Acute Cardio-renal Syndrome: Progression from Congestive Heart Failure to Congestive Kidney Failure

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Over the past few years, acute worsening of renal function has emerged as a powerful and independent predictor of adverse cardiac outcomes among patients hospitalized with acute heart failure exacerbation. This phenomenon has been recently termed acute cardio-renal syndrome. Acute cardio-renal syndrome is not uncommon, affecting roughly one third of acute decompensated heart failure patients. The mechanism of acute cardio-renal syndrome is poorly understood and difficult to elucidate in light of the complex and multifactorial comorbidities associated with acute heart failure syndrome. Acute cardio-renal syndrome is commonly explained by hypoperfusion of the kidney with intravascular volume depletion, hypotension and low flow state ("pre-renal syndrome"). This perception, however, is challenged by the actual hemodynamics present during acute cardio-renal syndrome characterized by hypervolemia, normal cardiac output, and elevated filling pressures of the systemic and venous circulation. This review discusses the long-standing and unnoticed evidence in support of the notion that right-sided failure with raised filling pressure of the renal vein by itself can indeed lead to acute worsening renal function with oliguria, azotemia, and reduced glomerular filtration rate.

Introduction

Due to significant advances in the care of patients with heart failure over the last two decades, their survival and quality of life have improved. Increased survival of patients with heart failure explains at least in part the continuous rise in overall prevalence of heart failure. As patients live longer, however, they are more likely to experience complications of the disease; one of the most clinically relevant is renal dysfunction. The following article reviews the role and pathophysiology of combined advanced heart failure and kidney disease which is called cardio-renal syndrome.

Definition of Cardio-renal Syndrome

The term "cardio-renal syndrome" lacks a universally accepted definition. In broader terms, cardio-renal syndrome describes the coexistence of renal dysfunction with cardiac disease. We differentiate between two subcategories of cardio-renal syndrome, the chronic and the acute. Chronic cardio-renal syndrome is the concomitant presence of chronic kidney disease and heart disease. Chronic kidney disease is associated with all-cause mortality among patients with chronic ischemic heart disease [1–4] and those with chronic, stable heart failure [4–8]. A glomerular filtration rate (GFR) of less than 60 mL/min/1.73 m^2 lasting for 3 months or more in duration [9], consistent with moderate kidney disease, predicts poor cardiac outcomes. The risk for cardiac death correlates with the severity of renal dysfunction (eg, severe chronic kidney disease with GFR < 30 mL/min/1.73 m^2 was more predictive than moderately reduced GFR), suggesting a J-shape curve for mortality risk starting at a level of less than 60 mL/min/1.73 m^2 [3]. It is estimated that chronic kidney disease has a prevalence of around 30% among patients with chronic heart failure [10]. The pathogenesis of renal dysfunction in these disease groups is poorly understood and difficult to define because its mechanism is complex and multifactorial in most cases. Nevertheless, the evidence of a cardio-renal connection [11,12] suggests that renal dysfunction triggers a systemic response that leads to the progression of left ventricular failure.

Lately, the acute manifestation of worsening renal function has been observed as a common and progressive complication of acute heart failure exacerbation. This is defined as acute cardio-renal syndrome. Almost one third of all patients hospitalized for acute decompensated heart failure develop worsening renal function [7,13,14], which

has shown to be a more pertinent prognostic marker for poor outcomes than baseline, stable renal dysfunction [7,8,14–16]. Any level of creatinine increase is prognostic [7]; however, recent studies have used a rise of more than 0.3 mg/dL over baseline [14,16,17] as the lower limit to classify for acute cardio-renal syndrome. Furthermore, increased blood urea nitrogen of greater than 50 mg/dL (17.84 mmol/L) was present in 20% of all patients with acute cardio-renal syndrome [8] and was the strongest predictor of in-hospital mortality in the ADHERE registry [18]. The rate of change in kidney function appears to be a powerful tool for the risk stratification of patients with heart failure beyond baseline kidney function and was associated with increased mortality but also predicted morbidity such as longer and more complicated hospitalization and greater likelihood of readmission. Acute cardio-renal syndrome has the potential of being reversed with appropriate and aggressive heart failure management [19] (Fig. 1) which supports the hypothesis that worsening heart failure is directly or indirectly involved in the pathogenesis of acute cardio-renal syndrome.

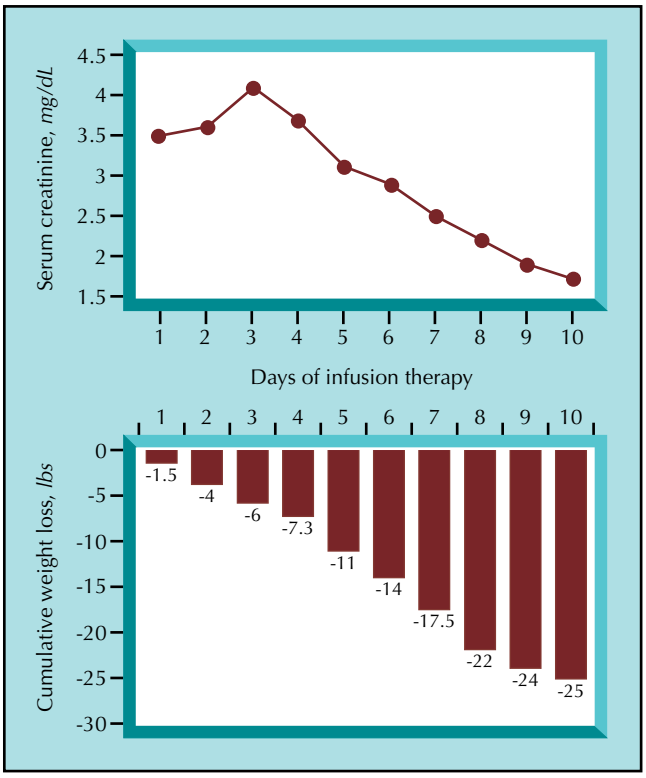

Figure 1. Acute cardio-renal syndrome treated with daily intravenous continuous infusion of furosemide. A patient with acute decompensated heart failure and worsening renal function was treated with outpatient intravenous furosemide infusion, 100 mg bolus three times in 1-hour intervals, and continuous infusion for 4 hours at a dose of 100 mg/h. Treatment was repeated daily until euvolemia was achieved. The patient diuresed effectively with an average net volume loss of 2.5 lbs/d. Acute cardio-renal syndrome was present at the start of treatment with elevated creatinine of 3.5 mg/dL. Creatinine rose further over the next 3 day s of furosemide treatment to a maximum of 4.1 mg/dL. Continuous aggressive diuresis, however, resulted in improvement of acutely worsening renal function to a baseline creatinine of 1.6 mg/dL after a total of 25 lbs of volume loss. (*From* Durango et al. [19].)

Etiology and Pathophysiology of Acute Cardio-renal Syndrome

Renal dysfunction in patients with acute heart failure exacerbation is complex and in many cases multifactorial as much as the heart failure syndrome itself. One potential cause of acute cardio-renal syndrome is worsening intrinsic kidney disease (eg, diabetic or hypertensive nephropathy) which could trigger the cascade of activation of the renin–angiotensin-II–aldosterone system, volume retention, and heart failure exacerbation [12]. Other potential causes for acute cardio-renal syndrome include certain classes of drugs that lead to decreased GFRs and urine output, such as angiotensin-converting enzyme inhibitors, angiotensin-II receptor blockers, anti-inflammatory drugs, and others. Prior history of renal dysfunction and/or heart failure is a risk factor for developing acute cardio-renal syndrome. Worsening renal failure usually occurs within the inital days of hospitalization [14] implying that acute cardio-renal impairment is related to inherent mechanism and the acute hemodynamic changes of heart failure itself.

Intuitively, the most commonly assumed yet least likely cause of acute cardio-renal syndrome is hypoperfusion of the kidney explained by hypotension or hypovolemia. In contrast to this assumption is the fact that the majority of patients hospitalized with acute cardio-renal syndrome are "warm and wet." These patients present with signs and symptoms of increased intravascular volume and biventricular filling pressures illustrated by dyspnea on exertion in 97%, central edema in 66% to 80%, and increased jugular venous pressure in 61% [8,14]. Even though hypovolemia is known to cause renal failure, hypervolemia is far more common in the acute decompensated heart failure population with worsening renal function than without. Of note, symptomatic hypotension is uncommon with an incidence of only 2.9% in acute cardio-renal syndrome [8], making low flow state a rather unlikely cause for worsening renal function. Even in the setting of low flow state, the autoregulatory mechanism of the kidney has a remarkable capacity to maintain its baseline GFR even at low cardiac index as low as 1.5 L/min/m^2 [20]. Renal function remains remarkably stable in most hypotensive patients with systolic blood pressure below 90 mmHg. In contrast, hypertension emerged as a predictor of worsening renal function.

Furthermore, severe left ventricular systolic function is not a predictor of worsening renal function and rarely leads to cardiogenic shock, which has an incidence of only 1% to 3% during acute decompensated heart failure [21]. In fact, almost one half (37%–55%) of patients with acute cardio-renal syndrome have preserved systolic function [8,14], making the argument for low flow state, hypotension, or hypoperfusion of the kidney as a primary cause of acute cardio-renal syndrome highly unlikely. In fact, in patients presenting with acute cardio-renal syndrome, there

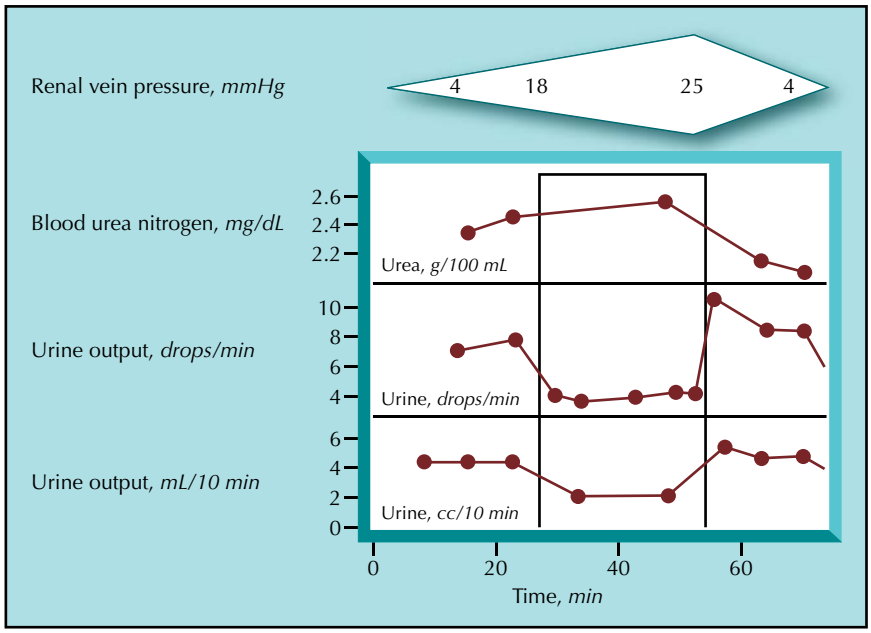

Figure 2. The effects of increased venous pressure on urine flow and renal function in a dog. Renal vein pressure was artificially raised from normal (4 mmHg) to a maximum of 25 mmHg. Renal function did not change until renal vein pressure increased to 20 mmHg resulting in rise of blood urea nitrogen and reduction in urine output. Blood urea nitrogen and urine flow returned to normal in response to normalization of renal vein pressures. (*Adapted from* Winton [37].)

is no correlation between renal deterioration and low cardiac output, low vascular filling pressures, or reduced renal perfusion [22]. Apparently, effective pharmacotherapy for heart failure has created a population of patients with acute decompensated heart failure who are "warm and wet," maintaining a relatively stable cardiac output despite severe symptoms, volume overload, and renal failure.

Even though diuretics are considered class I guideline-recommended treatment for symptomatic heart failure with or without preserved systolic function [23,24], their use in the management of acute cardio-renal syndrome remains highly controversial. Multiple studies found that diuretic use can be associated with worsening renal function, especially if combined with angiotensin-converting enzyme inhibitors [22]. Despite worsening renal function, aggressive intravenous furosemide infusion that is tailored to maximize urine flow and effective volume loss resulted in improved hemodynamics and heart failure symptoms and normalized renal function in most cases [19]. This supports the above findings that cardio-renal syndrome is a syndrome of hypervolemia and normal flow state. Unfortunately, diuretics are often given at subtherapeutic dosage and discontinued prematurely before hemodynamic improvement and euvolemia are achieved [25,26]. More than 50% of patients with acute decompensated heart failure have not lost any volume based on body weight at the time of discharge [25], exposing them to chronic high filling pressures and high risk of readmission. Therefore it is not surprising that multiple observational studies found aggressive yet ineffective diuretic use is associated with worsening renal function and increased morbidity and mortality [22,27,28].

As illustrated from the foregoing description, the major pathophysiology of acute cardio-renal syndrome is hypervolemia with elevated systemic filling pressures and normal flow state. Other mechanisms are less likely, even though several factors can co-participate. The most plausible explanation for acute cardio-renal syndrome should not be overlooked and require aggressive management that is focused on the hemodynamic derangement and restitution of euvolemia.

Elevated Renal Vein Pressure as Cause of Acute Cardio-renal Syndrome (Congestive Kidney Disease)

Despite the evidence, the concept of hypervolemia inducing renal failure appears contradicting especially because azotemia and rise in creatinine is considered the "paradigm" for the pre-renal syndrome. This constellation, however, is supported by a well established cause of renal dysfunction that has been ignored for many decades—high central venous pressure transmitted to the renal veins and kidneys. According to an elegant study by Winton [29••] (later confirmed by Firth et al. [30••]), hypervolemia and acute increase in renal vein pressure leads to profound azotemia combined with reduced glomerular fitration rate, urine output and sodium retention (Fig. 2). Cardiac output, renal blood flow, and mean arterial pressure were controlled at normal range and renal function remained stable until a threshold in renal vein pressure of 18 to 20 mmHg was achieved. Beyond this threshold, progressive deterioration of renal function occurred. Importantly, urine output and GFR improved when renal vein pressure returned to normal. Many other studies have shown that renal vein constriction results in reduced sodium excretion [31–34,35•] causing increased renal interstitial pressure and reduced GFR [32,35•]. Even the increase of intra-abdominal pressure by external abdominal cuff compression in normal human patients leads to a rise in renal vein pressure from

5 to 18 mmHg resulting in a 50% fall in urine output and 30% fall in GFR [36••]. Even though the exact mechanism is not known which increases renal vein pressure alters sodium handling and causes reversible azotemia and renal dysfunction, it is plausible to assume that increased renal vein pressure will cause extravasation, edema, and "congestion" of the kidneys as seen in congestive liver and gut edema. Congestion of the kidney combined with elevated renal interstitial pressure might be the mechanism by which tubular dysfunction, azotemia and renal failure occurs. These studies illustrate how hypervolemia and increased filling pressures as seen in acute cardio-renal syndrome can not only lead to worsening renal function but also drive the vicious cycle of further sodium retention, volume expansion, and heart failure exacerbation.

Conclusions

As shown in this review, acute cardio-renal syndrome is a common, progressive, and ominous complication of acute decompensated heart failure with a serious impact on morbidity and mortality. As a result of successful management of chronic heart failure over the last 20 years with improved survival, growing numbers of patients with advanced heart failure are expected to present with acute cardio-renal syndrome. The management of acute cardio-renal syndrome is challenging as it presents with a combination of aggravating renal dysfunction, diuretic refractoriness, and progressive heart failure symptoms that will require more aggressive and drastic interventions, like vasoactive therapy, ultrafiltration, hemofiltration, or mechanical circulatory support. Before these interventions can be used effectively, a better understanding of the pathophysiology of acute cardio-renal syndrome is necessary. The review of the current literature points to a paradigm shift towards the meaning of azotemia and reduced GFR in acute decompensated heart failure, suggesting that hypervolemia with right-sided failure and elevated renal vein pressure is the primary cause for congestion of the kidney and acute cardio-renal syndrome. Future randomized studies are required to confirm this hypothesis and to identify effective treatment for this challenging syndrome.

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