Review Article

Congestive Renal Failure: The Pathophysiology and Treatment of Renal Venous Hypertension

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ABSTRACT

Longstanding experimental evidence supports the role of renal venous hypertension in causing kidney dysfunction and "congestive renal failure." A focus has been heart failure, in which the cardiorenal syndrome may partly be due to high venous pressure, rather than traditional mechanisms involving low cardiac output. Analogous diseases are intra-abdominal hypertension and renal vein thrombosis. Proposed pathophysiologic mechanisms include reduced transglomerular pressure, elevated renal interstitial pressure, myogenic and neural reflexes, baroreceptor stimulation, activation of sympathetic nervous and renin angiotensin aldosterone systems, and enhanced proinflammatory pathways. Most clinical trials have addressed the underlying condition rather than venous hypertension per se. Interpreting the effects of therapeutic interventions on renal venous congestion are therefore problematic because of such confounders as changes in left ventricular function, cardiac output, and blood pressure. Nevertheless, there is preliminary evidence from small studies of intense medical therapy or extracorporeal ultrafiltration for heart failure that there can be changes to central venous pressure that correlate inversely with renal function, independently from the cardiac index. Larger more rigorous trials are needed to definitively establish under what circumstances conventional pharmacologic or ultrafiltration goals might best be directed toward central venous pressures rather than left ventricular or cardiac output parameters. (*J Cardiac Fail 2012;18:930–938*)

Key Words: Renal venous hypertension, congestive heart failure, cardiorenal syndrome, intra-abdominal hypertension.

There is accumulating evidence from studies of decompensated heart failure (HF) that there may be a component of the cardiorenal syndrome due to renal venous hypertension. The concept of passive renal congestion leading to depressed kidney function is not new and may have additional noncardiac causes. In the 1930s, investigators reported[1] a dog model in which acute renal vein obstruction was associated with kidney dysfunction, reduced renal blood flow, and sodium retention. By the 1960s it was recognized that renal venous hypertension occurred in chronic HF.[2] There was renewed interest in the 1980s with hypotheses exploring venous hypertension as a direct cause of sodium retention and edema.[3] More detailed studies were then facilitated by recent technologies that permitted the measurement of hormone levels for the renin-angiotensin-aldosterone system (RAAS), sympathetic nervous system (SNS), and cytokine pathways, vascular pressures, blood flow, baroreceptor and neural activity, and the effects of denervation (eg, sympathectomy) or antagonists to adrenergic vasoconstriction. The purpose of the present review is to examine the evidence for the proposed mechanisms by which venous hypertension might cause kidney dysfunction, and whether there are renal benefits from decongestion by pharmacologic or ultrafiltration (UF) therapies.

Pathophysiology of Renal Venous Hypertension and Renal Dysfunction (Table 1, Fig. 1)

Pressure-Related Effects

Much research has turned from pressure-related and receptor pathways resulting from "forward" HF to those originating from "backward" HF. An isolated rise in renal

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Table 1. Proposed Pathophysiology of the Effect of Renal Venous Hypertension on Kidney Function

Decreased transglomerular pressure gradient
Increased renal interstitial pressure
Renal arterial vasculature myogenic response:
Vasodilatation then vasoconstriction
Neural vasoconstrictive reflexes:
Intra- and extrarenal (eg, spinal)
Renal parenchymal hypoxia
Baroreceptor activation:
Right atrium and other (venous) vasculature
Atrial natriuretic peptide release
Renin-angiotensin-aldosterone system activation
Sympathetic nervous system activation
Decreased splanchnic venous blood capacitance
Endothelin release
Proinflammation cytokines and reactive oxygen species release
Renal arterial vascular smooth muscle hypertrophy
Glomerular hyperemia and sclerosis

venous pressure would lower the arteriovenous pressure gradient across the kidney, decrease the renal blood flow, and lower the transglomerular pressure gradients; however, the importance of intrarenal compensatory mechanisms were highlighted when blood flow was experimentally maintained by changes in arterial perfusion or pressure.[4] The renal venous hypertension, however, could also secondarily lead to parenchymal congestion within the confines of the nondistensible kidney capsule. Thus, there would be a rise in renal interstitial pressure that would affect the entire capillary bed and the tubules, possibly also involving local hypoxia. Compression of the tubules raises the luminal pressure, further attenuates the transglomerular pressure gradient, and lowers the glomerular filtration rate (GFR). These effects on the tubules and capillaries occur with venous pressure >15 mm Hg and have been known since animal investigations in the 1950s.[5] Based on dog studies, it appears that rises in renal venous pressure to the 10−20 mm Hg range are associated with an increase in interstitial pressure of ~ 6 mm Hg.[6] It is important to appreciate that a rise in renal interstitial pressure due to venous congestion is physiologically different than that caused by elevations in arterial pressure— which is associated with a natriuresis. The renal effects of rises in renal venous pressure to very high levels (ie, supraphysiologic, >30 mm Hg) have not been well studied in humans, but may be quite different based on animal investigations.[6]

Neural and Myogenic Mechanisms

The effects of renal venous hypertension have been challenging to elucidate in that there is added complexity due to secondary changes in filtration fraction and flow from baroreceptor, tubuloglomerular feedback (TGF), RAAS, SNS, and intrinsic vascular reflex pathways.[7] Regarding the latter, there is strong evidence that there are vascular ''myogenic'' responses to venous congestion that control the arterial microcirculation via neural reflexes. Abildgaard et al described how partially obstructed renal veins caused vasoconstriction and studied the effects of denervation or local instillation of an alpha-adrenoreceptor blocker.[8] In their model, the initial mild venous congestion raised interstitial tissue pressure, but perfusion was maintained by what was viewed as an adaptive intrinsic myogenic vasodilatory response. Further rises in venous hypertension, however, triggered maladaptive sympathetic vasoconstrictive neural reflexes that were both extrarenal (spinal cord via mechanoreceptors in the renal capsule) and intrarenal (receptors within the renal parenchyma). Surgical or pharmacologic sympathectomy was partially effective in

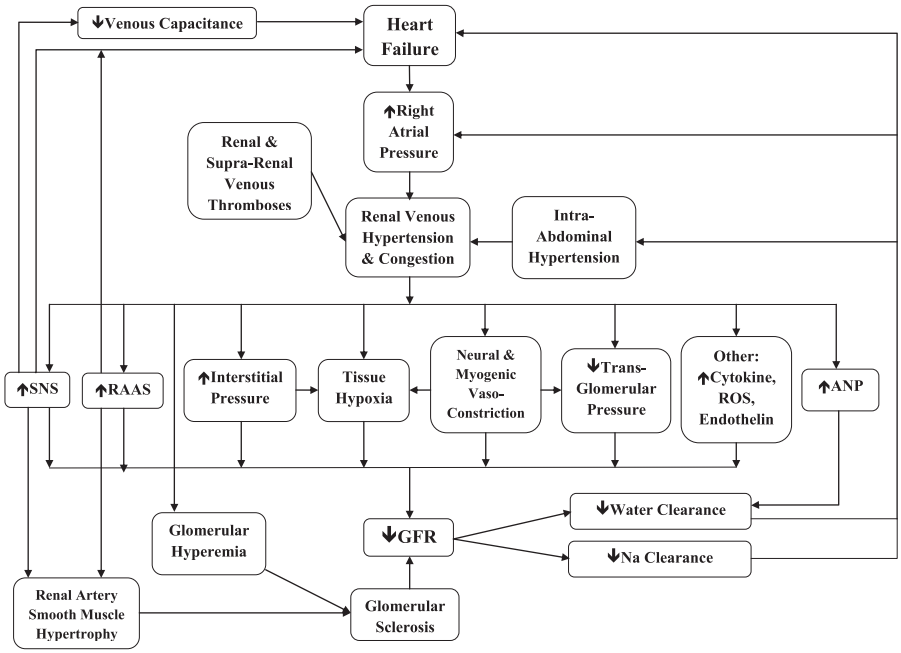

Fig. 1. Proposed pathophysiology of renal venous hypertension, congestion, and dysfunction. ANP, atrial natriuretic peptide; GFR, glomerular filtration rate; RAAS, renin-angiotensin-aldosterone system; ROS, reactive oxygen species; SNS, sympathetic nervous system.

preventing the adverse effects from the venous congestion. In other models of abdominal venous obstruction or cirrhosis, the activation of hepatic,[9] intestinal, and splenic[10] afferent neural pathways has been proposed to be associated with altered sympathetic outflow,[11] renin release, and decreased renal blood flow. Whether there is a similar intestinal-renal neural reflex remains controversial. Surgical or pharmacologic denervation in some renal and splenic venous hypertension models greatly attenuated the reduction in renal blood flow[10]; however, the literature is controversial in that in other models of renal interstitial hypertension, renal blood flow decreased despite kidney decapsulation and blockade of TGF and SNS pathways.[12]

Baroreceptor Mechanisms

Activation of mechanical baroreceptors would help explain renal dysfunction due to a variety of disorders resulting in renal venous hypertension: HF with high CVP; cirrhosis with portal hypertension and hepatorenal and splenorenal venous congestion; other mesenteric venous thrombotic conditions with intestinal-renal venous hypertension; intra-abdominal hypertension (IAH); direct pressure on the renal parenchyma; and obstruction at the renal veins by thrombi, tumors, trauma, or in experimental animal models. Stretch receptors in the atrium are of special interest. High atrial natriuretic peptide levels not only would be a marker of venous congestion, but there is also evidence that its beneficial natriuretic effects are attenuated in HF. High renal interstitial pressure due to venous congestion may impair preservation of GFR by loss of atrial natriuretic peptide's effects modulating TGF.[13] These proposed vascular baroreceptor neural networks would thus be extensive and complex, and there is no evidence that there would be a therapeutic role in HF by their ablation with surgical or the recently developed cryo- or radiofrequency techniques.

SNS and RAAS Mechanisms

In addition to the baroreceptor-associated, neural reflex, and natriuretic peptide pathways, there is longstanding evidence that renal venous congestion influences the sympathetic nervous system and RAAS systems. Early observations of sodium retention in models of venous obstruction were confounded by other hemodynamic changes present in HF. In a 1940s dog model of unilateral renal vein constriction, there was rapid ipsilateral retention of sodium and water that was independent of blood pressure, renal blood flow, or GFR.[14] Reports since the 1960s also showed that there was impaired salt excretion associated with decrements in GFR after renal venous constriction.[15,16] Although animal models such as these demonstrated that even mildly elevated renal venous pressure[17] can cause a rapid rise in plasma renin activity and aldosterone levels, it was difficult to exclude effects from changes in systemic hemodynamics. Subsequently, in a swine model of renal venous constriction in which there were no changes in cardiac index or systemic blood pressure, there still was a decline in renal blood flow and GFR as well as increases in plasma renin activity and aldosterone.[18] These acute changes occurred after 2 hours of venous hypertension to 30 mm Hg and were reversible. The authors thought that this was analogous to renal dysfunction in the abdominal compartment syndrome and then improvement upon decompression. The situation appears, however, to be more complex in that there may be differences across the various abdominal venous structures. For example, there may be increased adrenergic tone affecting renal perfusion and renin secretion resulting from portal hypertension and not from thoracic inferior vena cava constriction.[19]

Reports of elevated renal and systemic levels of angiotensin II[6,20] are consistent with not only increases in renin, but they may also be due to heightened SNS activity. It is not clear whether these pathways are involved locally when renal tissue hypoxia (perhaps exacerbated by interstitial edema) is proposed to trigger a decrease in GFR.[20]

Venous Capacitance Mechanism

Pathophysiology that involves neural and sympathetic nervous system pathways is particularly relevant regarding a recently advocated mechanism that involves splanchnic venous capacitance. Fallick et al[21] hypothesized that acute HF can result from increases in venous tone that cause decreased capacitance, increased venous return, higher effective blood volume, and thence cardiac decompensation. Short-term regulation of the splanchnic venous volume would thereby be regulated by sympathetic activity, predominantly alpha-adrenergic. Thus HF exacerbations or remissions occur with redistribution of the intravascular blood volume rather than from changes in total body salt or water. This model would lead to parallel changes in renal venous hypertension and kidney congestion. If this pathway is shown to be clinically relevant it could guide pharmacologic therapy, such as a greater focus on the use of alpha-adrenergic blockade, beta-blocker formulations with intrinsic alpha effects, and possibly sympatholytic interventional therapies involving radiofrequency or other ablative technologies.

Inflammation, Cytokine, and Other Mechanisms

In addition to the traditional renal venous hypertension effects on intra- and extrarenal hemodynamics, pressure profiles, and neurohumoral pathways, there has been a growing interest in inflammatory and endothelial cell activation. It has been proposed that in HF the endothelium changes from a quiescent redox profile to an activated proinflammatory, prooxidant, and provasoconstrictive state.[22] Deleterious effects on the heart and kidneys would then exacerbate this congestive pathophysiology, initiating a vicious cycle. It was theorized that venous congestion causes a biochemical signal to endothelial cells that changes their redox phenotype of reactive oxygen species, endothelin,[23] interleukin-6, tumor necrosis factor alpha, and nitric oxide bioavailability. These markers were increased in a dog model of acute fluid overload and venous

congestion.[24] The authors also provided preliminary evidence for proinflammatory endothelial cell changes after acute venous congestion of the forearm in humans.[22]

Effects on CKD

Beyond the diverse mechanisms for renal dysfunction due to acute renal venous congestion, there is also the important concern for the development of chronic injury that could cause or contribute to advancing CKD. In a canine model of renal venous hypertension induced by varying degrees of right-sided heart overload, there was glomerular hyperemia and sclerosis.[25] The investigators proposed that this injury was attenuated in animals that developed an adaptive increase in renal artery tone and hypertrophy of the vascular smooth musculature.

Renal Venous Hypertension in Human Disease

HF and the Cardiorenal Syndrome

Although the renal dysfunction associated with HF has traditionally been attributed to impaired cardiac output and kidney hypoperfusion, this relationship may not hold true across large cohorts of patients. For example, using the ADHERE (Acute Decompensated Heart Failure National Registry) database of 118,465 decompensated HF admissions, Heywood et al were not able to show an association between left ventricular systolic dysfunction and renal impairment.[26] Many recent trials have raised the possibility of alternative pathophysiologic mechanisms, with a growing interest in the effects of high right atrial pressures on renal venous congestion and hypertension. This was highlighted in the ESCAPE (Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterization Effectiveness) trial involving hospitalized decompensated HF patients in which kidney function did not correlate with cardiac index, pulmonary capillary wedge pressure, or systemic vascular resistance, but rather was (weakly) associated with right atrial pressure.[27] In Damman et al's retrospective analysis of 2,557 patients undergoing right heart catheterization, elevated central venous pressure (CVP) was associated with low estimated glomerular filtration rate (eGFR) independently from cardiac index, and it predicted mortality.[28] These investigators reported supportive findings in a study of 2,647 patients with systolic heart failure, in which depressed eGFR and mortality were associated with congestive findings such as ascites and elevated jugular venous pressure.[29] Similarly, Guglin et al[30] described catheterization findings in 178 HF patients wherein low eGFR correlated with high CVP and low renal perfusion pressure (mean arterial pressure − CVP), but not the cardiac index or left ventricular ejection fraction (LVEF). Echocardiogram data showed an association of renal impairment with peak tricuspid regurgitation velocity but not LVEF. Further complicating patient presentations are those with low cardiac index and HF in the setting of preserved ejection fraction, as well as having a range of vascular tone and perfusion across different various tissue beds.

The use of right atrial parameters (by direct measurement or by imaging) as markers for venous congestion−induced renal dysfunction is appealing, and there have been studies supporting that approach. For example, in Maeder et al's report of HF patients, the echocardiographic severity of tricuspid regurgitation was independently associated with the degree of renal dysfunction.[31] Nevertheless, a preponderance of studies analyzing right atrial pressures have demonstrated 2 major confounding factors that make it difficult to interpret these findings in HF: the extent of coexistent primary parenchymal renal disease, and the degree to which cardiac index is depressed. It has been suggested that elevations in right atrial pressure become clinically relevant only in states in which cardiac output is depressed. In a canine model of acute renal venous congestion (13 cm H_2O) the renal dysfunction (reduced blood flow, GFR, and sodium and water clearance) was ameliorated when transfusions normalized systemic hemodynamics.[32] In an important human study of cardiac dysfunction due to pulmonary hypertension, right atrial pressure (RAP) and renal blood flow independently correlated with iothalamate-measured GFR; however, the association with RAP and therefore venous congestion was most apparent in the low-renal-flow subjects.[20] In a series of 140 patients with acute HF it was only in those with hypotension that a high CVP on admission and discharge that there was a correlation with lower eGFR.[33] Low cardiac index might thus identify a population of patients who could potentially benefit from decongestive therapies guided by measurement of venous pressures. It has been suggested[20] that this stratification of patients at risk could explain the subset in the ESCAPE trial[34] whose renal function did not worsen when therapy was guided by RAP as opposed to clinical assessments.[35] A primary renal function dependence on cardiac output would suggest that venous congestion is of concern when ''warm'' HF patients move to ''cold'' (eg, with lower renal perfusion), with manifestations of elevated jugular venous pressure on physical exam and associated higher rates of hospitalization, HF progression, and mortality.[36,37] Therefore, the design of clinical trials studying the effects of lowering renal venous pressure would be challenging, because the results would be confounded if the intervention independently improved cardiac output.

Although studies of patients with varying degrees of reduced-EF HF have thus provided valuable lessons, the physiology and care of individuals with preserved-EF HF remains very challenging. In some HF populations, approximately one-half the patients have preserved EF and the diastolic dysfunction causes complex changes across the pulmonary vascular bed and right-sided cardiac structures. Right-sided heart failure would then be associated with reduced left ventricular end-diastolic and stroke volumes, thereby making the patients preload dependent.[38] In this situation, fluid removal protocols based on high CVP levels could be confounded by unintended deterioration in cardiac output. Complexities such as these highlight the potential therapeutic equipoise between treating the high CVP and

renal venous pressure while simultaneously maintaining preload, cardiac output, and renal perfusion.

Renal Venous Hypertension and Congestion in Noncardiac Diseases

Many of the concepts proposed for the renal dysfunction in HF are analogous to those for IAH: renal venous congestion with or without low cardiac output. In the 1940s, Bradley and Bradley studied the effects of abdominal compression devices in humans and induced IAH levels of up to 80 mm Hg.[39] At 20 mm Hg there was decreased renal plasma flow (from 621 mL/min to 488 mL/min), decreased GFR (from 117 mL/min to 88 mL/min), unchanged filtration fraction, increased water reabsorption, and decreased urine flow, changes which they hypothesized were due to renal venous hypertension. Those findings are consistent with reports of elevated plasma renin activity and aldosterone levels.[40] There has been a concern that some of the renal dysfunction with IAH is due to hypotension and low cardiac output. Nevertheless, when cardiac output is corrected by volume expansion in IAH dogs, renal blood flow and GFR were still $<25\%$ of normal.[41] Similarly, others have shown that with carefully maintained cardiac output there is still renal dysfunction with IAH as low as 15 mm Hg.[42] Nevertheless animal models with dramatic falls in cardiac output (eg, to 37% of normal with GFR down to 7%[41]) highlight why potentially profound systemic changes in severe IAH limit the utility of this model for studying kidney dysfunction in HF.

Treatment of Renal Venous Hypertension and Congestion

In light of the complex pathophysiology, crafting patient care guidelines that incorporate measures of both renal venous hypertension and left ventricular function is difficult and remains controversial. The frequent discordance between the cardiac index and right-sided pressures across the various cardiac disease entities (eg, with right, left, or biventricular dysfunction) might explain why in Mullins et al's series[43] the elevation in right atrial pressure at the time of acutely decompensated HF presentation did not correlate with renal dysfunction. Nevertheless, with treatment, those patients who did not have a fall in RAP were more likely to have worsened renal function and adverse clinical outcomes. Kidney dysfunction occurred less frequently when the CVP decreased to <8 mm Hg, and therefore its measurement was proposed as a way to stratify risk for renal impairment. This also has important implications for therapeutic interventions, such as extracorporeal UF, in which fluid removal could potentially be guided by monitoring of RAP. A report by Testani et al[44] described an association of venous congestion and right ventricular dysfunction with improved renal outcomes after UF. They theorized that kidney function improves in the subset of patients in whom decongestive therapy improves echocardiographic volume parameters, such as with vena cava collapse during inspiration. These findings are particularly relevant for patients with predominant or primary right ventricular failure in that therapies (eg, sildenafil) prescribed to improve outflow dynamics may have previously underappreciated secondary benefits from lowering renal venous pressure. Clinicians need to be mindful that with pathophysiology being different between acute and chronic venous hypertension, it is anticipated that there are also differences in the respective therapies.

Pharmacologic Treatment: Diuretic Therapy

The potential disadvantages of choosing diuretics to treat acute HF have been well studied and described in the literature.[45] These include maladaptive activation of TGF, activation of SNS and RAAS, and increased afterload.[46] Francis et al[47] have demonstrated that when chronic HF patients are given intravenous furosemide, there is a rise in systemic vascular resistance, plasma renin activity, and plasma levels of norepinephrine and arginine vasopressin. Nevertheless, diuretics have been the mainstay of HF treatment and are effective in many patients, which is consistent with a paradigm of decongestion that includes attenuating renal venous hypertension and kidney congestion. It is possible that the latter is due at least in part to the effects of loop diuretics on pathways distinct from a direct receptor-mediated natriuresis. These medications reportedly enhance the synthesis of prostaglandins which cause relaxation of smooth muscles and thence renal vasodilatation.[48,49] Similarly, the benefits of spironolactone therapy for advanced chronic HF (as reported by the Randomized Aldactone Evaluation Study) may not have been from its diuretic effect but rather neurohumoral from blockade of the RAAS.[50] This hypothesis was extended by the investigators in their report of the improved outcomes from eplerenone treatment being beyond that from diuretic or potassium effects and instead possibly due to other mechanisms from mineralocorticoid receptor antagonism.[51]

As in any diuretic regimen, future protocols designed to use diuretics to lower renal venous pressure would need to address the enhanced sodium reabsorption that can occur in the time intervals between short-acting loop diuretic doses. As shown by Wilcox et al,[52] a moderate salt intake (270 mEq/d) coupled with rebound salt hyperabsorption in the interdiuretic interval can negate any net natriuretic benefit from loop agents. Therefore, effective decongestion and potential decreases in renal venous hypertension would necessitate optimal salt restriction and/or longer-acting diuretics. A renal venous hypertension–directed approach using diuretics has yet to be investigated.

Pharmacologic and Interventional Treatments: Sympatholytic Therapies

The success of beta- and alpha-adrenergic blockade in the treatment of low cardiac output in HF could theoretically have benefits from lowering renal venous pressure, but these have not been independently rigorously investigated. However, alpha-adrenergic inhibition in particular

has additional appeal based on Fallick et al's[21] proposed splanchnic venous capacitance mechanism. If this pathway is shown to be of clinical magnitude, then, as described above, there might be pharmacologic or interventional treatments to ameliorate acute-on-chronic redistribution of splanchnic blood into the effective blood circulatory volume. Consistent with this paradigm are recent preliminary findings from Taborsky et al.[53] Following radiofrequency renal denervation, patients (n = 26) had higher ejection fraction (31% vs 25% in the control group; n = 25) and fewer HF hospitalizations (8 vs 18).

Mechanical Interventions

Analogous to there being unquantified benefits of pharmacologic HF therapy on relieving renal congestion, there are similar possible benefits from correcting valvular or other structural cardiac abnormalities that decrease cardiac output. This includes left-to-right shunts, such as acute ruptures of sinuses of Valsalva, which can acutely raise right-sided pressures and cause renal congestion.

Interventions for Intra-abdominal Hypertension

For IAH and the abdominal compartment syndrome, therapy has primarily involved procedures that directly lower pressure: paracentesis, gastrointestinal decompression, wall musculature paralytics, and of course decompressive abdominal wall surgery. Resolution of IAH is associated with rapid improvements in renal function, but effects on renal venous hypertension can not be dissociated from a wide range of other dramatic improvements, including cardiac output and blood pressure. It is possible that patients with decompensated HF develop enough ascites or interstitial tissue edema so as to raise intra-abdominal pressure, thereby developing a component of IAH in addition to other causes of the cardiorenal syndrome. Mullens et al[54] raised this hypothesis in a report of 40 decompensated HF patients treated with intense pharmacologic management. At baseline there was a mean intra-abdominal pressure of 8 ± 4 mm Hg, and 60% of the subjects had what were considered to be elevated intra-abdominal pressures at ≥8 mm Hg (well below the 12 mm Hg threshold for IAH or 20 mm Hg for abdominal compartment syndrome). For the latter subset, after treatment there were significant declines in abdominal pressure (from a mean of 10 mm Hg to 6 mm Hg) in some but not all patients. Only 10% of the subjects had the higher pressures typical of IAH, and those decreased from a mean of 15 mm Hg to 7 mm Hg. With treatment there were significant declines in CVP and wedge pressure as well as increased cardiac index and eGFR. Improvement in renal function, however, correlated only with decreases in the intra-abdominal pressure, not the hemodynamic variables. Beneficial renal effects from relieving these relatively low levels of "IAH" (especially in light of the multiple simultaneous confounding changes in central hemodynamics) would need to be rigorously confirmed. In that there are well established interventional (eg, paracentesis) and pharmacologic approaches to reduce IAH there are little data to support the use of extracorporeal fluid removal modalities. Nevertheless, a report by Bonfim et al supports a role for extracorporeal UF in IAH. They described 5 patients who underwent intermittent or extended HD treatments.[55] A mean of 14 kg was removed and the decrease in intra-abdominal pressures of ~8 mm Hg correlated with the "hydric balance." Similarly to IAH, there have yet to be rigorous studies addressing the effects on renal congestion and function after surgical or shunting procedures to relieve venous, portal, or mesenteric hypertension or thromboses.

Fluid Removal and "Decongestion" by Extracorporeal Ultrafiltration

Despite the above-described evidence for adverse renal effects from renal venous hypertension, it has been difficult to quantify benefits from its treatment in light of the therapies typically being confounded by other systemic effects. In the case of HF, eg, the heart and renal benefits from UF are associated not only with reduced RAP but also with improved cardiac output. A report by Marenzi et al[56] characterized hemodynamics during and after extracorporeal UF in 24 patients with refractory HF. With fluid removal up to ~5 L, there was progressive reduction in right atrial, pulmonary artery, and capillary wedge pressures, as well as increased cardiac output with improved New York Heart Association functional classification stage of HF. Notably, the subjects became more responsive to diuretics, which permitted a two-thirds reduction in furosemide dose. In that the vast majority of UF studies for HF were based on volume removed rather than venous hypertension parameters, this investigative group has provided a valuable approach with their protocols guided by RAP. For example, in the exercise capacity study of 26 patients with stable moderate HF, UF was adjusted based on right atrial measurements.[57] Fluid was removed in a single session until RAP decreased to 50% of baseline, and this resulted in ~600 mL/h for the 2 L of ultrafiltrate. In subsequent studies involving pulmonary function, this pressure-driven approach to UF protocols[58] explains the wide variation in UF volume: 1,250−2,600 mL.

Although the few studies that were guided by RAP provide some insights into the design of future trials for UF, the purported benefits from fluid removal have come mostly from investigations using other therapeutic targets. There are reports of protocols that have adjusted UF based on hemoconcentration, assessed by red packed cell volume,[56] but this is problematic for rigorous trials in that there is large variation of plasma refill rates across patient populations. Vascular refill rates may also vary during the course of a single UF session, declining as volume overload is ameliorated. This approach does not address hemodynamics after fluid shifts reach equilibrium, nor their ultimate effects on right atrial or renal venous hypertension.

The majority of studies purporting the HF benefits of ultrafiltration adopted protocol-driven UF rates rather than adjusting fluid removal by either RAP or

hemoconcentration, thereby being unable to dissociate venous pressure effects from other hemodynamic changes. Most of these investigations were facilitated by the development of a small simple portable device dedicated to isolated ultrafiltration, and data have been generated from inpatient and outpatient ''aquapheresis'' clinic experiences. In early small trials some subjects experienced worsening of their renal function with UF, which occurred in 45% of the 11 patients reported by Liang et al, 5 of whom ultimately needed dialysis.[59] Bartone et al[60] described serum creatinine rising from 1.9 mg/dL to 22 mg/dL, with levels increasing >0.5 mg/dL in 44% of the patients undergoing UF. These investigations highlight that potential kidney benefits from decongestion may be outweighed by overly aggressive UF rates and the induction of acute prerenal azotemia. The few single-center small series were followed by a multicenter randomized controlled trial (UNLOAD) of early inpatient treatment of acutely decompensated HF with the UF device compared with conventional care with intravenous diuretics.[61] Although perhaps owing in part to the highly protocolized medication dosing, the UF patients did have more weight loss over the first 2 days, but without better renal function, dyspnea scores, or length of hospital stay. Nevertheless, at 90 days after discharge UF was associated with fewer unscheduled visits and rehospitalizations, and it is unknown how much of this benefit can be attributed to relief of renal venous hypertension.

Peritoneal Dialysis Ultrafiltration

The literature regarding UF with the use of peritoneal dialysis adds little to directly support benefits mediated by reduction in renal venous pressure. While there are ongoing large trials, the current reports are mostly small single-center series. Some are confounded by many patients having underlying parenchymal renal disease (CKD of up to stage 5) or having undergone initial extracorporeal UF at the time of acute HF. UF with the use of peritoneal dialysis technology thus has a practical role only in chronic refractory HF, especially for individuals needing incremental solute clearance as their kidneys progressively fail from noncardiac causes. Even with these limitations, it is noteworthy that with UF there were improvements to echocardiographic or other cardiac parameters.[62–64] In that the cardiac measurements pertained to left ventricular function, it remains unproven whether changes in RAP may have contributed to the reported improvement in HF functional class, quality of life,[62–65] or hospitalization days.[62–64,66,67]

Conclusion

Longstanding observations of the adverse renal effects from venous hypertension have been explained by multiple pathophysiologic mechanisms, ranging from direct pressure to baroreceptor, neural, cytokine, systemic, and local hormonal factors. Relevant clinical entities include the cardiorenal syndrome in congestive HF, disorders (eg, renal, hepatic, or vena caval) of venous pressure or thromboses, and intra-abdominal hypertension. Renal congestion may also be an integral consequence of acute redistributions of blood volume, such as from changes in splanchnic venous capacity. Although the kidney improvements observed in trials using traditional pharmacologic strategies or UF have been attributed to improvement in cardiac output and renal perfusion, based on the physiology there is reason to hypothesize that there were benefits from reducing venous hypertension. The degree to which kidney function improves with relief of congestion by UF may depend on the preprocedure intrarenal hemodynamics driven by cardiac output and renal arterial perfusion. It is hoped that, by including measurements of RAP or other venous pressure parameters, future studies will be able to elucidate the extent and circumstances in which relief of venous hypertension by pharmaceutical or extracorporeal therapies will have clinically relevant benefits to kidney function.

Disclosures

None.

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