

STEVEN R. GOLDSMITH, MD\*

Division of Cardiology  
Hennepin County Medical Center  
Minneapolis, MN

# Vasopressin receptor antagonists: Mechanisms of action and potential effects in heart failure

## ■ ABSTRACT

Increased arginine vasopressin (AVP) secretion in heart failure may lead to vasoconstriction, left ventricular remodeling, and water retention—actions that promote afterload, preload, and hyponatremia and thereby cause disease progression. Interfering with AVP-mediated signaling pharmacologically may be beneficial in heart failure. Selective antagonism of the vasopressin 2 ( $V_2$ ) receptor may facilitate a safe diuresis and normalize low serum sodium levels, as demonstrated in preliminary clinical trials. Pure  $V_2$  antagonism, however, may stimulate AVP secretion and enhance  $V_{1a}$  signaling, while pure  $V_{1a}$  receptor antagonism may lead to unwanted  $V_2$  stimulation and secondary water retention and volume expansion. Combined  $V_{1a}$  and  $V_2$  receptor antagonism could potentially prove advantageous as a therapy for heart failure by acting synergistically to facilitate diuresis and improve hemodynamics.

## ■ KEY POINTS

AVP has multiple actions, mediated through the  $V_{1a}$  and  $V_2$  receptors, which could contribute to heart failure progression.

Interfering with AVP signaling may have clinical benefits in acute and chronic heart failure.

Facilitation of diuresis, a safe diuresis, and normalization of serum sodium are potential mechanisms of benefit of  $V_2$  antagonism in heart failure.

Combined  $V_{1a}$  and  $V_2$  antagonism has theoretic advantages as a therapeutic strategy, including synergy in improving hemodynamics, but this strategy needs to be tested clinically.

\*Dr. Goldsmith reported that he is a consultant to the Astellas corporation and is on the speakers' bureaus of the Astellas and GlaxoSmithKline corporations.

**A**N UNDERSTANDING OF the imbalances in the neurohormonal axis has prompted the greatest insights into the pathophysiology and treatment of heart failure to date. From a cardiorenal perspective, neurohormonal imbalances drive much of the sodium and water retention in this disease. These imbalances also contribute to abnormal loading conditions that predispose to a deterioration in hemodynamics and circulatory abnormalities. Even when volume is controlled, neurohormonal imbalances drive cellular and molecular processes that cause progression of this syndrome.

Therapy for heart failure today is built around interfering with two neurohormonal systems—the renin-angiotensin system and the sympathetic nervous system—with the addition of diuretics as needed for reducing volume expansion. Efforts to further exploit this neurohormonal approach may be warranted. Specifically, the possible contribution of the nonapeptide arginine vasopressin (AVP) to heart failure progression has recently been appreciated. This article reviews the actions of AVP and the evidence for AVP signaling in heart failure, and explores the therapeutic potential of interference with AVP signaling.

## ■ MECHANISMS FOR DISEASE PROGRESSION

Distinct load-dependent and load-independent mechanisms are responsible for disease progression in heart failure. The load-dependent mechanisms involve diastolic wall stress (eccentric hypertrophy) and systolic wall stress (concentric hypertrophy). The load-independent mechanisms come into play because of direct stimulation of processes at the cellular and intracellular level. The various neurohormones implicated in heart failure can contribute to disease progression by all of these mechanisms.

### Actions of AVP in heart failure

AVP may contribute to heart failure through several mechanisms because AVP has a complicated set of receptor systems (Table 1). The major actions of AVP in heart failure are mediated through the vasopressin 1a ( $V_{1a}$ ) and vasopressin 2 ( $V_2$ ) receptors.

**Consequences of  $V_{1a}$  activation.** The  $V_{1a}$  receptor is located on blood vessels and in the myocardium. It is a classic G-protein-coupled receptor, increasing intracellular calcium through the IP3 pathway. Its intracellular signaling pathway is similar to that of angiotensin II and the alpha-adrenergic portion of the sympathetic nervous system. The predictable consequences of  $V_{1a}$  activation are vasoconstriction (other than endothelin, it is the most potent vasoconstrictor in the body) and inotropic and mitogenic effects.

**Consequences of  $V_2$  activation.** The  $V_2$  receptor, located primarily on the renal tubule, is the receptor that governs water retention. When  $V_2$  receptors are activated, they change the expression of aquaporin channels in the renal collecting duct. The aquaporin channels translocate and then render the tubule more permeable to water so that water is retained.  $V_2$  receptors are also present on the endothelium and are linked in a complicated way to secretion of von Willebrand factor, so  $V_2$  receptors may contribute to hemostasis. Evidence is unequivocal that the  $V_2$  receptor also has an endothelium-dependent vasodilatory function. This function is not observed in normal humans until plasma AVP reaches fairly high levels; the plasma levels of AVP at which  $V_2$  receptors exert this action in patients with heart failure or in the presence of neurohormonal blockade is unknown.

### AVP signaling

In linking what is known about AVP signaling to potential progression of heart failure, AVP through the  $V_{1a}$  receptor could cause vasoconstriction, increase afterload, and thereby contribute to left ventricular (LV) remodeling and disease progression. AVP could also contribute to LV remodeling and disease progression directly through  $V_{1a}$  receptor activation. By triggering water retention, AVP stimulation of the  $V_2$  receptor could exacerbate preload, which could also lead to adverse LV remodeling and dis-

TABLE 1

### Actions of vasopressin

| RECEPTOR | SIGNALING                                                               | LOCATION      | ACTIONS                       |
|----------|-------------------------------------------------------------------------|---------------|-------------------------------|
| $V_{1a}$ | G-protein-coupled;<br>IP3 activation;<br>raises intracellular $Ca^{++}$ | Blood vessels | Vasoconstriction              |
|          |                                                                         | Myocardium    | Inotrope/mitogen              |
| $V_2$    | Adenyl cyclase                                                          | Renal tubule  | H <sub>2</sub> O retention    |
|          |                                                                         | Endothelium   | Hemostasis                    |
|          |                                                                         |               | Vasodilation<br>(high levels) |

ease progression. Another mechanism by which AVP could lead to disease progression is its possible contribution to hyponatremia.

The evidence for  $V_{1a}$  signaling in heart failure is the hemodynamic benefit achieved with acute and short-term  $V_{1a}$  antagonism in numerous animal models of congestive heart failure. The human data are extremely limited, however, and  $V_{1a}$  signaling may not be adequate for an effect to be observed in all settings.

Infusions of AVP in patients with chronic congestive heart failure produce hemodynamic deterioration (decrease in cardiac output and increase in systemic vascular resistance) with small changes in plasma AVP.<sup>1</sup> This effect is presumably mediated by the  $V_{1a}$  receptor, which causes vasoconstriction and deterioration of LV function. Early work by Creager et al with an intravenous (IV) AVP antagonist showed a drop in systemic vascular resistance in patients with heart failure following  $V_1$  antagonism.<sup>2</sup> Because these studies were performed in the 1980s, neither was conducted over a background of current standard therapy for heart failure, although other experimental evidence points to  $V_{1a}$  signaling being *more* potent in the presence of other neurohormonal blockade.

AVP has a mitogenic effect that could potentially contribute to remodeling. Stimulation of the  $V_{1a}$  receptor directly induces hypertrophic growth of neonatal myocytes in rat heart cells.<sup>3</sup>

### THERAPEUTIC POTENTIAL

No pure  $V_{1a}$  receptor antagonists are under development because competitive antagonism of the  $V_{1a}$  receptor alone may lead to unwanted  $V_2$  stimulation and secondary

By triggering water retention,  $V_2$  receptor stimulation could exacerbate preload

TABLE 2

**Predictive value of hyponatremia in patients hospitalized with heart failure\***

|                                         | HYPONATREMIC<br>PATIENTS<br>(n = 256) | NORMONATREMIC<br>PATIENTS<br>(n = 687) | P                  |
|-----------------------------------------|---------------------------------------|----------------------------------------|--------------------|
| 60-day mortality (%)                    | 16                                    | 7                                      | .0001 <sup>†</sup> |
| Readmission or death within 60 days (%) | 42                                    | 33                                     | .017               |

From the OPTIME-CHF trial.<sup>7</sup>

\* Hyponatremia defined as serum sodium  $\leq$  136 mEq/L at study baseline.

<sup>†</sup> Log-rank statistic.

AVP has a mitogenic effect that potentially contributes to remodeling

water retention and volume expansion.

As noted, the  $V_2$  receptor is linked to water retention, expansion of preload, diastolic wall stress, and ventricular remodeling. Unlike with the  $V_{1a}$  receptor, evidence is plentiful for the potential of  $V_2$  receptor antagonism in heart failure. All antagonists of the  $V_2$  receptor—tolvaptan, lixivaptan, and conivaptan—produce effective aquaresis and weight loss. Gheorghiade and colleagues demonstrated a significant net loss in volume with tolvaptan compared with placebo during hospitalization in patients admitted with worsening heart failure.<sup>4</sup> Regardless of AVP levels in heart failure, interfering with  $V_2$  signaling produces an aquaresis, making it theoretically possible that  $V_2$  receptor antagonists would be useful to relieve congestion.

### ■ SHORTCOMINGS OF LOOP DIURETICS IN HEART FAILURE

**Inefficient congestion relief.** As reviewed in previous articles in this supplement, loop diuretics, the current standard of therapy to relieve congestion, are ineffective and inefficient, especially in patients with severe heart failure or renal dysfunction.

**Neurohormonal stimulation.** Loop diuretics also activate the same neurohormonal forces that chronic heart failure treatment is designed to inhibit.

Administration of loop diuretics has clearly been shown to activate neurohormones, both acutely and chronically, in patients with con-

gestive heart failure. In animal studies, these drugs have the same effect; by comparison, administration of tolvaptan was not associated with this degree of neurohormonal activation, and attenuated that seen with furosemide when given together with this agent.<sup>5</sup> In heart failure, this “neurohormonal-sparing effect” could be important, if it can be demonstrated in patients.

**Heart failure exacerbation.** Data from an animal model indicate that excessive reliance on loop diuretics can exacerbate experimental heart failure.<sup>6</sup> In this study, animals with pacing-induced heart failure that were given furosemide had worse ventricular function and an acceleration of death compared with animals not given furosemide, despite relief of congestion and reduction of body weight with furosemide. The cause of death was not sudden death due to electrolyte depletion but a worsening of heart failure, as evidenced by the shortened time to left ventricular dysfunction in the furosemide group.

$V_2$  receptor antagonism in patients with heart failure may therefore have the benefit of a facilitated diuresis, leading to enhanced preload reduction, reduced wall stress, and diminished remodeling stimuli, assuming these effects can be demonstrated with long-term treatment.

### ■ HYPONATREMIA AND OUTCOMES

Hyponatremia is a marker for poor outcome in heart failure. Among heart failure patients treated with angiotensin-converting enzyme (ACE) inhibitors, diuretics, and beta-blockers, even a small decline in serum sodium levels, to 136 mEq/L or less, was associated with more than twice the risk of 60-day mortality and a significant increase in risk of readmission or death within 60 days compared with serum sodium levels greater than 136 mEq/L (Table 2).<sup>7</sup>

In a study of patients with end-stage heart failure, Italian investigators attempted to isolate the effect of an increase in serum sodium on clinical outcome.<sup>8</sup> They randomized 107 patients with refractory heart failure to receive an IV infusion of furosemide plus hypertonic saline solution 3% or an IV bolus of furosemide twice a day without hypertonic saline. Survival over a mean follow-up of 31 months was 55% in the group that received hypertonic saline compared with 13% in those that did

not receive hypertonic saline ( $P < .001$ ). This suggests that normalization of a low serum sodium may be another potential mechanism of benefit of  $V_2$  antagonism in heart failure.

The benefits of pure  $V_2$  antagonism, however, may come at a cost of stimulation of AVP secretion in response to rising plasma osmolality and an unwanted enhancement of  $V_{1a}$  signaling.

### ■ COMBINED $V_{1a}/V_2$ ANTAGONISM

Combined antagonism of the  $V_{1a}$  and  $V_2$  receptors may be a way to overcome some of the disadvantages with pure antagonism of either the  $V_{1a}$  or  $V_2$  receptor. The data are encouraging in the preclinical setting and in the acute clinical setting, but are lacking with chronic therapy.

Conivaptan is a combined  $V_{1a}/V_2$  receptor antagonist. Although it is orally and intravenously active, only the IV form is being developed and released. Conivaptan has been approved by the US Food and Drug Administration for treatment of euvoletic hyponatremia, making it the first AVP receptor antagonist to gain US marketing approval. A Phase 2 pilot study of conivaptan for treatment of acute congestive heart failure has been completed; data release is scheduled for late 2006.

Hemodynamics of combined antagonists. In an experimental model of heart failure, combining a  $V_{1a}$  antagonist with a  $V_2$  antagonist produced a synergistic effect in terms of increasing cardiac output and reducing systemic vascular resistance.<sup>9</sup> This study offered early evi-

dence that combined  $V_{1a}$  and  $V_2$  antagonism could result in more beneficial hemodynamic responses than a  $V_{1a}$  antagonist alone.

Potential synergy with ACE inhibition. In rats with experimental myocardial infarction,  $V_{1a}/V_2$  receptor antagonism with conivaptan given concomitantly with the ACE inhibitor captopril had a synergistic effect on reducing systolic blood pressure at 1 week.<sup>10</sup> This effect may represent an interruption of  $V_{1a}$  signaling if blood pressure is considered a surrogate for  $V_{1a}$  signaling. Combined therapy also led to a significant reduction in right ventricular weight as an index of remodeling, which probably represents a blocking of  $V_2$  signaling. These data suggest a potentially clinically meaningful effect on right ventricular compensation with the combination of ACE inhibition and dual  $V_{1a}/V_2$  receptor antagonism.

### ■ CONCLUSIONS

AVP clearly has multiple actions that could contribute to the progression of heart failure. Interfering with the  $V_{1a}$  and/or the  $V_2$  receptor-mediated actions of AVP could therefore be expected to be beneficial in the treatment of acute and chronic heart failure. Selective interference with only one set of receptors, however, could in theory trigger counterproductive increased signaling at the other sites. Combined  $V_{1a}$  and  $V_2$  antagonism might therefore be preferable as a therapeutic strategy, especially in the chronic setting, but this hypothesis has yet to be tested clinically.

Evidence is plentiful for the potential of  $V_2$  receptor antagonism in heart failure

### ■ REFERENCES

1. Goldsmith SR, Francis GS, Cowley AW Jr, Goldenberg IF, Cohn JN. Hemodynamic effects of infused arginine vasopressin in congestive heart failure. *J Am Coll Cardiol* 1986; 8:779–783.
2. Creager MA, Faxon DP, Cutler SS, et al. Contribution of vasopressin to vasoconstriction in patients with congestive heart failure: comparison with the renin-angiotensin system and the sympathetic nervous system. *J Am Coll Cardiol* 1986; 7:758–765.
3. Nakamura Y, Haneda T, Osaki J, et al. Hypertrophic growth of cultured neonatal rat heart cells mediated by vasopressin  $V(1A)$  receptor. *Eur J Pharmacol* 2000; 391:39–48.
4. Gheorghiade M, Gattis WA, O'Connor CM, et al. Effects of tolvaptan, a vasopressin antagonist, in patients hospitalized with worsening heart failure. *JAMA* 2004; 291:1963–1971.
5. Hirano T, Yamamura Y, Nakamura S, et al. Effects of the  $V(2)$ -receptor antagonist OPC-41061 and the loop diuretic furosemide alone and in combination in rats. *J Pharmacol Exp Ther* 2000; 292:288–294.
6. McCurley JM, Hanlon SU, Wei SK, et al. Furosemide and the progression of left ventricular dysfunction in experimental heart failure. *J Am Coll Cardiol* 2004; 44:1301–1307.
7. Klein L, Gattis WA, Leimberger JD, et al. Prognostic value of hyponatremia in hospitalized patients with worsening heart failure: insights from the Outcomes of a Prospective Trial of Intravenous Milrinone for Exacerbations of Chronic Heart Failure (OPTIME-CHF). *J Card Fail* 2003; 9:S83. Abstract.
8. Licata G, Di Pasquale P, Parrinello G, et al. Effects of high-dose furosemide and small-volume hypertonic saline solution infusion in comparison with a high dose of furosemide as bolus in refractory congestive heart failure: long-term effects. *Am Heart J* 2003; 145:459–466.
9. Naitoh M, Suzuki H, Murakami M, et al. Effects of oral AVP receptor antagonists OPC-21268 and OPC-31260 on congestive heart failure in conscious dogs. *Am J Physiol* 1994; 267:H2245–H2254.
10. Naitoh M, Risvanis J, Balding LC, et al. Neurohormonal antagonism in heart failure; beneficial effects of vasopressin  $V1a$  and  $V2$  receptor blockade and ACE inhibition. *Cardiovasc Res* 2002; 54:51–57.

Address: Steven R. Goldsmith, MD, Cardiology Division, Hennepin County Medical Center, 701 Park Avenue South, Minneapolis, MN 55415; srg\_hcmc@yahoo.com.