JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY
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PUBLISHED BY ELSEVIER INC.

VOL. 65, NO. 5, 2015
ISSN 0735-1097/$36.00
http://dx.doi.org/10.1016/j.jacc.2014.12.010

THE PRESENT AND FUTURE

STATE-OF-THE-ART REVIEW

Hyponatremia in Acute Decompensated Heart Failure

Depletion Versus Dilution

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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

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Manuscript received July 30, 2014; revised manuscript received November 30, 2014, accepted December 2, 2014.

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 ($t_{1/2}$ = 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 V_2 receptors in the collecting ducts of the nephron (Figure 1) (9). V_2 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 V_{1a} 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 tonicity gradient from the renal cortex toward the medulla, which is needed to concentrate the urine. Finally, another effect of V_{1a} receptor stimulation is promotion of prostaglandin synthesis in the collecting ducts. This counteracts V_2 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

ABBREVIATIONS AND ACRONYMS

ADHF = acute decompensated heart failure
AVP = arginine vasopressin
ENaC = epithelial sodium channel
GFR = glomerular filtration rate
MRA = mineralocorticoid receptor antagonist
Na^+ = sodium
TAL = thick ascending limb of Henle's loop

TABLE 1 Pathophysiology of Hyponatremia in Acute Decompensated Heart Failure

	Mechanism of Action
Dilutional hyponatremia	
Increased sensitivity of osmotic AVP release → Lower osmo-checkpoint*	Baroreceptor activation/angiotensin II
Increased nonosmotic AVP release	Baroreceptor activation/angiotensin II
Impaired AVP degradation	Liver and/or kidney dysfunction
Increased thirst	Baroreceptor activation/angiotensin II
Decreased distal nephron flow	Impaired glomerular filtration/Increased proximal tubular reabsorption
Depletional hyponatremia	
Low sodium intake	Salt-restricted diet
Exaggerated nonurinary sodium losses	Diarrhea, ascites
Exaggerated natriuresis	Diuretics, osmotic diuresis
Sodium shift toward the intracellular compartment	Potassium and/or magnesium deficiency

*This is the level of plasma osmolality that is pursued by the homeostatic mechanisms of the body.
AVP = arginine vasopressin.