Autonomic Modulation for the Management of Patients with Chronic Heart Failure

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Dysregulation of the autonomic nervous system in heart failure (HF) has received considerable attention during the past 3 decades, largely because of the well-recognized association between increased sympathetic activity and the elaboration of biologically active molecules, collectively referred to as neurohormones, that help to maintain cardiovascular homeostasis through increased volume expansion, peripheral arterial vasoconstriction, and increased myocardial contractility. However, high and sustained levels of these biologically active molecules (eg, norepinephrine, angiotensin II, aldosterone) are overtly toxic to the heart and circulation.[1] These and other insights have led to the clinical use of neurohormonal antagonists, such as angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, aldosterone antagonists, and β-blockers to treat patients with HF with a reduced left ventricular ejection fraction (LVEF).[1] The effectiveness of these pharmacological agents is predominantly because of their ability to directly antagonize the deleterious effects of excessive sympathetic and renin–angiotensin activation. However, the current guideline-directed medical therapy (GDMT) in patients with HF fails to completely restore normal autonomic balance disrupted as a part of HF pathophysiology.

During the last decade, a novel approach has generated widespread interest: modulation of the autonomic nervous system as a result of either a one-time intervention (eg, denervation) or of ongoing active therapy (eg, electric stimulation) as a means of further diminishing the sympathovagal imbalance that develops in HF.[2,3] Of note, therapeutic neuromodulation with device-based therapies, either with spinal cord stimulation (SCS) or vagal stimulation (VS), has been used safely in patients with chronic pain, epilepsy, and depression, since the 1980s. As noted above, HF with a reduced LVEF is associated with sustained activation of the sympathetic nervous system that is accompanied by a withdrawal of parasympathetic tone. Impaired arterial baroreflexes have been proposed as an important mechanism that contributes to the sympathovagal imbalance present in HF[4,5] (Figure 1). Blunting of the peripheral arterial and cardiopulmonary baroreceptors leads to a net increase in efferent sympathetic nerve activity that is accompanied by decreased efferent parasympathetic tone. Accordingly, interest has developed not only toward the reduction of sympathetic activity but also toward the possibility of augmenting vagal tone and reflexes.[6]

The first clinical report demonstrating the feasibility of performing chronic stimulation of the vagus in patients with severe HF[7] and its continuation in the first multicenter clinical trial[7,8] have paved the way for a series of clinical approaches having in common the acceptance of the concept[9] that deleterious autonomic imbalance is an appropriate target for treatment and that device-based autonomic modulation by simultaneously decreasing sympathetic and increasing parasympathetic activity may improve outcomes. Such a goal would not be possible with the current pharmacological approaches to HF.

Here, we review the experimental basis, rationale, design of ongoing clinical trials that are focused on autonomic modulation in HF, including VS, SCS, renal denervation, baroreceptor activation, and left cardiac sympathetic denervation (LCSD).

Vagal Stimulation

Chronic VS is already used clinically for the management of drug-refractory epilepsy[10] and, more recently, depression.[11] The potential salutary role of VS in the heart was first highlighted by a series of experimental studies culminating in the demonstration that VS prevented ventricular fibrillation induced by acute myocardial ischemia in the setting of a healed myocardial infarction.[12,13] In animal models of HF, VS increased survival,[14] improved ventricular function,[14–16] and has shown anti-inflammatory effects.[16] Indeed, the anti-inflammatory effects of VS after ischemia and reperfusion injury are accompanied by a reduction in the number of macrophages and apoptotic cells that is paralleled by decreased levels of circulating proinflammatory cytokines.[17] These data point to the likely clinical relevance of the so-called cholinergic anti-inflammatory reflex proposed by Tracey.[18]

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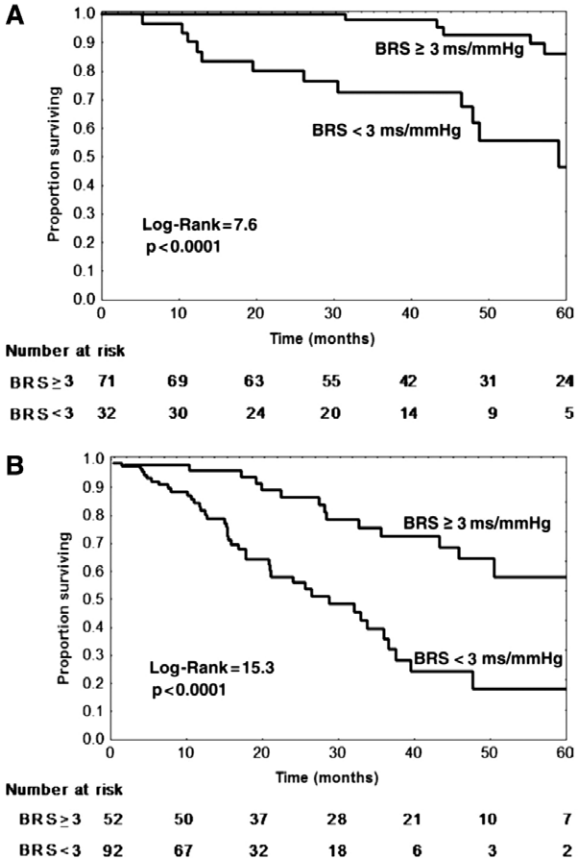

Figure 1. Kaplan–Meier survival curves according to dichotomized baroreflex sensitivity (BRS) in patients with heart failure (**A**) taking and (**B**) not taking β-blockers, with LVEF of 30% and 26%, respectively. Reprinted from La Rovere et al[4] with permission of the publisher. Copyright © 2009 American College of Cardiology Foundation. Published by Elsevier Inc.

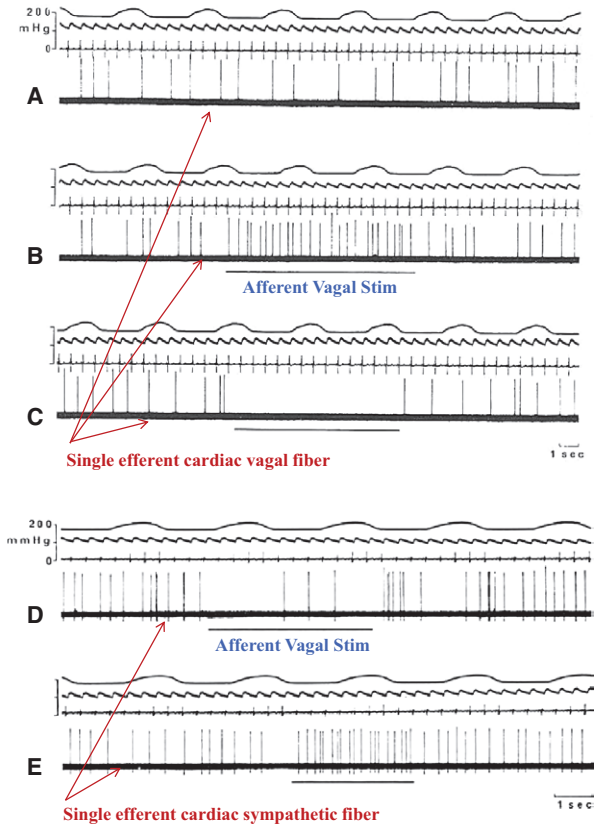

Figure 2. Effects of electric stimulation on the neural discharge of a single efferent cardiac vagal fiber in an anesthetized cat. **A**, Spontaneous activity, (**B**) electric stimulation (5 V,1.5 ms, 30 Hz) of the cut central end of the left cervical vagus, and (**C**) electric stimulation (10 V, 1.5 ms, 30 Hz) of the cut central end of the left inferior cardiac nerve. Effects of electric stimulation on the discharge of a single efferent cardiac sympathetic fiber in an intact, anesthetized cat. **D**, Electric stimulation (6 V,1.5 ms, 30 Hz) of the cut central end of the left vagus and (**E**) electric stimulation (10 V, 1.5ms, 30 Hz) of the cut central end of the inferior cardiac nerve. The tracings in each section are from top to bottom: respiration (positive-pressure inflation is an upward deflection), systemic arterial blood pressure, ECG, and neural activity. Reprinted from Schwartz et al[19] with permission of the publisher. Copyright © 1973, Wolters Kluwer Health.

In the clinical setting, VS is accomplished by placing an electrode cuff around the right or left cervical vagus, thereby stimulating both the vagal efferent and afferent fibers.[7,8] Experimentally, and importantly, stimulation of vagal afferent nerve fibers can have profound effects on the activity of the contralateral vagal efferent (increased activity) and bilaterally of cardiac sympathetic efferent nerve fibers (inhibition of activity), as shown in Figure 2.[19]

To date, 3 clinical studies of VS have been completed and published[20–22] (Table 1). The first-in-man single center study of VS involved 8 patients[7] and used the CardioFit 5000 device (BioControl Medical Ltd, Yehud, Israel), which is a closed-loop system comprised of a proprietary bipolar electrode

Table 1. Characteristics of 3 Just Completed or Ongoing Trials With Vagal Stimulation in Patients With HF

Study Name	Phase	Patients, n	NYHA	LVEF	QRS	Stimulation Side	Control Group	End-Point
ANTHEM-HF[20]	I to II	60	II–III	≤40%, LVEDD≥50 mm and <80 mm	≤150	R vs L	R vs L	LVESV; LVESD; LVEF
NECTAR-HF[21]	II	96	II–III	≤35%, LVEDD>55 mm	<130	R	Stimulation off	LVESD
INOVATE-HF[22]	III	650	III	≤40%, LVEDD 50–80 mm	NA	R	GDMT	Death+HF hospitalization

ANTHEM-HF indicates Autonomic Regulation Therapy via Left or Right Cervical Vagus Nerve Stimulation in Patients With Chronic Heart Failure; GDMT, guideline-directed medical treatment; HF, heart failure; INOVATE-HF, Increase of Vagal Tone in Heart Failure; L, left; LVEDD, left ventricular end-diastolic diameter; LVEF, left ventricular ejection fraction; LVESD, left ventricular end-systolic diameter; LVESV, left ventricular end-systolic volume; NA, not applicable; NECTAR-HF, Neural Cardiac Therapy for Heart Failure; NYHA, New York Heart Association class; and R, right. Reprinted from De Ferrari[23] with permission of the publisher. Copyright © 2014, Springer Science+Business Media New York.

that is surgically implanted around the right vagal nerve, and a right ventricular sensing lead that allows for VS to be synchronized so that the vagal nerve is stimulated after the QRS complex. This study was subsequently extended to a multicenter single-arm open-label phase II study that was designed to assess the safety and tolerability of chronic VS.[8] The first pilot study enrolled 32 patients in total (94% men; mean age, 56±11 years) with a history of chronic New York Heart Association (NYHA) class II to IV HF and a LVEF of 23±8%. The patients were already receiving GDMT, including β-blockers, angiotensin-converting enzyme inhibitors/angiotensin receptor blockers, and loop diuretics; 19 patients had an implantable cardioverter defibrillator. The stimulation intensity of VS, which was limited by patient symptoms of hoarseness or referred jaw pain, was progressively uptitrated to 4.1±1.2 mA (with 1–2 pulses per cardiac cycle). The resting heart rate decreased significantly during the study from 82±13 to 76±13 beats per minute. At 6 months, 59% of patients improved by at least 1 NYHA class and the Minnesota Living with Heart Failure (MLwHF) Questionnaire quality of life score improved from 49±17 to 32±19, as did the distance on the 6-minute walk test. Blinded 2-dimensional echocardiogram analyses disclosed a significant reduction in LV end-systolic volume and a significant increase in LVEF (from 22±7% to 29±8%), but a nonsignificant decrease in LV end-diastolic volume. A prespecified follow-up of a group of patients at 1 (n=23) and 2 years (n=19) showed that many of the beneficial effects of VS were maintained (Figure 3).

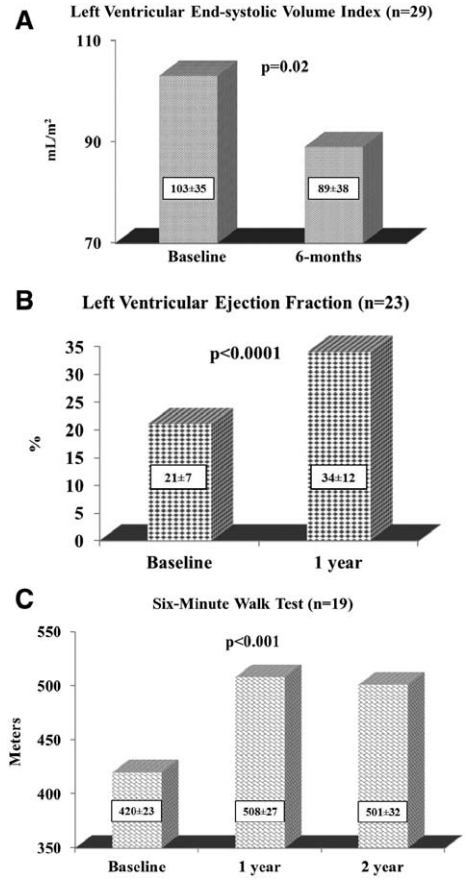

Figure 3. Effect of vagal stimulation over time: (**A**) change after 6 months in left ventricular end-systolic volume index in 29 patients; (**B**) in LVEF after 1 year in 23 patients; and (**C**) change in the 6-minute walk test after 2 years in 19 patients. Reprinted from De Ferrari et al[8] with permission of the publisher. Copyright © 2015, Oxford University Press.

A different technical approach with an open loop VS system that did not have an right ventricular sensing lead was used in the Autonomic Regulation Therapy via Left or Right Cervical Vagus Nerve Stimulation in Patients With Chronic Heart Failure (ANTHEM-HF) study.[20] This was an open-label phase II trial that enrolled 60 patients with NYHA class II and III HF, LVEF<40%, and QRS<150 ms, who were randomized to either left or right cervical VS. The stimulation intensity of VS was uptitrated during a 10-week period to reach 2.0±0.6 mA. The primary safety objective was the incidence of procedure and device-related complications. There were 2 coprimary efficacy end points: the first was LVEF, which, in the pooled analysis of right and left VS, increased by 4.5% (P<0.05). The relevance of this finding, however, is mitigated by the absence of significant change in the second end point, LV end-systolic volume, which decreased nonsignificantly by 4.1 mL. Although there was a trend toward greater improvement with right VS, these differences were not statistically significant (Figure 4). Overall, 77% of patients improved by at least 1 NYHA class at 6 months, with a significant improvement in the MLwHF score.

The Neural Cardiac Therapy for Heart Failure (NECTAR-HF) study was a phase II study enrolling patients with NYHA class II and III HF, an LVEF<35%, a QRS<130 ms, and LV end-diastolic diameter >55 mm. All 96 enrolled patients received a device implant and were randomized 2:1 to active treatment or sham treatment (with activation of the device only during the titration visits) for the first 6 months; thereafter, all patients received active treatment. The device used in NECTAR-HF also used a helical bipolar electrode and lacked an intracardiac right ventricular sensing lead, thus not allowing any regulation of stimulation on the basis of heart rate. The stimulation intensity was 1.4±0.8 mA. The primary efficacy end point, which was the change in LV end-systolic diameter at 6-month follow-up, was not significantly different (P=0.60) in the treatment and the control group.[21,24] Additional secondary end points, including LV end-diastolic dimension, LV end-systolic volume, LVEF, peak VO_2, and N-terminal of the prohormone brain natriuretic peptide, were not different between groups. However, there were statistically significant improvements in quality of life for the MLwHF Questionnaire (P=0.049) and the NYHA class (P=0.032) in the therapy group. Importantly, an assessment of blinding performed at 6 months revealed that 70% of the patients assigned to active treatment correctly guessed their randomization group, which was likely secondary to side effects of VS with this device.

The discrepancies in findings among the 3 VS studies warrant further discussion. A first issue is that each study used a different VS device. Whereas 2 of the devices were open-loop systems that were designed to treat patients with epilepsy, the VS device used in the CardioFit pilot trial was a closed-loop system that was designed for the treatment of HF. Probably, the most important issue is that each study used a different stimulation protocol and especially a different stimulation intensity and frequency. In agreement with the fact that lower frequencies allow greater amplitudes to be reached with

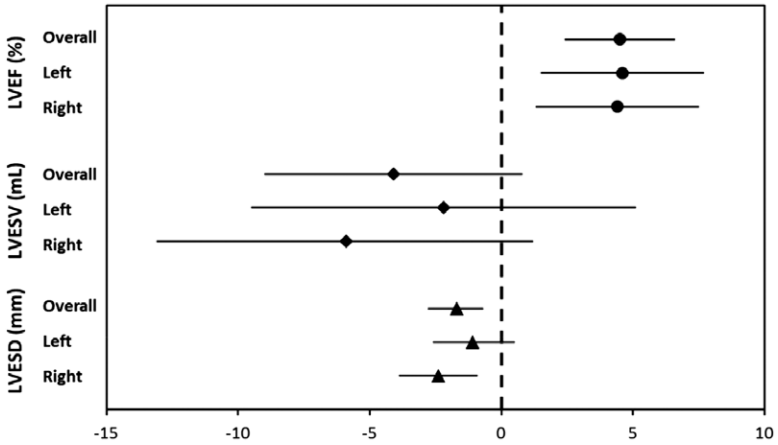

Figure 4. Mean and 95% confidence intervals of echocardiographic changes after 6 months of autonomic regulation therapy (overall, left-side treatment, and right-side treatment). LVEF indicates left ventricular ejection fraction; LVESV, left ventricular end-systolic volume; LVESD, left ventricular end-systolic diameter. Reprinted from Premchand et al[20] with permission of the publisher. Copyright @ 2014, Elsevier Inc.

tolerable side effects, the stimulation intensity did vary in the 3 studies being 1.3±08 mA in NECTAR-HF (range, 0.3–3.5), 2.0±0.6 mA in ANTHEM-HF (maximum intensity, 3 mA), and 4.2±1.2 mA in the CardioFit pilot trial (range, 1.1–5.5). With increases in stimulation intensity, the number of recruited vagus nerve fibers is progressively higher. Canine experimental studies have shown that intensities, such as those used in the NECTAR-HF study, albeit providing an improvement in LV function,[25] recruit only a minority of the fibers in the cervical vagus trunk.[26] Thus, it is likely that the lower intensity of VS in NECTAR-HF and ANTHEM-HF was not sufficient to adequately activate vagal fibers and that this could explain the different results. Finally, these differences may have been favored by the small number of patients involved in the trials.

The last VS clinical trial, which is still ongoing, is the Increase of Vagal Tone in Heart Failure (INOVATE-HF), which is an international, multicenter, randomized clinical trial designed to assess safety and efficacy of VS using the CardioFit system in patients with symptomatic HF who are on GDMT.[22] INOVATE-HF is randomizing 650 patients with NYHA class III symptoms, an LVEF ≤40% and LV end-diastolic dimensions 50 to 80 mm in a 3:2 ratio to either active treatment (implanted) or continuation of medical therapy (not implanted). The primary end point of the study is the composite of all-cause mortality or unplanned HF hospitalization equivalent, using a time to first event analysis. There are 2 coprimary safety end points: freedom from procedure and system-related complication events at 90 days and number of patients with all-cause death or complications at 12 months. This trial will complete enrollment in the first quarter of 2015.

Spinal Cord Stimulation

The concept for SCS originated following the revolutionary gate theory for the origin of pain, which suggested the possibility of suppressing pain by closing the gate through activation of large diameter afferent fibers.[27,28] Although the mechanisms of action of SCS are not completely understood, it seems that the mechanism of analgesia when SCS is applied in neuropathic pain states may be different from that involved in analgesia for peripheral ischemia.[29] In neuropathic pain states, experimental evidence shows that SCS alters the local neurochemistry in the dorsal horn, suppressing neuronal hyperexcitability, presumably by affecting the local concentration of several neurotransmitters and neuromodulators, most notably by increasing the levels of γ-aminobutyric acid.[30] However, in case of peripheral ischemic pain, analgesia seems to derive mostly from peripheral vasodilatation. Relevant here, SCS can be used for the treatment of refractory angina pectoris, in the absence of change in cardiovascular hemodynamics.[31] An antiadrenergic effect was thought to mediate the marked reduction in infarct size produced by prophylactic SCS, because this effect was blocked by α- or β-adrenergic blocking agents.[32] Olgin et al[33] suggested that SCS at the T1 to T2 level enhanced parasympathetic activity. SCS increased sinus cycle length and the AH interval, an effect that was abolished by bilateral vagal transection, and reduced the occurrence of VT/VF from 59% to 23% in a canine model in which ventricular arrhythmias were elicited by transient myocardial ischemia.[34] Subsequently, 28 dogs with HF induced by anterior myocardial infarction and rapid pacing were assigned for 5 weeks to no therapy, carvedilol, or SCS (delivered at T4/T5 region for 2 hours, 3× a day).[35] LVEF, that had declined to 18% after the induction of HF, recovered to 28%, 34%, and 47%, respectively, in the control, carvedilol, and SCS groups. Similar findings were observed with SCS in a porcine animal model of ischemia and reperfusion.[36]

Based on the above preclinical models, several clinical studies have been conducted in patients with HF. The Spinal Cord Stimulation for Heart Failure (SCS HEART) study[37] implanted a SCS device in 17 patients with NYHA class III HF, programmed to provide SCS for 24 hours a day (50 Hz at pulse width 200 μs). Patient safety was the primary end point of the study. Three patients required device reprogramming or repositioning because of back or neck discomfort. Significant improvements were observed at 6 months in NYHA class (2.1 versus 3.0), MLwHF Questionnaire (27±22 versus 42±26), LV end-systolic volume (137±37 versus 174±57 mL), and LVEF (37±8% versus 25±6%); overall 73% of patients had an improvement in ≥4 of 6 efficacy parameters. At 18-month follow-up, 2 patients (12%) died, 2 (12%) were hospitalized for HF and there continued to be no device–device interactions. Four patients (24%) with VT/VF before receiving the SCS therapy continued with VT/VF requiring implantable cardioverter defibrillator intervention, not confirming in this clinical setting the favorable antiarrhythmic effects observed in preclinical studies.[34,35]

The limitations of a small nonrandomized study were highlighted by the recent presentation of the results of the Determining

the Feasibility of Spinal Cord Neuromodulation for the Treatment of Chronic Heart Failure (DEFEAT-HF, NCT01112579), performed in 66 NYHA class III HF patients with a mean LVEF of 29±5%. Patients were randomized 3:2 to SCS or control, and after the 6-month visit, the control patients were crossed over to receive active therapy. The primary study end point was a reduction in the LV end-systolic volume index after 6 months of SCS therapy in the treatment arm versus the control arm. The results at 6 months show no difference between the active therapy arm and the control arm in LV end-systolic volume index, in peak VO_2, in N-terminal of the prohormone brain natriuretic peptide, and in all other parameters. The 12-month follow-up visit data will assess the effects of SCS for those enrolled in the therapy arm for a year, as well as the effects of SCS treatment for 6 months for those randomized from the control group to SCS treatment at 6 months.

After the negative results of the controlled study, it is presently unclear whether a phase III trial using this approach in patients with systolic HF will ever be performed.

Renal Denervation

Autonomic neural regulation of renal function has received increased attention during the past few years following the reports that catheter-based renal denervation could be safely performed by either radiofrequency energy or ultrasound delivery, thus representing a potentially useful procedure in all conditions associated with increased sympathetic activity. The renal sympathetic nervous system comprises both efferent and afferent renal nerves lying within and immediately adjacent to the wall of the renal artery. Although renal efferent nerves are distributed widely throughout the renal vasculature, renal afferent nerves are mainly located in the pelvic area. Renal sympathetic nerve activity is modulated in the central nervous system where information arising from all the different sensory receptors (also including signaling from renal sensory nerve fibers) is integrated. Increases in efferent renal sympathetic nerve activity reduce renal blood flow and decrease excretion of urinary sodium by activation of α_1-adrenoceptors, and increase renin secretion rate through activation of β_1-adrenoceptors.

Numerous studies have shown that increased renal efferent sympathetic activity plays an important role in the volume expansion that is observed in HF[38] by provoking renin release and the consequent increase in circulating and brain levels of angiotensin II.[39] HF also leads to diminished afferent renal sensory signaling, thereby blunting inhibitory reno-renal reflexes, which further contributes to increased renal sympathetic efferent activation.[40] In animal models, renal denervation improves volume-sensitive natriuresis, abolishes the decrease in mean renal blood flow and the increase in renal vascular resistance, and normalizes angiotensin II receptor expression.[41] In rats with postischemic HF induced by coronary artery ligation, structural and functional remodelling was partially prevented in denervated animals when compared with the control animal.[42] A still unsettled issue concerns the fact that reinnervation is expected to occur, soon or later, and it will also likely affect the afferent component of renal nerves.[43]

In patients with HF, the norepinephrine spillover from heart and kidneys is increased[44] and, specifically, increased renal sympathetic activity has been associated with all-cause mortality and heart transplants in these patients.[45]

Although several studies have been conducted in drug-resistant hypertensive patients,[46] the clinical experience with renal denervation in HF is far less. The REACH-Pilot study, the first-in-man in HF, evaluated 7 patients with symptomatic systolic HF (NYHA class III to IV) on maximal tolerated medical therapy.[47] There were no procedural complications and no significant hemodynamic disturbances were noted during the acute phase post renal denervation. All patients described themselves as symptomatically improved and had an increase in the 6-minute walking test. No hypotensive or syncopal episodes were reported during the 6-month follow-up period. However, none of these HF patients had a systolic blood pressure below 120 mm Hg. Several clinical trials are currently under way to evaluate the effects of renal denervation in patients with systolic HF and lower entry systolic blood pressure (Table 2). Based on studies in hypertensive patients showing that renal denervation may reduce left ventricular mass and improve diastolic function, a multicenter randomized controlled trial (DenervatIon of the renAl Sympathetic nerves in hearT failure with nOrmal Lv Ejection fraction, DIASTOLE) has been initiated to determine whether renal denervation, on top of medical treatment, is superior to medical treatment alone in improving echocardiographic parameters of diastolic function in patients with HF with preserved LVEF and hypertension.[48] Further studies in HF with preserved LVEF are listed in Table 2.

Baroreceptor Activation Therapy

As noted, HF with a reduced LVEF is associated with sustained activation of the sympathetic nervous system that is accompanied by a withdrawal of vagal tone. Preclinical and clinical studies have shown that electric stimulation of the baroreceptive fibers located in the carotid sinus leads to decreased sympathetic nerve activity and increased vagal tone.[49] In experimental HF models, chronic low-intensity carotid sinus stimulation resulted in decreased fibrosis and reverse LV remodeling in a canine coronary microembolization model[50] and improved survival in a canine model of pacing-induced HF.[51] These and other preclinical observations have led to interest in developing baroreceptor activation therapy (BAT) as novel treatment strategy in HF and to several trials (Table 3).

The technology for BAT is still evolving. The original Rheos system (CVRx Inc, Minneapolis, MN), which used 2 leads to stimulate the carotid sinus and had a battery life of ≈ 1 year, has been evaluated in 3 multicenter clinical studies in patients with resistant hypertension: the Device-Based Therapy in Hypertension Trial/Device-Based Therapy in Hypertension Extension Trial (DEBuT-HT/DEBuT-HET, NCT00710190 and 00710294, respectively) in Europe and the Rheos Feasibility Trial and Rheos Pivotal Trial (NCT00442286), which suggested greater efficacy of unilateral right-sided stimulation.[52] The second generation Barostim *neo* system consists of a single lead that requires less dissection of the carotid artery for implantation and has a battery life of 3 years. The Barostim *neo* system is also effective in treating resistant hypertension.[53]

BAT has been evaluated in patients with HF with a reduced LVEF. The Barostim Hope for Heart Failure (HOPE4HF) study (NCT01720160) is a feasibility study that is evaluating the effects of the Barostim *neo* system in 60 heart patients with

Table 2. Characteristics of Trials With Renal Denervation in Heart Failure

	Study/Acronym	Study Design	Patient Characteristic	Primary Outcome	Estimated Enrollment
Systolic HF					
NCT02085668	Renal Denervation in Patients with Chronic Heart Failure	Randomized Open label	NYHA II–III, LVEF 10%–40%, GFR≥30 mL/min per 1.73 m^2, BNP>100 pg/mL or NTproBNP>400 pg/mL, standard medical therapy, SBP>90 mm Hg	Safety of renal denervation with the Simplicity™ Catheter System, number of complications associated with the delivery and use of the Symplicity™ System	100
NCT01870310	Renal Denervation in Patients with Heart Failure and Severe Left Ventricular Dysfunction	Randomized Open label	NYHA II–IV, LVEF≤35%, standard medical therapy, SBP≥110 mm Hg	Change in serum NT-proBNP at 6 mo and 1 y from baseline in both groups	50
NCT01392196	Renal Denervation in Patients with Severe Heart Failure and Renal Impairment Clinical Trial/ SYMPLICITY-HF	Single group assignment Open label	NYHA II–IV, LVEF≤40%, GFR 30–75 mL/min per 1.73 m^2, GDMT, SBP>90 mm Hg	Safety of renal denervation in patients with HF as measured by adverse events	40
NCT02099903	Renal Denervation in Patients with Heart Failure Secondary to Chagas Disease	Randomized Open label	HF secondary to Chagas's disease, NYHA II–III, LVEF<40%, standard HF therapy, SBP>90 mm Hg	Composite: death, myocardial infarction, cerebrovascular event, need of intervention on renal arteries and renal function impairment (decrease in eGFR>30% from baseline)	30
NCT01954160	Study of Renal Denervation in Patients With Heart Failure/ PRESERVE	Randomized Open label	NYHA II–III, LVEF<40%, daily loop diuretic, GDMT, SBP≥110 mm Hg	Within-subject comparison of increase in urine sodium excretion after saline loading before RSD and 13 wk after RSD	64
NCT01402726	Renal Sympathetic Modification in Patients With Heart Failure/ SWAN-HF	Non-randomized Open label	NYHA II–IV, LVEF≤40% or ≥45%, eGFR≥45 mL/min	Composite cardiovascular events	200
NCT01790906	Renal Sympathetic Denervation for Patients With Chronic Heart Failure/RSD4CHF	Randomized Single blind	NYHA II–IV, LVEF≤35%	All-cause mortality, cardiovascular events	200
Diastolic HF					
NCT02041130	Renal Denervation in Heart Failure Patients with Preserved Ejection Fraction/RESPECT-HF	Randomized Open label	NYHA II–IV LVEF≥50%, evidence of LV diastolic dysfunction	Changes in left atrial volume index (LAVi) and left ventricular mass index (LVMi) on cardiac MRI between baseline and 6 mo	144
NCT02115230	Renal Denervation in Patients with Heart Failure with Normal LV Function	Randomized Open label	HF with normal LV function, LV hypertrophy, hypertension treated with at least 2 antihypertensive drugs	Change from baseline E/E′ at 12 mo+safety (composite of death, myocardial infarction, cerebrovascular events need of intervention on renal arteries, and renal function impairment)	40
NCT01583881	DenervatIon of the renAl Sympathetic nerves in hearT failure with nOrmal Lv Ejection Fraction/ DIASTOLE[48]	Randomized Open label	LVEF≥50%, evidence of LV diastolic dysfunction	Change from baseline E/E′ at 12 mo	60
NCT01840059	Renal Denervation in Heart Failure With Preserved Ejection Fraction/RDT-PEF	Randomized Open label	NYHA II–III, LVEF>50%	Change in symptoms, exercise function, biomarkers, LV filling pressure, LV remodeling	40

BNP indicates brain natriuretic peptide; eGFR, estimated glomerular filtration rate; GDMT, guideline-directed medical treatment; GFR, glomerular filtration rate; HF, heart failure; LV, left ventricular; LVEF, left ventricular ejection fraction; NTproBNP, N-terminal of the prohormone brain natriuretic peptide; NYHA, New York Heart Association class; and SBP, systolic blood pressure.

an LVEF≤35%, who are already receiving GDMT. Patients are randomized 1:1 to receive BAT plus GDMT or medical therapy alone. The primary outcome measure of the trial is safety and efficacy. The efficacy end points include change in LVEF, HF symptoms, quality of life, and HF hospitalizations. The Barostim *neo* System in the Treatment of Heart Failure Study (NCT01471860) is a European and Canadian randomized clinical trial that is being conducted in 150 patients with

Table 3. Characteristics of Trials With Baroreceptor Activation Therapy in HF

	Acronym	Study Design	Patient Characteristic	Primary Outcome	Estimated Enrollment
NCT00957073	Rheos HOPE4HF trial[49]	Randomized Open label	LVEF≥40%, symptomatic HF with elevated blood pressure	Cardiovascular death or heart failure event	540
NCT01471860	Barostim *neo* System in the Treatment of Heart Failure	Randomized Open label	NYHA class III HF and LVEF≤35%	Change from baseline in LVEF at 6 mo	150
NCT01484288	Baroreflex Activation Therapy in Heart Failure	Single center efficacy Study Open label	NYHA class III and LVEF<35% on GDMT	Changes in sympathetic nervous system activity at 6 mo from baseline	15
NCT01720160	Barostim HOPE4HF Study	Randomized Open label	On stable, HF GDMT for at least 4 wk before screening, LVEF≤35%	Safety and efficacy	60

GDMT indicates guideline-directed medical treatment; HF, heart failure; HOPE4HF, Hope for Heart Failure; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association class.

an LVEF≤35% and NYHA class III HF. Patients are randomized 1:1 to treatment with Barostim *neo* plus GDMT or GDMT alone. The primary efficacy end point is the change in LVEF at 6 months. There are also traditional secondary outcome measures. The primary safety end point is the rate of device and procedure-related complications. The NCT01720160 and NCT01471860 studies have just reported their results on 146 patients with NYHA class III HF and a LVEF ≤ 35% randomized to GDMT + BAT (n=76) or to GDMT alone (n=70).[54] Patients assigned to BAT, compared to the control group, after 6 months showed improvement in the 6-minute walk test, in a quality of life score, in the NYHA class ranking, and in NT-pro-BNP values. Despite a significant reduction in the rate of HF hospitalization from pre- to post-enrollment in the treatment group, there was no statistical difference between the treated and the control groups. Of some concern, echocardiogram analysis showed no significant difference in LVEF between BAT and control groups (p=0.15). The authors recognize the limitations due to lack of patient and investigator blinding leading to potential placebo effect and bias. Nonetheless, the overall results appear encouraging, suggesting safety of BAT in HF patients and possibly efficacy on some clinical parameters. A larger and controlled study seems warranted. The Baroreflex Activation Therapy in Heart Failure study (NCT01484288) is a single-center open-label study that has enrolled 11 patients with NYHA class III and LVEF<35% on GDMT. A progressive reduction in muscle sympathetic nerve activity and an improvement in quality of life and 6-minute walk test was noted at 6-month follow-up.[55] Although BAT studies using the older Rheo system in patients with HF and a preserved LVEF were interrupted (NCT00957073), studies using the newer Barostim *neo* System are under development.

Left Cardiac Sympathetic Denervation

The evidence that LCSD confers significant protection against life-threatening arrhythmias triggered by increased sympathetic activity[56] has led to interest in its role as a treatment for patients with advanced HF, as recently reviewed.[57] One of the features that makes LCSD a potentially interesting novel option for treating HF is that it improves sympathovagal imbalance by virtue of its synergistic action of not only reducing sympathetic activity but also of reciprocally increasing efferent vagal activity to heart[19,58] through the removal of the tonic inhibition exerted by cardiac sympathetic afferent fibers.[58,59] Thus, LCSD produces a simultaneous increase in vagal activity and in baroreceptive reflexes together with the expected reduction in sympathetic activity.

To date, the available clinical experience with LCSD is limited. The effects of high thoracic epidural sympathetic blockade were assessed in 40 NYHA class IV patients randomized to medical treatment only or to medical treatment+epidural block.[60] Overall, 17 of 20 patients treated by epidural sympathetic blockade improved to NYHA class III, whereas this occurred in 10 of 20 control patients (P<0.05). In the active treatment group after 30 days, LV end-diastolic diameter was reduced from 74±9 to 68±9 mm and LVEF was increased from 30±7 to 41±8%; both changes were statistically significant, whereas no change occurred in the control group.

LCSD, albeit not performed by removing the ganglia with a supraclavicular[61] or thoracoscopic[62] approach, as successfully performed for arrhythmia prevention, but by clipping the lower one third of the stellate ganglion and the T3 to T4 thoracic ganglia, was assessed in 10 NYHA class II and III patients, and compared with 5 control patients who were receiving GDMT.[63] Two patients in each group died within 6 months of follow-up; therefore, data were only available in 8 and 3 patients, respectively. Patients in the LCSD group showed a statistically significant improvement in the 6-minute walk test and echocardiographic LVEF improved from 25±10 to 33±8% (P=0.02). The extremely small number of patients together with the absence of a centralized blinded echocardiographic laboratory generates doubts about the reproducibility of these studies, but also raises interesting questions.[64]

Currently, the clinical data with LCSD in HF are still extremely small and are insufficient to draw any meaningful conclusions about the future of this therapeutic approach. However, we think that a larger pilot trial assessing the role of LCSD is warranted. The possible future clinical applications of LCSD may include the treatment of HF, particularly in patients who are intolerant to β-adrenergic blockade, and the prevention of life-threatening arrhythmias both in patients who have frequent implantable cardioverter defibrillator shocks, and as a primary prevention intervention in countries where financial limitations hamper the likelihood of receiving an implantable cardioverter defibrillator.

Overview and Conclusions

HF progresses, at least in part, because of increased activity of the sympathetic nervous system that is accompanied by concomitant withdrawal of parasympathetic activity. Despite the use of GDMT most patients will ultimately develop worsening HF and untoward clinical outcomes. Thus, there is a clear unmet medical need to develop additional therapies for patients with HF.

In the foregoing review, we have discussed the rationale for autonomic modulation of the failing heart, as well as summarized the recent clinical experience with VS, SCS, BAT, renal denervation, and LCSD. Neural stimulation is more complex than suspected by many clinicians and we call attention to 2 potential problems. One is related to the dose of stimulation; as with drugs, dosages may be either insufficient or excessive. Because the stimulation intensities tolerated by the patients vary significantly, without a careful titration phase, there is the risk that many patients receive an insufficient intensity (eg, see the VS studies) thus leading to negative results. The other comes from extrapolation to man of parameters used in experimental animals that are often anesthetized. The stimulation frequencies in some VS clinical studies are so high to have no relation with the physiological range of neural discharge of vagal efferent fibers, which is just 1 to 2 per s in baseline conditions.[58]

Given that all of the new technologies to modulate the autonomic nervous system are invasive, and therefore entail some procedural risk, it will be important to have a clearer understanding of the long-term consequences of device-based modulation of the autonomic nervous system in a HF population as the field matures. Importantly, each of the therapies discussed herein seems safe and potentially effective in exploratory clinical trials that have been conducted in small numbers of patients with HF (Tables 1–3). Of the emerging strategies for autonomic modulation, the only one that is currently being evaluated in a pivotal phase III clinical trial is VS in the INOVATE-HF trial. Although it is premature to speculate on which, if any, of these novel approaches will have a significant impact on clinical HF patient outcomes, it is clear that we have now entered an exciting new therapeutic era[53] that may in a near future allow clinicians to modulate the autonomic nervous system nonpharmacologically in patients with HF.

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References

1. Mann DL, Bristow MR. Mechanisms and models in heart failure: the biomechanical model and beyond. *Circulation*. 2005;111:2837–2849. doi: 10.1161/CIRCULATIONAHA.104.500546.
2. Schwartz PJ, De Ferrari GM. Sympathetic-parasympathetic interaction in health and disease: abnormalities and relevance in heart failure. *Heart Fail Rev*. 2011;16:101–107. doi: 10.1007/s10741-010-9179-1.
3. Lopshire JC, Zipes DP. Device therapy to modulate the autonomic nervous system to treat heart failure. *Curr Cardiol Rep*. 2012;14:593–600. doi: 10.1007/s11886-012-0292-8.
4. La Rovere MT, Pinna GD, Maestri R, Robbi E, Caporotondi A, Guazzotti G, Sleight P, Febo O. Prognostic implications of baroreflex sensitivity in heart failure patients in the beta-blocking era. *J Am Coll Cardiol*. 2009;53:193–199. doi: 10.1016/j.jacc.2008.09.034.
5. Floras JS. Sympathetic nervous system activation in human heart failure: clinical implications of an updated model. *J Am Coll Cardiol*. 2009;54:375–385. doi: 10.1016/j.jacc.2009.03.061.
6. Schwartz PJ, Vanoli E, Stramba-Badiale M, De Ferrari GM, Billman GE, Foreman RD. Autonomic mechanisms and sudden death. New insights from analysis of baroreceptor reflexes in conscious dogs with and without a myocardial infarction. *Circulation*. 1988;78:969–979.
7. Schwartz PJ, De Ferrari GM, Sanzo A, Landolina M, Rordorf R, Raineri C, Campana C, Revera M, Ajmone-Marsan N, Tavazzi L, Odero A. Long term vagal stimulation in patients with advanced heart failure: first experience in man. *Eur J Heart Fail*. 2008;10:884–891. doi: 10.1016/j.ejheart.2008.07.016.
8. De Ferrari GM, Crijns HJ, Borggrefe M, Milasinovic G, Smid J, Zabel M, Gavazzi A, Sanzo A, Dennert R, Kuschyk J, Raspopovic S, Klein H, Swedberg K, Schwartz PJ; CardioFit Multicenter Trial Investigators. Chronic vagus nerve stimulation: a new and promising therapeutic approach for chronic heart failure. *Eur Heart J*. 2011;32:847–855. doi: 10.1093/eurheartj/ehq391.
9. Schwartz PJ, La Rovere MT, Vanoli E. Autonomic nervous system and sudden cardiac death. Experimental basis and clinical observations for post-myocardial infarction risk stratification. *Circulation*. 1992;85 (1 Suppl):I77–I91.
10. Uthman BM, Reichl AM, Dean JC, Eisenschenk S, Gilmore R, Reid S, Roper SN, Wilder BJ. Effectiveness of vagus nerve stimulation in epilepsy patients: a 12-year observation. *Neurology*. 2004;63:1124–1126.
11. Shuchman M. Approving the vagus-nerve stimulator for depression. *N Engl J Med*. 2007;356:1604–1607. doi: 10.1056/NEJMp078035.
12. Vanoli E, De Ferrari GM, Stramba-Badiale M, Hull SS Jr, Foreman RD, Schwartz PJ. Vagal stimulation and prevention of sudden death in conscious dogs with a healed myocardial infarction. *Circ Res*. 1991;68:1471–1481.
13. De Ferrari GM, Vanoli E, Schwartz PJ. Vagal activity and ventricular fibrillation. In: Levy MN, Schwartz PJ, eds. *Vagal Control of The Heart: Experimental Basis and Clinical Implications*. Armonk, NY: Futura Publishing Co; 1994:613–636.
14. Li M, Zheng C, Sato T, Kawada T, Sugimachi M, Sunagawa K. Vagal nerve stimulation markedly improves long-term survival after chronic heart failure in rats. *Circulation*. 2004;109:120–124. doi: 10.1161/01.CIR.0000105721.71640.DA.
15. Sabbah HN, Rastogi S, Mishra S, Gupta RC, Ilsar I, Imai M, Cohen U, Ben-David T, Ben-Ezra O. Long-term therapy with neuroselective electric vagus nerve stimulation improves LV function and attenuates global LV remodelling in dogs with chronic heart failure [abstract]. *Eur J Heart Fail*. 2005;4(Suppl):166.
16. Zhang Y, Popovic ZB, Bibevski S, Fakhry I, Sica DA, Van Wagoner DR, Mazgalev TN. Chronic vagus nerve stimulation improves autonomic control and attenuates systemic inflammation and heart failure progression in a canine high-rate pacing model. *Circ Heart Fail*. 2009;2:692–699. doi: 10.1161/CIRCHEARTFAILURE.109.873968.
17. Calvillo L, Vanoli E, Andreoli E, Besana A, Omodeo E, Gnecchi M, Zerbi P, Vago G, Busca G, Schwartz PJ. Vagal stimulation, through its nicotinic action, limits infarct size and the inflammatory response to myocardial ischemia and reperfusion. *J Cardiovasc Pharmacol*. 2011;58:500–507. doi: 10.1097/FJC.0b013e31822b7204.
18. Tracey KJ. The inflammatory reflex. *Nature*. 2002;420:853–859. doi: 10.1038/nature01321.
19. Schwartz PJ, Pagani M, Lombardi F, Malliani A, Brown AM. A cardiocardiac sympathovagal reflex in the cat. *Circ Res*. 1973;32:215–220.
20. Premchand RK, Sharma K, Mittal S, Monteiro R, Dixit S, Libbus I, DiCarlo LA, Ardell JL, Rector TS, Amurthur B, KenKnight BH, Anand IS. Autonomic regulation therapy via left or right cervical vagus nerve stimulation in patients with chronic heart failure: results of the ANTHEM-HF trial. *J Card Fail*. 2014;20:808–816. doi: 10.1016/j.cardfail.2014.08.009.
21. Zannad F, De Ferrari GM, Tuinenburg AE, Wright D, Brugada J, Butter C, Klein H, Stolen C, Meyer S, Stein KM, Ramuzat A, Schubert B, Daum D, Neuzil P, Botman C, Castel MA, D'Onofrio A, Solomon SD, Wold N, Ruble SB. Chronic vagal stimulation for the treatment of low ejection fraction heart failure: results of the NEural Cardiac TherApy foR Heart Failure (NECTAR-HF) randomized controlled trial. *Eur Heart J*. 2015;36:425–433. doi: 10.1093/eurheartj/ehu345.
22. Hauptman PJ, Schwartz PJ, Gold MR, Borggrefe M, Van Veldhuisen DJ, Starling RC, Mann DL. Rationale and study design of the increase of vagal

tone in heart failure study: INOVATE-HF. *Am Heart J*. 2012;163:954–962.e1. doi: 10.1016/j.ahj.2012.03.021.
23. De Ferrari GM. Vagal stimulation in heart failure. *J Cardiovasc Transl Res*. 2014;7:310–320. doi: 10.1007/s12265-014-9540-1.
24. Camm AJ, Savelieva I. Vagal nerve stimulation in heart failure. *Eur Heart J*. 2015;36:404–406. doi: 10.1093/eurheartj/ehu363.
25. Hamann JJ, Ruble SB, Stolen C, Wang M, Gupta RC, Rastogi S, Sabbah HN. Vagus nerve stimulation improves left ventricular function in a canine model of chronic heart failure. *Eur J Heart Fail*. 2013;15:1319–1326. doi: 10.1093/eurjhf/hft118.
26. Castoro MA, Yoo PB, Hincapie JG, Hamann JJ, Ruble SB, Wolf PD, Grill WM. Excitation properties of the right cervical vagus nerve in adult dogs. *Exp Neurol*. 2011;227:62–68. doi: 10.1016/j.expneurol.2010.09.011.
27. Melzack R, Wall PD. Pain mechanisms: a new theory. *Science*. 1965;150:971–979.
28. Wall PD, Sweet WH. Temporary abolition of pain in man. *Science*. 1967;155:108–109.
29. Linderoth B, Foreman RD. Physiology of spinal cord stimulation: review and update. *Neuromodulation*. 1999;2:150–164. doi: 10.1046/j.1525-1403.1999.00150.x.
30. Stiller CO, Cui JG, O'Connor WT, Brodin E, Meyerson BA, Linderoth B. Release of gamma-aminobutyric acid in the dorsal horn and suppression of tactile allodynia by spinal cord stimulation in mononeuropathic rats. *Neurosurgery*. 1996;39:367–374.
31. Foreman RD, Linderoth B, Ardell JL, Barron KW, Chandler MJ, Hull SS Jr, TerHorst GJ, DeJongste MJ, Armour JA. Modulation of intrinsic cardiac neurons by spinal cord stimulation: implications for its therapeutic use in angina pectoris. *Cardiovasc Res*. 2000;47:367–375.
32. Southerland EM, Milhorn DM, Foreman RD, Linderoth B, DeJongste MJ, Armour JA, Subramanian V, Singh M, Singh K, Ardell JL. Preemptive, but not reactive, spinal cord stimulation mitigates transient ischemia-induced myocardial infarction via cardiac adrenergic neurons. *Am J Physiol Heart Circ Physiol*. 2007;292:H311–H317. doi: 10.1152/ajpheart.00087.2006.
33. Olgin JE, Takahashi T, Wilson E, Vereckei A, Steinberg H, Zipes DP. Effects of thoracic spinal cord stimulation on cardiac autonomic regulation of the sinus and atrioventricular nodes. *J Cardiovasc Electrophysiol*. 2002;13:475–481.
34. Issa ZF, Zhou X, Ujhelyi MR, Rosenberger J, Bhakta D, Groh WJ, Miller JM, Zipes DP. Thoracic spinal cord stimulation reduces the risk of ischemic ventricular arrhythmias in a postinfarction heart failure canine model. *Circulation*. 2005;111:3217–3220. doi: 10.1161/CIRCULATIONAHA.104.507897.
35. Lopshire JC, Zhou X, Dusa C, Ueyama T, Rosenberger J, Courtney N, Ujhelyi M, Mullen T, Das M, Zipes DP. Spinal cord stimulation improves ventricular function and reduces ventricular arrhythmias in a canine postinfarction heart failure model. *Circulation*. 2009;120:286–294. doi: 10.1161/CIRCULATIONAHA.108.812412.
36. Liu Y, Yue WS, Liao SY, Zhang Y, Au KW, Shuto C, Hata C, Park E, Chen P, Siu CW, Tse HF. Thoracic spinal cord stimulation improves cardiac contractile function and myocardial oxygen consumption in a porcine model of ischemic heart failure. *J Cardiovasc Electrophysiol*. 2012;23:534–540. doi: 10.1111/j.1540-8167.2011.02230.x.
37. Tse HF, Turner S, Sanders P, Okuyama Y, Fujiu K, Cheung CW, Russo M, Green MD, Yiu KH, Siu CW. Thoracic spinal cord stimulation for heart failure as a restorative treatment (SCS HEART study): First-in-human experience. *Heart Rhythm*. 2015;12:588–95. doi: 10.1016/j.hrthm.2014.12.014
38. Feng QP, Carlsson S, Thorén P, Hedner T. Characteristics of renal sympathetic nerve activity in experimental congestive heart failure in the rat. *Acta Physiol Scand*. 1994;150:259–266. doi: 10.1111/j.1748-1716.1994.tb09685.x.
39. Zucker IM. Neural mechanisms of sympathetic regulation in chronic heart failure. *Hypertension*. 2006;48:1005–1011.
40. Kopp UC, Cicha MZ, Smith LA. Impaired responsiveness of renal mechanosensory nerves in heart failure: role of endogenous angiotensin. *Am J Physiol Regul Integr Comp Physiol*. 2003;284:R116–R124. doi: 10.1152/ajpregu.00336.2002.
41. Clayton SC, Haack KK, Zucker IH. Renal denervation modulates angiotensin receptor expression in the renal cortex of rabbits with chronic heart failure. *Am J Physiol Renal Physiol*. 2011;300:F31–F39. doi: 10.1152/ajprenal.00088.2010.
42. Nozawa T, Igawa A, Fujii N, Kato B, Yoshida N, Asanoi H, Inoue H. Effects of long-term renal sympathetic denervation on heart failure after myocardial infarction in rats. *Heart Vessels*. 2002;16:51–56.
43. Mulder J, Hökfelt T, Knuepfer MM, Kopp UC. Renal sensory and sympathetic nerves reinnervate the kidney in a similar time-dependent fashion after renal denervation in rats. *Am J Physiol Regul Integr Comp Physiol*. 2013;304:R675–R682. doi: 10.1152/ajpregu.00599.2012.
44. Hasking GJ, Esler MD, Jennings GL, Burton D, Johns JA, Korner PI. Norepinephrine spillover to plasma in patients with congestive heart failure: evidence of increased overall and cardiorenal sympathetic nervous activity. *Circulation*. 1986;73:615–621.
45. Petersson M, Friberg P, Eisenhofer G, Lambert G, Rundqvist B. Long-term outcome in relation to renal sympathetic activity in patients with chronic heart failure. *Eur Heart J*. 2005;26:906–913. doi: 10.1093/eurheartj/ehi184.
46. Davis MI, Filion KB, Zhang D, Eisenberg MJ, Afilalo J, Schiffrin EL, Joyal D. Effectiveness of renal denervation therapy for resistant hypertension: a systematic review and meta-analysis. *J Am Coll Cardiol*. 2013;62:231–241. doi: 10.1016/j.jacc.2013.04.010.
47. Davies JE, Manisty CH, Petraco R, Barron AJ, Unsworth B, Mayet J, Hamady M, Hughes AD, Sever PS, Sobotka PA, Francis DP. First-in-man safety evaluation of renal denervation for chronic systolic heart failure: primary outcome from REACH-Pilot study. *Int J Cardiol*. 2013;162:189–192. doi: 10.1016/j.ijcard.2012.09.019.
48. Verloop WL, Beeftink MM, Nap A, Bots ML, Velthuis BK, Appelman YE, Cramer MJ, Agema WR, Scholtens AM, Doevendans PA, Allaart CP, Voskuil M. Renal denervation in heart failure with normal left ventricular ejection fraction. Rationale and design of the DIASTOLE (DenervatIon of the renAl Sympathetic nerves in hearT failure with nOrmal Lv Ejection fraction) trial. *Eur J Heart Fail*. 2013;15:1429–1437. doi: 10.1093/eurjhf/hft119.
49. Georgakopoulos D, Little WC, Abraham WT, Weaver FA, Zile MR. Chronic baroreflex activation: a potential therapeutic approach to heart failure with preserved ejection fraction. *J Card Fail*. 2011;17:167–178. doi: 10.1016/j.cardfail.2010.09.004.
50. Sabbah HN, Gupta RC, Imai M, Irwin ED, Rastogi S, Rossing MA, Kieval RS. Chronic electrical stimulation of the carotid sinus baroreflex improves left ventricular function and promotes reversal of ventricular remodeling in dogs with advanced heart failure. *Circ Heart Fail*. 2011;4:65–70. doi: 10.1161/CIRCHEARTFAILURE.110.955013.
51. Zucker IH, Hackley JF, Cornish KG, Hiser BA, Anderson NR, Kieval R, Irwin ED, Serdar DJ, Peuler JD, Rossing MA. Chronic baroreceptor activation enhances survival in dogs with pacing-induced heart failure. *Hypertension*. 2007;50:904–910. doi: 10.1161/HYPERTENSIONAHA.107.095216.
52. de Leeuw PW, Alnima T, Lovett E, Sica D, Bisognano J, Haller H, Kroon AA. Bilateral or unilateral stimulation for baroreflex activation therapy. *Hypertension*. 2015;65:187–192. doi: 10.1161/HYPERTENSIONAHA.114.04492.
53. Kuck KH, Bordachar P, Borggrefe M, Boriani G, Burri H, Leyva F, Schauerte P, Theuns D, Thibault B, Kirchhof P, Hasenfuss G, Dickstein K, Leclercq C, Linde C, Tavazzi L, Ruschitzka F; Document Reviewers. New devices in heart failure: an European Heart Rhythm Association report: developed by the European Heart Rhythm Association; endorsed by the Heart Failure Association. *Europace*. 2014;16:109–128. doi: 10.1093/europace/eut311.
54. Abraham WT, Zile MR, Weaver FA, Butter C, Ducharme A, Halbach M, Klug D, Lovett EG, Müller-Ehmsen J, Schafer JE, Senni M, Swarup V, Wachter R, Little WC. Baroreflex activation therapy for the treatment of heart failure with a reduced ejection fraction. *JACC Heart Fail*. 2015. doi: 10.1016/j.jchf.2015.02.006.
55. Gronda E, Seravalle G, Brambilla G, Costantino G, Casini A, Alsheraei A, Lovett EG, Mancia G, Grassi G. Chronic baroreflex activation effects on sympathetic nerve traffic, baroreflex function, and cardiac haemodynamics in heart failure: a proof-of-concept study. *Eur J Heart Fail*. 2014;16:977–983. doi: 10.1002/ejhf.138.
56. Schwartz PJ. Cardiac sympathetic denervation to prevent life-threatening arrhythmias. *Nat Rev Cardiol*. 2014;11:346–353. doi: 10.1038/nrcardio.2014.19.
57. De Ferrari GM, Schwartz PJ. Left cardiac sympathetic denervation in patients with heart failure: a new indication for an old intervention? *J Cardiovasc Transl Res*. 2014;7:338–346. doi: 10.1007/s12265-014-9541-0.
58. Cerati D, Schwartz PJ. Single cardiac vagal fiber activity, acute myocardial ischemia, and risk for sudden death. *Circ Res*. 1991;69:1389–1401.
59. Malliani A, Recordati G, Schwartz PJ. Nervous activity of afferent cardiac sympathetic fibres with atrial and ventricular endings. *J Physiol*. 1973;229:457–469.

60. Guo W, Liu F, Fu L, Qu R, Wang G, Zhang C. Effects of high thoracic epidural sympathetic blockade for the treatment of severe chronic heart failure due to dilated cardiomyopathy. *Acta Cardiol*. 2012;67:533–539.
61. Odero A, Bozzani A, De Ferrari GM, Schwartz PJ. Left cardiac sympathetic denervation for the prevention of life-threatening arrhythmias: the surgical supraclavicular approach to cervicothoracic sympathectomy. *Heart Rhythm*. 2010;7:1161–1165. doi: 10.1016/j.hrthm.2010.03.046.
62. Collura CA, Johnson JN, Moir C, Ackerman MJ. Left cardiac sympathetic denervation for the treatment of long QT syndrome and catecholaminergic polymorphic ventricular tachycardia using video-assisted thoracic surgery. *Heart Rhythm*. 2009;6:752–759. doi: 10.1016/j.hrthm.2009.03.024.
63. Conceição-Souza GE, Pêgo-Fernandes PM, Cruz Fd, Guimarães GV, Bacal F, Vieira ML, Grupi CJ, Giorgi MC, Consolim-Colombo FM, Negrão CE, Rondon MU, Moreira LF, Bocchi EA. Left cardiac sympathetic denervation for treatment of symptomatic systolic heart failure patients: a pilot study. *Eur J Heart Fail*. 2012;14:1366–1373. doi: 10.1093/eurjhf/hfs132.
64. Schwartz PJ. Autonomic modulation for chronic heart failure: a new kid on the block? *Eur J Heart Fail*. 2012;14:1316–1318. doi: 10.1093/eurjhf/hfs177.

KEY WORDS: autonomic nervous system ■ baroreceptors ■ spinal cord stimulation ■ sympathetic denervation ■ vagus nerve stimulation

Autonomic Modulation for the Management of Patients with Chronic Heart Failure

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