Novel devices

Non-pharmacological modulation of the autonomic tone to treat heart failure

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The autonomic nervous system has a significant role in the pathophysiology and progression of heart failure. The absence of any recent breakthrough advances in the medical therapy of heart failure has led to the evolution of innovative non-pharmacological interventions that can favourably modulate the cardiac autonomic tone. Several new therapeutic modalities that may act at different levels of the autonomic nervous system are being investigated for their role in the treatment of heart failure. The current review examines the role of renal denervation, vagal nerve stimulators, carotid baroreceptors, and spinal cord stimulators in the treatment of heart failure.

Keywords
Autonomic nervous system • Sympathetic nervous system • Parasympathetic nervous system • Renal denervation • Vagal nerve stimulator • Carotid baroreceptor stimulation • Heart rate variability • Baroreflex sensitivity • Spinal cord stimulation

Introduction

Heart failure (HF) remains a huge problem to the patient and the treating physician alike, with excessive morbidity and mortality.1 Despite the progress made with medical and device-based therapies, the number of annual admissions for HF continues to increase, posing a substantial burden on healthcare resources. The exponential increase in the total cost of HF is non-sustainable; an estimated total cost of USD $32 billion in 2013 is projected to increase by 120% to 70 billion by 2030.1 Attempts to retard the progression of HF have remained challenging, with implantable left ventricular assist devices and cardiac transplantation being fallback strategies. Both of these therapeutic modalities impose a great inconvenience to lifestyle coupled with significant financial challenges. Newer alternative strategies that may modulate the autonomic nervous system (ANS) to alleviate symptoms, while improving outcomes and reducing hospitalizations for HF are gaining traction as potential interventions. This review examines state-of-the-art non-pharmacological strategies to manipulate the renal nerves, vagus nerve, the carotid baroreceptors, and the spinal cord to control the progression of HF.

Autonomic nervous system, the neurohormonal axis, and heart failure

The interactions between the heart and the ANS have been known for several decades. The ANS has two primary components, the sympathetic and parasympathetic (Figure 1). The sympathetic nervous system (SNS) is the cardio-stimulatory pathway, which increases heart rate and force of contraction, while the parasympathetic nervous system (PNS) is the cardio-inhibitory pathway, and acts through reducing the heart rate, blood pressure, and contractility. Among other factors, it is the constant push and pull between these two limbs of the ANS, which regulates the heart rate, blood pressure, cardiac structure and function, and electrical stability of the myocardium.

Declining cardiac function is associated with a spectrum of compensatory mechanisms to preserve cardiovascular homeostasis. Two of the major participants in the neurohormonal system that are intricately intertwined in order to achieve stability are (i) the ANS and (ii) the renin–angiotensin–aldosterone system (RAAS).2,3 A reduction in cardiac output activates afferent stimuli from the baroreceptors to the central nervous system cardio-regulatory

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centres, which in turn leads to an activation of the sympathetic nervous pathway. Reduced renal perfusion, secondary to reduced forward flow activates the RAAS system via renin release. Importantly, renin facilitates the conversion of angiotensinogen to angiotensin I. Angiotensin-converting enzyme subsequently converts angiotensin I to angiotensin II. Although angiotensin II has a central effect on increasing sympathetic activity, it is also involved in sodium and water retention and has a systemic vasoconstrictive effect. It is noteworthy that these compensatory mechanisms are initially important to maintain cardiac output, but over the long term are detrimental through their adverse impact on the structural adaptive response of the heart.

Heightened sympathetic tone modulates heart rate, enhances AV conductance, as well as myocardial contractility, but when sustained over time it is associated with reduced cardiac sympathetic neuronal density and responsiveness. Sympathetic activation in turn increases the vasoconstrictor tone, accompanied by activation of the RAAS and the endothelin 1 and vasopressin system, which may be responsible for peripheral organ dysfunction and damage in the setting of congestive HF.

Perturbations of the sympathovagal balance with a preponderance of increased sympathetic activity besides being pro-arrhythmic can also be associated with nitric oxide dysregulation, increased inflammation with excess cytokine release and adverse remodelling of the heart. Several studies have also shown that diminished vagal activity and a heightened sympathetic activity reflected as an increased heart rate are predictors of high mortality in HF. More recently the SHIFT study has clearly demonstrated that high heart rate is a risk factor in patients with HF and that selective lowering of the heart rate improves outcomes. Of note, the beneficial impact of modulating the ANS is evident from the proven role of beta-blockers in blocking sympathetic activation and improving outcomes, along with stellate ganglionectomy, which is a useful modality for refractory ventricular arrhythmias. Inherent limitations of existing pharmacological strategies to more specifically modulate the limbs of the autonomic-cardiac circuit (e.g. selectively stimulate the vagus/parasympathetic tone), combined with commonly described side effects (bradycardia, fatigue, etc.) and intolerance to drugs has encouraged the evolution of innovative non-pharmacological interventions. Most of these interventions are currently under investigation, and include: spinal cord stimulation, vagal nerve stimulators, baroreceptor stimulation, and renal denervation. The jury is still out regarding which of any of these will improve clinical outcomes in patients with HF.

Worsening HF is in turn often associated with ionic and structural remodelling of the atrial and ventricular myocardium, increasing the

Figure 1 Organization of the autonomic nervous system demonstrating the salient interactions involving brain, heart, and kidney.
susceptibility to arrhythmias. This is accompanied by altered vagal and sympathetic discharges, both of which may serve as triggers for atrial and ventricular arrhythmias.10,16 Notably, autonomic innervation and modulation is different between the atrium and the ventricle. This is illustrated by the fact that the parasympathetic (vagal) limb is protective in the ventricle,11 while it contributes to the arrhythmogenicity of the atrial substrate.17 On the other hand, an up-regulation of the sympathetic nerves and beta-receptors in HF may afflict both the atria and ventricles, promoting arrhythmias.18

Measuring autonomic activity

Objectively quantifying autonomic activity is important, but fraught with limitations. Especially, while attempting to modulate the ANS, objective parameters to define the change in autonomic tone or a quantifiable surrogate for clinical outcomes is important. Available methods for measuring SNS activity may provide direct or indirect, and general or regional measures of sympathetic activity (see Table 1). One of the earliest neurochemical methods involves measuring ‘norepinephrine (NE) spillover’. Severe HF is characterized by regional and central SNS activation. Regional NE spillover can be calculated by radiotracers techniques that involve measuring isotope dilution, with plasma concentrations of NE from regional venous and arterial blood.18 Norepinephrine spillover although used to measure autonomic activity has many limitations and is impractical for routine clinical use. Importantly, there is considerable variation and heterogeneity in the way circulating and locally released catecholamines are handled by different tissues.19 Norepinephrine increase may not be reflective of increased production or secretion from the nerve terminal, but may just be secondary to a reduced clearance. Microneurography is another modality that enables the quantification of nerve firing within the skin and skeletal muscle vasculature and can be evaluated at the level of multiple or single fibres.20,21

Of note, its routine use in clinical practice has been precluded by its low reliability and the enormous amount of time used in its quantification.22 Most practical are several dynamic electrocardiographic variables that have been used as surrogates for ANS activity. It is well recognized that the beat-to-beat variability in heart rate and blood pressure is under direct influence of the autonomic tone.23,24 It is possible to distinguish the contribution of each of the limbs of the ANS, based on the physiology, that is, the vagal (parasympathetic) tone and sympathetic tone impact the heart rate in different frequency bands.25 The SNS modulates the low frequency (LF) variance in the heart rate as opposed to the PNS, which regulates the high frequency (HF) component of heart rate variability (HRV).25,26 It is noteworthy that the LF component of HRV may not exclusively reflect sympathetic, but also parasympathetic modulation of the heart rate.25 Notably, a variety of other factors inclusive of respiration, RAAS, and thermoregulations can affect these and other frequency bands of HRV.23–25 In particular, the computation of the LF/HF ratio may help to quantify the sympathovagal balance.26 Other measures that have been used to help quantify ANS activity include heart rate turbulence, entropy, and baroreflex control of heart rate, known as baroreflex sensitivity (BRS).27,28 It has also been proposed that diminished heart rate deceleration measured from Holter recordings reflects impaired autonomic regulation and can risk stratify patients post-myocardial infarction.29

Of note, in the setting of a high sympathetic tone, baroreceptor modulation of the heart is markedly reduced. Heart rate variability and BRS are viable strategies to measure acute ‘central’ and ‘reflex’ effects, providing an indirect assessment of autonomic function, while also having been proved to be valuable in monitoring the long-term clinical course and outcomes of patients.30,31 Recent data from the GISSI-HF trial28 showed that time domain measures (standard deviation of NN interval), frequency domain measures (VLF and LF), and non-linear measures of HRV and heart rate turbulence from Holter recordings in patients with HF were predictive of a long-term outcome.28 Other techniques to quantify autonomic activity are evolving exponentially and include imaging strategies such as MIBG and PET scanning,32–34 implantable sensors,34 and biomarkers.35

Device-based autonomic measurement

Recent work has shown that a spectrum of diagnostic measures available from within implantable devices may help predict the clinical course of the patient.34,36,37 Devices provide information regarding (i) rhythm disturbances (e.g. atrial fibrillation burden, ventricular ectopy, etc.), (ii) system information pertinent to the appropriate functioning (i.e. per cent pacing, lead thresholds, etc.), and (iii) HF diagnostics. The HF diagnostics include measures of physical activity, fluid accumulation (impedance measures), and autonomic activity. The baseline heart rate and measures of HRV (SDANN, HRV footprint) are automatically computed by the devices and can be trended.37 Some preliminary work has shown that changes in autonomic activity tracks favourable remodelling of the heart in patients receiving cardiac resynchronization therapy. There are several reports suggesting that baseline autonomic measures, inclusive of the mean heart rate, are predictive of an improved long-term outcome, inclusive of mortality.36–39 Therefore, implantable devices to modulate the ANS may have the potential to autoregulate the stimulation/pacing rates based on these measured parameters.

Renal denervation

A recent spate of studies has convincingly shown that renal denervation is a successful treatment strategy for treating refractory hypertension.39,40 However, it appears that the benefits of renal denervation are not restricted to blood pressure control alone, but in fact it has other positive effects via sympathetic tone modulation.41 This is exemplified by the underlying pathophysiology, where the heart and the kidney are intricately networked to maintain circulatory homeostasis (Figure 2). It is important to recognize that the kidney not only receives, but also disseminates sympathetic activity. Of note the efferent nerve fibres follow the renal arteries (within the adventitia), thereby innervating the kidney, its renal cortex, and terminating within the glomerular arteriole.42 Activation of the renal afferents that stimulate the hypothalamus is secondary to renal hypoxia, ischaemia, and concurrent intrinsic renal disease.43

Heart failure is associated with activation of the renal sympathetic efferent nerves, which causes renin release, sodium and water retention, and further reduced renal blood flow. Renal sympathetic activation in turn also results in higher levels of angiotensin II, which then affects the CNS and results in heightened global sympathetic tone. Additionally, the increased sympathetic tone contributes to an increased peripheral vascular resistance and remodelling, as well as left ventricular remodelling. Increased sympathetic activity is
### Table 1  Cardiac autonomic tests

<table>
<thead>
<tr>
<th>Tests</th>
<th>Measurement units</th>
<th>Description</th>
<th>Additional information</th>
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</thead>
<tbody>
<tr>
<td>Heart rate variability</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Frequency domain</td>
<td>Total power</td>
<td>Total variance in heart rate pattern</td>
<td>Useful for measuring sympathovagal balance and in risk stratification</td>
</tr>
<tr>
<td></td>
<td>Low-frequency (LF) power (0.04-0.15 Hz)</td>
<td>Sympathetic activity or both</td>
<td></td>
</tr>
<tr>
<td></td>
<td>High-frequency (HF) power (0.15-0.40 Hz)</td>
<td>Parasympathetic activity</td>
<td></td>
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<tr>
<td></td>
<td>LF/HF</td>
<td>Balance of sympathetic and parasympathetic activity</td>
<td></td>
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<tr>
<td></td>
<td>ms²</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>ms²</td>
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<td></td>
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<tr>
<td>Time domain</td>
<td>SDNN</td>
<td>Standard deviation of average R–R interval</td>
<td>Useful for risk stratification</td>
</tr>
<tr>
<td></td>
<td>RMSSD</td>
<td>Root of mean squares of difference between adjacent intervals</td>
<td></td>
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<tr>
<td></td>
<td>PNN50</td>
<td>Numbers of pairs of adjacent R–R intervals differing by &gt; 50 ms/total number of R–R intervals</td>
<td></td>
</tr>
<tr>
<td>Baroreflex Sensitivity</td>
<td>Cardiovascular baroreflex sensitivity</td>
<td>Index of baroreflex control of autonomic outflow. Close relationship with cardiac vagal tone</td>
<td>Limited availability, but useful in risk stratification and post-myocardial infarction prognostication</td>
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<td></td>
<td>ms/mmHg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Microneurography</td>
<td>Muscle sympathetic nerve activity</td>
<td>Measure of nerve activity using microelectrode in common peroneal nerve</td>
<td>Limited use. Low reliability and logistically challenging</td>
</tr>
<tr>
<td></td>
<td>Burst per 100 beats or bursts/minute</td>
<td>Measures efferent multi-fibre traffic in sympathetic nerves</td>
<td></td>
</tr>
<tr>
<td>Norepinephrine Levels</td>
<td>Norepinephrine spillover</td>
<td>Plasma NE levels are a sensitive guide to sympathetic nervous function</td>
<td>Limited availability and utility. Considerable variability in release and uptake of catecholamines in different tissues</td>
</tr>
<tr>
<td></td>
<td>Mol/min M²</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Scintigraphic Imaging</td>
<td>¹²³I-mIBG imaging</td>
<td>HMR (Heart to mediastinum ratio) of cardiac MIBG activity</td>
<td>Limited availability and standardization. Maybe useful in risk stratification</td>
</tr>
<tr>
<td></td>
<td>Washout rate</td>
<td>Myocardial sympathetic innervation imaging</td>
<td></td>
</tr>
</tbody>
</table>
associated with sodium retention, hypervolaemia, and further RAAS activation, thereby promoting the vicious cycle. In HF, SNS activation occurs after HF is manifested. In essential hypertension, the cause–effect relationship is reversed, with SNS activation presumably being important in the initiation and maintenance of hypertension. Whether blunting the SNS in HF, which may be an initial adaptive response, will translate into a long-term benefit needs further enquiry.

Typically, the pre-procedural evaluation of the patients involves screening of the renal artery anatomy to assess suitability of the intervention along with renal function tests. The imaging modalities that are used may include vascular ultrasound or magnetic resonance imaging, depending on the treating centre. The renal denervation procedure involves the delivery of low-energy radiofrequency applications within the renal artery. Currently, first generation devices use radiofrequency energy delivered via electrode catheters within the renal arteries. The catheters are positioned just proximal to the origin of the second-order renal artery branch. Typically, four to eight lesions are delivered circumferentially in different planes along the length of each of the two arteries. The energy source, the type of catheter being used, and the renal artery anatomy drive the numbers of lesions delivered. For safety reasons, these ablation lesions should be separated by at least 5 mm. Importantly, operators need to be experienced in renal angiography and, consequently, in acutely handling renal dissections or perforations. Of note, there are multitudes of direct radiofrequency ablation catheters (unipolar, bipolar, and multipolar), newer balloon-based technology, and alternative energy sources (e.g. cryo, laser, etc.) evolving. The multipolar and balloon-based catheters will significantly reduce the procedural time and the need for sedation and analgesia during the procedure.

The clinical impact of denervating the sympathetic afferent and efferent nerves to the renal arteries leads to a significant reduction in SNS activity. This facilitates the restoration of impaired natriuresis, improves LV filling pressures, and thereby improves LV function. Of note, within hypertensives, the blood pressure response to renal denervation varies significantly, with 8–37% of patients showing only minimal or no changes in blood pressure. There is still much to be understood, as to whether the contributing factors to this non-responsiveness are patient selection, incomplete denervation, or lack of the SNS contributing to the pathophysiology of hypertension in this subgroup of patients.

The REACH-Pilot study, directed at examining the safety of renal denervation, showed that, in a maximally treated HF population, there was no significant drop in blood pressure. In the seven patients with chronic HF who were studied, there were no hypotensive or syncopal episodes and renal function remained stable over a 6-month period. Although limited in size, the pilot study showed that there was a trend towards an improvement in symptoms and exercise capacity. This suggested that it might be safe to undertake randomized, blinded sham-controlled clinical trials in this patient population. Importantly, it must be recognized that all the patients selected for this study were normotensive to begin with. Early work randomizing 51 patients with NYHA class III and IV to renal denervation with optimal medical therapy vs. optimal medical therapy alone showed, over a follow-up period of 12 months, a trend towards reduced hospitalizations for HF and improvement in LV ejection fraction in the renal denervation arm. These preliminary results are encouraging, and will need to be substantiated by longer follow-up and larger randomized studies. The REACH study (NCT01538992), which is a prospective, double-blinded, randomized study on the safety and effectiveness of renal denervation in 100 patients with chronic systolic HF, is assessing its impact on functional improvement. Symplicity HF (NCT01392196) is studying 40 patients with NYHA class II or III HF, and with LVEF <40% on optimal medical therapy with mildly impaired renal function. These studies are recruiting patients with a baseline systolic blood pressure of at least greater than 100 mmHg.

Figure 2 Role of brain and kidney in activation of the renin–angiotensin–aldosterone system in hypertension, and heart failure.
Recent evidence to suggest that renal denervation may reduce left ventricular hypertrophy has created an interest in exploring its role in diastolic HF. The reduction in myocardial hypertrophy has been observed to be independent of the drop in blood pressure, suggesting that this may be a direct effect of modulating the ANS. Renal denervation may potentially provide other, non-blood pressure-lowering effects. Indeed, pilot studies indicate beneficial effects on glucose metabolism, atrial fibrillation, ventricular storm, heart rate reduction, etc. All these disease states represent important comorbidities, characterized by an increased sympathetic tone, having an impact on morbidity and mortality in HF patients.

Importantly, extrapolating the benefit of renal denervation in HF from hypertension studies should be done with caution. There are many unanswered questions, one of which is the long-term impact of renal artery damage in this frail patient group. Many of these patients already have declining renal function, and any additional damage may have a deleterious impact. Also, there may be substantial variability in the renal innervation patterns in HF patients and also individual differences in the contribution of the sympathetic tone to HF progression, which may influence the success of this procedure in this patient population. It is important to remember that sympathetic strategies may not always be most appropriate in HF patients. The MOXCON study testing a sympathetic agent, such as moxonidine, was prematurely stopped due to increased mortality. This was observed despite a significant reduction in norepinephrine levels. Although the study has its weaknesses and the mechanism of action between moxandine and RDN is not comparable, it should encourage us to pause and carefully examine the pathophysiology and implications of this intervention.

In summary, the role of sympathetic activity in the pathophysiology of HF is well accepted. There is a bidirectional signalling between the brain and the kidney, via the ANS mediated through the renal afferent and efferent nerves. Substantial clinical and experimental data implicate the benefit of renal denervation in reducing hypertension and left ventricular mass, and consequent improvement in diastolic function. Similarly, the role of RDN in treating systolic function and HF is under investigation, with preliminary evidence suggesting its benefit.

**Vagal nerve stimulation**

Experimental work done nearly 3 decades ago has shown that there is a strong association between depressed vagal reflexes (measured via BRS) and susceptibility to ventricular arrhythmias in the early post-infarction period. It was later via the ATRAMI (Autonomic Tone and Reflexes After Myocardial Infarction) study that the presence of this link was reinforced. This study showed that markers of autonomic activity (BRS and HRV) contributed to the risk stratification of patients after a myocardial infarction. In particular, a depressed BRS in patients with reduced heart function identified patients at high risk for cardiac and arrhythmic mortality. Vagal nerve stimulation (VNS), although a well-recognized clinical therapy for epilepsy and medically refractory depression, is currently under investigation as a therapy for HF and a spectrum of other conditions such as Alzheimer’s disease, anxiety, and obesity.

Much of its benefit has been shown to be mediated via anti-adrenergic effects that may occur at the central and peripheral level in addition to an observed anti-apoptotic and anti-inflammatory effect. Its role in congestive HF is fuelled by the evidence that reduced vagal activity in decompensated HF is associated with increased mortality. Experimental work has further elucidated that VNS is accompanied by an improvement in haemodynamics and mortality. Recent work has also shown that vagal stimulation, in a rat model of myocardial infarction-induced HF, not only significantly reduced arrhythmias, but also increased long-term survival. A mechanistic explanation is that vagal stimulation prevents a loss of connexin 43 induced by ischaemia, thereby improving electrical instability. Further work has shown the beneficial effects of VNS on structural remodelling, an improvement in ejection fraction accompanied by a significant reduction in inflammatory markers (i.e. TNF-alpha and interleukin-6).

The vagus nerve that innervates essentially all the organs in the neck, thorax, and abdomen originates in the medulla. The cervical vagus nerve contains both unmyelinated and myelinated nerve fibres. Afferents from the gastrointestinal tract, heart, and lungs outnumber the parasympathetic efferents to the visceral organs. The left vagus nerve gives rise to cardiac efferents that regulate cardiac contractility and the AV node, while efferents in the right vagus nerve are associated with the sinoatrial node and in regulating the heart rate. Notably, the mammalian vagal nerve fibres are divided into type A, B, and C fibres. The type of fibres recruited influences the clinical impact of VNS. Even though several thousand devices have been implanted, the exact mechanism for its clinical effect remains unclear. Of note, endovascular VNS may also be possible through stimulation of the coronary sinus ostium and/or superior vena cava, resulting in a slow heart rate and prolonged AV conduction.

The vagal nerve stimulation system is an implantable neurostimulator system that delivers electrical impulses via an asymmetric bipolar multi-contact cuff electrode around the vagus nerve in the neck. The stimulation electrode is tunnelled to the infracavicular region and attached to the pulse generator. (Figure 3). The system

![Figure 3 X-ray of a patient with a vagal nerve stimulator with a previously implanted implantable cardioverter defibrillator. The arrows show a lead attached to the vagus nerve on the right side and an additional right ventricular sensing lead connected to the vagal nerve stimulator device.](https://academic.oup.com/eurheartj/article-abstract/35/2/77/570996)
used in the CardioFit (BioControl Medical Ltd, Yehudi, Israel) study comprised an asymmetric bipolar multi-contact cuff electrode specifically designed to preferentially activate the vagal efferent fibres in the right cervical vagus nerve. The stimulation lead is designed to recruit efferent vagal B-fibres, with minimal recruitment of A-fibres, which when activated could have unwanted central side effects. The system also involves placement of a right ventricular sensing electrode to prevent excessive bradycardia from VNS. The implantation procedure often involves a multidisciplinary approach using the expertise of a surgeon and a cardiac electrophysiologist. The stimulation parameters, inclusive of the electrode design and stimulation intensities needed to stimulate the appropriate nerve fibres, are variable. It must be remembered that VNS in its present state results in activation of both the afferent and efferent nerve fibres, and the clinical benefit is a consequence of the balance achieved via stimulation and inhibition of the appropriate vagal nerve fibres. Gradual up-titration of the amplitude of stimulation is achieved, with targets of usually 5.5 mA and a heart rate reduction of 5–10 beats, without any side effects. Some common side effects include neck pain, coughing, swallowing difficulty, and voice alteration along with nausea and indigestion.

A recently performed open-label multi-centre pilot study in 32 patients with NYHA class II–IV and LVEF ≤ 35% demonstrated the positive impact of VNS on structural and functional endpoints. A substantial proportion of patients improved their NYHA class and 6-minute walk test, with an accompanying improvement in ejection fraction. The positive results in the pilot study have prompted a larger clinical trial, which is currently underway. The INcrease Of VAgal TonE in congestive heart failure (CHF) (INOVATE-HF) trial is a randomized, multi-centre (USA and European sites), open-label Phase III trial. This study aims to enrol 650 patients (NYHA class III, LVEF ≤ 40%, LV end-diastolic dimension 50–80 mm) in a 3:2 randomization scheme to active VNS therapy vs. standard of care (no implant). The primary efficacy endpoint of this trial is the composite endpoint inclusive of all-cause mortality or hospitalization for HF. Another multi-site study examining VNS in 250 patients is the randomized, double blind, Phase II trial, Neural Cardiac Therapy for Heart Failure Study (NECTAR-HF, NCT01385176), which is examining the clinical efficacy of direct right vagus nerve stimulation in HF patients.

The full reach of the therapeutic potential of this novel modality is still evolving. Any benefit of VNS may be a consequence of a multitude of mechanisms which include slower heart rate, blunting of the sympathetic axis, inhibition or down-regulation of the RAAS, and enhancing the signalling pathways, which facilitate restoration of the BRS, suppression of the pro-inflammatory cytokines, and suppression of the gap junction remodelling. Some of the challenges that exist are still centred on selecting the right patient and, more importantly, the appropriate pacing protocol. It could be speculated that those patients demonstrating a higher baseline sympathetic activity could be the ones showing an enhanced response, while those with a high scar burden may have a limited ability to remodel through neuromodulation. The issue of dose–response remains an unanswered question, as most studies have not addressed this. Although intravascular stimulation to recruit the vagal efferent fibres with appropriately positioned atrial pacing leads may be possible, there remain many technical challenges on this front pertinent to targeting, pain perception, and stimulation protocols.

In summary, there appear to be convincing preliminary data that VNS may be feasible, safe, and useful in patients with HF. The pilot studies have shown significant improvement in subjective and objective endpoints of HF, with results remaining to be confirmed in larger multi-centre randomized studies.

### Carotid baroreceptor stimulation

The carotid baroreflex circuit plays a critical role in blood pressure regulation via modulation of the sympathetic tone. The carotid baroreceptors are mechanoreceptors located in the carotid sinus, which are stretch sensitive to distension of the carotid wall. Simultaneously, the afferent signals from the baroreceptors go to the nucleus tractus solitarius located in the dorsal medulla of the brainstem. The conversion and processing of these signals occur in the ventrolateral medulla, from where the signals controlling the sympathetic tone are disseminated to the rest of the body. Importantly, activation of the carotid baroreceptor reduces sympathetic outflow and enhances the vagal tone.

Although ~50 years ago carotid sinus stimulation was studied as a treatment strategy for angina and hypertension, its use was abandoned due to technological limitations and an expanding array of pharmacological interventions. The resurgence of interest has been fuelled by more promising experimental work and technological advancements. The recent phase II non-randomized Device-based Therapy of Hypertension Trial (DEBuT-HT) in 45 patients with drug-resistant hypertension showed a significant drop in the mean BP (33/22 mmHg) after a 2-year follow-up. This was further evaluated in the Rheos system pivotal trial, which re-examined the impact of baroreceptor stimulation in 265 patients with severe hypertension on three anti-hypertensive medications. The results were mixed, with a moderate yet non-significant reduction in blood pressure. Multiple procedural adverse events (i.e. transient or permanent nerve injury, surgical or respiratory complications) were noted, implying the need for further technological refinement.

The emerging interest in the role of carotid baroreceptor stimulation (CBS) in HF is supported by its long-term benefit in hypertensive patients and the evidence of a depressed baroreflex control of heart rate in patients with HF. This depressed function is a direct consequence of abnormalities in the arterial baroreflex coupled with changes in the processing of central neuronal signals. Improving baroreflex function may reverse the neurohormonal excitation that accompanies CHF. Preclinical work has shown that baroreceptor stimulation was associated with lower plasma norepinephrine levels and enhanced survival in dogs with pacing-induced HF. In conjunction with this global reduction in sympathetic outflow, there may also be a reduction in the plasma angiotensin II levels.

As stated earlier, angiotensin II receptor blockade is considered the mainstream therapy for HF patients, thereby making a case for baroreceptor stimulation. Angiotensin II blockade contributes to inhibition of its direct mitogenic effects along with a reduction in its vascular resistance and extracellular volume, thereby retarding the adverse remodelling that accompanies progressive HF. It could also be speculated that the combined reduction in plasma norepinephrine and angiotensin II could lead to an enhanced endothelial function and, consequently, improved perfusion of vascular beds crucial to the remodelling process. It is unclear how much...
of the benefit is due to direct cardiac effects and may be more attributable to peripheral vascular and neurohormonal inhibition.

The benefit of baroreceptor activation can be obtained by either unilateral or bilateral carotid sinus stimulation. The most investigated Rheos system (CVRx., Inc., Minneapolis, MN, USA) has three components: an implantable pulse generator, carotid sinus leads, and the programmer (Figure 4A). Briefly, the pulse generator, which is similar to a pacemaker, is implanted in the infraclavicular region and is connected to two electrode leads that are connected to the perivascular tissue of the two carotid sinuses. The procedure requires a skilled and experienced team of vascular surgeons, hypertension specialists, and anaesthesiologists. The second generation (Barostimneo), with recent approval in Europe, consists of a pulse generator and only one carotid sinus electrode. The system comprises an electrode that is reduced in size and delivers less power, and thus with the potential for a simpler implant and lesser adverse effects.

There are a few ongoing studies examining the role of augmenting the baroreflex via baroreceptor activation in patients with diastolic and systolic HF. The CVRx® Rheos® Diastolic Heart Failure Trial is a prospective, randomized, double-blind trial to examine the safety/efficacy of this therapy in 60 patients. Another larger ongoing diastolic heart failure trial is the Rheos HOPE4HF Trial, which is an open-label randomized study examining the impact of bilateral baroreflex stimulation in 540 patients with diastolic HF (LVEF >40%). The Barostim HOPE4HF is another prospective randomized study evaluating the safety and efficacy of the Neo system in 60 subjects with a left ventricular ejection fraction <35%. Alternative strategies to examine the stimulation of carotid sinus nerves via endovascular stimulation with a catheter in the internal jugular vein are also being investigated (ACES II study, Acute Carotid Sinus Endovascular Stimulation Study). Some newer systems are also evaluating the placement of endovascular stents with external sources of energy to stimulate the carotid baroreceptors.

In summary, CBS through its modulation of the sympathovagal tone and its consequent effective reduction in blood pressure may have potential benefit in patients with HF. The data so far are preliminary and significant advances towards understanding the working mechanism, selecting the appropriate patients, and improving the technology still need to occur. Much work yet needs to be done on appropriate dose (stimulation) delivery, as well as understanding the benefits of unilateral vs. bilateral CBS, while limiting any potential adverse effects.

Spinal cord stimulation

Spinal cord stimulation (SCS) is an FDA-approved therapeutic modality for chronic pain syndromes and refractory angina. This therapy involves the placement of a stimulation electrode in the epidural space tunnelled to a pulse generator in the para-spinal lumbar region. (Figure 4B) The distal poles of the electrode are placed in the region of the fourth and fifth thoracic vertebrae. Spinal cord stimulation is applied at 90% of the motor threshold at a frequency of 50 Hz with a pulse width of 200 ms width for 2 h, three times a day. Several studies have shown that SCS may have a cardio-protective effect, largely mediated through a vagus-dependent mechanism, which reduces heart rate and blood pressure. Zipes and colleagues have shown that SCS at thoracic vertebra T1 may increase the sinus cycle length and prolong intracardiac conduction, both of which appear to be vagally mediated.

Preclinical work using a canine post-infarction HF model has also demonstrated that SCS administered during coronary artery balloon occlusion may reduce infarct size and suppress ventricular arrhythmias. The most robust evidence that SCS may have a role in the treatment of HF is the preclinical work undertaken by the same investigators in a chronic HF canine model. An elegant randomized study in canines involved the induction of HF, and then...
implantation of an implantable cardioverter defibrillator followed by left anterior descending coronary artery embolization to induce a myocardial infarction. Surviving animals entered the neuromodulation stage (stage 2). In this stage, the animals were equally randomized to receive SCS, medical therapy, or a combination of SCS and medical therapy over a 10-week period. Spinal cord stimulation was performed at T4, at 90% of the motor threshold, three times a day for 2 h each. A significantly greater decline in brain natriuretic peptide (BNP) and norepinephrine levels, along with a marked reduction in the number of spontaneous ventricular arrhythmias was observed in the SCS and the medical therapy group. Notably, there was an improvement in the LVEF, which was seen to be maximum in the groups receiving SCS. Similar findings were noted in an almost identical experiment in pigs. Continuous SCS was again associated with a reduction in NE and BNP and an improvement in the cardiac function in this species. Additional work has shown that this VT suppressing and LV remodelling effect may be site-specific to a particular spinal segment and stimulation threshold. Significant and similar effects may be obtained with stimulation at 90% of the motor threshold at the T1 or T4 level.99,100

On the basis of this preclinical work, there are a number of studies assessing the efficacy and safety of this modality in systolic HF patients. The SCS HEART (Spinal cord stimulation for Heart Failure, NCT01362725) study is a non-randomized, open-label safety study of 20 patients with NYHA class III or IV and LVEF between 20 and 35% on maximal medical therapy, with a dilated left ventricle. The DEFEAT-HF study (Determining the Feasibility of spinal cord neuromodulation for the treatment of chronic HF, NCT01112579) is an ongoing, randomized, single-blind study of 250 patients with HF. Another small, open-label, single-arm, safety and efficacy study (Trial of autonomic neuromodulation for treatment of chronic HF, TAME-HF, NCT01820130) is examining 20 HF NYHA class III patients, with LVEF < 35% and a narrow QRS, for its safety and impact on similar structural and functional endpoints.

**Evolution strategies**

Recent work has shown that endovascular cardiac plexus stimulation may increase LV contractility without increasing heart rate.104 The cardiac plexus lies within the adventitia of the great vessels between the ascending aorta and pulmonary artery. This plexus receives innervation from post-ganglionic sympathetic and pre-ganglionic parasympathetic cardiac autonomic nerves. Stimulation of these areas via an epivascular or endovascular route with a catheter in the right pulmonary artery has been shown to increase LV contractility and cardiac output with no accompanying heart rate increase. This is very preliminary work, but raises the possibility that selective recruiting of the cardiac plexus to alter the cardiac autonomic tone to improve cardiac function. Similar endeavours to stimulate the vagus nerve via minimally invasive transcatheter or endovascular approaches are being developed. Along with newer non-pharmacological interventions to modulate the ANS, there are continued advances in sensor strategies to measure autonomic activity. In the foreseeable future, implantable devices will be able to individualize the extent of autonomic modulation via automatic optimization and autoregulation algorithms.

**Conclusion**

The ANS is intricately intertwined with cardiac function and plays an important role in the progression of HF. Limited advances on the pharmacotherapy front have led to the development of innovative non-pharmacological interventions that can favourably alter the cardiac autonomic tone. Renal denervation, which disrupts the renal nerves from the renal artery, may alter the neurohormonal balance to facilitate favourable remodelling of the ventricles. VNS and CBS have been shown in separate pilot studies to improve functional status and ventricular function. Experimental work with SCS has also been shown to be beneficial in HF. Multiple clinical trials are currently evaluating the safety and efficacy of these therapeutic strategies in the treatment of HF. While being enthusiastic about these potential modalities, we need to be cognizant of the fact that these are invasive, investigational, and still beset with many unknowns. The era of non-pharmacological modulation of the ANS has dawned upon us. It, however, remains to be seen whether it lives up to our expectations.

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