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COMMENT

Renal venous hypertension to the regulation of pressure natriuresis in heart failure

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Keywords Heart failure · Renal medullary blood flow · Pressure natriuresis · Renal venous hypertension · Renal venous congestion

Pressure natriuresis relationship is well established by Author Guyton and his associates [1]. This mechanism play an important role in the blood pressure and body fluid control. Elevation of systemic blood pressure and body fluid increases renal blood pressure and stimulates urinary Na excretion thereby reduces bloody fluid and blood pressure. If pressure natriuresis is well maintained, blood pressure and body fluid should be well controlled.

Renal circulation has a unique morphology and function to regulate the pressure natriuresis. Autoregulation of total renal flow as well as cortical blood flow and glomerular filtration rate (GFR) is well maintained as shown by Romero et al. [2]. This mechanism helps maintaining glomerular and tubular function, urine volume and homeostasis. Then where does the kidney sense the change in blood pressure?

Renal medullary blood flow is about 10% or less of total renal blood flow [3]. Vasa recta plays a major role in regulation of the medullary blood flow. With its unique loop morphology, ascending and descending vasa recta sits side by side and oxygen is stolen from descending vasa recta to ascending vasa recta, which results in the hypoxia of renal medulla.

In contrast to the autoregulation of total and cortical blood flow together with GFR, medullary blood flow is well influenced by renal perfusion pressure [3]. There are numerous genes controlled under hypoxia inducible factors, such as erythropoietin, fibrotic factors, vascular endothelial growth factor and reactive oxygen species elements. Therefore, renal medulla plays an important role in the circulatory and oxygen sensors.

Cowley Jr. and his associates have established the role of medullary circulation to the regulation of pressure natriuresis [4]. Elevation of renal perfusion pressure increases medullary blood flow and vasa recta capillary pressure. Increase in vasa recta capillary pressure enhances interstitial hydrostatic pressure which could expand to the cortex. Elevated hydrostatic pressures in the cortex increases peritubular capillary pressure, thereby reduces Na reabsorption in the proximal tubules [5].

Tubules in the renal outer medulla such as thick ascending limb of Henle consumes oxygen to produce ATP in the mitochondria to activate Na-K ATPase pump and stimulate Na-K-2Cl cotransporter, which plays a major role in the reabsorption of NaCl and tubuloglomerular feedback [6]. Therefore, renal medullary tubules require oxygen in the limited blood flow and low oxygen. These tubules can synthesize nitric oxide and diffuse into surrounding vasa recta on the physiological range of vasoconstrictive substances such as angiotensin II. Physiological dose of angiotensin II does not reduce medullary blood flow and alter blood pressure. However, same dose of angiotensin II stimulates superoxide and blunt the diffusion of nitric oxide from tubules to vasa recta and reduces medullary blood flow and Na excretion in Dahl salt sensitive rats, thereby increases blood pressure [7]. Enhanced medullary oxidative stress expected to blunt pressure natriuresis which involve in the regulation of blood pressure and body fluid volume. In addition, increase in renal perfusion pressure or tubular salt loading also stimulates oxidative stress in the renal medulla which could also influence pressure natriuresis (Fig. 1A) [8].

Reduced Na excretion and worthening renal function is commonly observed in heart failure. Reduced renal function enhances volume overload and worthen the pathogenesis of

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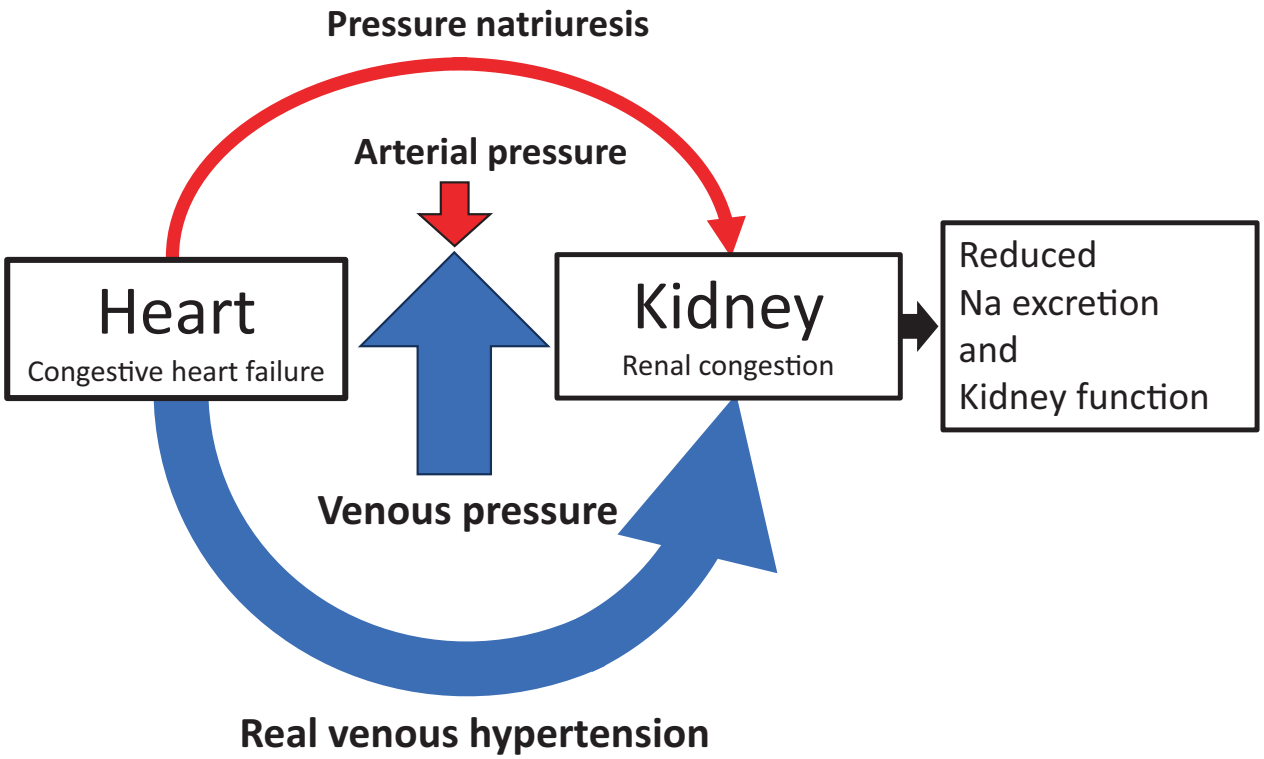
Graphical Opinion

Pressure natriuresis is reduced by renal venous hypertension in congestive heart failure.



heart failure. This cardiorenal connection mechanism and the underlining intrarenal circulation is still not fully understood.

With these backgrounds, Honetschlägerová et al. reports the role of heart failure in renal autoregulation and pressure natriuresis relationship [9]. They have found that autoregulatory capacity of renal blood flow and pressure natriuresis is well preserved in the model of aorto-caval fistula (ACF) (Fig. 1B). Cardiomyocyte is influenced by ACF, indicating the presence of heart failure. Although ACF in Ren-2 transgenic rats (TGR) demonstrated lower arterial pressure, renal blood flow urinaly flow and urinary Na excretion compared to sham operated TGR, well maintained autoregulatory capacity and improved slope of the pressure natriuresis relationship was observed. The balance between renal aortic pressure and those of venous pressure requires attention and may have influenced to the pressure natriuresis. We have recently established a model of renal congestion by ligation of inferior vena cava between renal veins. In this model, we have observed the increase in renal interstitial hydrostatic pressure, reduction of urine volume and renal medullary blood flow [10]. As shown in Fig. 1A, congestion of renal vein by heart failure reduces medullary blood flow and blunt pressure natriuresis. In addition, pericyte detachment associated with myofibroblast transition was observed in the renal congestive kidney which could explain the pathogenesis of worthening renal function in heart failure [11].

The major difference between ACF and venous ligation model is the presence of reduction of renal perfusion pressure and neurohormonal factors by heart failure. Pericyte detachment and pericyte myofibroblast transition with renal fibrosis are observed with reduced urinary Na excretion, medullary blood flow and increase in blood pressure of high salt fed Dahl salt sensitive rats [12]. Pericyte detachment and renal fibrosis was recovered by decapsulation, indicating that renal interstitial hydrostatic pressure is playing important role in the worsening renal function in renal venous congestion model. Renal pericyte detachment was also observed in autopsy patients with heart failure [12]. Together with the renal arterial pressure, renal venous congestion also play an important role in sodium excretion and renal injury in heart failure [13, 14].

Although TGR with ACF and salt fed Dahl salt sensitive rats are both rat model of hypertensive heart failure, there are several mechanisms that is different in TGR with ACF compared to Dahl salt sensitive rats. First, systemic plasma renin activity is lowered in salt fed Dahl salt sensitive rats.

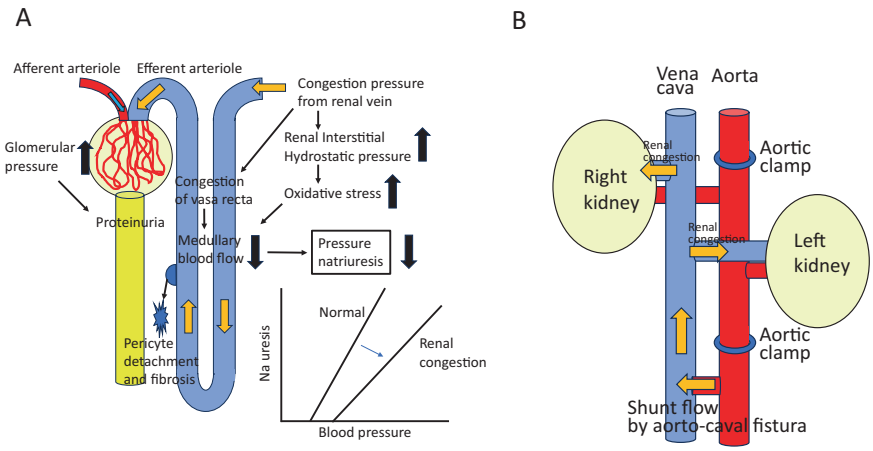


Fig. 1 Illustration of mechanisms proposed for heart failure induced renal congestion and pressure natriuresis. **A** Blunted pressure natriuresis by reduction of medullary blood flow by renal venous congestion. **B** Renal congestion by aorto-caval fistura

Second, systemic volume overload is expected to be higher in Dahl salt sensitive rats. Therefore, the results could be different if salt was loaded in TGR with ACF. Finally, there are technical issue that should be acknowledged. The experiment by Honetschlägerová et al. [9] reduced renal perfusion pressure by clamping of aorta above supra-mensentric artery or below left renal artery blanch. These are both expected to be above ACF as shown in Fig. 1B. Therefore, the flow of ACF could be reduced by aorta clamping, which could reduce renal venous pressure. Reduction of renal venous pressure could alter pressure natriuresis. Effect of changes in ACF by aorta clamping to the pressure natriuresis should be examined in the future study.

Pressure natriuresis is originally considered in a clinical state of arterial hypertension and urinary Na excretion. Venous hypertension such as volume overload and congestive heart failure should also be considered to the pathogenesis of pressure naturiuresis.

Compliance with ethical standards

Conflict of interest The authors declare no competing interests. The author reports lecture fees from Otsuka Pharmaceuticals, and endowed course support by Termo and JMS company.

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References

1. Guyton AC. Long-term arterial pressure control: an analysis from animal experiments and computer and graphic models. Am J Physiol. 1990;259:R865–R877.
2. Romero JC, Knox FG. Mechanisms underlying pressure-related natriuresis: the role of the renin-angiotensin and prostaglandin systems. State of the art lecture. Hypertension. 1988;11:724–38.
3. Cowley AW Jr. Role of the renal medulla in volume and arterial pressure regulation. Am J Physiol. 1997;273:R1–R15.
4. Cowley AW Jr. Renal medullary oxidative stress, pressure-natriuresis, and hypertension. Hypertension. 2008;52:777–86.
5. Cowley AW Jr. Long-term control of arterial blood pressure. Physiol Rev. 1992;72:231–300.
6. Kiroytcheva M, Cheval L, Carranza ML, Martin PY, Favre H, Doucet A, et al. Effect of cAMP on the activity and the phosphorylation of Na+,K(+)-ATPase in rat thick ascending limb of Henle. Kidney Int. 1999;55:1819–31.
7. Mori T, O'Connor PM, Abe M, Cowley AW Jr. Enhanced superoxide production in renal outer medulla of Dahl salt-sensitive rats reduces nitric oxide tubular-vascular cross-talk. Hypertension. 2007;49:1336–41.
8. Mori T, Ogawa S, Cowely AW Jr, Ito S. Role of renal medullary oxidative and/or carbonyl stress in salt-sensitive hypertension and diabetes. Clin Exp Pharm Physiol. 2012;39:125–31.
9. Honetschlägerová Z, Sadowski J, Kompanowska-Jezierska E, Maxová H, Táborský M, Kujal P, et al. Impaired renal autoregulation and pressure-natriuresis: any role in the development of heart failure in normotensive and angiotensin II-dependent hypertensive rats? Hypertens Res. 2023;46:2340–55.
10. Shimada S, Hirose T, Takahashi C, Sato E, Kinugasa S, Ohsaki Y, et al. Pathophysiological and molecular mechanisms involved in renal congestion in a novel rat model. Sci Rep. 2018;8:16808.
11. Matsuki T, Hirose T, Ohsaki Y, Shimada S, Endo A, Ito H, et al. Inhibition of platelet-derived growth factor pathway suppresses tubulointerstitial injury in renal congestion. J Hypertens. 2022;40:1935–49.
12. Ito H, Hirose T, Sato S, Takahashi C, Ishikawa R, Endo A, et al. Pericyte detachment and renal congestion involve interstitial injury and fibrosis in Dahl salt-sensitive rats and humans with heart failure. Hypertens Res. 2023;46:2705–17.
13. Ross EA. Congestive renal failure: the pathophysiology and treatment of renal venous hypertension. J Card Fail. 2012;18:930–8.
14. Mori T, Ohsaki Y, Oba-Yabana I, Ito S. Diuretic usage for protection against end-organ damage in liver cirrhosis and heart failure. Hepatol Res. 2017;47:11–22.