Vagal Nerve Stimulation: Basic Science and Experimental Studies

Optimal Titration Is Important to Maximize the Beneficial Effects of Vagal Nerve Stimulation in Chronic Heart Failure

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ABSTRACT

Background: Although vagal nerve stimulation (VNS) benefits patients with chronic heart failure (CHF), the optimal dose of VNS remains unknown. In clinical trials, adverse symptoms limited up-titration. In this study, we evaluated the impact of various voltages of VNS which were titrated below symptom threshold on cardiac function and CHF parameters in rat myocardial infarction (MI) models.

Methods and Results: We randomly allocated MI rats to vagal (VNS; n = 41) and sham (Sham; n = 16) stimulation groups. We stimulated the right vagal nerve with 20 Hz at 3 different voltages for 4 weeks. We defined Max as the highest voltage that did not evoke any symptom, Half as one-half of Max, and Quarter as one-fourth of Max. All 3 VNS groups significantly reduced biventricular weight compared with Sham ($P < .05$). In contrast, only Half decreased left ventricular (LV) end-diastolic pressure (Half: 17.5 ± 2.0 mm Hg; Sham: 24.2 ± 1.2 mm Hg; $P < .05$) and increased LV ejection fraction (Half: 37.9 ± 3.1%; Sham: 28.4 ± 2.3%,-$P < .05$) and LV maximum +dP/dt (Half: 5918.6 ± 2.0 mm/Hg/s; Sham: 5001.2 ± 563.2 mm Hg/s; $P < .05$). The number of large vagal nerve fibers was reduced with Max (Max: 163.1 ± 43.0 counts/bundle; Sham: 360.0 ±61.6 counts/bundle; $P < .05$), indicating significant neural damage by VNS.

Conclusion: The optimal titration of VNS would maximize benefits for CHF and minimize adverse effects. (*J Cardiac Fail 2016;22:631–638*)

Key Words: Vagal nerve stimulation, Chronic heart failure, Myocardial infarction.

Chronic heart failure (CHF) has a poor prognosis and is a major public health concern. Although new therapeutic strategies for CHF have been proposed in the past decades, approximately one-half of CHF patients die within 5 years.[1] Because the imbalance between sympathetic and parasympathetic nervous systems plays a major role in the pathogenesis of CHF,[2] there is increasing clinical interest in neuromodulation therapy to alter the autonomic imbalance.

Since Li et al[3] reported that vagal nerve stimulation (VNS) markedly improved the survival of CHF rats, many nonhuman animal studies have shown the favorable effects of VNS on CHF, such as decreases in heart rate and oxygen consumption,[4] reduction in inflammation through activation of nicotinic receptors,[5] attenuation of norepinephrine spillover in the left ventricle (LV),[6] suppression of free radical generation,[7] and sympatho-inhibition by activating the afferent arm.[8] Subsequent to these nonhuman studies, a few clinical trials of VNS therapy for CHF were conducted, but the

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outcomes were inconsistent.[9–11] Thus the efficacy of VNS for CHF in humans remains controversial. A nonrandomized clinical trial exploring VNS in 32 New York Heart Association functional class II–IV CHF patients found that VNS improved quality of life, exercise capacity, and LV ejection fraction (LVEF).[9] In contrast, the 1st randomized sham-controlled trial that investigated right-sided VNS for CHF patients (NECTAR-HF) failed to demonstrate significant beneficial effects on cardiac remodeling or functional capacity.[10] The results of NECTAR-HF raised many questions, such as patient selection, synergistic effects of medications, and the setting of electrical stimulation. In particular, incomplete understanding of the appropriate dosing of VNS makes it difficult to maximize the beneficial effects while minimizing the adverse effects.

In nonhuman studies, the doses of VNS were chosen at levels that reduce heart rate.[3] In contrast, the clinical trials showed that VNS-induced symptoms limited up-titration of the stimulating dose; consequently heart rate was not reduced in most cases.[9,10] On the other hand, a recent investigation in dogs revealed that VNS improved CHF independently from heart rate reduction.[12,13] This finding suggests that the heart rate–guided up-titration of VNS may be unnecessary and unrealistic in humans. To prove this hypothesis, we need to examine whether VNS below the symptom threshold yields any improvement in CHF. In the present study, we investigated the impact of subthreshold VNS that did not induce either symptoms or heart rate reduction on cardiac function and CHF parameters in rats.

Methods

Experiments and animal care were approved by the Committee on Ethics of Animal Experiment, Kyushu University Graduate School of Medical Sciences. The investigation conforms to the Guide for the Care and Use of Laboratory Animals published by the US National Institutes of Health (NIH publication no. 85-23, revised 1985).

Animal Preparation

We anesthetized 8-week-old male Sprague-Dawley rats (SLC, Japan) with a mixture of isoflurane in oxygen-enriched air. We ligated the left anterior descending coronary artery to create a large myocardial infarction (MI). One week after ligation, we performed echocardiography (SSA-380A; Toshiba, Japan) under anesthesia.[14] Rats with dilated LVs (LV diastolic dimension ≥9.5 mm) and reduced LVEF were included in subsequent experiments (Table 1). We attached a pair of stainless steel electrodes to the right vagal nerve at the neck level and implanted a pulse generator (ANRE-100; Anpex, Japan) to stimulate the vagal nerve. We also implanted a telemetry system (TA11PA-C40; Data Sciences International, USA) and inserted the pressure-sensing catheter in the abdominal aorta to record heart rate (HR) and blood pressure (BP).

Table 1. Body Weight (BW) and Echocardiographic Measurements at Baseline

Measurement	Sham	Quarter	Half	Max
BW, g	275.5 ± 4.8	264.4 ± 7.7	278.2 ± 4.7	268.8 ± 8.4
LVDd, mm	9.7 ± 0.1	9.6 ± 0.1	9.8 ± 0.1	9.6 ± 0.1
LVDs, mm	7.9 ± 0.2	7.9 ± 0.1	8.0 ± 0.2	7.9 ± 0.1
LVEF, %	41.8 ± 1.9	41.7 ± 1.8	42.0 ± 1.4	41.6 ± 1.8

Data are expressed as mean ± SEM. In each parameter (BW, LVDd, LVDs, and LVEF), there were no significant differences among the 4 groups. LVDd, left ventricular end-diastolic dimension; LVDs, left ventricular end-systolic dimension; LVEF, left ventricular ejection fraction. Sham, sham stimulation; Quarter, one-fourth of Max; Half, one-half of Max; Max, voltage just below the symptom threshold.

Protocol and Titration of VNS

One week after implantation, we randomized the rats into a VNS group (n = 41) and a sham group (Sham; n = 16). The VNS groups were divided into 3 groups depending on the voltage of VNS.

We determined the symptom threshold by observing symptoms such as respiratory twitching and abnormal behavior while changing the voltage of VNS. We defined the maximum voltage as the voltage just below the threshold (Max; n = 14). We defined the half-maximum voltage as one-half of Max (Half; n = 13) and quarter-maximum voltage as one-fourth of Max (Quarter; n = 14). Figure 1 shows the representative HR response of a rat during titration of VNS. VNS at Max, Half, and Quarter did not reduce HR during VNS. The voltage just above Max evoked symptoms in all rats without HR reduction, whereas a higher voltage (Max + 0.5 V) significantly reduced HR. The frequency was set at 20 Hz, pulse width at 0.18 ms, and duty cycle at 10 s/min. We titrated the VNS voltage once a week in every rat, readjusting the voltage if necessary. Each rat received chronic VNS for 4 weeks.

Echocardiographic and Hemodynamic Studies

At the end of the protocol (after 4 wk of VNS), we anesthetized the rats with isoflurane and recorded echocardiograms and hemodynamics under closed-chest condition. After performing echocardiography, we inserted a 2-F catheter-tipped micromanometer (SPR–320; Millar Instruments, USA) into the LV via the right carotid artery and recorded BP and LV pressure (LVP). We digitized LVP at 1 kHz with the use of a 16-bit analog-to-digital converter (Power Lab 16/35; AD Instruments, Australia) and stored the recording in a dedicated laboratory computer system. We calculated the first derivatives of LVP to estimate max +dP/dt and max −dP/dt as indexes of systolic function and diastolic function, respectively.

Neurohormonal Studies

We sampled blood for measurements of hormone concentrations at the end of the hemodynamic study. Plasma concentrations of norepinephrine and B-type natriuretic peptide (BNP) were measured.