Review Article

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KIDNEY RESEARCH AND CLINICAL PRACTICE

How should we treat acute kidney injury caused by renal congestion?

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Decreased kidney function is associated with increased risk of cardiovascular events and mortality, and heart failure (HF) is a well-known risk factor for renal dysfunction. Acute kidney injury (AKI) in patients with HF often is attributed to prerenal factors, such as renal hypoperfusion and ischemia as a result of decreased cardiac output. Another such factor is reduction of absolute or relative circulating blood volume, with the decrease in renal blood flow leading to renal hypoxia followed by a decrease in the glomerular filtration rate. However, renal congestion is increasingly being recognized as a potential cause of AKI in patients with HF. Increased central venous pressure and renal venous pressure lead to increased renal interstitial hydrostatic pressure and a reduction of the glomerular filtration rate. Both decreased kidney function and renal congestion have been shown to be important prognostic factors of HF, and adequate control of congestion is important for improving kidney function. Loop and thiazide diuretics are recommended as standard therapies to reduce volume overload. However, these agents are associated with worsening renal function even though they are effective for improving congestive symptoms. There is growing interest in tolvaptan, which can improve renal congestion by increasing excretion of free water and decreasing the required dose of loop diuretic, thereby improving kidney function. This review summarizes renal hemodynamics, the pathogenesis of AKI due to renal ischemia and renal congestion, and diagnosis and treatment options for renal congestion.

Keywords: Acute kidney injury, Cardio-Renal syndrome, Heart failure, Hemodynamics, Renal circulation, Venous congestion

Introduction

Decreased kidney function is associated with adverse outcomes in patients with heart failure (HF), and HF is a known risk factor for renal dysfunction [1,2]. Acute kidney injury (AKI) in patients with HF has been thought to be caused by renal hypoperfusion due to reduced cardiac output, decreased oxygen transport, and absolute or relative hypovolemia, which has a direct effect on renal autoregulation. Furthermore, in HF, arterial underfilling stimulates vasoconstrictor neurohormones, including the renin-angiotensin system (RAS), vasopressin, and catecholamines,

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leading to renal ischemia, hypoxia, and sodium retention and increasing volume overload.

Renal congestion has also been recognized as a potential cause of AKI in patients with HF. It has been reported that development of AKI in patients with acute decompensated HF is more strongly associated with venous congestion than with low cardiac output [3]. Recent studies suggest that both decreased renal function and renal congestion are major prognostic factors in HF [4–6]. It is important to increase or maintain kidney function as well as alleviate congestion to improve the prognosis of patients with HF. The pathophysiological mechanisms, prognostic markers, and treatment options for renal congestion and decreased kidney function in HF have not been fully elucidated. This review summarizes renal hemodynamics, the pathogenesis of AKI due to renal ischemia and renal congestion, and diagnostics and treatment options for renal congestion.

Renal hemodynamics

Although the kidneys weigh only ~150 g, they are highly perfused, with ~25% of cardiac output flowing into the two kidneys. As shown in Fig. 1, the renal artery branches into multiple (generally five) segmental arteries that enter the kidney at the renal hilum [7]. The branches of these segmental arteries become the interlobar arteries, which run between the lobes. Each interlobar artery becomes an arcuate artery that runs along the boundary between the cortex and the outer layer of the medulla, and an interlobular artery branches from each arcuate artery. Afferent arterioles branch off each interlobular artery and transport blood to the capillaries within the glomerulus, which is surrounded by Bowman's capsule. Systemic blood pressure decreases gradually until it reaches the glomerulus. The largest pressure gradient occurs in the afferent arteriole. Under normotensive conditions, systemic blood pressure has been found to decrease by ~30% at the proximal end

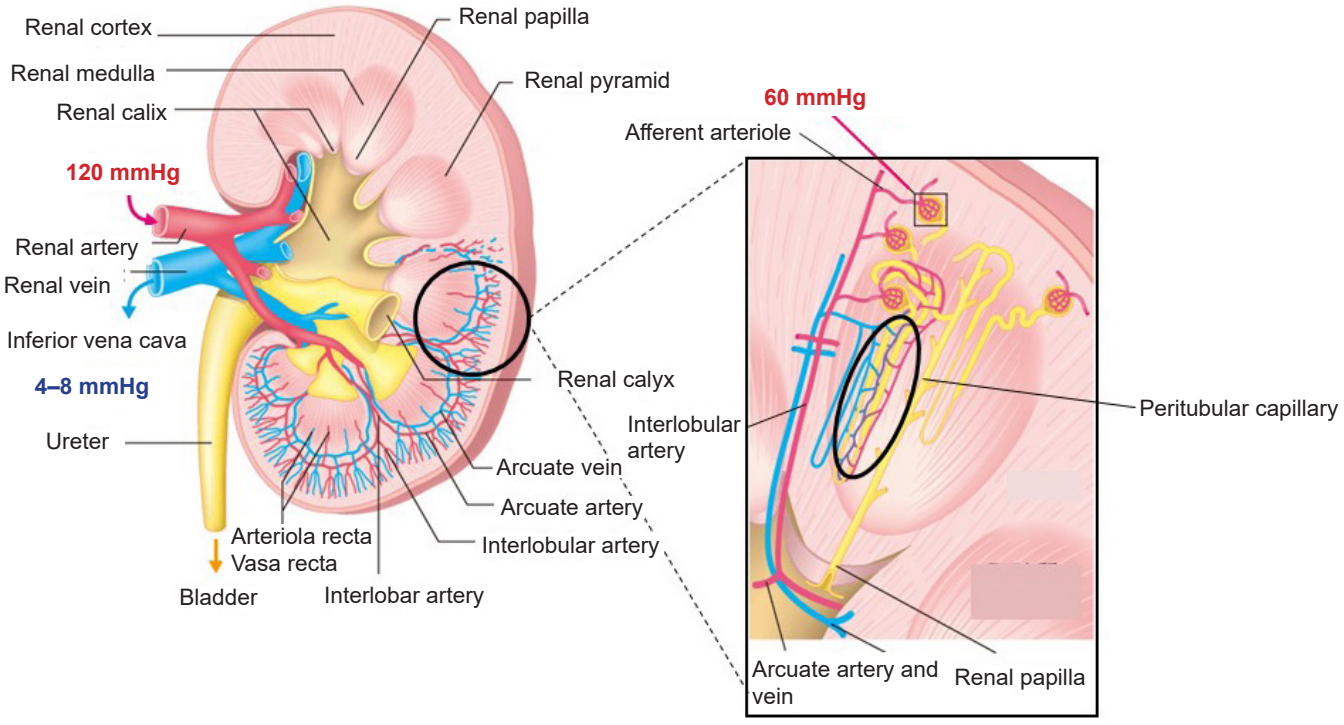

Figure 1. Renal hemodynamics. Blood vessels branching from the renal artery flow directly into the kidney with a systolic blood pressure of 120 mmHg. In the renal parenchyma, blood flows into the interlobar arteries, the arcuate arteries, and then into the interlobular arteries. Blood then flows from the interlobular arteries into the afferent arterioles to supply the glomerulus. The intraglomerular pressure is maintained at 60 mmHg.

of the most superficial afferent arterioles in a rat model [8]. Furthermore, the fractional pressure drop relative to the systemic blood pressure decreases with decreasing perfusion pressure, suggesting an autoregulatory mechanism in the afferent arterioles [8]. The calibers of the afferent arterioles, as well as their morphology and patterns of innervation, suggest that the cortical interlobular arteries are the principal sites of renal vascular resistance. Given that the length of the cortical interlobular arteries in the outer cortical circuits is greater than that in the circuits supplying the deeper cortex, the total preglomerular resistance in the most superficial circuits may be expected to be greater than in the juxtamedullary circuits. The efferent arterioles then branch into multiple peritubular capillaries (PTC). Studies in humans have demonstrated that blood pressure decreases significantly to 10–20 mmHg in the postglomerular circulation [9,10]. Blood flows from the cortical capillaries into the arcuate veins via the interlobular veins and then flows from the juxtamedullary glomeruli near the corticomedullary junction directly into the PTC, through the venules, and into the arcuate veins. Blood in the arcuate veins then flows through the interlobar veins, segmental veins, renal vein, and finally into the inferior vena cava (IVC). There is little further decrease in pressure, only 4–8 mmHg between the small intrarenal veins and the main renal vein [8]. The renal tubules consume significant oxygen when reabsorbing substances in the primary urine filtered by the glomerulus. Therefore, the capillaries after the efferent arteriole circulate as feeding vessels for the renal tubular cells. The pressure profile along the renal vasculature is shown in Fig. 2 [11].

Although 25% of cardiac output flows into the kidney, the distribution of blood flow within the kidney is uneven. As a result of its vascular and tubular anatomy, the kidney is hypoxic, especially in the renal medulla, where blood flow is less than in the cortex. The medulla is actively rendered hypoxic by a countercurrent mechanism whereby oxygen diffuses from the arteries into veins that run parallel to

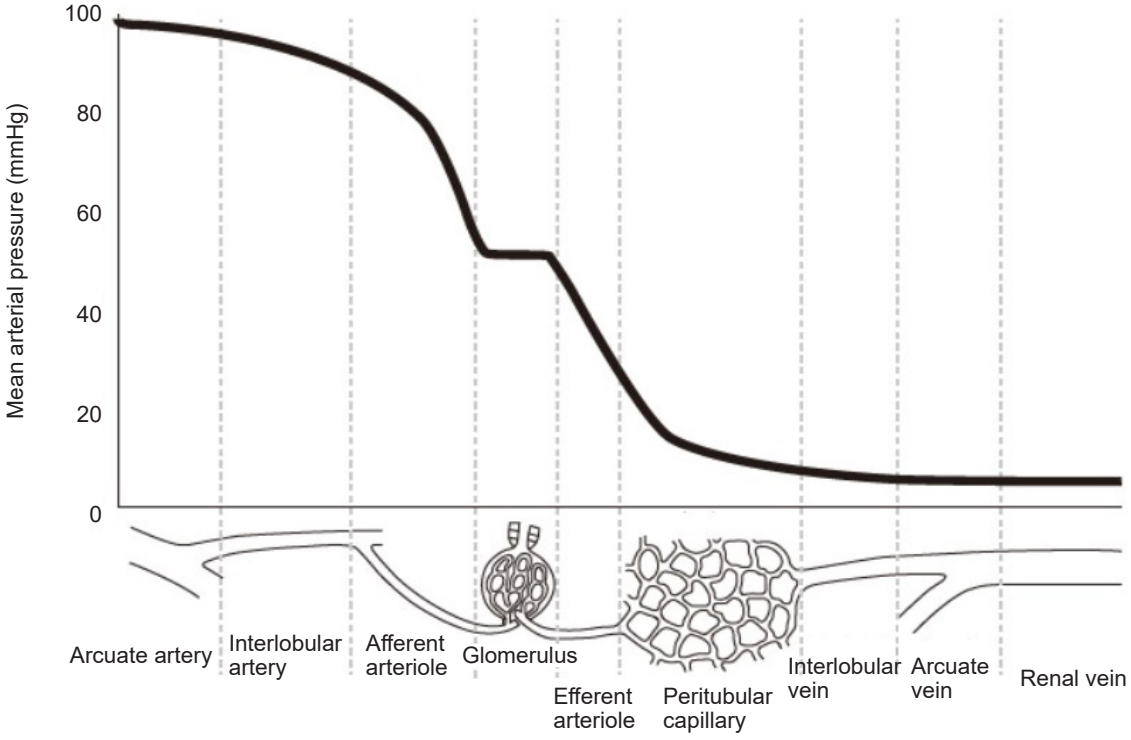

Figure 2. Hemodynamics and renal vasculature in a healthy kidney. Mean arterial pressure (MAP) is 100 mmHg in the arcuate artery and decreases to 50–60 mmHg in the glomerulus. Blood from the efferent arterioles flows into the peritubular capillaries and circulates in the tubule-interstitial area. MAP in the peritubular capillaries is further decreased. Finally, MAP decreases to single digits in the renal vein and inferior vena cava.

each other. Although the partial pressure of oxygen in the cortical renal tissue is 6.65–13.3 kPa (50–100 mmHg), it decreases with increasing depth, becoming as low as 1.3–2.9 kPa (9.8–21.8 mmHg) in the medulla, which is extremely hypoxic because of the high oxygen consumption in the renal tubules [12]. The collecting ducts and thin limbs of the loop of Henle, which are major tubules in the inner medulla, require little oxygen because they do not actively transport sodium. In contrast, the proximal tubules and thick ascending limbs in the outer medulla actively transport sodium and thus require large amounts of oxygen, indicating that the outer medulla is the region in the kidney most vulnerable to hypoxia. Na-K-2Cl cotransporters are present on the luminal side of the thick ascending limbs, and their activity is dependent on the concentration of sodium, which is pumped out of the tubules by basolateral Na-K ATPase. The Na-K ATPase activity is determined by oxygen-consuming mitochondrial adenosine triphosphate production. Furthermore, medullary blood flow accounts for no more than 10% of the total renal blood flow (RBF), and even small changes in medullary blood flow can cause hypoxia in the medulla [13,14]. The afferent arterioles in the glomerulus have an autoregulatory ability that maintains a constant glomerular blood flow and glomerular filtration rate (GFR) independent of renal perfusion pressure and is mediated by the myogenic response, tubuloglomerular feedback, the sympathetic nervous system, and the RAS.

Acute kidney injury caused by renal ischemia

Prerenal AKI accounts for ~70% of out-of-hospital AKI cases and ~40% of hospital-onset AKI cases. It is often associated with decreased intravascular volume as a result of gastrointestinal disease and bleeding or septic shock [15–17]. Therefore, it is important to confirm the dehydration status in the initial evaluation and to provide appropriate fluid replacement therapy. However, prerenal AKI is also present in pathologies in which RBF is reduced because of decreased cardiac output as a result of HF. Prerenal AKI associated with HF is classified as cardiorenal syndrome type 1 [18], which is thought to be caused by a decrease in RBF as a result of decreased cardiac output. However, no correlation has been found between the cardiac index and worsening renal function (WRF) during treatment of decompensated HF [3,4]. This finding suggests that a prerenal etiology of AKI, based on low forward flow, excessive diuresis, or excessive vasodilation, is unlikely to be the primary determinant of AKI. Patients with advanced HF and conditions such as hypertension and diabetes that contribute to development of intrinsic renal disease and disrupt renal autoregulation may be at increased risk for adverse outcomes [19]. In a study comparing the relationship between the cardiac index and GFR in patients with chronic HF, there was no significant difference in GFR between those with cardiac index of >2.0 L/min/m^2 vs. 1.5–2.0 L/min/m^2 (62 mL/min/1.73 m^2 vs. 67 mL/min/1.73 m^2) [20]. The GFR in the group with a cardiac index of <1.5 L/min/m^2 was 38 mL/min/1.73 m^2, which was significantly lower than that in the other groups. However, the filtration fraction, which is normally ~20%, increased to 35%, compensating for the decreased cardiac index and RBF in the group with a cardiac index of 1.5–2.0 L/min/m^2. This mechanism involved activation of the RAS by the juxtaglomerular apparatus and resistance in the efferent arterioles. However, a non-compensatory filtration fraction response was observed in the group with a cardiac index of <1.5 L/min/m^2, in which GFR was dependent on flow in the afferent arterioles despite stimulation of hemodynamic and hormonal pathways that would normally increase tone in the efferent arterioles [20]. Therefore, AKI in cardiorenal syndrome type 1 cannot be explained solely by decreases in the cardiac index and RBF. Indeed, GFR is maintained by renal autoregulation to some extent in response to changes in RBF. Even if the mean arterial pressure (MAP) increases from 75 to 160 mmHg, the GFR changes by less than 10% [21].

Additionally, the concept of normotensive ischemic AKI has been proposed as a pathological condition in which GFR is reduced and prerenal AKI develops, even in the absence of obvious hypotension [22]. The mechanism is considered to involve failure of renal autoregulation because of severe arteriosclerosis. Furthermore, renal tubular tissue damage in sepsis-related AKI has been thought to be the result of acute tubular necrosis due to renal ischemia caused by hypotension or renal vasoconstriction. However, a discrepancy between its pathophysiology and renal histopathology has been reported, and analysis of renal tissue specimens in particular has identified many cases of only mild tubular degeneration with no necrosis. Therefore, it is now believed that the main causes of this type of renal

damage are functional changes in microvessels and renal tubules associated with inflammation rather than structural changes [23]. Although blood pressure decreases in response to vasodilatation in the early stages of septic shock (i.e., "warm shock"), cardiac output is maintained. However, it has been confirmed that GFR decreases and RBF remains essentially unchanged or increases in this situation [24]. Therefore, the GFR is not thought to be determined by RBF but by dilatation of the afferent and efferent arterioles.

In patients with septic shock, guidelines for early goal-directed therapy recommend that the MAP be maintained at >65 mmHg because of the rapid decline in GFR that occurs when MAP decreases to <65 mmHg (Fig. 3) [21,25–28]. However, in patients with normotensive ischemic AKI, the target MAP may be set to an even higher level. A multicenter, randomized, controlled study was conducted in which patients with septic shock were divided according to target MAP of 65–70 or 80–85 mmHg. In patients with a history of hypertension, the group with MAP of 80–85 mmHg had significantly better renal survival in terms of doubling of serum creatinine level and the need for renal replacement therapy [29]. Therefore, even if the cardiac index and RBF decrease, GFR does not decrease, and a target MAP level of ≥65 mmHg is appropriate to prevent AKI. However, in patients with pre-existing severe atherosclerosis in the kidney, a target MAP of 80–85 mmHg may improve the renal prognosis.

Acute kidney injury caused by renal congestion

Renal congestion is now the focus of attention as the mechanism of AKI in acute HF. Renal congestion is a condition in which both central venous pressure (CVP) and intra-abdominal pressure (IAP) are elevated, resulting in retention of RBF because of elevated renal vein pressure. In a canine study in which the renal vein pressure was artificially increased from normal (4 mmHg) to a maximum of 25 mmHg, an increase in blood urea nitrogen level and a decrease in urine output were found when the renal vein pressure was increased to ≥20 mmHg. However, the blood urea nitrogen and urine output values returned to normal when the renal vein pressure was normalized [30]. Another study found that both CVP and renal vein pressure were higher in patients with congestive HF than in healthy subjects. Furthermore, in that study, pressure applied to the abdomen to raise the IAP to a mean of 20 mmHg in healthy subjects resulted in an increase in renal vein pressure from 5.8 to 18.3 mmHg and decreases in renal plasma flow, GFR, and urine output of 25%, 30%, and 50% from baseline, respectively [31].

Previous research has shown that renal venous congestion may contribute to the pathogenesis of cardiorenal failure [32]. Renal venous congestion has been shown to regulate RBF and sodium retention, with key factors of medullary blood flow and interstitial pressure. Renal interstitial fluid is produced by the medullary tubules, and one of its upstream origins is reabsorption from the collecting ducts into the venous capillaries in the cortex. Expansion of the kidney is limited because it is surrounded by Gerota's fascia. Congestion of renal interstitial flow and interstitial pressure can thus be increased by central or renal venous congestion [33,34]. An increase in interstitial hydrostatic pressure can lead to a reduction of medullary blood flow by

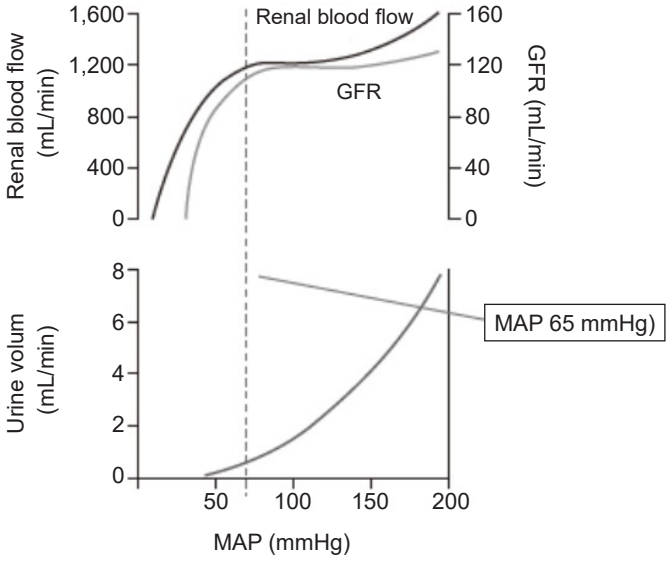

Figure 3. Relationships between MAP and blood flow in the kidney, GFR, and urine volume. In the upper panel the x-axis shows MAP, and the left and right y-axes show blood flow in the kidney and GFR, respectively. Urine volume is plotted against MAP in the lower panel. Blood flow in the kidney is associated with the GFR. When the MAP is >65 mmHg, normal GFR is maintained. However, when the MAP decreases to <65 mmHg, there is a rapid decrease in blood flow in the kidney and GFR, with a progressive decrease in urine volume.
GFR, glomerular filtration rate; MAP, mean arterial pressure.

compression of the venous capillaries, such as the vasa recta, and to a decrease in GFR by compression of the tubules. Therefore, the pressure in Bowman's capsule is increased because of compression of the lumens of the tubules [35]. The net filtration pressure at the glomerulus is determined by glomerular hydrostatic pressure minus the glomerular colloid osmotic pressure and the pressure in Bowman's capsule (Fig. 4). Thus, an increase in intratubular pressure causes an increase in Bowman's capsule pressure, which reduces the pressure gradient in the arterioles within the glomerulus and lowers the net filtration pressure, reducing the GFR.

Increased CVP is associated with a decrease in GFR and increased risk of mortality. A study in patients with cardiovascular disease found that the estimated GFR decreased when CVP exceeded 6 mmHg [4]. Another study involving 145 patients with advanced decompensated HF found that the CVP values at admission and after intensive care were significantly higher in patients with WRF, and that patients with a CVP of >8 mmHg were significantly more likely to have WRF [3]. Moreover, a decrease in CVP contributed to suppression of subsequent WRF, and there was no association of kidney function with impaired cardiac index at admission or improvement during hospitalization. The decline in GFR was not associated with systolic blood pressure or pulmonary capillary wedge pressure. Furthermore, a retrospective study in 178 patients with HF found that WRF was determined more by passive congestion than by reduced cardiac output [35]. Another study in patients with sepsis found that the mean CVP level was significantly higher in those who developed AKI than in those who did not (11 mmHg vs. 8.5 mmHg) [36]. Furthermore, there was a linear relationship between CVP level and risk of new or persistent AKI, even after adjustment for multiple variables. Most recent studies have confirmed the importance and independence of venous congestion as the primary hemodynamic cause of WRF [37–39]. It was also reported that there is no correlation between the cardiac index and GFR in patients awaiting cardiac transplantation [40].

Histopathological findings in an animal model of renal congestion

Renal congestion cannot be observed in conventional renal biopsy specimens because the blood vessels collapse during sample processing. Our group has examined the changes in the proximal tubules caused by renal congestion in a rodent model using an *in vivo* cryotechnique, whereby living tissue that is fully connected to the blood circulation is rapidly frozen *in vivo* and then excised [41]. Renal congestion was induced in both kidneys by ligating the IVC just above the branching renal veins (Fig. 5A). As

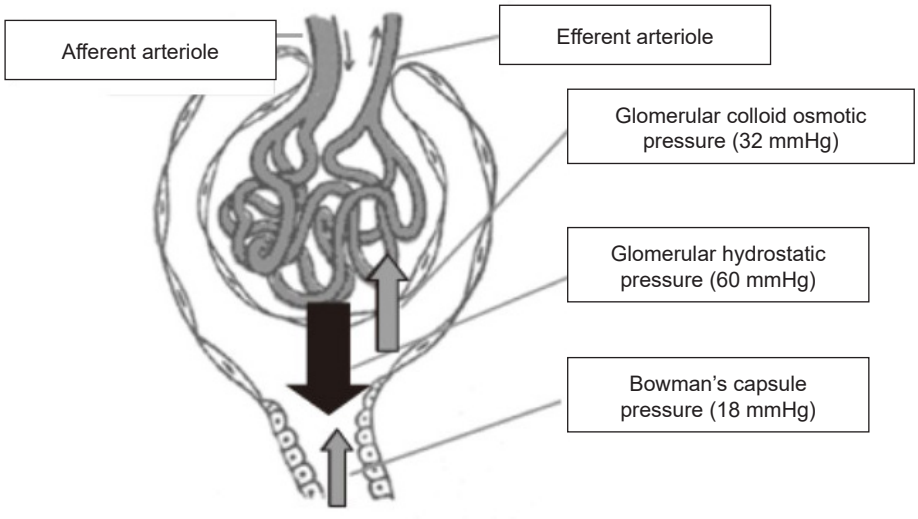

Figure 4. Glomerular hemodynamics. In the glomerulus, hydrostatic pressure is maintained at 60 mmHg, and colloid osmotic pressure is 32 mmHg. Bowman's capsule pressure, which is the internal pressure of the tubule, is 18 mmHg. Therefore, the net filtration pressure is 60 – 18 – 32 = 10 mmHg.

shown in Fig. 5B, the proximal tubules consisted of swollen cells, and in most cases, the lumens were closed by the *in vivo* cryotechnique. Many vacuoles were seen in the cytoplasm of cells in the proximal tubule and often contained cell debris. The interstitium was wide with dilated capillaries containing many erythrocytes, and marked basal striation was evident. However, as shown in Fig. 5C, the proximal tubule cells were swollen with indistinct lumens, the basal striation was unclear, the interstitium was narrow, and the PTC area could not be observed by conventional methods.

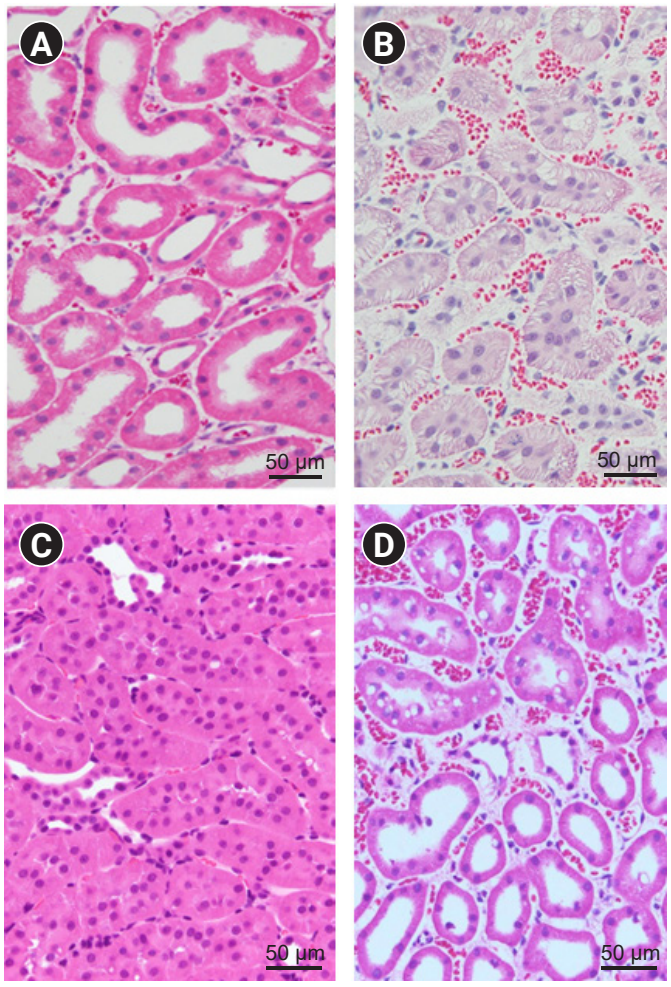

Figure 5. Light micrographs of samples from a normal control kidney and a model of renal congestion (H&E staining). (A) Findings in a normal control after using the *in vivo* cryotechnique. (B) After 5 minutes of inferior vena cava (IVC) clamping by the *in vivo* cryotechnique, the lumina are obstructed by swollen cells and ischemia-associated cell debris, and the peritubular capillaries can be confirmed. (C) After 5 minutes of IVC clamping by the conventional method, the tubular lumina are obstructed by swollen cells and ischemia-associated cell debris. However, peritubular capillaries cannot be confirmed. (D) After removing the IVC clamp, the renal congestion resolves, as can be seen by progression from the upper area to the lower area of the image. In the lower area, swollen cells have returned to cuboidal form, the cell debris has been removed from the tubular lumina, and the lumina are open.

Fig. 5D shows the findings after 5 minutes of congestion followed by 10 minutes of recirculation. After removing the IVC clamp, the renal congestion resolved and can be seen progressing from top to bottom in Fig. 5D. The proximal tubules shown in the upper area of this image are partially closed and contain small amounts of cell debris. However, in the lower area of this image, swollen cells have returned to their cuboidal form, the cell debris has been removed from the tubular lumina, and the lumina are open. These data demonstrate the importance of hemodynamics and suggest that renal dysfunction is reversible in many patients if the hemodynamics can be improved.

Rat models have demonstrated that elevated renal interstitial hydrostatic pressure caused by ureteral obstruction or aortic stenosis leads to renal injury [42–44]. A major cause of renal injury in these models has been fibrogenesis resulting from epithelial-mesenchymal transition [44,45]. The findings of another study in a subacute rodent model have suggested that increased renal interstitial hydrostatic pressure leads to compression of the PTC and renal tubules and detachment of pericytes because of multiple factors, including mechanical pressure, hypoxia, and reactive oxygen species [46]. Detachment of pericytes might be a trigger for pericyte-myofibroblast transition and cause expansion of the extracellular matrix. Therefore, it has been proposed that hypoxia, reactive oxygen species, and mechanical pressure can induce a pericyte-myofibroblast transition.

Pathophysiology of renal ischemia and renal congestion in acute kidney injury

Renal autoregulation is compromised when systemic blood pressure is decreased and renal perfusion pressure is <80 mmHg [20]. Therefore, left ventricular HF is thought to be related to reduced renal perfusion via diminished cardiac output, with underfilling of the arteries contributing to development of AKI in patients with HF [47]. Furthermore,

renal medullary blood flow decreases while ischemia and hypoxia increase in the outer medulla. Decreased renal perfusion pressure upregulates the sympathetic nervous system and the RAS. Angiotensin II and catecholamines further reduce renal plasma flow by inducing vasoconstriction of the glomerular arterioles [48]. However, angiotensin II constricts the efferent arterioles and increases intraglomerular pressure, maintaining GFR despite a decrease in renal plasma flow. Therefore, the filtration fraction and GFR are initially retained, although there is an eventual increase in the concentrations of angiotensin II and catecholamines. These increases result in enhanced preglomerular vasoconstriction, including in afferent arterioles, and lead to a decline in GFR [49,50]. This process activates reabsorption of sodium and water in the proximal tubules and leads to fluid retention.

In patients with right ventricular HF, increased CVP promotes renal congestion. In healthy subjects without HF or chronic kidney disease, a transient hypervolemic state leads to increased fluid and salt excretion, which result in decreases in both blood volume and cardiac output and a return of blood pressure to normal. However, in patients with HF, the elevated right atrial pressure and CVP resulting from hypervolemic conditions affect salt excretion by the kidneys, resulting in sodium retention and volume expansion [51]. Furthermore, decreases in medullary blood flow and GFR affect excretion of sodium and water during volume overload, and renal venous congestion reduces sodium and water excretion. Therefore, elevated renal venous pressure initiates a vicious cycle by causing sodium retention, plasma volume expansion, and further elevation of venous pressure (Fig. 6).

Higher systemic venous congestion leads to increased production of reactive oxygen species, tumor necrosis factor-α, endothelin-1, interleukin-6, vascular cell adhesion molecule-1, and intercellular adhesion molecule-1, which exacerbate endothelial dysfunction and dysregulation of nitric oxide, resulting in further neurohormonal activation and kidney injury [52–54]. Elevated IAP and congestion in the abdominal organs and interstitium may also contribute to renal congestion [55,56]. There is an inverse association between RBF and IAP. It has also been suggested that intra-abdominal venous hypertension may cause systemic hypotension and a decline in cardiac output [57]. Furthermore, alterations in the gut microbiota may be associated with AKI and renal congestion in patients with HF [58]. Entry of enterotoxins into the circulation may lead to further cardiac dysfunction and kidney injury because of intestinal barrier dysfunction resulting from congestion.

How should we assess renal congestion?

Renal congestion is often assessed by measurement of CVP [52,59]. The renal parenchyma is evaluated by ultrasonography, and a variety of indices of IVC diameter is used. However, no indices can be quantitatively evaluated with good reproducibility. Although we can use traditional markers, such as estimated GFR, and novel biomarkers, including cystatin C, neutrophil gelatinase-associated lipocalin, kidney injury molecule-1, and natriuretic peptides, which are useful for predicting the prognosis of HF and kidney dysfunction, none are specific for renal congestion. Natriuretic peptides are now routinely used, and high level of B-type natriuretic peptide (BNP) or N-terminal prohormone of BNP is associated with high filling pressures following volume overload [52]. BNP value has been shown to correlate with capillary wedge pressure and to serve as an indirect marker of renal dysfunction during treatment of acute HF [60]. However, natriuretic peptides are not specific for renal congestion and may reflect congestion specifically associated with HF.

Although there has long been a desire to use Doppler echocardiography for assessment of renal congestion, two studies have demonstrated that renal congestion can be assessed by intrarenal Doppler ultrasonography [61,62]. These studies assessed the arterial resistance index, venous impedance index, and intrarenal venous flow (IRVF) pattern in the interlobar arteries and veins and found that it was associated with mean right atrial pressure, suggesting a correlation with renal congestion. Furthermore, there was a significant association of the IRVF pattern with 1-year mortality. In recent years, ultrasonography has also been reported to be useful for assessment of renal congestion. Real-time contrast-enhanced ultrasonography (CEUS) is a novel imaging technique that can be used to visualize perfusion of the microvascular bed [63]. CEUS confirmed that impairment of renal parenchymal perfusion is accompanied by an increase in renal interstitial pressure in a rodent model of acute renal congestion. Furthermore, it has been reported that renal congestion can be evaluated by CEUS

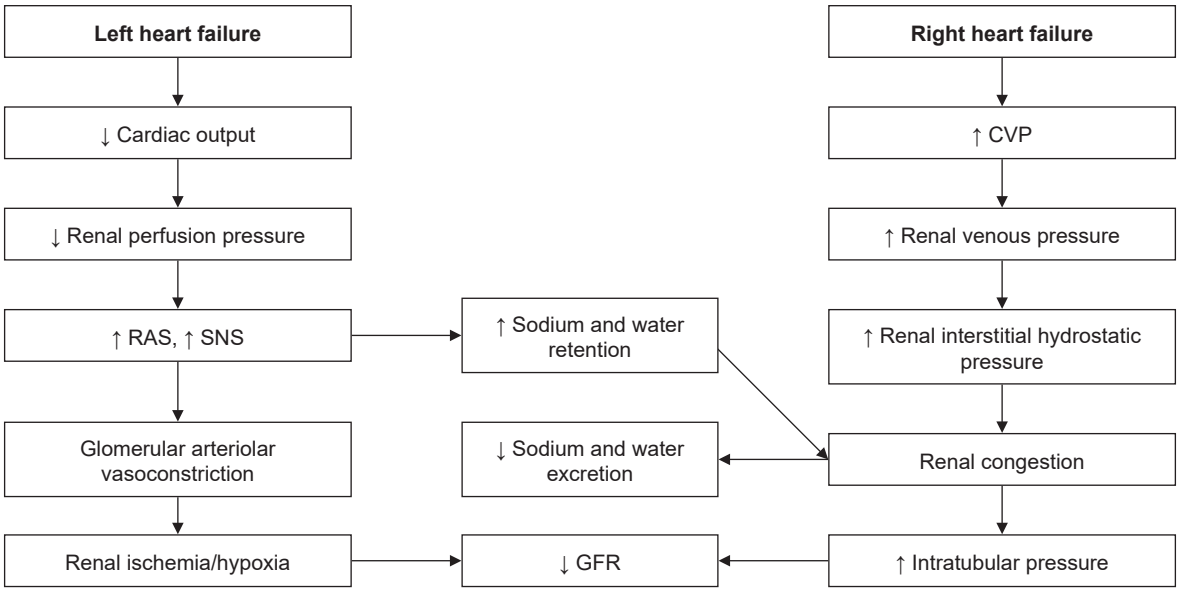

Figure 6. Mechanisms and pathophysiology of renal ischemia and renal congestion in HF. Left ventricular HF is related to reduced renal perfusion via diminished cardiac output. Decreased renal perfusion pressure upregulates the RAS and SNS. These increases result in enhanced vasoconstriction of afferent arterioles, and lead to a decline in GFR. This in turn activates proximal tubular sodium and water reabsorption, leading to more systemic and renal congestion. Right ventricular HF increases CVP and renal venous pressure. Renal congestion leads to increased renal interstitial pressure. Tubular compression raises the luminal pressure, further attenuating the transglomerular pressure gradient, and lowering the GFR. Renal congestion reduces sodium and water excretion. Therefore, elevated renal venous pressure initiates a vicious cycle by causing sodium retention, plasma volume expansion, and further elevation of venous pressure.
CVP, central venous pressure; GFR, glomerular filtration rate; HF, heart failure; RAS, renin-angiotensin system; SNS, sympathetic nerve system.

even in patients with HF, and that their renal congestion improves after treatment [64].

Treatment of renal congestion

Conventional diuretics

Water and salts filtered by the glomerulus are reabsorbed in several parts of the renal tubules, concentrating the urine. Approximately 70% of the filtered sodium is reabsorbed in the proximal tubules, 20% in the ascending loop of the limb of Henle, 7% in the distal tubules, and 3% in the collecting ducts. The effect of each diuretic is defined by sodium reabsorption at the active site of the renal tubules. From the viewpoint of natriuresis, loop diuretics have the strongest diuretic effect and are typically used to manage body fluid levels in patients with HF [65–68].

Loop diuretics inhibit the Na-K-2Cl cotransporter in the thick ascending limb of the Henle loop and increase sodium excretion. At the same time, loop diuretics increase the excretion of K^+, Ca^{2+}, Mg^{2+}, and titratable acid [69]. Loop diuretics are excreted into the tubular lumen via organic anion transporters in the proximal tubules and exert their effects as organic acids. Loop diuretics are absorbed from the intestine, are bound mainly to albumin, and are transported to the kidney. These diuretics are then secreted into the renal tubular lumen where they act on transporters from the renal tubular lumen side. The effects of loop diuretics are attenuated in patients with hypoalbuminemia because of a decrease in the concentration of serum albumin, which carries these agents to the proximal tubule. Furthermore, in patients with severe renal impairment and metabolic acidosis, excretion of loop diuretics into the lumen of the renal tubule via organic anion transporters is reduced, resulting in a decreased diuretic effect.

Administration of loop diuretics suppresses sodium

reabsorption in the loop of Henle, increasing the amount of sodium reaching the distal tubule and causing a compensatory increase in sodium reabsorption in the distal tubule. The distal tubules are expanded in a compensatory manner, leading to hypertrophy, and Na-K-2Cl cotransporter expression gradually increases [70]. As a result, the effects of loop diuretics are further decreased, and this is considered the main mechanism of diuretic resistance. Furthermore, loop diuretics increase the activity of vasoconstrictive mediators, including RAS, vasopressin, and catecholamine [71–74]. Administration of loop diuretics generally reduces RBF, particularly in the renal medulla. Therefore, the outer area of the medulla becomes more ischemic and the venous capillaries collapse despite ongoing renal congestion.

Higher doses of loop diuretics are reported to be associated with poor clinical outcomes, including WRF, in patients with HF [66,75]. Furthermore, it has been reported that the prognosis of patients with HF depends more on renal function than on the presence or absence of a history of myocardial infarction [76]. Therefore, correction of excess body fluid with maintenance of renal function is important during treatment of chronic HF.

There is controversy regarding whether administration of diuretics is harmful in patients with AKI. A recent report in 2022 suggested that use of diuretics was associated with worsening renal survival and mortality in patients with AKI [77]. In contrast, a meta-analysis found no association between use of diuretics and in-hospital mortality or need for renal replacement therapy in these patients [78]. However, higher doses of diuretics have been associated with increased risk of ototoxicity, including transient hearing loss and tinnitus [79].

The frequency of administration of loop diuretics is another issue. Theoretically, loop diuretics should be administered more frequently than twice a day or continuously. Furosemide has a short duration of action (<24 hours), and chronic administration leads to rebound sodium reabsorption. However, the Diuretic Optimization Strategies Evaluation trial found no difference between continuous therapy and bolus therapy [75,80]. Treatment with agents other than loop diuretics (e.g., thiazides or potassium-sparing diuretics) may be beneficial for decreasing activation of the RAS and the sympathetic nervous system and for reabsorption of sodium in the distal tubules [65].

Tolvaptan

Tolvaptan has been used in Japan for volume control in HF and decompensated cirrhosis with ascites. An aquaretic agent, tolvaptan has a mechanism of action that is different from that of the conventional natriuretics and is expected to overcome the disadvantages of loop diuretics. In patients with HF, furosemide decreases RBF and impairs renal function; switching to tolvaptan can attenuate the progression of renal dysfunction [78]. Unlike furosemide, tolvaptan does not cause a significant increase in plasma renin activity or vasopressin in patients with HF [81]. Intravascular volume is defined by serum osmotic pressure and colloid osmotic pressure. Tolvaptan increases free water excretion and serum osmolarity and promotes uptake of water from the interstitial fluid into capillaries [14]. These factors might be associated with maintenance of RBF despite a reduction in total body fluid. Therefore, tolvaptan can maintain RBF by preserving intracapillary volume. Furthermore, administration of tolvaptan has been shown to significantly reduce renal medullary pressure and CVP and improve renal dysfunction and renal fibrosis in Dahl salt-sensitive rats [82,83]. Tolvaptan blocks V2 receptors in the collecting ducts and inhibits reabsorption of water via aquaporin upstream of the interstitial fluid, which increases the renal interstitial hydrostatic pressure. Therefore, tolvaptan can reduce renal interstitial hydrostatic pressure by reducing interstitial fluid both upstream and downstream and may improve renal congestion by reducing volume.

A study in patients with HF and chronic kidney disease that included bioimpedance analysis has demonstrated that tolvaptan induces movement of water from inside cells to the extracellular space [84]. Therefore, there is increasing interest in tolvaptan as a treatment option for congestive HF, and positive effects on renal function have been reported in patients with advanced HF [85–87]. A randomized study that compared patients with new-onset acute HF receiving furosemide alone and those receiving furosemide with add-on tolvaptan has found a significantly lower incidence of WRF in the group that received add-on tolvaptan, especially in patients who had HF with reduced ejection fraction and renal impairment on admission [88]. Another randomized controlled study of 50 patients with HF and preserved ejection fraction has found greater improvement in congestive symptoms and better suppression of deteri-

oration of renal function in patients who received a combination of tolvaptan and loop diuretics than in those who received loop diuretics alone [89]. Therefore, many studies have demonstrated that tolvaptan has renoprotective effects in patients with HF regardless of whether ejection fraction. A meta-analysis has revealed that short-term add-on tolvaptan therapy can increase urine output, significantly reduce dyspnea, reduce body weight and edema, and increase serum sodium level compared to conventional diuretic therapy alone [90]. Furthermore, add-on tolvaptan therapy can significantly attenuate WRF and, when used in a low dose as add-on therapy (7.5–15 mg), significantly decrease the risk of WRF [90]. Tolvaptan is thought to exert a renoprotective effect by decreasing organ congestion while maintaining RBF without a significant reduction in circulating blood volume. Even in patients with stage G3–G5 chronic kidney disease, when the diuretic effect was not sufficient, use of add-on tolvaptan with regular furosemide was significantly associated with not only an increase in urine volume, but also a lower likelihood of developing AKI in comparison with only an increased dose of furosemide [91,92]. However, some studies have found that tolvaptan increases the incidence of WRF. The EVEREST (Efficacy of Vasopressin Antagonism in Heart Failure Outcome Study with Tolvaptan) study has found that tolvaptan mildly increased creatinine level, and the TACTICS (Targeting Acute Congestion with Tolvaptan in Congestive Heart Failure) study has reported that tolvaptan increased WRF [87,93,94]. Most studies of tolvaptan have been conducted in North America or Japan, and there are clear geographic disparities in the findings of these randomized controlled trials. The studies in Japan were carried out using low doses of tolvaptan (7.5–15 mg), whereas the North American studies used high doses [90,95]. A clear renoprotective effect has been observed at low doses but not at high doses.

Conventional diuretics can improve congestion rapidly but decrease the circulating blood volume, which leads to decreased RBF and impaired renal function and further activates the RAS and sympathetic nervous system [96]. There is a positive correlation between WRF and the dose of furosemide [97]. Therefore, the improvement in renal function resulting from add-on tolvaptan therapy can be attributed to a reduced dose of loop diuretic. Given that tolvaptan acts at the collecting duct, it is important to use a loop diuretic that suppresses reabsorption of water and sodium upstream (i.e., in the loop of Henle), allowing more primary urine to reach the collecting duct.

Ultrafiltration

Several guidelines state that ultrafiltration is a reasonable approach for patients with congestion refractory to diuretic therapy [98,99]. The UNLOAD (Ultrafiltration Versus Intravenous Diuretics for Patients Hospitalized for Acute Decompensated Heart Failure) trial compared the efficacy of diuretics with that of ultrafiltration in patients with congestive HF and found no significant between-group difference in congestive symptoms, prognosis, electrolytes other than potassium, or renal function [100]. However, after 48 hours, loss of body weight and fluid was significantly greater in the ultrafiltration group than in the diuretic group. Furthermore, there were fewer rehospitalizations and unscheduled hospital visits in the ultrafiltration group. Hypokalemia was significantly more common in the diuretic group. Another randomized controlled trial (CARRESS-HF [Cardiorenal Rescue Study in Acute Decompensated Heart Failure]) compared the efficacy of ultrafiltration with that of diuretics in patients with acute decompensated HF and WRF [101]. Although there was no between-group difference in changes in body weight, rehospitalization rate, or prognosis after 96 hours, there was less deterioration of renal function in the diuretic group. However, the average changes in serum creatinine levels was –0.04 mg/dL in the diuretic group and +0.23 mg/dL in the ultrafiltration group, and whether this difference is clinically significant requires further consideration. Furthermore, in CARRESS-HF, efficient stepwise pharmacologic therapy was less reasonably applied and compared with ultrafiltration delivered at a fixed rate of 200 mL/hr. The results of the subsequent CUORE (Continuous Ultrafiltration for Congestive Heart Failure) trial, which is the longest follow-up study of ultrafiltration in patients with congestive HF, were consistent with those of the UNLOAD trial [100]. In the CUORE trial, renal function was more stable in older patients with more severely depressed GFR in the ultrafiltration group than in their counterparts in the diuretic group. Furthermore, the incidence of readmission for HF was significantly lower in the ultrafiltration group [102].

It has also been reported that super high-flux membrane dialyzers can remove cytokines and inflammatory medi-

ators and improve cardiac function [103–105]. In Japan, continuous renal replacement therapy (CRRT) with a super high-flux dialyzer is used for acute blood purification [106]. Further research is needed to determine whether this modality is indicated in patients with HF.

Which should be prioritized–improvement of renal ischemia or relief of renal congestion?

The most common cause of right HF is prolonged left HF. Therefore, bilateral HF may be complicated by both renal ischemia and renal congestion. However, when renal ischemia and renal congestion coexist, it is unclear which should be prioritized. In patients with low cardiac output, CVP is an independent predictor of AKI. Furthermore, development of AKI in patients with HF is more strongly associated with venous congestion than with low cardiac output. Therefore, priority should be given to renal congestion. GFR can be increased by decreasing the renal interstitial pressure, which will decompress vessels and tubules in the renal medulla. Even at a low renal perfusion pressure, blood flow can resume in the PTC region, suggesting the possibility of recovery of kidney function.

Patients with HF and AKI who are resistant to diuretics are often treated by CRRT, in which a double-lumen dialysis catheter is inserted into the femoral vein or internal jugular vein. Although CRRT is administered on the assumption that treatment will be continued for 24 hours or longer, some patients show an increase in urine output several hours after initiation. The mechanism of this effect is thought to be relief of renal congestion when the blood in the IVC is moved to the extracorporeal circuit. In such patients, CRRT with a fixed fluid removal rate needlessly induces renal ischemia, which leads to prerenal kidney injury and a prolonged time until renal recovery. Therefore, CRRT could be discontinued in patients with an increased urine output a few hours after initiation of CRRT.

Future perspective for diagnosis and treatment of renal congestion

Renal congestion is a major factor in AKI in patients with HF and worsens the outcome of patients with HF. However, because renal congestion cannot be measured directly, it is difficult to detect and treat rapidly. It is necessary, therefore, to establish an easier approach than CVP measurement, such as using biomarkers and image diagnosis. Although a variety of therapeutic strategies for renal congestion has been used alone and in combination, no specific treatment strategies have been established. The pathophysiology of renal congestion is not fully understood. Multiple pathways are involved in renal congestion, and the factors may vary between patients. Therefore, an individualized diagnosis that focuses on prevention of AKI and improvement of renal congestion may be necessary. Further randomized clinical trials are needed to investigate the feasibility of diagnostic imaging and biomarkers for detection of renal congestion, determination of optimal treatment options, and individualization of treatment strategies.

Conclusions

First, patients with HF and AKI should be evaluated for fluid overload status. Appropriate fluid correction with diuretics may be effective in patients with congestion. Renal ischemia is the main cause of AKI in patients with HF, in whom administration of diuretics leads to a decrease in kidney function. However, when kidney function improves in patients with HF after administration of diuretics, the main cause of AKI is renal congestion. Loop diuretics are likely to cause hyponatremia, whereas tolvaptan alone is likely to cause hypernatremia. However, tolvaptan is usually administered with loop diuretics, so abnormal serum sodium concentration is unlikely to be encountered in clinical practice. In view of its ability to decrease renal congestion and improve renal hypoxia, tolvaptan may have an important role in reducing the risk of AKI in patients with HF.

Conflicts of interest

All authors have no conflicts of interest to declare.

Data sharing statement

The data presented in this study are available on request from the corresponding author.

Authors' contributions

Conceptualization, Investigation: MA, SH
Data curation: SH
Methodology, Project administration: MA
Supervision: HK
Writing–original draft: MA, SH
Writing–review & editing: HK
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