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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;*■■:■■–■■)

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.

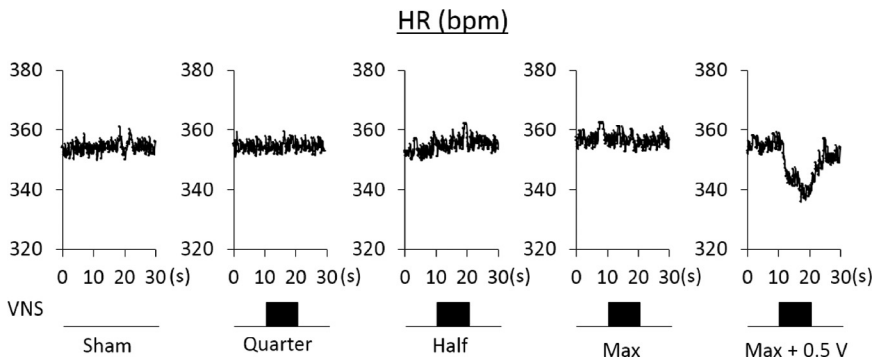

Fig. 1. Direct effect of vagal nerve stimulation (VNS) on heart rate (HR). Max, voltage just below the symptom threshold; Half, one-half of Max; Quarter, one-fourth of Max; Sham, sham stimulation. Subthreshold VNS up to Max did not reduce HR during stimulation. A higher symptom-evoking voltage (Max + 0.5 V) decreased HR.

Remodeling Study and Histologic Studies

After hemodynamic measurements, the heart and lung were excised, weighed, and then dissected and fixed in 10% buffered formalin. The LV was sliced from the apex to base into 4 transverse slices of 4 μm thickness and stained with the use of the Masson trichrome method. We digitized histologic images and estimated the size of MI as the ratio of the total length of MI lesion relative to the total circumferential length in 4 slices.[15]

We harvested the right vagal nerve from the site of electrode implantation. All samples were fixed in 2.5% glutaraldehyde, cut into 4-μm-thick sections, and stained with the use of toluidine blue. The number and diameter of myelinated fibers in the vagal trunk were analyzed under a microscope (Olympus, Japan). The fibers were classified as large (≥3 μm) or small (<3 μm).

Statistical Analysis

Results are expressed as mean ± SEM. One-way analysis of variance (ANOVA) was used to compare each parameter in 4 experimental groups (Max, Half, Quarter, and Sham). Post hoc Dunnett test was then performed to identify which group differences accounted for the significant overall ANOVA. A P value of <.05 was considered to be significant.

Results

Alteration of VNS Stimulation Setting

Table 2 presents weekly alterations of electrode impedance, stimulation voltage, and current. We derived the electrode impedance by applying a test voltage with a fixed amplitude (5 V) and measured the resultant current. The ratio of the test voltage to the current yielded the electrode impedance. The electrode impedance increased gradually in all groups. In most cases, we had to increase the stimulation voltage for titration. As a result, the stimulation current remained unchanged throughout the observation period in all groups. Although we used the same electrode and surgical procedure to attach the electrode to the vagal nerve, minute variations, such as connective tissue growing between the vagal fibers and the electrode, uncontrollable leakage of electricity and the involvement of sensory nerves in the vagal nerve and/or the electrode could not be avoided in some rats. In such cases, increasing the electrode impedance did not parallel the stimulation voltage of symptom threshold.

Effect of Chronic VNS on 24-Hour Averaged Heart Rate and Blood Pressure

Figure 2 shows the 24-hour averaged HR and mean BP during 4 weeks of VNS. Half reduced 24-hour averaged HR significantly compared with Sham from 1 to 4 weeks of VNS, and Max reduced HR at 3 and 4 weeks of VNS. The difference between Sham and Half reached 40 beats/min at the end of the study (P = .003). Mean BP averaged over 24 hours did not differ among the 4 groups (Sham: 86.5 ± 3.8 mm Hg; Quarter: 84.1 ± 1.6 mm Hg; Half: 89.7 ± 1.8 mm Hg; Max: 91.0 ± 2.1 mm Hg).

Effect of VNS on LV Function

Figure 3 shows the effect of VNS on LV function. Half did not decrease LV end-diastolic dimension (Half: 10.9 ± 0.2 mm; Sham: 11.1 ± 0.1 mm) but significantly decreased LV end-systolic dimension (Half: 9.1 ± 0.2 mm; Sham: 9.8 ± 0.2 mm; P < .05). As a result, Half significantly preserved LVEF compared with Sham (Half: 37.9 ± 3.1%; Sham: 28.4 ± 2.3%; P < .05). Furthermore, Half reduced LV end-diastolic pressure by 6.7 mm Hg compared with Sham (Half: 17.5 ± 2.0 mm Hg; Sham: 24.2 ± 1.2 mm Hg; P < .01) and showed the highest maximum LV +dP/dt. (Sham: 5001 ± 563 mm Hg/s; Quarter: 4988 ± 201 mm Hg/s; Half: 5918 ± 20 mm Hg/s; Max: 5351 ± 189 mm Hg/s; Half vs Sham: P < .05) and the lowest minimum LV −dP/dt. (Sham: −3632 ± 188 mm Hg/s; Quarter: −3595 ± 136 mm Hg/s; Half: −4342 ± 309 mm Hg/s; Max: −3903 ± 156 mm Hg/s; Half vs Sham: P < .05).

Effect of VNS on Other Parameters

Table 3 presents the effect of VNS on infarct size, body weight, organ weights, and neurohormonal factors. Infarct size and body weight were not different across groups at the

Table 2. Weekly Changes in VNS Settings

	Impedance (kΩ)					Stimulation Voltage (V)					Stimulation Current (mA)				
Weeks	0	1	2	3	4	0	1	2	3	4	0	1	2	3	4
Quarter	13.2 ± 1.0	25.0 ± 7.0	31.8 ± 10.1	29.3 ± 7.4	30.2 ± 7.3	0.5 ± 0.1	0.5 ± 0.1	0.7 ± 0.1	0.8 ± 0.1	0.8 ± 0.1	0.03 ± 0.007	0.03 ± 0.003	0.03 ± 0.003	0.03 ± 0.004	0.03 ± 0.003
Half	14.5 ± 1.0	20.9 ± 1.7	23.1 ± 2.0	25.9 ± 4.3	32.0 ± 6.9	1.1 ± 0.2	1.4 ± 0.3	1.9 ± 0.5	1.9 ± 0.4	2.0 ± 0.4	0.08 ± 0.01	0.08 ± 0.02	0.08 ± 0.02	0.07 ± 0.01	0.08 ± 0.02
Max	17.9 ± 1.9	24.3 ± 2.2	26.6 ± 3.2	33.8 ± 4.7	39.6 ± 9.2	1.8 ± 0.3	2.3 ± 0.5	2.9 ± 0.4	3.7 ± 0.7	3.7 ± 0.7	0.11 ± 0.03	0.11 ± 0.03	0.11 ± 0.01	0.10 ± 0.01	0.10 ± 0.01

Data are expressed as mean ± SEM. Weekly changes in electrode impedance, stimulation voltage, and current at each titration period. We derived the electrode impedance every week (see text for details). After knowing the electrode impedance, we stimulated the vagal nerve at various voltage amplitudes. The ratio of stimulation voltage to the electrode impedance yielded the stimulation current. Quarter, one-fourth of Max; Half, one-half of Max; Max, voltage just below the symptom threshold.

completion of the VNS protocol. Max, Half, and Quarter significantly reduced biventricular weight compared with Sham. Only Half significantly decreased lung weight compared with Sham, indicating improvement of pulmonary edema. Both Half and Max markedly decreased plasma BNP, a biomarker of aggravation of heart failure (Half: 157.4 ± 25.7 pg/mL; Max: 177.8 ± 27.6 pg/mL; vs Sham: 397.3 ± 37.5 pg/mL; both $P < .01$). Half reduced plasma norepinephrine, a marker of sympathetic nerve activity, by more than 50% compared with Sham (Half: 474.8 ± 58.6 pg/mL; Sham: 936.8 ± 126.2 pg/mL; $P < .01$).

Histology of Vagal Nerve

Figure 4 shows the effect of VNS on histologic damage of the vagal nerve. VNS did not change the number of small fibers (Sham: 1222.7 ± 293.9 counts/bundle; Quarter: 1086.8 ± 151.2 counts/bundle; Half: 1224.4 ± 108.6 counts/bundle; Max: 1312.5 ± 98.3 counts/bundle). However, Max significantly decreased the number of large fibers (Max: 163.1 ± 43.0 counts/bundle; Sham: 360.0 ± 61.6 counts/bundle; $P < .05$).

Discussion

This is the 1st study to elucidate the dose response of VNS below the symptom threshold regarding the effect on CHF. Major findings of this study are: (1) up-titration of VNS evoked symptoms before the level that reduced heart rate; (2) a VNS voltage at 50% of the symptom threshold (Half) significantly improved cardiac remodeling and heart failure compared with other voltages; and (3) a voltage just below the symptom threshold (Max) induced histologic injury to vagal nerve fibers.

Effect of VNS Voltages Below Symptom Threshold on Heart Failure

We compared the effect of chronic VNS at 3 different voltages below the symptom threshold. Max, Half, and Quarter did not elicit symptoms such as pain and respiratory twitching, and all 3 also did not reduce HR during stimulation, whereas the higher voltage (Max + 0.5 V) evoked both HR reduction and symptoms. Although all 3 voltages of VNS did not exhibit direct HR reduction during the period of titration, Half had the lowest 24-hour averaged HR among the 4 groups all through 4 weeks of chronic VNS. Because HR strongly correlates with the severity of heart failure,[16] this result indicates that Half improved heart failure. As shown in Fig. 3 and Table 3, Quarter failed to improve any parameter of CHF, indicating that a certain intensity level of VNS is required to achieve beneficial effects. Half, which was the voltage at 50% of the symptom threshold, clearly improved cardiac function, cardiac remodeling, and heart failure, whereas Max showed no significant improvement in these parameters except for biventricular weight and plasma BNP. These data suggest that optimal stimulus dose is required to maximize the beneficial effects of VNS for CHF. Using a stimulation intensity (current amplitude of 0.1–0.13 mA) sufficient to reduce HR,

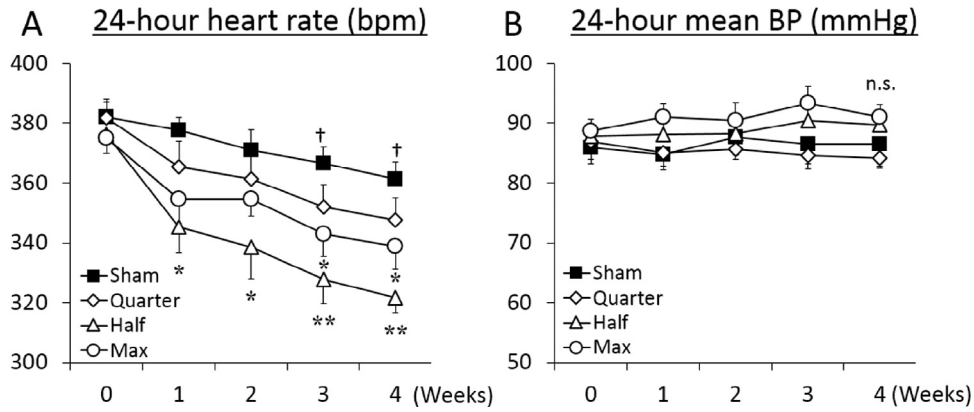

Fig. 2. Effects of vagal nerve stimulation (VNS) on (A) 24-hour averaged heart rate (HR) and (B) 24-hour mean blood pressure (BP) during 4 weeks of chronic vagal nerve stimulation. Max, voltage just below the symptom threshold; Half, one-half of Max; Quarter, one-fourth of Max; Sham, sham stimulation. (A) Half significantly decreased HR compared with Sham during 4 weeks of VNS. (B) Mean BP did not differ among the 4 groups. Data are expressed as mean ± SEM. $^{*}P < .05$, $^{**}P < .01$ vs Sham at the same period. $^{\dagger}P < .05$ vs Sham at 0 week. n.s., not significant.

Li et al[3] showed that chronic VNS improved cardiac function and survival in a rat model of heart failure after MI. In our study, we were not able to up-titrate VNS owing to adverse effects. At Max, which did not decrease HR, we found no benefit of chronic VNS on ventricular function. The differences in physiologic responses to VNS observed in Li et al's and our studies may be due to differences in electrode and stimulator (Li et al used a constant-current system). Therefore, we cannot directly interpret and compare the 2 findings.

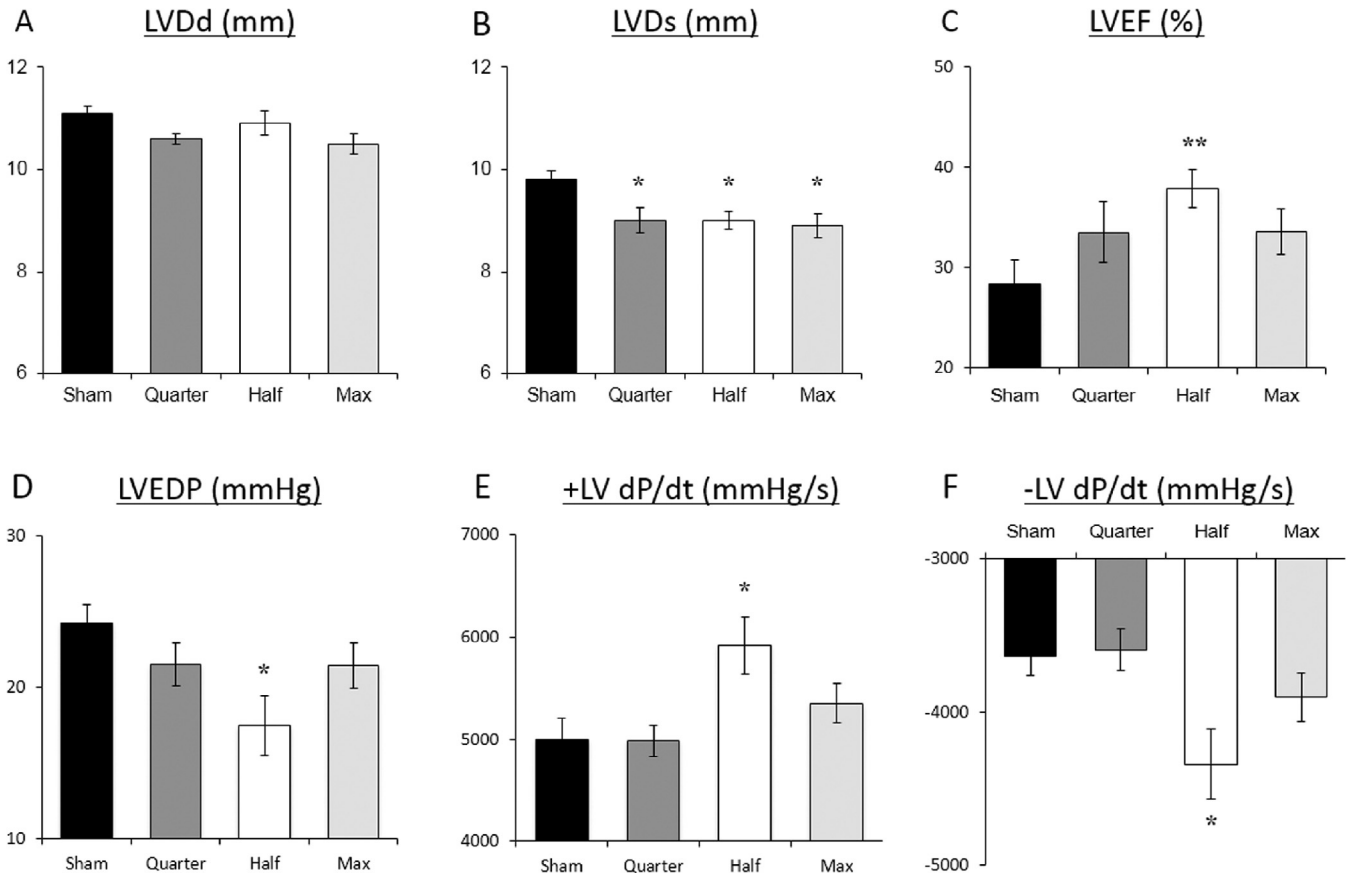

Fig. 3. Effects of vagal nerve stimulation on left ventricular (LV) function. Max, voltage just below the symptom threshold; Half, one-half of Max; Quarter, one-fourth of Max; Sham, sham stimulation. LVDd, left ventricular end-diastolic dimension; LVDs, left ventricular end-systolic dimension; LVEF, left ventricular ejection fraction; LVEDP, LV end-diastolic pressure. Half significantly increased LVEF. Half decreased LVEDP and showed the highest maximum LV +dP/dt and the lowest minimum LV −dP/dt. Data are expressed as mean ± SEM. $^{*}P < .05$, $^{**}P < .01$ vs Sham.

Table 3. Effects of Vagal Nerve Stimulation (VNS) on Other Parameters

Parameter	Sham	Quarter	Half	Max
MI size, %	46.9 ± 1.2	51.8 ± 2.3	48.0 ± 1.9	48.8 ± 1.6
BW, g	396.4 ± 9.7	382.6 ± 10.8	405.5 ± 13.2	382.6 ± 8.5
Biventricular weight, g/kg	3.7 ± 0.11	3.4 ± 0.06*	3.2 ± 0.11**	3.2 ± 0.12**
Lung weight, g/kg	9.7 ± 0.3	9.4 ± 0.8	6.7 ± 0.8**	8.3 ± 0.5
BNP, pg/mL	397.3 ± 37.5	372.9 ± 48.2	157.4 ± 25.7**	177.8 ± 27.6**
NE, pg/mL	936.8 ± 126.2	932.6 ± 179.9	474.8 ± 58.6**	631.9 ± 74.4

Data are expressed as mean ± SEM. MI, myocardial infarction, size normalized by LV circumferential length), BW, body weight, biventricular weight normalized by body weight; lung weight normalized by body weight; BNP, plasma B-type natriuretic peptide; NE, plasma norepinephrine. Infarct size and body weight were not different across groups at the completion of the VNS protocol. Sham, sham stimulation; Quarter, one-fourth of Max; Half, one-half of Max; Max, voltage just below the symptom threshold.

*$P < .05$, **$P < .01$ vs Sham.

Several possible mechanisms may explain why Half yielded better outcomes than Max. As shown in Fig. 4, chronic electrical stimulation at the maximum voltage caused significant neural fiber damage. Several modes of injury, such as compressive,[17] reperfusion,[18,19] and electrical damage to peripheral nerves secondary to implantation and electrical activation of electrodes have been reported.[20,21] In the present study, physical damage caused by compression and electrode attachment to the vagal nerve were conceivably the same in the 4 groups. We assume that the higher electrical intensity of Max may have induced neural damage. As for histologic investigation, Agnew et al[20] showed that electrical stimulation of feline peroneal nerves reduced the number of large myelinated fibers, whereas the smaller myelinated fibers were spared. Their findings are consistent with our observation that the maximum subthreshold voltage of VNS reduced the number of large fibers but not small fibers (Fig. 4). To clarify if the histologic neural damage parallels the function or sensitivity of vagal nerve, we examined the HR response to VNS at the highest voltage (10 V supramaximal) during titration as an indicator of loss of vagal nerve function. As shown in Fig. 5, supramaximal VNS in Max significantly attenuated the HR responder compared with other groups, indicating that Max induced a functional deficit of vagal nerve as well as an anatomic deficit. In addition, it is well known that the myelinated large vagal fibers play a pivotal role in the cardioprotective effects of VNS.[22] Therefore, electrical damage and loss of vagal myelinated fibers might have weakened the beneficial effects of Max. Another possible factor is the sensitivity of vagal nerve. The sensitivity and activity of vagal nerve vary daily or even hourly. Because we fixed the voltage of Max just below the symptom threshold, we cannot rule out the possibility that Max exceeded the threshold transiently. Persisting symptoms may evoke worsening of respiratory rhythm and stress-induced sympathetic activation, in turn leading to aggravation of CHF.

The Need for Investigation of Other Parameters to Optimize VNS

Apart from voltage, other stimulation parameters, such as frequency, duration, and duty cycle, should be considered to maximize the impact of VNS for CHF. In particular, frequency should be another important factor. Saku et al[8] reported that VNS at 20 Hz induced marked respiratory inhibition via the vagal nerve afferent pathway. In addition, we also evaluated how VNS frequency altered respiration, and clearly demonstrated that VNS at 5 Hz delivered higher voltage without obvious respiratory inhibition compared with VNS at 20 Hz.[23] These findings suggest that the frequency of VNS may alter the symptom threshold. Further investigations are needed to decide the optimal combination of stimulation parameters that balance the efficacy and adverse effects.

Clinical Implication

Several clinical trials of VNS for CHF have been reported, and stimulation parameters varied among them. In clinical trials, stimulation-related symptoms have limited up-

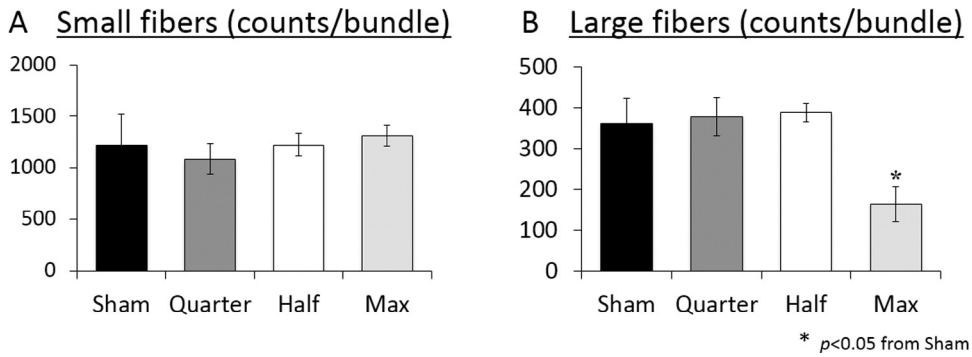

Fig. 4. Effect of vagal nerve stimulation (VNS) on histology of vagal nerve. Max, voltage just below the symptom threshold; Half, one-half of Max; Quarter, one-fourth of Max; Sham, sham stimulation. (A) VNS at all 3 voltages did not decrease the number of small fibers. (B) Max decreased the number of large fibers of the vagal nerve. Data are expressed as mean ± SEM. *$P < .05$ vs Sham.

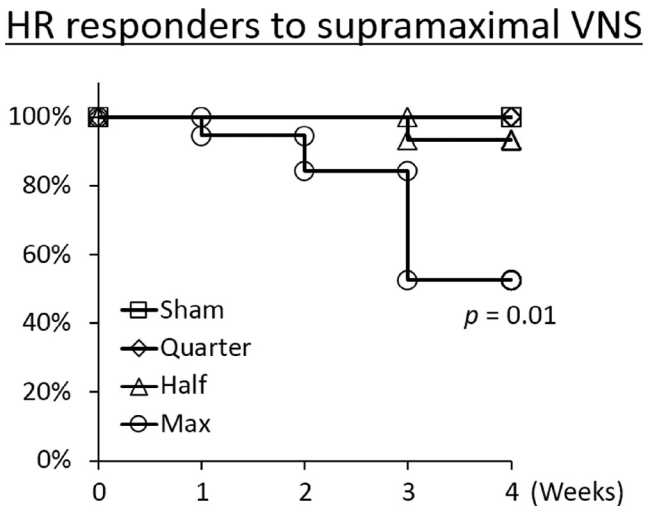

Fig. 5. The impact of acute supramaximal VNS (+10 V) on heart rate (HR) among the 4 groups. Max, voltage just below the symptom threshold; Half, one-half of Max; Quarter, one-fourth of Max; Sham, sham stimulation. We defined an HR responder as a rat showing HR reduction of >10 beats/min below the baseline and counted the number of responders once a week in each group. We estimated the rate of HR responders among 4 groups by means of the Kaplan-Meier method and compared them by means of log-rank test. Max halved the responder rate after 4 weeks. In contrast, the responder rate remained unchanged in Quarter and Half (Sham: 100%; Quarter: 100%; Half: 93.3%; and Max: 52.6% after 4 weeks of VNS; $P = .01$).

titration of VNS. De Ferrari et al[9] showed that adverse effects (discomfort and pain) prevented up-titration in 72% of the patients. In NECTAR-HF, the current amplitude used in VNS was less than one-half of the target current amplitude (4 mA) owing to side effects, resulting in a low current amplitude of 1.42 ± 0.80 mA.[10]

There have been no studies, including nonhuman investigations, that examined the dose-efficacy relationship of VNS below the symptom threshold. We demonstrated that one-half of the maximum subthreshold voltage outperforms the maximum subthreshold voltage. In the open-labeled ANTHEM-HF study, the VNS current amplitude was set below the symptom threshold with a safety margin (0.25 mA) to insure that the therapy was well tolerated.[11] This dose setting may be a reason why VNS in patients with CHF achieved significant improvement of LVEF and exercise tolerance in ANTHEM-HF. Titration of VNS considering both intensity and safety would maximize the beneficial effects and minimize the adverse effects in CHF patients. Taken together, we cannot support the notion that the stronger intensity the better.

Study Limitations

There are several limitations in this study. First, in studying the dose effects of VNS, many stimulation parameters other than the voltage are involved, such as frequency, duty cycle, timing to the cardiac cycle, and efferent/afferent nerve activation. In this study, we focused on the voltage. To develop VNS with maximum efficacy and minimum adverse effects, further investigations are needed to assess the effects of other stimulation parameters.

Second, because we focused on the impact of VNS on cardiac function and remodeling after MI, we did not fully evaluate the mechanistic insights of our findings. Zhang et al[13] reported that improvement of autonomic balance, inhibition of the renin-angiotensin system, and antiinflammatory effects mediate the therapeutic effects of VNS on CHF. It is conceivable that such mechanisms may also contribute to the beneficial effects of low-dose VNS in this study. Further investigations are needed to clarify the fundamental mechanism of low-dose VNS.

Third, we showed that the loss of vagal large fibers paralleled the beneficial effect of VNS on CHF at Max. Because the design of electrode and stimulus conditions in this study differ greatly from those in humans, we should be very careful to extrapolate this finding to VNS in human patients. On the other hand, VNS evokes similar physiologic responses in rats and in humans. Therefore, the symptom-guided up-titration method proposed in this study could serve as a practical indicator in determining the doses of VNS in patients.

Conclusion

Optimal titration maximizes the beneficial effects of VNS for CHF. A VNS voltage at 50% of the symptom threshold significantly improved CHF. The proposed titration procedure is potentially a practical clinical tool in determining the optimal dose of VNS.

Disclosures

None.

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