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ENDOCRINE SURGERY

What are normal quantitative parameters of intraoperative neuromonitoring (IONM) in thyroid surgery?

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Abstract

Purpose This study aimed at definition of normal quantitative parameters in intraoperative neuromonitoring during thyroid surgery that may serve as reference range values. Only few and single center studies described quantitative data of intraoperative neuromonitoring. Definition of normal parameters in intraoperative neuromonitoring is believed to be a prerequisite for interpretation of results and intraoperative findings when using this method. Moreover, these parameters seem important in regard to the prognostic impact of the method on postoperative vocal cord function.

Material and methods In a prospective multicenter study, quantitative analysis of vagal nerve stimulation pre- and postresection was performed in thyroid lobectomies. A standardized protocol determined set up and installation of neuromonitoring and defined assessment of quantitative parameters. Data of intraoperative neuromonitoring were respectively print-documented and centrally analyzed.

Results In six participating centers a total of 1,289 patients with 1,996 nerves at risk underwent surgery for benign and malignant thyroid disease. Median amplitude was significantly larger for the right vs. left vagal nerve, latency was significantly longer for left vs. right vagal nerve and duration of the left vs. right vagal nerve significantly longer. Age disparities were only present in form of significantly higher amplitude in patients below 40 years; however, there is no continuous increase with age. Regarding gender, there was significantly higher amplitude and smaller latency in women compared to men. Duration of surgery revealed a reduction of amplitude with operative time; contrarily, latency and signal duration remained stable. The type of underlying thyroid disease showed no influence on quantitative parameters of intraoperative neuromonitoring.

Conclusions Systematic data of multicenter evaluation on quantitative intraoperative neuromonitoring parameters revealed differences between left and right vagal nerves in regard to amplitude, latency and duration of signal, gender, and age. The nature of thyroid disease showed no significant influence on quantitative parameters of intraoperative neuromonitoring. This study presents for the first time collective data of a large series of nerves at risk in a multicenter setting. It seems that definitions of "normal" parameters are prerequisite for the interpretation of quantitative changes of intraoperative neuromonitoring during thyroid surgery enabling, interpretation of influence on surgical strategy and prediction of postoperative vocal cord function.

Keywords Intraoperative neuromonitoring · Thyroid surgery · Quantitative parameters · Definition normal values

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Introduction

Intraoperative neuromonitoring (IONM) is widely used as adjunct during thyroid surgery, aiming at unequivocal identification and functional control of the recurrent laryngeal nerves. IONM devices convert muscle activity into acoustic and electromyographical signals. During the past 10 years, the method has technically developed and remarkably spread while gaining strategic importance for intraoperative surgical decision making. Standards for the practical use of IONM are declared and algorithms for its use are designed. Even expert decisions in medico legal litigation affairs concerning thyroid surgery nowadays take IONM results and its management into consideration. However, despite these many fold practical aspects, quantitative parameters of IONM are not yet defined. Thus, interpretation of IONM findings and strategic surgical consequences remain uncertain.

Intraoperative neuromonitoring has evolved from cranial nerve monitoring as, e.g., facial nerve monitoring during parotid surgery [1]. During thyroid surgery, IONM aims at identification of the inferior recurrent laryngeal nerve (RLN), aiding dissection of the nerve as it is exposed within the surgical field, and most important, to suffice prognosis of the nerve's functional integrity with stimulation of the vagal nerve (VN), thus fully assessing the comprehensive current circuit.

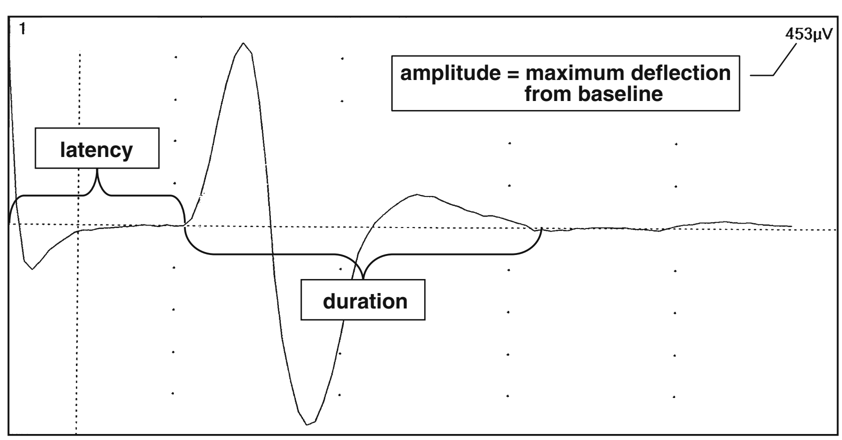
Early methods of IONM studies in humans using intramuscular electrodes placed transcutaneously found laryngeal muscle action with latency of 1.5 to 2.5 ms, amplitudes from 500 to 100 µV, and duration of 4 to 5 ms. Thyroarytenoid muscular activity demonstrated biphasic or triphasic pattern [2]. Measurement of spontaneous activity using hooked wire electrodes at stimulation with 0.2 to 0.5 mA showed activity of 40 to 160 µV [3]. Recruitment of activating muscle fibers depends on the intensity and frequency of the stimulation current, e.g., with stimulation at 30 Hz abductor activity predominates and at 40 Hz adductor activity prevails [4].

The improvement of RLN identification with use of IONM and without disadvantageous effect to the nerve's function was demonstrated in recent studies [5, 6]. However, due to pitfalls using this technology some ambiguity prevails concerning the superior type of electromyogram (EMG) registration and recording. Moreover, it remains unclear which quantitative EMG parameters should be selected to reliably predict postoperative vocal cord function (Fig. 1). EMG of the RLN and VN represents positive motor unit action potential indicating intact vocal cord mobility but as long as there is a minor form of continuity in the RLN-laryngeal muscle axis preserved, this may also conceal a partial loss of nerve or muscle function. This explains the observation that even in presence of intact electrophysiologic activation vocal cord palsy may be seen [7, 8]. In view of these unresolved issues it was the objective of this study to further enhance standardization of IONM by defining normal quantitative parameters and thereby precede utility and interpretation of IONM to improve intraoperative RLN management.

Methods

IONM was applied in six study centers (Berlin, Dresden, Hagen, Halle, Kaiserslautern, Kassel (German Neuromonitoring Study Group)) for elective consecutive thyroid surgeries with inclusion of unilateral and bilateral lobectomies following patients informed consent and approval by the institutional ethics committee. Subtotal, as well as any other restrictive resective procedures were excluded from the study. All patients underwent pre- and postoperative laryngoscopy to assess vocal cord function. Exclusively nerves at risk (NAR) with intact vocal cord mobility on obligatory pre- and postoperative laryngoscopy were included in this analysis. IONM was applied according to a strict study protocol applying a standardized set up using the noninvasive endotracheal tube surface electrodes monitoring the thyroarytenoid system of Medtronic, NIM 2 (Tolochenaz, Switzerland) with a pulse generator and constant current stimulation at four stimulations per second, stimulation duration of 100 µs and supramaximal stimulation at 2 mA. This system records EMG activity and monitors the thyroarytenoid laryngeal muscle that is innervated by the recurrent laryngeal nerve with EMG depiction, visible on a monitor and additional audio feedback. A filter system for avoidance of background low amplitude noise claims a preset 100 µV threshold for positive IONM EMG activity, and a suppressive circuitry halts IONM during cautery electrical activity to mute artificial

Fig. 1 Quantitative IONM parameters in EMG



EMG-printout depicting defined quantitative IONM parameters audio feedback [9, 10]. A Medtronic flextube (Medtronic, Tolochenaz, Switzerland) with circumferential deduction of IONM activity was used in all cases. This tube allows for a broader area of surface deduction; however, there is no discrimination of laterality in contrast to the bilaterally eccentrically electrode wire pairs of the nonflex tube. The choice of stimulation probes, monopolar or bipolar, single or reusable probes, and tip design used in this study was at the discretion of the individual surgeon as reports showed no relevant difference in the resulting quantitative EMG activity (monopolar 678 μV, bipolar 822 μV) [11]. It is however reported that bipolar probes are less exposed to current spread, therefore enabling a superior discrimination of structures within the surgical field [3]. Anesthesiology was introduced using short-acting nondepolarizing paralytic agent (succinylcholine at 2–2.5 mg/kg). Tube placement was performed with visual control for proper positioning at vocal cord level for the surface electrode contact. Control of impedance at <5 kΩ and imbalance <1 kΩ defined ideal electrode-mucosa contact for intraoperative electrophysiological monitoring [12]. A typical positioning of the tube with deduction of RLN stimulation in humans is at about the fourth to sixth tracheal ring, correlating to the tracheal tube measures of 20 to 22 cm. A baseline noise recording in IONM at 10 to 20 ms may be seen when the threshold is lowered accordingly. As muscle relaxation for introduction of anesthesia wears off, a coarse waveform of small amplitude represents the spontaneous respiratory activity varying between 30 and 70 μV that is usually muted by the 100 μV threshold preset. An increasing of coarseness and amplitude of these waveforms may be early indicative of patient's awakening from superficial anesthesia.

IONM quantitative parameters of the vagal and recurrent laryngeal nerves assessed were latency, amplitude, and duration. Latency is defined as time measured in milliseconds between stimulation artifact and onset of EMG activity. Amplitude is defined as the magnitude of EMG wave measured in microvolts. Duration is defined as latitude of the signal's waveform measured in milliseconds.

Discrimination between stimulation artifact and evoked response ("real EMG nerve signal") is made most reliably by the presence of latency that can only be registered by neural EMG activity. Additionally, wave configuration is different. While stimulation artifact is characterized by a sharp and early spike, neural EMG activity results in broader and later deformation of baseline with a typical biphasic course.

False positive EMG as, e.g., stimulation of a RLN with definite palsy resulting in an EMG activity with typical latency and wave form may be explained by shunting through the trachea directly to the subglottic electrodes or by an incomplete current block within the anatomically intact however functionally injured nerve fibers of the RLN or VN. Manipulation-induced potentials may occur throughout the case with stretching, mechanical manipulation, coagulation, fluid irrigation, or temperature changes. Repetitive or continuous spontaneous passive potentials should, however transient, be attended to as these may indicate neural stress and impending nerve injury.

Results

In six centers a total of 1,289 patients with 1,996 nerves at risk were included in the study. There was a ratio between female and male of 8:3 with a median age of 55 years (11–89). Indication to surgery included benign nodular goiter, autoimmune thyroid disease, and thyroid cancer. There were 1,139 (88%) primary and 150 (12%) recurrent surgical thyroid interventions performed.

All values are displayed as median $\tilde{x}$ with the 10th percentile P_{10} and 90th percentile P_{90}, cited as short form notation $\tilde{x}$ (P_{10}, P_{90}).

IONM parameters over all: vagal nerves

Evaluation of the total study population revealed median values for the left VN as follows: amplitude 460 μV (138.0, 1,240.5), latency 5.90 ms (5.00, 7.03), and duration 9.38 ms (7.42, 11.72). Median values for the right VN showed amplitude at 511 μV (168.3, 1,592.80), latency 3.91 ms (3.13, 4.69), and duration 8.59 ms (6.64, 11.72). Thus, median value of amplitude on the right VN is significantly ($p<0.001$) larger and latency significantly ($p<0.001$) shorter compared to the left VN, whereas duration was similar (Table 1).

IONM parameters over all: recurrent laryngeal nerves

Regarding the RLN, median values for the total study population revealed for the left RLN: amplitude at 719 μV (205, 1,766), latency 2.73 ms (1.95, 3.91), and duration 7.42 ms (5.47, 9.77). Median values for the right RLN showed amplitude 622.50 μV (206, 1,986), latency 2.73 ms (1.95, 3.91), and duration 7.42 ms (5.47, 10.16). Thus, median value of amplitude of left and right RLN showed no significant differences. Latency and duration were nearly identical between left and right RLN (Table 1).

IONM parameters according to indication to surgery: vagal nerves

According to indication to surgery, median values for the left VN showed for benign nodular goiter: amplitude at 448.50 μV (141, 1,194), latency 5.90 ms (5.00, 7.03), and duration 9.38 ms (7.42, 11.72). In the indication subgroup of autoimmune thyroid disease median values were: amplitude

Table 1 Overall quantitative IONM parameters as median with range of value from 10th percentile to 90th percentile (P_{10}, P_{90})

Nerve	Side	Nerves at risk (*n*)	Amplitude µV	Latency ms	Duration ms
Vagal	Left	(974)	460	5.90	9.38
			(138, 1,241)	(5.00, 7.03)	(7.42, 11.72)
	Right	(1,022)	512	3.91	8.59
			(168, 1,593)	(3.13, 4.69)	(6.64, 11.72)
Recurrent laryngeal	Left	(974)	719	2.73	7.42
			(205, 1,767)	(1.95, 3.91)	(5.47, 9.77)
	Right	(1,022)	623	2.73	7.42
			(207, 1,986)	(1.95, 3.91)	(5.47, 10.16)

476 µV (145.40, 1,487.40), latency 5.86 ms (5.08, 7.03), and duration 9.38 ms (6.64, 12.03). Median values for thyroid carcinoma revealed: amplitude 484 µV (110, 1,443), latency 5.86 ms (4.69, 7.03), and duration 8.98 ms (7.03, 13.28).

Median values according to the nature of thyroid disease for the right VN revealed: amplitude 491.50 µV (167, 1,539), latency 3.91 ms (3.13, 5.08), and duration 8.59 ms (6.64, 11.72). In the indication subgroup autoimmune thyroid disease median values were: amplitude 565 µV (186, 1,845), latency 3.91 ms (3.13, 4.69), and duration 8.98 ms (6.64, 11.52). Median values for thyroid carcinoma showed: amplitude 591.50 µV (172, 1,643), latency 3.52 ms (3.13, 4.69), and duration 8.98 ms (6.64, 13.55). Thus, nature of thyroid disease showed no relevant difference on IONM parameters for either right or left VN (Table 2).

IONM parameters according to indication to surgery: recurrent laryngeal nerves

Median values according to nature of thyroid disease for the left RLN were: amplitude 711 µV (206, 1,769), latency 2.73 ms (1.95, 3.91), and duration 7.42 ms (5.47, 9.77). In

Table 2 Indication to surgery and quantitative IONM parameters as median with range of value from 10th percentile to 90th percentile (P_{10}, P_{90})

Nerve	Side	Indication (*n*)	Amplitude µV	Latency ms	Duration ms
Vagal	Left	MNG (764)	449	5.90	9.38
			(141, 1,194)	(5.00, 7.03)	(7.42, 11.72)
		ATD (111)	476	5.86	9.38
			(145, 1,487)	(5.08, 7.03)	(6.64, 12.03)
		CA (99)	484	5.86	8.98
			(110, 1,443)	(4.69, 7.03)	(7.03, 13.28)
	Right	MNG (792)	492	3.91	8.59
			(167, 1,539)	(3.13, 5.08)	(6.64, 11.72)
		ATD (128)	565	3.91	8.98
			(187, 1,845)	(3.13, 4.69)	(6.64, 11.52)
		CA (102)	592	3.52	8.98
			(172, 1643)	(3.13, 4.69)	(6.64, 13.55)
Recurrent laryngeal	Left	MNG (764)	711	2.73	7.42
			(206, 1,769)	(1.95, 3.91)	(5.47, 9.77)
		ATD (111)	693	2.73	7.42
			(184, 1,880)	(1.95, 3.52)	(5.10, 9.77)
		CA (99)	733	2.73	7.42
			(205, 1,723)	(1.95, 4.30)	(5.87, 9.77)
	Right	MNG (792)	621	2.73	7.42
			(205, 1,879)	(1.95, 3.91)	(5.47, 10.00)
		ATD (128)	650	2.34	7.42
			(171, 2,168)	(1.95, 3.52)	(5.47, 10.55)
		CA (102)	628	2.73	7.81
			(219, 2,189)	(1.95, 3.91)	(5.47, 11.72)

MNG, multinodular benign goiter

ATD, autoimmune thyroid disease

CA, thyroid carcinoma

the indication subgroup of autoimmune thyroid disease median values were: amplitude 693 μV (184.00, 1,880.00), latency 2.73 ms (1.95, 3.52), and duration 7.42 ms (5.10, 9.77). Median values for thyroid carcinoma revealed: amplitude 733 μV (205.20, 1,723.00), latency 2.73 ms (1.95, 4.30), and duration 7.42 ms (5.87, 9.77).

According to indication to surgery, median values for the right RLN showed for benign nodular goiter: amplitude 621 μV (205, 1,879), latency 2.73 ms (1.95, 3.91), and duration 7.42 ms (5.47, 10.00). In the indication group autoimmune thyroid disease median values were: amplitude 650 μV (171, 2,168), latency 2.34 ms (1.95, 3.52), and duration 7.42 ms (5.47, 10.55). Median values for thyroid carcinoma revealed: amplitude 628 μV (218.80, 2,188.80), latency 2.73 ms (1.95, 3.91), and duration 7.81 ms (5.47, 11.72). Thus, nature of thyroid disease showed no relevant difference on IONM parameters for either right or left RLN (Table 2).

IONM parameters according to gender: vagal nerves

In regard to gender distribution for the total study group analysis revealed median values for the left VN in women: amplitude 502 μV (149, 1,310), latency 5.86 ms (4.69, 7.03), and duration 9 ms (7.03, 11.72). Contrary, in men median values for the left VN were: amplitude 323 μV (123, 882), latency 6.25 ms (5.10, 7.42), and duration 9.38 ms (7.81, 12.00).

For the right VN, median values in women showed: amplitude 583 μV (178, 1,826), latency 3.91 ms (3.13, 4.69), and duration 8.59 ms (6.64, 11.72). Contrary, in men median values for the right VN were: amplitude 386 μV (140, 1,012), latency 3.91 ms (3.13, 5.09), and duration 8.59 ms (7.03, 11.33). The IONM parameters for amplitude and latency reveal significant differences ($p<0.001$) between female and male subjects. For the left VN the duration was significantly ($p=0.013$) larger in the female patients (Table 3).

IONM parameters according to gender: recurrent laryngeal nerves

Analog analysis for the RLN in regard to gender showed for the left RLN in women: amplitude 771 μV (237, 1,827), latency 2.73 ms (1.95, 3.91), and duration 7.42 ms (5.47, 9.77). Contrary, in men median values for the left RLN were: amplitude 501 μV (162.80, 1,489.20), latency 2.73 ms (1.95, 3.91), and duration 7.82 ms (5.86, 9.77).

For the right RLN, median values in women showed: amplitude 836.50 μV (218.00, 2,163.80), latency 2.73 ms (1.95, 3.52), and duration 7.42 ms (5.47, 10.16). Contrary, in men median values for the right RLN were: amplitude 478 μV (172.20, 1,296.60), latency 2.73 ms (1.95, 3.91), and duration 7.42 ms (5.47, 9.77). Thus, median value of amplitude in women compared to men showed significantly ($p<0.001$) larger amplitude and latency for the left VN, whereas duration was similar (Table 3).

IONM parameters according to age: vagal nerves

In intention to reveal age-dependent differences, the study population was divided into three groups, under 40 years, older than 40 years, and under 60 years and older than 60 years. Regarding median values according to age groups, results for the left VN below 40 years were

Table 3 Quantitative IONM parameters in redo and primary thyroid surgery as median with range of value from 10th percentile to 90th percentile (P_{10}, P_{90})

Nerve	Side	Surgery (*n*)	Amplitude μV	Latency ms	Duration ms
Vagal	Left	Primary (857)	457	5.90	9.38
			(138, 1,228)	(5.00, 7.03)	(7.42, 11.72)
		Redo (117)	499	6.25	9.38
			(122, 1,414)	(5.08, 7.50)	(7.42, 11.80)
	Right	Primary (911)	510	3.91	8.59
			(168, 1,560)	(3.13, 4.69)	(6.64, 11.72)
		Redo (111)	513	3.91	8.98
			(159, 2,198)	(3.13, 5.08)	(6.64, 11.33)
Recurrent laryngeal	Left	Primary (857)	721	2.73	7.42
			(212, 1,767)	(1.95, 3.91)	(5.47, 9.77)
		Redo (117)	692	2.73	7.42
			(196, 1,768)	(1.95, 3.91)	(5.70, 9.77)
	Right	Primary (911)	620	2.73	7.42
			(204, 1,943)	(1.95, 3.91)	(5.47, 10.00)
		Redo (111)	665	2.73	7.81
			(220, 2,497)	(1.95, 3.72)	(5.47, 10.94)

amplitude 490 µV (141.20, 1.12220), latency 5.50 ms (5.00, 6.8560), and duration 9.38 ms (7.03, 12.50). In the group below 60 years it was found: amplitude 364.50 µV (131.60, 1.18420), latency 5.90 ms (5.08, 7.03), and 9.38 ms (7.03, 11.72). The age group above 60 years showed: amplitude 352 µV (124.80, 940.20), latency 6.25 ms (5.064, 7.42), and 9.38 ms (7.024, 11.72; Table 4).

For the right VN median values in the group below 40 years showed amplitude at 576 µV (155, 1,579), latency 3.52 ms (3.00, 4.32), and duration 8.59 ms (6.25, 11.72). In the group below 60 years it was found: amplitude 521 µV (169, 1,702), latency 3.91 ms (3.13, 4.69), and duration 8.59 ms (7.00, 11.72). The age group above 60 years showed: amplitude 460 µV (171, 1,550), latency 3.91 ms (3.13, 5.08), and 8.59 ms (6.64, 11.72). Thus, latency is significantly ($p<0.001$) shorter in the patient group below 40 years of age, whereas amplitude and duration are not influenced by age (Table 4).

IONM parameters comparing primary and redo surgery: vagal nerves

In regard to influence of prior surgery on IONM parameters, comparison of primary versus redo surgeries resulted in median values for the left VN in primary surgery: amplitude 457 µV (138, 1,228), latency 5.90 ms (5.00, 7.03), and duration 9.38 ms (7.42, 11.72). The left VN in redo surgeries showed: amplitude 499 µV (122, 1,414), latency 6.25 ms (5.08, 7.50), and duration 9.38 ms (7.42, 11.80).

The right VN in primary surgery revealed: amplitude 510 µV (168.20, 1,560.00), latency 3.91 ms (3.13, 4.69), and duration 8.59 ms (6.64, 11.72). The right VN in redo surgeries showed: amplitude 513 µV (158.60, 2,198.40), latency 3.91 ms (3.13, 5.08), and duration 8.98 ms (6.64, 11.33).

Thus, no relevant difference for IONM parameters of the VN in regard to primary versus redo surgery was found (Table 5).

IONM parameters comparing primary and redo surgery: recurrent laryngeal nerves

Comparison of primary versus redo surgery in regard to IONM parameters of the RLN showed for the left RLN in primary surgery: amplitude 721 µV (212.40, 1,767.00), latency 2.73 ms (1.95, 3.91), and 7.42 ms (5.47, 9.77). The left RLN in redo surgery showed: amplitude 692 µV (196.00, 1,768.00), latency 2.73 ms (1.95, 3.91), and duration 7.42 ms (5.70, 9.77).

The right RLN in primary surgery revealed: amplitude 620 µV (204.40, 1,943.00), latency 2.73 ms (1.95, 3.91), and 7.42 ms (5.47, 10.00). The right RLN in redo surgery showed: amplitude 665 µV (220.40, 2,496.80), latency 2.73 ms (1.95, 3.72), and duration 7.81 ms (5.47, 10.94).

Thus, no evident difference for IONM parameters of the RLN in regard to primary vs. redo surgery was found (Table 5).

Discussion

It is generally assumed that normal EMG configuration represents integrity of neural function and broad application of neurostimulation in neurosurgery and head and neck

Table 4 Gender and quantitative IONM parameters as median with range of value from 10th percentile to 90th percentile (P_{10}, P_{90})

Nerve	Side	Gender (*n*)	Amplitude µV	Latency ms	Duration ms
Vagal	Left	Male (267)	323 (123, 882)	6.25 (5.10, 7.42)	9.38 (7.81, 12.00)
		Female (704)	502 (149, 1,311)	5.86 (4.69, 7.03)	9.00 (7.03, 11.72)
	Right	Male (273)	386 (140, 1,012)	3.91 (3.13, 5.09)	8.59 (7.03, 11.33)
		Female (747)	583 (178, 1,826)	3.91 (3.13, 4.69)	8.59 (6.64, 11.72)
Recurrent laryngeal	Left	Male (267)	501 (163, 1,489)	2.73 (1.95, 3.91)	7.82 (5.86, 9.77)
		Female (704)	772 (237, 1,828)	2.73 (1.95, 3.91)	7.42 (5.47, 9.77)
	Right	Male (273)	478 (172, 1,297)	2.73 (1.95, 3.91)	7.42 (5.47, 9.77)
		Female (747)	699 (218, 2,164)	2.73 (1.95, 3.52)	7.42 (5.47, 10.16)

Table 5 Patient age and quantitative IONM parameters as median with range of value from 10th percentile to 90th percentile (P_{10}, P_{90})

Nerve	Side	Indication (*n*)	Amplitude µV	Latency ms	Duration ms
Vagal	Left	<40 years (170)	500 (147, 1,445)	5.86 (5.00, 6.64)	8.98 (6.64, 11.50)
		40–60 years (448)	455 (140, 1,261)	5.90 (5.06, 7.03)	9.38 (7.50, 12.09)
		>60 years (347)	443 (130, 1,186)	5.90 (5.00, 7.42)	9.37 (7.34, 11.72)
	Right	<40 years (178)	576 (155, 1,579)	3.52 (3.00, 4.32)	8.59 (6.25, 11.72)
		40–60 years (476)	521 (169, 1,703)	3.91 (3.13, 4.69)	8.59 (7.00, 11.72)
		>60 years (360)	461 (171, 1,550)	3.91 (3.13, 5.08)	8.59 (6.64, 11.72)
Recurrent laryngeal	Left	<40 years (170)	748 (263, 1,786)	2.73 (1.95, 3.91)	7.42 (5.47, 9.38)
		40–60 years (448)	692 (184, 1,769)	2.73 (1.95, 3.91)	7.42 (5.49, 9.77)
		>60 years (347)	721 (228, 1,767)	2.73 (1.95, 3.91)	7.42 (5.86, 9.77)
	Right	<40 years (178)	698 (234, 2,022)	2.34 (1.95, 3.52)	7.42 (5.47, 10.51)
		40–60 years (476)	610 (201, 2,071)	2.73 (1.95, 3.88)	7.42 (5.47, 10.47)
		>60 years (360)	612 (203, 1,845)	2.73 (1.95, 3.91)	7.42 (5.47, 9.91)

surgeries with comparative normal values is established. The present study aimed at establishing normal values for IONM in thyroid surgery and to establish thereby reference values for comparison. Only few studies investigated selective quantitative parameters of IONM in thyroid surgery in animal models or human subjects. There are no systematic studies available for a comprehensive review of factors (e.g., side differences, gender, age, indication) influencing quantitative IONM parameters to enable comparison with the data of the present study. Moreover, the specific IONM technique and devices utilized differ in the literature which may be a critical argument against comparison. Therefore, only selective findings may be elucidated with contributions of other investigations.

The possible influence of nerve length on quantitative IONM was subsidiary looked at by control of patients size. In a subgroup of 174 (13%) patients we found no correlation of patient size in centimeters with amplitude, latency, and duration of EMG with exception of a slightly increased duration of the right VN. This may not be clinically relevant. Maximum differences observed were 2 ms at 10 cm body length. This finding may also diminish potential influences assumed for the different levels of stimulation points in the short distances of the VN and RLN in thyroid surgery and evident interindividual differences of neck length independent of body length.

With a consecutive series of 1,996 nerves at risk in 1,289 patients recruited from six centers, a representative number of NAR were collected for analysis of basic quantitative IONM parameters in typically distributed surgical thyroid cases with proven intact vocal cord mobility. Over all "normal IONM parameters" in these NAR resulted in significantly greater median values of amplitude (511 vs. 460 µV) for the right VN compared to the left. We found no explanation for this finding. Contrary, latency of the left VN was observed to be significantly larger than on the right (5.9 vs. 3.9 ms), contributable to the anatomically longer course. Duration of the right and left VN (9.38 vs. 8.59 ms) was insignificantly different. Interestingly, quantitative IONM parameters of the RLN showed no evident differences when right and left sides were compared. Like in the VN, there was a similar difference observed in the RLN amplitude with greater amplitude of the left versus right RLN (719 vs. 622.5 µV).

These data compare to the few data on initial IONM parameters available. In a single center assessment, Randolph et al. described IONM quantitative parameters in 125 consecutive patients undergoing thyroid, parathyroid, and miscellaneous neck surgeries [10]. In this series, latency ranged from 2.87 ms (±0.9) at threshold to 3.3 ms (±1.0) at maximum stimulation. Latency for EMG activity stimulation of the RLN was about 3 to 4 ms. Latency for the VN was longer than in the RLN and the waveform of the ipsilaterally stimulated RLN was typically biphasic. Mean initial EMG amplitude at stimulation current at 1 mA was about 900 µV (maximum 1,800 µV, minimum 500 µV). A mean final stimulation threshold was 0.4 mA and maximum EMG amplitude at 0.8 mA. It must be acknowledged that amplitude strongly corresponds with the tube position.

In another investigation measuring EMG amplitudes during volitional speech in awake humans, spontaneous thyroarytenoid and cricothyroid responses were measured using transcutaneous monopolar intramuscular needles. EMG amplitude in this series ranged from 400 to 500 µV with a duration of 3.5 to 4 ms [13].

Basic IONM parameters in a porcine model established threshold of EMG response at 0.43±0.98 mA, and latency of the VN was 6.7±1.39 ms without relevant side difference. A correlation of increasing amperage with increasing amplitude above threshold was demonstrated and a peak value reached at 400 µV. Supramaximal stimulation in this study was seen at 0.8 mA without further signal increase and stable latency of 5.8 ms [14].

In another canine animal study, EMG parameters of IONM applying the endotracheal surface tube showed latency at 1.8±0.1 ms, maximal amplitude of 1,600±700 µV and duration at 2.7±0.4 ms. EMG threshold was between 0.1 and 0.2 mA and maximum amplitude was reached at 0.2 mA stimulus [15]. In comparison to human subjects these animal data show lower threshold values.

In a study using an IONM transligamental recording electrode during thyroid surgery in 502 NAR, Hermann et al. found stimulation threshold to range between 0.05 and 3 mA. It was observed that the vagal nerve was more sensitive to electrical stimulation than the recurrent nerve (0.159±0.004 mA; 0.357±0.008 mA). Interestingly, they found that an increase of stimulation current was necessary for vagal stimulation in patients who developed postoperative vocal cord palsy compared to intact functioning nerves (0.226±0.010 mA; 0.159±0.004 mA). Contrary, recurrent nerve stimulations thresholds shifted to the left, when postoperative function was impaired (0.231±0.016 mA; 0.359±0.008 mA) [16].

Contrary to expectation, we found no evident influence of age, gender, and thyroid disease on IONM parameters. It was hypothesized that IONM may reveal continuous decrease of IONM values with increasing age, however only amplitude in patients younger than 40 years was slightly larger compared to the remaining subjects while latency and duration showed no differences at all. Similarly, it was assumed that thyroid cancer and thyroiditis as well as redo surgery possibly influenced IONM parameters by direct or indirect change of the RLN conductibility due to alteration of the neighboring tissue or milieu. This was not demonstrated in the present data which showed no difference of IONM values comparing benign nodular goiter with thyroid cancer, autoimmune thyroiditis, and primary with redo surgery.

In several studies looking at electrophysiological parameters of IONM, the focus was held mainly on defining threshold values as indicator of postoperative neural function. Description of quantitative IONM parameters in human subjects, however scarce, compare to the findings of this study with variable amplitude and robust values for latency and duration depending on left and right sides. In this investigation it was however sought to establish normal values of IONM parameters as reference. Therefore, recruitment of all responding nerve fibers was assumed to best represent integer nerve function and to enable comparison which was achieved at supramaximal stimulation with 2 mA throughout the study. Stimulation of non-neural structures at a high enough stimulation current usually results in no amplitude when far away from the RLN or in low amplitude when close to structures that may carry current spread, e.g., blood vessels in proximity to the RLN. This phenomenon can also be diminished or eliminated by reducing the stimulation level and drying the surgical field. The substantial variability found in magnitude of the EMG amplitudes may be explained by influence through changes in nerve and stimulator probe contact (contact pressure, milieu of surgical field, overlying tissue) and changes in laryngeal electrode (tracheal tube) positioning. As there exists a dose–response correlation, the EMG amplitude may be increased with increasing stimulation current until supramaximal stimulation is individually gained [5, 17].

Although plain statistical analysis of the data derived from the present study reveals several significant differences, clinical evidence remains to be defined.

Whereas this study's observation of laterality with longer latency period and lower amplitude for the left VN may be explained by the anatomical course other differences remain to be elucidated. It is presently not understood, why IONM quantitative parameters show significantly larger amplitude and decreased latency for both VN in women compared to men.

Conclusions

The current study aimed to establish normal values of quantitative IONM parameters preceding the interpretation of intraoperative EMG findings and consequences on surgical strategy. Normal values derived from this large multicentric cohort study were as follows: median amplitude left VN 469 µV (range 138-1241), right VN 512 µV (range 168-1593); latency right VN 5.90 ms (range 5.00-7.03), left VN 3.91 ms (range 3.13-4.69); duration left VN 9.38 ms (range 7.42-11.7), right VN 8.59 ms (range 6.64-11.7). There was no influence of these "normal" quantitative IONM parameters found by age, indication, and prior surgery. A gender difference regarding amplitude and latency with higher value in women appears to be clinically insignificant.

The astounding stability of quantitative IONM parameters found in this study allow for assumption of intact preconditions for utilizing IONM in a chosen individual once the range of these "normal" values of IONM parameters is perceived. Primarily dissent IONM parameters call for investigation of technological set up and equipment as well as review of information regarding integrity of nerve function. Interpretation of EMG changes in a case with dissent parameters may be confined to mere nerve identification; however, consecutive influence on surgical strategy may be discouraged.

It is acknowledged, that implicit limitation of this study lies in the shortcoming of potential technical differences in the IONM device itself. It remains unclear whether quantitative parameters derived from other IONM devices arrive at similar values. It is furthermore acknowledged that this pioneering data need to be affirmed by further investigation. The prerequisites of established normal values of quantitative IONM parameters utilizing comparable IONM technology will prospectively be referred to when quantitative intraoperative changes of IONM are selected to predict postoperative functional nerve integrity and to define thresholds of impending neural impairment to possibly foreclose permanent damage.

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