JUSTIN L. GRODIN, MD, MPH
Division of Cardiology, Department of Internal Medicine, University of Texas Southwestern Medical Center, Dallas, TX

Hemodynamically, the kidney is at the heart of cardiorenal syndrome

In heart failure, the heart and the kidneys share a rocky relationship. Cardiac dysfunction can heighten renal dysfunction and vice versa—appropriately dubbed "cardiorenal syndrome."

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Although classically defined by a reduction in the glomerular filtration rate (GFR),[1] cardiorenal syndrome also encompasses complex neurohormonal, pharmacologic, and metabolic interactions affecting or affected by both glomerular and tubular function. Unfortunately, all of these maladaptive processes occur in heart failure and perpetuate a vicious circle of continued dual-organ dysfunction.

In heart failure, maladaptive processes perpetuate a vicious circle of dual-organ dysfunction

The central insult here is hemodynamic disarray from acute or chronic cardiac dysfunction, which can directly influence glomerular function. However, to understand the hemodynamic ramifications for glomerular function, we focus on the determinants of glomerular filtration.

DETERMINANTS OF GFR

The GFR is the rate of fluid flow between the glomerular capillaries and the Bowman capsule and is classically represented by the following equations[2]:

$$GFR = K_f \times (P_G - P_B - \pi_G + \pi_B)$$

$$K_f = N \times L_p \times S$$

K_f is the filtration constant, N the number of functional nephrons, L_p the hydraulic conductivity of the glomerular capillary, S the filtration area, P_G the hydrostatic pressure in the glomerular capillaries, P_B the hydrostatic pressure in the Bowman capsule, and π_G and π_B the colloid osmotic pressures within the glomerular capillaries and Bowman space, respectively.

Based on this relationship, the GFR is reduced when P_G is reduced in the setting of hypovolemia, hypotension, or renin-angiotensin system antagonist use or when P_B is increased in the setting of elevated central venous pressure or elevated abdominal pressure—all common in heart failure. With this understanding, one would assume that strategies to increase P_G (improve perfusion) and reduce P_B (reduce congestion) might ameliorate ongoing renal dysfunction and improve the GFR in heart failure.

In this issue, Thind et al[3] highlight the impact of hemodynamic derangements in heart failure with acute cardiorenal syndrome and provide an overview of its treatment. They review the complex relationship between progressive cardiac failure translating into accelerated neurohormonal responses (increases in sympathetic nervous system and renin-angiotensin-aldosterone system activation) and the impact of increased central venous pressure on progressive renal dysfunction. They also provide an overview of efforts to mitigate cardiorenal syndrome, after careful appraisal of volume status, through diuretic-mediated decongestion with aggressive use of loop diuretics (either in isolation or in the form of sequential nephron blockade with a thiazide

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or acetazolamide), and they highlight the lingering uncertainty regarding inotrope use.

VENOUS CONGESTION VS DECREASED CARDIAC OUTPUT

Returning to the GFR equation, it is clear that an imbalance in P_G and P_B can worsen glomerular function. Because cardiac dysfunction can lead to both venous congestion and decreased cardiac output, this leads to the question, "Of these, which is the more important driver of this imbalance and its effects on renal function?"

A compelling argument can be made for each side. On one hand, experiments over a half-century old in human models of venous congestion highlighted the profound impact of elevated venous pressure, which decreases electrolyte excretion (sodium included) and diminishes urine flow.[4,5] This has been replicated in more-contemporary decompensated heart failure cohorts in which worsening renal function was more closely associated with elevated central venous pressure rather than cardiac output.[6,7] On the other hand, early landmark experiments and more recent cohorts with heart failure have also shown that reductions in effective arterial blood volume, renal blood flow, and cardiac output are also associated with reductions in GFR.[5,8,9]

How then shall we reconcile whether cardiorenal syndrome is a "backward failure" (from central venous pressure) or a "forward failure" (from decreased perfusion) phenomenon?

The answer is complicated and is likely "both," with the major component being increased central venous pressure. To understand this construct, we must first exclude frank cardiogenic shock—when the hydraulic function of the heart fails to provide enough flow, leading to a catastrophic drop in mean arterial pressure that supersedes the kidney's ability to autoregulate renal blood flow.[10,11]

In patients with chronic heart failure and congestion who are not in shock, historical observations suggest that both intra-abdominal pressure (which increases renal venous pressure) and central venous pressure lead to reduced renal blood flow and increased renal vasomotor resistance (increase in afferent, intrarenal, and efferent vascular tone).[12–14] More recent observations from epidemiologic studies have largely replicated these findings. Central venous pressure remains essential to impacting renal function in heart failure,[6,15] and the impact of cardiac output on renal function remains uncertain.[16]

The relationship of intracardiac hemodynamics may also play a role in modifying renal function. Several reports recently described the relationship between both right- and left-sided filling pressures as being associated with worse renal function in heart failure.[17–19] Patients with a disproportionately higher right atrial pressure to pulmonary capillary wedge pressure have higher serum creatinine during and after decongestive therapies. Therefore, the concept of "right-sided heart failure" expands beyond the simple representation of "backward congestion" at the level of venous return. In fact, a higher ratio of right atrial pressure to pulmonary capillary wedge pressure may point to an inability of the venous and pulmonary circulations to provide adequate left ventricular preload. Therefore, a relatively underfilled left ventricle in the face of biventricular dysfunction may result in worsening renal function.

TREATMENT IS CHALLENGING

The treatment of cardiorenal syndrome is challenging. It is often accompanied by heightened azotemia, diuretic resistance, electrolyte abnormalities, and a spectrum of hemodynamic disarray. As Thind et al point out, there is, unfortunately, no firmly established treatment. While "sequential nephron blockade" (pharmacologically blocking multiple sites on the nephron simultaneously) is theoretically promising, there are no rigorously studied therapeutic strategies with proven efficacy.

On the other hand, mechanical removal of isotonic fluid with ultrafiltration showed early promise in decompensated heart failure, but enthusiasm diminished with results from the Cardiorenal Rescue Study in Acute Decompensated Heart Failure (CARRESS-HF) trial.[20] Ultrafiltration was roughly equivalent to aggressive pharmacologic therapy for fluid loss, was associated with higher serum creatinine levels, and was more challenging to administer.

Cardiorenal syndrome is likely both a 'backward failure' from central venous pressure and a 'forward failure' from decreased perfusion

Equally uncertain is the benefit of inotropic or vasoactive therapy, which directly alters cardiac hemodynamics. Low-dose dopamine or low-dose nesiritide is of no benefit toward enhancement of decongestion or renal protection when added to standard diuretic therapy.[21] Furthermore, routine use of inotropes is fraught with more arrhythmias and hypotension and is associated with dismal long-term outcomes.[22,23]

Alternative therapies that act directly on renal physiology—eg, rolofylline, a selective adenosine A1 receptor antagonist that may enhance renal blood flow, augment natriuresis, and break diuretic resistance—have been similarly disappointing.[24]

With so much uncertainty, more investigation into novel treatments for cardiorenal syndrome is clearly warranted.

However, because venous congestion is the hemodynamic hallmark of acute cardiorenal syndrome (increasing P_B), reducing central venous pressure remains the cornerstone treatment for cardiorenal syndrome. Additionally, efforts to preserve renal perfusion and avoid hypotension are prudent to maintain glomerular capillary hydrostatic pressure (P_G).

In light of these considerations, there is no "one size fits all" for the treatment of cardiorenal syndrome. Treatment should be based on thoughtful individualized strategies tailored to the underlying cardiorenal pathophysiology, and with the understanding that the kidney is at the heart of the matter.

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***ADDRESS**: Justin L. Grodin, MD, MPH, University of Texas Southwestern Medical Center, 5323 Harry Hines Blvd. Dallas, TX 75390-9047; justin.grodin@utsouthwestern.edu*