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Research Progress on Serum Sodium Concentration and Heart Failure Risk

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Abstract: ***Heart failure is one of the major chronic diseases worldwide, with increasing prevalence and healthcare burden. Hyponatremia is common among heart failure patients, with a prevalence ranging from 8% to 28%, and is associated with disease progression, as well as higher mortality and morbidity. The etiology is complex, involving neuroendocrine abnormalities, medication effects, and other factors. In both heart failure with preserved and reduced ejection fraction, hyponatremia is linked to higher mortality, though the mechanisms and impact differ. Treatment requires consideration of the type of hyponatremia, volume status, and severity of heart failure. Recently, vasopressin antagonists such as tolvaptan have shown promising therapeutic potential. This article reviews the relationship between serum sodium levels and heart failure risk, as well as treatment strategies, providing a reference for clinical practice.***

Key words: Heart failure, Serum sodium, Arginine Vasopressin**.**

1. Introduction

Hyponatremia refers to a condition where serum sodium concentration is below 135 mmol/L, and it is very common in heart failure (HF) patients [1]. The prevalence of hyponatremia among heart failure patients is between 8% and 28% [2]. Hyponatremia is associated with more severe congestion symptoms and poorer diuretic response in heart failure patients, and it can range from mild cognitive impairment to life-threatening conditions. Regardless of clinical presentation and left ventricular ejection fraction, hyponatremia is linked to increased mortality and morbidity in heart failure patients.

2. Causes and Influencing Factors of Hyponatremia

Hyponatremia is a common electrolyte disturbance in heart failure patients, and it is associated with multiple factors. First, heart failure patients often exhibit neuroendocrine abnormalities, such as activation of the sympathetic nervous system and the renin-angiotensin-aldosterone system (RAAS). These changes lead to electrolyte and acid-base imbalances, ultimately triggering hyponatremia [3]. Additionally, medications commonly used by heart failure patients, such as diuretics—especially thiazide diuretics—are common causes of hyponatremia [4]. These drugs interfere with the kidney's ability to concentrate urine, resulting in sodium loss. Heart failure patients may also experience inadequate renal blood flow, leading to a decrease in glomerular filtration rate, which further affects sodium excretion and water retention. Furthermore, reduced dietary intake of sodium in heart failure patients can contribute to the development of hyponatremia. Hyponatremia in heart failure patients is associated not only with short-term and long-term adverse outcomes but also with prolonged hospitalization, increased risk of readmission, and higher mortality rates [5-7].

The causes of hyponatremia are complex and varied, and they can be broadly divided into two categories: dilutional hyponatremia and depletion hyponatremia. Dilutional hyponatremia is primarily related to reduced renal blood flow and increased secretion of Arginine Vasopressin (AVP). Normally, elevated plasma osmolality stimulates the release of AVP, which activates the V2 receptors in the collecting ducts, promoting the translocation of aquaporin-2 channels and increasing free water reabsorption. In heart failure, reduced cardiac output activates pressure receptors, leading to the release of non-osmotic AVP, which causes antidiuretic effects and vasoconstriction. Although adequate renal blood flow can prevent hyponatremia in the presence of high AVP concentrations, insufficient renal blood flow leads to excessive free water reabsorption due to V2 receptor activation, causing dilutional hyponatremia. In heart failure, low osmolality fails to inhibit AVP release. Some evidence suggests that improving cardiac function may restore the normal regulation of AVP release [8]. On the other hand, depletion hyponatremia may result from diuretic therapy in heart failure. All commonly used diuretics in heart failure, including mineralocorticoid receptor antagonists (MRA), loop diuretics, and thiazide diuretics, work by increasing the excretion of sodium and chloride in the urine, which can lead to depletional hyponatremia.

3. The Relationship Between Hyponatremia and Heart Failure

3.1 Hyponatremia and Heart Failure with Preserved Ejection Fraction (HFpEF)

In HFpEF, hyponatremia is also an important clinical issue. HFpEF patients often have comorbid conditions such as obesity, hypertension, and diabetes, which may indirectly contribute to the occurrence of hyponatremia by affecting renal hemodynamics and hormonal regulation. Furthermore, diastolic dysfunction in HFpEF patients can lead to elevated cardiac filling pressures, which in turn impair renal perfusion, resulting in sodium and water retention [9]. Although the ejection fraction of HFpEF patients is relatively normal, their renal function may be compromised, leading to reduced sodium excretion.

However, there is still controversy regarding the relationship between hyponatremia and the prognosis of patients with HFpEF in clinical practice. A study explored the relationship between serum sodium levels and long-term mortality in

patients with HFpEF, suggesting that hyponatremia is a strong predictor of long-term mortality in HFpEF patients [10]. Some researchers have studied non-bedridden patients with heart failure to determine the prognostic significance of hyponatremia. They found that hyponatremia is associated with poor outcomes in these patients [11]. Another multicenter study investigated the association between hyponatremia at discharge and adverse outcomes in acute heart failure syndromes with preserved ejection fraction, suggesting that hyponatremia is closely related to all-cause mortality and all-cause heart failure death or rehospitalization in these patients [12]. However, data from the Korean Acute Heart Failure Registry indicated that hyponatremia is a significant risk factor for adverse in-hospital outcomes, but its long-term prognostic value is limited to patients with heart failure with reduced ejection fraction (HFrEF) and not applicable to HFpEF patients [13].

3.2 Hyponatremia and Heart Failure with Reduced Ejection Fraction

In patients with HFrEF, the incidence of hyponatremia is relatively high and is closely associated with the severity of the disease. The pathophysiological mechanism in HFrEF primarily involves impaired cardiac systolic function, which leads to reduced cardiac output and subsequently affects renal perfusion [14]. These hemodynamic alterations activate the renin-angiotensin-aldosterone system and the sympathetic nervous system, resulting in sodium and water retention, as well as increased release of arginine vasopressin [15]. The elevated release of AVP increases water reabsorption in the renal tubules, further diluting plasma sodium concentration and leading to hyponatremia.

Additionally, diuretics commonly used in HFrEF patients, especially thiazide and loop diuretics, may exacerbate hyponatremia by interfering with the kidney's ability to concentrate urine, thereby causing sodium loss [16]. Thiazide diuretics, for instance, act on the distal convoluted tubule of the nephron to inhibit sodium and chloride reabsorption, leading to increased urinary excretion of these electrolytes. Loop diuretics, on the other hand, inhibit the sodium-potassium-chloride cotransporter in the thick ascending limb of the loop of Henle, which also results in increased urinary sodium excretion. Both types of diuretics can contribute to hyponatremia by reducing the total body sodium content and promoting free water retention.

In HFrEF patients, hyponatremia is not only associated with short-term and long-term poor outcomes but is also linked to prolonged hospital stays, increased risk of readmission, and higher mortality rates [17]. Moreover, the presence of hyponatremia at the time of hospital admission or during hospitalization is an independent predictor of longer hospital stays and higher rates of readmission. This is particularly concerning given the already high burden of illness in patients with HFrEF. The increased risk of readmission not only places a significant strain on healthcare resources but also indicates a higher likelihood of disease progression and worsening heart failure symptoms. Additionally, hyponatremia has been identified as a strong predictor of mortality in HFrEF patients, both in the short term and long term. This underscores the importance of recognizing and effectively managing hyponatremia in the context of HFrEF to improve patient outcomes and reduce the overall burden of heart failure on the healthcare system.

4. Treatment of Patients with Hyponatremia with Heart Failure

The treatment of hyponatremia requires a comprehensive consideration of various factors, including the type of hyponatremia, the patient's volume status, and the severity of heart failure. Patients with heart failure who are admitted to the hospital and have hyponatremia, particularly when sodium levels further decline during their hospital stay, experience higher rates of all-cause mortality and cardiovascular mortality.

The treatment of hyponatremia combined with heart failure should be tailored based on symptoms and the severity of hyponatremia [18,19]. Common treatment approaches include fluid restriction and nonspecific strategies such as diuretics, isotonic or hypertonic saline, and V2 receptor antagonists [20]. For severe hyponatremia, the most critical complication is cerebral edema, which typically occurs in cases of acute hyponatremia—hyponatremia that develops within 48 hours. Due to the lack of counter-regulatory mechanisms, patients often present with neurological symptoms such as coma or seizures, caused by the shift of fluid from a hypotonic extracellular environment into the hypertonic brain tissue. Patients with severe symptoms require treatment in an intensive care unit and frequent monitoring [19]. European guidelines recommend a prompt infusion of hypertonic saline for patients with severe symptomatic hyponatremia, aiming for a rapid elevation of serum sodium levels [20]. However, in heart failure patients, the use of hypertonic saline may exacerbate symptoms, as the additional sodium load may lead to congestion [21,22]. Therefore, hypertonic saline therapy should only be applied to patients with severe neurological symptoms and is recommended to be administered alongside loop diuretics. Fortunately, acute hyponatremia is rare in patients with heart failure; the reduction in serum sodium is usually gradual, with mild or no symptoms.

For patients with mild hyponatremia, the focus is on pharmacological management. Currently, for heart failure patients with preserved renal function, the mainstay of treatment for chronic hyponatremia includes fluid restriction and the use of loop diuretics [23-25]. The choice of this therapeutic approach depends on the type of hyponatremia, specifically whether it is depletional or dilutional. In addition to fluid restriction and loop diuretics, other options include the combination of loop diuretics and hypertonic saline [22,26-28], which can be more effective in certain cases for correcting hyponatremia. Moreover, angiotensin-converting enzyme inhibitors are also used in the management of hyponatremia, as they improve renal hemodynamics and reduce sodium reabsorption [27]. Lastly, AVP receptor antagonists (such as tolvaptan) represent an emerging therapeutic option. By blocking the action of AVP, these agents reduce renal water reabsorption, thereby aiding in the correction of dilutional hyponatremia [28,29].

4.1 Tolvaptan and Heart Failure

AVP antagonists hold pathophysiological promise in the treatment of heart failure. Tolvaptan, a selective vasopressin V2 receptor antagonist, exerts its diuretic effect by binding to and blocking the activity of V2 receptors, thereby reducing water reabsorption without affecting solute absorption and excretion [30]. A meta-analysis evaluating the efficacy of tolvaptan in patients with acute heart failure showed that adding tolvaptan significantly reduced volume overload, as evidenced by improvements in dyspnea, weight loss, increased total urine output, and changes in urine volume relative to baseline.4 In the EVEREST trial (Efficacy of Vasopressin Antagonism in HF Outcome Study with Tolvaptan), while tolvaptan did not significantly reduce all-cause mortality in hyponatremic patients, it effectively increased serum sodium levels [31]. Additionally, a post hoc analysis of the EVEREST trial indicated that in the hyponatremia subgroup, tolvaptan was associated with weight loss and dyspnea relief [32].

In summary, hyponatremia is common among heart failure patients and is closely associated with poor prognosis. Its etiology is complex, involving multiple factors such as neuroendocrine abnormalities and medication effects. In both HFpEF and HFrEF patients, hyponatremia is linked to an increased risk of mortality, though the underlying mechanisms and impact vary. Treatment requires a comprehensive approach, and emerging therapies such as tolvaptan have shown promise. Future research should further explore its mechanisms to optimize treatment strategies and improve outcomes for heart failure patients.

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