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REVIEW

Safety of neural monitoring in thyroid surgery

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ABSTRACT

During thyroid surgery, the functional integrity of the recurrent laryngeal nerve (RLN) is not only threatened by direct nerve injury resulting from accidental transection, clipping or ligation. In fact, indirect trauma, e.g. traction and compression occurring repeatedly throughout gland dissection, contribute to long-term nerve impairment. In order to avoid RLN lesions and preserve nerve function the surgeon must adhere to and comply with a strict standardized intraoperative neuromonitoring (IONM) technique to preserve results, quality and safety.
IONM should be a team work between the surgeon and the anesthesiologist.

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1. Introduction

By conveying both information and emotion in a unique way, the voice represents the essential part of human communication.[1] Although modern thyroid surgery was inaugurated more than hundred years ago, recurrent laryngeal nerve (RLN) injury is still the most dreaded complication. In 1938 Lahey and Hoover first proposed routine identification of the RLN during thyroid surgery, which decreased RLN palsy rates effectively. Today, an overall palsy rate of approximately 11% remains in routine thyroid surgery; 0.5–2% in normal goiters and even up to 20% in cancer, Graves's disease or in redo-thyroidectomies.[2–6] Since approximately 5–7% of the world population suffer from thyroid disease, and approximately 10–15% have to undergo surgery, better RLN protection is clearly needed.[7]

In the late 1960s, intraoperative neuromonitoring (IONM) promised to eliminate RLN injury.[8] While RLN identification was improved by IONM, clinical evaluation showed no significant reduction of the palsy rates.[9–15] New insights into the mechanisms of RLN injury have revealed striking deficiencies of traditional (intermittent) IONM (I-IONM). RLN functional integrity is not only threatened by direct nerve injury resulting from accidental transection, clipping or ligation. In fact, indirect trauma e.g. traction and compression occurring repeatedly throughout gland dissection contribute to long-term nerve impairment.[16,17] Literally, "monitoring" implies watching and checking a condition or parameter over a period of time, allowing for performing necessary action.[18] I-IONM failed to provide this.

In order to overcome these deficiencies, some authors demanded "continuous" intraoperative neuromonitoring.[19,20] Meanwhile several groups presented their first results on real-time, continuous intraoperative neuromonitoring systems (C-IONM).[2–16,16–22] All of the presented C-IONM systems employ the vagus nerve for placement of the stimulation electrode. However, potential side effects of "continuous" vagal nerve stimulation within IONM are virtually unknown.

There is an increasing interest in IONM and in recent years numerous Institutions are beginning to perform more monitored thyroidectomies.[23,24] Attitudes changed with the introduction of non-invasive monitoring devices, the publication of randomized prospective trials, guidelines defining standards both for RLN and superior laryngeal nerve (SLN) monitoring, structured courses and description of clinical, legal and research implications.[2,25–30]

Therefore, it is important to acquaint surgeons with this device, providing them with an overview of the most important issues encountered in practice while offering them practical strategies and tips to improve the safety and quality of IONM performance. Furthermore, it is essential that the safety of a new procedure be established before it is widely used on patients.

International guidelines have been published with the intention to improve the quality and safety of monitoring and to discourage

inappropriate variations on the IONM technique both for the RLN and for the superior laryngeal nerve (SLN). [30,31]

Indeed, standardization has a fundamental role in increasing the security and success of a novel technique. [32] In this regard, the present paper aims to describe the key issues that must be addressed to ensure a safe introduction of I-IONM and C-IONM into clinical practice.

The questions that may arise are: What is different between thyroidectomies with and without IONM? Do these differences produce any side effects? Do side effects affect routine surgical practice?

In detail, concerns about IONM safety might arise from the following issues:

- Anesthesia
- Vagal nerve (VN) dissection and placement of stimulation probe
- Stimulation of the nerves
- Surgeon's methodology

2. Anesthesia

2.1. Induction and electromyography (EMG) – endotracheal tube insertion

Different IONM techniques have been proposed, including laryngeal palpation, glottic pressure monitoring, glottic observation, endo-scopically placed intramuscular vocal cord electrodes, intramuscular electrodes, endotracheal tube-based surface electrodes, and post-cricoid surface electrodes. [30]

The system of endotracheal tube-based surface electrodes has become popular for IONM of RLN in thyroid surgery because of its essential advantages, including ease of setup and use, noninvasive nature, and the capacity as a surface electrode to contact larger areas of the target muscles and summate EMG. [23,24,30]

Various authors have suggested to use larger size tubes, to avoid lubricants on the surface of the tube, or to use neuromuscular blocking agents, in order to achieve a perfect contact between the mucosa of the vocal cords (VC) and the surface electrodes, and to evoke and monitor EMG activity throughout the entire thyroidectomy. [33–43] Laryngeal injury, and particularly VC lesions caused by intubation and extubation, are related to some risk factors such as physical trauma itself from the tube, tube size, movement of the tube, duration of intubation, cuff pressure and design, and type of anesthesia. [33–43] The incidence of such damage is high, ranging from 3% to 73%. [33–43] As for thyroid procedures, one study found the incidence of VC injuries due to intubation and extubation to be higher than that of RLN injuries (31% vs. 6%). [36]

The use of neuromuscular blocking agents improves outcome as regards laryngeal injuries: without neuromuscular blockade the VC damage rate is about 42% as opposed to 8% with neuromuscular blockade. [33–43] It is important to assess whether there could be reasons to accept the high risk of VC damage during thyroidectomy without neuromuscular blockade. Pharmacodynamic studies on the effect of curare on the voluntary muscles demonstrate that the respiratory muscles are the least susceptible to its pharmacological effect. [33–43] While, on the one hand, curare has minor effects on the respiratory muscles and the effects are short-lived because of the fast washout due to the wide vascular perfusion of these muscles, on the other hand it appears clear that the risk of VC damage while intubating without curare for reasons of neuromonitoring is very high. [33–43] These conclusions were confirmed by the work of Marush et al. [41] who evaluated curare's efficacy for neuromonitoring. They concluded that laryngeal nerve monitoring is possible even during curare's effects, [41] so by using rocuronium or succinylcholine we can achieve excellent conditions for intubation. Thus, the use of neuromuscular blocking agents (NMBAs) in monitored thyroidectomy is essential to achieve clinically acceptable tracheal intubating conditions and to prevent laryngeal trauma.

As NMBAs can be a potential cause of false-negative responses during IONM, [33–43] it has been suggested to use a short-acting NMBA to allow adequate relaxation and ease of EMG endotracheal tube insertion during IONM, for instance 1–2 mg/kg succinylcholine. [43] However, succinylcholine, being a depolarizing NMBA, is associated with a variety of adverse effects, such as cardiac dysrhythmia, hyper-kalemia, and malignant hyperthermia. [43] Consequently, most anes-thesiologists use nondepolarizing NMBAs for reasons of safety. [33–43]

When nondepolarizing NMBAs are used, the NMBA dose and the time point of nerve stimulation are critical for successful IONM, although some studies have reported the feasibility of IONM after administration of a nondepolarizing NMBA during thyroid opera-tion. [33–43] One study [43] demonstrated that in patients who received two effective doses (ED) of rocuronium (0.6 mg/kg), 30 minutes after rocuronium injection the correlated twitch of neuromuscular transmission was < 5% and the rate of positive EMG response from vagal stimulation was only 53%; only at 55 minutes after rocuronium injection did the rate of positive EMG response reach 100% in these patients. Furthermore, the mean EMG amplitude was markedly lower from the time point of 30 to 60 minutes after rocuronium injection. [43] Therefore, 2 ED of rocuronium used for general anesthesia induction might cause a false-negative response at the early stage of the operation. We recommend that 1 ED of rocuronium (0.3 mg/kg) be used as the optimal dose for IONM without the application of neuromuscular transmission monitoring during thyroid surgery. Positive and high EMG signals were obtained in all patients at an early stage of operation and satisfactory intubation conditions were achieved in most patients. [43]

Moreover, after intubation of EMG endotracheal tube, significant change in electrode position may occur as the patient's neck position is changed from neutral to extended. Poor contact between the exposed electrodes and true vocal cords may happen and that can result in monitor dysfunction. The incidence of monitor dysfunction has been reported to range from 3.8% to 23%. [33–43] Malpositioning of the EMG endotracheal tube was found the most common cause of equipment-related problems in several studies. Lu et al. [38] reported that six cases (5.6%) of monitor dysfunction among 106 patients were all caused by the malpositioning of electrodes. Also, Dionigi et al. [44] reported that 15 patients (10%) needed further tube adjustment in-traoperatively because of nonoptimal contact between endotracheal surface electrodes and vocal cords. Therefore, routine verification of proper electrode position when the patient is fully positioned should be a standard procedure to substantially reduce the overall moni-toring problems encountered intraoperatively. [30,33–43] The presence of normal baseline and adequate measures of impedance as read on the monitor (impedance value < 5 kΩ; impedance imbalance < 1.0 kΩ) only imply adequate contact between the recording electrodes and the body, not necessarily correct positioning of the electrodes. Several assessments, such as respiratory variation, tap test, depth of EMG tube insertion and repeat laryngoscopy (direct laryngoscopy or fiber-optic laryngoscopy) have been promoted as tube-position verification tests, but repeat laryngoscopy after patient positioning represents the most accurate method and takes only a few minutes for tube positional assessment. [30]

2.2. Maintenance of anesthesia

It is of note that combinations of nitrous oxide and halogenated agents, or a combination of propofol and remifentanil, and in-travenous narcotics do not affect EMG readings. [30,37] In routine

clinical practice, most used are combinations of nitrous oxide and halogenated agents or a combination of propofol and remifentanil.[30,37] The depth of anesthesia from these agents must be sufficient to avoid any spontaneous activity of the vocal cords.[30,37] This level of anesthesia may be deeper than usually employed when neuromuscular blockage is used. If baseline EMG activity is substantially high because the level of anesthesia is too low, it will be difficult to differentiate spontaneous activity from intentionally evoked (i.e., stimulated) activity.

According to recent observations by Bacuzzi et al., propofol and remifentanil provide a rapid onset of anesthesia and rapid recovery, low incidence of postoperative nausea and vomiting, and can be used safely in patients susceptibile to malignant hyperthermia and greater depression of pharyngeal and laryngeal reflexes.[37] Thus, this drug combination may be suggested for proper maintenance of anesthesia in monitored thyroidectomy.

3. Vagal nerve (VN) dissection and probe placement for I-IONM and C-IONM

A better understanding of the anatomy of the carotid sheath and the VN may be useful not only to minimize complications but also to guarantee an accurate IONM. Recently there have been efforts to enhance the knowledge of the surgical anatomy of the carotid sheath and the vagal nerve, and to describe techniques for safe access to the carotid sheath.[45–47]

3.1. Surgical anatomy

Medial location of the common carotid artery (CCA) and anterolateral or lateral location of the internal jugular vein (IJV) are the most common configurations in the carotid sheath.[45–47] Few cases of medial IJV position are observed.[45–47] Tortuosity, kinking, or coiling of the extracranial carotid arteries may be observed with advancing age.[45–47] Neck anatomy can be altered by previous surgery (carotid stenting, cervical spine surgery, previous lymph node dissection, etc.).

The location of the VN in relation to the CCA and IJV is classified as anterior (A), posterior (P), posterior to internal jugular vein (Pj) or posterior to the common carotid artery (Pc).[45–47] Most VN lay in the posterior region of the carotid sheath in the groove between the two vessels. The P location of the VN is the most common configuration observed on either side, followed by the Pc (15%) and Pj (8%) locations. Less than 5% of cases with A location are observed overall.[45–47]

The above description is useful in the intraoperative setting. If the surgeon does not initially identify the VN, or is not confident with carotid sheath dissection as in the case of reoperative surgery, a large goiter, endoscopic thyroidectomy, or a hostile neck, VN identification may be safely expedited with an increase in probe-stimulation amplitude to 2–3 mA without initial blind dissection of the carotid sheath.[45–47]

3.2. Access to the carotid sheath

Access to the carotid sheath for VN stimulation can be achieved safely in three different ways[45]:

– *Anterior (or median) approach,* through and between the thyroid lobe medially and the infrahyoid muscles (strap muscles) laterally (sternohyoid, sternothyroid, thyrohyoid, and omohyoid). Positive identification of the carotid sheath is favored by gentle retraction and elevation of the thyroid gland in a medial direction and by using lateral countertraction on the sternothyroid muscle. This is the most

frequently used access and is commonly used for benign goiters and direct/cervical/neck endoscopic thyroidectomy.
– *Modified anterior (or intermedian) approach,* in between the sternothyroid muscle (medial) and the sternocleidomastoid muscle (SCM) (lateral). Identification of the carotid sheath is achieved by medial retraction of the thyroid gland and the sternothyroid muscle together and lateral elevation to some extent of the SCM. The technique is useful in re-do operations, thyroidectomy for cancer, and central and lateral compartment lymphadenectomies.
– *Lateral approach.* This access method is commonly used for remote (from the armpit) endoscopic thyroidectomy. Carotid sheath identification is guaranteed by a posterior approach, lateral and posterior to the SCM.[45]

3.3. Dissection and stimulation of the VN

In order to allow safe dissection and stimulation of VN, different approaches have been described.

3.3.1. Open technique

Nicely elevate the SCM freeing the muscle from the underlying IJV and CCA. Free the carotid sheath from any muscle fibers as these could interfere with the stimulation. VN is identified in the carotid sheath at the lower pole of the thyroid gland at a very early stage of the operation. By sharp dissection, open the carotid sheath. Begin to sweep fatty and areolar tissue in the carotid sheath. The VN is exposed by dissecting the carotid sheath from just a 10-mm to 15-mm pouch with dedicated tiny spatulas and debrider-aspirator (Karl Storz, Endoskope™, Tuttlingen, Germany). Thus, not all of the carotid sheath is completed and routinely inspected. Options for dissection and controlling of hemostasis during this stage must exclude any energy-based devices to prevent thermal injury to the VN. The VN is routinely stimulated with a current/intensity of 1-mA in the surgical field by the application of a stimulator probe. If VN is not initially identified, probe-stimulation amplitude is increased to 2–3 mA to expedite VN identification in the carotid sheath. Most stimulators have a 10 cm handle, and a 9 cm-long probe with a flexible and adaptable tip of 0.5 mm. The probe's design is useful for endoscopic cervical thyroidectomy: the flexible tip of the stimulating probe allows good access to neural structures in areas outside the surgeon's field of view.[45] The probe is insulated to the tip to prevent current shunting. Stimulation duration is set at 100 µs, frequency at 4 Hz, and event threshold at 100 µV. The monitor is set with a stimulation artifact suppression of 2.1 ms. Positive identification of VN is identified by an audible signal and is also seen as a corresponding bi-phasic waveform EMG signal of the IONM monitor (intact function of RLN). The technique described is useful in both conventional and endoscopic thyroidectomy and both for intermittent IONM and some continuous IONM probes (anchor probe). A negative EMG response following distal VN stimulation should lead to vagus stimulation at the upper pole of the thyroid lobe.[45] If this signal is positive, a non-RLN can be assumed and a complete mobilization of the vagus in these patients is required to identify the origin of the non-RLN. In detail, on the right side, the absence of an EMG signal at this early stage is considered suggestive of the presence of a non-recurrent laryngeal nerve (NRLN).[46] In the presence of a negative signal, the left vagus nerve must be also be checked to assess the position of the endotracheal tube, to minimize the possibility of a false-negative finding due to tube rotation. When NRLN is suspected, careful dissection of the vagus nerve is performed, including a check for signal cranially, close to the carotid bifurcation. When EMG is reported, dissection is oriented toward the likely location of the NRLN. Therefore, a check of the branch running to the laryngeal cartilage

is performed to assess the electric signal. Further confirmation of NRLN function is highlighted also by using the "laryngeal twitch" during neurostimulation. If there is a negative EMG response at this point, other problems, such as a technical defect, the application of muscle relaxants, or a nerve palsy, might be the reason for this phenomenon.[45]

3.3.2. Closed method

This technique was described in detail by Wu et al.[47] Instead of the conventional VN stimulation method, in which the VN is exposed and directly stimulated with 1.0 mA, a novel method of VN stimulation without vagus nerve exposure was applied.[45] A ball-tip probe is simply pressed onto the space between the CCA and IJV. When the nerve is deeply located, the probe can be pressed with force without fear of penetration injury to the carotid sheath. In detail, the carotid sheath was identified by gentle medical retraction of the thyroid lobe and laryngotracheal complex and by lateral countertraction on the sternothyroid muscle and sternocleidomastoid muscle. Without dissecting the carotid sheath to expose the vagus nerve, the ball-tip probe (nerve stimulator) is simply pressed and mapped onto the space between the CCA and IJV with a 3-mA stimulus current. In some cases of large goiters or re-do surgery, in which the carotid sheath is not directly visible, the surgeon can feel and palpate the periodic pulsation of the carotid artery, and the VN stimulation can be performed by stimulating around the carotid artery that is felt by the surgeon's finger.[45] The results of Wu et al. show that using a ball-tip nerve stimulator and 3-mA stimulus current for indirect VN stimulation is not only feasible but also reliable, rendering vagal stimulation simple and safe during IONM of the RLN.[47]

3.3.3. Circumferential 360° VN dissection

To recognize imminent RLN injury, thus avoiding nerve palsy and to overcome the main obstacle of standard (intermittent) IONM, i.e., diagnosis of loss of signal (LOS) when RLN lesion has already occurred, C-IONM has been developed in recent years.[16,20–22] Indeed, standard (intermittent) IONM limits the evaluation of the functional integrity of the RLN to the short time interval of stimulation and the site of direct stimulation. C-IONM benefits from special vagus electrodes and provides continuous "on-line" information on changes of amplitude and latency during dissection. C-IONM is able to test the integrity of the RLN during dissection, allows permanent evaluation of the RLN, and thus might perceive imminent RLN stress, risk, danger, and failure. Surgical maneuvers can be correlated to nerve function by synchronization of anatomy and function of the preoperative intact RLN.[16,20–22] Theoretically, in case of a weakening EMG signal the surgeon reacts early intraoperatively to the RLN stress/risk/danger/injury/failure and RLN injury becomes reversible.[16,20–22] Several C-IONM probes are available commercially, with differences in design, geometry, size, adaptability, versatility, hindrance and mode of stimulation (bipolar vs. monopolar).[16,20–22] The most common C-IONM probes have a closed design and geometry. This is essential to prevent any dislocation of the C-IONM probes and for an EMG signal that has stable amplitude and latency.[16,20–22] Therefore, they must surround the VN completely. Thus, a circumferential dissection of the VN is required: for optimal placement, the vagus nerve is dissected 360° at the carotid sheath by means of an approximately 15-20-mm pouch and subsequent gently positioning of the C-IONM probe. We suggest to avoid dissecting arterial and venous blood supply of the nerve while preparing its course. Keep the surgical field dry with a swab to avoid any artifacts and/or signal shunting. The authors agree that, ideally, C-IONM probes should be available in different sizes and optimized for different situations and distributions of the VN. In fact, VN position may differ between patients and the size

may increase during the surgical procedure for local edema.[16,20–22] If the surgeon doing the implantation has different sizes and adaptable C-IONM electrodes available in the operating room, then the most appropriate one for the patient can be selected at the time of implantation. Finally, visually inspect the C-IONM electrode to ensure that it is completely attached around the nerve, without pinching the nerve.

4. Stimulation of the nerves

In general, issues regarding safety of stimulation might be perceived to concern:

a. Direct trauma to the nerve by the stimulator itself.
b. Stimulation-induced tissue trauma due to
   – Intensity level (tissue is over-stimulated),
   – Stimulation rate (greater than physiologically tolerated),
   – Duration of the stimulation (fatigability).
c. Stimulation in pediatric patients and patients with co-morbidities.
d. Systemic effects of VN stimulation (VNS).

For items (a)–(c), there is robust evidence from the literature that stimulation is safe.[48] Therefore we will analyze only item (d) in detail.

4.1. Potential side effects of C-IONM via VNS

The relatively new technology of C-IONM via VNS is increasingly being applied in thyroid surgery. The required nerve stimulation and EMG recording technology has been approved according to international standards, but clinical side effects of continuous vagal nerve stimulation must be deduced from therapeutic VNS, even though different stimulation parameters are used in C-IONM. Generally, implantation and application of therapeutic VNS systems is considered safe, resulting in negligible mortality and low morbidity. The vagal nerve as a mixed cranial nerve comprises mostly parasympathetic fibers (20% afferents and 80% efferents).[49] Therapeutic VNS for epilepsy and depression relies on afferent stimulation. Typically, two helical bipolar platinum electrodes are wrapped around the left vagus nerve distal to the superior laryngeal nerve and superior and inferior cervical cardiac branches. The generator typically provides 0.5-ms pulses at 10–30 pulses per second (pps) for 30 seconds, every 2–4 minutes.[50] The current output is increased by 0.25–0.5 mA every 2–4 weeks until the optimum current output for stimulation is obtained.[51] Except for the stimulation rate and duration, the stimulation parameters in C-IONM are comparable.

The majority of reported side effects of VNS are temporary. They include voice alterations, dysphagia, altered breathing patterns and pain. As long as C-IONM is applied under general anesthesia during thyroid surgery, these side effects are clinically irrelevant. However, there have also been reports of cardiac arrhythmias or hemodynamic alterations that need to be considered in assessing the safety of C-IONM.[52–54] These events have been reported only rarely, and were attributed to increased parasympathetic activity.

We have performed a preliminary study to determine if heart rate variability analysis (HRVA) could be a suitable tool for measuring autonomous nervous system (ANS) activity and parasympathetic vs. sympathetic balance during C-IONM. Heart rate variability analysis proved to be suitable for identifying and quantifying cardiac effects. In the study, a unique parasympathetic alignment of ANS activity was observed.[55] The following results were obtained using a tripolar stimulation electrode, a supramaximal stimulation current of 0.5–5 mA, stimulation rate of 2–3 pps and a pulse width of 200 μs. In a series of 40 patients comparing HRVA in C-IONM vs. I-IONM we

demonstrated a reduction of overall ANS activity with induction of general anesthesia in both groups (I-IONM vs. C-IONM). Throughout the observed interval comprising VNS, ANS activity showed only little fluctuation. Also, both groups seemed to show the same course of ANS activity. However, detailed analysis revealed significant differences. [56]

4.1.1. Dynamics of the onset of ANS effects during VNS

Most cardiac complications from therapeutic VNS were reported at the onset of stimulation. [57,58] In our study, HRVA accordingly revealed a remarkably prompt and strong shift of the ANS balance toward vagal tone at the onset of VNS; for several minutes, only vagal activity could be detected, and no sympathetic response was noted. [59] This missing counteraction could be one reason why arrhythmia often occurs at the onset of VNS.

4.1.2. Persistence of the ANS effect during VNS

Although pre- and postoperative parasympathetic activity showed high concordance in both groups, parasympathetic activity consistently decreased during VNS for patients of the I-IONM group while it remained consistently high in the C-IONM group. After cessation of VNS, elevated parasympathetic activity was still recorded, resulting in significantly higher vagal tone than in individuals who had not received VNS during thyroid gland preparation. [60]

4.1.3. What influences ANS effects during VNS?

As mentioned above, the stimulation parameters for therapeutic VNS are almost the same as those for C-IONM. However, the stimulation rate is considerable higher in therapeutic VNS, and the stimulation current is incrementally increased by up to 0.5 mA at a time for weeks. Three case series [61–63] have shown that vagus nerve stimulation has the potential to change respiratory patterns during both wakefulness and sleep; in addition, dyspnea and voice changes occurred during VNS. There is evidence hinting that these changes or alterations depend on the stimulation rate, with higher stimulation rates resulting in more significant dyspnea and voice changes. [64] Therefore, we analyzed our C-IONM data with different currents and conducted an animal study testing different stimulation currents and rates.

In C-IONM patients we saw no significant correlation between stimulation current and elevated vagal nerve activity. The in-vivo experiments revealed that only stimulation currents above 10 mA led to a general increase of ANS activity. Interestingly, the stimulation rate has a reproducible and significant influence on heart rate. An increase in heart rate was observed upon stimulation rates above 10 pps. This was accompanied by an increased ANS activity, though mostly in the very-low-frequency domain (VLF). The physiological relevance of VLF is not well understood up to date. Our data suggest that stimulation currents beyond 10 mA and stimulation frequencies beyond 10 Hz provoke a systemic stress reaction, which could impact the safety of C-IONM.

4.2. Effects on the immune system

The immunomodulatory effects of VNS are potentially relevant for surgical patients, as the anti-inflammatory impact attributed to VNS might counteract regular wound healing. [65–69] Until now, no damage to the vagal nerve itself due to the demanding preparation of the vagal nerve has been reported for I-IONM or C-IONM. In carotic endartectomy, however, cranial and peripheral nerve injury is a common complication, occurring in 3–23%. [70] Two randomized controlled trials demonstrated that 8.6% and 6.3% of patients,

respectively, had at least one peripheral nerve injury. [71] Most of these injuries were temporary, but a potential risk for paralysis remains.

In addition to its influence on hemodynamics, VNS-induced parasympathetic predominance has been associated with strong immunomodulatory effects. [65,72–74] Cytokine release of TNF-α especially appears to be highly susceptible to VNS. [74,75] However, proinflammatory cytokines are crucial in postoperative wound healing. [68,69] Consequently, we analyzed serum concentrations of TNF-α before, during, and after the observation interval. Even though described in the literature, no attenuation of TNF-α release was detected in our study. Baseline values provided from every patient prior to surgery further validated the results of cytokine analysis. Blood samples obtained from septic patients in the intensive care unit at our institution were used as internal controls and demonstrated greatly elevated TNF-α serum levels. One could argue that relatively subtle, sterile, surgical trauma as in thyroid and parathyroid surgery does not induce a significant inflammatory response, and therefore no immunosuppressive effect of VNS could be identified. Therefore, in further studies additional analysis of high-mobility group protein B-1 (HMGB-1) could be valuable, as HMGB-1 levels are described to be strongly increased upon cell damage.

4.3. Effects on the lung and the upper intestine

Because of the fact that VNS for C-IONM was used only under general anesthesia, dyspnea or effects on respiratory pattern were negligible. Nausea and vomiting is another well-known side effect of therapeutic VNS, occurring in 2–20%. We did not observe post-operative nausea or vomiting related to C-IONM.

5. Surgeon's methodology

An adverse event is an undesired effect resulting from a new procedure. Such event may be related to the *technology* itself (i.e. malfunction) or to the *surgeon.* Indeed, the surgeon may cause unintended consequences due to inappropriate technique, incomplete learning curve, not using standardized methodology, low experience, and wanting behavior in acquiring and correctly integrating the new procedure.

Strict standardization is usefulness to maintain standards, to obtain better outcomes of surgical treatment, to verify safety of new technology, for technical training and surgical education, and for ratification, repeatability and interoperability.

The standardization of IONM was first proposed and applied by Chiang [8,30] and subsequently improved; it involves several discrete moments:

- *Structured informed consent* (discuss the possibility of staging thyroidectomy)
- *L1* : preoperative laryngoscopy
- *V1* : stimulation of the VN before dissection
- *R1* : stimulation of the RLN at first identification
- *R2* : stimulation of the RLN after complete hemostasis
- *V2* : stimulation of the VN at complete hemostasis
- *L2* : postoperative laryngoscopy
- *Printed EMG documentation*

If a standardized procedure is followed attentively, it supports any intraoperative surgical deliberations (such as the decision to stage thyroidectomy), it assists in modification of surgical technique (refinement) and consolidates the correct evaluation of the results (improvement). The surgeon must adhere to and comply with a strict standardized IONM technique to preserve results, quality and safety; appropriate stimulation protocols must be verified. High-quality IONM is fundamental for making any surgical deliberation, for

safety and to reduce false positive results. The role of the surgeon is critical to have excellent quality of IONM.

An unequivocal definition of normative EMG data is mandatory. The surgeon together with the anesthesiologist should optimize EMG signal, and in particular the *V1* signal, by means of appropriate verification of electrode materials and stimulation protocols, correct EMG tube position and proper use of induction and maintenance anesthesia drugs. Members of the IONM Study Group have proposed a proper definition/level for *V1* amplitude of >500 μV.[30] The *V1* signal is the prerequisite for the correct interpretation, diagnosis and verification of a functional intact RLN, for definition of a "significant" reduction of signal, "re-entry" signal, loss of signal (LOS) and again for the correct evaluation of the results.

6. Conclusion

The surgeon must adhere to and comply with a strict standardized IONM technique to preserve results, quality and safety.

IONM should be teamwork between the surgeon and the anesthesiologist. Verification of proper positioning of the electrodes and carefully delivering NMBAs during EMG endotracheal tube insertion are the key to safe IONM. According to a recent survey on most common agents used for induction and maintenance of anesthesia, NMBAs and propofol/remifentanil were used most frequently (80–96%) in routine clinical practice.[30] Therefore there are no substantial changes in the clinical practice with respect to anesthesia, both induction and maintenance. Hence, there are some advantages for the anesthesiologist in using IONM: (a) IONM indicates periods of light anesthesia, (b) IONM eliminates the need for visual assessment of VC function at the time of extubation and (c) IONM indicates the potential for bilateral vocal cord paralysis.

Appropriate stimulation protocols must always be verified before and during the surgical procedure. *I-IONM* is a safe procedure. There is a consensus about the fact that 1 mA stimulation intensity amplitude is safe.[30] Supramaximal stimulation with 2–3 mA should be used only to localize the RLN and/or the VN. The safety of VN stimulation has been demonstrated for IONM of the thyroid, parapharyngeal space operations, and treatment for intractable epilepsy.[30]

We have to emphasize that *C-IONM* should only be used by surgeons who are well trained or have ample experience with I-IONM. C-IONM via VNS with the regular parameters is safe; a distinct effect on parasympathetic activity is seen, but that seems to have no effect on heart rate, blood pressure and the other systems affiliated with the vagus nerve. Nevertheless, relevant effects could appear when using stimulation parameters "beyond 10", that is, >10 pps and >10 mA.

Disclosure statement
The authors have no conflicts of interest to declare.

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