Hyponatremia in Cardiac Resynchronized Therapy

– Is This a Novel Predictor of Response to Cardiac Resynchronization Therapy? –

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Cardiovascular diseases are recognized as the leading cause of death, both in Japan and worldwide, and almost all cardiovascular diseases eventually result in heart failure (HF). Further, the number of patients with HF has been increasing, together with worsened general severity of the condition. Given these circumstances, clinical investigations that focus on advanced stages of HF should be encouraged, and research into predictors of prognosis in this patient population have become more important in a variety of contexts.

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Hyponatremia is often seen in patients with HF as a result of general neurohumoral hyperactivation, particularly stimulation of arginine vasopressin (AVP) secretion. AVP plays a central role in the regulation of fluid and electrolyte balance, and decreased intravascular volume or pressure in patients with HF as a consequence of relatively low cardiac output triggers the secretion of AVP from the posterior pituitary gland. Secreted AVP binds to 3 types of AVP receptors: V1a, V1b, and V2. V1a receptors are located in the myocardium, liver, and vascular smooth muscle cells, V2 receptors are located predominantly in renal collecting ducts, which regulate free water reabsorption, and V1b receptors, also known as V3 receptors, are present in the anterior pituitary, where they mediate the release of adrenocorticotrophic hormone. Excess secretion of AVP in the condition of HF inappropriately stimulates both V1a and V2 receptors, resulting in increased vascular volume and/or pressure as a result of arterial vasoconstriction, as well as fluid retention that leads to dilutional hyponatremia.^{1,2} Thus, the degree of hyponatremia reflects the integrated severity of HF itself. The prevalence of hyponatremia in patients with HF is reportedly approximately 20% and depends on disease severity. Hyponatremia has been recognized as a powerful predictor of poor prognosis, including mortality and rehospitalization rates, in patients with HF.^{3–5}

In this issue of the Journal, Arao et al identify clinical predictive factors associated with adverse cardiac events occurring in patients with advanced HF, even after they underwent cardiac resynchronization therapy (CRT).⁶ Of 77 patients enrolled, 22 experienced HF events such as rehospitalization because of HF, implantation of a left ventricular assist device,

heart transplant, or cardiac death. Furthermore, 47% (36/77) of these patients demonstrated low serum sodium concentrations (<136 mmol/L), and multivariate Cox proportional hazard models revealed that hyponatremia was associated with future HF events after CRT.

Although the clinical use of hyponatremia as a predictive factor for future adverse cardiac events has been already documented in a variety of both inpatient and outpatient populations in subanalyses of large-scale multicenter cohort studies,^{7–9} the report by Arao et al provides further unique and useful information, especially because all enrolled patients underwent CRT as a result of being refractory to optimal medical therapy, and this population was much sicker than those in previous studies. In fact, whereas in the previous reports the proportion of patients with hyponatremia was approximately 20%, it was 47% (36/77) in the present study, reflecting these patients' critically severe condition.^{10,11} Another interesting point is that the results of the current study suggest the possibility of using clinical hyponatremia measurements as a supportive and additive parameter for identifying CRT responders. CRT is emerging as a standard therapy for patients with advanced HF complicated by systolic dysfunction and ventricular dyssynchrony who are refractory to optimal medical therapies. Although CRT has dramatically improved functional class and quality of life, approximately 30% of patients do not respond to this therapy. To date, several physiological parameters, such as electrocardiographic QRS duration and echocardiographic measures of mechanical dyssynchrony, have demonstrated an ability to identify CRT non-responders in single-center studies, but not yet in multicenter trials.^{12,13} In the report published in this issue of the Journal, hyponatremia independently predicted cardiac events in patients with CRT, whereas echocardiographic parameters did not. If the clinical course of CRT non-responders is thought to be defined by the development of HF events after CRT, hyponatremia that predates CRT might have potential in identifying this population. Simple but integrated clinical parameters such as the serum sodium concentration have been suggested as supportive and additive predictors of CRT responders.

Is hyponatremia a cause or effect of the worsening of HF? The answer may be both. Hyponatremia is generally caused by HF-related impaired hemodynamics leading to inappropriate release of AVP. Excessive use of loop and thiazide di-

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uretics is also an important cause of sodium hyperexcretion. Hyponatremia is therefore commonly viewed as simply a consequence of HF. Movagagh et al recently reported interesting data on the effects of hyponatremia on cardiac contraction using a cell-based assay.¹⁴ In cardiomyocytes, contraction is initiated by the opening of voltage-gated L-type Ca^{2+} channels (I_{Ca}). Influx of Ca^{2+} through I_{Ca} stimulates ryanodine receptors, which results in significant sarcoplasmic reticulum Ca^{2+} release. This process of Ca^{2+} -induced Ca^{2+} release (CICR) begins with I_{Ca} regulating cardiomyocyte contraction. Movagagh et al measured the Ca^{2+} currents of the I_{Ca} in a cell-based assay using cardiomyocytes and HEK 293 cells, with a number of low concentrations of extracellular Na^{+} that mimic the intracellular environment in the failing myocardium. The results of that study demonstrated that low extracellular Na^{+} concentrations between 100 and 135 mmol/L, which are concordant with the serum sodium concentrations associated with clinical hyponatremia, suppressed the I_{Ca} of cultured cells in a concentration-dependent manner. A suppressed I_{Ca} under the low extracellular Na^{+} conditions may partially explain the mechanism underlying further depression of cardiac contractility in patients with HF in the presence of hyponatremia, which in turn might cause future cardiac adverse events. However, the decreases in the difference of Na^{+} concentrations around the cell reverse the potential of Na^{+} and Ca^{2+} exchangers under the condition of extracellular low Na^{+} concentrations, which may lead to accumulated intracellular Ca^{2+} concentrations. Ca^{2+} overload via the Na^{+} and Ca^{2+} exchangers is thought to impair cardiac function. If hyponatremia acts as both a cause and effect in HF, AVP receptor blockade might improve the prognosis of HF patients with hyponatremia. However, the Efficacy of Vasopressin Antagonism in Heart Failure Outcome Study With Tolvaptan (EVEREST) trial did not demonstrate any improvement in long-term prognosis,¹¹ and thus more research to elucidate the clinical effectiveness of AVP receptor blockade in different settings is needed in the future.

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