

Safety of High-Current Stimulation for Intermittent Intraoperative Neural Monitoring in Thyroid Surgery: A Porcine Model

I-Cheng Lu, MD ; Pi-Ying Chang, MD; Gregory W. Randolph, MD, FACS, FACE; Hsiu-Ya Chen, NA; Kuang-Yi Tseng, MD; Yi-Chu Lin, MD; Feng-Yu Chiang, MD; Che-Wei Wu, MD, PhD 

Objectives: During monitored thyroidectomy, displacement of the recurrent laryngeal nerve (RLN) or vagus nerve (VN) in some complicated cases can increase the risk of injury. Although increasing the stimulus current can facilitate nerve mapping and localization, the safety of a high-current stimulus remains unknown. Therefore, this study evaluated the safety of a high-current stimulus in a porcine model.

Methods: Short-duration (1 minute), high-current (3, 5, 10, 15, 20, 25, and 30 mA at 4Hz) stimulus pulses were repeatedly applied to the RLN or VN in six anesthetized piglets. The safety of the high-current stimulus pulses was assessed in terms of hemodynamic stability during VN stimulation and in terms of nerve function integrity after VN and RLN stimulation.

Results: During VN stimulation with a high-current stimulus pulse, sinus rhythms in all six piglets showed stable heart rates, and mean arterial pressure was unaffected. High-current stimulation of the VN and the RLN did not affect electromyography amplitude or latency.

Conclusion: This porcine study showed that applying a short-duration, high-current stimulus pulse to the VN or RLN during monitored thyroidectomy has no harmful effects. In clinical practice, a short duration of high-current stimulus can be applied to facilitate neural mapping, especially in patients with disoriented nerve positions.

Key Words: Vagus nerve (VN) stimulation, recurrent laryngeal nerve (RLN) stimulation, high-current stimulus, intraoperative neural monitoring (IONM).

Level of Evidence: NA.

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INTRODUCTION

Recurrent laryngeal nerve (RLN) injury is a major complication of thyroid surgery. In recent decades, thyroid surgeons have increasingly used intraoperative neural monitoring to facilitate RLN identification, elucidate nerve injury mechanisms, predict postoperative vocal cord function, and aid thyroidectomy staging.^{1–6}

Suprathreshold vagal nerve (VN) and RLN stimulation is a recommended standard procedure before and after surgical dissection because it improves accuracy in

intraoperative neural monitoring (IONM) of the RLN.^{5,7,8} The standard practice when using IONM in thyroid surgery is to apply a stimulus current of approximately 1 to 2 mA to evoke the maximum electromyography (EMG) in a well-exposed VN or RLN.^{1,8,9} However, a higher stimulus current (supramaximal stimulation) may be required to increase identification sensitivity in surgical situations, for example: 1) to stimulate the VN without carotid sheath dissection,¹⁰ particularly when the VN is displaced by a huge goiter or when a troubleshooting algorithm requires contralateral VN stimulation¹; and 2) to map or localize a distorted RLN in cases involving a large goiter with substernal extension, a large Zuckerkandl tubercle, revision thyroidectomy, or thyroid cancer with major paratracheal node metastasis in the course of the nerve.^{11,12}

Stimulation of the VN is also considered a safe adjunct therapy for refractory epilepsy.^{13,14} The stimulus current typically used in anti-epileptic therapy is 0.25–4 mA applied for 30 seconds at a frequency of 20 to 30 Hz at 5-minute intervals.^{15,16} However, no studies have determined whether using a higher current for VN stimulation during neural mapping/localization causes hemodynamic instability or nerve injury. Therefore, the purpose of this study was to use a porcine model to evaluate the safety of using a high current to stimulate the VN or RLN.

MATERIALS AND METHODS

The study protocol was approved by the Institutional Animal Care and Use Committee of Kaohsiung Medical University

From the Department of Anesthesiology (I-C.L.); the Department of Otorhinolaryngology (C-W.W.), Kaohsiung Municipal Hsiao-Kang Hospital, Kaohsiung Medical University Hospital, Kaohsiung Medical University; the Faculty of Medicine, College of Medicine, Kaohsiung Medical University (I-C.L., F-Y.C., C-W.W.); the Department of Anesthesiology (P-Y.C., H-Y.C., K-Y.T.), Kaohsiung Medical University Hospital; the Department of Otolaryngology–Head and Neck Surgery (Y-C.L., F-Y.C.), Kaohsiung Medical University Hospital, Kaohsiung, Taiwan; and the Division of Thyroid and Parathyroid Endocrine Surgery, Department of Otolaryngology, Massachusetts Eye and Ear Infirmary; Department of Otology and Laryngology, Harvard Medical School (G.W.R.), Boston, Massachusetts, U.S.A.

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Send correspondence to Feng-Yu Chiang, MD, PhD, and Che-Wei Wu, MD, PhD, Department of Otolaryngology–Head and Neck Surgery, Kaohsiung Medical University, 100 TzYou First Road, Kaohsiung City 807, Taiwan. E-mail: fychiang@kmu.edu.tw; cwwu@kmu.edu.tw

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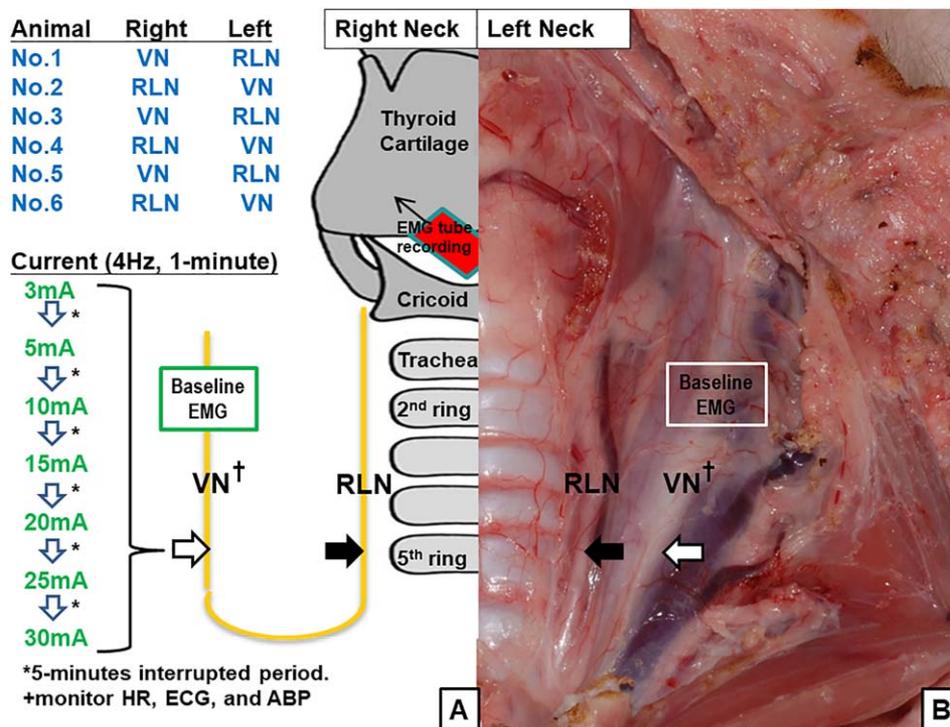


Fig. 1. Protocols for evaluating effects of high-stimulus currents. (A) The flowchart shows that one side of the neck was used for VN study ($n = 6$), and the contralateral neck was used for RLN study ($n = 6$). The baseline EMG responses were elicited and recorded by stimulating the proximal VN at the second tracheal ring level. A 1-minute stimulus current of 3 to 30 mA was used to stimulate the VN (white arrow) and RLN (black arrow) at the fifth tracheal ring level. Real-time HR, ECG tracing, and invasive ABP were monitored during VN stimulation (+ sign). Different stimulation levels were applied at 5-minute intervals (star sign). (B) Photograph of surgical anatomy of the piglet neck with identified VNs (white arrow) and RLNs (black arrow). ABP = arterial blood pressure; ECG = electrocardiography; EMG = electromyography; HR = heart rate; RLN = recurrent laryngeal nerve; VN = vagus nerve.

(KMUH) (Kaohsiung, Taiwan). All experiments were performed in piglets according to institutional guidelines that comply with national and international regulations for animal experiments. Six male pigs (age: 3–4 months, weight: 18–22 kg) were obtained from the Laboratory Animal Center of Kaohsiung Medical University. Electromyographic parameters in this pig model, including threshold, latency, amplitude, and evoked potentials, have shown good agreement with human data in previous studies.^{8,17}

Anesthesia and Monitoring

At 8 hours after fasting and 30 minutes before the experiment, each piglet was premedicated with intramuscular azaperone (4 mg/kg). General anesthesia was induced by inhalation of 2% to 4% sevoflurane via a hollow plastic bottle in a prone position. A bolus of propofol 1 mg/kg was administered intravenously with a 24-gauge peripheral intravenous catheter placed on the ear. Each piglet was then intubated with a size #6 EMG endotracheal tube (NIM Standard EMG Tube, Medtronic, Jacksonville, FL). The EMG endotracheal tube position was confirmed by the anesthesiologist. After the tube was fixed, the piglet was placed in the supine position with the neck extended. Anesthesia was maintained with sevoflurane 1% to 3% in oxygen. The lungs were ventilated in volume-control mode at a tidal volume of 8 to 12 mL/kg, and the respiratory rate was set to 12 to 14 breaths/minute. Body temperature was maintained with a circulating water mattress maintained at 40°C. The right femoral artery was catheterized for continuous monitoring of invasive blood pressure.

Physiologic monitoring included capnography, heart rate, electrocardiography (ECG) and oxygenation (SaO_2) (8100E, nGenuity, Criticare Systems, WI), and invasive blood pressure (HP78353A, Hewlett Packard, CT). No neuromuscular blocking agents were used during anesthesia.

Equipment Setting, Operation, and Experimental Design

The channel leads from the EMG tube were connected to the monitoring system (NIM-Response 3.0, Medtronic, Jacksonville, FL). The VN and RLN were stimulated by direct contact with a stimulation probe (Ball-Tip 1 mm, Medtronic, Jacksonville, FL). The monitoring system generated stimuli with a time window set to 50 ms, and an amplitude scale was set to 0.2 mV/division. The pulsed stimuli were 100 μs in duration and 4 Hz in frequency. The event capture was activated at a threshold of 100 μV .

After surgical disinfection, the neck and larynx were exposed by a midline vertical cervical incision. Bilateral VNs and RLNs were identified and carefully dissected. Figure 1 summarizes the design of the study. In each piglet, one side of the neck was used for VN study and the contralateral neck was used for RLN study. The baseline amplitude, latency, and waveform morphologies of EMG responses for the VN–RLN pathway were obtained and recorded on each side of the neck by stimulating the proximal VN at the second tracheal ring level.

After baseline neuromonitoring parameters were recorded, a continuous 1-minute stimulus was applied at the fifth

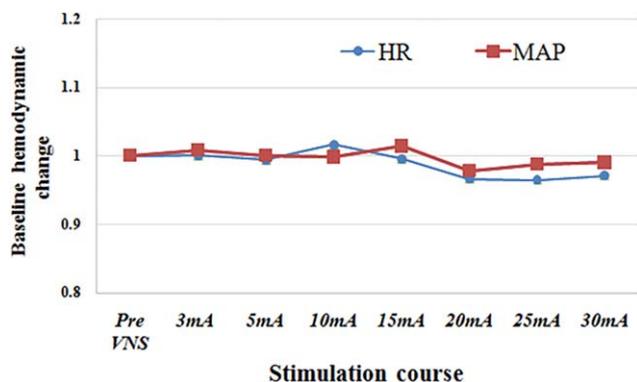


Fig. 2. Time course of hemodynamic status, including HR and MAP, during VNS with a high-current (3–30 mA, 4Hz, 1 minute) stimulus pulse. HR = heart rate; MAP = mean arterial pressure; VNS = vagus nerve stimulation. [Color figure can be viewed in the online issue, which is available at www.laryngoscope.com.]

tracheal ring level of the VN or RLN. At 5-minute intervals, current was progressively increased as follows: 3 mA, 5 mA, 10 mA, 15 mA, 20 mA, 25 mA, and 30 mA. Figure 1 shows that baseline EMG responses for the VN–RLN pathway from the proximal VN were confirmed and recorded before and after each stimulation level. To minimize changes in the EMG tube position caused by manipulation or traction, all EMG responses for one side were obtained before measuring the EMG responses on the contralateral side.

Safety Analysis

The safety of a high-current stimulus was assessed in terms of hemodynamic stability during VN stimulation and nerve function integrity after VN and RLN stimulation.

Hemodynamic stability during VN stimulation was evaluated by real-time monitoring of heart rate, ECG, and invasive arterial blood pressure (Fig. 1). Invasive arterial blood pressure was measured by cannulating a femoral arterial line with a 20-gauge catheter. Significant bradycardia and hypotension were defined as a 10% or larger decrease in heart rate and mean arterial pressure, respectively, compared to baseline. Effects of VN stimulation on autonomic nervous system activity were evaluated with a heart rate variability (HRV) analyzer. A wireless one-channel precordial ECG was recorded continuously

during the course of VN stimulation. Data were then transferred to a PC to filter out artifacts via automatic recognition (BEST EP2000-1, Xin Bo, Kaohsiung, Taiwan). A 5-minute observation interval was recorded and analyzed before and after the VN stimulation period. The HRV was analyzed by fast Fourier transformation method. The high-frequency (HF) band was defined as absolute values ranging from 0.13 to 0.41 Hz. The HF band is mainly used to detect vagal activity, which may be the mechanism of bradycardia induced by VN stimulation. The low frequency (LF) band was defined as absolute values ranging from 0.01 to 0.13 Hz.¹⁸ The LF band is mainly used to detect sympathetic efferent activity. The sympathetic–parasympathetic balance is expressed as the LF:HF ratio.¹⁹ The frequency bands for our pig model were based on a study by von Borell et al. and are widely accepted in the literature.²⁰

Nerve function integrity was evaluated by the comparing baseline EMG responses in the VN–RLN pathway proximal to the site of VN stimulation before and after each stimulation level (Fig. 1).

Statistical Analysis

All data were obtained prospectively, coded, and saved in a microsoft excel 2010 database (Microsoft, Redmond, WA). Data were expressed as mean with standard deviation. Statistical comparisons of continuous variables were performed by two-sample t-test. Categorical nominal variables were analyzed by chi-square test or Fisher exact test. All statistical tests were two-tailed, and a *P* value less than 0.05 was considered statistically significant.

RESULTS

Figure 2 shows the hemodynamic analysis results for the six piglets. Heart rate and mean arterial pressure were stable throughout the VN stimulation period. Figure 3 shows the hemodynamic characteristics revealed by ECG during VN stimulation with a high current (30 mA) in a single anesthetized piglet. The ECG tracing revealed sinus rhythm without arrhythmia. The HRV analysis showed that VN stimulation significantly decreased the LF:HF ratio compared to baseline (0.24 ± 0.06 vs. 0.82 ± 0.11 ; $P < 0.01$). Throughout the study, VN stimulation increased parasympathetic activity in all six piglets but did not evoke bradycardia or hypotension.

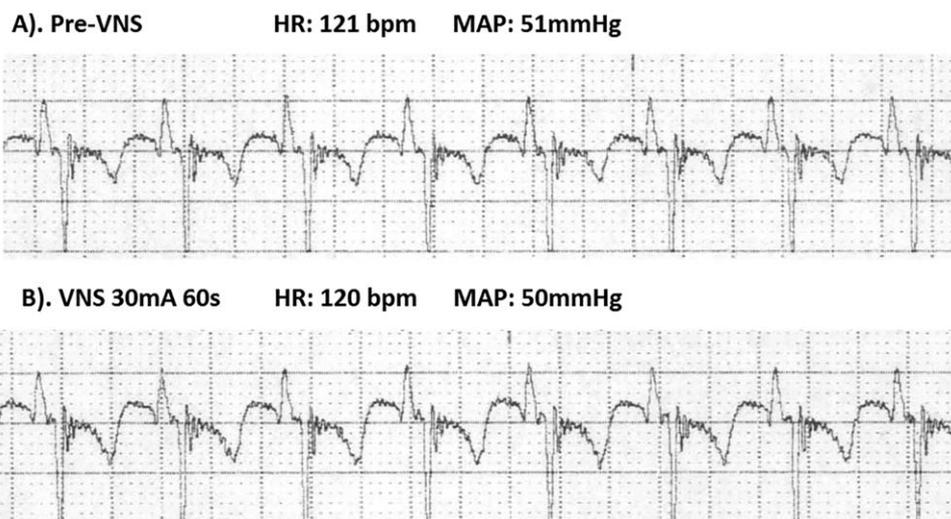


Fig. 3. Typical hemodynamic status and ECG tracing during VNS with a high current (30 mA, 60 seconds, 4 Hz) in a single anesthetized piglet. The ECG revealed sinus rhythm without arrhythmia. HR and blood pressure were unchanged. bpm = beats per minute; ECG = electrocardiography; HR = heart rate; MAP = mean arterial pressure; VNS = vagus nerve stimulation.

TABLE I.
Comparison of EMG Responses Before and After High-Stimulus Current of Vagus Nerve and Recurrent Laryngeal Nerve With High-Stimulus Current (3–30 mA, 4 Hz, 1 minute)

Subject	Baseline EMG Responses (before/after stimulation study) From Proximal VN Point*													
	3 mA		5 mA		10 mA		15 mA		20 mA		25 mA		30 mA	
Study Animal (Side)	Amplitude (μ V)	Latency (ms)	Amplitude (μ V)	Latency (ms)	Amplitude (μ V)	Latency (ms)	Amplitude (μ V)	Latency (ms)	Amplitude (μ V)	Latency (ms)	Amplitude (μ V)	Latency (ms)	Amplitude (μ V)	Latency (ms)
I. VN Stimulation Study[†]														
No. 1 (R)	1559/1620	5.5/5.5	1625/1652	5.5/5.5	1666/1623	5.5/5.5	1635/1698	5.3/5.5	1685/1673	5.3/5.3	1623/1699	5.5/5.5	1678/1709	5.5/5.5
No. 2 (L)	955/926	7.8/8.0	894/911	8.0/8.0	898/926	7.8/7.8	901/945	8.0/8.0	955/940	8.0/8.0	912/963	7.8/8.0	960/954	8.0/8.0
No. 3 (R)	756/785	5.5/5.5	786/803	5.8/5.8	770/723	5.8/5.8	753/740	5.5/5.5	788/769	5.5/5.5	779/789	5.4/5.5	780/795	5.5/5.5
No. 4 (L)	684/690	7.5/7.8	692/695	7.5/7.5	701/689	7.5/7.8	688/663	7.8/7.8	687/656	7.5/7.8	660/669	7.5/7.8	658/678	7.5/7.5
No. 5 (R)	998/976	5.5/5.5	1022/1005	5.3/5.3	979/998	5.5/5.5	1003/1102	5.3/5.5	996/977	5.3/5.5	982/995	5.5/5.5	1006/996	5.5/5.5
No. 6 (L)	828/823	7.3/7.3	835/844	7.3/7.3	856/849	5.3/5.3	844/832	7.3/7.3	855/868	7.3/7.3	870/856	7.3/7.3	866/854	7.3/7.5
II. RLN Stimulation Study[‡]														
No. 1 (R)	1956/2020	8.0/8.0	2089/2052	8.0/8.0	2070/2109	7.8/8.0	2056/2008	8.0/7.8	2074/7075	8.0/7.8	2011/2105	7.8/8.0	2009/2023	8.0/8.0
No. 2 (L)	1296/1337	5.5/5.5	1204/1311	5.5/5.5	1230/1326	5.5/5.3	1261/1316	5.3/5.5	1282/1354	5.5/5.3	1312/1313	5.5/5.5	1275/1323	5.5/5.5
No. 3 (R)	513/537	7.5/7.8	545/561	7.5/7.5	541/562	7.5/7.5	578/599	7.8/7.8	570/588	7.8/7.5	602/621	7.5/7.5	576/563	7.5/7.5
No. 4 (L)	984/984	5.5/5.5	1015/1011	5.5/5.8	993/967	5.8/5.8	974/959	5.5/5.5	929/951	5.5/5.5	965/1027	5.5/5.5	1096/1077	5.5/5.5
No. 5 (R)	718/732	7.3/7.3	688/694	7.5/7.5	685/702	7.3/7.3	695/711	7.3/7.3	731/731	7.3/7.3	750/707	7.3/7.5	748/774	7.5/7.5
No. 6 (L)	1044/1040	5.5/5.5	1086/1105	5.5/5.5	1174/1133	5.5/5.5	1275/1164	5.5/5.5	1176/1123	5.5/5.5	1202/1157	5.5/5.8	1101/1092	5.5/5.5

*Baseline EMG response was tested on the same point of the VN at the second tracheal ring level (Figure 1).

[†]The study was performed on the same point of the VN at the fifth tracheal ring level (Figure 1).

[‡]The study was performed on the same point of the RLN at the fifth tracheal ring level (Figure 1).
 EMG = electromyography; L = left; R = right; RLN = recurrent laryngeal nerve; VN = vagus nerve.

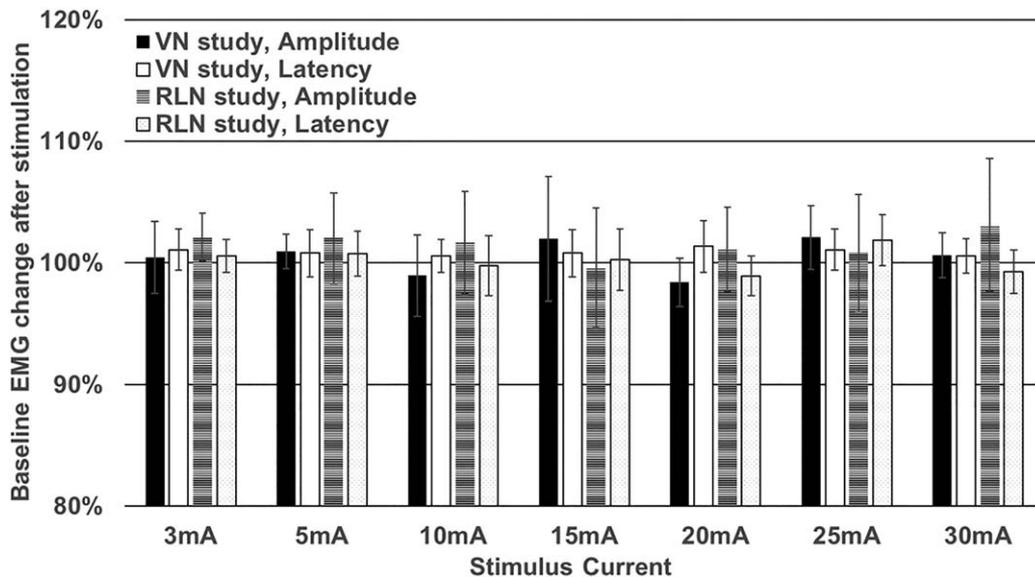


Fig. 4. Mean EMG changes from baseline after use of high-stimulus current for VN and RLN stimulation. Stimulation did not substantially decrease EMG amplitude and did not substantially prolong EMG latency. EMG = electromyography; RLN = recurrent laryngeal nerve; VN = vagus nerve.

In all piglets, baseline EMG amplitudes in the VN–RLN pathway proximal to the site of VN stimulation remained stable after a 1-minute, high-current (3–30 mA) stimulus was applied to the VN or RLN. Additionally, the stimulus did not significantly prolong latencies (Table I) (Fig. 4). That is, the high-current stimulus does not affect functional integrity in the VN or RLN.

DISCUSSION

An RLN injury resulting in postoperative vocal disability is among the most feared complications of thyroid surgery. Therefore, visual identification of the RLN during thyroid surgery is considered standard procedure because it is associated with lower RLN palsy rates.^{21,22} However, identifying the RLN may be complicated by various conditions, such as goitrous enlargement associated with fixation and splaying of the RLN to the under-surface of the enlarged thyroid gland. Identifying the RLN may also be complicated by paratracheal nodal disease in advanced stages.

One of the most useful applications of IONM during thyroid surgery is mapping neural information before visual identification of the RLN.^{1,12} In experimental studies and clinical reports, a 1 to 2 mA stimulus current is typically used to evoke EMG during IONM of a well-exposed VN or RLN.^{1,8,9} The typical clinical practice, however, is to use a stimulus current higher than 1 to 2 mA to stimulate the VN without dissecting the carotid sheath,¹⁰ and to map or localize the RLN before visual identification. A higher current is also used for nerve mapping in cases of VN displacement or RLN distortion caused by a large goiter with substernal extension, recurrent goiter, or thyroid cancer in advanced stage of paratracheal nodal metastasis.^{11,12} However, the literature shows limited data regarding whether using a

high current to stimulate the VN or RLN induces hemodynamic instability or nerve injury.

Therefore, this study used a reliable and well-established porcine model to investigate how a short-duration (1 minute), high-current (range: 3–30 mA) stimulus pulse in IONM affects hemodynamic stability and electrophysiologic EMG responses (Fig. 1). Analyses of hemodynamic status in all animals consistently revealed that VN stimulation did not destabilize heart rate or negatively affect mean arterial pressure throughout the VN stimulation period (Figs. (2 and 3)). In all experimental animals, analysis of the VN–RLN pathway also showed stable EMG responses in areas proximal to the site of VN stimulation (Table I) (Fig. 4).

The literature shows limited data regarding the safe range of stimulus current during IONM. A porcine model in our previous study showed no unwanted electrophysiological or cardiopulmonary effects of a continuous pulsatile current of 3 mA (pulse width: 100 μ s, frequency: 4 Hz, duration: 10 minutes) used to stimulate the VN and RLN. Another porcine study by Schneider et al.²³ similarly reported no vagal side effects during or after continuous VN stimulation with a 1.0 mA stimulus pulse (pulse width: 200 μ s, frequency: 3 Hz, mean duration: 280 minutes). In Yoo et al., however, a temporal pattern of continuous VN stimulation with a 2-mA stimulus pulse at a high frequency (20 Hz) induced bradycardia (defined as $\geq 10\%$ decrease in heart rate) in seven of eight anesthetized dogs.²⁴

In Ulmer et al., continuous VN stimulation with a 0.5- to 5-mA stimulus pulse (pulse width: 200 μ s, frequency: 2 Hz) for 81 minutes significantly decreased the LF:HF power ratio with parasympathetic predominance.²⁵ Friedrich et al. similarly reported that continuous VN stimulation significantly increased vagal activity. The authors also reported that parasympathetic

predominance was not associated with large changes in heart rate, sinus rhythm, or blood pressure.²⁶ Now that the use of IONM during thyroid surgery and parathyroid surgery is increasing worldwide, the risk of bradycardia or hemodynamic stability followed by increased vagal tone is a growing concern. Terris et al. reported an adverse cardiovascular event during continuous IONM in a healthy young female patient.²⁷ According to the literature, most side effects of VN stimulation are apparently related to the use of a high-frequency pulse or the use of continuous stimulation.

This study investigated how an intermittent, short-duration (1 minute), high-current (3 mA–30 mA) stimulus pulse used for neural mapping affects hemodynamic stability and electrophysiologic EMG responses in a porcine model of IONM. Hemodynamic status (indicated by heart rate and mean arterial pressure) remained stable throughout the duration of VN stimulation. The EMG amplitude, latency, and waveforms were also stable, which indicated good nerve function integrity. No cases of reduced amplitude or prolonged latency occurred.

Vagus nerve stimulation (VNS) therapy provides seizure-frequency reduction for patients with partial seizures refractory to antiepileptic medications from 1997. Although the mechanism of the VNS therapy for epilepsy remains unclear, it is believed that VNS increases the seizure threshold by modulation of afferent vagal activity. The output of VNS setting of the generator was quite different from neural monitoring for thyroid surgery. The typical activation settings were listed as follows: output current 0.25 mA increased gradually to 2 mA, frequency of 20 to 30 Hz, pulse width of 250 to 500 ms, and signal on for 30 seconds and off for 3 to 4 minutes. Settings may be changed as required for each patient?²⁸ A comparison of high (30 seconds every 5 minutes) and low (30 seconds every 90 minutes) vagal stimulation at the setting of 30 Hz frequency and 3.5 mA current showed better reduction rate in the high-stimulation group (50% vs. 13%).¹⁴ Adverse event resulted from VNS such as hoarseness, sore throat, cough, paresthesia, and headache were not observed in daily practice during short-term use of VNS therapy system.²⁹

There were certain limitations in this study: First, the sample size was relatively small in this pilot animal study. However, this model has proven useful and effective for evaluating electrophysiologic correlates of laryngeal EMG during IONM in previous studies,^{9,17} and there was a good reproducibility between tested animals. Second, healthy piglets undergoing an experimental protocol may not reflect the common landscape of thyroid surgery in humans with coronary heart disease, hypertension, and so forth. Patients with comorbidities may be more vulnerable to high-current stimulation and deserve further investigations in the future.

In fact, the clinical procedure for using an intermittent, higher-current stimulus pulse for VN or RLN mapping, or for early RLN identification during monitored thyroidectomy, can be performed very quickly (several seconds) and was previously reported as simple and safe.^{10–12} However, high current may increase

identification sensitivity but decreases its specificity as spatial precision decreases.⁹ Therefore, after the VN and RLN are identified, the stimulus current should still be reduced to the standard level of approximately 1 to 2 mA to minimize the potential for false shunting, artifact signals, nerve injury, or cardiopulmonary effects during IONM.

CONCLUSION

This porcine study showed that the use of intermittent, short-duration, high-current pulses to stimulate the VN or RLN caused no untoward cardiopulmonary effects or obvious EMG changes. In clinical practice, an intermittent, short duration of higher-stimulus current can be applied to facilitate neural mapping during monitored thyroidectomy, especially in patients with disoriented nerve positions. Although short duration of high-stimulus current is well tolerated, it only should be used for indirect VN or RLN mapping procedures. After the VN and RLN are identified, the standard stimulus current (1 or 2 mA) should be used to minimize the potential for false shunting, artifact signals, nerve injury, or cardiopulmonary effects.

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