Chronic vagal nerve stimulation for the treatment of human heart failure: progress in translating a vision into reality

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This editorial refers to ‘Chronic vagus nerve stimulation: a new and promising therapeutic approach for chronic heart failure†, by G.M. De Ferrari et al., on page 847

Heart failure resulting from cardiac ischaemia and/or tachycardia is accompanied by changes in autonomic tone that typically result in increased heart rate and a reduction in heart rate variability. In this setting, autonomic dysfunction is often accompanied by evidence of neurohormonal activation (increased plasma levels of norepinephrine, angiotensin II, and endothelin-1) as well as inflammatory biomarkers and cytokines (tumor necrosis factor-α and C-reactive protein), metabolic changes, and increased systemic and cardiac oxidant stress. As illustrated in Figure 1, these processes promote cardiovascular structural and electrical remodelling, leading to dilation of the cardiac chambers, increased interstitial fibrosis, pump failure, and an increased susceptibility to lethal ventricular arrhythmia.

Preclinical studies have been crucial to the elucidation of the role of the autonomic nervous system in cardiac function, and the dysfunction that accompanies ischaemia, infarction, and tachycardia-mediated cardiomyopathy. In 1984, Schwartz and colleagues showed that the autonomic nervous system had a critical role in the induction of ischaemia-induced lethal ventricular arrhythmias [ventricular tachycardia (VT)/ventricular fibrillation (VF)] in dogs with a healed myocardial infarction.1 This group showed that the sympathetic nervous system had a critical role in arrhythmogenesis, and that left stellectomy (which removes sympathetic input to the heart) essentially eliminated arrhythmogenesis in their model. Left stellectomy slows heart rate, but the authors showed that it was the combination of tachycardia plus acute ischaemia that was essential for arrhythmia induction. Recognition that pharmacological addition of β-adrenergic receptor blockers was able to slow heart rate, improve cardiac pump function, and reduce mortality in heart failure patients constitutes one of the major paradigm shifts in 20th century medicine.2 In the same canine model, Schwartz et al. demonstrated that the animals surviving acute ischaemia following exercise had a slower heart rate than those that did not survive.1 In follow-up studies, Billman et al. demonstrated that daily exercise could reduce the risk of arrhythmia in dogs previously vulnerable to ischaemic VT/VF.3 They inferred that either activation of the parasympathetic nervous system (mediated by the vagus) or deactivation of the sympathetic nervous system was likely to account for the heart rate slowing and enhanced survival. These studies suggested that daily exercise might improve function and reduce mortality in heart failure patients at risk for sudden cardiac death.

Anginal pain is a sign of acute cardiac ischaemia. β-Adrenergic receptor blockers and calcium channel blockers were originally developed as anti-anginal agents. In a bold and impressive study reported in 1967, Braunwald et al. demonstrated that vagal nerve stimulation (VNS; in the carotid sinus) could reproducibly attenuate angina symptoms and improve exercise capacity in two patients following myocardial infarction.4 For reasons that are unclear but probably related to the technical challenges of creating an implantable device at that time, further development of VNS paused until the supporting technology evolved. With the development of pacemaker and defibrillator technology, the essential elements needed to package and deliver VNS became feasible, and devices capable of delivering this treatment were commercially developed in the 1990s. Chronic VNS has been clinically approved for the treatment of epilepsy since 1997, and more recently approved for the treatment of depression.

In recent preclinical studies, chronic VNS has been shown to be effective in the treatment of both ischaemic and tachycardia-mediated heart failure.5,6 In a ventricular tachypacing model, our group showed that this intervention improved baroreflex sensitivity and cardiac function, and reduced chamber dimensions.5 Chronic VNS decreased circulating plasma catecholamine levels,
and the plasma levels of angiotensin II and C-reactive protein. These preclinical reports suggest that chronic VNS may be an effective treatment for preventing and/or reversing the autonomic causes of heart failure.

First-in-human heart failure studies with the new technology were recently reported, and studies have now reached the phase II stage. De Ferrari and colleagues now report the initial results of a 32 patient phase II study designed to test the feasibility, safety, tolerability, and initial efficacy of chronic VNS. Included patients had a left ventricular (LV) ejection fraction <35%, and were able to perform a 6-minute walk test. Exclusion criteria for the study included candidacy for cardiac resynchronization therapy (CRT) or history of atrial fibrillation or flutter (AF/AFL) in the previous 3 months. Here, the authors report that chronic VNS treatment (up to 1 year) was associated with significant improvements in LV ejection fraction, reduction in LV chamber volumes, and improvements in New York Heart Association (NYHA) class and 6-minute walk distance. The improvements progressed with time, and were sustained at 1 year follow-up. These results are encouraging, suggesting that the concept has clinical merit.

As nearly 40% of heart failure patients have AF/AFL and CRT is widely utilized, the study has initially characterized only a subset of the heart failure population. It will be of interest to determine whether VNS can provide benefits beyond those of CRT, as the side effects associated with VNS are not trivial. Minor side effects were common, particularly cough, dysphonia, and pain related to stimulation. Fortunately, most of these diminished with time. On a more sobering note, nearly half of the patients had serious adverse events, including three deaths and two device-related adverse events. It seems likely that some of these side effects are related to the learning curve associated with the delivery of a new technology.

In future studies, it will be of critical interest to determine the impact of VNS treatment on mortality. Also of interest is the impact of treatment on the development of AF, heart rate variability, and the biomarker profile. In individuals suffering from depression, VNS may have a dual benefit, and this should be monitored in future quality of life studies. A comparison of VNS with CRT, as well as an evaluation of the combined therapy (CRT/VNS) would be interesting.

It is relevant to note that increased exercise and modification of dietary lipids by increasing omega-3 fatty acid intake are alternative, non-invasive approaches that can enhance vagal tone, slow heart rate, and reduce mortality in heart failure patients. It is unclear whether the combined effects of these lifestyle changes with device therapy will be additive or asymptotic. From a simple cost perspective, both alternatives appear less expensive but more difficult to deliver than a device-based therapy. As the technology evolves, efforts should be made to compare the feasibility, efficacy, and cost of delivery of all available treatment options.

It is encouraging to see new therapies develop from old ideas. The study from De Ferrari and colleagues represents a useful and potentially important step in this process.

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References

Myocardial bridging causing infarction and ischaemia

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A 40-year-old woman with a long history of atypical chest pain and no cardiac risk factors was referred for cardiac work-up. Cardiac stress testing on a treadmill ergometer revealed T-wave inversion in leads V1–V3 and an intermittent left bundle branch block. The patient was subsequently referred to cardiac magnetic resonance imaging (MRI), which revealed normal myocardial perfusion at rest (Panel A). At maximum dobutamin stress (i.e. 85% of age-predicted maximum heart rate), impaired left ventricular contractility and delayed perfusion were observed in the anteroseptal myocardium (Panel B), indicating myocardial ischaemia. Delayed imaging revealed late enhancement in the subendocardial anteroseptal myocardium (arrow in Panel C), indicating a non-transmural myocardial scar. Invasive coronary angiography showed normal coronary arteries without systolic compression (images not shown); however, computed tomography coronary angiography (CTCA) revealed a myocardial bridging in the middle segment of the left anterior descending artery (arrow in Panel D). Finally, hybrid CTCA/99mTc-Tetrofosmin single-photon emission computed tomography images were acquired using a 1-day dobutamin-stress/rest protocol, which confirmed MRI results by displaying a partially reversible perfusion defect (ischaemia) in the anteroseptal myocardium (demonstrated by the arrowheads in Panel E at rest, Panel F at dobutamin stress).

This case illustrates a haemodynamic relevant myocardial bridging, causing a non-transmural myocardial infarction and a stress-induced myocardial ischaemia in a young female patient. The patient was subsequently treated with calcium-channel blockers and reported reduced chest pain in the clinical follow-up.