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The relevance of congestion in the cardio-renal syndrome

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Worsening renal function (WRF) during the treatment of acute decompensated heart failure (ADHF) occurs in up to a third of patients and is associated with worse survival. Venous congestion is increasingly being recognized as a key player associated with WRF in ADHF. Understanding the hemodynamic effects of venous congestion and the interplay between venous congestion and other pathophysiological factors such as raised abdominal pressure, endothelial cell activation, anemia/ iron deficiency, sympathetic overactivity, and stimulation of the renin–angiotensin–aldosterone system will help in devising effective management strategies. Early recognition of venous congestion through novel techniques such as bioimpedance measurements and remote monitoring of volume status combined with customized diuretic regimens may prevent venous congestion and perhaps avoid significant WRF.

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Acutely worsening renal function (WRF) in the setting of acute decompensated heart failure (ADHF), known as Type 1 cardiorenal syndrome, affects 25–45% of hospitalized patients.[1] Apart from increasing the complexity of managing such patients, WRF accompanying ADHF is now recognized as an independent predictor of mortality.[2,3] A retrospective analysis of the ADHERE database suggests that serum creatinine >2.75 mg/dl is a significant risk factor for mortality in patients with ADHF.[4] Although systemic underfilling leading to neurohumoral activation is likely a key event in heart failure (HF), WRF in ADHF is not always from hypoperfusion of the kidneys, but is now increasingly recognized to be associated with venous congestion.[5,6] A better understanding of the relationship between renal injury and venous congestion in ADHF will enable physicians to focus on the appropriate treatment strategy. Further, long-standing HF may be associated with significant renal fibrosis and consequent irreversibility despite hemodynamic improvement. Thus, preventing venous congestion and consequently acute episodes of WRF becomes an important long-term goal.[7] This review will focus on the role of venous congestion in WRF and examine the optimal management strategies in the treatment of these patients.

THE LINK BETWEEN VENOUS CONGESTION AND RENAL DYSFUNCTION

The pathophysiology of renal injury in ADHF is complex (Figure 1). Ljungman *et al.*[8] showed that renal blood flow is preserved until cardiac index falls below 1.5 l/min/m^2. In many patients, it is venous congestion rather than arterial underfilling that is associated with decreased renal blood flow and WRF. In the following sections, we will examine the pathophysiological links between venous congestion and WRF.

Hemodynamic effects and abdominal compartment syndrome

Renal perfusion pressure not only depends on arterial pressure but is also determined by the trans-renal perfusion pressure, which is equal to mean arterial pressure minus central venous pressure. As early as in 1861, Ludwig[9] found

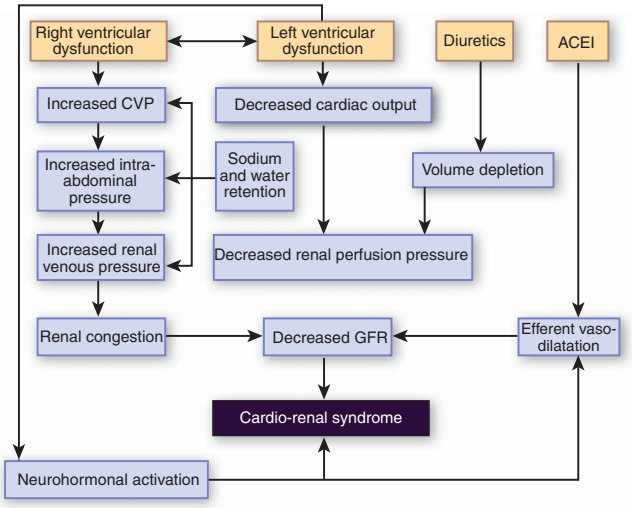

Figure 1 | Cardiorenal interactions in the pathophysiology of cardiorenal syndrome. ACEI, angiotensin-converting enzyme inhibitor; CVP, central venous pressure; GFR, glomerular filtration rate.

that if the renal vein pressure is raised beyond 10 mm Hg, it retards urinary flow. He attributed this to mechanical obstruction of the uriniferous tubules from compression by the surrounding venules. Winton[10] in 1931 showed that increased venous pressure was sufficient to produce a reduction of urine flow equal in amount to that produced by a decrease in arterial pressure on excised canine kidneys.

Clinically, Damman *et al*[11] and Drazner *et al*[12] have shown that increased central venous pressure and increased jugular venous pressure (JVP) on examination are associated with impaired renal function. In patients who had elective cardiac surgery, the preoperative presence of high central venous pressure was an independent predictor of acute kidney injury.[13–15] In the ESCAPE (Evaluation Study of Congestive heart failure and Pulmonary Artery Catheterization Effectiveness) trial, poor forward flow did not correlate with baseline creatinine—the only predictor was right atrial pressure.[16] The major studies linking venous congestion and renal dysfunction are summarized in Table 1.

The presence of venous congestion, visceral edema, ascites, and abdominal wall edema can lead to an increase in intra-abdominal pressure (IAP) in ADHF. In addition, gaseous distension of the bowel, urinary retention, and obesity and elevation of head end of the bed $>30^{\circ}$ can also raise the IAP. The normal IAP is usually <5–7 mm Hg, and a constant elevation of IAP >12 mm Hg defines intra-abdominal hypertension.[17,18] Renal blood flow is determined by the abdominal perfusion pressure, which is directly related to mean arterial pressure and inversely related to IAP.[19] The formula for abdominal perfusion pressure is as follows:

Abdominal perfusion pressure = mean arterial pressure − IAP (normal = 60 mm Hg). The prevalence of raised IAP in patients with ADHF is as high as 60%.[20,21] In one study, the greater the IAP was lowered, the more renal function improved, independent of hemodynamic changes.[18]

Neurohormonal effects

More recent neurophysiological studies indicate that increases in renal venous pressure and distension of intrarenal veins can stimulate mechanoreceptors and enhance local sympathetic renal nerve activity, resulting in intrarenal arterial vasoconstriction and a fall in glomerular filtration rate.[22–24] Conversely, increasing renal blood flow does not always translate into an increase in glomerular filtration rate.[25] These effects can be explained as being due to the neurohormonal regulation of the tone of the afferent and efferent arterioles. HF results in venous congestion and activation of the renin–angiotensin–aldosterone system (RAAS) and nonosmotic release of arginine–vasopressin and other neuroendocrine hormones, such as endothelin, which further promote congestion and renal function.[26]

Diuretic therapy in ADHF increases the delivery of sodium to the distal tubule stimulating adenosine secretion via tubuloglomerular feedback. Adenosine causes afferent arteriolar vasoconstriction, reducing renal blood flow. It also enhances sodium reabsorption in the proximal and distal tubules, with resultant venous congestion. Increased adenosine reduces glomerular filtration rate.[27] Although this pathway represents an appealing explanation, as it is susceptible to interruption with specific A1 adenosine receptor antagonists, a randomized trial comparing rolofylline, an adenosine receptor antagonist with placebo in patients hospitalized for acute HF, failed to prevent WRF.[28]

Endothelial activation and proinflammatory cytokines

The vascular endothelium is the largest endocrine/paracrine organ of the body. Endothelial cells that sense biomechanical forces can switch their synthetic profile from a quiescent state toward an activated state, which is pro-oxidant, proinflammatory, and vasoconstricting.[29] Circumferential stretch of venous endothelial cells from venous congestion activates endothelial cells (Figure 2). Under these circumstances, in addition to neurohormonal activation as outlined above, an increase in inflammation also occurs.[30] Concentrations of proinflammatory cytokines, such as such as tumor necrosis factor and interleukin-6, are increased and are imputed to impair myocardial function and accelerate HF progression, in addition to its deleterious effects on the kidneys.[31] They also stimulate renin secretion as a component of the systemic stress response and tubulo-interstitial inflammation, which may have effects on adaptive responses of glomerular hemodynamics, leading to impaired renal function.[32]

Iron deficiency

Activation of inflammatory cytokines is thought to be involved in the development of functional iron deficiency, because proinflammatory cytokines appear to be involved in the displacement of iron into cells of the reticuloendothelial system.[33,34] The acute-phase reactant hepcidin also has an important role in this regard.[35] Inflammatory cytokines and alterations in gut morphology[36] have a major role in the development of iron deficiency and anemia in HF.[37] The triad