Cardiorenal Syndrome: A Cardiologist's Perspective of Pathophysiology

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Summary

The cardiorenal syndrome has recently been defined as "disorders of the heart and kidney whereby acute or chronic dysfunction in one organ may induce acute or chronic dysfunction of the other." The syndrome is extremely common and independently associated with poor clinical outcomes. However, no pharmacological therapy has been shown to improve its outcomes. Unfortunately, the mechanisms that initiate the development of renal dysfunction in heart failure are still debated. This review tries to clarify some of the misunderstanding regarding the principle hemodynamic factors that drive the kidneys to retain salt and water.

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Introduction

Despite considerable advances in the clinical management of patients with heart failure (HF) and improvement in overall mortality, hospitalization rates remain high, with enormous costs to the health care system (1). HF accounts for 1%–2% of the total health care expenditure, and these costs are increasing (1). One of the factors that contribute to worse outcomes in HF is the presence or development of renal dysfunction during management of HF (2). Over the last decade, there has been a growing interest in the presence of renal dysfunction and CKD, often referred to as cardiorenal syndrome (CRS), as an important comorbidity in patients with HF. However, there has been a lack of clarity on how to define, classify, and indeed, manage CRS.

Definition and Classification of the CRSs

In 2008, a consensus conference under the auspices of the Acute Dialysis Quality Initiative (ADQI) proposed a definition and classification of CRS and discussed management strategies (3). The group recommended a simple generalized definition of CRS: "Disorders of the heart and kidneys whereby acute or chronic dysfunction in one organ may induce acute or chronic dysfunction of the other," and they suggested that the syndrome be classified into five distinct types depending on whether heart or kidney was the initial organ of insult (3). In types 1 and 2 CRS, worsening of HF in acute (type 1) or chronic HF (type 2) leads to worsening kidney function. In types 3 and 4 (termed acute and chronic renocardiac syndromes, respectively), AKI or CKD leads to worsening HF. In type 5 CRS, systemic conditions cause simultaneous dysfunction of the heart and kidney. This review is limited to a discussion of types 1 (acute) and 2 (chronic) CRS.

Prevalence and Incidence of Types 1 and 2 CRS

CKD is very common in patients with HF. In the Acute Decompensated Heart Failure National Registry (ADHERE), over 60% of patients admitted to US hospitals with acute decompensated HF (ADHF) had stage 3 (GFR<60 ml/min per 1.73 m²) or worse CKD (4). Similar findings have been reported in several other HF registries, surveys, and randomized trials in patients with ADHF. Moreover, during the management of ADHF, a majority of patients develops varying degrees of worsening renal function. In a study of approximately 1000 patients admitted with ADHF, serum creatinine increased by more than 0.1 mg/dl in over 70% of patients and more than 0.5 mg/dl in up to 20% of patients within 3 days of hospitalization (5). Most studies have used an increase in serum creatinine of ≥0.3 mg/dl or a ≥25% increase in serum creatinine from baseline to define acute or type 1 CRS. Using this definition, the prevalence of type 1 CRS is reported in the range of 27%–45% (6,7). The prevalence of CKD (type 2 CRS) is seen in 32%–50% of patients in the large chronic HF trials (8–12). Population-based surveys in North America have also found a similar prevalence of 38%–56% (13–15). Interestingly, a large study of over 6000 patients admitted to the Mayo clinic between 1987 and 2002 found a remarkable increase in the severity of renal dysfunction in patients admitted with ADHF (16). Because heart disease and CKD frequently coexist, it is often difficult to discriminate the primary from the secondary process. In such circumstances, the ADQI consensus conference recommended that these patients be classified as having both types 2 and 4 CRS (8).

Predictors of CRS

Several factors are associated with the presence of CKD in patients with chronic HF. In the Valsartan in Heart Failure Trial, age, men, diabetes, ischemic etiology of HF, low BPs, worse neurohormonal and proinflammatory profiles, presence of edema, and use of higher doses of diuretics were independently associated with the presence of CKD (12). Interestingly, the

variation of left ventricular (LV) ejection fraction was not associated with the presence of CKD. Indeed, in the CHARM trial (Candesartan in Heart Failure: Assessment of Reduction in Mortality and Morbidity), the presence of CKD was similar in patients with preserved (34%) and depressed LV function (33%) (10). Several factors have also been reported to independently predict the development of worsening renal function (type 1 CRS) during the treatment of ADHF. These factors include history of coronary artery disease, hypertension, diabetes mellitus, and history of prior HF. In addition, the presence of systolic hypertension, tachycardia, pulmonary edema, and use of high doses of diuretics at admission were independently related to the development of type 1 CRS (7,17–19).

Prognosis of CRS

Both types 1 and 2 CRS are independently associated with increased mortality and morbidity in patients with ADHF and chronic HF (4,9–11,13–15,20). In the ADHERE registry, the in-hospital mortality increased from 1.9% for patients with normal renal function to 7.6% for patients with severe renal dysfunction ($P<0.001$) (4). Although any increase in serum creatinine during treatment of ADHF is associated with worse prognosis, an increase in creatinine of >0.3 mg/dl was found to have the highest sensitivity and specificity for predicting in-hospital mortality and length of stay (5). Similar findings have been observed by several other studies (19). Therefore, both types 1 and 2 CRS are very common conditions and their presence is associated with worse short- and long-term adverse outcomes.

Pathogenesis of Renal Dysfunction in HF

Several mechanisms have been implicated in the pathogenesis of renal dysfunction and worsening renal function in HF. The hemodynamic consequences of reduced cardiac output (CO) with low renal perfusion and activation of the sympathetic and renin-angiotensin-aldosterone system (RAAS) probably play the most prominent role in initiating renal dysfunction, salt and water retention, and venous congestion. Venous congestion can in turn, further worsen renal function through several mechanisms as discussed below. Anemia, a common comorbidity in HF, can also worsen renal function (21). Drugs, such as blockers of RAAS used for the treatment of HF or nonsteroidal anti-inflammatory drugs and cyclosporine used for the management of comorbidities, may contribute to worsening renal function. Primary renal parenchymal disease related to longstanding diabetes and hypertension, common comorbidities in HF, may also worsen renal function, but often, the kidneys are intrinsically normal. Because of space constraints, this review is restricted to clarifying some of the misunderstanding of the role of hemodynamics in the development of renal dysfunction.

Role of Hemodynamic Abnormalities in the Pathogenesis of CRS

The syndrome of HF is characterized by neurohormonal activation, salt and water retention, and azotemia, regardless of the presence of kidney disease. The primary stimulus that signals or triggers the kidneys to retain fluid is debated. In

the early 1950s, Peters (22,23) developed the concept that, in congestive HF, despite increased blood volume, there is "underfilling of the arterial tree" that modulates renal retention of sodium and water (22,23). Peters (22,23) proposed a hypothetical effective arterial blood volume (EABV), a measure of fullness of the arterial tree, that he believed was reduced even when the blood volume was increased. This concept has been popularized as a unifying hypothesis to explain salt and water retention in low cardiac output and high cardiac output (cirrhosis and pregnancy) states (24). The problem is that EABV is a poorly defined entity that cannot be measured, and there are no known receptors where the body can directly monitor its adequacy. Because its validity as a hypothesis cannot be tested, the concept of EABV has remained hypothetical for over 60 years. In 1996, Michell (25) proposed that, because "effective blood volume has outlived its usefulness, it should be allowed to fade away from the textbooks" (25). The present review strongly supports this contention and provides evidence that a threat to the arterial BP and not "underfilling of the arterial tree" is the stimulus for the retention of salt and water by the kidney (24).

Another concern in the interpretation of previous studies is that most of them have investigated the mechanisms of fluid retention and renal dysfunction in HF patients who are receiving treatment. Treatment, particularly with diuretics, RAAS inhibitors, and β-blockers, has such profound effect on the mechanisms being tested that it becomes impossible to interpret these studies. Therefore, most of these data need to be set aside. In the late 1980s and early 1990s, a series of studies was done on patients with severe chronic low- or high-output HF who had never received any form of pharmacological treatment (26–31). Because these patients were untreated, it can be assumed that the insights into the mechanisms being tested were not being confounded by the effects of drugs. Figure 1 shows the average percent change from normal in a number of hemodynamic, neurohormonal, body fluid compartment, and renal function parameters in patients with severe untreated low-output dilated cardiomyopathy (27). In these patients, the LV systolic function was severely depressed, with approximately 50% decrease in the CO. The systemic vascular resistance (SVR) was increased by a factor of two, but the arterial BP remained within the normal range. There was variable increase in several circulating neurohormones, including norepinephrine, plasma renin activity, aldosterone, and atrial natriuretic peptide. The levels of arginine vasopressin were normal but inappropriately high relative to the low serum sodium seen in these patients. The renal blood flow (RBF) and GFR were decreased, and there was a significant increase in total body water, blood volume, extracellular volume, and total body exchangeable sodium.

From these data, it is possible to construct the sequence of events that leads to salt and water retention and development of renal dysfunction in patients with severe low-output HF (Figures 2 and 3) (32). A severe decrease in LV function causes a reduction in the CO and threatens the arterial BP, which lead to carotid sinus and aortic arch baroreceptor-mediated activation of several neurohormones. The parasympathetic tone is inhibited, and the sympathetic tone is enhanced, with subsequent activation of the RAAS.
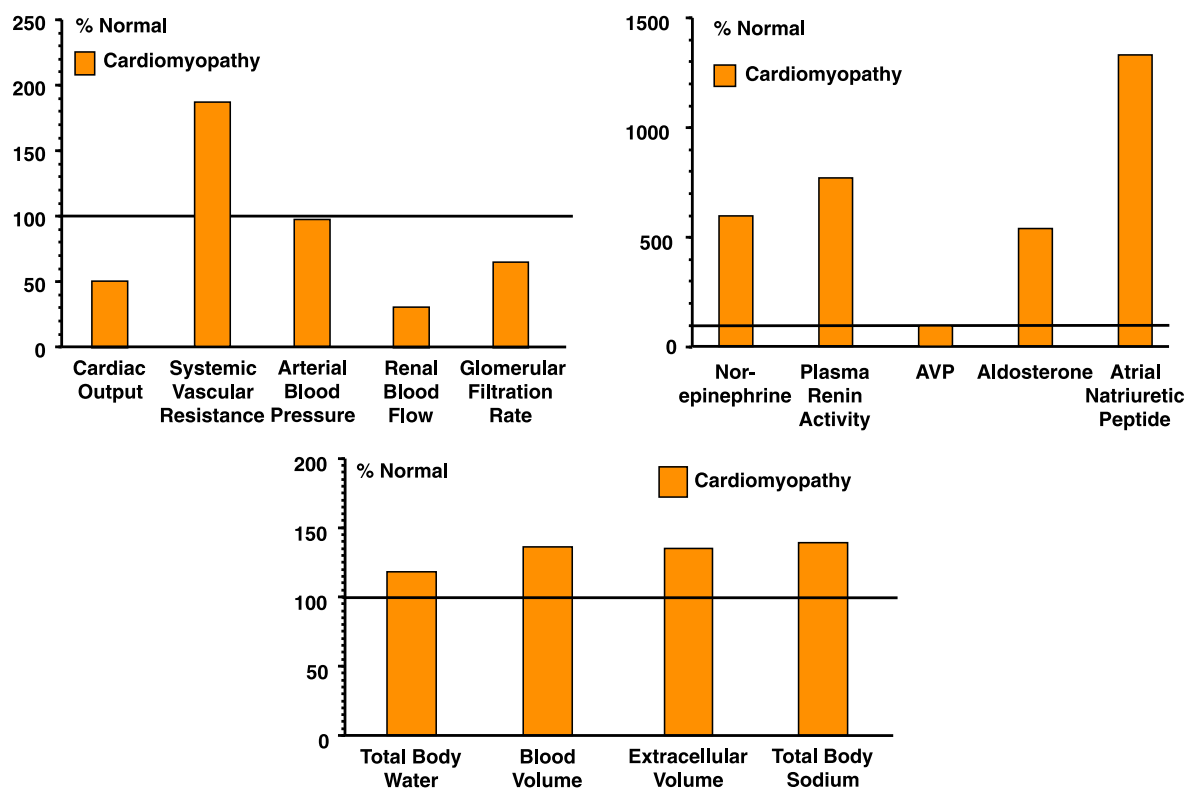
Figure 1. | Bar graphs showing hemodynamic, renal function, plasma hormones, and body fluid compartment data expressed as percent of normal in a group of patients with untreated congestive heart failure. Data are from reference 27. AVP, arginine vasopressin.

There is also a nonosmotic release of arginine vasopressin. The predominant effect of neurohormonal activation is one of severe vasoconstriction, with an increase in the SVR that is more marked in the splanchnic bed. The RBF decreases greater in proportion to the reduction in the CO. The dissociation between the decrease in CO and RBF suggests that the autoregulatory potential of the kidneys may be exhausted in HF. The GFR is also reduced but to a lesser extent than the RBF, suggesting a greater efferent than afferent arteriolar vasoconstriction. However, this assumption has been questioned from single nephron GFR measurements showing that renal autoregulation may also contribute to the relative preservation of the GFR when the RBF decreases (33). The changes in renal hemodynamics set the stage for the kidneys to start retaining salt and water, expanding the body fluid compartments, elevating the right- and left-sided filling pressures, and causing the release of natriuretic peptides. The net effect of these pathophysiological effects is that the arterial BP remains normal or is only mildly reduced in the untreated patient. Therefore, the compensatory mechanisms seen in low-output HF seem to be designed to preserve the arterial BP (34), which is maintained partly by an increase in SVR and partly by an expansion of the blood volume. Unfortunately, it occurs at the expense of renal function.

It has been argued that the reduced CO in HF decreases the intra-arterial volume, and this underfilling of the arterial system or decrease in EABV inactivates the high-pressure baroreceptors (23,24). Approximately 80% of the blood volume resides in the more compliant venous system, and only 20% is in the arterial circuit (35). Even if most of the increased blood volume in HF is accommodated in the compliant venous system, it is difficult to imagine how an underfilled arterial system would unload high pressure receptors in the aortic arch and the carotid sinus. Moreover, the neurohormonal response discussed above is not specific to low-output HF. An identical response is seen in other forms of HF, with increased CO (28–32). Figure 4 shows an example of severe untreated high-output HF caused by a large arteriovenous fistula. The CO in this case was increased by over 300% of normal because of severe vasodilation, with the SVR being only 20% of normal. The arterial BP was reduced. Despite the high CO, the neurohormonal response was identical to the response seen in severe low-output states, resulting in a similar decrease in renal function and salt and water retention (31). Similar finding are seen in other high or normal CO states with fluid retention, such as chronic severe anemia (30) and chronic obstructive pulmonary disease (29). In all high-output states, although the SVR is decreased, the renovascular resistance is increased, and the RBF and GFR are reduced, resulting in a similar pattern of renal dysfunction and fluid retention as seen in low-output HF (29,30). BP falls or is threatened in low-output states because of decrease in CO and high-output states because of a decrease in SVR. Interestingly, a similar neurohormonal profile is also seen in patients with pulmonary arterial hypertension, right ventricular infarction, and right ventricular failure (36). Although the initial triggers for neurohormonal activation in pulmonary hypertension
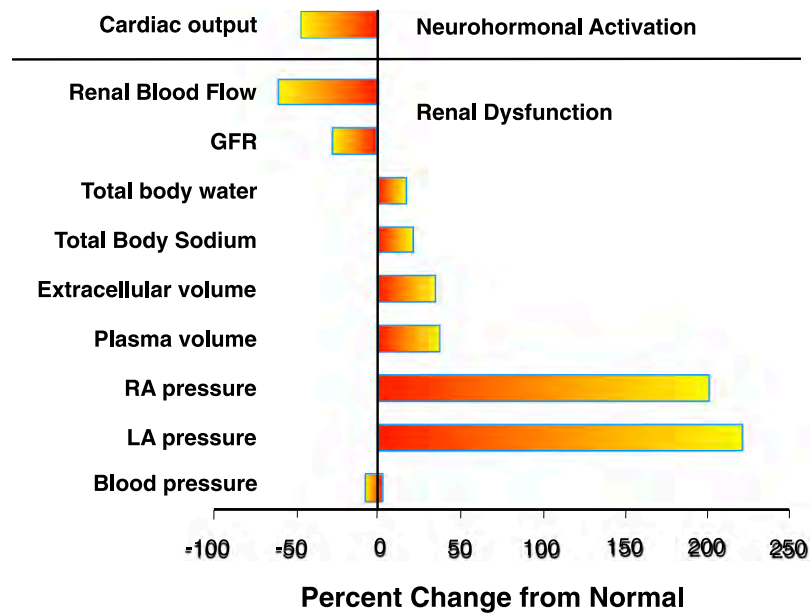
Figure 2. | **Compensatory changes in a number of hemodynamic and body fluid compartment parameters help to maintain a normal arterial BP in patients with untreated congestive heart failure**. This change occurs at the expense of renal dysfunction. Modified from reference 32, with permission. LA, left atrial; RA, right atrial.

have not been studied, it is likely that the mechanisms are similar to the mechanisms seen in low-output HF.

These studies, therefore, further support the notions that preservation or maintenance of the arterial BP is the main stimulus for the neurohormonal response seen in HF and that a threat to or a fall in the arterial BP and not underfilling of the arterial system or decrease in EABV is the most likely primary signal for the kidney to retain sodium and water and the development of renal dysfunction. Because EABV and arterial underfilling are ill-defined and hypothetical concepts that cannot be measured and for which there are no known receptors in the body, their continued use serves no useful purpose. It is the author's considered opinion that we should refrain from using these confusing and imaginary concepts.

If such disparate hemodynamics, as seen in the low- and high-output states, are associated with similar decreases in RBF and GFR and development of renal dysfunction, then routine measurement of hemodynamics may not be helpful in predicting which patients are likely to develop renal dysfunction or CRS. Indeed, hemodynamic measurements usually do not correlate well with the presence or development of renal dysfunction. In the Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterization Effectiveness Trial, which tested a hemodynamic-versus clinically guided strategy to improve outcomes in patients with ADHF, none of the classic baseline hemodynamic parameters like CO, pulmonary capillary wedge pressure, or SVR correlated with baseline renal function as measured by GFR or serum creatinine. Only venous or right atrial pressure correlated significantly but weakly with serum creatinine ($\rho=0.17$, $P=0.03$) and GFR ($\rho=-0.19$, $P=0.01$) (20). More importantly, none of the baseline or changes in hemodynamic parameters during in-hospital treatment of ADHF correlated with the development of worsening renal function as defined by increase in serum creatinine>0.3 mg/dl (20).

Role of High Venous Pressure in the Pathogenesis of CRS

Although the principle driving forces for changes in RBF and GFR in HF are the result of BP-mediated modulation of neurohumoral factors, the resulting fluid retention and increase in venous pressure can have important repercussions on renal perfusion (37–39). It has been know for several years that high central venous pressure (CVP) and even high intra-abdominal pressure from ascites may reduce GFR (40,41). Animal studies have consistently shown that increasing renal venous pressure by approximately 20–25 mmHg in the isolated dog or rat kidneys caused a profound decrease in renal perfusion accompanied by a sharp drop in the GFR, sodium excretion, and urine flow. Renal function promptly returned to normal when the venous pressure was lowered (37,42).

More recently, there has been a resurgence of interest in the role of increased venous pressure in patients with HF. Damman *et al.* (38) found that higher CVP was inversely related to GFR and independently associated with all-cause mortality. Similar findings were reported by Mullens *et al.* (39) in patients admitted with ADHF, and it was found that there was an incremental risk of developing worsening renal function (serum creatinine>0.3 mg/dl) with increasing CVP independent of the CO. The area under the receiver operating characteristic curve for predicting worsening renal function was 0.734 ($P<0.001$) for CVP and 0.552 ($P=0.60$) for CO. However, because only a few have studied the complexities of this issue, additional research is needed to clarify the exact role of increased venous pressure in the CRS.
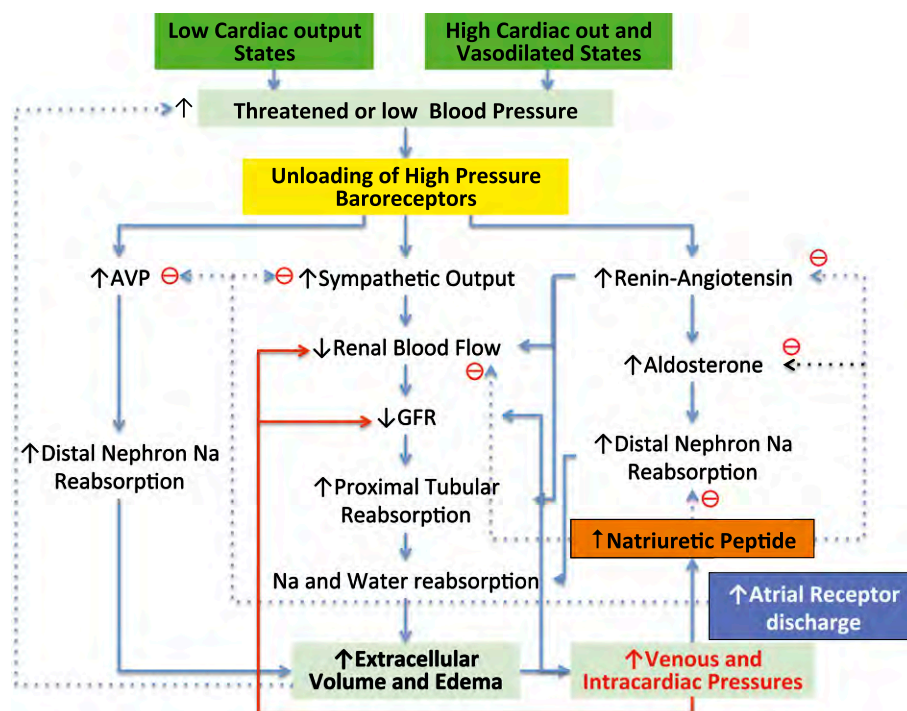
Figure 3. | Diagram showing the sequence of events that leads to salt and water retention by the kidney and development of renal dysfunction. Notice that, in both low and high cardiac output heart failure, the common stimulus seems to be a threat to the arterial BP. The direct effects of these mechanisms are shown by solid blue lines, and mechanisms that may help to improve renal function are indicated by the dotted blue lines and red symbol. The role of increased venous pressure in worsening renal function is shown in red lines. Modified from reference 32, with permission.

Why should an increase in venous pressure decrease renal function? Although several mechanisms have been suggested, the most plausible explanation is that an increase in renal venous pressure decreases the arteriovenous pressure gradient across the kidney and reduces the already compromised RBF, causing GFR to decrease (43). However, in normal kidneys, these changes might evoke a myogenic and tubuloglomerular autoregulation to stabilize the GFR. Because the kidneys have a tight capsule, an increase in venous pressure is also likely to increase renal interstitial pressure and therefore, the pressure in the renal tubules. Micropuncture studies on healthy rat kidneys have shown that elevation of the renal venous pressure beyond 15 mmHg caused a linear increase in the peritubular capillary and intratubular pressures (44). Because the intratubular pressure is one of the important driving forces for glomerular filtration, any increase in intratubular pressure is likely to oppose filtration, reduce the net ultrafiltration pressure, and decrease the GFR. It should be emphasized, however, that these theoretical explanations are based on acute experimental data in either normal intact animals or isolated kidneys, where the two components of renal autoregulation (*i.e.*, myogenic control of afferent arteriolar tone and tubuloglomerular feedback) might still be operative. It is unclear what roles these mechanisms play in HF patients with sympathetic and RAAS activation and when the RBF and GFR are already compromised. Hence, the exact mechanisms to explain the inverse relationship between high renal venous pressure and GFR in patients with HF are likely to be highly complex. Nevertheless, in patients with ascites or raised CVP, paracentesis or ultrafiltration has been shown to improve renal dysfunction (41). However, in the Cardiorenal Rescue Study in Acute Decompensated Heart Failure, ultrafiltration was not associated with improvement in renal function, although that study was not designed to address this particular question (45). Taken together, these experimental, epidemiologic, and clinical studies strongly support the view that renal venous pressure is an important determinant of renal hemodynamics and GFR. A rise in venous pressure can initiate a vicious cycle by causing sodium retention, expansion of plasma volume, and additional increase in venous pressure.

In addition to its effects on renal hemodynamics, high systemic venous congestion can activate endothelial dysfunction with production of reactive oxygen species, TNF-α, endothelin-1, IL-6, and other inflammatory cytokines (46,47), all of which worsen nitric oxide dysregulation, resulting in additional neurohormonal activation and renal dysfunction. Venous congestion may also trigger production of systemic endotoxins from the gut, and superimposed infection may also contribute to renal dysfunction (48).

Is the Renal Dysfunction Reversible?
Although hemodynamic abnormalities and poor renal perfusion play an important role in the pathogenesis of CRS, no pharmacological interventions have been shown to significantly improve renal function in patients with HF,
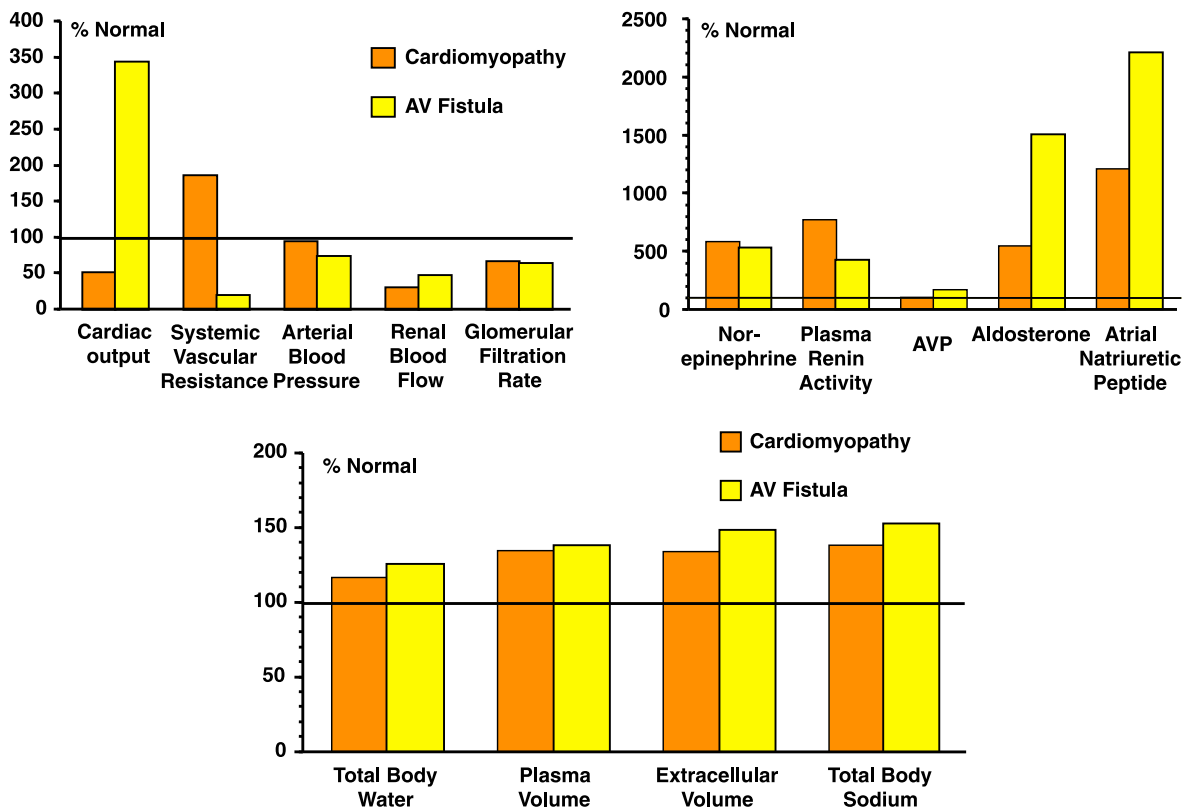
Figure 4. | **Bar graphs comparing the hemodynamic, renal function, plasma hormones, and body fluid compartment data of patients with untreated low-output heart failure with data from patients with untreated high-output heart failure because of a large arteriovenous fistula.** Despite dissimilar hemodynamics, the neurohormonal activation, fluid retention, and renal dysfunction were very similar in low- and high-output heart failure. Data are from references 27 and 31.

including rolofylline, an adenosine-receptor antagonist that is supposed to improve RBF (49). This finding raises the question of whether intrinsic kidney disease plays a more important role in the pathogenesis of CRS and whether CRS reverses when hemodynamics improves. However, several studies have shown a prompt improvement in renal function with placement of LV assist devices in patients with end stage HF (50). The role of hemodynamics was also investigated in 15 patients with chronic constrictive pericarditis, CRS, and severe fluid retention before and 8 weeks after pericardiectomy (28). Pericardiectomy rapidly normalized the hemodynamics and renal dysfunction. The cardiac index increased from 2.0±0.2 to 3.6±0.3 L/min per meter[2], the right atrial pressure fell from 22.1±1.2 to 5.3±0.7 mmHg, the effective renal plasma flow increased from 243±21 to 382±34 ml/min per 1.73 m[2], and the serum creatinine fell from 1.5 to 1.0 mg/dl (28). These data also underscore the importance of hemodynamics in the pathogenesis of CRS and show that, in many patients, the renal dysfunction is reversible if the hemodynamics can be improved.

Conclusions

CRS is very common in patients with chronic HF and ADHF, and it is independently related to poor clinical outcomes. Although several factors contribute to the pathogenesis of CRS, changes in hemodynamics with low renal perfusion and activation of the sympathetic and RAAS probably play the most prominent roles in initiating renal dysfunction. Increasing data suggest that elevated venous pressure is important in further worsening of renal function in HF. The exact prevalence of structural kidney disease in the CRS is unknown but likely to be high because of common association of diabetes and hypertension with HF. Finally, although in many patients, renal dysfunction may normalize if the pump function improves, in other patients, the underlying structural renal disease may contribute to permanent renal dysfunction. Additional studies are required to improve our understanding of the complex interactions between HF and renal dysfunction to enable us to devise better therapies for the CRS.

Disclosures

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