

# Neurohormonal modulation in chronic heart failure

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*A number of neurohormones are activated in chronic heart failure (CHF), which have either vasoconstrictor or vasodilator effects. Excessive neurohormonal production has deleterious effects in the long term, leading to progression of CHF through a variety of mechanisms including necrotic and apoptotic myocyte death, myocardial fibrosis, and continuous left ventricular remodeling. Neurohormonal activation begins early on in the natural history of CHF and soon after myocardial infarction, and is proportional to the severity of heart failure. Whereas findings from animal experiments suggest that the progression of CHF is associated with a worsening neurohormonal profile, there are insufficient human data to draw similar conclusions. Nevertheless, most studies indicate that high levels of neurohormones are predictive of a poor prognosis. ACE inhibitors reduce mortality in all stages of CHF, and the greatest benefit is seen in patients with the highest baseline level of neurohormones. Although data from the major randomized trials do not, as yet, support the hypothesis that ACE inhibitors act primarily through reduction of the levels of circulating neurohormones, other, indirect, data suggest that the progression of heart failure is related to excessive neurohormonal activation.*

**Keywords:** chronic heart failure; neurohormone; norepinephrine; epinephrine; plasma renin activity; angiotensin II; aldosterone; renin-angiotensin-aldosterone; arginine vasopressin; atrial natriuretic peptide; growth hormone; cortisol; ventricular remodeling; LV dysfunction

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Whenever the heart is damaged and cardiac output begins to fall, a number of neurohormones are activated to restore circulatory homeostasis.

However, once established, left ventricular (LV) dysfunction progresses relentlessly to symptomatic heart failure with high mortality.<sup>1</sup> Progression of heart failure is related to ventricular remodeling, a self-perpetuating process that remains poorly understood. The only agents that slow the development of heart failure and reduce cardiovascular mortality are angiotensin-converting enzyme (ACE) inhibitors, and possibly  $\beta$ -blockers, which may also act as neurohormonal modulators.<sup>1</sup> These findings have led to the neurohormonal hypothesis of the progression of heart failure.<sup>2</sup> According to this hypothesis, neurohormonal activation in chronic heart failure (CHF) is initially a beneficial and an adaptive response. Eventually, however, excessive production of neurohormones becomes maladaptive, leading to progression of heart failure through a variety of mechanisms including necrotic and apoptotic myocyte death and myocardial fibrosis with continuous LV remodeling.

In order to prove the neurohormonal hypothesis, Koch's postulates need to be fulfilled. It has to be demonstrated that: (i) neurohormones are activated in CHF; (ii) the degree of activation is proportional to the severity of heart failure; (iii) continuing neurohormonal activation is associated with progression of heart failure; (iv) the degree of neurohormonal activation is related to prognosis; (v) treatment decreases neurohormones; and, finally, (vi) that the decrease in neurohormones with treatment is proportional to the decrease in mortality. Are all these criteria met in heart failure? In this review, the neurohormones that are increased in heart failure will be briefly discussed and their beneficial and deleterious effects described. The neurohormonal hypothesis will then be addressed in light of the results of the major randomized trials.

## NEUROHORMONAL SYSTEMS ACTIVATED IN CHRONIC HEART FAILURE

Vasoconstrictor hormones	Vasodilator hormones
Sympathetic nervous system	Atrial and brain natriuretic peptides
Norepinephrine	Prostaglandins
Epinephrine	Kallikrein-kinin system
Renin-angiotensin-aldosterone system	Calcitonin gene-related peptide
Arginine vasopressin	

Table 1.

NEUROHORMONES  
IN CHRONIC HEART FAILURE

Two sets of neurohormones, with opposing effects, are activated in heart failure. The vasoconstrictor hormones are antinatriuretic and antidiuretic, and generally have growth-promoting properties. The vasodilator hormones, on the other hand, are natriuretic and diuretic and have antimitogenic effects. In CHF, the natriuretic and vasodilator effects are clearly overwhelmed by influences that lead to vasoconstriction and salt and water retention. We are now beginning to understand some of the other effects of these hormones, especially on cell growth and ventricular remodeling. A better understanding of these actions will help us design novel approaches to the management of heart failure. *Table 1* lists the neurohormones that have been well studied in heart failure.

## Vasoconstrictor hormones

*Sympathetic nervous system*

It has been known for many years that there is increased activity of the sympathetic nervous system (SNS) in heart failure.<sup>3</sup> Because direct measurement of cardiac SNS activity is difficult in man, plasma norepinephrine (NE), the main sympathetic neurotransmitter, has been used as an indirect estimate. Levels of the other catecholamines, like epinephrine, are not usually elevated in heart failure. Microneurographic recording of efferent postganglionic sympathetic nerve activity to skeletal muscle has confirmed a significant correlation between muscle sympathetic activity and NE spillover in the heart and kidney, in both normal subjects and patients with heart failure.<sup>4</sup> Sympathetic activity does not increase simultaneously in all organs. The earliest increase in sympathetic activity is detected in the heart, before an increase in renal and muscle sympathetic activity, and precedes the rise in plasma NE.<sup>5</sup>

Moreover, increased myocardial sympathetic activity occurs early in the natural history of left ventricular dysfunction, even before an increase in ventricular volume or end-diastolic pressure<sup>6</sup> and the onset of symptoms. Levels of NE are higher in patients with symptomatic heart failure and increase in proportion to the severity of the disease.<sup>7</sup>

Augmented sympathetic activity in heart failure is initially beneficial. It increases cardiac output and redistributes blood flow from the splanchnic area to the heart and skeletal muscles. Renal vasoconstriction leads to salt and water retention, which may help improve perfusion of vital organs. However, *sustained* sympathetic stimulation, as seen in heart failure, activates the renin-angiotensin-aldosterone system (RAAS) and other neurohormones, leading to progressive salt and water retention, vasoconstriction, edema, and increased preload and afterload. These developments, in turn, increase ventricular wall stress, resulting in higher myocardial oxygen demand and myocardial ischemia. Excessive sympathetic activity may also predispose to ventricular arrhythmias. Finally, NE has many direct effects on the cardiac myocytes, including induction of fetal gene programs, downregulation of calcium-regulating genes, myocyte hypertrophy, apoptosis, and necrosis. Therefore, although the initial sympathetic nervous system response appears to be adaptive and helps support blood pressure and cardiac output, prolonged and excessive sympathetic activation may have deleterious effects. Indeed, patients with heart failure and high plasma NE have been shown to have a worse prognosis,<sup>8</sup> and inhibiting the sympathetic activity is therapeutically beneficial.<sup>9</sup>

The mechanisms responsible for the excessive sympathetic activation in heart failure are not entirely clear.



Reduced clearance of NE due to low cardiac output probably contributes to the high circulating levels of plasma NE, but most of the increase is due to excessive NE secretion. The stimulus for this appears to be an early and sustained attenuation of cardiac and arterial baroreceptor control of sympathetic nerve activity due to a decrease in baroreceptor afferent discharge.<sup>10</sup> When heart failure is established, increased peripheral chemoreceptor sensitivity and augmented muscle mechanoreceptor discharge may further modulate sympathetic activity.<sup>10</sup>

### ***Renin-angiotensin-aldosterone system***

The importance of the RAAS in heart failure has been known for nearly 50 years. Renin, an enzyme released from juxtaglomerular cells of the kidney, cleaves the  $\alpha_2$ -globulin angiotensinogen produced in the liver to form the inactive peptide angiotensin I. ACE, which is widely expressed, converts angiotensin I to angiotensin II. Renin is released in response to a number of stimuli commonly observed in heart failure, eg, reduced renal perfusion pressure, increased renal sympathetic activity, decreased delivery of sodium to the macula densa, and diuretic use. Angiotensin II, the active product of renin activity, is a potent vasoconstrictor. In addition, it augments the presynaptic release of NE and stimulates the release of aldosterone, which promotes salt and water retention by the kidney. Angiotensin II also has direct effects on the kidney. It constricts the efferent arterioles and helps maintain the glomerular filtration rate (GFR); it also causes sodium reabsorption by direct action on the renal tubules. Indirectly,

through stimulation of thirst and vasopressin release, angiotensin II enhances water retention. In normal individuals, the RAAS is not activated and does not play a significant physiological role. However, in states of volume and salt depletion, during hypotension, and in heart failure, the RAAS is activated and exerts its vasoconstrictor and salt- and water-retaining effects.

Plasma renin activity (PRA) has generally been used as a measure of RAAS activity, because angiotensin II is relatively difficult to measure. PRA varies considerably in heart failure. In patients with asymptomatic LV dysfunction<sup>7</sup> or untreated mild heart failure,<sup>11</sup> PRA is normal, and is probably suppressed by atrial natriuretic peptide (see below). However, PRA is usually elevated in patients with untreated severe heart failure<sup>12</sup> and in patients on diuretics.<sup>11</sup> The elegant studies of Watkins et al<sup>13</sup> in dogs with inferior vena caval and pulmonary arterial constriction provide an explanation for the variability and lack of consistency of the RAAS in CHF. They showed that PRA increased immediately after constriction, but returned to normal as plasma volume and arterial blood pressure were restored to normal. The negative feedback control of the RAAS through blood volume and arterial blood pressure may explain the great variability in the activation of the RAAS in CHF. Therefore, RAAS activity in a subject would depend on the phase of fluid retention. Those who avidly retain salt and water would be expected to have higher RAAS activity than those who have reached a new steady state.

The initial beneficial effects of RAAS activation in heart failure—preservation of the GFR and blood pressure support—may become deleterious if excessive and prolonged, because it may worsen the loading conditions of the heart. In addition, instead of preserving GFR, RAAS activation reduces it by causing vasoconstriction in the afferent as well as the efferent arterioles. In the myocardium, RAAS activity and locally produced angiotensin II influence the behavior of the myocytes and fibroblasts, leading to myocyte hypertrophy, necrosis and apoptosis, and increased collagen turnover. Collectively, these adverse effects of RAAS activation may contribute to progressive ventricular remodeling and worsening heart failure.<sup>14</sup> The effectiveness of ACE inhibitors in reducing morbidity and mortality in heart failure may be related to their ability to block the deleterious effects of RAAS activity.

### ***Arginine vasopressin***

Arginine vasopressin (AVP) is another vasoconstrictor and water-retaining hormone with mitogenic properties

#### **SELECTED ABBREVIATIONS AND ACRONYMS**

<b>ANP</b>	atrial natriuretic peptide
<b>AVP</b>	arginine vasopressin
<b>BNP</b>	brain natriuretic peptide
<b>CGRP</b>	calcitonin gene-related peptide
<b>CHF</b>	chronic heart failure
<b>GFR</b>	glomerular filtration rate
<b>IGF-I</b>	insulin-like growth factor I
<b>NE</b>	norepinephrine
<b>NEP</b>	neutral endopeptidase
<b>NPR<sub>A</sub></b>	natriuretic peptide receptor A
<b>PRA</b>	plasma renin activity
<b>RAAS</b>	renin-angiotensin-aldosterone system
<b>SNS</b>	sympathetic nervous system

that may be potentially harmful in heart failure. However, relatively little is known about this hormone in heart failure. AVP is increased in some, but not all, patients with heart failure.<sup>7,12,15</sup> Under normal conditions, osmoreceptors are the primary determinant of AVP release. In heart failure, however, nonosmotic control of AVP release becomes more important. The important nonosmotic stimuli emanate from low- and high-pressure baroreceptors, angiotensin II, ANP, sympathetic activation, and central dopaminergic and prostaglandin-related stimuli. Some of these stimuli are abnormal in heart failure. Therefore, despite hyposmolar hyponatremia, which often occurs in severe CHF, and which should suppress AVP, levels remain inappropriately elevated. AVP acts on the vascular smooth muscle  $V_1$  receptors to cause vasoconstriction, and on  $V_2$  receptors in distal tubules and collecting ducts to enhance reabsorption of water. AVP probably contributes to vasoconstriction and fluid retention in heart failure, since infusion of a specific  $V_1$  receptor antagonist improves hemodynamics. High levels of AVP may also contribute to dilutional hyponatremia in severe heart failure, a feature indicating a poor prognosis. Additional studies with specific AVP antagonists are therefore required to establish whether inhibiting this vasoconstrictive system will also be beneficial.

### Vasodilator hormones

A number of endogenous vasodilators are involved in cardiovascular and renal homeostasis in heart failure. These important hormones are released from the heart (natriuretic peptides) and the kidney (prostaglandins and bradykinin). In addition, the vascular endothelium produces a potent vasodilator, endothelium-derived nitric oxide. However, the effects of all these endogenous vasodilators are significantly attenuated in heart failure.

#### *Atrial and brain natriuretic peptides*

Atrial natriuretic peptide (ANP) and brain natriuretic peptide (BNP) are a family of peptides that are synthesized primarily in atrial myocytes and released in response to atrial stretch. These peptides have natriuretic, vasodilator, and antimitogenic properties. They also antagonize most endogenous vasoconstrictors by reducing sympathetic activity and inhibiting renin and aldosterone release. The biological actions of these peptides are achieved by activating a common receptor termed natriuretic peptide receptor A ( $NPR_A$ ), coupled to cyclic guanosine monophosphate (cGMP). Levels of ANP and BNP are elevated early on in heart failure, along with SNS activity, preceding activation

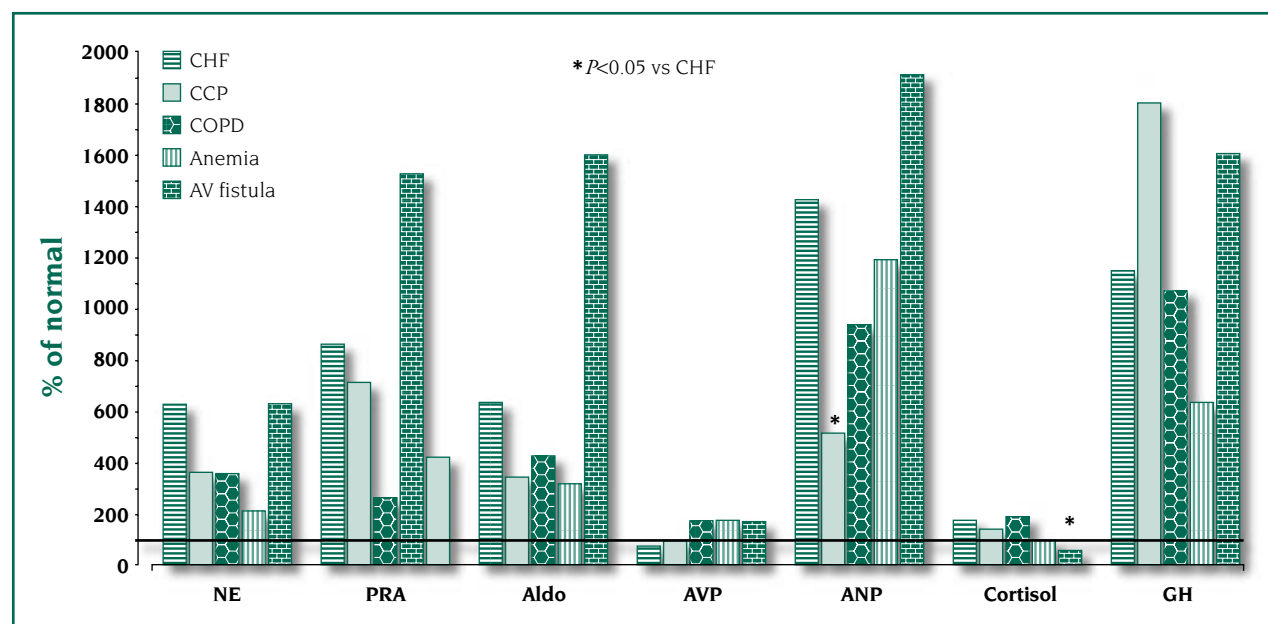
of the RAAS and before symptoms of LV dysfunction appear. Because of these findings, measurement of ANP/BNP is emerging as an important noninvasive marker of LV dysfunction and a screening tool in the population.<sup>16</sup> Animal studies suggest that the early increase in ANP is responsible for the maintenance of sodium balance and inhibition of the RAAS in asymptomatic LV dysfunction. As heart failure progresses, ANP and BNP levels increase, in proportion to the rise in atrial pressure and severity of LV dysfunction.<sup>17</sup> However, in severe heart failure, despite greatly increased levels of ANP and BNP, the natriuretic and vasodilator responses to them are attenuated. This may contribute to salt and water retention and systemic and renal vasoconstriction manifest in severe heart failure. The mechanisms responsible for the attenuated response are unclear and may be related to a number of factors, including a decrease in renal blood flow, increased renal sympathetic activity,  $NPR_A$  receptor downregulation, and enhanced enzymatic degradation of the peptides. Efforts to use these peptides as a therapeutic agent in CHF have, therefore, been disappointing.<sup>18,19</sup> Inhibition of neutral endopeptidase (NEP)<sup>24,11</sup>, the enzyme that degrades endogenous natriuretic peptides, potentiates the effects of endogenous peptides and has met with some success in CHF.<sup>20</sup> Because angiotensin II attenuates the effects of ANP, co-inhibiting NEP and ACE in heart failure may be an exciting therapeutic possibility.

### Intrarenal hormones

A number of intrarenal hormonal systems may be activated in CHF. The important ones are the arachidonic acid cascade and the kallikrein-kinin system.

#### *Prostaglandins*

The renal arterioles, glomeruli, and some parts of the renal tubules and collecting ducts synthesize the vasodilator prostaglandins  $PGI_2$ ,  $PGE_2$ , and  $PGF_{2\alpha}$ .<sup>21</sup> Renal glomeruli also synthesize thromboxane  $A_2$ , which causes platelet aggregation and vasoconstriction.<sup>21</sup> The prominent effect of prostaglandins is to protect the glomerular microcirculation during states of renal vasoconstriction by causing vasodilation, predominantly in the afferent arterioles, and also through promoting sodium excretion by directly inhibiting sodium transport in the distal tubules. Prostaglandin synthesis is increased during activation of the renin-angiotensin system and renal sympathetic systems, and in clinical and experimental heart failure.<sup>22</sup> Prostaglandins probably do not modulate renal hemodynamics or sodium excretion in normal



**Figure 1.** Changes in a variety of neurohormones in untreated patients with a low- and high-output state and edema.<sup>29</sup> The neurohormonal response is very similar. Aldo, aldosterone; Anemia, chronic severe anemia; ANP, atrial natriuretic peptide; AV fistula, arteriovenous fistula; AVP, arginine vasopressin; CCP, chronic constrictive pericarditis; CHF, congestive heart failure—dilated cardiomyopathy; COPD, chronic obstructive pulmonary disease; GH, growth hormone; PRA, plasma renin activity.

subjects, but may play a major role in situations with elevated RAAS and sympathetic activity, as in CHF. Consequently, inhibition of prostaglandins with cyclooxygenase inhibitors may induce a marked reduction in cardiac output and renal blood flow, an increase in peripheral vascular resistance, and sodium retention.<sup>22</sup>

### Kallikrein-kinin system

The distal tubules of the kidney synthesize kallikrein, a protease that cleaves kininogen to form bradykinin and kallidin. These peptides are degraded by the enzyme kininase II, which is the same as angiotensin-converting enzyme. Both bradykinin and kallidin produce vasodilation and natriuresis, and the former also stimulates the production of prostaglandins.<sup>23</sup> Although the exact role of this system in CHF is unknown, there is evidence that at least some of the beneficial effects of ACE inhibitors on hemodynamics and ventricular remodeling may be derived from an increase in bradykinin.<sup>24</sup>

### Other hormones

There has been recent interest in the role of growth hormone in heart failure. Growth hormone is secreted by the anterior pituitary and mediates its effects via insulin-like growth factor 1 (IGF-1). Levels of growth hormone are elevated in the syndrome of severe untreated low- and high-output heart failure as well as

in patients with cardiac cachexia.<sup>12,25</sup> The exact role of growth hormone in heart failure is not known. Treating heart failure with human growth hormone has been shown to be beneficial in some, but not all, studies.<sup>26</sup> Further research in this area is necessary before the exact role of growth hormone in CHF is established. Cortisol is another anterior pituitary hormone that is also elevated in various syndromes of CHF, possibly as part of a general stress response.<sup>12</sup>

Calcitonin gene-related peptide (CGRP), a potent vasodilator, is also released during heart failure.<sup>27</sup> CGRP is colocalized with substance P and vasoactive intestinal polypeptide (VIP) in parasympathetic nerve endings in the heart, blood vessels, and the nervous system. Short-term infusion of CGRP in patients with CHF is associated with beneficial effects.<sup>28</sup>

In addition to the neurohormonal activation described above, it has become evident during the last few years that other biologically active molecules, termed cytokines, are also oversecreted by cells in heart failure. Important among these are endothelins, tumor necrosis factor- $\alpha$ , and interleukin-6. These cytokines appear to exert deleterious effects on the heart and circulation, and may be involved in the progression of heart failure. The role of cytokines will not be described any further here, and will be discussed in this issue's Expert Answers section.

### Comment

The neurohormonal responses described above are seen in patients with heart disease and low-output CHF. However, an identical neurohormonal response and retention of salt and water also occurs in a number of conditions where the heart is entirely normal and the cardiac output may be even higher than normal. So-called "high-output" congestive heart failure is seen in diverse conditions with divergent hemodynamics, including chronic severe anemia, chronic arteriovenous fistula, beriberi, Paget's disease, and chronic obstructive pulmonary disease.<sup>29</sup> The common factor, in all forms of CHF, appears to be a tendency towards low arterial blood pressure. Blood pressure is "threatened" in low-output states because of low cardiac output and in high-output states because of a decrease in systemic vascular resistance. The neurohormonal response of the body is, however, similar (*Figure 1*). This response is not unique to low- or high-output syndromes of CHF. The same neurohormonal response is also seen when blood pressure is reduced for whatever reason, for example, during acute reduction of arterial pressure with nitroprusside,<sup>30</sup> and during physical exercise,<sup>31</sup> where blood pressure is threatened by marked vasodilation in exercising muscles.

These findings, therefore, support the theory<sup>32</sup> that the neurohormonal response evoked during CHF is the same as that evolved to support survival of the species under two main circumstances that threaten life, ie, hemorrhage and physical exercise. In these conditions, a short-term threat to blood pressure evokes a baroreceptor-mediated increase in sympathetic activity, which causes venoconstriction, tachycardia, stimulation of the myocardium, and regional vasoconstriction. When blood pressure is threatened by reduced cardiac output due to LV dysfunction, the body cannot distinguish whether the threat is from hemorrhage, exercise, or heart disease, and therefore uses the same stereotyped response for which it is programmed. In heart disease (and other sustained vasodilated high-output states), however, blood pressure is threatened over a prolonged period. Thus, the effector mechanisms continue to operate as long as the threat persists.

### THE NEUROHORMONAL HYPOTHESIS IN HEART FAILURE TRIALS

A number of the randomized controlled trials in heart failure have studied patients during different stages of

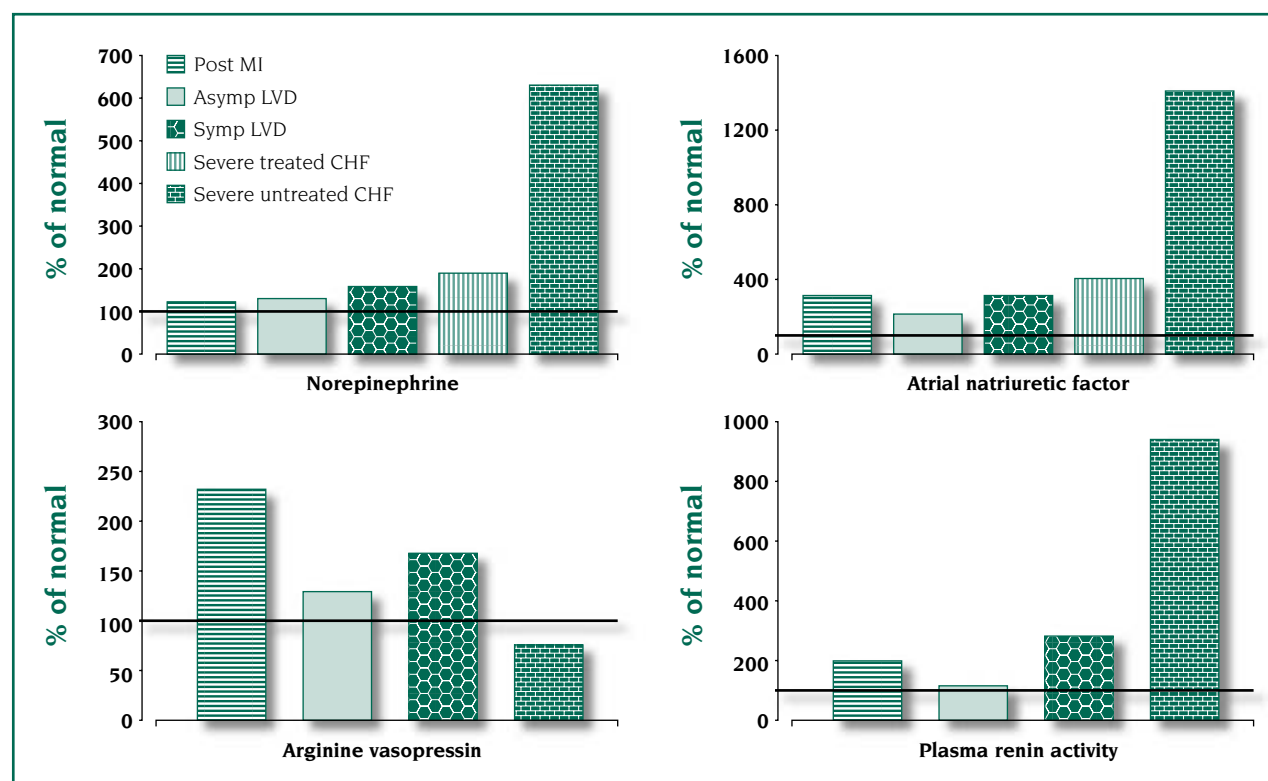
LV dysfunction. In some of these trials neurohormones were measured sequentially. These data have made a valuable contribution to our understanding of neurohormonal activation during the progression of heart failure. The following discussion attempts to analyze these trials from the neurohormonal standpoint.

### Neurohormonal activation is proportional to severity of LV dysfunction

Within hours of an acute myocardial infarction, plasma NE, angiotensin II, and ANP increased significantly and in proportion to the size of the myocardial infarct among the patients studied in CONSENSUS II (COoperative New Scandinavian ENalapril SURvival Study II).<sup>33</sup> Neurohormonal activation subsided within a week unless the patients developed LV dysfunction. In such patients, hormones remained elevated, in proportion to the severity of LV dysfunction.<sup>33</sup>

In the SAVE (Survival And Ventricular Enlargement) trial too, plasma NE, ANP, AVP, and PRA measured, on average, 12 days after myocardial infarction (519 patients, ejection fraction [EF] 31%±7%) were increased.<sup>34</sup> The Killip class recorded 72 hours after myocardial infarction was the most consistent predictor of increased neurohormone activity, independent of EF.<sup>35</sup> PRA was increased even in patients not taking diuretics. The SOLVD (Studies Of Left Ventricular Dysfunction) neurohormonal substudy compared the neurohormonal data in patients with asymptomatic LV dysfunction (EF <35%), symptomatic patients (New York Heart Association [NYHA] class II and III, EF <35%) and control subjects.<sup>7</sup>

This was the first study to clarify that plasma NE, ANP, and AVP are increased even in the asymptomatic patients with LV dysfunction. In symptomatic patients hormone levels were higher.<sup>7</sup> A similar increase in plasma NE and PRA was also seen in patients with mild-to-moderate heart failure in V-HeFT II (Vasodilator Heart Failure Trial II).<sup>36</sup> The patients in CONSENSUS I were the most severely affected (NYHA class IV) and had the greatest increase in neurohormones.<sup>37</sup> Only one small study<sup>12</sup> has reported neurohormone measurements in untreated patients with NYHA class IV CHF and evidence of severe salt and water retention and reduced renal blood flow. In these patients, plasma NE, PRA, aldosterone, and ANP were increased even more than that seen in the CONSENSUS patients.<sup>12</sup> *Figure 2* shows a progressive increase in a number of neurohormones with severity of heart failure.



**Figure 2.** Plasma hormones in different stages of left ventricular dysfunction. Data obtained from different studies and expressed as a percentage of normal. Post MI, post myocardial infarction patients studied in SAVE (Survival And Ventricular Enlargement) trial.<sup>34</sup> Asymp LVD and Symp LVD, asymptomatic and symptomatic left ventricular dysfunction patients studied in the prevention and treatment arm of Studies of Left Ventricular Dysfunction (SOLVD).<sup>7</sup> Severe treated CHF, NYHA class IV patients studied in CONSENSUS (COoperative North Scandinavian ENalapril SURvival Study).<sup>44</sup> Severe untreated CHF, untreated patients with end-stage cardiomyopathy.<sup>12</sup> A progressive increase in most neurohormones is seen in relation to the severity of the heart failure. Note that despite hyponatremia in the severe untreated CHF group, the arginine vasopressin levels were in the normal range. (Normal range = ———.)

The findings from large clinical trials, therefore, confirm that neurohormonal activation begins early on in the natural history of CHF and soon after myocardial infarction. Levels of the circulating neurohormones remain high in asymptomatic patients with LV dysfunction, and the degree of neurohormonal activation is proportional to the severity of heart failure.

### Progression of heart failure and increase in neurohormonal activation

Although the degree of neurohormonal activation appears to be related to the severity of heart failure, there are limited data demonstrating an increase in neurohormones with progression of heart failure. In the canine model of pacing-induced heart failure, plasma NE, aldosterone, ANP, and PRA increased progressively as LV dysfunction worsened and cardiac output fell.<sup>38</sup> The increase in ANP and NE in this model occurred much before the activation of the RAAS, at a stage comparable to asymptomatic left ventricular dysfunction in humans.<sup>39</sup>

There are very few studies that have reported sequential measurements of neurohormones in patients with heart failure. In one uncontrolled study of 22 patients receiving digoxin, diuretics, and vasodilators, a progressive increase in plasma NE was reported over a 2-year follow-up period.<sup>40</sup> In the SOLVD substudy, no significant change was seen in plasma NE, PRA, AVP, or ANP during a 1-year follow-up in patients with asymptomatic LV dysfunction or symptomatic heart failure.<sup>7</sup> It is important to point out that only patients who completed the 1-year follow-up were included in the study. Patients who died and who might have had more significant changes in neurohormones were excluded from the analysis.

In CONSENSUS I, too, no significant change was seen in the plasma NE, angiotensin II, PRA, and ANP in 126 patients on placebo followed for 6 weeks.<sup>37</sup> In V-HeFT II, despite an increase in EF in both the enalapril and hydralazine–isosorbide dinitrate groups, the corresponding levels of NE increased in both groups.<sup>41</sup> Thus, despite an apparent hemodynamic

improvement, NE levels increased. Moreover, the increase in NE did not seem to correlate with the change in EF, suggesting that there was no relationship between progression or regression of LV dysfunction and changes in hormones in V-HeFT II.

Thus, whereas animal experiments suggest that progression of heart failure is associated with a worsening neurohormonal profile, there are insufficient human data to draw similar conclusions.

### Neurohormones and prognosis of chronic heart failure

All the major heart failure trials except SAVE have shown a strong correlation between baseline plasma NE and total mortality. A significant but weaker correlation has also been shown for angiotensin II,<sup>33,42</sup> PRA,<sup>7,41</sup> and ANP.<sup>35,43,44</sup> Neurohormonal activation is also of prognostic value in patients early after myocardial infarction. In CONSENSUS II, plasma NE and angiotensin II levels measured 5 to 7 days after a myocardial infarction predicted the subsequent increase in ventricular volumes.<sup>42</sup> Similarly, in the SAVE trial, levels of PRA, aldosterone, NE, AVP, and ANP measured, on average, 12 days after myocardial infarction predicted adverse cardiovascular events at 1 year in a univariate analysis.<sup>35</sup> When considered as continuous variables, however, none of the hormones were predictors of cardiovascular mortality, development of CHF, or recurrent myocardial infarction.

The cutoff level beyond which NE is predictive of a poor prognosis has varied in different studies.

Rector et al<sup>8</sup> showed that patients with NE greater than 600 pg/mL fared worse than patients with NE values below that level. In the V-HeFT II study,<sup>41</sup> the cutoff point for poor prognosis was shown to be greater than 900 pg/mL. It is interesting that only 13% of the V-HeFT II cohort had NE levels greater than 900 pg/mL. Thus, the prognostic value of NE appears to be limited to a small number of subjects in any population with CHF.

Most data suggest, therefore, that high levels of NE, PRA, ANP, and angiotensin II predict a poor prognosis for patients with CHF. However, no linear correlation exists between neurohormone levels and cardiovascular mortality. These data do not support the idea that neurohormonal activation is responsible for the progression of CHF. In order to prove such a cause and effect relationship, it is essential to demonstrate that agents such as ACE inhibitors, which prevent or delay

the progression of heart failure and improve survival, act by attenuating neurohormonal activation.

The following section will discuss whether ACE inhibitors work by modulating neurohormones.

### ACE INHIBITORS AND NEUROHORMONAL ACTIVATION IN HEART FAILURE

#### *Do ACE inhibitors attenuate neurohormonal activation?*

ACE activity is increased in patients with CHF.<sup>33,42,44</sup> ACE inhibitor therapy decreases plasma angiotensin II,<sup>44</sup> but complete chronic suppression of angiotensin II is more difficult to achieve.<sup>42</sup> In CONSENSUS II, although enalapril caused sustained suppression of plasma ACE activity over the entire 6-month period of the trial, circulating angiotensin II was only partially blocked.<sup>42</sup> A number of factors, such as an increase in ACE binding sites and conversion of angiotensin I to angiotensin II through alternate non-ACE pathways, may account for this finding.<sup>45</sup> Because angiotensin II augments release of NE from sympathetic nerve endings, ACE inhibitors may be expected to reduce circulating NE. Uncontrolled studies in CHF show that ACE inhibitors either reduce<sup>38</sup> or have no effect<sup>42</sup> on circulating NE. In dogs with pacing-induced heart failure, ACE-inhibitor therapy attenuated the progressive increase in NE as compared to placebo.<sup>38</sup> In CONSENSUS, the mortality benefit with enalapril was accompanied by significantly decreased levels of NE, ANP, aldosterone, and angiotensin II in the ACE-inhibitor group, compared to the placebo group, even after only 6 weeks of treatment.<sup>37</sup> In V-HeFT II, the survival benefit with enalapril was accompanied by an attenuation in the rise in circulating NE.<sup>36,41</sup> In SOLVD, however, enalapril did not significantly influence neurohormone levels in patients with asymptomatic left ventricular dysfunction or symptomatic mild-to-moderate heart failure despite an improvement in prognosis.<sup>7</sup> Therefore, a consistent and long-term decrease in neurohormones has not been demonstrated in those randomized trials where a major mortality benefit of ACE inhibitor therapy was reported.

#### *Baseline neurohormonal activation determines the benefit of ACE inhibitors on mortality and progression of heart failure.*

Most data from randomized trials suggest that the greatest mortality benefit from ACE inhibitors is manifest in those patients who have the highest baseline levels of neurohormones. In CONSENSUS, enalapril reduced mortality only in those patients with NE, angiotensin II, aldosterone,



and AVP levels above the median, but had no effect on survival in those with neurohormone levels below the median.<sup>44</sup> Similarly, in V-HeFT II, the benefit of enalapril over hydralazine-isosorbide dinitrate was only seen in the patients with baseline NE levels greater than 900 pg/mL (13% of the total population) and PRA greater than 16 ng·mL<sup>-1</sup>·h<sup>-1</sup>. These findings could not be confirmed in SAVE.<sup>35</sup>

*Does the decrease in mortality with ACE inhibitors correlate with a corresponding change in neurohormonal activation?* There is only one study that has analyzed whether a change in neurohormones with ACE-inhibitor therapy causes a proportional decrease in mortality from CHF. Swedberg et al<sup>44</sup> did not find any correlation between the decrease in neurohormonal levels with enalapril at 6 weeks and the reduction in mortality at 6 months in CONSENSUS. However, the relationship between the change in the angiotensin II level and mortality was very impressive. Only 3 out of 44 patients with a decrease in angiotensin II greater than 16 pg/mL died as compared to 7 out of 37 in the group where angiotensin II fell by less than 16 pg/mL.

## CONCLUSIONS

A review of recent randomized clinical trials has shown that neurohormonal activation starts early on in the natural history of LV dysfunction and that levels of the circulating hormones increase in proportion to the severity of heart failure. In animals, progression of heart failure is associated with higher levels of neurohormones. Although similar data are not available in humans, most studies suggest that high levels of neurohormones predict a poor prognosis. ACE inhibitors reduce mortality in all stages of heart failure, and the greatest mortality benefit from ACE inhibitors is seen in those patients who have the highest baseline levels of neurohormones. However, a consistent and long-term decrease in neurohormones has not been demonstrated with ACE-inhibitor therapy. Finally, although data from the major randomized trials do not, as yet, support the thesis that ACE inhibitors mediate their effects primarily through reduction in circulating neurohormones, other, indirect, data do support the view that the progression of heart failure is related to the deleterious effects of excessive neurohormonal activation.

In the next section of this issue, we will turn our attention to the clinical applications of neurohormonal modulation in chronic heart failure. Claudio Ceconi poses a question with portentous implications: “**Is there a reliable marker of neuroendocrine response?**” while Henry Dargie defines priorities by asking: “**Is routine assessment of the neuroendocrine response clinically justified?**” and Gary Francis highlights the practical aspects by asking: “**What can and has been achieved by the pharmacological manipulation of neuroendocrine response?**”

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