Hyponatremia and Arginine Vasopressin in Early Stage of ST-Elevation Acute Myocardial Infarction
– Surrogate Markers or Therapeutic Targets? –
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Arginine vasopressin (AVP), also known as antidiuretic hormone (ADH), is a neuropeptide that plays an important role in circulatory and sodium homeostasis, and in regulating serum osmolality. It has been established that AVP expresses its physiological actions by binding to 3 different types of receptors, V₁a, V₁b and V₂. The V₁a receptor is the most widespread subtype and is found in vascular smooth muscle and myocardium. The activation of V₁a receptors results in vasoconstriction, increased afterload and hypertrophy. The V₂ receptors are located primarily in the renal collecting duct system and are the main mediators of ADH effects of water reabsorption. The V₁b receptors are mainly found in the anterior pituitary and mediate adrenocorticotropic hormone release. AVP levels have been reported to be inappropriately high in both acute and chronic heart failure (HF), and therefore AVP is thought to play a critical role in fluid retention and hyponatremia in patients with congestive HF.

In this issue of the Journal, Tada et al investigate the impact of hyponatremia (<136 mEq/L) on outcome in 140 consecutive patients with ST-elevation acute myocardial infarction (STEMI) in the era of primary intervention (1st study). Moreover, they also explore the contribution of the plasma AVP level to hyponatremia using an additional 65 patients with STEMI (2nd study). After careful evaluation of the patients’ backgrounds and prognoses, they conclude that hyponatremia is not infrequently (15–20%) found in the early phase of STEMI and is associated with HF in both short- and long-term outcomes. Through the 2nd study, they suggest that non-osmotic secretion of AVP could be involved in the hyponatremia in STEMI patients.

Hyponatremia has been well documented as predicting adverse clinical outcome in several common clinical entities, including myocardial infarction. Goldberg et al demonstrated that hyponatremia (<136 mEq/L) could be found in 11% of acute STEMI cases and was associated with a poor prognosis. Accordingly, Singla et al showed that 23% of patients with non-STEMI had hyponatremia (<135 mEq/L) and were significantly more likely to die or have recurrent myocardial infarction (2-fold) within 30 days after the primary infarction. The conclusion of the 1st study by Tada et al is consistent with those of previous reports. In spite of not a few confounding factors, such as aging, infarct size and diuretics use, for developing hyponatremia, it is reasonable to pay attention to the serum sodium level as an important prognostic indicator for developing HF in AMI.

It is important to note that Tada et al adopted their definition of hyponatremia (“early-developed hyponatremia”) at 72h after hospitalization. The measurement of the plasma AVP level was performed at the same time point in their 2nd study. Plasma AVP levels were significantly higher in the patients with early-developed hyponatremia than in those without hyponatremia (4.50±3.18 vs. 2.67±1.29 pg/ml, P=0.003), and the levels showed an inverse correlation with serum sodium levels (r=−0.28, P=0.02). By contrast, plasma osmolality or corrected plasma osmolality at 72h after hospitalization was not significantly different between the 2 groups. To clarify the mechanism of such non-osmotic release of AVP in STEMI patients, repetitive sampling of numerous neurohormonal molecules and frequent evaluation of physiological status might be required. Unfortunately, time sequential changes of the AVP level and plasma osmolality are not available in the present study.

The focused timing, 3–4 days after the onset of STEMI, is in a vulnerable phase of ventricular remodeling, a combination of infarct expansion and hypertrophy of residual non-infarcted myocardium. There are 2 important factors driving the process of left ventricular remodeling: ventricular loading condition and infarct-artery patency. Because most of the patients in the present study were successfully treated with a primary intervention, the loading condition (ie, elevated pressure and increased fluid volume) seems to be critical for ventricular remodeling and subsequent HF. Inappropriate secretion of AVP at this time may play an important role in increasing mechanical overload and the disruption of myocardial cells.

It is intriguing to now consider hyponatremia as a therapeutic target through suppression of AVP actions. AVP increases peripheral vascular resistance and thus elevates arterial blood pressure via V₁a receptors. Although this effect appears relatively small in healthy individuals, it becomes an important compensatory mechanism for restoring blood pressure in critical condition such as hypovolemic shock. As mentioned, elevation of the AVP level is thought to be associated with the pathophysiology of HF, especially with the
development of hyponatremia via V2 receptors. Therefore, it is quite natural to consider the development of AVP antagonists for the treatment of patients with congestive HF.

In Europe and the US, 2 AVP antagonists (‘vaptans’) are now available for the treatment of hyponatremia: conivaptan, a V1a- and V2-receptor blocker for intravenous use and tolvaptan, a selective V2-receptor blocker for oral administration. In the Japanese clinical settings, tolvaptan has been launched recently for the treatment of fluid retention in patient with HF refractory to conventional diuretics. It has been well documented that tolvaptan reduces pulmonary capillary wedge pressure, rapidly improving or normalizing the serum sodium concentration and sustaining the reduction in body weight. However, the Efficacy of Vasopressin Antagonism in Heart Failure Outcome Study With Tolvaptan (EVEREST) trial, in which HF patients within 48h of admission were randomly assigned to receive oral tolvaptan or placebo for a minimum of 60 days in addition to standard therapy, failed to show a beneficial effect on long-term mortality or HF-related morbidity, despite the significant benefits on dyspnea, edema, body weight and serum sodium level.

Although patients with AMI at the time of hospitalization were excluded from the EVEREST trial, two-thirds of the patients had ischemic HF etiology. In this issue of the Journal, Tada et al demonstrate that the plasma AVP level was significantly high in STEMI patients with “early-developed hyponatremia” and that the level inversely correlated with the serum sodium level. Given these findings, coupled with the adverse effect of hyponatremia, regulation of AVP actions in the early phase of STEMI using its antagonist might be an attractive option, and future investigation of vaptans under the STEMI setting seems to be warranted. The search for the optimal vaptan regimen (appropriate clinical settings, dose of drug, timing of control, etc) has just started.

References