Chronic Vagus Nerve Stimulation Improves Autonomic Control and Attenuates Systemic Inflammation and Heart Failure Progression in a Canine High-Rate Pacing Model

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Background—Autonomic dysfunction, characterized by sympathetic activation and vagal withdrawal, contributes to the progression of heart failure (HF). Although the therapeutic benefits of sympathetic inhibition with β-blockers in HF are clear, the role of increased vagal tone in this setting has been less studied. We have investigated the impact of enhancing vagal tone (achieved through chronic cervical vagus nerve stimulation, [VNS]) on HF development in a canine high-rate ventricular pacing model.

Methods and Results—Fifteen dogs were randomized into control (n=7) and VNS (n=8) groups. All dogs underwent 8 weeks of high-rate ventricular pacing (at 220 bpm for the first 4 weeks to develop HF and another 4 weeks at 180 bpm to maintain HF). Concomitant VNS, at an intensity reducing sinus rate ~20 bpm, was delivered together with the ventricular pacing in the VNS group. At 4 and 8 weeks of ventricular pacing, both left ventricular end-diastolic and -systolic volumes were lower and left ventricular ejection fraction was higher in the VNS group than in the control group. Heart rate variability and baroreflex sensitivity improved in the VNS dogs. Rises in plasma norepinephrine, angiotensin II, and C-reactive protein levels, ordinarily expected in this model, were markedly attenuated with VNS treatment.

Conclusions—Chronic VNS improves cardiac autonomic control and significantly attenuates HF development in the canine high-rate ventricular pacing model. The therapeutic benefit of VNS is associated with pronounced anti-inflammatory effects. VNS is a novel and potentially useful therapy for treating HF. (Circ Heart Fail. 2009;2:692-699.)

Key Words: autonomic nervous system • vagus nerve • vagus nerve stimulation • heart failure

A utonomic nervous system dysfunction, characterized by sympathetic activation and vagal withdrawal, is an important contributor to the progression of heart failure (HF)1-3. Extensive research has helped to define the role of sympathetic activation in HF4-7 and established the role of β-blockers as a beneficial therapeutic approach.8-10 Less attention has been paid to the role of vagal control. Clinical trials have demonstrated that diminished cardiac vagal activity and increased heart rate are predictors of a high mortality rate in HF,11,12 suggesting a detrimental role for vagal withdrawal in HF. Despite these findings, it remains unclear whether enhancing vagal control by cervical vagus nerve stimulation (VNS) can improve cardiac autonomic balance and favorably affect the clinical and neurohumoral or inflammatory aspects of HF.

Clinical Perspective on p 699

Normal function of the autonomic nervous system depends on the balance of sympathetic and vagal control, which is essential for maintaining hemodynamic homeostasis.13 Theoretically, the autonomic dysfunction in HF can be corrected or restored by enhancing vagal control. Improving vagal control by VNS may counteract sympathetic activation and its associated norepinephrine (NE) release, resulting in improved autonomic control. VNS can also reduce activity in the renin-angiotensin-aldosterone system.14,15 Inhibition of the renin-angiotensin-aldosterone system has been shown to be beneficial in HF treatment.16,17 Indeed, chronic VNS has been demonstrated to prolong survival in a rat myocardial infarction model.18 Moreover, early clinical data showed promising results of chronic VNS therapy in patients with advanced HF.19 This study was designed to test the hypothesis that enhanced vagal control achieved by chronic electric VNS can improve autonomic balance and attenuate HF development in a canine high-rate ventricular pacing-induced HF model.

Methods

Experiments were performed on 15 adult mongrel dogs (both sexes, body weight 22 to 27 kg). All dogs were implanted with a right
ventricular pacemaker and were randomized into control (n=7) and VNS (n=8) groups. A right cervical vagus nerve stimulator was implanted in VNS group dogs. The study was approved by the Institutional Animal Care and Use Committee and is in compliance with the “Guide for the Care and Use of Laboratory Animals” published by the National Institutes of Health.

**Implantation of Devices**

Following standard procedures, all dogs were anesthetized with thiopental (20 mg/kg IV), intubated, ventilated, followed by gaseous anesthesia (1% to 2% isoflurane/O2) using an Integra II SP Anesthesia Machine (DRE Inc, Louisville, Ky). Standard surface ECG leads (I, II, and III) were monitored continuously throughout the surgery. Body temperature was monitored with a rectal probe, and an electric heating pad under the animal and operating room lamps were used to maintain a body temperature of 36°C to 37°C.

Under sterile conditions, all dogs were implanted with a right ventricular pacemaker. Briefly, a bipolar screw-in endocardial pacing lead (model Tendril 1688TC/58 cm, St. Jude Medical, Inc, Sylmar, Calif) was implanted in the right ventricular apex through the right jugular vein under fluoroscopic guidance. The lead was connected to a custom high-rate pacemaker (St. Jude Medical), which can deliver high-rate ventricular pacing suitable for induction of HF.

Dogs in the VNS group were implanted with a right cervical vagus nerve stimulator. The right cervical vagus nerve was isolated, and a cervical VNS electrode (Cyberonics Inc, Houston, Tex) was placed around the nerve. The electrode was connected to a nerve stimulator (Cyberonics Inc). Both the right ventricular pacemaker and the nerve stimulator were buried in pockets at the neck area. A telemetric device (TL11-M2-D70-PCT, Data Sciences International, DSL, St. Paul, Minn) was implanted for monitoring ECG, blood pressure, and temperature, as described previously.

Animals were given a 2-week recovery period after device implantation. Standard postoperative care was performed daily until the incisions were healed.

**Initiation of High-Rate Ventricular Pacing and VNS Therapy**

After recovery from devices implantation, all dogs underwent 8 weeks of high-rate ventricular pacing. For the first 4 weeks, the pacing rate was set at 220 bpm to develop HF; the ventricular pacing rate was then reduced to 180 bpm for an additional 4 weeks. The pacing intensity was set at 3 times the threshold. This protocol rate was then reduced to 180 bpm for an additional 4 weeks. The ventricular pacing was verified daily by auscultation or palpitation. If there was any doubt, ventricular capturing was verified by ECG monitoring. There was no need for pacing intensity adjustments in these experiments.

**Animal Status Monitoring**

Animals were monitored daily. Because there are no generally accepted objective criteria for assessing the degree of pain or discomfort in animals, we followed accepted recommendations based on recognition of a departure from normal behavior and/or appearance of the animals. Any noticeable behavioral changes, including activity, appetite, and/or any signs of pain and distress in the animals were recorded on the animal’s log chart by our technician and the Biological Resource Unit staff personnel.

**Conscious Testing and Data Acquisition**

Data were acquired at 3 points in all dogs: baseline data before initiation of ventricular pacing, at 4 weeks of high-rate ventricular pacing, and at 8 weeks of high-rate pacing.

Data acquisition was performed in a dedicated conscious testing room, where dogs were lying on a coach in a quiet, dim-lighted environment, without any sedation or anesthesia. All data were acquired with the animals in a sinus rate by temporarily turning off both the ventricular pacemaker and the vagus nerve stimulator (in the VNS group), to permit spontaneous sinus rhythm to return. After a stabilization period of ≥15 minutes, the following data were acquired: echocardiography, ECG recording (for Heart Rate Variability [HRV] analysis), blood samples, and baroreflex sensitivity tests.

**Echocardiography**

Transthoracic 2-dimensional echocardiography was performed in the conscious state, with dogs lying in the left lateral decubitus position. Standard 2-dimensional short- and long-parasternal views, as well as 4-chamber, 2-chamber, and 3-chamber apical views were obtained in a standard manner using a 38 transducer coupled to a Vivid 7 echocardiographic machine (GE Medical, Milwaukee, Wis). Left ventricular (LV) end-diastolic, end-systolic volumes, and ejection fraction were measured by using a Simpson’s biplane equation. All volumes were measured in triplicate with averages reported.

**HRV**

According to the guidelines, both standard time and frequency domain HRV parameters were calculated from the 5-minute ECG data by means of custom written software. The time domain parameters include the standard deviation of the normal-to-normal intervals and the square root of the mean squared differences of successive normal-to-normal intervals.

For the frequency domain analysis, fast Fourier transform power spectrum was calculated with the method of Welch’s periodogram. The original tachogram (RR interval durations versus their consecutive number in a 5-minute recording) was first interpolated and then divided in 50%-overlapping segments of 128 intervals. After windowing (applying a Hamming window to each segment to account for boundary effects) and mean value subtraction, the discrete Fourier transform of each segment was computed. The resulting periodograms were averaged. Power within specific bands was calculated by integration of the area under the averaged power spectrum density curve. Specifically, we calculated low-frequency power (from 0.04 to 0.15 Hz), high-frequency power (0.15 to 0.40 Hz) in normalized units, and the ratio of low-frequency power to high-frequency power.

**Baroreflex Sensitivity Test**

Baroreflex sensitivity testing was performed according to methods described previously. Before testing, ventricular pacing was turned off to permit return of a spontaneous sinus rhythm. Heart rate and blood pressure were continuously monitored and recorded using the telemetry system. Dogs were given bolus injections of phenylephrine (10 μg/kg) to raise systolic arterial blood pressure by 30 to 50 mm Hg. Each RR interval was plotted as a function of the preceding systolic blood pressure. A linear regression analysis of these points was performed, and a regression coefficient (slope) was calculated. The slope was accepted only if the correlation coefficient was ≥0.8. At least 3 such measurements were performed, and the average of these slopes was taken as the baroreflex sensitivity (in ms/mm Hg).

**Biochemical Assay**

Venous blood samples were collected in ice-chilled tubes coated with EDTA (BD Vacutainer K2E, BD Diagnostics, Franklin Lakes, NJ). For angiotensin (Ang)-II samples, the aminopeptidase inhibitor bestatin (80 μL, Alpco, Salem, NH) was preadded to the tubes. Plasma was separated after centrifugation at 3000 rpm for 15 minutes in a refrigerated centrifuge at 4°C (Model 5702 RH, Hettich, Sylmar, Calif) and stored at −80°C for later analysis. Each sample was assayed in duplicate. Plasma levels of Ang-I, Ang-II, Ang-(1-7), and renin were determined using ELISA kits.
Plasma C-reactive protein (CRP, a systemic inflammatory marker) level was measured using a canine-specific high sensitivity CRP ELISA (KT-093, Kamiya Biomedical Company, Seattle, Wash), per the manufacturer’s directions. Samples were first diluted 1:1000. The assay detection range is 3.125 to 200 ng/mL.

Plasma NE concentrations were determined by a validated radioimmunoassay method supplied by American Laboratory Products Company (17-NORHU-R50, ALPCO, NH), and plasma was processed for radioimmunoassay method according to the manufacture’s published procedure. In brief, noradrenaline is extracted using a cis-diol-specific affinity gel and acylated to N-acylnoradrenaline and then converted enzymatically during the detection procedure into N-acylnormetanephrine; thereafter, using a specific antibody, standard radioimmunoassay method techniques are used. Plasma Ang-II contents were determined using a validated radioimmunoassay method supplied by American Laboratory Products (01-RK-A22, ALPCO). The plasma was processed and assayed using an antibody highly specific for Ang-II.

Statistical Analysis
Data are expressed as mean ± SD where appropriate. Data between the 2 groups at different points were compared using the 2-factor repeated-measures ANOVA with contrast analysis. The data analysis was performed with the use of statistical software (STATISTICA version 5.1, StatSoft Inc, Tulsa, Okla). Proper data transformations (logarithmic or square root) were performed before analysis for nonnormal distributed data. Unless otherwise specified, all statistical tests were 2-sided, and a P < 0.05 was required for statistical significance.

The authors had full access to the data and take responsibility for its integrity. All authors have read and agreed to the manuscript as written.

Results

VNS Effects on LV Function and Systemic Blood Pressure
All dogs in both the control and the VNS groups completed the 8-week experimental period. As shown in Figure 1, baseline LV function was comparable in control and VNS-treated dogs. However, at both 4 and 8 weeks of ventricular pacing, the LV end-diastolic and -systolic volumes were lower, and the LV ejection fraction was higher in the VNS group compared with the control group (all P < 0.05).

Systemic blood pressure at baseline and at 4 and 8 weeks pacing is shown in Figure 2. VNS did not affect systemic blood pressure level.

Prominent ascites was apparent in 3 of the control dogs, whereas no dogs in the VNS group had noticeable ascites.

VNS Effects on HRV
As shown in the Table, baseline HRV parameters were comparable between groups. At 4 and 8 weeks of ventricular pacing, the sinus cycle length was slightly longer (slower sinus rate) in the VNS group than that in the control group, but the difference was not statistically significant. Both time domain parameters (standard deviation of the normal-to-normal and the square root of the mean squared differences of successive NN intervals) were higher in VNS dogs than that in the control dogs (both P < 0.05). In the frequency domain, the low-frequency power was lower and high-frequency power was higher in the VNS dogs (both P < 0.05). The LF/HF ratio was lower in the VNS group dogs, although statistical significance was reached only at 4-week pacing. Taken together, HRV data indicate that VNS treatment enhanced the vagal control and autonomic balance compared with that in the control dogs.
VNS Effects on Baroreflex Sensitivity

Figure 3 (upper panel) shows an original telemetric ECG and blood pressure tracing recorded during baroreflex testing. After a bolus injection of phenylephrine (10 μg/kg), the resultant blood pressure increase was associated with prolongation of subsequent RR intervals, as expected.

On average, the baseline baroreflex sensitivity was similar in the 2 groups (Figure 3, lower panel). However, at both 4 and 8 weeks of pacing, baroreflex sensitivity was higher in the VNS dogs than in the control dogs (P<0.05).

VNS Effects on Plasma CRP, NE, and Ang-II Levels

As shown in Figure 4, plasma CRP levels increased significantly after high-rate ventricular pacing. VNS therapy markedly attenuated the increase in plasma CRP levels at both 4- and 8-week pacing (Figure 4, upper panel, P<0.05).

Plasma NE levels also increased after 4- and 8-week pacing. However, the levels were lower in the VNS group compared with that in the control group (Figure 4, middle panel, P<0.05).

Table. Time and Frequency Domain Heart Rate Variability Parameters in Control and Chronic VNS-Treated Dogs

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Baseline</th>
<th>4-wk Pacing</th>
<th>8-wk Pacing</th>
</tr>
</thead>
<tbody>
<tr>
<td>RR, ms</td>
<td>Control</td>
<td>VNS</td>
<td>Control</td>
</tr>
<tr>
<td></td>
<td>510.7±77.0</td>
<td>514.5±61.5</td>
<td>394.8±36.7</td>
</tr>
<tr>
<td>SDNN, ms</td>
<td>84.2±21.7</td>
<td>86.6±21.8</td>
<td>23.2±5.9</td>
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<tr>
<td>RMSSD, ms</td>
<td>68.9±10.6</td>
<td>69.3±17.2</td>
<td>17.0±4.6</td>
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<tr>
<td>LF, norm</td>
<td>35.2±12.5</td>
<td>36.2±12.3</td>
<td>72.1±8.6</td>
</tr>
<tr>
<td>HF, norm</td>
<td>64.8±12.5</td>
<td>63.8±12.3</td>
<td>27.9±8.6</td>
</tr>
<tr>
<td>LF/HF</td>
<td>0.70±0.33</td>
<td>0.63±0.34</td>
<td>3.03±1.79</td>
</tr>
</tbody>
</table>

SDNN indicates the standard deviation of the normal-to-normal (NN) intervals; RMMSD, the square root of the mean squared differences of successive NN intervals; LF, low-frequency power; HF, high-frequency power. Frequency domain parameters (LF, HF, and LF/HF) were logarithmic-transformed before the tests.

*P<0.05 compared with the control.

Figure 3. The upper panel shows an example of blood pressure and ECG traces recorded using the DSI telemetric device during baroreflex sensitivity test. The lower panel shows the average data at baseline, at 4- and 8-week ventricular pacing in control and VNS-treated dogs. *P<0.05 versus control group. W indicates week; VNS, vagus nerve stimulation.
We have studied the effects of chronic cervical VNS on cardiac autonomic control and HF development in a canine high-rate ventricular pacing model. VNS treatment significantly improved cardiac autonomic control and attenuated HF development. The VNS effect on HF is heart rate-independent in this model, because high-rate ventricular pacing was used to induce HF, and the pacing rate was not affected by VNS. In addition to the improved autonomic control (reflected by increased HRV, baroreflex sensitivity, and reduced plasma NE level), VNS treatment was also associated with reduced plasma CRP and Ang-II levels. Although it is known that inhibition of the renin-angiotensin-aldosterone system is beneficial in HF, the beneficial anti-inflammatory effect of cervical VNS during HF development has been less well studied.

**Autonomic Dysfunction in HF**

Activation of the sympathetic nervous system in patients with HF has been studied intensively, supporting the concept that sympathetic activation contributes significantly to the disease. Increased plasma NE levels and increased cardiac sympathetic nerve activity have been demonstrated in HF. Plasma NE concentration is elevated even in patients with asymptomatic LV dysfunction and increases further with the progression to overt HF. In patients with HF, total body NE spillover is doubled and cardiac NE spillover is increased 5- to 8-fold. The extent of elevation of NE concentration in patients with HF correlates directly with the severity of the LV dysfunction and inversely correlates with prognosis. The pathophysiological role of sympathetic activation in HF is highlighted by the beneficial effects of β-blocker therapy in this condition.

Both clinical and experimental data indicate diminished vagal control of the heart in HF. Functional withdrawal of parasympathetic activity exists even during the early stages of HF. With disease progression, vagal control of the heart is markedly reduced and cannot be significantly elicited even by strong reflex activation. Thus, the autonomic balance shifts from primarily vagal tone to sympathetic predominance in HF. Chronic withdrawal of vagal tone has been strongly associated with an increased risk of sudden death and arrhythmia. Patients with preserved vagal control have a lower risk of arrhythmia, independent of sympathetic activity. Impaired cardiac vagal activity is associated with a high incidence of sudden death in patients with HF. The Autonomic Tone and Reflexes After Myocardial Infarction and the Cardiac Insufficiency Bisoprolol II studies demonstrated that diminished cardiac vagal activity and increased heart rate were predictors of high mortality rate in HF. These data suggest a detrimental role for vagal withdrawal in HF as well.

**Therapeutic Effects of VNS in HF**

Theoretically, autonomic dysfunction (sympathetic activation and vagal withdrawal) in HF can be corrected or restored by inhibiting the sympathetic activity or enhancing the vagal control. Although the beneficial effect of sympathetic inhibition with β-blockers is clear, the effect of enhancing vagal tone on HF status has been less well investigated.
Studies have shown that increasing vagal tone by VNS has benefits in preventing ischemic arrhythmias and in treating coronary artery disease.\textsuperscript{36–38} In conscious dogs with an anterior myocardial infarction, Vanoli et al\textsuperscript{17} demonstrated that VNS significantly decreased ventricular fibrillation inducibility (from \approx 90\% to only 10\%). Further, VNS prolonged survival in a rat myocardial infarction model.\textsuperscript{18} A recent clinical observation showed promising clinical results of chronic VNS in patients with HF.\textsuperscript{19} Our results indicate that chronic VNS treatment attenuated the development of HF and produced significant therapeutic effects in a high rate ventricular pacing HF model. At both 4- and 8-week pacing, the LV end-diastolic volume and LV end-systolic volume were lower, and LV ejection fraction was higher in the VNS group compared with that in the control group (Figure 1). Improved function was associated with improved cardiac autonomic control, as demonstrated by HRV parameters, baroreflex sensitivity tests, and lower plasma NE levels. Thus, our data provide further detailed evidence of the beneficial effects of VNS in HF.

Possible Mechanisms Underlying the Effects of VNS in HF

VNS acutely evokes negative chronotropic, dromotropic, and inotropic effects on the heart. However, these acute effects cannot explain the observed beneficial effect of chronic VNS in HF. Current evidence suggests that the therapeutic effects of chronic VNS in HF may be mediated by the following pathways:

Improved autonomic balance: Vagal control of the heart is diminished in HF and dysfunctional ganglionic transmission may contribute to this abnormality.\textsuperscript{20} Defective ganglionic transmission has been reported to be prevented by repeated exposure with a nicotinic (N-) receptor agonist during the development of HF.\textsuperscript{40} Thus, VNS, by releasing acetylcholine, the natural N-receptor agonist, may prevent ganglionic malfunction in HF and improve autonomic control. Here, we have provided evidence that chronic VNS improved cardiac autonomic balance in HF as evidenced by increased HRV, baroreflex sensitivity, and reduced NE level in the VNS-treated dogs. Thus, improved autonomic balance is a likely contributor to the observed benefits.

VNS may inhibit the renin-angiotensin system: Vagal afferents from the cardiopulmonary region are reported to exert a tonic restraint on the release of renin.\textsuperscript{14} Vagal blockade significantly increased plasma renin activity in HF dogs.\textsuperscript{15} Our results show that VNS treatment reduced plasma Ang-II levels. Thus, inhibition of the renin-angiotensin system by VNS is an additional therapeutic pathway.

VNS has anti-inflammatory effects: VNS can suppress systemic inflammatory response through “the cholinergic anti-inflammatory pathway.”\textsuperscript{41–42} Our results clearly indicate that pacing induced HF promotes systemic inflammation, as evidenced by increased plasma CRP levels. VNS treatment markedly reduced CRP levels. VNS mediated inhibition of the inflammatory processes likely provide important benefits in HF treatment.\textsuperscript{43,44}

In addition, VNS may also have antioxidant effects.\textsuperscript{45} We have not evaluated this role in HF treatment yet.

Clinical Implication and Study Limitations

Our results show that chronic VNS improves cardiac autonomic control and attenuates HF development in a canine high-rate pacing model. Chronic VNS, by improving vagal control, may provide a novel therapeutic approach by which we can improve autonomic balance and HF treatment. Indeed, early clinical data provided some promising results of VNS therapy in patients with HF.\textsuperscript{19}

Because clinically pure tachycardia-induced HF likely constitutes only a small fraction of patients, the high-rate pacing model used in our study may have limited clinical counterpart. However, a similar autonomic malfunction has been demonstrated in this particular animal model and in patients with HF.\textsuperscript{1} Thus, knowledge gained from these animal experiments likely provides useful information to guide future clinical explorations.

A few technical limitations should be acknowledged. First, VNS was initiated simultaneously with rapid ventricular pacing. It may represent therefore a preventive or ameliorative measure rather than standard treatment. In addition, the effect of VNS treatment was tested in this study using a ventricular rapid-pacing model; it remains to be determined whether similar approach might influence HF development when rhythm is not accelerated. Second, the baroreflex sensitivity was evaluated only by phenylephrine injection; no vasodilators were used. Third, the blood pressures were obtained during the conscious testing when the ventricular pacing and the VNS were turned off. No data were acquired during ventricular pacing, or with VNS.

Although the side effects associated with chronic VNS were generally mild, because of the nature of animal studies, it is difficult to evaluate all potential side effects. Furthermore, the precise causes of some side effects are difficult to judge in animals. For example, whether reduced food intake in 3 animals was due exclusively to discomfort caused by VNS or was due to reduced appetite is not known. Similarly, prolapse of the third eyelid noticed in 2 animals may have been unique to those animals, and extrapolation to humans is obviously difficult. Clearly, the potential side effects associated with chronic VNS will eventually need to be addressed in patients. As an FDA-approved therapy, VNS has already been applied clinically in patients with drug-resistant epilepsy or depression.\textsuperscript{46} Thus, the clinical tolerability of chronic VNS seems likely.

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Disclosures

None.

References


CLINICAL PERSPECTIVE

Autonomic dysfunction, characterized by sympathetic activation and vagal withdrawal, contributes to the progression of heart failure (HF). The therapeutic benefits of sympathetic inhibition with β-blockers in HF have been established; however, the role of increased vagal tone in this setting has been less studied. We have investigated the impact of enhancing vagal tone (achieved through chronic cervical vagus nerve stimulation [VNS]) on HF development in a canine high-rate ventricular pacing model. It was found that chronic VNS treatment, at an intensity reducing spontaneous sinus rate by ∼20 bpm, significantly attenuated HF development in this animal model. The beneficial effect of VNS therapy was associated with an improved autonomic balance, reflected in increased heart rate variability, and baroreflex sensitivity. VNS therapy also reduced plasma norepinephrine and angiotensin II levels. In addition, VNS treatment significantly reduced plasma C-reactive protein (an inflammation marker) levels. Thus, we concluded that chronic VNS improves cardiac autonomic control and significantly attenuates HF development in the canine high-rate ventricular pacing model. Improving vagal control by VNS may provide a novel and potentially useful therapy in HF.