on a specific cardiovascular diagnosis (HF), it is surprising that the definition does not include an objective measure of cardiovascular dysfunction. To this point, investigators have examined the conjoined use of a biomarker of cardiac function (such as BNP or amino-terminal proBNP [NT-proBNP]) and measures of renal function or injury as a more refined way to phenotype CRS. This concept is supported by the fact that renal biomarkers of function or injury cannot likely differentiate WRF due to intrarenal congestion versus that from overdiuresis, for example. Indeed, BNP and NT-proBNP remain good predictor of ADHF and mortality in patients with renal dysfunction (60), and the combination of a natriuretic peptide and evidence for renal dysfunction identify a particularly higher risk patient, including those at risk for CRS. In this regard, as discussed above, severity of HF is a determinant of CRS, and data suggest that natriuretic peptides may predict CRS in the setting of HF. This concept was first proposed in work from the International Collaborative of NT-proBNP study, where WRF was more likely in those with markedly elevated NT-proBNP values; furthermore, prognosis was particularly worse in those with WRF associated with an elevated NT-proBNP (24). As noted above, combining BNP and NGAL was prognostic in the GALLANT study, but it is unclear whether this combination provides superior information for identifying the mechanism or risk for WRF in those with HF.

The term "kidney attack" has been proposed to highlight the possible uncoupling between aggressive care and renal injury and loss of function. When a kidney attack occurs, a variable number of nephrons may be damaged or impaired (61, 62). The subsequent loss of function will then depend not only on the total of nephrons injured but also on the renal functional reserve previous to the kidney attack (**Fig. 3**). Combing biomarkers of renal function and injury may therefore be use to stratify patients with ADHF and its kidney consequences.

Different Subtypes of Patients With Abnormalities of Renal Function

Combination use of biomarkers of renal function and renal injury may be useful to identify different subtypes of type 1 CRS with prognostic and therapeutic consequences. Considering this

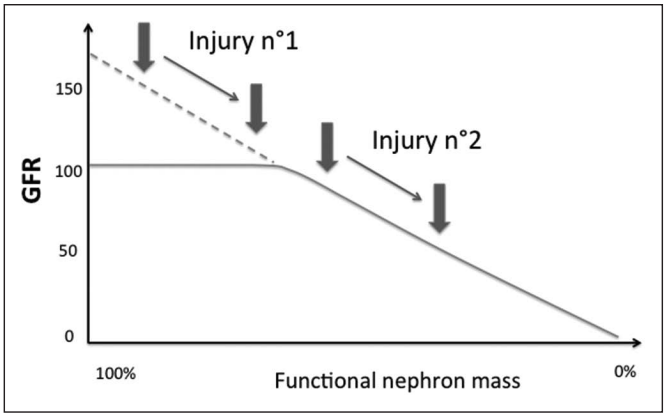

Figure 3. Representation of the renal function reserve according to the nephron mass. The scheme illustrates the different consequences to the same injury with respect to the functional reserve. Injury n°1 will leave within the normal range due to previous normal kidney structure and functional reserve. On the opposite, injury n°2 will be associated with a marked drop of glomerular filtration rate (GFR) because of the absence to functional reserve.

paradigm, it is important to consider the timing of renal function alteration with respect to treatment initiation. Although transient and slight decrease of GFR related to more aggressive decongestive treatment has been suggested to be associated with better outcome in patients receiving diuretics therapy for ADHF, sustained or persistent AKI associated with renal injury appears to be associated with worse outcome. Using this logic, it is intuitively obvious that different subtypes of acute CRS could be defined (**Fig. 4**), which might be discriminated using more sensitive biomarkers of renal injury. In this regard, biomarkers may better define prognosis and/or help guide treatments, particularly with respect to guiding intensity of diuretic therapy; indeed, what we refer to as subtype B-type I CRS could best benefit from the diagnostic value of biomarkers of renal injury. This large proportion of patients presenting with congestive signs and undergoing diuretic therapy or ultrafiltration have secondary increased of plasma levels of screat and BUN. Renal injury biomarker monitoring might help identifying those patients most likely to benefit from aggressive decongestive therapy; given the data by Testani et al (16), patients with a drop of GFR after aggressive diuresis might be differentiate in subtype B "injury–" and "injury+." Although subtype B "injury–" would reflect appropriate decongestive therapy and hemoconcentration along with slight decrease in GFR, subtype B "injury+" would help detecting patients with too aggressive diuresis and/or additional hit to the kidney. On the other hand, diuresis might be more precisely titrated in patients presenting to the emergency department with both positive renal function and renal injury biomarkers (type D) to guide the decongestive therapy (which will translate into a decrease in renal injury biomarkers levels) (35).

Another example where monitoring of renal injury might be of use is in the setting of ACE inhibitor or angiotensin receptor blockers initiation. These agents result in superior outcome in patients with HF although they may alter GFR (despite maintaining renal blood flow). Using our paradigm, clinicians might be able to more confidently titrate ACE inhibitors if guided with renal injury biomarker monitoring; patients developing a drop of their GFR might be more confidently kept on treatment if no ongoing renal injury was detected.

Beyond these applications, elevated biomarkers of renal injury in patients receiving adequate HF treatment could be used to increase physician awareness of potential nephrotoxic effects of noncardiovascular therapies or of a noncardiac cause of ongoing renal injury (e.g., sepsis).

The cost-effectiveness of a biomarker-guided evaluation and management strategy for CRS remains a matter of potential

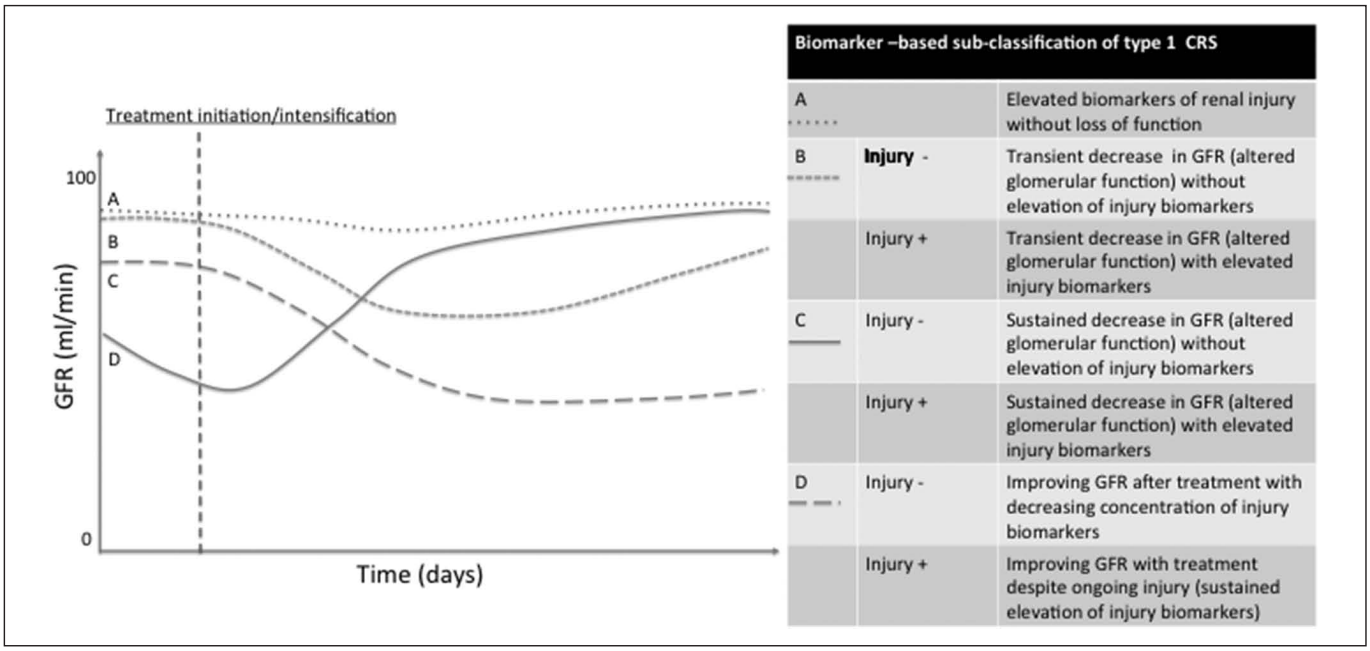

Figure 4. Proposition of different subtypes of acute cardiorenal syndrome with respect to change of renal function and renal injury biomarkers levels after initiation (or escalation) of treatment in acute decompensated heart failure patients. GFR = glomerular filtration rate, CRS = cardiorenal syndrome.

concern. Insights from the Acute Study of Clinical Effectiveness of Nesiritide in Decompensated Heart Failure (ASCEND-HF) provided useful data regarding the costs of acute decompensated HF episodes; in this study, mean length of stay from randomization to discharge was 8.5 and 8.6 days in the treatment and placebo groups, respectively. Cumulative mean costs at 30 days were ~$16,000, and at 180 days, cumulative costs were ~$25,000 (63). Specific data regarding costs of patients with and without CRS were not provided in ASCEND-HF; however, it is reasonable to assert affected patients have substantially higher costs of care. Although cost of biomarkers has to be taken into account in the management of these patients, the modest cost of these biomarkers appears to be rather low compared with the global cost of the treatment. Finally, a decrease in global cost can be expected if a biomarker-based management strategy proves to decrease the complications or decrease the global length of stay in these patients.

CONCLUSION AND FUTURE DIRECTIONS

With this review, we propose that different subtypes of patients with abnormalities of renal function exist in the context of ADHF. Such biomarkers may include those reflecting renal function and injury, likely to provide different information and better phenotype subgroups of patients with CRS and stratified according to outcome or response to treatment. In theory, a construct for patient care could be considered, where those patients with marked elevation of cardiac and renal biomarkers would receive the most aggressive efforts at decongestion, while lesser aggressive approaches might be taken for those with lower values of BNP or NT-proBNP, as an elevated renal injury marker might identify WRF due to other mechanisms, allowing for targeted strategies to improve outcome through different treatment. With the expected development of renoprotective therapies for use in patients with ADHF, such a monitoring and targeted therapy approach is likely to be realized. Further studies are needed to determine the prognostic and therapeutic implications of renal injury in patients with ADHF.

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