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EDITORIAL COMMENT

The Cardiorenal Syndrome

Do We Need a Change of Strategy or a Change of Tactics?*

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Two disparate analyses appear in this issue of the *Journal*: one evaluates hemodynamics associated with worsening renal function (WRF) in 145 patients hospitalized for acutely decompensated heart failure (ADHF) (1), and the other assesses the correlation between hemodynamics, renal function, and mortality in 2,557 patients undergoing right heart catheterization for various cardiovascular disorders (2). Despite the dissimilar patient populations, a strikingly similar message emerges: increased central venous pressure (CVP) is independently associated with renal dysfunction, WRF, and unfavorable outcomes. In the Dutch study, the detrimental effect of CVP on renal function and survival was greatest in those patients with preserved cardiac index (CI) (2).

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The discordance between cardiac performance and renal function challenges the notion that, in heart failure (HF), renal insufficiency usually represents hypoperfusion of the kidney as the result of poor forward flow or overzealous diuresis (3). Instead, growing evidence shows that hypervolemia by itself is independently associated with mortality (4,5). The authors of a study comparing blood volume measured by radiolabeled albumin with hemodynamics and outcomes in 43 nonedematous patients with HF demonstrated that 65% were hypervolemic (6). Importantly, blood volume was closely correlated with pulmonary capillary wedge pressure (PCWP) and independently predicted 1-year risk of death or urgent cardiac transplantation, both significantly greater in the hypervolemic patients (6). Observational data in patients with ADHF showed that pre-discharge reduction of PCWP <16 mm Hg, as opposed to an increased CI, predicted improved 2-year survival (7). Interestingly, in the Dutch study, increased CVP on admission, as well as insufficient reduction of CVP during hospitalization, were the strongest determinants for the development of WRF (1). In contrast, impaired CI on admission and improvement in CI after intensive medical therapy had little effect on WRF. These intriguing observations raise questions about our current management strategy for acute HF, which has been to lower cardiac filling pressures while maintaining or enhancing CI (8). What are the mechanisms by which venous congestion worsens renal function, and why is vigorous diuresis alone so often ineffective?

Normally, 85% of the total plasma volume resides in the venous circulation; only 15% is maintained in the arterial circuit. The primary regulation of renal sodium and water excretion and, thus, body fluid homeostasis, is modulated by the smaller arterial circulation, enabling the system responsible for the perfusion of the body's vital organs to respond to small changes in body fluid volume (9). Heart failure results in a decrease in CI and a decrease in intra-arterial blood volume. Arterial hypovolemia inactivates the high-pressure baroreceptors in the aortic arch and coronary sinus, attenuates the tonic inhibition of afferent parasympathetic signals to the central nervous system, and enhances sympathetic efferent tone, with subsequent activation of the renin-angiotensin-aldosterone system (RAAS) and nonosmotic release of arginine-vasopressin (AVP) (9). In the kidney, increased angiotensin II (Ang II) causes renal efferent arteriolar vasoconstriction, resulting in decreased renal blood flow (RBF) and increased filtration fraction. Together with renal nerve stimulation, the increased peritubular capillary oncotic pressure and reduced peritubular capillary hydrostatic pressure augment sodium reabsorption in the proximal tubule. Angiotensin II also directly stimulates proximal sodium reabsorption by activating sodium-bicarbonate cotransporters and apical sodium-hydrogen exchangers (10). Finally, Ang II promotes aldosterone secretion, which boosts sodium reabsorption in the distal nephron (9). Importantly, increased proximal sodium reabsorption decreases distal sodium and water delivery, stimulating macula densa cells to increase synthesis of renin that further amplifies neurohormonal activation (11). Enhanced renal sodium and water reabsorption predominantly fills the compliant venous circulation, increasing CVP and atrial pressures.

Normally, an increase in atrial pressure suppresses AVP release and enhances water diuresis, decreases renal sympathetic tone, and augments natriuretic peptide secretion. In patients with HF, these atrial–renal reflexes are overwhelmed by neurohormonal activation, evidenced by persistent renal sodium and water retention despite elevated atrial pressures (9). Transmission of venous congestion to the renal veins further impairs the glomerular filtration rate (GFR) (Fig. 1). The authors of an isolated mammalian kidney study from 1931 showed that increased renal venous pressure was associated with reduced RBF, urine flow, and

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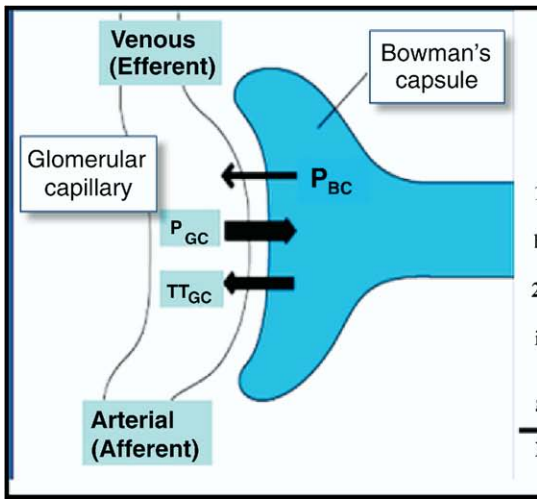

Forces	Normal: Afferent end of glomerular capillary (mmHg)	Normal: Efferent end of glomerular capillary (mmHg)	↑ RA pressure: Afferent end of glomerular capillary (mmHg)	↑ RA pressure: Efferent end of glomerular capillary (mmHg)
1. Favoring Filtration				
Glomerular-capillary hydrostatic pressure, P_{GC}	**60**	**58**	**55**	**63**
2. Opposing Filtration				
a. Hydrostatic pressure in Bowman's capsule, P_{BC}	**15**	**15**	**15**	**15**
b. Oncotic pressure in glomerular capillaries, π_{GC}	**21**	**33**	**21**	**33**
Net filtration pressure (1-2)	**24**	**10**	**19**	**15**
Filtration pressure:	*14 mmHg*		*4 mmHg*	

Figure 1 **Impact of Venous Congestion on Glomerular Net Filtration Pressure**

An illustration of the afferent and efferent pressures at a glomerular capillary in a patient with normal hemodynamics and a patient with increased right atrial (RA) pressure and venous congestion. P_{BC} = hydrostatic pressure in Bowman's capsule; P_{GC} = glomerular capillary hydrostatic pressure; π_{GC} = oncotic pressure in glomerular capillaries.

urinary sodium chloride excretion, abnormalities that were reversed by lowering renal venous pressure (12). Years later, hypervolemia experimentally induced in dogs directly decreased GFR, independent of CI and RBF (13). A contemporary study in patients with ADHF revealed that an increased intra-abdominal pressure from ascites and visceral edema was correlated with the severity of renal dysfunction and that reduction of intra-abdominal pressure improved renal function (14). Furthermore, in the ESCAPE (Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterization Effectiveness) trial, right atrial pressure emerged as the only hemodynamic variable correlated with baseline renal function, an independent predictor of mortality and HF hospitalization (15).

Despite these provocative data, it is premature to conclude that therapies specifically aimed at the reduction of CVP will actually reduce renal dysfunction or mortality in patients with HF. In the ESCAPE trial, therapy directed toward lowering measured PCWP and CVP produced no better outcomes than management aimed to reduce exam-based CVP (15). Also unknown are the specific CVP values that must be achieved to improve renal function and outcomes. Perhaps the strategy to reduce filling pressures in HF remains appropriate, but our heavy reliance on the tactic of diuretics to achieve this goal may critically impact renal function and outcome. Loop diuretics act in the thick, ascending limb of the loop of Henle, near the macula densa. Loop diuretics block sodium chloride uptake in the macula densa, independent of any effect on sodium and water balance, thereby stimulating the RAAS (16). This pathophysiology, and the growing literature documenting the adverse consequences of diuretic use on ADHF outcomes (17), has lead to exploration of other approaches. If fluid removal by an alternative therapy, such as ultrafiltration, does not exceed the interstitial fluid mobilization rate of 14 to 15 ml/min, further activation of the RAAS is avoided. Moreover, for the same fluid volume, more sodium is removed by isotonic ultrafiltration than by diuretic-induced hypotonic diuresis (18). Data from the UNLOAD (Ultrafiltration vs IV Diuretics for Patients Hospitalized for Acute Decompensated Congestive Heart Failure) trial on ADHF rehospitalization rates after ultrafiltration appear promising and await further confirmation in larger trials (19).

Acute HF decompensation identifies patients at an increased risk for rehospitalization and death (20). Poor outcomes after a single ADHF episode suggests that ADHF accelerates disease progression. Hypervolemia may be associated with myocardial edema which, together with RAAS activation, inflammatory cytokines, nitric oxide dysregulation, oxidative and mechanical stress, and inotrope-induced increase in myocardial oxygen consumption, create the "perfect storm," leading to myocyte injury or death. The pathologic events complicating ADHF also may cause acute renal injury by further reducing renal perfusion, oxygen delivery, GFR, and responsiveness to natriuretic peptides. In fact, renal dysfunction is the strongest predictor of poor outcomes in patients with HF, regardless of whether systolic function is decreased or preserved.

The cardiorenal syndrome recently has been classified according to whether the impairment of each organ is primary, secondary, or whether heart and kidney dysfunction occurs simultaneously as a result of a systemic disease, as outlined in Table 1 (21). A consensus definition of each type of cardiorenal syndrome may help to design random-

Table 1 Cardiorenal Syndrome

Type I: acute cardiorenal syndrome
Abrupt worsening of cardiac function (e.g., acute cardiogenic shock or acutely decompensated heart failure) leading to acute kidney injury.
Type II: chronic cardiorenal syndrome
Chronic abnormalities in cardiac function (e.g., chronic heart failure) causing progressive and potentially permanent chronic kidney disease.
Type III: acute renocardiac syndrome
Abrupt worsening of renal function (e.g., acute kidney ischemia or glomerulonephritis) causing acute cardiac disorder (e.g., heart failure, arrhythmia, ischemia).
Type IV: chronic renocardiac syndrome
Chronic kidney disease (e.g., chronic glomerular or interstitial disease) contributing to decreased cardiac function, cardiac hypertrophy, and/or increased risk of adverse cardiovascular events.
Type V: secondary cardiorenal syndrome
Systemic condition (e.g., diabetes mellitus, sepsis) causing both cardiac and renal dysfunction.

Adapted, with permission, from Ronco et al. (21).

ized controlled trials aimed at identifying pathophysiologically sound interventions targeting specific patient populations. At the outset, the precise relationships between CVP and renal function should be prospectively evaluated and confirmed. The next logical step will be to test the strategy that therapies specifically aimed at reducing CVP will favorably affect renal function, attenuate HF progression, and improve outcomes. Finally, the specific effects of different interventions, or tactics, should be tested in prospective randomized trials.

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