THE PRESENT AND FUTURE

STATE-OF-THE-ART REVIEW

Hyponatremia in Acute Decompensated Heart Failure
Depletion Versus Dilution

Frederik H. Verbrugge, MD,*  Paul Steels, MD,†  Lars Grieten, PhD,‡  Petra Nijst, MD,*  W.H. Wilson Tang, MD,∥  Wilfried Mullens, MD, PhD*  

ABSTRACT

Hyponatremia frequently poses a therapeutic challenge in acute decompensated heart failure (ADHF). Treating physicians should differentiate between depletional versus dilutional hyponatremia. The former is caused by diuretic agents, which enhance sodium excretion, often with concomitant potassium/magnesium losses. This can be treated with isotonic saline, whereas potassium/magnesium administration may be helpful if plasma concentrations are low. In contrast, as impaired water excretion, rather than sodium deficiency, is the culprit in dilutional hyponatremia, isotonic saline administration may further depress the serum sodium concentration. Because free water excretion is achieved by continuous sodium reabsorption in distal nephron segments with low water permeability, diuretic agents that impair this mechanism (e.g., thiazide-type diuretic agents and mineralocorticoid receptor antagonists) should be avoided, and proximally acting agents (e.g., acetazolamide and loop diuretic agents) are preferred. Vasopressin antagonists, which promote low water permeability in the collecting ducts and, hence, free water excretion, remain under investigation for dilutional hyponatremia in ADHF. (J Am Coll Cardiol 2015;65:480–92) © 2015 by the American College of Cardiology Foundation.

Hyponatremia, defined as a serum sodium (Na⁺) concentration <135 mEq/l, is the most common electrolyte disorder in hospitalized patients (1). Both admission and hospital-acquired hyponatremia are associated with an increased risk for adverse outcomes, including prolonged hospital stay, need for discharge to a short- or long-term care facility, and all-cause mortality (2). In a subanalysis from the OPTIMIZE-HF (Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients with Heart Failure) registry, including 47,647 patients with acute decompensated heart failure (ADHF), hyponatremia was present in ~20% upon admission (3). In addition, the incidence of hospital-acquired hyponatremia during decongestive treatment for ADHF is probably ~15% to 25% (4,5). Hyponatremia frequently poses an important therapeutic challenge in ADHF because simple administration of the depleted ion (as with other deficiencies) cannot be easily performed, and there is an obvious concern for harmful fluid overload. Moreover, the pathophysiology of hyponatremia in ADHF is often dilutional, rather than depletional (6,7). Importantly, ubiquitous use of powerful Na⁺-wasting diuretic agents in this context hampers differentiation between the 2 conditions, each of which requires a totally different approach. This review, therefore, aims to provide, on the basis of the currently

From the *Department of Cardiology, Ziekenhuis Oost-Limburg, Genk, Belgium; †Doctoral School for Medicine and Life Sciences, Hasselt University, Diepenbeek, Belgium; ‡Biomedical Research Institute, Faculty of Medicine and Life Sciences, Hasselt University, Diepenbeek, Belgium; and the ∥Department of Cardiovascular Medicine, Heart and Vascular Institute, Cleveland Clinic, Cleveland, Ohio. Dr. Verbrugge is supported by a PhD fellowship from the Research Foundation-Flanders. Drs. Verbrugge, Grieten, Nijst, and Mullens are researchers for the Limburg Clinical Research Program UHasselt-ZOL-Jessa, supported by the foundation Limburg Sterk Merk, Hasselt University, Ziekenhuis Oost-Limburg, and Jessa Hospital. Drs. Steels and Tang have reported that they have no relationships relevant to the contents of this paper to disclose.

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available evidence, a pathophysiology-based assessment and management strategy for the important clinical challenge of hyponatremia in ADHF.

**PATHOPHYSIOLOGY OF HYponatREMIA IN ADHF**

Table 1 provides a summary of the pathophysiology of hyponatremia in ADHF.

**Dilutional hyponatremia.** It is generally assumed that hyponatremia in ADHF is more often a problem of impaired water excretion than Na⁺ depletion (6,7). Two key events driving increased water retention and progression of hyponatremia in ADHF are increased nonosmotic release of arginine vasopressin (AVP) and insufficient tubular flow through diluting (distal) segments of the nephron. In many ways, this is the opposite of the situation in diabetes insipidus, where deficient AVP production and/or function in the presence of normal tubular flow results in very diluted urine, exaggerated water losses, and, ultimately, in hypernatremia, unless compensation occurs through increased water intake.

**AVP and regulation of plasma osmolality.** AVP, a cyclic octapeptide (1,099 D) with a 3-amino acid tail, is a key regulator of water homeostasis. AVP is synthesized in large-diameter neurons in the supraoptic and paraventricular nuclei of the anterior hypothalamus. After axonal transport into nerve terminals within the posterior lobe of the pituitary, AVP is released into the bloodstream in response to plasma hypertonicity (8). In healthy, normally hydrated persons, circulating AVP levels are very low (~1 pg/ml) because of its rapid degradation and excretion by the liver and kidneys (t½ = 15 to 20 min) (9). Consequently, hepatic dysfunction and renal insufficiency may contribute to increased plasma levels of AVP in ADHF. AVP exerts its water-retaining effects primarily through stimulation of high-affinity V₂ receptors in the collecting ducts of the nephron (Figure 1) (9). V₂ stimulation increases both the synthesis and availability of aquaporin-2 channels on the luminal side of these collecting ducts, which otherwise have low water permeability (10). The hypertonic environment of the renal interstitium subsequently provides a strong impetus for water reabsorption, resulting in decreased water excretion and, consequently, less diuresis. Importantly, this system is very sensitive to small changes in plasma AVP levels, which are difficult to detect, even by modern assays (11). At higher concentrations, the low-affinity V₁a receptor, which is expressed in the liver, collection ducts, and vasa recta of the nephron, is stimulated (Figure 1). This further enhances hypertonicity in the renal interstitium—hence antidiuresis—through increased hepatic urea production, improved medullary urea reabsorption in the collecting ducts, and reduced blood flow through the vasa recta (Figure 1) (12,13). The vasa recta are straight capillaries in the renal medulla with a hairpin loop. They receive a lower proportion of blood flow compared with the renal cortex, especially during antidiuresis. This is important, as high blood flow through the vasa recta washes out the tonic gradient from the renal cortex toward the medulla, which is needed to concentrate the urine. Finally, another effect of V₁a receptor stimulation is promotion of prostaglandin synthesis in the collecting ducts. This counteracts V₂ effects on aquaporin-2, thus stimulating water excretion (14). This latter effect may explain why some heart failure patients demonstrate a normal response to water loading, with production of adequately diluted urine, despite having elevated plasma AVP levels (15).

**Nonosmotic arginine vasopressin release in heart failure.** Several studies have demonstrated that AVP levels are generally elevated in heart failure (16-18). Moreover, aquaporin-2 expression was markedly up-regulated in a rat model of congestive heart failure (19), which would be expected to increase water permeability and reabsorption in the collecting ducts of the nephron. It is tempting to speculate that both events are causally related and promoting excessive free water reabsorption, leading to hyponatremia in ADHF. Certainly, baroreceptor activity, sympathetic overdrive, and angiotensin II, all stimulated by decreased effective circulatory...
Results of AVP in the Nephron

FIGURE 1

V_{2}-receptor effects: The primary effect of AVP on water homeostasis is mediated through stimulation of high-affinity V_{2} receptors, already with small increases in plasma levels (9). V_{2}-receptor stimulation in collecting duct cells results in increased production of AP2 channels and facilitates recruitment of these channels on the luminal membrane, which otherwise has low water permeability (10). Subsequently, water reabsorption is promoted as the renal interstitium is hypertonic and the basolateral membrane of collecting duct cells is highly permeable to water. Hypertonicity in the renal interstitium is accomplished through solute reabsorption in parts of the nephron that have relatively low water permeability, that is, sodium and chloride transport in the TAL and urea reabsorption in the medullary part of the collecting ducts through UT-A1 transporters.

V_{1a}-receptor effects: At high plasma levels, AVP further stimulates hypertonicity in the renal interstitium, and hence water reabsorption, through activation of the low-affinity V_{1a} receptor. First, this promotes both hepatic urea production and UT-A1 transport in the medullary part of the collecting ducts, resulting in higher urea concentrations and a stronger osmotic gradient in the renal interstitium. Furthermore, V_{1a} receptor stimulation causes vasoconstriction in the vasa recta, preventing wash-out of solutes from the renal medulla (12,13). On the other hand, V_{1a} receptor stimulation in collecting duct cells also promotes prostaglandin synthesis. Prostaglandins counteract the effects of V_{2} by impeding AP2 recruitment in these collecting duct cells (14). This somewhat preserves the diluting capacity of the distal nephron, even when AVP levels are high because of neurohumoral activation and nonosmotic AVP release. AP2 = aquaporin-2; AVP = arginine vasopressin; TAL = thick ascending limb of Henle’s loop.

Yet, with the GFR lowered to 43.2 l/day (30 ml/min), only 5% distal tubular flow because of increased proximal reabsorption in ADHF, maximal water intake without hyponatremia development would be decreased tremendously to 2.16 l/day (5% of 43.2 l/day) (28,29). The latter is even an overestimate, as it presumes that water permeability in the distal nephron is as low as with total AVP suppression, which is clearly not the case in ADHF (Figure 3A). An intriguing study by Bell et al. (30) further supports the concept of decreased distal nephron flow in AHDF. In this study, free water excretion was increased in ADHF patients with hyponatremia after infusion of 5% mannitol, an osmotic diuretic that enhances tubular flow through the
nephron. Mannitol exerts its diuretic effect through solvent drag and water retention in the tubular lumen, thereby also increasing distal delivery. Similar findings have been demonstrated in patients with cirrhosis, where the effective circulatory volume and renal perfusion are also impaired (31). However, it remains possible that correction of hyponatremia with mannitol in ADHF and cirrhosis is partly due to increased intravascular volume after infusion, suppressing baroreceptor tonus and, hence, nonosmotic AVP release (32).

**DEPLETIONAL HYponatremia.** Because increased Na⁺ avidity characterizes heart failure from the very beginning and is exacerbated by unrestrained neurohumoral up-regulation, Na⁺ depletion is relatively rare in ADHF not treated with diuretic agents (33,34). Still, osmotic diuresis because of hyperglycemia in the case of severe uncontrolled diabetes, gastrointestinal losses, and third-space losses may all contribute to a negative Na⁺ balance, especially if patients adhere scrupulously to the salt-restricted diets recommended by the guidelines (35-37). One group called these diets into question, demonstrating that heart failure patients adhering to such diets experienced increased hospitalizations and a higher mortality rate (38-40). However, it should be noted that these patients also received a high dose of diuretic agents (125 to 500 mg furosemide equivalents twice daily), increasing the risk of a negative Na⁺ balance. Indeed, the combination of very low dietary sodium intake and exaggerated losses might lead to progressive depletion of whole-body sodium stores.

**Loop diuretic-induced hyponatremia.** The use of powerful Na⁺-wasting loop diuretic agents is nearly ubiquitous in ADHF, with 88% of patients in ADHERE (Acute Decompensated Heart Failure Registry) receiving them (41). Moreover, 70% continue to receive daily maintenance therapy with loop diuretic agents, although many are probably not persistently volume-overloaded. Loop diuretic agents block the Na⁺/potassium/chloride cotransporter in the thick ascending limb of Henle’s loop (TAL). Na⁺ and chloride transport in the TAL, which has a relatively low water permeability, makes a crucial contribution to the hypertonicity of the renal interstitium, in addition to the other important factor, medullary urea transport in the collecting ducts (42,43). This hypertonicity, washed out by blood flow through the vasa recta with inhibition of TAL transport by loop diuretic agents, is the major driver of water reabsorption in the distal nephron. Because of this interference of loop diuretic agents with the renal capacity to concentrate urine, less free water is reabsorbed, resulting in production of hypotonic urine and, therefore, relative protection against hyponatremia (Figure 4A) (44). However, in conditions of profound volume depletion with strong neurohumoral activation and compromised renal blood flow, loop diuretic agents will fail to elicit meaningful water diuresis. Eventually, GFR and distal nephron flow will become depressed in the presence of strongly up-regulated AVP, creating the necessary environment for hyponatremia development (29).

**Other diuretic agents and hyponatremia.** Mineralocorticoid receptor antagonists (MRAs) are a cornerstone in the treatment of heart failure with reduced ejection fraction and are promising in selected patients with preserved ejection fraction...
(A) Through glomerular filtration, a healthy person forms 180 l of tubular fluid each day. As the proximal tubules, thin descending limb, and ascending limb of Henle’s loop all have high water permeability, reabsorption in these nephron segments is isotonic, and tonicity of the tubular fluid remains at 285 to 295 mOsm/l, equal to plasma. In contrast, the TAL has low water permeability. Thus, solutes in general and sodium/chloride in particular are reabsorbed without water, contributing to the hypertonicity of the renal interstitium. Consequently, osmolality is relatively stable (~150 mOsm/l) in the tubular lumen at the level of the macula densa, at which point 90% of reabsorption has occurred, with 10%, or 18 l, remaining on a daily basis (25). In the case of total AVP suppression, the distal nephron has very low water permeability, while sodium and chloride are continuously reabsorbed; therefore, urine can be diluted up to 30 to 60 mOsm/l. Consequently, almost 18 l of free water excretion can be achieved, which is the maximum a person can drink without developing plasma hypotonicity and hyponatremia. (B) Maximal free water excretion in a patient with heart failure and a GFR of 30 ml/min is considerably lower. In this case, 43.2 l of tubular fluid is formed each day. As proximal tubular reabsorption increases in heart failure, only 5% or 2.16 l of tubular fluid remains at the level of the macula densa, again with an osmolality of ~150 mOsm/l (25). As AVP is typically increased in heart failure and the minimal medullar tonicity is greater because of poor flow through the vasa recta, the osmotic gradient for water reabsorption is increased in the presence of a more leaky distal nephron. Thus, water is continuously reabsorbed, limiting maximal free water excretion to <1 l. This realistic example illustrates how difficult it can be for a patient to prevent hyponatremia progression with fluid restriction only. GFR = glomerular filtration rate; other abbreviations as in Figure 1.
(A) Loop diuretic agents block the sodium/chloride/potassium cotransporter in the TAL, interfering with the generation of hypertonicity in the renal interstitium and decreasing the osmotic gradient that promotes water reabsorption. Loop diuretic agents have no effect on sodium or chloride transport in the distal nephron, which has low water permeability, and they therefore do not interfere with the kidneys' capacity to produce hypotonic urine. (B) Thiazide-type diuretic agents block the sodium/chloride symporter, whereas MRAs inhibit ENaCs in the distal nephron. As both make a negligible contribution to the hypertonicity achieved in the renal interstitium, thiazide-type diuretic agents and MRAs do not interfere with the water reabsorption gradient. However, as sodium and chloride reabsorption in the relatively water-impermeable distal nephron is the mechanism of urinary dilution, this process is impaired, resulting in a higher urinary tonicity and, hence, lower free water excretion compared with loop diuretic agents. ENaC = epithelial sodium channel; MRA = mineralocorticoid receptor antagonists; other abbreviations as in Figure 1.
Hyponatremia in Decompensated Heart Failure

(45,46). Together with thiazide-type diuretic agents, often recommended as first-line therapy in case of loop diuretic resistance, they interfere with sodium reabsorption by ENaCs and Na\(^+\)/chloride cotransporters, respectively, in the distal convoluted tubules and collecting ducts (Figure 4B) (47). Thus, they have a direct effect on the diluting tubular segments of the kidneys and may cause hyponatremia, even without pronounced hypovolemia, as they generate less hypotonic urine (47-49). From a pathophysiological perspective, it is, therefore, prudent to avoid their use in any patient with hyponatremia—at least temporarily, until serum sodium levels are corrected—and to prefer a proximally working diuretic (e.g., acetazolamide) in such cases with volume overload and diuretic resistance (29).

**Potassium and magnesium depletion.** Both loop- and thiazide-type diuretic agents are a major cause of potassium and magnesium wasting in ADHF. This may have important implications, such as a higher risk of arrhythmic death (50). In addition, potassium depletion shifts Na\(^+\) towards the intracellular compartment to preserve cellular volume homeostasis, which may contribute to development of hyponatremia (51). Indeed, intracellular Na\(^+\) concentrations are higher in muscle cells of ADHF patients with hypokalemia (52). Furthermore, magnesium is critical for functioning of the Na\(^+\)/potassium ATPase that pumps Na\(^+\) out of cells; thus, hypomagnesemia may also exacerbate extracellular Na\(^+\) depletion.

**Initial Approach to Hyponatremia in Decompensated Heart Failure**

The Central Illustration presents a stepwise diagnostic and therapeutic approach to hyponatremia in decompensated heart failure.

**Confirm Plasma Hypotonicity.** In patients with hyponatremia, the first step is generally to assess whether plasma hypotonicity is present by measuring the plasma osmolality (reference value: 285 to 295 mOsm/l). This may not be necessary when hyponatremia is mild (serum Na\(^+\) concentration <130 mEq/l), asymptomatic, and easily corrected by empiric treatment. Elevated triglyceride or cholesterol levels, immunoglobulins, and monoclonal gammopathies—through laboratory artifacts—may all cause falsely low serum Na\(^+\) concentrations without affecting plasma osmolality (53-55). Additionally, the presence of effective osmoles raising serum osmolality—most notably glucose in uncontrolled diabetes and/or hyperosmolar radiocontrast media—may result in hyponatremia with normal, or even high, plasma tonicity (56,57). Indeed, the serum Na\(^+\) concentration decreases by approximately 2.4 mEq/l per 100 mg/dl increase in serum glucose (56). If these underlying causes are managed appropriately, hyponatremia is probably not associated with worse outcome (58).

**Avoid and Treat Depletional Hyponatremia.** In any patient with hypotonic hyponatremia, it is best to avoid thiazide-type diuretic agents, MRAs, and ENaC blockers (e.g., amiloride), as these medications interfere directly with the kidneys’ capacity to produce hypotonic urine. However, it should be stressed that this advice is purely on the basis of the pathophysiological rationale, as high-quality evidence is lacking. Further, potassium and magnesium stores should be replenished if serum levels are low. We propose aiming for serum potassium levels ≥4 mEq/l and magnesium levels ≥1.7 mEq/l (≥2 mg/dl) in ADHF patients presenting with hyponatremia, but this cutoff is arguably somewhat arbitrary.

**Distinguish Between Depletional and Dilutional Hyponatremia.** In ADHF, clinicians should differentiate between depletional hyponatremia, requiring the administration of saline, versus dilutional hyponatremia, where free water excretion should be promoted. Acute gastrointestinal or third-space losses, clinical signs of hypovolemia, and recent use of diuretic agents—especially at high doses or in combination therapy—increased the likelihood of depletional hyponatremia. In this case, production of hypotonic urine is promoted by the administration of isotonic saline, with subsequent normalization of serum sodium levels. In contrast, it would be impossible to correct dilutional hyponatremia with isotonic saline, as free water excretion is compromised and hypotonic urine production is impaired. One might consider a fluid challenge with 1 l of isotonic saline over 24 h to differentiate between these conditions, measuring the effect on serum sodium levels. However, this should be avoided in case of clear fluid overload and/or severe hyponatremia (serum sodium <125 mEq/l). Indeed, signs of volume overload indicate a component of dilutional hyponatremia, in which case an improvement is unlikely, and the risk of further deteriorating congestion is substantial. Further worsening of hyponatremia should certainly be avoided in patients with severe hyponatremia. Alternatively, one could measure urine osmolality, which should be adequately suppressed (<100 mOsm/l) in patients with depletional hyponatremia, but not in patients with dilutional hyponatremia. If urine osmolality is >150 mOsm/l, isotonic solutions should certainly be avoided, as administration would result in further worsening of
A flowchart with a stepwise diagnostic approach to hyponatremia in decompensated heart failure is presented. Therapeutic options are proposed according to the underlying pathophysiological culprit. AVP = arginine vasopressin.
hyponatremia. Finally, very low urinary Na\(^+\) and/or chloride concentrations (<50 mEq/l) are a relatively strong argument for electrolyte depletion.

**TREATMENT OF DEPLETIONAL HYponatREMIA**

As with other deficiencies, pure depletional hyponatremia is easily treated by administration of saline. Hypertonic saline will correct hyponatremia faster and with a lower water load than isotonic saline, which might be preferred in patients who are already normovolemic on clinical examination. However, if no severe hyponatremia symptoms are present, it is recommended to correct the serum Na\(^+\) concentration slowly, at a maximal rate of 5 mEq/l per day. If hyponatremia is profound (<125 mEq/l), correction up to 10 mEq/l per day is acceptable (59). At any time, increasing the serum Na\(^+\) concentration >10 mEq/l in 24 h should be avoided because of the risk of central pontine myelinolysis (60). Importantly, replenishment of potassium and magnesium stores through administration of supplements contributes to hyponatremia correction, and this should be taken into account when determining the correction rate (52,61). Although certainly not a substitute for frequent monitoring, the change in serum Na\(^+\) concentration with 1 l of infusate might be approximated by the following formula:

\[
\frac{([\text{Na}\text{]}_{\text{INFUSATE}} + [\text{K}\text{]}_{\text{INFUSATE}} - [\text{Na}\text{]}_{\text{SERUM}}])}{(\text{TBW} + 1)}
\]

with TBW = \(a\) \times body weight (kg), and \(a = 0.6\) in children and nonelderly men, 0.5 in nonelderly women and elderly men, and 0.45 in elderly women (62). Take for example a female patient, 50 years of age and weighing 62 kg, presents with a serum Na\(^+\) concentration of 130 mEq/l and a serum K\(^+\) of 3.5 mEq/l. This is presumably because of depletion, as she is on a high maintenance dose of furosemide (120 mg twice daily) and has no overt signs of volume overload. Infusion of 1 normal saline ([Na\(^+\)] = 154 mEq/l) with addition of 40 mEq K\(^+\) supplements would be expected to raise the serum Na\(^+\) concentration by 2 mEq/l ((154 mEq/l + 40 mEq/l − 130 mEq/l)/(0.5 × 62 + 1)). However, without K\(^+\) supplements, the increase would only be 0.75 mEq/l ((154 mEq/l − 130 mEq/l)/(0.5 × 62 + 1)).

**TREATMENT OF HYPOTONIC DILUTIONAL HYponatREMIA**

Acute treatment of hypotonic dilutional hyponatremia is focused on promoting free water excretion to restore normal serum sodium levels. However, for long-term treatment success, it is important to subsequently prevent a positive free water balance. This may be important, as the question whether hyponatremia in ADHF reflects a therapeutic target or is merely a marker of advanced disease has not been fully established. Indeed, studies looking at the prognostic effect of hyponatremia correction have yielded conflicting results (63,64). Madan et al. (63) demonstrated in a cohort of 322 ADHF patients with hyponatremia that long-term changes in serum Na\(^+\) concentration (assessed 60 to 270 days after hospital discharge) are significant predictors of mortality, with improving hyponatremia associated with better outcome. In contrast, after correction for disease severity markers, Lee et al. (64) found that normalization of hyponatremia at hospital discharge was not associated with improved survival (64). Obviously, confounding by different treatment strategies in both studies cannot be excluded, but a conservative interpretation is that only durable hyponatremia correction is potentially associated with improved outcome in ADHF. To achieve this, good heart failure management is often fundamental.

**ACUTE TREATMENT OF DILUTIONAL HYponatREMIA.** To promote free water excretion in a patient with ADHF and hypotonic dilutional hyponatremia, distal nephron flow should be increased, AVP levels should be lowered, or AVP effects should be antagonized.

**Loop diuretic agents with or without hypertonic saline.** The powerful inhibitory effect of loop diuretic agents on Na\(^+\) transport in the TAL increases the amount of tubular fluid presented to the distal nephron. Loop diuretic agents also reduce hypertonicity of the renal interstitium, further facilitating water excretion (Figure 4A) (44). Because loop diuretic agents are cheap and readily available, they remain the first-line therapy in ADHF with dilutional hyponatremia and volume overload. The addition of hypertonic saline to improve loop diuretic efficacy in ADHF is a controversial issue. Although counterintuitive from a pathophysiological point of view, some small studies have suggested more efficient decongestion and better renal preservation when loop diuretic agents are combined with hypertonic saline (Table 2) (65–70). Importantly, decreases in plasma renin activity, inflammatory markers, and even natriuretic peptide levels have been demonstrated with hypertonic saline administration in ADHF patients who receive loop diuretic agents (71,72). Still, it remains difficult to draw any firm conclusions, because the use of high doses of loop diuretic agents that might have induced these alterations might have confounded these improvements with sodium loading. As serum Na\(^+\) levels are more easily corrected, patients with hyponatremia might benefit more from the addition of hypertonic saline to loop
diuretic agents; however, this remains highly speculative. **Acetazolamide.** Alternatively, combination diuretic treatment with loop diuretics and acetazolamide ensures minimal tubular Na\(^+\) reabsorption proximal from the macula densa and maximal flow through the distal nephron (29). For this reason, if combination therapy is needed to overcome loop diuretic resistance in ADHF, acetazolamide should be preferred over thiazide-type diuretic agents, MRAs, or ENaC blockers.

**AVP antagonists.** AVP antagonists are the only medication class to directly promote free water excretion by prevention of aquaporin-2 channel availability in the collecting ducts of the nephron (73,74). Three oral V\(_2\) receptor antagonists (tolvaptan, satavaptan, and lixivaptan) have been tested for ADHF, with the former 2 shown to be efficacious in restoring serum Na\(^+\) levels in patients with volume overload and hyponatremia (75–78). Similar data are available for conivaptan, an intravenous agent that antagonizes both the V\(_2\) and V\(_1a\) receptors (74,79,80). Table 3 summarizes the currently available evidence on AVP antagonists in patients with ADHF and hyponatremia. Importantly, EVEREST (Efficacy of Vaso-pressin Antagonism in Heart Failure Outcome Study with Tolvaptan), including 4,133 patients with ADHF but without hyponatremia as an inclusion criterion, compared tolvaptan with placebo and was powered for clinical endpoint analysis (81). The overall trial did not show a significant reduction in all-cause mortality or readmission rates, but, interestingly, a subanalysis in patients presenting with pronounced hyponatremia (<130 mmol/l) suggested improved survival free from cardiovascular death or readmission (76,81). This promising finding warrants further study in an adequately powered, randomized clinical trial.

**LONG-TERM MANAGEMENT OF HYPOTONIC DILUTIONAL HYPONATREMIA. Water restriction.** Water restriction is uniformly recommended by the guidelines in ADHF patients with hyponatremia as it is in others with dilutional hypotonic hyponatremia (35–37,59). Whilst limiting free water intake certainly helps to prevent a positive free water balance, few data support its long-term efficacy, and adherence might be a problem. Indeed, thirst is a frequent, under-recognized, and distressing problem in heart failure, and many patients may find it difficult to comply with strict water restriction (<1 l) (82). Nevertheless, a recent study found that ADHF patients with mild hyponatremia had improvements in quality of life with such a strategy (83).

**AVP antagonists.** Although AVP antagonists are highly efficacious for short-term correction of hyponatremia, less is known about their long-term efficacy in providing a sustained correction of serum Na\(^+\) levels. In EVEREST, serum Na\(^+\) concentration increased more with tolvaptan compared with placebo during in-hospital stay (81). However, patients also reported feeling thirsty significantly more frequently, and the difference with serum Na\(^+\) levels in the placebo group disappeared after instillation of outpatient management, which suggests that patients may have drank more to compensate for increased water losses.

**Renin-angiotensin system blockers.** Renin-angiotensin system blockers are known to increase renal blood flow and decrease proximal tubular sodium reabsorption. Therefore, it is not surprising that they were among the first agents demonstrated to be effective in hypotonic dilutional hyponatremia in heart failure (84,85). Up-titration of renin-angiotensin system blockers should always be promoted for this indication if there are no contraindications, such as coexisting renal dysfunction.

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**Table 2** Studies on Hypertonic Saline in Patients With Acute Decompensated Heart Failure

<table>
<thead>
<tr>
<th>First Author (Ref. #)</th>
<th>n</th>
<th>Treatment</th>
<th>Outcome</th>
</tr>
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<tbody>
<tr>
<td>Paterna et al. (65)</td>
<td>60</td>
<td>IV furosemide 500-1,000 mg with vs. without 150 ml 1.4%-4.6% hypertonic saline BID</td>
<td>Increase in diuresis, natriuresis, and serum sodium levels; decrease in serum creatinine; and shorter hospitalization time with hypertonic saline</td>
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<tr>
<td>Licata et al. (66)</td>
<td>107</td>
<td>IV furosemide 500-1,000 mg with vs. without 150 ml 1.4%-4.6% hypertonic saline BID</td>
<td>Increase in diuresis, natriuresis, and serum sodium levels; decrease in serum creatinine; and improved survival with hypertonic saline</td>
</tr>
<tr>
<td>Paterna et al. (71)</td>
<td>94</td>
<td>IV furosemide 500-1,000 mg with vs. without 150 ml 1.4%-4.6% hypertonic saline BID</td>
<td>Increase in diuresis and natriuresis; decrease in BNP levels; shorter hospitalization time; and lower 30-day readmission rate with hypertonic saline</td>
</tr>
<tr>
<td>Parninello et al. (67)</td>
<td>133</td>
<td>IV furosemide 250 mg plus 150 ml 3% hypertonic saline BID vs. IV furosemide 250 mg BID plus low sodium diet (&lt;80 mmol)</td>
<td>Increase in diuresis, natriuresis, and serum sodium levels; improved renal function; and faster reduction of echo-PCWP with hypertonic saline</td>
</tr>
<tr>
<td>Paterna et al. (68)</td>
<td>1,771</td>
<td>IV furosemide 250 mg plus 150 ml 3% hypertonic saline BID vs. IV furosemide 250 mg BID plus low sodium diet (&lt;80 mmol)</td>
<td>Increase in diuresis, natriuresis, and serum sodium levels; decrease in serum creatinine; shorter hospitalization time; lower readmission rate; and improved survival with hypertonic saline</td>
</tr>
<tr>
<td>Issa et al. (69)</td>
<td>34</td>
<td>100 ml 7.5% hypertonic saline BID vs. placebo for 3 days</td>
<td>Improved in glomerular and tubular biomarkers with hypertonic saline</td>
</tr>
<tr>
<td>Okihara et al. (70)</td>
<td>44</td>
<td>500 ml 1.7% hypertonic saline vs. glucose 5% with 40 mg furosemide</td>
<td>Improved GFR and better diuresis with hypertonic saline</td>
</tr>
</tbody>
</table>

BID = twice daily; BNP = B-type natriuretic peptide; GFR = glomerular filtration rate; IV = intravenous; PCWP = pulmonary capillary wedge pressure.
TABLE 3: Studies on AVP Antagonists in Patients With Acute Decompensated Heart Failure and Hyponatremia

<table>
<thead>
<tr>
<th>First Author (Ref. #)</th>
<th>n/N</th>
<th>Treatment</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gheorghiade et al. (77)</td>
<td>71/254</td>
<td>Tolvaptan 30, 45, or 60 mg vs. placebo</td>
<td>Normalization of serum sodium after 24 h, greater decrease in body weight and edema, increased urine output with tolvaptan</td>
</tr>
<tr>
<td>Gheorghiade et al. (78)</td>
<td>51/319</td>
<td>Tolvaptan 30, 60, or 90 mg vs. placebo</td>
<td>Normalization of serum sodium with tolvaptan</td>
</tr>
<tr>
<td>Ghali et al. (79)</td>
<td>19/74</td>
<td>Conivaptan 40 or 80 mg vs. placebo</td>
<td>Normalization of serum sodium with conivaptan</td>
</tr>
<tr>
<td>Zeltser et al. (80)</td>
<td>28/84</td>
<td>Conivaptan 40 or 80 mg vs. placebo</td>
<td>Increase in serum sodium concentration with conivaptan</td>
</tr>
<tr>
<td>Konstam et al. (81)</td>
<td>1,157/4,133</td>
<td>Tolvaptan 30 mg vs. placebo</td>
<td>No effect on mortality or rehospitalization, significant increase in serum sodium with tolvaptan</td>
</tr>
<tr>
<td>Aronson et al. (75)</td>
<td>90/118</td>
<td>Satavaptan 25 or 50 mg vs. placebo</td>
<td>Increase in serum sodium concentration with satavaptan</td>
</tr>
</tbody>
</table>

Inotropes and vasodilator therapy. Increasing the effective circulatory volume in heart failure is expected to result in less nonosmotic AVP release and better renal blood flow, which, from a pathophysiological perspective, might help to correct dilutional hyponatremia. Because cardiac output in ADHF is rather insensitive to changes in cardiac pre-load—as the Frank-Starling mechanism is depleted—improvements can only be obtained through direct stimulation of contractility with inotropes or reducing afterload with vasodilator therapy. As the former treatment strategy is associated with increased mortality, afterload reduction probably remains the best option to increase the effective circulatory volume; however, its use is limited by low arterial blood pressure (86,87). Observational data have demonstrated that nitroprusside, titrated on arterial blood pressure and with conversion to oral hydralazine and nitrates, is feasible and potentially associated with better outcomes in ADHF (88,89). Alternatively, serelaxin, a vasodilator agent under investigation, might be of particular interest because of its specific renal vasodilator properties (90,91). The RELAX-AHF-EU (Effect of Serelaxin Versus Standard of Care in Acute Heart Failure Patients) trial is currently enrolling ADHF patients and is powered for clinical endpoint evaluation (92). Nevertheless, the specific effects of both inotropes and vasodilator therapy on hyponatremia remain insufficiently elucidated.

CONCLUSIONS

The pathophysiology of hyponatremia in ADHF is complex, and a 1-size-fits-all approach is therefore likely to fail. Appropriate differentiation between dilutional and depletional hyponatremia is crucial and depends on good history taking, clinical examination, and correct interpretation of laboratory results. A targeted, pathophysiology-based approach should help to treat this challenging condition efficiently, thereby minimizing adverse events.

REFERENCES

64. Lee SE, Choi DJ, Youn CH, et al., KorHF Registry. Improvement of hyponaetraemia during
hospitalisation for acute heart failure is not associated with improvement of prognosis: an analysis from the Korean Heart Failure (KoHF) registry. Heart 2012;98:1798-804.


KEY WORDS arginine vasopressin, distal, diuretics, kidney tubules, physiopathology, sodium