Clinical Aspects of Sympathetic Activation and Parasympathetic Withdrawal in Heart Failure

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Proposed reflex mechanisms for generalized neurohumoral activation in heart failure include decreased input from inhibitory baroreceptor afferent vessels and increased input from excitatory afferent vessels arising from arterial chemoreceptors, skeletal muscle metaboreceptors or the lungs. Not all subjects with left ventricular dysfunction have increased sympathetic nerve activity, but the magnitude of sympathoneural activation appears to independently predict survival. This association suggests both a causative mechanism linking sympathetic activation with adverse outcome and a therapeutic opportunity to improve the prognosis of such patients by inhibiting central sympathetic outflow.

Generalized sympathetic activation is not unique to heart failure, and its functional consequences appear to be both organ- and condition-specific. Sympathetic activation is present in other disorders such as mild hypertension, cirrhosis and aging that do not share the dim prognosis of congestive heart failure. The adverse effects of adrenergic activation on the diseased myocardium may be a function of the magnitude and time course of sympathetic activation in response to ventricular dysfunction, for cardiac-specific and generalization of activation of the sympathetic nervous system and for the stimulation or suppression of countervailing mechanisms capable of resisting its adverse effects is fundamental to the development of better therapies for congestive heart failure.

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Figure 1. Assessment of sympathetic and parasympathetic function in humans. Sympathetic function: arterial (A) or venous (V) plasma norepinephrine (PNE) and epinephrine (PE) concentrations (upper left); sympathetic nerve traffic to muscle (MSNA) or skin (lower left); total body norepinephrine \(\text{[3H]}\) spillover or regional norepinephrine spillover across the heart (A = aorta or arterial; CN = coronary sinus) (upper right), kidney (lower right) or leg (lower left); spectral analysis of heart rate variability (SA-HRV) (upper right). Parasympathetic function (upper right): bradycardic response to phenylephrine (baroreflex sensitivity; BRS); spectral analysis of heart rate variability (SA-HRV).

**Sympathetic and Parasympathetic Nervous Systems in Heart Failure**

**Sympathetic Nervous System**

Assessment of sympathetic function in humans. Efferent postganglionic sympathetic nerve traffic may be assessed directly in humans by inserting microelectrodes into superficial nerves innervating muscle or skin (9) or indirectly by recording potential effector responses to the neurally released norepinephrine, such as heart rate, blood pressure or regional blood flow and vascular resistance, or by quantitating venous or arterial catecholamine concentrations (10,11), norepinephrine spillover into plasma (12) or heart rate variability (13-15) (Fig. 1).

Each of these methods assesses different aspects of sympathetic function and has its advantages and limitations. The latter should be considered carefully when interpreting information acquired with these techniques. Any potential link between sympathetic activity and hemodynamics will be particularly tenuous in heart failure as a result of altered receptor responsiveness, cardiac and vascular structural alterations and concurrent activation of other vasoactive systems.

Norepinephrine concentrations can be determined simply and relatively inexpensively, but the values obtained have several shortcomings that limit their usefulness as measures of sympathetic nerve traffic in humans (10,11). Only a small fraction of neurally released norepinephrine appears in plasma, and that which is measured does not reflect neurotransmitter release, but rather the balance between norepinephrine spillover into plasma and its clearance (12,16). Values are weighted toward regional (for example, forearm) neurotransmitter spillover upstream from the sampling location (Fig. 1) (10,12). Because the sympathetic nervous system is capable of differential outflow, it should not be assumed that plasma norepinephrine concentrations measured from the antecubital vein provide an accurate estimate of sympathetic traffic to other hemodynamically important vascular beds (10-12). The issue of clearance is perhaps most important in the context of heart failure. Because norepinephrine clearance is a function of regional blood flow and inversely related to cardiac output (12), the interpretation of any increase in plasma norepinephrine concentrations in heart failure will be ambiguous. Does it represent increased norepinephrine release or markedly impaired clearance in patients with poor left ventricular function?

To address this question, Esler et al. (12) developed a radiotracer method of assessing total body norepinephrine spillover as an indirect but close approximation of neural norepinephrine release in conscious humans. By adapting this technique to estimate regional (that is, organ-specific) norepinephrine spillover, these investigators (12,17) were also able to determine whether sympathetic activation in heart failure is generalized or directed specifically toward the heart, kidney or other vascular beds.

The major strength of the microneurographic technique is that it permits direct quantitation of sympathetic nerve firing and its reflex control (9,18). Recordings are limited to superficial nerves, innervating muscular or cutaneous vascular beds. Because these nerves have different firing characteristics under basal conditions and in response to different stimuli, muscle sympathetic nerve burst frequency (influenced primarily by changes in baroreceptor afferent discharge) need not represent firing rates in other sympathetic nerves (9,10). It is therefore worth noting that Wallin et al. (19) recently obtained evidence in normal subjects at rest that interindividual differences in muscle sympathetic nerve discharge and cardiac norepinephrine spillover are proportional to each other. Their findings are consistent with the concept that a common mechanism influences the strength of sympathetic discharge to the heart and skeletal muscle.

The possibility that spectral analysis of heart rate variability might provide a noninvasive estimate of sympathetic drive to the heart has stimulated considerable interest (Fig. 1). However, there is as yet no clear consensus as to the optimal representation of cardiac sympathetic nerve traffic...
SYMPATHETIC ACTIVATION IN HEART FAILURE

by this method (14,15,20–22). Current analytic algorithms are limited by the need for heart rate variation for their application; such variation is lost in severe decompensated heart failure where sympathetic drive is highest, yet heart rate is fixed.

Evidence for generalized sympathoneural activation in heart failure. Plasma norepinephrine concentrations sampled during supine rest are elevated in patients with asymptomatic left ventricular dysfunction and increase further with the progression to overt congestive heart failure (13,23). At this later stage, total body norepinephrine spillover is on average double that of control subjects and norepinephrine clearance reduced by about a third (Fig. 2) (17).

Are these changes due to generalized increases in central sympathetic outflow or selective activation of sympathetic discharge to specific vascular beds? Certainly, the presentation of the patient in severe decompensated congestive heart failure suggests generalized sympathetic activation: tachycardia, tachypnea, diaphoresis, pallor, agitation and renal sodium retention. Biochemical and microneurographic evidence of increased sympathetic outflow to the kidneys, heart, skeletal muscle and adrenal glands confirms this clinical impression.

In normal subjects, approximately 25% of total body norepinephrine spillover arises from the kidney and about 2% from the heart (12). These two organs contribute approximately 60% of the increase in the total body rate of appearance of norepinephrine in plasma in congestive heart failure: renal norepinephrine spillover increases 2- to 3-fold and cardiac norepinephrine spillover >10-fold (Fig. 2) (12,17). Norepinephrine spillover into the leg circulation also doubles (24). Because the radiotracer kinetic technique quantitates the rate at which neuronally released norepinephrine appears in plasma rather than sympathetic nerve traffic or the rate of release of the neurotransmitter from sympathetic nerve endings, some of the increased spillover could be attributed to enhanced presynaptic modulation of neurotransmitter release by epinephrine (25) or angiotensin (26) or by decreased norepinephrine extraction within the neurovascular junction (12,27). This ambiguity was resolved by investigators (28,29) who obtained direct microneurographic evidence that efferent muscle sympathetic burst frequency is increased in congestive heart failure (Fig. 3) and correlates positively with plasma norepinephrine concentrations.

Epinephrine concentrations are increased in severe heart failure, denoting heightened adrenal sympathetic nerve activity and medullary catecholamine release (31). Increased plasma concentrations provide the substrate for its neuronal uptake and incorporation into sympathetic vesicles along with norepinephrine (30). Esler et al. (30) have documented cardiac epinephrine spillover, averaging 2 ng/min or 2% of the corresponding norepinephrine spillover, in untreated congestive heart failure (but not in healthy volunteers at rest) and higher levels of neuronal epinephrine release from their gut, liver, lungs and kidneys. Approximately 25% of their total plasma epinephrine appearance rate was due to regional overflows from these organs. This observation demonstrates that epinephrine can assume a neurotransmitter role in heart failure, in addition to its traditional action as a circulating hormone (31). This transformation may have important functional consequences in this condition: as a humoral agent, the predominant effect of epinephrine is postjunctionally mediated vasodilation, whereas as a cotransmitter, its predominant effect appears to be vasoconstriction mediated by stimulation of presynaptic beta-adrrenergic receptors that act to facilitate norepinephrine release (25).

Parasympathetic Nervous System

The parasympathetic control of heart rate may be assessed by quantitating the reflex bradycardic response to the pressor stimulus of phenylephrine (13) or by analysis of heart rate and its variability in the time (13) or frequency (14) domain (Fig. 1). Each of these methods confirms the initial demonstration by Eckberg et al. (32) of impaired parasympathetic control of heart rate in heart failure (20–22,33). Although low heart rate variability appears to be an independent risk factor for mortality after myocardial infarction (34), the prognostic importance of this abnormality in patients with heart failure has not been clearly established.

Similarly, the pathophysiologic implications of defective parasympathetic control of heart rate have not been fully investigated. It has been proposed that alterations in the parasympathetic component of heart rate variability spectra merely reflect greater sympathoexcitation in such patients.
Mechanisms for Generalized Sympathetic Activation and Parasympathetic Withdrawal in Heart Failure

Generalized sympathetic activation and parasympathetic withdrawal in heart failure have been attributed to alterations in inhibitory and excitatory influences on brainstem vasomotor neurons. These mechanisms are illustrated in Figure 5. The contribution of impaired inhibitory baroreceptor reflex mechanisms to these abnormalities of autonomic reflex control has been reviewed in depth by Thames et al. (36). Afferent inputs from carotid sinus and aortic arch "arterial high pressure" and the cardiopulmonary "low pressure" mechanoreceptors are the principal inhibitory influences on sympathetic outflow; discharge from arterial chemoreceptors and muscle "metaboreceptors" are the major excitatory inputs. The vagal limb of the baroreceptor heart rate reflex is also responsive to arterial baroreceptor afferent input. The integrated response to these competing influences in normal subjects at rest may be characterized as a relatively low sympathetic discharge and relatively high heart rate variability. Compensatory vagal and sympatho-

![Figure 3](image-url) Representative tracings of the electrocardiograms (upper tracings) and mean voltage neurograms of muscle sympathetic nerve activity (lower tracings) in three normal subjects (left) and three patients with heart failure (right). Adapted, with permission of the American Heart Association, from Leimbach et al. (28).

![Figure 4](image-url) Mean ± SE values for total body and regional norepinephrine spillover into plasma in 20 patients with congestive heart failure, 50 patients with essential hypertension and 35 patients with cirrhosis. Significant increases from reference values obtained from 28 healthy subjects (100%) are indicated by *p < 0.05 and **p < 0.01. Reproduced, with permission of the American Heart Association, from Esler et al. (12).
neural responses to acute perturbations in blood pressure are appropriate and brisk (Fig. 5, top panel).

Asymptomatic left ventricular dysfunction and its progression to overt congestive heart failure disturb this balance (Fig. 5, bottom panel). As the principal stimuli to arterial baroreceptor afferent discharge (that is, systolic blood pressure, pulse pressure and the rate of rise of blood pressure) become blunted and as the sensitivity of arterial, atrial and ventricular mechanoreceptors to stretch diminishes, inhibitory input from arterial and cardiopulmonary receptors will decrease (2,37-39). In decompensated heart failure, excitatory input, ordinarily quiescent, may arise from arterial chemoreceptors, skeletal muscle metaboreceptors and the lungs (37). Central regulation of parasympathetic outflow is also attenuated (40). The net response to this shift in the balance between inhibitory and excitatory afferent input includes a generalized increase in basal sympathetic outflow, parasympathetic withdrawal, blunted reflex parasympathetic and sympathetic control of heart rate and impairment of the reflex sympathetic regulation of vascular resistance (2,18,37).

Figure 5. Mechanisms for generalized sympathetic activation and parasympathetic withdrawal in heart failure. Under normal conditions (top panel) inhibitory (−) inputs from arterial and cardiopulmonary baroreceptor afferent nerves are the principal influence on sympathetic outflow. Parasympathetic control of heart rate is also under potent arterial baroreflex control. Efferent sympathetic traffic and arterial catecholamines are low and heart rate variability high. As heart failure progresses (bottom panel) inhibitory input from arterial and cardiopulmonary receptors decreases and excitatory (+) input increases. The net response to this altered balance includes a generalized increase in sympathetic nerve traffic, blunted parasympathetic and sympathetic control of heart rate and impairment of the reflex sympathetic regulation of vascular resistance. Anterior wall ischemia has additional excitatory effects on efferent sympathetic nerve traffic. See text for details. Ach = acetylcholine; CNS = central nervous system; E = epinephrine; Na+ = sodium; NE = norepinephrine.

Heterogeneity of Sympathetic Activation in Heart Failure

Nonetheless, many individuals with left ventricular dysfunction lack evidence for sympathetic activation (1,4,33,41). Viquerat et al. (42) documented arterial norepinephrine concentrations within their normal range in about one-third of their subjects with heart failure. The initial Studies of Left Ventricular Dysfunction (SOLVD) report (23) on baseline neurohormonal data described venous plasma norepinephrine concentrations below the median value for control subjects in ~25% of patients recruited to the asymptomatic arm and in about 15% of patients recruited to the treatment
Table 1. Some Potential Explanations of Variations in Sympathetic Nerve Activity in Patients With Heart Failure

<table>
<thead>
<tr>
<th>Patient age</th>
<th>Stage of disease</th>
<th>Severity of disease</th>
<th>Therapeutic interventions</th>
<th>Coexisting disorders</th>
<th>Sympathoinhibitory</th>
<th>Sympathoexcitatory</th>
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<tr>
<td></td>
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<td></td>
<td>Coexisting disorders: ischaemic heart disease, sleep-related breathing disorders</td>
<td>Sympathoexcitatory: sodium restriction, diuretic drugs, nonspecific vasodilators</td>
<td>Sympathoexcitatory: digitalis glycosides, beta-adrenergic antagonists, converting enzyme inhibition, physical conditioning</td>
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The majority of the young subjects with asymptomatic dilated cardiomyopathy that we have studied have muscle sympathetic nerve activity and plasma norepinephrine concentrations similar to those of age-matched normal volunteers (41).

Why is there such intersubject variation in sympathetic nerve activity in heart failure? Several factors could contribute to these variations in sympathetic traffic in patients with left ventricular dysfunction. Some of the more obvious examples appear in Table 1.

**Stage and severity of disease.** Abboud et al. (43) described three phases of autonomic disturbance in heart failure. In the early stage, decreased cardiac output activates the sympathetic and renin-angiotensin systems reflexively. In the middle stage, compensatory hypervolemia and cardiac enlargement stimulate baroreceptor afferent vessels, causing reflex suppression or normalization of sympathetic nerve activity. In the final stage, the restraining influence of cardiac and arterial baroreceptor afferent vessels on the sympathetic nervous system and the renin-angiotensin systems is impaired, resulting in generalized neurohumoral activation (Fig. 5).

Ferguson et al. (29) have quantitated disease severity with the use of balloon-tipped thermocution catheters in their study patients. They identified reduced cardiac performance and increased cardiac filling pressures as characteristics of patients with increased muscle sympathetic nerve activity. In contrast to Viquerat et al. (42), who did not uncover any convincing relation between arterial norepinephrine concentrations and the hemodynamic status of their patients, sympathetic burst frequency in the study of Ferguson et al. (29) was inversely related to left ventricular stroke work index and stroke volume index and directly related to pulmonary artery mean and diastolic pressures. The latter observation is particularly intriguing because it raises the possibility that mechanisms capable of sensing the severity of heart failure are preserved at this stage of the disorder (albeit responding paradoxically) and are potentially amenable to modulation.

**Coexisting disorders: ischaemic heart disease.** Myocardial infarction or ischemia can influence sympathetic outflow acutely or chronically through reflexive mechanisms, independent of any coexisting left ventricular dysfunction (39,44). Different sympathetic nerve activity could increase or decrease, depending on the nature and anatomic location of this insult. Prior myocardial infarction will interrupt the course of mechanoreceptor input to vagal afferents with inhibitory effects on sympathetic outflow (44,45) (Fig. 5).

Although not depicted in Figure 5, anterior wall ischemia elicits reflex sympathoexcitation by stimulating sympathetic afferent nerves (39,46–49) and, if arterial blood pressure decreases during this intervention, by unloading sinoaortic baroreceptors (50), whereas ischemia involving the infero-posterior wall of the left ventricle evokes a depressor reflex (39,47,48,51,52). Thus, it may not be appropriate to present data on ischemic and idiopathic dilated cardiomyopathy as if they arose from a common mechanism. Much of the evidence for increased sympathetic nerve traffic to muscle in congestive heart failure arises from studies of older patients with ischemic heart disease (28,29). Contrary evidence from young subjects with compensated idiopathic dilated cardiomyopathy (33,41) suggests that the cause of heart failure may also influence the time course or magnitude of sympathetic activation in patients with left ventricular dysfunction and, possibly, its adverse effects on the failing heart. For example, Bristow et al. (53) have described important functional differences in components of the beta-adrenergic receptor-0 protein-adenylate cyclase complex between ischemic and idiopathic dilated cardiomyopathy.

**Coexisting disorders: obstructive sleep apnea.** Sympathetic withdrawal during sleep typically results in a decrease in blood pressure of 20% to 25% from average waking levels (54–56). Heart failure is associated with briefer sleep duration, interrupted sleep and attenuation of the awake-asleep difference in blood pressure (57,58). Many patients with congestive heart failure also suffer from sleep-related breathing disorders, including obstructive sleep apnea (57). Apnea, hypoxia and hypercapnia, which develop recurrently in obstructive sleep apnea, can cause profound increases in muscle sympathetic nerve activity (59–61). Such disturbances in breathing during sleep will adversely alter afterload in the failing heart by generating extreme negative swings in intrathoracic pressure (57) and by preventing the normal nocturnal reductions in sympathetic drive and blood pressure (56). These nocturnal abnormalities may stimulate the development of left ventricular hypertrophy (62). Observations from our own (41) and other (63) laboratories raise the possibility that apneic episodes during sleep trigger a sustained non-baroreflex-mediated increase in central sympathetic outflow that carries over into the daytime when subjects are awake and breathing spontaneously. Unremitting exposure by day and at night to such sympathoexcitation could contribute synergistically to the development or aggravation of congestive heart failure, but would not be responsive to conventional pharmacologic treatment.
Adverse Effects of Adrenergic Activation on the Diseased Myocardium and Peripheral Circulation

Any supportive effect of this generalized increase in central sympathetic outflow on the heart and peripheral circulation in congestive failure is eventually superseded by a number of functional organ-specific consequences with potentially adverse implications (Table 2, Fig. 5).

Myocardium. Daly and Sole (7) reviewed the time course of changes in myocardial sympathetic innervation and catecholamine content with the initiation and progression of experimental heart failure. In the hamster model of dilated cardiomyopathy, early increases in cardiac norepinephrine turnover, tyrosine hydroxylase and dopamine beta-hydroxylase activity and cardiac dopamine stores are followed by depletion of myocardial norepinephrine content and destruction of sympathetic nerve terminals. Other contributors to this symposium have discussed in detail the adverse effects of adrenergic drive on cardiac structure and function. These include downregulation of myocardial beta,-adrenergic receptor number, decreased beta-adrenergic responsiveness to endogenous or exogenous agonists (64), trophic and toxic effects on cardiac myocytes (65), exacerbation of arrhythmias predisposing to sudden death and impairment of ventricular diastolic and systolic function (Table 1). Daly and Sole (7) placed particular emphasis on the topography of altered myocardial norepinephrine content and sympathetic innervation in experimental heart failure; these investigators postulated that nonuniform distribution of these derangements would disturb the temporal coordination of mechanical contraction and relaxation, alter the dispersion of refractoriness and the duration and configuration of the cardiac action potential and consequently exacerbate any underlying mechanical or electrophysiologic dysfunction in such patients.

Peripheral circulation. Excessive sympathetic drive to the periphery can exacerbate the hemodynamic derange-

ments of heart failure by increasing both preload and afterload (Fig. 5). For example, elevated effluent renal sympathetic nerve activity will exacerbate congestion by activating the renin-angiotensin system, stimulating tubular reabsorption of sodium and water, decreasing renal blood flow and glomerular filtration rate and blunting the renal responsiveness to atrial natriuretic peptide (2,66,67). Augmented adrenergic drive to muscle will sustain afterload at inappropriately high levels, whereas secondary hypertrophy of smooth muscle in resistance vessels will amplify neurogenic vasoconstrictor responses to sympathetic input (7,68,69). Reductions in muscle blood flow by these mechanisms below levels required to meet local metabolic demands may increase sympathetic outflow reflexively, particularly during exercise, by stimulating excitatory metaboreceptor afferents (Fig. 5) and possibly contribute to the impaired functional capacity of such patients (2,69).

In summary, there are many cardiac and peripheral mechanisms by which sympathetic activation could adversely influence prognosis in heart failure. However, any attempt to establish a causal relation between sympathetic activation and mortality on this basis must contend with the awkward observation that sympathetic activation is not unique to heart failure, but is present in other disorders that do not share its poor prognosis.

Other Conditions of Generalized Sympathetic Activation

Sympathetic excitation and parasympathetic withdrawal are not specific to heart failure: There is biochemical or microneurographic evidence, or both, of increased sympathetic outflow to the kidneys, heart, skeletal muscle and adrenal glands in young subjects with borderline and mild essential hypertension (12,70-73), in patients with cirrhosis and ascites (12,74), in subjects with obstructive sleep apnea even when studied while awake (63) and in healthy elderly persons (70,75) (Fig. 6). Hypertension and aging are also characterized by impaired parasympathetic control of heart rate (76). Cardiac and renal norepinephrine spillover are 1.5 to 3-fold higher in young subjects with hypertension than in age-matched normotensive control subjects (12) (Fig. 4). Renal norepinephrine spillover is increased threefold in patients with cirrhosis, whereas cardiac norepinephrine spillover is five to seven times higher than in control subjects (12) (Fig. 4). Indeed, subjects with cirrhosis and ascites display a profile of generalized neurohumoral activation not unlike that of the patient with heart failure (74,77): Atrial natriuretic factor is increased (78), the heart rate is rapid, and varies little, and increases in muscle sympathetic nerve activity correlate positively with elevated venous norepinephrine and epinephrine concentrations and with plasma renin activity (74).

The reflex and central mechanisms responsible for increased sympathetic outflow and parasympathetic with-

| Table 2. Potential Adverse Effects of Sympathetic Activation in Heart Failure |
|------------------------------|---------------------------------|
| Cardiac                     | Myocyte hypertrophy             |
|                              | and fibrosis                    |
|                              | Nonuniform depletion of norepinephrine stores |
|                              | Nonuniform destruction of sympathetic innervation |
|                              | Arrhythmias                     |
|                              | Impaired diastolic function      |
|                              | Impaired systolic function       |
| Renal                       | Increased tubular reabsorption of sodium |
|                              | Activation of renin-angiotensin system |
|                              | Increased renal vascular resistance |
|                              | Attenuated response to natriuretic factors |
| Vascular                    | Neurogenic vasoconstriction      |
|                              | Vascular hypertrophy             |
Figure 6. Increased muscle sympathetic nerve activity (MSNA) is not specific to heart failure. Reproductions of 40-s segments on the electrocardiogram (ECG) and mean voltage neurograms of muscle sympathetic nerve activity in four of our subjects with other conditions of sympathetic activation: a healthy elderly (>70 years) subject (upper left) and three young (<40 years) subjects with, respectively, mild hypertension, sleep apnea (studied while awake) and cirrhosis with ascites.

Organ-specific responses. Three important cardiac-specific factors are worth noting. First, and perhaps most fundamental, is that regardless of the etiology of ventricular dysfunction and in contrast to these other conditions, both the primary stimulus to and the target of increased cardiac sympathetic drive is a diseased myocardium. Second, the increase in cardiac norepinephrine spillover relative to that in other vascular beds appears to be greater in congestive failure than in cirrhosis or primary hypertension (12) (Fig. 4). Reasons for this observation have not been fully elucidated, but could include more intense neural drive to the heart, greater withdrawal of the inhibitory influence of acetylcholine (35) and augmentation of the facilitatory influence of epinephrine (3,30,31,70) on cardiac norepinephrine release and possibly (this issue remains controversial) decreased neuronal norepinephrine uptake (12,27,86,87). Third, the effects of prolonged intense adrenergic stimulation on myocardial norepinephrine stores and sympathetic nerve terminals are heterogeneous (7). The diseased heart, with its altered geometry and patchy distribution of fibrosis and necrosis, will be particularly sensitive to any nonuniform destruction of sympathetic or parasympathetic innervation. Such pathologic inhomogeneity may have profound mechanical, electrophysiologic and prognostic implications for patients with heart failure (7).

The differing vascular responses to increased muscle sympathetic activity in congestive heart failure, mild hypertension and cirrhosis, described earlier, reinforce the concept that condition- or organ-specific factors may also amplify or oppose neuroeffector transduction of this increased adrenergic drive. Neurogenic vasoconstriction can be amplified geometrically by structural changes in resistance vessels (68) and opposed by potent endothelially mediated vasodilation (88). The latter mechanism is impaired in both hypertension (89) and heart failure (90,91) and may be augmented in cirrhosis (92). On the basis of these observations, one could propose that interventions that improve endothelially mediated vasodilation might benefit patients with congestive heart failure.
heart failure by countering the vasoconstrictor response to their increased sympathetic drive.

The response of the kidneys to increased renal sympathetic nerve activity (Fig. 5) appears to be more homogeneous (66). We have documented an inverse relationship between muscle sympathetic nerve activity and both the fractional excretion of sodium (74) and the natriuretic response to a 2-h infusion of atrial natriuretic peptide (67) in patients with cirrhosis and ascites. These derangements in renal function and responsiveness to atrial natriuretic peptide appear common to both cirrhosis and congestive heart failure (67,93-95). However, increased renal sympathetic nerve activity alone cannot account for these changes: renal norepinephrine spillover is increased in young subjects with essential hypertension (12) (Fig. 4), but they do not suffer from edema or ascites as a consequence.

In summary, neither the adverse effects detailed in Table 2 nor the poor prognosis of patients with heart failure can be attributed exclusively to increased central sympathetic outflow. The functional consequences of sympathetic activation appear to be condition- and organ-specific. Of these, the adverse effects of intense cardiac sympathetic activation on a diseased myocardium may be most important, and interventions that preferentially attenuate adrenergic drive to the heart may be of particular benefit. Thus far, the hypothesis that inhibiting efferent sympathetic nerve activity will improve the prognosis of patients with congestive heart failure has not been tested directly.

Modulation of Sympathetic Activity in Heart Failure

The only drugs shown to reduce the incidence of death in congestive heart failure thus far are converting enzyme inhibitors and nonspecific vasodilators (96-99), but the mortality rate in treated patients remains disappointingly high. In those with severe heart failure enrolled in the Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS) (97), the 6-month mortality rate was 48% in the placebo-treated group and 29% in the enalapril-treated group (97). The impact of converting enzyme inhibition on survival of patients with less severe expression of their congestive heart failure has been modest: in the SOLVD Treatment Study (98), the mortality rate was 39.7% in the conventionally treated group and 35.2% in the enalapril-treated group; that is, mortality benefit was provided to only 4.5/100 patients after 41 months of treatment, and in the SOLVD Prevention Trial (100), converting enzyme inhibition attenuated the progression of asymptomatic left ventricular dysfunction to congestive heart failure but had no significant effect on mortality. Although the positive effects of long-term converting enzyme inhibition on survival may be greatest in subjects with highest norepinephrine concentrations (3,5), the SOLVD neurohumoral substudy data presented by Benedict et al. (101) elsewhere in this symposium do not reveal any short-term or long-term effect of angiotensin-converting enzyme inhibition with enalapril on mean values for plasma norepinephrine concentrations. Thus, it is not clear whether sympathoinhibition is one of the mechanisms by which converting enzyme inhibition interrupts disease progression or improves the prognosis of asymptomatic or symptomatic patients.

The SOLVD, CONSENSUS and other recent trials have had a major positive impact on our understanding and management of congestive heart failure. These trials have also emphasized the need to develop additional interventions to improve the poor prognosis, even after treatment, of these patients. Packer (8) recently summarized the limitations of early attempts to antagonize the peripheral effects of neurolymphatically released norepinephrine. The alpha-1 antagonist prazosin, for example, has no demonstrable effect on mortality (96) and, until recently clinicians have been reluctant to prescribe beta-adrenergic antagonist drugs for such patients out of concern that they will further impair contractile function. The principal drawback of this adrenergic antagonist approach is its limited objective, which is to shield the heart, kidney and peripheral vasculature from the potentially harmful effects of neurally released norepinephrine rather than to attenuate sympathetic outflow to these organs. It is difficult to maintain a consistently effective shield with long-term treatment and, perhaps more important, the neuroeffector response to other neurotransmitters released by noradrenergic nerves innervating the heart will not be blocked by these antagonists. One such neurotransmitter is the neuropeptide Y, a potent inhibitor of efferent vagal neurotransmission (102) and a coronary and peripheral vasconstrictor with a more sustained duration of action than that of norepinephrine (103).

To attain additional benefit, it may be necessary to attenuate adrenergic drive directly by developing and applying interventions that attenuate central sympathetic outflow or norepinephrine synthesis (104) or release. Neural norepinephrine release may be reduced by several distinct mechanisms: by augmentation of inhibitory baroreceptor input, suppression of excitatory influences, inhibition of sympathetic traffic centrally and presynaptic inhibition of neurotransmitter release (Fig. 7).

Obviously, the first approach would not be feasible if reflex sympathetic activation due to baroreceptor dysfunction were an inevitable and irreversible consequence of heart failure. However, evidence from several sources indicates that the restraining influence of inhibitory arterial and cardiopulmonary mechanoreceptor afferents on sympathetic outflow is suppressed, rather than irreversibly damaged in congestive heart failure. For example, cardiac unloading with lower body negative pressure can evoke a reflex sympathoinhibitory response in some patients with congestive failure; this paradoxical observation has been attributed to a decrease in left ventricular end-diastolic volume and wall stress, a resultant increase in left ventricular fractional shortening and an inotropically mediated increase in ventric-
Figure 7. Attenuation of sympathetic outflow in heart failure. Potential mechanisms include: 1) augmenting inhibitory baroreceptor input by sensitization or stimulation of arterial and cardiopulmonary baroreceptor afferents; 2) decreasing excitatory afferent input from arterial chemoreceptors, skeletal muscle or lungs; 3) central inhibition of sympathetic outflow; 4) inhibition of ganglionic neurotransmission; and 5) prejunctional inhibition of norepinephrine or epinephrine release. In addition, the neuroeffector response to increased adrenergic drive can be blocked by alpha- and beta-adrenoceptor antagonists. Abbreviations as in Figure 5.

The arterial baroreflex control of heart rate also appears to be functionally rather than structurally impaired because it can be restored by treatment of decompensated heart failure by bed rest, salt restriction, diuretic drugs and vasodilators (such treatment may also blunt excitatory influences on sympathetic outflow) (106), by reversal of canine heart failure (107) or by heart transplantation in humans (108). Nonpharmacologic approaches should also prove effective: the benefits of long-term exercise training of selected subjects with congestive heart failure include reduction of total body norepinephrine spillover and normalization of the parasympathetic and sympathetic control of heart rate variability (109). Atrial natriuretic peptide, which inhibits sympathetic outflow in normal subjects through either a central or a ganglionic mechanism (110), also has inhibitory effects on norepinephrine and epinephrine release that are not attenuated in experimental canine heart failure (111); its potential sympathoinhibitory actions in congestive heart failure in humans remain to be explored.

Digitalis glycosides, angiotensin-converting enzyme inhibitors and beta-adrenoceptor antagonists may exert part of their beneficial actions in congestive heart failure through similar mechanisms. Activation of Na⁺, K⁺-ATPase at the neuronal membrane can cause acute peripheral baroreceptor resetting (112). Digitalis is said to cause a reflex sympathoinhibition that has been attributed to sensitization of cardiopulmonary mechanoreceptors (113) (this observation has been disputed [114]) and in some subjects with congestive heart failure, digitalis normalizes the reflex vasodilator response to cardiac unloading (105). In experimental heart failure, ouabain also appears to sensitize arterial baroreceptor nerve endings (38). The effects of long-term treatment with digitalis glycosides on sympathetic nerve traffic have not been reported.

Angiotensin-converting enzyme inhibitors (and angiotensin II antagonists) improve the parasympathetic control of heart rate (115) and should antagonize the facilitative effects of angiotensin II on central sympathetic outflow and inhibit norepinephrine release at the neuroeffector junction, where it is subject to modulation by prejunctional angiotensin II receptors (26). Despite these potential sympathoinhibitory mechanisms, it has been difficult to demonstrate any short-term or long-term effect of angiotensin-converting enzyme inhibition with enalapril on mean values for plasma norepinephrine concentrations (101) or any inhibitory effect of acute administration of captopril or enalaprilat on total body norepinephrine spillover in subjects with congestive heart failure (116). Thus, the mechanism or mechanisms responsible for the beneficial effect of long-term converting enzyme inhibition on survival remain open to investigation.

The role of beta-adrenergic receptor antagonists in dilated cardiomypathy is discussed elsewhere in this symposium (117). In addition to shielding the heart against the potentially toxic effect of increases in neurally released or circulating catecholamines (Table 2), this class of drugs may dampen central sympathetic outflow (118). An additional benefit of beta-blockade may be that proposed by Daly and Sole (7): Beta-adrenergic blockade should improve the temporal coordination of excitation and contraction between innervated and denervated segments by restoring the uniformity of neural stimulation of the heart.

Conclusions

The time course over which organ-specific or generalized sympathetic activity begins to increase after the development of left ventricular dysfunction has not been characterized. Because the primary derangement in subjects with such dysfunction is cardiac, sympathetic drive to the heart may be increased early in the course of this disorder before there is any obvious increase in muscle sympathetic burst frequency, total body norepinephrine spillover or plasma norepinephrine concentration. Activation of adrenergic
drive to the diseased myocardium may be the causative mechanism linking sympathetic activation to adverse outcome, and interventions that selectively modulate sympathetic outflow to the heart may exert the greatest benefit, particularly if administered early before the development of generalized sympathetic activation. In this respect, the recent observation by Bristow et al. (119) that beta-adrenergic blockade with carvedilol selectively attenuates adrenergic drive to the failing heart is particularly interesting and could serve as the basis for future tests of this concept.

Activation of the sympathetic nervous system appears to independently predict adverse outcome in patients with left ventricular dysfunction, but increased central sympathetic outflow is not specific for this condition. It is present in other disorders that do not share the dim prognosis of patients with congestive heart failure. The adverse effects of adrenergic activation on the diseased myocardium may be a function of the magnitude and time course of the increase in cardiac sympathetic nerve activity, the mechanical and electrophysiological consequences of nonuniform abnormalities of cardiac innervation in the failing heart and the absence of specific protective countervailing forces present in other conditions also characterized by adrenergic activation. Furthermore, not all patients with left ventricular dysfunction have increased sympathetic nerve activity. Greater understanding of the mechanisms responsible for the heterogeneity of sympathetic activation in response to ventricular dysfunction, for cardiac-specific and generalized activation of the sympathetic nervous system and for the stimulation or suppression of compensatory mechanisms capable of resisting its adverse effects is fundamental to the development of better therapies for congestive heart failure.

References


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