Activation of the sympathetic nervous system (SNS) and inhibition of the parasympathetic system have long been recognized as manifestations of the clinical syndrome of heart failure (HF), presumably as a consequence of hemodynamic changes associated with the alteration in cardiac function. The possibility that this autonomic imbalance contributes directly to the progression of the disease process was postulated in the 1990s with evidence that inhibition of the sympathetic drive through β-receptor blockade favorably affected the course of the disease. Numerous drugs and devices that interfere with this activation pattern have since been studied as therapeutic means to alter the natural history of HF. The purpose of the present review is to re-explore the basic cellular mechanisms of enhanced sympathetic activity, to examine the data supporting a contributory role of these autonomic functional alterations on the course of HF, to evaluate the evidence for clinical effectiveness of these pharmacological and device interventions critically, and to consider the future role of autonomic nervous system modifiers in the management of this increasingly common and lethal disease process.

The cardiac autonomic nervous system consists of 2 branches, the sympathetic and the parasympathetic systems, that work in a delicately tuned, yet opposing fashion in the heart. These branches differ in their neurotransmitters and exert stimulatory or inhibitory effects on target tissue via adrenergic and muscarinic receptors. Both sympathetic and the parasympathetic branches of the autonomic nervous system are composed of afferent and efferent, as well as interneuronal fibers. Sympathetic innervation originates mainly in the right and left stellate ganglia. These fibers travel along the epicardial vascular structures of the heart into the underlying myocardium and end as sympathetic nerve terminals reaching the myocardiun. The optimal counteraction of the excessive sympathetic activity is still unclear. A profound decrease in adrenergic support with excessive blockade of the sympathetic nervous system may result in adverse outcomes in clinical HF. In this review, we analyze the data supporting a contributory role of the autonomic functional alterations on the course of HF, the techniques used to assess autonomic nervous system activity, the evidence for clinical effectiveness of pharmacological and device interventions, and the potential future role of autonomic nervous system modifiers in the management of this syndrome. (Circ Res. 2014;114:1815-1826.)

Key Words: autonomic nervous system ■ heart failure ■ norepinephrine ■ receptors, adrenergic
endocardium. Parasympathetic effects are carried by the right and left vagus nerves, originating in the medulla. The vagus nerve further divides into the superior and inferior cardiac nerves, finally merging with the postganglionic sympathetic neurons to form a plexus of nerves at the base of the heart, known as the cardiac plexus.

The 2 mediators of the SNS, norepinephrine and epinephrine, derive from 2 major sources in the body: the sympathetic nerve endings, which release norepinephrine directly into the synaptic cleft, and the adrenal medulla, whose chromaffin cells synthesize, store, and release predominantly epinephrine and norepinephrine on acetylcholine stimulation of the nicotinic cholinergic receptors present on their cell membranes. Thus, all of the epinephrine in the body and a significant amount of circulating norepinephrine derive from the adrenal medulla, and the total amount of catecholamines presented to cardiac adrenergic receptors (ARs) at any given time is composed of these circulating norepinephrine and epinephrine plus norepinephrine released locally from sympathetic nerve terminals. Norepinephrine is released into synaptic clefts in response to acetylcholine stimulation of the nicotinic cholinergic receptors present on their cell membranes.

Norepinephrine is released into synaptic clefts in response to neuronal stimulation through fusion of presynaptic storage vesicles with the neuronal membrane. Norepinephrine stimulates presynaptic α2-ARs, which provide a negative feedback on exocytosis, and the postsynaptic β-ARs. In the synaptic cleft, most norepinephrine undergoes reuptake into nerve terminals by the presynaptic norepinephrine transporter and recycles into vesicles or is metabolized in the cytosol by monoamine oxidase. A small fraction of ≈20% diffuses into the vascular space, where it can be measured in coronary sinus blood. Norepinephrine spillover can also be measured in the blood and used to infer sympathetic outflow to the heart. Norepinephrine is released into the circulation by the adrenal medulla and affects both the myocardium and the peripheral vessels.

Adrenoceptors mediate the central and peripheral actions of the primary sympathetic neurotransmitter—norepinephrine—and the primary adrenal medullary hormone—epinephrine. The ARs are divided into 3 families, the α1-ARs, the α2-ARs, and the β-ARs, each of which is further subdivided in several subtypes. In the heart, the 2 main ARs are the β-ARs, which comprise ≈90% of the total cardiac ARs, and α1-ARs, which account for ≈10%.

Evidence from cell, animal, and human studies demonstrates that α1-ARs mediate adaptive and protective effects in the heart and activate pleiotropic downstream signaling to prevent pathological remodeling in HF. These effects may be particularly important in chronic HF, when catecholamine levels are elevated and β-ARs are downregulated and dysfunctional.

It is now generally accepted that, in the human heart, β1- and β2-ARs coexist; the existence of a third heart β-AR is to date mainly supported by the anomalous pattern of nonconventional partial agonists. β1-AR is the predominant subtype in the myocardium, representing 75% to 80% of total β-AR density, followed by β2-AR. Activation of cardiac β-ARs increases heart rate, myocardial contractility, impulse conduction through the atrioventricular node, and pacemaker activity of the sinoatrial node.

The interpretation of catecholamine effects has recently been re-examined in light of the demonstration of the expression of the β3-AR in cardiovascular tissues in humans and in several animal species. This isotype was known to mediate lipolysis and thermogenesis in adipose tissue. In the heart, contrary to β1 and β2 isotypes, it mediates a negative inotropic effect when activated with high concentrations of agonist ex vivo. Given its differential expression in cardiac tissue, the β3-AR is an attractive target for therapeutic modulation in several cardiomyopathies.

The concept of biased agonism has recently been proposed with the demonstration that G-protein–coupled receptors activate complex signaling networks and can adopt multiple active conformations on agonist binding. As a consequence, the efficacy of receptors, which was classically considered linear, is now recognized as pluridimensional. Biased agonists selectively stabilize only a subset of receptor conformations induced by the natural unbiased ligand, thus preferentially activating certain signaling mechanisms. Such agonists reveal the intriguing possibility that one can direct cellular signaling with unprecedented precision and specificity and support the notion that biased agonists may identify new classes of therapeutic agents that have fewer side effects.

Acetylcholine, the transmitter of the parasympathetic system, is stored in vesicles and is released by parasympathetic stimulation, activating postsynaptic muscarinic, and preganglionic nicotinic receptors. These effects are terminated by rapid degradation by acetylcholinesterase. Parasympathetic stimulation decreases heart rate by decreasing sinoatrial node discharge rate and atrioventricular node conduction velocity with minimal or no effect on cardiac contractility. There is evidence that stimulation of the local muscarinic receptors in the heart inhibits norepinephrine release from adrenergic nerve terminals; therefore, cardiac muscarinic receptors may play a role in the local modulation of cardiac sympathetic activity in HF.

Alterations in autonomic function occur in several interrelated cardiac conditions, including hypertension, myocardial ischemia, HF, cardiac arrhythmias, and sudden cardiac death.

**Autonomic Nervous System in HF**

Most of the data about the role of the SNS in the development and prognosis of HF were obtained from studies on subjects with dilated ventricles and reduced ejection fraction (EF). One of the first responses to myocardial injury or to alterations in cardiac loading is activation of the SNS, resulting in both increased release and decreased uptake of norepinephrine at
adrenergic nerve endings. Sympathetic outflow from the central nervous system in HF affects several key organs, including the heart, the kidney, and the peripheral vasculature. In the acute setting, catecholamine-induced augmentation of ventricular contractility and heart rate help maintain cardiac output. Increased sympathetic activity also leads to systemic vasoconstriction and enhanced venous tone, both of which initially contribute to maintenance of blood pressure by increasing systemic vascular resistance and ventricular preload. Renal vasoconstriction (mediated primarily by angiotensin II) occurs at the efferent arteriole, producing an increase in filtration fraction that allows glomerular filtration to be relatively well maintained, despite a fall in renal blood flow. Both noradrenaline and angiotensin II stimulate proximal tubular sodium reabsorption, which contributes to sodium retention and volume expansion characteristic of HF. The heart responds to the increase in venous return with an elevation in end-diastolic volume that results in a rise in stroke volume via the Frank–Starling mechanism. Chronic sympathetic stimulation induces myocyte enlargement, interstitial growth, and remodeling that increase myocardial mass and may lead to enlargement of the left ventricular (LV) chamber.26,29

The elevated SNS outflow and norepinephrine and epinephrine levels in chronic HF lead to chronically elevated stimulation of the cardiac β-AR system, which has detrimental repercussions for the failing heart. Extensive investigations during the past 3 decades have helped delineate the molecular alterations afflicting the cardiac β-AR system that occur during HF, and it is now well known that, in chronic human HF, cardiomyocyte β-AR signaling and function are significantly deranged and the adrenergic reserve of the heart is diminished.30–32 Cardiac β-AR dysfunction in human HF is characterized at the molecular level by selective reduction of β1-AR density at the plasma membrane (downregulation) and by uncoupling of the remaining membrane β1-ARs and β2-ARs from G proteins (functional desensitization).31 In addition, emerging evidence suggests that β2-AR signaling in the failing heart is different from that in the normal heart (ie, is more diffuse and noncompartimentalized and resembles the proapoptotic diffuse cAMP signaling pattern of the β1-AR).33 Importantly, myocardial levels and activities of the most important, versatile, and ubiquitous G-protein–coupled receptor kinases (GRKs), GRK2 and GRK5, are elevated both in humans and in animal models of HF.34–38 The current consensus is that in chronic HF, the excessive amount of SNS-derived catecholamines stimulating cardiac β-ARs extracellularly triggers the GRK2 upregulation inside the cardiomyocytes, thus leading to a reduction in cardiac β-AR density and responsiveness and resulting in cardiac inotropic reserve depletion.39,40 This GRK2 elevation possibly serves as a homeostatic protective mechanism aimed at defending the heart against excessive catecholaminergic toxicity. Thus, elevated SNS activity in chronic HF causes enhanced GRK2–mediated cardiac β1-AR and β2-AR desensitization and β1-AR downregulation, which leads to the progressive loss of the adrenergic and inotropic reserves of the heart, the hallmark molecular abnormality of this disorder.41

It has been known for many years that chronic exposure to catecholamines is toxic to cardiac myocytes.42 Many studies demonstrated a high plasma norepinephrine concentration concomitant with a depressed iodine 123 metaiodobenzylguanidine (123I-MIBG) reuptake in HF, and this phenomenon has been explained as sympathetic denervation.43 In 1992, Mann et al44 demonstrated that at the cellular level, adrenergic stimulation leads to cAMP-mediated calcium overload of the cell, with a resultant decrease in cardiomyocyte viability. Kimura et al45 have recently suggested that the cardiac sympathetic nerve density is strictly regulated by the nerve growth factor expression and demonstrated in an experimental rat model that long exposure to high plasma norepinephrine concentration caused myocardial nerve growth factor reduction, followed by sympathetic fiber loss. It has been suggested that the sympathetic nerve endings are probably damaged by norepinephrine-derived free radicals,46 and that antioxidant therapy may prevent the toxic effects of norepinephrine on the sympathetic nerve terminals.47,48 Norepinephrine-mediated cell toxicity was also attenuated by β1-AR blockade and mimicked by selective stimulation of the β2-AR, whereas the effects mediated by the α-AR were relatively less apparent.49

Communal et al49 examined the mechanism by which norepinephrine caused cell death in ventricular myocytes cultured from adult rat hearts. Exposure to norepinephrine for 24 hours caused DNA fragmentation consistent with apoptosis. Norepinephrine-stimulated apoptosis was abolished by the β2-AR antagonist propranolol but not by the α1-AR antagonist prazosin.46,48 Stimulation of β1-ARs increases apoptosis via a cAMP-dependent mechanism, whereas stimulation of β2-ARs inhibits apoptosis via inhibitory G-protein (Gi) pathway.49–52 Although hyperstimulation or overexpression of β1-ARs has detrimental effects in the heart,53,54 there are new data suggesting chronic β-adrenergic signaling can be cardioprotective.54

Extensive research in the rat model of dilated cardiomyopathy after induction of myocardial infarction showed that prolonged treatment with the β2-AR agonist, fenoterol, in combination with the β1-AR blocker, metoprolol, is more effective than β1-AR blocker alone and as effective as β1-AR blocker with angiotensin-converting enzyme inhibitor with respect to survival and cardiac remodeling.55 This combined regimen of a β2-AR agonist and a β1-AR blocker might be considered for clinical testing as alternative or adjunct therapy to the currently accepted HF arsenal.

Preclinical data point to protective effects of overexpressed β3-ARs against LV remodeling in the setting of neurohormonal or postschemic stress. Theoretically, one could conceive the benefit of using β3-AR agonists to prevent adverse remodeling in these conditions. Recently, a study showed preliminary encouraging data using a β3 agonist, BRL37344, in mice submitted to transaortic constriction56 although the specificity of this molecule as an agonist for the murine β3-AR is somewhat disputed.57 Sorrentino et al58 have recently demonstrated in a postinfarction murine model that nebivolol, a β2-AR, and likely β1-AR biased agonist,59 which was previously shown to activate β3-AR in the human ventricle,60 improves LV function and survival early after myocardial infarction likely beyond the effects provided by conventional β1-receptor blockade.58 The Study of the Effects of Nebivolol Intervention on Outcomes and Rehospitalisations in Seniors with Heart Failure (SENIORS) trial demonstrated the effect of nebivolol on all-cause mortality or cardiovascular hospitalization in elderly patients with HF.61
Less is known about the role of the para-SNS in the pathophysiology of HF. Parasympathetic outflow to the heart is reduced in patients with HF,\textsuperscript{62,63} resulting in increased heart rate and decreased heart rate variability (HRV), both of which are correlated with increased mortality.\textsuperscript{64} Muscarinic receptor stimulation in the failing human left ventricle was shown to have an independent negative lusitropic effect and at antagonize the effects of β-adrenergic stimulation.\textsuperscript{55}

### Autonomic Nervous System in HF With Preserved EF

Approximately one half of patients presenting with HF have normal or near-normal LVEF.\textsuperscript{65,66} These patients with HF and preserved EF (HFpEF) have been reported to experience an overall prognosis and pattern of functional decline similar to that of patients with HF and reduced LVEF.\textsuperscript{68} Patients with HFpEF are, however, older, and their functional decline is characterized by impaired ventricular relaxation and reduced compliance of the ventricles. The resulting impairment of diastolic filling may in time lead to congestive HF.\textsuperscript{69,70} To date, no established effective treatment strategies are known. Partly, this can be explained by a lack of knowledge on mechanisms. Various physiological mechanisms have been implicated in the pathogenesis of HFpEF, including increased passive ventricular stiffness, because of enhanced extracellular collagen deposition and intrinsic alterations in myocyte cytoskeletal proteins,\textsuperscript{71} impaired active myocardial cardiac relaxation related to altered myocyte calcium handling and reduced myocardial energy reserve,\textsuperscript{27,31} abnormal ventricular–vascular coupling and pulsatile load as a consequence of diminished aortic compliance,\textsuperscript{74} and impaired renal handling of salt and water because of increased neurohormonal activation.\textsuperscript{75}

Data on autonomic nervous system in HFpEF are limited. In patients with hypertension, SNS hyperactivity may contribute to the development of LV diastolic dysfunction and thus increase HF risk.\textsuperscript{76} Several preclinical and clinical studies have shown a relationship between an elevated SNS activity and the development of diastolic dysfunction or HFpEF.\textsuperscript{77–79}

On the basis of the relationship between the SNS and HFpEF, we have suggested that modulation of the SNS may result in an improvement of the clinical status of patients with HFpEF. Although there have been no randomized clinical trials investigating the role of β-blockers in patient with HFpEF, the SENIORS trial enrolled subjects with both reduced and preserved EF.\textsuperscript{61} In the subgroup of 752 patients with a LVEF of ≥35%, treatment with nebivolol showed no significant benefit on the primary end point of all-cause mortality or cardiovascular hospitalizations.\textsuperscript{80} The denervation of the renal sympathetic nerves in HF with normal LVEF (Denervation of the renAI Sympathetic nerves in heartT failure with nOrmal Lv Ejection fraction [DIASTOLE]; ClinicalTrials.gov Identifier NCT01583881) will investigate whether renal sympathetic denervation is an effective means to modulate the detrimental effects of the SNS in patients with HF with normal EF.\textsuperscript{91}

### Techniques Used to Assess Autonomic Nervous System Activity

The following techniques have been used to assess autonomic nervous system activity: analysis of heart rate and blood pressure, measurement of norepinephrine spillover, microneurography, and imaging of cardiac sympathetic nerve terminals.

### Analysis of Heart Rate and Blood Pressure

#### Heart Rate Variability

Beat-to-beat HRV can serve as a noninvasive marker of autonomic input to the heart. HRV is markedly reduced in patients with HF, and the reduction in HRV is related to the severity of HF and its prognosis.\textsuperscript{72,83} The underlying physiological mechanism of decreased HRV is likely to be an alteration in the cardiac sympathetic–parasympathetic balance, characterized by a relative sympathetic dominance probably secondary to reduced parasympathetic activity.\textsuperscript{84} The estimation of HRV by ambulatory monitoring provides prognostic information beyond that of traditional risk factors.\textsuperscript{85} Studies have shown that HRV strongly predicts sudden cardiac death in patients with chronic HF,\textsuperscript{86} and that β-blocker therapy with bisoprolol induced a significant increase in HRV.\textsuperscript{57}

#### Baroreflex Sensitivity

Baroreceptor-heart rate reflex sensitivity (BRS) assesses the integrity of the carotid and aortic baroreceptors in response to changes in blood pressure. Abnormalities in baroreceptor function are intrinsic to the pathophysiology of HF.\textsuperscript{88} Experimental\textsuperscript{89} and clinical\textsuperscript{62} studies demonstrated that the carotid sinus baroreceptor sensitivity is diminished in HF. The site or sites within the baroreflex arc that is responsible for the depressed baroreflex in HF are not clearly identified. Patients with HF were shown to exhibit reduced elevation in heart rate when parasympathetic restraint is abolished by atropine and diminished sensitivity of the baroreceptor reflex, characterized by a severe reduction in the heart rate slowing for any given elevation of systemic arterial pressure.\textsuperscript{62} In contrast to the increase in heart rate and plasma norepinephrine levels during nitroprusside infusion in normal subjects, patients with HF also exhibited neither an increase in plasma norepinephrine nor an increase in heart rate during nitroprusside infusion (Figure 1).\textsuperscript{90} A depressed BRS conveys independent prognostic information that is not affected by the modification of autonomic dysfunction brought about by β-blockade.\textsuperscript{91}

#### Heart Rate Turbulence

The phenomenon of heart rate turbulence (HRT) refers to sinus rhythm cycle-length perturbations after isolated premature ventricular complexes. The physiological pattern of HRT consists of brief heart rate acceleration (turbulence onset) followed by more gradual heart rate deceleration (turbulence slope) before the rate returns to the pre-ectopic level. Physiological investigations confirm that the initial heart rate acceleration is triggered by transient vagal inhibition in response to the missed baroreflex afferent input caused by hemodynamically inefficient ventricular contraction. A sympathetically mediated overshoot of arterial pressure is responsible for the subsequent heart rate deceleration through vagal recruitment. Two large studies (UK-HEART [United Kingdom Heart Failure Evaluation and Assessment of Risk] trial and Muerte Subita en Insuficiencia Cardiaca [MUSIC] study) investigated the prognostic role of HRT in patients with HF.\textsuperscript{92,93} In the UK-HEART trial,\textsuperscript{93} abnormal turbulence slope was an independent predictor of HF decompensation. In the
MUSIC study. HRT predicted all-cause mortality and sudden death in patients with HF. The HRT pattern is blunted in patients with reduced BRS. La Rovere et al analyzed the relationship between measures of HRT and the BRS in patients with HF, who also had a direct evaluation of their hemodynamic status by right heart catheterization and suggested HRT might be regarded as a surrogate measure of BRS.

Norepinephrine Spillover

Most norepinephrine released into the synaptic cleft of the AR undergoes reuptake into nerve terminals by the presynaptic norepinephrine transporter, where it recycles into presynaptic vesicles or is metabolized in the cytosol by monoamine oxidase. A small amount of the transmitter escapes neuronal uptake and local metabolism and diffuses or spills over into the blood vessels, where it can be measured to infer the level of sympathetic outflow.

Depletion of cardiac norepinephrine content was the first objective evidence of sympathetic derangement in HF. In 1963, Chidsey et al reported a significant diminution in the myocardial norepinephrine concentrations observed in patients with chronic congestive HF. They also reported increased plasma norepinephrine levels and urinary excretion of norepinephrine in patients with HF. In 1984, Cohn et al reported that plasma norepinephrine levels provide a better guide to prognosis in patients with chronic congestive HF than other commonly measured indices of cardiac performance (Figure 2). A more recent analysis of both plasma norepinephrine and plasma brain natriuretic peptide indicated that brain natriuretic peptide had a stronger association with morbidity and mortality than norepinephrine, and that changes in these neurohormones over time are associated with corresponding changes in morbidity and mortality. It should be noted that measurement of plasma norepinephrine levels represents a crude assessment of SNS activity as only ≈20% of norepinephrine released at the nerve terminals may enter the bloodstream where it undergoes clearance from the circulation. A higher plasma norepinephrine concentration in patients with HF was shown to be secondary to both increased release and reduced its clearance. In conditions, such as congestive HF, where clearance is likely to be abnormal, the rate of spillover is a more accurate index of sympathetic activity than the total plasma norepinephrine concentration.

The analysis of plasma kinetics of norepinephrine can be used to estimate sympathetic nervous activity for the body as a whole and for individual organs. There is marked regional variation in sympathetic nerve activity in patients with HF. Cardiac and renal norepinephrine spillover are increased, whereas norepinephrine spillover from the lungs is normal. Adrenomedullary activity is also increased in patients with HF. The finding of increased cardiorenal norepinephrine spillover has important pathophysiologic and therapeutic implications.

Microneurography

Microneurography uses metal microelectrodes to investigate the neural traffic in myelinated and unmyelinated efferent and afferent nerves directly. This technique has been used in clinical neurophysiology to evaluate the neural mechanisms of autonomic regulation, motor control, and sensory functions in physiological and pathological conditions. Microneurography has also been used to analyze the muscle sympathetic nerve activity. Studies have shown that increased muscle sympathetic nerve activity is associated with increased mortality rate in patients with HF.

Imaging of Cardiac Sympathetic Nerve Terminals

The use of radiolabeled catecholamine analogs to image cardiac sympathetic nerve terminals dates back ≈30 years. Recently, several radiolabeled compounds have been proposed for noninvasive imaging of cardiac neuronal function. The catecholamine analog 123I-MIBG is the tracer most commonly used to map myocardial presynaptic sympathetic innervation and activity. Cardiac neuronal distribution and function can be imaged with standard γ-cameras and positron emission tomography.

Figure 1. Response of plasma norepinephrine (PNE) and heart rate (HR) to nitroprusside (NP) infusion in normal subjects (▲) and patients with congestive HF (CHF; ◆). Symbols above the control columns (C) indicate a significant difference between normal subjects and patients with CHF; symbols in NP columns indicate significant changes from control during NP infusion. *P<0.01, †P<0.05. Mean values±SEM are shown. Reprinted from Olivari et al.

Figure 2. Predicted survival curves based on initial measurement of plasma norepinephrine. Reprinted from Cohn et al. Copyright 1984. Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.
tomography scanners. $^{109}$ $^{123}$I-MIBG cardiac imaging has been shown to carry independent prognostic information for risk stratification of patients with HF in a complementary manner to more commonly used biomarkers, such as LVEF and brain natriuretic peptide. $^{110}$ β-blockade and renin–angiotensin–aldosterone system inhibition are associated with an increase in $^{123}$I-MIBG uptake and a reduced washout. $^{7}$ Imaging of the cardiac autonomic nervous system has recently entered large-scale clinical trials and has supported a prognostic value in HF. $^{111,112}$

Interventions Targeting the Autonomic Nervous System in HF

Pharmacological Blockade of the SNS

β-blockers reverse ventricular remodeling $^{113,114}$ and reduce mortality in patients with HF. $^{115–117}$ The use of 1 of the 3 β blockers proven to reduce mortality (eg, bisoprolol, carvedilol, and sustained-release metoprolol succinate) is, therefore, recommended for all patients with current or previous symptoms of HF with reduced EF. $^{118}$

The association between the degree of sympathetic activation and mortality $^{99,100}$ raised the possibility that more complete adrenergic blockade might produce even greater benefit on outcomes. Moxonidine, a mixed central agonist that stimulates both α2- and imidazoline-receptors $^{119}$ and which greatly reduces circulating catecholamines, $^{120}$ was used to test this hypothesis in the Moxonidine in Congestive Heart Failure (MOXCON) trial. $^{121}$ The study had to be terminated early with only 1934 of the planned 4533 patients randomized because of a 38% higher mortality in the moxonidine group. Hospitalizations for HF and myocardial infarctions were also increased. The increase in mortality and morbidity was accompanied by significant decrease in plasma norepinephrine by moxonidine (~18.8%) when compared with that by placebo (+6.9%). $^{121}$

The MOXCON findings suggest that central inhibition of the SNS may not be safe in patients with HF. It is conceivable that receptor inhibition might be better tolerated than central suppression of the cardiac stimulation and peripheral vasoconstrictor effects of the SNS. $^{121}$ It is also possible that the pharmacological benefit of β blockade in HF is at least partly achieved through a mechanism different than that resulting from a decrease in sympathetic nerve traffic. Renin inhibition by β1 receptor blockade with reduction in angiotensin II levels may be an important mechanism for the efficacy of β blockers. $^{122}$ Another possible reason for the failure of moxonidine in the MOXCON trial might have been the reported α2-AR desensitization and downregulation that accompanies HF, which renders α2-ARs dysfunctional, thus increasing sympathetic outflow and limiting efficacy of α2-AR sympatholytic agonists. $^{7,123}$

Another example of the association between marked sympatoexcitatory effect and adverse outcomes was seen in the Beta-Blocker Evaluation of Survival Trial (BEST), $^{124}$ which is the only β-blocker HF trial that failed to demonstrate mortality benefit. In BEST, patients receiving bucindolol, who had a decrease in norepinephrine of >224 pg/mL from baseline to 3 months, had a 169% increase in mortality when compared with patients who had no significant change in norepinephrine. $^{125}$

β-blocker trials in patients with HF have demonstrated differences in outcomes by geographic region. In Metoprolol Controlled-Release Randomized Intervention Trial in Heart Failure (MERIT-HF), metoprolol succinate showed a significant 34% risk reduction in mortality when compared with placebo. $^{115}$ This risk reduction was nearly identical to the significant mortality risk reductions observed with bisoprolol in Cardiac Insufficiency Bisoprolol Study (CIBIS)-II (34%) and carvedilol in Carvedilol Perspective Randomized Cumulative Survival (COPERNICUS) trial (35%), both were compared with placebo. $^{116,117}$ In contrast, BEST showed a nonsignificant 13% risk reduction in mortality in patients treated with bucindolol versus placebo. $^{124}$ MERIT-HF, CIBIS-II, and COPERNICUS were international trials with the majority of recruitment outside the United States, whereas BEST recruited only patients in the United States and Canada (97.7% and 2.3%, respectively). The geographic diversity among these trials created an opportunity to examine whether outcome differences by region were present. A recent post hoc analysis of large β-blocker trials suggested that a difference in response to β-blocker therapy may exist between patients in the United States and in other parts of the world. $^{126}$ Among US patients, the reduction in mortality associated with β-blocker therapy was of lesser magnitude than that observed in the overall trial results, and it was not statistically better than placebo. This geographic difference in treatment response may be a reflection of population differences, genetics, cultural or social differences in disease management, or low power and statistical chance.

Questions remain as to the mechanism of the beneficial effect of β-blockers in patients with HF and whether they work through diminishing sympathetic overactivity or exclusively through cardiac slowing. In patients with mild to severe chronic HF, elevated resting heart rate is associated with an increased risk of all-cause mortality and cardiovascular mortality. $^{127,128}$ Similarly, investigators of the systolic HF treatment with the I, inhibitor ivabradine trial (SHIFT) study observed that patients with chronic HF and in sinus rhythm who had the highest heart rate were at a 2-fold greater risk of cardiovascular death or hospitalization for HF when compared with patients with the lowest heart rate. $^{129}$ In this trial, treatment with ivabradine was associated with an average reduction in heart rate of 15 bpm from a baseline value of 80 bpm and a significant reduction of the risk of cardiovascular death or hospital admission for worsening HF. $^{130}$ Patients with heart rates higher than the median were at increased risk of an event and received greater event-reducing benefit from ivabradine than did those with heart rates lower than the median. $^{130}$ These finding suggests that the magnitude of benefit associated with ivabradine varies directly with pretreatment heart rate. This conclusion is in line with a meta-analysis of β-blocker trials in chronic HF, suggesting that there is an association between the magnitude of heart rate reduction and outcome. $^{131}$ Although these findings support the idea that heart rate plays an important part in the pathophysiology of HF and that heart rate modulation can interfere with the progression of the disease, it is possible that the higher heart rates represent a sicker population in which the benefit of the drug would be easier to demonstrate.

Although SHIFT emphasized the importance of isolated heart rate reduction on outcomes in patients with HF, several β-blocker trials could not establish any relationship between the baseline heart rate and the efficacy of β-blocker therapy with either nonselective agents $^{132,133}$ or selective agents. $^{134,135}$
In the MERIT-HF, metoprolol controlled release/extended release significantly reduced mortality and hospitalizations independent of resting baseline heart rate, achieved heart rate, and change in heart rate. The reduction in mortality with bisoprolol, when compared with placebo, was not influenced by heart rate changes in the CIBIS-II as well. It is likely that β-blocker therapy may counteract the deleterious effects of tachycardia in the failing heart so that this variable loses its prognostic significance.

**Effect of Cardiac Resynchronization Therapy on Cardiac Autonomic Function**

Several studies have shown that cardiac resynchronization therapy (CRT) improves sympathetic function in patients with HF accompanied by reduced systolic function. Biventricular pacing was shown to reduce muscle sympathetic nerve activity when compared with right ventricular pacing or right atrial pacing. These beneficial effects persisted ≤6 months after resynchronization therapy. Cha et al examined the effect of CRT on neurohormonal integrity by studying cardiac presynaptic sympathetic function, as determined by nuclear cardiac imaging modalities (123I-MIBG scintigraphy), in patients with HF who received CRT and found that CRT reverses cardiac autonomic remodeling by upregulating presynaptic receptor function, as evidenced by increased 123I-MIBG heart/mediastinum ratio and attenuated heart/mediastinum washout rate, with concomitantly improved HRV. Najem et al found that sympathetic inhibition induced by chronic CRT is acutely reversed when patients are shifted from a synchronous to a nonsynchronous mode; this was observed only in patients who responded to CRT, even more than a year after initiation of the therapy. The mechanism by which CRT inhibits sympathetic activity is intriguing because correction of the electric and mechanical dysynchrony with biventricular pacing does not directly block the SNS. It is probable that biventricular pacing improves cardiac function over time and thus reduces sympathetic drive.

**Exercise Training and Autonomic Nervous System in HF**

Studies in experimental HF have shown that exercise training in animals improves cardiac β-AR signaling and function, increases adrenergic and inotropic reserves of the heart, and helps restore normal SNS activity/outflow and circulating catecholamine levels. Exercise training is known to increase resting vagal tone and to decrease sympathetic drive in healthy individuals. Coats et al showed that a similar beneficial change could be induced in patients with HF. Exercise not only improved peak oxygen uptake in patients with HF but also associated with a reduction in markers of SNS activation (norepinephrine spillover and HRV). In the HF: A Controlled Trial Investigating Outcomes of Exercise Training (HF-ACTION) trial, the largest randomized controlled trial of exercise training in patients with HF and reduced LV function, exercise training provided a nonsignificant reduction in the risk of the primary end point of all-cause mortality or all-cause hospitalization.

**Use of Devices to Modulate Autonomic Nervous System in HF**

**Renal Sympathetic Denervation**

Sympathetic outflow to the kidneys is activated in patients with essential hypertension. Efferent sympathetic outflow stimulates renin release, increases tubular sodium reabsorption, and reduces renal blood flow. Afferent signals from the kidney modulate central sympathetic outflow and thereby directly contribute to neurogenic hypertension.

Recently developed endovascular catheter technology enables selective denervation of the human kidney, with radiofrequency energy delivered in the renal artery lumen, accessing the renal nerves located in the adventitia of the renal arteries. A first-in-man study of this approach performed in a 59-year-old man with uncontrolled hypertension showed reduction of sympathetic activity and renin release in parallel with reductions of central sympathetic outflow. Muscle sympathetic nerve activity decreased from 56 bursts per minute at baseline to 41 bursts per minute at 30 days and 19 bursts per minute at 1 year. Furthermore, from baseline to 30 days, total body norepinephrine spillover decreased by 42%, and renal norepinephrine spillover decreased by 75% and 48% in the right and left kidney, respectively. Finally, mean office blood pressure decreased from 161/107 mm Hg at baseline to 141/90 at 30 days and 127/81 mm Hg at 1 year, despite the withdrawal of 2 antihypertensive medications. This fall in blood pressure was accompanied by a reduction in LV mass measured using cardiac MRI.

A subsequent randomized controlled trial (SYMPLICITY HTN-2 trial [renal sympathetic denervation in patients with treatment-resistant hypertension]) showed that catheter-based renal denervation can safely be used to reduce blood pressure substantially in treatment-resistant patients with hypertension. Renal sympathetic denervation was also shown to reduce LV hypertrophy and to improve cardiac function in patients with resistant hypertension. The pivotal study, the SYMPLICITY HTN-3 trial was, however, terminated prematurely because it failed to achieve its primary efficacy end point of change in office systolic blood pressure at 6 months. The SYMPLICITY HTN-3 study was a single-blinded, randomized, designed to evaluate the safety and effectiveness of renal denervation in patients with treatment-resistant hypertension. In this trial, people receiving the investigational treatment were compared with a sham-control group that did not receive treatment.

Experimental studies suggested that renal denervation could be beneficial for improving the neurohormonal dysregulation of chronic HF. Davies et al have recently reported the results of a pilot study of 7 patients with chronic systolic HF, who underwent bilateral renal denervation and were followed up for 6 months. The study found no procedural or postprocedural complications. A randomized trial with appropriate concealment of treatment is required to address the potential benefits of renal denervation in HF, and such a trial is currently underway in chronic systolic HF (REACH [Renal Artery Denervation in Chronic Heart Failure study], ClinicalTrials.gov Identifier NCT01639378).

**Baroreflex Sensitization**

Baroreflex sensitization devices have been commercialized and are currently undergoing clinical testing. The Rhoes (CVRx, Minneapolis, MN) implantable carotid sinus stimulator has been studied in patients with severe hypertension refractory to drug therapy. Implantation involves both carotid

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sinuses being surgically exposed and electrodes being placed around the carotid adventitial surface bilaterally. The leads are subcutaneously tunneled and connected to an implantable stimulation device placed in the subclavian subcutaneous position on the anterior chest wall. Electric baroreflex activation is then initiated on both carotid sinuses simultaneously with incremental voltage increases until the chronic stimulation level is achieved.159

A recent European multicenter feasibility study showed that the Rheos device sustainably reduces blood pressure in patients with resistant hypertension, and that this unique therapy offers a safe individualized treatment option for these high-risk individuals.160 There are currently several trials underway examining the role of baroreceptor activation therapy in patients with HF.161

Vagal Nerve Stimulation

An approach that could further advance the neurohormonal and autonomic imbalance hypothesis in HF is the improvement of autonomic regulatory function by vagal nerve stimulation. Reduced vagal activity is associated with increased mortality in patients with HF,162 and many investigators have shown that restoration of autonomic regulatory function by vagal nerve stimulation improves survival in animal models of HF.163-165 More recently, a multicenter, open-label phase II safety and feasibility study was reported with the use of right cervical vagal nerve stimulation synchronized to the cardiac cycle (CardioFit System; BioControl Medical, Yehud, Israel).166 The Autonomic Neural Regulation Therapy to Enhance Myocardial Function in Heart Failure (ANTHEM-HF) study will use the Cyberonics vagal nerve stimulation therapy system to provide additional information on the role of autonomic regulation therapy in patients with LV dysfunction and chronic symptomatic HF.167

Future Directions

Despite remarkable insights into the role of the autonomic nervous system in the syndrome of HF, several issues remain poorly understood and in need of further investigation. The issue of paramount importance is whether activation of the autonomic nervous system is the driver of HF or merely a consequence of the disease. Some other important questions include (1) What is the optimal counteraction of the activation of the SNS in chronic HF? (2) What is the mechanism of the heterogeneity of response to β-blocker therapy? (3) Are there new pharmacological mechanisms that could be exploited? (4) If drugs are properly used, are devices still necessary? (5) At what stage of the HF syndrome the adaptive sympathetic activation becomes deleterious and begins playing a critical role in the progression of the disease? (6) Could preventive strategies at that stage be more effective? (7) What preventive strategy would be most effective? Prospective intervention studies are needed to reach a verified consensus on how measurements and modulation of autonomic nervous system should be incorporated into the diagnosis, risk assessment, and treatment of patients with HF.

Disclosures

None.

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