Abstract: Heart failure (HF), the leading cause of death in the western world, develops when a cardiac injury or insult impairs the ability of the heart to pump blood and maintain tissue perfusion. It is characterized by a complex interplay of several neurohormonal mechanisms that become activated in the syndrome to try and sustain cardiac output in the face of decompensating function. Perhaps the most prominent among these neurohormonal mechanisms is the adrenergic (or sympathetic) nervous system (ANS), whose activity and outflow are enormously elevated in HF. Acutely, and if the heart works properly, this activation of the ANS will promptly restore cardiac function. However, if the cardiac insult persists over time, chances are the ANS will not be able to maintain cardiac function, the heart will progress into a state of chronic decompensated HF, and the hyperactive ANS will continue to push the heart to work at a level much higher than the cardiac muscle can handle. From that point on, ANS hyperactivity becomes a major problem in HF, conferring significant toxicity to the failing heart and markedly increasing its morbidity and mortality. The present review discusses the role of the ANS in cardiac physiology and in HF pathophysiology, the mechanisms of regulation of ANS activity and how they go awry in chronic HF, methods of measuring ANS activity in HF, the molecular alterations in heart physiology that occur in HF, along with their pharmacological and therapeutic implications, and, finally, drugs and other therapeutic modalities used in HF treatment that target or affect the ANS and its effects on the failing heart. (Circ Res. 2013;113:739-753.)

Key Words: β-blockers ■ adrenal glands ■ adrenergic nervous system ■ cardiac sympathetic nerve terminals ■ catecholamine ■ heart failure ■ hyperactivation ■ myocytes, cardiac ■ receptors, adrenergic ■ synaptic transmission
Heart failure is a clinical syndrome that occurs over time after a cardiac injury or chronic stress causing a decline in contractile function of this pumping efficiency of the heart. It is marked by a dynamic interplay between underlying myocyte dysfunction and compensatory mechanisms that are neurohumoral in nature as these signals attempt to stimulate the pump to maintain cardiac output. Among these neurohormonal mechanisms, elevated activities of the adrenergic (or sympathetic) nervous system (ANS), of the renin–angiotensin–aldosterone system (RAAS), and of several cytokines play central roles. These systems are initially activated to compensate for the reduced cardiac function and to maintain cardiac output. However, upon long-term presence of the initial insult to the heart muscle, cardiac function ultimately succumbs to their deleterious effects on myocytes and other cells of the heart, leading to cardiac decompensation and progressively worsening function and the inability to sustain daily life activities. The present review discusses the role of the ANS in HF pathophysiology and therapeutics, starting with a discussion of its role in normal cardiac function.

ANS and Cardiac Function

The ANS exerts a plethora of cardiovascular effects, including heart rate increase (positive chronotropy, predisposing to arrhythmias), increase in cardiac contractility (positive inotropy), accelerated cardiac relaxation (positive lusitropy), decrease in venous capacitance, and constriction of resistance and cutaneous arteries (Figure 1). All of these effects aim to increase cardiac performance to prepare for and enable the body’s so-called fight-or-flight response. Conversely, the mirror branch of the autonomic nervous system, the parasympathetic (cholinergic) nervous system, slows the heart rate (bradycardia) through vagal nerve impulses, with minimal or no effect on cardiac contractility. This is because the cardiac ventricles, whose contraction is responsible for pumping the blood into the systemic and pulmonary circulations, receive almost exclusively adrenergic fiber innervations, whereas the cholinergic fibers follow the vagus nerve under the endocardium, primarily reaching the atria with limited ventricular connections. Therefore,
whereas heart rate can be controlled (in opposing fashion) by both autonomic branches, cardiac contraction/relaxation is controlled almost solely by the ANS (Figure 1).

The ventricular ANS innervation presents as gradient pattern from base to apex.2 Afferent, efferent, and interconnecting neurons comprise the neuronal system of the heart.3 Several reflex responses regulate ANS outflow to the heart and to the peripheral circulation, such as the carotid baroreceptors (mediating ANS inhibition), cardiorespiratory baroreceptors (e.g., the Bezold–Jarisch reflex, also mediating ANS inhibition), and peripheral chemoreceptors (mediating ANS activation).4,7

ANS activation in the cardiovascular system translates into release of the 2 catecholamines that mediate its effects, that is, norepinephrine (or noradrenaline) and epinephrine (or adrenaline), and this can occur via the following mechanisms (Figure 2): (1) norepinephrine released by cardiac sympathetic nerve terminals located in the sinus and atroventricular nodes (resulting in tachycardia and acceleration of atroventricular conduction) and in the left ventricle (resulting in an increased force of contraction); (2) epinephrine (and to a much lesser extent norepinephrine) released into the circulation by the adrenal medulla, modulating both myocardium and peripheral vessels; and (3) local release of norepinephrine and epinephrine by various peripheral ANS’s that can synthesize and release these catecholamines in an autocrine/paracrine manner and are located in blood vessels and in cardiac myocytes themselves.8,9

**Adrenergic Receptors in the Cardiovascular System**

**Cardiac Adrenergic Receptor Signaling and Regulation**

The ANS neurotransmitters norepinephrine and epinephrine mediate their effects in cells and tissues by binding to specific cell surface adrenergic receptors (ARs), which belong to the superfamily of G-protein-coupled receptors (GPCRs) or 7 transmembrane-spanning receptors or heptahelical receptors. Approximately 80% of norepinephrine put forth by ANS nerve terminals is returned by the norepinephrine transporter type 1, whereas the remainder spills over to become circulating in nature.10 The receptors for both ANS catecholamines are divided into 3 types and 9 total different subtypes, as follows: 3 α AR subtypes (α1A, α1D, α1F); 3 α AR subtypes (α2A, α2C, α2D); and 3 β AR subtypes (β1, β2, β3).11 All ARs primarily signal through heterotrimeric G proteins. The human heart contains all 3 β AR subtypes.12 β1AR is the predominant subtype in the (normal, healthy) myocardium, representing 75% to 80% of total β AR density, followed by β2AR, which comprises ≈15% to 18% of total cardiomyocyte β ARs, and the remaining 2% to 3% is β3 ARs (under normal conditions).13 The principal role of β ARs in the heart is the regulation of cardiac rate and contractility in response to norepinephrine and epinephrine. Stimulation of β1 ARs (mainly) and stimulation of β2 ARs (to a lesser extent) increases cardiac contractility (inotropy), frequency (chronotropy), rate of relaxation (lusitropy), acceleration of impulse conduction through the atrioventricular node (dromotropy) as well as increased pacemaker activity from the sinoatrial node.14 β ARs are largely silent during normal cardiac physiology;15 however, when they are activated they can produce negative inotropy, which opposes effects from activated β1 ARs and β2 ARs, and this involves the nitric oxide synthase pathway.16 Thus, the β3AR can act as a “fuse” against cardiac adrenergic overstimulation.17 Agonist-occupied and activated β ARs generally cause the exchange of guanosine triphosphate for GDP on the Gs subunit of heterotrimeric G proteins, resulting in the dissociation of the heterotrimer into active Gs and free Gαs subunits (always associated together, a heterodimer that functions essentially as a monomer), which can transduce intracellular signals independently of each other.14 The most powerful physiological mechanism to increase cardiac performance is activation of cardiomyocyte β1 ARs and β2 ARs, which, in turn, activate Gs proteins.
(stimulatory G proteins). G\textsubscript{s}-protein signaling stimulates the effector adenylyl cyclase, which converts ATP to adenosine 3',5'-monophosphate or cAMP, which as a second messenger causes the activation of the cAMP-dependent protein kinase (G-protein kinase A [PKA]). PKA is the major effector of cAMP (there is also Epac, exchange protein directly activated by cAMP, which can be activated by cAMP independently of PKA), and by phosphorylating a variety of substrates, it ultimately results in significant increase in free intracellular Ca\textsuperscript{2+} concentration, which is the master regulator of cardiac muscle contraction (Figure 3).\textsuperscript{19} Among the main targets of PKA phosphorylation in the cardiac myocyte are the following: the cell membrane–located L-type calcium channels and the sarcoplasmic reticulum–located ryanodine receptors, and these 2 molecules both lead to increased cellular Ca\textsuperscript{2+};\textsuperscript{19} phospholamban, a negative modulator of sarcoplasmic/endoplasmic reticulum Ca\textsuperscript{2+}-ATPase whose phosphorylation by PKA deinhibits sarcoplasmic/endoplasmic reticulum Ca\textsuperscript{2+}-ATPase, thus accelerating Ca\textsuperscript{2+} reuptake by the sarcoplasmic reticulum after contraction and increasing sarcoplasmic reticulum Ca\textsuperscript{2+} stores available for the next contraction;\textsuperscript{19} hyperpolarization-activated cyclic nucleotide-gated channels, which generate the hyperpolarization-activated cation inward current (If), that can alter and modulate cardiac pacemaker cells;\textsuperscript{20} troponin I and myosin binding protein-C, which regulate myofilament Ca\textsuperscript{2+} sensitivity and relaxation;\textsuperscript{21} and phospholemman, closely associated with Na\textsuperscript{+}/K\textsuperscript{+}-ATPase and inhibiting its function, whose phosphorylation by PKA relieves this inhibition and stimulates the sodium pump, thereby accelerating cardiac muscle repolarization and relaxation (Figure 3).\textsuperscript{22} Moreover, PKA can phosphorylate the βARs themselves (and other GPCRs) in the heart, causing functional desensitization and uncoupling of the receptor, which is known as heterologous or agonist-independent desensitization.\textsuperscript{23}

Of note, β\textsubscript{2}AR also mediates the effects of catecholamines in the heart, but in a qualitatively different manner from β\textsubscript{1}AR, because it can also couple to the adenylyl cyclase inhibitory G-protein (G\textsubscript{i}). In fact, this switching of β\textsubscript{2}AR signaling from G\textsubscript{s} to G\textsubscript{i} proteins is postulated to be induced by the phosphorylation of the β\textsubscript{2}AR by PKA.\textsuperscript{23} Nonetheless, it is now generally accepted that, in the heart, β\textsubscript{2}AR signals and functions in a substantially different way compared with β\textsubscript{1}AR.\textsuperscript{24–26} Importantly, whereas β\textsubscript{1}AR activation enhances cardiomyocyte apoptosis, β\textsubscript{2}AR exerts antiapoptotic effects in the heart.\textsuperscript{24–27} This essential difference between the 2 receptor subtypes is ascribed to the signal of β\textsubscript{2}AR through G\textsubscript{i} proteins.\textsuperscript{25} Studies using transgenic mice, β\textsubscript{2}AR-selective stimulation, and adenoviral-mediated β\textsubscript{2}AR overexpression have demonstrated the protective effects of β\textsubscript{2}AR signaling in the myocardium, including improved cardiac function and decreased apoptosis. Conversely, hyperstimulation or overexpression of β\textsubscript{1}AR has detrimental effects in the heart.\textsuperscript{27,28}

Both α\textsubscript{2}ARs and βARs, like the majority of GPCRs, are subject to agonist-promoted (homologous) desensitization.
and downregulation, a regulatory process that diminishes receptor response to continuous or repeated agonist stimulation.9,30 At the molecular level, this process is initiated by receptor phosphorylation by a family of kinases, termed GPCR kinases (GRKs), followed by binding of β-arrestins (β-arrs) to the GRK-phosphorylated receptor. The β-arrs then uncouple the receptor from its cognate G proteins, sterically hinder its further binding to them (functional desensitization), and subsequently target the receptor for internalization.9,30 Across all mammalian species, GRK2 and GRK5 are the most physiologically important members of the GRK family because they are expressed ubiquitously and regulate the majority of GPCRs. They are particularly abundant in neuronal tissues and in the heart.31,32

Importantly, the differences between the 2 predominant cardiac βARs, that is, β1AR and β2AR, in terms of their signaling properties might take quite a different shape and have a much larger bearing on pathophysiologic implications in the setting of human HF; for instance, and as discussed in more detail in subsequent sections, β2AR is selectively downregulated (ie, functional receptor number reduced) in human HF, thus shifting the aforementioned stoichiometry of βAR:β2AR toward 50:50 in the failing heart from ≈75%:20% in the normal, healthy heart.33,34 However, β2AR is also nonfunctional and does not signal properly in the failing heart.32–34 In addition, emerging evidence suggests that β2AR signaling in the failing heart is quite different from that in the normal heart (ie, is more diffuse and noncompartmentalized and resembles the proapoptotic diffuse cAMP signaling pattern of the β1AR).35 Therefore, this stoichiometric shift in favor of the supposedly good β2AR in HF seems unable to help the heart improve its structure and function.

The human heart also expresses α1AARs and α1B ARs, albeit at much lower levels than βARs (≈20% of total βARs).36 How important a role cardiac α1 ARs play in cardiac physiology is still a matter of debate. In contrast, their role in regulation of blood flow by inducing constriction in the smooth muscle wall of major arteries (eg, aorta, pulmonary arteries, mesenteric vessels, coronary arteries) is well-known and indisputable.37 The α1 ARs couple to the Gq/11 family of heterotrimeric G proteins, thereby activating phospholipase C-β. Phospholipase C-β generates the second messengers, inositol 1,4,5-trisphosphate (IP3) and 2-diacylglycerol (DAG), from the cell membrane component, phospholipid phosphatidylinositol (4,5)-bisphosphate. IP3 binds specific receptors in the sarcoplasmic reticulum membrane, which causes release of Ca2+ from intracellular stores, whereas DAG activates PKC and transient receptor potential channels (Figure 3). The end result is again raised intracellular [Ca2+], which leads to contraction (vasoconstriction; Figure 3).

Finally, regarding α2 AR subtypes, α2A ARs are known to be present in vascular smooth muscle, causing constriction of certain vascular beds, whereas centrally located α2 ARs can inhibit sympathetic outflow (presynaptic inhibitory autoreceptors) and thus lower systemic blood pressure.38,39 The release of norepinephrine from cardiac sympathetic nerve terminals is controlled by both presynaptic α2 ARs and α2C ARs,40 and genetic deletion of both of these α2 AR subtypes leads to cardiac hypertrophy and HF because of chronically enhanced cardiac norepinephrine release, as well as enhanced norepinephrine and epinephrine secretion from the adrenal medulla.8,41,42

AR Polymorphisms and Cardiac Function

There are some important genetic polymorphisms in human βAR and αAR genes, which have been associated with HF phenotypes and interaction with β-blocker therapy, a mainstay of HF standard of care, and can significantly influence cardiac function. Thus, it would be useful to briefly discuss these polymorphisms and their functional consequences for the heart. The Arg389Gly human β1AR gene polymorphism is probably the best-studied AR gene polymorphism to date; it is associated with significantly elevated adenylate cyclase/PKA activities and, hence, β1AR-stimulated cardiac contractility in the Arg389 variant carriers (compared with Gly389 carriers).43 Another human β1AR polymorphism is the Ser49Gly variation, which is associated with increased agonist-promoted receptor downregulation for the Gly49 over the Ser49 variant.44 A lower prevalence of ventricular arrhythmias has been associated with the Gly389 allele.45 Of note, African American HF patients with an enhanced activity mutation (Leu41) of GRK5, the second (after GRK2) major cardiac GRK, demonstrate improved survival (explained by this GRK5 mutant acting as a genetic β-blocker).46 Additionally, the Gly49 allele of the human β1 AR gene has been shown to confer enhanced survival benefit in response to β-blocker treatment47 and significant reduction in left ventricular end-diastolic diameter48 compared with Ser49 homozygous carriers. Ameliorated cardiac adverse remodeling has been reported for Arg389 homozygous HF patients treated with the β-blocker carvedilol49 and for Arg389Gly heterozygous carriers.50 There are also negative studies, however, reporting no associations of these polymorphisms with any cardiac outcome.51–53 Further adding to the confusion, a dependency of whether the Ser49Gly polymorphism has any bearing on dilated cardiomyopathy outcomes on the dose of the β-blocker has been reported, according to which the Gly49 allele associates with worse outcomes than Ser49 allele homozygosity at low β-blocker doses; however, at higher doses, genotype apparently has no effect.54 On the other hand, HF patients carrying the Arg389 genotype had a larger agonist-dependent ventricular contractility and better survival (adjusted for age, sex, and race) than Gly389 carriers in a β-Blocker Evaluation of Survival Trial subcohort.55

The human β1AR gene is known to display 2 variations that are in linkage disequilibrium (and thus constitute a haplotype), Gly16Arg and Gin27Glu, which affect receptor downregulation, and a third polymorphism, Thr164Ile, which confers impaired receptor–G-protein coupling and reduced adenylate cyclase–mediated signaling.56 Finally, a 4-amino-acid deletion in the human α1C AR gene (Del322–325) leads to increased norepinephrine release from CNS cardiac nerve terminals,57 and this polymorphism, in combination with the β1AR Arg389Gly polymorphism, has been used for patient stratification based on the clinical response to the β-blocker bucindolol into “very favorable,” “favorable,” and “unfavorable” response genotypes.58 The latter polymorphism (β2 AR Arg389Gly) also belongs to a set of 3 genetic polymorphisms that were recently shown to serve as predictors of appropriate
implantable cardioverter-defibrillator shock therapies in HF patients. In conclusion, human AR genetic polymorphisms may prove to be useful tools in guiding the individual tailoring (personalization) of HF therapy in the future.

Assessment of ANS Activity
Plasma norepinephrine measurements represent the usual crude method to assess ANS function/activity levels, because the latter depends on the rate of immediate norepinephrine reuptake as well as norepinephrine clearance from the circulation. The two standard techniques to assess human ANS activity are radiotracer measurements of regional noradrenergic spillover and microneurography (microelectrode measurements of postganglionic nerve activity). These techniques can discern central from peripheral contributions of increased plasma norepinephrine levels and facilitate precise assessment of the regional (eg, cardiac) sympathetic nerve function, both under physiological and pathological conditions. Cardiac neuronal function is visualized with γ-cameras and positron emission tomography scanners using radiolabeled norepinephrine analogs. ANS activity or its pharmacological inhibition can also be measured with [123I]-labeled metadobenzylguanidine (MIBG), an analogue of norepinephrine. [123I]-labeled MIBG cardiac imaging has also been shown to carry independent prognostic information for risk stratification of HF patients in a complementary manner to ejection fraction and B-type natriuretic peptide.

Regulation of ANS Outflow and Activity in Health and in Chronic HF
Cardiac Sympathetic Efferent Nerves
There are several mechanisms by which the ANS controls cardiac function. The first one to be documented historically is through the aortic arch and carotid sinus (high pressure) and cardiopulmonary (low pressure) baroreceptor reflexes. Aside from these baroreceptor inputs, additional factors that act within the central nervous system play a role in regulation of cardiac ANS activity. In particular, suprabulbar subcortical monoaminergic neurons and brain stem angiotensin II have attracted interest for their ability to regulate ANS outflow in HF (Figure 2). Norepinephrine turnover in subcortical regions in HF is significantly higher than that in the cortex and higher than that in healthy subjects. Moreover, the rate of subcortical norepinephrine release correlates well with global ANS activity, as measured by total body norepinephrine plasma spillover. Angiotensin II–dependent ANS activation plays an important role in adverse hemodynamic and left ventricular remodeling responses to myocardial infarction, possibly through superoxide formation. Thus, part of the benefit of RAAS modulators in HF might derive from centrally mediated suppression of ANS activity.

As the heart becomes progressively unresponsive to the stimulatory effects of catecholamines, chronic stimulation of cardiac ANS nerve terminals leads to chronically elevated norepinephrine release from the heart (increased norepinephrine spillover). Presynaptic α2ARs present on cardiac ANS nerve terminals and acting as norepinephrine release–inhibiting autoreceptors play a crucial role in regulation of cardiac norepinephrine release from sympathetic nerves. Knockout mice lacking either the α2AR or the α2C/AR subtype show significantly enhanced cardiac ANS activity and circulating catecholamine levels, as well as significantly worse heart function and clinical indices, during the course of surgical pressure overload by means of transverse aortic constriction–induced HF compared with age-matched wild-type HF mice. Moreover, double α2A/α2C/AR knockout mice exhibit even worse cardiac phenotypes than single α2C/AR knockout mice; by 4 months of age, they spontaneously develop cardiomyopathy (without stress or any specific insult). In HF patients, the expected inhibitory effects of α2AR stimulation on norepinephrine spillover are markedly blunted, thereby contributing to the increase in cardiac norepinephrine spillover observed in chronic HF. In addition, the human α2C/AR Del322–325 variant that displays impaired signaling and sympathoinhibitory function is alone associated with increased risk of HF in homozygous African American carriers, especially when cooccurred with the hyperfunctional cardiac β2AR Arg389 variant, with the most probable mechanism being attenuated autoinhibitory feedback of, and thus enhanced norepinephrine release from, the cardiac sympathetic nerves. In fact, even in healthy humans, the α2C/AR Del322–325 variant is associated with increased sympathetic nervous and adrenomedullary hormonal activities during both supine rest and pharmacologically evoked catecholamine release. Thus, presynaptic inhibitory α2-adrenergic autoreceptors crucially regulate ANS cardiac nerve activity and norepinephrine release into the heart, and any dysfunction of these receptors attributable to either genetic polymorphisms or increased desensitization/downregulation translate into increased morbidity and mortality in chronic HF (Figure 2). Perhaps the crucial role of presynaptic α2ARs in regulating norepinephrine release from cardiac ANS nerves stems from the fact that they are the only presynaptic ARs that can inhibit norepinephrine release; presynaptic βARs (of the β1,AR subtype, mainly) are facilitatory autoreceptors enhancing norepinephrine release at sympathetic nerve terminals, a phenomenon whose inhibition may contribute to the therapeutic benefit of β-blockers in HF (Figure 2).

Adrenal Glands
Circulating epinephrine and norepinephrine derive from 2 major sources in the body: the cardiac sympathetic nerve endings, which release norepinephrine directly onto the cardiac muscle, and the adrenal medulla, whose chromaffin cells synthesize, store, and release epinephrine (mainly) and norepinephrine on acetylcholine stimulation of the nitrergic cholinergic receptors present on their cell membranes (Figure 2). Epinephrine represents ≈80% of the total adrenal catecholamine secretion under normal conditions, with norepinephrine representing the other ≈20%. However, these percentages vary widely depending on the physiological condition of the adrenal gland and of the whole body. 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 ARs at any given time is composed of these circulating norepinephrine and epinephrine plus norepinephrine released...
locally from sympathetic nerve terminals within the heart. The secretion of catecholamines from the adrenal glands is regulated in a complex manner by a variety of cell membrane receptors present in chromaffin cells. Many of these receptors are GPCRs, including, similarly to cardiac ANS nerve endings, α2ARs that inhibit secretion (inhibitory presynaptic autoreceptors) and βARs that enhance it (facilitatory presynaptic autoreceptors); Figure 2). Of note, although various presynaptic autoreceptors and heteroreceptors facilitate (increase) adrenal catecholamine secretion, for example, βARs, muscarinic cholinergic receptors, angiotensin II-ergic, histaminergic, and adrenomedullin receptors, the α2ARs are the only receptor type reported to date to inhibit adrenal catecholamine secretion.8,42,76

An increase in GRK2 expression and activity has been documented in several cardiovascular diseases, including increased cardiac expression in HF77–79 and increased expression in some vascular beds in hypertension.80 A few years ago, we reported that GRK2 expression and activity are increased also in the adrenal medulla during HF.81 Specifically, our studies over the past few years have established that adrenal GRK2 upregulation is responsible for severe adrenal α2AR dysfunction in chronic HF, which causes a loss of the sympathoinhibitory function of these receptors in the adrenal gland, and catecholamine secretion is thus chronically elevated (Figure 2).81–85 This emerging crucial role for adrenal GRK2 in HF is underlined by the fact that its specific inhibition, via adenosinomediated βAR kinase carboxyl terminal adrenal gene delivery, leads to a significant reduction in circulating catecholamine levels, restoring not only adrenal but also cardiac function in HF.81 Additional evidence for the crucial role of adrenal GRK2–regulated α2ARs in regulating adrenal ANS tone in HF comes from the phenylethanolamine-N-methyl transferase–driven GRK2 knockout mice.82 These mice, which do not express GRK2 in their adrenal medullae from birth, display decreased ANS outflow and circulating catecholamines in response to myocardial infarction, which translates into preserved cardiac function and morphology over the course of the ensuing HF.82 Of note, elevated GRK2–dependent α2AR dysfunction during HF might also occur in other peripheral sympathetic nerve terminals of the heart (Figure 2) and of other organs, thus contributing to the increased norepinephrine release and spillover, as well as to the presynaptic α2AR dysfunction in ANS neurons observed in chronic HF.72,86

Effects of ANS Overactivity in Chronic HF
Myocardial systolic dysfunction is associated with neurohormonal hyperactivity as a compensatory mechanism to maintain cardiac output in the face of declining cardiac function. The neuronal part of this response is represented by ANS cardiac nerve terminals, whereas the hormonal (or humoral) part is represented by increased secretion and elevated circulating levels of certain hormones, the most prominent being epinephrine and norepinephrine, along with the RAAS hormones (ie, angiotensin II and aldosterone).83 ANS hyperactivity is evidenced by increased plasma norepinephrine and epinephrine levels, elevated (central) sympathetic outflow, and heightened NE spillover.84 Cardiac norepinephrine spillover in untreated HF patients can reach ≤50-fold higher levels than those of healthy individuals under maximal exercise conditions.85 The information on chronic ANS activation in HF with preserved left ventricular ejection fraction (ie, diastolic HF) is very limited but certainly can participate in increased HF risk.86 In systolic HF, patients may actually have decreased ANS neuronal density and function, resulting in decreased norepinephrine concentration within the heart, in addition to decreased postsynaptic βAR density, due to depletion of cardiac ANS neuronal norepinephrine stores and decreased norepinephrine presynaptic reuptake secondary to norepinephrine transporter downregulation.81,82

Effects on Cardiac ARs
The elevated ANS outflow and norepinephrine and epinephrine levels in chronic HF lead to chronically elevated stimulation of the cardiac βAR system, which has detrimental repercussions for the failing heart. Extensive investigations over the past 3 decades have helped delineate the molecular alterations afflicting the cardiac βAR system that occur during HF, and it is now well-known that, in chronic human HF, cardiomyocyte βAR signaling and function are significantly deranged and the adrenergic reserve of the heart is diminished.33,34,93 Cardiac βAR dysfunction in human HF is characterized at the molecular level by selective reduction of βAR density at the plasma membrane (downregulation) and by uncoupling of the remaining membrane βARs and βARs from G proteins (functional desensitization).33 Importantly, myocardial levels and activities of the most important, versatile, and ubiquitous GRKs, GRK2 and GRK5, are elevated both in humans and in animal models of HF.32,77–79.94–77 The current consensus is that in chronic HF the excessive amount of ANS-derived catecholamines hitting cardiac βARs extracellularly triggers the GRK2 upregulation inside the cardiomyocytes, thus leading to a reduction in cardiac βAR density and responsiveness and resulting in cardiac inotropic reserve depletion.85,86 This GRK2 elevation possibly serves as a homeostatic protective mechanism aimed at defending the heart against excessive catecholaminergic toxicity. However, several studies soon refuted this assumption, demonstrating that GRK2 upregulation is detrimental for the heart and causes the functional uncoupling of βARs in vivo.84 This finding prompted investigations of the role GRK2 plays in cardiac function, which revealed that cardiac GRK2 is an absolutely critical regulator of cardiac βAR–dependent contractility and function. Specifically, cardiomyocyte-restricted overexpression of GRK2 to the same level of upregulation found in human HF (ie, 3-fold to 4-fold) markedly attenuated βAR signaling and contractile reserve, showing that GRK2 is the main culprit for the functional desensitization of cardiac βARs in HF (Figure 3).87 The proof for this was provided by studies of the in vivo inhibition of cardiomyocyte GRK2, which were enabled by the development of the βAR kinase carboxyl terminal mini-gene, which blocks cell membrane translocation and hence activation of GRK2, and its cardiomyocyte-specific expression in vivo in transgenic mice by virtue of the α-myosin heavy chain gene promoter.87 GRK2 inhibition in vivo in the heart with βAR kinase carboxyl terminal (or its partial genetic deletion) enhances cardiac contractility both
at baseline and after adrenergic stimulation, reverses the contractile and βAR dysfunctions, and preserves or even augments cardiac function and survival in HF.97–102 On the down side, loss of cardiac GRK2 can predispose the heart to catecholamine toxicity, exactly because it works, in essence, as a positive inotropic therapy.103 In summary, elevated ANS activity in chronic HF causes enhanced GRK2-mediated cardiac β2AR and β3AR desensitization and βAR downregulation, which leads to the progressive loss of the adrenergic and inotropic reserves of the heart, the hallmark molecular abnormality of this disease (Figure 3).104

With regard to the other major AR type expressed in the heart, α1ARs in HF may function compensatorily to preserve cardiac contractility, but their involvement in cardiac pathophysiology appears limited to situations of cardiac hypertrophy that ultimately lead to HF.105 For instance, in the presence of pressure overload, cardiac α1ARs get activated and promote cardiomyocyte survival (ie, block apoptosis), protecting against adverse remodeling and decompensation to HF.106,107

**ANS Cardiotoxicity**

ANS cardiac toxicity is well-documented. For instance, intravenous infusion of isoproterenol (a standard nonsubtype selective βAR full agonist) or norepinephrine results in acute contraction band lesions attributed to relative hypoxia, calcium overload, elevation of cAMP, activation of α- and βARs, and formation of reactive oxygen species.108,109 Chronic catecholaminergic stimulation has been shown in animals to cause cardiac fibrosis, to reduce adrenergic and inotropic reserves, and to induce cardiac apoptosis and dysfunction via left ventricular dilatation.110,111 Moreover, norepinephrine induces cardiac apoptosis via both β2AR-mediated and reactive oxygen species/tumor necrosis factor/caspase–mediated signaling pathways.112,113 A perfect example of catecholamine-induced cardiac toxicity leading to cardiac dysfunction is found in stress (Takotsubo) cardiomyopathy; high circulating levels of epinephrine trigger a form of myocardial stunning, which includes the signaling switch of the cardiac β2AR from Gs to Gi proteins, especially in the region of the apical myocardium, where βAR density is highest,114 thus negatively affecting inotropy.115

**ANS Therapeutics in HF**

**β-Blockers**

β-blockers (Table) comprise first generation agents (nonsubtype selective, competitive blockers of both the β1- and β2ARs, eg, propranolol); second generation agents (much higher affinity for the β1- than for the β2AR, eg, atenolol, metoprolol); and third generation agents (subtype-selective, eg, celiprolol, nebivolol, or nonselective, eg, bucindolol, carvedilol, labetalol). The latter ones can also block α1ARs, thereby causing peripheral vasodilation (bucindolol, carvedilol, labetalol). Celiprolol possesses β2AR agonist properties, whereas nebivolol can also induce nitric oxide synthesis.116 Cardioselectivity, that is, selectivity for the β1AR over the β2AR subtype, is dose-dependent and decreases with increasing dosage. Both subtype-selective and subtype-nonselective agents have negative chronotropic and inotropic effects. β1AR-selective agents have a lesser inhibitory effect on the β2AR and thus are less likely to cause peripheral vasodistraction (and bronchoconstriction).116 β2AR-selective agents carry less risk for limiting exercise performance, since they spare the β2AR which increases skeletal muscle blood flow (via vasodilation) in response to exercise. Finally, some β-blockers are mixed βAR agonists/antagonists (or partial agonists); in other words, at low concentrations they antagonize the receptors, but at high concentrations they actually activate βARs (act as agonists), causing cardiac stimulation. These β-blockers possess (the so-called) intrinsic sympathomimetic activity, for example, pindolol, alpenrolol, and oxprenolol, and inhibit the effects of catecholamines through the high-affinity binding state of the myocardial β2AR while mimicking catecholamines when binding to the low-affinity state of the cardiomyocyte β2AR.117

The β-blockers with intrinsic sympathomimetic activity have a high propensity for arrhythmias and should not be used for chronic HF treatment. The majority of β-blockers are partially or completely metabolized by CYP2D6, a gene with considerable genetic variability.118 All β-blockers are approved for chronic HF treatment (Table).119 Conversely, they are all contraindicated in acute HF (because of the acute decrease in cardiac output they cause).119 Chronic β-blocker therapy reverses cardiac adverse remodeling (reverse remodeling), reduces hospitalization rates, improves patient survival, reduces risk of arrhythmias (sudden cardiac death), improves coronary blood flow to the heart (relieves angina), and protects the heart against cardiotoxic overstimulation by the catecholamines. All of these effects result in a decrease in the oxygen/energy and metabolic demands of the heart (cardiac workload is decreased) and in an increase in its oxygen/energy supply, thereby improving, in the long-term, left ventricular function and performance. Various molecular mechanisms underlying these effects have been postulated as follows: (1) direct antagonism of catecholaminergic cardiotoxic effects; (2) cardiac βAR up-regulation and restoration of their signaling and function, that is, increase in adrenergic and inotropic reserves of the heart, partly via cardiac GRK2 downregulation;120 (3) suppression of the elevated cardiotoxic, adverse remodeling–promoting, and proapoptotic neurohormonal systems (RAAS, endothelin); (4) coronary blood flow enhancement (as a result of diastolic prolongation); and (5) restoration of the reflex controls on the heart and the circulation.121 In addition, restoration of adrenal GRK2–α1AR–catecholamine secretion axis and suppression of norepinephrine release from cardiac ANS endings might contribute to the beneficial effects of β-blockers in chronic HF, as well.74,85

**α-Blockers**

In human HF, the α1-blocker prazosin led to worse outcomes than vasodilators combination of hydralazine and isosorbide dinitrate (BiDil), possibly due to the fact that prazosin causes feedback sympathetic activation, which may diminish any potential benefit reaped from vascular smooth muscle α1AR inhibition-induced vasodilation (Table).121,122 Adding to the inappropriateness of α1AR blockers for HF therapy, the doxazosin arm in the antihypertensive and lipid-lowering treatment
to prevent heart attack trial (ALLHAT) was terminated early because of higher rate of HF-related events (Table).124

**Centrally Acting Sympatholytic Agents**

Central nervous system-localized α-ARs inhibit ANS outflow via an autocrine negative feedback mechanism.39 Clonidine is a centrally acting α-AR agonist that can attenuate cardiac and renal sympathetic tone in HF (sympatholytic). It exerts its sympathoinhibitory effects without apparent negative clinical outcomes (Table).125 However, clinical trials are needed to fully evaluate whether it can have a place in the HF therapeutic armamentarium. Another centrally acting sympatholytic agent, moxonidine, also an imidazoline derivative like clonidine, has been used in clinical trials for HF. Moxonidine is an α2AR agonist as well as an agonist at the putative imidazoline receptors.126,127 It causes marked reductions in plasma norepinephrine,128 and it failed in clinical trials because it was found to increase HF-related mortality (Table).129 As a possible explanation for this, excessive sympatholysis to a point that was incompatible with life was postulated. However, another explanation might have been the reported α2AR desensitization and downregulation that accompanies HF,72 which renders

### Table. Overview of ANS-Related Therapeutics in HF

<table>
<thead>
<tr>
<th>Therapeutic Modality</th>
<th>Mechanism of Action in HF</th>
<th>Effect on ANS Function</th>
<th>Effect on HF Phenotype</th>
<th>Clinical Outcome, Indication in HF</th>
<th>Other Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>β-Blockers</td>
<td>Cardiac β1AR antagonism, ANS neuronal β1AR antagonism; ↓ cardiac and renal GRK2; ↑ PNS outflow/activity</td>
<td>↓ Outflow/activity</td>
<td>Reversed adverse remodeling; ↓ arrhythmias; ↑ cardiac blood flow; protection against CA toxicity; ↓ cardiac oxygen, metabolic, and energy demand/supply ratio</td>
<td>↓ All-cause and cardiac mortalities; ↓ adrenergic and inotropic reserves, chronic HF; especially after MI</td>
<td>Contraindicated in acute HF; certain polymorphisms in cardiac β1AR and GRK5 genes affect response; individual agents not equal: carvedilol–metoprolol seem superior in HF</td>
</tr>
<tr>
<td>α-Blockers</td>
<td>VSM α1AR (and α2AR) antagonism</td>
<td>↑ Outflow/activity (reflex response to α1AR blockade)</td>
<td>Worsening of HF; ↑ HF incidence; ↑ HF morbidity and mortality</td>
<td>↑ Cardiac morbidity and mortality (prazosin–doxazosin)</td>
<td>Contraindicated in HF</td>
</tr>
<tr>
<td>Centrally acting sympatholytic agents</td>
<td>Central ANS and adrenal α1AR (and putative imidazoline receptor) agonism</td>
<td>↓ Outflow/activity</td>
<td>↓ Cardiac and renal ANS tones in HF; ↓ cardiac oxygen, metabolic and energy demand/supply ratio (?)</td>
<td>No clinical deterioration (clonidine) but ↓ mortality (attributable to excessive sympatholysis?) with moxonidine; benefit questionable</td>
<td>Contraindicated in acute HF; central ANS and adrenal α1ARs desensitized/downregulated in chronic HF (attributable to ↑ GRK2), so efficacy might be limited</td>
</tr>
<tr>
<td>RAAS-modulating agents</td>
<td>↓ AngII production, AngII and Aldo antagonism, leading to ↓ NE release and ↑ NE reuptake from ANS neurons</td>
<td>↓ Outflow/activity</td>
<td>Well-established benefits in reversed adverse remodeling and ↓ cardiac oxygen, metabolic, and energy demand/supply ratio</td>
<td>↓ All-cause and cardiac mortalities, chronic HF, especially after MI</td>
<td>Part of benefit in chronic HF attributable to ANS outflow/activity lowering</td>
</tr>
<tr>
<td>Sympathomimetics</td>
<td>Cardiac β1AR agonism or PDE3 inhibition, leading to ↑ cardiac and VSM cAMP levels</td>
<td>Indirect ↓ outflow/activity via improved cardiac hemodynamics but potential ↑ NE release from ANS neurons; net effect unknown</td>
<td>Positive inotropy for acute HF; ↑ arrhythmias; ↑ cardiac oxygen, metabolic, and energy demand/supply ratio</td>
<td>↑ All-cause and cardiac mortalities; ↓ adrenergic and inotropic reserves and cardiac β1AR signaling/function over time (attributable to ↑ cardiac GRK2), acute HF only (cardiogenic shock); Contraindicated in chronic HF; PDE3 inhibitors (milrinone) provide additional (direct) vasodilatory benefit</td>
<td></td>
</tr>
<tr>
<td>Exercise training</td>
<td>Improved hemodynamics, ↑ cardiac β1AR signaling/function, ↓ cardiac and renal GRK2, ↑ ANS neuronal and adrenal α1AR function</td>
<td>↓ Outflow/activity</td>
<td>Improved arterial and chemoreflex controls; ↑ cardiac blood flow; ↓ CA toxicity; ↓ cardiac inflammation</td>
<td>↓ All-cause and cardiac mortalities; ↑ adrenergic and inotropic reserves; ↓ cardiac ANS tone</td>
<td>Undergoing investigation for chronic HF treatment</td>
</tr>
<tr>
<td>Cholinergic system stimulation</td>
<td>↓ HR and cardiac NE release, ↑ cardiac function, ↓ adverse remodeling</td>
<td>↓ Outflow/activity</td>
<td>Improved arterial and chemoreflex controls; ↓ arrhythmias; ↑ CA toxicity</td>
<td>↓ Cardiac ANS tone; undergoing investigation for chronic HF treatment, especially along with β-blockers</td>
<td>Cholinergic system function (bradycardia and vasodilatation) ↓ in chronic HF; benefit in HF significantly enhanced by β-blockers</td>
</tr>
</tbody>
</table>

Aldo, aldosterone; ANS, adrenergic nervous system; AngII, angiotensin II; AR, adrenergic receptor; CA, catecholamine; GRK, G-protein-coupled receptor kinase; HF, heart failure; HR, heart rate; MI, myocardial infarction; NE, norepinephrine; PDE3, phosphodiesterase type III; PNS, parasympathetic nervous system; RAAS, renin–angiotensin–aldosterone system; VSM, vascular smooth muscle.
α-ARs dysfunctional, increasing sympathetic outflow in HF and limiting efficacy of α₂-AR sympatholytic agonists (Table).

RAAS-Modulating Drugs

Hyperactivation of the RAAS is another neurohormonal hallmark of chronic HF, and the degree of its activation correlates with prognosis. Angiotensin II enhances the release and inhibits the reuptake of norepinephrine at ANS nerve endings (Figure 2). Angiotensin-converting enzyme inhibitors, by decreasing angiotensin II and aldosterone levels, increase plasma renin activity and also decrease circulating catecholamines and vasopressin because of the hemodynamic improvements they bring about. Plasma aldosterone levels may be elevated 20-fold in some patients with HF, and this heightened serum level is due to increased production by the adrenal glands, which is a consequence of high plasma angiotensin II. Our laboratory recently has identified another mechanism for the enhanced cardiotoxic aldosterone production by the adrenal cortex in HF: enhanced activity of adrenal β-arrestin1, a cofactor of GRKs in receptor desensitization, at the AT₁R angiotensin II receptor. In addition to its electrolyte, hemodynamic, and metabolic effects, aldosterone has several direct detrimental effects on the myocardium, promoting cardiac adverse remodeling and HF progression, and also mediates several of the cardiotoxic effects of angiotensin II in the cardiac muscle (eg, myocardial fibrosis, increased oxidative stress, inflammation). With regard to the ANS in HF, aldosterone, like angiotensin II, can increase norepinephrine reuptake from ANS presynaptic neurons, thereby contributing to the enhanced ANS outflow in chronic HF (Figure 2). Some of the beneficial effects of aldosterone antagonists, such as spironolactone and eplerenone, in human HF thus may derive from suppression of this effect of aldosterone on the ANS (ie, partial sympatholysis; Table).

Sympathomimetics (AR Agonists)

Dopamine, dobutamine, and milrinone (its congener amrinone has been withdrawn from the market) represent the most commonly used sympathomimetic drugs (adrenergic agonists) used as positive inotropes for acute HF (Table). All positive inotropes lead to cAMP accumulation inside cardiomyocytes, which increases contractility via elevation of intracellular free Ca²⁺ concentration (Figure 3). Dopamine and dobutamine achieve that by binding to and activating cardiac β₁-ARs, whereas milrinone blocks phosphodiesterase type 3 (cAMP-specific phosphodiesterase), thereby preventing cAMP degradation. Of course, the elevation of intracellular free Ca²⁺ inside cardiomyocytes predisposes to arrhythmias (major adverse effect of positive inotropes). All 3 inotropes produce a vasodilatory effect and can cause a reduction in blood pressure; this is especially the case for milrinone, because there are no β₁-ARs in vascular smooth muscle (β₁-AR is the β₁AR subtype there; Table). Finally, the effects of dobutamine and dopamine are blunted when the patient is already using β-blocker therapy. In that case, non-β-AR-related inotropes are preferred, such as milrinone or glucagon (which can also increase cAMP in cardiomyocytes through its own G₁-protein-coupled receptor). Despite the straightforward rationale for using positive inotropes in HF (decrease in cardiac output, hence administration of an agent that will directly increase it), clinical trials have clearly demonstrated that sympathomimetics significantly increase mortality in chronic HF. Therefore, they are used only in acute HF management, such as in cardiac hypoperfusion or shock (Table).

Another therapeutic strategy involving sympathomimetics in HF is combined β₁-AR blockade with simultaneous β₂-AR stimulation with clenbuterol (a β₂-AR-selective agonist), which has been shown to help reverse severe HF in selected patients requiring left ventricular assist devices. The rationale for this approach was based on studies demonstrating that clenbuterol is able to improve left ventricular function by affecting cardiac cell morphology, excitation-contraction coupling, and calcium sensitivity. However, a recent trial demonstrated that clenbuterol leads to increases in lean mass, in lean mass-to-fat ratio, and in muscle strength, resulting in increased exercise capacity of chronic HF patients (presumably via enhanced vascular smooth muscle β₂-AR–dependent vasodilation, which increases skeletal blood flow), and it is, in fact, used in sports medicine as a performance-enhancing drug. Therefore, determination of the ultimate role of clenbuterol in HF therapy requires further investigations in larger prospective trials.

Nondrug Therapeutic Modalities Affecting ANS in HF

Exercise Training

Intolerance to exercise is a major symptom of chronic HF; and skeletal myopathies can certainly contribute to the reduced functional capacity in HF. ANS activation serves as a coordinator of cardiac and vascular muscle to maintain adequate blood pressure during exercise. However, enhanced ANS activity can also lead to peripheral myopathies that are often seen in HF, and this can be due, in part, to ANS-mediated vasconstriction that limits blood flow to skeletal muscle both at rest and during exercise, leading to hypoperfusion/ischemia, release of ROS, and chronic inflammation. On the other hand, exercise training has been shown to improve centrally mediated hemodynamic parameters and skeletal muscle performance that can lead to a reflex reduction in ANS activity in HF patients, alone or in conjunction with β-blocker therapy, resulting in reductions of all-cause and cardiovascular mortalities (Table). The postulated mechanisms for these positive results after exercise training in HF include improvements in reflex controls in arteries, decreased and abnormal central ANS outflow, increases in blood flow peripherally, and reduction in circulating proinflammatory cytokines. Additionally, studies from our laboratory and others in experimental HF animals have shown that exercise training improves cardiac βAR signaling and function, increases adrenergic and inotropic reserves of the heart ameliorating cardiac contractility and function, and helps restore normal ANS activity/outflow and circulating catecholamine levels, partly via normalization of GRK2 activity and restoration of sympathoinhibitory α₂-AR function in the adrenal gland (Table).

Cholinergic System Modulation

Vagus nerve afferent activation from the periphery can modulate efferent adrenergic and cholinergic neurons centrally and
at the baroreceptors. Moreover, cholinergic neurons exert tonic inhibition of adrenergic neuron activation and of nor-
epinephrine release from presynaptic ANS nerve terminals. The well-known cardiovascular effects of the parasym-
thetic nervous system, that is, heart rate reduction (brady-
cardia, indirectly via inhibition of the ANS and directly by
hyperpolarization and pacemaker activity suppression of the
sinoatrial node) and vasorelaxation (indirectly via nitric oxide
synthesis), are significantly attenuated in chronic HF, which leads to, among other consequences, lifting of the har-
ness of ANS activation that the cholinergic system normally
imposes and, thus, (indirect) enhancement of ANS outflow
(Table). Clinical and experimental data suggest that β-
blockade augments reflex vagal nerve control of heart rate
in HF via suppression of the cardiac sympathetic presynap-
tic β2AR–facilitated norepinephrine release. Additionally,
muscarinic cholinergic M2 receptors (M2 muscarinic cholin-
ergic receptors) are upregulated in the left ventricular free
wall, resulting in reduced heart rate variability. Finally,
vagus nerve stimulation therapy, combined with chronic
β-blocker therapy, has been shown to further improve left
ventricular function and reverse remodeling beyond what is
achieved with β-blockers alone (Table).

Conclusions

A vast number of studies over the past few decades have estab-
lished the crucial role of activated ANS in the compensatory
response of the circulation to retain its hemodynamic stability
in the face of a cardiac insult and, when this fails, its exces-
sive activation that accelerates HF progression and poses se-
vere toxicity on the chronically failing heart. Additionally, the
benefits of β-blockers and other therapeutic modalities that
mitigate or protect the heart against this ANS hyperactivity
are also well-documented. Several recent developments in the
basic cardiovascular research field that are at various stages of
preclinical testing to ultimately reach the bedside in HF ther-
apeutics also aim at reducing the activity and the detrimen-
tal effects of the ANS on the failing heart. Among these are
sympatholytic agents (α1 AR agonists), polymorphic variants
of cardiac ARs that confer better prognosis in HF or better
responses to current HF treatments, new sympathoinhibitors
that seek to augment the function of the seemingly cardioprotective β2AR while simultaneously blocking the cardiotoxic
β1 AR (eg, clenbuterol), activation of the cardiac parasympa-
thetic nervous system, and, last but not least, augmentation of cardiac βAR–dependent function without the accompanying
elevation of ANS activity/outflow. The latter is pursued with the
promising GRK2 inhibition therapeutic approach, which poses to improve cardiac adrenergic and inotropic reserves by
restoring cardiac βAR signaling and function (ie, to provide
positive inotropy) while keeping the ANS outflow at bay by
restoring or augmenting central, cardiac, and adrenal symp-
pathoinhibitory α1 AR function. Further understanding of the
mechanisms of ANS activation and of the repercussions this has on regulation of cardiac function and structure in chronic
HF is most certainly bound to provide the clinicians of the fu-
ture with some desperately needed, newer, and better weapons
in the battle against this devastating disease.

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