Continuous Vagal Intraoperative Monitoring Prevents Recurrent Laryngeal Nerve Paralysis by Revealing Initial EMG Changes of Impending Neuropraxic Injury

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Declaration:

I Eimear Phelan declare that

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- it is entirely the candidates (Eimear Phelan) own work (where work has been carried out jointly, the work of others has been acknowledged within the text
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Summary:

- The larynx is the phonating mechanism, specifically designed for voice production.

- Through movement of the cartilages, the larynx varies the opening between the vocal cords and thereby varies the pitch of sounds produced by the passage of air through them.

- The human larynx receives innervations from the vagus nerve via the superior laryngeal nerve (SLN) and the recurrent laryngeal nerve (RLN).

- The reported prevalence of recurrent laryngeal nerve injuries after thyroid surgery varies widely- the average temporary vocal cord palsy (VCP) rate is approximately 9.8%. The rate of permanent VCP ranges from 0%- 18.6%.

- Due to the RLN vulnerability and variable anatomic course, the chief controversy in thyroid surgery for years revolved around the issue of RLN preservation through visual identification during surgery.

- Several single centre and multicentre studies have confirmed that RLN integrity is preserved significantly more often with routine visual identification than without it.

- Various intraoperative medical devices have been developed over the past two decades or so to help identify the RLN. Essentially these devices convert laryngeal muscle activity into audible plus or minus visual electromyographic (EMG) signals

- Recent studies have shown the intraoperative nerve monitoring (IONM) can help improve RLN identification and may also help to recognize impending nerve injury.

- Studies consistently show a high negative predictive value of 92-100% for IONM.- Thus patients with a negative IONM (intact nerve function) after thyroid surgery generally will not have a RLN palsy.

- The risk of RLN dysfunction is substantial with a loss of IONM signal.

- Injury to the RLN usually results from severing, crushing, suturing, stretching or tearing the main trunk or its branches.

- Current IONM devices only allow the surgeon to intermittently stimulate and assess RLN function which allows the nerve to be theoretically at risk for damage in-between stimulations.

- The main advantage of a continuous nerve monitor device is that it has the potential to identify injury to the RLN earlier and thus the nerve trauma maybe reversible

- The *Medtronic* Automatic Periodic Stimulation (APS) electrode provides periodic, low-level stimulation of the vagus nerve and is designed to potentially allow detection of recurrent nerve injury via early warning of changes in nerve amplitude and latency waveforms.

- To identify clinically relevant significant adverse EMG signal changes we categorized EMG signals based on vagal evoked signal amplitude and latency waveform characteristics. Single events were defined as EMG changes affecting either amplitude or latency.

- Combined events (CE) were defined as concordant changes in both signal amplitude and latency and are stratified below into mild (mCE) and severe CEs (sCE).

- We hypothesized that such combined events may more reliably track with impending neuropraxia

- VCP is the outcome of neural injury which can be identified by an intraoperative progression of increasing severe adverse evoked EMG events. Our study shows CIONM allows identification of the EMG changes (sCE) heralding imminent RLN injury.

Index:

Chapter: **Page:**

- Introduction
- Materials & Methods
- Results
- Discussion
- Conclusion

Chapter 1: Anatomy and Physiology of the Human Larynx, Recurrent Laryngeal Nerve and Vagus Nerve

The larynx is the phonating mechanism, specifically designed for voice production. Phonation is defined as the utterance of sounds with the aid of the vocal cords. Through movement of the cartilages, the larynx varies the opening between the vocal cords and thereby varies the pitch of sounds produced by the passage of air through them. These sounds are translated into intelligible speech by articulatory and resonating structures i.e. the lips, tongue and mouth. The larynx is located in the anterior part of the neck. In adult males it approximately 5cm in length, it is shorter in women and children and situated slightly more superior in the neck.

Skeleton of the larynx:

The laryngeal cartilage is comprised of nine cartilages that are joined by various ligaments and membranes. Three cartilages are paired (arytenoid, corniculate, cuneiform) and three are single (cricoids, thyroid, epiglottis).

Thyroid Cartilage- this is the largest of the cartilages and is composed of two quadrilateral laminae. The inferior two thirds are fused anteriorly in the median plane to form the laryngeal prominence. Just superior to the laryngeal prominence, the two thyroid laminae diverge anteriorly to form the thyroid notch. The posterior border of each thyroid lamina projects superiorly to form the superior horn and inferiorly as the inferior horn. The superior border of the thyroid cartilage is attached to the hyoid bone by the thyrohyoid membrane. The inferior horns of the thyroid cartilage articulate with the cricoid cartilage at special facet joints which allow the thyroid cartilage to tilt or glide anteriorly or posteriorly.

The Cricoid Cartilage: this is shaped like a signet ring with its band facing anteriorly. The posterior (signet) part of the cricoid is called the lamina and the anterior part (band) is called

the arch. The cricoid is stronger and thicker than the thyroid cartilage. The cricoid forms the the inferior part of the anterior and lateral wall and most of the posterior wall of the larynx. The cricoid cartilage is attached to the inferior margin of the thyroid cartilage by the cricothyroid ligaments and to the first tracheal ring by the cricotracheal ligament.

Arytenoid Cartilages: these paired cartilage shaped like three sided pyramids, articulate with the lateral parts of the superior border of the lamina of the cricoid cartilage. Each cartilage has an apex superiorly, a vocal process anteriorly and a muscular process laterally. The apex is attached to the aryepiglottic fold, the vocal process to the vocal ligament and the muscular process to the posterior and lateral cricoarytenoid muscles.

Corniculate & Cuneform Cartilages: These small cartilaginous nodules are in the posterior part of the aryepiglottic folds. These cartilages are attached to the apices of the arytenoid cartilages. The cuneiform cartilages lie in the aryepiglottic folds and are approximated to the tubercle of the epiglottis when the inlet of the larynx is closed during swallowing.

Epiglottic Cartilage: a thin cartilage which is shaped like a leaf and gives flexibility to the epiglottis. The epiglottis is situated posterior to the root of the tongue and hyoid bone and anterior to the inlet of the larynx. The epiglottis forms the superior part of the anterior wall and the superior margin of the inlet to the larynx. The broad superior end is free and its tapered inferior end is attached to the thyroepiglottic ligament, located in the angle formed by the thyroid laminae. The anterior surface of the epiglottic cartilage is attached to the hyoid bone by the hyoepiglottic ligament.

The Interior of the Larynx:

The Vocal Cords: the vocal cords are concerned with voice production. The apex of each wedged shaped vocal fold projects medially into the laryngeal cavity and its base lies against the lamina of the thyroid cartilage. Each vocal cord consists of the vocal ligament, the conus elasticus, muscle fibres and a covering of mucous membrane. The glottis refers to the vocal folds, rima glottidis (aperture between the vocal cords) and the narrow part of the larynx at the level of the vocal cords. The glottis is the part of the larynx most directly concerned with voice production. The shape of the rima glottidis varies according to the position of the vocal folds. The vocal folds are closely approximated during speaking so that the rima glottidis is a narrow slit. Variation in tension and length of the vocal cords, in the width of the rima glottidis and in intensity of the expiratory effort produces changes in pitch of the voice.

Muscles of the Vocal Cords: these muscles open and close the rima glottidis.

- **Adductors of the vocal folds**- the lateral cricoarytenoid muscle (arises from lateral part of cricoid cartilage and inserts into the muscular process of the arytenoids cartilage). The lateral cricoarytenoid muscles pull the muscular processes anteriorly, rotating the arytenoids so that there vocal processes swing medially. This adducts the vocal cords and narrows the rima glottidis.

- **Abductors of the vocal cords**- the posterior cricoarytenoid muscle are the principle abductors of the vocal cords (arises from posterior surface of the lamina of the cricoid cartilage and insert into the muscular process of the arytenoids cartilage). They rotate the arytenoids cartilages, moving them laterally and widening the rima glottidis.

- **Tensors of the vocal cords**- the main tensors are the cricothyroid muscle (located on external surface of the larynx between the cricoid and thyroid cartilages). These

muscles pull or tilt anteriorly the thyroid cartilage on the cricoid cartilages. As a result, the vocal ligaments are elongated and tightened and the pitch of the voice is raised.

- **Relaxers of the Vocal Cords-** the principle relaxers are the broad thyroarytenoid muscles (arise from posterior surface of the thyroid cartilage and insert onto the arytenoids cartilage). A band of its inferior deeper fibres, called the vocalis muscle passes to the vocal process of the arytenoids cartilage. The thyroarytenoid muscles pull the arytenoids cartilage anteriorly, slackening the vocal ligaments. The vocalis muscles produce minute adjustments of the vocal ligaments (i.e. during whispering). They also relax parts of the vocal cords during phonation and singing. [1]

Innervation of the Human Larynx:

The human larynx receives innervations from the vagus nerve via the superior laryngeal nerve (SLN) and the recurrent laryngeal nerve (RLN). The SLN arises from the distal end of the nodose ganglion and travels inferiorly, initially deep to then medial to the carotid artery.[2] The nerve divides into a large internal branch and a small external branch, approximately 1.5cm inferior to the nodose ganglion or more inferiorly either at the level of the greater cornu of the hyoid bone or within the carotid bifurcation. Rarely, the SLN may branch immediately before the internal branch pierces the thyrohyoid membrane.[3] (Fig1)
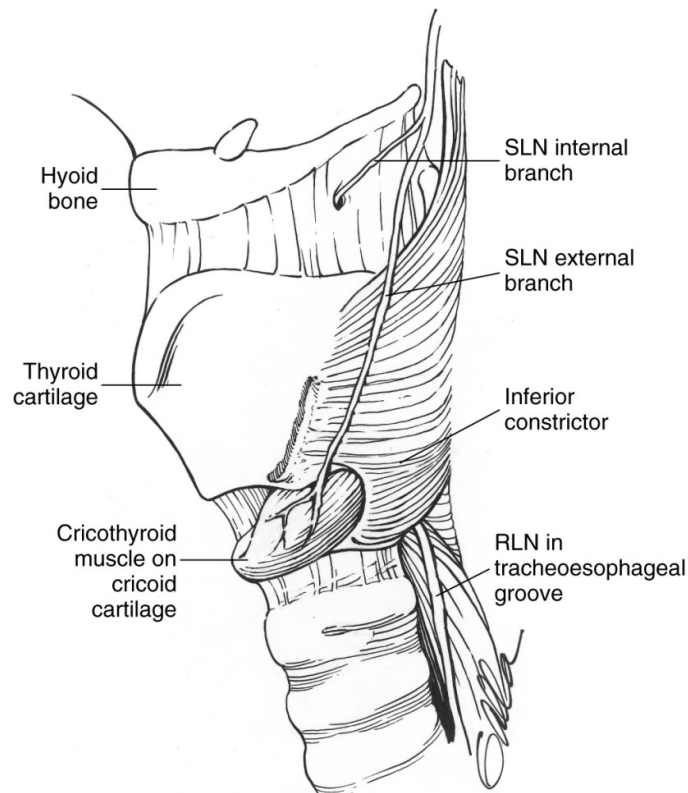
Figure1-Superior laryngeal nerve laryngeal entry point

The internal SLN which is 1-2mm in diameter descends above the superior thyroid artery on the thyrohyoid membrane and enters the upper edge of the inferior pharyngeal constrictor muscle. Within the thyrohyoid membrane or just external to it, it divides into several branches (2-5 branches) and descends along the aryepiglottic fold. The most superior branches supply the mucosa of the vallecula and the epiglottis (sensory fibres). The middle divisions descend in the medial wall of the pyriform sinus and supply the intralaryngeal mucosa (posterior commissure and subglottis) with sensory fibres and the interarytenoid muscle with motor fibres, anastomosising with the arytenoids branches of the RLN. This anastomosis usually occurs within the muscle.[4] The most inferior branch of the internal SLN runs postero-inferiorly, on the surface of the posterior cricoid muscle (PCA) and joins the posterior branch of the RLN, forming Galens anastomosis. This supplies the mucosa of the postcricoid area and the cervical oesophagus.[5] (Fig.2)
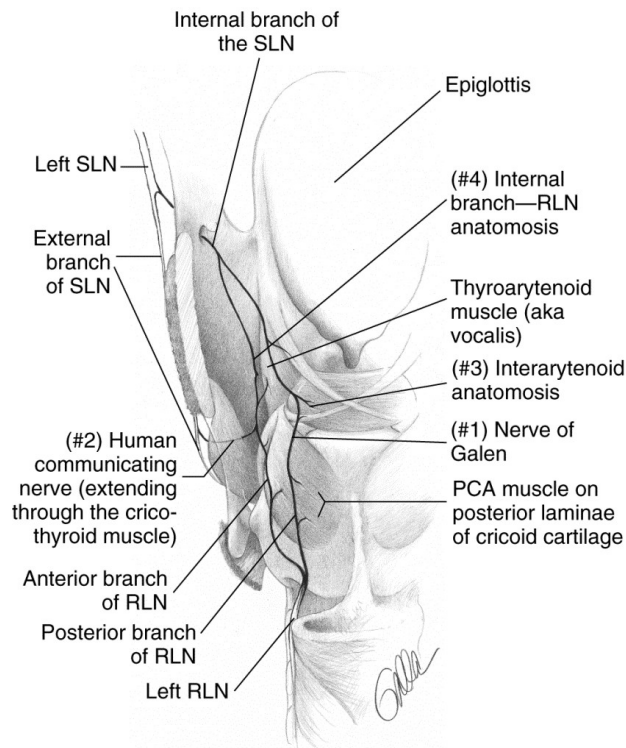

Figure 2- Divisions of Superior Laryngeal and Recurrent Laryngeal Nerve

The external SLN which measures 0.2mm in diameter passes posterior to the sternothyroid muscle deeper to the superior thyroid artery. It descends on the fascia or within the inferior pharyngeal constrictor muscle, sending branches to the pharyngeal plexus.[6]

Occasionally, close to the superior third of the thyroid lamina the external SLN communicates with the main trunk of the internal SLN through an anastomosis running through a thyroid foramen. This foramen is at the level of the oblique line of the thyroid cartilage or just under its lower edge- depending on the size of the thyroid gland. The external SLN curves anteriomedially and reaches the cricothyroid muscle, lying medial to the superior thyroid artery.[2] Occasionally the nerve may be adherent to the artery and its branches (15%) , looped around them (6%).[6] Before entering the cricothyroid muscle, the nerve bifurcates, supplying both the oblique and rectus bellies of the muscle (motor fibres).

The RLN which is 1mm in diameter derives from the vagus nerve. On the right side it winds around the subclavin artery and gradually runs closer to the trachea as it ascends towards the trachea- oesophageal groove. On the left side, it passes lateral to the ligamentum arteriorsum, behind the aortic arch and enters the tracheo – oesophageal groove in the chest running parallel to the trachea in a slightly deeper plane than on the right side. During their ascent towards the larynx, branches (with motor and /or sensory fibres) are distributed to the oesophagus, the trachea, and the inferior pharyngeal constrictor - more numerous on the left side. (Fig.3)
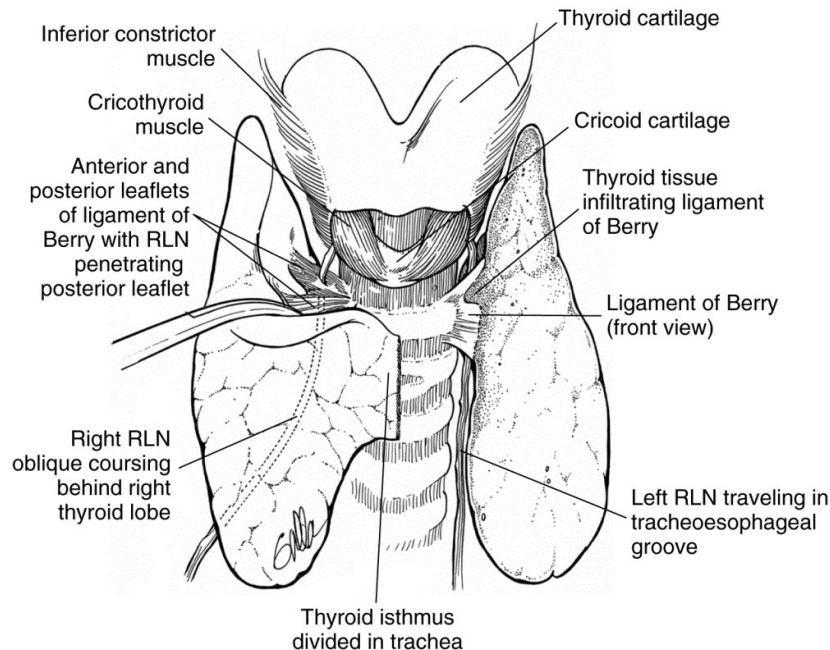
Figure 3 shows a front-view anatomical diagram of the larynx and thyroid with the following labels: Inferior constrictor muscle, Cricothyroid muscle, Anterior and posterior leaflets of ligament of Berry with RLN penetrating posterior leaflet, Right RLN oblique coursing behind right thyroid lobe, Thyroid cartilage, Cricoid cartilage, Thyroid tissue infiltrating ligament of Berry, Ligament of Berry (front view), Left RLN traveling in tracheoesophageal groove, Thyroid isthmus divided in trachea.

Figure 3- Recurrent laryngeal nerve

Rarely, the RLN may pass directly to the larynx (inferior laryngeal nerve) without recurring.[7] Non recurrent RLNs are reported to occur in 0.5% of the population. [8] At the lower pole of the thyroid gland, the nerve may cross either posteriorly or anteriorly to the inferior thyroid artery or it may pass between its branches. On the right side, there is an equal chance of finding the nerve in each of these locations, while on the left it is more likely to lie posterior to the inferior thyroid artery.[9]

Extralaryngeal bifurcation of the RLN is well recognized, it tends to occur in relationship to the ligament of Berry, within the last 1-2cm of the RLN prior to entry into the larynx. It occurs in approximately 36 – 70 % of patients and is more common on the right then the left.[10, 11, 12,] Some authors have suggested that the motor branches are solely in the anterior branch and sensory fibers in the posterior division. [13] These branches usually have a similar diameter, if not, the anterior branch is thicker.[14] The anterior RLN branch (motor) approaches the larynx behind and close to the posterior face of the cricothyroid joint, separated from the

capsule by only 1-2mm of connective tissue. At the level of the inferior thyroid cornu, the nerve gives off at least two main branches, passing medially between the PCA and the posterior lamina of the cricoid cartilage. The first branch supplies the PCA muscle while the second branch supplies fibres of the interarytenoid muscle. Thus, the anterior branch of the RLN carries both adductor and abductor fibres. The interarytenoid muscle (IA) is innervated by both RLNs which cross the midline with considerable overlapping.[15] After supplying the branches to the PCA and IA muscles, the anterior branch of the RLN curves anteriorly and enters the pyriform sinus. It divides finally into its terminal branches for the lateral cricoarytenoid and thyroarytenoid muscles. The anterior branch of the RLN terminates in the thyroarytenoid muscle (TA), forming the densest anastomotic network seen in any of the laryngeal muscles, especially near the vocal ligament. This reflects the rapidity of the glottic closure reflex (lateral region of TA muscle) and the delicate adjustments during phonation (medial region of TA muscle).[16] The posterior branch of the RLN passes into the lateral wall of the piriform sinus or more medially into the postcricoid area and terminates in the hypopharyngeal mucosa. During its course it supplies a number of sensory branches to the laryngeal mucosa below the level of the vocal folds.

Histological Asymmetry of the RLN:

The right and left RLNs display asymmetric lengths- in men the average length of the left RLN is 43cm and the right is 32cm, giving an average difference of 11cm (range 5.7- 15cm). This asymmetry between the lengths also occurs in animal species.[17, 18] This asymmetry arises because the right and left RLNs take different routes to the larynx as previously described. When the right and left RLNs are compared, the differences in parameters, such as length and route to the larynx are well described. Studies have shown that despite these differences, the arrival of motor impulses is simultaneous in both sides of the laryngeal musculature.[17] Jotz et al analyzed a number of morphometric parameters including intraperineural area,

intraperineural perimeter, fibre area, fibre density (number of fibres/mm2) and total number of fibres that are involved in the intensity and velocity of nerve conduction in human right and left RLNs. Measurement of the fibre area demonstrated the existence of a significant difference between the right and left RLNs.[19]

The fibre area in the right nerve was 21% larger than the left (p=0023). There was also a significant difference (11%, p=0.0009) between the fibre perimeter of the right and left nerves. The mean total number of nerve fibres in the right RLN was 795 ± 376 fibres/nerve and the left was 1204 ± 493 fibres/nerve. The conduction velocity is related to fibre area, and increases in fibre area are responsible for increases in the velocity of impulse conduction.[20, 21] Jotz et als findings suggest that the conduction velocity is higher in the right RLN when compared to the left RLN. There study suggests that the left nerve could present a slight delay in the conduction velocity when compared with the right nerve. However, this slight delay is likely insignificant as it does not alter the mobility of the intrinsic muscles of the larynx which control the left vocal cord. This longer latency in the left RLN cannot be explained by its longer length alone, but probably is also due to the reduced fibre area compared to the right RLN.[19]

Chapter 2- Thyroid Surgery and Recurrent Laryngeal Nerve Injury:

The reported prevalence of recurrent laryngeal nerve injuries after thyroid surgery varies widely. A recent analysis of 27 articles which reviewed over 25,000 patients undergoing thyroidectomy found the average temporary vocal cord palsy (VCP) rate was 9.8%. The rate of permanent VCP varied tenfold, depending on the method of examining the larynx- range 0%- 18.6%. [22]The Scandinavian Quality Registrar for thyroid and parathyroid surgery, reporting on 40 endocrine surgeons in 2008, noted an immediate VCP rate of 4.3%.[23] In the UK British Association of Thyroid and Endocrine Surgeons audit (BAETs), a VCP rate of 2.5% was found. However, both the Scandinavian and British quality registers derive from surgeon reported data without routine post operative laryngeal exam. The rate of VCP doubled when patients in the Scandinavian Quality Registrar were subjected to routine laryngeal exam as opposed to postoperative laryngoscopy that was performed only in patients with persistent and severe voice changes.Thus it is highly likely that the rate of both temporary and permanent VCP is underestimated.[23, 24] Low rates of VCP quoted to patients by surgeons are often derived from reported series of patients treated at high volume expert centres with favourable published results. In the USA, 50% of thyroid surgery is performed by surgeons who perform less than five procedures per year.[25] A 6 year review of jury verdict reports of endocrine malpractice litigation from the US Civil Court system showed that 50% of adverse events were related to thyroid surgery, of which 70% involved the RLN. [26]

It is well recognized that both subjective and objective post operative voice changes commonly occur in patients after thyroidectomy with intact vocal cord mobility i.e. no vocal cord palsy. These symptoms are transient and generally consist of voice fatigue or difficulty with high pitch. Typically these symptoms self resolve within 3-6 month post op.[27] One retrospective analysis at a mean of 4 years after uncomplicated thyroid surgery i.e. no VCP, in

a cohort of 60 patients identified a high prevalence of nonspecific voice changes (28%) and impaired swallow (15%).[28] The proposed mechanisms for voice alteration with grossly normal vocal cord mobility/RLN function are- partial/subclinical RLN dysfunction and or a partial/subclinical external branch SLN dysfunction. Others factors may include- endotracheal tube vocal cord /laryngeal injury, regional scarring, laryngeal tethering.[28]

Vocal Cord Paralysis without Voice Symptoms: VCP can be asymptomatic due to variable remaining cord function, variability in paralytic cord position and variability in contralateral cord compensation. It is common, that in permanent VCP, symptoms improve due to contralateral cord compensation. This may lead to one thinking incorrectly that the VCP has resolved.[29] In a recent study of 98 patients with VCP, voice was normal in 20%. Overall, nearly one third of patients with VCP were or became asymptomatic. [30]

Preoperative Vocal Cord Assessment- The Rationale:

There are several reasons in favor of routine preoperative and postoperative laryngeal exam. Firstly, as discussed above, one third or more of patients with unilateral RLN paralysis are asymptomatic, voice changes cannot be relied on as a predictor of vocal cord function. Two recent studies investigating pre operative voice changes and VCP found sensitivity of voice change predicting VCP ranging from 33% to 68% and a positive predictive value in one study of only 38%.[31] Randolph et al demonstrated that the presence of preoperative RLN palsy had an excellent predictive value for finding invasive thyroid cancer at surgery (sensitivity 76%, specificity 100%). Preoperative recognition of VCP is essential in planning thyroid surgery i.e. if the RLN is found to be invaded during surgery. Also nerve injuries not detected preoperatively will be assumed to be due to surgery on postoperative review. Despite this information, the Scandinavian Quality Registrar indicates that preoperative laryngeal exam was performed just over half of the patients in the database. This figure was slightly higher in

patients for thyroid cancer surgery.[23] The BAETS audit found preoperative laryngeal exam was performed in only 38% of patients prior to thyroid surgery. [24]

Post Operative Vocal Cord Assessment: The Rationale

Due to the divergence in voice symptoms and objective vocal cord function, routine postoperative laryngeal exam is required in all patients undergoing thyroid surgery. This allows surgeons to have accurate information regarding their surgical outcomes. The Scandinavian Quality Registrar data shows that the documented postoperative rate of VCP doubles if postoperative laryngeal exam is performed routinely rather than in only symptomatic patients. Post operative vocal cord palsy has significant implications in patients for whom contralateral surgery may become necessary i.e. for cancer recurrence

Identifying the RLN during Thyroid Surgery:

Due to the RLN vulnerability and variable anatomic course, the chief controversy in thyroid surgery for years revolved around the issue of RLN preservation through visual identification during surgery. Lahey (Boston, 1938) and Riddell (London, 1956) were strong advocates of routine RLN dissection and visualization during thyroidectomy. [32, 33] Several single centre and multicentre studies have confirmed that RLN integrity is preserved significantly more often with routine visual identification than without it.[29, 34] Routine visual identification of the RLN is regarded as the gold standard of care in thyroid surgery. [35] Despite significant improvements in RLN preservation through visual identification, RLN palsy rates continue to vary widely, depending on the respective thyroid disease (0.2%-25%), the type of surgery (initial or reoperation, 0.6% vs. 3.6%), the extent of resection (subtotal/partial or total lobectomy: 0.7% vs. 1.3%) and the surgeons personal experience (0.6%- 1.4%).[34] Various intraoperative medical devices have been developed over the past two decades or so to help identify the RLN and measure its neurophysiological function before and after thyroid

resection. Essentially these devices convert laryngeal muscle activity into audible plus or minus visual electromyographic (EMG) signals.(Fig.1) There are a variety of different techniques which have been described in the literature but can be divided into two main categories-

1. Without EMG documentation- RLN stimulation with observation of posterior cricoarytenoid contraction or palpation [36]

2. With EMG documentation- RLN stimulation with registration of the elicited laryngeal muscle activity through endoscopic insertion of electrodes into the vocal fold, with the use of endotracheal surface of electrodes [35]
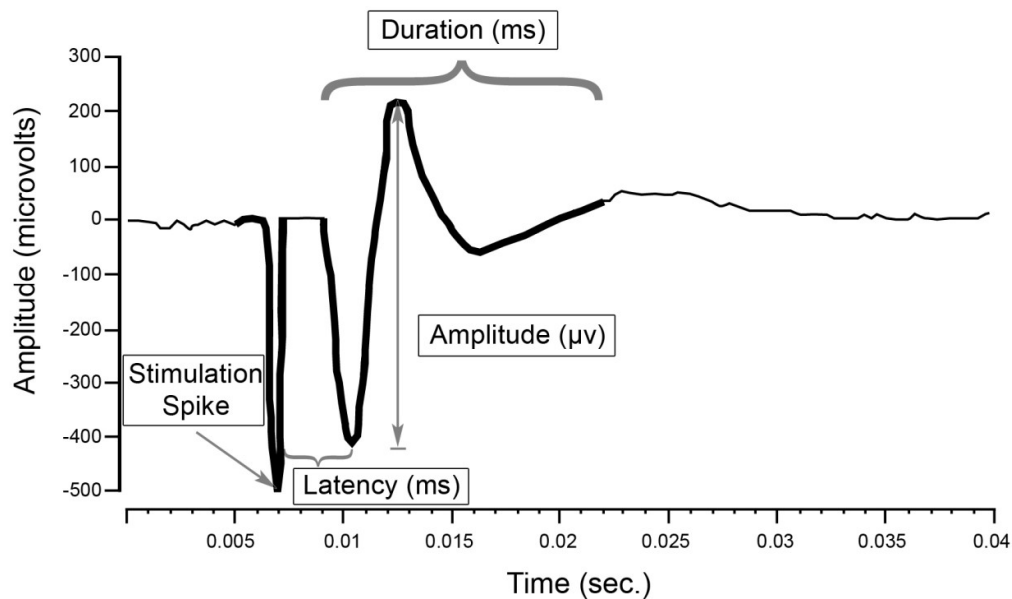

Figure1- Electromyographic (EMG) Signal

Recent studies have shown the IONM can help improve RLN identification and may also help to recognize impending nerve injury. Chan et al looked at 1000 RLNs at risk during thyroidectomy both primary and reoperative thyroid surgery. The outcome of 501 RLNs with the use of neuromonitoring was compared with that of 499 nerves that were operated by routine identification only. The incidences of RLN paralysis were compared between the 2 groups. There was no significant difference in postoperative, transient, and permanent paralysis rates between the neuromonitoring and control groups. However, in subgroup analysis, the postoperative RLN palsy rate was higher during reoperative thyroidectomy (19% vs. 4.6%; $P = 0.019$) in the control group but not in the neuromonitoring group (7.8% vs. 3.8%; $P > 0.05$). Neuromonitoring of the RLN during thyroid surgery could not be demonstrated to reduce RLN injury significantly, compared with the adoption of routine visual RLN identification. [37]

Chan et al conducted a prospective study to validate the ability of IONM to predict post operative vocal cord palsy. This involved 271 nerves at risk and patients were placed into two groups- low risk (primary surgery for benign disease), high risk (malignancy and recurrent disease).The incidence of postoperative nerve palsy in the low risk and high risk groups was 4.4% and 7.8%, respectively. There were 241 true-negative (positive signal and no cord palsy), 15 false-positive (negative signal but no cord palsy), 8 true-positive (negative signal and cord palsy), and 7 false-negative (positive signal but cord palsy) results, as correlated with the postoperative assessment. The sensitivity, specificity, and positive and negative predictive values were 53%, 94%, 35%, and 97%, respectively. For the high risk group, the sensitivity and positive predictive value increased to 86% and 60%, respectively. Chan et al based on their study findings recommended use of IONM in high risk cases as opposed to routine use.[38] Barczynski et al looked at whether routine identification of the RLN during thyroid surgery reduces injury and whether IONM is helpful. 1000 patients were allocated to one of two groups- standardized protection or additional nerve monitoring. Transient and permanent RLN injuries

were found respectively in 38 and 12 nerves without RLN monitoring ($P = 0·011$) and 19 and

8 nerves with RLN monitoring ($P = 0·368$). The prevalence of transient RLN paresis was lower

in patients who had RLN monitoring by 2·9 per cent in high-risk patients ($P = 0·011$) and 0·9

per cent in low-risk patients ($P = 0·249$). The negative and positive predictive values of RLN

monitoring in predicting postoperative vocal cord function were 98·9 and 37·8 per cent

respectively. Nerve monitoring decreased the incidence of transient but not permanent RLN

paresis compared with visualization alone, especially in high-risk patients.[39] Dralle et al based

on a systematic appraisal of the literature concluded that recurrent laryngeal nerve palsy rates

tended to be lower with IONM than without it, but that this difference was not statistically

significant. Studies consistently showed a high negative predictive value of 92-100% for

IONM. Thus patients with a negative IONM (intact nerve function) after thyroid surgery

generally will not have a RLN palsy. The risk of RLN dysfunction is substantial with a loss of

IONM signal. The positive predictive value in these tests was generally low and highly variable

(10-90%), depending on the outcome of interest (transient or permanent RLN palsy). Dralle et

al also highlighted that there was ambiguity in interpretation of a positive IONM test (negative

IONM signal with postoperative RLN palsy on laryngeal examination). In contrast, elicitation

of an intact IONM signal at the end of surgery provides reasonable assurance that any

postoperative voice changes were unrelated to RLN dysfunction.[40] As suggested by the above

studies, there is some evidence that IONM may provide additional benefits beyond those

afforded by visual nerve identification. In experienced hands, the RLN palsy rates is so low

the prohibitively large numbers of patients would be needed to achieve statistical power. Dralle

has studied issues of statistical power necessary to prove that rates of paralysis are lower with

the application of neural monitoring. His studies have suggested that a researcher would need

9 million patients per arm for benign multinodular goiter and approximately 40,000 patients per

arm for thyroid cancer for such studies to be conducted with statistical power if typical rates of

nerve paralysis are used for calculation. However, there seems to be a strong trend toward improved RLN protection with the use of IONM with visual identification remaining the gold standard. [41]

There are still some issues to resolve with regard to the use and interpretation of IONM which include-

1. There is no consensus about which electrodes to use for EMG recording- intralaryngeal vocal fold electrodes, transcricoid membrane needle electrodes, tube surface or post cricoids surface electrodes

2. Which method is the best for recording nerve action- continuous or intermittent nerve stimulation

3. Which quantitative electromographic parameters should be selected as possible predictors of post operative vocal cord palsy- amplitude, latency combined or isolated measurements.

Standardization of intra-operative nerve monitoring of recurrent laryngeal nerve:

The lack of standardized procedures of IONM during thyroid surgery may lead to highly variable results which can cause misleading results and conversely increase the risk of RLN injury. Thus standardization of IONM is essential. Chiang et al applied a standardized IONM on 289 patients/ 435 nerves at risk undergoing thyroid surgery. They found that applying a standardized procedure was useful and eliminated false IONM results and elucidated the mechanism of RLN injury. All patients were intubated with a *Medtronic* Nerve Integrity Monitor (NIM) standard reinforced EMG endotracheal tube. The tube was placed so it was well in contact with the vocal cords. When the patients head was positioned in full extension

the impedance electrodes were checked (the impedance of each electrode should be < 5Ω and an impedance imbalance <1.0Ω). The presence of normal baseline, impedance <5.0Ω and impedance imbalance <1.0Ω only suggests proper connection of wires and good electrode – mucosa contact, but this does not mean the IONM is working. A Prass monopolar stimulation probe (*Medtronic)* was used for nerve stimulation during thyroid surgery. Stimuli were generated from a NIM 2.0 monitor with a stimulation of between 1-2 mA for the vagus and RLN. The event capture was activated with a threshold of 100μV. In this study Chiang et al applied the four step procedure of IONM to test the RLN and vagus nerve.[42]

- Step 1: V1 signal- an original electromyographic (EMG) signal was obtained from the vagus nerve before identification of the RLN. Equipment failure was considered if a V1 signal could not be elicited.

- Step 2: R1 signal – the signal was obtained from the RLN, which was first identified at the tracheoesophageal groove.

- Step 3: R2 signal – the signal was obtained by stimulating its most proximally exposed portion after Berry's ligament was completely dissected out from the RLN.

- Step 4: V2 signal – the final testing of the vagus nerve was performed after complete hemostasis of the surgical field. The stimulation and event threshold of R1, R2 and V2 signals were the same as those of V1 signal.

Signals were interpreted in the following way-

Unchanged Signal- V1, R1 signals and R2, V2 signals were obtained successfully with the same stimulation level during surgery and there was no apparent change between the comparisons.

Loss of Signal (LOS) - the original signal was obtained from the vagus nerve, but it could not be elicited from the RLN or vagus nerve after dissection of the RLN. When R2 and V2 signals were lost after complete dissection of the RLN, this meant that the RLN may have been injured during manipulation. An effort was made to identify the disrupted point of nerve conduction and where possible elucidate the mechanism of injury. The disrupted point of nerve conduction could be located by the following procedure- (a) the RLN was tested from the distal portion of the RLN at the entry point of larynx (b) conversely, the RLN was tested from the proximal portion of the exposed nerve and then the upper portion until a response was elicited. This generally permitted the point of nerve disruption to be located.

Laryngeal Examination:

All patients have preoperative and postoperative laryngeal examinations.

Functional Integrity of RLN:

Functional integrity was confirmed with the registration of EMG signals (as outlined in the four step procedure- V1, R1, V2, R2)

Chiang et al had 417 nerves with unchanged R2 and V2 signals and all cases showed normal vocal cord function postoperatively. Eighteen nerves experienced loss of EMG signals and the cause of the nerve injury was identified with the application of the standardized IONM protocol. One nerve injury was due to inadvertent transaction and resulted in permanent vocal cord palsy. Twelve of this nerve injuries were caused by overstretching the RLN at the region of Berry's ligament. Two RLNs (0.8%) developed temporary palsy and both were due to stretch injury. In this study, RLNs with loss of EMG signal caused by overstretching can regain full, partial or no recovery, and the outcome of cord mobility can be normal, weakened or fixed.[43] Several potential pitfalls of IONM have been reported- equipment malfunction (defect in the device or electrodes), improper set up of equipment, misuse of muscle relaxant,

anatomic variation of RLN, shunt stimulus which can cause misleading information. Monitoring set up problems are the most common cause of false IONM results.[44, 45] In Chiang et als study, malposition of electrodes was the main cause of equipment failure.[43] The position of the endotracheal tube electrodes could displace and not be detected when the patient's neck is fully extended post intubation.[46] Thus being certain of the correct position of the endotracheal tube electrodes before using IONM is important. This can be achieved by-

 1. Visual check using fibreoptic laryngoscopy

2. Check for respiratory variation - after intubation and after the paralytic agent from induction has worn off but before the inhalation plane of anaesthesia is too deep, there is a window that occurs, typically just before the patient starts to move spontaneously or ''buck.'' During this window, a coarsening of the monitor baseline can be seen, with small waveforms typically varying from 30 to 70 mV. This activity is termed ''respiratory variation of the baseline''. For this variation to be present on both channels, the endotracheal tube must be in good position at the level of the vocal cords.[46]

Yap et al demonstrated the effect of head and neck movement and Trendelenberg tilt on endotracheal tube position relative to the carina. Inward movement of the endotracheal tube tip (shortening of the distance between the carina and tube tip) resulted from neck flexion with a mean of 5.5mm. Neck extension resulted in an outward movement (increased distance from carina to tip of endotracheal tube) of the endotracheal tube of a mean of 6.3mm but up to 21mm inward and 33mm outward. Neck rotation or Trendelenberg alone did not show a trend towards inward or outward movement. This study highlighted that for any given postural change in any one patient, the direction and magnitude of endotracheal displacement is variable.[48]

A Learning Curve for IONM in Thyroid Surgery:

Dionigi et al conducted a study which looked at the initial experience and learning curve of IONM during thyroid surgery. This involved 152 consecutive patients / 304 nerves at risk, who were divided into approximately three groups of fifty patients. The vagus and RLN were indentified in all patients. Ninety percent of patients had successful IONM with initial endotracheal tube placement. Ten percent needed adjustmenet of their endotracheal tube. In over 50% of patients tube malrotation was the main cause of initial IONM failure. The success rates of prompt IONM technique improved from group 1 (80%) to group 3 (98%, p<0.05). The study demonstrated that IONM success rates were affected by the extent of both surgical and anaesthesiological experience. The learning curve for successful use of IONM and performance of a safe surgical technique in identifying the RLN was seen after approximately 50 cases.[49]

Chapter 3: Normative Vagal and Recurrent Laryngeal Nerve Electrophysiological Data:

Intraoperative nerve monitoring devices are designed to convert laryngeal muscle activity into an audible and visual electromyograghic (EMG) signal following stimulation of either the vagus nerve or RLN. There is limited information available in the literature on the normal intra operative neuromonitoring nerve parameters such as nerve amplitude and latency in either humans or animal models. The earliest data in humans in 1978, used transcutaneously placed electrodes and demonstrated a laryngeal muscle action potential with a latency of 1.5-2.5ms, amplitudes ranged from 100-500μv with a duration of 4-5ms.[50]

Chiang et al's porcine model demonstrated a dose response curve with increasing EMG amplitude as the stimulating current increased. The maximum EMG amplitude of both the vagus and RLN stimulation was 989μv (+/- 365 SD) and 1015μv (+/- 209 SD) respectively, which was obtained at <1mA stimulation current. Latencies of the left (8.45ms) and right (6.52ms) vagus nerves were different and latencies of the right and left RLN were 3.28ms and 3.23ms, respectively. The mean stimulus threshold for response was 0.24mA in the vagus nerve and 0.21mA in the RLN. Chiang found no adverse neural or cardiopulmonary safety of repetitive vagus and RLN stimulation during IONM.[51]

Scott et al in their canine studies, found the average canine RLN threshold to be between 0.1 and 0.2mA with a steeply up sloping threshold stimulation curve. Interestingly, this study did demonstrate evidence of increased latency and decreased amplitude in injured nerves which improved towards normal as the nerve function recovered. [52, 53]

Dralle's group in Germany analyzed normal quantitative parameters in 1,996 nerves at risk, in patients who underwent thyroid surgery in six participating centers. The aim of the study was to define the normal quantitative parameters in IONM which may serve as reference range

values. The median amplitude was significantly larger for the right vagus nerve (512μv, range 168-1,593) vs. the left vagus nerve (460μv, range 138-1,241). Latency was also significantly longer on the left (5.90 ms, range 5.00 – 7.03ms) vs. the right vagal nerve (3.91ms, range 3.13-4.69ms). The median RLN amplitude was larger on the left (719 μv, range 205 - 1,767 μv) vs. the right RLN (623μv, range 207-1,986μv). The latency of right and left RLN was the same (2.73ms). Interestingly, this study showed gender differences, with significantly higher amplitude (502μv vs. 323μv) and shorter latencies (5.86ms vs. 6.25ms) in women compared to men but no differences preferable to patient morphologic size or age. Threshold data was not obtained.[54]

Massachusetts Eye and Ear Infirmary (Boston, USA) Normative Human Vagal Nerve and RLN Data:

We conducted a prospective intraoperative nerve monitoring study performed at the Department of Otolaryngology, Division of Thyroid and Parathyroid Surgery, Massachusetts Eye and Ear Infirmary (MEEI), Boston over an 8 month period of time. Internal review board (IRB) approval was obtained prior to commencing this study and all participating patients were adequately counseled and consented.

All patients who were scheduled for routine thyroid, parathyroid or neck exploration surgery were invited to participate. All patients who consented to participate in this study had a preoperative and postoperative laryngeal examination to assess vocal cord function. Any patient with an abnormal preoperative laryngeal examination was excluded. IONM was applied using a standardized IONM set up using the noninvasive surface electrode endotracheal tube and the Medtronic NIM 2.0 monitor with a surgeon controlled hand held stimulating probe. The stimulating probe was set to 4 stimulations per seconds with a stimulation duration 100ms and a supramaximal stimulation of between 1-2mA. [47]

This system monitors EMG activity in the thyroarytenoid muscle following stimulation of either the vagus or RLN, with EMG depiction visible on the monitor with audio feedback. A filter system is set at 100µv to avoid low amplitude background noise and a suppressive circuitry temporarily halts IONM during electrocautery which mutes artificial audio feedback. Anesthesia was induced with a short acting paralyzing agent and paralytic agents were avoided during the remainder of the case consistent with international guidelines.[47] The endotracheal tube was inserted under visual control to ensure electrode contact with the vocal cords. Following final positioning of the patient, the patient was allowed to briefly lighten from their anesthesia to confirm the presence of good respiratory variation. Deeper anesthesia

was then immediately induced using a non paralyzing IV agent. Impedance of the electrodes was also checked, with electrode impedance of <5kΩ and impedance imbalance <1kΩ. The vagus and RLN were stimulated with the stimulating probe at 1-2 milliamps. IONM parameters which were recorded for the vagus and RLN included –

1. Amplitude of the evoked response (initial at the beginning of surgery and final at the completion of surgery)

 2. Latency of the evoked response

 3. Stimulation Threshold of the response.

For the purpose of this study the following definitions were accepted (see figure 1):

- **Latency** - defined as time measured in milliseconds (ms) between the stimulation artifact and onset of EMG activity.

- **Amplitude** - defined as the maximum deflection from the baseline of the EMG wave measured in microvolt's (µv).

- **Stimulation threshold** - defined as the lowest level of neural stimulation measured in milliamps (mA) that generates a reproducible evoked EMG response (one with a conserved waveform morphology) with amplitude >100µv.
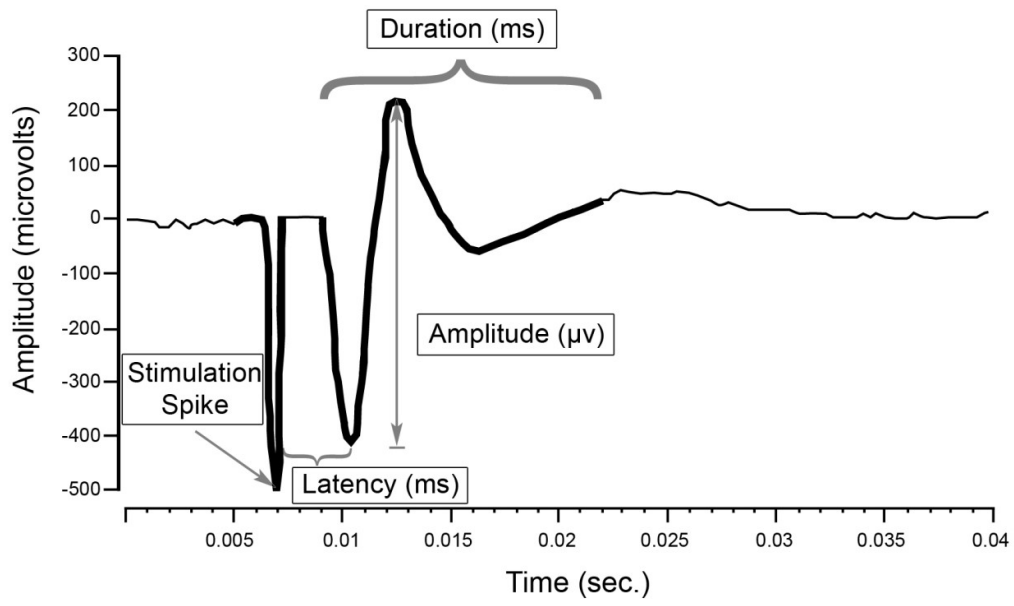
Figure 1- Electromyographic Signal (EMG)

MEEI Normative Data Study Results:

The total number of patients who participated in this study was 58 patients -39 female and 19 male with an average age of 52.6years (range 16-92 years). The most commonly performed surgical procedure which allowed identification and stimulation of the vagus nerve and or RLN was a total thyroidectomy (22/58, 37.9%). All patients had normal post operative laryngeal examination. The results for RLN and vagal latency, threshold of stimulation and amplitude are presented below.

Latency:

The right RLN mean latency was 3.19ms (n= 5, range 2.47- 4.25ms) and the left RLN mean latency was 3.70ms (n=3, range 2.50 - 4.34ms).The right vagus mean latency was 6.77ms (n=9, range 4.25 - 9.50ms) and the left vagus mean latency was 7.67ms (n=9, range 6.10 – 10.00ms). There was no statistical significance between the right and left side for either the RLN or vagus nerve - there was a trend towards significance between the right and left vagus nerve, but due to small numbers in this group this was not achieved. However, when comparing the RLN with the vagus nerve, there was statistical significance for both right and left side (RLN vs. Vagus, right: p=0.0001, RLN vs. Vagus, left: p<0.0001). **Table 1**

Table 1. Latency

Latency (ms)	Right RLN	Left RLN	Right Vagus	Left Vagus
Mean ± SD	3.19 ± 0.72	3.70 ± 1.04	6.77 ± 1.83	7.67 ± 1.33
Range	2.47- 4.25	2.5 - 4.34	4.25 - 9.50	6.1 - 10.0
No. of Patients	5	3	9	9

Right vs. Left, RLN: p = 0.44

Right vs. Left, Vagus: p = 0.25

RLN vs. Vagus, Right: p = 0.001*

RLN vs. Vagus, Left: p < 0.001*

Comparisons based on two-sample Student t-tests.

Stimulation Threshold:

The right RLN mean threshold intensity was 0.51mA (n= 6, range 0.25 - 1.40mA) and the left

RLN mean threshold intensity was 0.61mA (n=5, 0.25 – 1.00mA). The right vagus mean

threshold was 0.41mA (n=7, range 0.25 – 0.85mA) and the left vagus mean threshold was

also 0.41mA (n= 5, range 0.10 - 0.80mA). There was no statistical significance between the

RLN and vagus nerve or right and left side. **Table 2**

Table 2. Stimulation Threshold

Threshold (mA)	Right RLN	Left RLN	Right Vagus	Left Vagus
Mean ± SD	0.51 ± 0.44	0.61 ± 0.30	0.41 ± 0.20	0.41 ± 0.25
Range	0.25 -1.40	0.25 -1.00	0.25 – 0.85	0.1 – 0.80
No. of Patients	6	5	7	5

Right vs. Left, RLN: p = 0.68

Right vs. Left, Vagus: p = 0.99

RLN vs. Vagus, Right: p = 0.60

RLN vs. Vagus, Left: p = 0.29

Comparisons based on two-sample Student t-tests.

Amplitude:

The right RLN mean amplitude was 783μv (SD+/- 512microV) and the left RLN mean amplitude was 604μv (SD +/- 504micro V). There was no statistical difference between the right and left mean RLN. The right vagus mean amplitude was 717μv (SD +/- 479microV) and the left vagus mean amplitude was 420μv (SD +/-255microV). The right vagus mean amplitude was significantly higher than the left vagus mean amplitude and this was statistically significant. (Student t-test, not paired, p=0.0031). **Table 3**

Vagus Amplitude vs. RLN Amplitude:

The right RLN mean amplitude (n= 35, 783μv +/- 512) was compared to the right vagus mean amplitude (n=34, 717μv +/- 479), but no statistical difference was identified. A similar finding was noted when the left RLN mean amplitude (n= 34, 604μv +/- 504) was compared to the left vagus amplitude (n= 31, 420μv +/- 255). **Table 3**

Table 3. Mean RLN and Vagus Amplitude

Mean Amplitude (μv)	Right RLN	Left RLN	Right Vagus	Left Vagus
Mean ± SD	783 ± 512	604 ± 504	717 ± 479	420 ± 255
Range	177 - 2391	169 - 1947	75 - 1825	74 - 925
No. of Patients	35	34	34	31

Right vs. Left, RLN: p = 0.15

Right vs. Left, Vagus: p = 0.003*

RLN vs. Vagus, Right: p = 0.58

RLN vs. Vagus, Left: p = 0.07

Comparisons based on two-sample Student t-tests.

Male vs. Female:

The female RLN mean amplitude was 739μv (n=50, range 135 – 2391μv) and the male RLN mean amplitude was 581μv (n= 19, range 109 – 1670μv). The mean female vagus amplitude was 573μv (n=44, range 74 -1610μv) and the male vagus mean amplitude was similar with an amplitude of 581μv (n=21, range 175 – 1825μv).

There was no statistical significance when male and female mean amplitudes were compared for either the RLN or vagus nerve. **Table 4**

Table 4. Male vs. Female

Mean Amplitude (μv)	RLN - Male	RLN - Female	Vagus - Male	Vagus - Female
Mean ± SD	581 ± 448	739 ± 532	581 ± 449	573 ± 401
Range	109 - 1670	135 - 2391	175-1825	74 -1610
No. of Patients	19	50	21	44

Male vs. Female, RLN: p = 0.26

Male vs. Female, Vagus: p = 0.94

RLN vs. Vagus, Male: p = 0.99

RLN vs. Vagus, Female: p = 0.09

Comparisons based on two-sample Student t-tests.

Initial RLN Amplitude vs. Final RLN Amplitude:

The initial RLN mean amplitude was compared to the final RLN mean amplitude and no

statistical difference was identified for either the right or left side (right initial RLN vs. right

final RLN: p=0.279, left initial RLN vs. left final RLN: p=0.995). **Table 5**

Table 5. Initial vs. Final RLN Amplitude

Mean Amplitude (μv)	Right Initial RLN	Right Final RLN	Left Initial RLN	Left Final RLN
Mean ± SD	693 ± 638	807 ± 606	500 ± 469	508 ± 507
Range	86 - 2237	86 - 2275	30 - 2049	92 - 2237
No. of Patients	34	32	33	31

Right Initial vs. Final, RLN: p=0.279

Left Initial vs. Final, RLN: p= 0.995

Comparisons based on two-sample Student t-tests.

Initial Vagal Amplitude vs. Final Vagal Amplitude:

A similar finding was seen when the initial vagus mean amplitude was compared to the final

vagus mean amplitude (right vagus initial vs. right vagus final: p=0.192, left vagus initial vs.

left vagus final: p=0.318). **Table 6**

Table 6. Initial vs. Final Vagus Amplitude

Mean Amplitude (μv)	Right Initial Vagus	Right Final Vagus	Left Initial Vagus	Left Final Vagus
Mean ± SD	663 ± 503	847 ± 570	444 ± 296	371 ± 261
Range	75 - 1797	166 - 1804	82 - 1256	80 - 1137
No. of Patients	33	15	30	21

Right Initial vs. Final, Vagus: p= 0.192

Left Initial vs. Final, Vagus: p= 0.318

Comparisons based on two-sample Student t-tests.

Latency:

Our study confirmed similar findings regarding latency. We defined latency as the time from stimulation artifact to first wave peak differing from Dralle's group's definition.[54, 55](Figure 1) In our study mean latency of the left vagus (7.67ms) was significantly longer than the right vagus (6.77ms). Also vagal latencies were significantly longer than latency of the right and left RLN which were similar (left RLN 3.19ms and right RLN 3.70ms). This difference in vagal and RLN waveform latency and the significant difference between left and right vagal waveform latencies has significant implications in terms of documentation of neural integrity at the completion of lobectomy. Subsequent to the specimen being sent off the table, a timed waveform of vagal stimulation in the mid-neck at the level of the larynx provides clear-cut documentation as to vagal and RLN status. This timed waveform if recorded for documentation clearly identifies that the vagus nerve was stimulated and due to the unique latency of the left versus right vagus nerve aside that is being tested. Such vagal stimulation provides documentation that the entire neural circuit is intact.

Threshold

The threshold intensity for the right RLN (0.51mA) was similar to the left RLN (0.61mA), and both the right and left vagus threshold intensities (0.41mA for both right and left vagus). This threshold intensity for stimulation of human RLN in vagal nerves coupled with the proven safety of repetitive neural stimulation in this study at 1 to 2 mA together lead us to recommend that standard neural stimulation during thyroid surgery of the human RLN and vagus nerve should be performed approximately 1 to 2 mA. This provides a robust but safe level of neural stimulation. There is no added safety to stimulating at lower levels which brings the risk of incomplete or inadequate neural stimulation leading the surgeon to potentially disregard a structure that may in fact be neural.

Amplitude

With respect to amplitude we found there is a dose response curve in terms of EMG amplitude starting at a low level when the nerve is stimulated near threshold with a small but definable evoked waveform and increasing to a stable super maximal stimulation amplitude which cannot be increased despite increasing stimulation current level . Stimulation at 1 to 2 mA provides such super maximal stimulation amplitude levels desirable during thyroid surgery. The variability in the magnitude of the EMG amplitudes obtained during the course of thyroidectomy may be caused by several major factors: (1) variation in nerve-stimulating electrode probe contact (this 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 are also likely involved to some degree (6) variable exact position of motor fibers within the nerve relative to position of the stimulating probe (i.e. eccentric position of motor

fibers within the vagus nerve), and (7) sex, age and other morphologic characteristics of the patient. It should be noted that the amplitudes we found to evoke stimulation of the recurrent laryngeal nerve and vagus there during stimulation thyroid surgery are quite similar to cord polarization amplitudes occurring spontaneously during volitional speech shown to be in the 400 to 500µv range.[56] It seems that stimulation during routine thyroid surgery results in neural and core elements that are within normal physiologic speech ranges. The mean amplitude was higher in the right vagus 717µv vs. the left vagus 420µv which was statistically significant and is consistent with the work of Dralle's group described above.The mean amplitude of the right RLN 783µv was higher than the left RLN 604µv but this was not statistically significant. Dralle's group found greater amplitudes in the left versus right RLN.[54] Further we found no statistically significant difference overall between RLN amplitudes and vagal amplitudes when compared within each side.

Safety of Stimulation and Surgical Dissection

Repeated stimulation had no adverse affect on evoked EMG parameters or untoward effects on postoperative vocal cord mobility (we had normal post operative vocal cord examination in all patients). Further, there were no adverse cardiopulmonary consequences to repetitive vagal stimulation.

Male vs. Female

With regard to gender difference between male and female nerve amplitudes, in our study the female RLN mean amplitude (739µv) was higher than the male RLN mean amplitude (581µv). The mean female vagus amplitude (573µv) and the male vagus mean amplitude (581µv) were similar. There was no statistical significance when male and female mean amplitudes were compared for either the RLN or vagus nerve. Dralle's group showed similar values for both male and female RLN mean amplitudes.[54] In contrast to our study, the males

in Dralle's study group had lower values for vagus nerve amplitudes (male left vagus 323μv, male right 386μv) and there was significant statistical difference between males and females for both RLN and vagus nerve amplitudes. However, this finding is likely to be clinically insignificant.[54]

Conclusion:

This study (MEEI Data) highlights the electrophysiological/EMG differences and similarities between the RLN and vagus nerve. In summary the latency of the evoked waveform is significantly different RLN versus vagus and left versus right vagus. These latency differences are significant enough to allow, based on latency analysis of the evoked waveform ,identification of the nerve being stimulated based on waveform analysis, which has potential documentation implications .The stimulation threshold for the bilateral RLN's and vagus nerves are between 0 .4- 0.5mA, suggesting intraoperative initial neural stimulation at 1 to 2 milliamps represents super maximal stimulation level. Repetitive neural stimulation and surgical dissection in this series did not affect RLN or vagus electrophysiologic stimulation parameters or postoperative vocal cord function. Normative amplitude measurements for bilateral RLN and vagus nerve stimulation are presented - as there is limited data available in the literature on normal RLN and vagal EMG signals generated during thyroid surgery. Of all of the advantages of IONM, the prediction of postoperative vocal cord paralysis is perhaps the one which can be most strategically employed in the prevention of bilateral vocal cord paralysis. In order to recognize when signal loss has occurred during neural monitoring one must, of course, have a complete understanding of normative data. In short we must appreciate what the normal signal during vagal and RLN stimulation is if we are to completely understand injury states where the signal is lost or altered. Recent International IONM Study Group recommends routine measurement of amplitude, latency and threshold and recognition of wave form morphology at beginning, during and completion of surgery for

RLN and vagus. Our study provides further data on normative RLN and vagal EMG reference values towards that end. [47, 57] *(Paper Presented at American Academy Otolaryngology-Head Neck Surgery, San Francisco 2011, Irish Otolaryngology Society Meeting, Ireland 2011)*

Chapter 4: Electromyograghic Changes in Injured Recurrent Laryngeal Nerves

Injury to the RLN usually results from severing, crushing, suturing, stretching or tearing the main trunk or its branches. [58, 59]

Nerve injuries may be divided into 3 categories- neurapraxia, axonotmesis or neuromesis according to the Seddon classification. Neuropraxia is defined as a local, transient conduction block along a nerve without axonal degeneration. The injury may be short term or take months to resolve. Axonotmesis involves axonal injury and is characterized by distal axonal degeneration, although the nerve sheath remains anatomically intact. Neuromesis occurs when the nerve is transected, resulting in degeneration of the distal axon. [60, 61]

The process of demyelination and axonal degradation that occurs after axonal injury is called wallerian degeneration. The Sunderland classification expands on the Seddon classification by further subdividing degrees of axonotmesis injury depending on loss of endoneurium, loss of perineurium or loss of epineurium. [60, 61, 62] Neuropraxic injuries often results in recovery without any surgical intervention such as nerve repair or grafting in contrast to neurotmesis. Electrodiagnostic evaluations such as nerve conduction studies and EMG can be used to evaluate peripheral nerve injuries and provide information in regard to the location and severity of the injury. Volitional and evoked EMG can be performed on patients with peripheral nerve injuries to determine the extent of nerve injury. Fibrillation potentials are typically seen after days to weeks, whenever there is axonal injury and wallerian degeneration. Motor unit action potentials are seen after nerve injury if some axons have been spared. Thus, if the peripheral nerve injury is incomplete, one can see fibrillation potentials with motor unit action potentials. The absence of motor unit action potentials raises two possibilities- 1. The nerve may be transected 2. The nerve may be anatomically intact, but

there may be a complete conduction block. Evoked EMG would show no motor response, as long as the site of stimulation is proximal to the site of injury. As the degenerated and spontaneously fibrillating muscle fibres become reinnervated by surviving axons of the motor neurons, fibrillation potentials disappear. If the lesion is primarily segmental demyelination with conduction block, motor unit action potentials will reappear as the demyelinated nerve segment becomes remyelinated, allowing nerve conduction. The successful transmission of an evoked waveform suggests that a nerve axon is anatomically intact, thus ruling out nerve transection (neurotmesis). In adults with laryngeal nerve injury, volitional EMG has been used to classify the nerve injury and to determine prognosis.[63, 64] If an adult who has sustained an RLN injury undergoes laryngeal EMG approximately three months post injury and this examination demonstrates the presence of fibrillations or the absence of EMG activity in the thyroarytenoid muscle- there is a greater than 90% chance that the injury represents neurotmesis and that vocal cord paralysis is permanent.[64] In the same scenario described above- if some degree of electrical activity is noted in the thyroarytenoid muscle three months after injury, the significance of the activity is unclear.[64] There has been renewed interest in evoked laryngeal EMG in patients with known vocal cord palsy. Quantitative measures such as threshold, amplitude, latency and wave duration may be altered post injury.[60, 65]

Scott et al performed a pilot canine study with the aim of testing whether intraoperative spontaneous laryngeal EMG and evoked laryngeal EMG could distinguish between healthy and injured RLNs. They also tested whether serial spontaneous and evoked laryngeal EMG recordings provided valuable information in regard to the likelihood of vocal cord palsy recovery or the timing of recovery following surgical injury of the RLN. Six canines were divided into two groups- four animals sustained a standardized crush injury to the left RLN and two animals underwent resection of a 1cm segment of the left RLN. Spontaneous and evoked laryngeal EMG were performed. As evoked laryngeal EMG was performed,

quatitative measures of threshold, amplitude, wave duration and latency were measured. The EMG data was correlated with vocal cord mobility as assessed by direct laryngoscopy. All four canines who underwent crush injuries to the RLN developed a transient left vocal cord palsy which fully recovered by week six. In the transection group- one canine developed bilateral vocal cord palsy (accidental contralateral nerve injured) and was euthanized. The second canine developed a left vocal cord palsy which did not resolve by week ten when the animal was sacrificed. Spontaneous and evoked laryngeal EMG of the thyroarytenoid muscle was performed on all animals before nerve injury and at one week time intervals until the recovery of vocal cord motion. After nerve transection and double crush injury, a pattern of fibrillations was observed which persisted until the week before the return of vocal cord mobility, when electrical silence was noted. Early laryngeal EMG fibrillations are probably explained by an initial period of muscle denervation which occurs in both axonotmesis and neurotmesis (transection). The subsequent pattern of electrical silence followed by low amplitude motor unit action potentials is probably due to muscle reinnervation. As recovery continues, more coordinated firing of motor units is evident on EMG. *The timing of this change to electrical silence is very important – muscle atrophy leads to a decline in spontaneous electrical discharge and the only way to differentiate between early reinnervation and the electrical silence seen with chronic muscle atrophy following permanent vocal cord paralysis is to place the examination within the temporal context of the injury.* [66] At weekly intervals, open stimulation of both RLNs was performed to assess for an evoked EMG response. An abnormal evoked response, with decreased amplitude, increased latency and increased stimulation threshold was observed in all four animals in the crush group at week 5/6. As vocal cord motion recovered, threshold, latency and amplitude values changed and approached normal values (two animals). Evoked EMG in the transection group had no response. [67, 68]

Xu et al performed a canine study to characterize various RLN injuries in twenty beagles. The canines were divided into three groups – complete injury (transection), incomplete injury and control. In the complete injury group, a 1cm RLN segment was resected. Within the incomplete injury group there was three sub groups- ligation subgroup, half section group, crush subgroup. The characteristics of the RLN surgical injuries were evaluated by endoscopic examination and laryngeal EMG immediately after surgery and at 1, 3, 6 and 12 months after the procedure. Histopathological examinations were also performed at 1, 3, 6 and 12 months after surgery. The vocal cords were completely immobile in both the transection and ligation subgroup. This continued for more than six months in most of the vocal cords in the transection group. All of the vocal cords in the ligation subgroup had limited activity more than six months post surgery. Various forms of vocal cord mobility were observed in the half section group more than six months after injury - 20% were fixed and 80% had limited movement. In the crush subgroup, 50% had limited movement and 50% had normal activity immediately after injury. After RLN injury the average muscle fibre diameter and the average muscle bundle of the affected muscles were decreased. The average number of muscular cell nuclei per square inch increased. These changes were especially apparent between 6- 12 months after injury and were significantly different when compared to the control group. With regards to observed electrophysiological changes observed, electrical silence was seen in the vocal cords of the transection and ligation subgroup. Fibrillation potentials were seen in the transection group one week later and these increased over a 1- 3 month period. However, after 3-6 months the fibrillation potentials were decreasing. No reinnervation potentials were observed in the transection group. Increasing recruitment activity and increasing reinnervation potentials were observed in the ligation subgroup. These continued in the ligation subgroup over a six month period. In the crush and half section subgroup, normal and low amplitude motor unit potentials were observed. From six to twelve

months, a reinnervation potential was observed. With regards to evoked potential laryngeal EMG analysis, there were no significant evoked potentials in the ligation and half section subgroups in the early period. Evoked potentials with lower amplitudes could be detected in the later period. The amplitudes of the ligation subgroup were lower than those observed in the half section subgroup. The mean amplitude of the evoked potentials in the crush group showed no significant difference from that of the control group but the latency period increased significantly from 1- 3 months after injury. [69]

Xu et al demonstrated that the degrees of nerve injury in order of decreasing severity to be caused by transection, ligation, half section and crush. As the extent of injury increased, the average diameter of the muscle fibres and the average diameter of the muscle bundles decreased and the number of muscular nuclei per square inch increased especially at 6- 12 months. After nerve transection the vocal cords were fixed immediately with no improvement over time. No vocal cords recovered normal movement in the ligation subgroup, whereas some vocal cords recovered normal movement and no vocal cords were fixed in the crush subgroup. [70]

Mu & Yang simulated RLN injury during neck surgery in a canine model. Twenty canines were randomly divided into 1 of four groups- half section, double crush with a haemostat, permanent ligation with nylon suture or complete section (a 1cm segment of nerve was removed)The aims of the study were to obtain information on the laryngeal EMG patterns in the affected laryngeal muscles (thyroarytenoid and posterior cricoarytenoid muscle) after varying injuries to the RLN, to clarify whether vocal cord palsy caused by half section, crush and ligation of the RLN would disappear partially or completely and how long it would take. In addition, Mu et al correlated laryngeal EMG findings with vocal cord mobility. Before and immediately after the injuries to the RLNs, the laryngeal EMG was examined and vocal cord movement was inspected. This same follow up exam was made at weekly intervals for 4-6

months. After three months post RLN injury, the EMG motor unit potentials and vocal cord

movements on the side of nerve injury were back to normal in the canines that had their RLN

partially sectioned or double crushed. In the canines that had their RLN ligated with a suture

or complete nerve section, neither their EMG nor vocal cord movements returned to normal.

Recovery from RLN palsy was complete by 3 months after nerve impairment if over half of

the nerve fibres remained intact.[71]

Chapter 5: Continuous Intra Operative Nerve Monitoring (CIONM)

Intra operative nerve monitoring has been used to add to visual information and to facilitate localization and identification of the RLN during thyroid /neck surgery. The main limitation with hand held intermittent intra operative nerve monitoring using a conventional stimulation probe – is that the RLN is at risk for damage *between* stimulations. Thus, a real time continuous nerve monitoring system would be desirable. Lamadé et al performed a study on fifty five patients undergoing thyroid and or neck surgery using the first continuous intraoperative nerve monitoring (CIONM) device. The device was developed for continuous transtracheal intraoperative monitoring and in situ detection of the RLN during surgery. The new system was based on a double-balloon endotracheal tube with integrated atraumatic stimulating and tracing electrodes. The recurrent laryngeal nerve was stimulated transtracheally and laryngeal muscle action potentials were recorded. Laryngeal muscle action potentials were recorded continuously and responded sensitively to tension and pressure to the nerve. There were no accidental permanent RLN palsies. Lamadé et al concluded that the new system offered five advantages: 1. it was atraumatic, 2. it was easy to use, 3. it could monitor continuously with an audio feedback to the surgeon, 4. it worked outside the surgical field; and 5. it was highly sensitive, even indicating reversible irritation to the nerve.[72] However, due to economic and technical issues this system was not introduced for widespread clinical use. In 2007, Lamadé et al presented a new system for CIONM of the RLN- a vagal electrode. This was a pilot study involving only seven patients. The electrode was designed as a hybrid cuff electrode with a tripolar electrode arrangement. The electrode was fully implantable and atraumatic. A hand held probe was also used during the study to intermittently stimulate the RLN during dissection in addition to the vagal electrode. This was used to assist in localisation of the RLN and any structure suspicious for the RLN could be stimulated prior to dissection. Both endotracheal surface electrodes and bipolar needle

electrodes were used as sensing electrodes for laryngeal EMG activity. Real time signal analysis was performed and the surgeon was provided with both visual and acoustic feedback. Following identification and isolation of the vagal nerve, the vagal electrode was placed tension free around the vagus nerve. All patients underwent a pre and postoperative vocal cord laryngoscopy. The average time for electrode placement was 5.8mins. The vagus nerve was stimulated for a mean of 63mins (range 55-99). In all seven patients stable EMG signals were recorded throughout the surgery. No patient experienced any complications – there was no change in heart rate intraoperatively and all had normal postoperative vocal cord movement. During this pilot study it was noted that stretch or tension on the nerve during manipulation of the thyroid gland resulted in signal depression of up to 60% which resolved within seconds on removal of the tension/stretch. Lamadé et al suggested that such trauma to the RLN may be recognised early by use of CIONM and thus allow the surgeon to react accordingly. [73]

Schneider et al also recognised the limitations of conventional hand held stimulation electrodes and conducted a CIONM feasibility study on twenty three pigs using a specially designed vagal electrode. This t shaped bipolar electrode was fully implantable during surgery and was self stabilising between the vagal nerve and cervical vessels. A foot switch system allowed the surgeon to switch from CIONM to hand held stimulation as required. During this study the RLN s were traumatised either by mechanical (traction, compression) or thermal injury (heat). Traction using a pulley system was applied to six pigs/twelve RLNs (max 350g), compression injury was performed in another six pigs/twelve nerves at risk using a pressurised inflated cuff (max 280mmHg). In five pigs, heat of up to $55°C$ was applied to the RLN with a platinum heater and an integrated temperature sensor. In six pigs, the vagal nerve threshold and latency were determined. The stimulation intensity was set at 0.1mA and gradually increased by 0.1mA to an upper limit of 1.0mA. A vagal nerve biopsy was taken to

elucidate any morphological changes in the vagal nerve caused by the anchor electrode. Results of this study demonstrated that the vagal electrode was easy to apply and on average took less than one minute. The mean time of continuous vagal nerve stimulation was 280 ± 60 mins with $0.5 – 1.0$ mA. No adverse cardiorespiratory side effects were observed. There was no further increase in signal amplitude above 0.8mA stimulation intensity. In the stimulation only group (six pigs, twelve nerves at risk), pathological evaluation of the vagus nerve was consistent with an intact large calibre nerve, without interruptions of nerve conductivity, microcirculation or haemorrhage. Only minor epineural oedema and nonspecific diffuse epineural and perineural accumulation of leucocytes were seen histologically. Traction trauma to six pigs/twelve nerves at risk resulted in an amplitude decrease of $59\% \pm 15\%$ with increasing traction. The latency increased in eight nerves at risk by approximately $15\% \pm 16.3\%$. Six RLNs exhibited complete loss of signal at 1,500mN (~150g) with only two showing recovery of signal at the end of the experiment. Compression trauma (12 nerves at risk) caused amplitude decrease by $40\% \pm 23.8\%$ with increasing compression in ten nerves. Three nerves had complete loss of signal at 200mmHg or greater and only one had signal recovery at the end of the experiment. The latency was increased by $14\% \pm 21\%$ in ten nerves and unchanged in two nerves. Thermal injury to the RLN in ten nerves at risk resulted in an amplitude decrease by $48\% \pm 18\%$ with increasing heat. Three nerves showed complete loss of signal at $50\,^{\circ}$C without recovery. The latency was increased by $15\% \pm 12.1\%$ in six nerves and unchanged in two nerves. Of all the nerves at risk , 12 nerves (38%) had complete loss of signal during application of the simulated trauma, return of signal was only seen in 3 of the nerves (9%). In all cases of total signal loss, the RLN could be stimulated with a hand held electrode distal to the injury, producing a positive EMG signal but no response was found proximal to the site of nerve injury. Schneider et al did not correlate amplitude changes, latency changes or loss of signal with post operative vocal cord function. Thus it is unknown

whether these electrophysiological changes would have been associated with either a temporary or permanent vocal cord palsy. However, this study does support the idea that increasing stress to the RLN results in electrophysiological changes that could be monitored continuously intraoperatively. Perhaps, initial electrophysiological changes may prove as an early warning to the surgeon and prevent further irreversible nerve damage.[74]

Safety of Continuous Intra Operative Nerve Monitoring:

Prolonged vagal nerve stimulation has become an important treatment modality for medically refractive epilepsy, depression, anxiety and Alzheimers disease. Cardiac and respiratory side effects were detected after longterm stimulation weeks to months later; no complications were seen in these patients after short term stimulation. [75, 76, 77] Studies have shown that stimulation frequencies of 50Hz and above cause major irreversible damage to the vagus nerve. For clinical use of vagal stimulation, frequencies range from 20 to 30Hz.[76] In general, a stimulation of between 1-2 Hz is typically used in IONM. Schneider et al did not see any cardiorespiratory side effects after 280 min of stimulation. Wu et al conducted a study on eight piglets to assess the optimal electrical intensity for reliable stimulation and safety of repetitive RLN and vagal stimulation during IONM. The RLN and or vagus nerve were stimulated using a current of 0.1 – 1.0 mA (a stepwise increase of 0.1 mA), 1.5, 2.0, 2.5 and 3.0mA - 100μs duration and were repeated at 4 pulses/sec).The baseline amplitude, latency and waveform morphologies of the EMG response were observed and recorded. Following the above, the vagus nerve and RLN were then stimulated continuously for ten minutes (3.0mA, 4 pulses/sec, and duration 100μs). Any changes in amplitude, latency and threshold of the EMG signal or cardiovascular parameters were recorded. Wu et al demonstrated that neither the vagus nor RLN amplitude changed when one compared continuous stimulation (ten minutes) with baseline stimulation. The amplitude of the continuously stimulated vagus nerve (987±365μV) was 99.7% of the baseline vagus amplitude signal. The final amplitude of

the continuously stimulated RLN (1024±214µV) was 99.8% of the baseline RLN amplitude signal. In addition, there were no changes in threshold or latency between the two groups, nor were there any observed changes in heart rate, rhythm or bronchospasm. [78]

Chapter 6: Study Proposal

Continuous Vagal Intraoperative Monitoring Prevents Recurrent Laryngeal Nerve Paralysis by Revealing Initial EMG Changes of Impending Neuropraxic Injury: A Prospective, Multicentre Study

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Introduction:

Recurrent laryngeal nerve (RLN) paralysis is one of the most serious surgical complications which can occur in patients undergoing surgery for thyroid pathology. This can result in significant post-operative morbidity such as voice and swallowing dysfunction. Bilateral RLN nerve injury can result in dyspnoea and life threatening glottic obstruction. [40, 44]

The prevalence of vocal cord injury post thyroid surgery varies widely depending on the reporting institution and whether or not pre and post-operative laryngoscopy is performed. A recent study showed a temporary vocal cord palsy rate of approximately 10% and permanent vocal cord palsy rate ranged from 0-18.6%.[22] Descriptions of electrical recurrent laryngeal nerve monitoring date back to animal and human studies performed by Shedd et al. in 1966.[79, 80] While advances have been made since Shedd's introduction of intralaryngeal balloon spirography, the issue of intraoperative nerve monitoring (IONM) in thyroid surgery remains

controversial.[81, 82] Current IONM devices only allow the surgeon to intermittently stimulate and assess RLN function which allows the nerve to be theoretically at risk for damage in-between stimulations. Any inadvertent retraction of the RLN as the thyroid gland is being manipulated can cause 'blind' damage and deterioration in neural function.[67, 82] Debates on usage of the nerve monitoring system lie in questions of its reliability, sensitivity and specificity, and cost.[73,74,83] The first continuous nerve monitor was described by Lamade et al.[72] The main advantage of a continuous nerve monitor device is that it has the potential to identify injury to the RLN earlier and thus the nerve trauma maybe reversible. Additionally, to achieve detection of the maximal length of nerve that would be at risk, the electrode would best be placed as proximally as possible. In the case of RLN nerve monitoring, the electrode would be placed on the vagus nerve. The device, however, has not gained mainstream favour due to cost, technical difficulty, and availability.[67, 73, 74, 83]

Dr. Randolph has advocated the use of IONM for many years. In addition, the Thyroid and Parathyroid Surgical Unit at MEEI which has an established history of intraoperative nerve monitoring has recently written international guidelines.[47]

The *Medtronic* Automatic Periodic Stimulation (APS) electrode provides periodic, low-level stimulation of the vagus nerve and is designed to potentially allow detection of recurrent nerve injury via early warning of changes in nerve amplitude and latency waveforms. The APS electrode once installed automatically stimulates the vagal nerve approximately every six seconds (10 times /minute). The APS electrode provides both visual and audible feedback via a monitor. Any change in electrophysiological response from the nerve would allow the surgeon to take appropriate action and thus prevent further nerve injury. This is not available with current technology. Of note continuous vagal nerve stimulation has been shown to be safe in treatment of refractory epilepsy.[84]

Standard IONM:

Intraoperative neural monitoring (IONM) has been routinely applied in head and neck surgery and has been increasingly recognized as an adjunct to visual nerve identification, as an aid in intraoperative management and in prognostication of postoperative nerve function over the past two decades in thyroid and parathyroid surgery.[29,35,36,44] Recent studies show approximately 53% of US general surgeons and 65% of US otolaryngologists use IONM in some or all of their cases and a recent survey of German surgical departments found over 92% routinely utilize IONM during thyroidectomy.[79, 80] The value of IONM information for surgeons is highlighted by its more common use in expert settings by surgeons with higher volume practices of >100 cases per year.[80]

Multidisciplinary organizational support for neural monitoring is also accumulating. German practice guidelines and the International Neural Monitoring Study Group recommend IONM for all cases of thyroid surgery.[47,81] American Academy of Otolaryngology and Head and Neck Surgery (AAOHNS) in its recently published guidelines for voice optimization during thyroid surgery suggest IONM is an option for patients undergoing thyroid surgery due to proven utility in three distinct areas: 1) improvement in recurrent laryngeal nerve (RLN) identification time, 2) reduction of temporary vocal cord palsy (VCP) rates and 3) avoidance of bilateral VCP

(through prognostication of postoperative vocal cord function). These AAOHNS guidelines suggest special utility for IONM in cases of 1) bilateral thyroid surgery, 2) revision thyroid surgery and 3) surgery in the setting of an existing RLN paralysis.[82] Two recently published American Thyroid Association (ATA) Surgical Affairs Committee consensus statements (on outpatient thyroid surgery and on optimal surgical management of goiter) note that neural monitoring is helpful in confirming intact neural function at the end of surgery and that this

may impact on discharge planning.[83, 84] American Head and Neck Society (AHNS) guidelines for the management of invasive thyroid cancer state that IONM provides important intraoperative and postoperative functional information which impacts on timing of contralateral surgery and need for tracheotomy and recommends IONM be considered for all cases of thyroid cancer especially if there is preoperative RLN dysfunction.[85]

Continuous Vagal Monitoring and Neural Injury Prevention:

Current IONM formats allow the surgeon to intermittently stimulate and assess RLN function. While this has significant utility, such intermittent stimulation monitoring format could potentially allow the RLN to be at risk for damage in-between stimulations.[53,86] This dynamic may underlie data suggesting current IONM formats are limited in ability to *prevent* neural injury.[36,81,86,41,42,87-89] An IONM format that provides information regarding impending injury would address this issue.

The potential advantage of a continuous nerve monitoring format (CIONM) is that it has the potential to monitor the entire vagus and RLN functional integrity in real-time throughout surgery and could identify EMG signals associated with early-impending injury states.[73,74,90] Initial studies on CIONM with a vagal nerve electrode have suggested such monitoring is not associated with significant adverse neural, cardiac, pulmonary or gastrointestinal vagal side effects.[53, 72, 73, 91-93]

For continuous vagal neural monitoring to have proven utility it must provide accurate detection of EMG changes which are A.) Considered adverse EMG events in that they are associated with impending VCP, B.) Easily recognized by the surgeon intraoperatively and C.) Nascent so that they are reversible with modification of the associated surgical maneuver with a resolution of EMG changes.

Further we must be able to segregate such EMG changes of impending neural injury from EMG changes which are artifactual such as those associated with endotracheal tube position

or other equipment problems. We report one of the largest prospective continuous vagal monitoring studies investigating novel EMG outcome parameters (we define as "combined events") associated with imminent neuropraxic nerve injury, their relationship to intraoperative surgical maneuvers and postoperative VCP.

Study Outline: This is a prospective, non - randomized observational study. An internal review board (IRB) application has been approved.

We propose to use an APS electrode in a series of hundred and two adult patients undergoing thyroid surgery at MEEI and Halle Germany with the intention of relating intraoperative electrophysiological changes to post- operative laryngeal function. We hope to demonstrate that vagal nerve waveform changes, specifically amplitude and latency changes can be correlated with impending and frank nerve injury. Potentially, the results of this study could have implications on intraoperative vagal nerve monitoring in the future.

Materials and Methods:

Written informed consent was obtained from each patient in this nonrandomized prospective observational trial. Patients with preexisting RLN paralysis, non-recurrent laryngeal nerve, amplitude <500μV and age under 18 years were excluded. All patients had a preoperative and post-operative laryngoscopy to assess vocal cord function and repeated serially if abnormal. We followed all patients, male and female, who underwent operations for various thyroid diseases, all performed by a single endocrine surgeon (Dr. Gregory Randolph, MEEI Boston, Dr. Henning Dralle, Halle, Germany). Patients were also stratified to low-risk and high-risk groups according to the anticipated technical difficulty and inherent risk of morbidity due to the nature of the particular procedure. The low-risk group included patients undergoing primary surgery for benign pathology, and the high-risk group consisted of those undergoing re-operative surgery or completion thyroidectomy for recurrent disease or malignancy.

Information on the patient's demographics, indication for surgery, operative details including recorded neuromonitoring signals (vagus and recurrent laryngeal nerve amplitude and latency values) pathology reports, and postoperative outcome were collected prospectively. Intraoperative nerve monitoring was set up in the standard way using a *Medtronic* NIM 3.0 nerve monitor. All patients following general anesthesia induction were intubated with a standard electromyographic (EMG) endotracheal tube. Following induction and intubation no further neuromuscular blocking agents were administered. Correct positioning of the EMG endotracheal tube between the vocal cords was confirmed by the presence of good respiratory variation (as seen on the NIM monitor) and or direct laryngoscopy. All IONM set up and practices (including trouble shooting algorithm) was as recommended by the International Neural Monitoring Study Group.[47] Intra-operatively the APS electrode was installed onto the vagus nerve. The carotid sheath was dissected in a manner consistent with current medical standards. The vagal electrode resides within the carotid sheath in close proximity to the vagus nerve. The APS electrode was then switched on and RLN monitoring commenced as the thyroid gland was manipulated. The surgeon may as required intermittently directly stimulate the RLN or vagus nerve using the traditional hand held stimulator. Besides a small extension of vagal nerve dissection, no major changes have been made from the traditional neck surgeries with nerve monitoring.

The prospective electrophysiological nerve data was saved in a Microsoft Excel database. Upon completion of prospective data collection, data was anonymized and stored in a password-protected MS Access database, and statistically analyzed. We investigated evoked vagal nerve waveform amplitude and latency changes (alone and combined) during thyroid surgery using a size 2 or 3 vagal electrode (**Figure 1A and 1B**) and a NIM 3.0 monitor (APS vagal electrode system Medtronic, Jacksonville Fl) and correlate these with intraoperative

maneuvers, and post- operative laryngeal function to determine parameters of impending and definitive nerve injury.

Definition of Adverse EMG Events:

To identify clinically relevant significant adverse EMG signal changes we categorized EMG signals based on vagal evoked signal amplitude and latency waveform characteristics. Single events were defined as EMG changes affecting either amplitude or latency. Combined events (CE) were defined as concordant changes in both signal amplitude and latency and are stratified below into mild (mCE) and severe CEs (sCE). We hypothesized that such combined events may more reliably track with impending neuropraxia as opposed to other technical issues such as endotracheal tube malpositioning (which could affect amplitude in isolation).We defined amplitude and latency changes as follows:

- **Mild Combined Event (mCE)**- amplitude decrease of >50 – 70 % with a concordant latency increase of 5-10%

–**Severe Combined Event (sCE)**- amplitude decrease of >70% with an concordant latency increase of >10%

– **Loss of Signal (LOS)** – complete loss of recognizable RLN electromyographic signal (amplitude < 100 µV) intraoperatively as defined by the International Neural Monitoring Study Group.[47]

Installation of the APS electrode required exposure of less than 1cm segment of vagus nerve.The APS electrode, keeping the enclosure tabs open with forceps was positioned on the nerve starting at a 45° angle and sliding it over the vagus (see **Figure 1A and 1B**).
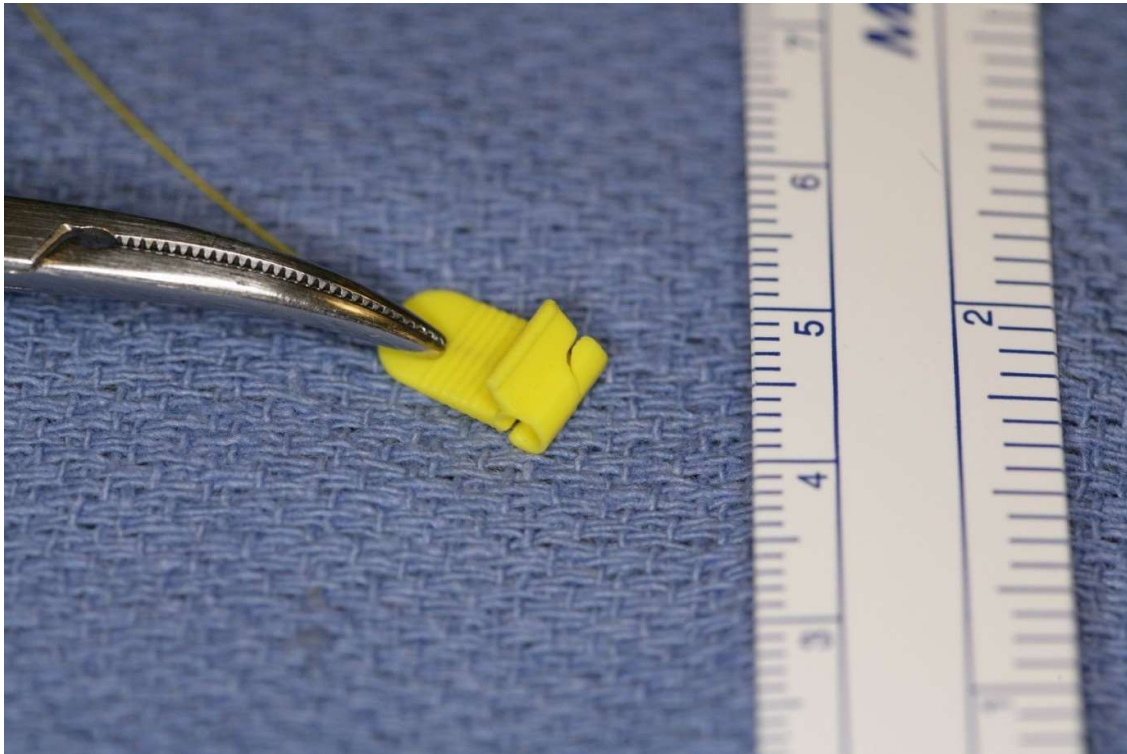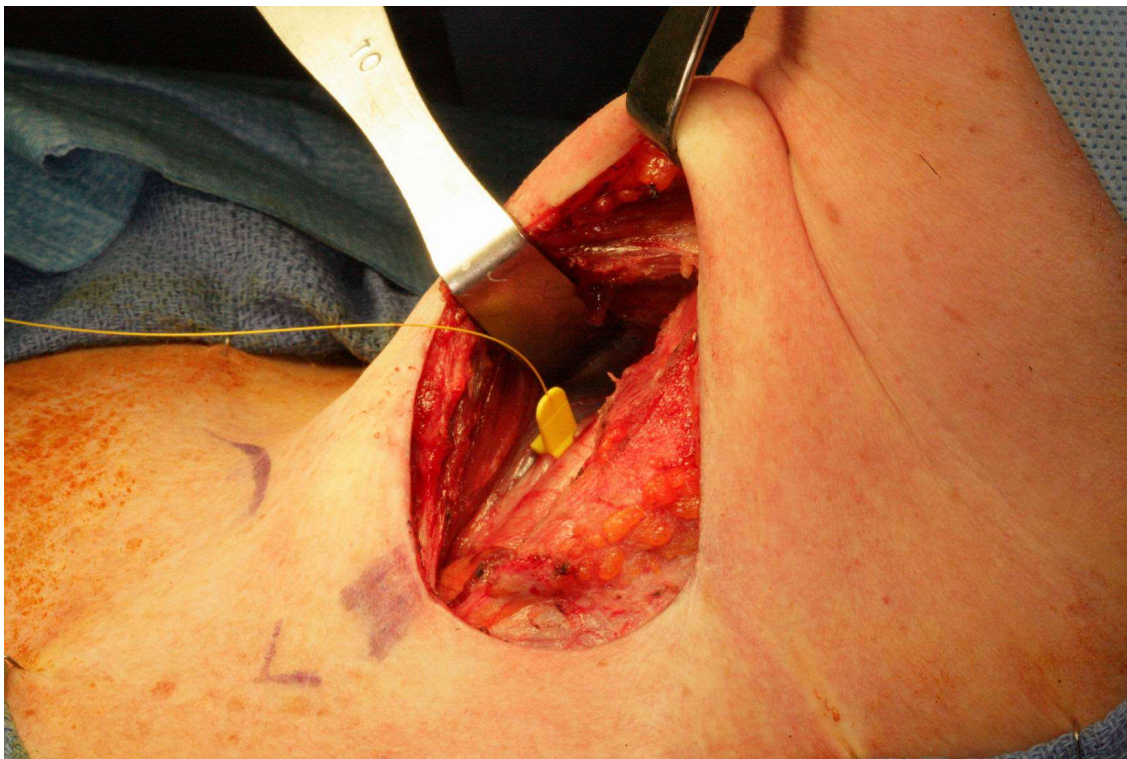
Figure 1A. APS Electrode

Figure1B. APS Electrode Installed on Vagus Nerve

After connecting the APS electrode to the monitor baseline values for latency and amplitude were automatically calibrated. If the baseline amplitude was less than 500 µV the anesthesiologist repositioned the endotracheal tube such that a waveform of greater than 500 µV was achieved as an initial baseline. If at the initial phases of the case amplitude and latency alarms engaged and this was not during a surgical maneuver and was felt to be artifactual then the tube was repositioned and a new amplitude and latency baseline was re-calibrated. The APS electrode provides periodic, low-level stimulation of the vagus nerve of 1mA every six seconds (10 times/minute, pulse duration 100µsec). The frequency of stimulation can be programmed. Amplitude and latency waveforms were displayed separately and upper limit threshold for latency and a lower limit threshold for amplitude were defined as separate alarm lines. In addition acoustic signals alerted the surgeon that preset alarm threshold of amplitude or latency had been violated or that the electrode had been dislocated.

Surgical Behavior

As part of our surgical protocol if significant adverse EMG changes occurred temporally associated with a given surgical maneuver, then that maneuver was immediately aborted and the surgical maneuver as well as the EMG changes were documented and observed to determine recovery. At the end of the surgery, removal of the APS electrode and the stimulation of the vagus nerve - proximal and distal to electrode contact sites were performed to exclude electrode induced vagal segmental injury.

Data Analysis

Receiver Operating Characteristic (ROC) curves were constructed treating the number of sCE or mCE as continuous variables in a non-parametric analysis (data distribution were skewed) with the presence or absence of VCP as the gold standard. The standard error for the area under the curve was calculated according the algorithm described by Delong.[94] Sensitivity and

specificity were defined according to standard definitions for binary and nonbinary diagnostic tests, while predictive values were calculated according to Bayesian theory.[95] Associations between the presence/absence of VCP and categories of sCEs and mCEs were evaluated with Fisher's exact test. Statistical analysis was performed using Stata 12.0(College Station, TX). Predictive values were calculated according to Bayes theorem with standard conditional probabilities.[96] Pre-test probabilities were estimated based on the prevalence calculations from within the study data.The intermediate pre-test probability was selected as the point estimate of prevalence (5.9%). The low and high pre-test probabilities were selected using the 95% CI for the prevalence point estimate (2.2%, 12.4%).

Results:

In this prospective study 102 cases, including 73 females and 29 males with average age 52.7years (14-82 years) were enrolled in two tertiary thyroid cancer referral centers. Almost half (47%) of surgery was for thyroid cancer and 21% surgeries were revision thyroid cancer surgery. All patients had successful stable evoked potentials through vagal and RLN neural stimulation. Repositioning of the endotracheal tube to increase baseline EMG amplitude at the beginning of the case was required in several patients to obtain a minimum threshold of 500 µV per our study protocol and generally took only several minutes and was always feasible.There were no cases of stimulation evoked nerve injury. The average number of vagal 1 mA stimulations was 602 stimulations (112-2257 stimulations). In our series we had no cases of intraoperative adverse cardiac, pulmonary or gastrointestinal adverse effects (including bronchospasm or bradycardia). In the majority of cases a size 2 APS electrode was installed. On average the APS electrode installation time was 21 sec (10-60 sec) and removal was safe and required 7sec (3-20 sec). Electrode placement and removal were technically straight forward in all patients. The average number of electrode dislocations was 0.3 (range 0-3) per case. Stimulation of proximal and distal vagal segments relative to the electrode

placement at the end of the case after electrode removal showed no evidence of intraoperative vagal nerve surgical injury in any patient due to dissection of the vagus or placement of the electrode.

Vagus and RLN normative amplitude and latency values in patients with normal postoperative vocal cord function:

The average vagal initial baseline amplitude was 1185 µV (496-3542 µV) .The amplitudes and latencies for patients with normal postoperative vocal cord function are illustrated (**Table 1**).There was no significant difference between pre and post-surgery amplitude or latency of the vagus or RLN suggesting repetitive vagal stimulation and surgical neural dissection was never associated with nerve injury. Left vagal latency was significantly longer than right vagal latency and vagal latency was significantly longer overall than RLN latency. This is consistent with prior work and suggests that timed vagal evoked waveforms at the completion of lobectomy could serve documentation purposes in that the characteristic left and right vagal latency defines the waveform as vagal stimulation which implies entire vagal-RLN nerve pathway testing.[44]

Table 1.
Amplitude and Latency Values for Patients with Normal Vocal Cord Function

Nerve (n =102)	Pre Resection Amplitude (µV)	Latency (msec)	Post Resection Amplitude (µV)	Latency (msec)
Right Vagus	**1260** (500 – 3542)	**4.56** (2.63 – 7.50)	**1210** (80 – 3800)	**4.46** (2.63 – 7.63)
Left Vagus	**1052** (400 – 3121)	**7.21** (4.75 – 9.79)	**1063** (198 – 2700)	**7.21** (4.88 – 9.75)
Right RLN	**1386** (280 – 5163)	**2.72** (2.20 – 4.50)	**1320** (100 – 4600)	**2.66** (1.75 – 4.75)
Left RLN	**1300** (109 – 3800)	**2.77** (2.00 – 4.00)	**1306** (116 – 3000)	**2.80** (2.00 – 6.63)

- Vagus Pre Resection Amplitude + Latency *vs.* Post Resection Amplitude + Latency – NS
- RLN Pre Resection Amplitude + Latency *vs.* Post Resection Amplitude + Latency – NS
- Left Vagus Latency Significantly *Higher* than Right Vagal Latency, **p < 0.0001**
- RLN Latency Significantly *Shorter* than Right or Left Vagal Latency, **p < 0.0001**

Postoperative Vocal Cord Function: The Relationship between adverse EMG (CE and LOS)

Of the 6 cases which developed VCP there was no significant correlation between whether the RLN had >1 branch or a specific relation (ventral or dorsal) to the inferior thyroid artery. In patients with isolated amplitude or isolated latency changes there were no cases of VCP.

A. Severe Combined Events (sCE)

ROCs were created for both sCE and mCE. The area under the ROC curve for sCE was 0.84 (95% CI 0.65, 1.0: **Figure 2**) suggesting overall accuracy of the sCE test result. At the threshold value of one event the sensitivity of sCE is 83.3% with a specificity of 79.2% for VCP. At the threshold value of 7sCEs, the sensitivity and specificity are 66.7% and 91.7% respectively for VCP. sCE as a test for VCP showed a PPV of 33% and the NPV of 97%.When evaluating sCE according to categories of VCP there is a significant association between the number of sCE and VCP (Fisher's exact p = .001) (see **Table 2**). In the 80 patients without sCEs there was only one VCP whereas in the remaining 22 patients with multiple sCE there were five VCPs. Of the 6 cases which developed a temporary VCP, 83% developed sCE during surgery and the average number of sCEs for this VCP group was 29 (1-124 events)**.** Of the remainder 96 cases who had a normal post-operative vocal cord examination, only 20% developed sCEs during surgery. The average number of sCEs for this group was 3.5 (range 1-79) (see **Table 2).**

The area under the ROC curve (not shown) for mCE was only 0.74 (95% CI 0.54, 94) suggesting a low accuracy for this test relative to VCP. Even at a threshold of 19 mCE events the sensitivity and specificity of mCE was only 66.7% 82.3% respectively.
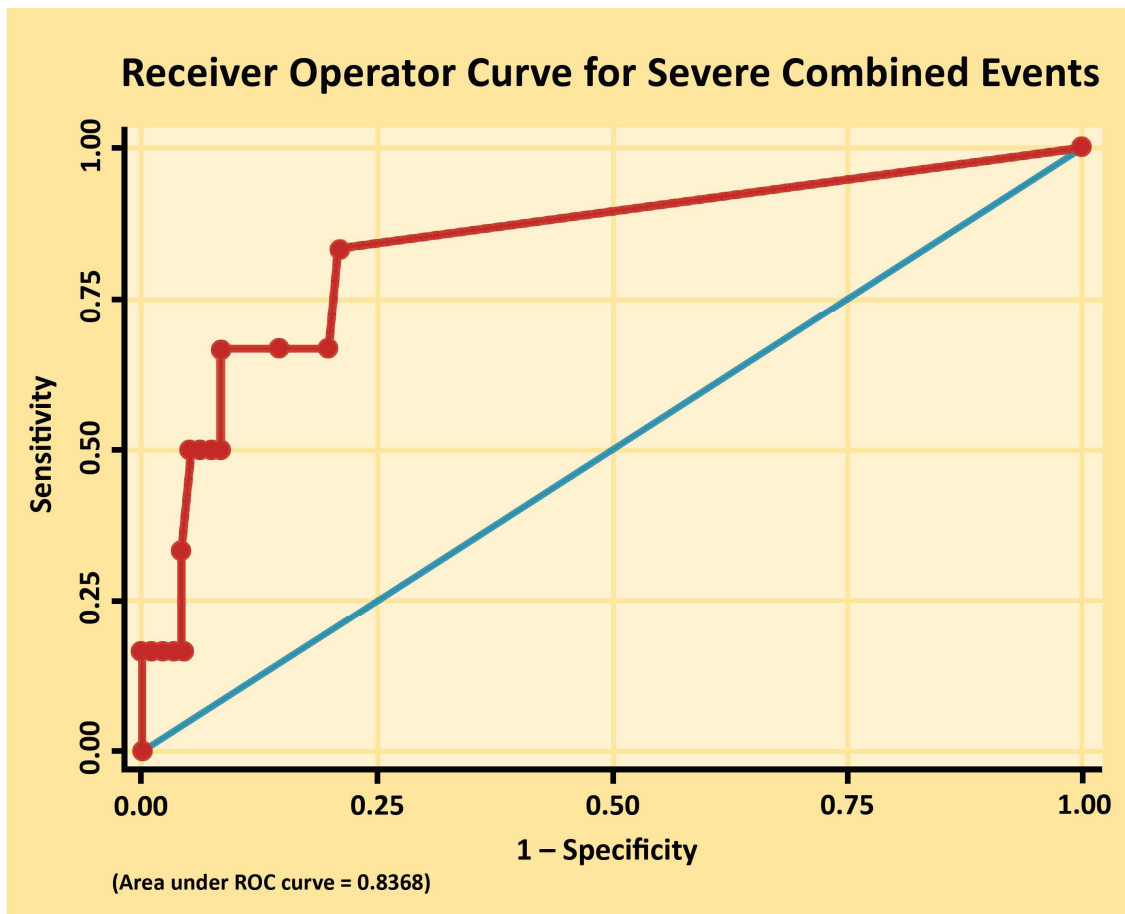
Receiver Operator Curve for Severe Combined Events

(Area under ROC curve = 0.8368)

Figure 2:

Table 2.
Vocal Cord Paralysis Group vs. No Vocal Cord Paralysis Group: Combined Events and Loss of Signal

Vocal Cord Palsy (VCP)	Severe CEs % occurring/average #	LOS % occurring
VCP (N = 6)	Occurring 83% Average # 29.3 (range 0 – 124)	83%
No VCP (N = 96)	Occurring 20% Average # 3.5 (range 1 – 79)	1%

p = 0.001 (Severe CEs)   p < 0.001 (LOS)

SCE (>7)   Sensitivity 66.7%   Specificity 91.7% for VCP

LOS   Sensitivity 83%   Specificity 99% for VCP

Table 3A. **LOS and VCP**

Test status	Disease status Present	Absent	Total
Present	5	1	6
Absent	1	95	96
Total	6	96	102

| 3B		95% Confidence Interval		
Prevalence	Pr (A)	5.9%	2.2%	12.4%
Sensitivity	Pr (+|A)	83.3%	35.9%	99.6%
Specificity	Pr (−|N)	99%	94.3%	100%
Likelihood ratio (+)	Pr (+|A) / Pr (+|N)	80	11	581
Likelihood ratio (−)	Pr (−|A) / Pr (−|N)	.168	.0281	1.01
Odds ratio	LR (+) / LR (−)	475	32.8	−
Positive predictive value	Pr (A|+)	83.3%	35.9%	99.6%
Negative predictive value	Pr (N|−)	99%	94.3%	100%

B. Loss of Signal (LOS)

If LOS is considered as a binary test for VCP its sensitivity is estimated at 83.3% (95% CI 35.9%, 99.6%) with a specificity of 99% (95% CI 94.3%, 100%). LOS showed a PPV of 83% and a NPV of 98% for VCP. Thus a positive LOS test indicates that VCP is highly likely.

When evaluating LOS according to categories of VCP, there is a significant association between LOS and VCP. (Fisher's exact p <0 .001) (**Table 2, 3A,3B**).

There were 6 (5.9%) cases of postoperative temporary VCP (no cases of permanent VCP). Of these 6 cases of VCP, 5 cases (83.3%) developed LOS. One temporary VCP had no combined events or LOS recorded intra operatively. **(Figure 3)**

Figure 3- No combined events, Latency and amplitude graph
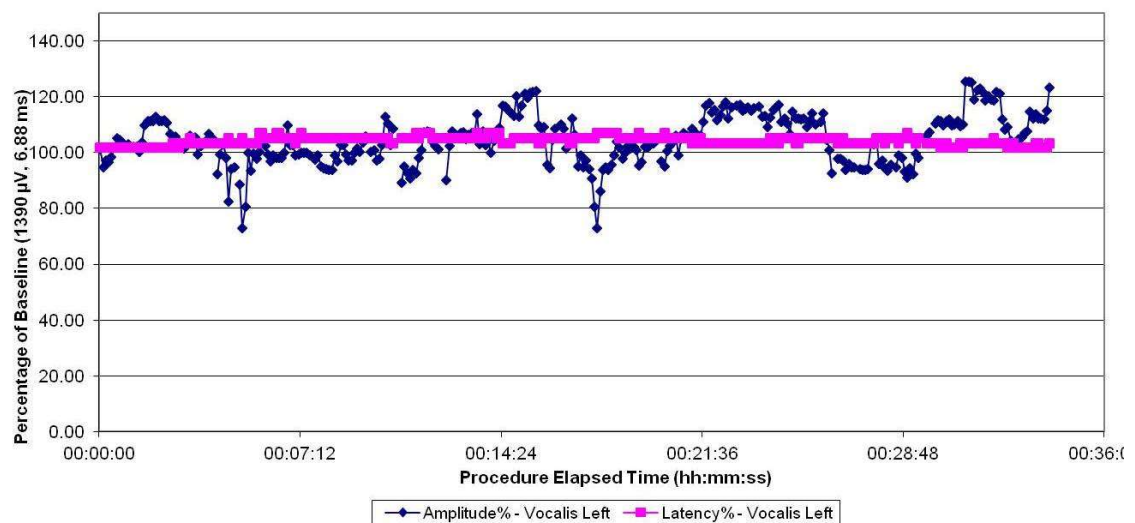
We hypothesize that neural injury in this case occurred after the vagal electrode was removed and thus the adverse EMG changes were not recorded. Of the 6 patients who developed LOS, 1 case had recovery of signal and 5 cases did not recover signal by the end of surgery. For the normal postoperative glottic function group only 1% had LOS (and this recovered). LOS therefore was found to be a grave finding - only 17% of those with LOS recovering

intraoperatively. In the one case where LOS recovered intraoperatively the LOS was felt to be due to a global type 2 lesion secondary to traction and vocal cord movement was normal post operatively. LOS when it occurred was localized to a discrete segment of RLN (the RLN entry site/ligament of berry region) in 1 case (i.e. **Type I** neural injury) (**Figure 4)**, and a global lesion in 4 cases (i.e. **Type II** neural injury).[47] The suspected mechanism of injury to the RLN in the LOS cases was believed to be due to traction in 2 cases, coagulation in 1 case, cold irrigation in 1 case and unknown in 2 cases .Interestingly, in the irrigation LOS case, initial amplitude and latency changes were seen after the completion of surgery during irrigation of the surgical field with cold saline and this patient had VCP for nearly 3 months.
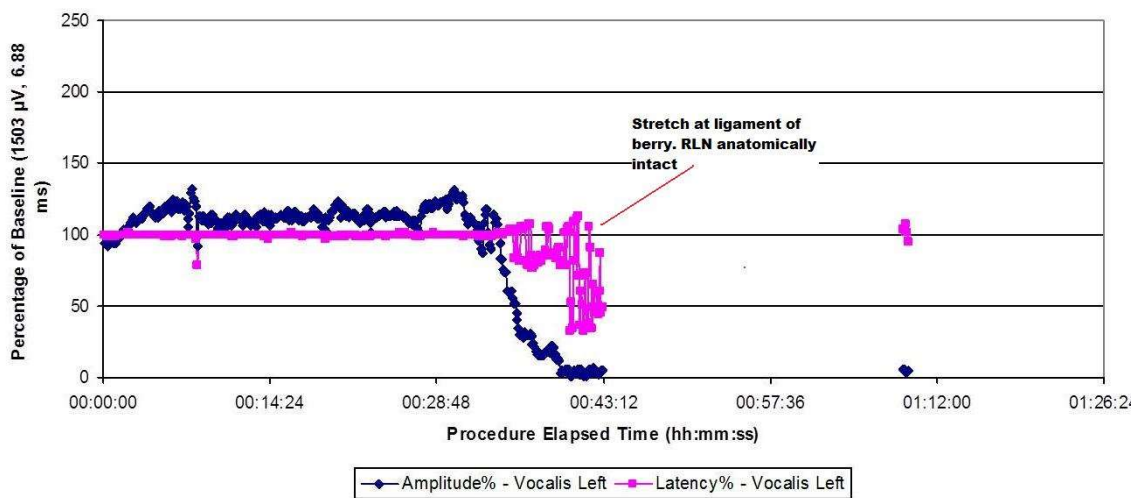

Figure 4. Loss of signal, Stretch at ligament of berry.

Modification of the surgical maneuver and EMG change resolution:

For patients with significant adverse EMG changes of multiple sCEs, immediate modification of the surgical maneuver resulted in resolution of those EMG changes in nearly 77% of such cases **(Figure 5**). Typically, during a case in which adverse EMG events (i.e., CEs) occurred, a surgical maneuver could be implicated. Subsequently, a relatively short period of alteration of the surgical maneuver—which we termed "relaxation time"—resulted in prompt improvement in the EMG waveform, usually over a few minutes. However when LOS was present, modification of the surgical maneuver was associated with resolution of the EMG changes in only 17%.
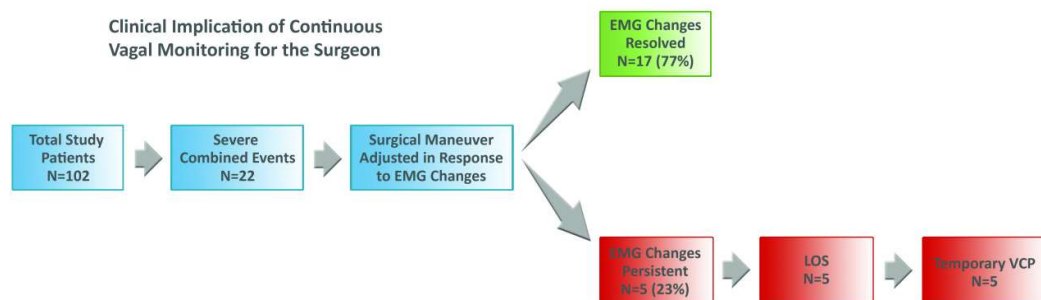

Figure 5.

Discussion:

This series represents two thyroid cancer tertiary care units, each with nearly 50% of patients undergoing surgery for thyroid cancer with 20% representing revision surgery. In all 102 patients a continuous vagal monitoring format successfully allowed safe vagal data recording. The vagal electrode with stimulation levels at 1 mA yielded supra-maximal stimulation in all patients. Endotracheal tube repositioning to obtain initial amplitude baseline > 500 µV (from which decreased amplitude changes can be readily appreciated) was occasionally necessary and was readily achieved. Repetitive neural stimulation, vagal dissection and vagal electrode placement was safe in all patients.

CIONM Efficacy in Prevention of RLN Injury:

Impending nerve injury to the facial nerve during skull base neurologic surgery may result in dramatic induced EMG changes but such passive surgical maneuver associated traumatic EMG changes are not reliably present during RLN traumatic dissection in thyroid surgery.[44] This inherent disadvantage of current formats of intermittent IONM may be in part underpinning (along with issues of statistical power) the inability to diminish RLN paralysis rates with current IONM formats.[39, 40] CIONM of vagal nerve on the other hand offers realtime ongoing intraoperative assessment of the entire length of the vagal- RLN nerve segment at risk for intraoperative surgical injury. Although various vagal electrodes are available for CIONM there is still uncertainty regarding the electrophysiologic thresholds indicative of imminent RLN injury.[73,74,90,97]

 For the CIONM format to be of surgical utility it must meet several criteria:

1- It must incorporate existing monitoring standards of preoperative and postoperative laryngeal exam, routine vagal stimulation, recognition of standard normative

recording parameters and application of standard equipment trouble shooting algorithm as has been outlined by the International Neural Monitoring Study Group Guideline.[47]

2- It must differentiate artifactual EMG changes (such as those which accompany endotracheal tube intraoperative displacement) from EMG changes truly reflecting impending neuropraxic injury.

3- EMG changes must track with impending neuropraxic injury, must be clearly recognized intraoperatively but must be nascent so as to be completely reversible once the associated surgical maneuver is aborted.

We feel our definition of a severe combined event (sCE = amplitude reduction > 70% with concordant latency increase of > 10%) appears to meet the above criteria #3.

Adverse EMG Events Tracking with VCP are Identifiable with CIONM

Our study showed certain intraoperative EMG changes are "adverse" in that they are associated with VCP. The two adverse EMG parameters we found are sCE as well as LOS. We found that both were statistically associated with VCP. It should be noted that these EMG changes are easily recognizable intraoperatively. The evidence is as follows:

A. sCE: The area under the ROC curve for sCE is 0.84 (95% CI 0.65, 1.0: **Figure 2**) suggesting an overall accuracy of the sCE test result. At threshold value of seven events the sensitivity and specificity for VCP are 66.7% and 91.7% respectively with a PPV of 33% and a NPV of 97%. When evaluating a number of sCE according to VCP categories there is a significant association between the number of sCE and VCP (Fisher's exact p = .001**).** The total number of sCE in the VCP group was 29 and in the no VCP group was 3.5. The percent

of patients having sCEs in the VCP group was 83% and only 20% in the no VCP group.Milder forms of combined events (i.e. mCE) in isolation, as well as isolated amplitude and latency changes were not associated with VCP. In the 80 patients without sCEs there was only one VCP whereas in the remaining 22 patients with multiple sCE there were five VCPs. Thus sCE represents a robust adverse EMG event tracking with VCP.

B. LOS: If LOS is considered as a binary test then its sensitivity for VCP is estimated at 83.3% (95% CI 35.9%, 99.6%) with a specificity of 99% (95% CI 94.3%,100%) with a PPV of 83% and a NPV of 98%. Evaluation of LOS with respect to VCP and no VCP categories shows significant association between the number of LOS and VCP (Fisher's exact p <0 .001). Thus LOS is a good test for VCP with a PPV of 83% and a NPV of 99% (assuming our groups prevalence of VCP).

LOS was highly associated with postoperative VCP with 83% of VCP is being associated with preceding LOS opposed to only 1% of the no VCP group. In the single case of VCP without LOS we hypothesize a post stimulation injury. Also interestingly in the single case of recovery of LOS, VCP did *not* occur postoperatively. While sCEs may be reversible, the development of LOS is significantly more worrisome: LOS was reversible in only one of six individuals (17%) whereas sCE was reversible in nearly 73%. Other workers have disputed this finding but their findings may be explained by less strict definitions of LOS and application of IONM trouble shooting algorithm is important in the accurate delineation of LOS introperatively.[47] We therefore think it is reasonable to consider LOS, in general, as a nonrecoverable adverse EMG event and when present highly predictive of VCP. True LOS represents a robust adverse EMG event tracking with VCP. VCP is the outcome of neural injury which can be identified by an intraoperative progression of increasing severe adverse evoked EMG events. The most typical sequence of adverse EMG events leading to VCP was

multiple sCE with evolution to complete LOS. Again sCEs (generally reversible) and LOS (generally not reversible) track robustly with VCP and are easily identifiable intraoperatively. We suggest that the presence of sCEs suggest impending RLN injury and should warrant modification of the associated surgical maneuver whenever possible. With the implementation of such an algorithm we estimate 73% of VCP which would result from the evolution of sCE to complete LOS and VCP, could be prevented.

Studies on Type and Method of Injury:

Injury to the RLN can result from severing, compressing, stretching, or heating the main trunk or its branches.[58,59] Nerve injuries may be divided into 3 categories- neuropraxia, axonotmesis or neuromesis according to the Seddon classification.[61] Of our five cases of nonreversible LOS one was a Type I segmental injury at the ligament of Berry/nerve entry site and 4 were Type II global injuries.[47]Two of the five injuries were thought to be caused by traction, one of the five injuries was by coagulation and interestingly one of the five injuries was thought to be associated with cold irrigation. In this case surgery had been completed and the onset of adverse EMG changes was coincident with the irrigation of cold saline after all surgical maneuvers had been completed. As a result we now ensure irrigation with body temperature saline at our institution.

Literature:

In 2007, Lamadé et al in a pilot study noted that stretch or tension on the nerve during manipulation of the thyroid gland resulted in signal depression of up to 60% which resolved within seconds on removal of the tension/stretch. Lamadé et al suggested that such trauma to the RLN may be recognized early by use of CIONM and thus allow the surgeon to react accordingly.[72] Lamadé et al concluded in a study on 55 patients with CIONM that the new system offered five advantages.[73] Schneider et al recognized the limitations of conventional

hand held stimulation electrodes and conducted a CIONM feasibility study on 23 pigs using a specially designed vagal electrode. During applied trauma, EMG changes such as amplitude decreases and or latency increases were recorded. Schneider et al did not correlate amplitude changes, latency changes, or LOS to postop VCP.[74] Schneider et. al. in their series of 52 patients studied combined events (with their definition being different than ours- amplitude changes of > 50% and latency changes > 10%).They found, consistent with our data, no cases of VCP with isolated amplitude or latency changes. All CEs occurred during either traction or cautery with almost 80% being referable to traction injury. Multiple CE occurred in 13 patients. VCP reliably occurred if multiple CE were associated with ensuing LOS intraoperatively. However in patients with initial adverse EMG changes modification of the surgical maneuver associate with those changes averted VCP in 70% cases, which is very similar to our findings.[90]

The vagal electrode we used meets many CIONM requirements including electrode geometry, applicability, easy removal, low stimulation current, and signal stability rendering it a potential useful instrument for CIONM. However a number of issues need to be the addressed. Latency measurement can be hampered by latency "jumping" which represents an artifactual system measurement error of latency caused by atypical triphasic evoked waveforms and maybe also associated with low amplitudes waveforms below 350 μV.[25] Baseline amplitude changes may also occur during the surgery and be associated with slowly evolving changes in endotracheal tube placement through surgical manipulation and retraction. Such changes may require re-calibrating an amplitude and latency baseline during the surgery.

Safety

Our series demonstrates that continuous IONM is safe. Despite the average number of vagal stimulations being 602 for patient (with a maximum in one patient of 2300) at 1 mA with

pulse duration of 100 µsec there were no cases of amplitude or latency adverse changes or VCP resulting from neural stimulation injury and no cases of adverse cardiac, pulmonary or gastrointestinal side effects.

Electrode installation on the vagus was technically straightforward taking an average of 21 seconds with removal taking an average of 7 seconds. Testing the vagus proximal to the segment occupied by the electrode after its removal showed no adverse effects from either vagal dissection or vagal electrode placement in any patients. The electrode was easily managed during surgery within the surgical field with the average number of dislocations being <1 per case (0-2).

Groves and Brown showed it takes more than 2 mA or more to elicit a cardiopulmonary response from the c fibers of the vagus nerve.[76] Low level vagal stimulation at frequencies less than 30 Hz have not been associated with subsequent adverse vagal nerve effects such as central headache and numbness, cardiac arrhythmias, bradycardia, pulmonary bronchospasm or gastrointestinal side effects of nausea and vomiting.[73, 76,98,99]

Conclusion:

VCP is the outcome of neural injury which can be identified by an intraoperative progression of increasing severe adverse evoked EMG events. Our study shows CIONM allows identification of the EMG changes (sCE) heralding imminent RLN injury which empowers the surgeon to promptly initiate corrective action to preserve the nerves functional integrity by reversing the surgical maneuver associated with these early but adverse EMG changes.Our initial data suggests that in nearly 77% of cases of such adverse EMG changes,modification of the surgical maneuver results in a resolution of the adverse EMG changes and averts VCP. The identification of such EMG events is therefore of great importance.

In conclusion, this study demonstrates the potential usefulness of a CIONM device to monitor the RLN and potentially warn the surgeon of impending RLN injury. Our findings would suggest that sCE represent a clear but reversible adverse EMG change and when allowed to continue may progress to LOS (which is significantly less recoverable) and to postoperative VCP. Such monitoring is well-tolerated and un-associated with vagal/RLN injury, pulmonary, gastrointestinal or cardiac adverse sequels. Isolated EMG changes in either amplitude or latency which may derive from endotracheal tube position or equipment and related problems did not predict VCP. Clearly further work is required to optimize CIONM definition of meaningful warning threshold values. NPV and PPV of various adverse EMG parameters are strongly related to the underlying prevalence of VCP in the study population and so this needs to be taken into account as our adverse EMG parameter candidates of sCE and LOS are applied to different surgical populations. Also we appreciate that the development and time course of the EMG adverse changes as a result of surgical trauma will likely vary with the nature of the given surgical trauma and with the amount and time course of delivery of that trauma to the nerve. Our study was limited in the forms of trauma that were identified and studied in this series of patients.[100]

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