Pathogenesis of AVP Release
In several animal models of low-output and high-output cardiac failure and in congestive heart failure in humans, it has been demonstrated that plasma AVP, renin activity, aldosterone and norepinephrine are significantly increased. Renal excretion of sodium and water is predominantly regulated by the integrity of the arterial circulation, which is determined by cardiac output and peripheral vascular resistance. Several baroreceptors on the high pressure side of the circulation can sense arterial underfilling, and they are found in the left atrium, carotid sinus, aortic arch and renal afferent arterioles. Reduction in baroreceptor sensitivity occurs because of a decrease in systemic arterial pressure, stroke volume, renal perfusion or...
Peripheral vascular resistance. In the state of cardiac failure, cardiac output is decreased in association with reduced stroke volume despite an increase in total circulatory volume. We propose the hypothetical term “effective circulatory blood volume”, which is involved in the sensitivity of baroreceptors. A decrease in effective circulatory blood volume impairs the sensitivity of baroreceptors, which leads to an increase in the activity of the sympathetic nervous system, activation of the renin-angiotensin-aldosterone (R-A-A) system, and the non-osmotic release of AVP.

Increased AVP release could be a major factor in impaired water excretion. AVP2 is excreted into urine, in both the soluble and membrane-bound form. The fraction of AVP2 excreted into the urine is approximately 3% of the AVP2 protein present in collecting duct cells. We clarified a positive correlation of urinary AVP2 excretion with plasma AVP levels in normal subjects and heart failure patients. Urinary excretion of AVP2 was progressively increased in patients with heart failure according to progression of NYHA class.

### Hyponatremia, Plasma AVP Levels and Prognosis

Gheroghiade et al demonstrated that hyponatremia less than 135 mmol/L was not infrequently found in 19.7% of 48,612 patients with congestive heart failure. As noted earlier, baroreceptor-mediated activation of AVP, R-A-A, and catecholamines increases water and sodium retention, resulting in increased circulatory blood volume. Water retention is more predominant than sodium retention, thus creating dilutional hyponatremia.

Essentially, excessive circulatory blood volume augments cardiac preload in the failing heart, and further deteriorates the impairment in cardiac contraction. In this issue of the Journal, Imanura et al demonstrate the poor prognosis in patients with stage D heart failure. They focused on plasma AVP levels, and divided the patients into 2 groups according to a cut-off level of plasma AVP of 5.3 pg/ml. Kaplan-Meier analysis showed a significant difference between groups in terms of overall survival over 2 years. Cox regression analysis clarified that higher plasma AVP levels were significantly associated with decreased survival. The observation is basically similar to that of poor prognosis in hyponatremic patients with heart failure. In our recent study, a low serum Na concentration was only associated with the occurrence of heart failure events, among the varying humoral and cardiac parameters, during the follow-up period (mean 601 days) in patients with heart failure receiving cardiac resynchronization therapy.

Hyponatremia is derived from excessive circulatory blood volume because of impaired water excretion, and thus is dilutional hyponatremia. We believe that the related circulatory blood volume expansion per se could deteriorate the already reduced cardiac contraction in the failing heart. In contrast, non-osmotic release of AVP is mediated through reduced baroreceptor sensitivity, which senses the effective circulatory blood volume and cardiac output in congestive heart failure. Namely, an alteration in plasma AVP level is closely linked to baroreceptor sensitivity. Thereafter, an elevation in the plasma AVP level could relate to water retention, increased circulatory blood volume and further dilutional hyponatremia. However, AVP hypersecretion may be indirectly associated with worsening cardiac function and survival in the pathological state of heart failure.

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**Figure 2.** Pathogenesis of increased circulatory blood volume and deterioration of cardiac dysfunction. AVP, arginine vasopressin; R-A-A, renin-angiotensin-aldosterone.

**Impaired Water Excretion and Aquaporin2 (AQP2)**

Two studies using animal models of congestive heart failure have shown the enhanced hydro-osmotic action of AVP. The AQP2 water channel is located in renal collecting duct cells, and AQP2 is regulated by AVP, namely, short- and long-term regulation. Short-term regulation by AVP has been shown to involve cellular trafficking of AQP2 from cytosolic vesicles to the apical membrane of collecting duct cells. AQP2 per se then permeates water from the apical space to the cells. In addition, AVP stimulates the expression of AQP2 mRNA, followed by the synthesis of AQP2 protein (long-term regulation). Non-suppressable AVP release is remarkably involved in abnormal antidiuresis in pathological states of heart failure. Chronic excess AVP may be closely linked to abundant AQP2 protein in collecting duct cells. Thus, long-term regulation of AQP2 could be a major factor in impaired water excretion.

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**Cardiac Dysfunction**

- Reduced Sensitivity of Baroreceptors
  - ↑ AVP
  - ↑ R-A-A System
  - ↑ Sympathetic Nerve

**Impaired Water Excretion**

- ↑ Circulatory Blood Volume
  - Hypervolemic (Hyponatremia)
  - Euvolemic (Normonatremia)
  - ↑ Cardiac Preload

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The cardiac index gradually decreased according to the progression of NYHA class. However, it is as yet undetermined how the baroreceptors sense the decrease in effective circulatory blood volume linked to low cardiac output in congestive heart failure.

We verified an elevation of plasma AVP levels in congestive heart failure. Plasma AVP levels increased gradually in association with higher New York Heart Association (NYHA) class. The cardiac index gradually decreased according to the severity of NYHA class, and the plasma AVP level had a negative correlation with cardiac index. Increased AVP release was closely linked to the afferent pathways of the baroreceptors, which were stimulated by reduced effective circulatory blood volume as noted earlier (Figure 1).
AVP in HF

References


