Neuroendocrine Response in Heart Failure

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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. 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 β-blockers, which may also act as neurohormonal modulators. These findings have led to the neurohormonal hypothesis of the progression of heart failure. According to this hypothesis, neurohormonal activation in chronic heart failure (CHF) is initially a beneficial and 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, myocardial fibrosis, and continuous left ventricular 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.
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 I lists the neurohormones that have been well studied in heart failure.

**NEUROHORMONAL SYSTEMS ACTIVATED IN CHRONIC HEART FAILURE**

<table>
<thead>
<tr>
<th>Vasoconstrictor hormones</th>
<th>Vasodilator hormones</th>
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</thead>
<tbody>
<tr>
<td>Sympathetic nervous system</td>
<td>Atrial and brain natriuretic peptides</td>
</tr>
<tr>
<td>Norepinephrine</td>
<td>Prostaglandins</td>
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<tr>
<td>Epinephrine</td>
<td>Kallikrein-kinin system</td>
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<tr>
<td>Renin-angiotensin-aldosterone system</td>
<td>Calcitonin gene–related peptide</td>
</tr>
<tr>
<td>Arginine vasopressin</td>
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Table 1.

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 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.

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, and inhibiting the sympathetic activity is therapeutically beneficial.

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.\(^{10}\) When heart failure is established, increased peripheral chemoreceptor sensitivity and augmented muscle mechanoreceptor discharge may further modulate sympathetic activity.\(^{10}\)

**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\(^2\) or untreated mild heart failure,\(^{11}\) 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\(^{12}\) and in patients on diuretics.\(^{11}\) The elegant studies of Watkins et al\(^{13}\) 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.\(^{14}\) 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.
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. 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 hypoosmolar hyponatremia, which often occurs in severe CHF, and which should suppress AVP, levels remain inappropriately elevated. AVP acts on the vascular smooth muscle V1 receptors to cause vasoconstriction, and on V2 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 V1 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 (NPRA), 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. 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.

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, NPRA receptor downregulation, and enhanced enzymatic degradation of the peptides. Efforts to use these peptides as a therapeutic agent in CHF have, therefore, been disappointing. Inhibition of neutral endopeptidase (NEP)24.11, the enzyme that degrades endogenous natriuretic peptides, potentiates the effects of endogenous peptides and has met with some success in CHF. Because angiotensin II attenuates the effects of ANP, coininghiting 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 PGI2, PGE2, and PGF2α. Renal glomeruli also synthesize thromboxane A2, which causes platelet aggregation and vasoconstriction. 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. Prostaglandins probably do not modulate renal hemodynamics or sodium excretion in normal
untreated low- and high-output heart failure as well as hormone are elevated in the syndrome of severe by the anterior pituitary and mediates its effects via

There has been recent interest in the role of growth dynamics and ventricular remodeling may be derived from an increase in bradykinin.24

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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.12,25 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.26 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.12

Calcitonin gene–related peptide (CGRP), a potent vasodilator, is also released during heart failure.27 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.28

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–α, 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.

Figure 1. Changes in a variety of neurohormones in untreated patients with a low- and high-output state and edema.29 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 obstructive pulmonary disease; CHF, congestive heart failure—dilated cardiomyopathy; COPD, chronic obstructive pulmonary disease; GH, growth hormone; PRA, plasma renin activity.
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. 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. 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, and during physical exercise, where blood pressure is threatened by marked vasodilation in exercising muscles.

These findings, therefore, support the theory 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 vasoconstriction, 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 programed. 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). 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.

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. The Killip class recorded 72 hours after myocardial infarction was the most consistent predictor of increased neurohormone activity, independent of EF. 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. 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. 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). The patients in CONSENSUS I were the most severely affected (NYHA class IV) and had the greatest increase in neurohormones. Only one small study 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. Figure 2 shows a progressive increase in a number of neurohormones with severity of heart failure.
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. 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.

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. 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.

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. 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. 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, PRA, and ANP. 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. 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. 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. 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, 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. ACE inhibitor therapy decreases plasma angiotensin II, but complete chronic suppression of angiotensin II is more difficult to achieve. 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. 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. 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 or have no effect on circulating NE. In dogs with pacing-induced heart failure, ACE-inhibitor therapy attenuated the progressive increase in NE as compared to placebo. 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. In V-HeFT II, the survival benefit with enalapril was accompanied by an attenuation in the rise in circulating NE. 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. 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. 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⁻¹·h⁻¹. These findings could not be confirmed in SAVE.35

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 al44 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 neurohormonal response?” while Henry Dargie defines priorities by asking, “Is routine assessment of the neurohormonal 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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Neuroendocrine Response in Heart Failure

Expert Answers to Three Key Questions

1. Is there a reliable marker of neuroendocrine response?
   C. Ceconi

2. Neuroendocrine response in heart failure: is routine assessment clinically justified?
   H. Dargie

3. What has been and can be achieved by pharmacological manipulation of neuroendocrine responses?
   G.S. Francis
A variety of endogenous neurohormonal systems are activated in patients with chronic congestive heart failure (CHF), and are thought to play an important role in the pathophysiology and progression of the disease. The fact that angiotensin-converting enzyme (ACE) inhibitors and β-blockers have been well demonstrated in clinical use to effectively counteract the neuroendocrine response lends credence to this hypothesis. Yet, in spite of the pathophysiological importance and therapeutic implications of circulating hormonal factors, the assessment of neurohormones has, so far, only been carried out at a research level and has found little application in the management of patients with CHF in the clinical setting. This state of affairs is reflected in the guidelines published by the most prestigious cardiological Societies. For example, the Task Force on Heart Failure of the European Society of Cardiology concludes that “… in individual patients, these predictors (neurohormones) are inaccurate and difficult to interpret.”

Several factors could explain these difficulties, in particular: (i) certain therapies alter plasma concentrations of neurohormones in a complex fashion, which results in limited diagnostic use; (ii) norepinephrine levels rise with age, and healthy subjects over the age of 75 may have norepinephrine plasma concentrations in ranges similar to those found in heart failure.

For its part, the Committee on the Evaluation and Management of Heart Failure (for the American College of Cardiology / American Heart Association [ACC/AHA] Task Force on Practice Guidelines) concluded that “… there is little evidence that measurements of circulating hormonal factors assist in the routine assessment of patients. Furthermore, such measurements have not been shown to guide the rational selection of a specific therapeutic intervention in patients with heart failure.”

Based on these premises, it is not surprising that the use of neurohormonal evaluation in the clinical setting is extremely rare. Statistics from a survey carried out in various cardiology units in Italy have shown that only less than 4% of patients with CHF undergo neurohormonal assessment. The reasons for the dichotomy between the fundamental pathophysiological role and the remarkable potential prognostic value of the neurohormones on the one hand, and the poor clinical applicability on the other hand, needs careful analysis.
WHAT ARE THE FACTORS LIMITING THE CLINICAL USE OF NEUROENDOCRINE EVALUATION?

Undoubtedly, the great complexity and practical problems involved in the measurement of neurohormones render its routine application difficult.

Difficulties in the collection and storage of samples

The majority of neurohormones have a rather short plasma half-life and undergo rapid catabolism after sampling. This is particularly the case for paracrine mediators such as angiotensin II and kinins, for which sophisticated and complex collection procedures are required. The chemical instability of the hormone molecules also contributes to making the preservation of these compounds difficult. For instance, in the case of norepinephrine, enzymatic catabolism and auto-oxidation must be counteracted by the addition of appropriate stabilizing agents and storage at -80°C, in order to ensure stability of plasma samples of about 90% at 3 months.

Technical difficulties of measurement

While assay methods for some neurohormones (eg, aldosterone) are easy and already available for clinical chemistry laboratories, other compounds involve complex procedures. For instance, measurement of neuropeptides necessitates solid-phase extraction before immunoassay. Another example is the assay of catecholamines, which usually involves high-performance liquid chromatography (HPLC) with electrochemical detection of liquid/liquid or liquid/solid affinity separation of plasma samples. This procedure has largely replaced the time-consuming and tedious radioenzymatic assay, but it is complex and delicate and not applicable on a routine basis. Finally, direct immunoassay of plasma samples is often used, as, for instance, in the case of angiotensin II. However, the interpretation of circulating peptide-like immunoactivity of plasma and its relationship with true peptide levels remain controversial. Angiotensin can be very accurately assayed, but this requires solid-phase extraction of plasma samples and HPLC separation followed by immunoassay of eluate fractions, a procedure that has been used only in small clinical trials.

High costs

This is self-evident and needs no further elaboration.

Wide ranges of neurohormone levels in homogenous populations

Wide ranges in values in homogenous populations with wide overlaps among groups of patients despite differences in the clinical severity of CHF are typically found. This concept is graphically represented in Figure 1, which shows the individual plasma norepinephrine levels and mean values according to the New York Heart Association (NYHA) classes of an homogenous population of patients with CHF. It is clear that, although norepinephrine plasma values increase with the progression of the disease, there is an extensive overlap of values that makes their interpretation quite difficult. This is also the main reason why plasma norepinephrine as a prognostic predictor was used as a discrete, and not a continuous variable in clinical studies.

Interpretative misconceptions and difficulties

As already mentioned, several factors, including age and therapy, can directly influence the neuroen-
There is a reliable marker of neuroendocrine response? - Ceconi

docrine response, making the interpretation of results even more difficult. Furthermore, the relationship between neuroendocrine activation and central hemodynamics is complex. For instance, the relationship between circulating hormones and cardiac function is poor. Figure 2 shows what happens in the case of ejection fraction and plasma norepinephrine (r=0.172) and atrial natriuretic peptide (r=0.251), and the same paradigm can be applied to all neurohormones. Apart from pathophysiological considerations on the relative role of central and peripheral factors in triggering humoral responses, this concept is important inasmuch as it once again highlights the fact that the recruitment of the neuroendocrine system is in itself an unfavorable event in the natural history of CHF and an independent prognostic factor.

**Multiplicity of neurohormonal systems**

The multiplicity of the neurohormonal systems activated in the different pathophysiological situations makes it necessary to assay many parameters, each of which has its own implications. This latter point is relevant due to the extreme complexity of hormonal responses in CHF. Neurohormones of particular interest in terms of clinical prognosis include: (i) plasma norepinephrine as an index of sympathetic activation; (ii) atrial natriuretic peptide (ANP) and brain natriuretic peptide (BNP), which are correlated with central hemodynamics and circulatory homeostasis; and (iii) the components of the renin-angiotensin-aldosterone system (RAAS) as an index of electrolytic and volemic adaptation. A general interpretation of the above considerations could be that the intrinsic nature of neurohumoral adaptation—which is transient and has complex pathophysiological correlates—constitutes, together with the practical difficulties, the major limitation in the use of neurohormones as a routine screening tool in clinical practice.

**INDIRECT APPROACHES TO THE MEASUREMENT OF NEUROENDOCRINE ACTIVATION**

To overcome these problems, efforts have been made to identify indirect indices of neuroendocrine hyperactivity. In this context, for instance, power spectral analysis has emerged as an effective method for studying sympathetic influences on the cardiovascular system.

The following looks at some of the possible approaches that can be
used for the indirect assessment of neuroendocrine activation: (i) evaluation of changes concomitant or associated with the activation of a neurohumoral system; (ii) measurement of neurohormonal metabolism by-products; and (iii) measurement of substances cosecreted with neurohormones. These approaches can be considered as effective candidates for routine clinical use and can constitute a stimulating basis for research.

**Evaluation of changes concomitant or associated with the activation of a neurohumoral system**

The best example of this approach is neither new nor original. Indeed, the measurement of plasma renin activity (PRA)—a rate-limiting step in the activation of the circulating angiotensin-aldosterone cascade—has been used for decades in clinical practice as an index of the activation of this neuroendocrine cascade. Pretreatment PRA values have been shown to be an independent prognosticator in several ACE-inhibitor trials.

**Measurement of by-products of neurohormonal metabolism**

Natriuretic peptides are a good example of the clinical application of the measurement of neurohormonal metabolism by-products. It has been shown that measurement of the inactive N-terminal portion of the ANP precursor—and, more recently, of the BNP precursor—had far greater sensitivity as an indicator of left ventricular function or a prognostic predictor than the corresponding active hormone fragment. The fact that the N-terminal portion of ANP is more chemically stable and has a slower catabolism than ANP gives it a distinct advantage over ANP in terms of measurement in clinical practice.

The use of the N-terminal fragments of atrial and brain natriuretic peptides (NT-ANP and NT-BNP, respectively) has been investigated mainly in the context of myocardial infarction where it has been shown to be of value in complementing standard prognostic indicators used in risk stratification after acute myocardial infarction. Both NT-ANP and NT-BNP are strongly and independently correlated with long-term survival after myocardial infarction, with the added advantage of good in vitro stability and simplicity of analysis. Clinical studies have shown that NT-BNP is remarkably well correlated with central hemodynamics in comparison with other neuroendocrine indices of left ventricular dysfunction.

**Measurement of substances cosecreted with neurohormones**

Another approach seeks to identify the possible correlations between substances cosecreted along with the neurohormones and specific neuroendocrine responses. This is best exemplified by neuropeptide Y—a peptide that is stored with the catecholamines both in the peripheral sympathetic nerve terminals and in the adrenal medulla—and that is cosecreted with the circulating catecholamines. In CHF, an increase in plasma neuropeptide Y immunoreactivity has been shown to occur concomitantly with the increase in plasma norepinephrine.

Another substance that appears to fit the description of cosecreted molecules is chromogranin A. This is a 49-kd acidic protein, originally discovered in the chromaffin granules of the adrenal medulla, but which has also been found in nearly all neuroendocrine cells and tissues. The increase in circulating levels of chromogranin A is a diagnostic marker of neuroendocrine tumors, such as pheochromocytoma and carcinoid tumor. More recently, chromogranin A has been reported to be increased in CHF, this increase being proportional to the clinical severity of the syndrome. Because of its wide distribution, chromogranin A has been proposed as a marker of general neuroendocrine activation. Further studies are warranted for the clinical validation of this promising approach.

**CONCLUSIONS**

Congestive heart failure is a common and serious disorder, neuroendocrine assessment appears to have great potential usefulness in complementing the information provided by the limited number of tools currently available for the screening of asymptomatic phases, the follow-up of treatments, and the prognostic stratification of these patients. Today, despite some still unresolved controversies, interest in research into neuroendocrine activation continues unabated. This is probably due to the fact that the usefulness of other prognostic factors is restricted by their limitations in terms of accuracy and availability of low-cost blood tests for the prognostic evaluation of patients with CHF (such as cholesterol for dyslipidemic disorders and blood glucose for diabetes). Thus, a stimulating incentive for further research remains.
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Neuroendocrine response in heart failure: is routine assessment clinically justified?

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The most prominent components of the neuroendocrine response in heart failure are the catecholamines, the renin-angiotensin system, endothelin, and the atrial (ANP) and brain (BNP) natriuretic peptides. Their potential clinical applications include: (i) use as markers in the diagnosis of heart failure and in the screening of asymptomatic left ventricular dysfunction; (ii) use as predictors of specific cardiac events, including death; and (iii) use in tailoring and following up the treatment of heart failure patients. Until now, the major impediment that has put off the use of neuroendocrine assessment in clinical practice has been the lack of availability of reliable and cost-effective assay techniques, but this problem seems to be on the verge of being resolved as far as the natriuretic peptides are concerned.

The short answer to this intriguing question is “no”; or perhaps, “not yet!” This is as surprising as it is disappointing given the huge, and increasing, volume of research data that has accumulated about the importance of the neuroendocrine response in recent years, not only as a marker of the heart failure state, but also in direct pathophysiological terms, in determining progression and, therefore, clinical outcome.¹

Many humoral factors are considered under the “neuroendocrine” banner (Table I), but, in terms of perceived clinical importance or possible imminent routine measurement, this article will concentrate on the most prominent candidates. These are the catecholamines, the various components of the renin-angiotensin system, endothelin, and the natriuretic peptides, and they will be considered under the headings of diagnosis, prognosis, and treatment.

**DIAGNOSIS**

All four of the major components of the neuroendocrine response have been reported to be increased in heart failure, with the degree of activation being roughly proportional to the severity of the underlying condition.²³ In terms of diagnosis, however, it is the natriuretic peptides that, at present, hold center stage. Of these peptides, both atrial natriuretic peptide (ANP), especially N-terminal ANP, and brain natriuretic peptide (BNP) have been found to be consistently elevated, not only in a variety of clinical heart failure situations,

**COMPONENTS OF THE NEUROENDOCRINE RESPONSE**

<table>
<thead>
<tr>
<th>Norepinephrine</th>
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<tr>
<td>Epinephrine</td>
<td>Leptin</td>
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<td>Renin</td>
<td>ß-Endorphin</td>
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<td>Angiotensin II</td>
<td>Calcitonin gene–related peptide</td>
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<tr>
<td>Aldosterone</td>
<td>Cortisol</td>
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<tr>
<td>Atrial natriuretic peptide</td>
<td>Growth hormone</td>
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<tr>
<td>Brain natriuretic peptide</td>
<td>Neurokinin A</td>
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<tr>
<td>Endothelin</td>
<td>Neuropeptide Y</td>
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<tr>
<td>Arginine vasopressin</td>
<td>Substance P</td>
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<tr>
<td>Tumor necrosis factor–α</td>
<td>Vasoactive intestinal polypeptide</td>
</tr>
</tbody>
</table>

*Table 1.*

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**Keywords:** natriuretic peptide; brain natriuretic peptide; left ventricular dysfunction; neuroendocrine response

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but also in asymptomatic cardiac dysfunction. Consequently, natriuretic peptides could be considered as potentially useful biochemical markers in a number of important clinical scenarios.

Why should we need a biochemical, or indeed any other, aid to the diagnosis of heart failure? The reason is that the clinical diagnosis of heart failure remains unsatisfactory, both in terms of accurately confirming or excluding the presence of the heart failure state. This should not be surprising given the poor sensitivity and specificity of the individual clinical components that suggest heart failure. The size of the problem was emphasized in a recent epidemiological survey of heart failure and left ventricular systolic dysfunction (LVD) in the community. This showed that of those subjects with symptomatic LVD, that is to say, “heart failure” by the criteria of the European Society of Cardiology’s Working Group on Heart Failure, only 60% were being treated at all and only 30% with an angiotensin-converting enzyme (ACE) inhibitor. In addition, previous surveys have drawn attention to the problem of the false diagnosis of heart failure in patients presenting with some of its features, especially breathlessness. Thus, it would seem that most patients with true heart failure either have not been recognized, or the underlying cause has not been identified and properly treated, and that many patients are receiving treatment for something they do not have.

The potential clinical usefulness of assaying plasma concentrations of natriuretic peptides in a clinical setting has been demonstrated in a number of clinical situations including the differential diagnosis of dyspnea in the emergency room, the identification of significant LVD in post-myocardial infarction (MI) patients, and, most recently, in a study of incident cases of heart failure in a single health district. In this study, ANP and BNP were found to have a clinically acceptably high sensitivity and specificity of 97% and 84%, respectively, in diagnosing heart failure, with negative and positive predictive values of 97% and 70%, respectively. These encouraging data suggest that these peptides could be useful in diagnosing and excluding heart failure in a general setting and thereby inform the clinical decision to refer individual patients for further investigation. However, this needs to be tested in an appropriately designed prospective study.

**SCREENING**

Natriuretic peptides, perhaps uniquely in the neuroendocrine response, are also elevated in the absence of clinical signs and symptoms in patients with LVD, especially systolic LVD. This raises the possibility that they might also be useful in identifying patients with important, but asymptomatic, LVD who would benefit from appropriate investigation and treatment (Figure 1). The sensitivity and specificity of BNP in detecting such patients from the general population is very acceptable in terms of a screening test, especially when the patients most likely to have LVD are considered, such as those with clinical evidence of coronary heart disease (CHD) those with hypertension, diabetes, or other vascular disease (sensitivity and specificity of 89% and 73%, respectively). In the scenario, the positive predictive accuracy of BNP is relatively low, but the negative predictive accuracy is 98%, indicating a “rule out” role for BNP in order to refine the group of patients who should go forward for further investigation, which, in most cases, would initially be an echocardiogram. Not only would this be clinically justifiable,
it could also have important cost implications, since most patients referred to open or rapid-access echocardiography services seem not to have important abnormalities of cardiac function or structure. A normal BNP value would obviate the need for referral for echocardiography in the first instance, and at least until alternative causes of the presenting symptom had been excluded.17 This approach also requires validation in a prospective study, perhaps in comparison with the ECG as the initial test that indicates a strong likelihood of underlying cardiac dysfunction. Evidence to date is very encouraging, and, to facilitate this approach, newer and more rapid assays are being developed so that all doctors who see patients with possible heart failure, and especially general practitioners, can avail themselves of this advance in technology.18

### PROGNOSIS

The ability to predict important clinical outcomes such as death itself, but also the risk of potentially preventable specific cardiac events, including the need for hospitalization, would be of considerable importance. Not only would this facilitate the identification of patients who might benefit from a greater degree of surveillance or indeed intervention, but it would also help health care purchasers and providers in planning the clinical needs of cohorts of patients.

Since the demonstration of the graded poorer prognosis of patients with increasing concentrations of plasma norepinephrine levels many years ago,19 similar attempts at prognostication have been made, not only with catecholamines,20 but also with several other components of the neuroendocrine response including renin, angiotensin, aldosterone, the natriuretic peptides, and, most recently, endothelin.21-24

Many other clinical, hemodynamic, echocardiographic, and biochemical measurements also have been found to have prognostic value, but their usefulness has never been tested in a prospective clinical setting.25,26 Simply to find, in a logistic regression analysis, factors with independent predictive value is of limited value in an individual patient, as pointed out by Jay Cohn in a paper entitled "Prognostic factors in heart failure: poverty among a wealth of variables."27 Logistic regression analyses have their strengths and weaknesses. Clearly, they are heavily influenced by the type and number of factors entered into the model, though consistent trends from different studies can indicate the most likely contenders for clinical prognostication, which obviously is more relevant to the individual patient rather than groups of patients. In the SAVE (Survival And Ventricular Enlargement) substudy, ANP was a powerful predictor of cardiovascular mortality and of the development of heart failure28; in patients with heart failure, BNP was superior to ANP in predicting mortality and was an independent predictor29; and in an elderly population, BNP also was an independent predictor as well as being the most powerful—this was in a population thought to be free of cardiovascular disease.30 Again, these studies used logistic regression and Kaplan-Meier curves to demonstrate the prognostic association and give little indication of the sensitivity and specificity or of the levels that indicate a prognostic effect. However, since the assays for natriuretic peptides are becoming more generally available, prospective studies of the value of different concentrations of various peptide markers will shortly become available.

Similar data are now available for endothelin. Thus, in heart failure patients, endothelin-1 (ET1) was an independent predictor of mortality and was superior in this respect to ANP and also norepinephrine.24 Big ET1, in another study, has also been found to predict mortality independently, while ANP, aldosterone, and renin had no additional prognostic value.23 Although these studies are small, the comparative data with respect to other neuroendocrine markers are interesting, though by no means conclusive. Should these data be confirmed in larger prospective studies, then the development of user-friendly assays for endothelin may become as justified as for the natriuretic peptides.

### TREATMENT

There are potentially two situations where neuroendocrine assays could inform the treatment process. Firstly, the CONSENSUS (COoperative North Scandinavian ENalapril SUrivial Study) results suggest that it was only in patients with neuroendocrine activation that enalapril had a significant benefit on mortality.21 Thus, it could be argued that, for example, if the renin-angiotensin or sympathetic nervous systems were not activated, then an ACE inhibitor or a β-blocker would not be justified. However, these data from CONSENSUS can only be regarded as hypothesis-generating, and such an approach would have to be addressed in an appropriately designed randomized trial. This certainly would be an interesting approach to the tailoring of treatment, but one that is unlikely to be tested because of the complexities involved.
A related approach would be to use measurements of the degree of activation of the particular therapeutic target of an individual agent to determine if that agent in that patient at that dose was effectively suppressing that system, and, if not, to increase the dose until effective suppression had occurred. The most logical target for this regimen would be the ACE inhibitors, the chronic use of which has often been demonstrated to have been associated with escape or incomplete suppression of the renin-angiotensin system. The recently presented ATLAS (Assessment of Treatment with Lisinopril And Survival) trial suggests that higher doses of lisinopril, which presumably were associated with greater suppression of angiotensin II, had a more beneficial effect on outcome than did conventional doses. The tailored approach using individually measured levels of angiotensin II would be a refinement to the somewhat “blunderbuss” ATLAS approach. In this context, it is of interest that larger doses of ACE inhibitors are not always associated with more pronounced hemodynamic effects, though they certainly produce much greater suppression of the renin-angiotensin system. This raises issues concerning the separation of the hemodynamic from the neuroendocrine effects, and, generally, supporting the notion that neuroendocrine measurements are indeed a logical way to approach the use of specific agents targeted at its specific components.

The general theme of neuroendocrine measurement in treatment monitoring is based on the philosophy that, in the treatment of patients with heart failure, there are no easily measurable and reproducible clinical parameters that tell us whether the individual patient is being optimally treated—in contrast to the treatment of hypertension where the dose of the antihypertensive medication is titrated against the blood pressure. Attempts at tailoring therapy against what might be regarded as an equivalent hemodynamic variable, the pulmonary capillary wedge pressure (PCWP), do suggest considerable clinical benefit in that those patients in whom the PCWP could be brought below 16 mm Hg had a considerably improved survival, and, in further support of the neuroendocrine hypothesis, those patients being treated with captopril had a significantly better outcome than those on hydralazine/nitrates, despite a similar reduction in filling pressure.

An alternative approach would be to titrate treatment against some marker that would be an indicator of the overall degree of the heart failure state. Such a marker could be one or more of the natriuretic peptides used as a “biochemical Swan-Ganz catheter.” Attractive as this idea may sound, there are some practical difficulties, not least of which might be the fact that β-blockers raise levels of natriuretic peptides in patients with heart failure and so could confuse the interpretation of the response. Nevertheless, this, or a similar approach, is a further potentially legitimate reason for measuring these peptides in clinical practice.

**PRACTICALITIES**

Before any measurement can be adopted into clinical practice, certain criteria must be satisfied. For a biochemical test, the assay should be accurate, reproducible, user-friendly, and affordable. In terms of standardization, assay technology is probably furthest advanced with the natriuretic peptides. In addition, there is recent evidence that, for BNP at least, the samples can be sent through the post without prior preparation such as spinning down to retrieve plasma or serum.
or freezing, there being little degradation in samples kept at room temperature (Figure 2). Obviously, samples should be able to be “turned around” in a reasonably short time rather than being held back to be assayed in batches as is the case with most of the neuroendocrine assays under consideration at present. Assay technology, however, is being improved all the time towards a level of clinical accuracy and acceptability as will render estimation of a number or “neuroendocrine panel” of candidates eminently possible.

Casual samples rather than those requiring to be taken after resting for periods of time are much preferable, and this may be one of the practical problems in measuring catecholamines, for example.

**CONCLUSIONS**

There is an inherent logic to the concept of measuring certain components of the neuroendocrine—or perhaps more logically termed, the biochemical—responses that have given useful information about various aspects of heart failure and left ventricular dysfunction. The perception of the meaning or impact of these elevated levels has shifted in recent years from their simply being markers of the presence or severity of cardiac dysfunction to the probability that increased plasma concentrations could have pathophysiological consequences—beneficial in the case of the natriuretic peptides and detrimental in the cases of catecholamines, angiotensin II, aldosterone, and endothelin.

Probably the major reason for the delay in applying the concept of neuroendocrine assessment in clinical practice has been the lack of availability of good, cheap, and accurate assay techniques. That should be much less of a barrier in the near future as assay technology advances to the point where the determining factor in the adoption into clinical practice of any of the various contenders will depend purely on their clinical utility. The future could be very exciting indeed as more and more therapeutic agents are being developed against specific targets of pathophysiological importance whose effectiveness could be enhanced and indeed evaluated by measurements of an appropriate biochemical marker. At the present time, the natriuretic peptides are nearest the transfer from the scientific laboratory to clinical practice.

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What has been and can be achieved by pharmacological manipulation of neuroendocrine responses?

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Research into therapeutic strategies to manipulate the neuroendocrine responses activated in heart failure has been intense. Alongside classic drugs with proven efficacy such as β-adrenergic blockers and angiotensin-converting enzyme inhibitors, alternative strategies are being developed to block the sympathetic nervous system, the renin-angiotensin system, endothelin, as well as numerous cytokines and enzyme systems known to play a major role in the pathogenesis of heart failure. These include angiotensin II-receptor blockers (whose role is still controversial), monoclonal antibodies to block tumor necrosis factor-α, endothelin-receptor blockers, matrix metalloproteinase blockers, neutral endopeptidase blockers, and aldosterone blockers. Most of these agents are currently undergoing clinical trials, the results of which are eagerly awaited.

Keywords: neurohormone; heart failure; cytokine; heart failure treatment

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Although it has been known since the time of Starling that there is an exuberant neuroendocrine response to the failing circulation, recognition of the importance of this problem has only come about in the past 15 to 20 years. It now seems clear that there are a host of neurohormones and cytokines that are important in the pathogenesis of heart failure.1 Given the somewhat spectacular success of the angiotensin-converting enzyme (ACE) inhibitors for the treatment of heart failure, intense interest has developed regarding alternative strategies to block excessive neuroendocrine and cytokine responses (Table I). Most of the successes to date have been related to inhibition of the adrenergic nervous system through β-blockers and attenuation of the renin-angiotensin system with the use of ACE inhibitors. However, new strategies are now developing that are designed to block endothelin, a vasoconstrictor-mitogenic neurohormone known to be increased in patients with heart failure. Specific antibodies have developed against tumor necrosis factor-α (TNF-α). Matrix metalloproteinase (MMP) inhibitors are also being studied in an attempt to abrogate excessive slippage between myocardial fibers, a mechanism presumed to be operative during left ventricular remodeling. This overview is designed to briefly discuss some of these strategies and suggest new potential therapies for modulating neurohormone, cytokine, and enzyme activity in heart failure.

ADRENERGIC NERVOUS SYSTEM INHIBITORS

There is a considerable amount of data to indicate that increase in circulating plasma norepinephrine levels is a potent and reliable indicator of a poor prognosis in patients with congestive heart failure.2 More than a simple marker of severe heart failure, plasma norepinephrine has consistently been demonstrated to correlate with the severity of the disease and provide independent prognostic information. The precise mechanism whereby plasma norepinephrine is increased in patients with heart failure remains to be determined. The most recent data would suggest that excessive spillover or release of norepinephrine is the dominant mechanism,3,4 but the genesis of this perturbation is unclear.

The β-adrenergic blockers have emerged as the most promising form of new therapy for the treatment of congestive heart failure.
Although their use in heart failure dates back to experience with these drugs in Scandinavia during the 1970s, there has always been a serious concern that adding negative inotropic agents to the failing circulation may exacerbate the clinical syndrome. New data with the nonselective ß-adrenergic blocker carvedilol indicate that the need for hospitalization and mortality is reduced with the cautious introduction and careful titration of this drug in patients with New York Heart Association class II and III heart failure. Carvedilol is somewhat unique in that it has little selectivity, is a potent antioxidant, and has peripheral vasodilating properties modulated through α-adrenergic blocking activity. Unlike metoprolol, there is no increase in membrane-bound β-adrenergic receptor density following the use of carvedilol. Although the precise mechanism of action of carvedilol is undoubtedly complex, its long-term use is associated with a reduction in the progression of heart failure.

Additional strategies designed to block the sympathetic nervous system are now emerging. Drugs that inhibit tyrosine hydroxylase, an enzyme step in the synthesis of norepinephrine, are currently under study. To date, it is unclear whether this strategy will have any noticeable advantage over that of conventional ß-receptor blockers. There is additional interest in the use of centrally acting antiadrenergic agents such as moxonidine and clonidine. Clonidine acts on α₂-adrenergic receptors to inhibit the flow of sympathetic traffic from the brain to the periphery. Moxonidine acts on a specific imidazoline-1 receptor in the brain and potently inhibits central nervous system sympathetic drive to the periphery. The renin-angiotensin system is also partially blocked by moxonidine. Although these drugs are currently marketed for the treatment of hypertension, they may have potentially beneficial effects in the treatment of heart failure. More clinical studies will be necessary to better position these therapies.

ACE INHIBITORS

The ACE inhibitors have emerged as the treatment of choice for patients with congestive heart failure. They are now undoubted as beneficial therapy in patients with functional class I to IV heart failure. Virtually all patients with left ventricular dysfunction and heart failure should be treated with an ACE inhibitor unless there is an obvious contraindication such as shock, hyperkalemia, or a rapidly rising serum creatinine. There is seemingly a trend for patients to be underdosed with ACE inhibitors, and most experts now recommend that these agents be titrated to the doses used in the large clinical trials. For example, enalapril should be

Table I. Neurohormone/cytokine/ enzyme manipulation in heart failure.
titrated to 10 mg twice a day, captopril to 75 mg three times a day, and lisinopril should be used in doses of 20 mg per day. Obviously, not all patients will tolerate maximal doses, and individual patients will still require an adjustment of dosage.

Despite extensive investigation over the past two decades, the precise mechanism whereby ACE inhibitors benefit patients with heart failure is incompletely understood. Data are emerging to suggest that prolonged inhibition of the renin-angiotensin system does not occur with these agents, and there is likely an “escape” phenomenon despite persistent therapeutic efficacy. There has long been a belief that ACE-inhibitor-associated incremental changes in bradykinin at the tissue level may have important pharmacologic activity, but this has never been proven conclusively to be an operative long-term mechanism. Clearly, their benefit is not simply a matter of afterload reduction, since there are numerous agents that reduce peripheral vascular resistance, but fail to demonstrate the obvious benefits of ACE inhibitors. It may be that their antiadrenergic properties, although relatively modest, are an important adjunctive mechanism.

ANGIOTENSIN II–RECEPTOR BLOCKERS

Angiotensin II-(Ang II) receptor blocking drugs are now being widely used to treat hypertension. Their role in the management of patients with heart failure has been less well defined. These interesting agents are not a simple substitute for ACE inhibitors, but their usage continues to grow both for the treatment of hypertension and heart failure. Because there are no definitive long-term survival data in patients with heart failure treated with Ang II blockers, and because there are many uncertainties regarding their potential antiremodeling properties, the Ang II blockers should be reserved for the treatment of hypertension until more data become available. Nonetheless, there remains widespread interest in their use, and they may well emerge as an important treatment for patients with heart failure, either added to or in lieu of ACE inhibitors.

REDUCTION OF TNF-α

There is a growing awareness that TNF-α is important in the pathogenesis of left ventricular remodeling. Circulating levels are increased in patients with heart failure, and this cytokine is well known to stimulate myocardial growth and hypertrophy. It is possible that much of the excessive TNF-α is produced locally by the cardiac myocyte. In addition to promoting myocyte hypertrophy, an essential component of left ventricular remodeling, TNF-α may also modulate programmed cell death or apoptosis. There is much interest in developing tissue-specific therapies to reduce TNF-α. Both amiodarone and digoxin are associated with reductions in circulating levels of TNF-α, but whether this mechanism is important in the management of patients with heart failure remains to be conclusively demonstrated. It is likely that tissue-specific monoclonal antibodies will be developed that effectively block excessive TNF-α, and clinicians must eagerly await the results of these intended studies.

ENDOTHELIN-RECEPTOR BLOCKERS

Endothelin (ET) is a potent vasoconstrictor substance that is endogenously released in patients with heart failure. In addition to promoting peripheral vasoconstriction and adding to the afterload stress of heart failure, endothelin has important mitogenic effects including both myocyte hypertrophy and enhancement of the interstitial cardiac matrix. It seems quite likely that endothelin is important in the progressive left ventricular remodeling that characterizes heart failure. Animal studies have suggested that the introduction of endothelin-receptor blockers following experimental acute myocardial infarction is associated with a lessening of left ventricular remodeling and an improvement in survival. Whether or not specific endothelin-receptor blockade is more important than nonspecific blockade of both receptors has yet to be carefully worked out. Bosentan, a nonspecific ETα and ETβ blocker, is associated with acute hemodynamic improvement. Undoubtedly, more specific ET-receptor blockers, including ET-converting-enzyme inhibitors, will emerge in the near future.

MATRIX METALLOPROTEINASE BLOCKERS

The complex problem of left ventricular remodeling has been the subject of numerous experimental and human investigations. There is now a growing awareness that the cardiac myocytes are held together by a precise network of interstitial collagen struts, which are important in the overall mechanical function of the left ventricle in vivo. Heart failure, particularly as a result of myocardial infarction, is associated with dissolution of these interstitial collagen struts. This enzymatic step is largely mediated by a series of matrix metalloproteinases (MMPs). The net result is that the individual cardiac...
myocytes may slip apart, a process known as “myocardial slippage.” It is believed by some that myocardial slippage is responsible in part for the cavity dilation that occurs during progressive left ventricular remodeling. Agents that specifically block the activity of these MMPs have been developed and are currently being studied in patients with cancer in order to prevent metastasis. It is likely that they will be investigated in experimental heart failure as antislippage agents.

NEUTRAL ENDOPEPTIDASE INHIBITORS

Although atrial natriuretic peptide (ANP) has not emerged as an important treatment for patients with heart failure, drugs designed to block the degradation of ANP are currently under both experimental and clinical investigation. The neutral endopeptidase (NEP) inhibitors have been associated with increased plasma levels of atrial natriuretic factor (ANF), and in principle should improve renal blood flow and natriuresis. NEP inhibitors are currently undergoing clinical trials and may eventually have a role as therapeutic agents for the treatment of heart failure.

ALDOSTERONE BLOCKERS

Lastly, the strategy of blocking aldosterone may be an important adjunctive treatment for patients with heart failure. Aldosterone is known to be associated with deposition of both the replacement and interstitial fibrosis that occurs during progressive left ventricular remodeling. A large, randomized controlled clinical trial has recently been completed and indicates that spironolactone improves survival in patients with advanced heart failure.

CONCLUSION

In summary, there is no question that excessive neuroendocrine and cytokine activity is very important in the pathogenesis of the heart failure syndrome and may be the driving force behind progressive left ventricular remodeling. Armed with this information, the pharmaceutical industry has begun to develop numerous therapeutic agents designed to manipulate these neuroendocrine cytokine and enzyme responses. It is clear that ACE inhibitors and β-adrenergic blockers stand out as classic examples of how neuroendocrine modulators may emerge as important therapy. In the near future we will likely see more data regarding the potential use of other neuroendocrine and enzyme modulators, including new strategies designed to block the sympathetic nervous system, the renin-angiotensin system, endothelin, as well as numerous cytokines and enzyme systems known to be important in the genesis of heart failure.

REFERENCES


Neuroendocrine Response in Heart Failure

Summaries of Ten Seminal Papers

1. Augmentation of the plasma norepinephrine response to exercise in patients with congestive heart failure

2. The renin-angiotensin-aldosterone system in congestive failure in conscious dogs

3. Heart atrial granularity: effects of changes in water-electrolyte balance

4. Atrial natriuretic peptide elevation in congestive heart failure in the human
   J.C. Burnett Jr and others. *Science.* 1986

5. Edema of cardiac origin. Studies of body water and sodium, renal function, hemodynamic indexes, and plasma hormones in untreated congestive cardiac failure

6. Prostaglandins in severe congestive heart failure. Relation to activation of the renin-angiotensin system and hyponatremia

7. Plasma norepinephrine as a guide to prognosis in patients with congestive heart failure

8. Congestive cardiac failure: central role of the arterial blood pressure
   P. Harris *Br Heart J.* 1987

9. The neurohormonal hypothesis: a theory to explain the mechanism of disease progression in heart failure
   M. Packer. *J Am Coll Cardiol.* 1992

10. Comparison of neuroendocrine activation in patients with left ventricular dysfunction with and without congestive heart failure. A substudy of the Studies of Left Ventricular Dysfunction (SOLVD)
    G.S. Francis and others. *Circulation.* 1990
starling expounded his Law of the Heart in 1915. Its almost biblical resonance and authority dominated physiological thought through two world wars. “The mechanical energy set free on passage from the resting to the contracted state depends (…) on the length of the muscle fiber.” The Law had, however, the characteristic defect of a purely benchtop experiment extrapolated into the complex world of a man’s body in action. And, eventually, Sarnof and Berglund in the 1950s showed that a whole family of Starling’s curves relating cardiac output to filling pressure could be derived at different degrees of sympathetic stimulation. By 1965, Hamilton and Richards could state: “Without the coordinating stimulus of the central nervous system and the hormonal control governed by this system, the truly isolated heart seems to vary its pumping function between that of a normal resting animal and that of a heart in an animal moribund in the last stages of shock.”

In normal life, the greatest increases in cardiac output are to be found during physical exercise, so that it was reasonable to imagine that this increase would be made possible by increased sympathetic stimulation. By 1965, von Euler and Hellner showed that the excretion of norepinephrine in the urine was increased during exercise in normal men.

These were also the years in which, following the introduction of cardiac catheterization by Cournand and Richards, the cardiac output was being measured in man under all sorts of conditions. In patients with congestive cardiac failure, the cardiac output was low and did not increase to the normal extent during exercise. Was this because there was an inadequate sympathetic stimulus during exercise? Or was there increased sympathetic outflow, but the damaged heart was unable to respond?

Measurements of norepinephrine in the blood had to wait, as is often the case, for a reliable method; but in 1961, von Euler and Lishajko published their fluorometric technique. Thus, by 1962, when Chidsey had moved from Cournand’s laboratory, where we had worked together, to Braunwald’s laboratory, the stage was set to investigate the role of the sympathetic in patients with congestive cardiac failure at rest and during exercise. The paper by Chidsey, Harrison, and Braunwald is a precisely designed and executed study that left no doubts and was to suffer the fate of a classic—always referred to, but seldom read. It is worth reading for its simple and unambiguous writing, and to see what it was like in the good old times when editors had more space for original data than for glossy ads.

They studied five normal subjects and 10 patients with heart disease, of whom 9 had rheumatic heart disease and one cardiomyopathy. Seven of the patients were in congestive cardiac failure.

The normal subjects undertook exercise first at a moderate level for 6 minutes and then at a more intense level for 6 minutes. The cardiac patients undertook only the moderate level of exercise. The oxygen uptake rose from 151 to 477 mL·min⁻¹·m⁻² in normal subjects during moderate exercise, and from 159 to 463 mL·min⁻¹·m⁻² in the patients with congestive cardiac failure. Patients therefore undertook the same moderate exercise as the normal subjects. But the heart rate, which rose from 69 to 104 beats/min in the normal subjects, increased from 88 to 142 beats/min in the patients with congestive cardiac failure. In the normal subjects, the arterial norepinephrine rose from 0.28 to 0.46 g/L; in the patients with congestive cardiac failure it rose from 0.63 to 1.73 g/L. In the patients without failure, the levels of norepinephrine were within the normal range under both conditions. Epinephrine was not affected.

“It is concluded that the excessive augmentation of the plasma norepinephrine response to exercise in patients with congestive heart failure reflects an increased response of the sympathetic nervous system and that this response may have an important supportive role in such patients.” The results were too good for any statistics.

Adolf Eichmann is hanged for his Nazi war crimes; James Watson, Francis Crick, and Maurice Wilkins share the Nobel Prize for Medicine; and Marilyn Monroe dies, aged 36
The renin-angiotensin-aldosterone system in congestive failure in conscious dogs

L. Watkins Jr, J.A. Burton, E. Haber, J.R. Cant, F.W. Smith, A.C. Barger

*J Clin Invest.* 1976;57:1606-1617

These aptly designed experiments, quoted much less often than their importance warrants, were carried out in the mid-seventies.

By that time, a role of the renin-angiotensin-aldosterone system in congestive cardiac failure was suspected, but the measurement of plasma renin activity and aldosterone in patients with the clinical condition had given diverse results. It seemed that the renin-angiotensin-aldosterone system was stimulated in some patients, but not in others.

Watkins and his colleagues had already studied dogs in which congestive cardiac failure had been induced by pulmonary artery ligation and tricuspid incompetence, but they appreciated that, by the time the animals had recovered from the effects of the operation, the initial neurohumoral response to the cardiac damage may well have passed off. They therefore sought to reproduce the hemodynamic conditions of cardiac failure by implanting inflatable balloons around the pulmonary artery or the inferior vena cava of dogs, so that at a later date congestive cardiac failure might be initiated in conscious animals. The cuffs were then maintained inflated for a period of 2 weeks.

The immediate effect of inflating the cuffs was a fall in arterial pressure. This was accompanied by an increase in plasma renin activity, plasma aldosterone, and water intake, and by near total sodium retention. In the days succeeding a moderate degree of inflation, the body weight and plasma volume increased, and ascites and edema developed. As the plasma volume increased, the arterial pressure became restored to normal and plasma renin activity, plasma aldosterone, and renal excretion of sodium also returned to normal values. In animals with more severe constriction, the arterial pressure did not recover, and the levels of plasma renin activity and plasma aldosterone remained high throughout.

In the early days following a moderate degree of constriction, when plasma renin activity was high, the intravenous injection of a converting enzyme inhibitor caused an abrupt decrease in arterial pressure, but later, when the level of plasma renin activity had returned to normal, this did not happen. Chronic infusion of the converting enzyme inhibitor prevented the restoration of arterial pressure and suppressed the increase in plasma aldosterone, while sodium retention was less than in control experiments.

It was noted that the above effects were much greater in inferior vena caval constriction than in pulmonary artery constriction. It is interesting to follow the way in which authors attempted to explain this. "A growing body of evidence," they write, "suggests that the cardiopulmonary pressures (atrial, pulmonary venous, or ventricular end-diastolic) may modify the release of renin." It wasn't a bad attempt. De Bold's paper ([see review page 220](#)) on the atrial granules appeared just 3 years later, and subsequent research would point to the influence of atrial natriuretic peptide. The peptide would have been released during constriction of the pulmonary artery as the right atrial pressure rose, but constriction of the inferior vena cava was accompanied by a decrease in right atrial pressure and a decreased stimulus for release of atrial natriuretic peptide.

These studies revealed the feedback mechanism through which the renin-angiotensin-aldosterone system operates in congestive cardiac failure. The initial threat to the arterial pressure evokes an increased plasma renin activity and plasma aldosterone. Angiotensin II is of immediate help in maintaining the arterial pressure by peripheral arterial vasoconstriction. Then, in the period which follows, the expansion of the plasma volume through the sodium-retaining properties of aldosterone and the action of angiotensin II to increase thirst completes the restoration of the arterial pressure and the system shuts off.

1976

The United States celebrates its Bicentennial year;
Milton Friedman (USA) is awarded the Nobel Prize in Economic Sciences;
and Benjamin Britten, the English composer, dies, aged 63
Heart atrial granularity: effects of changes in water-electrolyte balance

A.J. de Bold


The discovery of the function of the atrial granules and their production of atrial natriuretic peptide has been one of the most exciting stories of modern cardiology. Suddenly the heart, thought of since time immemorial only as a pump, became an endocrine organ.

The presence of granules in the atrial myocytes had been described by Jamieson and Palade in 1964 when the heart was first being studied under the electron microscope. They were referred to as “atrial specific granules,” and it was noted that they had the appearance of secretory granules. But it was not until 1976 that Marie, Guillemot, and Hatt proposed that the granules had a function in the volume sensitivity of the atria. To my mind, Pierre-Yves Hatt, who also described the juxtaglomerular apparatus in the kidney, has never been accorded the recognition due to him for this seminal observation.

But it was de Bold who, by applying careful electron microscopical morphometric techniques to the study of the atria of rats under experimental conditions, was able to assert with confidence their relation to salt and water balance. Using these techniques, the granularity of the myocytes could be expressed as the percentage volume occupied by granules. As de Bold pointed out, the distribution of the granules in the cell was so irregular that it would take large changes in their numbers to be evident by simple inspection. Preliminary experiments had shown that “as much as near doubling in granularity as detected by the morphometric method used in the present investigations is not detectable by subjective microscopic evaluation.”

The mathematical basis of such morphometric techniques had been developed by Gomez in the 1950s. That colorful and vulnerable Cuban genius had been found by Courmand in Paris and brought to New York, where he developed the methods of morphometry in order to estimate the surface area of the alveolar membrane and the volume of emphysema in the lungs—and demonstrated its general application by predicting the number of string beans in a frozen packet from a cross section.

In de Bold’s original paper, rats were subjected to a number of different experimental conditions involving salt and water balance. These comprised: adrenal regeneration hypertension, bilateral adrenalectomy, injections of desoxycorticosterone, water deprivation, adding salt to the drinking water, and salt restriction. Separate control groups were used for each type of experiment.

Neither adrenalectomy nor adrenal regeneration hypertension had any significant effect on the granules. Adding sodium chloride to the drinking water under various other experimental conditions consistently reduced the atrial concentration of granules, but the differences were not statistically significant. However, sodium restriction, which increased the hematocrit from 45% to 52%, caused a significant increase in granularity from an average of 2.95% granules to 3.67%. Water deprivation, increasing the hematocrit from 44% to 54%, also caused a significant increase in granularity from 2.54% granules to 3.62%.

In the case of water deprivation, there was a significant correlation between the hematocrit and the granularity. In animals receiving desoxycorticosterone plus salt loading, there was a significant fall in atrial cell granularity from 2.74% granules to 2.03%.

Thus, de Bold started with no more than a general hint from previous workers, and set up a limited number of well-designed fishing experiments to investigate it numerically, being rewarded with the clear-cut answer that was to start a new epoch in cardiology. He ends with the modest comment that this and previous work “suggest that atrial specific granules are likely related to water-electrolyte balance and this appears a useful working hypothesis to further define the physiological role of these organelles.”

Mother Teresa is awarded the Nobel Peace Prize; Maria Pintassilgo becomes Portugal’s first female Prime Minister; and Lord Mountbatten is killed by an IRA bomb blast, aged 79
Atrial natriuretic peptide elevation in congestive heart failure in the human


Science. 1986;231:1145-1147

Following de Bold’s discovery of the relation of the atrial granules to water and electrolyte balance, atrial natriuretic peptide was identified, its chemical composition established, and the molecule synthesized. When given to animals, it was found to cause natriuresis, a decrease in arterial pressure, and inhibition of the renin-angiotensin-aldosterone system. Assays for atrial natriuretic peptide were developed, and it could be shown that increasing the intracardiac pressure in conscious dogs led to an increase in the plasma concentration of the peptide.

At this point it was not certain what role atrial natriuretic peptide might play in the pathophysiology of heart disease. One suggestion, which appeared plausible, was that there was a suppression of the production or liberation of the peptide in congestive cardiac failure. After all, this condition was notable for the massive retention of salt and water in the body, so it was difficult to see why the body in its “wisdom” should decide on an increased level of atrial natriuretic peptide in the blood. This paper was the first to investigate such a hypothesis.

The authors were careful first to develop a sensitive radioimmunoassay for human atrial natriuretic peptide, using radiiodinated purified synthetic peptide, and to validate the method in the laboratory. They then used the method to assay the concentration of atrial natriuretic peptide in the plasma of four groups of subjects. These comprised normal controls, patients with cardiovascular disease but normal cardiac filling pressures, patients with cardiovascular disease and raised cardiac filling pressures, and patients with cardiovascular disease and raised cardiac filling pressures and congestive cardiac failure. All cardiac therapy was withheld on the day of investigation.

The results were unequivocal. Instead of the expected diminution in plasma concentration of atrial natriuretic peptide in congestive cardiac failure, there was a striking increase. There is nothing, as Popper would have told us, so convincing as disproving your hypothesis. The mean figures were 45 pg/mL in normals, 52 pg/mL in patients with cardiovascular disease but normal cardiac filling pressures, 232 pg/mL in patients with cardiovascular disease and raised cardiac filling pressures, and 445 pg/mL in patients with cardiovascular disease and raised cardiac filling pressures.

Taken in conjunction with the preceding experiments on animals, it could be concluded that distention of the cardiac chambers gave rise to an increased release of atrial natriuretic peptide into the plasma.

But what was the role of the mechanism in the pathogenesis of congestive cardiac failure? And, if the action of the peptide is to cause natriuresis and vasodilation, why is it so ineffective in that condition? The authors conclude that their study “establishes that, in human subjects, congestive heart failure reflects not an atrial natriuretic peptide deficiency state, but rather a compensatory increase in peptide release.” With hindsight we may now, I think, add that this “compensatory” mechanism is ineffective because the body has been programmed to consider the maintenance of the blood pressure more important than the limitation of the blood volume.

1986

The World Wildlife Fund celebrates its 25th birthday; Yellow balls are used for the first time at the Wimbledon Championships; and Henry Moore, British sculptor, dies, aged 88
Edema of cardiac origin. Studies of body water and sodium, renal function, hemodynamic indexes, and plasma hormones in untreated congestive cardiac failure

I.S. Anand, R. Ferrari, G.S. Kalra, P.L. Wahi, P.A. Poole-Wilson, P.C. Harris

Circulation. 1989;80:299-305

By the early 1980s, a great deal of fragmented information was available concerning the neurohumoral response in congestive cardiac failure (see review of Harris page 225). The information, however, was incomplete in a number of ways. The first problem was that, in the affluent West, it was rare to find a patient who had not yet received some treatment, and one could not be sure to what extent previous treatment had influenced or even initiated the neurohumoral responses that had been reported. To get round this, therapy could be withdrawn for a few days; but again it was not clear to what extent the observations might be the results of a recovery from chronic diuretic therapy. In addition, nearly all had congestive cardiac failure due to a damaged heart, and there was virtually no information concerning patients with a "high output failure." Would the neurohumoral response be the same in them?

The present study—the first of a series intended to fill these essential gaps in our knowledge—was carried out on eight patients with severe congestive cardiac failure. Two had ischemic heart disease and six had dilated cardiomyopathy. The hemodynamic measurements were a measure of the extreme severity of the condition—cardiac index 1.8 L/min·m⁻², heart rate 115 beats per minute, pulmonary wedge pressure 30 mm Hg, right atrial pressure 15 mm Hg—but the mean aortic pressure was maintained at 100 mm Hg.

In addition to standard hemodynamic procedures, measurements of renal function, plasma volume, total body water, and exchangeable sodium were performed to complete the physiological picture and confirm the presence of retention of saline in the body. There were significant changes in all, which showed that the retention of water in the body was distributed preferentially in the extracellular space, including the blood plasma. Renal plasma flow was greatly diminished, while glomerular filtration rate was diminished to a lesser extent, indicating vasoconstriction of the glomerular efferent vessels. The observations support (but do not prove) the hypothesis that the control mechanisms operating in congestive cardiac failure are directed to the maintenance of the arterial pressure.

The neuroendocrine measurements in the plasma were aldosterone, vasopressin, growth hormone, prolactin, cortisol, norepinephrine, epinephrine, and renin activity. The values were compared with measurements taken in the same laboratory from normal subjects of the same ethnic population. The findings confirmed that in untreated congestive cardiac failure there is a striking increase in plasma renin activity, aldosterone, norepinephrine, and atrial natriuretic peptide. Unexpected findings were increases in growth hormone and cortisol. Epinephrine, which seems to reflect emotional rather than hemodynamic stress, was not affected. Neither was vasopressin. However, the release of vasopressin is controlled by both baroreceptor and osmotic stimuli. In congestive cardiac failure, these two factors are operating in opposite directions: hyponatremia and hypo-osmolarity reducing vasopressin release, while a decreased baroreceptor stimulus increases it. The level of plasma vasopressin may, therefore, have been abnormally high in relation to the hyponatremia.

The results established a primary database with which to compare other forms of congestive cardiac failure. Subsequent studies using the same techniques were to show a similar neurohumoral response in the "high output failure" associated with chronic respiratory disease or anemia. Together they provided evidence that the response is evoked to maintain the arterial pressure, whether it is threatened by a reduced cardiac output or by a decreased peripheral resistance.

1989

The 200th anniversary of the French Revolution is celebrated in Paris; Batman celebrates his 50th birthday (31 December); and San Francisco is devastated by an earthquake that leaves at least 90 people dead
Prostaglandins in severe congestive heart failure: relation to activation of the renin-angiotensin system and hyponatremia

V.J. Dzau, M. Packer, L.S. Lilly, S.L. Swartz, N.K. Hollenberg, G.H. Williams


This paper was published in 1984. That was around the time when atrial natriuretic peptide had appeared on the horizon. Since then, there has been a great deal of interest in atrial natriuretic peptide as a natriuretic and vasodilator liberated in excess into the plasma in congestive cardiac failure. Some of the prostaglandins, which are the subject of this paper, are also vasodilators and promote salt and water excretion by the kidneys, but they have, by contrast, been little followed up.

Underperfusion of the kidneys or the heart releases prostaglandins I₂ (prostacyclin) and E₂, whose vasodilator activity helps to restore blood flow. The infusion of vasoconstrictor hormones, such as angiotensin II, norepinephrine, or vasopressin, also stimulates prostaglandin synthesis, which attenuates the vasoconstriction.

Prostaglandins E₂ and I₂ are highly unstable, and, in this study, their more stable metabolites were measured in the plasma as an indication of their overall rate of biosynthesis in the body. Such measurements were made in a group of 38 patients with severe congestive cardiac failure, as shown by the cardiac output, pulmonary wedge pressure, and left ventricular ejection fraction. Treatment with diuretics and vasodilators had been withdrawn 3 to 5 days before the study. The measurements of prostaglandin metabolites were related to plasma levels of renin activity and angiotensin II, and to serum sodium concentration.

The stable metabolites used were prostaglandin E₂-M for prostaglandin E₂ and 6-keto-prostaglandin F₁α for prostaglandin I₂. The mean plasma concentrations of both metabolites were greatly increased in the patients with congestive cardiac failure, as was plasma renin activity. However, individual values of all three ranged from normal to extremely high. Plasma concentrations of E₂-M correlated directly with plasma renin activity and plasma angiotensin II, while concentrations of 6-keto-prostaglandin F₁α correlated with angiotensin II.

Serum sodium concentration had an important bearing on hormonal levels. Patients with hyponatremia (Na <135 mmol) had increased concentrations of E₂-M, 6-keto-prostaglandin F₁α and angiotensin II, and an increased plasma renin activity. The patients with hyponatremia also had an increased blood urea and creatinine.

Seven patients were placed on a diet of 10 mmol sodium a day, and eight patients were placed on a diet of 80 mmol daily. These dietary manipulations did not affect the above correlations, but the absolute values of the various measurements under these conditions are not given.

To assess the importance of prostaglandins in congestive cardiac failure, the authors studied the effects of indomethacin in 23 patients. This nonsteroidal, anti-inflammatory drug inhibits the enzyme cyclooxygenase that generates the cyclic endoperoxides from arachidonic acid. In this way, it inhibits the synthesis of both E₂ and I₂. Not all prostaglandins and endoperoxides are vasodilators—some are vasoconstrictors—but Wennalm (*Clin Sci*, 1978) had shown that the infusion of indomethacin in normal man caused a reduction in cardiac output and an increase in systemic vascular resistance.

Indomethacin caused a considerable and significant decrease in cardiac output and increase in pulmonary wedge pressure, systemic arterial pressure, and systemic arterial resistance in those patients with a low serum sodium, in the patients with a normal serum sodium, the effects were in the same direction, but of less magnitude and not statistically significant.

This paper provides impressive evidence of a role played by vasodilator prostaglandins in congestive cardiac failure. It is surprising that its implications have not been explored further. The caveat against the use of nonsteroidal anti-inflammatory drugs in congestive cardiac failure is borne out by clinical experience.

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1984

Peggy Ashcroft wins an Oscar (Best Supporting Actress) for “Passage to India”;
Jayne Torvill and Christopher Dean win an Olympic Gold for ice-dancing in Sarajevo;
and The Nobel Peace Prize is awarded to Desmond Tutu, Bishop of Johannesburg.
 Plasma norepinephrine as a guide to prognosis in patients with congestive heart failure

J.N. Cohn, T.B. Levine, M.T. Olivari, V. Garberg, D. Lura, G.S. Francis, A.B. Simon, T. Rector


In this neat prospective study, Jay Cohn, Gary Francis, and their colleagues show for the first time that, in patients with clinical congestive cardiac failure, plasma norepinephrine is a better predictor of prognosis than hemodynamic measurements. They studied 106 patients with congestive cardiac failure; 60 had coronary heart disease, while the rest had cardiomyopathy or "volume-overload lesions." The objective was to see if, during follow-up, their prognosis could be related to initial hemodynamic and hormonal measurements, all performed at rest. Any vasodilators had been withdrawn 48 hours before, and digoxin and diuretics were withheld on the day of the study. Mean values for right atrial and pulmonary wedge pressures were abnormally high, while the systemic arterial pressure and cardiac output were low. The mean plasma levels of norepinephrine and of renin activity were abnormally high, and the serum sodium was low. Over a period of 62 months, 60 patients died. Of these, 17 died suddenly and unexpectedly, 11 died suddenly after a worsening of the congestive cardiac failure, and 27 died with progressive congestive cardiac failure.

The main analysis was between the patients dying and those surviving. Plasma norepinephrine (P<0.001), plasma renin activity (P=0.01), stroke work index (P=0.03), serum sodium (P=0.05), and heart rate (P=0.05) could be identified as potential predictors of survival. But, when the simultaneous predictive utility of these measurements was analyzed, only plasma norepinephrine emerged as an independent factor of importance (P=0.002).

Why should plasma norepinephrine be a better predictor than direct hemodynamic measurements of cardiac function? The authors first review evidence that plasma norepinephrine reflects sympathetic activity in the body, and they point to the stability of the measurement of plasma norepinephrine in their patients. Emotional stress, which has immediate hemodynamic effects, influences epinephrine rather than norepinephrine. Hemodynamic measurements are labile, and particularly the arterial pressure may vary widely in patients of middle age and beyond. In a damaged heart, the cardiac output may actually be brought back to normal by an increased sympathetic activity, and sympathetic activity may be seen as a response "when depression of pump function is perceived by the body as impairing organ function."

In order to determine whether higher plasma levels of norepinephrine are associated with a greater mortality, Cohn et al divide the plasma norepinephrine levels arbitrarily into terciles and show that this results in statistically distinguishable survival curves, with survival decreasing as plasma norepinephrine increases. Sympathetic activity in the heart itself has been shown to favor arrhythmias, so that the increased sympathetic activity that is revealed by a high plasma norepinephrine may not only be a reflection of a poor cardiac pump function, but may itself be a cause of sudden death. If that were important, one would expect the initial plasma norepinephrine to have been higher in patients dying suddenly than in those dying from progressive congestive cardiac failure. The data do not bear that hypothesis out. In an analysis to distinguish between the patients dying suddenly and those dying from progressive congestive cardiac failure, plasma norepinephrine and renin activity were found to be significantly higher and the stroke-work index significantly lower in the patients dying of progressive congestive cardiac failure. The authors, however, are careful to point out that the limited number of deaths provided only a limited statistical power and that the clinical selection of patients dying of unheralded arrhythmias is much less certain than overall mortality.

To what extent could the level of plasma norepinephrine be influenced by cardiac therapy? We can only tell you, say the authors, that the patients received conventional therapy. For most of them, this consisted of digoxin, furosemide, and a vasodilator drug.

Indian troops storm the Golden Temple of Amritsar, held by Sikh extremists; Band Aid is created by Bob Geldof, to help victims of the Ethiopian famine; and US author and playwright Lillian Hellman dies, aged 77
Congestive cardiac failure: central role of the arterial blood pressure

P. Harris
Br Heart J. 1987;58:190-203

The history of the changing concepts of the mechanisms of formation of peripheral edema in cardiac patients goes back to 1832 when Hope proposed that an overworked ventricle first hypertrophies and then dilates, damming up the blood behind it, resulting in increased venous pressure, which is transmitted ultimately to the capillaries, where edema is formed. This theory convincingly explained the formation of pulmonary edema, but not the massive peripheral edema found in severe congestive heart failure.

By the beginning of our century, Starling and Mackenzie had rejected the “backward failure” theory in favor of a forward failure due to impaired nutrition of the capillaries from a diminished cardiac output. Landis eventually showed that capillary pressure was increased, which made the backward failure theorists happy. But both forward and backward theories implied a diminution in blood volume, and this was shown to be increased. In the 1940s, cardiac catheterization confirmed that the cardiac output in patients with congestive failure was usually decreased. But it revealed a disconcerting group of patients who had an increased cardiac output. Here was disaster for the backward failure theorists and a serious dilemma for the forward failure proponents.

It took a long time for the theorists to realize what was obvious to any clinician: that edema and oliguria implied a retention of water in the body. In the 1940s, attention swung finally to the kidneys, and Merrill showed that reduced urinary volume and lack of urinary sodium were associated with a reduction in renal blood flow. But then a mysterious increase in tubular reabsorption of sodium was found. This led to the discovery of aldosterone and its eventual link to the renin-angiotensin-aldosterone system.

The urine had been known to be highly concentrated for a century. Robinson and Farr showed in 1940 that it contained an antidiuretic substance, but it was not until 1974 that this was identified as vasopressin. The influence of the sympathetic system on the heart was also known in the 19th century, but it took Sarnoff and Berglund in 1954 to show its physiological importance, while its particular importance in congestive failure had to wait a further 6 years to be revealed (see review of Chidsey et al, page 218). Thus, there emerged a combination of neurohumoral agents that together would stimulate the heart and cause peripheral vasoconstriction and retention of saline. Then came the discovery of atrial natriuretic factor (see review of de Bold, page 220), a peptide with natriuretic and vasodilator properties that circulated in high concentration in congestive failure. Although it is clear that its influence is quite outweighed by that of the vasoconstrictor agents, one is left with a nagging doubt about how the “wisdom of the body” could have got so mixed up.

The thesis proposed in this article is that the neurohumoral response in congestive failure arose during evolution for preservation of arterial pressure during hemorrhage. In this condition, both the arterial and the venous pressures fall, so that the release of atrial natriuretic peptide is diminished simultaneously with a stimulation of the sympathetic and renin-angiotensin-aldosterone systems, and the total neurohumoral response is coordinated. During evolution, the warm-blooded animals developed a high arterial pressure, which permitted the distribution of blood flow by regional vasoaction. This was essential during exercise when an overriding diversion of blood flow to the limbs might be necessary. The threat to the system was leakage from the high pressure, and the responses that we see in congestive failure evolved to deal with that contingency.

The body is not prepared for the threat to the arterial pressure from a damaged heart or from severe sustained vasodilatation that occurs in “high output failure,” and it responds in the way it has been programmed. It maintains the arterial pressure by cardiac stimulation, vasoconstriction, and an increased blood volume, and overrides the opposing neurohumoral influences from the resulting distention of the atria.

Van Gogh’s “Irises” are sold for 53.9 US dollars; Australian Pat Cash wins the Men’s Singles at Wimbledon; and Fred Astaire, US dancer and actor, dies, aged 88
The neurohormonal hypothesis: a theory to explain the mechanism of disease progression in heart failure

M. Packer


This review of the literature concerning the role of neurohumoral stimulation in congestive heart failure attempts to answer the question: do systemic vasodilators or myocardial stimulants reduce mortality?

First to be reviewed are the vasodilators. The Veterans Administration Heart Failure Trial (V-HeFT) showed that prazosin produced a greater decrease in arterial pressure than isosorbide dinitrate, but no effect on mortality, whereas the combination of isosorbide with hydralazine, although relatively ineffective on the arterial pressure, reduced mortality by 28%. Minoxidil and the calcium channel blockers are potent vasodilators, but worsen the prognosis. ß-Agonists and phosphodiesterase inhibitors have the advantage of stimulating the myocardium as well as causing vasodilation. However, their long-term use has been associated with an increase rather than a decrease in mortality. Treatment with milrinone in the Prospective Randomized Milrinone Survival Evaluation (PROMISE) trial resulted in a 28% increase in mortality.

Packer next explores the hypothesis according to which the progressive deterioration in patients with congestive failure would be due to the direct effects of neurohumoral stimulation. Both norepinephrine and angiotensin II have effects on hemodynamics and water and salt balance that might increase the disability of the heart. Since the 1950s it had been known that massive doses of catecholamines could cause myocardial necrosis, and more recently that angiotensin II had a direct deleterious effect on the myocardium. What then, are the effects of long-term blockade of these systems?

The findings of the North Scandinavian Enalapril Survival Study (CONSENSUS), published in 1987, were striking. Enalapril, which decreased plasma angiotensin II by inhibiting converting enzyme, reduced total mortality by 40% at 6 months and 31% at 1 year. Subsequent trials with this and other converting enzyme inhibitors gave similar results. These beneficial effects could simply have been due to the drugs’ potent vasodilatory effects, but two points argue against this. First, the reduction in mortality was greatest in patients with the highest neurohumoral activation. Second, the Veterans Administration Heart Failure Trial II (V-HeFT II), comparing enalapril and the hydralazine/isosorbide dinitrate combination, showed that the hemodynamic effects were greater with hydralazine/isosorbide dinitrate while the neurohumoral effects were greater with enalapril, and that mortality was significantly lower with the latter.

Physicians were long scared to give ß-blockers to patients with congestive failure, since increased sympathetic activity was thought to be necessary to support cardiac output. Eventually, however, trials showed that ß-blockers were beneficial, probably by suppression of arrhythmias, since they particularly reduced the risk of sudden death, a risk increased by milrinone. Since phosphodiesterase inhibitors increase intracellular cyclic AMP and ß-blockers reduce it, these two types of drugs may be acting on the same biochemical mechanism.

Among the drugs used in the treatment of congestive cardiac failure, a good case is made that relief of the myocardial effects of norepinephrine and renin-angiotensin-aldosterone stimulation is more effective than relief of hemodynamic over-burden. However, the review is based on the treatment of patients with ischemic heart disease. In this disease, the scope for surgery is limited, and treatment relies on drugs. Do the same principles apply to valvular heart disease? Few would deny the effectiveness of surgery in such conditions, but even here there comes a point after which surgery fails to prevent the progression of congestive cardiac failure.

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**1992**

The European parliament celebrates its 40th anniversary; Emma Thompson wins an Oscar (Best Actress) for her role in “Howard’s End”; and Anthony Perkins, who starred in “Psycho”, dies, aged 60.
Comparison of neuroendocrine activation in patients with left ventricular dysfunction with and without congestive heart failure.  
A substudy of the Studies of Left Ventricular Dysfunction (SOLVD)


Circulation. 1990;82:1724-1729

This study was a spin-off from SOLVD (Studies of Left Ventricular Dysfunction), a large trial testing the effects of the converting enzyme inhibitor enalapril in patients with a low left ventricular ejection fraction (<35%). Most of the patients had ischemic heart disease.

There were two sections of the trial. The first section, called the “prevention group,” consisted of patients with left ventricular dysfunction who did not require diuretics or digitalis for control of clinical congestive cardiac failure. A certain number, however, were being treated with diuretics for hypertension or with digitalis for arrhythmia. In this group, the object of the trial was to see if enalapril prevented the development of congestive cardiac failure and reduced mortality.

The second section of the SOLVD trial, called the “treatment group,” consisted of patients with left ventricular dysfunction who had symptomatic congestive cardiac failure requiring treatment with digitalis, diuretics, or vasodilators that were not converting enzyme inhibitors. The object of this section of the trial was to see if enalapril prevented the development of congestive cardiac failure and reduced mortality.

There was a placebo division for each section of the trial, and it had been planned to measure plasma renin activity, norepinephrine, atrial natriuretic peptide, and vasopressin in each patient before randomization into placebo or treatment division. This paper gathers together the results of those measurements and compares them in the prevention group and treatment group. In addition, a control group had been studied simultaneously with the recruitment of patients into the trial. Thus, for each measurement there were three groups: prevention group, treatment group, and control. There was a total of 151 patients in the prevention group, 81 patients in the treatment group, and 56 persons in the control group. The results are summarized in Table I.

<table>
<thead>
<tr>
<th>Measurement</th>
<th>Control</th>
<th>Prevention</th>
<th>Treatment</th>
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<tr>
<td>Norepinephrine (ng/mL)</td>
<td>317</td>
<td>422</td>
<td>507</td>
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<tr>
<td>Renin activity (ng·mL⁻¹·h⁻¹)</td>
<td>0.6</td>
<td>0.7</td>
<td>1.4</td>
</tr>
<tr>
<td>Vasopressin (ng/mL)</td>
<td>1.8</td>
<td>2.2</td>
<td>3.0</td>
</tr>
<tr>
<td>Atrial natriuretic peptide (ng/mL)</td>
<td>48</td>
<td>103</td>
<td>146</td>
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Table I. Median values of neuroendocrine parameters in SOLVD.

In each case, the value for the prevention group was significantly greater than that of the control group, and the value for the treatment group significantly greater again that of the prevention group. Of these statistical tests for significance, the least impressive was a P value of 0.03 in the comparison of plasma renin activity between the control group and the prevention group. Could this be accounted for by the fact that 20% of the patients in the prevention group were receiving diuretics for hypertension?

To look into this, the authors reanalyzed their data according to diuretic use. Whether the patients were on diuretics or not made no significant difference in the results for norepinephrine, atrial natriuretic peptide, or vasopressin; but there was a significant increase in the plasma renin activity in patients taking diuretics in both the prevention group and the treatment group. “It is, therefore, likely,” say the authors, “that activation of the renin-angiotensin-aldosterone system (...) is in part related to diuretic use.”

Neuroendocrine stimulation, involving both vasoconstrictor and vasodilator systems, “occurs at a symptomless or mildly symptomatic stage of left ventricular dysfunction and therefore is not likely to be a simple consequence of worsening congestion. Our data suggest that there is additional progressive neuroendocrine activation as patients progress from early asymptomatic or mildly symptomatic left ventricular dysfunction to symptomatic heart failure.”

The final, prophetic sentence is: “Neuroendocrine activation appears to precede overtly symptomatic heart failure and may therefore contribute to its development.”

Macauley Culkin is left “Home Alone”;
The Hubble space telescope is put into orbit around the earth;
and John McEnroe is banished from the Australian Open for bad behavior.
# Neuroendocrine Response in Heart Failure

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