Heart failure (HF) is among the most common causes of hospitalization, and its incidence will likely increase in an aging population of “survivors” (1). Pharmacological treatment targeted at neurohormonal activation has improved survival, but mortality remains substantial in patients with HF, thus warranting the search for novel therapeutic approaches. Novel agents under investigation for the treatment of HF include arginine vasopressin (AVP) receptor antagonists (RA). Udelson et al. (2), in this issue of the Journal, report the effects of an AVPRA, tolvaptan, on left ventricular (LV) remodeling in patients with systolic HF.

**AVP in Heart Failure**

Arginine vasopressin serves primarily to regulate the body’s water content and blood pressure by influencing water excretion by the kidney and controlling vascular tone. Its release is triggered by low effective blood volume and hypernatremia. During arterial underfilling, the carotid artery, aortic arch, and left atrium baroreceptors sense a decrease in pressure and stimulate the release of AVP.

However, because atrial pressures increase in patients with HF, the Henry-Gauer atrial reflex might be expected to suppress AVP; therefore, arterial baroreceptors must override the activation of atrial receptors to maintain the nonosmotic release of AVP. Exquisitely sensitive “high” and “low” threshold hypothalamic osmoreceptors sense small changes in extracellular fluid osmolality and, by releasing AVP, stimulate thirst and water reabsorption at the kidney, respectively.

The AVP acts on specific receptor (R) subtypes termed V_{1A}R, V_{1B}R (also known as V_{3}R) and V_{2}R. The adrenocortical V_{1A}R mediate the aldosterone secretagogue effect of AVP; in vascular smooth muscle cells and cardiomyocytes the V_{1A}R activation triggers vasoconstriction and increased contractility, respectively. In the anterior pituitary, V_{1B}R mediates the release of adrenocorticotropic release (3). The renal collecting ducts V_{2}R respond to AVP by increasing free water re-absorption (3). Essential in this cascade is the aquaporin-2 (AQP-2) water channels, which allow water molecules to traverse the apical membrane of the principal cells in response to the osmotic gradient generated by the countercurrent urinary concentrating mechanism. Plasma AVP levels correlate directly with AQP-2 expression and, in HF with high circulating AVP levels the AQP-2 protein levels increase and become detectable in the urine, suggesting that urinary AQP-2 measurement may be a marker of the AVP activation and thereby of HF status (3).

**Pathophysiological Considerations**

Patients hospitalized for HF are categorized into 2 main groups: the first entails patients who present with systemic congestion, mostly as the result of systolic LV dysfunction (“cardiac” failure); the second comprises patients with pulmonary congestion despite a preserved systolic function, because of volume redistribution from the systemic to the pulmonary circulation (“vascular” failure) (1). In both cases, arterial underfilling triggers baroreceptor-mediated neurohormonal activation of the sympathetic nervous system, the renin-angiotensin-aldosterone system, and the nonosmotic release of AVP.

Because over the long term these neurohumoral reflexes have deleterious consequences, a therapeutic strategy targeted at the neurohumoral activation has been exploited. Hence, a combination of angiotensin-converting enzyme inhibitors or AT_{1}R blockers, aldosterone inhibitors, and beta-blockers, represents the standard approach to treat HF, besides diuretics and digoxin. Unfortunately, such an optimized combination does not generally resolve congestion in patients with HF, which is troublesome because persistent congestion predicts mortality (4). Furthermore, the ability of loop diuretics, the mainstay of current treatment for HF congestion, to correct volume overload and decrease body weight is limited by adverse effects, such as hyponatremia and worsening renal insufficiency.

Circulating AVP levels are elevated early on in patients with congestive HF; they are proportional to the severity of HF and predict cardiovascular mortality. These increased AVP levels are both paradoxical and inappropriate because they induce not only free water reabsorption by the kidney despite an already edematous state, but also aldosterone secretion and increased systemic vascular resistance and pulmonary capillary wedge pressure via V_{1A}R-mediated arterial vasoconstriction. Presumably, these effects are more detrimental in the failing heart, which has an intrinsic inability to tolerate small changes in load. Furthermore, retention of water in excess of sodium may lead to hyponatremia, which is an ominous prognostic indicator and carries...
subtle neurological defects that are reversible with correction of the hyponatremia.

Hence, AVPRA might represent the ideal strategy to treat congestion, as it might be expected to increase water loss and lower filling pressures without negatively affecting blood pressure, heart rate, electrolytes, renal function, neurohormones, or clinical outcomes.

**AVPRAs**

Until recently, the potential benefits of AVPRA in the treatment of HF could not be investigated for the lack of effective and well-tolerated nonpeptide agents. Newly developed compounds (for review, see Verbalis [5]) targeting the V$_{1A}$R/V$_2$R (conivaptan) or the V$_2$R (mozavaptan, lixivaptan, sativaptan, and tolvaptan) are now being tested. They not only decrease congestion and correct hyponatremia but, in contrast with other neurohormonal modulators, also prevent LV remodeling and progression of LV dysfunction.

Tolvaptan, the oral, once-daily, nonpeptide AVPRA used by Udelson et al. (2), binds to the V$_2$R with a 29:1 affinity over the V$_{1A}$R (3). Like lixivaptan (6), tolvaptan, reduces edema, body weight, corrected hyponatremia (7), lowered urinary AQP-2 excretion, and increased solute-free water excretion in patients with HF. Unlike furosemide, tolvaptan increases renal blood flow, decreases renal vascular resistance, improves glomerular filtration rate, and does not affect sodium and potassium excretion (3), thus approaching the features of an ideal drug to correct congestion in patients with HF. Not unexpectedly, these favorable effects were associated with thirst, polyuria, and increased urinary frequency (2).

**Does Tolvaptan Improve LV Remodeling?**

This question received a negative answer by Udelson et al. (2), which does not detract from the importance of the study. The results are sound because of the use of state-of-the-art study design and careful methodology for assessing the LV changes. Moreover, negative studies are important as they can avoid investigators from wasting time, energies, and resources in useless studies. Power calculations, which are very helpful in connection with negative findings, were furnished: the study was designed to have a reassuring (>80%) power to detect a difference of 4.5 ml/m$^2$ in LV end-diastolic volume. Although recruitment of a larger number of patients was planned, a dropout rate greater than expected was recorded. Thus, with the actual sample size (180 patients) and the pooled observed standard deviation, the recorded average difference (1.74 ml/m$^2$) favoring tolvaptan would require more than 1,000 patients to achieve statistical significance. Proof of statistical significance for such small beneficial effect would therefore require a much larger study. The lack of significance likely reflects the ineffectiveness of tolvaptan of improving LV remodeling, but additional factors also could explain the negative findings. The authors chose a dose of tolvaptan at the lowest range of the spectrum therapeutically explored so far in HF studies, albeit equal to that used in the ongoing long-term outcomes trial (8). This dose was selected because of the lack of a dose-dependency for correction of congestion, and of the higher rate of side effects observed at higher doses (4,9). Whether a greater tolvaptan dose might reduce LV end-diastolic volume remains therefore to be ascertained.

An increase of AVP level was observed in the tolvaptan group as compared to placebo patients, which suggests effective AVP displacement from V$_2$R. This result is at variance with a previous report, in which tolvaptan effectively lowered congestion (9), suggesting that the relationship between changes in AVP concentrations, presumed effects at the receptor level, and clinical effects is complex. Information on plasma tolvaptan levels, which would be of interest for a better understanding of the mechanisms underlying effective V$_2$R blockade, was unfortunately not available.

Noteworthy, AVP adversely affects LV remodeling and the progression of HF through at least 5 actions, mostly occurring through V$_{1A}$R, which are not blocked by tolvaptan: (1) V$_{1A}$R signaling can increase vascular resistance and thereby LV afterload LV; (2) V$_{1A}$R signaling can directly cause cardiomyocyte hypertrophy, thereby directly influencing LV remodeling; (3) V$_{1A}$R signaling can cause coronary vasoconstriction, thereby leading to ischemia; (4) V$_2$R signaling can contribute to inappropriate volume expansion, thus increasing ventricular preload; and (5) V$_2$R signaling can contribute to hyponatremia, an independent predictor of adverse outcome in patients with congestive HF (10).

Hence, no beneficial effects of tolvaptan on at least 3 mechanisms, which are relevant for LV remodeling, can be expected. Likely, the small decrease of load-dependent indexes of LV remodeling observed at week 54 could be attributable mainly to the V$_2$R-mediated aquaretic effects of the drug lowering blood volume. This interpretation is supported by the prompt disappearance of the small difference of LV end-diastolic volume between tolvaptan- and placebo-treated patients 1 week after tolvaptan withdrawal, which suggests a functional rather than a structural drug-related effect (2).

Theoretically, there might also be concerns on the long-term effects of V$_2$R specific antagonists: competitive displacement of AVP from V$_2$R could increase AVP plasma levels and, therefore, enhance V$_{1A}$R activation. By increasing osmolality, a potent V$_2$R antagonist also could induce AVP secretion. Indeed, most studies have reported an increase in plasma AVP after administration of receptor antagonists. Whether this increase exerts detrimental effects via unblocked receptor sites remains to be demonstrated. Nonetheless, data in experimental HF, and in class III and IV HF patients documented the benefit of combined if V$_{1A}$R and V$_2$R, at least acutely and short term. If V$_{1A}$R signaling contributes to the pathophysiology of congestive
HF, then an increase in $V_{1a}R$-mediated effects during $V_2R$ blockade might be harmful. Furthermore, $V_{1a}R$ signaling can be amplified in the presence of diminished activity of the renin-angiotensin-aldosterone system and the sympathetic nervous system (10). Because patients with HF usually are treated with agents inhibiting these systems, even more concern about these potential effects exists. Thus, even if the net effect of using $V_2R$ antagonists is positive, ongoing stimulation of $V_{1a}R$ may work against an even greater potential beneficial effect, which might be seen if both receptor sites were blocked. Further research aimed at comparing the effects of combined $V_2R$ plus $V_{1a}R$ with $V_2R$ blockade not only on LV volumes, but also on LV hypertrophy and fibrosis, is therefore necessary.

In a post-hoc analysis tolvaptan reduced the composite end point of death or hospitalization, after adjustment for confounders (2), which accords with results in renal dysfunction or severe congestion patients in the ACTIV in CHF (Acute and Chronic Therapeutic Impact of a Vasopressin 2 Antagonist [Tolvaptan] in Congestive Heart Failure) trial (4). Although useful for generating hypothesis, these findings should be taken cautiously, because both studies were underpowered to investigate this question. In summary, the success of treatment of HF targeted at neurohormonal activation has narrowed the space for showing further therapeutic improvement. Hence, only very large well-designed studies might demonstrate significant benefits on survival and surrogate end points. Available data indicate that tolvaptan is safe and effective in correcting congestion without adversely affecting electrolyte status, hemodynamics, and renal function.

A large trial ongoing named EVEREST (Efficacy of Vasopressin Antagonism in Heart Failure Outcome Study with Tolvaptan) investigates whether tolvaptan improves survival in patients with chronic HF. Mount Everest (8,848 m), the highest mountain in the Himalayas named for the British Surveyor General of India Sir George Everest, was successfully climbed, for the first time, by Hillary and Norgay in 1953. More than 4,000 people had attempted to climb Everest thereafter; ~20% of them were successful, and more than 140 died trying, thus making the difficulties of climbing Mount Everest legendary. Hopefully, the EVEREST study will not prove a winter attempt to climb the Everest’s tip but rather as successful as Hillary’s and Norgay’s attempt.

Acknowledgments
The secretarial assistance of Mrs. Carla Franceschin and the support of FORICA (The FOundation for advanced Research In Hypertension and CArdiovascular diseases) are gratefully acknowledged.

Reprint requests and correspondence: Dr. Prof. Gian Paolo Rossi, Internal Medicine 4, University Hospital, 35126 Padova, Italy. E-mail: gianpaolo.rossi@unipd.it.

REFERENCES