Awareness of the Vasopressin System in Heart Failure
– Lessons From a Novel Aquaretic Agent –

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In 1983, Goldsmith et al demonstrated that arginine vasopressin (AVP) levels were increased in patients with congestive heart failure (CHF). The vasopressin system as well as renin-angiotensin-aldosterone/sympathetic nervous systems should be recognized as important compensatory systems in CHF. AVP is well known as a stress hormone, acting as a neuromodulator and neurotransmitter to converge behavioral regulation. In addition, AVP, which is stimulated by plasma osmolality, decreased arterial pressure, and reduced blood volume, increases the water permeability of the collecting duct, thereby promoting water reabsorption.

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tubules via V2 receptors and modulates the glomerular capillary ultrafiltration coefficient and glomerular cell contraction via V1 receptors. The V2 receptors are located on the basolateral membrane of renal collecting tubules, which functionally couple to the adenylate cyclase mediated through Gs protein and increase cAMP. Aquaporin-2 (AQP2), which is a water channel, is exocytosed and trafficked to the apical plasma membrane. These reactions mediate water transport across the renal collecting ducts, leading to increased water permeability (Figure). A proportion of the internalized AQP2 is excreted into the urine, which positively correlates with plasma AVP level.

Interestingly, it is known that changes in the urinary excretion of AQP2 can be used as an index of the action of AVP on the kidney. From these findings, the following concept can be speculated: urine AQP2 as well as urine osmolality could be good indices of the action of AVP and also good predictors of response to tolvaptan, which is a selective V2 receptor antagonist. In fact, Imamura et al have clarified that both urine AQP2 and urine osmolality are good predictors of tolvaptan-responders, defined as increased urine output after initiation of tolvaptan in CHF. These great findings were derived from the authors’ minute understanding of the role of the vasopressin system in cardiorenal syndrome. In other words, studying the action of tolvaptan made the authors realize and understand how important the vasopressin system is in CHF.

Congestion (ie, cardiac pulmonary edema and fluid retention) is the main pathophysiological condition in hospitalized CHF patients. Acute exacerbation in CHF causes increased release of not only angiotensin II but also both adrenocorticotropin (ACTH) and AVP. Angiotensin II and ACTH increase the aldosterone level, which induces sodium retention, and AVP causes water retention (Figure). In terms of management of congestion, both pathways are so important, but little attention has been paid to the vasopressin system in CHF. Increases in AVP levels cause organ congestion as well as systemic congestion. When sustained, the reserve function of organs is lost, causing poor outcome in hospitalized CHF patients. Thus, natriuresis and aquarexis are essential from the viewpoint of appropriate management of congestion. On the other hand, appropriate evaluation of congestion must be performed for appropriate management. The Acute Heart Failure Committee of the Heart Failure Association of the European society of Cardiology and the European Society of Intensive Care Medicine recommend systematic assessment and grading of congestion including clinical and hemodynamic congestion. It is necessary to evaluate the degree of congestion in each CHF patient before discharge. Recently, an interim result of post-marketing surveillance in Japan was reported and confirmed the efficacy and safety of tolvaptan for management of clinical and organ congestion in hospitalized CHF patients in the real-world clinical setting. Therefore, combined therapy with furosemide and tolvaptan is recommended during the early stage of CHF hospitalization.

From the studies conducted by Imamura et al, we have learnt the lessons of unrealized pathophysiology in CHF. Based on these considerations and new findings, we have to do better with management and try to improve outcomes in patients with CHF.

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