Cardiorenal Syndrome
New Perspectives

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Maintenance of blood volume, vascular tone, and hemodynamic stability depends on a set of elegant interactions between the heart and kidney. For some time, physicians have recognized that severe dysfunction in either of these organs seldom occurs in isolation. However, only recently have we attempted to define and apply the widespread concept of the cardiorenal syndrome (CRS). Despite our growing use of the term, there is still some debate as to its true definition. More important, the process itself remains enigmatic; our understanding of the complex physiological, biochemical, and hormonal derangements that encompass the CRS is woefully deficient and may lead to improper medical management of patients.

Because renal dysfunction portends such a dismal prognosis in cardiac failure and vice versa, there has been a recent surge of interest in identifying precise pathophysiological connections between the failing heart and kidneys. Understanding the mechanisms involved in the CRS will allow us to target therapies that interrupt this dangerous feedback cycle.

In 2004, a working group of investigators at the National Heart, Lung, and Blood Institute defined the CRS as a state in which therapy to relieve heart failure (HF) symptoms is limited by further worsening renal function.[1] Although this definition is succinct and understandable and probably reflects the most common use of the term, some authors argue that it is simplistic to the point of being inaccurate.[2] Several groups have recently proposed that the definition of CRS be broadened in an attempt to stress the complex and bidirectional nature of pathophysiological interactions between the failing heart and kidneys. That is, each dysfunctional organ has the ability to initiate and perpetuate disease in the other organ through common hemodynamic, neurohormonal, and immunologic/biochemical feedback pathways.

Proper use of the term *CRS* should correct a common misunderstanding: that kidney dysfunction in HF is a direct consequence of impaired renal blood flow in the setting of depressed left ventricular systolic function. Recent investigations do not support this as the sole derangement in CRS. Increasing evidence supports the roles of central venous congestion, neurohormonal elaboration, anemia, oxidative stress, and renal sympathetic activity as other potential contributors to this complex syndrome. This review stresses the ways in which the heart and kidney interact, often in a deleterious manner.

Epidemiology and Outcomes in Combined Cardiorenal Disease: The Scope of the Problem

Prevalence of Renal Disease in Patients With HF

In the Acute Decompensated Heart Failure National Registry (ADHERE) of >105 000 individuals admitted for acute decompensated HF, 30% had a history of renal insufficiency, 21% had serum creatinine concentrations >2.0 mg/dL, and 9% had creatinine concentrations >3.0 mg/dL.[3] McAlister et al[4] found that only 17% of 754 outpatients with HF had creatinine clearances >90 mL/min. In their cohort, 39% with New York Heart Association (NYHA) class IV symptoms and 31% with NYHA class III symptoms had creatinine clearance <30 mL/min. These numbers are striking when one considers the complexity of treating volume overload in those with coexistent renal disease and that there are >1 million hospital admissions for decompensated HF in the United States annually.

Impact of Renal Disease on Clinical Outcomes in Patients With HF

Renal dysfunction is one of the most important independent risk factors for poor outcomes and all-cause mortality in patients with HF. Baseline glomerular filtration rate (GFR) appears to be a stronger predictor of mortality in patients with HF than left ventricular ejection fraction or NYHA functional class. Both elevated serum creatinine on admission and worsening creatinine during hospitalization predict prolonged hospitalization, rehospitalization, and death.[5,6] Even small changes in creatinine <0.3 mg/dL are common (Figure 1) and have been associated with increased mortality and prolonged hospitalization.[7]

HF Outcomes in Patients With Renal Disease

On the basis of estimates provided by the Third National Health and Nutrition Examination Survey (NHANES III), almost 8 million individuals living in the United States have a GFR <60 mL/min.[8] Patients with chronic renal insufficiency are at strikingly higher risk for myocardial infarction, HF with systolic dysfunction, HF with preserved left ventric-

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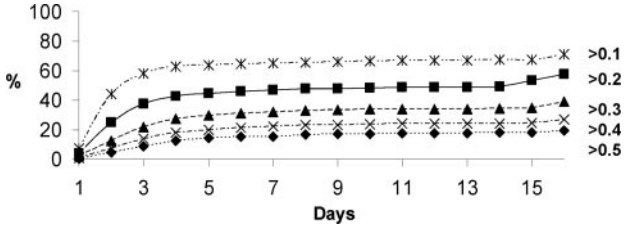

Figure 1. The frequency and time course of developing an increase in creatinine in patients hospitalized with HF. The percent of patients with an increase (by that time in the hospitalization) in creatinine of at least the value indicated is shown. Worsening renal function is common in patients with HF. Reprinted from Gottlieb et al.[7]

ular ejection fraction, and death resulting from cardiac causes compared with individuals with normal GFR.[9] A recent meta-analysis suggests that individuals with primary renal disease are more likely to eventually die of cardiovascular causes than renal failure itself.[10] This is not just secondary to atherosclerotic disease; in a multicenter cohort study of 432 patients, 31% planning to initiate hemodialysis had HF symptoms, and 33% of such patients had estimated left ventricular ejection fraction <40%.[11] Patients with HF and new hemodialysis had a median survival of only 36 months compared with 62 months in patients without HF. Furthermore, 25% who did not have HF symptoms on initiation of dialysis developed these symptoms after a median follow-up of 15 months. Conversely, reversal of renal dysfunction can improve cardiac function. In a study of 103 hemodialysis patients with HF and left ventricular ejection fraction <40%, the mean ejection fraction increased from 32% to 52% after renal transplantation, and 70% had normalization of cardiac function.[12]

Hypertensive heart disease and HF with a normal ejection fraction are common among individuals with advanced and end-stage renal disease. One study showed that there is echocardiographic evidence of left ventricular hypertrophy in 45% of individuals with creatinine clearance <24 mL/min and in 70% of those planning to initiate hemodialysis.[13] Renal disease patients with left ventricular hypertrophy have accelerated rates of coronary events and markers of uremia compared with those with normal left ventricular mass, and a high proportion of these individuals develop clinical HF.[14]

Traditional and Emerging Hypotheses for the Pathophysiology of Cardiorenal Failure

Evolutionary mechanisms designed to maintain constant blood volume and organ perfusion under continuously changing conditions are clearly responsible for CRS. Unfortunately, when primary cardiac or renal dysfunction develops, the renin-angiotensin-aldosterone system (RAAS), pressure-sensing baroreceptors, cellular signaling, and sympathetic nervous system mechanisms turn from friend to foe. Attempting to understand the nature of these normal physiological mechanisms gone awry is key to developing a multimodal approach to preserving function in both organs.

The Low-Flow-State Hypothesis

Traditional reasoning held that the progressive decline in GFR observed in HF primarily reflects inadequate renal perfusion secondary to reduced cardiac output. Many surmised that inadequate renal blood flow or perfusion pressure prompts renin release by the juxtaglomerular cells of the afferent arterioles through low-flow states in the ascending limb of the loop of Henle and pressure-sensing baroreceptors. Renin release and RAAS activation confer extreme sodium avidity, volume retention, decreased glomerular perfusion (ie, afferent arteriolar constriction), and profibrotic neurohormone increases, leading to ventricular remodeling. On one hand, this reasoning is not incorrect because all of the above conditions are observed in HF (neurohormonal stimulation, decreased fractional excretion of sodium, myocardial fibrosis). Experience would also suggest that, by augmenting contractility, heart rate, and cardiac index, inotropes can lead to short-term improvement in urine output, mental status, and other clinical indicators of organ perfusion. However, recent investigations suggest that this viewpoint is extremely limited and management of patients with CRS based solely on the low-flow theory does not lead to improved outcomes.

A recent large trial of pulmonary artery catheter–guided management of 433 individuals admitted with acute decompensated congestive heart failure (Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterization Effectiveness [ESCAPE]) found no correlation between baseline renal function and cardiac index.[15] Furthermore, improvement in cardiac index did not result in improved renal function, prevention of death, or prevention of rehospitalization. This notion is supported by the findings of multiple other investigations in which improved cardiac index or decreased pulmonary capillary wedge pressure during pulmonary artery catheter–guided therapy failed to predict improvement in renal function.[16–18] Collectively, these data do not support poor forward flow and altered hemodynamics as primary determinants of progressive renal failure in the HF population.

Intraabdominal and Central Venous Pressure Elevation

The relationship between blood pressure, cardiac output, and systemic vascular resistance is summarized by the Poiseuille law: Cardiac flow is dependent on a sufficient pressure gradient across the body's capillary networks. HF is marked by an elevation in central venous pressure, which attenuates the gradient across the glomerular capillary network. Indeed, there is increasing evidence to support roles for elevated renal venous pressure and intraabdominal pressure (IAP) in the development of progressive renal dysfunction in patients with HF.

The suggestion that elevated renal venous pressure can retard both renal blood flow and urine formation dates back to investigations performed >100 years ago.[19,20] In one such early experiment, Winton[20] observed that urine formation by isolated canine kidney was markedly reduced at renal venous pressures of 20 mm Hg and abolished at pressures >25 mm Hg. Renal blood flow was also diminished in proportion to the decrease in pressure gradient across the afferent and efferent renal circulations, probably caused by the increased efferent arterial pressure. Rising renal venous pressure limited urine formation and renal blood flow more

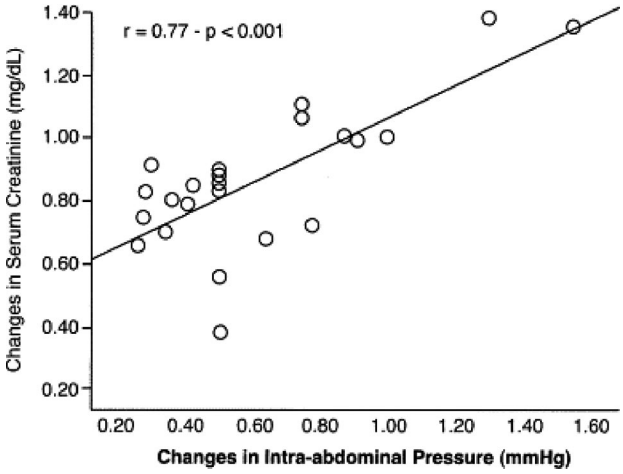

Figure 2. The relationship between changes in IAP with diuresis and the change in serum creatinine. The close relationship suggests that increased IAP may cause renal dysfunction. Reprinted with permission from Mullens et al.[17]

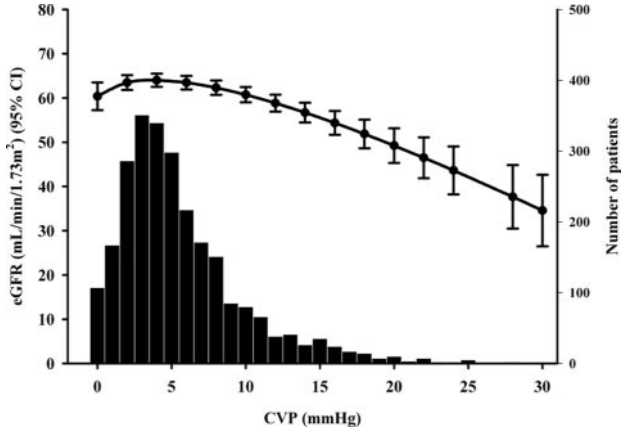

Figure 3. Distribution of central venous pressure (CVP) and the relationship between CVP and estimated GFR in 2557 patients. CVP has repeatedly been shown to correlate well with renal dysfunction in patients with HF. Reprinted with permission from Damman et al.[27]

than a reduction in arterial pressure. Elevation of renal venous pressure from extrinsic compression of the veins has also been shown to compromise renal function.[21] More than 60 years ago, Bradley and Bradley[22] showed that abdominal compression to produce IAP of 20 mm Hg in normal individuals markedly reduced GFR and renal plasma flow. These relationships are supported by modern in vivo animal models.[23] In recent years, there has also been increasing recognition that oliguric acute renal dysfunction frequently accompanies abdominal compartment syndrome in surgical and trauma patients.[24] These changes are promptly reversed by abdominal decompression and may be associated with subsequent polyuria.

An international panel recently defined elevated IAP as pressure $\geq$8 mm Hg and intraabdominal hypertension as pressure $\geq$12 mm Hg.[25] In a recent study, 24 of 40 consecutive patients admitted for acute decompensated HF (mean left ventricular ejection fraction, 19%) had an IAP $\geq$8 mm Hg.[17] None of the 40 patients in the cohort complained of abdominal symptoms at study entry. Patients with elevated IAP had significantly lower baseline GFR compared with those with normal IAP, and the degree of reduction in IAP after diuresis predicted an improvement in renal function (Figure 2). Other initial hemodynamic parameters such as pulmonary capillary wedge pressure and cardiac index were not different between patients with elevated IAP and those with normal IAP. The concept that venous congestion, not arterial blood flow, is an important mediator of cardiorenal failure is supported by the findings of the Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterization Effectiveness trial, in which only baseline right atrial pressure, not arterial blood flow, correlated with baseline serum creatinine.[15]

In considering whether elevated IAP in congestive heart failure is a true culprit in the development of progressive renal dysfunction or an innocent bystander, several mechanisms by which abdominal pressure might contribute to CRS have been explored. Elevation of renal parenchymal pressure does not appear to have significant effects on GFR or renal blood flow. This was shown in studies of isolated porcine kidneys subjected to increasing amounts of extrinsic pressure.[26] In contrast, elevated central and renal venous pressures offer a stronger explanation for the relationship between elevated IAP and renal dysfunction. Elevating renal venous pressure by 30 mm Hg for 2 hours in intact porcine kidneys resulted in a substantial reduction in renal blood flow and GFR.[23] Furthermore, patients with HF with impaired renal function at baseline or worsening renal function during hospitalization have significantly elevated central venous pressure relative to those with less renal impairment[18,27] (Figure 3). In one study of intensive medical therapy directed at volume reduction, hemodynamic profiles were monitored in all patients with pulmonary artery catheters, and only elevated central venous pressure correlated with worsening versus preserved renal function.[18] The role of elevated central and renal venous pressures is further supported by the association of elevated jugular venous pulsations on physical examination with higher baseline serum creatinine and increased risk for hospitalization and death caused by pump failure.[28] Finally, the association of tricuspid regurgitation with renal dysfunction was recently examined in 196 consecutive patients with HF.[29] The authors found that patients with at least moderate tricuspid regurgitation by transthoracic echocardiography had lower estimated GFR and that a linear relationship existed between severity of tricuspid regurgitation and degree of GFR impairment.

Sympathetic Overactivity

The adverse consequences of sympathetic nervous system activity are well known. Sustained elevated adrenergic tone causes a reduction in β-adrenergic receptor density, particularly β_1, within the ventricular myocardium, as well as uncoupling of the receptor from intracellular signaling mechanisms. Less well appreciated are the systemic effects of renal sympathetic stimulation. As left ventricular systolic failure progresses, diminished renal blood flow and perfusion pressure (whether from arterial underfilling or renal venous congestion) lead to baroreceptor-mediated renal vasoconstric-

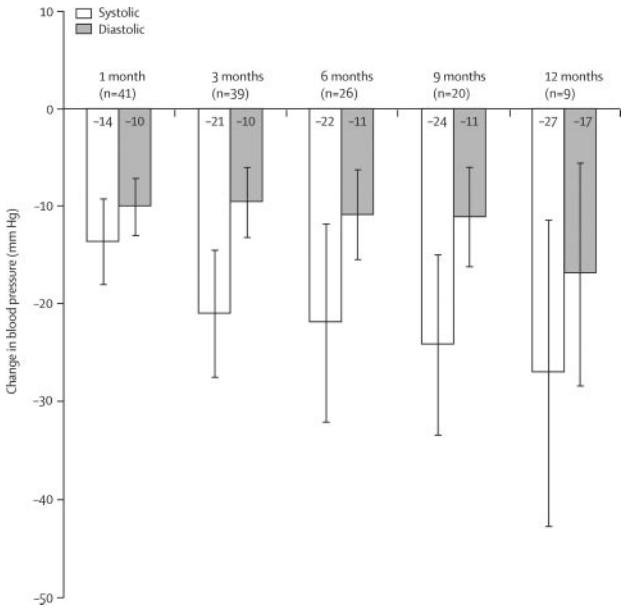

Figure 4. The change in blood pressure after radiofrequency ablation of renal sympathetic nerves. The decrease in blood pressure suggests systemic effects from renal sympathetic nerve activity. Reprinted with permission from Krum et al.[31]

tion, activation of the renal sympathetic nerves, and release of catecholaminergic hormones. This problem is compounded in patients with HF with advanced renal insufficiency because there is reduced clearance of catecholamines by the kidneys.[30]

There are now good data to suggest that the renal sympathetic activation leads to direct vascular effects. A recent pilot study of catheter-based renal sympathetic denervation in patients with resistant hypertension found significant improvements in GFR in 24% of patients undergoing the procedure.[31] Bilateral renal nerve ablation has also been shown to reduce renal norepinephrine spillover, renin activity, and systemic blood pressure 12 months later[32] (Figure 4). Although this intervention has not been tested specifically in an HF population, denervation could possibly affect renal function and halt renal sympathetic nerve-mediated progression of cardiac failure related to elaboration of catecholamines and the RAAS. Further investigation into this exciting concept is needed to determine whether it is clinically relevant.

Renin-Angiotensin-Aldosterone Axis and Renal Dysfunction

The extreme sodium avidity and ventricular remodeling conferred by RAAS elaboration in HF are a maladaptive response to altered hemodynamics, sympathetic signaling, and progressive renal dysfunction. The benefits of angiotensin-converting enzyme (ACE) inhibition and aldosterone antagonism through blockade of the intracardiac RAAS, reduction in adrenergic tone, improvement in endothelial function, and prevention of myocardial fibrosis are well described in cardiac failure; RAAS inhibition has been a main focus of therapy in HF for the last 2 decades and has led to improved outcomes for many patients. Unfortunately, little is known about the long-term benefits or adverse effects of RAAS inhibition on kidney function in HF.

ACE inhibitors and angiotensin receptor blockers have important renoprotective effects in hypertensive patients with nondiabetic renal disease and individuals with diabetic nephropathy.[33] In contrast, whether there is a renoprotective role of ACE inhibitors and angiotensin receptor blockers in systolic HF that is independent of direct preservation of ventricular function has not been established. ACE inhibitors and angiotensin receptor blockers cause dose-dependent increases in angiotensin II (AT-II).[34] This may contribute to the phenomenon described as escape from ACE inhibition.[35] Significantly, AT-II directly contributes to kidney damage. AT-II upregulates the cytokines transforming growth factor-β, tumor necrosis factor-α, nuclear factor-κB, and interleukin-6 and stimulates fibroblasts, resulting in cell growth, inflammation, and fibrotic damage in the renal parenchyma.[36,37]

Oxidative Injury and Endothelial Dysfunction

Neurohormones are strong precipitants and mediators of an oxidative injury cascade that leads to widespread endothelial dysfunction, inflammation, and cell death in the CRS. AT-II seems to be particularly important in this process, exerting many deleterious effects through the activation of NADPH oxidase and NADH oxidase. AT-II activates these 2 enzymes within vascular smooth muscle cells, cardiac myocytes, and renal tubular epithelial cells, generating superoxide, a reactive oxygen species.[38–40] Reactive oxygen species have many unfavorable effects in living tissues and likely contribute to the processes of aging, inflammation, and progressive organ dysfunction. Growing evidence supports oxidative injury as a common link between progressive cardiac and renal dysfunction. Because both primary cardiac failure and primary renal failure lead to elaboration of the RAAS, activation of oxidases by AT-II in one organ has the potential to lead to progressive dysfunction in the secondary organ through reactive oxygen species generation.

Inactivation of nitric oxide is a particularly important effect of superoxide and other reactive oxygen species. Decreased bioavailability of nitric oxide may partially explain the endothelial dysfunction observed in vascular smooth muscle and abnormal contractile properties of cardiac myocytes in HF. There is heightened NADPH oxidase activity in explanted failing hearts compared with healthy hearts awaiting implantation,[39] and high-dose antioxidant agents attenuate left ventricular remodeling after experimental ligation of the left anterior descending coronary artery.[41] Dahl salt-sensitive rats with systolic HF have substantial elevations in AT-II and NADPH oxidase expression and reduced nitric oxide production in kidney tissue compared with control animals without experimental HF.[42] Interestingly, these changes were prevented with the ACE inhibitor imidapril. Other groups have shown that both ACE inhibitors and angiotensin receptor blockers increased the availability of nitric oxide through upregulation of superoxide dismutase.[43] These observations provide a good example of dysfunction in a secondary organ, in this case kidney, associated with primary disease in another organ.

Erythropoietin and the Cardiorenal-Anemia Syndrome

Anemia is common in individuals with chronic kidney disease and HF and may contribute to the abnormal renal oxidative state; hemoglobin is an antioxidant. Although anemia should induce increased erythropoietin, there is evidence that decreased concentrations in patients with CRS may directly exacerbate the renal abnormalities. Therefore, the combination of anemia and decreased erythropoietin may exacerbate the underlying factors causing CRS.

The high frequency of anemia in CRS and HF has repeatedly been demonstrated.[44] In the Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients With Heart Failure (OPTIMIZE-HF) registry, 51% of the nearly 50 000 patients with HF had hemoglobin ≤12 g/dL and 25% had hemoglobin between 5 and 10.7 g/dL.[45] Patients with HF with anemia had increased mortality, length of hospital stay, and hospital readmission rates compared with nonanemic patients with HF. It should be noted that anemia in advanced kidney diseases is due to an absolute deficiency in erythropoietin production. HF alone, on the other hand, may be marked by insensitivity to elevated erythropoietin concentrations secondary to sustained inflammation.[46] Patients with both HF and kidney disease, however, may have low erythropoietin concentrations.

The lack of erythropoietin could exacerbate HF in multiple ways.[47] In cardiac cells, erythropoietin can prevent apoptosis and increase the number of cardiomyocytes.[48] Similar observations have been made in renal cells.[49] Although it is unclear what effect erythropoietin has on nitric oxide synthesis, it does appear to decrease oxidative stress.[47] Small studies suggest that these actions might exert clinical benefit. In a single-center prospective trial, 32 anemic NYHA class II to IV patients were randomized to receive erythropoietin and intravenous iron or routine management. After a mean follow-up of 8 months, patients with active treatment demonstrated improved ejection fraction by multigated acquisition, decreased diuretic requirements, unchanged serum creatinine, and improvements in NYHA functional class. Control patients had worsened ejection fraction, worsening serum creatinine, and deterioration in NYHA functional class.[50] Unfortunately, this study was not placebo controlled or blinded. Other studies have focused on clinical benefits and have not carefully evaluated possible mechanisms.

At this point, it is therefore unclear whether anemia is a marker of progressive heart and renal failure or a true mediator of the CRS. Further long-term study is needed to address the interesting possibility that treatment of anemia in HF may improve renal function. Studies of patients with advanced renal disease suggest that partial correction of anemia leads to improved quality of life, reduced progression to end-stage renal disease, and reduced mortality.[51] Because aggressive correction of anemia in this population has been associated with high rates of adverse events,[52] exploring the utility of correcting anemia in patients with HF should be done with caution.

Other Renal Targets

Arginine vasopressin is a nonapeptide that is released by oncotic stimuli but also by blood pressure and cardiac factors. Concentrations are increased in HF and could lead to water retention and hyponatremia.[53] Furthermore, it has vasoactive effects (mainly through V_1 receptors) that could be important. More clearly relevant to patients with HF is that activation of the V_2 receptor increases the permeability to water of the renal collecting tubular cells, resulting in water retention. Vasopressin antagonists have been shown to lead to more aquaresis and resolution of hyponatremia, with some weight loss and improvement in overall fluid balance. However, these effects have not resulted in clear demonstrable clinical benefit or improvement in renal function.[54] At present, vasopressin appears important as a cause of water retention in some patients but does not appear integral to renal function in these patients.

The importance of adenosine as a mediator of the CRS is also not known. Adenosine-A_1 receptors are found in afferent arterioles, juxtaglomerular cells, the proximal tubule, and thin limbs of Henle, and GFR and urine output could improve by countering the effects of adenosine. Indeed, adenosine concentrations are increased in patients with HF.[55] Initial studies suggested that this mechanism was important. An adenosine-A_1 antagonist, BG9719, maintained creatinine clearance while permitting diuresis.[56] In a crossover study of another adenosine-A_1 antagonist, rolofylline, GFR increased by 32% with active drug, and renal plasma flow increased by 48%.[57] Unfortunately, the pivotal Prophylaxis of Thromboembolism in Critical Care Trial (PROTECT), recently presented at the European Society of Cardiology (2009), showed no beneficial effects in patients with acute decompensated HF. The reason for the very different results between the early studies and PROTECT is unknown. It could reflect the lack of importance of adenosine as a mediator of the CRS or could indicate problems with the drug or the particular patient population studied.

In contrast to most of the neurohormones discussed, there is no suggestion that endogenous natriuretic peptides worsen cardiac or renal function. However, the lack of response of many patients with HF raises questions as to why endogenous natriuretic peptides are not effective. With stimulation of cGMP, these substances (both endogenous and pharmacological) would be expected to increase urine output and to improve renal blood flow. However, it is unclear what their effects are in patients with HF. Possible reasons for different actions include the consequences of lowered blood pressure, altered degradation leaving inactive peptides that are nonetheless assayed, and changes in the target.[58]

Therapeutic Implications

Factors Influencing Medication Use

Cardiac failure and renal failure have synergistic effects that magnify the poor outcomes associated with either disease alone. However, physicians may also have a role in these poor outcomes in that we are often reluctant to prescribe or titrate valuable medications.[16,59] Slight elevation in creatinine concentration during diuretic treatment of decompensated congestive HF may be seen as depletion of intraarterial volume or "overdiuresis" and limit more aggressive diuresis. Such patients are frequently discharged from the hospital

with inadequate resolution of symptoms and thus have high short-term rehospitalization rates.

Inpatients with acute decompensated HF are often not started on ACE inhibitor therapy at discharge for fear of worsening serum creatinine.[60] Recognition that elevated serum creatinine portends worse outcomes in HF prompts physicians to be concerned about the renal effects of these agents. However, the benefits of ACE inhibitor use are clear and outcomes are extremely poor in individuals with HF in whom ACE inhibitors are held. Although it is possible that the prognostic importance of the lack of ACE inhibitors is partly reflective of the severity of disease in these patients, it must also be recognized that ACE inhibitors and angiotensin receptor blockers can lead to decreased renal function even in patients who benefit from their use; mean serum creatinine increased even though outcomes were better in the Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS).[61] With diuresis, serum creatinine is more likely to increase in patients receiving ACE inhibition and in those with the lowest blood pressures.[61] These data suggest that some increase in creatinine should be tolerated with the use of ACE inhibition, and other interventions (such as decreased diuresis) might be needed to accomplish this. The advantage of ACE inhibitors in delaying progression and death in HF is undeniable, and their use should be encouraged unless detrimental effects are clearly proven.

Fluid Removal and Renal Effects

Diuretics are commonly used in HF and appear necessary, but there are suggestions that they might be detrimental. Furosemide decreases GFR in many patients.[56] Higher doses of loop diuretics are also associated with elevated serum creatinine and reduced survival in the HF population, but this might just reflect the need to use higher doses in the sickest patients.[62] More disturbing are their effects on neurohormones known to worsen outcome.

Furosemide can increase fibrosis by its known stimulation of the renin-angiotensin-aldosterone axis. For example, banding of the rat aorta above the renal arteries induces RAAS and reactive fibrosis in the heart, kidneys, and blood vessels.[63] Even more worrisome is a pig study of tachycardia-induced cardiomyopathy. Animals randomized to furosemide reached the end point of systolic dysfunction significantly sooner than placebo animals. Although serum aldosterone did not rise in the placebo group, it was significantly increased in the furosemide group. In addition to activating the RAAS, furosemide can also inhibit renal tubular 11β-hydroxy-steroid dehydrogenase-2, which would allow cortisone to activate the renal mineralocorticoid receptor.[64] The possible adverse effects of diuretics are just starting to be explored, and better knowledge of how to use them is essential. Nevertheless, they will remain the mainstay of treatment until other interventions are proven to be safer and more effective.

Worsening serum creatinine, azotemia, and metabolic contraction alkalosis often limit conventional diuresis in patients with HF. Continuous venovenous ultrafiltration is emerging as a possible alternative to pharmacological diuresis in these scenarios and may offer greater ease and efficacy of volume and sodium reduction without further compromising renal function.[65] Although routine use of ultrafiltration has not been shown to lead to better renal outcomes,[65,66] if the ultrafiltration rate does not exceed the interstitium to intravascular refill rate ($\approx$15 mL/min), it is possible that the more steady fluid removal will prevent renal dysfunction.

The effects of nesiritide on both fluid status and renal function in patients with HF are controversial. Although nesiritide does have natriuretic effects and improves GFR in normal individuals, the effects in patients with HF are more questionable.[67] Indeed, a meta-analysis suggested that it might worsen renal function.[68] Even if it does not have direct adverse renal effects, blood pressure or diuretic actions could lead to such an outcome. The Acute Study of Clinical Effectiveness of Nesiritide in Decompensated Heart Failure Trial (ASCEND) is an ongoing large study that should clarify the effects of this agent in patients with HF.[69]

Inotropes

Considering the multiple causes of CRS in patients with HF, it is not surprising that the data for inotropes as treatment are mixed. It is true that dobutamine and milrinone have been shown to increase cardiac index and renal blood flow in most studies,[70] and after open heart surgery, the increase in renal blood flow is proportional to the increase in cardiac index.[71] However, the clinical consequences are not clear, with urine output and outcomes not having shown improvement in many studies.[72–74] The hypothesis that routine use of inotropic therapy will permit more effective diuresis and treatment in patients with HF was conclusively tested and rejected in the Outcomes of a Prospective Trial of Intravenous Milrinone for Exacerbations of Chronic Heart Failure (OPTIME) study.[75] OPTIME did not evaluate patients who were deemed too ill to be randomized; thus, this population has never been studied in a randomized fashion. Of note, however, is the fact that the patients with the worst renal function in OPTIME, while having the poorest outcome, did not show any benefit with milrinone.[73]

Selective increases in renal blood flow have been evaluated with dopamine and fenoldopam. Despite multiple studies, no clinical benefit has been demonstrated.[76] Although dopamine has occasionally been shown to improve renal function, it appears that this improvement might be secondary to increased cardiac output rather than a local effect.[77] Improved renal function has not been demonstrated with fenoldopam, which appears to increase cardiac output secondary to vasodilation.[78]

Inotropic therapy will continue to be used in patients with worsening renal function presumed to be secondary to decreased cardiac output. Although this treatment regimen still needs to be tested (albeit the impediments to randomized studies in this population are obvious), the routine use of inotropes or other adrenergic stimulating agents for acute decompensated HF is not indicated. Other inotropic drugs are being developed, and evaluating their renal effects will be important.

Conclusions

Fortunately, the importance of the CRS has recently been realized, and investigations looking at both the cause and the

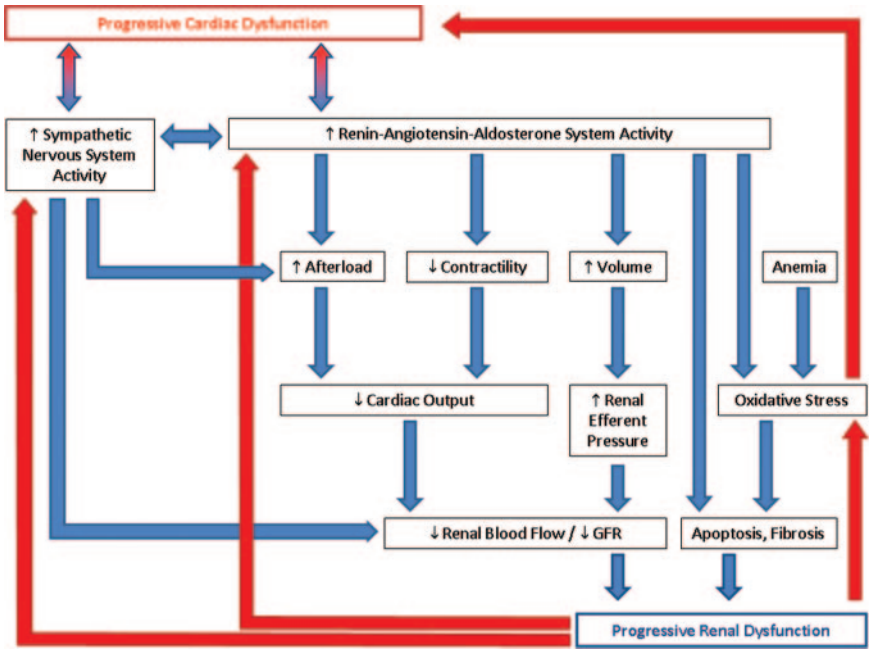

Figure 5. Postulated mechanisms underlying the relationship between HF and renal dysfunction. Blue arrows indicate pathways by which HF may lead to renal failure. Red arrows indicate pathways by which renal failure may lead to HF. The relative importance of these mechanisms (and additional mechanisms not discussed) is not known (ie, boxes are not drawn to scale).

treatment are ongoing. At present, however, interventions to treat the renal problems are lacking; no agents have been shown to directly improve renal function in patients with HF. Figure 5 illustrates many of the possible mechanisms related to the interaction between HF and renal dysfunction. Our improved understanding of the mechanisms behind CRS should be considered when evaluating these patients with a poor prognosis and complex dilemmas.

Disclosures

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