

STATE-OF-THE-ART PAPER

The Sympathetic Nervous System in Heart Failure

Physiology, Pathophysiology, and Clinical Implications

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Heart failure is a syndrome characterized initially by left ventricular dysfunction that triggers countermeasures aimed to restore cardiac output. These responses are compensatory at first but eventually become part of the disease process itself leading to further worsening cardiac function. Among these responses is the activation of the sympathetic nervous system (SNS) that provides inotropic support to the failing heart increasing stroke volume, and peripheral vasoconstriction to maintain mean arterial perfusion pressure, but eventually accelerates disease progression affecting survival. Activation of SNS has been attributed to withdrawal of normal restraining influences and enhancement of excitatory inputs including changes in: 1) peripheral baroreceptor and chemoreceptor reflexes; 2) chemical mediators that control sympathetic outflow; and 3) central integratory sites. The interface between the sympathetic fibers and the cardiovascular system is formed by the adrenergic receptors (ARs). Dysregulation of cardiac beta₁-AR signaling and transduction are key features of heart failure progression. In contrast, cardiac beta₂-ARs and alpha₁-ARs may function in a compensatory fashion to maintain cardiac inotropy. Adrenergic receptor polymorphisms may have an impact on the adaptive mechanisms, susceptibilities, and pharmacological responses of SNS. The beta-AR blockers and the inhibitors of the renin-angiotensin-aldosterone axis form the mainstay of current medical management of chronic heart failure. Conversely, central sympatholytics have proved harmful, whereas sympathomimetic inotropes are still used in selected patients with hemodynamic instability. This review summarizes the changes in SNS in heart failure and examines how modulation of SNS activity may affect morbidity and mortality from this syndrome. (J Am Coll Cardiol 2009;54:1747-62) © 2009 by the American College of Cardiology Foundation

Heart failure is a clinical syndrome that develops in response to an insult resulting in a decline in the pumping capacity of the heart. This is subsequently characterized by the continuous interaction between the underlying myocardial dysfunction and the compensatory neurohumoral mechanisms that are activated. Among many, these include the sympathetic nervous system (SNS), the renin-angiotensin-aldosterone axis, and the cytokine system (1). These systems are initially able to compensate for the depressed myocardial function and preserve cardiovascular homeostasis. However, their long-term activation has deleterious effects on cardiac structure and performance, leading to cardiac decompensation and heart failure progression.

SNS and Normal Cardiac Function

The SNS has a wide variety of cardiovascular actions, including heart rate acceleration, increase in cardiac con-

tractility, reduction of venous capacitance, and constriction of resistance vessels. On the contrary, the parasympathetic nervous system affects the cardiovascular system by slowing heart rate through vagal impulses (Fig. 1). The cardiac sympathetic nerve fibers are located subepicardially and travel along the major coronary arteries representing the predominant autonomic component in the ventricles. The parasympathetic fibers run with the vagus nerve subendocardially after it crosses the atrioventricular groove and are mainly present in the atrial myocardium and less abundantly in the ventricular myocardium (2). The ventricular sympathetic innervation is characterized by a gradient from base to apex (3). The cardiac neuronal system is made up of spatially distributed cell stations comprising afferent, efferent, and interconnecting neurons behaving as a control system (4). The neurons are in constant communication with each other and each neuronal cell station is involved in cardio-cardiac reflexes that control spatially organized cardiac regions.

The sympathetic outflow to the heart and peripheral circulation is regulated by cardiovascular reflexes. Afferent fibers are usually carried toward the central nervous system by autonomic nerves, whereas efferent impulses travel from the central nervous system toward different organs either in autonomic or

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**Abbreviations
and Acronyms**

AR = adrenergic receptor
ATP = adenosine triphosphate
cAMP = 3',5'-cyclic monophosphate
EPI = epinephrine
MIBG = metaiodobenzylguanidine
NE = norepinephrine
SNS = sympathetic nervous system

somatic nerves. The main reflex responses originate from aortic arch and carotid baroreceptors (SNS inhibition), cardiopulmonary baroreceptors (diverse reflexes including the Bezold-Jarisch reflex, SNS inhibition), cardiovascular low-threshold polymodal receptors (SNS activation), and peripheral chemoreceptors (SNS activation) (5). The effect of SNS activation on the periphery is mediated by 4 pathways (6): 1) norepinephrine (NE) releasing neurons through the right stellate

ganglion reaching the sinus and atrioventricular nodes (resulting in an increase in heart rate and shortening of atrioventricular conduction) and through the left stellate ganglion reaching the left ventricle (resulting in an increase in contractile strength and blood pressure); 2) epinephrine (EPI), released in circulation by the adrenal cortex affecting both the myocardium and peripheral vessels; 3) direct effect on peripheral vessels through local release of EPI and NE; and 4) circulating NE, which can act in multiple locations (e.g., increase in heart rate during exercise of heart transplant recipients) (7).

Cardiovascular Adrenergic Receptors (ARs)

The sympathetic transmitters NE and EPI bind to specific ARs, which are specialized macromolecules embedded in the cell membrane. Approximately 80% of NE released by the sympathetic nerve terminals is recycled by the NE transporter 1, whereas the remainder clears into circulation (8). Both NE and EPI exert their biological actions via activation of 9 different AR subtypes, 3 α_1 -receptors (α_{1A} , α_{1B} , and α_{1D}), 3 α_2 -receptors (α_{2A} , α_{2B} , and α_{2C}), and 3 beta-receptors (β_1 , β_2 , and β_3) (9). All ARs have 7 transmembrane receptors that signal primarily via interaction with heterotrimeric G proteins.

The human heart contains β_1 , β_2 , and β_3 receptors (10). The β_1 - and β_2 -AR subtypes are expressed at a ratio of 70:30, and their stimulation increases cardiac contractility (positive inotropic effect), frequency (positive chronotropic effect), and rate of relaxation (lusitropic effect) as well as impulse conduction through the atrioventricular node (positive dromotropic effect). β_3 -ARs are predominantly inactive during normal physiologic conditions (11); however, their stimulation seems to produce a negative inotropic effect opposite to that induced by β_1 - and β_2 -ARs, involving the nitric oxide synthase pathway (12), acting as a “safety valve” during intense adrenergic stimulation (13). Agonist-induced activation of beta-ARs catalyzes the exchange of guanosine triphosphate for guanosine diphosphate on the G_{α} -subunit of G proteins, resulting in the dissociation of the heterotrimer into active G_{α} - and $G_{\beta\gamma}$ -subunits, which

are competent to signal independently (14). The heterogeneity of G-protein alpha subunit, of which there are ≈ 20 subtypes (G_s , G_i , G_q , G_o , and so on), is the central basis of G-protein coupled receptor signaling.

In the human heart, activation of β_1 - and β_2 -ARs is the most powerful physiologic mechanism to acutely increase cardiac performance. β_1 -ARs activate G_s proteins whereas β_2 -ARs use both G_i and G_s proteins. G_s signaling acts as a “receptor-accelerator,” and G_i signaling as a “receptor-brake” (15). G_s signaling stimulates the effector enzyme, adenylyl cyclase, resulting in dissociation of adenosine 3',5'-cyclic monophosphate (cAMP), which in turn binds to cAMP-dependent protein kinase A. Targets of protein kinase A-induced phosphorylations in the AR signaling pathway are: 1) the L-type calcium channels and ryanodine receptors, both leading to an increase in Ca^{2+} entry into the cell (16); 2) the hyperpolarization-activated cyclic nucleotide-gated channels, which generate the hyperpolarization-activated cation inward current (I_h) affecting the initiation and modulation of rhythmic activity in cardiac pacemaker cells (17); 3) phospholamban, a modulator of the sarcoplasmic reticulum associated ATP-dependent calcium pump, which accelerates Ca^{2+} reuptake by the sarcoplasmic reticulum accelerating cardiac relaxation (18); 4) troponin I and myosin binding protein-C, which reduce myofilament sensitivity to Ca^{2+} accelerating the relaxation of myofilaments (18); and 5) phospholemman, a subunit of Na^+/K^+ -ATPase, relieving its inhibitory influence and resulting in the stimulation of the sodium pump (19) (Fig. 2).

Moreover, protein kinase A phosphorylates beta-ARs, resulting in partial uncoupling and desensitization of the receptor to further agonist stimulation (*heterologous desensitization*). G_i signaling decreases cAMP levels, activates mitogen-activated protein kinase, and contributes to the regulation of receptor signaling and activation of nuclear transcription.

The human heart also expresses α_{1A} - and α_{1B} -ARs at lower levels ($\approx 20\%$) than those of beta-ARs (20). It is unknown whether cardiac α_1 -ARs play a major role under physiologic conditions. Moreover, the α_1 -ARs heavily populate major arteries (including the aorta, pulmonary arteries, mesenteric vessels, and coronary arteries) and activation of these receptors by NE and EPI is a major contributor to the regulation of blood flow by vasoconstriction (21). Both α_{1A} - and α_{1B} -AR subtypes couple to the G_q family of heterotrimeric G proteins, which, in turn, activate phospholipase C_b . Phospholipase C_b hydrolyzes phosphatidylinositol (4,5) biphosphate to generate the second messengers inositol [1,4,5]-trisphosphate and 2-diacylglycerol. Inositol [1,4,5]-trisphosphate contributes to the regulation of intracellular Ca^{2+} responses, whereas 2-diacylglycerol activates some of the isomers of protein kinase C as well as some of the transient receptor potential channels (Fig. 3). Stimulation of vascular α_{2B} -ARs

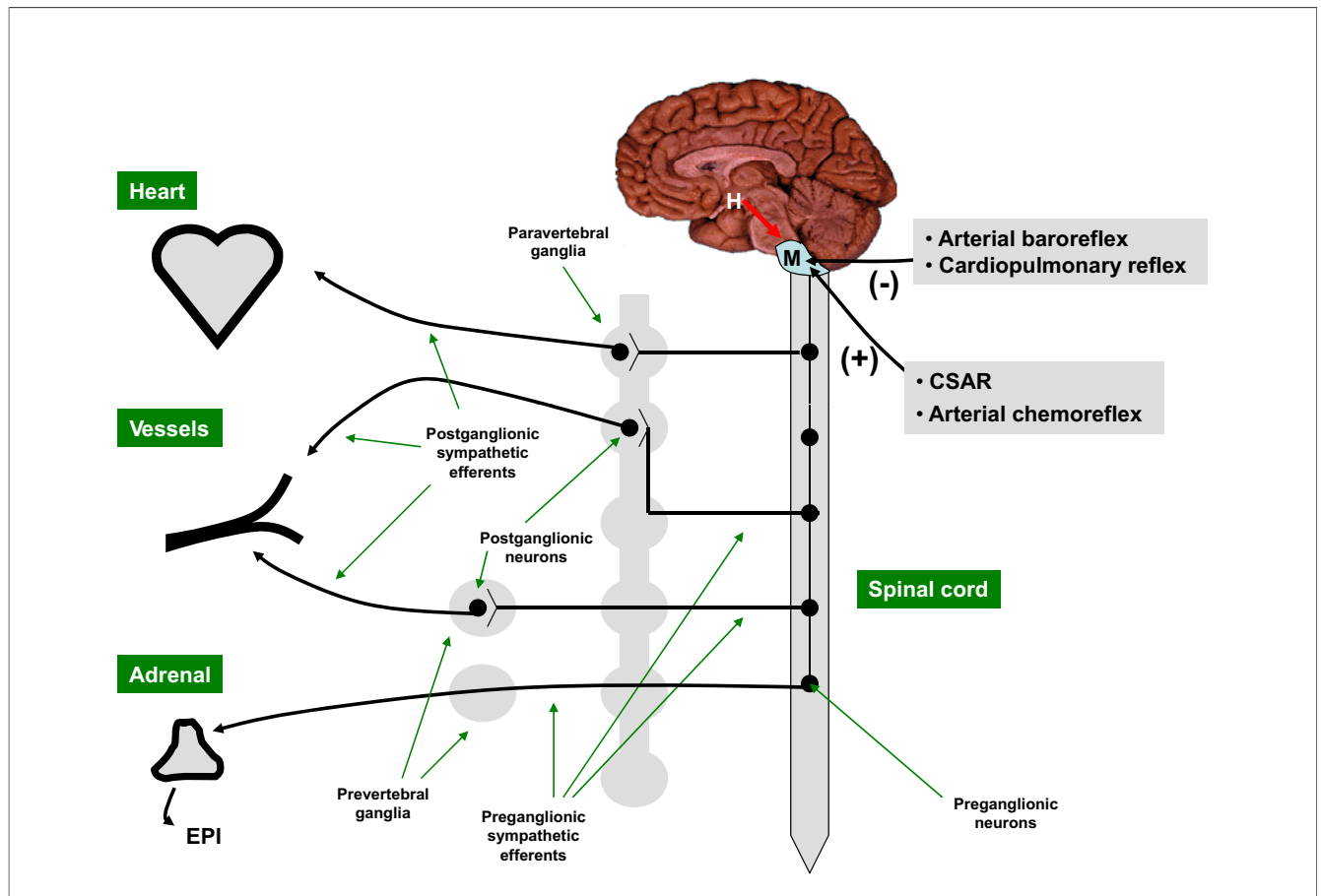


Figure 1 The Sympathetic Nervous System

The most important level of integration of sympathetic nervous system efferent activities to the cardiovascular system resides in the *dorsolateral reticular formation of the medulla*. The hypothalamus modifies the activity of the medullary centers and is important in stimulating cardiovascular responses to emotion and stress. The motor outflow of the sympathetic nervous system is formed by 2 serially connected sets of neurons. The first set (*pre-ganglionic neurons*) originates in the brain stem or the spinal cord, and the second set (*post-ganglionic neurons*) lies outside the central nervous system in collections of nerve cells called *sympathetic ganglia*. The sympathetic pre-ganglionic neurons originate in the lateral horns of the 12 thoracic and the first 2 or 3 lumbar segments of the spinal cord (*thoracolumbar outflow*). The axons of these neurons (short, myelinated) exit the spinal cord in the ventral roots and then synapse on either sympathetic ganglion cells or chromaffin cells in the adrenal gland that release epinephrine (EPI). The sympathetic ganglia can be divided into 2 major groups: 1) the *paravertebral* (3 in the cervical region including the right and left stellate ganglia, 10 to 11 in the thoracic region, 4 in the lumbar region, and a single, unpaired ganglion lying in front of the coccyx), which lie on each side of the vertebrae and are connected to form the sympathetic chain or trunk; and 2) the *pre-vertebral (pre-aortic)*, which provide axons that are distributed with the 3 major gastrointestinal arteries arising from the aorta. The predominant neurotransmitter of the sympathetic pre-ganglionic neurons is *acetylcholine*, whereas the predominant neurotransmitter of most sympathetic post-ganglionic neurons is *norepinephrine*. Sympathetic activity is attenuated (-) by the arterial baroreflex and the cardiopulmonary reflex and increased (+) by the cardiac sympathetic afferent reflex (CSAR) and the arterial chemoreceptor reflex. H = hypothalamus; M = medulla.

causes a transient vasoconstriction, whereas activation of central α_{2A} -ARs leads to a decrease in blood pressure by inhibiting central sympathetic outflow (22). The release of NE from sympathetic nerves is controlled by pre-synaptic α_{2A} - and α_{2C} -ARs. Both pre-synaptic α_{2} -ARs are essential, as deletion of α_{2A} - and α_{2C} -ARs leads to cardiac hypertrophy and failure due to chronically enhanced catecholamine release.

Assessment of SNS Activity

Activity of SNS is difficult to evaluate in the clinical setting. Plasma NE measurement represents a crude guide to assess sympathetic neural function because it depends on the rate

of immediate NE reuptake as well as NE clearance from circulation (23). Likewise, frequency analysis of heart rate variability signals, although easily performed noninvasively, has been shown to have limitations (24). Indeed the low-frequency spectral power (approximately 0.05 to 0.15 Hz), in addition to cardiac sympathetic nerve traffic, depends on other factors, including multiple neural reflexes, cardiac AR sensitivity, post-synaptic signal transduction, and electrochemical coupling (25). Two state-of-the-art techniques that best quantify sympathetic nerve activity in humans are radiotracer measurements of regional NE spillover and microneurography (microelectrode direct measurements of post-ganglionic sympathetic nerve activity—the

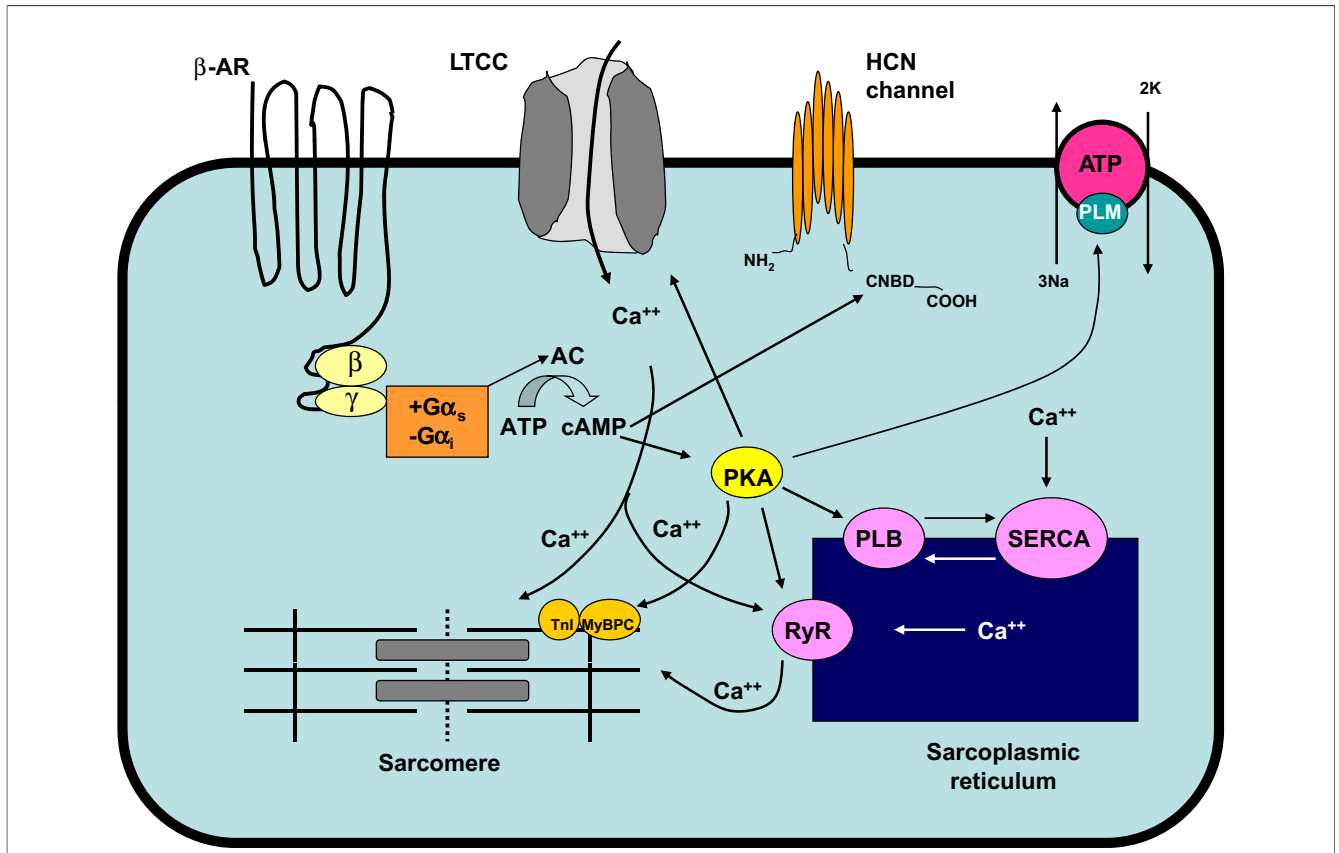


Figure 2 Beta-AR Signaling

The major intracellular effect of the sympathetic transmitters norepinephrine and epinephrine is mediated by formation of 3',5'-cyclic monophosphate (cAMP), which increases the activity of the cAMP-dependent protein kinase A (PKA). PKA mediates a series of phosphorylations in diverse intracellular substrates, including the L-type Ca^{++} channels (LTCC), hyperpolarization-activated cyclic nucleotide-gated (HCN) channels, sarcoplasmic ryanodine receptors (RyR), phospholamban (PLB), myofibrillar proteins troponin I (TnI), cardiac myosin-binding protein C (MyBPC), and phospholemman (PLM). AC = adenylyl cyclase; AR = adrenergic receptor; ATP = adenosine triphosphate; CNBD = cyclic nucleotide-binding domain; $G_{\alpha_{i}}$ and $G_{\alpha_{s}}$ = G protein alpha-subunit subtypes; SERCA = sarcoendoplasmic reticulum.

proximate neural stimulus to NE release) (26,27). These assessments allow discrimination between the central or peripheral contribution of increased plasma NE levels and precise estimation of the regional sympathetic neural function, both under physiological and pathological conditions.

Neural imaging techniques allow direct visualization of sympathetic innervation of human organs, thus providing information on the in vivo metabolism of NE in different cardiovascular beds. Cardiac neuronal distribution and function can be imaged with standard gamma-cameras and positron emission tomography using radiolabeled analogs of NE (28); whereas, post-synaptic beta-AR distribution and density can be determined using positron emission tomography (29). Although technical improvements have allowed for a more precise assessment of human adrenergic function, no technique so far available can be viewed as the "gold standard" (30). Limitations of the various techniques may be reduced if these methods are seen as being complementary and are employed in combination.

Cardiac sympathetic neuronal activity or its pharmaceutical inhibition can also be noninvasively assessed by the use of

^{123}I -metaiodobenzylguanidine (MIBG), an analogue of NE (31), using semiquantitative analyses, namely early heart-to-mediastinum ratio, late heart-to-mediastinum ratio, and myocardial washout. Beta-blockade and renin-angiotensin-aldosterone inhibition are associated with an increase in ^{123}I -MIBG uptake and a reduced washout. Data from a systematic meta-analysis suggest that patients with decreased late heart-to-mediastinum or increased myocardial ^{123}I -MIBG washout have a worse prognosis than those patients with normal semiquantitative myocardial MIBG parameters (32). A prospective study that compared the predictive value of cardiac ^{123}I -MIBG imaging for sudden cardiac death with that of the signal-averaged electrocardiogram, heart rate variability, and QT dispersion in patients with mild-to-moderate heart failure demonstrated that ^{123}I -MIBG was the only powerful predictor of sudden cardiac death independently of left ventricular ejection fraction (33). Finally, the recently presented ADMIRE-HF (AdreView Myocardial Imaging for Risk Evaluation in Heart Failure) trial demonstrated that ^{123}I -MIBG cardiac imaging carries additional independent prognostic information for risk-

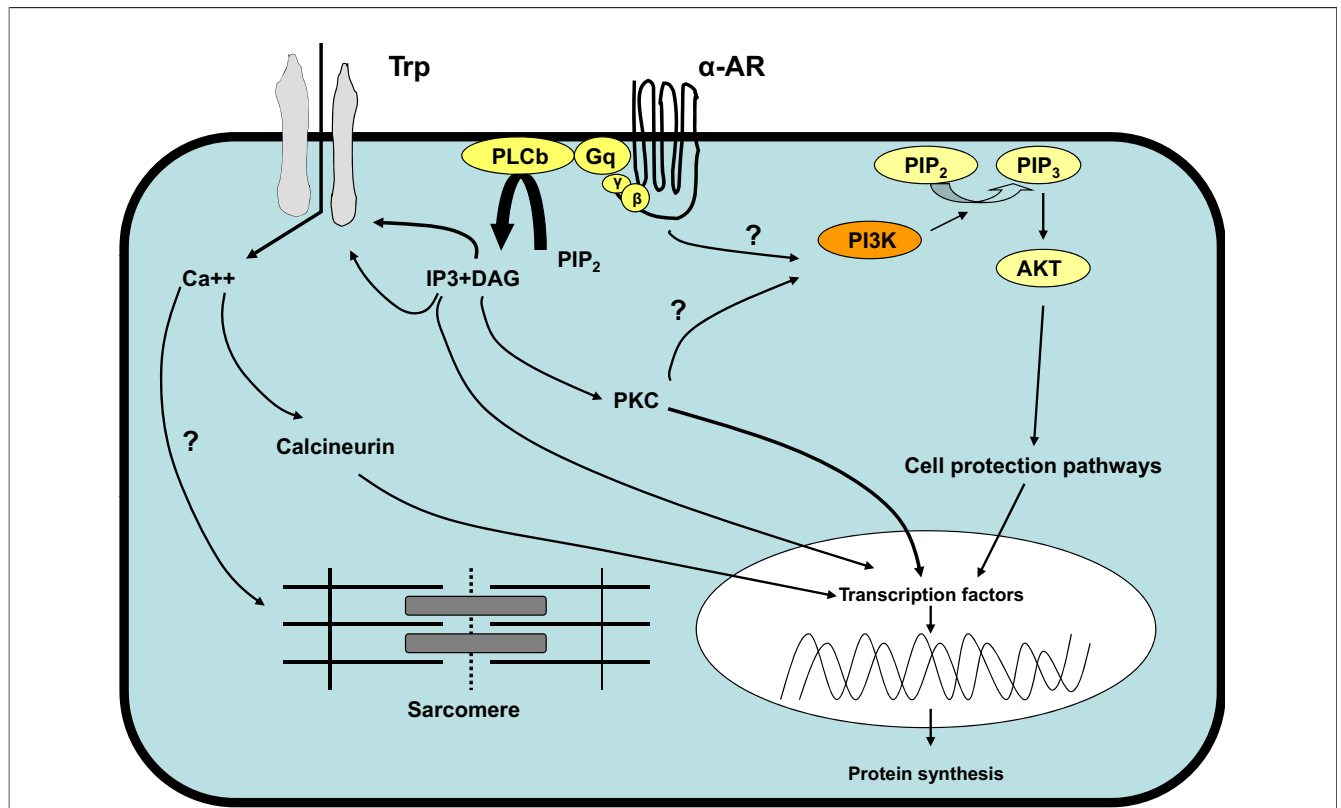


Figure 3 Alpha₁-AR Signaling

Agonist-induced stimulation of alpha₁-ARs activates G_q and phospholipase C_β (PLC_β), resulting in hydrolysis of phosphatidylinositol bisphosphate (PIP₂), to generate inositol trisphosphate (IP₃) and diacylglycerol (DAG). DAG, in turn, activates protein kinase C (PKC) to initiate a series of phosphorylations that alter channel activity and induce transcriptional changes. Moreover, IP₃ interacts with perinuclear inositol trisphosphate receptors (IP₃R) disinhibiting growth-related gene transcription. Both PIP₂ and DAG increase the permeability of the transient receptor potential (Trp) channel to Ca²⁺, which enters the cell and activates calcineurin to initiate downstream growth signaling pathways. Ca²⁺ entry through transient receptor potential channels may also act on myofilaments enhancing contractile responses. The alpha₁-AR also transactivates epithelial growth factor receptors, resulting in formation of phosphoinositide 3-kinase (PI₃K) and phosphatidylinositol trisphosphate (PIP₃), activation of the Akt pathway, and initiation of cell-survival signaling pathways. Abbreviations as in Figure 2.

stratifying heart failure patients on top of commonly used markers such as left ventricular ejection fraction and B-type natriuretic peptide (34).

Heart Failure and SNS Hyperactivity

Myocardial systolic dysfunction is associated with neuro-humoral hyperactivity aiming at preservation of cardiac output. The neuronal limb of this response is represented by SNS, whereas the humoral limb is represented by the increased secretion of certain hormones, the most important being those forming the renin-angiotensin-aldosterone axis (35). Sympathetic hyperactivity is evidenced by increased plasma NE levels, central sympathetic outflow, and NE plasma spillover from activated sympathetic nerve fibers (36). Indeed, application of isotope dilution methods for measuring cardiac NE plasma release indicate that in untreated heart failure patients, cardiac NE spillover is increased as much as 50-fold, similar to levels seen in healthy hearts during maximal exercise (37). There is limited information

regarding chronic SNS activation in heart failure with preserved left ventricular ejection fraction (diastolic heart failure) (38). However, the findings of a recent study indicate that, in patients with hypertension, SNS hyperactivity (increased muscle sympathetic nerve traffic) may contribute to the development of left ventricular diastolic dysfunction and account for the increased cardiovascular risk (39).

In contrast to the increased muscle sympathetic nerve activity and NE spillover, patients with systolic heart failure may have decreased neuronal density, decreased neuronal function resulting in decreased NE concentration within the cardiomyocytes, or a combination, besides a reduction in post-synaptic beta-receptor density (40). The mechanism for decreased intracellular NE concentration is unclear. Experimental studies suggest reduced neuronal NE transporter expression and/or activity in association with heightened release (41). Moreover, complementary animal and human studies demonstrated a reduction in the myocardial content and rate of release of the nerve growth factor in

heart failure, which in turn modifies the expression of NE transporter in cell culture models (42).

Mechanisms of SNS hyperactivity in heart failure. The sympathetic hyperactivity observed in heart failure is closely related to abnormalities in cardiovascular reflexes. The sympathoinhibitory cardiovascular reflexes such as the arterial baroreceptor reflex are significantly suppressed, whereas the sympathoexcitatory reflexes, including the cardiac sympathetic afferent reflex and the arterial chemoreceptor reflex, are augmented (43). Moreover, in heart failure, the cardiac neuronal hierarchy undergoes remodeling and the spatially organized reflexes acting in isolation may destabilize efferent neuronal control of regional cardiac electrical and/or mechanical events. Also, the central nervous system may receive input from a variety of sources in the body and activate mechanisms that play a major role in progressive cardiac remodeling and dysfunction (Fig. 4) (44,45). For example, it has been demonstrated that the angiotensin-II and aldosterone produced locally in the brain affect SNS activation and progression of systolic heart failure (46,47). It seems that angiotensin-II initiates a positive feedback mechanism leading to up-regulation of the angiotensin II type 1 receptor, nitric oxide inhibition, and increased production of superoxide anion through the action of reduced nicotinamide adenine dinucleotide phosphate oxidase, lead-

ing to increased sympathetic outflow and disease progression (48,49).

SNS hyperactivity and cardiac ARs. Prolonged SNS activation adversely affects excitation-contraction coupling (50) and enhances apoptotic pathways (51), playing a central role in the progression of chronic heart failure. A striking feature of heart failure is a characteristic set of molecular alterations in the components of the beta-AR signaling pathway, including a decrease in beta₁-AR density and messenger ribonucleic acid, uncoupling of beta₁-AR from G_s, increased G_i protein and messenger ribonucleic acid, and impaired compartmentalization of cAMP/protein kinase A signaling (52-54). Beta₁-AR abnormalities have been attributed to the recruitment of both beta-AR kinase 1 and phosphoinositide 3-kinase to the ligand-activated receptor complex (55,56). In addition, the levels of both G_i signaling proteins and the G-protein receptor kinases are increased. It seems that beta-AR desensitization is a predominantly protective adaptation, which follows the increase in NE plasma levels that keeps intracellular cAMP concentration constant (57). This is further supported by the fact that overexpression of human beta₁-ARs in transgenic mice initially augments cardiac function but eventually leads to pathologic hypertrophy and heart failure (58).

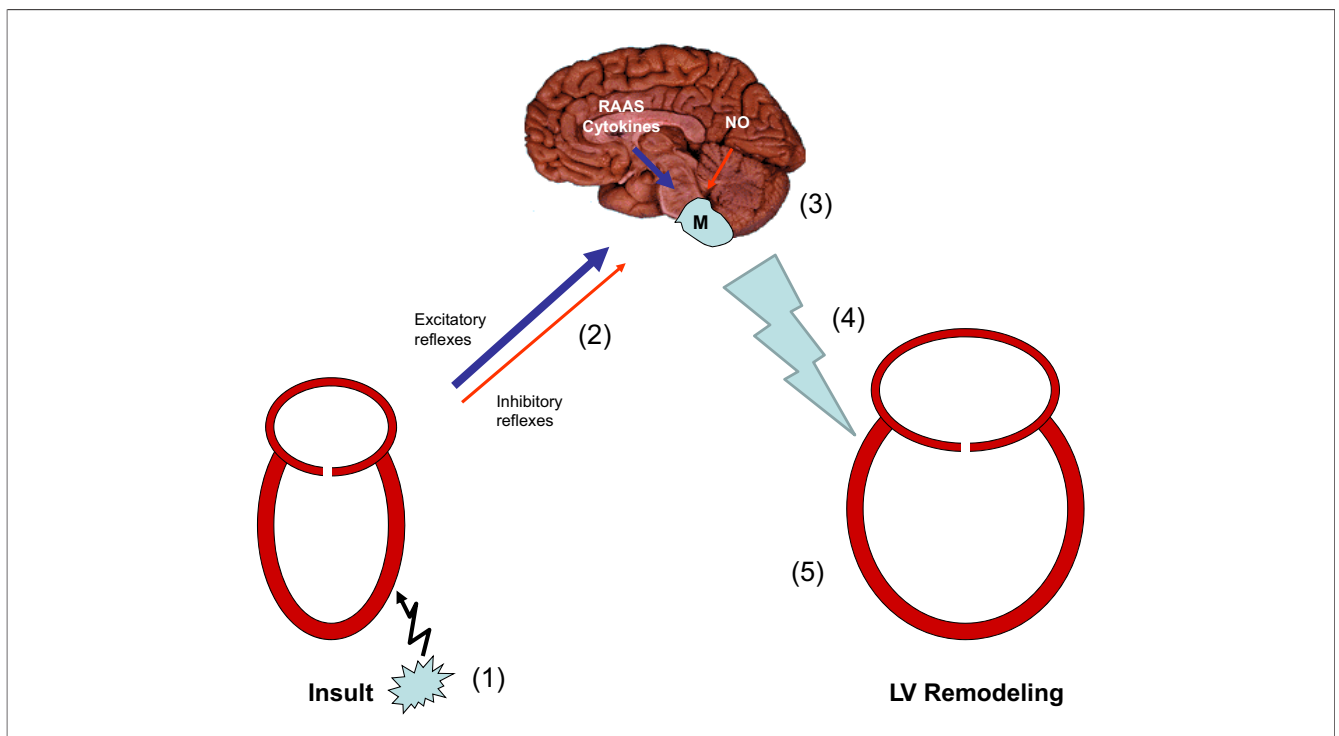


Figure 4 Sympathetic Activation in Systolic Heart Failure

(1) An insult causes cardiac dysfunction and decreases cardiac output. (2) Attenuation of inhibitory sympathetic cardiovascular reflexes and augmentation of excitatory sympathetic cardiovascular reflexes is associated with increased sympathetic input in the central nervous system. (3 and 4) Central facilitation of the augmented cardiovascular sympathetic afferent reflex mediated by an increase in angiotensin II and cytokines and a decrease in nitric oxide (NO) contributes to tonic increases in sympathetic output. (5) The chronic increase in sympathetic output is associated with structural and functional changes in the cardiomyocytes and the interstitium leading to left ventricular (LV) dilation and systolic dysfunction (LV remodeling). m = medulla; RAAS = renin-angiotensin-aldosterone system.

The role of beta₂-ARs in heart failure has not been delineated clearly. There is no significant change in the levels of beta₂-ARs in the failing heart, and studies in transgenic animals have demonstrated that, in contrast to the early cardiomyopathy resulting from low-level (≈5-fold) cardiac overexpression of beta₁-ARs, even a 100-fold overexpression of beta₂-ARs in the mouse heart significantly increases cardiac contractile force without any cardiomyopathic consequences; extremely higher levels of overexpression (up to 350-fold) are needed to induce pathological changes (59). Moreover, because beta₂-AR signaling contributes to an increase in the levels of G_s, it has been suggested that this may activate a protective antiapoptotic pathway in the setting of catecholamine excess. Indeed, in a recent experimental study, selective inhibition of G₁-signaling in response to myocardial ischemia was associated with a marked enhancement of myocardial infarct size and apoptotic signaling (60). The role of beta₃-ARs in heart failure has not been elucidated. However, it has been proposed that in heart failure there is an excess of beta₃-AR signaling, which exerts a negative inotropic effect by increasing nitric oxide production and inhibiting calcium transients (61,62).

Alpha₁-ARs may function in a compensatory fashion to maintain cardiac inotropy in the heart involved in both developmental cardiomyocyte growth as well as pathological hypertrophy (63). In the presence of pressure overload or with myocardial infarction, activation of alpha₁-ARs, particularly the alpha_{1A}-subtype, also appears to produce important pro-survival effects at the level of the cardiomyocyte and to protect against maladaptive cardiac remodeling and decompensation to heart failure (64,65). Recent evidence suggests that alpha₂-AR deficiency is associated with elevated catecholamine levels, cardiac hypertrophy, fibrosis, and eventually heart failure (66).

Catecholamine cardiotoxicity. Catecholamine-induced cardiotoxicity is well known. Intravenous infusions of isoproterenol or NE result in acute contraction band lesions attributed to relative hypoxia, increased sarcolemmal permeability, calcium overload, elevation of cAMP, activation of alpha-ARs, activation of beta-ARs, and formation of oxidative catecholamine metabolites (67,68). Chronic catecholamine administration in rats causes interstitial fibrosis, reduces beta-AR-mediated inotropic responses, promotes myocyte apoptosis, and induces pump dysfunction primarily through left ventricular dilation (69,70). Moreover, exposure to NE of both adult and neonatal rat cardiac myocytes stimulates apoptosis via the adrenergic and the reactive oxygen species–tumor necrosis factor–caspase signaling pathways (71,72). Of note, catecholamines may induce oxidative damage through reactive intermediates resulting from their auto-oxidation, irrespective of their interaction with ARs, thus representing an important factor in the pathogenesis of catecholamine-induced cardiotoxicity (73).

Catecholamine surge has been implicated in the pathogenesis of stress (Takotsubo) cardiomyopathy or apical

ballooning (74). It has been hypothesized that stress cardiomyopathy is a form of myocardial stunning, produced by the high levels of circulating EPI, which trigger a negative inotropic switch in intracellular signal trafficking in ventricular cardiomyocytes, from G_s protein to G₁ protein signaling via the beta₂-AR (75). This effect is magnified at the apical myocardium, where beta-AR density is greatest (76).

AR Polymorphisms

Marked variability in disease phenotype and response to treatment suggests a potential disease-modifying role for common genetic variants in heart failure. Functional polymorphisms in beta- and alpha-AR genes, which have been associated with heart failure phenotypes and interaction with beta-blockers, are under pharmacogenomics, the study of variations of deoxyribonucleic acid and ribonucleic acid characteristics as related to drug response, and pharmacogenetics investigations. Common polymorphisms of the beta₁-ARs are: 1) the arginine to glycine switch at codon 389 (Arg389Gly), associated with significantly lower adenylyl cyclase activity in response to agonist than the Arg389 variant (77); and 2) the serine to glycine switch at codon 49 (Ser49Gly), associated with increased agonist-promoted down-regulation and adrenergic coupling than the Ser49 variant (78). Likewise, common polymorphisms of the beta₂-ARs are: 1) the glycine to arginine switch at codon 16 (Gly16Arg), resulting in reduced agonist-promoted down-regulation (79); 2) the glutamine to glutamic acid switch at codon 27 (Gln27Glu), which is more resistant to receptor down-regulation; and 3) the threonine to isoleucine switch at codon 164 (Thr164Ile), demonstrating impaired receptor coupling and reduced adenylyl cyclase activation (80). Finally, a deletion mutation of amino acids 322 to 325 (alpha_{2C}del322-325) in alpha₂-AR gene leads to increased NE release (81).

A lower prevalence of ventricular arrhythmias has been attributed to the Gly389 allele (82) and improved survival has been reported for African-American heart failure patients with the G-protein receptor kinase 5–Leu41 variant (83).

Therapeutic impact of beta-AR polymorphisms. Many studies have examined the impact of the aforementioned polymorphisms in response to beta-blockade among heart failure patients. Preliminary studies in patients treated with various beta-blockers have demonstrated a survival benefit (84) and a significant reduction in left ventricular end-diastolic diameter (85) for those who carried the Gly49 allele as compared to the Ser49 homozygous patients. A similar reversal of the remodeling process has been reported for Arg389-homozygous heart failure patients treated with carvedilol as compared with Gly389-homozygous (86) and Arg389Gly-heterozygous patients (87). However, neutral results have also been reported. For example, no survival benefit was observed for the Ser49Gly or the Arg389Gly patients treated with carvedilol (79,88), bisoprolol (79), or

metoprolol (88), and for the Arg389-homozygous or Gly389 patients treated with metoprolol CR/XL (89). Finally, a dose-dependent response to beta-blockade has been reported, whereby low doses in patients carrying the Gly49 allele portend worse outcomes than in Ser49-homozygous patients, whereas in higher doses, genotype-dependent differences are not observed (90).

More recent data, however, suggest improvement in the therapeutic effect of bucindolol by pharmacogenetic targeting. In the deoxyribonucleic acid substudy of the BEST (Beta Blocker Evaluation of Survival Trial) (91), patients carrying the Arg389 genotype had a greater agonist-promoted ventricular contractility and improved age-, sex-, and race-adjusted survival than the Gly389 carriers (92). Combinations of the beta₁-AR (codon 389 Arg→Gly) and alpha_{2C}-AR (322-325 WT→del) polymorphisms were recently used to stratify patients according to the clinical response to bucindolol into “very favorable,” “favorable,” and “unfavorable” genotypes (Table 1) (93). Finally, a combination of 3 genetic polymorphisms (the Arg389 allele included) acted as a predictor of appropriate shock therapies in patients with and without heart failure carrying an implantable cardioverter-defibrillator, thus identifying those at high risk for sudden cardiac death (94). In this respect, the use of genetic polymorphisms as potential tools to guide therapeutic strategies seems a promising new approach.

Therapeutic Implications

Inhibition of SNS activity. BETA-BLOCKERS. Beta-blockers can be broadly classified into generations: 1) *first generation*, which are nonselective and competitively block both the beta₁- and beta₂-AR (propranolol, nadolol, timolol); 2) *second generation*, with much higher affinity for the beta₁- than for the beta₂-AR (atenolol, metoprolol, bisoprolol); and 3) *third generation*, which may be selective (celiprolol, nebivolol) or nonselective (bucindolol, carvedilol, labetalol) but all cause peripheral vasodilation mediated via alpha₁-AR blockade (bucindolol, carvedilol, labetalol), beta₂-AR agonism (celiprolol), or nitric oxide synthesis (nebivolol) (95). Cardioselectivity of beta-blockers is dose-dependent and decreases with larger doses. Both selective and nonselective agents have negative chronotropic and inotropic effects. Selective agents have a less inhibitory affect on the beta₂-receptors and are less likely to cause peripheral vasoconstriction (96). Exercise performance may be impaired to a lesser extent by beta₁-selective agents, partially because beta₂-

blockade tends to blunt the exercise-induced increase in skeletal muscle blood flow. Finally, there are beta-blockers that at low concentrations antagonize the cardiostimulant effects of catecholamines but at high concentrations cause cardiostimulation. These cardiostimulant beta-blockers (e.g., pindolol, alprenolol, oxprenolol), widely known as nonconventional partial agonists, antagonize the effects of catecholamines through a high-affinity site (beta_{1H}AR), but cause cardiostimulation mainly through a low-affinity site (beta_{1L}AR) of the myocardial beta₁-AR (97). Nonconventional partial agonists are considered potentially arrhythmogenic and should not be used for heart failure treatment.

The majority of beta-blockers are partially or totally metabolized by CYP2D6, whose gene has more than 90 different variants (98). Individuals homozygous for non-functional alleles are considered poor metabolizers. Several inconsistencies have been reported regarding the genotype-phenotype correlations for intermediate or extensive metabolizers (99). Poor metabolizers treated with metoprolol have a 5-fold higher risk for adverse effects (100), whereas the adverse effects of carvedilol and bisoprolol are less influenced by the genetic background (101,102).

Among all beta-blockers, bisoprolol (except in U.S.), carvedilol, and metoprolol succinate (except in Canada) are almost universally approved for the treatment of chronic heart failure (Table 2) (103-114). Chronic beta-blocker therapy improves left ventricular performance and reverses left ventricular remodeling, reduces risk of hospitalization, and improves survival. Various protective mechanisms linked with SNS antagonism have been attributed to beta-blockers, namely: 1) inhibition of catecholamine cardiotoxic effects; 2) beta₁-AR up-regulation (carvedilol is an exception); 3) attenuation of neurohumoral vasoconstrictive, growth-promoting, and pro-apoptotic systems (renin-angiotensin-aldosterone system, endothelin); 4) subendocardial coronary flow enhancement (as a result of diastolic prolongation); 5) restoration of the reflex control on the heart and circulation; and 6) improved myocardial performance (by reducing heart rate and oxygen demand) (115).

ALPHA-BLOCKERS. In the Veterans Administration Cooperative Study (116), heart failure patients receiving the alpha₁-blocker prazosin experienced worse outcomes than did those receiving the combined vasodilator therapy of hydralazine and isosorbide dinitrate. Prazosin chronic use has been reported to increase catecholamine

Table 1 Outcomes by Beta₁ and Alpha_{2C} Genotype in the BEST Genetic Substudy

End Point	Beta ₁ 389Arg/Arg + Alpha _{2C} 322-325 WT or DEL Carrier (n = 493)	Beta ₁ 389Gly Carrier + Alpha _{2C} 322-325 WT/WT (n = 413)	Beta ₁ 389Gly Carrier + Alpha _{2C} 322-325 DEL Carrier (n = 134)
All-cause mortality	0.62 (0.39-0.99)*	0.75 (0.48-1.17)	1.04 (0.43-2.54)
Cardiovascular mortality	0.52 (0.31-0.88)*	0.60 (0.36-0.97)*	1.11 (0.45-2.78)
Heart failure hospitalization	0.56 (0.39-0.82)†	0.77 (0.53-1.13)	0.73 (0.35-1.53)

Data presented as relative risk (95% confidence interval). *p < 0.05; †p < 0.01.

Arg = arginine; BEST = Beta-Blocker Evaluation of Survival Trial; DEL = deletion; Gly = glycine; WT = wild type.

Table 2 Large Randomized Trials With Beta-Blockers and the ACC/AHA Guidelines Recommended Doses

Beta-Blocker	Trial(s)	Year	n	Benefit	Initial Daily Dose(s) (103)	Maximum Dose(s)
Metoprolol	MDC (104)	1993	383	All-cause mortality or morbidity was 34% lower in the metoprolol than in the placebo group (HR: 0.66; 95% CI: 0.62 to 1.06; $p = 0.058$). The change in LVEF from baseline to 12 months was significantly greater with metoprolol than with placebo (0.13 vs. 0.06; $p < 0.0001$)	5–10 mg twice	100 mg twice
Metoprolol CR/XL	MERIT-HF (105)	1999	3,991	All-cause mortality was 34% lower in the metoprolol CR/XL group than in the placebo group (7.2% vs. 11.0%; HR: 0.66; 95% CI: 0.53 to 0.81; $p = 0.00009$)	12.5–25 mg once	200 mg once
Carvedilol	U.S. Carvedilol HF Study Group (106)	1996	1,094	All-cause mortality was 65% lower in the carvedilol than in the placebo group (3.2 vs. 7.8%; HR: 0.65; 95% CI: 0.39 to 0.80; $p < 0.001$)	3.125 mg twice	25 mg twice
	Australia/New Zealand HF Research Collaborative Group (107)	1997	415	All-cause mortality or morbidity was 26% lower in the carvedilol than in the placebo group (104 vs. 131; HR: 0.74; 95% CI: 0.57 to 0.95)		
	CAPRICORN (108)	2001	1,959	All-cause mortality was lower in the carvedilol than in the placebo group (12% vs. 15%; HR: 0.77; 95% CI: 0.60 to 0.98; $p = 0.03$)		
	COPERNICUS (109)	2001	2,289	Carvedilol reduced the combined risk of death or hospitalization for a cardiovascular reason by 27% ($p = 0.00002$) and the combined risk of death or HF hospitalization by 31% ($p = 0.00004$)		
	COMET (110)	2003	3,029	All-cause mortality was lower in the carvedilol than in the metoprolol group (34% vs. 40%; HR: 0.83; 95% CI: 0.74 to 0.93; $p = 0.0017$)		
Bisoprolol	CIBIS (111)	1994	641	All-cause mortality did not reach statistical significance: 67 patients died on placebo, 53 on bisoprolol (HR: 0.80; 95% CI: 0.56 to 1.15; $p = 0.22$). Bisoprolol reduced HF hospitalization ($p < 0.01$) and improved the functional status		
	CIBIS II (112)	1999	2,647	All-cause mortality was 34% lower with bisoprolol than on placebo (11.8% vs. 17.3%; HR: 0.66; 95% CI: 0.54 to 0.81; $p < 0.0001$)	1.25 mg once	10 mg once
	CIBIS III (113)	2005	1,010	This study demonstrated that it may be as safe and efficacious to initiate treatment for CHF with bisoprolol as with enalapril		
Nebivolol*	SENIORS (114)	2005	2,128	All-cause mortality or cardiovascular hospital admission occurred in 332 patients (31.1%) on nebivolol compared with 375 (35.3%) on placebo (HR: 0.86; 95% CI: 0.74 to 0.99; $p = 0.039$)	1.25 mg once	10 mg once

*Not endorsed in the ACC/AHA 2005 heart failure guidelines.

ACC/AHA = American College of Cardiology/American Heart Association; CAPRICORN = Carvedilol Post-Infarct Survival Controlled Evaluation; CHF = chronic heart failure; CI = confidence interval; CIBIS = Cardiac Insufficiency Bisoprolol Study; COMET = Carvedilol or Metoprolol European Trial; COPERNICUS = Carvedilol Prospective Randomized Cumulative Survival; HF = heart failure; HR = hazard ratio; LVEF = left ventricular ejection fraction; MDC = Metoprolol in Dilated Cardiomyopathy; MERIT-HF = Metoprolol CR/XL Randomized Intervention Trial in Congestive Heart Failure; SENIORS = Study of the Effects of Nebivolol Intervention on Outcomes and Rehospitalisation in Seniors with Heart Failure.

levels, diminishing any potentially beneficial action mediated through inhibition of the α_1 -receptor (117). In the ALLHAT (Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial) study (118), the doxazosin arm was terminated early because of the higher heart failure incidence.

Centrally acting agents. Central α_2 -ARs are possible targets of treatment, because their excitation inhibits SNS activation (119). *Clonidine* is a centrally acting agent with α_2 -agonist actions. In modest doses, it significantly

attenuates cardiac and renal sympathetic tone in heart failure patients. Interestingly, chronic clonidine administration exerts marked sympathoinhibitory effects without further clinical deterioration (120). Large clinical trials, however, are needed to evaluate the prospective of its broader use in chronic heart failure.

The centrally acting sympatholytic agent *moxonidine* has also been used in heart failure patients. Moxonidine acts through both α_2 and imidazoline receptors (121,122). It causes a marked dose-related reduction in plasma NE (123),

accompanied by evidence of reverse remodeling. However, in clinical trials, it led to increased mortality (124). Most likely, the harmful effects of sympatholysis are observed in hemodynamically unstable heart failure patients, who may need the adrenergic drive and, therefore, are pre-disposed to the adverse effects of adrenergic withdrawal (125). Beta-AR inhibition can be easily reversed by NE competition, which allows recruit adrenergic drive when needed to support cardiac function.

Renin-angiotensin-aldosterone system modulating agents. The renin-angiotensin-aldosterone system is activated in heart failure and the degree of activation correlates with prognosis. Angiotensin-II and aldosterone production enhances the release and inhibits the uptake of NE at nerve endings (126,127). *Angiotensin-converting enzyme inhibitors* have a predictable effect in increasing plasma renin and decreasing angiotensin-II and aldosterone levels, whereas NE and vasopressin reduction is attributed to the hemodynamic improvement (128). Plasma aldosterone levels may be elevated as high as 20-fold in patients with heart failure, primarily due to increased production by the adrenal glands following stimulation by the high plasma angiotensin-II concentrations. In addition to its electrolyte and metabolic effects, aldosterone promotes the development of myocardial fibrosis, facilitating the remodeling process and disease progression. Besides decreasing NE uptake, aldosterone has a negative effect on endothelial function and increases plasminogen activator inhibitor-1 levels. Two trials have shown benefit with aldosterone antagonists in heart failure patients and may be partially related to their effect on NE (129,130).

SNS stimulation. Dobutamine and milrinone represent the most commonly used inotropes targeting increase in cAMP levels (131). Dobutamine stimulates cAMP production by adenylate cyclase through the beta-adrenergic pathway, whereas the phosphodiesterase inhibitor milrinone prevents cAMP breakdown. Increased intracellular cAMP leads to an increase in endomyocyte calcium release. Elevated calcium levels enhance cardiac contractility through optimizing actin-myosin binding. However, increased calcium levels are also responsible for inotropic therapy side effects, especially arrhythmogenesis. Both inotropes produce a vasodilatory effect and can cause a reduction in arterial pressure; this is more prominent with milrinone (132). Finally, the effects of dobutamine are blunted when the patients are already on beta-blocker therapy (133).

Despite the clinical rationale for using inotropes for the failing heart, clinical trials conducted in chronic heart failure demonstrated disappointing results, with inotropic use significantly increasing mortality (134–136). For acute heart failure, the OPTIME-CHF (Outcomes of a Prospective Trial of Intravenous Milrinone for Exacerbations of Chronic Heart Failure) study compared 48-h intravenous infusion of milrinone with placebo in patients without absolute indication for inotropic therapy;

milrinone was associated with increased morbidity and similar mortality rate compared with placebo (137). In the PROMISE (Effects of Oral Milrinone on Mortality in Severe Chronic Heart Failure) trial (136), 1,088 patients with severe chronic systolic heart failure were assigned to double-blind treatment with 40-mg oral milrinone daily or placebo, on top of conventional treatment including digoxin, diuretics, and an angiotensin-converting enzyme inhibitor. Despite its beneficial hemodynamic actions, long-term therapy with oral milrinone increased the morbidity and mortality of patients with severe chronic systolic heart failure. Likewise, the ADHERE (Acute Decompensated Heart Failure National Registry) database (138) showed a worse clinical course in acute heart failure patients receiving inotropes compared to vasodilators. In accordance with these findings, inotrope use should only be considered for the subgroup of acute heart failure patients with clinically evident hypoperfusion or shock, or as a bridge to more definitive treatment, such as revascularization or cardiac transplantation. However, this subgroup represents the minority of those with acute heart failure ($\approx 10\%$).

Combined SNS inhibition and stimulation. Combined beta₁-inhibition with beta₂-stimulation with *clenbuterol* has been proposed as a treatment modality to achieve sustained reversal of severe heart failure in selected patients requiring left ventricular assist devices (139). The rationale for this approach was based on experimental studies demonstrating that clenbuterol treatment, alone or in combination with mechanical unloading, improved left ventricular function at the whole-heart and cellular levels by affecting cell morphology, excitation-contraction coupling, and myofilament sensitivity to calcium (140). After optimization of medical therapy and achieving a constant left ventricular size for at least 2 weeks, clenbuterol was administered at an initial dose of 40 μg twice daily, then at a dose of 40 μg 3 times daily, and finally at a dose of 700 μg 3 times daily. The dose was adjusted to maintain resting heart rate at a level below 100 beats/min. Prior to clenbuterol initiation, carvedilol was replaced by the selective beta₁-blocker bisoprolol.

It should be taken into consideration, however, that in a recent small, randomized controlled study, clenbuterol use in patients with chronic heart failure was associated with a significant increase in both lean mass and lean/fat ratio as well as in muscle strength, and a decrease in exercise duration (141). Thus, the effectiveness of clenbuterol in heart failure patients should be further evaluated in larger prospective trials.

Exercise. Exercise intolerance is a characteristic of patients with chronic heart failure, and skeletal myopathy contributes to the limitation of functional capacity in heart failure (142). SNS activation and myogenic reflex engagement moderate the heart and muscle vasculature to maintain adequate blood pressure during exercise (143). However, sympathetic overactivity contributes to the skeletal myop-

athy seen in heart failure, because SNS-mediated vasoconstriction at rest and during exercise restrains muscle blood flow, arteriolar dilation, and capillary recruitment, leading to underperfusion, ischemia, release of reactive oxygen species, and chronic inflammation (144). Due to the presence of exercise intolerance, heart failure patients are often counseled to limit their physical activity. However, this advice may be inappropriate, because current evidence suggests that exercise training improves central hemodynamics, peripheral muscle function, and symptoms and reduces sympathetic activity even in patients treated with beta-blockers (145,146). The HF-ACTION (Heart Failure—A randomized Controlled Trial Investigating Outcomes of exercise training) study (147), the first large, randomized, controlled trial to evaluate the effects of exercise training in heart failure patients, demonstrated that exercise training is safe and offers clinical benefits in this patient population. Specifically, exercise training was associated with an 11% reduction in all-cause mortality or hospitalization, a 9% reduction in cardiovascular mortality or cardiovascular hospitalization, and a 15% reduction in cardiovascular mortality or heart failure hospitalization. The mechanisms for these beneficial effects of exercise in heart failure patients proposed include: 1) improvement in arterial and chemoreflex control; 2) significant reduction in central sympathetic outflow; 3) correction of central nervous system abnormalities; 4) increase in peripheral blood flow; 5) reduction of circulating cytokines; and 6) increase in muscle mass (148). Recent experimental evidence suggests that the exercise training-induced beneficial effects on autonomic activity in heart failure may be due to an up-regulation in central antioxidative mechanisms and suppressed central pro-oxidant mechanisms (149).

Parasympathetic modulation. There is a complex, often antagonistic, interaction between the parasympathetic nervous system and the SNS mediated partially by the second messenger's cAMP and cyclic guanosine monophosphate. Indeed, vagus nerve afferent activation, originating peripherally, can modulate efferent sympathetic and parasympathetic function centrally and at the baroreceptor level. Moreover, efferent vagus nerve activation can have tonic and basal effects that inhibit sympathetic activation and release of NE at the pre-synaptic level. Cardiovascular effects of parasympathetic activation include heart rate reduction (indirectly by inhibition of the SNS and directly by hyperpolarization of sinus node cells) and vasorelaxation (through nitric oxide synthesis) or vasoconstriction (direct activation of smooth muscle) (150). The activity and physiological effects of the parasympathetic nervous system are attenuated in heart failure, including lack of attenuation of SNS activity (151). Clinical and experimental data suggest that beta-blockade in heart failure can augment reflex vagus nerve control of heart rate, by blocking cardiac sympathetic pre-junctional β_2 -AR that facilitate NE release (152), and by increasing the density of M_2 receptors, especially in endocardial tissues of the left ventricle free wall (153),

resulting in improved heart rate variability measurements (154). Finally, there are experimental studies that suggest that repeated exposure with a nicotinic agonist during the development of heart failure results in not only preserved but also supranormal effects of parasympathetic stimulation on the sinus node and that vagus nerve stimulation therapy, when combined with chronic beta-blockade, elicits an improvement in left ventricular function and remodeling that is additive to that achieved with beta-blockade alone (155,156).

Other treatment modalities. DIGOXIN. Digoxin increases cardiac contractility in heart failure patients by reversibly inhibiting the alpha subunit of the sodium-potassium ATPase, reducing the transmembrane sodium gradient and indirectly inhibiting the sodium-calcium exchanger. Thus, it allows calcium to accumulate in cardiac myocytes and be taken up by the sarcoplasmic reticulum (157). In addition, digoxin improves baroreceptor function, decreases sympathetic tone, and increases parasympathetic tone, favorably influencing autonomic balance in heart failure (158–160). In heart failure patients with atrial fibrillation, the combination of digoxin and a beta-blocker controls heart rate, and for heart failure patients in sinus rhythm, digoxin should be considered as an adjunct therapy for uncontrolled symptomatology (161).

POSITIVE AIRWAY PRESSURE. Continuous or bi-level positive airway pressure has been employed for the treatment of obstructive or central sleep apneas, which are highly prevalent in heart failure. Obstructive sleep apnea may affect heart failure through mechanical, adrenergic, and vascular mechanisms, whereas central sleep apnea likely arises as a consequence of heart failure (162,163). Treatment of heart failure patients with coexisting obstructive sleep apnea by continuous positive airway pressure improves baroreflex sensitivity during wakefulness, augments left ventricular ejection fraction, and lowers blood pressure and heart rate (164). The result may be even better with the use of bi-level positive airway pressure (165). Evidence also supports the use of positive airway pressure for improving several parameters of cardiovascular function in heart failure patients with coexisting central sleep apnea. Studies in this patient population have shown that continuous positive airway pressure attenuates central sleep apnea, improves nocturnal oxygenation, increases left ventricular ejection fraction, lowers NE levels, and increases the 6-min walking distance (166). Moreover, its early institution reduces the frequency of central sleep apnea episodes and may prolong heart transplant-free survival (167).

Conclusions

The role of activated SNS in maintaining hemodynamic stability in the face of acute injury to the cardiovascular

system is well known. Similarly, its role in heart failure progression and the benefits of beta-blocker therapy are well documented. Several newer developments related to the SNS are at various stages of research and clinical application. Genetic polymorphisms in the ARs may prove to be one of the earliest clinical applications for personalized medicine, both in terms of risk prediction, and pharmacogenomic application and drug response. There has been a growing interest in the use of SNS activity assessment by ¹²³I-MIBG imaging leading to an ongoing clinical trial. Role of alpha ARs in modulating cardiac function is unfolding and has potential therapeutic applications. Newer drugs that may modify the SNS, such as combined beta₁-inhibition and beta₂-stimulation with clenbuterol has sparked interest in patients with advanced heart failure requiring mechanical assist device support. Understanding SNS functioning in further details and its modulation will continue to provide pathophysiologic and therapeutic insights for heart failure management.

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Key Words: heart failure ■ sympathetic nervous system ■ adrenergic receptor ■ beta-blockers ■ sympatholytics ■ sympathomimetic inotropes.