

## A Patient with Heart Failure and Worsening Kidney Function

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### Abstract

There is high prevalence of CKD, defined by reduced GFR, in patients with heart failure. Reduced kidney function is associated with increased morbidity and mortality in this patient population. The cardiorenal syndrome (CRS) involves a bidirectional relationship between the heart and kidneys whereby dysfunction in either may exacerbate the function of the other, but this syndrome has been difficult to precisely define because it has many complex physiologic, biochemical, and hormonal abnormalities. The pathophysiology of CRS is not completely understood, but potential mechanisms include reduced kidney perfusion due to decreased forward flow, increased right ventricular and venous pressure, and neurohormonal adaptations. Treatment options include inotropic medications; diuretics; ultrafiltration; and medications, such as  $\beta$ -blockers, inhibitors of the renin-angiotensin-aldosterone system, and more novel treatments that focus on unique aspects of the pathophysiology. Recent observational studies suggest that treatments that result in a decrease in venous pressure and lead to hemoconcentration may be associated with improved outcomes. Patients with CRS that is not responsive to medical interventions should be considered for ventricular assist devices, heart transplantation, or combined heart and kidney transplantation.

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### Case Presentation

Our patient is a 56-year-old man with ischemic cardiomyopathy who has had several admissions for worsening shortness of breath, lower-extremity edema, and increased abdominal girth. He was readmitted with the same symptoms.

His medical history is significant for coronary artery disease, coronary artery bypass surgery performed 9 years before admission, mitral and tricuspid valve repair, atrial fibrillation with failed cardioversion, non-sustained ventricular tachycardia with an implantable cardiac defibrillator, pulmonary hypertension, severe hyperlipidemia treated with lipid apheresis using an arteriovenous fistula, and CKD with a baseline creatinine level of 1.5–2 mg/dl.

Outpatient oral medications included furosemide, 60 mg in the morning and 40 mg in the evening; carvedilol, 12.5 mg twice daily; hydrochlorothiazide, 25 mg daily; digoxin, 0.125 mg daily; aspirin, 81 mg daily; mexiletine, 150 mg three times daily; and warfarin, 3 mg daily. He had intolerance to angiotensin-converting enzyme (ACE) inhibitors and statins.

Pertinent physical examination findings included BP, 130/74 mmHg; heart rate, 84 beats/min; respiratory rate, 18 breaths/min; and weight, 88.7 kg (increased >10 kg during the last few months). Jugular venous pressure was elevated to the angle of the jaw with the patient at 45 degrees. Heart rate was irregular, with a II/VI systolic murmur loudest at the left sternal border. There were bibasilar crackles, tense ascites, and 2+ pitting edema bilaterally up to the knees. He had an arteriovenous fistula in his left arm.

Laboratory results were as follows: sodium, 131 mEq/L; potassium, 3.8 mEq/L; chloride, 89 mEq/L; HCO<sub>3</sub>, 32 mEq/L; BUN, 54 mg/dl; creatinine, 2.1 mg/dl; eGFR, 35 ml/min per 1.73 m<sup>2</sup>; aspartate aminotransferase, 17 IU/L; alanine aminotransferase, 14 IU/L; alkaline phosphatase, 92 IU/L; total bilirubin, 1.2 mg/dl; international normalized ratio, 2.0; and hemoglobin, 8.9 g/dl. Result on a urine dipstick was negative for blood or protein.

Echocardiography showed an ejection fraction of 25% with moderate to severe global hypokinesis of the left ventricle. The right ventricle was normal in size, with normal thickness, and systolic function was mildly reduced. The left atrium was mildly dilated, and the right atrial size was normal. There was a bioprosthetic mitral valve. There was moderate eccentric tricuspid regurgitation without other valvular stenoses or regurgitation. Right ventricular systolic pressure was elevated at 50–60 mmHg.

### What Was the Differential Diagnosis of CKD in This Patient?

Given the negative urinary dipstick result, intrinsic kidney disease was less likely. CKD due to heart failure or the cardiorenal syndrome (CRS), therefore, was high on the differential diagnosis list. However, other diseases to consider would be renovascular disease, prior atheroembolic disease, tubulointerstitial disease, and myeloma kidney. However, the history, other laboratory data, and the physical examination are not suggestive of these diseases. The most likely

diagnosis, therefore, was CRS with both left- and right-sided heart failure causing CKD.

## Cardiorenal Syndrome

### Definition

CRS has been difficult to define because it encompasses many complex physiologic, biochemical, and hormonal abnormalities. In 2004 the National Heart, Lung, and Blood Institute defined it as (1): “the result of interactions between the kidneys and other circulatory compartments that increase circulating volume and symptoms of heart failure and disease progression are exacerbated. At its extreme, cardio-renal dysregulation leads to CRS in which therapy to relieve congestive symptoms of heart failure is limited by further decline in renal function.” Some authors have argued that this definition is too simplistic, and additional definitions have been developed. Ronco *et al.* defined five classes of CRS (2): type 1, acute decompensated heart failure resulting in AKI; type 2, chronic heart failure resulting in CKD; type 3, AKI resulting in acute decompensated heart failure; type 4, CKD resulting in chronic heart failure; type 5, codevelopment of CKD and heart failure due to a systemic illness.

### Pathophysiology

Several pathophysiological mechanisms have been hypothesized to play a role in CRS.

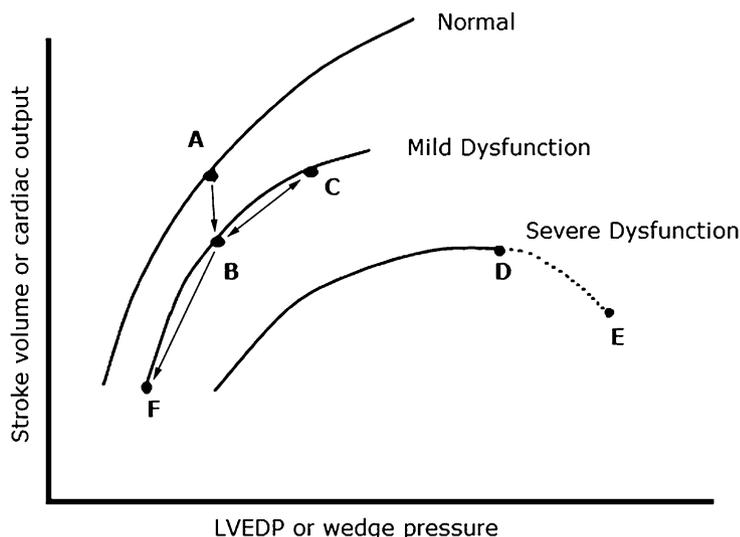
**Reduced Kidney Perfusion or “Reduced Forward Flow.”** In Figure 1 this is represented by moving from the “normal heart” curve to a curve with mild heart failure (A→B). At any level of left ventricular end-diastolic pressure there is lower stroke volume and, therefore, decreased perfusion. The neurohumoral adaptations to reduced kidney perfusion result in stimulation of the renin-angiotensin-aldosterone system (RAAS) and the sympathetic nervous

system, as well as vasopressin and endothelin release, all of which promote systemic vasoconstriction and further decrease in GFR. However, it is clear that not all patients with heart failure and decreased kidney function have hypotension or a reduction in cardiac output (3,4), many patients with hypotension do not have reduced kidney function, and, furthermore, increasing reduced cardiac output does not necessarily materially improve kidney outcomes (5). Therefore, decreased forward flow is clearly not the sole contributor to CRS and cardiorenal interactions cannot be explained solely by pressure/volume diagrams.

**Increased Venous Pressure or “Back Pressure.”** Animal data support the concept of venous congestion being transmitted to the renal veins and causing a decline in GFR (6). Hypothesized mechanisms include reduced transglomerular pressure gradients, myogenic and neural reflexes, baroreceptor stimulation, activation of the RAAS and sympathetic nervous system, and enhanced proinflammatory pathways (7).

High central venous pressure (CVP) is a risk factor for death (3,8) and has been associated with lower eGFR at baseline and decline in eGFR (3). For example, in a study of 145 patients with decompensated heart failure, kidney function declined less frequently when CVP was <8 cm (3), and the ability of CVP to stratify risk was independent of heart rate, pulmonary wedge pressure, systolic BP, cardiac index, and eGFR. Other studies, however, have not reproduced these findings (9,10), and a recent editorial has highlighted the complexity of interpretation of epidemiologic studies evaluating the relationships between CVP and progression of kidney disease (11).

Higher intra-abdominal pressure is also associated with worse kidney function at baseline in heart failure, and patients with reduction of intra-abdominal pressure through decongestion or diuresis had improvement in kidney function (12). The high abdominal pressure and its relationship



**Figure 1. | Starling curves demonstrating varying pressure/volume relationships in patients with normal cardiac function, mild cardiac disease, and severe cardiac disease.** Examples of different scenarios: A→B, Development of mild cardiac dysfunction. B→C, Increased left ventricular end diastolic pressure (LVEDP) in someone with mild cardiac dysfunction. C→B, Diuresis with associated decreased stroke volume with mild cardiac dysfunction. B→F, “Excessive diuresis” D→E, Negative limb of starling curve with severe cardiac dysfunction. There is debate as to whether the negative limb exists and is compatible with life.

to AKI are reminiscent of the abdominal compartment syndrome, which was initially described after abdominal surgery or trauma but is now recognized to have several causes (7,13,14).

**Other Factors.** Right ventricular dilatation and dysfunction may adversely affect kidney function through an elevation in venous pressure, as discussed above (15), as well as through impairing left ventricular filling (16) and, therefore, forward output. Another mechanism that had previously been hypothesized to explain worsening kidney function in heart failure, as well as improvement in kidney function with diuresis, is the negative limb of the Starling curve (Figure 1, D→E). There is, however, debate as to whether the negative limb exists and is even compatible with life (17,18). Finally, although not a cause of cardiorenal syndrome *per se*, diuresis may be excessive such that there is volume depletion (Figure 1, B→F) with low capillary wedge pressure, low CVP, and decreased stroke volume, and, therefore, a decline in GFR.

### Prevalence

Approximately 30%–60% of patients with heart failure reach criteria for having CKD (eGFR < 60 ml/min per 1.73 m<sup>2</sup>). In a systematic review of 80,000 hospitalized and nonhospitalized individuals with heart failure, 29% had kidney impairment (19), while in the Acute Decompensated Heart Failure National Registry (ADHERE) database, which has >100,000 individuals, approximately 30% had creatinine values >2 mg/dl (20). The broad ranges in prevalence of CKD are related to varying definitions, differences in the observed time at risk, and the heterogeneity of selected populations being studied. There is also a 20%–30% incidence of AKI during treatment for heart failure (21–24).

### Effect of Baseline Kidney Function and Change in Kidney Function on Prognosis

Many studies have demonstrated that worse baseline kidney function is a powerful independent risk factor for adverse outcomes in heart failure (19,21,22). This is true both in heart failure with preserved ejection fraction (also called diastolic dysfunction) as well as in heart failure with reduced ejection fraction (25).

The relationship between change in kidney function and outcomes is complex. Several studies (5,21,26) suggest that worsening kidney function may also be a risk factor for adverse outcomes in patients with heart failure. For example, in one study of 1004 consecutive patients admitted with a primary diagnosis of heart failure, decline in kidney function of >0.3 mg/dl occurred in 27% of individuals and was associated with increased risk of complications, longer hospitalizations, and in-hospital death (21). Not all studies have reported an association of worsening kidney function with worse outcomes (27,28). For example, in the Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterization Effectiveness (ESCAPE) trial, a creatinine increase of >0.3 mg/dl or a 25% decline in eGFR were associated with a 30%–50% increase in mortality, although this finding was not statistically significant (29). Improved kidney function was also associated with higher mortality (4) in the ESCAPE trial, particularly in patients with recurrent AKI after discharge (30).

In combination, these data suggest that there may be different pathophysiologic processes resulting in worsening kidney function, and each may carry different prognostic implications. For example, a decline in kidney function due to worsening heart failure is associated with poor prognosis. In contrast, if a decline in kidney function reflects adequate diuresis or decongestion (see below), or is due to the hemodynamic effect of a medication, such as an ACE inhibitor, an angiotensin-receptor blocker (ARB), or an aldosterone blocker, it may be associated with improved outcomes. Data in support of this include those from the ESCAPE trial, where hemoconcentration was associated with decongestion and deterioration in kidney function, but also improved survival (28). Similar findings have been noted in an analysis of the Efficacy of Vasopressin Antagonism in Heart Failure Outcome Study with Tolvaptan (EVEREST Trial), in which hemoconcentration was associated with greater risk of worsening kidney function but decreased risk of death (27). Hemoconcentration achieved later during the hospitalization was particularly associated with improved survival (31). Similarly, in the Studies of Left Ventricular Dysfunction (SOLVD) or in the Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study (EPHESUS), despite an early decline in kidney function during treatment with RAAS blockade, ACE inhibitors or aldosterone blockers were associated with better outcomes than placebo (32,33).

### Hospital Course

Early during admission, the patient underwent right-heart catheterization, which showed a right atrial pressure of 28 mmHg, pulmonary capillary wedge pressure of 38 mmHg, mean pulmonary artery pressure of 52 mmHg (pulmonary artery systolic pressure of 72 mmHg and diastolic BP of 25 mmHg), and cardiac index, measured by Fick equation, of 3.41 L/min per m<sup>2</sup>. Occlusion of the patient's left arteriovenous fistula reduced the cardiac index only slightly.

The patient began receiving an intravenous furosemide drip at 10 mg per hour, which was increased to 40 mg per hour (Table 1), together with intermittent use of a thiazide diuretic. Therapeutic and diagnostic paracentesis was performed twice, with removal of a total of 5.0 L of fluid. Creatinine, however, reached a peak of 2.7 mg/dl when the weight was 74.2 kg. Urine specific gravity was 1.010 while the patient was receiving a diuretic, the pH was 6.5, and no blood or protein was seen. Microscopy showed no casts or cells. Fractional excretion of urea (FeUrea) was 41%. Fractional excretion of sodium (FeNa) was not measured. Renal ultrasonography showed an 11.4-cm left kidney and an 11.1-cm right kidney, without hydronephrosis.

A nephrology consultant noted that the patient was breathing comfortably, his BP was 116/66 mmHg, his heart rate was 92 beats/min, oxygen saturation was 99% on room air, lungs were clear to auscultation, and edema had decreased to 1+. Although he was thought to have slight volume overload, given the increased serum creatinine the recommendation was to continue diuretics to maintain net even fluid balance.

### Discussion of AKI in This Patient

This patient developed AKI while undergoing diuresis. As alluded to earlier and discussed in more detail later, AKI

**Table 1. Changes in serum creatinine and weight, timing and dose of furosemide, and timing of paracetemes during the hospitalization**

Variable	Hospital Day														
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
Creatinine (mg/dl)	2.08	2.02	2.29	2.08	2.42	2.60	2.49	2.37	2.46	2.49	2.70	2.42	2.40	2.48	2.62
Weight (kg)	88.7	87.6	86.3	85.1	84.5	84.5	84.5	78.9	76.7	76.6	74.2	74.2	75.2	75.9	75.9
IV furosemide	10 mg/hr	20 mg/hr					40 mg/hr					Hold	80 mg IV	80 mg IV	Discharge
Paracetemes (L)							3	2							

IV, intravenous.

in the setting of decongestion has been associated with improved prognosis in some studies (27,28). The exact pathophysiologic cause of AKI in our patient cannot be determined, but possibilities include decreased forward perfusion and diuretic-induced neurohormonal activation. The worsening of kidney function despite diuresis and paracetemes suggests that increased venous pressure was not the primary cause.

We have been traditionally taught that “prerenal” azotemia is associated with low FeNa (<1%) and bland urine sediment, while intrinsic renal disease due to acute tubular necrosis (ATN) is associated with high FeNa (>2%) and granular casts. These distinctions, however, are likely neither very sensitive nor specific, and there may be overlap, particularly when there is tubular damage (granular casts) with low FeNa. This suggests the ability of nondamaged parts of the nephron to conserve sodium. Overlap may also occur during diuretic therapy, when the FeNa may be high in the setting of prerenal pathophysiology. In the latter setting, the FeUrea may be more accurate in distinguishing ATN from prerenal azotemia (34). Given the bland urine sediment and the clinical presentation, the cause of AKI was consistent with CRS, although one cannot rule out some component of ATN because the FeUrea was equivocal—it was above the threshold of 35% used to define “prerenal” azotemia.

No trial data support target rates of diuresis in patients with heart failure. From a pathophysiologic standpoint, diuresis should not significantly exceed interstitial fluid mobilization rate so as to avoid hypotension and further neurohormonal activation. In practice, it is reasonable to initially target a net negative balance of about 1 L per day, but this is highly variable and should be modified by the clinical urgency, hemodynamic stability, and kidney function response.

**Are There Evidence-Based Treatments for the Patient?**

The patient was discharged with a prescription for torsemide, 100 mg twice daily, in place of furosemide and hydrochlorothiazide. Spironolactone, 50 mg daily, was added while he was in the hospital. Because of the ACE inhibitor allergy, isosorbide mononitrate, 90 mg daily, and hydralazine, 75 mg three times daily, were also added and titrated. Carvedilol was continued. A low-salt diet was recommended, as were daily weight checks and frequent evaluation of electrolytes, BUN, and creatinine. At discharge, the patient’s weight was 75.9 kg, with a creatinine of 2.62 mg/dl (eGFR, 26 ml/min per 1.73 m<sup>2</sup>).

**Interventions to Improve Cardiac Function**

**Inotropes.** Inotropic drugs, such as milrinone, dobutamine, and levosimendan (not approved in the United States), increase cardiac output, while dopamine increases kidney blood flow at a dose of 2–10 µg/kg per minute and cardiac output in the range of 5–10 µg/kg per minute. Although milrinone, dobutamine, and levosimendan are often used in clinical practice to manage CRS in patients with reduced cardiac index, no large trials demonstrate kidney, cardiovascular, or mortality benefit with use of these medications. For example, in the Outcomes of a Prospective Trial of Intravenous Milrinone for Exacerbations of Chronic Heart Failure,

milrinone treatment led to a minor improvement in eGFR but the 60-day mortality and readmission rates were similar between the milrinone and placebo groups (5,35). Similarly, in the ROSE Acute Heart Failure Randomized Trial (ROSE AHF), which included 360 patients with acute heart failure and eGFR < 60 ml/min per 1.73 m<sup>2</sup>, low-dose dopamine did not enhance decongestion or improve kidney function when added to diuretic therapy (36).

**Vasodilators.** Prior studies had raised concern regarding adverse kidney outcomes and mortality with use of nesiritide in patients with heart failure. A randomized trial of 7141 individuals found no difference in death, hospitalization rate, or kidney function with use of nesiritide versus placebo (37). Similarly, in the ROSE AHF, low-dose nesiritide had no effect on decongestion or kidney function when added to diuretic therapy (36).

**Cardiac Resynchronization.** In an observational study of 490 individuals who underwent cardiac resynchronization, the presence of CKD was associated with a lower likelihood of response to cardiac resynchronization, defined by a decrease in left ventricular end-systolic volume >15% at 6-month follow-up. Those who did respond had preservation in kidney function, while nonresponders had worsening kidney function (38).

### Treatment of Congestion

Although not proven in large randomized trials, low sodium intake is a mainstay of treatment to avoid volume expansion. Other treatments are as follows:

**Diuretics.** Diuretics are generally the first-line treatment for volume overload. Many patients need aggressive diuresis, and several studies suggest that normalizing volume may be beneficial, despite worsening kidney function (28,39). For example, hemoconcentration, a proxy for diuresis, has been associated with favorable prognosis in several studies (27,28,39). Diuretic resistance is frequently a problem in the CRS. Various methods have been used to circumvent this problem, including intravenous diuretics, use of higher and more frequent dosing of loop diuretics, use of torsemide or bumetanide rather than furosemide given their more reliable absorption and longer half-life (torsemide), and incorporation of diuretics acting at different sites along the nephron (*e.g.*, adding thiazide to loop diuretics).

Meta-analyses of small trials suggested that continuous infusion of loop diuretics may increase urine output compared with bolus injections (40). However, some of the best data come from the Diuretic Strategies in Patients with Acute Decompensated Heart Failure trial, which randomly assigned 308 patients to bolus injection or continuous infusion, as well as to a low dose (equivalent to prior oral dose) or a high dose (2.5 times the prior oral dose). In this study there was no significant difference in efficacy (global assessment of symptoms) and safety (worsening of kidney function) between the continuous versus the bolus infusion. High-dose therapy was associated with greater weight loss and relief of dyspnea, but also more frequent worsening of kidney function (41). In interpreting this trial, it is important to note that the continuous infusion group did not receive a loading dose, which is usual practice in some centers.

Use of hypertonic saline along with diuresis has been suggested as a way to limit the neurohormonal upregulation associated with diuretics alone. Small double-blind random-

ized studies have shown improvement in hemodynamics, quicker relief of congestion, shorter hospitalization time, and reduction in brain natriuretic peptide and troponin release with this combination (42). Additional larger trials are needed.

**Vasopressin Receptor Antagonists.** Antidiuretic hormone levels are elevated in heart failure and through V2 receptors promote water retention. Tolvaptan is a vasopressin V2 receptor antagonist, which leads to increased free water clearance. In the EVEREST trial, 4133 patients were randomly assigned to tolvaptan or placebo. Serum sodium levels significantly increased with tolvaptan, but the primary outcomes of hospitalization with heart failure or all-cause and cardiovascular mortality did not differ between groups (43).

**Ultrafiltration.** In the Ultrafiltration versus Intravenous Diuretics for Patients Hospitalized for Acute Decompensated Heart Failure (UNLOAD) study (44), 200 patients with heart failure were randomly assigned to ultrafiltration or diuretics. Ultrafiltration produced greater weight loss than diuretics and reduced 90-day resource utilization for heart failure. One critique of the trial was that the diuretic doses used were below what one would use in standard of care, although similar results were noted in the Relief for Acutely Fluid Overloaded Patients with Decompensated Congestive Heart Failure trial. The most recent study to evaluate this issue incorporated changes in diuretic doses and randomly assigned 188 patients with acute decompensated heart failure, as well as decline in kidney function and congestion, to stepped pharmacologic therapy or ultrafiltration (Cardiorenal Rescue Study in Acute Decompensated Heart Failure). The primary outcome was a bivariate change in kidney function and body weight. Stepped pharmacologic therapy was superior to ultrafiltration for preservation of kidney function, despite similar weight loss (45). A critique of this trial was that the mechanism of implementation of ultrafiltration differed from that of the UNLOAD trial. Thus, the utility of ultrafiltration remains unresolved and additional trials are ongoing.

### Other Interventions for Patients with Reduced Ejection Fraction

**$\beta$ -Blockers.** In a meta-analysis of patients with heart failure and CKD,  $\beta$ -blocker treatment reduced the risk of all-cause and cardiovascular mortality but increased the risk of bradycardia and hypotension (46).  $\beta$ -Blockers need to be introduced with caution, if at all, in patients with cardiogenic shock or decompensated heart failure because they may precipitate worsening of symptoms.

**ACE Inhibitors or ARBs.** ACE inhibitors and ARBs often result in mild, short-term declines in eGFR, but they should not be discontinued for this reason (32,33). For example, in a secondary analysis of the SOLVD trial, among the individuals randomly assigned to enalapril, the initial decline in kidney function was not associated with adverse outcomes. In fact, patients who continued to receive enalapril despite initial worsening of kidney function had decreased mortality compared with the placebo group (32). ACE inhibitors or ARBs must be introduced with caution, if at all, in patients with declining kidney function because they may precipitate further GFR reduction. Similarly, in patients with declining kidney function, ACE inhibitors or ARBs at times need to be held given their effect on inhibiting

efferent arteriolar vasoconstriction, and thereby promoting additional decline in GFR.

**Aldosterone Antagonists.** A *post hoc* analysis of the Randomized Aldactone Evaluation Study demonstrated that the absolute benefit of spironolactone was greatest in patients with an eGFR < 60 ml/min per 1.73 m<sup>2</sup>, and that worsening kidney function was associated with mortality only in the placebo group (47). Similarly, in the Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure, eplerenone was safe in those at high risk for worsening kidney function or hyperkalemia (48); in EPHEUS, eplerenone induced a more frequent early decline in eGFR, which did not affect its benefit on cardiovascular outcomes (33). Despite these reassuring *post hoc* analyses, given the risk of hyperkalemia (49), caution should be exercised in use of aldosterone blockers in patients with decreased GFR who are being treated with ACE inhibitors or ARBs or those with baseline high potassium values.

**Hydralazine and Nitrates.** In patients with heart failure and reduced ejection fraction who cannot tolerate or are allergic to ACE inhibitors or ARBs, hydralazine and nitrates are recommended (50,51).

**Adenosine Antagonists.** Adenosine levels are increased in heart failure and are known to alter levels of nitric oxide as well as other vasodilators. Rolofylline activates the adenosine 2 receptor, which leads to vasodilation and increased renal medullary blood flow. Rolofylline was compared with placebo in a randomized trial of 2033 patients hospitalized with heart failure and reduced kidney function. However, the composite of survival, heart failure status, and changes in kidney function did not differ between groups (52).

### Patient Follow-Up

Unfortunately, our patient continued to have recurrent admissions for heart failure and AKI, with creatinine reaching as high as 4 mg/dl on several admissions. He ultimately required hospitalization and continued inotropic support. His eGFR was labile but generally fluctuated between 15 and 30 ml/min per 1.73 m<sup>2</sup>.

### What Is the Evidence to Support Left Ventricular Devices from the Kidney Standpoint?

Implantable and percutaneous assist devices can be used as a bridge for transplantation or, alternatively, as destination treatments for patients with CRS. Only a few studies have evaluated kidney function after insertion of these devices, and although they may be useful in improving kidney function in the short term (53–56), this has been less clear in the longer term (55,57). Our patient was not a candidate for a left ventricular assist device given his advanced right-sided heart failure. A biventricular assist device may have been considered but carries significant morbidity.

### Is There a Role for a Heart Transplant or a Simultaneous Heart and Kidney Transplant?

Our patient was considered for a heart transplant but because an eGFR < 25–30 ml/min per 1.73 m<sup>2</sup> or a creatinine level > 2.5 mg/dl are relative contraindications to heart transplant alone, the question arose as to whether he should receive a kidney transplant at the same time. There remains

no standardized guidelines for when to perform simultaneous heart and kidney (SHK) transplants, even though as many as 30% of heart transplant recipients have an eGFR < 45 ml/min per 1.73 m<sup>2</sup> before their transplant (58).

Lower eGFR is a risk factor for death after heart transplant (59). Five years after a heart transplant alone, 11% of recipients will require RRT or have an eGFR < 30 ml/min per 1.73 m<sup>2</sup> (60). The decrease in kidney function is likely multifactorial, but the kidney toxicity of calcineurin inhibitors probably plays a role. If nonreversible CKD precedes the heart transplant, it is reasonable to assume that kidney function will be more likely to progress in the setting of calcineurin inhibitor use.

In a recent analysis from the Organ Procurement and Transplantation Network/United Network for Organ Sharing databases, which identified 16,710 heart transplants alone and 263 SHK transplants between 1998 and 2007, recipients of SHK had a lower risk of death compared with recipients of heart transplant alone. This was, however, true only in patients who required dialysis before transplant. The authors concluded that SHK should be considered in heart transplant candidates with kidney failure requiring dialysis, but that for kidney disease not requiring dialysis, further study is needed (61). Another study from the United Network for Organ Sharing identified 26,183 heart transplant recipients and 593 SHK recipients and noted that heart transplant recipients with eGFR < 37 ml/min per 1.73 m<sup>2</sup> had worse survival than SHK recipients (59).

Determining who has kidney dysfunction that is reversible and is likely to improve with advanced therapies, such as heart transplant, is difficult to determine. If a patient is known to have intrinsic kidney disease—by having > 500–1000 mg of protein per day, small kidneys, or active urine sediment—then it is less likely that the kidney dysfunction will fully reverse after transplant. Improvement in kidney function with inotropes or with assist devices suggests a component of reversibility; however, the converse may not necessarily be true, and a lack of response to inotropes or a ventricular assist device does not necessarily indicate irreversibility. The presence of comorbid conditions, such as hypertension and diabetes, is probably not helpful because these conditions may or may not contribute to the decreased GFR. High BUN-to-creatinine ratio (62), right ventricular dysfunction (63), and abnormal liver function test results (64) have been associated with reversible kidney dysfunction in a few studies, but their predictive value before heart transplant is less clear. Decisions are relatively straightforward regarding placement on a SHK list when ESRD predates the heart failure but are more challenging regarding listing for heart transplant alone or an SHK in a nondialysis patient with no overt intrinsic kidney disease but with an eGFR of 15–30 ml/min per 1.73 m<sup>2</sup>.

### Patient Follow-Up

Our patient received an SHK transplant after being hospitalized for approximately 6 months. He is doing well, with a serum creatinine of 0.9 mg/dl (eGFR > 60 ml/min per 1.73 m<sup>2</sup>).

### Questions

*Osama Amro, MD, Nephrology Fellow, Tufts Medical Center:* Will kidney biopsy help risk stratify as to who may benefit from SHK?

M.J.S.: There is only one study of which I am aware that has evaluated this question. Thirty heart transplant candidates with an eGFR < 40 ml/min per 1.73 m<sup>2</sup>, proteinuria > 500 mg/d, or a history of amyloid underwent kidney biopsy (65). The degree of fibrosis on kidney biopsy did not correlate with eGFR or proteinuria. On the basis of the biopsy results, approximately half were listed for SHK and half for heart transplant alone. Eight patients had ischemic nephropathy by pathology, with seven of the eight having < 500 mg of proteinuria, and four of the eight having significant atrophy/fibrosis, suggesting that chronic hypoperfusion may lead to structural abnormalities. The conclusion was that a kidney biopsy may help determine chronicity of kidney disease and help differentiate intrinsic disease from kidney hypoperfusion. The risks and benefits of a kidney biopsy should therefore be considered in cases where either defining the extent of atrophy/fibrosis or delineating the etiology of the decreased GFR will alter management.

Pranav Garimella, MD, Nephrology Fellow, Tufts Medical Center: What is the role of biomarkers in CRS?

M.J.S.: This is an ongoing area of investigation, with serum natriuretic peptides probably being best studied. Levels of natriuretic peptides can be used for diagnosis of heart failure in the setting of decreased GFR, although thresholds may need to be modified, as increased levels may be due to the kidney dysfunction itself. Higher levels of natriuretic peptides are associated with worse prognosis in the CRS, as they are in patients with heart failure but without CKD. Although some studies have suggested that repeated measurements of natriuretic peptides should be used to guide therapy in heart failure, this has not been sufficiently evaluated in the specific subgroup with CRS.

Pranav Garimella, MD, Nephrology Fellow, Tufts Medical Center: What is the utility of invasive monitoring, especially given that target rates of fluid removal are unknown?

M.J.S.: The utility of invasive monitoring was evaluated in the ESCAPE trial, which randomized 433 patients with decompensated heart failure to therapy guided by clinical assessment and invasive monitoring using a Swan-Ganz catheter or by clinical assessment alone (66). At 6 months there was no difference in the primary endpoint of days alive out of the hospital. There was also no significant difference in mortality. Routine use of invasive monitoring, therefore, is not currently recommended, although a subset of patients in whom clinical assessment is inadequate may still benefit.

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#### Disclosures

None.

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