

## Review Article

# Embryology of the non-recurrent laryngeal nerve and advancements in detection prior to surgery

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## ABSTRACT

The non-recurrent laryngeal nerve (NRLN) is an uncommon anatomical variant of the recurrent laryngeal nerve (RLN). A right-sided NRLN is exceedingly more common than a left-sided NRLN, and almost all are associated with abnormalities of the aortic arch, especially a right aberrant subclavian artery (ASCA). The NRLN has a strong embryological basis, resulting from the premature obliteration of the right fourth aortic arch. Absence of this structure during longitudinal development allows the laryngeal nerve to migrate superiorly, ultimately branching from the cervical vagus nerve without entering the mediastinum. Despite a low prevalence, the presence of a NRLN is associated with a six to eight-fold increase in iatrogenic injury during surgeries of the thyroid, parathyroid and carotid structures. Pre-operative ultrasound for identification of an ASCA and thus the presence of a NRLN has demonstrated a clinically-significant reduction in the risk of laryngeal nerve damage intra-operatively. Intraoperative nerve monitoring (IONM) has also been shown as an effective alternative approach for detection of a NRLN intra-operatively. Further prospective studies exploring the effectiveness of these strategies in identifying a NRLN would be beneficial.

**Keywords:** Embryology, Non-recurrent laryngeal nerve, Ultrasound, Thyroid surgery

## INTRODUCTION

The RLNs originate from the vagal trunk, supplying fibres to the cardiac plexus and to the mucosa of the trachea and oesophagus, but exhibit unique courses as they ascend to supply structures of the larynx.<sup>1,2</sup> The right RLN branches from the vagal trunk at the level of the 1<sup>st</sup> or 2<sup>nd</sup> thoracic vertebrae. Continuing inferiorly into the superior mediastinum, it then normally hooks around the right subclavian artery to ascend behind the right common carotid artery and pretracheal fascia in the tracheoesophageal groove, invested by tracheoesophageal fascia at its superior aspect.<sup>1,2</sup> The right RLN has an equal probability of lying anterior or posterior to the inferior thyroid artery.<sup>1</sup> The left RLN divides from the vagal trunk at the 4<sup>th</sup> or 5<sup>th</sup> thoracic

vertebrae, continuing into the superior mediastinum before passing over the aortic arch to hook around the ligamentum arteriosum.<sup>1,2</sup> Its proceeding course is much like that of the right, ascending behind the pretracheal fascia in the tracheoesophageal groove invested in tracheoesophageal fascia superiorly.<sup>1,2</sup> The left RLN is more likely to lie posterior to the inferior thyroid artery.<sup>1</sup>

Both the right and left RLN pass behind the cricothyroid joint underneath the inferior constrictor to supply the structures of the larynx.<sup>1,2</sup> The terminal portions of these nerves often divide into an anterior branch which gives motor supply to the intrinsic muscles of the larynx (excluding cricothyroid), and a posterior branch which provides sensory innervation to the laryngeal mucosa below the vocal folds.<sup>1,2</sup>

The unique courses of the RLNs can be understood by examining their embryological origins. During normal embryological development, branches from the vagus nerve innervate the sixth pharyngeal arches bilaterally.<sup>3,4</sup> These branches have close anatomical relationships to the developing vascular structures of the sixth aortic arches, lying underneath the arches in the horizontal plane. As the foetus continues to develop, the heart and aortic structures are displaced caudally into the thoracic cavity, resulting in the 'hooking' of these vagus branches (right and left RLN) around the sixth aortic arches.<sup>3,4</sup> Bilateral regression of aortic arch structures during development inform the course of the RLN in the adult. On the right, regression of the distal portion of the fifth and sixth aortic arches cause the right RLN to migrate superiorly and hook around the right subclavian artery. On the left, the distal portion of the sixth aortic arch persists as the ductus arteriosus resulting in the hooking of the left RLN around the ligamentum arteriosum to ascend to the larynx.

## ANATOMY AND EMBRYOLOGICAL BASIS OF THE NRLN

A NRLN is a variant of the normal anatomy described above; it is much more commonly seen on the right than the left, and almost always in association with abnormalities of the aortic arch, especially an aberrant right subclavian artery.<sup>5-7</sup> Since being first described by Stedman in 1823, the entry of the nerve into the larynx directly after branching from the cervical vagus nerve has been recognised as posing a significantly increased risk of iatrogenic injury during neck surgery.

The largest meta-analysis to date describing the prevalence of a right NRLN analysed fifty-three studies (including 33,571 right NRLNs) and reported a pooled prevalence estimate of 0.7% (95% CI 0.6-0.9).<sup>5</sup> This same meta-analysis estimated the prevalence of the left NRLN at 0.004%. More recent prospective studies by Le (incidence right NRLN 0.74% in 2158 patients) and Wang (incidence right NRLN 0.39% in 18,433 patients) echoed this estimate.<sup>8,9</sup>

The most commonly used classification system for NRLN proposed by Toniato describes three subtypes:<sup>10</sup> type 1, in which the NRLN arises directly from the vagus nerve and enters the larynx with the superior thyroid vasculature; type 2a, in which the NRLN traverses anteriorly over the trunk of the inferior thyroid artery and; type 2b, in which the NRLN enters the larynx behind or between the branches of the inferior thyroid artery. A literature review by Polednak investigated the prevalence of each subtype using the Toniato system-in 88 right NRLNs, type 2 (69.3%) occurred more commonly than type 1 (30.7%).<sup>11</sup>

A recent classification system proposed by Hong however has begun to gain favour with surgeons due to its superior detail and utility for surgical approach. Hong describes four subtypes; descending, in which the NRLN

descends from the vagus trunk; vertical, where the nerve passes vertically to the cricothyroid joint; ascending, where the nerve passes upward to the cricothyroid joint, and; V-shaped, in which the NRLN descends before ascending to the cricothyroid joint.<sup>12</sup> Only one review by Le has investigated the frequency of each of Hong's NRLN subtypes-in 16 cases of NRLN, the ascending type (37.5%) occurred most commonly, followed by vertical and V-shaped (25%) and descending (12.5%).<sup>13</sup>

Strong evidence exists for an embryological basis of right NRLN. The meta-analysis by Henry used the presence of an ASCA concurrently with a right NRLN as a secondary outcome-in 136 patients with right NRLN, 89.3% also had an ASCA.<sup>5</sup> Smaller reviews by Natsis and Bakaliniis found 98-100% of patients with an ASCA had a right NRLN.<sup>6,7</sup> There are only 16 reported cases of patients with NRLN in the absence of arterial abnormalities.<sup>14</sup> An ASCA arises due to errors in aortic arch development. In these cases, the right fourth aortic arch and proximal portion of the right dorsal aorta are obliterated. Due to absence of the right fourth aortic arch, the would-be right RLN branches migrate superiorly during longitudinal development, branching directly from the vagus nerve at a cervical level.<sup>3,4</sup> Consequently, the NRLN is not found in the trachea-oesophageal groove arising from the mediastinum as with the RLN. Due to the obliteration of the right fourth aortic arch, the right subclavian artery is formed by the distal portion of the right dorsal aorta and the seventh intersegmental artery.<sup>3</sup> In this orientation, the artery originates below the left subclavian artery and crosses the midline behind the oesophagus to supply the right upper limb. Although normally asymptomatic, ASCA can manifest clinically as dysphagia, dyspnoea and retrosternal pain in 7-10% of patients.<sup>15</sup> As mentioned above, the left NRLN is exceedingly rare and requires the concurrent existence of a left subclavian artery with a lusoria course and situs inversus viscerum, in the absence of a ductus arteriosus.<sup>5-7</sup>

Despite these numerous NRLN subtypes, all variants supply the larynx by passing posterior to the cricothyroid joint and through the deep fibres of the inferior constrictor, as with the RLN, before dividing into anterior and posterior branches.<sup>13</sup> The NRLN also provides extra-laryngeal branches to the mucous membrane and muscular wall of the oesophagus and trachea.

## SURGICAL CONSIDERATIONS OF THE NON-RLN AND ADVANCEMENTS IN DETECTION

The NRLN is a major risk factor for iatrogenic injury in carotid, thyroid and parathyroid surgery. The reported rate of RLN injury following thyroid surgery is 3-7%; in a review of 6000 thyroid surgeries involving patients with NRLN, the rate of iatrogenic injury to the nerve approached 13%, a six-fold increase.<sup>10</sup> A more recent retrospective study by Iacobone found an eight-fold increase in the rate of iatrogenic laryngeal nerve injury between NRLN and RLN (14.3% vs. 1.7%).<sup>16</sup> The low

pre-operative probability of an NRLN, and its propensity for misidentification as fibrous tissue or the inferior thyroid artery are the predominant reasons for this increased risk. Numerous surgical strategies to avoid iatrogenic RLN injury have been suggested; diligent dissection and identification of the RLN bilaterally; palpation of the nerve in the tracheoesophageal groove; ligation of the upper thyroid vessels at the margin of thyroid gland, and; the classic adage 'no structure passing medially from the carotid sheath to the trachea should be ligated except the middle thyroid veins until the nerve has been identified'. Unfortunately, considering the course of the NRLN and relationship to surrounding structures as detailed above, such strategies are often ineffective.

The use of pre-operative imaging to identify possible ASCA and therefore NRLN has been suggested as a strategy to reduce intra-operative injury. Pre-operative ultrasound has been established as a tool to predict NRLN. Iacobone allocated patients undergoing primary neck surgery (n=1477) to either receive a pre-operative ultrasound (n=878) or not (n=599) for identification of an ASCA.<sup>16</sup> Sixteen patients who underwent ultrasound (USS) had an ASCA identified, and all 16 were found to have a right NRLN intra-operatively. Furthermore, patients who received a USS had a reduced risk of laryngeal nerve damage (1.8% vs. 4.2%,  $p<0.05$ ) and NRLN palsy.<sup>16</sup> Numerous other studies support the predictive value of USS for NRLN; Devèze et al, Huang et al, Yetisir et al, Satoh et al and Wang et al all state the sensitivity of USS for NRLN prediction between 84-100%.<sup>18-21</sup> The use of computed tomography (CT) and magnetic resonance imaging (MRI) have also been suggested for identification of ASCA pre-operatively. Several studies found the predictive utility of these modalities for NRLN to be equal or outperforming USS.<sup>16,21</sup> However, these investigations have substantial costs, invasiveness and adverse events; their appropriateness as screening tests in a large population for rare entities such as ASCA and NRLN is therefore questionable. The affordability, accessibility and safety of USS only bolster its potential for use as a standardised pre-operative investigation in neck surgery to reduce NRLN damage.

IONM is an alternative approach to identify and protect nervous structures during neck surgery. IONM records the electromyographic signal of the intrinsic muscles of the larynx to indicate the function of the RLN. Meta-analysis by Bai et al evaluated 34 studies and found IONM increased the correct identification of the RLN and reduced the incidence of total, transient and permanent RLN injury.<sup>22</sup> Wang et al has performed the largest study to date, involving 73 patients with NRLN.<sup>8</sup> By utilising an algorithm based on the electromyographic profiles for NRLN, Wang et al achieved a sensitivity of 96.7% for the detection of NRLN.<sup>10</sup> When combined with pre-operative CT identification of ASCA, this algorithm approached 100% sensitivity and specificity. Other case-studies support the utility of IONM in the early

identification of NRLN.<sup>23,24</sup> Although large studies involving NRLN detection are lacking, IONM has been shown to improve identification of nervous structures and post-operative outcomes in neck surgery, and in conjunction with USS could be considered a desirable tool in reducing the risk of injury to a NRLN.

## CONCLUSION

Although uncommon, the NRLN remains an important anatomical consideration in neck surgery. As its presence increases the rate of iatrogenic nervous injury by six to eight-fold early identification of a NRLN is crucial to improving post-operative outcomes. A detailed knowledge of the embryological basis of the NRLN, in particular the association between a right NRLN and ASCA, allows for pre-operative prediction of NRLN. Pre-operative ultrasound detection of an ASCA and IONM have shown promise in improving NRLN detection and reducing iatrogenic NRLN injury. Further research should be conducted to establish the most effective tools in identifying a NRLN, such that neck surgery and its associated risks can continue to be improved.

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