Review

Hyponatremia in Heart Failure: Revisiting Pathophysiology and Therapeutic Strategies

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ABSTRACT

Hyponatremia is frequently encountered in patients with heart failure (HF), and its association with adverse outcomes is well-established in this population. While hyponatremia is an independent marker for severity of HF, it is not certain whether it has a causal impact on the progression of the disease. There are no universally accepted consensus guidelines regarding therapeutic strategies for HF-associated hyponatremia and volume overload; current societal guidelines do not address management of this complication. Whereas thiazide diuretics are known to induce or worsen hyponatremia in this setting through a number of mechanisms, loop diuretics can be considered a readily available first-line pharmacologic therapy. Consistent with pathophysiology of the disease and mechanisms of action of loop diuretics, available clinical evidence supports such an approach provided that patients can be closely monitored. Use of vasopressin receptor antagonists is an emerging therapeutic strategy in this setting, and the efficacy of these agents has so far been shown in a number of clinical studies. These agents can be reserved for patients with HF in whom initial appropriate loop diuretic therapy fails to improve serum sodium levels.

Scope of the Problem

Hyponatremia, the most common electrolyte abnormality in hospitalized patients, is associated with increasing morbidity and mortality in various clinical settings, including heart failure (HF). In an analysis of the Organized Program To Initiate Life-Saving Treatment In Hospitalized Patients With Heart Failure (OPTIMIZE-HF) study comprising data on 47 647 admissions for acute decompensated HF (ADHF), 19.7% of the patients presented with hyponatremia, defined as a serum sodium (Na) level <135 mEq/L.[1] This subgroup of patients demonstrated significantly worse outcomes and was more likely to require dialysis and inotropic agents. The in-hospital mortality rate was also significantly higher compared with those patients with normal serum Na levels (6% vs 3.2%, $P < 0.0001$). Nearly half of the study population had preserved left ventricular ejection fraction (LVEF), suggesting that presence of hyponatremia is an independent predictor of outcomes in HF patients with both preserved as well as reduced LVEF, a concept that has been confirmed by other authors.[2,3] In another study on more than 4000 patients, Lee et al demonstrated that chronic hyponatremia (defined as serum Na level <136 mEq/L) increased the 30-day mortality by 53% and the 1-year mortality by 46% in patients admitted with a primary diagnosis of HF.[4] In addition to its impact on survival, in a study on patients with a discharge diagnosis of HF in 49 US academic medical centers, hyponatremia was shown to significantly increase the hospital length of stay.[5] HF being the most common reason for hospitalization in patients age >65 years, and with an annual cost exceeding $33 billion, even a slight increase in length of stay is likely to portend a significant adverse impact on the health-care economy. It is still not certain whether hyponatremia, an established marker for severity of HF, has also a causal effect on the progression of the disease. Current therapeutic approaches for HF-related hyponatremia are mainly derived from our understanding of the pathophysiology of the disease.

Pathophysiologic Mechanisms

Although the precise mechanisms are not yet clear, a number of factors contribute to hyponatremia in the setting of HF. These factors are either related to the underlying pathophysiology of the disease or due to the therapeutic strategies. With regard to volume status, 3 types of hyponatremia exist: hypovolemic, euvolemic, and hypervolemic. HF-associated hyponatremia is generally of the hypervolemic type; there is a disproportionate retention of both Na and water, with the increase in body fluid volume exceeding that of total Na content, resulting in low serum Na concentration. Decreased renal perfusion, activation of the renin-angiotensin-aldosterone system (RAAS), decreased delivery of Na to distal tubules (due to decreased glomerular filtration rate [GFR] and enhanced Na absorption in the proximal tubules), and impaired response to natriuretic peptides are among the factors leading to Na

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retention. Arterial underfilling (due to decreased cardiac output or peripheral vascular resistance) is sensed by baroreceptors that are located in various anatomic positions (eg, the carotid sinus, aortic arch, and renal afferent arteries) and activates the sympathetic nervous system (SNS), which results in diminished renal water (Table 1) and Na excretion. Enhanced activation of SNS leads to increased tubular reabsorption of Na, RAAS activation, and decrease in both GFR and Na filtration.[6] It has also been suggested that exhaustion of B-type natriuretic peptide synthesis might be the cause of Na retention in patients with dilated heart and advanced disease.[7] The impaired water excretion is due to: (1) enhanced reabsorption of the water in the proximal tubules, and (2) disturbance in the diluting capacity of the distal nephron. Enhanced activation of SNS in HF contributes to increased absorption of water in proximal tubules, with resultant reduced delivery to distal tubules (diluting section). Nonosmotic release of arginine vasopressin (AVP) is thought to play a crucial role in impairment of dilutional capacity of the distal nephron. Indeed, several studies on HF have shown disproportionate elevated serum AVP levels in relation to plasma osmolality.[8] Interestingly, acute water loading does not suppress the AVP levels in these patients, indicating discordance between AVP release and plasma osmolality.[8] Indeed, while the sensitivity of the osmotic control remains intact, it is reset, hence leading to persistent elevation in serum AVP levels in the presence of hyponatremia and hypo-osmolality. It should also be noted that angiotensin II is an inducer of thirst, further complicating the clinical picture through excessive free water intake by HF patients. The imbalance between compensatory mechanisms aiming at preservation of circulatory integrity in HF (eg, RAAS and SNS) can lead to disproportionate reabsorption of water, and hyponatremia. It is also noteworthy that renal dysfunction is a common comorbidity in HF, and disturbance in tubular function and free water excretion can lead to hyponatremia in a subset of patients with concomitant renal dysfunction. Finally, whether differential distribution of Na and a shift toward extravascular space (eg, pleural or peritoneal cavity) can play a role in development of hyponatremia in those patients with overt volume overload and congestion is to be explored. The mechanisms of Na and water retention are summarized in Table 1.

A number of therapeutic agents (eg, thiazide diuretics) can lead to development of hyponatremia in these patients. There are 3 requirements for maximal renal excretion of electrolyte-free water in the kidney: (1) delivery of enough fluid to the diluting segment of the nephron (eg, distal tubules), (2) intact mechanisms for reabsorption of the electrolytes in the diluting segment, and (3) water impermeability of collecting ducts due to absence of AVP.[9] Thiazide diuretics block sodium-chloride transport in the distal tubules, connecting segment, and possibly early cortical collecting tubules, therefore significantly impairing free water clearance. Whereas increased Na loss and disturbance in diluting capacity of the kidney remain the major mechanisms for thiazide-induced hyponatremia, reset osmostat (ie, normal diluting capacity at a lower serum Na level) secondary to intracellular potassium (K) depletion might also be responsible in certain cases. Normally, negative luminal charge (secondary to reabsorption of Na) induces K secretion in the distal tubules and cortical collecting ducts. Thiazide diuretics therefore portend a significant kaliuretic effect by enhancing increased delivery of Na to this part of the nephron. In addition, chloride (Cl) depletion due to blockade of Na-Cl cotransporter can also independently lead to increased kaliuresis.[9] The resultant intracellular K depletion causing reset osmostat might be the etiology of hyponatremia in certain cases of stable HF-associated hyponatremia. Not surprisingly, thiazide diuretics are considered one of the most common etiologies of hyponatremia. In a review of 129 patients with hyponatremia, Sonnenblick et al reported that the majority of cases (63%) were related to thiazide diuretics.[10]

Table 1. Mechanisms of Na and Water Retention in HF

Sodium	Water
Decreased renal perfusion	Enhanced SNS activation
Enhanced activation of RAAS	Increased resorption in proximal tubules
Enhanced SNS activation	Nonosmotic release of AVP
Decreased Na delivery to distal tubules	
Impaired response to natriuretic peptides	
Low level of BNP	

Abbreviations: AVP, arginine vasopressin; BNP, B-type natriuretic peptide; HF, heart failure; Na, sodium; RAAS, renin-angiotensin-aldosterone system; SNS, sympathetic nervous system.

Spironolactone, especially when used concomitantly with other diuretics, can be a contributing factor in the development of hyponatremia in patients with HF. While the exact mechanisms are not yet well understood, it has been suggested that excessive natriuretic response might result in volume loss, decrease in GFR, and enhanced reabsorption of water in proximal tubules.[11] In a study on 114 patients initiated on spironolactone therapy for HF, Sligl et al reported discontinuation of this medication in 7 patients (6%) due to development of dehydration/hyponatremia.[12]

Indapamide has been used for treatment of hypertension, often in combination with other drugs. It facilitates the action of nitric oxide and stimulates prostacyclin production, as well as affecting the proximal segment of the distal tubules, interfering with the transport of Na ions across the tubular

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cells.[13] Therefore, it portends a renal adverse effect profile similar to that of thiazide diuretics. Its use, especially if concomitant with blockers of RAAS, hydrochlorothiazide, or other drugs that can potentially reduce serum Na levels (eg, selective serotonin reuptake inhibitors), might cause hyponatremia in patients with HF.

Finally, it should be noted as a reminder that common comorbidities such as diabetes with uncontrolled hyperglycemia might play a role in the development or worsening of hyponatremia in these patients. Moreover, other noncardiac causes of hyponatremia such as hypothyroidism (eg, amiodarone induced) might coexist in patients with HF and need to be considered in the diagnostic and therapeutic approaches. The causes of hyponatremia are summarized in Table 2.

Conventional Management Strategies

Management of hyponatremia remains challenging, with only few therapeutic options available.[14] Traditionally, patients are advised to restrict their free water intake. Since enhanced RAAS activation is a known feature of HF, and angiotensin is a known mediator of thirst, fluid restriction is both uncomfortable and unsuccessful in many cases. Loop diuretics remain the mainstay of therapy in HF patients with edema and congestive symptoms. They inhibit the transport of Na-K-Cl in the thick ascending limb of the loop of Henle. Many physicians have reservations about using loop diuretics in the setting of HF-associated hyponatremia, with the fear of further decreasing serum Na levels. However, in contrast to thiazides, loop diuretics generally interfere with the concentrating ability of the kidneys, hence increasing free water excretion and improving hyponatremia. Although Na excretion leads to a reduction in total body Na content, the urine produced by loop diuretics is hypotonic and contains only about 60 mEq/L Na.[15] Therefore, while decreasing both total body water volume and Na content, the net effect of loop diuretics on fluid and electrolyte balance is expected to be a gradual increase in serum Na concentrations.

It is noteworthy, however, that in certain circumstances use of loop diuretics might not result in improvement of hyponatremia. Since loop diuretics significantly increase the delivery of Na to macula densa, they lead to further activation of RAAS. Angiotensin II is a known mediator for AVP secretion and can therefore promote retention of water and exacerbation of hyponatremia.[16] Moreover, long-term use of diuretics or extrarenal loss of Na (eg, chronic diarrhea secondary to edema of the intestinal epithelium) could eventually reduce total body Na content; loop diuretics might contribute to worsening of hyponatremia by further Na depletion (hypovolemic hyponatremia). Concomitant administration of low-dose isotonic saline solution might be helpful in this specific setting, with close monitoring of urine output and urine osmolality. In the study by Sonnenblick et al, loop diuretics were implicated in 6% of the cases with severe hyponatremia.[10] It is imperative to closely monitor serum Na levels in any HF patients for whom loop diuretics are used to treat hyponatremia.

Table 2. Causes of Hyponatremia in HF

Activation of neurohormonal axis (ie, nonosmotic release of AVP, RAAS, SNS)
Increased thirst due to high levels of angiotensin II
Disturbance in renal diluting mechanisms and water excretion
Increased Na excretion (due to initially elevated levels of natriuretic peptides)
Medications (eg, thiazide diuretics and spironolactone)
Comorbidities (eg, uncontrolled hyperglycemia and hypothyroidism)

Abbreviations: AVP, arginine vasopressin; HF, heart failure; Na, sodium; RAAS, renin-angiotensin-aldosterone system; SNS, sympathetic nervous system.

Newer Management Strategy

Hypertonic saline has been used in severe cases of hyponatremia due to various etiologies. In a study on 9 patients with ADHF and hyponatremia (mean serum Na level 131 mEq/L), Issa et al did not report any worsening in pulmonary congestion with use of hypertonic saline, and found an increase in urine output and reduction in serum blood urea nitrogen (BUN) with no significant change in weight.[17] In a randomized single-blind study on 107 patients with refractory HF, Licata et al used intravenous (IV) furosemide combined with small volumes of hypertonic saline, and compared the results with those of patients who received only IV furosemide.[18] While the first group showed significant improvement in their hyponatremia (increase in serum Na from 135.8 to 142.3 mEq/L, $P < 0.001$), serum Na levels decreased in those patients who received furosemide alone (134.8 to 130.2 mEq/L, $P < 0.007$). Importantly, use of hypertonic saline was not associated with increased congestion and change in HF functional class. Moreover, readmission rate and hospital mortality were significantly lower in those patients who received hypertonic saline. This therapeutic strategy has also been mentioned in the most recent guidelines of the Canadian Cardiovascular Society for efficient decongestion through use of high-dose diuretics while limiting the risk of hyponatremia.[19] The beneficial effects of hypertonic solution and high-Na diet can be related to the effect on prostacyclin synthesis and nitric oxide-dependent vasodilation as well

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as various other cytokines and neurohormonal changes.[20] Such a counterintuitive approach underscores the need for a precise and comprehensive understanding of the pathophysiologic mechanisms that underlie HF and fluid-electrolyte balance in this setting; there are still concerns about its safety, however, and it is not currently considered a routinely recommended treatment strategy. Larger studies with long-term follow-up are needed to confirm the results of these trials before its widespread use.[21,22] Current guidelines recommend that this strategy be used only under the supervision of a physician with extensive expertise in its application.[19] Similarly, a more recent therapeutic approach comprising high-dose oral furosemide and higher daily Na intake associated with fluid restriction has been reported to portend beneficial effects with very promising results in chronic HF patients; it is also likely to lower the incidence of hyponatremia in this patient population.[23–26]

Vasopressin receptor antagonists (VRA), also called aquaretics or vaptans, represent the emerging strategy for treatment of HF-associated hyponatremia. Three types of vasopressin receptors have been identified with distinct functions: V1a, V1b, and V2. Vasopressin increases blood volume and decreases Na concentration by promoting free water retention through the V2 receptors on principal cells of the renal cortical collecting ducts. With currently no available therapy to reduce secretion of vasopressin, interest has turned to blockade of its receptors. VRA, originally used for the correction of hyponatremia in the context of syndromes of inappropriate antidiuretic hormone (ADH) secretion or cirrhosis, are potentially capable of ameliorating fluid overload and hyponatremia in HF patients through excretion of electrolyte-free water. The VRA that have been most extensively studied are the selective V2 receptor antagonists tolvaptan, satavaptan, and lixivaptan, in addition to the dual V1a/V2 receptor antagonist conivaptan. Tolvaptan has been more frequently tested in trials of HF patients.

In 2001, Udelson et al published the results of a randomized, placebo-controlled study using short-term therapy with conivaptan to define hemodynamic and urinary responses in patients with stable HF.[27] Conivaptan significantly increased urine output in a dose-dependent manner during the first 4 hours after the injection. Urine osmolality was significantly reduced compared with placebo, without any change in plasma osmolality. However, the change in serum Na level was not significantly different from placebo. Later, Gheorghiade et al evaluated the effects of different dosage regimens of tolvaptan in a randomized trial on 254 patients with chronic HF.[28] The authors reported that the changes in serum Na levels were significantly different between tolvaptan groups and the placebo group at all time points; in hyponatremic patients, normalization was seen in 82% and 40%, respectively, at the last assessment during treatment. Tolvaptan was used in another randomized controlled trial on 319 patients with worsening HF and an LVEF of <40%.[29] Different oral dosing regimens were used for up to 60 days. Patients with hyponatremia (21.3%) showed rapid increase, and often normalization, in serum Na, which was sustained throughout the study.

Recently, the results of the Efficacy of Vasopressin Antagonism in Heart Failure Outcome Study With Tolvaptan (EVEREST) studies in ADHF were published.[30] These large, randomized, double-blind, placebo-controlled studies tested the benefit of tolvaptan in 3 clinical trials: 2 identical short-term and 1 longer-term safety and outcome protocol. More than 4000 patients from 20 countries were included. The tolvaptan group showed sustained reduction in body weight, as well as sustained normalization of serum Na levels in patients with baseline hyponatremia, but it did not show any beneficial effect on long-term mortality or HF-related morbidity. It is not clear whether V1/V2 receptor antagonists portend outcome benefits that are not seen with tolvaptan or other V1 receptor antagonists. The results of randomized controlled trials that exclusively used VRA in patients with HF are summarized in Table 3.

While the results support a beneficial impact on serum Na levels, lack of evidence on long-term beneficial effects, absence of disease-modifying properties, risk of overcorrection, and cost are among the concerns that have so far hindered widespread use of VRA. It is noteworthy that impact on hyponatremia has not been the primary endpoint in the HF trials, and these agents have frequently been used concomitantly with conventional therapy. Indeed, patients included in these trials were not all hyponatremic, indicating that similar favorable results (eg, hemodynamic changes) can also be seen in HF patients without hyponatremia. As outlined in Table 2, most studies did not report the baseline Na levels and did not include analysis specific to hyponatremic patients. However, other trials supporting the efficacy of VRA in the treatment of euvolemic or hypervolemic hyponatremia have often included a significant number of HF patients.[36] The Treatment of Hyponatremia Based on Lixivaptan in NYHA Class III/IV Cardiac Patient Evaluation (BALANCE) trial is an ongoing large-scale multicenter study that will specifically focus on the subgroup of HF patients with hyponatremia and will evaluate the impact of lixivaptan on all-cause mortality and morbidity in these patients.

Practical Therapeutic Approach

In order to prevent the development of hyponatremia in patients with HF, they should be instructed to avoid excessive consumption of Na-free fluids as well as concurrent use of medications with the potential side effect of lowering serum Na levels. As deterioration in renal function is a potential cause of hyponatremia in these patients, preservation of renal function is likely to help prevent the decrease in serum Na. Once hyponatremia is

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Table 3. Summary of Studies on VRA in Heart Failure

Study	Drug	No. of Patients	Study Population	Study Design	Baseline Serum Na (mEq/L)	Change in Serum Na	Urine Findings	Comment
Udelson et al (2001)[11]	Conivaptan	142	NYHA class III, IV HF	Randomized, double-blind, placebo-controlled; single IV dose (10, 20, or 40 mg)	137	No significant change	Dose-dependent increase in UOP; decrease in urine osmolality	Favorable changes in hemodynamics. Renal function not reported.
Gheorghiade et al (2003)[12]	Tolvaptan	254	Chronic stable HF	Randomized, double-blind, placebo-controlled; once-daily dose (30, 45, or 60 mg) for 25 d	NR	Small mean increase (<4 mEq/L) for tolvaptan groups vs small decrease in placebo group (<1 mEq/L) in overall population	Urine osmolality increase in tolvaptan groups	Normonatremic patients: an acute transient increase in serum Na levels. Hyponatremic patients: a greater increase in serum Na. No significant change in renal function.
Gheorghiade et al (2004)[13]	Tolvaptan	319	ADHF; LVEF <40%	Randomized, double-blind, placebo-controlled; daily dose (30, 60, or 90 mg) for up to 60 d	139	Small mean increase (2.77–3.5 mEq/L) for drug groups vs small decrease (0.2 mEq/L) in placebo group	NR	Hyponatremic patients (21.3%): rapid increase in serum Na sustained throughout the study. Significant reduction in body weight in drug groups. No significant change in renal function.
Abraham et al (2006)[15]	Lixivaptan	42	Chronic HF, NYHA class II, III	Randomized, double-blind, placebo-controlled; single dose (10, 30, 75, 150, 250, or 400 mg)	NR	Significantly higher at 2 and 4 h with doses of 150 and 250 mg	Significant increase in UOP; dose-dependent decrease in urine osmolality for all lixivaptan groups	Significant solute-free water excretion during the first 2 h. No significant change in BUN.
Costello-Boerrigter et al (2006)[16]	Tolvaptan	14	Stable HF, NYHA class II, III; LVEF <40%	Randomized, open-label, placebo-controlled, crossover; single dose (30 mg), followed by furosemide (80 mg) on d 5	NR	No significant change compared with furosemide or placebo	Tolvaptan and furosemide significantly increased urine flow; both significantly decreased urine osmolality	Furosemide significantly decreased renal blood flow compared with both tolvaptan and placebo. No change in GFR.

continued

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Table 3. (*continued*)

Study	Drug	No. of Patients	Study Population	Study Design	Baseline Serum Na (mEq/L)	Change in Serum Na	Urine Findings	Comment
Konstam et al (2007)[14]	Tolvaptan	4133	ADHF	Randomized, double-blind, placebo-controlled; daily dose (30 mg) for a minimum of 60 d	NR	Hyponatremic patients: significant increase (5.49 mEq/L) at d 7 or discharge, which was maintained through 40-wk treatment	NR	Significant decrease in body weight. Significant decrease in BUN and significant increase in serum creatinine levels. No impact on long-term mortality or HF-related morbidity.
Udelson et al (2007)[17]	Tolvaptan	240	NYHA class II, III HF	Randomized, double-blind, placebo-controlled; daily dose (30 mg) for 1 y	140	No significant change	NR	No significant change in weight. No significant change in renal function.
Goldsmith et al (2008)[18]	Conivaptan	170	ADHF	Randomized, double-blind, placebo-controlled; 20 mg loading dose followed by 2 continuous IV infusions of 40, 80, or 120 mg/d	NR	Dose-dependent increase of 1.38–2.4 mEq/L	Dose-dependent increase in UOP	No significant change in body weight. No significant change in renal function.
Udelson et al (2008)[19]	Tolvaptan	181	NYHA class III, IV HF	Randomized, double-blind, placebo-controlled; single dose (15, 30, or 60 mg)	NR	No significant change	Dose-dependent increase in UOP; significant decrease in urine osmolality	Favorable but modest changes in filling pressures. No significant change in renal function.

Abbreviations: ADHF, acute decompensated heart failure; BUN, blood urea nitrogen; GFR, glomerular filtration rate; HF, heart failure; IV, intravenous; LVEF, left ventricular ejection fraction; Na, sodium; NR, not reported; NYHA, New York Heart Association; UOP: urine output.

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Table 4. Practical Therapeutic Approach to Hyponatremia in HF

Establish the diagnosis of HF-related hypervolemic hyponatremia via history, physical exam, and laboratory studies; rule out noncardiac causes (eg, hyperglycemia, medications, and diarrhea).
Limit Na-free fluid intake (replace IV medication carriers to isotonic Na-containing solution in the inpatient setting).
Prescribe IV loop diuretics with close monitoring of serum Na (can be accompanied by simultaneous administration of hypertonic or isotonic saline solution in selected patients under supervision of an experienced physician).
Prescribe oral or IV VRA with close monitoring of serum Na to avoid rapid increase in serum Na and overcorrection.
Institute RRT (eg, hemodialysis), especially in patients with concomitant severe renal dysfunction.

Abbreviations: HF, heart failure; IV, intravenous; Na, sodium; RRT, renal replacement therapy; VRA, vasopressin receptor antagonist.

encountered, it is necessary first to rule out noncardiac causes such as medications (eg, selective serotonin reuptake inhibitors), laxative use or diarrhea, and syndrome of inappropriate secretion of ADH (eg, postoperative pain and nausea). The diagnostic approach to hyponatremia is out of the scope of this article. Once the diagnosis of HF-associated hypervolemic hyponatremia is established, fluid restriction can be recommended, especially if there is a suspicion of excessive intake of solute-free water. The next step would be instauration of loop diuretic therapy while closely monitoring serum Na levels. A subset of patients with HF presents with diuretic resistance, a term that is commonly used but still lacks a widely accepted definition. Strategies available to enhance diuretic responsiveness in hospitalized patients include progressive escalation of the dose, use of IV route, and infusion rather than bolus administration. These strategies ideally should be tried before a patient without sufficient increase in urine output can be considered resistant to diuretics. In case of suspicion for "hypovolemic" HF-related hyponatremia based on the history and laboratory results (eg, low urine Na concentration despite use of diuretics in a patient with severe diarrhea and hypotension), isotonic IV solution alone or in combination with a loop diuretic can be used to simultaneously replenish intravascular volume while increasing free water clearance. It is important to note that administration of isotonic fluid alone to a hyponatremic patient with high urine osmolality can paradoxically reduce serum Na levels in the presence of inappropriately elevated AVP levels. If hyponatremia does not improve despite therapy, cautious use of VRA is indicated. Rapid rise in serum Na level and overcorrection are potential adverse consequences, although they have not been reported in clinical trials. In cases of concomitant severe renal dysfunction and refractory volume overload, extracorporeal therapy such as hemodialysis using low-concentration Na dialysate (to avoid rapid correction) is indicated. However, volume overload or other indications in these severe cases frequently mandate use of dialytic therapy even before serum Na reaches a critically low level. While ultrafiltration is efficient at rapid removal of fluid and improvement in congestive symptoms, it cannot treat hyponatremia; a renal-replacement therapy technique using exchange or substitution fluid (eg, hemodialysis) is needed for this purpose.[37] The therapeutic approach to hyponatremia in HF is summarized in Table 4.

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