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 HF7 and its continuation in the first multicenter clinical trial8,9 have paved the way for a series of clinical approaches having in common the acceptance of the concept 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 epilepsy10 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
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. 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.

To date, 3 clinical studies of VS have been completed and published (Table 1). The first-in-man single center study of VS involved 8 patients and used the CardioFit 5000 device (BioControl Medical Ltd, Yehud, Israel), which is a closed-loop system comprised of a proprietary bipolar electrode cuff around the right or left cervical vagus, thereby stimulating both the vagal efferent and afferent fibers.

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.

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

<table>
<thead>
<tr>
<th>Study Name</th>
<th>Phase</th>
<th>Patients, n</th>
<th>NYHA</th>
<th>LVEF</th>
<th>QRS</th>
<th>Stimulation</th>
<th>Side</th>
<th>Control Group</th>
<th>End-Point</th>
</tr>
</thead>
<tbody>
<tr>
<td>ANTHEM-HF</td>
<td>I to II</td>
<td>60</td>
<td>II–III</td>
<td>≤40%</td>
<td>≤150</td>
<td>R vs L</td>
<td></td>
<td>LVEDD≥50 mm and &lt;80 mm</td>
<td>LVEF; LVESD; LVESD</td>
</tr>
<tr>
<td>NECTAR-HF</td>
<td>II</td>
<td>96</td>
<td>II–III</td>
<td>≤35%</td>
<td>&lt;130</td>
<td>R</td>
<td></td>
<td>LVESD</td>
<td>Stimulation off</td>
</tr>
<tr>
<td>INOVATE-HF</td>
<td>III</td>
<td>650</td>
<td>III</td>
<td>≤40%</td>
<td>NA</td>
<td>R</td>
<td></td>
<td>GDMT</td>
<td>Death+HF hospitalization</td>
</tr>
</tbody>
</table>

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 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.

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 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 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).

A different technical approach with an open loop VS system that did not have a 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%, QRS<150 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 Additional secondary end points, including LV end-diastolic dimension, LV end-systolic volume, LVEF, peak VO₂, 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...
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 cases 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 al33 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) study37 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 VO₂, 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 α₁-adrenoceptors, and increase renin secretion rate through activation of β₁-adrenoceptors.

Numerous studies have shown that increased renal efferent sympathetic activity plays an important role in the volume expansion that is observed in HF by provoking renin release and the consequent increase in circulating and brain levels of angiotensin II. HF also leads to diminished afferent renal sympathetic nerve signaling, thereby blunting inhibitory reno-renal reflexes, which further contributes to increased renal sympathetic efferent activation. 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. 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. 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.

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

Although several studies have been conducted in drug-resistant hypertensive patients, 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. 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 mmHg. 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 renAI Sympathetic nerves in hearT failure with nOmal 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. 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. In experimental HF models, chronic low-intensity carotid sinus stimulation resulted in decreased fibrosis and reverse LV remodeling in a canine coronary microembolization model and improved survival in a canine model of pacing-induced HF. 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 Rhoes 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 NCT00710294, respectively) in Europe and the Rhoes Feasibility Trial and Rhoes Pivotal Trial (NCT00442286), which suggested greater efficacy of unilateral right-sided stimulation. 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.

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

<table>
<thead>
<tr>
<th>Study/Acronym</th>
<th>Study Design</th>
<th>Patient Characteristic</th>
<th>Primary Outcome</th>
<th>Estimated Enrollment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systolic HF</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NCT02085668</td>
<td>Randomized</td>
<td>NYHA II–III, LVEF &gt; 35%, GFR ≥ 30 mL/min per 1.73 m², BNP &gt; 100 pg/mL or NT-proBNP &gt; 400 pg/mL, standard medical therapy, SBP &gt; 90 mmHg</td>
<td>Safety of renal denervation with the Simplicity™ System</td>
<td>100</td>
</tr>
<tr>
<td>NCT01870310</td>
<td>Randomized</td>
<td>NYHA II–IV, LVEF ≥ 35%, standard medical therapy, SBP ≥ 110 mmHg</td>
<td>Change in serum NT-proBNP at 6 mo and 1 y from baseline in both groups</td>
<td>50</td>
</tr>
<tr>
<td>NCT01392196</td>
<td>Single group assignment</td>
<td>NYHA II–IV, LVEF ≥ 40%, GFR 30–75 mL/min per 1.73 m², GDMT, SBP &gt; 90 mmHg</td>
<td>Safety of renal denervation in patients with HF as measured by adverse events</td>
<td>40</td>
</tr>
<tr>
<td>NCT02099903</td>
<td>Randomized</td>
<td>HF secondary to Chagas’s disease, NYHA II–III, LVEF &lt; 40%, standard HF therapy, SBP &gt; 90 mmHg</td>
<td>Composite: death, myocardial infarction, cerebrovascular event, need of intervention on renal arteries and renal function impairment (decrease in eGFR &gt; 30% from baseline)</td>
<td>30</td>
</tr>
<tr>
<td>NCT01954160</td>
<td>Randomized</td>
<td>NYHA II–III, LVEF ≥ 40%, daily loop diuretic, GDMT, SBP ≥ 110 mmHg</td>
<td>Within-subject comparison of increase in urine sodium excretion after saline loading before RSD and 13 wk after RSD</td>
<td>64</td>
</tr>
<tr>
<td>NCT01402726</td>
<td>Non-randomized</td>
<td>NYHA II–IV, LVEF ≥ 40% or ≥ 45%, eGFR ≥ 45 mL/min</td>
<td>Composite cardiovascular events</td>
<td>200</td>
</tr>
<tr>
<td>NCT01790906</td>
<td>Randomized</td>
<td>NYHA II–IV, LVEF ≥ 35%</td>
<td>All-cause mortality, cardiovascular events</td>
<td>200</td>
</tr>
<tr>
<td>Diastolic HF</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NCT02041130</td>
<td>Randomized</td>
<td>NYHA II–IV, LVEF ≥ 50%, evidence of LV diastolic dysfunction</td>
<td>Changes in left atrial volume index (LAVi)</td>
<td>144</td>
</tr>
<tr>
<td>NCT02115230</td>
<td>Randomized</td>
<td>HF with normal LV function, LV hypertrophy, hypertension treated with at least 2 antihypertensive drugs</td>
<td>Change from baseline E/E′ at 12 mo and death (composite of myocardial infarction, cerebrovascular events, need of intervention on renal arteries, and renal function impairment)</td>
<td>40</td>
</tr>
<tr>
<td>NCT01583881</td>
<td>Randomized</td>
<td>LVEF ≥ 50%, evidence of LV diastolic dysfunction</td>
<td>Change from baseline E/E′ at 12 mo</td>
<td>60</td>
</tr>
<tr>
<td>NCT01840059</td>
<td>Randomized</td>
<td>NYHA II–III, LVEF ≥ 50%</td>
<td>Change in symptoms, exercise function, biomarkers, LV filling pressure, LV remodeling</td>
<td>40</td>
</tr>
</tbody>
</table>

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; NT-proBNP, 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

<table>
<thead>
<tr>
<th>Acronym</th>
<th>Study Design</th>
<th>Patient Characteristic</th>
<th>Primary Outcome</th>
<th>Estimated Enrollment</th>
</tr>
</thead>
<tbody>
<tr>
<td>NCT00957073</td>
<td>Rheo HOPE4HF trial&lt;sup&gt;46&lt;/sup&gt;</td>
<td>Randomized Open label</td>
<td>LVEF≥40%, symptomatic HF with elevated blood pressure</td>
<td>540</td>
</tr>
<tr>
<td>NCT01471860</td>
<td>Barostim neo System in the Treatment of Heart Failure</td>
<td>Randomized Open label</td>
<td>NYHA class III HF and LVEF&lt;35%</td>
<td>150</td>
</tr>
<tr>
<td>NCT01484288</td>
<td>Baroreflex Activation Therapy in Heart Failure</td>
<td>Single center efficacy Study Open label</td>
<td>NYHA class III and LVEF&lt;35% on GDMT</td>
<td>15</td>
</tr>
<tr>
<td>NCT01720160</td>
<td>Barostim HOPE4HF Study</td>
<td>Randomized Open label</td>
<td>On stable, HF GDMT for at least 4 wk before screening, LVEF&lt;35%</td>
<td>60</td>
</tr>
</tbody>
</table>

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).<sup>54</sup> 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.<sup>55</sup> 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<sup>56</sup> has led to interest in its role as a treatment for patients with advanced HF, as recently reviewed.<sup>57</sup> 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<sup>19,58</sup> through the removal of the tonic inhibition exerted by cardiac sympathetic afferent fibers.<sup>58,59</sup> 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.<sup>60</sup> 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±4 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<sup>61</sup> or thoracoscopic<sup>62</sup> 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.<sup>63</sup> 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.<sup>64</sup>

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 ß-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 era53 that may in a near future allow exciting new therapeutic era53 that may in a near future allow clinicians to modulate the autonomic nervous system nonpharmacologically in patients with HF.

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Disclosures
Dr Mann is a consultant for BioControl Medical Ltd and Medtronic, Dr Schwartz for BioControl Medical Ltd, and Dr De Ferrari for Boston Scientific. Dr La Rovere reports no conflicts.

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