Intraoperative Monitoring: Normative Range Associated With Normal Postoperative Glottic Function

Diana Caragacianu, MD; Dipti Kamani, MD; Gregory W. Randolph, MD

Objectives/Hypothesis: Despite increasing use of intraoperative nerve monitoring (IONM), there is limited information on normative electrophysiologic electromyographic (EMG) parameters. The objective of this study was to define normative parameters of recurrent laryngeal nerve (RLN) intraoperative neuromonitoring during thyroid surgery associated with normal postoperative vocal cord function.

Study Design: Prospective data collection in a tertiary care center.

Methods: Quantitative analysis of evoked waveform amplitude and threshold was performed on 125 patients with 167 nerves at risk. Values were displayed as a mean with 5th percentile and 95th percentiles (5th–95th). Postoperative vocal cord function in all patients was documented.

Results: All patients had normal postoperative laryngeal function (group I–normal) except for two patients who had postoperative transient vocal cord paralysis (group II–abnormal/outlier). The final amplitude between 247 and 3607 μV at the end of dissection/end of surgery was associated in all group I patients with a normal postoperative neural function. Final intraoperative amplitude measures for group II averaged just 97.5 μV, significantly different than our normative ranges obtained for group I, and fell outside of the group I 5% to 95% percentile range (P = .016). Final amplitude adequately predicted postoperative RLN impaired function immediately after surgery.

Conclusions: We propose IONM EMG data criteria that predict normal postoperative vocal cord function monitoring and provide information about nerve functioning at the end of the operation, thereby allowing adaptation of the surgical strategy when a bilateral procedure is indicated to avoid bilateral nerve paralysis.

Key Words: Intraoperative nerve monitoring, recurrent laryngeal nerve, normal parameters, postoperative glottis and/or recurrent laryngeal nerve function, bilateral vocal cord palsy, complications of thyroid surgery.

Level of Evidence: 4

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INTRODUCTION

Unilateral vocal cord paralysis can be associated with voice changes severe enough to necessitate change in vocal function and also significant dysphagia and aspiration potentially resulting in pulmonary complications.1 Bilateral vocal cord paralysis results in loss of airway and tracheotomy. Surgical exposure and visualization of the recurrent laryngeal nerve (RLN) is the gold standard to prevent injury.2,3 However, visual judgment that the RLN is structurally intact does not guarantee normal nerve function postoperatively.4–6 Intraoperative nerve monitoring (IONM) during thyroid and parathyroid surgery is increasingly recognized as an adjunct to visual nerve identification. Recent studies show approximately 53% of general surgeons and up to 65% of otolaryngologists use IONM in some or all of their cases.9,10 The perceived value of IONM by surgeons is made clear by its more common use in expert settings by surgeons with higher volume practices of >100 cases per year.10

Organizational support for neural monitoring is also becoming evident. German practice guidelines suggest IONM be considered for all cases of thyroid surgery and that monitoring has a role in RLN identification, prognostication of postoperative neural function, and avoidance of bilateral vocal fold paralysis, with proven utility in revision surgery.11 In addition the International Neural Monitoring Study Group, which has published detailed guidelines on RLN monitoring, recommends neural monitoring in all patients undergoing thyroid surgery.12 Soon to be published American Academy of Otolaryngology and Head and Neck Surgery (AAOHN) guidelines suggest IONM is an option for patients undergoing thyroid surgery due to 1) proven improvement in RLN identification time, 2) reduction of temporary paralysis rates, and 3) avoidance of bilateral vocal cord paralysis (through prognostication of postoperative vocal cord function). These AAOHN guidelines suggest special utility for neural monitoring in cases of 1) bilateral thyroid surgery, 2) revision thyroid surgery, and 3) surgery in the setting of an existing RLN paralysis.13

From the Division of Thyroid and Parathyroid Surgery (D.C., D.K., G.W.R.), Massachusetts Eye and Ear Infirmary, Boston, Division of Surgical Oncology Endocrine Surgical Service (G.W.R.), Massachusetts General Hospital, Boston, Massachusetts, U.S.A.

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Send correspondence to Gregory W. Randolph, MD, Department of Otolaryngology, Division of Thyroid and Parathyroid Surgery, Massachusetts Eye and Ear Infirmary, 243 Charles St., Boston, MA 02114. E-mail: gregory.randolph@meei.harvard.edu

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Caragacianu et al.: IONM Range for Normal Glottic Function
One of the most important roles of intraoperative nerve monitoring is in the prevention of bilateral vocal cord paralysis. Aside from the obvious significant morbidity and potential mortality of bilateral cord paralysis, it is also the source of significant medicolegal activity, with a recent review describing plaintiff awards of $2.5 million. The utility of incorporating IONM data, including loss of signal, in the surgical plan is well documented by the work of Goretzki et al. A retrospective analysis of 1,333 patients undergoing surgery for benign bilateral disease using IONM showed that loss of neural monitoring signal on the first side of dissection caused the surgical strategy to be changed to successfully prevent bilateral RLN palsy in all patients when the information was used. This was compared to a group in which the neural monitoring information was not used and surgery was continued; in this group 17% of patients developed bilateral vocal fold paralysis.

Several studies show how poor the surgeon is at visually judging RLN injury intraoperatively, with only 10% to 14% of injured nerves being identified intraoperatively by the surgeon as being injured. Numerous recent studies show negative predictive value (NPV) of >95% (i.e., good neural function) is highly correlated with preservation of satisfactory electromyographic (EMG) activity at the completion of surgery. These emerging data suggest that the role of IONM in avoidance of bilateral paralysis by accurate predication of postoperative function of the first side of thyroidectomy is perhaps the most important advantage of IONM.

Clear definition of normative quantitative intraoperative EMG parameters associated with postoperative normal cord function is needed for effective prognostication of postoperative glottic function. We aimed to provide electrophysiologic reference range values for threshold stimulation and amplitude of evoked action potential in the setting of RLN preservation and normal postoperative vocal cord function.

MATERIALS AND METHODS

With institutional review board approval, 125 consecutive thyroid surgeries placing 167 RLNs at risk, performed by a single surgeon (G.W.R.) in a tertiary surgical practice were included.

All patients underwent pre- and postoperative laryngoscopy to assess vocal cord function. All patients who had normal pre- and postoperative laryngeal exams constituted group I–normal, and two patients who had abnormal postoperative vocal cord function constituted group II–abnormal/outlier. IONM was applied according to strict study protocol with standardized setup in accordance with published International Neural Monitoring Study Group guidelines. In all patients there was effective electrode placement, successful neural identification, and stimulation with evoked EMG recording.

The following measures of amplitude were assessed at 1 mA and 2 mA stimulation: initial, final, minimal, maximal. The final measurement was obtained after all surgery was completed on the first side and results from stimulation of the RLN proximal to all neural dissected segments. Amplitude represents the summed motor action unit potentials of the ipsilateral vocal cord muscle as recorded by cordal surface electrodes at the level of the glottis. Threshold is defined as the current that, applied to the nerve, first starts to trigger recognizable minimal EMG activity of >100 μV (Fig. 1).

RESULTS

All patients had normal postoperative laryngeal function (designated as group I–normal) except for two patients who had postoperative transient vocal cord paralysis of 6 to 8 weeks duration (designated as group II–abnormal/outlier).

IONM quantitative parameters assessed included measures of amplitude and threshold. All values are displayed as mean with the 5th percentile and 95th percentile (5th–95th).

Group I–Normal Data

Characteristics of evoked amplitude during surgery at 1-mA stimulation. For group I–normal, at a suprathreshold stimulation current of 1 mA, mean initial amplitude was 898 μV (5th percentile, 144 μV; 95th percentile, 2,050 μV) and mean final amplitude was 1,179 μV (5th percentile, 247 μV; 95th percentile, 3,607 μV). The full range of the final amplitude was 152 μV to 3,843 μV (Table I).

The initial amplitude with a value between 144 and 2,050 μV demonstrates that the system is functional and that the nerve is correctly identified and is functional.
The final amplitude at the end of dissection/end of surgery between 247 and 3,607 μV was associated with a functional nerve at the end of surgery in all group I patients.

**Characteristics of evoked amplitude during surgery at 2-mA stimulation.** To identify the ideal stimulus strength, in group I–normal, 73 nerves underwent 2-mA stimulation. A t test analysis showed no difference between 1-mA stimulation and 2-mA stimulation with regard to amplitude. We also evaluated 22 subjects who received both 1-mA and 2-mA stimulation. Again, there was no statistically significant higher amplitude with 2 mA versus 1 mA, therefore normal range criteria is accomplished using 1-mA values (Table II).

**Threshold stimulation values.** In group I–normal, the mean threshold stimulation current was determined in a subset of patients (n = 36) with a mean of 0.37 mA (5th percentile, 0.15 mA; 95th percentile, 0.80 mA). The mean threshold amplitude was 562 μV (5th percentile, 215 μV; 95th percentile, 1,018 μV) (Table III). Threshold amplitude of 562 μV (5th percentile, 215 μV; 95th percentile, 1,018 μV) was significantly lower than maximal amplitude of ~1,800 μV (P = .0001) at 1 mA (Table IV).

Correlation coefficient analysis of all variables (initial amplitude, final amplitude, difference and percent difference of initial vs. final, minimal amplitude, maximal amplitude, difference and percent difference of minimal vs. maximal) found no relationship between threshold stimulus level and any of these amplitude measures.

**Group II Abnormal/Outlier Data**

The amplitudes of group II–abnormal/outlier are shown in Table V. Average initial amplitude was 378 μV, and average maximum value was 1,521 μV. These initial and maximum values are well within the group I–normal 5% to 95% range. However, for group II–abnormal/outlier, the final intraoperative parameters of RLN stimulation at 1 mA were markedly different than our normative ranges obtained from group I and fell outside of the group I–normal 5% to 95% range. Group II–abnormal/outlier’s final amplitude at end of surgery had a mean of 97.5 μV. This is significantly lower than the group I’s normative range (P = .016). In these patients, final amplitude accurately predicted postoperative RLN impaired function immediately after surgery. Statistical analysis was done using the Kruskal-Wallis test.

**DISCUSSION**

It is known that normal EMG configuration of an evoked potential from vocal cord muscle (thyroarytenoid muscle) implies functional integrity of the RLN. Numerous recent studies show high correlation between preservation of satisfactory EMG activity at the completion of surgery and normal postoperative vocal cord function with NPV of >95%. However, what constitutes satisfactory EMG activity, and what is the normal amplitude range when cordal function is preserved?

Examination of our data revealed that despite the wide range of amplitude there are reliable evoked amplitude potentials that can be used to predict normal vocal cord function. If testing at the completion of the first side of surgery falls within these parameters, normal cord function can be expected in 100% of the patients (Fig. 2). To provide a useful and safe normative lower limit for final amplitude, we excluded the values that fell under the 5th percentile (i.e., <250 μV). The lowest value in group I for final amplitude was 152 μV, and the average for group II final amplitude was 97 μV. We could have chosen 100 μV or 125 μV as our lower limit to provide absolute separation of patients with and without

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**TABLE I.**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Mean</th>
<th>SD</th>
<th>Range, 5th–95th</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial amplitude</td>
<td>898</td>
<td>644</td>
<td>144–2,050</td>
</tr>
<tr>
<td>Final amplitude</td>
<td>1,179</td>
<td>890</td>
<td>247–3,607</td>
</tr>
<tr>
<td>Minimal amplitude</td>
<td>492</td>
<td>343</td>
<td>152–1,362</td>
</tr>
<tr>
<td>Maximal amplitude</td>
<td>1,791</td>
<td>1,096</td>
<td>451–3,843</td>
</tr>
</tbody>
</table>

SD = standard deviation.

**TABLE II.**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Mean</th>
<th>SD</th>
<th>Range, 5th–95th</th>
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<tbody>
<tr>
<td>Initial amplitude</td>
<td>802</td>
<td>690</td>
<td>150–2,274</td>
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<tr>
<td>Final amplitude</td>
<td>862</td>
<td>571</td>
<td>160–1,803</td>
</tr>
<tr>
<td>Minimal amplitude</td>
<td>439</td>
<td>335</td>
<td>110–1,137</td>
</tr>
<tr>
<td>Maximal amplitude</td>
<td>1,468</td>
<td>1,198</td>
<td>270–4,003</td>
</tr>
</tbody>
</table>

SD = standard deviation.

**TABLE III.**

| Threshold and Amplitude at Threshold Information in a Subset of Group I. |
|-----------------------------|----------------|------|----------------|
| Threshold, mA              | 36             | 0.37 | 0.17           |
| Amplitude at threshold      | 26             | 562  | 304            |

SD = standard deviation.

**TABLE IV.**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Mean</th>
<th>SD</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial</td>
<td>248</td>
<td>513</td>
<td>.034</td>
</tr>
<tr>
<td>Final</td>
<td>791</td>
<td>997</td>
<td>.0013</td>
</tr>
<tr>
<td>Minimum</td>
<td>−27</td>
<td>538</td>
<td>.82</td>
</tr>
<tr>
<td>Maximum</td>
<td>1,400</td>
<td>1,125</td>
<td>.0001</td>
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</tbody>
</table>

SD = standard deviation.
vocal cord paralysis. However, those values are nearly inseparable given the wide ranges of amplitudes seen with IONM, and we intentionally wished to provide in our IONM criteria a clear-cut range that would guarantee normal cord function in 100% of patients. All of our injured nerves fell well outside of this range. We recognize rare patients with low values at this threshold may have normal cord function.

Our two patients with vocal cord paralysis had initial and maximal amplitude values within the normal range, which demonstrated clearly that the nerve was functional and the recording system was working at the beginning of surgery. However, at the conclusion of the operation, the final amplitude values were outside the 5% to 95% range (P = .016). These data from the group II–abnormal/outlier demonstrated that despite the wide range and variability of normal amplitudes of evoked EMG responses, it is possible to detect the stimulation change in a nerve that has become neuropraxic. At the conclusion of surgery, the amplitude of 97.5 μV is significantly below the normative range of 247 μV to 3,607 μV (Fig. 2). Statistical analysis for the two outliers was done using the nonparametric Kruskal-Wallis test, as used by studies on quantitative parameters in facial nerve monitoring, where the population is a small sample size and without assumption that they follow a normal distribution.

Our data in Table I represent a systematic approach to interpretation of intraoperative evoked amplitudes. These data are concordant with other studies evaluating normative parameters for RLN monitoring. Lorenz et al.24 also showed similar values for maximal amplitude from 205 μV to 1,986 μV at 2 mA, similar to our data at 1-mA and 2-mA stimulation. Julien et al.,25 demonstrated with 1-mA stimulation a mean initial amplitude of 910 μV and a mean final amplitude of 821 μV, with a range of 100 to 2,906 μV. Obtaining suitable initial evoked amplitude is critical for two reasons: 1) demonstrating that the monitoring system is functional and 2) documenting a functioning nerve at the beginning of the operation. The initial baseline is essential to allow for further interpretation, including loss of signal at the completion of the first side of surgery. The final stimulation provides prognostic information.23,26,27 Other data supporting amplitude as a prognostic parameter are the data of Matthies et al. and Acioly et al. in facial nerve monitoring.26,27

In addition to establishing a range of normative parameters, these data also confirm that intraoperative nerve monitoring repetitive stimulation at the level of 1 to 2 mA is safe and has no adverse effect on the nerve's functional integrity. Initial and final amplitude did not

<table>
<thead>
<tr>
<th>Variable</th>
<th>Average, mV</th>
<th>P Value</th>
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<tbody>
<tr>
<td>Initial amplitude</td>
<td>378</td>
<td>.12</td>
</tr>
<tr>
<td>Final amplitude</td>
<td>97.5</td>
<td>.016</td>
</tr>
<tr>
<td>Minimal amplitude</td>
<td>97.5</td>
<td>.021</td>
</tr>
<tr>
<td>Maximum amplitude</td>
<td>1,521</td>
<td>.79</td>
</tr>
</tbody>
</table>

*Statistical analysis was done using the Kruskal-Wallis test of this population with small sample size and without assumption that they followed a normal distribution.

![Amplitude Measures Demonstrating Normal Range Associated With Normal Vocal Cord Function](image-url)

Fig. 2. Amplitude measures demonstrating normal range associated with normal glottis function. EMG = electromyography; Max = maximum; Min = minimum. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

**Neural Monitoring Success Criteria**

(A) Initial Setup Criteria
- Average initial stimulation at 1mA ideal 900μV – must be > 150μV

(B) Final Prognostic Criteria
- Final average stimulation at 1mA, 1200μV – must be > 250μV
- Final average threshold ideal at 0.37mA – must be less than 0.80μV
  - "Final" = after all surgery is done on one side, do vagal stimulation.
  - If A and B are met, expect normal postoperative vocal cord function, contralateral surgery can be considered.
  - If A and B are not met, consider neural injury, especially if there is a gradient of evoked waveform around possible injured segment with less than 100μV for evoked EMG proximal to injury; consider mapping the nerve injured segment and consider delay and staging of the contralateral surgery.
change with surgical dissection and repetitive stimulation, indicating that these are not harmful to the nerve. Many patients had repeated stimulations >100 times. In concordance with multiple other studies on the RLN and facial nerve monitoring, our findings demonstrate that multiple stimulations throughout the case and surgical dissection does not injure the nerve, and does not dampen the motor unit action potential. Further dissection does not injure the nerve, and does not prevent trauma, and an adequately visualized nerve does not imply a functional nerve. We note the two nerves injured in this study looked grossly normal and intact. Neural monitoring represents a new and accurate functional assessment of the nerve that is significantly more precise than visual inspection of the nerve. Several studies have shown how poor the surgeon is at visually judging RLN injury intraoperatively, with only 10% to 14% of injured nerves being identified by the surgeon as being injured.5,6

In our study we found neural stimulation of 2 mA was equivalent in terms of amplitude generation to stimulation at lower levels of 1 mA. Therefore, we recommend initial stimulation when mapping the nerve at 2 mA, and then once the nerve is visualized reducing stimulation to 1 mA. Julien et al. also demonstrated that there was no difference in amplitude before and after dissection with 1 mA-, 1.5 mA-, 2 mA-, and 2.5-mA stimulation. However, we feel that for the purpose of mapping out the RLN, 2 mA depolarizes a greater sphere of tissue around the probe tip and has utility in the initial search of the nerve.

Our study does show that there is a wide range of amplitude correlating with normal vocal cord function. The magnitude of evoked EMG amplitudes during intraoperative monitoring may vary significantly within a patient and among patients. The substantial variability in the magnitude of the EMG amplitudes obtained during the course of thyroidectomy is likely caused by several major factors: 1) variation in nerve-stimulating electrode probe contact, which in turn may result from variation in contact pressure by the handheld probe; 2) variation in overlying soft tissue and fascia on the nerve; 3) variation in degree of moisture (blood and tissue fluid shunting) in the operative field; 4) variation in laryngeal electrode/endotracheal tube position; 5) temperature and degree of nerve desiccation; 6) variable exact position of motor fibers within the nerve relative to the position of the stimulating probe (i.e., eccentric position of motor fibers is known within the vagus nerve); 7) sex, age, and other morphologic characteristics of the patient; and 8) subtle degrees of vocal cord dysfunction that may not have been detected on preoperative fiberoptic exam. Recurrent laryngeal nerve neuropathy is known in many clinical settings to be graded. It is possible that one of the sources of EMG variability in our normal group is subtle degrees of neuropathy that were not detected on fiberoptic exam that may have been detected with more sophisticated postoperative laryngeal voice lab evaluation or voice survey instrument. However, despite the variation, we feel our data demonstrate that a clinically useful normative range can be established and used for surgical decision making (Fig. 2).

Threshold is another electrophysiologic parameter and may be important to understand as part of a functioning system and part of interpretation of IONM. Our values of threshold stimulation had a mean of 0.37 mA, ranging from 0.15 to 0.80 mA, consistent with previously published values. We found the amplitude response at threshold stimulation is significantly less than maximum stimulation amplitude levels when stimulated at 1 mA. Also similar to these publications, our data show no relationship between threshold stimulation and amplitude of evoked potential.

Noteworthy are the studies by Snyder et al. and Chiang et al. showing 75% of neural injuries occur through stretching of the ligament of Berry, and that the typical scenario is that neural injury occurs in the setting of a visually intact nerve. Visualization does not prevent trauma, and an adequately visualized nerve does not imply a functional nerve. We note the two nerves injured in this study looked grossly normal and intact. Neural monitoring represents a new and accurate functional assessment of the nerve that is significantly more precise than visual inspection of the nerve. Several studies have shown how poor the surgeon is at visually judging RLN injury intraoperatively, with only 10% to 14% of injured nerves being identified by the surgeon as being injured.5,6

Limitations

One limitation of our study is that even though we had a large group for analysis of normative EMG, the number of injured nerves in this human series is very small. Animal studies will likely provide a better environment to determine the EMG electrical signature of injured nerves.

Our study concentrated on specific EMG parameters, focusing on amplitude and threshold. Other EMG parameters may also be useful in providing functional prognostication but have not been thoroughly studied. We chose amplitude and threshold as these are readily available to surgeons with currently available monitoring equipment. From our study, amplitude appears to be very robust in identification of normal vocal cord function and most reliable as a normative parameter for prognostication. Of the EMG parameters, latency and conduction speed are other useful variables in nerve monitoring. Latency has been shown not to correlate well with postoperative motor outcome in spinal cord, facial EMG studies, and vagal studies. We recognize that low amplitude at the completion of surgery may be due to equipment-related issues, and that it is extremely important to adhere to standard equipment troubleshooting algorithms and existing IONM guidelines to keep positive predictive values high. Furthermore, we recognize that one of the sources of EMG amplitude variability in our normal group may be subtle degrees of laryngeal dysfunction not seen on fiberoptic exam.

CONCLUSION

The results of this study demonstrate the utility of normative parameters for intraoperative RLN monitoring. Evoked EMG amplitude is a valid parameter to assess nontransection nerve injury. Based on these detailed data, we can formulate intraoperative EMG criteria, which when present imply normal vocal cord function postoperatively. These criteria are divided into 1)
initial/setup criteria, which inform the surgeon that the nerve has been appropriately identified and that the monitoring system is working, and 2) final/prognostic EMG parameters, which if satisfied correlate with normal vocal cord function postoperatively. If our criteria are met, surgeons may confidently move to the second side of surgery during planned bilateral thyroid surgery (Fig. 2).

Monitoring provides information about nerve functioning during and at the end of the operation, thereby allowing adaptation of the surgical strategy when a bilateral procedure is indicated. In such a case the surgeon can consider deferring second side surgery to avoid the risk of bilateral vocal cord paralysis. The surgeon can also stimulate the affected RLN from the distal-most segment near the laryngeal entry point, sequentially stimulating the nerve retrograde and may be able to then identify the neuroparotic segment. This has great learning implications and may also result in identification of the source of nerve injury, such as suture entrapment of the nerve, which can then be treated.

BIBLIOGRAPHY