Disturbances in cardiovascular neural regulation, influencing both disease course and survival, progress as heart failure worsens. Heart failure due to left ventricular systolic dysfunction has long been considered a state of generalized sympathetic activation, itself a reflex response to alterations in cardiac and peripheral hemodynamics that is initially appropriate, but ultimately pathological. Because arterial baroreceptor reflex vagal control of heart rate is impaired early in heart failure, a parallel reduction in its reflex buffering of sympathetic outflow has been assumed. However, it is now recognized that: 1) the time course and magnitude of sympathetic activation are target organ–specific, not generalized, and independent of ventricular systolic function; and 2) human heart failure is characterized by rapidly responsive arterial baroreflex regulation of muscle sympathetic nerve activity (MSNA), attenuated cardiopulmonary reflex modulation of MSNA, a cardiac sympathoexcitatory reflex related to increased cardiopulmonary filling pressure, and by individual variation in nonbaroreflex-mediated sympathoexcitatory mechanisms, including coexisting sleep apnea, myocardial ischemia, obesity, and reflexes from exercising muscle. Thus, sympathetic activation in the setting of impaired systolic function reflects the net balance and interaction between appropriate reflex compensatory responses to impaired systolic function and excitatory stimuli that elicit adrenergic responses in excess of homeostatic requirements. Recent observations have been incorporated into an updated model of cardiovascular neural regulation in chronic heart failure due to ventricular systolic dysfunction, with implications for the clinical evaluation of patients, application of current treatment, and development of new therapies. (J Am Coll Cardiol 2009;54:375–85) © 2009 by the American College of Cardiology Foundation

Sympathetic nervous system activation in chronic human heart failure (HF) has implications for both disease progression and survival (1,2). The prevailing model, as illustrated in the Journal in 1993 (3), assumes that this begins when left ventricular systolic dysfunction elicits reflexively a generalized increase in sympathetic outflow directed at all vascular beds. Its subsequent augmentation plus concurrent diminution of reflex vagal heart rate (HR) modulation are attributed primarily to dysfunction of 2 sets of sympathoinhibitory reflexes engaged by stimulation of mechanoreceptor afferents: 1) arterial baroreceptors, which stretch less as systolic and pulse pressures diminish; and 2) cardiopulmonary baroreceptor reflexes, which may be damaged by prior myocardial infarction, stimulated less as inotropy diminishes, or altered by ventricular dilation (3).

However, recent investigations have identified afferent, central neural, and efferent sympathoexcitatory mechanisms not addressed by this model, plus a selective, rather than generalized, alteration in autonomic regulation early in HF, with attenuation of heart rate variability (HRV) (4) and a selective elevation of cardiac norepinephrine spillover (CNES) (5) preceding rises in total body norepinephrine spillover (TNES), renal norepinephrine spillover (RNES), and muscle sympathetic nerve activity (MSNA). Also, the model does not inform why MSNA burst frequency (or HR-corrected burst incidence) in many patients with profound ventricular systolic dysfunction is similar to that of age- or sex-matched healthy subjects (5,6). Often, sympathetic excitation is present only when other clinical characteristics such as impaired exercise capacity (6,7), sleep-related breathing disorders (Fig. 1) (8), or ischemic heart disease (9) coexist. Importantly, at left ventricular ejection fractions below 35%, this no longer correlates with nerve firing rate (6–8,10). These observations, which argue against ventricular systolic dysfunction per se as the princi-
pal stimulus to sympathetic activation, have implications for the clinical evaluation of patients, application of current treatment, and development of new therapies.

The purpose of this review is 2-fold: 1) to propose a contemporary model that integrates newer knowledge concerning mechanisms responsible for temporal, regional, and individual heterogeneity of sympathetic activation in human HF due to left ventricular systolic dysfunction; and 2) to discuss the implications of this model for the investigation and management of the HF patient, and for future clinical trial design and recruitment. Several of these concepts also might apply to patients with HF, but relatively preserved systolic function, in whom the sympathetic nervous system would not appear to be as active as in systolic dysfunction, and HRV not as depressed (11–14).

Stimuli to Sympathetic Activation and Augmented Neural Norepinephrine (NE) Release

Our present understanding of the diversity of sympathoexcitatory mechanisms engaged by HF arises primarily from the application of NE kinetic methodology (which quantifies total body, cardiac, renal, brain, or forearm NE spillover into plasma) (2,15,16) and from microneurographic recordings obtained from sympathetic fibers innervating muscle or cutaneous vascular beds (17,18). By contrast, HRV reflects the fidelity with which post-junctional sinoatrial receptors respond to oscillations in sympathetic and vagal nerve discharge, rather than the absolute magnitude of neurotransmitter released (19). Mechanical stretch of the sinoatrial node, for example by high right atrial pressure, will also decrease HRV (20). In conscious paced sheep, directly recorded cardiac sympathetic nerve firing rate increases markedly as HF develops, without affecting low-frequency HR spectral power (21). Consequently, in human HF, HRV analysis provides neither direct nor definitive mechanistic information concerning cardiac autonomic regulation.

Afferent Mechanisms

Arterial baroreceptor reflexes. Arterial baroreflex-mediated HR responses to drug-induced blood pressure (BP) changes are clearly diminished in human HF (22–24). Such impairment also foreshortens survival (25). However, efferent vagal and sympathetic responses to arterial baroreceptor stimulation are not invariably concordant: with both healthy aging (26) and primary hypertension (27) arterial baroreflex regulation of HR is attenuated, yet reflex modulation of MSNA is preserved. In an ovine model of pacing-induced HF in which cardiac sympathetic nerve activity (CSNA) was recorded directly, burst frequency was increased, and the baroreceptor regulation of HR profoundly impaired, likely as a result of both altered pre-synaptic vagal ganglionic neurotransmission (28) and blunted sinoatrial responsiveness to the neurotransmitter NE (29), whereas the reflex control of CSNA did not differ from normal sheep (21).

In the paced-canine model, electrical stimulation of the carotid sinus nerve to increase baroreceptor afferent input elicits a significant fall in plasma NE concentration (30), yet sinoaortic baroreceptor denervation has no effect on the time course of changes in hemodynamics and plasma NE concentrations as HF develops (31). Therefore, in this preparation, the set point for sympathetic vasoconstrictor tone is increased centrally, rather than as a consequence of diminished baroreceptor stimulation, resetting, or reflex gain; the functional sympathomodulatory capacity of this reflex is preserved.

In chronic human HF, the presence of a significant inverse relationship between stroke work index and MSNA (32) suggests that the arterial baroreflex retains the capacity to modify efferent sympathetic outflow about a higher set point in response to changes in cardiac output or BP. Attenuation of efferent MSNA responses to pharmacological baroreceptor perturbation has not been observed consistently (22,33,34), but there are several limitations to the interpretation of sympathetic responses to vasoactive drugs. These infusions will alter cardiac loading conditions, with
unpredictable effects on low-pressure mechanoreceptor nerve firing. Induced BP changes are of relatively slow onset, whereas arterial baroreceptors transduce best high-frequency oscillations (35). Nitric oxide donors such as nitroprusside may inhibit directly sympathetic neurotransmission (36). Importantly, because HR responses to these induced changes in BP are attenuated, the potential magnitude of concurrent variations in HR-dependent variables, such as sympathetic burst frequency, will be constrained as a direct consequence. Conversely, if MSNA responses expressed as absolute or relative increase in discharge frequency (bursts/min) (23) are recalculated as HR-independent variables (e.g., change in bursts/100 cardiac cycles), values for arterial-MSNA baroreflex gain do not differ appreciably between HF and healthy control subjects (18).

Independent, but complementary, methods provide additional evidence that arterial baroreflex control of sympathetic nerve activity is relatively intact in HF. Key observations include: 1) preserved MSNA pulse-synchronicity (37); 2) immediate reflex augmentation of MSNA burst amplitude and duration in response to the long diastolic period following a ventricular ectopic complex (18,38), with subsequent post-extrasystolic suppression of MSNA proportional to the diastolic pressure overshoot (39); 3) MSNA tracks reflexively pulsus alternans (37); 4) reflex reductions in MSNA when diastolic pressure rises modestly upon left or biventricular pacing (40); 5) similar inhibition of MSNA by aortic and ventricular mechanoreceptor stimulation in subjects with normal and impaired ventricular systolic function (41); 6) similar reflex increases in TNES in patients and control subjects with nitroprusside infusion to achieve comparable baroreceptor unloading (42); and 7) similar gain, in subjects with and without HF, of the cross-spectral transfer function between BP (stimulus) and MSNA (response) across all frequency bands (35).

By contrast, renal studies evaluating responses to hypotension induced by nitroprusside revealed an 85% increase in RNES in healthy controls, but no net change in HF, albeit from a nearly 3-fold higher baseline (16). What is uncertain is whether this finding represents a ceiling effect (i.e., RNES cannot increase further, as suggested by ovine renal sympathetic nerve data [43]), or the integrated response to combined arterial and cardiopulmonary receptor unloading. In another study, low-dose nitroglycerin reduced pulmonary pressures selectively without altering RNES in either HF or healthy subjects, whereas a higher hypertensive dose elicited a significant reduction only in those with systolic dysfunction (44).

Cardiopulmonary reflexes. Cardiopulmonary baroreceptor reflexes elicit sympathoinhibition when stimulated by increased filling pressures, chamber volume, or inotropy, and sympathoexcitation when unloaded, for example, by lower body negative pressure (LBNP). Dunlap et al. (33), who infused phenylephrine at the peak depressor response to nitroprusside, observed similar gains in the arterial baroreflex control of MSNA in healthy and HF subjects, whereas reflex responses to stimuli that raised and lowered cardiac filling pressure without affecting systemic pressure were attenuated. These investigators concluded that the fundamental regulatory defect in human HF was impairment of cardiopulmonary (not arterial) baroreflex-mediated inhibition of sympathetic discharge (33,34).

However, increased cardiac filling pressure appears to stimulate in addition an ordinarily quiescent “low-pressure” excitatory reflex, arising from myelinated cardiac vagal (45,46) and/or cardiac sympathetic afferent nerves (47), that excites specifically cardiac adrenergic discharge. In normal dogs, a cardiac sympathetic afferent reflex can be potentiated by acute volume expansion (48,49), and in a pacing-induced canine HF model, Zucker’s group has demonstrated also sensitization of cardiac sympathetic afferents responsive to chemical stimuli, and amplification of the central gain of the cardiac sympathetic afferent reflex through an angiotensin II–mediated mechanism (48,50). Several observations in human HF are consistent with this concept: 1) the selective increase in cardiac norepinephrine spillover (CNES) in mild HF (5); 2) forearm vasoconstriction in response to saline infusion in mild HF, but not in control subjects (51); 3) significant positive relationships between left ventricular filling pressures or pulmonary artery pressures, on the one hand, and either CNES or MSNA (15,32); 4) attenuation, in patients with impaired systolic function, of the reflex increase in CNES elicited by a hypertensive infusion of nitroprusside (42); 5) paradoxical reductions in CNES when nitroprusside lowered both atrial and arterial pressure of patients with severe secondary pulmonary hypertension (52); 6) in HF patients, a paradoxical fall in CNES (but no change in TNES) when atrial and ventricular transmural pressure were reduced acutely by continuous positive airway pressure (CPAP) (53), or when atrial pressure was reduced selectively by nonhypotensive LBNP (54); and 7) absence of any significant reflex increase in CNES (present when ventricular systolic function is normal) in response to hypotensive LBNP (54).

Pulmonary reflexes. The classical model (3) discounts the entrainment of MSNA by breathing in HF. Although this is preserved (35,55), neural silence with inspiration requires higher tidal volumes than in healthy subjects (55). Patients with low tidal volume and high respiratory frequency exhibit a high burst incidence (56). Brief periods of apnea elicit marked increases in MSNA (38). Rapidly adapting vagal sensory receptors located in the airways respond to lung inflation and deflation, and also to increases in left atrial pressure and extravascular pulmonary fluid volume (57). Peripheral chemoreceptor reflexes. The contribution of arterial chemoreceptors to sympathetic activation in experimental HF models has been reviewed in detail (58). In healthy humans, brief exposure to hypoxia elicits sustained increases in MSNA, persisting long after reoxygenation (59). Augmented peripheral chemoreceptor sensitivity to hypoxia, present in perhaps 40% of treated HF patients (60,61), is associated with several autonomic disturbances
with prognostic implications. These include higher plasma NE, impaired arterial baroreflex control of HR, but loss of HRV, very low-frequency oscillations in breathing during both sleep and wakefulness, enhanced ventilatory responses to exercise, and an increased propensity to nonsustained ventricular tachycardia (60–62).

Di Vanna et al. (63) reported increased MSNA responses to hypoxic (peripheral) and hypercapneic (central) chemoreceptor stimulation in the New York Heart Association (NYHA) functional class II to III HF patients compared with controls. However, in 2 studies, inhalation of 100% O\textsubscript{2} (to suppress peripheral chemoreceptor input) had no effect on mean MSNA values, suggesting that chemoreceptor-mediated sympathoexcitation may not be as prevalent in the broader HF population (64,65). These experiments were conducted in resting subjects; this mechanism is augmented by exercise (66).

**Sleep-related breathing disorders.** During nonrapid eye movement sleep, MSNA, BP, and HR normally fall (67,68), whereas vagal activity and the arterial baroreflex control of HR increase (69,70). The briefer and interrupted sleep characteristic of systolic dysfunction (71) increases the integrated (24 h) adrenergic burden upon the failing heart and circulation.

Sleep–related breathing disorders, potent stimuli to acute and sustained sympathoexcitation, are also absent from the current model (3), yet sleep apnea is present in the majority of symptomatic patients. Approximately one-third exhibit obstructive sleep apnea (OSA), and one-third central sleep apnea (CSA) (72,73). By deactivating pulmonary stretch receptors and stimulating peripheral and central chemoreceptors by hypoxia and hypercapnia, each pause in breathing during sleep elicits profound increases in MSNA (74). This sympathetic excitation is independent of and in addition to any reflex responses to mechanoreceptor unloading resulting from pump failure or systemic hypotension. Inspiratory efforts against a collapsed upper airway, as occurs in OSA will generate extreme negative swings in intrathoracic pressure (i.e., an abrupt increase in left ventricular afterload). Because the failing heart is more sensitive to increases in afterload, obstruction provokes an acute fall in stroke volume and diastolic BP (75). This unloading of arterial baroreceptors elicits a reflex increase in MSNA of greater intensity in HF than in subjects with normal ventricular function, who are better able to maintain stable systemic BP in the face of this mechanical stimulus (41). Arousal, which terminates an apneic event, is accompanied by a further rise in central sympathetic outflow and BP plus vagal withdrawal (74,76). These cycles of apnea and arousal expose the failing heart and peripheral circulation each night to repetitive surges of central sympathetic outflow and NE release far greater than required for circulatory homeostasis.

Sympathoexcitation carries over into wakefulness (8,74). Grassi et al. (77) identified higher daytime MSNA in HF patients with obesity or hypertension, but did not report the prevalence of sleep apnea in these high-risk populations (72,78). Compared with HF patients without sleep apnea, in those with coexisting OSA, MSNA was 11 bursts/100 heart beats higher (Fig. 1); in a subset studied in a randomized controlled trial, MSNA fell by 12 bursts/100 heart beats after OSA was abolished (8,79). These data provide important evidence in human HF for convergence, on central sympathetic neurons, of input from 2 independent sympathoexcitatory influences that increase MSNA through a process of additive summation (80) (Fig. 2). This additional OSA-mediated sympathoexcitation could accelerate HF mortality rates (73).

Compared with HF patients otherwise matched, but without sleep-related breathing disorders, those with CSA have greater nocturnal urinary NE excretion and plasma NE concentrations while awake (81). MSNA during wakefulness is also increased (8). Mansfield et al. (82) attributed higher rates of CNES and TNES in HF patients with CSA to greater hemodynamic decompensation, but because subjects were dichotomized using a very low apnea–hypopnea index (>5 events/h vs. >15 events/h), a direct comparison with microneurographic findings is uninformative.

**Myocardial ischemia and infarction.** Myocardial ischemia and prior infarction have the potential to exert an acute or chronic effect on sympathetic outflow that is both additive to and independent of the magnitude of systolic dysfunction (83,84). If cardiac output, and hence BP, fell as a consequence of ischemia, unloading of sinoaortic baroreceptors should elicit a further reflexive increase. When studied 6 months after myocardial infarction, patients with relatively preserved ejection fraction (mean 52%) had higher MSNA burst incidence than coronary artery disease patients or healthy control subjects (85). Ischemic patients exhibit higher plasma NE concentrations than dilated cardiomyopathy patients (86). Grassi et al. (87) reported virtually identical values for MSNA in these 2 populations; in a comparison involving younger patients (by 5 to 10 years) with lower mean ejection fractions (22% vs. 33%), MSNA was significantly higher in those with ischemic cardiomyopathy (9).

**Reflexes arising from skeletal muscle.** Several neural mechanisms, arising from skeletal muscle, have the capacity to increase the set point for central sympathetic outflow in HF at rest or during exercise. These include: 1) a sympathoexcitatory reflex, stimulated by adenosine, with the participation of angiotensin acting via the AT\textsubscript{1} receptor as a neural intermediary (88,89); 2) increases in local venous pressure (90); 3) activation, in HF, of a muscle mechanoreflex (91) elicited by passive exercise; and 4) a muscle metaboreflex elicited by both isotonic and isometric handgrip (6,89). The latter is activated at a lower workload in HF than in age-matched healthy control subjects, and intensifies in those in whom predicted exercise VO\textsubscript{2} peak falls below 56% (6). An important consequence is that values for
plasma NE acquired at rest do not predict the magnitude of sympathetic activation during exercise. **Excitatory reflexes arising from the kidney.** In patients with chronic renal failure, an afferent signal from the uremic kidney stimulates MSNA (92). This reflex may become functionally important in patients with renal insufficiency or right HF.

**Central Integration and Interactions**

The initial concept that the central nervous system simply integrates information from these several afferent inputs, and then transmits output passively, has been superseded by evidence demonstrating its active contribution to the autonomic disturbances of HF (93). In experimental HF models, Zucker’s group has documented central augmentation of cardiac sympathetic afferent reflex regulation of renal sympathetic nerve activity, arising from increases in central angiotensin II and in rostral ventral lateral medulla (VLM) angiotensin AT1 receptor and NAD(P)H oxidase subunit gene expression, with consequent generation of reactive oxygen species, plus a decrease in local synthesis of neuronal nitric oxide (which exerts sympathoinhibitory actions at several brain sites) (94,95). The hypotheses proposed by these investigators are: 1) the set point for sympathetic outflow is elevated as a consequence of central enhancement of cardiac reflex gain, rather than loss of arterial baroreceptor input (31,96); and 2) increased central angiotensin II initiates this positive feedback loop by generating reactive oxygen species that alter neuronal excitability by modulating ion channel function (95).

Sympathetically mediated increases in renal renin release could amplify such positive feedback by increasing plasma angiotensin II, which interacts with the arterial baroreflex at several sites within and without the blood–brain barrier to inhibit vagal discharge and increase central sympathetic outflow (97–99). In dogs without HF, peripheral infusion of angiotensin II attenuates the hypotensive response to chronic carotid baroreceptor stimulation (100); its chronic central infusion potentiates the cardiac sympathetic afferent reflex (101).

Aldosterone of adrenal origin has been reported to stimulate the brain renin–angiotensin system by increasing paraventricular (hypothalamic) nucleus angiotensin AT1 receptor mRNA, protein, and NAD(P)H oxidase subunit gene expression and plasma NE concentrations (102). In rats with experimental HF, intracerebroventricular infusion
of spironolactone reduced renal sympathetic nerve firing and augmented its arterial baroreflex regulation (103). A recently described central cytokine-mediated sympathoexcitatory pathway can also be attenuated by mineralocorticoid receptor blockade (104).

In human HF, Esler’s group has demonstrated significant increases in internal jugular venous spillover of metabolites of NE and epinephrine (15,105), with a positive correlation between brain NE turnover and cardiac NE spillover (105). Aggarwal et al. (106) detected 4-fold higher suprabulbar subcortical turnover of NE and a tendency to lower cortical NE turnover in treated patients, compared with control subjects, and a significant correlation between subcortical NE turnover and TNES in HF. These authors propose that activation of noradrenergic neurons projecting rostrally from the brain stem mediates this sympathoexcitation. Could chronic sleep disruption exacerbate this centrally mediated increase in adrenergic drive?

In a recent report, 47% of 60 consecutive patients with treated NYHA functional class I to III HF exhibited increased CO₂ sensitivity (61). HF progression augments ventilatory and sympathetic neural responses to central chemoreceptor stimulation by hypercapnia (61,63,107,108). Within-breath sympathoinhibition is attenuated (108). An increase in the gain of the central chemoreflex response to CO₂ could perpetuate the cyclical breathing oscillations characteristic of CSA (109); during apneas, sympathoexcitation is exaggerated (108). MSNA remains high after waking (8,81).

**Efferent Mechanisms**

In the hamster dilated cardiomyopathy model, early increases in cardiac tyrosine hydroxylase and dopamine beta-hydroxylase activity are followed by NE depletion and destruction of sympathetic nerve terminals (110). In the paced-rabbit model, ventricular systolic dysfunction and increases in synaptic and plasma NE precede reversible reductions in cardiac NE uptake and transporter density and subsequent reductions in myocardial beta-receptor density (111). In patients with NYHA functional class II to IV HF, both NE uptake-1 carrier density (112) and the fractional transmyocardial extraction of NE fall by 30% (5); consequently NE spillover into the coronary sinus rises disproportionately to neuronal release (113). Abnormal cardiac NE uptake can be improved with chronic beta-adrenoceptor blockade (114).

Neural release of NE and acetylcholine may be modified by agents acting on pre-junctional receptors. Alpha₂-adrenoceptor agonists, such as clonidine, inhibit NE release, with left ventricular (115), but not forearm, alpha₂-adrenoceptors (116) retaining this property in human HF. In experimental preparations, stimulation of pre-junctional AT₁ receptors facilitates sympathetic ganglionic neurotransmission, and neural and adrenal catecholamine release (97), but it has proven difficult to replicate this action in humans (117). NE release and adrenal catecholamine secretion also can be facilitated if pre-junctional beta₂-adrenoceptors are stimulated by epinephrine (118). Circulating activating antibodies against beta₁- and/or beta₂-adrenoceptors, present in some patients with dilated cardiomyopathy, can mimic sympathoexcititation (119). In a retrospective genetic-association study, Small et al. (120) described a 6-fold greater risk of HF in African-American subjects homozygous for the hypofunctioning pre-junctional alpha₂C Del322-325 polymorphism, and a 10-fold increase in those also homozygous for the hyperfunctional post-junctional beta₁ Arg329 receptor, but provided no direct functional data concerning cardiac NE release or post-junctional adrenergic responsiveness in this population. By contrast, in healthy subjects, variability in the NE response to the selective alpha₂-agonist dexmedetomidine was unaffected by genotype (121), and in a cohort of patients with severe HF, Kaye et al. (122) detected no relationship between the alpha₂C Del322-325 or beta₂-adrenoceptor polymorphism and cardiac NE release. The relationship between NE release and HR was steeper in beta₂-adrenoceptor Arg 16 homozygotes, implying greater post-junctional responsiveness.

Muscarinic receptors on adrenergic nerve endings also attenuate NE release when stimulated by acetylcholine (123,124). Its intracoronary infusion in subjects with ventricular systolic dysfunction decreased cardiac NE spillover, an effect not seen in control subjects with normal left ventricular systolic function. Receptor blockade with atropine had no effect in the HF group, but increased CNES in control subjects (125). Conversely, NE and Neuropeptide Y released from sympathetic nerve endings inhibit acetylcholine release by stimulating vagal pre-junctional receptors (126,127).

**A New Model**

Thus, sympathetic activation in the setting of impaired systolic function reflects the net balance and interaction between appropriate reflex compensatory responses to impaired systolic function and excitatory stimuli that elicit adrenergic responses in excess of homeostatic requirements, pivoting upon a higher set point of central neural origin. Figure 3 integrates these concepts into a model in which: 1) arterial baroreceptor reflex regulation of HR by the vagus nerve is impaired; 2) arterial baroreflex regulation of MSNA is rapidly responsive to changes in diastolic BP, retains the capacity to modulate generalized sympathoexcitation (42), and responds to the perception of diminished pulsatile arterial mechanoreceptor stretch by adjusting, as required, a centrally established set point for sympathetic outflow; 3) pulmonary mechanoreceptor-mediated entrainment of sympathoexcitatory outflow persists; 4) the conventional inhibitory ventricular baroreceptor reflex control of MSNA is blunted; but 5) elevated filling pressures can increase CNES early in the course of HF by stimulating a cardiac-specific sympathoexcitatory reflex.
The time course and magnitude of hemodynamic compromise affecting these several baroreflex-mediated mechanisms could account for the considerable variation between patients with left ventricular systolic dysfunction with respect to the prevailing level of sympathetic activity and its organ-specific nature. If the progression to symptomatic HF is slow or if relatively normal stroke volume and BP can be maintained by increases in left ventricular end-diastolic volume, rather than cardiac filling pressure, increasing ventricular mechanoreceptor firing could maintain reflexively plasma NE concentrations, MSNA, TNES, and RNES within the normal range. Increasing cardiac filling pressure to maintain stroke volume and systemic arterial pressure would have several consequences: activation of the cardiac sympathetic reflex, itself causing a reduction in arterial baroreflex vagal HR modulation (47), plus an atrial stretch-induced decrease in high-frequency HRV (20). Afferent, central, and ganglionic (28) inhibition of parasympathetic tone would attenuate the restraining influence of acetylcholine on cardiac NE release. Importantly, these are the first abnormalities detected in human HF and those linked most closely to prognosis.

Chronically, increased cardiac NE release initiates sino-atrial beta1-adrenoceptor down-regulation and altered cardiac beta-adrenoceptor signal transduction, destruction of sympathetic terminals, and attenuation of NE reuptake (128). Should stroke volume alone not support systemic BP, HR will rise, through arterial baroreflex-mediated vagal withdrawal, and cardiac NE release will increase further; over time, arterial baroreceptor unloading by declining systemic pressure will elicit generalized neurohumoral activation.

If the initial insult, such as an infarct, causes a sudden drop in cardiac output and BP, arterial baroreceptor unload-
ing will immediately activate the sympathetic and renin-angiotensin systems and decrease vagal tone reflexively to compensate. Concurrent augmentation of afferent mechanoreceptor or chemoreceptor nerve traffic, and peripheral angiotensin, aldosterone, or cytokines could activate central sympathoexcitatory pathways (93). Pulmonary congestion, altered lung mechanics, and increased work of breathing will increase further central sympathetic outflow (56).

Importantly, in a significant number of patients, additional nonbaroreflex-mediated excitatory stimuli, including coexisting sleep apnea, myocardial ischemia, and obesity, reflexes from exercising muscle, and/or alterations in central integration or efferent autonomic regulatory systems may supervene to elevate the set point for central sympathetic outflow or neurotransmitter release at rest, during exercise, or during sleep in excess of levels required to maintain hemodynamic stability, with important pathological consequences. Inflammation may induce an additional nonneuronal source of catecholamines (129).

Contemporary disease-based HF therapies such as beta-adrenoceptor antagonists, angiotensin-converting enzyme inhibitors, angiotensin receptor antagonists, and digitalis counter, directly or indirectly, the adverse effects of excessive cardiac and systemic sympathetic activity and augment vagal tone to improve symptoms, prognosis, or both. Beta-adrenoceptor antagonists address the earliest autonomic disturbances identified in HF by countering the adverse effects of cardiac sympathetic overactivity, by augmenting tonic and reflex HR modulation (130,131), and by antagonizing beta-adrenergic–mediated stimulation of renin release, thereby lowering circulating concentrations of angiotensin II (132). In some, contemporary therapy appears sufficient to restore sympathetic activity toward values obtained in healthy control subjects, whereas in others, particularly if nonbaroreflex stimuli to sympathetic nervous system activation and increased NE release are not targeted, high sympathoadrenal activity may persist.

Figure 3 suggests several strategies, acting upon afferent, central, or efferent components of these baroreceptor- and nonbaroreceptor-mediated mechanisms that might be tested in the future. Data from several small trials suggest that relief of congestion by diuresis-diminishing plasma NE (133) could also reduce the risk of death (134). In early mild HF with elevated left atrial pressure, diuretics, natriuretic peptides (135), or ultrafiltration (136), administered judiciously to avoid systemic hypotension, baroreceptor unloading, and reflexive increases in sympathetic activity or renin release (137), might prevent or delay reflexively increased CNES (54). A functionally important central angiotensin II-AT₁ receptor-aldosterone-reactive oxygen species excitatory pathway provides new opportunities to modulate (avoiding ablation [138]) sympathetic outflow. If present, adjunctive therapy directed at myocardial ischemia, deconditioning, obesity, uremia, or sleep apnea, that concurrently diminishes sympathetic tone or augments tonic or reflex vagal HR modulation could be considered (10,79,139,140).

Contemporary drug management of HF has no impact on OSA. By contrast, the sympathoinhibitory and vagotonic effects of CPAP during sleep (140,141) alone may be sufficient to benefit patients with coexisting OSA. In randomized trials lasting 1 month involving HF patients with OSA, nightly CPAP abolished apnea and improved ejection fraction (142) and lowered systolic BP, HR, and MSNA after waking (79,142). The latter finding is consistent with elimination of an independent stimulus to sympathetic excitation (Fig. 2). Abolition of apneas by CPAP may also reduce mortality (73).

In a 3-month randomized trial involving HF patients with CSA, nightly CPAP suppressed apnea and reduced nocturnal urinary NE by 41%, to values in HF patients without CSA. CPAP also reduced plasma NE during wakefulness by 22% (81). In a a post hoc efficacy analysis of data from a long-term trial involving 258 HF patients with CSA, CPAP improved significantly transplant-free survival of those in whom apnea was suppressed below the inclusion criterion of 15 apneic or hypopneic events/h (143).

Therapies such as beta-adrenergic antagonism and angiotensin-converting enzyme inhibition that diminish noradrenergic drive, augment the vagal modulation of HR, or both, prolong and improve the quality of life. However, patients without evidence of residual sympathetic activation while receiving contemporary therapy may not benefit and might be harmed by adding sympathoinhibitory or sympatholytic drugs (138). Without detailed clinical evaluation, and hypothesis-driven trials, one cannot be certain that the magnitude of adrenergic activation in a particular HF patient is best managed with proven sympathomodulatory therapies alone, or whether there is an opportunity for additional intervention, directed at patient-specific sympathoexcitatory mechanisms such as elevated left atrial pressure, myocardial ischemia, deconditioning, or sleep apnea.

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