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# Electrical vagus nerve stimulation for the treatment of chronic heart failure

■ **ABSTRACT**

Autonomic dysregulation is a feature of chronic heart failure (HF) and is characterized by a sustained increase of sympathetic drive and by withdrawal of parasympathetic activity. Both sympathetic overdrive and increased heart rate are predictors of poor long-term outcome in patients with HF. Pharmacologic agents that partially inhibit sympathetic activity, such as beta-adrenergic receptor blockers, effectively reduce mortality and morbidity in patients with chronic HF. In contrast, modulation of parasympathetic activation as a potential therapy for HF has received only limited attention because of its inherent complex cardiovascular effects. This review examines results of experimental animal studies that provide support for the possible use of electrical vagus nerve stimulation (VNS) as a long-term therapy for the treatment of chronic HF. The review also addresses the effects of VNS on potential modifiers of the HF state, including proinflammatory cytokines, nitric oxide elaboration, and myocardial expression of gap junction proteins. Finally, the safety, feasibility, and efficacy trends of VNS in patients with advanced HF are reviewed.

**A**utonomic imbalance characterized by sustained sympathetic overdrive and by parasympathetic withdrawal is a key maladaptation of the heart failure (HF) state. This autonomic dysregulation has long been recognized as a mediator of increased mortality and morbidity in myocardial infarction and HF.[1,2] Sympathovagal imbalance in HF can lead to increased heart rate, excess release of proinflammatory cytokines, dysregulation of nitric oxide (NO) pathways, and arrythmogenesis. Diminished vagal activity reflected in increased heart rate is a predictor of high mortality in HF.[3,4] Sustained increase of sympathetic activity contributes to progressive left ventricular (LV) dysfunction in HF and promotes progressive LV remodeling.[5,6] Pharmacologic agents that reduce heart rate, such as beta-blockers and, more recently, specific and selective inhibitors of the cardiac pacemaker current I*f*, have been shown to improve survival and prevent or attenuate progressive LV remodeling in animals with HF.[4,5,7,8]

During the past two to three decades, the emphasis on modulation of neurohumoral activation for treatment of chronic HF gave rise to angiotensin-converting enzyme inhibitors, beta-adrenergic receptor blockers, and aldosterone antagonists. In recent years, renewed interest has emerged in modulating parasympathetic or vagal activity as a therapeutic target for treating chronic HF. An alteration in cardiac vagal efferent activity through peripheral cardiac nerve stimulation can produce bradycardia and can modify atrial as well as ventricular contractile function.[9,10]

Electrical vagus nerve stimulation (VNS) was shown to prevent sudden cardiac death in dogs with myocardial infarction and to improve long-term survival in rats with chronic HF.[11,12] VNS has also been shown to suppress arrhythmias in conscious rats with chronic HF secondary to myocardial infarction.[13]

This article focuses primarily on the effects of chronic VNS on LV dysfunction and remodeling in dogs with HF produced by multiple sequential intracoronary microembolizations[14] or by high-rate ventricular pacing[15] and on the safety, feasibility, and efficacy trends of VNS in patients with advanced HF.[16]

■ **VNS IN DOGS WITH MICROEMBOLIZATION-INDUCED HEART FAILURE**

The CardioFit VNS system (BioControl Medical, Yehud, Israel), used in dogs with coronary microembolization-induced HF, delivered electrical stimulation to the right cervical vagus only when the heart rate increased beyond a preset level, thus operating on a negative-feedback loop **(Figure 1)**. The
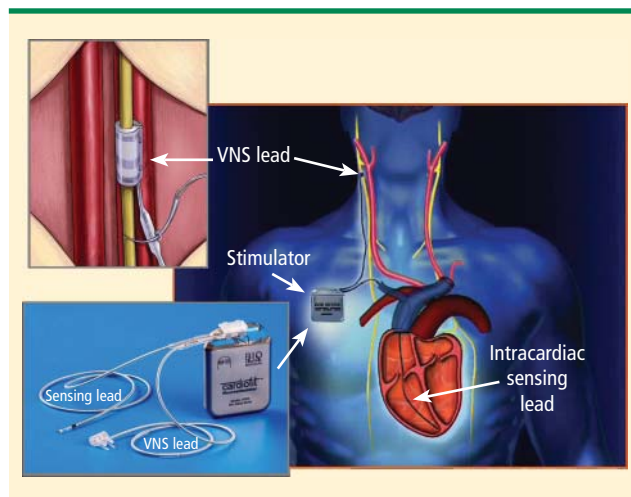
**FIGURE 1.** Right: Depiction of an implanted CardioFit vagus nerve stimulation (VNS) device showing the position of the VNS lead on the right vagus nerve, the intracardiac pacing lead in the right ventricular apex, and the implantable CardioFit neurostimulator in the right subclavicular region. Top left: Positioning of the CardioFit stimulation lead around the right vagus nerve. Bottom left: The CardioFit VNS implantable neurostimulator, sensing lead, and VNS lead.

Courtesy of BioControl Medical, Ltd., Yehud, Israel

### TABLE 1
**Indices of LV systolic and diastolic function in control and VNS-treated dogs before (PRE) and 3 months after (POST) initiating therapy[17,33]**

| | Control (n = 6) | | VNS (n = 7) | |
| --- | --- | --- | --- | --- |
| | **PRE** | **POST** | **PRE** | **POST** |
| LV EF (%) | 33 ± 1 | 29 ± 1* | 34 ± 1 | 41 ± 1* |
| LV EDV (mL) | 56 ± 2 | 60 ± 2* | 58 ± 1 | 57 ± 3* |
| LV ESV (mL) | 37 ± 1 | 42 ± 2* | 38 ± 2 | 34 ± 3* |
| NT-proBNP (pg/mL) | 487 ± 11 | 546 ± 126* | 554 ± 84 | 260 ± 24* |
| LVEDP (mm Hg) | 14 ± 1 | 15 ± 1 | 15 ± 1 | 11 ± 2* |
| PE/PA | 2.0 ± 0.2 | 1.8 ± 0.2 | 2.0 ± 0.3 | 2.4 ± 0.4 |
| DT (msec) | 91 ± 1 | 85 ± 4 | 94 ± 5 | 111 ± 10* |
| EDWS (g/cm²) | 54 ± 3 | 57 ± 4 | 60 ± 5 | 46 ± 7* |

DT = deceleration time of early rapid mitral inflow velocity; EDV = end-diastolic volume; EDWS = left ventricular end-diastolic circumferential wall stress; EF = ejection fraction; ESV = end-systolic volume; LV = left ventricular; LVEDP = left ventricular end-diastolic pressure; NT-proBNP = N-terminal pro-brain natriuretic peptide; PE/PA = ratio of peak early rapid mitral inflow velocity (PE) to peak of mitral inflow velocity during left atrial contraction (PA); VNS = vagus nerve stimulation

* $P < .05$ vs PRE.

stimulation lead was a modified bipolar cuff electrode designed to activate vagus cardioinhibitory B fibers while maintaining a large degree of unidirectionality with respect to low threshold fibers recruited in the 1- to 2-mA range. The lead is attached to a model 5000 electrostimulator fitted with a processing unit that adjusts the impulse rate and intensity to keep the heart rate within the desired range. Maximal stimulation current, pulse width, and operation algorithm are controlled by the physician programmer via wireless communication. A standard pacemaker bipolar ventricular electrode, also attached to the model 5000 electrostimulator, was used in all the animal studies for sensing the intracardiac electrocardiogram (ECG).

### Monotherapy with VNS
Dogs with HF and LV ejection fraction of approximately 35% were randomized to 3 months of active VNS monotherapy (CardioFit on, n = 7) or to no therapy at all (sham-operated control, CardioFit off, n = 6). The feedback on-demand heart rate control was set to reduce basal heart rate by 10%.[17] Long-term (3 months) VNS monotherapy significantly improved LV ejection fraction and significantly decreased LV end-systolic and end-diastolic volumes compared with controls **(Table 1)**.[17] The reduction in LV size was in line with an observed decrease in plasma levels of N-terminal pro-brain natriuretic peptide (NT-

proBNP). In VNS-treated dogs, heart rate assessed using ambulatory ECG Holter monitoring showed a reduction of minimum, average, and maximum heart rate by 1, 10, and 28 beats per minute, respectively, compared with changes of heart rate in control dogs of 2, 1, and 0.5 beats per minute, respectively.

Long-term VNS therapy also elicited improvements in indices of LV diastolic function. VNS significantly decreased LV end-diastolic pressure **(Table 1)**, increased deceleration time of rapid mitral inflow velocity, tended to increase the ratio of peak mitral inflow velocity during early LV filling to peak mitral inflow velocity during left atrial contraction (PE/PA), and significantly reduced LV end-diastolic circumferential wall stress, a determinant of myocardial oxygen consumption **(Table 1)**. These measures suggest that VNS can reduce preload, improve LV relaxation and improve LV function without increasing myocardial oxygen consumption.

### VNS in combination with beta-blockade
The effects of VNS in combination with beta-blockade were examined in dogs with HF. Dogs with LV ejection fraction of approximately 35% were randomized to 3 months of therapy with a beta-blocker alone (metoprolol succinate, 100 mg once daily, n = 6) or to

metoprolol (100 mg once daily) combined with active VNS with CardioFit (n = 6). As with the monotherapy study, the CardioFit VNS system was operated in the feedback on-demand heart rate responsive mode. Dogs were started on oral metoprolol therapy 2 weeks prior to randomization to VNS therapy. After randomization, all dogs continued to receive metoprolol succinate once daily for the duration of the study.[18]

In HF dogs receiving background therapy with metoprolol, the addition of VNS increased LV ejection fraction and decreased LV end-systolic volume compared with dogs treated with metoprolol alone **(Table 2)**.[18] These findings suggest that the addition of VNS improves LV systolic function beyond that seen with beta-blockade alone. Adding VNS therapy to metoprolol also elicited improvements in indices of LV diastolic function. Combination therapy resulted in greater lowering of LV end-diastolic pressure and LV end-diastolic wall stress and greater increase in deceleration time of rapid mitral inflow velocity compared with metoprolol alone.

The improvements in LV systolic and diastolic function with combination therapy were associated with important changes in heart rate. Twenty-four–hour ambulatory ECG Holter monitoring studies showed no differences in minimum and average heart rate between dogs treated with metoprolol and those treated with combination therapy with VNS. Maximum heart rate, however, was significantly lower in

dogs treated with the combination therapy (114 ± 12 vs 149 ± 8 beats/min, $P < .05$). These observations suggest that preventing heart rate escape at the high end may further improve LV systolic function compared with beta-blockade alone. This added benefit of the combination of VNS and beta-blockade was likely the result of reducing the adverse impact of increased cardiac workload and increased myocardial oxygen consumption elicited by the heart rate increase.

## VNS and left ventricular remodeling

In addition to improving LV systolic and diastolic function, long-term VNS in dogs with coronary microembolization-induced HF led to important changes in cellular and structural markers of LV remodeling.[19] Compared with untreated HF dogs, dogs treated with VNS as monotherapy showed a significant decrease in volume fraction of replacement and interstitial fibrosis; a decrease in oxygen diffusion distance, measured as half the distance between two adjoining capillaries; a decrease in myocyte cross-sectional area, a measure of cardiomyocyte hypertrophy; and an increase in capillary density **(Figure 2)**. These histomorphometric measures are often, if not always, adversely affected by the HF state. Their amelioration by VNS suggests that this form of therapy can help preserve myocardial structural integrity through direct or indirect action on the failing myocardium.

## VNS and proinflammatory cytokines, nitric oxide, and gap junction proteins

Elevation of proinflammatory cytokines occurs in HF and is associated with increased morbidity and mortality. Electrical VNS has been shown to decrease the release of various cytokines, including tumor necrosis factor (TNF)-alpha and interleukin (IL)-6.[20] In dogs with microembolization-induced HF, LV tissue levels of TNF-alpha and IL-6 are elevated compared with LV tissue from normal dogs **(Table 3)**. Long-term monotherapy with VNS normalizes protein expression of both TNF-alpha and IL-6 in LV myocardium.[21]

Nitric oxide (NO) is formed by a family of NO synthases (NOS). The three isoforms of NOS identified to date are endothelin NOS (eNOS), inducible NOS (iNOS), and neuronal NOS (nNOS). The three isoforms have differing characteristics and roles:

**eNOS.** NO produced by eNOS plays an important role in the regulation of cell growth and apoptosis[22] and can enhance myocardial relaxation and regulate contractility.[22,23]

**iNOS.** Overexpression of iNOS in cardiomyocytes in mice results in peroxynitrite generation associated with fibrosis, LV hypertrophy, chamber dilation,
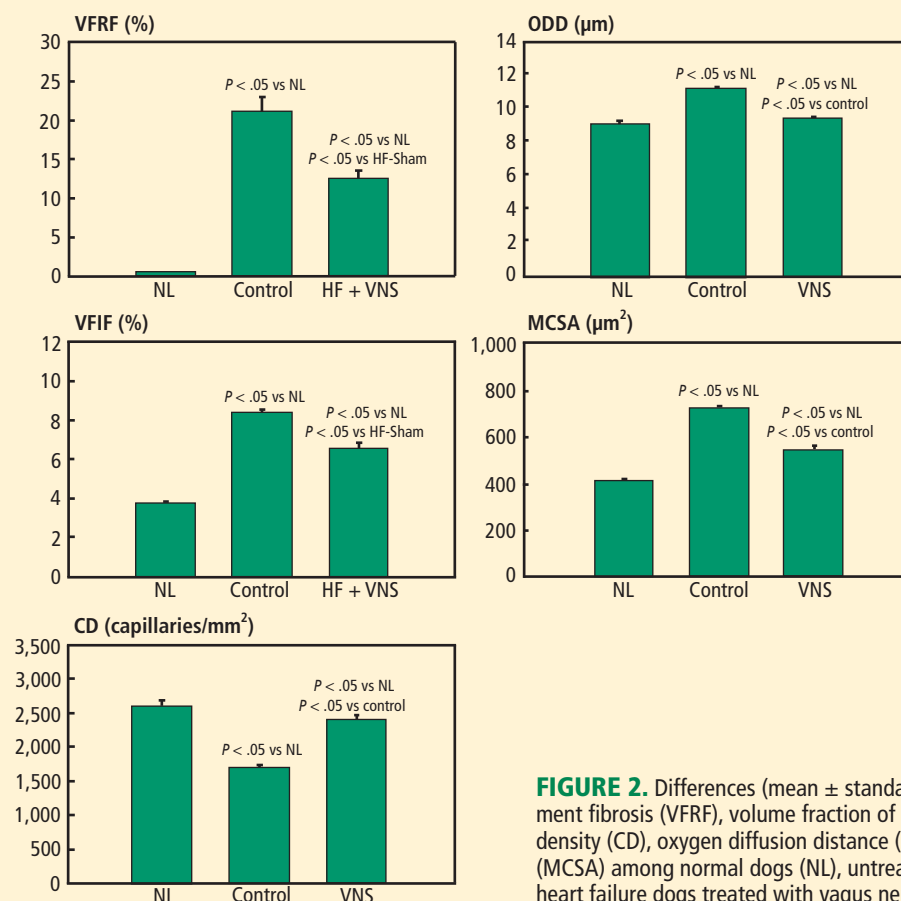
**FIGURE 2.** Differences (mean ± standard error) in volume fraction of replacement fibrosis (VFRF), volume fraction of interstitial fibrosis (VFIF), capillary density (CD), oxygen diffusion distance (ODD), and myocyte cross-sectional area (MCSA) among normal dogs (NL), untreated heart failure dogs (control), and heart failure dogs treated with vagus nerve stimulation (VNS).[33]

cardiomyopathic phenotype, heart block, and sudden cardiac death.[24]

**nNOS.** nNOS has been shown to be upregulated in the human failing heart and in rats following myocardial infarction.[25] In rats with HF, inhibition of nNOS leads to increased sensitivity of the myocardium to beta-adrenergic stimulation,[26] suggesting a role for nNOS in the autocrine regulation of myocardial contractility.[26]

In dogs with coronary microembolization-induced HF, mRNA and protein expression of eNOS in LV myocardium is significantly downregulated compared with normal dogs; therapy with VNS significantly improves the expression of eNOS **(Table 3)**.[27] Both iNOS and nNOS are significantly upregulated, and their expression tends to be normalized by long-term VNS therapy.[27]

Gap junction proteins or connexins are reduced or redistributed from intercalated disks to lateral cell borders in a variety of cardiac diseases, including HF.[28] This so-called "gap junction remodeling" is considered highly arrhythmogenic. In mammals, gap junctions exclusively contain connexin-43 (Cx43). Reduced expression of Cx43 occurs in the failing human heart and has been shown to result in slowed transmural conduction and dispersion of action potential duration with increased susceptibility to arrhythmia and sudden cardiac death.[29,30] In dogs with coronary microembolization-induced HF, mRNA and protein expression of Cx43 in LV myocardium was shown to be markedly downregulated compared with normal dogs, and long-term therapy with VNS was associated with a significant increase in the expression of Cx43 in LV myocardium **(Table 3)**.[31]

### ■ VNS IN DOGS WITH RAPID PACING–INDUCED HEART FAILURE

Electrical VNS as a potential therapy for HF was examined in dogs with HF secondary to high-rate ventricular pacing using the Cyberonics VNS system (Cyberonics Inc., Houston, TX), which does not operate on a negative feedback mechanism.[15] In this

**TABLE 3**

**mRNA expression of proinflammatory cytokines, NOS, and connexin-43 in LV myocardium of normal (NL) dogs, untreated HF dogs (Control), and HF dogs treated with VNS[21,27,33]**

|  | NL (n = 6) | Control (n = 6) | VNS (n = 7) |
|---|---|---|---|
| TNF-$\alpha$ (du) | 173 ± 14 | 399 ± 12* | 202 ± 21† |
| IL-6 (du) | 75 ± 9 | 246 ± 23* | 116 ± 19† |
| eNOS (du) | 1.44 ± 0.15 | 0.51 ± 0.02* | 0.90 ± 0.03† |
| iNOS (du) | 1.68 ± 0.15 | 4.05 ± 0.14* | 2.69 ± 0.28† |
| nNOS (du) | 1.55 ± 0.11 | 4.41 ± 0.52* | 1.98 ± 0.20† |
| Cx43 (du) | 218 ± 16 | 11 ± 2* | 106 ± 5† |

Cx43 = connexin-43; du = densitometric units; eNOS = endothelial nitric oxide synthase; HF = heart failure; IL-6 = interleukin-6; iNOS = inducible nitric oxide synthase; LV = left ventricular; nNOS = neuronal nitric oxide synthase; TNF-$\alpha$ = tumor necrosis factor-alpha; VNS = vagus nerve stimulation.

* $P < .05$ vs NL; † $P < .05$ vs control.

study, VNS therapy was delivered continuously for the duration of the study with a duty cycle of 14 seconds on and 12 seconds off. VNS signals were delivered to the right cervical vagus nerve at a frequency of 20 Hz and a pulse width of 0.5 msec.[15] Dogs were randomized to control (n = 7) or to monotherapy with VNS (n = 8) and followed for 8 weeks. All measurements were made approximately 15 minutes after temporarily turning off the ventricular pacemaker and the vagus nerve stimulator.[15] VNS therapy resulted in a significant decrease in LV end-diastolic and end-systolic volumes and a significant increase in LV ejection fraction compared with controls.[15] This improvement was associated with significant reduction in plasma levels of norepinephrine, angiotensin II, and C-reactive protein. The study also demonstrated the effectiveness of VNS in restoring baroreflex sensitivity, thus improving cardiac autonomic control.[15] Because rapid pacing was maintained throughout the study except for short periods when measurements were made, one can argue that the benefits of VNS therapy in this model of HF are independent of heart rate.[15]

### ■ SAFETY AND TOLERABILITY OF VNS IN PATIENTS WITH ADVANCED HEART FAILURE

In patients with HF, reduced vagal activity is associated with increased mortality.[1] Vagal withdrawal has also been shown to precede episodes of acute decompensation.[32] In a recently published study, De Ferrari et al, on behalf of the CardioFit Multicenter Trial

Investigators, examined the safety and tolerability of chronic VNS in 32 patients with symptomatic HF and severe LV dysfunction using the CardioFit system.[16] The CardioFit system used in this study differed from that used in dogs with microembolization-induced HF in that it did not operate on a negative feedback principle. A bradycardia limit causing interruption of VNS was set at 55 beats/min. A 3-week uptitration period was used to maximize current amplitude and duty cycle based on patient sensation. The intensity of the stimulation reached 4.1 ± 1.2 mA at the end of the titration period.[16]

This multicenter, open-label, phase 2 trial involved 3 to 6 months of followup with an optional 1 year followup. The results suggested that VNS may be safe and tolerable in HF patients with severe LV dysfunction. Trends for efficacy were also favorable, bearing in mind the nonrandomized and unblinded nature of the study design. The study showed significant improvements in New York Heart Association HF classification, 6-minute walk test, LV ejection fraction, and LV systolic volumes.[16]

### ■ CONCLUSIONS

A wealth of preclinical and clinical studies supports the concept that electrical VNS can favorably modify the underlying pathophysiology and course of evolving HF. In animals with HF, VNS improves LV function, attenuates LV remodeling and may prevent arrhythmias that provoke sudden cardiac death. VNS derives these potential clinical benefits from multiple mechanisms of action that include reduced heart rate and normalization of sympathetic overdrive. VNS also appears to have a favorable impact on other signaling pathways that are likely to elicit beneficial effects in patients with HF. These include restoration of baroreflex sensitivity, suppression of proinflammatory cytokines, normalization of NO signaling pathways, and suppression of gap junction remodeling. At present, there is no evidence to implicate a single mechanism of action for the benefits derived from VNS. Instead, it is likely that all of the mechanisms listed above act in concert to elicit the global benefit seen with VNS. In humans with HF, VNS may be safe, feasible, and apparently well tolerated. Full appreciation of its efficacy in treating chronic HF must await completion of pivotal randomized clinical trials.

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