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Selective Control of Physiological Responses by Temporally-Patterned Electrical Stimulation of the Canine Vagus Nerve

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***Abstract*—Vagus nerve stimulation (VNS) is effective for treating epilepsy and depression, and has emerging indications for anxiety and heart failure. However, stimulation-evoked side effects remain a challenge for long-term compliance. We investigated the feasibility of reducing VNS side effects by using a temporally-modified stimulation pattern. In 4 anesthetized canines, we measured changes in both the heart rate and evoked laryngeal muscle activity. Compared to baseline, we found that a 5% duty cycle (measured by the number of pulses per second of stimulation) could still evoke a 21% reduction in heart rate; whereas compared to continuous stimulation (3 mA, 300 µs pulsewidth, 20 Hz) the same 5% duty cycle reduced the evoked laryngeal muscle activity by 90%. The results of this study indicate that temporally-patterned stimulation may provide an effective tool for optimizing VNS therapy.**

I. Introduction

VAGUS nerve stimulation (VNS) is approved by the Food and Drug Administration for treating intractable epilepsy and depression and is under investigation for treating heart failure [10-13]. Although studies support clinical effectiveness [1], the precise mechanism(s) by which VNS achieves therapeutic efficacy remain unclear. As a consequence, programming the stimulation parameters generally involves titration of a number of key variables [2-4]: ≤ 3.5 mA, 100-500 µs, 20–50 Hz, and 30–90 s on/5–10 min off. The lack of definitive guidance for clinicians limits both the overall effectiveness and patient compliance to VNS therapy.

Maximizing therapeutic efficacy is further confounded by both the complex innervation pattern of the vagus nerve – which includes the upper and lower airways, heart, and visceral organs [5, 6] – and the broad range of axon diameters within the nerve trunk. The mammalian vagus nerve contains approximately 20,000 myelinated axons including large (A-type) and small (B-type) diameter fibers [7], with the vast majority of all fibers (65–85%) being unmyelinated C-fibers [8, 9]. As a consequence, VNS therapy is often limited by stimulation-evoked side effects including voice hoarseness, cough, and pain.

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We examined the feasibility of using temporally-modified stimulation patterns as a potential means of mitigating side effects of VNS therapy for treating heart failure [10-13]. The objective of this study was to modulate various physiological responses such as heart rate and laryngeal muscle activation by applying different temporal patterns of stimulation to the vagus nerve.

II. Methods

All surgical and experimental protocols were approved by the Institutional Animal Care and Use Committee of Duke University. The study included 4 mongrel dogs (female, weight = 18-21 kg) that were fasted and medicated (Fentanyl patch, 50-75 µg/hr).

A. Anesthesia

Each animal was sedated (thiopental sodium, 20 mg/kg, i.v.) and anesthetized with isofluorane (1–5%) during surgery and propofol (i.v., 0.2–0.8 mg/kg/min) during nerve stimulation. Analgesia was provided by supplemental fentanyl (i.v., 10–15 µg/kg/hr). Heart rate and blood pressure were monitored to assess the depth of anesthesia. Continuous infusion of lactated ringer's solution (i.v., 10 mL/kg/hr) was maintained. At the end of the study, the animals were euthanized with pentobarbital (i.v., 0.2 mg/kg).

B. Instrumentation

A ventral incision exposed the right cervical vagus nerve for implantation of a bipolar helical nerve electrode at the level of the thyroid cartilage. A tripolar nerve cuff electrode was implanted approximately 8 cm distal to the stimulating electrode, and a pair of stainless steel wires was inserted into the posterior cricoarytenoid muscle. Constant current pulses (Pulsar-6bp, FHC, Inc.) were delivered through the bipolar helical electrodes and the evoked compound nerve action potential (CNAP) and laryngeal electromyogram (EMG) were measured. Both signals were filtered (CNAP = 100 Hz–30 kHz, EMG=30-3kHz) and amplified (CNAP = 100,000, EMG =1000) using a low-noise voltage preamplifier (SR560, Stanford Research Systems). The electrocardiogram (ECG) was measured with surface electrodes, the arterial blood pressure (BP) was measured by catheterizing the femoral artery, and the left ventricular pressure (LVP) was measured via an endoventricular catheter

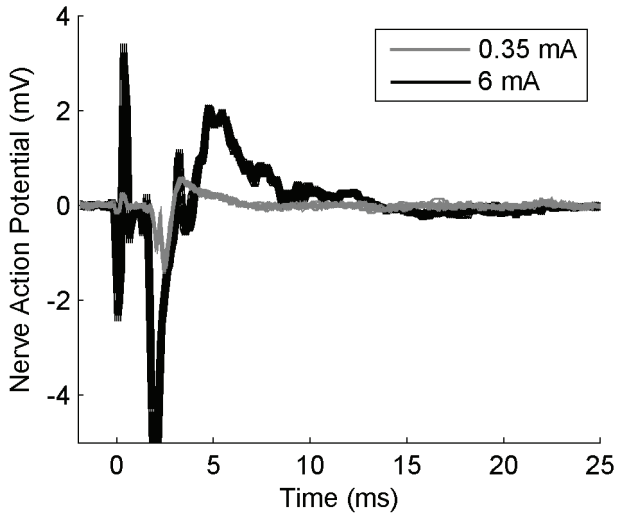

Figure 1. Compound nerve action potentials evoked by electrical stimulation of the right vagus nerve at 0.35 mA (A-fiber) and 6 mA (A- and B-fiber). Neuromuscular block was achieved with I.V. succinylcholine chloride. [Stimulus artifact @ t = 0 ms]

(SPC-454F Mikro-Tip Catheter Pressure Transducer, Millar Instruments, Inc.). All signals were sampled (20 kHz) and recorded (DASH 8Xe, Astro-Med, Inc).

C. Experimental Protocol

The stimulus thresholds for activating myelinated (A- and B-) fibers in the right cervical vagus nerve were determined in each animal by recording the CNAP and EMG evoked in response to trains of monophasic current pulses delivered via the bipolar helical electrode: amplitude = 0.02–10 mA, pulsewidth = 300 μs, frequency = 1 Hz, number of pulses = 20. The stimulating helical electrode was connected in a proximal anode/distal cathode configuration [14]. The effect of vagus nerve stimulation on cardiac function was also studied in each animal, specifically changes in the ECG in response to 20 or 30 second trains of current pulses delivered via the helical electrode: amplitude = 0.2–50 mA, pulse width = 300 μs, and frequency = 5–50 Hz.

D. Data Analysis

The evoked electroneurogram (ENG) and EMG signals were quantified by calculating the rectified average of the post-stimulus response [14]. The stimulation threshold for activating A- or B- fibers of the canine vagus nerve was defined as the intensity at which a 10% increase in evoked activity was measured. Changes in cardiac function during vagus nerve stimulation were quantified by heart rate (HR, beats per minute), BP (average pressure), and ventricular contractility (VC, mmHg/s). The VC was calculated by averaging the rate of pressure increase during each ventricular contraction over the 20 or 30 second duration of stimulation.

All data are expressed as the mean ± standard error, unless otherwise specified. Statistical analysis used an initial one-way ANOVA followed by a Tukey multiple comparison test.

III. Results

Electrical stimulation of the vagus nerve resulted in the recruitment of myelinated axons (Figure 1), where activation of larger diameter A-fibers occurred at a lower threshold (0.6 ± 0.1 mA, n = 4) than activation of smaller B-fibers (2.8 ± 0.6 mA, n = 4). C-fiber activity was also recorded at amplitudes above 10 mA (data not shown).

A. Stimulation of Vagus Nerve Branches

In three dogs, the vagus nerve was surgically separated into the recurrent laryngeal nerve (RLN) and thoracic component of the vagus nerve (tVN). Selective electrical stimulation of the RLN evoked laryngeal EMG activity in conjunction with A-fiber activity recorded from the cervical vagus nerve trunk (Figure 2). In contrast, stimulation of the tVN resulted in the activation of only myelinated B-fibers at larger stimulation amplitudes.

B. Efferent VNS evokes bradycardia

VNS also elicited marked changes in heart rate. As shown in figure 3, stimulation of the nerve in one dog with a 30-second train of pulses (20 Hz, 3 mA) resulted in a marked change in cardiac function (bradycardia: 10% decrease in HR). The stimulus amplitude required to evoke bradycardia (4.3 ± 1.2 mA, n = 4) was consistently equal to or greater than the threshold for activating B-fibers. Following transection of the right vagus nerve, electrical stimulation of the cranial cut end of the nerve failed to evoke bradycardia; while the

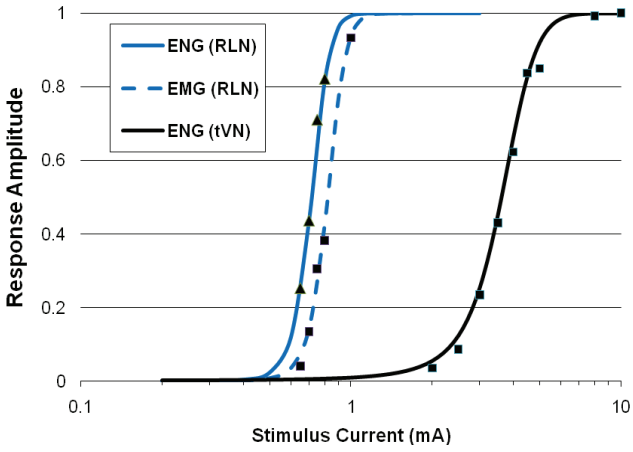

Figure 2. Recruitment curves of myelinated A-fibers and laryngeal EMG in response to stimulation of the RLN branch (blue lines). Electrical stimulation of the thoracic component of the vagus nerve (tVN) elicited B-fiber activity.

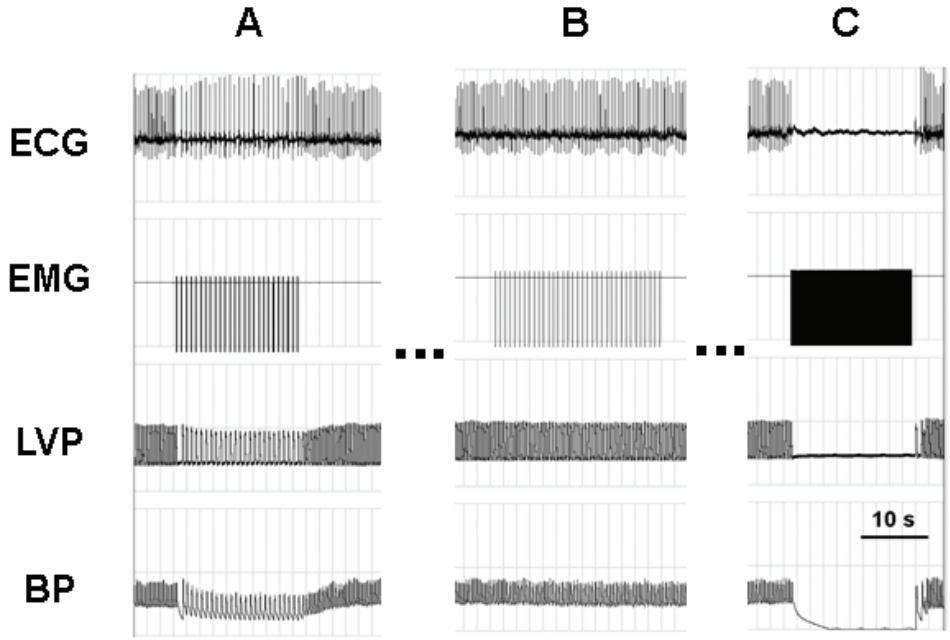

Figure 3. Changes in the duty cycle of vagus nerve stimulation – A (0.12%), B (0.03%), and C (continuous, 0.6%) – evoked differential responses in the electrocardiogram (ECG), laryngeal muscle (EMG), left ventricular pressure (LVP), and arterial blood pressure (BP). In this example, the stimuli were 3 mA pulses applied at 20 Hz. It is noted that asystole was observed at or below 5 mA in only one animal.

same stimulus applied to the caudal cut end continued to evoke bradycardia. This suggests that stimulation-evoked changes in heart rate were the result of stimulation of efferent fibers in the vagus nerve.

C. Selective Modulation of Cardiac Function

As shown in Figure 3, the duty cycle of the stimulus pulse train (3 mA, 20 Hz) was varied from 0.03%, 0.12%, and 0.6% by applying 1, 4 and 20 pulses per second of stimulation, respectively. Compared to baseline (no stimulation, 111 beats per minute), VNS at 0.12% and 0.03% duty cycle evoked a 46% and 21% reduction in heart rate, respectively (Figure 3 A-B). Both the mean BP (50%, 35%) and LVP contractility (41%, 32%) also decreased during stimulation at 0.12% and 0.03% duty cycles, respectively.

The laryngeal EMG evoked by VNS was also markedly reduced when compared to continuous stimulation. A 76% decrease in EMG activity was achieved at 0.12% duty cycle; while a 0.03% duty cycle resulted in a 90% reduction in laryngeal EMG. It is noted that cardiac modulation always occurred at or above amplitudes that evoked maximum EMG responses.

IV. Discussion

The responses evoked by temporally-patterned vagus nerve stimulation support the feasibility of selectively modulating cardiac function, while minimizing the potential side effects associated with co-activation of laryngeal muscles. We confirmed that the large diameter vagal A-fibers are derived from the recurrent laryngeal nerve (RLN), which is consistently activated at therapeutic stimulation intensities (≥ B-fiber threshold) [2, 15]. We also found that modulation of cardiac function (i.e., bradycardia) could be achieved with minimal laryngeal EMG activity by adjusting the duty cycle of the applied train of pulses.

Although the precise role of VNS-evoked bradycardia in the treatment of heart failure remains unclear [10, 16-18], the stimulation level (amplitude and frequency) at which the heart rate is reduced has been used as a reference point for setting the stimulation parameters for VNS [11]. Given this physiological target, we chose to limit the number of pulses per second of duty cycle on-time, instead of varying the on-time (2 to 30 seconds) with continuous (e.g., 20 Hz) stimulation [4, 19]. Not only did our stimulation method achieve significant bradycardia, but it also markedly reduced the mean activity level of the laryngeal muscles. While this is expected to improve the side-effect profile of VNS therapy, further work is needed to validate the therapeutic effects.

The stimulation thresholds required to evoke neural responses from myelinated A- and B- fibers in this study were similar to previous work in rats [20], dogs [14], and pigs [21]. However, we were unable to observe any indirect component of the vagal ENG, as reported by Ordelman et al [21]. As shown in Figure 1, only A- and B-fiber responses were measured within the 20 ms post-stimulus window. And while laryngeal muscle artifacts were commonly observed within the 8 and 15 ms window, these disappeared from the ENG following neuromuscular block (IV succinylcholine chloride). Further, nerve transection distal to the recording electrode did not change the response; while transection between the stimulating and recording electrodes abolished all evoked activity.

V. Conclusion

Temporally-modified patterns of VNS can achieve the effect of evoking bradycardia, while minimizing activation of the laryngeal muscles (i.e., side effects). This novel approach provides a practical alternative to a more invasive surgical procedure that would require access to the tVN located distal to the subclavian artery. Moreover, temporally patterned VN stimulation may also be effective for treating intractable epilepsy and depression. Further work is needed to determine the clinical feasibility of this approach.

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