Can we Modulate the Autonomic Nervous System to Improve the Life of Patients with Heart Failure? The Case of Vagal Stimulation

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Abstract

An imbalance of the autonomic nervous system, with reduced vagal and increased sympathetic activity, contributes to pathogenesis and clinical deterioration in heart failure (HF). Experimental studies have demonstrated that vagal stimulation (VS) has an antifibrillatory effect that has proved beneficial in animal models of HF. The potential value of chronic VS in man was first investigated with an implantable neuro-stimulator capable of delivering low current pulses with adjustable parameters to stimulate the right vagus. The results of a pilot study and a small multicentre clinical trial of VS in HF patients appeared to show a favourable clinical effect, and feasibility and safety data were encouraging. An ongoing pivotal clinical trial will provide a definitive assessment of the efficacy and usefulness of chronic VS in HF patients. This approach represents a new and exciting possibility for the management of HF that will provide clinicians with a novel tool to modulate non-pharmacologically the autonomic nervous system in patients with moderate-to-advanced HF.

Keywords

Heart failure, autonomic nervous system, vagal stimulation

Disclosure: Peter Schwartz is a consultant for BioControl Medical Ltd.

Acknowledgement: The Author is grateful to Pinuccia De Tomasi for her expert editorial support.

Received: 27 June 2014 **Accepted:** 29 July 2014 **Citation:** *Arrhythmia & Electrophysiology Review* 2014;**3**(2):120–2 **Access at:** www.AERjournal.com

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Despite the clear improvements in clinical outcomes brought about by medical therapy with β -blockers, ACE inhibitors and aldosterone antagonists, as well as by device therapy with cardiac resynchronisation, many patients with chronic heart failure (HF) remain symptomatic despite optimal medical therapy. Symptomatic HF can have devastating consequences for the quality of life of individuals, and impacts on their families as well as the wider community. HF represents a major socio-economic burden due to the huge number of individuals affected worldwide.

Whenever situations like this occur in medicine, the medical community is keen to explore novel means of treatment, and one such approach has attracted widespread interest. Although original, its background goes back 30 years to the recognition that the autonomic nervous system can be dysfunctional in HF^{1,2} and that this dysfunction is characterised by an autonomic imbalance, with reduced vagal and increased sympathetic activity.³ Initially, the augmented cardiac adrenergic drive supports the performance of the failing heart. However, long-term activation of the sympathetic nervous system is deleterious and β -adrenergic blocker treatment is beneficial.⁴ The realisation that decreased vagal activity could be as important as increased sympathetic activity in causing cardiovascular morbidity and mortality^{5,6} focused interest toward the possibility of producing benefit also by augmenting vagal tone and reflexes. Eventually clinical cardiologists realised the potential inherent in approaches that modulate the autonomic nervous system to obtain a higher vagal and a lower sympathetic activity.³

The first clinical report demonstrating the feasibility of performing chronic stimulation of the vagus in patients with severe HF⁷ gave the green light for a series of clinical endeavours to modulate the autonomic nervous system. These are still in their infancy but appear full of promise. The first-in-man study and its continuation in the first multicentre clinical trial of chronic vagal stimulation (VS)^{7,8} have paved the way for a diversity of clinical approaches that all seek to address autonomic imbalance by modulating the autonomic nervous system both to decrease sympathetic and increase vagal activity.⁹

Initial work with VS^{7,8} has been followed by other approaches, all interesting and potentially useful. They include spinal cord stimulation, baroreceptor activation and renal denervation.^{10,11} This article will provide a succinct review of the rationale behind VS, results of the first-in-man study, its evolution, and the current situation.

Experimental Background

A number of experimental studies laid the foundation for the current translational attempts. Evidence was obtained from post-myocardial infarction (MI) dogs⁵ and then from post-MI humans,¹² that depressed baroreflex sensitivity (BRS) is associated with higher risk for sudden cardiac death. As BRS is largely a marker of vagal activity, this implied that conditions associated primarily with impaired vagal reflexes, but also with increased sympathetic reflexes, can predispose to life-threatening arrhythmias. Direct right VS performed in conscious dogs with a healed MI during a transient

coronary occlusion performed in an exercise stress test¹³ was found to reduce the occurrence of ventricular fibrillation from 100 % to 10 % ($p < 0.001$).¹⁴ The transition towards HF was provided by two large studies that demonstrated an inverse relationship between New York Heart Association (NYHA) class and BRS, with a higher mortality in HF patients with depressed BRS.¹⁵ This predictive value of impaired vagal reflexes was present also among patients treated with β -blockers.¹⁶ When experimental studies on the effect of VS in animals with HF began to be published,^{17–19} there was no reason to delay initiation of VS studies in man.

In contrast with the wide experience of VS in epilepsy, which is conducted through stimulation of the left vagus, the right vagus would be the natural choice for stimulation when targeting the heart itself. As one has to stimulate the intact vagus, the electrical stimulation will activate both efferent and afferent fibres. But what are the consequences of activating the afferent vagal fibres? The answer to this question was provided 40 years ago when it was demonstrated, by recording single vagal and sympathetic fibres directed to the heart, that stimulation of vagal afferent fibres produces a reflex increase in the activity of the contralateral vagus and a reflex inhibition of cardiac sympathetic efferent activity.²⁰ Thus, at clinical level we can expect stimulation of the right vagus to result not only in the direct and reflex activation of vagal efferent fibres but also in the reflex inhibition of cardiac sympathetic efferent traffic. This synergistic effect is likely to contribute significantly to the results observed clinically.

Additional considerations are relevant. In HF there is an increased density of cardiac muscarinic receptors, likely to be secondary to reduced tonic vagal activity.²¹ While postganglionic vagal nerve transmission seems to be intact in HF, pre- to post-ganglionic parasympathetic efferent neurotransmission via nicotinic acetylcholine receptors seems to be impaired.²¹ These nicotinic receptors are agonist-dependent and chronic exposure to a nicotinic agonist during HF can re-establish efferent parasympathetic neural control of the sinus node.²² These data enhance the pathophysiological rationale for the use of electrical pre-ganglionic cervical vagal nerve stimulation to re-establish the diminished cardiac vagal tone in chronic HF.

Clinical Translation

Based on the experimental background and rationale, we moved into the clinical arena with a single centre study involving eight severely diseased patients, as appropriate for a non-traditional approach. This was the first-in-man study with chronic vagal stimulation for heart failure.⁷ The encouraging preliminary results showed the technique to be safe and achievable, and possibly beneficial. It was logical to continue with a multicentre single-arm open-label interventional phase II study.⁸ The pilot study enrolled 32 patients in total (94 % men; mean age 56 ± 11 years) with a history of chronic HF in symptomatic NYHA class II–IV and average left ventricular ejection fraction (LVEF) of 23 ± 8 %. The patients were on optimal medical therapy; and 19 had an implantable cardioverter-defibrillator (ICD).

These patients underwent implantation of the CardioFit 5000 system (BioControl Medical Ltd, Yehud, Israel), including; an implantable neurostimulator capable of delivering low-current electrical pulses (with adjustable parameters); a proprietary cuff with a bipolar electrode placed over the right vagus nerve; and an intracardiac sensing electrode placed in the right ventricle. This enables suppression of

nerve stimulation when heart rate falls below a pre-determined value. The stimulator is designed to sense the heart rate (via an intracardiac implanted electrode) and to deliver stimulation at preset delays from the R wave.

Following an up-titration phase, the stimulation intensity reached 4.1 ± 1.2 mA and was limited by discomfort or pain. Adverse events were limited, and as a rule, disappeared by lowering stimulation intensity. The heart rate changes observed during VS were modest but baseline resting heart rate decreased significantly during the study from 82 ± 13 to 76 ± 13 beats per minute. Most patients (59 %) improved by at least one NYHA class at six months. Quality of life markedly improved at six months (from 49 ± 17 to 32 ± 19 on the Minnesota Living with Heart Failure Questionnaire). The same was found for the six-minute walk test with an increase at three months from 411 ± 76 to 470 ± 99 m and subsequent stability. The blinded echocardiogram analysis disclosed a significant reduction in LV end-systolic volume, and a significant increase in LVEF (from 22 ± 7 % to 29 ± 8 %). A group of 23 patients continued their follow-up with active VS revealing significant maintenance and even magnification of the favourable effects of VS at one year (especially LVEF, from 21–34 %).

This first human experience of chronic VS in patients with HF suggested that the treatment is feasible, safe and tolerable and leads to a subjective clinical improvement. The continuation of data collection in a subset of 19 patients has proved that these effects are preserved at two-year follow-up, a strong argument against a major role for a possible placebo effect. As of today, this represents a major difference from other approaches, be they spinal cord stimulation, baroreceptor activation or renal denervation.

These two clinical studies^{7,8} were ground-breaking as they represented the first attempt to modify the autonomic control of the heart in man with the objective of altering the downhill course of heart failure. Their encouraging results stimulated the design of a formal, randomised clinical trial. The INOVATE-HF (INcrease Of VAgal TonE in CHF) study (NCT01303718) is an international, multicentre, randomised clinical trial designed to assess safety and efficacy of vagus nerve stimulation using the CardioFit System in patients with symptomatic HF who are on optimal medical therapy.²³ This ongoing study is enrolling patients with NYHA Class III symptoms, LVEF ≤ 40 % and end-diastolic dimensions between 50 and 80 mm. Patients are randomised in a 3:2 ratio to either active treatment (implanted) or continuation of medical therapy (not implanted). The primary efficacy end point of the study is the composite of all-cause mortality or unplanned HF hospitalisation equivalent, using a time to first event analysis. The study will continue until a pre-specified number of clinical and safety events have been accumulated and the 500th enrolled patient has been followed for at least one year or for a maximum of 4.5 years. There are two co-primary safety end points: freedom from procedure and system-related complication events at 90 days; and the number of patients with all-cause death or complications at 12 months. After the randomisation and optimisation period, the clinical status of all subjects is evaluated at three-monthly intervals during 18 months post-implant and every six months thereafter. At the time of writing the number of enrolled patients exceeds 460.

Other clinical studies based on vagal stimulation include the Neurocardiac Therapy for Heart Failure study (NECTAR-HF)²⁴ and the Autonomic Neural Regulation Therapy to Enhance Myocardial

Function in Heart Failure (ANTHEM-HF) study.²⁵ Preliminary results from these two trials will be presented in September 2014.

Conclusion

It is evident that management of HF has entered a new phase of hope. As yet nobody can say whether or not the novel approach to

modulate the autonomic nervous system by increasing vagal and decreasing cardiac-bound sympathetic activity will be successful. However, there is undoubtedly merit in exploring this physiologically-based attempt to improve the life of patients with heart failure. Within the next few years INOVATE-HF and the other ongoing studies will provide a clear answer. ■

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