INVESTIGATION OF OPTIMAL INTENSITY AND SAFETY OF ELECTRICAL NERVE STIMULATION DURING INTRAOPERATIVE NEUROMONITORING OF THE RECURRENT LARYNGEAL NERVE: A PROSPECTIVE PORCINE MODEL

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Abstract: Background. Intraoperative neuromonitoring (IONM) of the recurrent laryngeal nerve (RLN) has recently been more frequently applied in thyroid surgery. However, concerns have been raised regarding the safety and optimal intensity of electrical nerve stimulation.

Methods. Eight piglets were enrolled, and electrically evoked electromyography (EMG) was recorded from the vocalis muscles via endotracheal surface electrodes. The baseline EMG was measured and continuous pulsatile stimulations were performed on the vagus nerve and RLN for 10 minutes. Changes of EMG waveform and cardiopulmonary status were analyzed.

Results. A dose–response curve existed with increasing EMG amplitude as stimulating current was increased, with maximum amplitude elicited on vagal and RLN stimulation at <1 mA. No obvious EMG changes and untoward cardiopulmonary effects were observed after the stimulation.

Conclusions. Electrical stimulation is safe during IONM in this porcine model. Minimal current that required generating the maximal evoked EMG, approximately 1 mA in this study, can be selected to minimize the risk of nerve damage and cardiopulmonary effects.

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Keywords: intraoperative neuromonitoring; recurrent laryngeal nerve; safety; thyroid surgery; porcine model
Injury to the recurrent laryngeal nerve (RLN) remains a significant source of morbidity during thyroid operations, and it ranks among the leading reasons for medicolegal litigation of surgeons. Unilateral injury can cause significant paralytic dysphonia and dysphagia, in which bilateral injury—a potentially life-threatening problem—places the airway at risk. Routine identification of the RLN has been reported to be associated with lower rates of nerve injury and is regarded as the gold standard of care.

Visual identification of the nerve may sometimes be difficult, especially in cases in which previous surgery, large tumors, or bleeding may impede visualization. Intraoperative neuromonitoring (IONM) has been applied to add to visual information and to facilitate localization and identification of the RLN during thyroid surgery. IONM has been used as a means not only to localize and identify the RLN, but also to predict cord function and to elucidate the mechanism of injury during surgical dissection of the RLN.

In addition to RLN stimulation, vagal stimulation has been recommended by some authors as a standard procedure intraoperatively, to ensure that neural testing is not performed distal to the site of RLN injury. IONM thus implies repetitive direct electrical stimulation of the vagus nerve and the RLN throughout the operation. Concerns have been raised regarding the safety of repetitive electrical nerve stimulation on the vagus and the RLN. In addition, there is no consensus about which stimulation intensity level should be used to obtain a safe and reliable evoked electromyographic (EMG) response.

A prospective human study with repetitive nerve stimulation for investigating the optimal safe stimulus intensity has not been performed. The aim of this study was to develop a pig model to investigate the optimal electrical intensity for reliable stimulation and safety of repetitive RLN and vagal stimulation during IONM.

MATERIALS AND METHODS

Animal and Anesthesia. Duroc–Landrace male piglets (n = 8; weight, 18–20 kg) were obtained through the laboratory animal center of Kaohsiung Medical University. The animal-use protocol was approved by the Institutional Animal Care and Use Committee of Kaohsiung Medical University (protocol no. 97146). Piglets were fasted for 8 hours but were allowed water before the experiment.

Piglets were anesthetized with intravenous thiopental (15 mg/kg), after which a nerve integrity monitor (NIM) EMG endotracheal tube (Medtronic Xomed, Jacksonville, FL) size #6 was inserted by a single anesthesiologist (IC Lu) without administration of a neuromuscular blocking agent. The tube was placed with the middle of exposed electrodes well in contact with true vocal cords under a direct laryngoscope. General anesthesia was maintained with sevoflurane (1% to 2%), and the piglets were control ventilated. Physiological monitors, including electrocardiography (EKG), oximetry, end-tidal CO₂, and airway pressure, were continuously monitored.

Equipment Setting. The channel leads from the NIM EMG reinforced endotracheal tube were connected to the NIM-Response 1.0 monitor (Medtronic Xomed). A Prass monopolar probe (Medtronic Xomed) was used in direct contact with the vagus nerve and RLN for nerve stimulation. The stimuli were generated from the NIM-Response 1.0 monitor for vagal and RLN stimulation. The NIM-Response 1.0 monitor was set to run with a 50-ms time window and an amplitude scale at 0.2 mV/division. Event capture was activated with a threshold at 100 µV. Peak-to-peak amplitudes of evoked EMG activities were read directly on the monitor screen.

Operation and Experimental Design. After surgical disinfection, a midline vertical cervical incision was made for exposure of the neck and the larynx. Bilateral vagus nerves and RLNs were identified and dissected free from overlying soft tissue and fascia (see Figure 1).

Each nerve was stimulated using a current of 0.1 to 1.0 mA (stepwise by 0.1-mA increments), 1.5, 2.0, 2.5, and 3.0 mA, and the baseline amplitude, latency, and waveform morphologies of EMG response were observed and recorded. The pulsed stimuli were 100 µs in duration and were repeated at 4 pulses/second (4 Hz). The stimulus current that first evoked a clear-cut EMG activity of >100 µV was also recorded and defined as the nerve stimulus response threshold.

After the documentation of baseline neuromonitoring parameters, the vagus nerve was continuously stimulated for 10 minutes (3.0 mA; 4 Hz; width, 100 µs) with a 2-second interval
between each minute for recording the EMG signal. Then the RLN was also continuously stimulated with the same electrical current level and time. All changes in amplitude, latency, and threshold of the EMG signal and EKG monitoring (heart rate and rhythm) were recorded.

All the testing and recording were performed completely on 1 site before testing the other side to minimize the change of the electrodes’ contact resulting from manipulation or traction. The nerve stimulation field was maintained bloodless by meticulous dissection. No electrical cautery was used with bleeding vessels around the nerve.

RESULTS

Baseline EMG Activities. The mean vagal and RLN stimulation thresholds were 0.24 mA (range, 0.1–0.3 mA) and 0.21 mA (range, 0.1–0.3 mA), respectively. The amplitudes of EMG signals at different nerve stimulation levels are shown in Table 1. There was a positive correlation between the stimulus current and the resultant laryngeal EMG amplitude (see Figure 2). As expected, EMG amplitude reached a plateau as stimulating current was increased. The minimal stimulus current that could evoke a maximal response was 0.7 mA in the vagus nerve and 0.5 mA in the RLN (Table 1 and Figure 2). Latencies of the left and the right vagus nerves differed as expected (based on differential lengths) and were 8.45 ms on the left and 6.52 ms on the right. Latencies of the left and the right RLNs were 3.28 and 3.23 ms, respectively.

EMG Changes after Continuous and Repetitive Nerve Stimulation. After continuous pulsatile vagal stimulation for 10 minutes, the amplitudes of the EMG signal from the vagus nerve measured 987/365 lV, which was 99.7% compared with the neuromonitoring signal of the baseline amplitudes (Table 1), and was not significantly lower (p = .25; Figure 3). The final

<table>
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<tr>
<th>Stimulus level, mA</th>
<th>No. of response</th>
<th>EMG amplitude, μV</th>
<th>%*</th>
<th>No. of response</th>
<th>EMG amplitude, μV</th>
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<tr>
<td>0.1</td>
<td>2</td>
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<td>50.5</td>
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Abbreviation: EMG, electromyography.
*Mean percentage of response using amplitude from 3.0-mA stimulation as reference.
†After repetitive stimulus.
amplitudes after continuous stimulation of the RLN were measured at $1024 \pm 214 \, \mu V$, which was 99.8% compared with the EMG signal of the baseline RLN amplitudes (Table 1), and was not significantly lower ($p = .70$; Figure 3). In addition, the latency and threshold of the signals were constant throughout the entire period of nerve stimulation.

**Changes of Cardiopulmonary Status.** Throughout the entire period of nerve stimulation, there were no changes of sinus rhythm or marked changes in heart rate. The end-tidal CO$_2$ was kept at 40 to 55 mmHg, and peak airway pressure was kept at $<15 \, \text{cmH}_2\text{O}$.

**DISCUSSION**

Although several techniques to monitor RLN function have been described and reviewed,$^7,14$ most rely on EMG recordings derived from the laryngeal musculature after stimulation of the RLN with electrical current. EMG recordings can be subdivided into 4 separate techniques: (1) needle electrodes inserted into vocalis muscles by direct laryngoscope or (2) through the cricothyroid ligament; and (3) surface electrodes placed against the postcricoid area or (4) surface electrodes attached to endotracheal tubes to contact the vocal cord directly. We selected the endotracheal surface electrode system for use because of the essential advantages apparent during human work and in other animal studies, including ease of setup and use, noninvasive nature, capacity as a surface electrode to contact larger areas of the target muscle, and summated EMG.

Similar to EMG monitoring of the facial nerve, which is commonplace in surgery of the temporal bone and parotid gland, IONM of the RLN is now gaining acceptance. However, several pitfalls$^{11}$ and lack of standardization$^{14}$ continue to limit the utility of this technology. Currently, estimates suggest that nearly 25% of U.S. thyroid surgery is performed with IONM. Some researchers$^{7,8,14,15}$ have worked on
formulation guidelines or standards of IONM, which may help to solve the potential pitfalls and ease the application and interpretation of IONM. Multiple workers have also declared the safety of repetitive vagus nerve stimulation during thyroidectomy. Most results are based on the clinical experience or retrospective review, and there is still no consensus about which intensity of electrical current should be used as a safe and optimal stimulation to obtain a reliable evoked EMG response.

In this porcine model, we showed that the EMG assessment through endotracheal surface electrodes is sensitive for detecting an evoked response to low-level neural stimulation current. We also showed that a dose–response curve exists with increasing EMG amplitude as stimulating current was increased and that maximum EMG amplitude can be obtained on both vagus nerve and RLN stimulation at <1 mA (see Figure 2). This study also verified the neural and cardiopulmonary safety of repetitive vagus nerve and RLN stimulation during IONM. This information will greatly help to reduce the concerns of nerve injury for thyroid surgeons and to facilitate formulation of a valid guideline for the use of electrical stimulation during IONM.

In this study, the mean stimulus threshold for response was 0.24 mA in the vagus nerve and 0.21 mA in RLN, similar to that in other clinical human studies using the same device. In our clinical experience of more than 400 human nerves, when proper position of electrodes was confirmed by fiber-optic laryngeal examination and the nerve stimulation area was bloodless and free of fascia, the EMG response could be elicited with a stimulation level of 0.3 mA from both the vagus nerve and the RLN. A limitation of our study was the small number of animals and thus the limited number of EMG samples. We intended this study to be an initial pilot study to generate initial normative porcine samples. We intended this study to be an initial pilot study to generate initial normative porcine samples. In this study, we chose the pig as the model for investigation because the pig's larynx structure is comparable to that of humans, and recent studies have shown that the neuromonitoring parameters of pig are comparable to those of humans. Indeed, the EMG activities recorded in this study, including the threshold, latency, amplitude, and the dose–response curve between the EMG amplitude and stimulating current, are also comparable to the human data reported by Randolph. However, translation of these data to humans should still be done with caution. One thing that must also be noted is that the EMG data, especially the amplitude, is
a very inconstant parameter because it changes under different circumstances, such as manipulation on the trachea, dislocation of the tube electrodes, tissue preparation, and changes in the operation field including bleeding, which clearly reduces the sensitivity of stimulation. To minimize this potential bias, all the testing and recording in this study were performed completely on 1 site before testing the other side, to avoid the change of electrodes’ contact resulting from manipulation or traction. In addition, no electrical cautery was used during preparation of the nerves; the surgical field was maintained strictly bloodless, and the nerves to be stimulated were dissected free of fascia. We believe that these principles, while applied during IONM in clinical practice, will allow EMG parameters to become more reliable and provide accurate prediction of postoperative vocal cord function.

CONCLUSION
In summary, we demonstrated the sensitivity and safety of electrical nerve stimulation during IONM in this study. Although repetitive higher current is well tolerated, minimal current that required generating the maximal evoked EMG, which showed approximately 1 mA in this study, should be selected to minimize the potential risk of nerve damage and false results during IONM.

Acknowledgments. The animal use protocol was approved by the Institutional Animal Care and Use Committee of Kaohsiung Medical University (protocol no. 97146).

REFERENCES