Parasympathetic Nervous System and Heart Failure
Pathophysiology and Potential Implications for Therapy

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A bundant evidence links sympathetic nervous system activation to outcomes of patients with heart failure (HF).1 In contrast, parasympathetic activation has complex cardiovascular effects that are only beginning to be recognized. In particular, the pathophysiological roles of normal and disordered parasympathetic innervation in patients with HF are not understood as comprehensively.2-5

In the present article, we review cardiovascular responses to parasympathetic activation, address the modulating factors that can affect parasympathetic function, discuss the role of the vagus nerve in ventricular dysfunction, and consider how activation of the parasympathetic nervous system may have important therapeutic implications for patients with congestive HF.

Structure of the Parasympathetic Limb of the Autonomic Nervous System

The parasympathetic nervous system originates from medial medullary sites (nucleus ambiguous, nucleus tractus solitarius, and dorsal motor nucleus) and is modulated by the hypothalamus. Vagal efferents extend from the medulla to postganglionic nerves that innervate the atria via ganglia located in cardiac fat pads with neurotransmission that is modulated via nicotinic receptors. Postganglionic parasympathetic and sympathetic cholinergic nerves then affect cardiac muscarinic receptors (the Figure).6-8

Vagus nerve afferent activation, originating peripherally, can modulate efferent sympathetic and parasympathetic function centrally and at the level of the baroreceptor.

Efferent vagus nerve activation can have tonic and basal effects that inhibit sympathetic activation and release of norepinephrine at the presynaptic level. Acetylcholine release from parasympathetic nerve terminals will activate ganglionic nicotinic receptors that in turn activate muscarinic receptors at the cellular level. Cardiovascular effects include heart rate reduction by inhibition of the sympathetic nervous system and by direct hyperpolarization of sinus nodal cells. Parasympathetic activation can affect atrioventricular nodal conduction mediated predominantly through the left vagus nerve. Furthermore, muscarinic receptors on blood vessel walls can cause vasorelaxation through a nitric oxide (NO)-modulated pathway but can also cause vasoconstriction by directly activating smooth muscle.6-8 Therefore, although the sympathetic nervous system has global effects on cardiovascular physiology in an all-or-none type of response, the parasympathetic nervous system can have selective modulation at various levels.

Parasympathetic/Sympathetic Interactions

The sympathetic and parasympathetic nervous systems are not “opposites”; rather, the interactions are complex.9 A dynamic interaction occurs between them; these interactions are modulated partially by secondary messengers (cAMP and cGMP). The parasympathetic nervous system can inhibit sympathetic nerve traffic presynaptically. Likewise, sympathetic activation can inhibit parasympathetic activation presynaptically.

Vagal “tone” (tonic parasympathetic activation) predominates over sympathetic tone at rest. Under normal physiological conditions, abrupt parasympathetic stimulation will inhibit tonic sympathetic activation and its effects at rest and during exercise. This response is known as “accentuated antagonism.”10-12 In a static13 or dynamic14 state, elevated sympathetic tone is overridden by intense vagus nerve discharge.

In HF, observations in ventricular myocardium manifest at the level of cardiac myocyte function provide insights into the relationship of sympathetic and parasympathetic function. The effect of intracoronary acetylcholine to inhibit a β-adrenergic–stimulated increase in the first derivative of left ventricular pressure over time is preserved, suggesting that the postreceptor pathway is intact. However, these same experiments indicate a reduction in tonic parasympathetic activation in HF because intracoronary atropine increased the response of the first derivative of left ventricular pressure over time to dobutamine in normal patients (indicating presence of significant parasympathetic tone) but not in HF (suggesting less parasympathetic tone in the heart).15-18

β-Adrenergic stimulation causes apoptosis of cardiac myocytes.19 This effect, mediated by protein kinase A and requiring calcium entry via voltage-dependent calcium channels, may contribute to the progression of myocardial failure. Muscarinic receptor stimulation opposes this action by a
G(i)-mediated signaling pathway that opposes actions of adenylyl cyclase. Carbachol, a muscarinic agonist, can prevent β-adrenergic receptor–stimulated apoptosis and therefore may indicate that muscarinic activation can improve outcomes in HF by this mechanism.20

**Muscarinic Receptors**

Muscarinic receptors reside in both the atria and ventricles but have a greater density in the former.6 They occur more in the endocardium than in the epicardium. Muscarinic receptors exist on T tubules in cardiomyocytes, coronary arteries (including small vessels), and endothelial cell membranes of capillaries. Muscarinic receptors are abundant on sinoatrial and atrioventricular nodal cells.

The known effects of the parasympathetic nervous system on cardiac function, heart rate, and atrioventricular nodal conduction appear modulated generally via M2 receptors. M2 and M4 receptors may be colocalized on various cardiac structures, yet their role in modulating measurable physiological responses in humans remains uncertain. The different muscarinic receptor subtypes can have different effects. The M2 receptor will markedly slow the heart rate (mediated in part by G-protein inwardly rectifying potassium [GIRK] channels), shorten atrial action potentials, increase smooth muscle contraction, inhibit the funny current, activate the G-protein–gated atrial potassium channel (Iₖ,ACh), and decrease contractility directly. The M3 and M4 receptors are upregulated in congestive HF; the former can activate the potassium channel IKM3, and the latter will activate GIRK1 and Iₖ,ACh.

Antibodies to the M2 receptor have been identified in patients with dilated cardiomyopathy and may influence the development of atrial fibrillation.5,21–25 In an animal model, autoantibodies have been associated with remodeling in HF, but it is not certain how the two are related.26 M2 receptor predominance also was observed to shift to M3 and M4 receptors. Cardiac M3 receptors may affect heart rate and cardiac repolarization, modulate inotropic effects, protect against ischemic injury, regulate cell-cell communication, and have antiarrhythmic and proarrhythmic effects.27 A potential role for the M3 receptor in initiating and maintaining atrial fibrillation in HF has been proposed.28 M3 receptor activation may have an opposite effect on heart rate compared with M2 receptor activation. The role of M2 receptors remains unclear,29 but they appear to modulate different repolarization currents.

**Nicotinic Receptors**

Nicotinic receptors reside on the postganglionic parasympathetic neuron and therefore can affect vagus nerve activity.
Nicotinic receptors do not directly stimulate or directly affect organs, but they are responsible for ganglionic transmission and ultimately are responsible for end-organ parasympathetic activation. Decreased synaptic transmission in parasympathetic ganglia may contribute to abnormal parasympathetic function in HF. In part, attenuated parasympathetic control in HF is located within the peripheral efferent limb within the parasympathetic ganglion in a canine HF model.30

Nicotinic receptors mediate synaptic ganglionic transmission and upregulate in response to chronic exposure to agonist. Repeated exposure of ganglionic neurons to a nicotinic agonist to prevent loss of parasympathetic control in HF has been tested. Despite decreased ganglionic function leading to reduced parasympathetic control in HF, repeated exposure to a nicotinic agonist during HF development resulted in preserved, even supernormal, effects of parasympathetic stimulation.30,31

Types of Vagus Nerve Fibers
Much of the understanding of the histology of the fiber type in the cervical vagus nerve is derived from animals (canine, feline, and other mammals).32–34 Although differences can be found in the distribution of the fascicles by species in the cervical vagus, the quantitative relations between the various types and functions of fibers are similar.4 Afferent fibers predominate and include slowly conducting unmethylated C fibers and small-diameter A-delta fibers that underlie the sensation of referred neck and jaw pain experienced in angina pectoris. The C fibers in efferent fascicles contribute to tonic cardio-inhibition and are mediated by muscarinic receptors. Efferent fascicles also contain large myelinated A-beta fibers that belong to the laryngeal bundle and cardio-inhibitory A-delta fibers that excite postganglionic neurons in the cardiac fat pads via nicotinic receptors. Theoretically, at least, preferential stimulation is needed to effect cardio-inhibition without generating other effects or eliciting pain.7,8,32–39

Central Influences on Parasympathetic Innervation
Parasympathetic innervation may be modulated by a number of centrally mediated mechanisms. Central γ-amino butyric acid (GABA) mechanisms may promote vagus nerve withdrawal. In particular, it appears that GABA inhibits vagus nerve outflow40 mediated through the GABAA receptor.41 Centrally acting opioids (enkephalins) interrupt vagus nerve–induced bradycardia through a muscarinic effect. Mu-opioid receptors and opioid-like receptors (ORL-1) within the nucleus ambiguus suggest that opioids modulate synaptic transmission to cardiac vagal neurons. A mu-selective endogenous agonist, D-Ala2,N-Me-Phe4,Gly5-ol-enkephalin (DAMGO), and nociceptin decrease glycinergic inputs to vagal neurons in the nucleus ambiguus, suggesting central modulation of parasympathetic activation.52 Decreases in glycinergic transmission increase parasympathetic activity and may be a mechanism by which opioids not only induce bradycardia but also influence atrial fibrillation.43 Serotonin, neuropeptides, and even cannabinoids can modulate parasympathetic function centrally.44–46

Heart Rate Control
As noted, heart rate control by the parasympathetic nervous system is relatively complex. Activation from the central nervous system of vagal preganglionic nerves can, via nicotinic receptors, activate the vagal postganglionic nerve. The subsequent release of acetylcholine stimulates the muscarinic receptors, which, in turn, activate NO synthase (NOS) through guanylate cyclase to inhibit the L-type calcium channel. The M2 receptor can indirectly activate IKACh to slow the sinus rate. Additionally, M2 receptors on the presynaptic sympathetic nerve terminal will inhibit norepinephrine release.21–23,26

Heart Rate and Outcomes
Resting heart rate in a normal heart generally is governed by a parasympathetic mechanism. Epidemiological data indicate that the resting heart rate, a measure of vagus nerve function, predicts mortality. The higher the vagus nerve activity is, the slower the heart rate is, the greater the increase in the parasympathetic component of heart rate variability is, and the better the outcome is. In HF, heart rate is less regulated by parasympathetic activation. A summary of data on resting heart rate and cardiovascular disease indicates a robust relationship between increased heart rate and adverse outcomes.47

Evaluation of Parasympathetic Activation
Parasympathetic function is difficult to measure directly. Parasympathetic effects can be measured crudely by responses to vagus nerve stimulation (Valsalva or similar maneuvers) and blockade (atropine or antimuscarinic, M2 receptor blocker)48,49 or physiological observations such as reduced heart rate or respiratory sinus arrhythmia. More sophisticated measurements are similarly indirect and noninvasive such as evaluation of heart rate variability, heart rate recovery from exercise,50 and spectral turbulence.51,52

Several lines of evidence suggest that heart rate variability is a marker, albeit nonspecific, of autonomic tone and that heart rate turbulence may be a marker of baroreceptor sensitivity.53 The high-frequency components of heart rate variability are associated with vagus nerve/parasympathetic effect, whereas the low-frequency components are due to sympathetic and parasympathetic activation. Of note, differences exist between the ratios of low-frequency to high-frequency components, depending on the cause of HF.54 Baroreflex sensitivity, which reflects in part parasympathetic innervation, also is difficult to measure directly. It may reflect central vagal output and include input from the carotid sinus, aortic and atrial receptors, and left ventricular (LV) mechanoreceptors.55

Alteration of Parasympathetic Control in HF
Parasympathetic activation and its physiological effects are attenuated in HF. Data indicate that changes in vagus nerve control of heart rate become apparent at a very early developmental stage of LV dysfunction, which may provide important prognostic information in patients at risk for developing progressive myocardial dysfunction.56
Nitric Oxide

The mechanism(s) by which NO influences cardiac function are difficult to conceptualize in that the NO molecule appears to have diverse and often opposing effects. Nevertheless, any interaction between the parasympathetic nervous system and NO is relevant to the pathophysiology of HF. The observations of Hare et al are particularly relevant in that the inotropic response to dobutamine on contractility could be attenuated by vagal stimulation in normal instrumented canines. The infusion of the NOS inhibitor Nω-monomethyl-L-arginine reduced the impact of vagus nerve inhibition, whereas infusion of the NOS substrate arginine had the opposite effect. Hence, NO is involved in parasympathetic regulation of myocardial contractility.

The complexity of the interactions is heightened by the heterogeneity of expression and effects of different types of NOS expressed in endothelial cells and cardiac myocytes where NO exerts a variety of location-specific effects. Expression of NOS isoforms is markedly altered in humans with HF and in animals with experimentally induced HF. Expression of neuronal NOS and inducible NOS is significantly increased in humans and animals with HF, whereas expression of endothelial NOS is decreased.

The increase in autonomic imbalance in HF may be related in part to an endothelial NOS promoter polymorphism (thymidine-to-cytosine transition [T-786C]). Those homozygous for this polymorphism had heart rate variability measures suggesting more sympathetic and less parasympathetic activity. In HF, NO influences cardiac function in seemingly opposite directions.

The concept that NO acts from site-specific modes of signaling through NOS isoforms that are spatially located to different organs provides an explanation for these divergent effects. Dysregulation of the NO pathway can have a direct adverse impact on worsening of the HF state, particularly with respect to LV performance. Studies in dogs with coronary microembolization–induced chronic HF have shown that long-term vagus nerve stimulation can improve LV systolic function and is associated with normalization of mRNA and gene expression of NOS. Additional studies are needed to explore further the mechanism(s) through which vagus nerve stimulation acts to modulate NO and its isoforms.

Cytokines

Cytokine production by the immune system contributes importantly to both health and disease. The nervous system, via an inflammatory reflex of the vagus nerve, can inhibit cytokine release and thereby prevent tissue injury and cell death. The antiinflammatory effects of vagus nerve stimulation are likely mediated through activation of the α-7 nicotinic acetylcholine receptor. Activation of this receptor by the acetylcholine inhibits the release of high-mobility group box 1 (HMGB1), a mediator of inflammation, from macrophages.

Persistent inflammation, involving increased levels of inflammatory cytokines, plays a potential pathogenic role in the progression of LV dysfunction and remodeling in HF. However, results from placebo-controlled studies with tumor necrosis factor-α antibodies suggest no improvement or even adverse effects resulting from such therapy, underscoring the challenges in developing treatment modalities that can modulate the cytokine network in HF patients. The injection of lipopolysaccharides in animals that underwent vagus nerve stimulation resulted in reduced macrophage release of inflammatory cytokines (tumor necrosis factor-α, interleukin [IL]-18, and IL-6) without affecting the release of IL-10, an antiinflammatory cytokine. However, vagus nerve transaction removed this protection. In human macrophage cell cultures, acetylcholine inhibited tumor necrosis factor-α release when the cultures were exposed to lipopolysaccharide. These results suggest that the vagus nerve may play a role in an antiinflammatory response.
Moreover, when vagus nerve activity is decreased or absent, cytokines are overproduced. Findings in human studies are consistent with the hypothesis that diminished vagal antiinflammatory signals can allow cytokine overproduction. In experimental models of inflammatory diseases, vagus nerve stimulation attenuates the production of proinflammatory cytokines and inhibits the inflammatory process. From a pharmacological perspective, nicotinic agonists are more efficient than acetylcholine at inhibiting the inflammatory signaling and the production of proinflammatory cytokines.

### Other Modulators

A number of other modulators may affect parasympathetic function, including histamine, capsaicin, substance P, bradykinin, adenosine, natriuretic peptides, oxygen free radicals, and stretch receptors. For example, histamine released from immunoreactive mast cells, located on ganglia adjacent to parasympathetic postganglionic neurons in guinea pigs, results in stimulation of \( H_3 \) receptors. The ensuing local inflammatory response activates parasympathetic neurons rapidly.

Bradykinin activates ventricular C-fiber afferents. Captopril enhances chemosensitive vagus nerve afferent discharge in HF but not in control animals; bradykinin enhanced the afferent response in both groups. Indomethacin significantly inhibits resting discharge and nearly abolishes the afferent responses to lower doses of bradykinin in HF. The cyclooxygenase system contributes to the enhanced bradykinin responsiveness of cardiac chemosensitive endings in HF.

Arachidonic acid metabolites and oxygen free radicals can modulate cardiac afferent sensitivity in HF. However, although heart rate variability measures and IL-6 levels correlate, no correlations were found with parasympathetic tone as measured by heart rate variability.

### Parasympathetic Activation: A New Treatment Paradigm?

Given the importance of the vagus nerve in parasympathetic innervation of the heart, vagal stimulation becomes an obvious potential target. Either direct or indirect vagus nerve stimulation could have direct beneficial effects on remodeling and clinical outcomes. This is supported by results of studies of the time course of sympathetic imbalance and LV dysfunction in dogs with rapid pacing-induced HF. In these studies, Ishise and colleagues showed a close relationship between cardiac dysfunction and autonomic dysregulation during the development of HF.

### Potential Mechanisms

The exact mechanisms and precise targets are likely to be varied but could include a reduction in heart rate, improvements in heart rate variability and baroreflex sensitivity parameters, changes in NO or cytokine expression, direct antiarrhythmic effects, or other electrophysiological or central modulation (the Table). As noted, vagus nerve stimulation may have antiinflammatory effects, as suggested by inhibition of release of tumor necrosis factor-\( \alpha \), IL-1, IL-6, IL-18, and intracellular HMGB1 protein. A cholinergic anti-inflammatory pathway in HF may exist. Parasympathetic activation may increase acetylcholine, dopamine, NO, endorphins, antioxidants, and other factors. Acetylcholine has been shown to attenuate the release of proinflammatory cytokines and tumor necrosis factor-\( \alpha \), IL-1, IL-6, and IL-18 but not the antiinflammatory cytokine IL-10.

Antiarrhythmic effects of vagus nerve stimulation are possible, as seen in animal models. Right cervical vagus nerve stimulation after myocardial infarction in a rat model suppressed the occurrence of ventricular ectopy. When a pharmacological approach with pyridostigmine (30 mg orally 3 times daily for 2 days) was used in a double-blind, crossover protocol that included patients with HF in sinus rhythm, active therapy resulted in a 65% reduction in ventricular ectopic activity (\( P=0.03 \)) and an improvement in heart rate variability parameters (\( P<0.05 \)).

### Therapeutic Strategies to Enhance Parasympathetic Tone

Currently, evidence is available that some existing therapies may exert benefit through a favorable impact on parasympathetic tone. For example, angiotensin-converting enzyme inhibitors may have a muscarinic effect. Cardiac vagal activity may be mediated by angiotensin II activity, and its suppression may be associated with improved sodium handling, although these data are in dispute. Small clinical studies have assessed the impact of angiotensin-converting enzyme inhibitors on baroreflex function and parasympathetic function but differ by agent studied, technique used, and population evaluated. Studies showing a favorable effect include quinapril in the post–myocardial infarction setting and captopril (but only at low doses). Whether this effect is a reflection of improved hemodynamics or a primary effect is not clear.

Recent data suggest that \( \beta \)-blockade with metoprolol or carvedilol in HF can augment reflex vagus nerve control of heart rate by blockade of cardiac sympathetic prejunctional \( \beta_2 \) receptors that facilitate norepinephrine release. In an animal model of HF, the density of \( M_2 \) receptors was increased in the carvedilol-treated group, especially in endocardial tissues of the LV free wall. Clinically, the putative role of carvedilol in the modulation of parasympathetic activity was inferred as a result of improvements in heart rate variability measurements.

Statins and fish oil may alter heart rate variability and heart rate in a beneficial fashion. Although statins may improve autonomic balance, they may also alter the substrate that triggers atrial fibrillation. Abnormal heart rate variability
measures seen in rabbits with pacing-induced congestive HF are reversed and return toward normal with simvastatin therapy. In double-blind trials, scopolamine can regulate parasympathetic control in HF120,121 as measured by heart rate variability122 and improved baroreflex sensitivity.123 Despite this, little, if any, additional clinical benefit was observed.

Furthermore, the degree to which these observations will translate into improvements in clinical status is not yet known. For example, the impact of parasympathetic stimulation on systolic and diastolic function, ventricular shape and size, the substrate for ventricular arrhythmia, and the risk of sudden death needs to be explored.

Could Direct Parasympathetic Stimulation Be Beneficial in HF?
The effect of chronic electric stimulation of the vagus nerve on cardiac remodeling and long-term survival in an animal model of chronic HF after myocardial infarction has been evaluated.124 After 6 weeks of right vagus nerve stimulation in a rat HF model to lower heart rate 20 to 30 bpm, treated rats had improved hemodynamic measures and a 73% relative risk reduction in death. Vagus nerve stimulation also effectively suppressed arrhythmias, including the occurrence of premature ventricular contractions within 1 to 2 days.92 Conversely, vagal blockade increased renin activity and vasopressin levels, suggesting that vagal afferent activity is increased and effectively suppresses renin and vasopressin in HF.

In an open-chest dog model of HF, vagus nerve stimulation appeared to slow the ventricular rate during atrial fibrillation. Electrophysiological, echocardiographic, and hemodynamic measurements were obtained during sinus rhythm, atrial fibrillation, and atrial fibrillation with vagus nerve stimulation. Vagus nerve stimulation produced slowing of the ventricular rate and significant reversal of pressure and contractile indexes. Slowing of the ventricular rate during AF by selective ganglionic stimulation of the vagus nerve that innervates the atrioventricular node successfully improved hemodynamic responses.125 Additional data support the use of epicardial fat pad stimulation in animals with induced atrial fibrillation over standard atrioventricular nodal ablation and pacing.126,127

In a recent pilot study, the effects of direct selective right vagus nerve electrical stimulation on LV function were examined in dogs with chronic HF using a new implantable system that also incorporates a right ventricular lead to monitor heart rate (CardioFit, BioControl Medical, Yehud, Israel). Results demonstrate that long-term (3 months) monotherapy with vagus nerve stimulation prevents progressive increases in LV end-diastolic volume, reduces LV end-systolic volume, and significantly increases LV ejection fraction.128 In addition to preclinical studies, vagus nerve stimulation therapy when combined with chronic β-blockade elicited an improvement in LV function and remodeling that was additive to that achieved with β-blocker alone.129 This device is currently being investigated in a study of New York Heart Association class II and III patients130 and will be examined further in a large-scale clinical trial.

Potential Drawbacks of Vagus Nerve Stimulation
Parasympathetic nerve stimulation shortens the atrial refractory period in an inhomogeneous fashion and can affect atrioventricular nodal conduction and ventricular contractility. As currently conceptualized, for vagus nerve stimulation to be effective, it needs to incur activation of the proper fibers and presumably the proper efferent fibers. Afferent activation is probably unnecessary in congestive HF.

Theoretically, augmentation of parasympathetic activity could be detrimental even though little clinical evidence supports this. When patients with terminal HF die, they may experience profound bradycardia or asystole instead of ventricular tachycardia or fibrillation; however, it is not at all clear that this is due to a primary parasympathetic mechanism.131

Summary
Autonomic regulation of the heart has an important influence on the progression of HF. Although elevated sympathetic activity is associated with an adverse prognosis, a high level of parasympathetic activation confers cardioprotection by several potential mechanisms. These parasympathetic actions on the heart are mediated not only by the direct consequences of cardiac muscarinic receptor stimulation but also by a multitude of indirect mechanisms. Direct vagus nerve stimulation has only recently been investigated in human subjects with HF and could provide new insights into how parasympathetic activation affects disease progression and clinical outcomes.

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