Laryngeal Adductor Reflex in Laryngeal and Brainstem Surgeries to Predict Postoperative Outcome

Maria J. Téllez1*, Catherine F. Sinclair2, and Sedat Ulkatan3

1Department of Intraoperative Neurophysiology, Mount Sinai West Hospital, USA
2Department of Otolaryngology Head and Neck Surgery, Mount Sinai West Hospital, USA
3Department of Intraoperative Neurophysiology, Mount Sinai West Hospital, USA

Abstract

The larynx has three critical functions in humans: protection of the lower airway, respiration, and phonation. The laryngeal adductor reflex (LAR) protects the airway inlet from penetration by activation of adductor muscles via a brainstem reflex, and the vagus nerve. The LAR consists of short-latency R1 and long-latency R2 components, both bilateral, in awake humans and patients under general anesthesia. A novel non-invasive methodology for eliciting the LAR in patients under general anesthesia was introduced for intraoperative monitoring purposes. A major intraoperative monitoring breakthrough that the LAR offers is its ability to assess the integrity of both sensory and motor functions of laryngeal and vagus nerves and intrinsic brainstem pathways and nuclei within the medulla and correlate intraoperative LAR results with postoperative laryngeal outcomes. In neck endocrine and vagus schwannoma surgeries, monitoring the LAR improved rates of transient vocal fold paralysis and laryngeal outcome. The LAR has been used to monitor posterior fossa and brainstem tumor surgeries in adults and pediatric patients. All patients with LAR loss or a significant and permanent LAR amplitude decrement by the end of the surgery showed postoperative laryngeal dysfunction with zero false-negative cases. The LAR has become a critical method to reduce laryngeal complications and enhance safety during resection of complex posterior fossa and brainstem lesions and thyroid and parathyroid masses. The main limitation of the LAR is methodologic and related to displacements of the endotracheal tube during surgery.

ABBREVIATIONS

LAR: Laryngeal Adductor Reflex; ISLN: Internal Superior Laryngeal Nerve; VN: Vagus Nerve; RLN: Recurrent Laryngeal Nerve

INTRODUCTION

The larynx has three critical functions in humans: protection of the lower airway, respiration, and phonation.

Phylogenetically viewed [1,2], the larynx's primary and most primitive function is a contractile sphincter, protecting the lower airway from foreign body penetration. Next, the larynx acquires the capacity to actively expand the laryngeal inlet to enhance ventilatory flow requirements when necessary. Mammals' phonation, which uses the larynx as a flutter valve, is the latest phylogenetic acquisition. However, protection is the primary function, and laryngeal physiology studies provide supportive evidence that volitional respiratory and voice tasks do not suppress or modulate laryngeal adduction [3,4].

The protective closure of the larynx occurs by reflexive activation of laryngeal adductor muscles via a brainstem reflex called the laryngeal adductor reflex (LAR) [5]. The LAR has been extensively studied in cats and other mammals and, more recently, in humans [5-11].

Laryngeal mucosa receptors for LAR elicitation

Stimulation of the laryngeal mucosa mechanoreceptors, innervated by the internal superior laryngeal nerve (ISLN), branch of the vagus nerve (VN), elicits the LAR. Studies using mechanical stimuli (e.g., air pulse, microdroplets, and touch) to activate the reflex have yielded variable results due to lack of control on excitatory summation for reaching the necessary threshold, requiring an air-pulse stimulus to last at least 100 milliseconds to elicit the LAR [7,12-14]. By contrast, direct activation of distal nerve fibers by electrical mucosal stimulation bypasses the mechanoreceptors. It can effectively elicit a LAR response with a stimulus that only lasts few milliseconds, thereby allowing for a more objective assessment of LAR behavior [15-18].

The greatest density of LAR sensory receptors and afferent nerve fibers in humans exists in the posterior supraglottis over the medial surface of the arytenoid cartilages, followed by the epiglottic tip (Figure 1). These are the locations where an
inhaled foreign body would first touch the laryngeal mucosa. Topographical differences in the density of the supraglottic sensory receptors likely represent a peripheral control point that allows for adequate airway protection when required without over-enthusiastic reflex elicitation during routine volitional tasks. For instance, the absence of receptors on the membranous aspect of the true vocal folds likely prevents the phonatory process from being disrupted by inappropriate LAR activation during speech [19].

Electromyographic components of the electrically elicited LAR

The electromyographic components of the electric LAR have been revisited in recent studies on awake subjects [20] and patients under general anesthesia [5,16,17]. These studies give evidence that the LAR consists of short-latency R1 and long-latency R2 components, both bilateral, regardless of the stimulating side, in awake humans and patients under general anesthesia, contradicting previously published studies (Figure 2) [7]. This bilateral R1 component can be elicited at all anesthesia depths in 100% of patients if anesthesia is maintained total intravenous, and inhalational agents and muscle relaxants are avoided.

Reflex arc of the LAR

When the LAR is elicited by electrical mucosa stimuli, the bilateral lateral cricoarytenoid and thyroarytenoid muscles innervated by the RLN (a branch of the VN) contract, resulting in vocal fold adduction and closing the glottic inlet.

The afference portion of the LAR comprises the ipsilateral (relative to the stimulus) ISLN to the ipsilateral nucleus tractus solitarius within the medulla oblongata. From here, the ipsilateral R1 project to the ipsilateral nucleus ambiguous, while the contralateral R1 is thought to project to the contralateral nucleus ambiguous via the reticular formation. The LAR’s efferent portion comprises the vagus and RLN nerves with subsequent adductor muscle contraction, bilaterally. The brainstem pathways of the R2 responses remain hypothetical but possibly travel from the medulla to the upper midbrain within the reticular formation [2,8,21].

The LAR as an intraoperative monitoring tool to predict postoperative laryngeal functional outcomes

In 2017 we introduced a novel non-invasive methodology for eliciting the LAR in patients under general anesthesia for intraoperative monitoring purposes [17,22]. This methodology’s uniqueness is that the entire LAR is elicited and recorded with the electrodes attached to the endotracheal tube, continuously every 1-2 seconds, without the need for additional electrodes in the operative field.

With currently available endotracheal tube electrodes, simultaneous recording of ipsi- and contralateral components of the LAR is technically challenging. Therefore, stimulation is performed using electrodes on one side of the tube, and recording is performed using the electrodes on the opposite side (Figure 3). The side of laryngeal mucosal stimulation versus recording is dictated by which nerve is at risk during the surgery.
Figure 2 The R1 component of the laryngeal adductor reflex (LAR) is a bilateral response despite different methodological approaches and consciousness states. In awake subjects, an ipsi-(iR1) and contralateral (cR1) short-latency components, and an ipsi-(iR2) and contralateral (cR2) long-latency components, relative to the stimulating side, are consistently recorded. In patients under total intravenous anesthesia (TIVA), in addition to iR1 and cR1 components, iR2 and cR2 components can be recorded, never previously recorded under general anesthesia. These R2 components tend to fade during surgery. From Kathleen S, Francesco S, Jay LS, Vedran D. Neurophysiology in Neurosurgery: A Modern Approach. 2020, with permission.

For example, in neck endocrine surgeries, the RLN is at risk of injury. In these cases, the recording electrodes are on the side of the tube ipsilateral to the operative field (the side where the RLN is at risk), and the stimulating electrodes are on the side of the tube contralateral to the operative field. This setup allows contralateral (relative to the stimulating side) R1 and R2 components to be recorded from muscles innervated by the RLN at risk. In cases where the proximal VN or lower brainstem is at risk of injury, both afferent and efferent fibers of the reflex arc are at risk of injury. In these cases, the stimulating and recording electrodes should be alternatively shifted from one side of the tube to the other to monitor adduction from the right and left laryngeal muscles.

Expertise in correct placement and securing of the endotracheal tube are critical to ensure correct electrode location relative to the vocal folds given intraoperative tube displacement represents a critical limitation of this methodology.

Several LAR studies in neck and brainstem surgeries have given evidence that the LAR is highly sensitive to surgical maneuvers that stretch or compress any reflex arc’s neural structures. Such maneuvers result in a decrement in the LAR amplitude or, in extreme cases, complete signal loss. Complete signal loss correlates with postoperative vocal fold paralysis. These studies have also shown that LAR decrements can be easily reversed by corrective measures such as tissue release, surgical pause, and saline irrigation. A major intraoperative monitoring breakthrough that the LAR offers is its ability to assess the integrity of both sensory and motor functions of laryngeal and vagus nerves and intrinsic brainstem pathways and nuclei within the medulla and correlate intraoperative LAR results with postoperative laryngeal outcomes.

<table>
<thead>
<tr>
<th>CONSCIOUS STATE</th>
<th>STIMULATION</th>
<th>RECORDING</th>
<th>TRACES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Awake</td>
<td>Right ISLN</td>
<td>Hookwires into the Vocal folds</td>
<td><img src="image1.png" alt="Image" /></td>
</tr>
<tr>
<td>TIVA</td>
<td>Right ISLN</td>
<td>Endotracheal tube electrodes NIM Trivantage</td>
<td><img src="image2.png" alt="Image" /></td>
</tr>
<tr>
<td></td>
<td>Left laryngeal Mucoza</td>
<td>Hookwires into the Vocal folds</td>
<td><img src="image3.png" alt="Image" /></td>
</tr>
<tr>
<td>TIVA</td>
<td>Endotracheal tube electrodes INOMED (posterior electrodes)</td>
<td>Endotracheal tube electrodes INOMED (lateral electrodes)</td>
<td><img src="image4.png" alt="Image" /></td>
</tr>
</tbody>
</table>
Intraoperative LAR monitoring in head and neck surgeries

In neck endocrine surgeries, the RLN is at risk of injury due to its proximity to the thyroid operative bed. Injury to this nerve causes vocal fold dysfunction, which can result in dysphonia and aspiration. Rates of RLN injury likely approach 10% and have been grossly underestimated due to variable postoperative laryngeal examination practices and the poor predictive value of voice symptoms for vocal fold function [23]. The first observational case historical-control study examining RLN injury rates before and after implementing the LAR at a single center by a single surgeon during these surgeries gave evidence that monitoring with the LAR improved rates of transient vocal fold paralysis paresis over the intermittent mapping of the RLN alone. Traction-related injuries of the RLN in the LAR group (205 nerves) were reduced to zero, compared with five in the intermittent mapping group (130 nerves). Rates of permanent RLN paralysis were low and comparable between groups and occurred abruptly due to cautery [22,24].

Extracranial schwannomas of the VN are benign tumors commonly found in the parapharyngeal space of the neck. Most schwannomas grow off a single nerve fascicle displacing and stretching the rest of nerve fibers over the tumor, compromising the overall nerve function. When they become symptomatic, surgical resection is recommended. Postoperative results vary according to the surgical technique and range from normal function (up to 45%) to hoarseness (up to 60%), dysphagia (up to 16%), and vocal fold palsy or paralysis (up to 54%) [25]. By using the LAR, we were able to map and monitor sensory ISLN fibers intimately associated with the tumor, in addition to motor RLN fibers. All patients in this small series had normal postoperative swallow function and normal vocal fold function [26]. Interestingly, for the first time, the VN’s sensory fibers were identified separately.
from motor fibers by mapping VN fibers over the tumor’s surface with a hand-held monopolar probe and eliciting the LAR [27].

**Intraoperative monitoring LAR results on posterior fossa and brainstem lesions surgeries**

Surgery for posterior fossa and brainstem complex lesions is associated with a high risk of postoperative neurological deficits depending on the lesion location and planned extent of resection. Multimodal intraoperative monitoring techniques support surgical teams in maximizing the extent of tumor resection while minimizing postoperative neurological deficits and in recommending the correct timing for discontinuing further surgical resection. One common theme across published studies on posterior fossa and brainstem surgeries relates to postoperative lower cranial nerve dysfunction, particularly related to VN and medulla injuries. These complications can cause significant morbidity, including aspiration, which increases the risk of comorbidities and escalates the threat of postoperative death [13,28-30].

In a multicenter study that included 53 patients undergoing posterior fossa and brainstem lesion surgeries, the LAR successfully monitored the VN and its brainstem reflex pathway [31]. Stimulating the laryngeal mucosa contralateral to the tumor side and recording the LAR ipsilateral to the tumor side provided data on the motor integrity of the VN at risk. Stimulating the laryngeal mucosa ipsilateral to the tumor provided sensory information of the VN at risk and was recorded on the contralateral vocal fold muscle (Figure 4). If both VNIs were at risk of injury due to a midline lesion location, the right and left LAR were assessed alternatively during surgery.

In 30% of the patients, the LAR showed a significant change or loss during surgery, raising an intraoperative monitoring alert. All patients with LAR loss except one (due to a technical problem) or a permanent LAR amplitude decrement >50% at closing compared to opening baseline showed postoperative laryngeal dysfunction. In this series, severe laryngeal dysfunction, such as aspiration and permanent swallowing problems, occurred in only 5.6% of the patients representing a significant reduction from the percentage of patients reported in previously published studies. Patients presenting with a LAR amplitude decrement that recovered by the end of the surgery presented no neurological deficits. This study demonstrated that monitoring the VN’s sensory component with the LAR is beneficial not only in peripheral nerve surgeries but also in the posterior fossa and brainstem surgeries for detecting laryngeal mucosa hypoaesthesia and anticipating possible swallowing dysfunction. This study presented zero false-negative cases, indicating that if the LAR amplitude is stable during surgery, resection is progressing safely without a VN or lower brainstem injury.

![Figure 4](image-url)

**Figure 4** Schematic illustration of the methodology for eliciting the laryngeal adductor reflex in a patient with a right vagus schwannoma tumor. Panel A: The electrical stimulation of the laryngeal mucosa on the side contralateral to the tumor carries sensory information to the brainstem via the left internal superior laryngeal nerve (iSLN), and activation of motor neurons located on both nucleus ambiguus will follow. By recording the contraction of vocal muscles on the right side (ipsilateral to the tumor), the LAR provides data on the motor integrity of the vagus nerve at risk, so the LAR is called motor-LAR. Panel B: Stimulation of the laryngeal mucosa ipsilateral to the tumor provides sensory information of the vagus nerve at risk by the iSLN on the right side, activation of motor neurons located on both nucleus ambiguus will follow. The LAR recorded on the contralateral vocal fold muscle is called sensory-LAR. From Tellez MJ, Mirallave-Pescador A, Seidel K, Urriza J, Shoakazemi A, Raabe A et al. Neurophysiological monitoring of the laryngeal adductor reflex during cerebellar-pontine angle and brainstem surgery. Clin Neurophysiol. 2021;132(2):622-631, with permission.
The LAR allows nuances in laryngeal behavior to be uncovered. For instance, normal postoperative vocal fold motility while the patient says “eee” under laryngoscope examination does not exclude laryngeal hypoesthesia and therefore does not rule out a higher risk of aspiration. Hypoesthesia is only confirmed by lightly touching the supraglottis and verifying a lack of clinical LAR elicitation. Another nuance is that automatic functions such as swallowing, coughing, and aspiration have been demonstrated to occur through separate pathways than voluntary functions such as speech [32,33]. As such, disruption of the reflexive intrinsic LAR medullary pathway with a spared corticobulbar tract may not significantly affect voluntary speech due to the bilateral nucleus ambiguous innervation for this function [34,35]. For that reason, for monitoring surgeries of intrinsic brainstem lesions, where segmental and suprasegmental pathways are at risk of injury, a combination of LAR and vocal fold corticobulbar motor evoked potential monitoring may improve neurophysiological guidance [36].

The LAR has been used to monitor VN pathways in pediatric patients during the removal of fourth ventricle tumors by a modified methodology that uses hook wire electrodes to stimulate and record the reflex [37]. Preservation of LAR correlated with the absence of VN neurological deficits. The Costa et al. (2018), report has significant implications for LAR monitoring, such as pursuing a more controlled total intravenous anesthesia and developing LAR-specific endotracheal tubes for children.

**DISCUSSION & CONCLUSION**

The LAR represents a non-invasive method for intraoperatively monitoring laryngeal, VN, and lower brainstem structures with high predictive value to foresee postoperative laryngeal dysfunction during neck endocrine and posterior fossa and brainstem surgeries [38]. The main limitation of the LAR is methodologic and related to displacements of the endotracheal tube during surgery. Inadequate contact of endotracheal tube electrodes with laryngeal mucosa due to incorrect endotracheal tube size selection for the individual patient’s laryngeal anatomy is another potential limitation, as is the current inadequacy of existing tube designs.

Overall, damage to vagal LAR nuclei or the LAR brainstem interneuron network undoubtedly has different and more complex effects on the LAR compared with direct peripheral cranial nerve injury. In peripheral neck or extra-axial brainstem surgeries, LAR loss occurs due to damage to the peripheral motor (VN or RLN) or sensory (VN or ISLN) final pathway and renders the intrinsic laryngeal muscles entirely paralytic or the mucosa hypoesthetic. This injury results in immediate postoperative findings and symptoms, including vocal fold paralysis, dysphagia, and aspiration. However, when a complete unilateral LAR loss during intra-axial brainstem surgery occurs with retention of corticobulbar pathway function, the patient may exhibit no significant deficits in voluntary speech and swallowing functions.

The LAR has become a critical method to reduce laryngeal complications and enhance safety during resection of complex posterior fossa and brainstem lesions, vagus nerve schwannomas, and thyroid and parathyroid masses and likely has a bright and expansive future ahead of it.

**REFERENCES**


