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COMMENT

Sodium glucose cotransporter 2 inhibitor as a promising therapy for congestive kidney injury

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Heart failure is a major health burden that causes high morbidity and mortality rates. Heart failure often coexists with numerous comorbidities and has direct consequences for other organs, especially the kidneys [1]. Furthermore, worsening of the kidney function and acute kidney injury (AKI) are associated with increased mortality in patients with heart failure [2]. The question of how AKI occurs in the setting of heart failure still remains to be completely elucidated. Reduced cardiac output causes a significant decrease in kidney blood supply [3]. Decreased kidney blood supply induces activation of the renin-angiotensin-aldosterone system and sympathetic nervous system, contributing to systemic vasoconstriction and further decreasing kidney blood supply. Maladaptive conditions triggered by low cardiac output have long been believed to play an important role in the development of kidney injury in patients with heart failure. However, Mullens et al. reported that kidney congestion detected by increased central venous pressure is the most important determinant of the development of worsening of the kidney function, independent of the cardiac output index, in patients with advanced decompensated heart failure [4]. Since the kidneys are enveloped by a tight capsule, increased central/kidney venous pressure results in attenuation of the transglomerular pressure gradient and subsequent lowering of the glomerular filtration rate [5, 6]. Furthermore, kidney venous congestion possibly induces multiple mechanisms, such as local hypoxia, inflammation, and endothelial activation, which contribute to further kidney injury [6]. The concept that kidney congestion plays a pivotal role in the development of AKI in heart failure is now widely accepted.

In this issue of *Hypertension Research*, Endo et al. investigated the protective effect of a sodium glucose cotransporter 2 inhibitor (SGLT2), tofogliflozin, in a rat hemi-renal vein congestion model induced by inferior vena cava (IVC) ligation between renal veins [7]. The authors recently developed a novel rat model of AKI [8]. IVC ligation between renal veins can induce an acute increase in pressure of the left renal vein and AKI, including decreased urine output, tubulointerstitial fibrosis and podocyte injury, which is attenuated by stripping the kidney capsule. A microarray analysis revealed increases in extracellular factors, notably extracellular matrix expansion and tubular injury, and decreases in the regulation of vasoconstriction in congestive kidneys. Furthermore, the authors found that transgelin and platelet-derived growth factor receptors, which are both responsible for pericyte-myofibroblast transition, were highly expressed in the pericytes and surrounding interstitial cells of congestive kidneys in comparison to control kidneys. Additionally, pericyte detachment with expansion of the vasa recta was observed in congestive kidneys, but not in control kidneys. These results provide novel insights into the possible role of the pericyte-mesenchymal transition in the pathogenesis of kidney congestion. The current IVC ligation model has some advantages over standard experimental models for cardiorenal syndrome, such as high salt-loaded Dahl salt-sensitive rats or DOCA salt rats [9]. First, in this model, selective elevation of left kidney vein pressure can be induced. The major advantage of the current model is that arterial underfilling and subsequent compensating factors, such as the activated renin-angiotensin-aldosterone system, sympathetic nervous system, and neurohormonal peptide,

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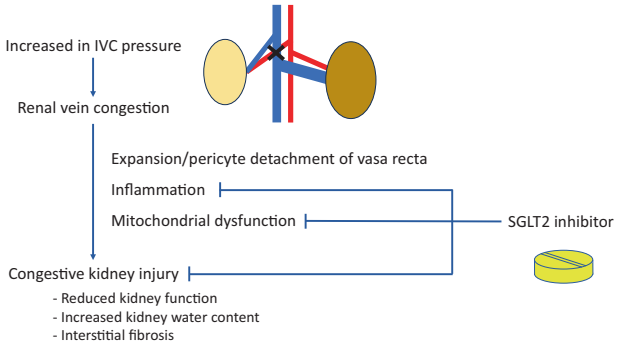

Fig. 1 Schematic illustration of the study concept. Renal vein congestion induced by IVC ligation results in congestive kidney injury, including kidney dysfunction, increased kidney water content, and kidney interstitial fibrosis. The development of congestive kidney injury due to increased pressure of the renal vein is associated with multiple mechanisms, including expansion of the vasa recta, pericyte detachment in the vasa recta, kidney tubulointerstitial inflammation, and mitochondrial dysfunction. The SGLT2 inhibitor tofogliflozin attenuates congestive kidney injury possibly via the amelioration of kidney inflammation and mitochondrial dysfunction. IVC inferior vena cava, SGLT2 sodium glucose cotransporter 2

are preferably omitted. Thus, we can observe a pure effect of the predominant kidney congestion on kidney injury in the current model. Second, the pressure of the left vein increased to approximately 20 mmHg immediately after ligation and decreased to approximately 10 mmHg on postoperative day 3, possibly due to the formation of collateral circulation. Therefore, the IVC ligation model is preferable for evaluating pathophysiology in the acute phase of congestive kidney failure. In the present study [7], Endo et al. confirmed that the kidney weight and percentage of water content (defined as the difference between wet kidney weight immediately after sacrifice and dry kidney weight after drying up), kidney interstitial fibrosis, increased profibrotic and proinflammatory markers, and reduced mitochondrial markers with an abnormal mitochondrial structure in the left congested kidney at 3 days after surgery. The authors confirmed that the phenotypes induced by IVC ligation were improved by short-term tofogliflozin treatment (from the day before IVC ligation until 2 days after IVC ligation). Although tofogliflozin treatment attenuated the enhanced expression of transgelin and platelet-derived growth factor receptor B in the congested kidney, it did not affect the expansion of the vasa recta or the detachment of pericytes. As the authors pointed out, further experiments using a chronic kidney congestion model may be needed to evaluate the effects of SGLT2 inhibitors on long-term kidney congestion. Additionally, studies to confirm the pleiotropic effects of SGLT2 inhibitors to standard diuretics in patients with congestive kidney injury are promising Fig. 1.

In the past decade, numerous randomized control trials and real-world studies have shown that SGLT2 inhibitors improve mortality, cardiovascular events (especially heart failure), and kidney outcomes in patients with chronic diseases, including diabetes, CKD with albuminuria, and heart failure [10]. More recently, population-based studies revealed that the use of SGLT2 inhibitors was associated with a lower incidence of AKI in patients with diabetes [11, 12]. The EMPALSE study showed that the initiation of SGLT2 inhibitor treatment in hospitalized patients with acute heart failure resulted in a statistically significant and clinically meaningful benefit within 90 days after randomization [13]. These studies suggested that the therapeutic target of SGLT2 inhibitors has expanded not only in patients with chronic-phase of diseases, but also in those with acute-phase diseases, such as AKI or acute heart failure. Further studies to assess the utility of SGLT2 inhibitors and elucidate their related mechanisms in AKI and acute heart failure would provide clinically useful insights.

Compliance with ethical standards

Conflict of interest The authors declare no competing interests.

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