Review

Water and Sodium Regulation in Heart Failure

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Heart failure is the pathophysiological state characterized by ventricular dysfunction and associated clinical symptoms. Decreased cardiac output or peripheral vascular resistance lead to arterial underfilling. That is an important signal which triggers multiple neurohormonal systems to maintain adequate arterial pressure and peripheral perfusion of the vital organs. The kidney is the principal organ affected when cardiac output declines. Alterations of hemodynamics and neurohormonal systems in heart failure result in renal sodium and water retention. Activation of sympathetic nervous system, renin-angiotensin-aldosterone system and non-osmotic vasopressin release stimulate the renal tubular reabsorption of sodium and water. Dysregulation of aquaporin-2 and sodium transporters also play an important role in the pathogenesis of renal sodium and water retention.

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Introduction

Heart failure is the pathophysiological state characterized by ventricular dysfunction and associated clinical symptoms. It is a major cause of cardiovascular mortality and morbidity[1]. Decreased systolic or diastolic cardiac function results in abnormal circulatory hemodynamics, activation of a variety of neurohormonal systems and retention of sodium and water[2]. The integrity of the arterial circulation is determined by cardiac output and peripheral vascular resistance. Decrease in cardiac output or peripheral arterial vasodilatation causes arterial underfilling. That is an important signal which triggers multiple neurohormonal systems to maintain adequate arterial pressure and peripheral perfusion of the vital organs[3]. The kidney is the principal organ affected when cardiac output declines. The kidney plays an important role in the maintenance of body fluid volume which is regulated by multiple neurohormonal systems. Alterations of hemodynamics and neurohormonal systems in heart failure result in renal sodium and water retention[4]. This review discusses the pathophysiologic mechanisms of sodium and water retention in heart failure.

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Activation of neurohormonal systems

In heart failure, the sympathetic nervous system (SNS) is activated. It has been demonstrated by an increase in plasma concentrations of catecholamine in patients with heart failure[5, 6]. Increased catecholamine secretion plays a role in the maintenance of blood pressure in heart failure. In addition, activation of SNS contributes to renal sodium and water retention in heart failure. In the kidney, SNS plays a stimulatory role in renal tubular reabsorption of sodium and water[7]. Previous studies have demonstrated a direct effect of renal nerve activation on renal sodium and water reabsorption across the proximal tubular epithelium. Adrenergic innervations in the basement mem-

brane of renal tubular epithelial cells were demonstrated[8, 9]. Low-frequency electrical stimulation of the renal nerves resulted in an antidiuretic and antinatriuretic response in the absence of changes in glomerular filtration rate (GFR) or renal plasma flow[8]. Moreover, the protein expression of aquaporin (AQP) water channels was decreased in the denervated kidney[10]. Renal denervation decreased sodium and water retention in experimental heart failure[11]. In addition, the activation of renal nerves stimulates the renin-angiotensin-aldosterone system (RAAS) by stimulating renin release[3, 12].

In heart failure, the RAAS is stimulated. Plasma renin activity, angiotensin II and aldosterone concentrations are increased[13]. Angiotensin II is an important mediator of sodium and water retention in patients with heart failure. Angiotensin II directly enhances proximal tubular reabsorption of sodium and water[14]. Angiotensin II receptor blocker treatment resulted in natriuresis in experimental heart failure[15]. In addition, it was demonstrated that aldosterone antagonist spironolactone increased urinary sodium excretion in patients with heart failure[16].

In the kidney, natriuretic peptides (NPs) increase the GFR and urinary sodium excretion by afferent arteriolar vasodilation and efferent arteriolar constriction[17]. Moreover, NPs inhibit sodium and water reabsorption induced by angiotensin II action in the proximal tubule and they directly inhibit sodium reabsorption in the collecting duct[18, 19]. NPs also inhibit renin release and aldosterone synthesis[20]. The NPs are increased in heart failure[21, 22]. However, the renal responses of NPs were blunted in patients with heart failure[23]. The resistance may be due to down-regulation of renal NP receptors, secretion of inactive immunoreactive NPs, increased degradation of NPs by neutral endopeptidase in the proximal tubule or decreased sodium delivery to the collecting duct as a result of increased sodium reabsorption in the proximal tubule[3].

Arginine vasopressin (AVP) is an antidiuretic hormone which is synthesized in the hypothalamus, stored in the posterior pituitary gland and released in response to increased osmolality or volume depletion. In the kidney, AVP causes antidiuresis by activating vasopressin V2 receptors on the basolateral membrane of the principal cells in the collecting duct. This process results in passive water reabsorption along the osmotic gradient. In heart failure, AVP secretion occurs despite a normal or even low plasma osmolality (non-osmotic AVP release)[24]. Arterial underfilling in heart failure contributes to the breakdown of baroreceptor-mediated suppression of AVP. In addition, angiotensin II stimulates the release of AVP by the stimulation of the thirst center of the brain[3, 12]. Thus, the dysregulation of AVP plays an important role in the development of hypoosmolar hyponatremia in patients with heart failure.

Dysregulation of AQP and sodium transporters

In the kidney, AQP water channels allow the movement of water across the tubular epithelium. AQP1 is abundant in the proximal tubule and descending thin limb and is essential for urinary concentration[25]. AQP2 is exclusively expressed in the principal cells of the connecting tubule and collecting duct[26]. It is regulated in the short-term and long-term by the AVP/Cyclic adenosine monophosphate (cAMP) pathway to increase osmotic water reabsorption[27, 28]. AQP3 is present in the basolateral membranes of collecting duct principal cells and represents exit pathways of water reabsorbed via AQP2 in the apical membranes[29].

In experimental heart failure, up-regulation of AQP2 has been documented. Nielsen et al. reported increased expression and targeting of AQP2 in association with hyponatremia in experimental heart failure[30]. Xu et al. also demonstrated up-regulation of AQP2 in chronic heart failure rats[31]. In this study, the expression of AQP2 massenger RNA and protein was increased in associated to increased plasma AVP levels in heart failure rats. V2 receptor antagonist treatment induced a significant diuresis, decrease in urinary osmolality and increase in plasma osmolality in heart failure rats. Up regulation of AQP2 in heart failure is inhibited by the treatment of V2 receptor antagonist. Moreover, it was demonstrated that V2 receptor antagonism decreases urinary AQP2 excretion in patients with chronic heart failure[32]. These results suggest that upregulation of vasopressin and AQP2 plays an important role in

the development of water retention and hyponatremia in heart failure.

The renal sodium transporters play a critical role in the sodium reabsorption and regulation of extracellular fluid volume. The renal tubular sodium reabsorption is basically linked to the activity of Na^+,K^+-ATPase that is heavily expressed in the basolateral membrane throughout the nephron segments[33]. The proximal tubule reabsorbs approximately two-thirds of the filtered sodium load. In this segment, type 3 Na^+/H^+ exchanger (NHE3) is mainly responsible for apical sodium reabsorption[34]. The bumetanide-sensitive $Na^+/K^+/2Cl^-$ cotransporter (NKCC2) is localized at the apical membrane of the thick ascending limb and mediates the apical NaCl transport in this water impermeable segment[35]. In the distal convoluted tubule, the thiazide-sensitive Na^+/Cl^- cotransporter (NCC) is involved in the apical movement of sodium[36]. On the other hand, epithelial sodium channel (ENaC) is expressed in the connecting tubule and collecting duct[37].

Recently, altered regulations of renal sodium transporters in heart failure have been documented. Torp et al. demonstrated that the expression of NKCC2 was increased in heart failure rats. This change was decreased by losartan treatment. In addition, heart failure rats had increased basal and AVP stimulated cAMP accumulation in the thick ascending limb, which was abolished by losartan treatment[38]. These results may suggest that up-regulation of NKCC2 in heart failure rats plays a role in the increased sodium reabsorption in the thick ascending limb. The NKCC2 expression may be regulated by an interaction between V2 receptor and angiotensin II receptor. In addition, it was demonstrated that the expressions of AQP2, NHE3, NKCC2 and α-ENaC were increased in heart failure rats, which were reversed or prevented by candersartan treatment[39]. These findings suggest that angiotensin II and the dysregulation of AQP2 and sodium transporters plays an important role in the pathogenesis of renal sodium and water retention in heart failure.

Conclusions

In heart failure, activation of SNS, RAAS, resistance to NPs and non-osmotic vasopressin release stimulate the renal tubular reabsorption of sodium and water. Dysregulation of AQP2 and sodium transporters also play an important role in the pathogenesis of renal sodium and water retention.

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