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REVIEW

Congestive nephropathy: a neglected entity? Proposal for diagnostic criteria and future perspectives

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Abstract

Venous congestion has emerged as an important cause of renal dysfunction in patients with cardiorenal syndrome. However, only limited progress has been made in differentiating this haemodynamic phenotype of renal dysfunction, because of a significant overlap with pre-existing renal impairment due to long-term hypertension, diabetes, and renovascular disease. We propose congestive nephropathy (CN) as this neglected clinical entity. CN is a potentially reversible subtype of renal dysfunction associated with declining renal venous outflow and progressively increasing renal interstitial pressure. Venous congestion may lead to a vicious cycle of hormonal activation, increased intra-abdominal pressure, excessive renal tubular sodium reabsorption, and volume overload, leading to further right ventricular (RV) stress. Ultimately, renal replacement therapy may be required to relieve diuretic-resistant congestion. Effective decongestion could preserve or improve renal function. Congestive acute kidney injury may not be associated with cellular damage, and complete renal function restoration may be a confirmatory diagnostic criterion. In contrast, a persistently low renal perfusion pressure might induce renal dysfunction and histopathological lesions with time. Thus, urinary markers may differ. CN is mostly seen in biventricular heart failure but may also occur secondary to pulmonary arterial hypertension and elevated intra-abdominal pressure. An increase in central venous pressure to $>$6 mmHg is associated with a steep decrease in glomerular filtration rate. However, the central venous pressure range that can provide an optimal balance of RV and renal function remains to be determined. We propose criteria to identify cardiorenal syndrome subgroups likely to benefit from decongestive or pulmonary hypertension-specific therapies and suggest areas for future research.

Keywords Cardiorenal syndromes; Heart failure; Intra-abdominal hypertension; Pulmonary hypertension; Venous congestion

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Introduction

Renal dysfunction in heart failure (HF) has traditionally been considered to result from decreased renal perfusion and associated neural and hormonal changes. Recently, persistent venous congestion was identified as a major contributor.[1,2] High central venous pressure (CVP) initiates a vicious cycle of hormonal and endothelial activation, hepatic dysfunction, ascites, increased intra-abdominal pressure (IAP), intestinal mucosal ischaemia (with translocation of bacterial toxins), inflammation, oxidative stress, excessive renal tubular sodium reabsorption, and volume overload, leading to further right ventricular (RV) stress.[3,4] Ultimately, renal replacement therapy may be required to relieve congestion.[5] This sequence of

events appears to be crucial in the pathophysiology of RV failure in patients with pulmonary arterial hypertension[6] and, more commonly, those with biventricular HF.[7,8]

Despite evidence that unresolved congestion leads to adverse renal and overall outcomes in HF[1,9]—whereas effective decongestion preserves or even improves renal function[10,11] and improves survival[12]—this haemodynamic phenotype of renal dysfunction is still not clearly defined. This is partly because patients with concomitant HF and chronic kidney disease (CKD) are commonly diagnosed with cardiorenal syndrome (CRS), a heterogeneous and controversial clinical entity encompassing a spectrum of disorders mediated by multiple haemodynamic and non-haemodynamic factors.[13] Many patients with CRS have hypertension and/or diabetes,[14] so albuminuria and renal dysfunction[15–17] generally lead to diagnosis of hypertensive nephrosclerosis or diabetic nephropathy without a corroborating kidney biopsy.[18,19] In patients with CRS, undetected congestion caused by HF and pulmonary hypertension (PH) may converge with other pathophysiological mechanisms to aggravate renal dysfunction. Early identification of patient subgroups having cardiac plus renal dysfunction, and phenotyping of underlying kidney disease mechanisms, may enable tailoring of therapy.

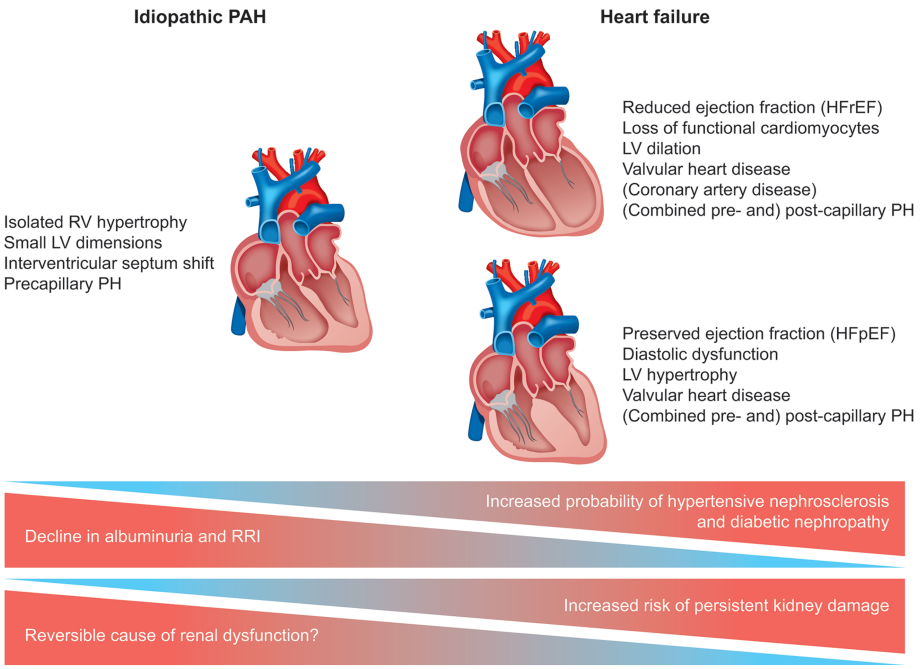
We propose the term congestive nephropathy (CN) to describe the neglected clinical entity of renal dysfunction that is associated with venous congestion as well as decreased renal perfusion.[20] Similar to obstructive nephropathy,[21] CN appears to be reversible in early stages. Whether long-term congestion will result in tubular atrophy and renal fibrosis remains unknown. This review aims to (i) summarize current understanding of CN and its impact on the development of CKD, (ii) suggest criteria to characterize patient subgroups likely to benefit from decongestion, and (iii) identify areas for future research.

Clinical scenarios associated with congestive nephropathy

HF is likely the most common condition associated with CN; others include PH of any origin, isolated tricuspid regurgitation,[22] and congenital heart disease.[23,24] CN should also be suspected in patients who show improved renal function after decongestion by diuretics, HF-specific and PH-specific therapy, or mechanical means (e.g. paracentesis of ascites).

Various factors associated with renal dysfunction are encountered frequently in patients with pulmonary arterial hypertension and HF (*Figure 1*).

Figure 1 Congestive nephropathy in pulmonary arterial hypertension and heart failure. Various factors and co-morbidities related to renal dysfunction appear frequently in patients with PAH and HF. HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; LV, left ventricular; PAH, pulmonary arterial hypertension; PH, pulmonary hypertension; RRI, renal resistance index; RV, right ventricular.



Heart failure

One seminal study on acute decompensated HF found that high CVP on admission (or insufficient reduction after hospitalization) is a stronger predictor of renal dysfunction than cardiac index.[1] Another study by the same group, however, found no association between CVP and serum creatinine during treatment of HF.[25] Registry data show no association between ejection fraction in HF and renal dysfunction.[26,27] The ESCAPE trial revealed that improvement in cardiac index is not associated with renal outcomes,[28] and observational studies show that increased CVP is associated with decreased kidney function and increased mortality.[1,2] Importantly, RV diastolic pressure and pulmonary arterial diastolic pressure are comparably increased in HF patients with reduced or preserved ejection fraction.[29] In the presence of PH with RV dysfunction and relatively preserved cardiac index, CVP elevation is associated with a reduced glomerular filtration rate (GFR).[20] Overall, however, patients with congestion plus hypoperfusion have worse GFR and renal outcome and higher mortality than patients with isolated congestion or hypoperfusion.[20,26,27,30–32]

Pulmonary hypertension due to left heart disease

PH is the most common precursor of RV failure,[33] being reported in 40–75% of patients with reduced ejection fraction and 36–83% of patients with preserved ejection fraction[34]; the actual prevalence is probably higher because PH may manifest only upon stress (e.g. during exercise or fluid challenge)[35] Importantly, impaired renal venous flow (indicative of renal venous congestion) and reduced GFR have been described in HF without echocardiographic evidence of PH or RV dysfunction, suggesting that congestion may be present even without clinically detectable RV failure.[36]

Chronic kidney disease and heart failure

The effect of severity and duration of venous congestion and volume overload on CKD remains largely unexplored. Studies have shown that a high HF hospitalization rate (reflecting persistent congestion) is associated with long-term decline in GFR,[37,38] and that decongestive therapies improve overall outcome.[9] Furthermore, volume overload is reported to be associated with renal disease progression.[39,40] Whether the risk of CKD can be mitigated by relieving congestion (without precipitating low cardiac output) and achieving euvolaemia (using combination diuretic therapy to overcome diuretic resistance) needs to be determined, as also the CVP range that provides the optimum balance of RV and renal function in patients with HF.

Chronic kidney disease and pulmonary hypertension

CKD, per se, can cause cardiac dysfunction and failure.[13] PH often coexists with CKD; the prevalence increases with increasing CKD stage, suggesting an interdependent relationship.[3,36,41–43] In a recent study on patients with CKD undergoing right heart catheterization (n = 1873), 68% had PH, with post-capillary PH being the predominant phenotype. Among those with post-capillary PH, 64% had HF (33% with reduced ejection fraction and 31% with preserved ejection fraction), suggesting HF as the most prevalent cause of PH.[44] Interestingly, pre-capillary PH was found in 16% of patients,[44] indicating that CKD itself may cause pulmonary vascular remodelling in predisposed patients.[45] CKD-induced PH may result from volume overload, endothelial dysfunction, decreased bioavailability of nitric oxide, and increased endothelin-1 levels.[3] In patients on dialysis, blood exposure to dialysis membrane and shunting via arteriovenous fistulae may also contribute.[3] Acute worsening of renal function in pulmonary arterial hypertension has been found to be strongly associated with RV failure and mortality.[46–49]

Congenital heart disease, cardiac surgery, and isolated tricuspid regurgitation

In patients with Fontan circulation, renal function is inversely related to CVP[23,50]; these patients have high baseline albuminuria and tubular damage biomarker levels, with the latter linked to adverse outcomes.[23,51] Interestingly, however, renal dysfunction tends to be delayed,[52] probably owing to renal compensatory mechanisms during adolescence. Meanwhile, in children undergoing surgery for congenital heart disease, CVP rather than cardiac output is associated with worsening of postoperative renal function.[24] Venous congestion and decreased renal perfusion pressure are also associated with increased risk of acute kidney injury in adults undergoing cardiac surgery[53,54] and heart transplantation[55]; congestion in this setting may be a sign of underlying right HF.

Impaired renal function is a predictor of mortality in adults with isolated tricuspid regurgitation.[22] In retrospective studies, high preoperative serum creatinine was strongly associated with mortality in adult patients with tricuspid regurgitation receiving surgical and medical management.[56,57]

Increased intra-abdominal pressure

The splanchnic veins contain anywhere between 20% and 50% of the total blood volume.[58] As a result of sympathetic nerve overactivity in HF, vasoconstriction in this compartment forces movement of venous blood to the circulating compartment, which contributes to HF decompensation; this may be

particularly important in acute HF.[58–60] As an additional component, high IAP compresses intra-abdominal and intrathoracic blood vessels, compromising microvascular blood flow.[61] Diminished venous drainage results in renal, intestinal, and mesenteric venous congestion, oedema, and ischaemia.[62]

In healthy volunteers, increased IAP by means of external abdominal compression results in increased renal venous pressure and CVP, and decreased renal blood flow, GFR, tubular function, and urine output.[63] CRS is commonly associated with increased IAP, especially when ascites is present. The impact of increased IAP on renal dysfunction in acute HF has been described in small studies.[64–66] In a seminal study involving patients with acute HF with reduced ejection fraction, an elevated IAP (≥8 mmHg) at admission was present in 60% of the study population ($n = 40$) and was associated with renal dysfunction.[65] Furthermore, a strong correlation ($r = 0.77$; $P < 0.001$) was observed between reduction in IAP at baseline and improvement in renal function, independent of haemodynamic changes.[65] Another study reported a similar association between increased IAP (≥12 mmHg) and renal dysfunction in patients with acute HF with mid-range ejection fraction and preserved ejection fraction.[66] Furthermore, in that study, a persistent increase in IAP at 72 h was associated with a longer length of hospital stay and 1 year mortality.[66]

Microcirculatory disturbance occurs when IAP reaches 10–15 mmHg.[61] In animal models, renal dysfunction commences at IAP of 10 mmHg,[67,68] and anuria occurs at IAP of 30 mmHg.[69,70] Such changes are not seen in animals with isolated elevation of intrarenal parenchymal pressure due to renal compression.[71] In models of abdominal compartment syndrome, reversal of reduced cardiac output by volume expansion does not improve renal function, suggesting that high renal venous pressure is principally responsible for renal dysfunction in the setting of increased IAP.[72]

Congestive nephropathy

Pathophysiology

Table 1 provides an overview of key studies of the pathophysiology of renal venous congestion. Much of the evidence comes from animal experiments and cannot be entirely extrapolated to humans. Animal models show an association between increased renal venous pressure and reduced renal blood flow,[76] with congestion being a more important determinant of renal dysfunction than perfusion.[77]

Elevation of CVP is directly transmitted to the renal veins because venous vascular resistance is negligible. As the encapsulated kidney has little room to expand, renal interstitial hydrostatic pressure increases (*Figure 2*).[78] This increase may initially be prevented by a compensatory increase in renal lymphatic flow,[79–81] but continuing elevation of CVP will progressively reduce venous and lymphatic outflow and also late-stage arterial inflow.[81,83]

As the post-glomerular vascular and tubular network is a low-pressure system,[88–90] increases in renal interstitial pressure cause compression or occlusion of vessels and tubules, resulting in reduced tubular secretion and reabsorption.[63,82,84,85] The renin–angiotensin–aldosterone system and the sympathetic nervous system are activated, leading to sodium and urea retention, interstitial oedema, endothelial dysfunction, reduced nitric oxide availability, increased production of inflammatory cytokines and reactive oxygen species, and reduced GFR.[71,75,77,83,85,86,91] The inflammatory response is also enhanced,[92] and the resulting increase in arterial stiffness and myocardial cell dysfunction further worsens renal dysfunction. Increased endothelial permeability results in fluid extravasation (e.g. into lung alveoli) and absorption of pro-inflammatory endotoxin from the bowel.[92] Circulating lipopolysaccharide levels may amplify the systemic inflammation and induce acute kidney injury in this setting.[92]

In animals[75] and humans,[2] a curvilinear relationship exists between CVP and GFR: as CVP increases, GFR first increases slightly then falls sharply. The early increase in GFR is presumably due to increased glomerular hydrostatic pressure consequent to elevated proximal peritubular capillary pressure, which results in increased efferent arteriolar pressure.[2,75,83] This phenomenon is comparable with the autoregulatory mechanism of the glomerulus, where efferent arteriole vasoconstriction leads to increased glomerular hydrostatic pressure and GFR. Increased renal venous pressure (e.g. during hydration) may initially lead to an increase in GFR by inducing glomerular hyperfiltration, as long as proximal tubular pressure remains below glomerular net ultrafiltration pressure (normally ~20 mmHg).[73–75] This assumption is supported by intrarenal Doppler ultrasonography studies showing increased GFR in the early stage of renal venous congestion.[74] Later, glomerular filtration progressively decreases and comes to a standstill during systole. In consequence, renal venous pressure dips only occur during RV diastolic filling.[73,74] Sodium and fluid retention also aggravate HF, further decreasing mean circulatory filling pressure and elevating renal venous pressure. Concomitant renovascular disease or treatment with renin–angiotensin–aldosterone system inhibitors and nonsteroidal anti-inflammatory drugs may further interfere with maintenance of GFR. Of note, rat models suggest that hormonal factors may also be involved in the decrease of GFR, implicating pathways other than a simple reduction of the renal arteriovenous pressure gradient.[87]

Proteinuria

In CN due to isolated RV failure (e.g. due to pulmonary arterial hypertension), a gradual increase in albuminuria is seen

Table 1 Studies examining renal function and glomerular haemodynamics related to venous congestion or elevation of intra-abdominal and renal parenchymal pressure

Study	Design	Cohort	Methods	Findings
Bradley *et al*., 1947[63]	Prospective interventional single centre	17 healthy individuals; mean GFR 115 ± 19 mL/min	External abdominal compression at 80 mmHg (resulting in intra-abdominal pressure approx. 20 mmHg), invasively measured renal venous pressure in 9 individuals	Abdominal compression is associated with renal venous pressure elevation and reduction of GFR and tubular activities (maximal glucose reabsorption and maximal diodrast excretion)
Damman *et al*., 2009[2]	Retrospective observational single centre	2557 patients with broad spectrum of cardiovascular disease undergoing right heart catheterization; mean estimated GFR 65 ± 24 mL/min/1.73 m^2	Association of renal function with invasive haemodynamics; median 10.7 year follow-up evaluating all-cause mortality	Estimated GFR increases slightly as central venous pressure increases from 1 to 6 mmHg, whereas it falls sharply when central venous pressure rises above 6 mmHg; central venous pressure is an independent determinant of mortality
Iida *et al*., 2016[73]	Prospective observational single centre	217 stable patients with HF (30% with preserved ejection fraction) and 38 healthy individuals; mean estimated GFR 64 ± 26 mL/min/1.73 m^2	Characterization of Doppler-derived intrarenal venous flow patterns according to invasive haemodynamics, echocardiography, and renal function; 1 year follow-up evaluating cardiovascular mortality and HF-related hospitalization	Intrarenal venous flow patterns are associated with central venous pressure rather than cardiac index; discontinuous intrarenal venous flow patterns are independently associated with adverse outcomes
Husain-Syed *et al*., 2019[74]	Prospective observational single centre	205 patients with suspected or prediagnosed PH undergoing right heart catheterization; PH excluded in 40 patients; 165 patients diagnosed with PH group 1–5	Characterization of Doppler-derived intrarenal venous flow patterns and renal venous stasis index according to invasive haemodynamics, echocardiography, renal function, volume status, and intra-abdominal pressure; median 1 year follow-up evaluating composite endpoint of PH progression	Estimated GFR increases from renal venous stasis index = 0 to first tertile, but then decreases from second tertile of renal venous stasis index onwards; similar trend observed across intrarenal venous flow patterns
Experimental				
Winton 1931[76]	Prospective interventional	One dog model with isolated perfused kidneys	Ligature of renal veins (renal venous pressure of >20 mmHg)	Significant association between increased renal venous pressure, reduced renal blood flow, and reduced urine output; pressure in the vein is transmitted to the fluid in the distal portions of the tubules
Blake *et al*., 1949[84]	Prospective interventional	22 intubated and anaesthetized dogs	Clamping of left renal vein (stepwise increase of renal vein pressure <600 mm saline), followed by reperfusion	Renal venous pressure elevation <350 mm saline leads to a significant decrease in free water and sodium excretion due to increased renal tubular reabsorption; further elevation (<600 mm saline) leads to reductions in renal blood flow and GFR

(*Continues*)

Table 1 (continued)

Study	Design	Cohort	Methods	Findings
Hall *et al.*, 1951[82]	Prospective interventional	15 intubated and anaesthetized dogs	Ligature of left renal veins to allow comparison of congestive left kidneys with non-congestive right kidneys (renal venous pressure of baseline, 10, 20, and 30 cm H_2O)	Significant decrease in creatinine clearance and sodium and potassium excretion secondary to renal venous pressure elevation
Haddy *et al.*, 1958[79]	Prospective interventional	98 intubated and anaesthetized dogs	Compression of renal vein; cannulation of renal hilar lymph vessel [renal venous pressure of approx. 7 (baseline) and stepwise increase >25 mmHg]	Significant increase in renal lymph flow rate and renal vascular resistance secondary to venous pressure elevation
Lebrie *et al.*, 1960[80]	Prospective interventional	Intubated and anaesthetized dogs	Partial occlusion of inferior vena cava above renal veins with balloon catheter [renal venous pressure of approx. 4 (baseline) and stepwise increase >25 cm H_2O]; cannulation of renal capsular lymph vessels	Significant increase in renal lymph flow and decrease in urine output and sodium excretion secondary to venous pressure elevation
Burnett *et al.*, 1980[85]	Prospective interventional	Ten intubated and anaesthetized dogs	Clamping of left renal vein [renal vein pressure of approx. 5 (baseline), 10, 20, 30, and 40 mmHg]; measurement of renal interstitial pressure	Renal venous pressure elevation in the presence of volume expansion leads to a gradual increase in renal interstitial pressure and gradual decreases in renal blood flow, GFR, and sodium excretion
Burnett *et al.*, 1982[86]	Prospective interventional	Intubated and anaesthetized Sprague–Dawley rats	Micropuncture tubular segmental analysis during left renal vein clamping in presence and absence of volume expansion (no data on renal venous pressure)	Significant increase as with decrease in fractional sodium excretion in euvolaemia vs. volume expansion; decreased proximal tubule sodium reabsorption in both volume states
Firth *et al.*, 1988[75]	Prospective interventional	One rat model with isolated perfused kidneys	Ligation of renal vein (venous pressure of 0, 6.25, 12.5, 18.75, and 25 mmHg)	GFR increases slightly as venous pressure increases from 0 to 6.25 mmHg, but GFR and sodium excretion fall sharply when venous pressure rises above 6.25 mmHg, with these changes being reversible when venous pressure returns to baseline
Rohn *et al.*, 1996[81]	Prospective interventional	Intubated and anaesthetized dogs	Partial occlusion of inferior vena cava above renal veins with balloon catheter [renal venous pressure 3.5 (baseline) and stepwise increase >27.2 cm H_2O]; cannulation of renal lymph vessels	Significant increase in renal lymph flow and renal interstitial pressure secondary to renal venous pressure elevation, but increase >27.2 cm H_2O leads to impaired lymphatic outflow

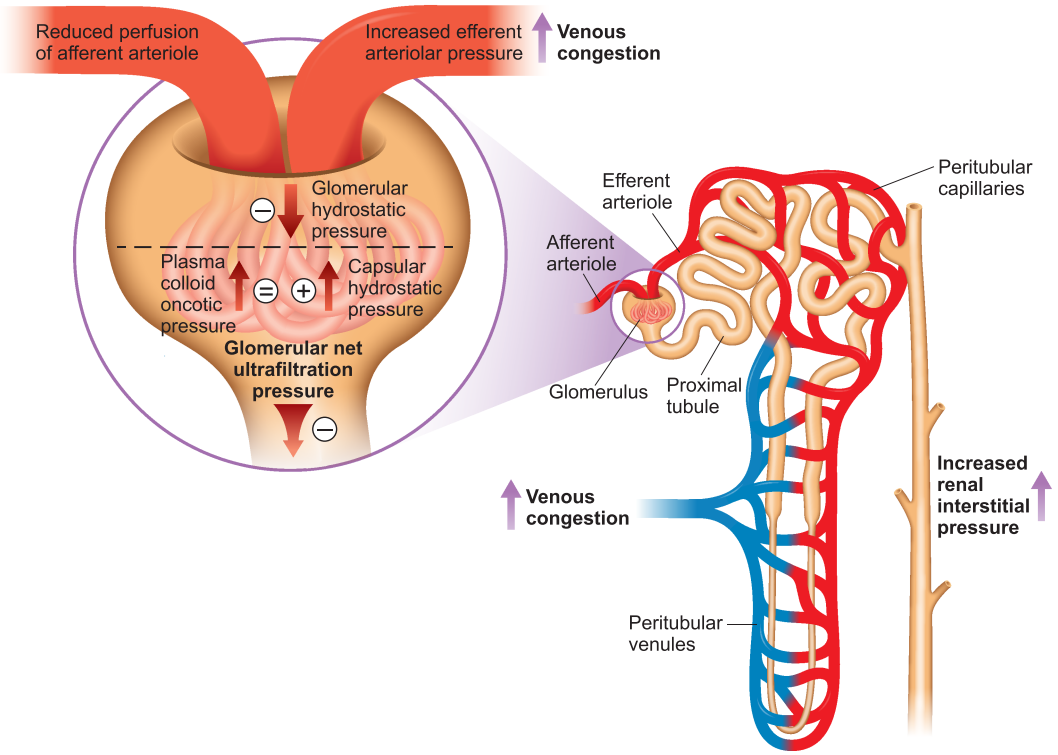
(*Continues*)

Table 1 (continued)

Study	Design	Cohort	Methods	Findings
Doty *et al*., 1999[83]	Prospective interventional	Eight swine	Renal vein constriction (renal venous pressure of baseline and 30 mmHg)	Venous pressure elevation leads to significant decreases in renal blood flow and GFR and increases in plasma aldosterone and plasma renin activity, with these changes being reversible when renal venous pressure returns towards baseline
Doty *et al*., 2000[71]	Prospective interventional	Yorkshire swine (n = 6) vs. sham-operated swine (n = 6)	Renal parenchymal compression (30 mmHg for 2 h)	Renal blood flow, GFR, plasma aldosterone or plasma renin activity are not affected by isolated elevation of renal parenchymal pressure
Li *et al*., 2012[77]	Prospective interventional	Intubated and anaesthetized mice vs. sham-operated mice (C57BL/6)	Clamping of renal artery, vein, or both (whole pedicle) for 30–45 min followed by reperfusion	Renal vein clamping for 30 min induces a more pronounced decrease in renal blood flow and higher serum creatinine elevation than renal artery or pedicle clamping; at 24 h, renal vein clamping is associated with significantly increased pro-inflammatory mediators (interleukin-6, keratinocyte-derived chemokine, granular-colony stimulating factor, and monocyte chemoattractant protein-1) compared with sham surgery
Shimada *et al*., 2018[78]	Prospective interventional	Intubated and anaesthetized Sprague–Dawley rats vs. sham-operated rats	Ligature by suture of inferior vena cava between renal veins to allow comparison of congestive left kidneys with non-congestive right kidneys; measurement of cortical renal interstitial hydrostatic pressure	Significant increase in renal interstitial hydrostatic pressure secondary to venous pressure elevation compared with sham surgery
Huang *et al*., 2018[87]	Prospective interventional	83 intubated and anaesthetized Lewis rats	Surgical left renal vein constriction [renal venous pressure of approx. 1 (baseline), 10, and 20 mmHg]	Elevation of renal venous pressure decreases ipsilateral renal blood flow and GFR, with the reduction being abolished by high salt diet but not renal denervation; the authors postulate that acute renal venous pressure elevation induces renal vasoconstriction and decreased GFR likely via the renin–angiotensin system rather than via the renal nerves

GFR, glomerular filtration rate; HF, heart failure; PH, pulmonary hypertension.

Figure 2 Venous congestion and glomerular haemodynamics. Renal venous congestion caused by intravascular congestion or an increase in intra-abdominal pressure can lead to a build-up of renal interstitial hydrostatic pressure through peritubular capillary congestion and development of interstitial oedema. This presumably leads to increased efferent arteriolar pressure, which may initially result in glomerular hyperfiltration; however, further increases in renal venous pressure with decreases in renal perfusion pressure ultimately reduce glomerular filtration rate.



with increasing severity of congestion, although the increase probably remains within the physiological range.[74,93] Tubular dysfunction, chronic tubulointerstitial damage,[94] and increased levels of atrial natriuretic peptides,[95] which directly reduce proximal tubular reabsorption, may increase proteinuria. In contrast to patients with isolated RV failure, patients with HF commonly exhibit high levels of albuminuria (probably due to the presence of hypertensive nephrosclerosis, diabetic nephropathy, or renovascular disease).[96] A rapid increase in renal venous pressure may transiently increase proteinuria by causing acute glomerular and tubular dysfunction. Such functional albuminuria is probably common in HF and may be the consequence of congestion.[97] *Table 2* provides an overview of studies reporting proteinuria related to venous congestion or IAP elevation.

Histopathological findings

Studies in rodent models investigating the effects of congestion on renal histopathology report predominant congestion in peritubular capillaries, which, in the normal state, are almost invisible. These studies also report pericyte detachment, potentially resulting in dysregulated cortex and medullary circulation, hypoxia, and tubular injury, while chronic renal congestion may lead to tubular atrophy and fibrosis.[78,102] Renal histopathological findings from rodent models and a case report of a patient with idiopathic pulmonary arterial hypertension are described in *Table 3*. Histopathological studies in humans with isolated CN are scarce because decreased GFR is usually attributed to nephrosclerosis and diabetic nephropathy.[107,108] Kidney biopsy is also often avoided because of an unproven increased risk of biopsy-associated haemorrhage.

Is congestive nephropathy a reversible condition?

In animal models, congestion-induced renal dysfunction resolves completely when venous pressure is restored to basal levels with the extent of resolution depending on the duration and severity of congestion.[75,84] Improvement in renal function has been reported in a patient with HF after decongestion by peritoneal dialysis.[109] A recent post hoc analysis showed that sildenafil treatment in patients with pulmonary arterial hypertension improved renal function and reduced PH-related morbidity.[110] Whether renal function improved owing to the effect of sildenafil on the pulmonary vasculature and right

Table 2 Studies reporting proteinuria related to venous congestion or elevation of intra-abdominal pressure

Study	Design	Cohort	Methods	Findings
Bradley *et al*., 1947[63]	Prospective interventional single centre	17 healthy individuals; mean GFR 115 ± 19 mL/min	External abdominal compression at 80 mmHg (resulting in intra-abdominal pressure approx. 20 mmHg), invasively measured renal venous pressure in 9 individuals	Transient proteinuria and renal venous pressure elevation (from mean 5.8 to 18.3 mmHg) during abdominal compression
Vesely *et al*., 2001[95]	Prospective interventional single centre	24 patients with HF with reduced ejection fraction and New York Heart Association functional class III; patients with serum creatinine levels >1.5 mg/dL were excluded	Infusion of long-acting natriuretic peptide, vessel dilator, and kaliuretic peptide for a duration of 60 min	2-fold to 7-fold increase in albuminuria, 2-fold to 5-fold increase in proteinuria, and 25-fold to 40-fold increase in urinary β_2-microglobulin (marker of proximal tubular reabsorption); authors postulate that part of the mechanism of the observed enhanced protein excretion is the inhibition of proximal tubular reabsorption of protein
Koyama *et al*., 2013[97]	Prospective observational single centre	115 patients admitted for acute HF (preserved and reduced left ventricular ejection fraction); mean baseline estimated GFR 48 ± 23 mL/min/1.73 m^2	Spot urinary albumin-to-creatinine ratio measured on Days 1 and 7 of hospitalization	Increased albuminuria at admission with significant decrease within 7 days of treatment of cardiac decompensation; these changes were paralleled by decreases in N-terminal pro-b-type natriuretic peptide levels, but not with baseline nor with changes in renal function
Navaneethan *et al*., 2016[98]	Prospective observational multi-centre	2959 patients with non-dialysis-dependent chronic kidney disease (estimated GFR: 20–70 mL/min/1.73 m^2) and preserved left ventricular ejection fraction; PH present in 21%; patients with New York Heart Association functional class III/IV HF were excluded	Median 4.1 year follow-up evaluating cardiovascular and renal outcomes, and all-cause mortality	24 h proteinuria comparable between those with and without PH (mean, 200 vs. 200 mg; $P = 0.10$), the overall higher-than-normal values likely reflecting the high prevalence of concomitant cardiovascular disease and diabetes in both cohorts
Jotwani *et al*., 2018[100]	Prospective observational dual centre	Random sample of 776 participants including cardiovascular disease and HF cases	Median 12.4 year follow-up evaluating incident cardiovascular disease, HF, and all-cause mortality	Higher urinary alpha-1 microglobulin and urinary neutrophil gelatinase-associated lipocalin levels are associated with elevated risk of incident cardiovascular disease and all-cause mortality; no significant association with HF
Husain-Syed *et al*., 2019[74]	Prospective observational single centre	205 patients with suspected or prediagnosed PH undergoing right heart catheterization; PH excluded in 40 patients; 165 patients diagnosed with PH group 1–5	Evaluation of baseline morning spot urinary protein-to-creatinine, albumin-to-creatinine, and α1-microglobulin-to-creatinine ratios; median 1 year follow-up evaluating composite endpoint of PH progression	Gradual increase in proteinuria, albuminuria, and α1-microglobulin excretion with increasing severity of congestion, although the increase remains within the physiological range

(*Continues*)

Table 2 (continued)

Study	Design	Cohort	Methods	Findings
Nickel *et al*., 2019[93]	Prospective observational dual-centre	283 patients with pulmonary arterial hypertension, 18 unaffected carriers of mutations in the gene encoding bone morphogenetic protein receptor type 2, 68 healthy controls (2 independent cohorts); patients with diabetes mellitus and estimated GFR $<$ 60 mL/min/1.73 m^2 were excluded	Morning spot urinary albumin-to-creatinine ratio	Gradual increase in albuminuria with increasing severity of congestion, although the increase remains within the physiological range (below the threshold of microalbuminuria) and is statistically non-significant in this study; urinary albumin-to-creatinine ratio $>$ 10 μg/mg significantly associated with higher odds of death or lung transplantation
Garimella *et al*., 2019[99]	Prospective multi-centre open-label clinical trial	Patients with high systolic blood pressure and high risk for cardiovascular events; 2337 selected non-diabetic patients with estimated GFRs $<$ 60 mL/min/1.73 m^2; patients with HF were excluded	Median 3.8 year follow-up evaluating a composite cardiovascular outcome	Lower urinary uromodulin excretion (which is associated with higher odds of tubular atrophy and fibrosis[151]) and higher urinary alpha-1 microglobulin levels are associated with elevated risk of HF
Experimental				
Winton 1931[76]	Prospective interventional	One dog model with isolated perfused kidneys	Ligature of renal veins (renal venous pressure of $>$20 mmHg)	Gradual increase in proteinuria during renal venous pressure elevation; proteinuria normalizes when renal venous pressure returns to baseline
Doty *et al*., 1999[83]	Prospective interventional	Eight swine	Renal vein constriction (renal venous pressure of baseline and 30 mmHg)	Renal venous pressure elevation leads to significantly increased proteinuria, with the finding being reversible when venous pressure returns towards baseline
Shimada *et al*., 2018[78]	Prospective interventional	Intubated and anaesthetized Sprague–Dawley rats vs. sham-operated rats	Ligature by suture of inferior vena cava between renal veins to allow comparison of congestive left kidneys with non-congestive right kidneys	3 days after surgery, significantly increased urinary albumin-to-creatinine ratio in the congestive left kidneys, potentially associated with observed podocyte injury and slit diaphragm disruption
Cops *et al*., 2018[101]	Prospective interventional	Intubated and anaesthetized Sprague–Dawley rats (n = 7) vs. sham-operated rats (n = 6)	Permanent surgical constriction (20 gauge) of thoracic inferior vena cava (increasing central venous pressure to a mean of 17 mmHg)	12 weeks after surgery, plasma creatinine, plasma cystatin C, urinary albumin, glomerular surface area, and width of Bowman capsule increased significantly in the inferior vena cava group compared with the sham group; no difference in the acute tubular damage biomarker kidney injury molecule-1

GFR, glomerular filtration rate; HF, heart failure; PH, pulmonary hypertension.

Table 3 Studies reporting renal histopathological findings related to venous congestion, elevation of intra-abdominal pressure or obstructive nephropathy

Study	Design	Cohort	Methods	Findings
Faustinella *et al.*, 1997[103]	Single-centre case vignette	34-year-old woman with idiopathic pulmonary hypertension; systolic pulmonary arterial pressure > 74 mmHg, 24 h proteinuria 5 g, and creatinine clearance 70 mL/min	Diagnostic kidney biopsy including immunohistologic and ultrastructural evaluation	Glomerulomegaly, mesangial hypercellularity and sclerosis, focal tubular atrophy, and interstitial fibrosis and inflammation; the authors postulate that elevation of central venous pressure, with passive congestion and glomerular capillary hypertension, is primarily responsible for the observed changes
Experimental				
Schachtrupp *et al.*, 2002[67]	Prospective interventional	Intubated and anaesthetized domestic pigs	CO_2 pneumoperitoneum (intra-abdominal pressure of 15 mmHg for 24 h)	Low-grade proximal tubular epithelial necrosis was observed
Sato *et al.*, 2003[104]	Prospective interventional	Mice vs. sham-operated mice (wild-type and Smad3-null)	Double-ligation of right proximal ureter[a]	Wild-type mice showed tubulointerstitial fibrosis associated with epithelial–mesenchymal transition of the renal tubules and collagen accumulation; this was prevented by lack of Smad3
Li *et al.*, 2012[77]	Prospective interventional	Intubated and anaesthetized mice vs. sham-operated mice (C57BL/6)	Clamping of renal artery, vein, or both (whole pedicle) for 30 min followed by reperfusion	At 24 h after renal vascular clamping, both kidney function and histologic injury are the most severe in the renal vein clamping group
Chang *et al.*, 2013[105]	Prospective interventional	Mice (ICR)	Intraperitoneal injection of albumin and normal saline (intra-abdominal pressure of 0, 5, 10, or 20 cm H_2O)	Increasing degrees of diffuse interstitial oedema, renal tubular lumen collapse, and interstitial inflammation were observed with increasing intra-abdominal pressure
Shimada *et al.*, 2018[78]	Prospective interventional	Intubated and anaesthetized Sprague–Dawley rats vs. sham-operated rats	Ligature by suture of inferior vena cava between renal veins to allow comparison of congestive left kidneys with non-congestive right kidneys	3 days after surgery, congestive left kidneys showed lesions in peritubular capillaries with pericyte detachment, up-regulated pathways involved in extracellular matrix expansion and induction of expression of tubular injury markers (kidney injury molecule-1) in stressed tubules; renal decapsulation ameliorated the tubular injury and profibrotic effects in the cortical region only
Owji *et al.*, 2018[102]	Prospective interventional	28 intubated and anaesthetized Sprague–Dawley rats	Bilateral clamping of the renal artery, vein, or both (whole pedicle) for 30 min followed by 2 h reperfusion; $n = 7$ in each group	At ~2 h after renal vascular clamping, both kidney dysfunction and histologic tubular injury were the most severe in the renal vein

(*Continues*)

Table 3 (continued)

Study	Design	Cohort	Methods	Findings
				clamping group, with distinctive haemorrhagic congestion of peritubular capillaries in the cortex and medulla
Cops *et al.*, 2018[101]	Prospective interventional	Intubated and anaesthetized Sprague–Dawley rats (n = 7) vs. sham-operated rats (n = 6)	Permanent surgical constriction (20 gauge) of thoracic inferior vena cava (increasing central venous pressure to a mean of 17 mmHg)	12 weeks after surgery, glomerular surface area and width of Bowman capsule increased significantly in the inferior vena cava group compared with the sham group; no difference in the acute tubular damage biomarker kidney injury molecule-1

[a]Experimental ureteral obstruction provides a model of obstructive nephropathy resulting in tubular injury and renal fibrosis.[106]

ventricle (and the resultant reduction in venous congestion) or owing to its direct vasodilatory and remodelling effect in the renal vasculature, or both, remains unknown.

Decongestion may not be effective in patients with pre-existing CKD or long-standing renal hypoperfusion or venous congestion, owing to the presence of irreversible tubulointerstitial damage. In studies on patients with end-stage HF (43–49% of whom had ischaemic cardiomyopathy), the majority had improved renal function after implantation of a ventricular assist device (VAD), but the likelihood of improvement was lower in those with more severe preimplant renal dysfunction and diabetes.[111–113] Renal function improvement was probably owing to decreased venous congestion, increased systemic perfusion, and decreased hormonal activation.[114,115] In VAD recipients with improved renal function, renal Doppler ultrasonography showed decreased mean peak systolic velocity and increased mean end-diastolic velocity, which together lowered the renal resistance index. The likely explanation is that reduction of venous congestion-induced elevated renal interstitial pressure led to an increase in the cross-sectional area of interstitial vessels and improved diastolic flow.[116] Renal function did not improve in some cases probably owing to underlying CKD (secondary to longstanding hypertension, diabetes, or renovascular disease), ongoing volume overload, or persistent low cardiac output despite VAD implantation.

In patients with acute HF, lowering of increased IAP by decongestive therapy can improve renal function, presumably by alleviating abdominal congestion.[65] In acute HF with ascites, paracentesis reduces IAP and volume overload and thereby improves renal function.[64] Paracentesis of ascites also improves renal function in patients with pulmonary arterial hypertension[117] and hepatorenal syndrome.[118] In patients with HF and refractory ascites, peritoneal dialysis is an alternative to repeated paracentesis. However, evidence on the benefits of peritoneal dialysis in this setting comes mostly from observational single-centre studies.[119] Of note, peritoneal dialysis may temporarily increase IAP by generating an 'artificial ascites' through dialysate dwelling within the peritoneal cavity. However, the mean IAP with the classical intraperitoneal volume of 2 L in adult patients undergoing peritoneal dialysis is within the high-normal range (9 ± 2 mmHg).[120] Factors associated with increased IAP include dialysate volume (IAP increases by 1.0 ± 0.3 mmHg for each 500 mL of infused volume) and body mass index.[121] There are no studies on IAP in CRS patients on peritoneal dialysis.

Diagnostic markers for congestive nephropathy

CN is a potentially reversible subtype of renal dysfunction, characterized by RV failure or volume overload. Decongestion

may help to reverse renal dysfunction by improving RV function, lowering CVP/renal venous pressure, or lowering IAP/renal interstitial pressure. Notably, clinico-biological presentation of CN may change with the severity of RV failure and/or volume overload, and with the duration of abnormal renal haemodynamics. Congestive acute kidney injury may not be associated with cellular damage, and complete renal function restoration may be a confirmatory diagnostic criterion. In contrast, a persistently low renal perfusion pressure might induce renal dysfunction and histopathological lesions with time. Thus, urinary markers may differ.

Diagnosis of CN is challenging because there is no gold standard to assess renal venous congestion. Many patients with CN have normal left ventricular ejection fraction, and the symptoms and signs of volume retention may quickly resolve with diuretic therapy. Moreover, the signs and symptoms of right HF are often nonspecific. Regardless, the diagnosis of acute kidney injury, volume overload, cardiac dysfunction, and any evidence of CKD must be pursued to establish potential reversibility of renal dysfunction by decongestion.

Clinical evaluation

Initial assessment would include the evaluation of symptoms, signs, and history; this is in accordance with the clinical practice guidelines of the European Society of Cardiology for HF[122] and PH.[6] Cardinal clinical symptoms/signs include recurrent short-term weight gain due to volume overload; jugular venous distension; diuretic resistance (i.e. poor response to high doses of diuretics or need for combination of diuretics for sequential nephron segment blockade to achieve effective decongestion); previous unscheduled hospitalization for volume overload; and clinical/ultrasonographic signs of volume overload (bilateral ankle oedema, anasarca, pleural effusion, and/or ascites). If initial evaluation suggests HF/PH, advanced workup is necessary to demonstrate functional or structural alterations of the heart and the kidney as the underlying cause. CN may be suspected when high levels of natriuretic peptides[6,122] occur in combination with imaging signs of right HF and evidence of renal dysfunction.[123–125] Because this may refer to a large proportion of patients with HF, further diagnostic testing would be required to rule out other intrinsic causes of renal dysfunction.

Imaging: assessment of renal venous congestion

There is no method to measure renal venous congestion directly in the clinical setting. A wireless implantable haemodynamic monitoring system is available that measures pulmonary arterial pressure continuously; these data can be used by clinicians to assess congestion. The device has been shown to reduce HF-related hospitalizations in outpatients with HF[8]; however, availability and cost, and the invasive procedure for implantation, are major limitations. Currently, assessment of congestion is based on the CVP (inferior vena cava size and collapse), right atrial and RV size, and tricuspid annular plane systolic excursion (as a surrogate for RV systolic function), as well as parameters of RV–pulmonary circulation coupling.[123,126,127] In the non-acute setting, congestion is usually assessed by observing whether renal function improves with decongestion.

Intrarenal Doppler ultrasonography can be useful for evaluating renal congestion as it can identify intrarenal venous flow patterns that predict diuretic response and adverse outcomes in HF, PH, and cardiac surgery.[36,53,73,74] Doppler intrarenal venous flow has shown stronger independent associations with adverse outcomes than invasive haemodynamic measurements,[73,74] suggesting that intrarenal venous flow may be an integrative marker of renal congestion. However, classification of discontinuous intrarenal venous flow patterns into different categories may miss important changes within those categories; a continuous measure may provide a more objective assessment of renal congestion.[74] Intrarenal Doppler ultrasonography may be useful for guiding HF-specific and PH-specific therapy, evaluating treatment response, and identifying patients at risk for adverse outcomes, but there are few studies examining dynamic changes in intrarenal venous flow.[36] So far, there have only been a few single-centre reports on the use of Doppler ultrasonography to investigate renal congestion. No study has examined the correlation of invasively measured renal venous pressure with alterations in Doppler-measured intrarenal venous flow. Of note, renal venous congestion does not necessarily indicate right HF, because tricuspid insufficiency with intact RV function may also induce congestion. Moreover, discontinuous intrarenal venous flow patterns have been described in obstructive nephropathy[128] where they are at least partly explained by increased renal interstitial pressure consequent to ureteral obstruction. Also, it remains unknown whether volume overload in absence of cardiac dysfunction (e.g. due to acute kidney injury) may also cause renal venous congestion. In our opinion, any Doppler-derived discontinuous intrarenal venous flow is indicative of CN and calls for cardiac evaluation. It should be noted that ultrasound is relatively insensitive for detecting fibrotic changes. In a preclinical model, kidney elasticity estimation by ultrasound surface wave elastography (reflecting the combination of venous congestion, renal fibrosis, and altered renal compliance) correlated well with transcatheter measurement of kidney intracapsular pressure and IAP,[129] but this has not yet been confirmed in human studies. The use of other imaging techniques (e.g. magnetic resonance imaging) to assess renal venous congestion has not been described.

Other potentially useful diagnostic tests may include assessments of congestive hepatopathy secondary to HF

(e.g. with Doppler-derived portal venous flow alterations or liver stiffness measurement with transient elastography), but there are still limited data on their correlation with indices of RV failure and Doppler-derived intrarenal venous flow.[53,130]

Assessment of volume status

Among patients hospitalized for acute HF and deteriorating renal function, outcome is worse in those with residual congestion at discharge than in those without congestion.[9] What remains unknown is how underlying intrinsic renal insufficiency can be distinguished from the dynamic changes in GFR that commonly occur in the course of HF and during its management with diuretics and HF medications. Overall, it may be difficult to classify the patient with right HF to a CKD stage because serum creatinine elevation may also be due to congestion-induced renal dysfunction or hypovolaemia resulting from excessive diuretic use. In both scenarios, achieving optimal volume status would allow more accurate estimation of baseline renal function and CKD stage. However, determining and maintaining the ideal volume status in patients with right HF is one of the most challenging problems in nephrology. A combination of different tools may be necessary to assess volume status, and monitoring of renal function during therapy would be needed to confirm the initial assessment. Of note, while ultrasonographically measured inferior vena cava diameter is used for assessment of intravascular volume, the diameter is also influenced by RV function and is thus a reflection of preload rather than tissue hydration.[131] Elevated levels of natriuretic peptides are indicators of intravascular and intracardiac congestion (e.g. atrial fibrillation),[58] but they are also influenced by medication; moreover, accumulation can occur in patients with renal dysfunction.[122] Therefore, natriuretic peptide levels must always be interpreted in the context of clinical findings. Carbohydrate antigen (CA)-125 has potential value in HF as it is released by epithelial serous cells (pericardium, pleura, and/or peritoneum) in response to mechanical (hydrostatic pressure) or cytokine stimuli.[132] Furthermore, CA-125 production is not influenced by age or renal function, which circumvents some of the limitations of natriuretic peptides.[133] Elevated levels of CA-125 are found in two-thirds of acute decompensated HF cases,[132,133] correlate with the severity of acute HF,[132–134] and relate to increased morbidity and mortality rates.[132] The CHANCE-HF study examined the use of CA-125-guided therapy vs. standard of care in patients with acute HF and found a lower rate of rehospitalization for acute decompensated HF in the CA-125-guided group. Notably, patients allocated to the CA-125 group were more frequently visited than patients in the standard of care group and received ambulatory administration of intravenous furosemide based on their CA-125 levels.[135] Bioimpedance analysis is a non-invasive technique to aid the clinical assessment of body mass and cellular water composition by bioelectrical impedance measurements, resistance, and reactance.[136] In patients with acute HF, bioimpedance analysis is a good predictor of length of hospital stay and correlates well with levels of natriuretic peptides and E/e′ ratio.[137,138] Furthermore, serial evaluation of bioimpedance analysis seems to be useful in monitoring volume status variations and the efficacy of decongestive therapy in HF.[139,140]

Clinical chemistry: assessment of renal function

Equations using serum creatinine to calculate estimated GFR may overestimate renal function in patients with CN because of the high prevalence of non-GFR determinants such as cardiac cachexia (with reduced creatinine generation) and low creatinine level due to serum dilution in patients with CRS.[141] Creatinine clearance may also be unreliable because incorrect collection/sampling may influence the GFR value. GFR equations based on cystatin C, which unlike serum creatinine is independent of muscle mass, may be superior for estimation of renal function.[141] However, diagnosis of CN does not necessarily require evidence of reduced renal function. Renal venous congestion precedes renal function decline as measured by established biomarkers such as serum creatinine and cystatin C[74]; experimental studies suggest that early congestion is accompanied by a dramatic increase in lymphatic flow, which prevents any increase in renal interstitial pressure until full saturation.[79,80] This may particularly be the case in patients without intrinsic kidney damage (e.g. due to long-standing hypertension and diabetes). Finally, different trajectories of changes in serum creatinine in acute HF have been described,[142] and further research is needed to evaluate their prognosis in terms of long-term renal outcome and overall mortality.

Assessment of hormonal activation and biomarkers

There is no single laboratory marker of hormonal activation that has high discriminative power for CN; a combination of different markers may improve diagnostic accuracy. Increased blood urea nitrogen-to-creatinine ratio and dilutional hyponatraemia have been proposed as surrogate markers of hormonal activation as they reflect the disproportionate tubular reabsorption of urea and free water.[143] Persistent hypokalaemia (despite potassium substitution) and inverse

urine sodium-to-potassium ratio indicate diuretic resistance due to hyperaldosteronism secondary to right HF. Hormone levels (e.g. renin, angiotensin II, and aldosterone) could support a diagnosis of CN, but antihypertensive medications may influence these parameters. In patients with HF, persistently low fractional excretion of sodium in urine despite use of potassium-wasting diuretics suggests diuretic resistance and sodium retention, probably attributable to activationvof sodium chloride transport along the distal nephron.[144]

Several novel tubular damage biomarkers have been identified, but their value in acutely decompensated HF may be limited to distinguishing serum creatinine elevation due to kidney damage from functional serum creatinine fluctuations.[145] Research on biomarkers in HF (e.g. soluble ST2, galectin-3, copeptin, and adrenomedullin) has not yet found any that can be recommended for clinical practice.[122] However, galectin-3 may be of interest in CN as it is associated with the development and progression of CKD and predicts development of HF.[146,147]

Directions for future research

Experimental

Future animal models should clarify the impact of long-standing venous congestion on renal pathology and renal function. Detailed immunohistologic and ultrastructural studies are needed. Only one study has examined the effects of congestion on the kidney, and that was in a rat model of abdominal venous congestion for up to 12 weeks,[101] which was too short for detailed analysis. In animal models, ligation of the inferior vena cava between the renal veins can generate collateral circulation, which would lower inferior vena cava pressure and relieve renal venous congestion; thus, alternative models need to be developed to study long-term effects.[148,149]

Clinical

In patients with CRS and persistent and/or progressive renal dysfunction despite adequate decongestion, we believe renal biopsy might be considered as it may help to identify patient subsets likely to have improvement in residual renal function after restoration of cardiac function by segregating those with reversible from those with irreversible tubulointerstitial damage. Further studies are needed to determine if CVP is a suitable metric to capture CN. Research is also needed to validate the role of intrarenal Doppler ultrasonography in the management of HF and PH and evaluation of volume status. Intrarenal Doppler ultrasonography performed at baseline and throughout therapy could help establish specific Doppler-derived renal congestion targets indicative of optimal volume and RV status in individual patients, similar to the strategies used to guide medication adjustment in studies of pulmonary artery sensors.[150] Intrarenal Doppler ultrasonography studies should include patients requiring renal replacement therapy for diuretic-resistant volume overload and acute kidney injury to evaluate the severity of renal congestion and to identify when, during renal replacement therapy, improvement in residual renal function will permit discontinuation of renal replacement therapy.

Conclusions

Prognosis varies widely among patients with concomitant cardiac and renal dysfunction, so it is important to identify high-risk patients who might benefit from intensive monitoring and therapy. The adverse impact of congestion on renal function has long been recognized, but it is still not given due consideration in clinical practice. Early decongestion can improve renal function and outcome. Clear definition of this haemodynamic phenotype of renal dysfunction will help physicians identify patients likely to benefit from specific management strategies. We suggest the term CN for a potentially reversible subtype of renal dysfunction associated with declining renal venous outflow and progressively increasing renal interstitial pressure. Discontinuous venous flow patterns on intrarenal Doppler ultrasonography may indicate CN and the need for detailed cardiac evaluation. Further research is needed to validate the role of intrarenal Doppler ultrasonography in the management of HF and PH, to address the challenge of evaluating and optimizing volume status, and to identify the CVP value that provides the best balance of RV and renal function.

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Conflict of interest

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