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Vagus nerve stimulation: A new approach to reduce heart failure

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Abstract

Autonomic imbalance with increased adrenergic and reduced parasympathetic activity is involved in the development and progress of heart failure (HF). Experimental data have demonstrated that stimulation of the vagus nerve is able to reverse ventricular remodeling of the failing heart. There is also evidence that increasing parasympathetic activity may stimulate the production of nitric oxide, and reduce the devastating inflammatory process involved in HF. Vagus nerve stimulation (VNS) has been successfully applied for many years to treat drug resistant epilepsy. The first study of right vagus stimulation in patients with advance HF has proven the feasibility and safety of this new approach. Long term follow-up of increased vagal tone over 12 months with a specially designed stimulating system (CardioFit, BioControl, Yehud, Israel) has demonstrated that symptoms of HF can be significantly diminished, left ventricular ejection fraction increased, and ventricular volumes reduced. These recently published data are very promising and may offer another approach for patients with advanced HF already treated with optimal medical therapy. A prospective randomized trial with a larger patient cohort is needed to confirm these beneficial results of VNS. (Cardiol J 2010; 17, 6: 638––643)

Key words: vagus nerve stimulation, heart failure, autonomic imbalance

Introduction

Despite significant progress in medical treatment of congestive heart failure (HF) in recent years, particularly with consequent prescription of angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, beta-blocker and aldosterone antagonists mortality remains high once the patient has reached an advanced stage of HF [1]. Treatment of the failing heart must relieve disabling symptoms, should be directed to the underlying disease, and will concentrate on strategies to interrupt the ventricular remodeling process. With cardiac resynchronization therapy a very successful non-medical approach using biventricular pacing was added to the armamentarium for HF treatment although limited to patients with a wide QRS complex and mechanical dyssynchrony. New techniques rather than new drugs are on the horizon to treat or reverse the progressively impairing structural changes of the failing myocardium.

Autonomic imbalance

There is ample experimental and clinical proof that HF goes along with autonomic imbalance demonstrating increased sympathetic activity and a reduced parasympathetic activation [2–4]. In the early stage of myocardial injury and hemodynamic impairment increased sympathetic activity may be

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beneficial to maintain cardiac output and support myocardial performance. However, in the long-term run the compensatory preponderance of increased beta-adrenergic stimulation leads to deterioration of ventricular performance, structural remodeling with increased apoptosis of myocytes, deposition of fibrous tissue leading to ventricular dilatation, and a higher risk of electrical instability [5, 6]. At the same time parasympathetic activation with its beneficial effects is significantly attenuated with progressing HF, measurable particularly by loss of heart rate (HR) control.

The interaction between the sympathetic and parasympathetic system with both afferent and efferent fibers is rather complex and far from being completely understood. Evidence exists that the parasympathetic system is involved in the regulation of endothelial nitric oxide (NO) expression, and dysregulation of NO pathways due to reduced vagal ganglionic transmission impairs contractility and cardiac function, leading to worsening of HF [7]. Another important finding is the fact that parasympathetic activity can inhibit inflammatory cytokine release and may help to prevent tissue injury and cell death by its anti-inflammatory response [8, 9]. Therefore diminished vagal activity will promote harmful cytokine over-production.

Clinical evaluation of reduced parasympathetic activity in HF patients is difficult and can only be done indirectly by observation of increased resting HR, diminished HR variability, particularly the high frequency component, or the ratio of low frequency to high frequency components. Another parameter which reflects vagal activity is the baroreceptor sensitivity [10]. Baroreceptor sensitivity is found significantly depressed in HF and was found as a predictor of increased risk of ventricular tachycardia/ventricular fibrillation and overall mortality (ATRAMI study) [11, 12].

Heart failure is closely linked with the occurrence of life-threatening ventricular tachyarrhythmias, promoted by increased sympathetic activity, reduced parasympathetic tone or both. Experimental animal data in conscious dogs clearly demonstrate that increasing vagal tone by means of right vagus nerve stimulation (VNS) can prevent ventricular tachyarrhythmias in a model with healed myocardial infarction, exercise testing and intermittent ischemia [13]. Of note is the fact that the observed anti-fibrillatory effect was independent from HR reduction.

In summary currently available experimental and clinical data indicate that HF is associated with reduced vagal activity. Withdrawal of parasympathetic tone increases propensity to life-threatening arrhythmias and promotes structural remodeling. Therefore it seems only logical that VNS may become another approach to treat HF and to reverse ventricular remodeling.

Experimental results of vagus nerve stimulation

The first important animal model of VNS in HF was reported in 2004 by Li et al. [14]. Rats developed HF after anterior myocardial infarction and were randomized to VNS or to a sham stimulated group. Stimulation was performed for 10 s every minute with stimulus intensity able to reduce HR by 20–30 bpm. A significant improvement of left ventricular function and decreased mortality from 50% to 14% compared to sham treated animals was observed after 140 days. Similar beneficial results of improved left ventricular function with VNS were found in a canine model of microembolization induced HF [15]. Recently Zhang et al. [16] demonstrated in another canine model with high rate ventricular pacing induced HF that chronic VNS over 12 weeks was able to reduce ventricular volumes and increased left ventricular ejection fraction (LVEF) significantly. Heart rate reduction did not play a role in this model since both, treated and control group were constantly paced at the same rate. Important findings were presented by Sabbah et al. [17] with their microembolization HF model. Low intensity vagus stimulation with no HR decrease improved left ventricular function, and showed significant decrease of harmful biomarkers of HF.

Vagus nerve stimulation for epilepsy

Vagus nerve stimulation for drug refractory seizures in epilepsy patients was introduced more than 20 years ago, and its safety and efficacy has been described by various authors [18, 19]. The Cyberonics vagus nerve stimulator system (Cyberonics Inc. Houston, TX, USA) consists of an implantable pulse generator and a helical bipolar lead attached to left cervical portion of the vagus nerve. Until today about 50,000 patients have been treated for epilepsy with this device. Recently VNS has also been applied for treatment of drug resistant depression [20].

Vagus nerve stimulation

The neurostimulator (CardioFit 5000, BioControl Medical, Yehud, Israel) delivers low-current

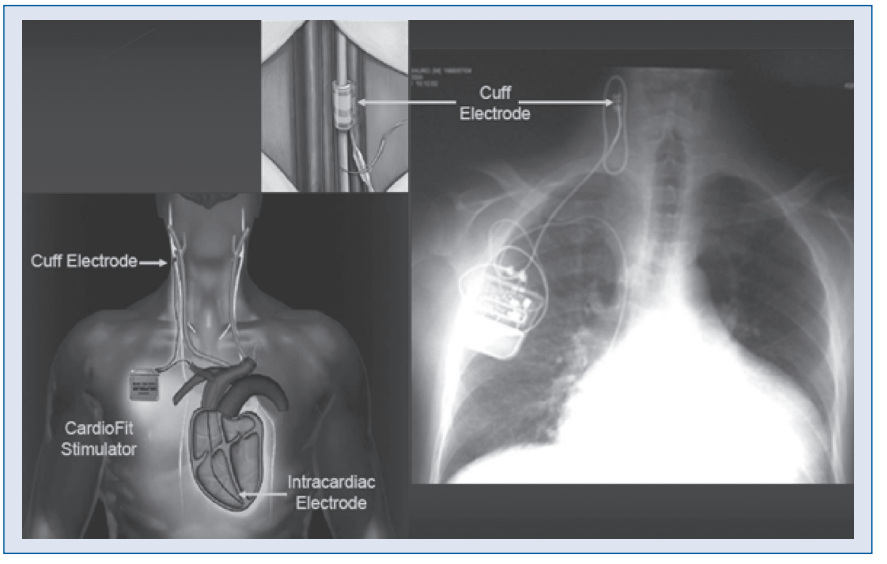

Figure 1. Design of the CardioFit vagus-nerve stimulation system. Upper left small panel: Cuff electrode placed around the right vagus nerve. Left lower panel: CardioFit pulse generator, cuff electrode at the right vagus nerve; right ventricular sensing lead at the right ventricular apex. Right lower panel: Chest X-ray of a patient with the CardioFit vagus nerve stimulation system in place. There is a wide loop of the lead from the vagus nerve insertion to the pulse generator in order to avoid stretching of the electrode with head or shoulder movement (design of the CardioFit vagus nerve stimulation system [BioControl, Yehud, Israel], reproduced with permission: Conf Proc IEEE Eng Med Biol Soc, 2009; 1: 2037.

electrical pulses. The right vagus nerve is exposed through a latero-cervical incision under general anesthesia; the generator is implanted subcutaneously in the right sub-clavicular region just like a regular pacemaker (Fig. 1). The device senses the HR by means of a right ventricular electrode. Pulses are delivered to the right vagus nerve via a stimulation lead that contains an asymmetric bipolar multi-contact cuff electrode placed around the nerve about 2–3 cm below the carotid artery bifurcation. Pulses are delivered at a programmable preset delay from the R-wave. If the HR drops below a programmed rate, stimulation is interrupted. Action potentials in the vagus nerve are produced by cathodic induction with simultaneously applying asymmetric anodal blocks activating more efferent than afferent vagus-nerve fibers. A 3 week up-titration phase to reach the maximum tolerable current amplitude (from 0.5 to 5.0 amp) begins about 3–4 weeks after device implantation. Stimulus strength is limited by patient symptoms (pain, cough, dysphonia) and HR dropping. The relationship between stimulation "on" and stimulation "off" will be progressively prolonged to a maximum of 10 s "on" and 30 s "off", depending on the patient's tolerance. Heart rate reduction with nerve stimulation should be limited to not more than 10 bpm below the basic HR.

With careful up-titration of vagus stimulation unpleasant side effects can be diminished. The most frequent adverse effects are mild cough, particularly at the beginning of the stimulus strength up-titration (about 50%), pain at the nerve stimulation side (about 50%) or at the right mandible region, voice alteration or dysphonia (about 20%). Dramatic HR decrease can hardly occur because nerve stimulation is interrupted with significant (> 10 bpm) drop of HR.

First human study with vagus nerve stimulation

Based on the available impressive results of VNS in animal models of HF, Schwartz et al. [21] were the first to launch a single center pilot study with a single arm open-label intervention to demonstrate the feasibility, tolerability and safety of VNS in patients with advanced HF. The first part of this study enrolled only 8 patients, later the phase II study was extended to a multi-center phase II trial with altogether 32 patients. The secondary endpoint of this small study looked also at clinical effectiveness of VNS over 6 months with optional extended follow-up over 1 year.

After 6 month a moderate but significant decrease of the resting HR was noted in 29 patients.

Table 1. Long-term follow-up of 23 patients (modified from [22]).

Variable	Baseline	12 months	P
Heart rate [bpm]	85 ± 14	76 ± 11	0.003
Heart rate variability (pNN50)	4.6 (1.8–8.4)	7.4 (3.2–24.0)	0.001
6-minutes hall walk test [m]	405 ± 92	472 ± 139	0.012
LVESVI [mL/m^2]	100 ± 40	80 ± 44	0.009
Left ventricular ejection fraction (%)	21.1 ± 7.5	34.1 ± 12.5	< 0.0001
MLwHF score	47 ± 19	30 ± 24	0.001
NYHA I/II/III/IV	0/14/9/0	10/10/3/0	< 0.001
LVEDVI [mL/m^2]	126 ± 47	118 ± 56	0.36

Seven parameters were found significantly improved after 12 month of vagus-nerve stimulation, except the left ventricular end-diastolic volume index (LVEDVI); LVESVI — left ventricular end-systolic volume index; MLwHF score — Minnesota Living with Heart Failure Quality of life score

An improvement of the Minnesota Living with Heart Failure Quality of life score (MLwHF), an increase of the 6-minutes walking test and a significant reduction of the left ventricular end-systolic volume (LVESV) were observed. There were fewer patients in NYHA class III after 6 months, and at this time the LVEF showed a trend to improvement.

Of the 32 patients enrolled into the study (mean age 56 years, 94% male, 62% coronary artery disease) 23 patients were followed over 1 year [22]. Two patients died between 6–12 months, one of end stage HF, the other one after an acute myocardial infarction. One patient underwent heart transplant. Two patients stopped VNS. A significant improvement in NYHA class, an increased 6-minutes walk test, continued improvement of MLwHF score, a significant increase of LVEF and LVESV index were observed. Heart rate variability showed a significant increase of pNN50. Resting HR continued to be slightly but significantly lower than at the time of VNS onset (Table 1).

How can we explain these findings?

Increased parasympathetic tone with reduced HR and improved HR variability, even beyond additional beta-blocker therapy, may have contributed to the beneficial results although drop of resting HR was rather moderate over the course of the study. Most likely an actively produced anti-adrenergic effect of VNS may be responsible for the measurable clinical improvement. Although not specifically evaluated, anti-apoptotic and anti-inflammatory effects as well as potentially increased NO production may all have added to the positive outcome with impressive improvement of LVEF as a sign of reverse remodeling.

Indication for vagus nerve stimulation

The first VNS in humans selected patients with structural heart disease, ischemic as well as non-ischemic cardiomyopathy, reduced LVEF and clinical symptoms of advanced HF (NYHA class II–III). Patients had to be in sinus rhythm with a resting HR between 60–110 bpm and needed to be on stable optimal treatment. Excluded were patients with asthma, chronic obstructive pulmonary disease, history of gastro-intestinal bleeding, peptic ulcer, insulin-dependent diabetes mellitus, glaucoma, and significantly prolonged AV-conduction (PR > 240 ms). All enrolled patients were no candidates for cardiac resynchronization therapy.

Since future trials will need randomization and longer follow-up time in order to evaluate the clinical effectiveness of chronic VNS, it seems advisable to enroll patients with stable HF conditions but in a less advanced stage of failure (i.e. NYHA class IV should be excluded). Before we know the results of long-term parasympathetic stimulation on the AV node, patients with atrial fibrillation should also be excluded. It would be interesting, however, to find out if VNS is able to prevent occurrence of atrial fibrillation, or if increased vagus tone may promote the onset of atrial fibrillation because of potential inhomogeneous shortening of the atrial refractory period.

Potential VNS patients are also potential candidates for implantable cardioverter-defibrillator (ICD) therapy. In fact, more than 50% of the enrolled patients in the initial study had previous ICD implantation, and ICD shocks occurred during follow-up. This indicates that patients for VNS should not be excluded because of their implanted ICD. There were no interactions noted between the two electrical devices.

Vagus nerve stimulation can be considered as "add-on" therapy to optimal medical therapy for HF. It may not be restricted for any specific underlying disease process except significant valve disease or an acute coronary syndrome. Its effect in patients with advanced renal disease or insulin-dependent diabetes mellitus needs to be investigated in more detail. Although experimental data demonstrated anti-fibrillatory effects on the ventricular level, a significant anti-arrhythmic effect of VNS in patients with HF has to be assessed in the future.

Unanswered questions

The most important question in VNS relates to the mechanism of its beneficial effect. Heart rate reduction may be important and reflects the anti-adrenergic effect of increased vagus tone. However, recent experimental data and the clinical outcome of the first application in patients demonstrate that the advantageous effect is measurable even without clinically relevant HR reduction. The improved HR variability clearly shows that there is increased parasympathetic activity. The acute effectiveness of VNS is difficult to asses, and therefore prediction of response becomes uncertain. An effective anti-apoptotic mechanism, an increased production of endothelial NO and the anti-inflammatory effect may well be the major contributor to the observed reverse remodeling action of VNS.

The most effective and tolerable dose of VNS as well as the optimal stimulation mode still needs to be determined. It is unclear if exclusively efferent or both types, efferent and afferent vagus fibers need to be stimulated. It may be technically challenging to separate the two types of fibers with the current or even future stimulation devices. It is also unanswered if the right vagus nerve is more important than the left sided nerve, and if even better results may be achieved with both nerves stimulated, although this may be technically more difficult to do. Will it be more appropriate to apply continuous stimulation instead of pulse-synchronous stimuli? The optimal number of pulses per cycle, the stimulus amplitude and the maximum current needs to be established. We don't know the most appropriate relationship between stimulation time and stimulation pause. Which is the best titration parameter, either HR reduction or tolerable symptoms such as pain or cough?

The device that was used for the first patient study needed a right ventricular sensing lead, but it may not even need an extra intra-cardiac lead at all? All these questions and uncertainties have to be elaborated in future studies with advanced VNS device technology.

Future directions of vagus nerve stimulation

The important physiologic role of autonomic balance for the heart, and the possibility to restore its imbalance by increasing the vagus tone through electrical stimulation has been well established, particularly for patients with HF, not yet, however, for better arrhythmia control.

Non-pharmacologic treatment of HF as "add-on" approach has opened a whole new field of research and clinical practice [23]. Large experience and excellent results are available with cardiac resynchronization therapy. Cardiac contractility modulation has been introduced for HF treatment; however, a broad application with this technique is still missing [24]. Carotid baroreceptor stimulation for the treatment of drug-resistant hypertension seems to be another promising electrical approach [25]. A different place to increase parasympathetic activity in order to have a beneficial impact on HF and/or ventricular arrhythmias is the spinal cord stimulation. Studies using this technique have started, but results in patients with HF are not yet available [26].

The recently published data of the first phase II study of VNS are quite promising. A larger multicenter randomized trial to confirm the initial results will be launched soon, and technical progress of nerve stimulators is predictable. New experimental results on the molecular and cellular level of remodeling predict the potential benefit of VNS in patients [27]. Questions how to transform this approach into a simple to do therapy for a broad spectrum of HF patients, how to predict responders or non-responders, and how to make it a cost-effective treatment need to be answered in the future.

Conclusions

The pathophysiologic mechanism of autonomic imbalance and the beneficial effect of VNS to correct it have long been recognized. First clinical data are now available. They confirm the feasibility, safety and tolerability of VNS. Although the results of the clinical effectiveness of the new approach are derived from a small group of patients, they are promising, and will open a new field of clinical research in order to improve HF symptoms, to reverse ventricular remodeling, and to prevent HF progression.

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