

Review Article

Hyponatremia and Congestive Heart Failure: A Marker of Increased Mortality and a Target for Therapy

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Heart failure is one of the most common chronic medical conditions in the developed world. It is characterized by neurohormonal activation of multiple systems that can lead to clinical deterioration and significant morbidity and mortality. In this regard, hyponatremia is due to inappropriate and continued vasopressin activity despite hypoosmolality and volume overload. Hyponatremia is also due to diuretic use in an attempt to manage volume overload. When hyponatremia occurs, it is a marker of heart failure severity and identifies patients with increased mortality. The recent introduction of specific vasopressin-receptor antagonists offers a targeted pharmacological approach to these pathophysiological derangements. Thus far, clinical trials with vasopressin-receptor antagonists have demonstrated an increase in free-water excretion, improvement in serum sodium, modest improvements in dyspnea but no improvement in mortality. Continued clinical trials with these agents are needed to determine their specific role in the treatment of both chronic and decompensated heart failure.

1. Introduction

Heart failure (HF) is an increasingly common condition, with recent American data revealing a 1 in 5 lifetime risk for both sexes, and over 5 million currently affected patients [1]. In addition to being common, morbidity and mortality attributable to HF continue to rise with over 1.1 million hospital discharges and 1 in 8 death certificates mentioning heart failure in 2006 [1]. HF has an annual mortality of 20% per year after diagnosis, and its estimated economic burden in the United States in 2009 was \$37.2 billion [1].

Although HF manifests primarily with cardiopulmonary symptoms, hyponatremia is very common in this patient population. In fact, hyponatremia (variably defined as serum sodium <134–136 mmol/L) is present in over 20% of patients admitted to hospital with HF [2, 3]. Not only is it a common occurrence, but it has repeatedly been shown to be a marker of increased mortality in the HF population [3, 4].

As will be discussed in this paper, both the maladaptive neurohormonal and renal changes as well as diuretic treatment of HF contribute to the development of hyponatremia [2–4]. In particular, the posterior pituitary hormone vasopressin leads to renal water retention and hyponatremia. As such, the recently developed vasopressin antagonists present an attractive target for the management of hyponatremia in HF [5].

2. Physiology of Water Handling

To appreciate the pathophysiology of hyponatremia in HF, it is important to understand the basic physiology of renal salt and water handling. With the exception of psychogenic polydipsia and low dietary solute intake, essentially all cases of true hyponatremia represent a failure to excrete maximally dilute urine. In the presence of normal renal function, this

failure is most often related to the action of vasopressin (AVP).

AVP is a hormone synthesized in the supraoptic (SON) and paraventricular nuclei of the hypothalamus and is released from the posterior pituitary [6]. Its effects are multiple and related to the affected receptor (Table 1). Binding to the V_{1a} receptor leads to vascular smooth muscle contraction [7] while V_2 receptor activation in the renal medulla leads to free water reabsorption by the collecting duct. Binding to V_2 receptors, located on the basolateral membrane of the cortical collecting duct cells, leads to increased aquaporin 2 (aqp-2) mRNA levels and translocation of aqp-2 to the apical membranes [6]. This increases tubular water permeability and allows water to move from the tubule to the medullary interstitium (down a concentration gradient), resulting in net reabsorption of free water. This movement of water is passive and relies upon a hypertonic renal medulla, the generation of which is partly dependant on the activity of the NKCC (sodium-potassium-2 chloride) channels in the ascending loop of henle [8]. Absence of AVP activity (such as in diabetes insipidus) leads to loss of high volume dilute urine.

AVP release is mediated by both osmotic as well as cardiac output and intravascular volume stimuli. Osmoreceptors present in the SON are exceedingly sensitive to changes in serum osmolality demonstrating alterations in AVP release in response to a 1% fluctuation in serum osmolality [9]. This sensitivity serves to keep serum osmolality tightly controlled with a threshold for AVP release of approximately 280 mOsm/Kg [9]. The nonosmotic stimuli for AVP release consist of reductions in cardiac output, intravascular blood volume, or blood pressure [9]. These stimuli, mediated through high (aortic arch and carotid sinus) and low (left atrial) pressure baroreceptors [10], enhance the secretion of AVP for any given osmotic stimulus [9, 10]. In effect, AVP will be released at a lower plasma osmolality when decreased intravascular volume, cardiac output or blood pressure are detected.

Recently, AVP has been shown to be a potent and independent regulator of the thiazide-sensitive $\text{Na}^+\text{-Cl}^-$ cotransporter (NCC) [11, 12]. This action is mediated through the V_2 -receptor and its clinical effects are, as yet, not clear but implicate AVP in the handling of sodium as well as water.

3. Pathophysiology of Hyponatremia in Heart Failure

In the normal physiologic state, alterations in serum osmolality serve as the primary control for AVP release. However, in conditions that lead to nonosmotic stimulation of AVP release, these stimuli may take precedence resulting in the acceptance of a lower serum osmolality [9]. Such is the case in HF where a decrease in cardiac output leads to a continued release AVP despite a reduction in osmolality, thus leading to hyponatremia. Multiple studies have demonstrated increased levels of AVP in HF leading accompanied by inadequate inhibition when exposed to a decrease in serum osmolality

[13, 14]. Indeed, data in the Studies of Left Ventricular Dysfunction (SOLVD) show a progressive incremental increase in AVP levels with worsening HF symptoms [15]. It has also been shown that the density of AVP positive neurons in the SON is increased by as much as 30% in patients with HF [16].

A number of other neurohormonal abnormalities contribute to abnormalities in renal sodium (Na) and water handling. Arterial underfilling (from decreased cardiac output) detected by baroreceptors in the aortic arch, carotid sinus and afferent renal arterioles leads to activation of the sympathetic nervous system (SNS) and the renin-angiotensin-aldosterone system (RAAS) [2]. While the activation of these systems acts to preserve systemic perfusion pressure in patients with HF, it is a long-term maladaptive response that leads to avid Na and water retention in multiple nephron segments. This overload of Na and water may worsen cardiac function thus perpetuating the cycle of Na and water retention. In addition, angiotensin II is a potent inhibitor of thirst, which may lead to increased free water intake and exacerbation of hyponatremia [17].

Reductions in glomerular filtration rate are common in patients with HF and can eventually lead to a reduced capacity for water and Na excretion. It has been shown that the filtered load of Na decreases in parallel with declining GFR in patients receiving diuretics [18]. While salt intake in these patients exacerbates volume overload and HF, they are also at risk of worsening hyponatremia with increased free water intake.

Although a mainstay in the therapy of HF, diuretics can also cause hyponatremia. These drugs increase Na and water excretion thereby alleviating congestive symptoms and theoretically helping to optimize cardiac contractility. It is interesting to note that despite their widespread use, diuretics have not been shown to improve survival in HF patients [19]. Diuretics are prescribed in 85–100% of symptomatic and 16–35% asymptomatic patients with reduced left ventricular function [20–22]. Loop diuretics are the most commonly utilized diuretics and exert their salt wasting effects by inhibiting the NKCC channel in the thick ascending loop of Henle. Other diuretics used frequently in HF include thiazide diuretics and spironolactone. Thiazides inhibit the Na-Cl cotransporter in the distal convoluted tubule while spironolactone prevents activation of the mineralocorticoid receptor on the principal cells of the cortical collecting duct. Of these 3 classes, loop diuretics offer the most potent increase in Na and water excretion and thus are important agents in the treatment of states of volume overload.

In the general population, diuretic-induced hyponatremia is very common, with thiazides accounting for the 63% of the cases of severe hyponatremia, loop diuretics for 6%, and spironolactone for 1% [23]. The incidence of hyponatremia with thiazide diuretics may be as high as 11% in the elderly [24]. Several features may contribute to hyponatremia: (1) stimulation of AVP release secondary to diuretic-induced volume contraction, (2) decrease in GFR from intravascular volume contraction, (3) inhibition of urinary dilution capacity due to interference with Na absorption in the distal segments, and (4) hypokalemia induced intracellular shift of Na [24]. The thiazide effect in the distal

TABLE 1: The actions of vasopressin and its receptors.

| Receptor | Location | Action |
|-----------------|-------------------------|-------------------------------------|
| V _{1a} | Vascular smooth muscle | Vasoconstriction |
| | Platelets | Myocardial hypertrophy |
| | Myometrium | Aggregation |
| V _{1b} | Anterior pituitary | Uterine contraction |
| V ₂ | Renal collecting tubule | Adrenocorticotropin hormone release |
| | Vascular endothelium | Induction of aquaporin-2 |
| | | Free water absorption |
| | | Release of von Willebrand factor |
| | | Release of factor VIII |

nephron accounts for its association with hyponatremia. Conversely, loop diuretics may be spared from causing hyponatremia by their effect on the NKCC co-transporter, which helps maintain the hypertonic medullary interstitium. A reduction in the tonicity in this area decreases the gradient for free water movement out of the tubules via aqp-2 channels and may therefore lessen the risk of hyponatremia as compared to thiazides.

Owing to their disruption of the medullary concentration gradient, loop diuretics may actually lead to an increase in Na in hyponatremic patients [25]. If, however, there is incomplete amelioration of the concentration gradient, administration of loop diuretics can still cause hyponatremia. This likely relates to further stimulation of the RAAS due to increased distal Na delivery thereby increasing angiotensin II, a well-known stimulant of AVP secretion [26].

4. Epidemiology of Hyponatremia in Heart Failure

Given the number of neurohormonal changes in patients with HF, it is not surprising that hyponatremia is very common in this population. With Na and water retention and decreased GFR from activation of the RAAS and SNS in the context of increased AVP levels, continued intake of hypotonic fluids may lead to hyponatremia. Of all patients admitted to hospital with a diagnosis of HF, 18–27% will have hyponatremia (Na < 135 mmol/L) on admission [27, 28].

Not only is hyponatremia common, it is also a strong marker of increased morbidity and mortality in HF patients. Lee and Packer [29] analyzed 30 clinical, hemodynamic, and biochemical variables and their association with survival in 203 consecutive patients with severe HF. The most powerful predictor of cardiovascular mortality was pretreatment serum Na, with hyponatremic patients having a substantially shorter median survival than patients with a normal serum Na (164 versus 373 days, $P = .006$). Similarly, in the Outcomes of a Prospective Trial of Intravenous Milrinone for Exacerbations of Chronic Heart Failure (OPTIME-CHF) study, both in hospital and 60-day mortality rates were highest for patients with the lowest admission serum Na [27]. In the Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients with Heart Failure (OPTIMIZE-HF) registry, patients with hyponatremia had significantly

higher in-hospital and follow-up mortality rates and longer hospital stays [30]. In this study, for each 3 mmol/L decrease in serum Na below 140 mmol/L at admission, the risk of in-hospital mortality and follow-up mortality increased by 19.5% and 10%, respectively. More recently, the importance of persistent hyponatremia in HF patients was described in a cohort of patients enrolled in the Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterization Effectiveness (ESCAPE) [31]. Hyponatremia in this study was associated with higher 6-month mortality after covariate adjustment (hazard ratio(HR), for each 3 mmol/L decrease in serum Na, 1.23; 95% confidence interval (CI), 1.05–1.43; $P = .01$). After controlling for baseline variables and clinical response, patients with persistent hyponatremia had an increased risk of all-cause mortality (31% versus 16%; HR, 1.82; $P = .04$), HF rehospitalization (62% versus 43%; HR, 1.52; $P = .03$), and death or rehospitalization (73% versus 50%; HR, 1.54; $P = .01$) compared with normonatremic patients.

It is unclear whether this increased mortality directly related to hyponatremia or if the sodium abnormality is a marker of a more severe underlying illness. It is likely that it reflects a greater activation of the RAAS and SNS with higher levels of AVP leading to increased mortality. It has in fact been shown that patients with hyponatremia have higher circulating levels of catecholamines, renin, angiotensin, aldosterone, and AVP [32]. It is also feasible that the presence of hyponatremia limits options in terms of diuretic management and could potentially alter HF therapy leading to differences in mortality. Moreover, hyponatremia associated with diuretic use may be accompanied by multiple other metabolic abnormalities such as hypokalemia and hypomagnesemia that could increase mortality. In addition, severe hyponatremia and its correction can respectively lead to cerebral edema and the osmotic demyelination syndrome, both of which are associated with high morbidity and mortality.

5. Management of Hyponatremia in Heart Failure

Management of hyponatremia in heart failure demands a multifaceted approach including optimization of cardiac function (including prevention of volume overload and neurohormonal blockade), preservation of renal function,

and maintenance of appropriate fluid intake. In addition, the relatively newly developed vasopressin antagonists potentially offer an attractive therapeutic strategy for dealing with hyponatremia in HF. Of utmost importance in any patient with hyponatremia is to ensure adequate monitoring of serum Na levels, as rapid changes in either direction can have dire consequences.

5.1. Optimization of Cardiac Function. Perhaps a simplistic view of managing hyponatremia in HF is to ensure adequate cardiac output. Ideally, this would reduce the stimulation of baroreceptors and lessen the activation of the SNS and RAAS resulting in less renal avidity for Na and water and lower levels of AVP.

While detailed management of HF is beyond the scope of this paper, inhibition of the SNS and RAAS with β -blockers (BB) and angiotensin converting enzyme inhibitors (ACEi) or angiotensin receptor blockers (ARB) remain the cornerstone of chronic HF management [33]. These agents break the maladaptive cycle of neurohormonal activation and via multiple mechanisms lead to improved preservation of cardiac function [33]. They also lead to a reduction in left ventricular afterload facilitating an improvement in cardiac output. In addition, blockade of the aldosterone action with spironolactone or eplerenone decreases hospitalizations and mortality in patients with New York Heart Association (NYHA) class III and IV HF [34, 35]. In patients with acute exacerbations of HF, afterload reduction with ACEi and nitrates and utilization of positive inotropic agents may be used to improve cardiac output [36] thus increasing Na levels in hyponatremic patients.

As previously discussed, diuretics remain a mainstay of HF treatment and have complex effects on serum Na levels. Increasing Na and water loss can ease congestive symptoms and, especially in combination with afterload reduction and increased inotropy, can improve cardiac output in the volume-overloaded patient [36]. This is usually accomplished with loop diuretics, or a combination of loop and thiazide diuretics, and can lead to increased Na levels in the hyponatremic patient. It is important to note, however, that excessive diuresis leads to hypovolemia, activation of the SNS and RAAS, and decreased renal function. This effect can worsen cardiac function and lead to impaired renal Na and water handling resulting in hyponatremia from increased AVP release. In addition, a single bolus of furosemide has been associated with an increase in plasma renin activity, norepinephrine, and AVP leading to increased left ventricular filling pressure and decreased stroke volume [37]. This response to furosemide is potentially detrimental to the HF patient.

Diuretic use has been associated with increased mortality in both chronic and acute exacerbations of HF [38, 39]. It is difficult, however, to delineate a cause and effect relationship, and despite a lack of evidence for their effectiveness, diuretics will likely remain an important component of HF management for the foreseeable future. Due to the complex physiology of HF, the effect of loop diuretics on serum Na can be difficult to accurately predict thus making frequent monitoring of serum Na very important.

In addition, nonpotassium sparing diuretics may lead to significant hypokalemia, hypomagnesemia, and decreased renal function. It is therefore prudent to ensure adequate monitoring of these parameters when using these agents.

5.2. Preservation of Renal Function. Patients with impaired renal function have a decreased capacity for Na and water excretion thus placing them at an increased risk of developing hyponatremia. Efforts to maintain normal renal function including blood pressure control, limiting use of nephrotoxic medications and contrast dye, and avoiding excessive diuresis may help to limit the risk of hyponatremia. In patients whose renal function is sufficiently poor to maintain appropriate Na and water balance, renal replacement therapy (hemodialysis or peritoneal dialysis) can remove excessive Na and water and maintain normal sodium levels.

5.3. Maintenance of Appropriate Fluid Intake. With high levels of circulating AVP, HF patients will have a limited capacity to excrete excess dietary free water. It thus follows that HF patients with hyponatremia should limit dietary water intake. The degree of limitation necessary will be patient specific and dictated by the degree of neurohormonal activation in each patient. Again, frequent monitoring will help ensure an appropriate rise in serum Na in response to the intervention.

5.4. Vasopressin Antagonists. Given the primary role of AVP in free water retention and the development of hyponatremia, antagonism of AVP action would seem like a rational therapeutic option in hyponatremic HF patients. As vasopressin also leads to vasoconstriction and cardiomyocyte hypertrophy [7], blocking its actions may have further beneficial effects in HF.

A number of such drugs have been developed and target either V_2 receptors selectively or a combination of V_2 or V_{1a} receptors. These agents lead to a selective loss in renal free water losses termed *aquaresis*. To date, no studies have shown a reduction in mortality with use of the vasopressor antagonists in HF.

Preclinical studies in animals and humans showed that administration of a V_2 receptor antagonist leads to an increase in free water excretion with little increased Na loss and no compensatory activation of the RAAS [40–42]. These positive results have led to a number of clinical trials of these agents in HF patients.

Georgiade et al. compared tolvaptan to placebo in 254 NYHA class III or IV outpatients who continued to receive standard HF therapy [43]. Patients received either 1 of 3 oral doses of tolvaptan (30, 45, or 60 mg/day) or placebo for a total of 25 days. Although all patients treated with tolvaptan had an increase in serum Na, the 28% who had baseline had hyponatremia the greatest rise. 80% of tolvaptan-treated patients with hyponatremia had normalization of serum Na on day 1 compared to 40% of those receiving placebo. These patients also had significant reductions in body weight with an improvement in HF symptoms. A similar study in 319 patients randomized patients to 1 of 3 tolvaptan doses (30, 60, or 90 mg) or placebo, in addition to standard HF

treatment for 60 days [28]. Patients in the tolvaptan group had small increases in serum Na; the greatest rise in Na was seen in the 21.3% of patients with baseline hyponatremia. Tolvaptan-treated patients also had a significant decrease in body weight at 24 hours (median 2.05 Kg in the highest dose group) with no changes in heart rate, blood pressure, renal function, or development of hypokalemia.

A larger study of 4133 patients assessed both- short and long-term outcomes in patients admitted with acutely decompensated HF [44, 45]. Patients were randomized to receive Tolvaptan 30 mg/day or placebo in addition to standard HF care. Short-term outcomes at 7 days revealed no difference in the primary outcome of global clinical status. Similar to the previous studies, however, the tolvaptan group did have a significant decrease in body weight and dyspnea. Of note, treatment with tolvaptan also led to significant increases in thirst, polyuria, and hypernatremia (1.4% versus 0%). The long-term follow-up trial over a mean of 9.9 months, found no difference in all-cause mortality, cardiovascular death, or HF hospitalizations between the groups. Improvements in dyspnea and serum Na were maintained throughout followup with similar side effects to those seen in the short-term trial. A subgroup analysis of the 8% of the patients with baseline hyponatremia found serum Na to be increased by 5.5 mmol/L and 1.8 mmol/L in the tolvaptan and placebo groups, respectively.

Similar short-term outcomes of increased urine output and serum sodium were found in patients with stable HF receiving lixivaptan, another V_2 -receptor antagonist [46]. Ascending single doses of the drug were used and produced a dose-dependent increase in urine output but no long-term outcomes with this agent have been published.

Antagonism of the V_{1a} receptors in addition to the V_2 receptors has the added theoretical benefit of decreasing afterload by inhibiting AVP-mediated smooth muscle contraction. Conivaptan is one such agent with FDA approval for treatment of hypervolemic hyponatremia. In a randomized, double-blind, placebo-controlled, multicenter study, 84 patients with hyponatremia were randomized to receive 1 of 2 doses of conivaptan (20 mg bolus followed by 96 hour infusion of either 40 or 80 mg/day) or placebo, in addition to standard HF treatments [47]. Both doses of conivaptan were associated with significant increases in serum Na. Na levels increased by 6 mmol/L or were normalized in 69% of the 40 mg/day dose and 88.5% of the 80 mg/day dose by day 4, whereas only 20.7% of the placebo group achieved this goal.

Several studies of conivaptan in HF patients have yielded similar results to those with V_2 -receptor antagonists [48–50]. Recipients of conivaptan had increases in urine output with decrease in left- and right-sided filling pressures and had minimal side effects. When compared with furosemide alone, a combination of furosemide and conivaptan produced a dose-dependent increase in urine output [50]. In addition, combination with higher doses of conivaptan (80 or 120 mg/day) led to small but significant increases in serum Na.

The precise role of vasopressin antagonists in the management of hyponatremic HF patients remains unclear. While no effects on mortality have been seen in clinical trials,

there are clear improvements in symptoms in the majority of studies. To date, there have been no studies directly comparing the effects of V_2 and combined V_2/V_{1a} -receptor antagonists which remains an interesting clinical question. It is important to note that in all of the aforementioned studies, vasopressin antagonists have been used in conjunction with usual HF treatment (including diuretics), and have not been studied as a replacement for loop diuretics.

6. Conclusion

Hyponatremia in HF is a frequent occurrence related to the activation of a multitude of neurohormonal pathways including the SNS, RAAS, and particularly the increased release of AVP. In addition to being common, hyponatremia is associated with increased mortality in the HF population. The treatment has traditionally consisted of RAAS and SNS blockade in combination with loop and thiazide diuretics and dietary water restriction. While this approach can be effective, diuretics have several detrimental metabolic side effects and may potentially worsen hyponatremia and cardiac function. Vasopressin antagonism represents a logical goal in the management of hyponatremia in the HF population. These agents have been shown to increase serum Na and free water clearance and improve HF symptoms, but have not yet been found to reduce long-term mortality. More trials are necessary to define an exact role for the vasopressin antagonists in HF patients.

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