Novel Interventional Therapies to Modulate the Autonomic Tone in Heart Failure

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ABSTRACT

Heart failure (HF) represents a significant and expanding public health burden associated with increasing prevalence and exponential growth in related healthcare costs. Contemporary advances in both pharmacological and nonpharmacological therapies have often been restricted in application and benefit. Given the critical role of the autonomic nervous system (ANS) in maintaining cardiovascular homeostasis in the failing heart, there has been increasing interest in the role of ANS modulation as a therapeutic modality in HF. In this review, we highlight the anatomy of the ANS and its role in the pathophysiology of HF, as well as metrics of its assessment. Given the limitations associated with pharmacological ANS modulation, including lack of specificity and medication intolerance, we focus in this review on contemporary nonpharmacological ANS modulation therapies. For each therapy—vagal nerve stimulation, carotid baroreceptor stimulation, spinal cord stimulation, and renal denervation—we review the rationale for modulation, pre-clinical and clinical assessments, as well as procedural considerations and limitations. We conclude by commenting on novel technologies and strategies for ANS modulation on the horizon. (J Am Coll Cardiol HF 2015;3:786–802) © 2015 by the American College of Cardiology Foundation.

Heart failure (HF) represents a significant and expanding public health burden affecting nearly 25 million patients globally (1,2). In the United States alone, the prevalence of HF is nearly 6 million and is estimated to double by the year 2030 (2). Although contemporary strategies in the management of HF have improved survival after diagnosis, overall mortality remains high because nearly one-half of patients die within 5 years (3). The expanding prevalence of HF, coupled with improved survival after diagnosis, has framed an exponential growth in HF-related costs, estimated to range between $30 and $60 billion, and are expected to more than double in the next 20 years (2,4).

In the face of rising HF morbidity, mortality, and costs, there have been important contemporary advances in both pharmacological (5) and nonpharmacological therapies (6), although their application and benefit are often restricted to a subset of patients (7). In this context, given the long-recognized relationship between autonomic nervous system (ANS) function and HF, there is increasing interest in ANS modulation as a therapeutic modality. In this review, we highlight the anatomy of the ANS and its role in the pathophysiology of HF, as well as metrics of its assessment. We then review contemporary nonpharmacological ANS modulation therapies in HF before commenting on novel technologies and strategies on the horizon.

ANATOMY, REFLEXES, AND REGULATION OF THE ANS

In its most reductive form, the ANS primarily comprises 2 systems: the sympathetic and parasympathetic. The sympathetic nervous system (SNS) serves a predominant cardioacceleratory function, and its activation is associated with augmentation of heart rate (HR), increased ventricular contraction, and enhanced atrioventricular conductivity. In counterbalance, the parasympathetic nervous system (PNS) serves a predominant cardioinhibitory function associated with attenuation of HR and ventricular contraction, reduced arterial stiffness, and increased venous capacitance. The dynamic interaction of these 2 limbs of the ANS, modulated by physiological inputs and reflexes, ultimately regulates the hemodynamic and electrical functions of the heart and vascular system (Central Illustration).

Understanding the anatomy of the ANS is critical to defining the scope of its therapeutic targeting and modulation (Figure 1A). The SNS output is located in the spinal column (first thoracic to fourth lumbar segments), extending rostrally and caudally to the adjacent paravertebral ganglia forming the sympathetic trunk. SNS signals are carried via pre-ganglionic neurons to post-ganglionic ganglia, which are either located directly on viscera (adrenal cortex, smooth muscle cells of blood vessels) or, in the case of myocardial input, organized into 2 major ganglia (superior cervical and stellate) (9). For myocardial SNS
ABBR EVIATI ONS AND ACRONYMS

ANS = autonomic nervous system
CBS = carotid body stimulation
HF = heart failure
HRR = heart rate recovery
HRV = heart rate variability
NE = norepinephrine
NO = nitric oxide
NYHA = New York Heart Association
PET = positron emission tomography
PNS = parasympathetic nervous system
RAAS = renin-angiotensin-aldosterone system
SNS = sympathetic nervous system
VNS = vagal nerve stimulation
VTA = ventricular tachyarrhythmia

input, post-ganglionic fibers coalesce into cardiac nerves (superior, middle, inferior) whose sympathetic fibers extend to the heart and travel subepicardially. For peripheral SNS inputs, stimulation of post-ganglionic ganglia leads to secretion of epinephrine from the adrenal cortex or local release of epinephrine and norepinephrine (NE) near peripheral vessels. Secretion of these sympathetic transmitters bind adrenergic receptors in the myocardium (predominantly β-receptors with chronotropic, lusitropic, inotropic, and dromotropic effects) and periphery (α-receptors with vasoconstrictive effects) to exert their end-organ influence (10).

By contrast, PNS visceral innervation is reflected by regional nerve inputs (oculomotor, facial, glossopharyngeal, vagal, sacral). Myocardial PNS innervation is via the vagus nerve with pre-ganglionic origins in the central nervous system (medulla, nucleus ambiguous). The vagus nerve and its branches synapse on myocardial ganglionated plexuses located within the epicardial fat pads of the atria and ventricles, with additional concentration of inputs involving the vena cava, coronary sinus, and ostia of the pulmonary veins. The concentration of PNS innervation is generally greater in the atria compared with the ventricles, where PNS fibers extend subendocardially into the ventricular muscle (11). Peripherally, PNS inputs on blood vessels can lead to vasorelaxation (via nitric oxide [NO] pathways) or vasoconstriction (via activation of smooth muscle) (12).

The extracardiac inputs of both the SNS and PNS further interact with a complex network of intrinsic cardiac neurons (approximately 43,000 in the adult heart) known as the epicardial neural plexus (9) (Figure 1B). Through organization into ganglionated subplexuses on the surface of atria and ventricles (with proximity to both the sinoatrial and atrioventricular nodes) (8), the epicardial neural plexus adds an additional layer of cardio-cardiac regulation of autonomic function (13).

The homeostatic functions of the ANS are modulated by autonomic reflexes as well as integration with neurohormonal axes. Stress-sensitive baroreceptors (mechanoceptors) are present in both high-pressure arterial (carotid sinus, aortic arch) and low-pressure venous systems (atria/pulmonary arterial interface, systemic veins), whereas chemoreceptors responsive to changes in arterial oxygen and carbon dioxide concentration are present both peripherally (carotid sinus, aortic arch) and centrally (brainstem). There are additional low-threshold polymodal receptors (sensitive to both mechanical and chemical stimuli) present in the walls of all cardiac chambers that stimulate SNS output in the setting of reduced receptor activity (10). The ANS is further modulated through bidirectional feedback from the renin-angiotensin-aldosterone system (RAAS). For example, reduced renal perfusion (reflective of reduced cardiac output) is associated with release of renin and downstream synthesis of angiotensin II (ATII), which functions centrally to increase SNS activity (14,15) while also inhibiting baroreflex-mediated suppression of SNS tone (16,17). Inversely, increased SNS output leads to increased renin secretion (14).

AUTONOMIC FUNCTION AND HF. The ANS plays a critical compensatory role in maintaining cardiovascular homeostasis in the failing heart. Reduction in cardiac output leads to stimulation of multiple cardiovascular reflexes (low-flow stimulation of arterial baroreceptors, increased blood volume stimulation of venous baroreceptors, and reduced activity of intramyocardial receptors) and activation of neurohormonal axes (reduced renal perfusion and RAAS stimulation) culminating in stimulation of the SNS. Increased SNS activity is well described in patients with systolic HF (18) and has recently been implicated in the pathogenesis of HF with preserved ejection fraction (19,20). Increased sympathetic inputs maintain cardiac output initially via positive inotropic and chronotropic effects. Over time, however, chronic activation of the SNS and withdrawal of PNS input lead to progressive myocardial dysfunction, neurohormonal activation, and increased susceptibility to malignant arrhythmias. Indeed, more than 3 decades ago, Cohn et al. (21) demonstrated that plasma NE levels were independently predictive of mortality in patients with systolic HF. Chronic activation of SNS inputs leads to reduced cardiac neuronal density and responsiveness (22), dysfunction of SNS reflexes including augmentation of excitatory arterial baro- and chemoreceptor inputs (23), as well as subcellular myocardial dysfunction (increased apoptosis, abnormal calcium handling, increased interstitial fibrosis) (23–25). In addition to abnormalities of the SNS, withdrawal and attenuation of PNS input has also been implicated in the pathogenesis of HF (12). PNS alterations include reduced vagal ganglionic activity as well as loss of PNS receptor density and neurotransmitter activity (12,26). Sympathovagal imbalance in HF, including loss of PNS inhibition of SNS reflex arcs (27–29), has been associated with increased resting HR and worse clinical outcomes in HF (30). Reduced PNS activity may...
further contribute to HF pathogenesis through dysregulation of NO signaling (12,31,32) as well as loss of PNS inhibition of inflammatory cytokine release (33,34) and RAAS activation (35).

Electrophysiologically, HF is associated with neuronal and ionic channel remodeling (36,37) as well as abnormal SNS and PNS discharges (38). SNS-mediated effects on the electrical refractory period, spatial heterogeneity of electrical remodeling, ionic channel remodeling, and aberrancy of intracellular calcium handling may underlie the increased risk of ventricular tachyarrhythmias and sudden cardiac death in patients with HF (39,40). PNS influences in HF are more complex as vagal stimulation has been shown to reduce ventricular ectopy and ventricular tachyarrhythmias (41), whereas increased atrial PNS tone has been associated with atrial fibrillation (37).

**MEASURING AUTONOMIC FUNCTION.** Objective assessment and quantification of ANS activity is essential to defining ANS pathology as well as targeting and assessing the efficacy of ANS interventions. Conceptually, ANS activity can be measured directly or indirectly and reflect general or regional assessment (Table 1). Historically, SNS activity was measured via plasma NE levels utilizing radioimmunoassay of regional venous or arterial blood (21,42,43). Unfortunately, plasma NE levels are at best a crude assessment of SNS function subject to the heterogeneity of synthesis, reuptake and clearance of NE in different tissue beds (44,45). More direct quantification of SNS activity includes microneurography, which measures post-ganglionic SNS neuronal activation of SNS activity includes microneurography, which measures post-ganglionic SNS neuronal activity. Positron emission tomography using either time-domain (variation in R-R intervals) or frequency domain (spectral analysis assessing distribution of R-R intervals) methods (59). Frequency domain measures of HRV (e.g., the ratio of low- and high-frequency variance, which are under SNS and PNS control, respectively) may reflect sympathovagal balance (61), although the relationship between discrete measures of HRV and limbs of the ANS is not always linear and is further subject to influence from non-ANS inputs (respiration, thermoregulation) (58,60). Provocation (including exercise) has also been utilized to assess ANS function including, for example, post-exercise HR recovery, which is thought to reflect parasympathetic reactivation and SNS withdrawal (59). Each of these electrical variables—resting HR, time and frequency domain measures of HRV, and HR recovery—has demonstrated prognostic utility in patients with and without cardiovascular disease (39,55,59,62). Of particular practical interest, intracardiac devices have the capacity to measure multiple noninvasive electrical surrogates of ANS function (e.g., resting HR, HRV) (63). Device-based measures of ANS surrogates have been shown to predict HF hospitalization and mortality (64,65) and may offer future opportunities to dynamically regulate stimulation and pacing rates in response to these parameters.

**NONPHARMACOLOGICAL MODULATION OF ANS IN HF.** Given the implicate role of the ANS in the pathogenesis of HF, there has been expanding interest in the role of ANS modulation as HF therapy. The salutary effects of established pharmacotherapies for HF, including β-blockade and RAAS inhibitors, are thought, in part, to be related to modulation of ANS tone and related reductions in arrhythmia and favorable ventricular remodeling (10). Indeed, the mortality benefit associated with β-blockade in HF is closely related to the degree of HR reduction (30), and therapies targeted at elevated resting HR in HF have been associated with improved clinical outcome as shown with use of ivabradine in the SHIFT (Systolic Heart Failure Treatment with the IR Inhibitor Ivabradine)
CENTRAL ILLUSTRATION  Autonomic Dysfunction and Heart Failure Pathogenesis

SNS Activation
- Subcellular myocardial dysfunction (abnormal calcium handling, apoptosis)
- ↑ Interstitial fibrosis
- Synergistic activation of excitatory SNS reflexes
- ↑ Arrhythmia susceptibility
- ↑ Peripheral vascular resistance

RAAS Activation
- ATII-mediated ↑ central SNS output
- ATII-mediated ↑ carotid body chemoreceptor sensitivity
- Abnormal sodium and water homeostasis
- Pathologic LV remodeling

PNS Withdrawal
- NO dysregulation
- ↑ Inflammatory cytokines
- ↑ Resting HR
- ↑ Arrhythmia susceptibility
- Loss of inhibition of SNS reflexes

PROGRESSIVE HEART FAILURE

(Lower left) Schematic demonstrating the synergistic relationships between autonomic imbalance, neurohormonal activation, and the pathogenesis of heart failure.
(Lower right) Schematic highlighting the interactions between the central nervous system, heart, and kidneys. Anatomic sites of autonomic modulation are highlighted.

ATII = angiotensin II; AV = atrioventricular; HR = heart rate; LV = left ventricular; NO = nitric oxide; PNS = parasympathetic nervous system; RAAS = renin-angiotensin-aldosterone system; SA = sinoatrial; SNS = sympathetic nervous system.

trial (66). There are important limitations, however, of pharmacological strategies to modulate ANS tone, including lack of specificity in modulating discrete limbs of the ANS and frequent side effects associated with medication intolerance. For example, although the centrally acting agent moxonidine was shown to significantly reduce plasma NE in select patients with HF (67), it was associated with increased mortality in randomized controlled assessment (68), highlighting the potential dangers associated with nonspecific sympatholysis in HF (69). These limitations have spurred the development of nonpharmacological approaches of ANS modulation, including vagal nerve stimulation (VNS), spinal cord stimulation (SCS), baroreceptor stimulation, and renal denervation.

**VAGAL NERVE STIMULATION**

Myocardial input of the PNS is organized via the vagus nerve—the left and right vagus nerves responsible for regulation of cardiac contractility and sinoatrial function (9,70). More than 4 decades ago, Braunwald et al. (71) demonstrated dysfunction of the PNS in HF. Subsequent elegant animal models of HF suggested that VNS was associated with normalization of abnormal ANS surrogates (HRV, baroreflex sensitivity, plasma NE) and improved survival (72,73). Importantly, the salutary influence of vagal nerve modulation in HF almost certainly extends beyond influence on autonomic measures (resting HR, HRV) and includes its impact on ventricular NO signaling, inflammatory cytokine activation, and neurohormonal activation (12). For example, NO is known to modulate parasympathetic influences on ventricular contractility (74), and VNS-associated improvement in left ventricular (LV) systolic function is closely correlated with normalization of NO expression (75).

Similarly, vagal nerve stimulation has been shown to reduce expression of multiple inflammatory cytokines (e.g., tumor necrosis factor [TNF]-α, interleukin [IL]-6, IL-1), which have been implicated in the pathogenesis of HF, including aberrant β-adrenergic signaling, increased myocyte apoptosis, increased myocardial fibrosis, and ultimately, adverse LV remodeling (76,77).

Implantation of a vagal nerve stimulator involves the coordinated expertise of a surgeon and electrophysiologist. Stimulation of the vagal nerve is accomplished via an implantable stimulator system that delivers electrical impulses via a bipolar cuff electrode around the vagus nerve in the neck approximately 3 cm below the carotid bifurcation (Figure 2A). At this level, the vagus nerve comprises both afferent and efferent fibers organized into 1 of 3 types (A-C), each with distinct stimulation thresholds, conductive properties, and organ targets. The efficacy of VNS turns on the ability of the device to selectively stimulate and inhibit appropriate vagal nerve fibers. Strategies for selective targeting include electrode design as well as modulation of stimulation intensities and waveforms. For example, the CardioFit VNS system (BioControl Medical, Yehudi, Israel) utilizes a multicontact electrode designed to preferentially activate vagal efferent fibers in the right cervical vagus nerve. The stimulation lead was designed to recruit myocardial-specific efferent vagal B-fibers with minimal recruitment of vagal A-fibers that could lead to unwanted central side effects (78). The system additionally incorporates a right ventricular lead to provide backup pacing in the event of VNS-mediated bradycardia. Following implantation of the vagal cuff, the stimulation lead is subsequently tunneled to an infraclavicular pocket (Figure 2B). The efficacy of myocardial vagal nerve targeting is confirmed by up-titration of the amplitude of stimulation (target usually ~5.5 mA) associated with a reduction in HR of 5 to 10 beats and without side effects (neck pain, coughing, swallowing difficulty, nausea) (79,80). Of note, alternative procedural approaches to VNS that have shown early promise include endovascular stimulation at the coronary sinus ostium and/or superior vena cava (81).

The first human study of VNS employed the aforementioned CardioFit system in 8 patients with HF, demonstrating safety as well as significant improvements in HF symptoms and LV end-systolic volumes (82). De Ferrari et al. (79) subsequently led an open-label multicenter trial of the CardioFit device in 32 patients with symptomatic HF and reduced LV ejection (left ventricular ejection fraction [LVEF] <35%) showing significant improvements in functional status and favorable LV remodeling (improved LVEF, reduced LV systolic volumes). These initial favorable studies led to 3 randomized controlled assessments of VNS, including NECTAR-HF (Neural Cardiac Therapy for Heart Failure), ANTHEM-HF (Autonomic Neural Regulation Therapy of Enhance Myocardial Function in Heart Failure), and INOVATE-HF (Increase of Vagal Tone in Congestive Heart Failure) (83–85) trials (Table 2). The NECTAR-HF study enrolled 96 patients with symptomatic HF, depressed LVEF, and dilated LV cavity and randomized patients in a 2:1 fashion using a sham-controlled design (83). VNS was achieved via a vagal cuff lead (NCT lead, Boston Scientific Corporation, Marlborough, Massachusetts) without use of a sensing right ventricular lead, and thus activation and inactivation were unrelated
to cardiac cycle. Preliminary 6-month follow-up identified no significant difference in the primary efficacy endpoint of change in LV end-systolic dimension, although patients undergoing VNS did demonstrate significant improvements in subjective quality-of-life scores and improvement in New York Heart Association (NYHA) functional class (62% vs. 45% in the VNS vs. control groups, p = 0.032). The lack of VNS efficacy in the NECTAR-HF study may be related to multiple factors, including enrollment of a relatively “stable” HF population (baseline N-terminal pro-B-type natriuretic peptide [NT-proBNP] was 879 to 882 pg/ml across study groups), suboptimal delivery of stimulation current (average of 1.4 mA, which was lower than ~4 mA current in trials demonstrating VNS efficacy), use of a helical bipolar electrode stimulating both afferent and efferent vagal fibers (in contrast to the asymmetric, preferential stimulation of efferent fibers utilized previously), and suboptimal modulation of vagal myocardial inputs (nonsignificant changes in resting HR and variable improvement in indices of HRV).

The ANTHEM-HF study was an open-label assessment of 60 patients with symptomatic HF and reduced LVEF (<40%) randomized to right versus left vagal nerve stimulation (84). VNS was accomplished via the VNS Therapy System (Cyberonics, Houston, Texas) using a pulse frequency lower than that used in the NECTAR-HF study (10 vs. 20 Hz). Similar to the NECTAR-HF study, and unlike the CardioFit system, VNS was performed without intracardiac sensing and was thus untimed to the cardiac cycle. In the entire study population, there were modest, but significant, improvements in the primary efficacy endpoints of change in LVEF (+4.5%) and reduction in LV end-systolic volume (~4.1 ml) at 6 months. NYHA functional class improved in 77% of patients. ANS surrogates were variably affected with improvement in time-domain measures of HRV but no significant change in resting HR or plasma NE and ATII. The incidence of serious therapy-related adverse events was very low (~2%). The ongoing INOVATE-HF study is a multicenter phase III trial that aims to enroll 650 patients with symptomatic HF, dilated LV cavity, and depressed LVEF (≤40%) who will be randomized in a 3:2 fashion to VNS or standard therapy (no implant) (85). The study will utilize the CardioFit VNS system, delivering 1 to 2 pulses per cardiac cycle (timed via intracardiac sensing lead).

Taken together, the results and design of VNS studies to date highlight several unanswered challenges in utilizing VNS in HF. Optimal patient selection is important to consider because patients with limited neurohormonal derangement (as seen in the NECTAR-HF study) may not experience incremental benefit when compared with goal-directed medical therapy. Furthermore, whether patients with baseline increased SNS activity are most likely to benefit remains an open question. The range of stimulation sites (right vs. left), stimulation protocols (timed vs. untimed to cardiac cycle, variability of current delivery), and lead design (asymmetric vs. symmetric activation of afferent and efferent vagal fibers) frame open questions and challenges in improving the efficacy of VNS in HF. Finally, given the protean
influences of VNS on intersecting pathway of HF pathogenesis—from innate immunity and proinflammatory cytokines to NO signaling—additional work elucidating the impact of VNS on these pathways will likely enhance patient selection and improve the ability to assess the efficacy of different VNS targeting strategies. For example, the ongoing NoSIRS pilot study (Effects of Transvenous Vagus Nerve Stimulation on Immune Response, NCT01944228) will examine the impact of VNS on TNF-α expression before and after exposure to endotoxin in healthy volunteers (86).

**CAROTID BARORECEPTOR STIMULATION**

The carotid baroreflex arc plays a significant role in sympathovagal balance and is implicated in the regulation of blood pressure and HR (87,88). The carotid body and carotid sinus are innervated by both the PNS (vagus and glossopharyngeal fibers) and SNS (via nearby cervical sympathetic ganglia), and contain both chemoreceptors (predominantly in the carotid body; responsive to oxygen and carbon dioxide tension, blood pH, hypoglycemia) as well as stretch-sensitive mechanoreceptors (predominantly in the carotid sinus; responsive to increase in blood pressure) (89). Stimulation of the carotid sinus mechanoreceptors results in afferent signals to the dorsal medulla of the brainstem and, ultimately, attenuation of SNS and augmentation of vagal outflow reflected by reduction in system blood pressure and HR (89–91). Stimulation of carotid body chemoreceptors is associated with augmentation of SNS tone (17). Given the close relationship between carotid baroreceptor activation and blood pressure modulation, there has been long-standing historical interest in the efficacy of carotid body stimulation (CBS) in patients with hypertension (92). Initial enthusiasm nearly a half century ago was tempered by technological limitations as well as the advent of effective pharmacotherapy.

In patients with HF, there is reduced sensitivity of the normal inhibitory function of carotid baroreceptors, related to primary alterations within the carotid body as well as dysfunction of central nervous system processing, ultimately resulting in excessive sympathetic tone (93–96). Additionally, the neurohormonal (RAAS) activation associated with HF may further exacerbate SNS activity via ATII-mediated augmentation of carotid chemoreceptor sensitivity (96,97). Therapeutically, stimulation of the carotid body in canine models of HF is associated with normalization of ANS surrogates (reduced plasma NE, normalized expression of cardiac β-receptors) as well as favorable LV reverse remodeling (improved LVEF, reduced LV volumes) (94). CBS may further ameliorate HF via reduction in plasma ATII levels (91,95) with related improvements in extracellular volume regulation, endothelial function, and favorable ventricular remodeling (17,98).

Renewed contemporary interest in CBS as a therapy in HF has been catalyzed by technological advances and improvement in implant techniques. Implantation is performed under the direction of a multi-disciplinary team of vascular surgeons, cardiologists, and anesthesiologists. The most investigated Rhoes system (CVRx, Minneapolis, Minnesota) has 3 components: an implantable pulse generator, carotid sinus leads, and an external programmer (Figure 3A). Stimulation can be targeted to either or both carotid sinuses (e.g., a newer-generation system [Barostim neo, CVRx] consists of a single carotid sinus electrode). Stimulation leads are typically targeted to the carotid sinus of the common carotid artery approximately 5 mm from the carotid bifurcation. Leads are connected to an implantable pulse generator that is placed within an infraclavicular pocket. The electrode is standardly tested for hemodynamic
FIGURE 2 Vagal Nerve Stimulation

(A) Examples of leads associated with available vagal nerve stimulation (VNS) systems. (B) Chest radiograph of patients with a vagal nerve stimulator (VNS) and previously implanted implantable cardioverter-defibrillator. Highlighted is the sensing lead of the VNS system located in the right ventricle. CRT = cardiac resynchronization therapy device.
TABLE 2 Comparison of Randomized Controlled Comparisons of Vagal Nerve Stimulation in HF

<table>
<thead>
<tr>
<th>Study</th>
<th>INOVATE-HF (Ongoing)</th>
<th>ANTHEM-HF</th>
<th>NECTAR-HF</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>650</td>
<td>60</td>
<td>96 (87 with paired data)</td>
</tr>
<tr>
<td>NYHA functional class</td>
<td>III</td>
<td>II–IV</td>
<td>II–IV</td>
</tr>
<tr>
<td>Ejection fraction</td>
<td>≤40%</td>
<td>≤40%</td>
<td>≥35%</td>
</tr>
<tr>
<td>LVEDD</td>
<td>50–80 mm</td>
<td>50–80 mm</td>
<td>≥55 mm</td>
</tr>
<tr>
<td>QRS width</td>
<td>&lt;120 ms</td>
<td>&lt;130 ms</td>
<td>≥150 ms</td>
</tr>
<tr>
<td>Trial design</td>
<td>Randomized 3:2 (implant vs. no implant)</td>
<td>Open label, randomized right vs. left VNS</td>
<td>Randomized 2:1 (VNS on vs. off)</td>
</tr>
<tr>
<td>Control</td>
<td>Optimal medical treatment</td>
<td>Right vs. left</td>
<td>Stimulation off</td>
</tr>
<tr>
<td>Device used</td>
<td>CardioFit System, BioControl Medical, Israel</td>
<td>Demipulse model 103, Cyberonics, United States</td>
<td>Precision, Boston Scientific, United States</td>
</tr>
<tr>
<td>Side stimulated</td>
<td>Right</td>
<td>Right and left</td>
<td>Right</td>
</tr>
<tr>
<td>Stimulation protocol</td>
<td>Target output: 1.3–5.5 mA, titrated on/off times to maximum of 10 s on/30 s off</td>
<td>Target output 1.5–3.0 mA (average achieved 2.0 mA), frequency 10 Hz, pulse width 130 µs, 14 s on/66 s off</td>
<td>Target output: maximal 4 mA (average achieved 1.4 mA), frequency 20 Hz, pulse width 300 µs, 10 s on/50 s off</td>
</tr>
<tr>
<td>Intracardiac lead</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Study duration</td>
<td>18 months</td>
<td>6 months</td>
<td>6 months</td>
</tr>
<tr>
<td>Primary efficacy endpoints</td>
<td>Death or HF hospitalization (up to 5.5 years)</td>
<td>Change in LVESV and LVEF at 6 months</td>
<td>Change in LVESV from baseline at 6 months</td>
</tr>
<tr>
<td>Primary efficacy endpoint met</td>
<td>Trial ongoing</td>
<td>Yes, LVEF improvement of 4.5% (95% CI 2.4–6.6)</td>
<td>No</td>
</tr>
</tbody>
</table>

CI = confidence interval; HF = heart failure; LVEDD = left ventricular end-diastolic dimension; LVEF = left ventricular ejection fraction; LVESD = left ventricular end-systolic dimension; LVESV = left ventricular end-systolic volume; NYHA = New York Heart Association; VNS = vagal nerve stimulation.

response utilizing an incremental voltage protocol. Similar to VNS, there are myriad stimulation parameters including sequence (continuous, burst) as well as impulse duration and amplitude. Despite these technological advances, contemporary trials utilizing these systems have been associated with adverse events (surgical complications, hypoglossal nerve injury, and respiratory complications), suggesting need for further technological refinement (102).

The evaluation of efficacy of CBS in HF is in its nascent stages. Recently, Gronda et al. (103) reported a single-center, open-label evaluation of CBS in 11 patients with symptomatic HF and depressed LVEF (<40%). Utilizing the Barostim neo system targeting a single carotid sinus, the study assessed a primary efficacy endpoint of muscle sympathetic nerve activity at 6 months. CBS was associated with significant reduction in SNS activity in parallel with modest improvements in functional status, quality of life, and LVEF. Extending these findings, the recently reported Barostim HOPE4HF study randomized 146 patients to goal-directed medical therapy alone versus the addition of CBS via the Barostim neo system (104). There was no standard dosing protocol, with device stimulation intensity incremented over a 3-month period unless associated with excessive reductions in HR or blood pressure. At 6-month follow-up, compared with patients with medical therapy, CBS was associated with modest, but significant, improvement in functional endpoints (e.g., 6-min walk distance, quality-of-life score, NYHA functional class), reduction in natriuretic peptide concentration, and a trend to reduction in days of HF hospitalization. There was no significant difference in LV reverse remodeling between the 2 groups. Ongoing studies involving CBS in HF include the Rheos Diastolic Heart Failure trial (CVRx, NCT00718939) and the ongoing Rheos HOPE4HF (Hope for Heart Failure, CVRx, NCT00957073) trial, both of which are randomized controlled assessments of CBS in patients with relatively preserved LVEF (<40%) (105,106). Endpoints include major adverse cardiac events, changes in LV mass index, and safety. Alternative strategies to carotid sinus stimulation including endovascular stimulation are being tested, for example, in the ACES II study (Acute Carotid Sinus Endovascular Stimulation II Study, Medtronic, Minneapolis, Minnesota, NCT01458483) (107).

Although early efficacy assessments of CBS in HF are promising, and technological evolution of the device and implant system has improved safety, there remain significant questions regarding the role of unilateral versus bilateral stimulation, selection of patients with carotid baroreceptor dysfunction, and optimization of stimulation protocols (impulse duration, frequency, sequence).
SPINAL CORD STIMULATION

SCS is a well-established therapy for chronic pain syndromes and refractory angina (108). Implantation typically occurs under conscious sedation with percutaneous insertion of a multipolar 8-electrode lead into the epidural space at the mid-thoracic level (109) (Figure 3B). Stimulation is applied typically at 90% of the motor threshold with a set of frequency (usually ~50 Hz) and pulse width (usually ~200 ms) for a prescribed duration of time (either cyclic or continuously). For patients with implantable-cardioverter defibrillators, the potential presence of SCS-induced myopotentials as well as interference with ventricular fibrillation detection warrant interrogation and, if needed, reprogramming of the stimulator at the time of implant.

SCS is thought to mediate cardioprotective effects via augmentation of parasympathetic tone through an unknown mechanism postulated to include modulation of higher-order PNS processing (110). Given the demonstrated influence of SCS on autonomic function, there has been increasing interest in its role as a therapy for HF (111). Consistent with its postulated effects on PNS tone, SCS has been shown to increase atrial refractory period and decrease the inducibility of atrial fibrillation in a tachy-pacing canine model (112). In addition, SCS has been shown to reduce the incidence of ventricular tachyarrhythmias in several post-infarction animal models (113,114). The most robust evidence of the efficacy of SCS in HF includes a randomized assessment of thoracic SCS in a post-infarction canine model of HF (115). Over 10 weeks, SCS was performed at the T4 level, 3 times a day for 2 h each, at 90% of the motor threshold. SCS was associated with significant decrement in ANS surrogates (plasma NE) and neurohormonal activation (reduced NT-proBNP), as well as significant improvement in LVEF. Stimulation at 60% of the motor threshold and at a higher thoracic level (i.e., T1) was also shown to significantly reduce ambulatory HR in a similar canine model (116).

The efficacy of SCS as HF therapy in humans has been mixed (117). The SCS HEART (Spinal Cord Stimulation for Heart Failure) study was an open-label, nonrandomized assessment of safety and efficacy of SCS in 22 patients (17 patients and 5 controls who did not consent to implant) with symptomatic HF, reduced LVEF (20% to 35%), and dilated LV cavity (118). The SCS device (Eon Mini Neurostimulation System, St. Jude Medical, Plano, Texas) included 2 percutaneous leads covering the high-thoracic space (T1 to T3), set at 90% to 110% of the paresthesia threshold, and delivering therapy continuously (24 h/day). At 6-month follow-up, SCS was associated with statistically significant improvement in functional class, quality-of-life scores, metrics of LV reverse remodeling (improved LVEF, reduced LV volumes), and peak oxygen consumption. The procedure was well tolerated, with no acute complications. In contrast to the favorable results of the SCS HEART study, preliminary results of the single-blind, phase II efficacy study DEFEAT-HF (Determining the Feasibility of Spinal Cord Neuromodulation for the Treatment of Chronic Heart Failure, NCT01112579) were generally null (118). The DEFEAT-HF study randomized 66 patients with symptomatic HF, depressed LVEF (<35%), and dilated LV cavity in a 3:2 fashion to SCS for 12 h per day or no activation for 6 months. A single, 8-electrode lead (Medtronic lead model 3777) was utilized at 90% of the motor threshold. There was no significant improvement in the primary efficacy endpoint of LV end-systolic volume index, and no difference in secondary endpoints, which included peak oxygen consumption, change in NT-proBNP, change in functional status, or major adverse cardiac events (death, HF hospitalization).

The neutral results of the DEFEAT-HF trial raise several questions regarding the implementation of SCS in HF. Whether more continuous SCS exposure (24 h in the SCS HEART study vs. 12 h in the DEFEAT-HF study) or multiple electrode poles are associated with greater benefit is unknown. There remains no standardized “dose” of SCS in HF, and dose studies of electrode output in humans may be warranted. Finally, whether SCS benefits select patients with HF (e.g., ischemic cardiomyopathy, as was utilized in animal models) or whether efficacy is related to duration of HF and degree of pathological LV remodeling remain questions for future investigation.

RENAL DENERVATION

In patients with HF, there is bidirectional feedback between the ANS and RAAS. The reduced renal perfusion associated with HF leads to stimulation of the RAAS with ATII-mediated increases in central SNS output (14,15) as well as ATII-mediated modulation of carotid body chemoreceptor sensitivity (16,17). Inversely, efferent sympathetic fibers innervating the renal cortex and terminating within the glomerular arteriole lead to increased renin secretion and maladaptive handling of sodium and water (14,119). Additionally, renal afferents...
responsive to renal hypoxemia and ischemia may
directly trigger increased central SNS output (120).
The synergistic relationship between autonomic and
neurohormonal dysfunction in HF is thought to be
an important mediator of progressive pathological
ventricular remodeling, increased peripheral vas-
cular resistance, and abnormal sodium and water
homeostasis.

Although initially assessed in patients with
resistant hypertension, there has been growing

(A) Schematic diagram of patient with carotid body stimulation system. The top panel shows the location of the baroreflex activation lead and implantable pulse generator. The lower panel shows the first-generation CVRx Rheos device (left) and the single-lead second-generation Rheos device. Adapted, with permission, from Gassler et al. (99) and Karunaratne et al. (100). (B) Chest radiograph of patient with spinal cord stimulator device (red arrow) and previously implanted biventricular pacemaker-implantable cardioverter-defibrillator. Adapted with permission from Kang et al. (101).
interest in the use of renal denervation as therapy in HF (121). Pre-procedural evaluation includes assessment of renal arterial anatomy and renal function testing (122). The proceduralist must be experienced in renal angiography as well as management of acute complications such as renal dissections or perforation. Denervation is accomplished via circumferential, low-energy radiofrequency applications within the renal artery, typically positioned just proximal to the origin of a second-order renal artery branch. In general, 4 to 8 applications are applied along the length of each renal artery, although individual anatomy and catheter technology affect the total number of lesions delivered. Given the recent demonstration of the lack of benefit associated with renal denervation in patients with resistant hypertension (123), there is significant interest in the use of novel procedural approaches (e.g., more distal renal artery ablation; increase in number of ablative lesions) as well as consideration of optimal patient selection and trial design. Procedural innovation in renal denervation includes the use of different ablation catheter designs (unipolar, bipolar, multipolar), balloon-based application technology, use of alternative energy sources (cryo, laser, ultrasound), and alternative ablative agents (ethanol) (123,124).

Pre-clinical models of HF demonstrated improvements in sodium handling and cardiac output, as well as decrease in angiotensin receptor density following renal denervation (121). The first human demonstration of renal denervation safety and efficacy in HF was in the REACH (Renal Artery Denervation in Chronic Heart Failure) pilot study (125). In 7 patients with symptomatic systolic HF, depressed LVEF and normotension at baseline, renal denervation was well tolerated as reflected by nonsignificant reduction in blood pressure, no episodes of syncope or hypotension, and no significant change in renal function at 6 months. In this limited study, patients experienced significant improvement in subjective quality-of-life measures and 6-min walk distance. These results in patients with systolic HF remain to be validated in larger randomized studies with longer follow-up, including the SYMPLICITY-HF study (Renal Denervation in Patients with Chronic Heart Failure and Renal Impairment, NCT01392196) and the RSD4CHF trial (Renal Sympathetic Denervation for Patients with Chronic Heart Failure, NCT01790906) (126,127).

Additionally, given the demonstrated relationship between renal denervation and regression of LV hypertrophy (128,129), there are ongoing trials assessing the efficacy of renal denervation in patients with HF and preserved ejection fraction. Of interest, in previous trials of patients with resistant hypertension, regression of myocyte hypertrophy was only partly dependent on decrement in blood pressure, suggesting a more direct relationship between autonomic modulation and HF pathogenesis (129). The ongoing DIASTOLE trial (Denervation of the Renal Sympathetic Nerves in Heart Failure with Normal LV Ejection Fraction, NCT01583881) will randomize 60 patients with HF and LVEF ≥50% to renal denervation or continued optimal medical therapy. Efficacy endpoints include measures of LV remodeling (change in LVEF, LV mass) as well as multiple ANS surrogates (MIBG washout, HRV) (130). Similarly, the ongoing SWAN-HF study (Renal Sympathetic Modification in Patients with Heart Failure, NCT01402726) will randomize 200 patients with symptomatic HF (both reduced and preserved ejection fraction) to renal denervation or continued medical therapy with a primary endpoint of composite cardiovascular events (131). Finally, given the potential benefits of renal denervation on ventricular and atrial arrhythmias (132,133), glucose metabolism (134), and sleep apnea (135), there may be an additional role for this strategy in managing relevant comorbidities implicated in the pathogenesis and exacerbation of HF.

In summary, preliminary work suggests that renal denervation is safe and tolerated in patients with HF, although its ultimate efficacy and tolerability remains to be tested in larger studies. Sympathetic tone plays an important compensatory role in HF, and historic trials of nonspecific pharmacological sympatholysis have been associated with increased mortality (68,69). Heterogeneity of sympathetic renal innervation and the presence of comorbid renal dysfunction in patients with HF will also need to be considered in the application of renal denervation for this population.

**FUTURE STRATEGIES OF NEUROMODULATION IN HF**

There are several technologies on the horizon that may further shape the landscape of neuromodulation in HF. First, there is expanding interest in the role of tragus stimulation as an alternative, less-invasive method of vagal nerve stimulation (136). In a pre-clinical model of post-infarction cardiomyopathy, tragus stimulation was associated with attenuation of ANS surrogates (plasma NE) and neurohormonal activation (NT-proBNP), as well as improvement in LV function (137). Similar efforts to
stimulate the vagus nerve through less invasive means include endovascular stimulation (e.g., within the superior vena cava) (138). Second, although the strategies discussed in the previous text have focused exclusively on extracardiac autonomic modulation, another area of intense investigation involves modulation of the intrinsic cardiac neural plexus that lies on the epicardial surface of the heart as well as within the adventitia of the great vessels between the ascending aorta and pulmonary artery (9,12). Endovascular cardiac plexus stimulation in preliminary pre-clinical work was associated with augmented LV contractility and cardiac output without influence on vascular resistances, central venous pressure, or HR (139). Given the anatomic organization of the intrinsic neural plexus, the ability to selectively modulate components of the intrinsic cardiac nervous system offers the speculative possibility of truly targeted autonomic modulation (e.g., sinoatrial node in sick sinus syndrome vs. ventricular myocardium in cardiomyopathy). Third, given the ability of implantable devices to measure surrogates of ANS function, we anticipate the development of pacing and stimulation technologies dynamically responsive to ANS tone. Finally, there is increasing evidence that HF is often accompanied by central sleep apnea (CSA), which in turn increases morbidity and mortality (140). Mechanistically, CSA is mediated via the respiratory control center, which is sensitive to the increased sympathetic drive and overactive chemoreceptors observed in HF. The respiratory control center regulates the blood CO₂ and also sends signals to the diaphragm via the phrenic nerves to control the pattern of breathing. Notably, every episode of CSA also activates the SNS, perpetuating the vicious cycle. Treating the CSA accompanying HF may in fact offset some of the accompanying autonomic imbalance and novel transvenous pacing of the phrenic nerve (via axillary or subclavian vein access of the left pericardiophrenic or right brachiocephalic vein) has been associated with a promising efficacy in mitigating apneic episodes and improving sleep apnea indices (141). The long-term clinical impact of phrenic nerve pacing in HF patients remains to be proven.

CONCLUSIONS

The ANS plays a critical role in the pathogenesis of HF. As acknowledged at the outset, the reductive “yin-yang” formulation of the SNS and PNS components of the ANS does not reflect the complex and integrative relationships among autonomic function (extracardiac and intracardiac), neurohormonal activation, innate immune system activation, and subcellular functions (e.g., NO signaling). Continued translational efforts focused on refining our understanding of the complex interactions between neurohormonal and ANS dysfunction, as well as insight into regional autonomic regulation, will only augment the development of ANS targeting technologies in HF. Experience to date with non-pharmacological ANS therapy highlights ongoing challenges for improving patient selection, optimization of implant or denervation strategies, and refinement of stimulation protocols. As technological capabilities and scientific understanding converge, effective modulation of the ANS may transform the landscape of HF.

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nerve traffic, baroreflex function, and cardiac hae-

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