REVIEWS

Clinical Challenge of Hyponatremia in Heart Failure

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Hyponatremia is a significant and independent predictor of outcomes including rehospitalization and mortality in patients with both acute decompensated heart failure (HF) and chronic HF. Even modest degrees of hyponatremia are associated with a poorer prognosis. Treatment options include fluid restriction and the vaptan class ("aquaretics") in select patients. *Journal of Hospital Medicine* 2012; 7:S6–S10. © 2012 Society of Hospital Medicine

Hyponatremia, defined as a serum $[Na^+] \leq 135$ mEq/L, occurs in 20-30% of patients with acute decompensated heart failure (HF)[1–3] and has been independently associated with a poor prognosis. In clinical trials of acute decompensated HF, the reported mean serum sodium is often normal or near normal, but a significant proportion of study subjects can have serum sodium values that approach 130 mEq/L or lower.[3] However, despite the association between hyponatremia and clinical outcomes like hospitalization and mortality, data from studies are sparse about the impact of drug or device interventions in the hyponatremic cohort, since patients are generally not stratified at the time of randomization by the value of baseline serum sodium.

HYPONATREMIA AND PROGNOSIS

Hyponatremia has long been recognized as a potential prognostic marker in heart failure, highlighted by Packer and Lee in 1986.[4] Subsequently, a wealth of data derived from clinical trials, registries, and observational databases support the concept that hyponatremia is an independent predictor of both short- and long-term outcomes.[1–3,5–11] As reviewed by Jao and Chiong,[3] this relationship holds in patients on optimal evidence-based medical therapy, including treatment with antagonists of the renin-angiotensin system and beta blockers. In the Organized Program To Initiate Lifesaving Treatment In Hospitalized Patients With Heart Failure (OPTIMIZE)[2] HF Registry of nearly 50,000 patients, in-hospital and 60-day mortality rates were higher in patients with lower serum sodium levels on admission (cut-off point of 135 mEq/L). In-hospital death and the combined endpoint of death or re-hospitalization increased significantly for each 3 mEq/L decrease in serum $[Na^+]$ below 140 mEq/L. Patients with hyponatremia were more likely to have lower systolic blood pressures and receive intravenous inotropic agents; lengths of stay were also longer.

Similar findings were reported in the Evaluation Study of Congestive Heart Failure and Pulmonary Acute and Chronic Therapeutic Impact of a Vasopressin 2 Antagonist (Tolvaptan) in Congestive Heart Failure (ACTIV in CHF)[10] trial.[11] For example, in the former, Gheorghiade and colleagues tracked serum sodium levels in 433 hospitalized patients who had acute decompensated HF and examined the proportion free from a major event (defined as death and/or HF hospitalization).[1] There was a clear association between the event rate and serum sodium level. Patients whose hyponatremia persisted from hospital admission to discharge were at higher risk relative to those whose hyponatremia was corrected during the hospital stay.

However, whether the way in which the serum sodium improvement is achieved has a bearing on outcomes is not known. In the studies comparing outcomes in patients with heart failure and hyponatremia versus normonatremia, no mention is made about how the patient arrived at either state. Despite this limitation, the findings are incontrovertibly consistent. Hyponatremia on discharge (prior to or after the adoption of renin-angiotensin-aldosterone system (RAAS) antagonists or beta blockers) is a marker for poorer outcomes, as is another laboratory abnormality frequently observed in patients hospitalized with heart failure: an elevated creatinine.

Additionally, serum sodium obtained shortly after hospitalization is a potent predictor of re-hospitalization[12] and persistently poor health-related quality-of-life.[13] The impact on longer-term outcomes can also be demonstrated in multiple prognostic models[6,8,9] in which serum sodium is a risk factor for adverse outcomes. For example, using the Seattle Heart Failure Model, overall prognosis worsens for each 1 mEq decline in serum sodium when all other variables are

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kept constant.[8] This observation suggests that, in terms of prognosis, the value of serum sodium functions as a continuous not a binary variable.

HYPONATREMIA AND HF PATHOPHYSIOLOGY

The reasons underlying hyponatremia in heart failure are complex, but a key component is the non-osmotic release of arginine vasopressin (AVP) in response to stimulation of carotid baroreceptors. This phenomenon occurs as a result of arterial underfilling (both lower blood pressure and lower cardiac output). AVP is one member of a family of "neurohormones" and cytokines that are upregulated in heart failure (eg, norepinephrine, renin, angiotensin, aldosterone, endothelin, and tumor necrosis factor-alpha). Levels of AVP are increased most markedly in patients with advanced symptoms (ie, New York Heart Association Class III and IV),[14] and this leads to impaired free water handling in the renal tubules and a hypervolemic form of hyponatremia. The reasons underlying the upregulation are debated, but likely reflect a short-term hemodynamic adaptation that is designed to augment cardiac output by increasing circulating volume. In addition, multiple neurohormones have been shown to promote progressive ventricular dilation, referred to as remodeling. For example, chronic elevations of norepinephrine contribute to a multitude of genotypic and phenotypic changes at the level of the myocyte. The short-term benefits of neurohormonal upregulation are offset by maladaptive responses in the long term, and this observation likely explains a major part of the clinical benefits seen with drugs such as angiotensin converting enzyme inhibitors, aldosterone antagonists, and beta blockers.

It is also clear that the development and management of patients with hyponatremia and heart failure are frequently complicated by the presence of other factors that impact sodium and water handling. Heart failure often occurs in older patients with renal dysfunction who are on medications that can exacerbate hyponatremia, such as diuretics, non-steroidal anti-inflammatory agents, antidepressants, and opiate derivatives. In addition, other conditions like hypothyroidism may coexist and contribute to the hyponatremic state. It is therefore crucial for the clinician to consider these possibilities when a patient with heart failure presents with or develops hyponatremia, and in particular to critically evaluate the potential role of concomitant medications that can cause a syndrome of inappropriate antidiuretic hormone secretion (SIADH)-like picture.

HYPONATREMIA AND RESOURCE USE

As with other markers of poor outcome in heart failure, such as worsening renal insufficiency, chronic obstructive lung disease, and other comorbidities, hyponatremia is associated with longer lengths of stay (LOS) and cost. In an analysis of approximately 116,000 patients hospitalized with HF and grouped at admission by serum [Na^+], risk-adjusted mortality, LOS, and attributable cost were highest for patients with severe hyponatremia compared to patients with normonatremia.[15] In addition, Amin and colleagues recently demonstrated that length of stay in the intensive care unit and associated costs were greater (21% and 23%, respectively) in patients who had an International Classification of Diseases, 9th revision, Clinical Modification (ICD-9-CM) code for hyponatremia compared to those that did not.[16]

CONSIDERATIONS FOR PATIENTS HOSPITALIZED WITH HEART FAILURE WITH AND WITHOUT HYPONATREMIA

A number of significant management challenges exist during the hospitalization phase of acute decompensated heart failure. Among other tasks, the clinician should evaluate the potential cause of the decompensation (eg, medication noncompliance, dietary noncompliance, increased metabolic demand from pneumonia or other infection, worsening renal failure, diuretic resistance, iatrogenic fluid overload) and decide whether the patient is fluid overloaded, in a low cardiac output state contributing to end-organ perfusion, or both. Manifestations of worsening heart failure other than dyspnea may be present. For example, mental status changes in an elderly patient may reflect fluid overload with or without low cardiac output, but the differential diagnosis also includes impaired clearance of drugs due to liver congestion or worsening renal function (eg, digoxin toxicity), hyponatremia (potentially mediated through cerebral edema), low cardiac output, occult infection, cerebrovascular accident, and other complications of coronary heart disease.

Key components of the physical exam include the presence of jugular venous distention,[17] a more sensitive and specific finding than pulmonary rales in chronic or acute-on-chronic heart failure. While the mainstay of therapy for fluid overload remains diuretic therapy, we have only recently learned in a definitive way from the Diuretic Optimization Strategies Evaluation (DOSE)[18] study that the method of administration (bolus vs continuous intravenous infusion and high dose vs low dose) matters, albeit slightly. Patients who receive high doses of loop diuretic have greater dyspnea relief and weight loss but are at greater risk for developing worsening renal function.

Certain key clinical markers, when present on admission, place the patient in an at-risk group for a longer length of stay (Table 1). In addition to new or established hyponatremia, these include a creatinine value above baseline, marked antecedent weight gain, and hypotension. During the hospitalization, development of new hyponatremia or worsening of established hyponatremia, worsening renal function (often

TABLE 1. Complicating Factors Associated With Prolonged Length of Stay in Heart Failure

Hyponatremia
Worsening renal failure
Advanced age
Comorbidities
Marked antecedent weight gain
Lack of (early) resolution of weight gain
Hypotension
Organ hypoperfusion

simply defined by an increase in baseline creatinine by 0.3 mg/dL or more), lack of dyspnea relief, and lack of weight loss, increase the complexity of decision-making. A proportion of these higher-risk patients may benefit from the initiation of intravenous vasoactive therapy, mechanical fluid removal (eg, with ultrafiltration), or the use of a vaptan (or "aquaretic"), depending on the particular presentation and profile. Occasionally, mechanical support will be needed but this option only applies to a limited subgroup.[19] However, aside from ventricular assist devices, none of these options have been associated with improved survival.

Despite this limitation, the immediate goal of care in the acute setting is symptom relief. Thus, although neither intravenous dobutamine nor milrinone have been shown to decrease mortality, both are recognized as palliative options in patients with advanced or end-stage symptoms[20,21]; for example, milrinone, due to its inodilator characteristics, may improve symptoms and end-organ perfusion while mitigating against an increase in pulmonary vascular resistance. However routine use in the management of acute decompensated heart failure is discouraged, based on the Outcome of a Prospective Trial of Intravenous Milrinone for Exacerbations of Chronic Heart Failure (OPTIME-CHF)[2] Trial.[22] Similarly, the routine use of nesiritide cannot be recommended, based on the neutral findings of the recently published Acute Study of Clinical Effectiveness of Nesiritide in Decompensated Heart Failure (ASCEND-HF)[23] study, though subsets of patients may still be candidates for this therapy.

Ultrafiltration appears to function well as an adjunct to fluid and salt removal as demonstrated in the Ultrafiltration versus Intravenous Diuretics for Patients Hospitalized for Acute Decompensated Congestive Heart Failure (UNLOAD)[24] study, though a number of limitations have been cited.[25] It should be strongly considered for patients who have developed refractory fluid overload and anasarca, especially if responsiveness to loop diuretics is blunted.

For hypervolemic hyponatremia, the standard approach has been fluid restriction, but this can require a prolonged and at times uncomfortable prescription for patients to follow. Hypertonic saline is contraindicated in most cases, given the salt load and

risk of exacerbating fluid overload. Data for demeclocycline are sparse.[26] The vaptan class is an interesting option, in large part because of the significant free water loss that can be achieved through the competitive antagonism of V_2 receptors in renal tubules. Competitive binding to this receptor leads to a reduction in the deposition of new water channels (or aquaporins) on the luminal side of the tubule, resulting in a marked reduction in water reuptake from the urine.[27] Indeed, data for tolvaptan, an orally available vaptan, suggest that short-term treatment can increase urine output, weight loss, and serum sodium level.[28] In both the Acute and Chronic Therapeutic Impact of a Vasopressin 2 Antagonist (Tolvaptan) in Congestive Heart Failure (ACTIV) and Efficacy of Vasopressin Antagonism in Heart Failure: Outcome Study With Tolvaptan (EVEREST)[29] studies,[28] a number of favorable short-term effects were seen such as dyspnea relief and weight loss, but in the latter study, the trial did not meet 1 of its 2 prespecified co-primary endpoints (change on a visual analog scale) in an embedded analysis of acute treatment effects. Further, EVEREST failed to show any meaningful impact on posthospitalization morbidity and mortality when tolvaptan was administered chronically.[30] It is also noteworthy that in both trials, inclusion criteria required the presence of symptomatic heart failure rather than hyponatremia; in fact, in EVEREST only 11.5% of patients had a serum sodium level less than 135 mEq/L. To date, there are no long-term prospectively collected data on the impact of the vaptan class in heart failure accompanied by hyponatremia.

Despite these caveats, the judicious use of vaptans may have a role in heart failure; at the very least, serum sodium increases by, on average, 5.2 mEq/L.[31] Fluid restriction should be liberalized and serum sodium should be monitored frequently in the first few days of therapy to avoid rapid correction of serum sodium, which can lead to an unusual neurological complication (osmotic demyelination syndrome).[32]

OUTPATIENT MANAGEMENT CONSIDERATIONS

Patients who have chronic hyponatremia or who are at risk for worsening of preexisting hyponatremia should be closely monitored during the early postdischarge period, in part to detect further decreases in the serum sodium level and deterioration in overall clinical status. Worsening of hyponatremia may occur in the outpatient setting due to intentional or unintentional increased free water intake, initiation of new medications, exacerbation of the underlying condition, infection, or related conditions. Similar to the inpatient setting, the outpatient management of patients with fluid overload and hyponatremia can be difficult. Further study is required and clinical trials are needed to assess whether the chronic administration of a

vaptan in this particular patient population will impact prognosis relative to fluid restriction alone.

Regardless of serum sodium, a frequently advocated intervention in long-term management is daily weight monitoring which has become a gold standard, especially for patients with advanced symptoms. As shown in EVEREST, lean body weight increases prior to re-hospitalization for HF were 1.96, 2.07, and 1.97 kg, compared with 0.74, 0.90, and 1.04 kg, respectively, in patients who were not re-hospitalized ($P < 0.001$ for all groups).[33] Recently, use of invasive hemodynamic monitoring, largely on the basis of the Cardio-MEMS Heart Sensor Allows Monitoring of Pressure to Improve Outcomes in NYHA Class III Heart Failure Patients (CHAMPION)[34] trial, has been advocated as a potential breakthrough in outpatient management because increased right-sided pressures, rather than weight gain, may precede a heart failure exacerbation.[35,36] It is, however, worthwhile to emphasize that routine hemodynamic monitoring with pulmonary artery catheterization has not been shown to be effective in the inpatient setting,[37] despite the attractiveness of "knowing the numbers." Additionally, the data supporting the use of serial measurements of biomarkers (in particular, brain natriuretic peptide or its precursor) as a surrogate for filling pressures are conflicting, and therefore this approach is not at present considered standard of care.[38]

Studies also suggest that postdischarge adherence and the intensity of follow-up for patients recently admitted for HF may be critical to ensure optimal outcomes. From a practical standpoint, the presence of defined risk factors should lead clinicians to adopt a selective approach to postdischarge monitoring. For those patients deemed to be at risk, reasonable options include outpatient medication titration, more frequent nurse contact, and focused efforts at increasing patient self-efficacy, all of which can be targeted in the context of a HF disease management program or HF clinic.[39,40] A recent consensus paper outlines the components that should be considered in the establishment of a clinic devoted to the care of patients with heart failure.[40] Given increasing reimbursement pressures, these clinics may provide a mechanism to increase quality of care in the outpatient setting while decreasing risk of readmission for "preventable" heart failure exacerbations. However, other nonphysiological factors influence readmission rates, and not all of these factors can be easily addressed in a traditional medical model.[41]

SUMMARY

Hyponatremia, in addition to declining renal function, persistent dyspnea, and weight gain, is a major clinical concern during and following hospitalizations for acute decompensated heart failure. Low serum sodium (especially below 130 mEq/L) can contribute to symptoms, complicate diagnostic and therapeutic decision-making, and significantly prolong length of stay and associated costs. Early recognition of the underlying etiologies, aggressive fluid restriction, and removal of medications that might exacerbate hyponatremia are key steps. The vaptan class is now a useful adjunct in select patients with hyponatremia and fluid overload who do not respond to standard approaches such as fluid restriction.

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