

STATE-OF-THE-ART PAPERS

Vasopressin Antagonism in Heart Failure

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Treatment of chronic heart failure (HF) is based on interference with the renin-angiotensin-aldosterone system and the adrenergic nervous system. Diuretics are used in volume-expanded patients. Insights from clinical trials and registries establish the need to consider correcting both cardiac loading conditions and nonload-related biological factors if HF therapy is to be optimized. Arginine vasopressin (AVP) represents a potentially attractive target for therapy in both acute and chronic HF. Excessive AVP secretion could contribute to both systolic and diastolic wall stress via V1a- and V2-mediated effects on the peripheral vasculature and on water retention. Arginine vasopressin also may directly and adversely affect myocardial function due to the effect of V1a activation on myocardial contractility and cell growth. Last, AVP may contribute to hyponatremia, a powerful predictor of poor outcome in HF. The development of effective nonpeptide antagonists to both the V1a and V2 receptors for AVP now allows for testing the hypotheses that interfering with AVP-mediated signaling could be beneficial in HF. This review summarizes the theoretical rationale for further development of such therapy, reviews the status of current compounds under development, and suggests key issues that need to be addressed as these agents undergo further clinical testing. (J Am Coll Cardiol 2005;46:1785–91) © 2005 by the American College of Cardiology Foundation

Therapy for chronic heart failure (HF) is currently based on pharmacologic interference with the renin-angiotensin-aldosterone system (RAAS) and the adrenergic nervous system, together with diuretics as needed. This treatment has reduced the expected annualized mortality in HF to 5% to 6% per year in stable, well-compensated patients (1,2). There are, however, many patients who clearly need additional support. Such patients are characterized by persistent congestion, frequent readmissions, renal failure, and hyponatremia (3–6).

Acute decompensated heart failure (ADHF) also remains a challenge. Data from the Acute Decompensated Heart Failure National registry (ADHERE) show that shortness of breath and edema are the major causes for admission to the hospital in patients with known HF (6). Therapy for ADHF is frequently suboptimal, with 60-day readmission rates in the range of 17% to 22% and 60-day mortality as high as 22% in patients with severe congestion and/or even mild renal impairment (5). Loop diuretics remain the prime intervention in ADHF. While retrospective data suggest better outcomes in patients treated with vasodilators as compared to inotropes (6), and while one vasodilator, nesiritide, may be less arrhythmogenic than dobutamine (7) and marginally superior to low-dose nitroglycerin for symptom relief (8), no additional therapy has yet been proven to be of adjunctive value in outcomes-driven prospective, placebo-controlled trials. The patient with renal insuffi-

ciency remains a challenge, even with the use of newer treatments like nesiritide (9).

In view of the success of neurohormonally guided treatment, further exploitation of this approach seems reasonable, both for chronic and acute HF. In theory, the antidiuretic hormone arginine vasopressin (AVP) is an attractive target, but until recently there have not been effective intravenous and oral antagonists to its effects. The recent development of such agents provides the opportunity to test the possibility that interference with AVP might be useful in the treatment of HF.

AVP IN HF

Treatment of chronic HF clearly needs to include both optimizing cardiac loading conditions, and the correction of nonload-related variables that contribute to progressive ventricular remodeling and failure (10). At least some of these variables must be improved by angiotensin-converting enzyme inhibition, angiotensin receptor blockade, beta-adrenergic blockade, and aldosterone antagonists because these treatments improve the outcome in HF despite minimal if any effects on loading conditions or hemodynamics. Comprehensive neurohormonal inhibition actually improves the basic biology of the heart, including partial reversal of the ventricular remodeling process at both the phenotypic and genotypic levels (11,12).

Similar considerations may apply to ADHF. Although there are far fewer data, the routine use of inotropic support is not supported by available trials (13), and there are no true outcomes studies with any vasodilator. Diuresis remains the key intervention for most patients with ADHF, yet diuretics can produce harm both acutely and chronically via electrolyte disturbances, neurohormonal stimulation, and worsen-

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Abbreviations and Acronyms

ADHF = acute decompensated heart failure
 AVP = arginine vasopressin
 HF = heart failure
 RAAS = renin-angiotensin-aldosterone system

ing renal function (14–16). Diuretics have been reported to actually hasten the development of overt HF in experimental HF (17), and the intensity of their use in chronic HF is associated with poor outcome (18).

Arginine vasopressin was one of the candidate “pathogens” in the original paper describing the “neurohumoral axis” in HF (19). Arginine vasopressin is a nonapeptide synthesized in the hypothalamus, stored in the posterior pituitary for release in response to both osmotic and nonosmotic factors. The dominant stimulus for AVP secretion in all species is serum osmolality (20). Nonosmotic factors including cardiac filling pressure, arterial pressure, and other influences, such as the effects of adrenergic stimuli and angiotensin II in the central nervous system, all can modulate the osmotic control of AVP to varying degrees in different species (20).

For reasons as yet unexplained, plasma AVP levels are inappropriately high in both acute and chronic HF (21–25). An early study with a bioassay showed elevated AVP in patients with HF due to a mix of etiologies (21). Later, radioimmunoassays of AVP in patients with both stable HF and ADHF associated with left ventricular systolic dysfunction confirmed frankly elevated or incompletely suppressed AVP levels (22–25). These reports were before the introduction of converting enzyme inhibitors and beta-blockers, however, and a recent study described plasma AVP levels in stable chronic HF patients that were lower than in the earlier work (26). No recent data regarding AVP levels in ADHF have been published.

Plasma AVP is elevated in the presence of left ventricular dysfunction even in the absence of clinical HF (27). As with other neurohormones, elevated plasma AVP correlates with poor outcomes (28). If the therapeutic experiences with the RAAS and the adrenergic nervous system are predictive, excessive AVP secretion may prove to be a contributor to the syndrome and not just a marker of severity.

Arginine vasopressin has many effects. Its major actions relevant to HF relate to signaling at the V1a and V2 receptors (29) (Table 1). The V1a receptor is a G-protein-

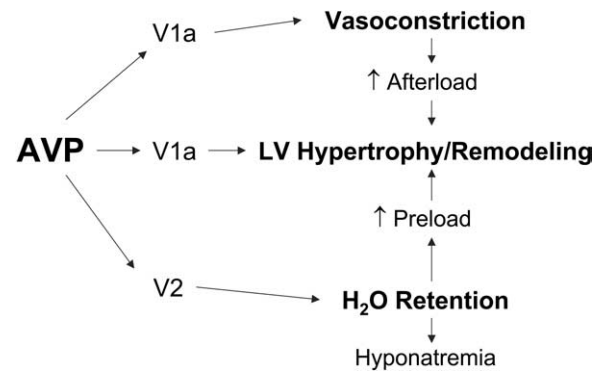


Figure 1. Vasopressin could aggravate the progression of heart failure by adversely affecting ventricular remodeling, worsening clinical congestion, and contributing to hyponatremia. V1a effects would be predominantly those causing arterial vasoconstriction, increasing afterload, and adversely affecting ventricular structure and function. Direct myocardial V1a effects could also be present. V2 effects could lead to excessive circulatory congestion, adversely affecting myocardial structure and function via increasing preload. V2 effects would also lead to hyponatremia. AVP = arginine vasopressin; LV = left ventricular.

coupled receptor which, when activated, increases intracellular calcium through the inositol triphosphate pathway (30). The result is constriction of smooth muscle (30) and a positive inotropic effect in cardiac muscle (31). Prolonged V1a stimulation leads to synthesis of proteins involved in cellular hypertrophy both in vascular and myocardial tissue (32).

Activation of the V2 receptor alters the expression of aquaporin channels and thereby increases the permeability to water of the renal collecting tubular cells (33), resulting in water retention. V2 receptors may also subserve endothelium-dependent vasodilation, but probably not at normal physiologic levels (34).

Excess AVP secretion could contribute to the pathophysiology of HF by several distinct load-dependent and load-independent mechanisms (29) (Fig. 1). V1a receptor stimulation could cause constriction of both arteries and veins and so contribute to increased myocardial afterload and preload. Increases in loading conditions may contribute to ventricular remodeling and progressive HF. Sustained V1a stimulation could also directly contribute to myocardial hypertrophy and aggravate adverse remodeling. Because the intracellular signaling pathway for the V1a receptor resembles that for angiotensin II, any adverse myocardial and vascular effects from V1a stimulation would likely be more prominent in the presence of agents that interfere with the generation or effects of angiotensin II. V1a stimulation could also cause coronary vasoconstriction and contribute to myocardial ischemia. Recently, an endothelium-dependent mechanism by which AVP may be synthesized in the heart has been described (35). If this can be confirmed in humans, plasma levels of AVP might underestimate the magnitude of V1a-mediated myocardial and coronary effects. There may be an interesting parallel here with the systemic and organ-specific synthesis of angiotensin II.

Table 1. Actions of Vasopressin

Receptor	Signaling	Location	Actions
V1a	G-protein, IP3	Blood vessels Myocardium	Vasoconstriction Inotrope/mitogen
V2	Adenyl cyclase	Renal tubule Endothelium	H ₂ O retention Vasodilation (high concentrations)

The predominant actions of vasopressin as relates to heart failure involve activation of the V1a and V2 receptors. See text for details.

The V2 receptor stimulation by AVP could contribute to volume expansion and therefore to increased cardiac preload. Increased preload exacerbates diastolic wall stress, in turn aggravating eccentric remodeling. If water accumulates to a greater degree than sodium, hyponatremia results. Hyponatremia is a marker for poor outcome in HF, even in the modern era (5). While generally assumed to be simply a marker for advanced disease, hyponatremia could be an active contributor to both morbidity and perhaps disease progression. For example, the only available treatment for hyponatremia is water restriction, which is often poorly tolerated by sick patients, thereby adversely affecting quality of life. Hyponatremia may have another more insidious contribution to poor outcome in severe HF by limiting the intensity of therapy with diuretics, angiotensin-converting enzyme inhibitors, and angiotensin receptor blockers. And hyponatremia could theoretically adversely affect myocyte function via increased cellular water content, as happens in the brain. An extremely provocative recent investigation reported that chronically correcting serum sodium with the combination of hypertonic saline and loop diuretics was associated with improved outcome in a population of patients with very severe HF (36). This study should certainly prompt further investigation of the nature of the relationship between hyponatremia and poor outcome in HF.

EXPERIMENTAL STUDIES OF AVP ANTAGONISM

Acute V1a antagonism produces hemodynamic improvement in animal models of HF (37-39). There is currently no long-term experience with a pure V1a antagonist. Most studies have involved only the use of the V1a antagonist, but one (in the pacing model) demonstrated synergism with the combination of a V1a antagonist and an angiotensin II antagonist (40). This is a potentially important observation in view of the common intracellular signaling pathways for AVP and angiotensin II. As well, many prior studies conducted under other conditions consistently showed more potent effects of V1a antagonism in the absence of activity of the adrenergic nervous system and the RAAS (41-43).

Administration of a V2 antagonist in animal models of HF yields a sustained diuresis that is largely an "aquaresis" (44). Combined administration of V1a and V2 antagonists in the pacing model of HF and the use of a mixed V1a/V2 antagonist in the postmyocardial infarction rat model of HF have resulted in greater hemodynamic benefit than with selective antagonism (39,45-47). When given chronically in experimental postmyocardial infarction HF, a combined V1a/V2 antagonist produced significant effects on right ventricular, but not left ventricular, weight beyond that seen with an angiotensin-converting enzyme inhibitor (48). The available experimental literature, while sparse, therefore suggests active V1a and V2 signaling in models of left ventricular dysfunction and HF.

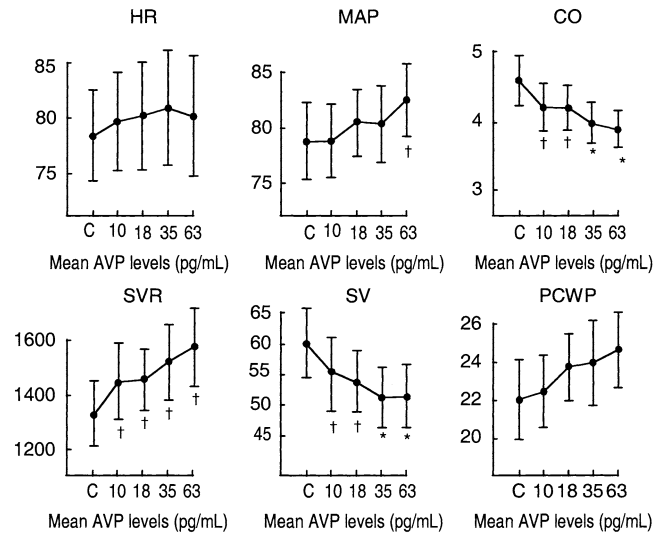


Figure 2. Hemodynamic effects of infused arginine vasopressin (AVP) in patients with chronic heart failure. CO = cardiac output; HR = heart rate; MAP = mean arterial pressure; PCWP = pulmonary capillary wedge pressure; SV = stroke volume; SVR = systemic vascular resistance. * $p < 0.01$; † $p < 0.05$. Adapted from Goldsmith SR, et al. *J Am Coll Cardiol* 1986;8:779-83.

HUMAN STUDIES

V1 antagonists. Infusion of exogenous AVP in patients with chronic stable HF produced acute hemodynamic deterioration, presumably via V1a effects (49) (Fig. 2). Single-dose studies with an intravenous peptide V1a antagonist showed evidence of V1a signaling by demonstrating a fall in systemic vascular resistance and improvement in cardiac output in HF patients with elevated AVP levels (50). Administration of the same V1a antagonist also reduced blood pressure in patients with resistant hypertension, despite relatively low AVP levels (51). This was an important observation because it suggests that, especially in the face of other vasoactive treatments, plasma levels of AVP may not predict the hemodynamic response to an effective antagonist.

Development of nonpeptide V1a antagonists has been difficult, because compounds that have seemed promising in animals have been shown to be partial agonists in humans (52). Preliminary work has been done with relcovaptan (SR 49059, Sanofi Recherche, Paris, France) (53), in both hypertension and HF, but there is no published information regarding these studies, and the compound is not currently undergoing further clinical evaluation. As of this writing, we know of no other pure V1a antagonist being developed for HF.

V2 antagonists. The issue of species-dependent partial agonism has also plagued the development of V2 antagonists. However, several effective agents have been tested (33). Lixivaptan (VPA 459, originally Wyeth-Ayerst, now Cardiokine, Philadelphia, Pennsylvania), tolvaptan (OPC-41061, Otsuka, Rockville, Maryland), and SR 121463 (Sanofi Recherche) have all been investigated in phase I and

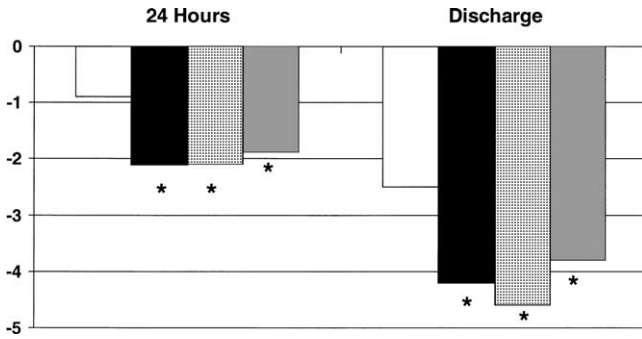


Figure 3. Effects of tolvaptan relative to placebo on body weight at 24 h (the primary end point of the study) and at discharge in the Acute and Chronic Therapeutic Impact of a Vasopressin (ACTIV) trial. * $p < 0.05$ vs. placebo. Adapted from reference 55. **White bars** = placebo; **black bars** = tolvaptan 0 mg; **dotted bars** = tolvaptan 60 mg; **grey bars** = tolvaptan 90 mg.

II trials. Tolvaptan is now in phase III studies for both HF and hyponatremia.

Acute and chronic studies with these agents in patients with HF demonstrate brisk and sustained increases in urine output and free water clearance (54,55), thereby establishing the presence of clinically measurable V2 signaling in human HF. The V2 antagonists may be viewed as the first new class of diuretic agents since the development of furosemide, but they are “aquaretics,” not “saliuretics.” With time, osmotic shifts lead to modest sodium excretion, but the predominant effect remains water excretion. There is no depletion of other electrolytes, and, in experimental studies, less stimulation of renin, aldosterone, and catecholamines than is seen with a comparable diuresis produced by furosemide (56).

Only one of these compounds, tolvaptan, has thus far been studied for longer than a few days in humans. The drug was given for 30 days to patients with mild clinical HF of diverse etiologies, some with hyponatremia (54). A sustained water diuresis was achieved, with body weight remaining below baseline, and only a modest, if any, rise in

serum sodium for the group as a whole. Patients who were hyponatremic maintained an improvement in serum sodium. The drug was well tolerated, with thirst the only major side effect reported.

A subsequent investigation with tolvaptan focused on patients with ADHF with ejection fraction less than 40%. This investigation, Acute and Chronic Therapeutic Impact of a Vasopressin Antagonist in Congestive Heart Failure (ACTIV in CHF) (55), was placebo-controlled, included a 60 day follow-up, and had two primary end points: 1) in-hospital body weight 24 h after drug administration; and 2) worsening HF at 60 days. There was a significantly greater reduction in body weight during the first 24 h in the group receiving tolvaptan. The body weight further decreased by discharge in the tolvaptan groups (Fig. 3). This difference was maintained during follow-up. However, while body weight declined on tolvaptan, there were no statistically significant differences in the signs and symptoms of clinical congestion. At 60 days, there was no difference in worsening HF between the groups. Patients randomized to tolvaptan used less furosemide and maintained a lower body weight, and there were no differences in heart rate, blood pressure, or renal function. If serum sodium was low, it normalized and remained so throughout the study period (Fig. 4). Although not powered for mortality, an intriguing post-hoc analysis suggested a reduction in mortality in the higher-risk patients (those with “severe” congestion and/or blood urea nitrogen >29 mg/dl).

There were significant side effects reported during the study with drop-out rates of nearly 33% in patients assigned to tolvaptan (for a variety of reasons, although excessive thirst was common). While AVP levels from the two arms of the study have not yet been reported, and while there was no worsening of HF in either arm of the study, it is interesting that while body weight decreased on active

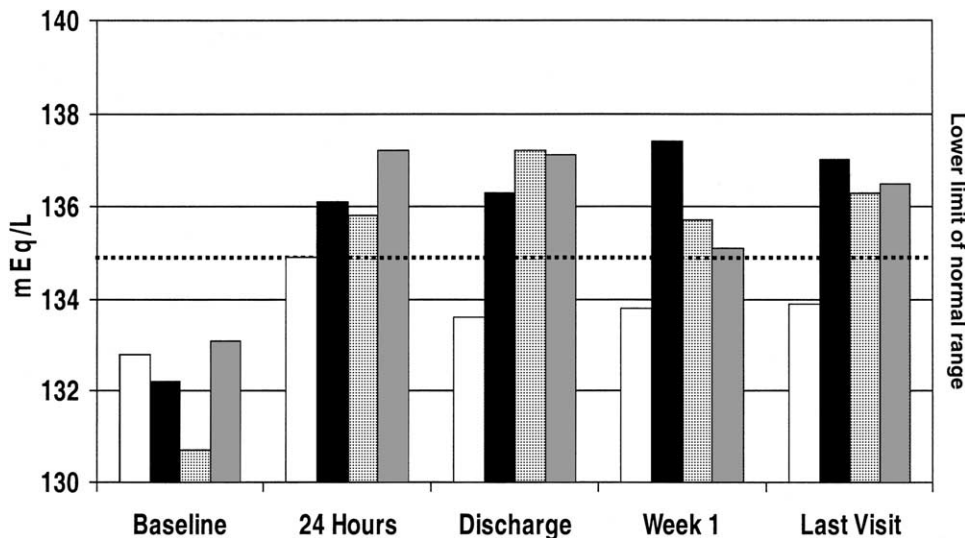


Figure 4. Effect of tolvaptan on serum sodium in those patients presenting with initial sodium under 135 mEq/ in the Acute and Chronic Therapeutic Impact of a Vasopressin (ACTIV) trial. Adapted from reference 55. **White bars** = placebo; **black bars** = 30 mg; **dotted bars** = 60 mg; **grey bars** = 90 mg.

treatment, blood pressure did not fall. This is unusual with significant diuresis in HF, and could suggest the unmasking of a V1a effect from endogenously stimulated AVP.

These results, while provocative and raising some unanswered questions, led to the initiation of a mortality trial of tolvaptan, which began enrollment in late 2003 (Efficacy of Vasopressin Antagonism in Heart Failure: Outcome Study with Tolvaptan [EVEREST]). The results of a phase II trial with this compound, in which ventricular remodeling was the primary end point, were presented at a "Late-Breaking Trials" session during the meeting of the Heart Failure Society of America in September 2005. The results did not show a beneficial effect of tolvaptan on ventricular remodeling versus placebo after approximately one year of treatment. However, the drug was well-tolerated, and a post-hoc Kaplan-Meier analysis of time to readmission or death was favorable for the tolvaptan group (Udelson et al., unpublished data, September 2005).

Combined V1a/V2 antagonists. To date, only one effective combined V1a/V2 antagonist (Conivaptan, or YM087, Yamanouchi Pharma, Surrey, United Kingdom) (57) has been evaluated in humans. This compound has demonstrated not only V1a- and V2-blocking effects in the peripheral circulation and kidney (57), but also the ability to block the recently described myocellular effects of V1a stimulation (58). Phase III trials have been completed with conivaptan in hyponatremia with a pending application to the Food and Drug Administration for approval. The V1a receptor antagonism of the compound would not be expected to contribute directly to an effect on hyponatremia, but, because many patients with hyponatremia have HF, if V1a signaling is important, this could be viewed as an added benefit.

There is as yet limited information regarding this compound in patients with HF. A large single-dose experience in patients with chronic stable HF showed that acute administration of conivaptan produced a fall in cardiac filling pressures together with a water diuresis (26). There were no effects of the compound on blood pressure, cardiac output, or systemic vascular resistance, suggesting that the predominant effect may have been V2 receptor-related. The patients studied had relatively normal AVP levels, however, making it less likely that a major V1a effect would be seen acutely. And it is not clear whether the early fall in filling pressures could be accounted for solely by the diuretic effect. If filling pressures declined before diuresis, a venorelaxant effect could have occurred. A positive effect on cardiac output could also have been masked by a preload-related decline in stroke volume. Interpreting these hemodynamic results is therefore complicated, but it is clear that the acute administration of this compound reduces cardiac filling pressures and causes an aquaresis. Current plans for conivaptan are focused on treatment for ADHF, and hyponatremia, but only for acute use in view of significant cytochrome P450 interactions. A phase II pilot trial in ADHF has been

completed with the results to be available in 2005, while positive results in phase III hyponatremia trials (59) have led to an active new drug application with a response expected in late 2005. Many of the patients in those phase III trials had HF, so more information about the effect of conivaptan in HF should be forthcoming from the detailed analysis of that experience.

PATHOPHYSIOLOGIC AND PRACTICAL CONSIDERATIONS FOR FUTURE STUDIES

Because effective antagonists of both the V1a and V2 receptors are now available, several key issues must be considered in their future development. Clearly, both V1a- and V2-mediated effects are demonstrable in severe and/or decompensated HF; therefore it is reasonable to consider either or both types of antagonists in these settings. A pure V1a antagonist might produce arterial vasodilation, acute hemodynamic improvement, and, chronically, a reduced afterload-related stimulus to ventricular remodeling. It might also diminish venoconstriction and adverse direct myocardial stimulation from AVP. All V1a effects may be more important in the setting of other neurohormonal antagonists. However, if plasma AVP levels rose in the presence of a competitive V1a antagonist, unwanted water retention could occur, with either congestion or hyponatremia or both as a consequence. On the other hand, while a pure V2 antagonist will produce a sustained aquaresis, if AVP levels increased in response to the presence of a competitive antagonist, or due to increased osmolality, unwanted acute vasoconstriction and/or direct myocardial stimulation from V1a activation might occur.

The foregoing considerations may favor the use of combined antagonists, both for acute and chronic HF, although the relative contribution of each type of receptor antagonist might vary depending on the setting in which it is evaluated. When evaluating the long-term effects of selective antagonists, it might be helpful to carefully assess the impact of such agents on plasma AVP levels and AVP-mediated signaling at the unblocked receptor sites. Such studies would enhance understanding of the full physiologic effects of these agents, and address the issues mentioned regarding safety.

The rationale for acute and chronic use of a V1a antagonist is straightforward. The rationale for acute use of V2 antagonists is also obvious: the rationale supporting the chronic use of such agents, unless in the setting of persistent congestion, perhaps less so, but worth considering. First, there may simply be a beneficial effect on preventing congestion, alone or in combination with loop diuretics. Clearly, persistent congestion is a major clinical issue for many patients, and a major indicator of poor outcome (6,55). The clinical trials and registries indicate that prevention and relief of congestion is currently suboptimal. Reducing congestion would obviously be desirable to reduce morbidity and expense, but as well might reduce the

stimulus for maladaptive ventricular remodeling from excessive preload. An effective aquaretic agent might also lead to a more effective overall diuresis by rapidly encouraging the movement of water and then electrolyte out of cells into the vascular space and so ultimately to the kidney where it may be excreted. The net result might be an effect on total body congestion and ventricular preload produced more easily than with the isotonic diuresis produced by loop diuretics alone.

Next, as discussed in the previous text, there are demonstrable adverse effects of high doses of loop diuretics on electrolytes, neurohormonal balance, and renal function (14-16). High-dose diuretic use is also correlated with poor outcome in HF (18). It is therefore possible that a loop-diuretic-sparing effect as a result of V2 antagonism could lead to a safer, as well as a more effective, reduction in ventricular preload. Combining a V2 antagonist with other newer approaches such as natriuretic peptides and/or adenosine antagonists could, in theory, lead to even less reliance on loop diuretics, especially in the setting of renal insufficiency (16).

Lastly, effective V2 antagonists would be of significant potential benefit in patients with HF and hyponatremia. As already discussed, hyponatremia, even mild hyponatremia, confers a significantly worse outcome in HF (5), and it may be that safely and simply correcting this condition could improve outcomes in this group of patients.

CONCLUSIONS

The development of AVP antagonists for acute and chronic HF rests on a strong theoretical basis, but there are important unanswered questions and unresolved issues. Merely demonstrating a desirable pharmacologic effect is not sufficient to warrant adoption of a new class of therapy for either acute or chronic HF. The benchmark for chronic use is either a positive effect on mortality, or at least a strong effect on morbidity with neutral effects on mortality. There is currently no consensus for what constitutes a rationale for adopting a new treatment for ADHF, but it will undoubtedly become necessary to meet some combination of clinical, biological, and economic end points. At a minimum, such treatment should acutely improve the clinical status of patients (i.e., congestion) while not adversely affecting biological variables known to be associated with poor outcome. It is also critical that no delayed adverse effects on mortality or morbidity be seen. For all of the reasons discussed in this review, it should be clear that targeting AVP has the real potential to be a useful additional therapy in both acute and chronic HF.

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