Vagal nerve stimulation in heart failure

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This editorial refers to ‘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’, by F. Zannad et al., on page 425.

It has been estimated that the prevalence of heart failure with a reduced ejection fraction exceeds 20 million patients worldwide—about 2% of the general population in the Western world—and that the annual incidence is >2 million patients per year. The mortality of heart failure exceeds that of many malignancies. Significant healthcare improvements have been made with regard to pharmacological therapy, cardioverter defibrillator implantation, and biventricular pacing, but the risk of mortality remains high, and many patients remain very symptomatic, as evidenced by frequent hospitalizations, reduced exercise tolerance, and degraded quality of life.

Patients with congestive heart failure have a major disturbance of autonomic function: heightened sympathetic and reduced parasympathetic activity. Induced heart failure leads to this imbalance and, in turn, the imbalance leads to aggravation of heart failure. The overactive sympathetic system can be addressed by treatment with beta-adrenergic blockade or inhibitors of the renin–angiotensin–aldosterone system, and reduced parasympathetic activity can be bolstered to some extent by physical training and low dose digoxin.

Several relatively new and experimental non-pharmacological interventions which target specific aspects of autonomic imbalance (e.g. renal denervation, cardiac contractility modulation, spinal cord stimulation, and carotid sinus nerve stimulation) are being actively investigated.

It is also possible to stimulate the vagus nerve directly to improve parasympathetic tone and reflexes. It has been shown that vagal nerve stimulation (VNS) leads to improved left ventricular haemodynamics, increased heart rate variability, better vagal reflexes, and greater nitric oxide expression. VNS also results in improvement of the renin–angiotensin system, reduced heart rate, modulation of inflammatory cytokines, less likelihood of spontaneous or induced ventricular arrhythmias, and reduced mortality. This wealth of data led ineluctably to the hypothesis that vagal nerve stimulation might improve the outlook of patients with congestive heart failure.

There have been two previous reports of the use of VNS in patients with heart failure. A single-centre pilot study of eight patients with severe heart failure [seven in New York Heart Association (NYHA) class III] showed that right-sided VNS with the CardioFit system (BioControl Medical, Yehud, Israel), synchronized at 70 ms after the R wave with a duty cycle of no more than 25%, was safe and tolerable. Sinus bradycardia was noted but was not a limiting factor since it was patient discomfort that generally prevented further increase of the stimulus intensity. There were significant and clinically important improvements in NYHA class, quality of life, and echocardiogram-derived end-systolic volume when compared with baseline values.

Since the results were favourable, this study was extended to include a further 24 patients from multiple centres. The results of the larger study were equally compelling [significant improvements in NYHA class, quality of life, 6 min walk test (from 411 ± 76 to 471 ± 111 m), left ventricular ejection fraction (from 22 ± 7 to 29 ± 8%), and left ventricular systolic volumes]. Some serious adverse events were noted that were thought to be due to the implantation procedure, and some expected minor side effects such as a hoarse voice and coughing which were attributable to the stimulation were noted early in the post-implant phase but could be eliminated by adjustment of the stimulus intensity. The success of this trial, together with a substantial basic science evidence-base, set the scene for further clinical studies.

The NECTAR-HF (NEural cardiac TherApy foR Heart Failure) trial which is now reported is the first randomized trial which has assessed the value of VNS in patients with heart failure. In this study, patients with symptomatic heart failure despite optimal medical therapy (NYHA class II–III), a left ventricular ejection fraction ≤35%, and a left ventricular end-diastolic diameter ≥55 mm were recruited. There was no specific criterion about QRS duration, but patients should not have been candidates for any form of pacing (although some did have biventricular devices). The Boston Scientific VNS system [a vagal cuff lead and an implantable pulse generator—Precision™ (Boston Scientific Corporation, St. Paul, MN, USA)] was implanted in all patients but was randomly activated in only...
two out of three for the initial 6-month part of the study. The stimulation frequency was delivered at 10 Hz and operated independently of the cardiac cycle, but with a duty cycle (% of time stimulating) of 15%, and a maximum output of 4 mA.

Vagal nerve stimulation was not associated with any significant reduction of heart rate, and echocardiographic variables did not improve significantly. Quality of life was better in those undergoing active stimulation, but blinding was not perfect in the trial since some patients could sense the stimulation. It is not clear from either the design paper or the present report why the estimate of the sample size was reduced from the original estimate of 250 (https://clinicaltrials.gov/ct2/results?term=NECTAR-HF&Search=Search) to 96, but it seems unlikely from the reported results that a larger trial would have made much difference. However, it might well be that a 6-month period of comparison was too short to allow differences between active treatment and standard of care to emerge.

The second part of the trial, which follows patients—all undergoing active stimulation—for up to 18 months, was designed to assess the long-term safety of VNS. It is not certain that this part of the trial will be continued if there is no efficacy value, but continued application of the treatment may have a benefit that can be demonstrated by comparing pre-stimulation values with longer term on-treatment measurements.

The INNOVATE-HF (INcrease Of VAgal TOnE in Heart Failure) trial is a large ongoing trial which is assessing the effect of right vagal nerve stimulation with the Cardiofit system (as used in the previous successful reports) on cardiovascular outcomes (all-cause mortality and heart failure hospitalizations) in patients with a narrow QRS complex (<120 ms) and class III NYHA symptoms despite optimal medical therapy. The trial plan is to recruit up to 650 patients, randomized 3:2 to active therapy vs. standard of care (no sham procedure is involved), and is expected to follow patients for at least 1 year. On the other hand, ANTHEM-AF (Autonomic Neural regulation TTherapy To Enhance Myocardial function in Heart Failure) is recruiting 60 NYHA class II–III patients with a QRS width ≤150 ms and a left ventricular ejection fraction ≤40% to assess the safety of the procedure and to evaluate efficacy of VNS with the Cyberonics VNS Therapy System (Cyberonics, Houston, TX, USA). The primary endpoint of this early study with another stimulator that is not synchronized to the R-wave is to be focused on safety, but left ventricular end-systolic volume, left ventricular end-systolic diameter, and ejection fraction are to be compared with measurements at baseline.

The three trials (NECTAR-HF, ANTHEM-HF, and INOVATE-HF) employ different stimulators and different electrodes, and are assessing different outcomes in different patients (Table 1). The details of the stimulation protocols are not completely clear and it is not certain whether the protocols together with the electrode spacing, polarity, and positioning are more likely to recruit afferent or efferent vagal fibres, whether sympathetic activity will also be suppressed, and what effect there should be on ventricular contractility. The partial results from the NECTAR-HF trial should not dissuade investigators from continuing with their trials. There is considerable autonomic disturbance in heart failure; the excess of sympathetic activity and the withdrawal of vagal activity clearly contribute to the progression of ventricular remodelling and

<table>
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<tr>
<th>Table 1</th>
<th>Comparison of NECTAR-AF with INOVATE-AF and ANTHEM-AF</th>
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<tr>
<td><strong>NECTAR-HF</strong></td>
<td><strong>INOVATE-HF</strong></td>
</tr>
<tr>
<td><strong>Stimulator</strong></td>
<td>Precision Boston Scientific</td>
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<tr>
<td><strong>Electrode lead</strong></td>
<td>Single lead with three helical cuffs; bipolar stimulation</td>
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<td><strong>Number of patients</strong></td>
<td>87 with paired data</td>
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<td><strong>Inclusion criteria</strong></td>
<td>Stable NYHA class II–III despite optimal medical therapy</td>
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<td><strong>Stimulation protocol (maintenance)</strong></td>
<td>20 Hz, maximum 4 mA (nearly cycle)</td>
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<td><strong>Duration of follow-up</strong></td>
<td>Stage 1: 6 months</td>
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LVEDD, left ventricular end-diastolic dimension; LVEF, left ventricular ejection fraction; LVEDV, left ventricular end-systolic volume; NYHA, New York Heart Association.
worsening of heart failure. Redressing sympathovagal balance in heart failure is feasible and should be advantageous, but only more data, carefully collected, analysed, and promulgated, will tell us if, when, and how to do this.

Conflict of interest: none declared.

References