Electrical Interaction between Implantable Vagus Nerve Stimulation Device and Implantable Cardiac Rhythm Management Device*

Imad Libbus PhD, Scott T. Mazar MSEE, Scott R. Stubbs BSEE, Bruce H. KenKnight PhD

Abstract— **Background: Autonomic regulation therapy via vagus nerve stimulation (VNS) was recently approved as a therapy for chronic heart failure, and will likely be utilized in patients who are also indicated for cardiac rhythm management device implantation. This study is designed to assess the degree to which VNS is likely to cause interference in the cardiac sensing of an implantable cardiac rhythm management device.**

Methods: A VNS stimulation lead and a cardiac sensing lead were placed in a simulated biological medium. A nonconductive carrier frame was used to position the leads at a precise electrode spacing. Stimulation was delivered through the VNS Therapy lead at a maximum output current and a variety of combinations of stimulation frequencies from 5-30 Hz and stimulation pulse widths from 130-1000 µs. The electrode spacing began at 0 cm and was increased in 1 cm increments until the measured signal dropped below the cardiac rhythm management device noise floor for sensing. The test was conducted with both bipolar and unipolar sensing.

Results: In the bipolar sensing configuration, the maximum sensed signal amplitude was 687 µV at an electrode separation of 0 cm, signal frequency of 30 Hz, pulse width of 1000 µs, and output current of 3.5 mA. In the unipolar sensing configuration, the maximum amplitude was 406 µV. In both configurations, the measured signal with maximum stimulation intensity decreased significantly with electrode separation, and dropped below the noise floor at an electrode spacing of 3.0 cm. The sensed signal amplitude was further attenuated at lower stimulation amplitudes and pulse widths.

Conclusion: Even at maximum neural stimulation intensity of 3.5 mA, at an electrode separation of at least 3.0 cm, neural stimulation did not result in a detectable level of interference with either bipolar or unipolar sensing. Because this separation is significantly smaller than the minimum electrode separation of 15 cm in clinical practice, VNS Therapy is not expected to interfere with the function of implantable cardiac devices.

I. Introduction

The Vagus Nerve Stimulation (VNS) Therapy system (LivaNova, Houston, TX) is an implantable system that delivers chronic electrical stimulation to the vagus nerve in the neck. The VNS Therapy system has had over 100,000 patient implants over the past 25 years for the treatment of epilepsy and depression, and has recently received regulatory approval for the treatment for chronic heart failure. Patients with cardiac disease are more likely to also have other implanted cardiac devices, such as implantable pacemakers, implantable cardioverter defibrillators (ICDs), and cardiac resynchronization therapy (CRT) devices, all of which sense electrical activity in the heart and deliver stimulation to the heart.

The presence of both an implantable neurostimulator and an implantable cardiac device raises the concern that stimulation from the VNS Therapy system would be detected by the implantable cardiac device, leading to inappropriate delivery of therapy. Interference between the two devices could lead to high-frequency vagus nerve stimulation being detected by the cardiac device, triggering a change in cardiac pacing or the inappropriate delivery of a high-voltage shock.

The current study is designed to assess the degree to which stimulation from the VNS Therapy system is detected by an implantable cardiac device. A tank filled with normal saline was used to simulate the biological medium, and the VNS Therapy system electrodes (stimulation lead) and cardiac device electrodes (sensing lead) were placed in the tank at various separation distances. At each separation distance, stimulation was delivered through the stimulation lead, and the resulting signal was measured with the sensing lead. The amplitude of the sensed signal as a function of separation distance was used to assess the degree to which VNS is likely to cause interference in the cardiac sensing of an implantable cardiac rhythm management device.

II. Methods

All testing was performed and verified by an independent testing laboratory (TUV Rheinland of North America, Boxborough, MA). Calibration of all instruments was verified prior to testing.

A. Test Setup

The human torso was simulated with a plastic tank (56 cm x 38 cm x 36 cm) filled with 0.9% sodium chloride solution (Baxter International, Deerfield, IL), as shown in Figure 1. The bath was heated to a stable temperature of 37 °C with an immersion heater (TH-500, Finnex, Chicago, IL) and temperature controller (WS-1500EB, Aubur Instruments, Alpharetta, GA) prior to the initiation of testing. A small immersion circulation pump (FT-70-O, Fountain Tech, Santa Maria, CA) was used to minimize temperature stratification. The heater and pump were turned off while recordings were being made.

Bar clamps were used to create a rigid frame to which a digital caliper was affixed. A carrier frame was attached to the caliper and used to position the VNS lead (PerenniaFLEX

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I. Libbus is with LivaNova, Minneapolis, MN USA (phone: 763-416-3960; e-mail: imad.libbus@livanova.com).

S. T. Mazar is with LivaNova, Minneapolis, MN USA (e-mail: scott.mazar@livanova.com).

S. R. Stubbs is with LivaNova, Minneapolis, MN USA (e-mail: scott.stubbs@livanova.com)

B. H. KenKnight is with LivaNova, Minneapolis, MN USA (e-mail: bruce.kenknight@livanova.com)

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Model M304, Cyberonics, Inc., Houston, TX) and the cardiac sensing lead (Acuity Model 4555 Steerable Lead, Boston Scientific, Natick, MA). Electrode separation was confirmed with a second digital caliper (CD-6, Mitutoyo Corp., Kawasaki, Japan).

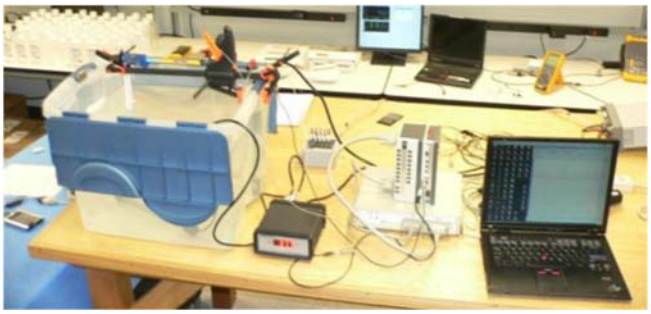

Figure 1. Experimental test setup.

Testing was performed in two phases: in a configuration that simulates bipolar cardiac sensing and in a configuration that simulates unipolar cardiac sensing. The vast majority of modern implantable cardiac devices use bipolar sensing; the unipolar configuration test was performed for completeness. For bipolar sensing, an electrode separation of 0 cm was defined as a position at which the centers of the bipolar electrodes were aligned; for unipolar sensing, an electrode separation of 0 cm was defined as a position at which the unipolar electrode was at the mid-point of the bipolar VNS stimulation lead, with parallel electrode orientation.

In the bipolar configuration, signals were measured using a cardiac lead, with measurements made from the lead tip to the lead ring (i.e. standard bipolar sensing). In the unipolar configuration, signals were measured from the lead tip to a simulated pulse generator (PG) metallic shell; a wire was welded to a VNS Therapy PG (DemiPulse Model M103, Cyberonics, Inc., Houston, TX), which is approximately the same size as a pacemaker PG, and the PG was placed in a location that approximates the location of an implanted PG relative to the VNS stimulation lead.

The cardiac lead was connected to a data acquisition system (MP100 system with ECG100B amplifier, Biopac Systems, Goleta, CA). The Physician's Manual of the ART system delivering VNS recommends that chronic stimulation be applied at a signal frequency of 5-10 Hz, a stimulation pulse width of 250 μs, and a maximum output current amplitude of 2.5-3.0 mA; however, to measure the maximum level of interference that could be measured, the maximum stimulation parameters of the device were use in this test. Using the VNS programmer, the VNS system was set at its maximum output current amplitude (3.5 mA) and sequentially programmed to combinations of stimulation frequency between 5 and 30 Hz and stimulation pulse width between 130 and 1000 μs. One of the programmed settings was the maximum stimulation intensity of the VNS system (30 Hz, 1000 μs). The electrode spacing began at 0 cm and was increased in 1 cm increments. At each electrode spacing, the measurements were repeated at each combination of stimulation frequency and pulse width until the measured signal dropped below the noise floor (defined as the recorded signal amplitude at VNS output current amplitude of 0 mA).

B. Calibration

A signal generator (33220A, Agilent Technologies, Santa Clara, CA) was used to provide a known reference signal to the data acquisition system. The generator output was attenuated with a 60 dB attenuator (8495B, Agilent Technologies, Santa Clara, CA) and verified with a True RMS Multimeter (289, Fluke Corp., Everett, WA).

III. RESULTS

The stimulation delivered by the VNS Therapy system was detected by the cardiac sensing lead over a range of stimulation parameters. The VNS Therapy system delivers a train of stimulation pulses at a programmed frequency, amplitude, pulse width, and duty cycle (Figure 2). At frequencies of 10 Hz and higher, the output current gradually increases over approximately 2 seconds to the programmed output current the beginning of each train of stimulation pulses; at the end of each train of stimulation pulses, the output current gradually decreases over approximately 2 seconds from the programmed output current to zero.

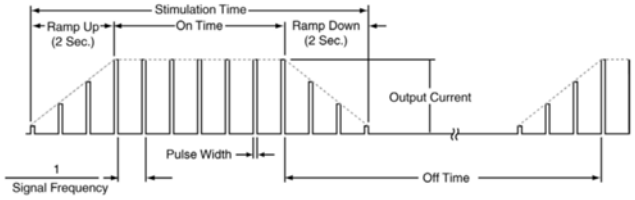

Figure 2. VNS stimulation waveform.

The ramp-up and ramp-down were also observed in the sensed signal at high stimulation intensity and close electrode separation (Figure 3).

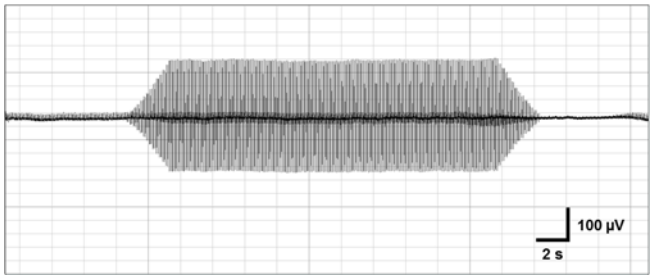

Figure 3. Example sensed signal.

In the bipolar sensing configuration, the sensed signal amplitude was dependent on stimulation amplitude, pulse width, and electrode separation, and reached a maximum of 687 μV at an electrode separation of 0 cm, a signal frequency of 30 Hz, a pulse width of 1000 μs, and an output current of 3.5 mA (Figure 4). The noise floor with bipolar sensing (sensed signal amplitude at a stimulation amplitude of 0 mA) was 9.6 μV. The stimulation frequency had minimal effect on the amplitude of the sensed signal. The measured signal decreased significantly with electrode separation, and dropped below the noise floor at electrode separations above 3.0 cm.

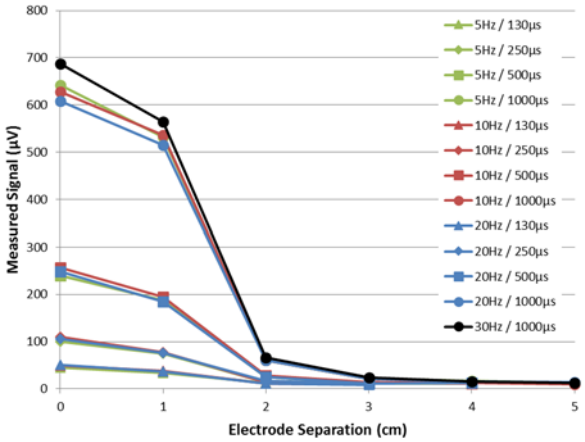

Figure 4. Measured signal amplitude, bipolar sensing

In the unipolar sensing configuration, the sensed signal amplitude was also dependent on stimulation amplitude, pulse width, and electrode separation, and reached a maximum of 406 µV at an electrode separation of 0 cm, a signal frequency of 30 Hz, a pulse width of 1000 µs, and an output current of 3.5 mA (Figure 5). The noise floor with unipolar sensing (sensed signal amplitude at a stimulation amplitude of 0 mA) was 10.0 µV. The stimulation frequency also had minimal effect on the amplitude of the sensed unipolar signal. The measured signal decreased significantly with electrode separation, and dropped below the noise floor at electrode separations above 3 cm.

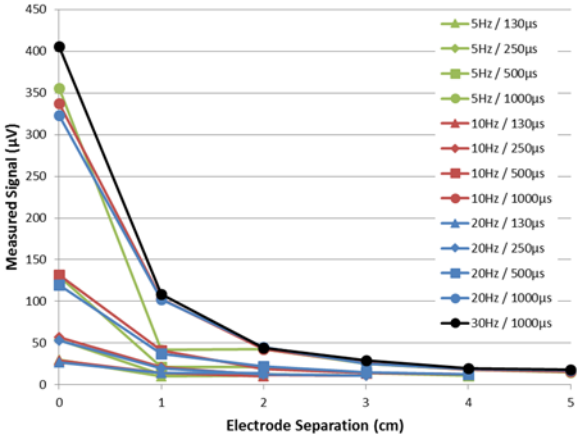

Figure 5. Measured signal amplitude, unipolar sensing

IV. Discussion

Patients with heart failure frequently meet the clinical indications for implantation of cardiac rhythm management devices [1]. Therefore, heart failure patients may be implanted with both a VNS Therapy system for the treatment of heart failure and a cardiac rhythm management device for the treatment of atrial or ventricular arrhythmias. This study was designed to assess the degree to which stimulation from the VNS Therapy system would be detected by an implantable cardiac device through a bipolar sensing lead and through a unipolar sensing lead.

Cardiac device sensing is accomplished through a sequence of signal processing stages. The high-frequency component (> 100 Hz) is not part of the cardiac signal, and is removed, removing most electromagnetic interference (EMI). A threshold comparison is then performed. The comparison input value is either a static, or created dynamically as a function of time and the previously detected cardiac signal. The dynamic case is called Automatic Gain Control (AGC), and is used to adjust the gain of the sense amplifier following a cardiac pacing pulse which may transiently change the cardiac beat morphology. Determination of input values is important because it ensures that beat sensing only occurs on the depolarization segment of the cardiac input signal; repolarization artifacts are rejected to prevent spurious beat detection. AGC also allows ICD sensitivity to increase, enhancing ventricular fibrillation (VF) detection.

Bipolar and unipolar sensing yield similar sensed voltages during normal sinus rhythm [5]. Bipolar signals average 11.8 ± 6.0 mV (range: 3.3 to 31.3 mV), and unipolar signals average 12.2 ± 5.2 mV (range: 4.0 to 29.2 mV). Bipolar sensing is generally considered to provide superior non-physiologic EMI rejection and reduced T-wave sensing artifact as compared to unipolar sensing.

It has been previously reported that external electrical stimulation devices, such as transcutaneous electrical nerve stimulation (TENS) devices, can interfere with the proper function of implantable cardiac devices. Wayar and colleagues reported cases of electrical interference in two patients from commercial muscle stimulators used for abdominal training, in which stimulation was detected by implantable ICDs and resulted in inappropriate delivery of high-voltage shocks [2]. Pyatt and colleagues reported the case of a patient with an implantable ICD who experienced interference during the use of a TENS device, resulting in dizziness and bradycardia [3].

The degree of interaction between implantable cardiac devices and other implantable stimulators has also been assessed. Enggaard and colleagues examined five patients with both an ICD and an implantable spinal cord stimulator (SCS) for refractory angina [4]. In these patients, the maximum tolerable level of spinal cord stimulation was applied during ICD implantation to exclude interference with the ICD; during up to 72 months of follow-up, chronic SCS therapy did not result in any cases of inappropriate defibrillator shocks. In contrast, a case of potential interaction between an SCS and an ICD was reported by Schimpf and colleagues [6]. In this case report, no artifacts or oversensing could be detected during standard spinal cord stimulator, even at the highest ICD sensing sensitivity; however, at a maximal output which caused significant discomfort for the patient, intermittent signals were detected by the ICD on both the atrial and ventricular channels.

VNS Therapy has been approved for the treatment of epilepsy for over 20 years, and several case studies have been reported in patients implanted with both a VNS Therapy device and a cardiac device (pacemaker or ICD). Cáceres and colleagues reported on an epilepsy patient who was implanted with a cardiac pacemaker (Medtronic KDR-731) after a post-ictal cardiac arrest [7]. The VNS Therapy system was implanted on the left cervical vagus nerve, and VNS therapy was tested at near-maximal stimulation parameters (3.5 mA

amplitude, 30 Hz frequency, 500 μs pulse width). During this test, the pacemaker was programmed to its most sensitive setting. Communication between the cardiac pacemaker and its programmer was not affected by the VNS Therapy device and or its programmer, and subsequent pacemaker checkups over 30 months did not show any evidence of electrical interference from the VNS Therapy. A similar experience was reported by Müller and colleagues in a patient implanted with both a VNS Therapy system and an ICD (Biotronik Lumax 340 VR-T XL) [8]. After ICD implantation, the patient was monitored continuously for one week with a cardiac monitor, then with daily ECGs for 22 weeks, including three 24-hour ECGs. During this time, the ICD functioned normally, and there was no evidence of interference from the VNS Therapy system.

A. Device Interaction

In the present study, we used a saline tank as a simulated biological medium, and precisely controlled the electrode separation to determine the separation-dependent signal over a range of stimulation parameters. As the test shows, even at maximum stimulation parameters (3.5 mA, 30 Hz, 1000 μs), the measured interference drops below a detectable level in both the bipolar and unipolar configurations when the vagus nerve stimulation electrodes and the cardiac electrodes are separated by at least 3.0 cm.

To determine the minimum separation between vagus nerve stimulation electrodes and cardiac electrodes that would be encountered in clinical practice, we made calculations based on published anatomical data. According to the VNS Therapy physician's manual, the vagus nerve stimulation electrode is implanted in the C3-C4 region. In the recumbent position, when gravity is not exerting downward pressure on the heart, the heart lies at the level of T6-T9 [9]. Therefore, electrode separation was conservatively estimated to be the minimum distance between C4 and T6.

For each vertebral body and intervertebral disc between C4 and T6, the minimum values of human anatomical height were calculated using published values one standard deviation below the mean [10]. These heights were summed to determine the minimum separation between the VNS Therapy electrode and the cardiac electrode. This calculation yielded a minimum electrode separation of 15.3 cm. When the minimum electrode separation (15.3 cm) is compared with the maximum separation at which measured interference drops below a detectable level (3.0 cm), it is clear that, with a significant safety margin, stimulation delivered by the VNS Therapy system would not be detected by an implantable cardiac device with either bipolar or unipolar sensing, and therefore does not pose a risk of interaction.

B. Clinical Experience

Several clinical studies have been recently published in which heart failure patients were implanted with a cervical VNS system and given chronic stimulation for up to 12 months. In the CardioFit Multicenter Trial, 19 of 32 patients (59%) had received ICD implantation prior to enrolling in the study; the authors reported that no interaction was observed between the VNS system and the ICD, including no episodes of oversensing possibly related to VNS [11]. In the NECTAR-HF Study, 56 of 63 therapy patients (89%) had received ICD or CRT-D implantation prior to enrolling in the study; all ICD shocks and anti-tachycardia pacing events were adjudicated to be unrelated to interference from the VNS system [12]. In the ANTHEM-HF Study, none of the 60 patients had an ICD implant at enrollment; two patients were implanted with ICDs during the study, and no device interaction was observed between the VNS system and the ICDs. In these three studies, a total of 77 patients had both an implantable VNS system and an implantable cardiac device, and none of these patients reported any interference or interaction between the two systems [13].

V. Conclusion

The interference between VNS Therapy stimulation and cardiac sensing was assessed in a simulated biological medium. Even at maximum neural stimulation intensity, provided that the electrode separation is greater than 3.0 cm, neural stimulation did not result in a detectable level of interference with either bipolar or unipolar sensing.

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