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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 beta$_1$-AR signaling and transduction are key features of heart failure progression. In contrast, cardiac beta$_2$-ARs and alpha$_1$-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 contractility, 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 alpha$_1$-receptors (alpha$_{1A}$, alpha$_{1B}$, and alpha$_{1D}$), 3 alpha$_2$-receptors (alpha$_{2A}$, alpha$_{2B}$, and alpha$_{2C}$), and 3 beta-receptors (beta$_1$, beta$_2$, and beta$_3$) (9). All ARs have 7 transmembrane receptors that signal primarily via interaction with heterotrimeric G proteins.

The human heart contains beta$_1$, beta$_2$, and beta$_3$ receptors (10). The beta$_1$- and beta$_2$-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). Beta$_3$-ARs are predominantly inactive during normal physiologic conditions (11); however, their stimulation seems to produce a negative inotropic effect opposite to that induced by beta$_1$- and beta$_2$-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$_{alpha}$-subunit of G proteins, resulting in the dissociation of the heterotrimer into active G$_{alpha}$- and G$_{beta\text{-}gamma}$-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 beta$_1$- and beta$_2$-ARs is the most powerful physiologic mechanism to acutely increase cardiac performance. Beta$_1$-ARs activate G$_s$ proteins whereas beta$_2$-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, adenyl cyclase, resulting in dissociation of adenosine triphosphate (ATP) into the second messenger 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$_f$) 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 alpha$_{1A}$- and alpha$_{1B}$-ARs at lower levels (≈20%) than those of beta-ARs (20). It is unknown whether cardiac alpha$_1$-ARs play a major role under physiologic conditions. Moreover, the alpha$_1$-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 alpha$_{1A}$- and alpha$_{1B}$-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) bisphosphate 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 alpha$_{2B}$-ARs