

REVIEW

Significance of Hyponatremia in Heart Failure

Christina Chrysohoou, MD, Dimitris Tousoulis, MD,
Christodoulos Stefanadis, MD

ABSTRACT

Hyponatremia is a common clinical condition among hospitalized heart failure patients, associated with increased morbidity and mortality. The pathophysiological mechanisms that relate heart failure with hyponatremia are complex, involving beyond renal dysfunction, neurohormonal activation and diuretic treatment. The pituitary hormone vasopressin seems to play a central role leading to renal water retention and hyponatremia. Although therapeutic strategies (water restriction, hormone inhibition) have been shown to increase serum sodium concentration and improve symptoms, no beneficial effect has been detected on clinical outcome. This fact urges the need for the conduction of further clinical trials, in order to determine the causality between short- and long-term outcome and serum sodium concentration in heart failure patients.

First Cardiology Department, School of
Medicine, University of Athens, Athens,
Greece

KEY WORDS: *heart failure;*
hyponatremia; arginine vasopressin;
electrolyte abnormalities

ABBREVIATIONS

AVP = arginine vasopressin
HF = heart failure
NKCC = Na-K-Cl cotransporter
RAAS = renin-angiotensin-aldosterone
SIADH = syndrome of inappropriate
antidiuretic hormone
hypersecretion

Corresponding author

Christina Chrysohoou, MD, PhD
46 Paleon Polemiston St.,
166 74, Attica, Greece
Tel. +30-210-9603116,
Fax. +30-210-9600719
E-mail: chrysohoou@usa.net

Manuscript received February 5, 2012;
revised manuscript received February
29, 2012; re-revised manuscript received
March 13, 2012; accepted March 16,
2012

INTRODUCTION

Hyponatremia represents one of the most common clinical metabolic disorders in patients with chronic heart failure. Hyponatremia, which is generally defined as Na concentrations below 135 meq/l, occurs in 10-20% of heart failure (HF) patients.¹ Several studies have revealed the prognostic role of serum Na concentrations on the clinical course of HF.²⁻⁵ The Acute Decompensated Heart Failure registry (ADHERE), which included 158,168 HF patients, showed a prevalence of 5% among patients on admission with serum sodium levels <130 meq/L. Those low Na concentrations were associated with increased mortality and morbidity.⁶ In the Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients with Heart Failure (OPTIMIZE-HF) registry, including 48,162 HF patients, 19.7% of the patients had hyponatremia on admission, which was also associated with prolonged hospitalization and higher in-hospital mortality.⁷ Recently, from the Duke Databank for Cardiovascular Diseases, 10% of the 1,045 patients, who were identified with HF and systolic dysfunction, had hyponatremia. Those hyponatremic patients were older, more likely to have anemia, higher heart rate and levels of blood urea nitrogen, lower blood pressure, and more severe HF; while the multiaadjusted analysis revealed that low serum Na was associated with poor cardiovascular outcome.⁸ Although the incidence of hyponatremia in hospitalized patients is well described, in stable outpatients the available data are limited. In

Conflict of Interest: none declared

the Danish Heart Failure Clinics Network, which included 2883 patients, the prevalence of hyponatremia was 17%, which was lower than in most previous studies of hospitalized patients.⁵ Another study in a smaller outpatient population reported a hyponatremia ($\text{Na}^+ < 135 \text{ mEq/L}$) prevalence of 13%, and in the Spanish MUSIC-study the prevalence of hyponatremia

(where it was unusually defined as $\text{Na} < 138 \text{ mmol/L}$) was found to be 38% (Table 1).^{9,10}

PATHOPHYSIOLOGICAL MECHANISMS

The renin-angiotensin-aldosterone (RAAS) system plays a crucial role in the progression of heart failure. The RAAS is

TABLE 1. Studies of Association of Hyponatremia with Heart Failure Outcomes

Study	No of patients	Type of patients	Outcome	[Na] cut-off	HR (95%CI)
DDCD ⁸	1,045	Hospitalized patients with chronic systolic HF (NYHA II-IV)	4.5-year all-cause mortality, 4.5-year CV mortality and rehospitalization	[Na] <135 mmol/L	1.45 (1.09-1.93) 1.45 (1.13-1.86)
HFSS ⁸	268	Outpatients with systolic HF (NYHA III-IV)	1-year mortality	[Na] per 1-mmol/L change (value after medical therapy optimization)	1.05 (1.00-1.08)
EFFECT ²	2624	Hospitalized patients with systolic and diastolic HF (NYHA II-III)	30-day and 1-year mortality	[Na] <136 mmol/L	1.53 (1.14-2.05), for 30-day mortality; 1.46 (1.19-1.80), for 1-year mortality
UK-HEART ²³	553	Outpatients with systolic HF (NYHA II-III)	5-year mortality	[Na] per 2-mmol/L change [Na] <140 mmol/L (baseline value)	1.13 (1.05-1.19)
Seattle Heart Failure Model ⁴	1125	Hospitalized patients with systolic HF (NYHA II-IV)	1-, 2-, and 3-year mortality	[Na] <138 mol/L	1.05 (1.005-1.097)
MUSIC ¹⁰	992	Outpatients with systolic and diastolic HF (NYHA II-III)	4-year mortality for total, cardiac, and pump failure mortality	[Na] <138mmol/L	1.35 (1.03-1.77), for cardiac mortality; 1.60 (1.12-2.29), for pump failure mortality
ESCAPE ²⁴	433	Hospitalized patients with systolic HF (NYHA III-IV)	6-month mortality	[Na] per 1-mmol/L change, [Na] <130 mmol/L	0.93 (0.87-0.99)
OPTIME-CHF ²⁵	949	Hospitalized patients with systolic HF (NYHA III-IV)	60-day mortality	[Na] per 5-mmol/L change	0.75 (0.60-0.95)
Danish Heart Failure Clinics Network ⁵	3465	Outpatients with systolic HF	4.5years mortality	[Na] <136 mmol/L	HR 1.5 (1.2–1.9)

CI = confidence intervals; CV = cardiovascular; DDCD = Duke Databank for Cardiovascular Diseases; EFFECT = Enhanced Feedback for Effective Cardiac Treatment; ESCAPE = Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterization Effectiveness; HF = heart failure; HFSS = Heart Failure Survival Score; HR = hazard ratio; MUSIC = Multi-Sensor Monitoring in Congestive Heart Failure; NYHA = New York Heart Association (classification); OPTIMISE-CHF = Outcomes of a Prospective Trial of Intravenous Milrinone for Exacerbations of Chronic Heart Failure; UK-HEART = United Kingdom Heart Failure Evaluation and Assessment of Risk Trial.

stimulated by a decrease in renal blood flow and by low blood salt concentration. RAAS is also stimulated by the increase in sympathetic tone that results from the decrease in arterial baroreceptor stretch in heart failure. The excess of angiotensin II in heart failure causes systemic and arteriolar vasoconstriction, increase in aldosterone concentration, and increased thirst, which further exacerbates hyponatremia. The angiotensin and sympathetic pathways increase systemic vascular resistance and increase preload and arterial filling. The stimulation of vasopressin release activates the movement of aquaporin-2 water channels to the apical membrane of the collecting duct where passive water reabsorption occurs. Additionally, aldosterone causes water and sodium reabsorption at the level of the collecting duct. Furthermore, in patients with heart failure, there is a decrease in transport of sodium and water to the collecting duct, due to arterial underfilling and low circulating blood volume, which impairs the kidney's ability to excrete dilute urine.¹¹ It is important to emphasize that excess water intake, due to social interaction, especially in younger heart failure patients, can be another important reason for the occurrence of water imbalance and hyponatremia. Furthermore, excess water intake is noted in chronic psychiatric patients when treated with certain antipsychotic medications, which are often used in heart failure patients with depression and increase thirst through anticholinergic side effects.

Inappropriate arginine *vasopressin* (AVP) release is another explanation of hyponatremia. This situation represents excess release of AVP, despite low serum osmolality. Myocardial remodeling in response to excessive water reabsorption which expands ventricular preload and alterations in gap junction function can contribute to lower osmolality in patients with even normal renal function. In this condition, although the serum sodium remains low, the total body sodium is elevated and there is increased extracellular fluid volume. Low circulating blood volume has been proposed as the unifying etiology for this contradiction in volume states. In heart failure, the decrease in effective arterial filling leads to a decrease in baroreceptor stretch, a mechanism that mediates vasopressin release.¹² Vasopressin release is mediated by both osmotic as well as cardiac output and intravascular volume stimuli. Those stimuli, mediated through high (aortic arch and carotid sinus) and low (left atrial) pressure baroreceptors enhance the secretion of AVP for any given osmotic stimulus. This hormone is synthesized in the supraoptic and paraventricular nuclei of the hypothalamus and is released from the posterior pituitary. Its effects are multiple and related to the affected receptor. Vasopressin binding to the V1a receptor (in the vascular smooth muscle cells, myometrium and platelets) leads to vascular smooth muscle contraction; while V2 receptor activation in the renal medulla leads to free water reabsorption by the collecting duct. Binding of vasopressin to V2 receptors, located on the basolateral membrane of the cortical collecting duct cells, leads to increased aquaporin 2 mRNA levels and

translocation of aquaporin-2 to the apical plasma membrane, which increases tubular water permeability and allows water to move from the tubule to the medullary interstitium, resulting in net reabsorption of free water.^{13,14} The lack of suppression of AVP release despite hypo-osmolality plays a pivotal role in the development of hyponatremia in patients with heart failure. This is due to the fact that water balance regulation is primarily designed to control serum osmolality and to a lesser extent blood volume. For that reason AVP starts to rise after a 1% increment in serum osmolality, compared to a 5–10% decrease in blood volume. Eventually, the need to return the perfusion pressure to normal limits leads to an inability of AVP suppression, at the cost of hyponatremia. Interestingly, Waikar et al illustrated that in patients with end-stage renal disease, the neurohormonal activation of advanced heart failure does not lead to water retention and hyponatremia through a vasopressin-mediated mechanism. Thus, any effect must be mediated by neurohormonal effects on thirst.¹⁵

Diuretic use is another cause of hyponatremia in HF patients. Loop diuretics are the most commonly utilized diuretics and exert their salt wasting effects by inhibiting the Na-K-Cl cotransporter (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.¹⁶ Amiodarone can also cause hyponatremia, most probably due to a syndrome of inappropriate antidiuretic hormone hypersecretion (SIADH)-induced mechanism. Although this phenomenon occurs only rarely, it should be recognized by clinicians as a possible serious adverse effect of this drug. The mechanism of SIADH-induced hyponatremia secondary to amiodarone is unclear. One possible mechanism includes alterations on channel-modulating properties on renal or neural tissues.¹⁷

HYPONATREMIA: MARKER OR MEDIATOR?

All these complex pathogenetic mechanisms of hyponatremia in HF patients lead to the crucial dilemma if hyponatremia reflects a mediator and not an independent marker of survival.¹⁸ Along with this thought comes the fact that in patients with HF hyponatremia is associated with higher levels of plasma renin, angiotensin II, aldosterone, epinephrine, norepinephrine, dopamine, and cortisol, and a greater degree of impairment of renal and hepatic blood flow. In patients hospitalized for heart failure, hyponatremia also is associated with lower systolic blood pressure, higher brain natriuretic peptide, and higher likelihood of using inotropic agents. In these conditions, hyponatremia is mediated by nonosmotic release of AVP and reduced free water clearance by the kidney, which in

turn may reflect the severity of the underlying disease process through mechanisms such as reduced glomerular filtration rate and activation of the sympathetic nervous system. Additionally, in many studies, those patients with hyponatremia had higher prevalence of diabetes mellitus and were under higher-dose requirements of loop diuretics than normonatremic patients.¹⁹ It is possible that hyponatremia might simply be a marker for high vasopressin levels, which, through the stimulation of V1a receptors, could alter outcome in chronic HF.²⁰ Therefore, it is difficult to prove a causal association between hyponatremia and poor clinical outcomes in congestive heart failure patients, due to the high likelihood of confounding by disease underlying severity.

MANAGEMENT OF HYPONATREMIA

Hyponatremia can be classified according to the measured plasma osmolality as isotonic, hypertonic or hypotonic. Hyponatremia with a normal plasma osmolality usually indicates pseudohyponatremia, while hyponatremia because of a high plasma osmolality is typically caused by hyperglycemia. The syndrome of inappropriate ADH (SIADH) secretion should be suspected in any patient with euvolemic hyponatremia with a urine osmolality above 100 mOsm/kg and urine sodium concentration above 40 mEq/l. Management of hyponatremia includes optimization of medical therapy (RAAS antagonists, β -blockers), preservation of renal function in normal limits 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.²¹ Feldman et al¹⁹ have recently demonstrated a role for V1a-mediated signaling in the development of HF, which supports a role for V1a blockade in the treatment of patients with elevated levels of vasopressin; although it has not yet been established whether the normalization of hyponatremia (by fluid restriction or specific drugs) leads to a better prognosis.

The Acute and Chronic Therapeutic Impact of a Vasopressin Antagonist in Congestive Heart Failure (ACTIV in CHF) trial using tolvaptan and the Efficacy of Vasopressin Antagonism in Heart Failure Outcome Study with Tolvaptan (EVEREST) trial, as well as the DILIPO-study where the short and long-term treatment of dilutional hyponatremia with satavaptan, a selective AVP V2-receptor antagonist, was examined, revealed positive results of AVP antagonist efficacy in increasing serum sodium concentrations. However, improvement of clinical symptoms or survival was not reported in any of those studies.^{21,22} EVEREST was a prospective, international, multicenter, randomized, double-blind, placebo-controlled study, which enrolled 4133 heart failure patients (2072 received tolvaptan and 2061 received placebo). The first primary end point (all cause mortality) was not different; 25.9% vs 26.3% in the tolvaptan vs placebo groups (hazard ratio 0.98; 95% confidence intervals-CI 0.87–1.11; $P = 0.68$). The second

primary end point (death from cardiovascular causes or first hospitalization for HF) was reached in 42% of the patients on tolvaptan compared with 40.2% in the placebo group (hazard ratio 1.04; 95% CI 0.95–1.14; $P = 0.55$). Improvement in the patient-assessed dyspnea score at day 1 was seen in 74.3% of tolvaptan patients with dyspnea at baseline compared with 68.0% in the placebo group ($P < 0.001$). Additionally, improvement was noted in edema, total body weight and renal function in the tolvaptan group compared to placebo.²² Those results, despite the neutral effect of tolvaptan on cardiovascular and total outcome among patients with systolic HF, provide a basis for its use to correct moderate to severe hyponatremia among outpatients with systolic HF, in order to achieve rapid clinical improvement and reduce length of hospitalization.

CONCLUSION

Hyponatremia represents a serious clinical condition in patients with advanced heart failure, which is associated with adverse outcome (Table 1).^{2,5,8,10,23-25} As the pathophysiological mechanisms are complex, treatment strategies that have been used are limited and associated with adverse effects. Among them, dietary fluid restriction, diuretic therapy, and neurohormonal blockade are the traditional recommendations, but their efficacy is poorly documented. Even the use of vasopressin antagonists has shown neutral results on clinical outcome. It seems rational that future studies addressing the effect of vasopressin antagonists or other therapeutic approaches on outcome in HF patients are needed, in order to determine the causality between hyponatremia and heart failure physical history.

REFERENCES

1. Farmakis D, Filippatos G, Parissis J, Kremastinos DT, Gheorghide M. Hyponatremia in heart failure. *Heart Fail Rev* 2009;14:59-63.
2. Lee DS, Austin PC, Rouleau JL, Liu PP, Naimark D, Tu JV. Predicting mortality among patients hospitalized for heart failure derivation and validation of a clinical model. *JAMA* 2003;290:2581-2587.
3. Kearney MT, Nolan J, Lee AJ, et al. A prognostic index to predict long-term mortality in patients with mild to moderate chronic heart failure stabilised on angiotensin converting enzyme inhibitors. *Eur J Heart Fail* 2003;5:489-497.
4. Levy WC, Mozaffarian D, Linker DT, et al. The Seattle Heart Failure Model: prediction of survival in heart failure. *Circulation* 2006;113:1424-1433.
5. Balling L, Schou M, Videbæk L, Hildebrandt P, Wiggers H, Gustafsson F, for the Danish Heart Failure Clinics Network. Prevalence and prognostic significance of hyponatraemia in outpatients with chronic heart failure. *Eur J Heart Fail* 2011;13: 968-973.

HYPONATREMIA IN HEART FAILURE

6. Fonarow GC, Heywood JT, Heidenreich PA, Lopatin M, Yancy CW, ADHERE Scientific Advisory Committee and Investigators. Temporal trends in clinical characteristics, treatments, and outcomes for heart failure hospitalizations, 2002 to 2004: findings from Acute Decompensated Heart Failure National Registry (ADHERE). *Am Heart J* 2007;153:1021-1028.
7. Gheorghiade M, Abraham WT, Albert NM, et al, OPTIMIZE-HF Investigators and Coordinators. Relationship between admission serum sodium concentration and clinical outcomes in patients hospitalized for heart failure: an analysis from the OPTIMIZE-HF registry. *Eur Heart J* 2007;28:980-988.
8. Bettari L, Fiuzat M, Shaw LD, et al. Hyponatremia and long-term outcomes in chronic heart failure. An observational study from the Duke databank for cardiovascular diseases. *J Cardiac Fail* 2012;18:74-81.
9. Dewolfe A, Lopez B, Arcement LM, Hebert K. Low serum sodium as a poor prognostic indicator for mortality in congestive heart failure patients. *Clin Cardiol* 2010;33:E13-17.
10. Vazquez R, Bayes-Genis A, Cygankiewicz I, et al, MUSIC Investigators. The MUSIC Risk score: a simple method for predicting mortality in ambulatory patients with chronic heart failure. *Eur Heart J* 2009;30:1088-1096.
11. Sica DA. Sodium and water retention in heart failure and diuretic therapy: basic mechanisms. *Cleve Clin J Med* 2006;73(suppl 2):S2-7.
12. Schrier RW. Water and sodium retention in edematous disorders: role of vasopressin and aldosterone. *Am J Med* 2006;119 (suppl 1):S47-53.
13. Nielsen S, Kwon TH, Christensen BM, Promeneur D, Frøkiær J, Marples D. Physiology and pathophysiology of renal aquaporins. *J Am Soc Nephrol* 1999;10:647-663.
14. Farmakis D, Filippatos G, Kremastinos DT, Gheorghiade M. Vasopressin and vasopressin antagonists in heart failure and hyponatremia. *Curr Heart Fail* 2008;5:91-96.
15. Waikar SS, Curhan GC, Brunelli SM. Mortality associated with low serum sodium concentration in maintenance hemodialysis. *Am J Med* 2011; 124: 77-84.
16. Sica DA, Gehr TWB. Diuretic combinations in refractory oedema states: pharmacokinetic- pharmacodynamic relationships. *Clin Pharmacokin* 1996;30:229-249.
17. Shavit E, Sherer Y. Hyponatremia induced by amiodarone therapy. *Isr Med Assoc J* 2007;9:564-565.
18. Ghali JK, Tam SW. The critical link of hypervolemia and hyponatremia in heart failure and the potential role of arginine vasopressin antagonists. *J Card Fail* 2010;16:419-431.
19. Li X, Chan TO, Myers V, et al. Controlled and cardiac-restricted overexpression of the arginine vasopressin V1A receptor causes reversible left ventricular dysfunction through Gαq-mediated cell signaling. *Circulation* 2011;124:572-581.
20. Liamis G, Milionis H, Elisaf M. A review of drug induced hyponatremia. *Am J Kidney Dis* 2008; 52:144-153.
21. Aronson D, Verbalis JG, Mueller M, Krum H. Short- and long-term treatment of dilutional hyponatremia with satavaptan, a selective arginine vasopressin V2-receptor antagonist: the DIL-IPO study. *Eur J Heart Fail* 2011;13:326-336.
22. Konstam MA, Gheorghiade M, Burnett JC, et al. Efficacy of Vasopressin Antagonism in Heart Failure Outcome Study With Tolvaptan (EVEREST) Investigators. Effects of oral tolvaptan in patients hospitalized for worsening heart failure: the EVEREST Outcome Trial. *JAMA* 2007;297:1319-1331.
23. Kearney MT, Fox KA, Lee AJ, et al. Predicting death due to progressive heart failure in patients with mild-to-moderate chronic heart failure. *J Am Coll Cardiol* 2002;40:1801-1808.
24. Gheorghiade M, Rossi JS, Cotts W, et al. Characterization and prognostic value of persistent hyponatremia in patients with severe heart failure in the ESCAPE Trial. *Arch Intern Med* 2007;167:1998-2005.
25. Klein L, O'Connor CM, Leimberger JD, for the O-CHFI. Lower serum sodium is associated with increased short-term mortality in hospitalized patients with worsening heart failure: results from the outcomes of a prospective trial of intravenous milrinone for exacerbations of chronic heart failure (OPTIME-CHF) study. *Circulation* 2005; 111:2454-2460.