Neurohormonal interactions and adaptations in congestive heart failure

MILTON PACKER, M.D.

When I was a boy of fourteen, my father was so ignorant I could hardly stand to have the old man around. But when I got to be twenty-one, I was astonished at how much he had learned in seven years.

Mark Twain

When cardiac output falls after an insult to the myocardium, a number of neurohormonal mechanisms are activated to preserve circulatory homeostasis. Although originally viewed as a beneficial compensatory response, the endogenous release of vasoconstrictor neurohormones appears to play a deleterious role in the development of congestive heart failure. Activation of the sympathetic nervous and renin-angiotensin systems causes an increase in loading conditions in the failing ventricle and may accelerate progression of the underlying disease. These neurohormones may interact with (and exacerbate) the electrolyte abnormalities seen in heart failure, which may underlie the pathogenesis of ventricular arrhythmias. By these mechanisms, neurohormonal activation contributes importantly to the symptoms of heart failure as well as to the high mortality of patients with this disorder.1

Why are these neurohormones released in patients with heart failure when their effects are so detrimental? Physiologists have hypothesized that the circulation is limited in its capacity to respond to circulatory stress (e.g., a reduction in cardiac output). According to this theory, the mechanisms that are activated in heart failure are identical to those triggered in response to intravascular volume depletion, but with an important difference. The release of neurohormones is generally successful in reversing the hemodynamic abnormalities seen in hypovolemic states, and consequently, neurohormonal activity subsides. In contrast, neurohormonal activation in heart failure not only fails to correct but may exacerbate the hemodynamic abnormalities in this disorder, and thus the release of neurohormones continues unabated and initiates a series of self-reinforcing events that lead to progressive left ventricular dysfunction and death. According to this view, the circulation remains vulnerable to prolonged neurohormonal activation because it never evolved the means to effectively modulate endogenous vasoconstrictor activity.

Over the past several years, however, we have learned that this view of neurohormonal activity in patients with heart failure is too simplistic. Although the endogenous release of neurohormones can exert deleterious hemodynamic and metabolic effects, these substances also play an important beneficial role in the support of systemic blood pressure, cardiac contractility, and glomerular filtration rate. Furthermore, many of the neurohormones released in heart failure are capable of interacting with one another, so as to potentiate or attenuate specific physiologic actions. Finally, prolonged neurohormonal activation is accompanied by changes in end-organ responsiveness that can significantly modify the effects of neurohormonal agonists. All of these interactions can be viewed as mechanisms by which the circulation can adapt to and limit the effects of endogenous vasoconstrictor neurohormones in chronic heart failure. We now realize that the physiologic responses in heart failure are substantially more complex than we had previously imagined, and this complexity distinguishes heart failure from the...
more simple reactions evoked during hypovolemia. A close look at these neurohormonal interactions and adaptations permits us to formulate specific hypotheses regarding the sequence of events that may occur during the evolution and progression of the heart failure state.

Release of neurohormones from the central nervous system

Any change in cardiac performance that threatens cerebral blood flow is detected by sensory receptors in the heart and great vessels. These receptors normally send impulses to the central nervous system that are inhibitory to the activation of two vasoconstrictor mechanisms—the sympathetic nervous system and the release of vasopressin from the pituitary. When stimulated by a fall in cardiac output or systemic blood pressure, however, these central baroreceptors act to decrease the number of tonic inhibitory impulses, thereby triggering the release of neurohormones from the central nervous system. The sympathetic nervous system and vasopressin interact to increase systemic blood pressure and intravascular volume, and thereby support cerebral perfusion. Normal feedback regulation of these two systems is dependent on the stimulation of high-pressure arterial and atrial baroreceptors, which restores tonic inhibition of neurohormonal activity, if arterial or atrial pressure rises as a consequence of excessive systemic vasoconstriction or intravascular volume expansion.

Abnormalities of central neurohormonal regulation in heart failure. In congestive heart failure, however, the ability of atrial and arterial baroreceptors to suppress sympathetic activity and the release of vasopressin from the central nervous system is markedly impaired.2 Left atrial receptors are no longer appropriately activated by the increase in atrial pressure that follows volume expansion, and the firing rate of left atrial receptors for a given level of atrial pressure is diminished. The cause for this abnormal baroreceptor sensitivity is unknown but may be related to changes in atrial compliance as well as to disruption and fragmentation of atrial receptor endings. Similar abnormalities of arterial baroreflex function have been demonstrated in both experimental and clinical heart failure; stimulation of arterial baroreflexes in these patients may enhance rather than inhibit sympathetic activity.3 This baroreflex dysfunction greatly impairs the ability of the circulation to limit the release of vasoconstrictor neurohormones, even though the threat to cerebral perfusion may have subsided. Consequently, most patients with heart failure demonstrate an excessive activation of the sympathetic nervous system at rest or during exercise; such activity is usually assessed clinically by an increase in plasma norepinephrine.

Adaptations to prolonged adrenergic stimulation in heart failure. How does the circulation respond to this sustained overactivity of the sympathetic nervous system? Immediately after the onset of heart failure, the signs of heightened adrenergic activity are readily apparent: patients with acute heart failure have a marked tachycardia and show clinical evidence of cutaneous and renal vasoconstriction. In contrast, despite high circulating levels of catecholamines, the heart rate is usually not elevated in patients with chronic heart failure, and signs of excessive peripheral vasoconstriction can no longer be easily discerned. Such observations suggest that some adaptation to prolonged sympathetic stimulation occurs in chronic heart failure; most notably, the ability of the failing heart to respond to endogenous or exogenous catecholamines becomes markedly attenuated.4 5 This reduced responsiveness is not related to a loss of (or a defect in the) myocardial contractile elements, since the failing myocardium responds normally to digitalis and calcium, but appears to be related to a specific intracellular deficiency of cyclic AMP in the failing heart.5

The cause of this intracellular myocardial deficiency of cyclic AMP remains controversial but is most likely related to defects in the β-adrenergic pathway that have been identified in both experimental and clinical heart failure. The failing myocardium becomes depleted of catecholamines, possibly because of defects in the synthesis and uptake of norepinephrine.6 In addition, the density of β-adrenergic receptors is markedly decreased in failing human hearts, and this receptor loss is accompanied by a proportional decrease in the activity of adenylate cyclase and in agonist-stimulated muscle contraction.7 A similar reduction in β-receptor density and in catecholamine responsiveness has been observed in the peripheral lymphocytes of patients with heart failure, and this tissue has been used to assess changes in adrenergic responsiveness in this disease. In the ventricular myocardium, this receptor down-regulation appears to selectively affect the β2-receptor, such that selective β2-agonists can no longer mediate a full positive inotropic response.8 In contrast, selective β2-agonists retain full inotropic activity in patients with heart failure mediated through a β2-receptor population that is not significantly reduced; these β2-receptors may serve an important supportive role in the failing myocardium.

Does β-adrenergic receptor loss completely explain the diminished response to catecholamines seen in this
disorder? In dogs with heart failure, catecholamine resistance appears to be related to a defect in the guanine nucleotide binding proteins that couple β-receptors to adenylate cyclase (rather than to a loss of the β-receptors themselves). In patients with heart failure, the positive inotropic effects of glucagon (as well as norepinephrine) are markedly attenuated, yet this agent activates adenylate cyclase (and increases intracellular cyclic AMP) by an effect on the guanine nucleotide binding proteins that is independent of the β-receptor. Both observations suggest that a defect in receptor-cyclase coupling may contribute to the catecholamine resistance observed in some patients with heart failure. The existence and nature of a defect in receptor-cyclase coupling remains controversial, however. In lymphocytes of patients with heart failure, there is reduction in the stimulatory G protein (Gs) that promotes cyclase activation; a similar reduction in Gs (but preserved concentrations of Gi, the inhibitory component that inhibits Gs action) has been noted in the ventricular myocardium of dogs in heart failure. In contrast, studies in failing human hearts have produced conflicting results, with some studies reporting decreased concentrations of Gs and impaired Gi function and others noting normal Gi function but an increase in Gi. Further studies are clearly needed; nevertheless, the available data suggest that the Gi/Gs ratio is reduced in heart failure and may contribute to the resistance seen to endogenous and exogenous catecholamines in these patients.

What factors are responsible for these changes in the β-adrenergic pathway in congestive heart failure? These alterations appear to be the direct consequence of the marked sympathetic overactivity in these patients, since both a decrease in the density of β-receptors as well as functional uncoupling of these receptors from adenylate cyclase can result from prolonged exposure to catecholamines. In fact, the degree of “down-regulation” of myocardial β-receptors in patients with heart failure correlates closely with the concentration of norepinephrine measured in the coronary sinus; such increased exposure to norepinephrine, an agonist with selectivity for the β1-receptor, may explain why myocardial β1-receptors are selectively reduced in this disease. These defects in the receptor-cyclase complex may be restored toward normal by interventions that attenuate (or block) the activity of the sympathetic nervous system in heart failure (e.g., converting-enzyme inhibitors and β-blockers). Conversely, such abnormalities may be exacerbated after an increase in adrenergic activity, as is seen during exercise or as a result of progression of the heart failure state. This latter observation may explain why the magnitude of the reduction in β-receptor density and in the Gi/Gs ratio is related to the severity of the hemodynamic impairment in heart failure and why these measurements (as with other measures of adrenergic activity and catecholamine responsiveness) have prognostic significance.

It is noteworthy that a similar reduction in catecholamine responsiveness does not appear to be present in most noncardiac organs in congestive heart failure. Catecholamines do not become depleted in the kidney, and sympathetic neurotransmitter activity is augmented (rather than attenuated) in the peripheral blood vessels. Hence, catecholamine desensitization in response to prolonged sympathetic activity appears to occur relatively selectively in the myocardium. Nevertheless, the peripheral vasoconstrictor effects of sympathetic activation may still be limited in chronic heart failure by the release of endogenous vasodilators, most notably the release of atrial natriuretic peptide. This factor appears to be a particularly effective antagonist of adrenergic vasoconstriction in the renal circulation.

Effect of pharmacologic interventions on adrenergic responsiveness. Is this reduction in catecholamine responsiveness in the failing myocardium a beneficial or deleterious response to prolonged sympathetic overactivity in the patient with heart failure? Insofar as norepinephrine can exert direct arrhythmogenic effects and may accelerate progression of the underlying disease by a toxic action on myocardial cells, any “down-regulation” of β1-receptors may protect the failing heart from the adverse effects of this hormone. On the other hand, to the extent that the sympathetic nervous system acts to support myocardial contractility, any decrease in catecholamine responsiveness may exacerbate the hemodynamic abnormalities seen in heart failure. We can attempt to distinguish between these two possibilities by observing the hemodynamic and clinical reaction to specific therapeutic interventions.

β-Adrenergic agonists. β-Adrenergic agonists have been a notably unsuccessful approach to the treatment of heart failure. Although hemodynamic benefits may follow the administration of single doses of these drugs, long-term treatment is accompanied by a further reduction in β-receptor density and loss of initial hemodynamic improvement. Consequently, neither prenalterol nor pirbuterol have proved to be effective agents in placebo-controlled trials. It is noteworthy, however, that the abrupt withdrawal of these β-agonists after long-term treatment is not accompanied by worsening congestive heart failure; this observation sug-
suggests that the reduction in receptor density that accompanies long-term therapy with β-agonists does not adversely affect myocardial contractility. On the other hand, when attempts are made in patients with heart failure to stimulate the β-receptors but at the same time prevent the occurrence of receptor down-regulation (as with the intermittent use of intravenous dobutamine), serious arrhythmias may be observed and survival may be adversely affected.21

**Phosphodiesterase inhibitors.** In normal myocardium, phosphodiesterase inhibitors produce potent positive inotropic effects due to their ability to increase intracellular cyclic AMP by inhibiting its degradation. The ability of these drugs to enhance contractility in the failing heart is impaired, however, because basal intracellular levels of cyclic AMP are so markedly reduced.2 These agents may also exert positive inotropic effects by inhibiting the G, component of the guanine nucleotide binding proteins22; if so, the altered G/ ratio in heart failure may contribute to the reduced inotropic activity of these drugs. Despite blunting of their positive inotropic effects, the phosphodiesterase inhibitors can produce significant increases in myocardial cyclic AMP in heart failure. Unfortunately, this effect appears to be achieved without a compensatory decrease in the activity of the β-adrenergic pathway; in fact, the density of β-receptors may increase if treatment produces hemodynamic improvement. The end-result resembles the changes that occur during intermittent dobutamine; not surprisingly, these agents have also been implicated in producing arrhythmias and in adversely affecting survival in patients with chronic heart failure.

**β-Adrenergic-blocking drugs.** β-Adrenergic-blocking drugs have produced favorable effects in some patients with chronic heart failure. Hemodynamic and clinical improvement has been demonstrated in controlled clinical trials with metoprolol and bucindolol. Long-term treatment with β-blockers is associated with up-regulation of β-receptors as well as improved catecholamine responsiveness,16 but it is not clear that such changes are important in mediating the benefits of β-blockade in these patients, since the up-regulated receptors remain pharmacologically blocked and since other β-blockers (i.e., xamoterol) may produce hemodynamic and clinical benefits without producing an increase in β-receptor density. In fact, up-regulation of β-receptors may be deleterious if these receptors are not pharmacologically shielded; this may explain the hemodynamic deterioration that has been observed in patients with heart failure after the abrupt withdrawal of β-blocking drugs.

These clinical observations suggest that the selective reduction in myocardial responsiveness to catecholamines in chronic heart failure is a beneficial adaptive response that protects the failing ventricle from the deleterious effects of prolonged sympathetic stimulation. This hypothesis may explain why therapeutic interventions that increase myocardial cyclic AMP without a compensatory decrease in the activity of the β-receptor pathway may produce adverse clinical effects in these patients.

**Release of neurohormones from the kidney**

Any change in cardiac performance that threatens renal blood flow is detected by sensory receptors in the renal arterioles; this baroreceptor stimulation leads to the release of renin from the kidney, an effect that may be potentiated by the reduction in distal tubular sodium chloride transport and by the stimulation of the renal sympathetic nerves.2 The subsequent formation of angiotensin II acts on the efferent arterioles to increase glomerular hydraulic filtration pressure (and to preserve renal function), despite the reduction in renal perfusion pressure.23 Should excessive activation of the renin-angiotensin system occur and result in an increase in systemic and atrial pressures, normal operation of arterial and atrial baroreceptors would lead to the release of atrial natriuretic peptide as well as to a reduced stimulation of the renal sympathetic nerves, both of which would act to reduce renin release.

**Abnormalities of renal neurohormonal regulation in heart failure.** Unfortunately, the normal functioning of the atrial and arterial baroreceptors is markedly impaired in congestive heart failure, and thus atrial distension does not suppress renal sympathetic activity in this disorder.24 In fact, activation of the renin-angiotensin system may exacerbate this abnormality in baroreceptor function, since angiotensin II can directly attenuate baroreceptor sensitivity.2 In addition, the ability of atrial distension to stimulate the release of atrial natriuretic peptide is impaired in chronic heart failure, as is the ability of the peptide to suppress renin release.25, 26 These combined defects interfere with the capacity of the failing circulation to limit the release of renin from the kidney, particularly in the face of a persistent stimulus to such release (as a result of the low renal perfusion pressure). Consequently, most patients with congestive heart failure demonstrate an excessive activation of the renin-angiotensin system at rest or during exercise. Once formed, angiotensin II may potentiate the effects of other vasoconstrictor hormones in heart failure, specifically by facilitating the central and peripheral effects of the sympathetic nervous sys-
tem and by enhancing the release of vasopressin from the pituitary; all three systems may then act in concert to greatly exacerbate loading conditions in the failing heart.

Adaptations to activation of the renin-angiotensin system. How does the circulation respond to sustained activation of the renin-angiotensin system? In acute heart failure, activation of the renin-angiotensin system results in marked systemic vasoconstriction and sodium retention, but as the acute phase subsides, plasma renin activity declines toward normal and the vasoconstrictor effects of angiotensin II become less apparent. As in the case of catecholamines, we might suspect that prolonged exposure to angiotensin II might lead to a reduction in tissue responsiveness to the hormone, but this possibility has not been explored in either experimental or clinical heart failure. On the other hand, the response to and the degree of activation of the renin-angiotensin system may be limited in patients with heart failure by the release of specific counter-regulatory hormones, particularly the release of the vasodilators prostaglandin E₂ and atrial natriuretic peptide.

Renal hypoperfusion is a potent stimulus to the release of both renin and prostaglandins from the kidney. Consequently, patients with hyponatremic heart failure (who have the most compromised renal perfusion) show the highest plasma renin activity and highest circulating levels of prostacyclin and prostaglandin E₂. Both hormones are further released in response to diuretic therapy and to stimulation of the renal sympathetic nerves, and once formed within the kidney, both prostaglandins and angiotensin II stimulate the intrarenal release of each other. How do these hormones interact? Both prostaglandins and angiotensin II increase glomerular hydraulic filtration pressure and thus act to preserve glomerular filtration rate — the prostaglandins by a dilating action on the afferent arteriole and angiotensin II by a constricting effect on the efferent arteriole. Yet, at nearly all other sites, the actions of the renal prostaglandins oppose those of angiotensin II. Prostacyclin and prostaglandin E₂ antagonize the actions of angiotensin II on the systemic blood vessels and decrease loading conditions in the failing heart. In addition, prostaglandins may directly inhibit sodium reabsorption in the renal tubules; they may antagonize the dipsogenic effects of angiotensin II; and they may oppose the actions of angiotensin II–mediated vasopressin release in the collecting duct.

Effect of pharmacologic interventions on renal hormonal release

Cyclooxygenase inhibitors. The importance of prostaglandins in limiting the actions of angiotensin II in heart failure may explain the effects of cyclooxygenase inhibitors in these patients. Indomethacin produces notable systemic vasoconstriction and hemodynamic deterioration in patients with heart failure because of the unopposed action of angiotensin II and other systemic vasoconstrictor hormones. Cyclooxygenase inhibition results in a marked reduction in renal blood flow in low-output states, unless the actions of angiotensin II are simultaneously blocked. Indomethacin may also produce notable sodium and water retention in patients with heart failure. These adverse effects of prostaglandin inhibition are most likely to be seen in patients with hyponatremic heart failure, who have the highest circulating levels of prostaglandins and the most compromised renal perfusion.

Converting-enzyme inhibitors. Because of angiotensin's numerous interactions with other neurohormones, converting-enzyme inhibitors may produce hemodynamic and clinical benefits in patients with heart failure by a number of different mechanisms. By inhibiting the facilitatory actions of angiotensin II on norepinephrine and vasopressin release from the central nervous system, converting-enzyme inhibitors may not only reduce the effects of angiotensin II but may decrease the activity of all three vasoconstrictor systems. All vasoconstrictor hormonal activity may be further suppressed if the decline in angiotensin II acts to enhance baroreceptor sensitivity. The unopposed vasodilator actions of prostaglandins may also contribute to the hemodynamic improvement seen in patients treated with converting-enzyme inhibitors; in fact, converting-enzyme inhibition may stimulate prostaglandin synthesis directly by an action that is independent of angiotensin II. This increase in renal prostaglandins may contribute importantly to the increase in sodium and free water excretion that is seen after converting-enzyme inhibition.

Diuretics. The interaction between prostaglandins and angiotensin II in heart failure is potentiated by the administration of diuretics. Both hormones are released from the kidney during diuretic therapy but exert opposite effects on the systemic vasculature. This may explain why intravenous furosemide has been reported to cause vasodilation in some reports but vasoconstriction in others. Both hormones may also modify the natriuretic response to furosemide, which is potentiated and attenuated by converting-enzyme and cyclooxygenase inhibition, respectively.

These observations suggest that in patients with severely compromised renal perfusion, the release of prostaglandins by the kidney acts as an adaptive response that counteracts the deleterious effects of the
renin-angiotensin system. Prostaglandins may not limit the response to angiotensin II in patients with less severe heart failure, however, whose renal blood flow is only modestly reduced. Under these circumstances, atrial natriuretic peptide may function as the primary antagonist of the renin-angiotensin system (see below). As the condition of the patient deteriorates and renal blood flow is progressively reduced, however, the intrarenal actions of the atrial peptides become attenuated, and renal prostaglandins become increasingly important as an antagonist of angiotensin II action. It is noteworthy that both prostaglandins and atrial natriuretic factor oppose nearly all of the systemic and intrarenal actions of the renin-angiotensin system except angiotensin’s constrictor effects on the efferent arteriole. Such an action must be preserved if the renin-angiotensin system is to preserve glomerular filtration rate. In fact, both prostaglandins and atrial natriuretic peptide act synergistically (on the afferent and efferent arterioles, respectively) to further increase glomerular hydraulic filtration pressures, and in so doing, both hormones enhance (rather than attenuate) this important intrarenal action of angiotensin II. These observations suggest that endogenously released vasodilators do not act as nonspecific vasoconstrictor antagonists but instead may exert their effects selectively to protect both the failing heart and the hypoperfused kidney.

Release of neurohormones from the heart

Any change in cardiac performance that increases cardiac filling pressures is detected by stretch receptors in the right and left atria; this baroreceptor stimulation leads to the release of atrial natriuretic peptides from the heart, an effect that may be potentiated by activation of the sympathetic nervous system. Once released, atrial peptides exert potent direct vasodilator and natriuretic actions by virtue of their ability to increase intracellular cyclic GMP; these effects unload the distended heart and reduce its energy consumption. In addition, atrial peptides antagonize the actions of most endogenous vasoconstrictor systems. Under experimental conditions, atrial natriuretic peptide inhibits the release of norepinephrine from nerve terminals as well as the vasoconstrictor actions of norepinephrine on systemic vessels; it also enhances baroreceptor sensitivity and thereby reduces central activation of the sympathetic nervous system. Atrial peptides suppress the formation of renin and oppose the systemic vasoconstrictor actions of angiotensin II as well as angiotensin’s ability to stimulate thirst and the secretion of aldosterone and vasopressin. Atrial peptides inhibit the release of vasopressin as well as its vasoconstrictor effects on systemic vessels and its antidiuretic effects on the collecting duct. All of these observations suggest that atrial natriuretic factor functions as a versatile neurohormonal antagonist. This antagonism not only ameliorates cardiac distension but may also attenuate any adverse effect of endogenous vasoconstrictors on the kidneys. This may explain why, despite a similar reduction in cardiac output, renal function is less impaired in subjects with cardiac failure than in subjects with hypovolemia.

Abnormalities of cardiac neurohormonal regulation in heart failure. How does the circulation respond to this marked increase in the circulating level of atrial natriuretic peptide? Atrial peptides exert important natriuretic and renin-suppressive effects in acute heart failure, but as the heart failure state enters its chronic phase, the normal functioning of the atrial stretch receptors becomes impaired, and consequently, the ability of atrial distension to increase the release of natriuretic peptides is blunted. This defect may be enhanced by a decrease in myocardial catecholamine responsiveness, since β-adrenergic receptors may be an important determinant of peptide release during periods of physiologic stress. As a result, although the circulating levels of atrial natriuretic peptide are markedly increased in heart failure, the slope of the atrial pressure/response curve is shifted such that the circulating level of atrial peptide is reduced for a given level of atrial pressure. This attenuated release of atrial peptides may significantly potentiate the release and the actions of vasoconstrictor hormones in patients with chronic heart failure.

It is noteworthy that as the atrial content of natriuretic peptides becomes depleted in heart failure, natriuretic peptides are synthesized in ventricular myocytes (as well as in the atria), and this source may contribute substantially to the circulating level of atrial peptides. In fact, important baroreceptor mechanisms for hormonal release and suppression are located in the ventricles as well as the atria. The localization of natriuretic peptides in the ventricular myocardium appears to represent regression to a more primitive evolutionary state, since natriuretic peptides are normally found in the ventricles only in nonmammalian species, but disappear from the ventricles in higher forms of life unless heart failure supervenes.

Adaptation to increased circulating levels of atrial natriuretic peptide. Although atrial peptides exert potent natriuretic effects in acute heart failure, patients with chronic heart failure demonstrate marked sodium retention, despite the very high circulating levels of
atrial peptides. These observations suggest that patients with heart failure may adapt to the physiologic effects of atrial natriuretic peptide over time. As in the case of catecholamines and angiotensin II, a decrease in the density of atrial peptides receptors has been proposed to explain this hormonal resistance; the number of receptors for atrial natriuretic peptide on circulating platelets is reduced in heart failure.41 Yet, the physiologic relevance of this finding remains unclear, since it is not known whether patients with heart failure have a generalized reduction in responsiveness to the hormone.

There is growing evidence, however, that the actions of atrial peptides on the kidney are markedly attenuated in patients with chronic heart failure. The infusion of atrial natriuretic peptide produces little change in urinary sodium or water excretion in these patients and fails to suppress the secretion of renin from the juxtaglomerular cells.26 Attenuation of the renal response to atrial natriuretic peptide appears to be directly attributable to the decrease in renal blood flow seen in these patients, since responsiveness to the peptide can also be attenuated experimentally by clamping the renal artery.36 It is unknown, however, whether renal hypoperfusion impairs the effects of atrial peptides because of its hemodynamic consequences or because such hypoperfusion leads to the intrarenal release of vasoconstrictors (norepinephrine and angiotensin II), which may oppose the actions of atrial natriuretic peptide within the kidney.42 It is possible that a similar release of vasoconstrictors in the systemic circulation may oppose the extrarenal effects of the atrial peptides as well.

Effect of pharmacologic interventions on atrial peptide release. A number of pharmacologic interventions that improve cardiac performance can cause a decrease in the circulating level of atrial natriuretic peptide, presumably as a consequence of a drug-induced decline in right and left atrial pressure. This reduced release of atrial peptides is not necessarily accompanied by sodium retention, however. If therapy improves renal blood flow or decreases the activity of counteractive endogenous vasoconstrictor hormones, the reduced level of atrial peptides may be more effective in eliciting a natriuretic response than the higher levels seen before treatment. The role of atrial natriuretic peptide in mediating the changes in sodium balance that are seen after treatment with conventional vasodilator and inotropic drugs remains to be determined.

Neurohormonal interactions in heart failure: a hypothesis

Preliminary observations in experimental animal preparations (simulating heart failure in patients) suggest that the neurohormonal interactions and adaptations outlined in this review may play an important role in the sequence of events that occurs during the development of heart failure.27, 31, 43 Based on these concepts, we can formulate a hypothetical model of heart failure progression that can be critically evaluated in future studies.

Phase I. After an acute insult to the myocardium, the sympathetic nervous and the renin-angiotensin systems are activated, leading to support of systemic blood pressure and cardiac output. Atrial and arterial baroreceptors are functioning normally during this acute phase, and thus any excessive increase in arterial and atrial pressure leads to baroreflex-mediated inhibition of the sympathetic nervous system and the release of atrial natriuretic peptide. This release of atrial peptides limits the vasoconstrictor effects of the sympathetic nervous system and inhibits any adrenergically mediated activation of the renin-angiotensin system.43 As a consequence of these interactions, circulatory homeostasis may be achieved without notable changes in systemic vascular resistance or in sodium balance, unless the degree of myocardial injury is large.

Phase II. Should these hemodynamic changes persist and heart failure enter a chronic phase, specific events may occur that may alter this homeostatic balance between endogenous vasoconstrictors and vasodilators. Among the most important is the desensitization of atrial and arterial baroreceptors. The resulting baroreflex dysfunction limits the ability of an increase in atrial pressure to inhibit the activation of the sympathetic nervous system or to stimulate the release of atrial natriuretic peptide. Atrial desensitization shifts the balance of circulatory homeostatic mechanisms to a new (albeit unstable) equilibrium in which vasoconstrictor forces become increasingly dominant and vasodilator forces become progressively attenuated. This loss of normal baroreceptor function is an important event in patients with congestive heart failure and has prognostic significance.44

Phase III. With increasing dominance of the systemic vasoconstrictor factors, cardiac output declines - a decline that may be exacerbated by the progressive loss of myocardial responsiveness to endogenous catecholamines that results from alterations in the β-adrenergic pathway. Consequently, blood flow to peripheral organs (particularly to the kidney) is reduced; the fall in renal blood flow is potentiated by persistent stimulation of the renal sympathetic nerves. The decline in renal blood flow and the increase in renal adrenergic activity act to blunt the intrarenal effects of atrial natriuretic peptide. As a consequence of these events, renin is released by the
kidney, and sodium retention occurs. The resulting systemic vasoconstriction and increase in intravascular volume interact to increase loading conditions in the failing heart, which may contribute importantly to a progressive deterioration in cardiac performance.

**Phase IV.** Continued progression of the severity of heart failure leads eventually to a critical reduction in renal blood flow, which triggers the release of both renin and prostaglandins by the kidney; both hormones interact to preserve glomerular filtration rate, despite the marked decrease in renal perfusion pressure. Renal perfusion is so severely compromised at this stage that atrial natriuretic peptide may no longer be able to exert important intrarenal effects, and consequently prostaglandins may assume the role of antagonizing the intrarenal effects of systemic vasoconstrictor hormones.

Unlike the atrial peptides, however, prostaglandins increase (rather than decrease) the release of renin from the juxtaglomerular cells and thus may lead to further activation of endogenous vasoconstrictor systems. The reduction in renal blood flow to the critical levels seen in phase IV represents another milestone in the progression of chronic heart failure; this may explain why hypotension — the clinical marker of severe renal hypoperfusion — has prognostic significance in patients with this disorder.45

During the final stages of heart failure, activation of endogenous vasoconstrictor systems is likely to produce deleterious effects on the energy balance of the failing heart. Down-regulation of myocardial hormone receptors may reduce the adverse mechanical, electrophysiologic, and metabolic effects of this prolonged increase in neurohormonal activity.

**Therapeutic implications**

Can the interactions and adaptations described in this review be successfully modified to improve the clinical outcome of patients with heart failure? Three therapeutic approaches seem promising.

**Baroreceptor sensitization.** Since baroreflex dysfunction plays a central role in the activation of vasoconstrictor systems in heart failure, any therapeutic intervention that acts to restore baroreceptor responsiveness should lead to a reduction in neurohormonal activity. Two commonly used interventions may act in part by this mechanism: digitalis and the converting-enzyme inhibitors. Digitalis may improve baroreflex function by a direct stimulatory effect on atrial and arterial receptors.2,37 Converting-enzyme inhibitors, on the other hand, appear to have the same effect because of their ability to decrease the inhibitory effects of angiotensin II on baroreflex sensitivity.46 Both interventions may enhance baroreceptor responsiveness indirectly by improving cardiac performance. As a consequence of these actions, both digitalis and the converting-enzyme inhibitors may reduce endogenous vasoconstrictor activity in chronic heart failure; this effect may contribute importantly to the hemodynamic and clinical improvement that follows treatment with these drugs.

**Potentiation of endogenous vasodilator mechanisms.** Since both prostaglandins and atrial natriuretic peptide act to minimize the effects of systemic vasoconstrictor activity, therapeutic interventions that enhance the release or potentiate the effects of these endogenous vasodilators may produce symptomatic benefits. By increasing the renal production of prostaglandins, potent diuretics (such as furosemide) can antagonize the sodium retention seen in heart failure. Unfortunately, both diuretics and the prostaglandins may activate vasoconstrictor hormones and thus may be limited in their capacity to produce clinical improvement. Recent studies have attempted to increase vasodilator and natriuretic activity in heart failure by the direct infusion of atrial natriuretic factor; in addition, new agents are being developed to inhibit the metabolic breakdown of the peptide. Unfortunately, the activity of atrial natriuretic factor may be limited in heart failure not by a deficiency in peptide formation or release but by a reduction in renal blood flow. Hence, the natriuretic effects of endogenous atrial peptide may be most effectively enhanced by interventions that selectively increase renal blood flow (e.g., fenoldopam) or that inhibit the intrarenal effects of endogenous vasoconstrictors (e.g., converting-enzyme inhibitors).

**Antagonism of endogenous vasoconstrictor hormones.** The most direct approach to treating the excessive vasoconstriction seen in heart failure is to administer systemic vasodilator drugs. Direct-acting agents produce marked short-term hemodynamic and clinical benefits in these patients, but tolerance develops to many of these drugs during long-term treatment. Two mechanisms appear to underlie the development of tolerance to vasodilator therapy — a reduction in end-organ responsiveness to the drug and antagonism of drug action by the release of vasoconstrictor neurohormones.47 Both mechanisms are strikingly similar to those utilized by the circulation to limit the response to endogenous neurohormonal systems. Tolerance rarely develops to drugs that interfere with endogenous neurohormonal vasoconstrictor activity (e.g., converting-enzyme inhibitors and β-blockers); this may contribute to the high frequency of favorable responses seen in patients with chronic heart failure treated with these drugs.
Conclusion

If vasoconstrictor neurohormones play a detrimental role in the development of congestive heart failure, how can the circulation respond to limit the consequences of this excessive neurohormonal activity? The baroreflex mechanisms that are normally used to control the release of neurohormones are impaired in heart failure. As a result, the circulation must rely on secondary mechanisms — the release of endogenous vasodilators and an alteration in tissue hormonal responsiveness — to maintain homeostasis. Unlike baroreceptor stimulation (which causes a generalized decrease in neurohormonal activity), these secondary mechanisms appear to selectively limit the effects of the vasoconstrictor systems in specific organs. Unfortunately, these adaptive responses become progressively limited in their counterregulatory capacity as heart failure progresses, and thus the vasoconstrictor forces play an increasingly dominant role in the late stages of the disease. This shift in the balance between endogenous vasoconstrictor and vasodilator hormones appears to be an important determinant of the clinical outcome of these patients. It is likely that most therapeutic interventions in heart failure produce hemodynamic and clinical benefits at least in part by restoring this neurohormonal balance — by interfering with the actions of the vasoconstrictor systems or by potentiating the effects of endogenous vasodilators. Further attempts to modulate the neurohormonal interactions in chronic heart failure will undoubtedly lead to new approaches to the treatment of these severely ill patients.

References

Neurohormonal interactions and adaptations in congestive heart failure.

M Packer

Circulation. 1988;77:721-730
doi: 10.1161/01.CIR.77.4.721

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1988 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/77/4/721.citation