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The role of vasopressin in congestive heart failure

ABSTRACT

Neurohormonal abnormalities contribute to the pathophysiology of congestive heart failure (CHF). Successful approaches to improving the prognosis of patients with CHF are based largely on therapeutic interruption of activated neurohormonal systems. The use of antagonists and inhibitors of the renin-angiotensin-aldosterone and sympathetic nervous systems has significantly improved clinical outcomes in CHF. Excessive secretion of arginine vasopressin (AVP) has the potential for deleterious effects on various physiologic processes in CHF. Inhibition of AVP through vasopressin receptor antagonist therapy is a potentially beneficial new therapeutic approach to CHF.

KEY POINTS

Stimulation of vasopressin type 1A (V_{1A}) receptors results in vasoconstriction and a positive inotropic effect. Stimulation of vasopressin type 2 (V_2) receptors leads to increased water retention.

Plasma AVP levels are increased or incompletely suppressed in patients with CHF.

Hyponatremia is associated with poor outcomes in CHF and may be caused or aggravated by excess AVP.

AVP antagonism, either with a combined V_{1A}/V_2 antagonist or a pure V_2 antagonist, is a logical and promising therapeutic option in acute and chronic CHF.

ALTHOUGH BY NO MEANS FULLY CLEAR, our understanding of the pathophysiology of congestive heart failure (CHF) has evolved greatly over the past 2 decades. Among the chief insights is that hemodynamic derangements do not fully explain the syndrome since hemodynamically oriented therapy is not sufficient, and is sometimes even harmful. Recent attention has focused on the role of neurohormonal imbalances as important contributors to both load-dependent and load-independent processes that may aggravate CHF.[1]

Among neurohormonal targets for therapy in CHF, arginine vasopressin (AVP) has attracted much recent interest. Indeed, it is increased AVP secretion in heart failure, and its potential to promote hyponatremia and other effects that can lead to CHF progression, that makes CHF a topic of interest for this supplement. This article reviews the role of AVP as it relates to CHF and the potential benefits of AVP antagonism as a new therapeutic option for patients with CHF.

NEUROHORMONES IN HEART FAILURE

Under normal circumstances, acute activation of neurohormonal systems helps preserve circulatory homeostasis and maintain arterial pressure. Chronic excess of these neurohormones, however, plays an important role in the development and progression of CHF. This role has been clearly established by the therapeutic success achieved with agents that are active in interfering with the renin-angiotensin-aldosterone system (RAAS) and the sympathetic nervous system. Angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor antagonists, aldosterone antagonists, and beta-blockers have all provided significant clinical benefits in patients with CHF.[2–9]

The question now is whether further intervention in CHF based on neurohormonal

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TABLE 1

Site of action and physiologic effects of AVP receptor subtypes

RECEPTOR SUBTYPE	SITE OF ACTION	PHYSIOLOGIC EFFECTS
V_{1A}	Vascular smooth muscle Cardiac myocytes	Vasoconstriction Positive inotropy/mitogen
V_{1B} (V_3)	Anterior pituitary	ACTH and beta-endorphin release
V_2	Renal collecting ducts	Free water reabsorption

ACTH = adrenocorticotropic hormone
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mechanisms would be useful. Recent studies with endothelin antagonists have not shown benefit, nor has the long-term approach of increasing natriuretic peptide signaling by combining endopeptidase inhibition with an ACE inhibitor.[10,11] A remaining candidate hormone for therapeutic targeting is AVP, which was one of the three neurohormones proposed as possible contributors to the pathophysiology of CHF in the first paper written describing the "neurohumoral axis" in CHF.[12]

Plasma AVP levels correlate with adverse outcome in CHF

PHYSIOLOGY OF AVP

Arginine vasopressin has three distinct receptor subtypes (Table 1).[13,14] From a cardiovascular perspective, the most important receptors are the vasopressin type 1A (V_{1A}) and vasopressin type 2 (V_2) receptors.

V_{1A} receptors are located on vascular smooth muscle and cardiac myocytes. These are G protein–coupled receptors, which increase intracellular calcium via the inositol triphosphate pathway. This increase in intracellular calcium results in vasoconstriction and a positive inotropic effect.[15] Stimulation of the V_{1A} receptor also promotes the synthesis of contractile protein in myocytes.[16] Stimulation of the V_{1A} receptors in vascular smooth muscle could therefore increase systemic vascular resistance, increasing impedance to ventricular emptying (ie, afterload) and thereby adversely affect ventricular function in heart failure. Sustained increases in afterload also contribute to myocardial remodeling and progressive failure. Direct stimulation of the myocyte over time may have the same effect.

V_2 receptors mediate their effects via adenyl cyclase–dependent signaling in the renal collecting ducts. Activation of these receptors increases water retention, which is accomplished by upregulation of the aquaporin-2 water channels.[17] This upregulation results in an increased movement of water from the collecting ducts back into the plasma, increasing free water reabsorption, which leads to increased water retention. This effect, if sustained, may contribute to volume expansion that exacerbates diastolic wall stress in CHF, another mechanism that may contribute to ventricular remodeling and dysfunction. Depending on the balance of factors influencing water and sodium intake and excretion, V_2 receptor–mediated water retention may also contribute substantially to hyponatremia, a common condition in moderate and severe CHF.

ROLE OF AVP IN HEART FAILURE

Plasma AVP levels are increased, or at least incompletely suppressed, in patients with chronic stable CHF and acute decompensated CHF[18–23] (Figure 1). As with other neurohormones, plasma AVP levels correlate with adverse outcome in CHF and tend to be much higher in severe CHF, or soon after major insults such as myocardial infarction (MI). A cause-and-effect relationship between inappropriate AVP levels and CHF progression has not yet been proven, but if experience with the other neurohormonal systems is a guide, increased AVP is likely not just an epiphenomenon.

As discussed above, a number of mechanisms related directly to the physiologic effects of AVP could underlie pathophysiologic contributions (Figure 2). AVP could potentially contribute directly and indirectly to well-characterized load-dependent and load-independent mechanisms that may aggravate progressive ventricular remodeling and failure, as well as the expression of the clinical heart failure syndrome. Congestion, in particular, is a hallmark of decompensated or severe CHF, and the volume retention secondary to excessive AVP secretion adds to the volume retention of sodium and water caused by aldosterone and other renal mechanisms. Likewise, hyponatremia, which is associated with poor outcome in CHF, may be caused or aggravated by excessive AVP levels.

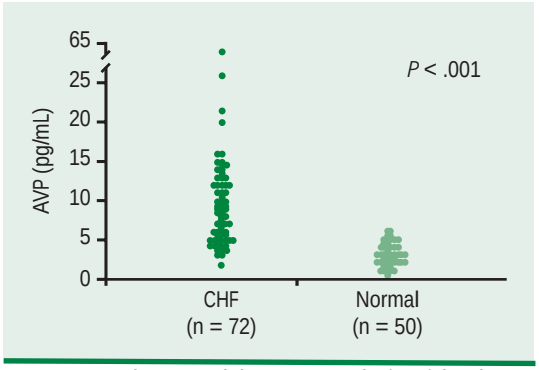

FIGURE 1. Plasma arginine vasopressin (AVP) levels, although heterogeneous, are two to three times greater in patients with mild to moderate congestive heart failure (CHF) compared with controls without cardiovascular disease. Reprinted, with permission, from reference 13.

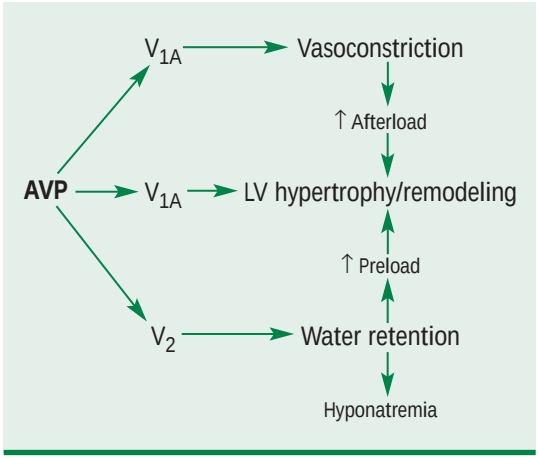

FIGURE 2. The actions of arginine vasopressin (AVP) are mediated through the vasopressin type 1A (V_{1A}) and vasopressin type 2 (V_2) receptors. The consequences of V_{1A} activation are vasoconstriction, increased afterload, and left ventricular (LV) hypertrophy and remodeling. V_2 activation promotes water retention, leading to volume expansion and potentially hyponatremia.

Interfering with either or both the V_{1A} and V_2 receptors could therefore, at least theoretically, be of substantial value in chronic or acute CHF.

Ultimately, before a definitive role for AVP in chronic or acute CHF is established, we must establish not just a potential pathophysiologic role and adequate hormone levels or signaling, but evidence that interfering with hormone secretion or effect has a clinically important benefit. This process is just beginning with AVP, but preliminary experimental and clinical results are encouraging.

Experimental models

Many studies in several animal models of CHF have shown acute and moderately sustained beneficial effects of V_{1A}, V_2, and combined V_{1A} and V_2 antagonism.[24–32] A more recent study by Naitoh and colleagues[33] assessed the long-term effect of dual V_{1A} and V_2 receptor blockade either alone or in combination with an ACE inhibitor in a well-accepted animal model of post-MI remodeling. They found that blockade of V_{1A} and V_2 receptors was associated with increased free water excretion, and, when combined with an ACE inhibitor, a degree of reduction in right ventricular mass not achieved with ACE inhibition or AVP blockade alone.

These results establish an active degree of AVP signaling in this setting, and suggest that although blockade of V_{1A} and V_2 receptors alone may be of limited utility, a synergistic effect may occur when combined with an ACE inhibitor. Synergy between these two drug classes is relevant clinically in that any benefit of AVP antagonists would have to occur over a background of ACE inhibitor therapy. Other studies on the vascular effects of AVP blockade also suggest important synergies between V_{1A} blockade and interventions that interrupt the RAAS.[31,34,35]

A synergistic effect may occur with AVP antagonism and ACE inhibition

Effects in clinical CHF

Reports of the effects of AVP antagonists in clinical CHF are limited. AVP signaling, however, has been shown to be adequate to produce a hemodynamic effect in patients with CHF. Exogenous infusion of AVP produces a fall in cardiac output and an increase in systemic vascular resistance, among significant hemodynamic changes (Figure 3).[20,21,36] Following acute administration of a V_{1A} antagonist, plasma levels of vasopressin correlate inversely with the percentage change in systemic vascular resistance in patients with chronic stable CHF.[37] Additionally, acute administration of a pure V_2 antagonist has been shown to produce a marked increase in water excretion.[38,39]

No clinical experience with sustained administration of either a pure V_{1A} antagonist or a combined V_{1A}/V_2 antagonist has been reported to date. Administration of a V_2 antagonist (tolvaptan) in the setting of acute decompensated CHF is associated with superior early weight loss and a sustained reduction in body weight after up to 60 days of administration.[40]

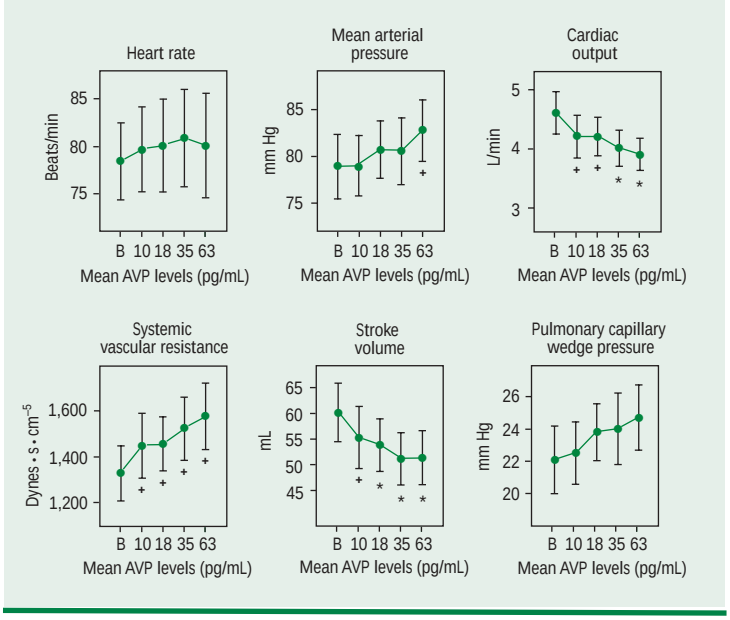

FIGURE 3. Stepwise infusion of exogenous vasopressin led to acute hemodynamic deterioration in a group of 11 patients with chronic stable congestive heart failure, including increases in heart rate, mean arterial pressure, systemic vascular resistance, and pulmonary capillary wedge pressure and decreases in cardiac output and stroke volume. AVP = arginine vasopressin; B = baseline. Reprinted, with permission, from reference 36.

Serum sodium, when low, remained corrected. This report is encouraging in that it demonstrated sustained effects of a V_2 antagonist in clinical CHF. However, there were significant tolerability issues regarding thirst, and a somewhat surprising lack of change in blood pressure despite the significant effect on body weight. Plasma AVP levels have not been reported from this study, but one may expect that they rose in the group of patients on active treatment. A vasoconstrictive effect from unopposed V_{1A} stimulation could therefore have accounted for the lack of fall in blood pressure.

The final article in this supplement reviews in detail the available clinical trials of all AVP antagonists in late-stage development, both in CHF and in other conditions associated with hyponatremia.

CONSIDERATIONS FOR DRUG DEVELOPMENT

With several AVP antagonists under active development for CHF, and potentially more on the way, several factors must be considered in future studies. How to measure efficacy is a major concern, and this decision will depend on the type of compound and the study setting. Mortality is the ultimate endpoint for testing therapies for chronic CHF, and a mortality study with tolvaptan is under way. Given the current low mortality rate in stable CHF, demonstrating a benefit of any new treatment on this endpoint may be a challenge. Hence, looking for benefits on surrogate endpoints such as ventricular remodeling may also be crucial. For both acute and chronic CHF, morbidity and cost of care are also reasonable endpoints, and here the effects of V_2 or combined antagonists may be particularly valuable given the potential benefits of these agents on congestion and hyponatremia.

For chronic CHF, the type of antagonist studied may be important. As noted before, the reasons to expect benefit from a V_{1A} antagonist are many, assuming adequate signaling is present. But a pure V_{1A} antagonist may lead to elevated AVP levels and unwanted water retention, which would not be desirable, particularly in patients with well-compensated CHF. Likewise, a pure V_2 antagonist, although useful acutely, may lead over time to unwanted V_{1A} stimulation. When AVP levels rise in response to increased osmolality in patients with normal serum sodium levels who receive a V_2 antagonist, any level of adverse endogenous AVP stimulation from the V_{1A} side is obviously enhanced. For long-term studies, therefore, it would seem most desirable to combine V_{1A} and V_2 antagonism, whereas for acute decompensated CHF, a pure V_2 antagonist may be equally useful. These are the types of issues that will need to be resolved with additional clinical studies.

CONCLUSIONS

There is now adequate theoretical justification to pursue AVP antagonism in acute and chronic CHF. AVP is a logical target both in terms of conventional hemodynamic understanding of CHF and in view of the successes of neurohormonally based therapy. Excessive AVP levels are present in clinical CHF, and acute studies with AVP antagonists in both experimental and clinical settings are encouraging. Many issues remain unresolved, however, and much work will be required in the coming years before a meaningful role for AVP in the pathophysiology of CHF can be definitively established.

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