who becomes volume depleted, whether it be from overly aggressive diuresis or an intercurrent volume-depleting illness. Third, ACE inhibitors or ARBs may induce acute kidney injury in patients with high-grade bilateral renal artery stenosis or stenosis of a dominant or a single kidney renal artery; in patients with extensive atherosclerotic disease in smaller preglolemular vessels; or in patients with significant luminal narrowing of different arterioles, as occurs with poorly treated hypertension or chronic calcineurin inhibitor use. More often than not, the complex nature of renal function changes in the CRS patient requires that ACE inhibitor or ARB therapy be temporarily stopped.

Many CRS patients are on the cusp of needing dialysis as their disease moves forward in what is sometimes an almost inexorable fashion; therefore, it must be determined whether a patient’s clinical status has deteriorated enough that dialysis will be soon needed and, if so, which form of central access should be used for temporary dialysis. Once dialysis starts and a patient is brought to a euclidean state and electrolyte abnormalities are corrected, a determination can be made as to whether dialytic intervention was merely a bridge therapy until improvement or whether long-term dialysis plans need to be initiated. The prevailing blood pressure often dictates the form of long-term dialysis that is considered. Maintenance hemodialysis can prove challenging in CRS patients with significant hypertension, and in such patients peri-tional dialysis may be the better dialytic modality (8). Of note, once end stage renal failure is determined to be present, it is not uncommon to have a role reversal in which the nephrologist becomes the primary health care provider and the cardiologist offers learned consultation.

References
1. Ronco C, et al. Cardiorenal syn-
2. Sarraf M, Masoumi A, Schrier RW. Cardiorenal syndrome in acute de-
3. Gerlag PG, van Meijl JH. High-dose furosemide in the treatment of refrac-
4. Thomson MR, et al. Continuous versus intermittent infusion of furosemide in acute decompensat-
5. Sica DA, Gehrz TW. Diuretic combi-
6. Costanzo MR, et al. Ultrafiltration Versus Intravenous Diuretics for Pa-
tients Hospitalized for Acute Decom-
pen.sated Heart Failure (UNLOAD) Investigators. Ultrafiltration is asso-
7. Schoolwerth A, et al. Considerations in angiotensin converting enzyme inhibitor therapy. Circula-
8. Krishnan A, Oreopoulos DG. Perito-
nal dialysis in congestive heart fail-
Domenic Sica, MD, is professor of medi-
cine and pharmacology and chairman of the section of clinical pharmacology and hypertension, division of nephrology, at the Virginia Commonwealth University Health System.

Figure 1
Heart-kidney interactions

Cardiorenal Syndrome: The Cardiologist’s Viewpoint

By Inder S. Anand, MD

Most cardiologists consider the coexistence of heart failure and chronic kidney disease (CKD) (1) or worsening of renal function (WRF) defined as an increase in serum creatinine >0.3 mg/dL (2) during treatment of acute decompensated heart failure (ADHF) as a reasonable working definition of cardiorenal syndrome (CRS). Others consider the presence of diuretic refractoriness despite persistent hypervolemia, inability to handle sodium load, and inability to use adequate doses of heart failure medications as important components of CRS. However, these variables have never been included in the definition because they are difficult to study. This brief review limits discussion to patients with type 1 (acute) and type 2 (chronic) CRS as proposed in a recent classification of CRS (3).

Prevalence and prognosis of cardiorenal syndrome

The prevalence of CKD (type 2 CRS) has been reported in the range of 32–50 percent in the large chronic heart failure trials (4–9). Population-based surveys in North America have found a similar prevalence of 38–56 percent (10–12). Gottlieb et al. found that the sensitivity and specificity for the prediction of poor outcomes with WRF, defined as a rise in serum creatinine of 0.8 mg/dL during ADHF (type 1 CRS), were 81 percent and 62 percent, respectively (2). Using that definition, the prevalence of type 1 CRS is reported in the range of 27–45 percent in previous studies (13–15). However, in the ADHERE registry, the prevalence of CKD (GFR < 60 mL/min/1.73 m2) was as high as 65 percent (16).

The presence of CKD or the development of WRF are significant independent predictors of mortality and morbidity in patients with ADHF and chronic heart failure (4–12, 16–17). In the ADHERE registry, the in-hospital mortality increased from 1.9 percent for patients with normal renal function to 7.6 percent for patients with severe renal dysfunction (p < 0.0001) (16).

Predictors of cardiorenal syndrome

Several factors are associated with the presence of CRS in patients with chronic heart failure. In the Val-HeFT trial, the independent predictors for the presence of CRS were age, male gender, diabetes, ischemic etiology of heart failure, low blood pressures, worse neurohormonal and proinflammatory profile, presence of edema, and use of higher doses of diuretics (9). Left ventricular ejection fraction did not predict the presence of CRS. Indeed, the presence of CRS was similar in patients with preserved (54 percent) or depressed (53 percent) left ventricular function in the CHARM trial, which studied the effects of the angiotensin receptor blocker candesartan in patients with depressed and preserved ejection fraction (6). The pathogenetic mechanisms responsible for the development of WRF during ADHF are not clear. Published studies have reported that baseline serum creatinine, coronary artery disease, hypertension, history of diabetes mellitus, use of calcium channel blockers, pulmonary edema, and high doses of diur-
etics are associated with its development (14,18–20). However, it is unclear whether the development of WRF is related to a pre-renal, intravascular volume depleted state, induced by intensive diuresis during the management of ADHF, or the result of a complex interaction involving heart failure treatment in the setting of intrinsic kidney disease. Other factors considered important in the pathogenesis of CRS are poor renal perfusion owing to low cardiac output, high venous pressure, systemic and renal vasoconstriction (21,22).

Classical studies have taught us that low cardiac output activates catecholamine and the renin-angiotensin system, causing an increase in systemic and renovascular resistance, leading to a decrease in renal blood flow and GFR and to retention of salt and water (21). However, several hemodynamic studies in patients with ADHF have found that cardiac output is not necessarily low in these patients, although none of these studies directly assessed renal hemodynamically

In low cardiac output states, auto-regulatory mechanisms help to maintain coronary and cerebral perfusion at the expense of other major organs including the kidneys, liver, and skeletal muscles.
The Cardiologist’s Viewpoint

Continued from page 13

ics. In a study of 48 patients with ADHF, Weinfield et al. did not find low cardiac output or estimated renal perfusion pressure (mean arterial minus CVP) in patients who developed CRS during heart failure treatment (23). In the Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterization (ESCAPE) trial, cardiac output, pulmonary capillary wedge pressure, and systolic blood pressure did not correlate with renal function. Only right atrial pressure correlated weakly with baseline serum creatinine (r = 0.165, p = 0.03) (17).

Role of increased venous pressure in cardiorenal syndrome

Over 60 years ago Bradley and Bradley (24) showed that an increase in intra-abdominal pressure (IAP) to >80 mm Hg obtained by applying a tight abdominal binder in normal volunteers caused an immediate decrease in effective renal plasma flow (ERPF), GFR, and urine output. Removal of the abdominal binders rapidly normalized the ERPF, GFR, and urine output. It is unclear whether raising the abdominal pressure caused an increase in renal venous pressure. However, in a series of elegant studies on isolated perfused kidney, Firth et al. (22) provided evidence that when arterial pressure is kept constant, an increase in renal venous pressure leads to a decrease in GFR.

In patients with ADHF, there is a potential for ascites and visceral edema that might increase the IAP. Intra-abdominal hypertension (IAH) (IAP >8 mm Hg) is associated with intra-abdominal organ dysfunction. The role of IAP in the pathogenesis of ADHF was recently investigated by Mullens et al. (25) in 40 patients with ADHF (LVEF 19 ± 9 percent, serum creatinine 2.0 ± 0.9 mg/dL), 50 percent of whom had elevated IAH. Elevated IAP was associated with worse renal function (p = 0.009). Intensive medical therapy resulted in improvement in both hemodynamic measurements and IAP. A strong correlation (r = 0.77, p < 0.001) was observed between reduction in IAP and improvement in renal function. However, changes in IAP or renal function did not correlate with changes in any hemodynamic variables (Figure 1). It appears, therefore, that elevated IAP is prevalent in a large number of patients with ADHF and is associated with impaired renal function. However, it is unclear whether high IAP is related to raised venous pressure.

To determine whether increased venous pressure rather than impairment of cardiac output is primarily associated with the development of WRF in patients with ADHF, the same investigators (26) studied 145 consecutive patients admitted with ADHF (age 57 ± 14 years, cardiac index 1.9 ± 0.6 L/min/m², LVEF 20 ± 8 percent, serum creatinine 1.7 ± 0.9 mg/dL). WRF developed in 40 percent of these patients. Patients who developed WRF had a higher central venous pressure (CVP) on admission (18 ± 7 mm Hg versus 12 ± 6 mm Hg, p < 0.001) after intensive medical therapy (11 ± 8 mm Hg versus 8 ± 5 mm Hg, p = 0.04). High venous pressure was the most important hemodynamic factor driving WRF in ADHF.

Is cardiorenal syndrome reversible?

In low cardiac output states, auto-regulatory mechanisms help to maintain coronary and cerebral perfusion at the expense of other major organs including the kidneys, liver, and skeletal muscles. The resulting poor renal perfusion contributes to renal dysfunction and has been considered important in the pathogenesis of CRS (21,22). However, studies in patients with chronic heart failure or ADHF have failed to show significant correlation between hemodynamic alterations and renal dysfunction apart from high venous pressure. These findings raise the question of whether intrinsic kidney disease plays a more important role in the pathogenesis of CRS and whether CRS reverses when hemodynamics improve.

Butler and colleagues (27) assessed the relationship between renal function in 220 patients who underwent left ventricular assist device placement. Creatinine clearance (CrCl) increased significantly within a week of left ventricular assist device placement suggesting that renal dysfunction is reversible even in patients with severe end stage heart failure (Figure 2).

Further support for the reversible nature of CRS comes from studies in patients with chronic constrictive pericarditis. The body fluid compartments, neurohormones, renal function, and hemodynamics were measured in 15 patients with CRS and constrictive pericarditis before and eight weeks after pericardiectomy. Pericardiectomy rapidly normalized the hemodynamics, neurohormones, body fluid compartments, and renal dysfunction. The cardiac index increased from 2.0 ± 0.2 to 3.6 ± 0.3 L/min/m², right atrial pressure fell from 22.1 ± 1.2 mm Hg to 5.3 ± 0.7 mm Hg, ERPF increased from 245 ± 21 to 582 ± 34 L/min/1.73 m², and serum creatinine fell from 1.5 to 1.0 mg/dL (28). Taken together, these data underscore the importance of hemodynamics in the pathogenesis of CRS and demonstrate that in many patients renal dysfunction is reversible if the hemodynamics can be improved.

Conclusions

CRS is very common in patients with ADHF or chronic heart failure and is an independent predictor of poor clinical outcomes. The exact prevalence of structural kidney disease in CRS is unknown but is likely to be high because of the common association of atherosclerotic CV disease, diabetes, and hypertension with heart failure. Although low cardiac output-induced neurohormonal activation in heart failure reduces renal blood flow and is probably an important factor contributing to renal dysfunction, the exact role of hemodynamic mechanisms is not entirely clear.

Increasing data suggest that elevated venous pressure may contribute to renal dysfunction in heart failure. In many patients, renal dysfunction does normalize when the pump function improves. In others, the underlying structural renal disease may contribute to permanent renal dysfunction. Further studies are required to improve our understanding of the complex interactions between heart failure and renal dysfunction to enable us to devise better therapies for CRS.

Inder S. Anand, MD, DPhil, is professor of medicine, University of Minnesota Medical School, and director of the heart failure program at the VA Medical Center in Minneapolis, MN.

References


Figure 1

Intra-abdominal pressure (IAP) is increased in a significant number of patients with ADHF. The left half of the graph shows that elevated IAP is associated with worse renal function. Note a strong correlation between reduction in IAP and improved renal function in patients with baseline elevated IAP (Redrawn from Mullens et al. J Am Coll Cardiol 2008; 51:300–6).

Figure 2


Effect of Left Ventricular Assist Device on Renal Function (n=220)
Anemia Management in Cardiorenal Disease

By Donald S. Silverberg MD, Dov Wexler MD, Adrian Iaina, MD, and Doron Schwartz, MD

Anemia is common in congestive heart failure (CHF) and is associated with increased mortality, morbidity, and progression of renal failure. The two most common causes of the anemia are associated renal failure, which causes depression of erythropoietin production in the kidney, and excessive cytokine production, which can also cause depression of erythropoietin production in the kidney as well as depression of the erythropoietic response in bone marrow.

Cytokines can induce iron deficiency by increasing hepcidin production from the liver, which both reduces gastrointestinal iron absorption and reduces iron release from iron stores located in the macrophages and hepatocytes. Many studies of anemia in CHF with erythropoiesis stimulating agents (ESA) and oral or IV iron—but also with IV iron without ESA—have shown positive effects on the anemia as well as on hospitalization, fatigue and shortness of breath, cardiac and renal function, quality of life, exercise capacity, and reduced beta natriuretic peptide. These studies have not demonstrated an increase in cardiovascular damage related to the therapy. Adequately powered, long-term placebo-controlled studies of ESA and of IV iron in CHF are still needed to examine hard cardiovascular endpoints.

Prevalence and significance of anemia in CHF

In a recent meta-analysis of 34 studies of anemia in CHF (1) including a total of 153,180 patients, 29.2% were anemic (using the authors’ own criteria), and the adjusted hazard ratio (HR) for death was 1.46. In these anemic CHF patients, there was no difference between systolic or diastolic CHF in prevalence of anemia or mortality. Another recent meta-analysis looked at 21 prospective clinical studies of anemia in CHF that studied 97,699 patients (2) (Table 1). In the six studies that considered mortality, anemia was linked to a significantly higher risk of death (1.46, p < 0.001). In three of the four studies that looked at CHF hospitalization rates, the rates were higher among anemic patients. In five studies that evaluated effectiveness of left ventricular ejection fraction (LVEF), anemic patients had a 0.53 percent lower LVEF than nonanemic patients, p < 0.001. In 16 of the 21 studies that used multivariate analysis, an independent relationship between anemia and all outcomes in CHF was found. These studies suggest, but do not prove, that anemia plays a causal role in the worsening of CHF.

What causes the anemia in CHF?

Anemia associated with CHF is most likely due to a combination of several factors (3,4):

Chronic kidney disease (CKD)

CKD is associated with reduced production of erythropoietin (EPO) in the kidney; the renal damage seen in many cases of CHF is probably mainly a result of reduced renal blood flow caused by the reduced cardiac output leading to hypoxic renal damage. Perhaps the most dramatic evidence of the role of CHF in renal failure is the improvement of renal function seen after successful cardiac resynchronization therapy when cardiac function is improved. Treatment of CHF with beta blockers is associated with an improvement in CHF and with an improvement in renal function and anemia (5). These data suggest that the better CHF is treated, the slower will be the progression of renal failure.

Elevated cytokines causing abnormalities in EPO and iron metabolism

Cytokines elaborated in CHF, especially tumor necrosis factor alpha (TNFα) and interleukin-6 (IL-6), can cause four hematological abnormalities (6):

- reduced EPO production in the kidney leading to inappropriately low levels in the blood for the degree of anemia present
- reduced erythropoietic response of the bone marrow to ESA
- hypoxia of the kidney leading to anemia
- Cytokines elaborated in CHF, especially tumor necrosis factor alpha (TNFα) and interleukin-6 (IL-6), can cause four hematological abnormalities (6):
- reduced EPO production in the kidney leading to inappropriately low levels in the blood for the degree of anemia present
- reduced erythropoietic response of the bone marrow to ESA
- hypoxia of the kidney leading to anemia
- Cytokines elaborated in CHF, especially tumor necrosis factor alpha (TNFα) and interleukin-6 (IL-6), can cause four hematological abnormalities (6):
- reduced EPO production in the kidney leading to inappropriately low levels in the blood for the degree of anemia present
- reduced erythropoietic response of the bone marrow to ESA
- hypoxia of the kidney leading to anemia