Renal dysfunction is a common and often progressive complication of heart failure (Figure 1). Renal function is defined by a descriptive term—"switch"—in the patient with heart failure. It can change relating to patient volume status, concomitant medications, and adequacy of pump function, with all factors influenced by the background level of renal function. When corrective measures are taken in patients who experience a "bump" in serum creatinine levels, and renal function returns to baseline, all is well from a nephrologist’s perspective—at least for the moment. Patients who experience transient deterioration in function would be viewed as having a moment of poor cardiac and renal crosstalk, but not necessarily cardiorenal syndrome (CRS).

A recent classification of CRS into categories, although arbitrary, provides needed perspective for the nephrologist on the sorting of the sometimes puzzling bidirectional nature of kidney–heart interactions (Figure 1). Five subtypes of CRS have been proposed that reflect the temporal nature of organ interactions as well as the primary and secondary pathology of kidney–heart crosstalk.

Type 1 CRS (acute cardiorenal syndrome) is an abrupt worsening of cardiac function, such as acute decompensated heart failure, leading to acute kidney injury. Type 2 CRS (chronic cardiorenal syndrome) comprises chronic abnormalities in cardiac function, such as chronic advanced stage heart failure causing progressive and permanent chronic kidney disease. Type 3 CRS (acute renocardiac syndrome) is an abrupt worsening of renal function, such as nephrotic syndrome, provoking an acute cardiac disorder, such as heart failure or coronary ischemia. Type 4 CRS (chronic renovascular syndrome) comprises chronic kidney disease of any origin contributing to structural and functional cardiac abnormalities and a heightened risk of cardiovascular events. Type 5 CRS (secondary cardiorenal syndrome) is a systemic condition, such as sepsis, causing both cardiac and renal dysfunction (1).

Nephrologists who treat patients with CRS should assume that cardiac function has been optimized with available medications and device therapies. If these corrective measures do not result in any meaningful improvement in renal function and electrolyte status, the nephrologist enters into the fray in a more defined way. Mindful of the diverse ways in which the kidney may be affected by cardiac dysfunction, the nephrologist should adopt a systematic treatment approach that optimizes diuretic therapy, corrects electrolyte abnormalities, stabilizes blood pressure, and manages anemia (Table 1). Of these treatment considerations, optimizing diuretic therapy and stabilizing renal function are by far the most important and are where the nephrologist best fits in.

Most patients with CRS are significantly volume overloaded and are typically viewed as being diuretic refractory or diuretic resistant (2). In heart failure patients who respond poorly to conventional doses of a loop diuretic, high-dose therapy may prove effective. In one study, daily doses of 500 to 2000 mg of intravenous furosemide were administered to a series of patients with heart failure and refractory edema. With this regimen, a diuretic response was elicited, body weight was reduced, and heart failure class was improved. Similar studies have reported improved furosemide efficacy in refractory heart failure when high doses of oral furosemide are administered (3). Administering a loop diuretic as an infusion, rather than as bolus therapy, is another treatment strategy that can improve the diuretic response in the heart failure patient with diuretic resistance. A significantly greater diuresis/natriuresis is observed frequently when a continuous loop diuretic infusion is given compared with intermittent bolus administration; this differential benefit is accomplished at lower peak loop diuretic concentrations. When continuously infused, this method of loop diuretic delivery results in a more effective delivery of the drug to its site of action in the nephron (4).

Diuretic combinations can also be used in heart failure patients who are otherwise refractory to loop diuretics alone. The process of combining diuretics that work at different nephron segments is called sequential nephron blockade. Because of structural adaptation occurring in the distal nephron with prolonged loop diuretic therapy, the combination of a distal-acting diuretic and a loop diuretic is particularly effective in such patients.

Numerous reports have demonstrated significant clinical improvements accompanied by additional clinical improvement with the addition of metolazone to a loop diuretic (usually furosemide) in heart failure patients previously resistant to loop diuretic therapy alone. Metolazone is particularly effective because its duration of action is quite prolonged, it is lipophilic with a large volume of distribution, and it remains effective in advanced stage renal failure (5). Spironolactone has also been used in combination with loop diuretics and thiazide-type diuretics and has improved the diuretic response in diuretic refractory heart failure patients; however, the risk of hyperkalemia is greater in the cardiac patient, and spironolactone should be given cautiously if at all. Recent clinical studies of intravenous dopamine, natriuretic peptide infusion, or oral adenosine or vasopressin antagonists have all been ineffective in reliably improving the response to diuretic therapy in patients with evolving CRS. A final issue with volume control in the CRS patient is that of isolated ultrafiltration, which can be performed by a nephrologist in a dialysis unit setting (although this procedure has recently become commonplace in heart failure units in a nephrologist-independent manner).

The ultrafiltration device used in heart failure units is 0.12 m² and can be used with either peripheral or central access in that the required blood flow is 30 to 40 mL/min (total filter set volume of 33 mL). Up to 500 mL of isotonic fluid can be removed hourly, and the filters last for one to two days on average. Several recent clinical trials have demonstrated the safety and feasibility of ultrafiltration in the management of acute decompensated heart failure. Ultrafiltration may be more effective at removing fluid than standard diuretic therapy, and it has been associated with some beneficial long-term results (6). However, it remains to be determined whether ultrafiltration is truly nephroprotective, what its actual safety profile is, and what its real cost-effectiveness is. An additional issue with isolated ultrafiltration is the extent to which dialysis unit staff should provide support for non–dialysis unit procedures occurring elsewhere in the hospital.

Because renal impairment in the setting of CRS is a very important indicator of adverse outcome, every effort should be made to prevent any significant (>25 percent of basal value) rise in serum creatinine levels consequent to diuretic unloading therapy. Unfortunately, this proves quite difficult, and diuretic therapy is often stopped because of the degree to which serum creatinine “bumps” with even modest unloading. Renal function can deteriorate suddenly when renin–angiotensin–aldosterone system inhibitor therapy has been begun. In addition, it can acutely change in patients receiving chronic therapy, particularly patients with systolic heart failure who have a low pretreatment mean arterial pressure value as well as some pre-existing level of renal failure.

In most patients who experience worsening renal function with renin–angiotensin–aldosterone system inhibitor therapy, one or more of three main mechanisms can be implicated (7). First and most importantly, if the mean arterial pressure falls to levels that are insufficient to sustain renal perfusion or that provoke substantial reflex renal sympathetic nerve activity, renal function will worsen. Angiotensin-converting enzyme inhibitor–related hypotension is generally more common with long-acting agents or in situations in which the pharmacologic half-life of an angiotensin-converting enzyme (ACE) inhibitor is inordinately prolonged, as occurs when the degree of renal insufficiency is underestimated and an ACE inhibitor cleared predominantly by renal pathways is given. Second, ACE inhibitor or angiotensin receptor blocker (ARBs) are more likely to cause acute kidney injury in the patient with heart failure.

Table 1. Nephrologic considerations in patients with cardiorenal syndrome

| 1 | Consultation for diuretic refractory patients with acute heart failure with need for bridging extracorporeal therapy |
| 2 | Management of prerenal azotemia when significant |
| 3 | Management of clinically significant hyperkalemia or hyponatremia |
| 4 | Consultation for appropriate drug dosing and drug interactions in renal insufficiency |
| 5 | Management of severe hypertension and pulmonary edema associated with diastolic dysfunction |
| 6 | Management of acute heart failure in anuric end stage renal disease patients |
| 7 | Long-term management of pre–end stage renal disease patients with severe cardiomyopathy who are in pulmonary edema or with acute kidney injury |
| 8 | Increasing anemia awareness and management |

The Kidney Cardiac Link

Cardiorenal Syndrome: The Nephrologist’s Perspective

By Domenic Sica
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 cardiorenal syndrome (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 is related to hypervolemia, leading to a decrease in renal blood flow. Angiotensin-converting enzyme (ACE) inhibitor therapy (17) may improve renal perfusion at the expense of other major organs. 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 pressure, 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 (34 percent) or depressed (33 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 pathogenic 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 diuretics 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 diuretic 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 hemodynamics. Continued on page 14.

References
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