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Hyponatremia and Vasopressin Antagonism in Congestive Heart Failure

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Summary

In a national heart failure registry, hyponatremia (serum sodium <130 mEq/L) was initially reported in 5% of patients and considered a risk factor for increased morbidity and mortality. In a chronic heart failure study, serum sodium level on admission predicted an increased length of stay for cardiovascular causes and increased mortality within 60 days of discharge. Hyponatremia in patients with congestive heart failure (CHF) is associated with a higher mortality rate. Also, by monitoring and increasing serum sodium levels during hospitalization for CHF, patient outcomes may improve. This review describes the pathophysiology of hyponatremia in relation to CHF, including the mechanism of action of vasopressin receptors in the kidney, and assesses the preclinical and clinical trials of vasopressin receptor antagonists—agents recently developed to treat hyponatremia. In hospitalized patients with CHF, hyponatremia plays a major role in poor outcomes. Vasopressin receptor antagonists have been shown to be safe and effective in clinical trials in patients with hyponatremia.

Key words: congestive heart failure, euvolemia, hypervolemia, V_{1a} and V_2 receptor antagonists

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Introduction

Approximately 5 million people in the United States are affected by congestive heart failure (CHF), resulting in more than 1 million hospital admissions per year.[1] Because heart failure (HF) occurs at a higher incidence among the elderly and can cause disabling symptoms, it has become an increasingly important clinical problem. In the Adhere (Acute Decompensated Heart Failure Registry) National Registry, hyponatremia (serum sodium <130 mEq/L) at clinical presentation was noted in 5% of patients with HF and was considered a risk factor for increased morbidity and mortality.[2]

Hyponatremia and Congestive Heart Failure

Hyponatremia is generally defined as a serum sodium <135 mEq/L; however, if the serum sodium concentration falls below 120 mEq/L or shows rapid decline, nonspecific symptoms may appear (e.g. headache, lethargy, or nausea).[3,4] In a study of patients with HF,[5] and serum sodium $\leqslant$ 135 mEq/L is associated with increased mortality in hospitalized patients.[6] CHF patients with hyponatremia have been known to display high circulating levels of catecholamines, renin, angiotensin II, aldosterone, and vasopressin.

In a retrospective analysis of the OPTIME-CHF (Outcomes of a Prospective Trial of Intravenous Milrinone for Exacerbations of Chronic Heart Failure) study, serum sodium on admission was an important predictor of increased number of days of hospitalization for cardiovascular causes and increased mortality within 60 days of discharge.[7]

Mechanisms Causing Hyponatremia in Heart Failure

Renin-Angiotensin-Aldosterone System

The initial stages of HF involve an expansion of intravascular volume and weight gain that prevents

volume depletion when persistent salt and water retention produces extravascular volume expansion.[8] Renin-angiotensin-aldosterone activation is sensitive to low cardiac output (CO) and low renal perfusion (Fig. 1).[8] The stimulus is primarily hypotension (arterial underfilling), and once compensated, the renin-angiotensin-aldosterone system (RAAS) shuts down. However, the basal activity of the RAAS is increased in most patients with HF.[9]

Increased amounts of aldosterone in urine and plasma correlate with the retention of sodium and water at renal and extrarenal sites.[8] In healthy subjects on a normal diet, the aldosterone secretion rate is 100–175 μg (277–485 nmol) per day, but in patients with HF, the aldosterone secretion rate may be as high as 400–500 μg (1100–1400 nmol) per day. Decreased metabolic clearance of aldosterone by the underperfused liver further contributes to increased plasma concentrations of aldosterone in patients with HF.[8] In healthy subjects, high doses of aldosterone initially increase renal sodium and water retention, which leads to expansion of extracellular fluid by 1.5 to 2 liters, as in patients with primary hyperaldosteronism.[9] However, patients with primary hyperaldosteronism and healthy subjects who have been given aldosterone avoid the salt-retaining effects of aldosterone and do not develop edema.[8] This escape mechanism of sodium retention does not occur in patients with CHF, as they continue to retain sodium and water in response to aldosterone.[9] The mechanisms responsible for this phenomenon have not been fully explained, though increased alpha adrenergic and angiotensin-II stimulation decrease sodium delivery to the collecting ducts, thereby promoting persistent aldosterone-mediated salt and water retention in patients with HF.[9]

The Role of Arginine Vasopressin

In addition to the RAAS, the enhanced release of arginine vasopressin (AVP) can lead to hyponatremia in patients with HF, which is associated with two underlying mechanisms: (i) the abnormal feedback mechanism, and (ii) baroreceptor feedback.[10–14] Enhanced AVP secretion and binding to the V_2 receptor results in free-water retention and hyponatremia.[14]

Arginine Vasopressin is synthesized in the supraoptic and paraventricular nuclei in the hypothalamus and stored in the posterior lobe of the pituitary (Fig. 2).[9,11] Its major renal effect is to augment the water permeability of the luminal membranes of the cortical and medullary collecting tubules, promoting water reabsorption. The major stimuli to AVP are hyperosmolarity and circulating volume depletion. AVP release is decreased with hypoosmolality.[11] In patients with CHF, there is a deviation in the feedback mechanism, and hypoosmolality is consistently associated with high plasma

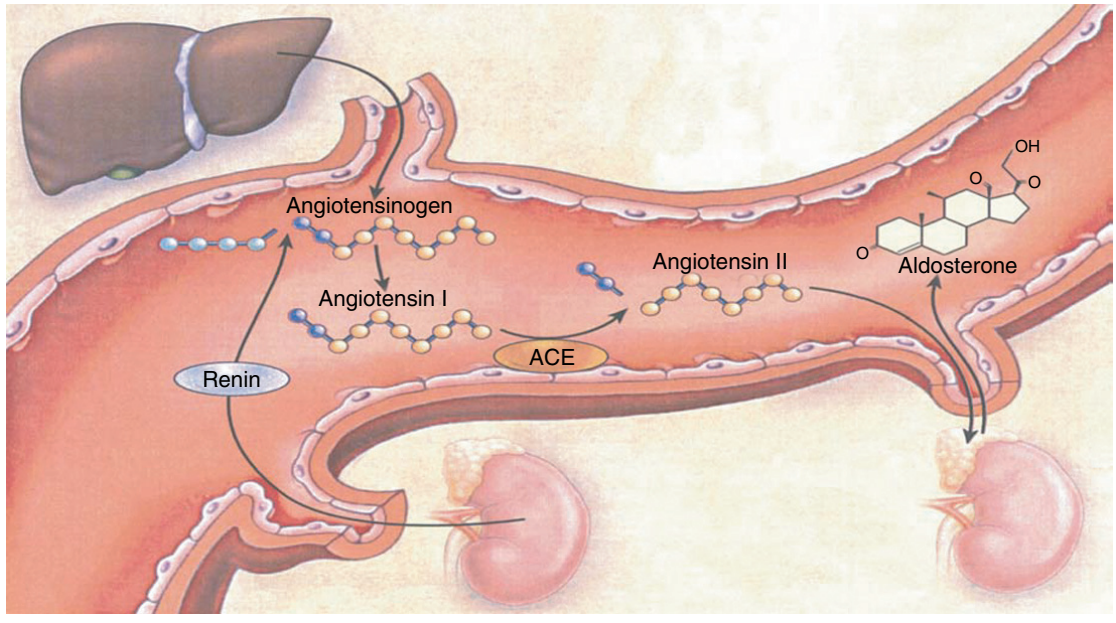

FIG. 1 The RAAS. Angiotensinogen, the precursor of all angiotensin peptides, is synthesized by the liver. While in circulation, it is cleaved by renin, which is secreted into the lumen of renal afferent arterioles by juxtaglomerular cells. Renin cleaves four amino acids from angiotensinogen, thereby forming angiotensin I. In turn, angiotensin I is cleaved by the angiotensin-converting enzyme (ACE), which is bound to the membrane of endothelial cells, to form angiotensin II. In the zona glomerulosa of the adrenal cortex, angiotensin II stimulates the production of aldosterone. Aldosterone production is also stimulated by potassium, corticotropin, catecholamines (e.g., norepinephrine), and endothelins. Reprinted with permission from reference 8. 2001 Massachusetts Medical Society. All rights reserved.

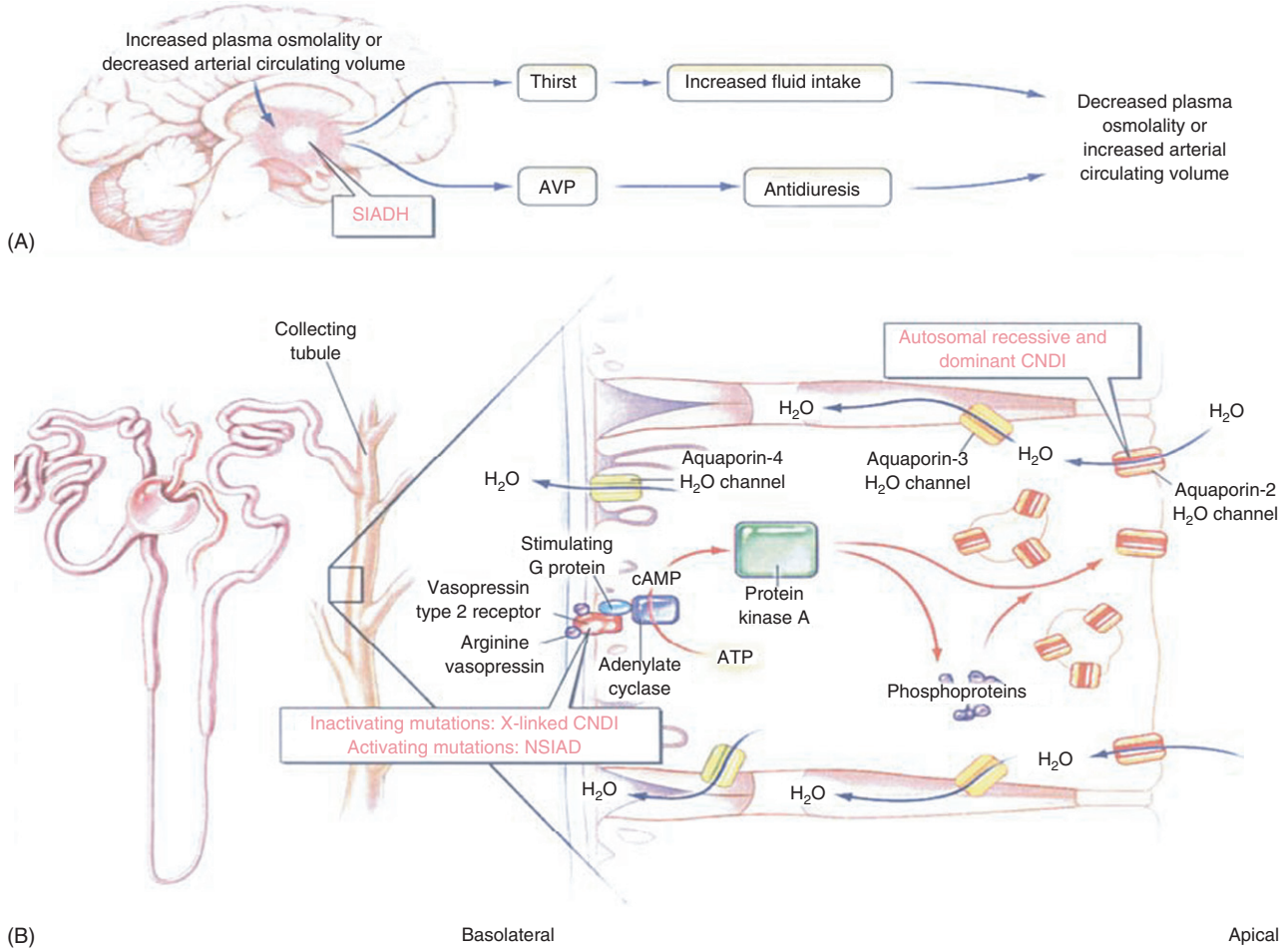

FIG. 2 Physiology of water homeostasis in humans (panel A) and pathway of AVP signaling in renal collecting duct cells involved in regulating water excretion (panel B). AVP = arginine vasopressin; cAMP = cyclic adenosine monophosphate. Reprinted with permission reference 11. 2005 Massachusetts Medical Society. All rights reserved.

AVP.[10] The degree of hyponatremia and hypoosmolality is more severe in patients with detectable AVP levels than in those with undetectable AVP levels.[12] A baseline evaluation of the SOLVD (Studies of Left Ventricular Dysfunction) database demonstrated an incremental increase in plasma AVP concentrations from asymptomatic and symptomatic patients with left ventricular dysfunction.[14]

The inappropriate increase in AVP may be due to the nonosmotic baroreceptor-mediated pathway. This happens because low CO in patients with HF causes reduction in arterial pressure, which unloads carotid sinus and aortic arch baroreceptors, thereby triggering the RAAS, the sympathetic nervous system, and AVP secretion in an effort to increase sodium and water retention.[12,13] These baroreceptors are stimulated to reduce arterial pressure by at least 10%.[14] Thus, nonsuppressible, nonosmotic release of AVP is found despite hypoosmolality.

AVP binds to three types of receptors, classified based on the second messenger system to which they are coupled (Table 1).[14] The V_{1a} and V_{1b} receptors are linked to the phosphoinositol signaling pathway, with intracellular calcium acting as the second messenger. The V_2 receptor is linked to the adenylate cyclase signaling pathway with intracellular cyclic adenosine monophosphate (cAMP) acting as the second messenger.[14]

AVP triggers vasopressin V_2 receptors located on the principal cells of the collecting duct, leading to translocation of aquaporin-2 (AQP-2) water channels and subsequent water reabsorption. AVP also increases AQP-2 synthesis.[14] In a study of 65 patients with HF and 8 control subjects, urinary excretion of AQP-2 was exaggerated in the patients with HF compared with that of controls.[15] There were positive correlations between plasma AVP levels and urinary excretion of AQP-2 in patients with CHF.

TABLE 1 Vasopressin receptors

Receptors	Location	Effects of AVP
V_{1a}	Lymphocytes and monocytes	Coagulation factor release
	Platelets	Platelet aggregation
	Adrenal cortex	Glycogenolysis
	Vascular smooth muscle cells	Vasoconstriction
V_{1b}	Anterior pituitary	Adrenocorticotropic hormone and beta-endorphin release
V_2	Principal cells of the renal collecting duct	Free-water retention

Abbreviations: AVP = arginine vasopressin.
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Role of Diuretic Therapy

Diuretics are commonly used in patients with HF, and hyponatremia is an occasional but potentially serious complication of diuretic therapy. In a review of 129 cases of severe diuretic-induced hyponatremia (<115 mEq/L), investigators concluded that thiazides were the cause in 94%.[16] Advanced age was not associated with a higher tendency for hyponatremia in this study. In the majority of patients who received thiazides, excess AVP activity, hypokalemia, and excess water intake were findings which, singly or together, appeared to contribute to the development of hyponatremia.[16]

Thiazides act in the renal cortex of the distal tubule, thus they do not interfere with AVP-induced water retention. The combination of increased sodium and potassium excretion and enhanced water reabsorption can result in the excretion of urine with a sodium-plus-potassium concentration higher than that of the plasma. Loss of this fluid can promote the development of hyponatremia independent of the degree of water intake. Loop diuretics, which act in the medullary and cortical aspects of the thick ascending limb, often worsen hyponatremia by isotonic diuresis with salt loss.[17] Diuretics can cause the depletion of potassium and magnesium, which can lead to life-threatening cardiac arrhythmias, particularly in the existence of digitalis therapy.

Role of Vasopressin Receptor Antagonists in Hyponatremia

Given the central role of AVP in causing hyponatremia in patients with CHF, decreasing vasopressin activity has been a therapeutic focus. With no current therapy to decrease production of AVP, attention was turned to decreasing the effect of AVP by blocking the receptor. In 1992, an orally active, nonpeptide V_2 receptor antagonist (OPC-31260) was described for the first time.[18,19] Since then, clinical studies of several different agents have demonstrated a potential role of vasopressin receptor antagonism in the treatment of hyponatremia (Table 2).[14,19–24]

Tolvaptan (OPC-41061)

Tolvaptan, a selective V_2 receptor antagonist, can help achieve dose-dependent production of dilute urine.[19] The effects of tolvaptan, an oral agent with a half-life of 6 to 8 hours, were evaluated in 83 patients with HF (NYHA class II-III) in a randomized, controlled trial.[20] Patients were removed from baseline diuretics and randomized to placebo (n = 21), monotherapy with tolvaptan 30 mg (n = 20), monotherapy with furosemide 80 mg (n = 22), or both tolvaptan and furosemide (n = 20) once daily for 7 days. Tolvaptan reduced body weight and lessened edema without concomitant diuretic therapy compared with placebo.[20]

ACTIV in CHF (Acute and Chronic Therapeutic Impact of a Vasopressin antagonist in Congestive Heart Failure) was a dose-ranging, phase 2 trial of 319 patients with left ventricular ejection fraction of less than 40% who were hospitalized for HF despite standard therapy.[21] Patients were randomized to 30, 60, or 90 mg/day of oral tolvaptan or placebo in addition to standard therapy. The study drug was continued for up to 60 days. Results demonstrated that treatment with tolvaptan increased net fluid loss, resulting in a greater decrease in body weight than with standard therapy alone. Tolvaptan also improved serum sodium levels in patients with hyponatremia.[21]

The EVEREST (Efficacy of Vasopressin Antagonism in Heart Failure Outcome Study with Tolvaptan) trial is evaluating mortality, morbidity, and patient-assessed global clinical status in patients treated with tolvaptan compared with those given standard care. Patients are randomized 1:1 to tolvaptan 30 mg/day or placebo for a minimum of 60 days. Time to all-cause mortality and time to cardiovascular mortality or hospitalization for HF are the endpoints.[25] As of November 29, 2005, 3,712 patients have been registered globally.[26]

Lixivaptan (VPA-985)

Lixivaptan is an orally active vasopressin V_2 receptor antagonist. Its affinity for V_2 receptors is approximately one hundred-fold higher than for V_{1a} receptors, and it produces little or no effect at the V_{1b} receptors.[27] In a double-blind, placebo-controlled study that randomized 21 patients with CHF (NYHA class II–III) to placebo (n = 6) or lixivaptan 30 (n = 5), 75 (n = 5), or 150 mg (n = 5) after overnight fluid deprivation, all doses of lixivaptan were found to increase urine flow and serum sodium concentration.[22] In a randomized, double-blind,

TABLE 2 Arginine vasopressin antagonists in development for the treatment of hyponatremia

	Tolvaptan (OPC-41061)	Lixivaptan (VPA-985)	Conivaptan (YM-087)
Receptor subtype specificity	V_2	V_2	V_{1a}/V_2
Selectivity index in humans (K_i V_{1a}: K_i V_2)	29 : 1	100 : 1	10 : 1
Proposed route of administration for heart failure	Oral	Oral	IV
Urine volume effects	Increased	Increased	Increased
Urine osmolality effects	Decreased	Decreased	Decreased
Sodium excretion/24 h	No change	No change at low doses	No change

Abbreviations: AVP = arginine vasopressin, IV = intravenous.
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placebo-controlled, phase 2 multicenter trial of lixivaptan in hospitalized hyponatremic patients (serum sodium <132 mEq/L), 14 of these patients were diagnosed with CHF.[19] After randomization, patients were placed on a restricted fluid intake of 1,200 mL/day and either lixivaptan (50 or 100 mg twice daily [b.i.d.]) or placebo for upto 7 days. Compared with placebo, lixivaptan significantly increased serum sodium concentration (to normal levels), and no adverse effects were reported.[19]

Studies have shown that specific V_2 receptor antagonists can increase the plasma vasopressin level. For example, lixivaptan (250 mg b.i.d.) almost tripled the vasopressin concentration of patients in one study ($p<0.05$).[28] One could hypothesize that increased V_{1a} activity and the resulting vasoconstriction, release of coagulation factors, and platelet aggregation would be deleterious to patients with HF. Therefore, one could predict that blocking V_{1a} receptors in addition to V_2 receptors may provide better outcomes in this patient population.[29]

Conivaptan (YM-087)

After a 20 mg intravenous (IV) loading dose, conivaptan, a nonpeptide V_{1a}/V_2 receptor antagonist, produced a mean C_{max} of 619 ng/mL.[30] Following the loading dose and a continuous infusion of 20 or 40 mg/day for 4 days, conivaptan demonstrated a relatively short elimination half-life (median 6.7 hours).[30] Conivaptan has been well tolerated with no serious side effects in studies with normal controls.[23,24] Common adverse events have included headache, hypokalemia, and thirst; clinically significant changes in blood pressure and pulse have not been observed.[23,24,30] The drug IV conivaptan was studied in patients with the syndrome of inappropriate antidiuretic hormone secretion (SIADH; n = 4) and CHF (n = 4) with a serum sodium of 120 to 132 mEq/L. Initially, all patients were given 20 mg of IV conivaptan. The majority of patients received 20 and 30 mg on day 1 and 40 mg IV b.i.d. on days 2 and 3. The data from this study showed an increase in serum sodium from baseline along with an increase in free-water clearance and decrease in urine osmolality. There were no drug-related adverse events.[23]

Conivaptan therapy for hyponatremia (115 to <130 mEq/L) was evaluated in a multicenter, parallel-group efficacy study of 84 patients randomized to placebo or a 20 mg IV bolus followed by 40 or 80 mg/day IV infusion for 4 days.[31,32] Both IV conivaptan dosages significantly increased serum sodium within 24 h compared with placebo ($p<0.001$) and improved the effective water clearance (electrolyte-free water excretion or aquaresis) on day 1 compared with placebo ($p<0.05$). Conivaptan was well tolerated throughout the 4-day study.[31,32]

In an efficacy report that combined three randomized, placebo-controlled trials of conivaptan in patients with CHF (N = 241), conivaptan (40 and 80 mg) treatment in one IV and two oral formulations was shown to improve serum sodium concentration (area under the curve) from baseline to the end of the study compared with placebo.[33] Adverse events were similar between treatment and placebo groups and included headache, nosebleed, pyrexia, worsening CHF, renal failure, and infusion site reactions in the IV trial.[33]

Conivaptan has also produced favorable changes in hemodynamics and urine output in patients with HF.[34] The effects of a single IV dose of conivaptan (10, 20, or 40 mg) were studied in 142 patients with symptomatic HF (NYHA class III–IV).[34] Compared with placebo, conivaptan 20 and 40 mg significantly reduced pulmonary capillary wedge pressure and right atrial pressure. There was significant dose-dependent increase in urine output and decrease in urine osmolality. This study reported favorable short-term hemodynamic and renal effects with no relation to vasopressin activation, suggesting that AVP receptor antagonism may play a future role in the treatment of hyponatremia in HF.[34]

Conclusion

In patients with CHF, AVP plays a major role in causing hyponatremia. Observation of vasopressin regulation and its effect on vasopressin receptors in the renal collecting duct has provided a basis for the development of vasopressin receptor antagonists. A number

of these agents have recently been studied in animal models and small-scale human trials. Tolvaptan and conivaptan, in particular, have shown great potential for treating hyponatremia. It is clear that hyponatremia is an independent predictor of poor outcomes; it remains to be seen in future studies if correcting hyponatremia improves these outcomes. As a potential treatment for hyponatremia, vasopressin receptor antagonists may prove valuable by promoting electrolyte-free water clearance (aquaresis) and increasing serum sodium in patients with hyponatremia secondary to HF.

References

1. *American College of Cardiology/American Heart Association Task Force on Practice Guidelines*. ACC/AHA 2005 guideline update for the diagnosis and management of chronic heart failure in the adult 2005; 112: e154–e235
2. Adhere® Registry: Insights from the Adhere Registry: data from over 100,000 patient cases. 2005 www.adhereregistry.com
3. Oren RM: Hyponatremia in congestive heart failure. *Am J Cardiol* 2005;95(9 suppl 1):B B 2–7
4. Goh KP: Management of hyponatremia. *Am Fam Phys* 2004; 69:2387–2394
5. Dargie HJ, Cleland JGF, Leckie BJ, Inglis CG, East BW, et al.: Relation of arrhythmias and electrolyte abnormalities to survival in patients with severe chronic heart failure. *Circulation* 1987;75(suppl 4):498–4107
6. Chin MH, Goldman L: Correlates of major complications or death in patients admitted to the hospital with congestive heart failure. *Arch Intern Med* 1996;156:1814–1820
7. Klein L, O'Connor CM, Leimberger JD, Gattis-Stough W, Piña IL, et al.: for the OPTIME-CHF Investigators: Lower serum sodium is associated with increased short-term mortality in hospitalized patients with worsening heart failure. *Circulation* 2005;111:2454–2460
8. Weber KT: Aldosterone in congestive heart failure. *New Engl J Med* 2001;345:1689–1697
9. Schrier RW, Abraham WT: Hormones and hemodynamics in heart failure. *New Engl J Med* 1999;341:577–585
10. Goldsmith SR, Francis GS, Cowley AW, Levine B, Cohn JN: Increased plasma arginine vasopressin levels in patients with congestive heart failure. *J Am Coll Cardiol* 1983;1:1385–1390
11. Knoers N: Hyperactive vasopressin receptors and disturbed water homeostasis. *New Engl J Med* 2005;352:1847–1850
12. Szatalowicz VL, Arnold PE, Chaimovitz C, Bichet E, Berl T, et al.: Radioimmunoassay of plasma arginine vasopressin in hyponatremic patients with congestive heart failure. *New Engl J Med* 1981;305:263–266
13. Schrier RW, Ecder T: Unifying hypothesis of body fluid volume regulation: implications for cardiac failure and cirrhosis. *Mt Sinai J Med* 2001;68:350–361
14. Lee CR, Watkins ML, Patterson JH, Gattis W, O'Connor CM Jr, et al.: Vasopressin: a new target for the treatment of heart failure. *Am Heart J* 2003;146:9–18
15. Funayama H, Nakamura T, Saito T, Yoshimura A, Saito M, et al.:Urinary excretion of aquaporin-2 water channel exaggerated dependent upon vasopressin in congestive heart failure. *Kidney Int* 2004;66:1387–1392
16. Sonnenblick M, Friedlander Y, Rosin AJ: Diuretic-induced severe hyponatremia. Review and analysis of 129 reported patients. *Chest* 1993;103:601–606
17. Goldsmith SR: Current treatments and novel pharmacologic treatments for hyponatremia in congestive heart failure. *Am J Cardiol* 2005;95(9 suppl 1):B B 14–23
18. Yamamura Y, Ogawa H, Yamashita H, Chihara T, Miyamoto H, et al.:Characterization of a novel aquaretic agent, OPC-31260, as an orally effective, nonpeptide vasopressin V_2 receptor antagonist. *Brit J Pharmacol* 1992;105:787–791
19. Palm C, Reimann D, Gross P: The role of V2 vasopressin antagonists in hyponatremia. *Cardiovasc Res* 2001;51:403–408
20. Udelson JE, Orlandi C, O'Brien T, Sequeira RF, Ouyang J, et al.: Vasopressin receptor blockade in patients with congestive heart failure: results from a placebo controlled, randomized study comparing the effects of tolvaptan, furosemide, and their combination [abstract] *J Am Coll Cardiol* 2002;156A
21. Gheorghiade M, Gattis WA, O'Connor CM, Adams KF Jr, Elkayam U, et al.: for the ACTIV in CHF Investigators: Effects of tolvaptan, a vasopressin antagonist, in patients hospitalized with worsening heart failure: a randomized controlled trial. *JAMA* 2004; 291:1963–1971
22. Abraham WT, Oren RM, Crisman TS, Robertson AD, Shakar S, et al.: Effects of an oral, nonpeptide, selective V2 receptor vasopressin antagonist in patients with chronic heart failure. *J Am Coll Cardiol* 1997;29(2 suppl A):169A
23. Abraham W, Koren M, Bichet DG, Verbalis JG, Klapholz M, et al.: Treatment of hyponatremia in patients with SIADH or CHF with intravenous conivaptan (YM 087), a new combined vasopressin V_1/V_2 receptor antagonist. *Eur Heart J* 2000;21:345
24. Abraham W, Suresh DP, Wagoner LE, Haas GJ, Nelson C, et al.: Pharmacotherapy for hyponatremia in heart failure: effects of a new combined V_{1A}/V_2 vasopressin receptor antagonist, conivaptan (YM087) administered orally. *Eur Heart J* 2000;21:345
25. Gheorghiade M, Orlandi C, Burnett JC, Demets D, Grinfeld L Jr, et al.: Rationale and design of the multicenter, randomized, double-blind, placebo-controlled study to evaluate the efficacy of vasopressin antagonism in heart failure: outcome study with tolvaptan (EVEREST). *J Card Fail* 2005;11:260–269
26. EVEREST North American Update. Otsuka Maryland Research Institute. November 29, 2005
27. Chan PS, Coupet J, Park HC, Lai F, Hartupee D, et al.:VPA-985, a nonpeptide orally active and selective vasopressin V_2 receptor antagonist. *Adv Exp Med Biol* 1998;449:439–443
28. Wong F, Blei AT, Blendis LM, Thuluvath PJ: A vasopressin receptor antagonist (VPA-985) improves serum sodium concentration in patients with hyponatremia: a multicenter, randomized, placebo-controlled trial. *Hepatology* 2003;37:182–191
29. Goldsmith SR, Gheorghiade M: Vasopressin antagonism in heart failure. *J Am Coll Cardiol* 2005;46:1785–1791
30. Vaprisol® (conivaptan hydrochloride injection) [package insert]. Deerfield, Ill: Astellas Pharma US, Inc; 2006
31. Verbalis JG, Bisaha JG, Smith N: *Novel Vasopressin V_{1a} and V_2 Antagonist Conivaptan Increases Serum Sodium Concentration and Effective Water Clearance in Hyponatremia Presented at: American Society of Nephrology Renal Week 2004*. October 27, 2004-November 1, 2004; St. Louis, Mo
32. Verbalis JG, Bisaha JG, Smith N: Novel vasopressin V_{1a} and V_2 antagonist (conivaptan) increases serum sodium concentration and effective water clearance in patients with hyponatremia [abstract]. *J Card Fail* 2004;10(suppl 1):S27
33. Verbalis J, Ghali J, Gross P, Long W, Smith N: Novel vasopressin V_{1a} and V_2 antagonist (conivaptan) increased serum sodium concentration in patients with hyponatremia secondary to congestive heart failure [abstract]. *J Card Fail* 2005;11(suppl 6):S120
34. Udelson JE, Smith WB, Hendrix GH, Painchaud CA, Ghazzi M, et al.:Acute hemodynamic effects of conivaptan, a dual V_{1a} and V_2 vasopressin receptor antagonist, in patients with advanced heart failure. *Circulation* 2001;104:2417–2423