Neural-Mediated Laryngopharyngeal Reflux Disease and the Role of Esophageal Dysmotility

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KEYWORDS

• Laryngopharyngeal reflux • LPR • Neural-mediated LPR • Esophageal dysmotility

KEY POINTS

- Neural-mediated LPR involves vagally mediated mechanisms, where shared esophageal-airway innervation triggers sensory and motor reflexes, causing symptoms rather than being primarily driven by direct refluxate exposure.
- Functional laryngeal disorders and hypersensitivity should be considered, particularly in treatment-resistant patients.
- Upper esophageal sphincter abnormalities, ineffective esophageal motility, and large peristaltic breaks are reported in patients with LPR, but nonspecific for the diagnosis of LPR.
- High-resolution manometry is not a first-line diagnostic tool. If available, high-resolution impedance manometry may provide the association of pharyngeal bolus flow and swallowing function.

INTRODUCTION

Laryngopharyngeal reflux (LPR) is defined as the retrograde flow of gastric contents into the upper aerodigestive tract.[1] Unlike gastroesophageal reflux disease (GERD) typically presenting with heartburn (HB) and regurgitation, LPR is characterized by persistent symptoms such as chronic cough (CC), burning sensation in the throat, dysphonia, globus sensation, mucus sensation, frequent throat clearing etc.[2] An important finding of LPR is the absence of endoscopically detected erosive esophagitis or typical symptoms in most patients. The diagnosis is challenging due to the nonspecific nature of symptoms and clinical findings, compounded by low response to proton-pump inhibitor (PPI)-therapy in many cases.

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Abbreviations	
AET	acid exposure time
CC	chronic cough
CGRP	calcitonin gene-related peptide
GERD	gastroesophageal reflux disease
HB	heartburn
HRIM	high-resolution impedance manometry
HRM	high-resolution manometry
IEM	ineffective esophageal motility
IRP	integrated relaxation pressure
LES	lower esophageal sphincter
LPR	laryngopharyngeal reflux
MII-pH	multichannel intraluminal impedance-pH
PCI	proximal contractile integral
PPI	proton-pump inhibitor
RFS	reflux finding score
RSI	reflux symptom index
SAP	symptom associated probability
TLESR	transient lower esophageal sphincter relaxation
UES	upper esophageal sphincter

The pathophysiology of LPR is multifactorial involving disruption of physiologic barriers such as the lower esophageal sphincter (LES), esophageal clearance influenced by esophageal peristalsis, saliva and gravity, and upper esophageal sphincter (UES) dysfunction. Additionally, exposure to reflux components including pepsin, bile salts, and pancreatic enzymes, contributes to tissue damage in this highly susceptible tissue.[3] Furthermore, indirect injury through vagally mediated reflexes by stimulating mucosal chemoreceptors in the lower esophagus, leads to laryngeal mucus secretion, cough, globus sensation, and throat clearing. Neural-mediated LPR may also present as increased laryngeal sensitivity or UES abnormalities.[4,5] Esophageal dysmotility such as transient LES relaxation or LES hypotonia allows the reflux of gastric contents into the esophagus and further into the larynx and pharynx resulting in troublesome symptoms and/or complications.[6]

The diagnosis of LPR requires a multidisciplinary approach involving otolaryngologists and gastroenterologists in some cases pulmonologists. Flexible laryngoscopy is often the initial test to exclude other laryngeal pathologies, while 24-h multichannel intraluminal impedance-pH (MII-pH) is considered to be the gold standard for detecting reflux episodes affecting the upper and lower respiratory tract mucosa.[7] However, in a previous study, we demonstrated that using pathologic parameters for GERD, MII-pH was not the most effective diagnostic tool for identifying LPR.[8] Recent guidelines advocate for ambulatory reflux monitoring off -PPI treatment, particularly in patients without typical GERD symptoms.[9] However, 50% to 60% of patients with isolated laryngeal symptoms lack evidence of reflux disease and do not respond to antireflux therapies.[9,10] Neural-mediated mechanisms, including autonomic dysfunction and laryngeal hypersensitivity, along with esophageal dysmotility may further contribute to the complexity of diagnosing LPR. This article aims to explore neural-mediated LPR and the role of esophageal dysmotility.

NEURAL-MEDIATED LARYNGOPHARYNGEAL REFLUX

Neural-mediated LPR involves vagally mediated mechanisms rather than direct exposure of laryngeal tissues to refluxate. Transient lower esophageal sphincter relaxation (TLESR) is one of the main mechanisms responsible for both physiologic and

pathologic reflux. TLESR is primarily triggered after a meal, as gastric vagal mechanoreceptors in the upper stomach activate vagal afferent pathways to the brainstem, which subsequently signal to inhibitory neurons in the LES through vagal efferents.[11] The shared vagal innervation of the esophagus and airways facilitates sensory signal transmission from the esophagus to the brainstem (afferent pathways) and initiates motor reflexes (efferent pathways) affecting the larynx and pharynx. Additionally, sensitization of the nucleus tractus solitarius in the brainstem may contribute to a reverse association, leading to cough-induced reflux[12] (**Fig. 1**).

The Role of Autonomic Nerve Dysfunction in Laryngopharyngeal Reflux

The autonomic nervous system plays a key role in regulating esophageal and gastric peristalsis, and the tone of UES and LES. In GERD, autonomic nerve dysfunction has been associated with impaired LES competence, increased transient relaxations and delayed gastric emptying.[13] Peristalsis in the proximal esophagus is controlled by the central nervous system through vagal innervation. The UES is a high-pressure zone, which represents the barrier against LPR and the refluxate to reach the pharynx. The laryngopharynx lacks the effective clearance function. Therefore, if reflux cannot

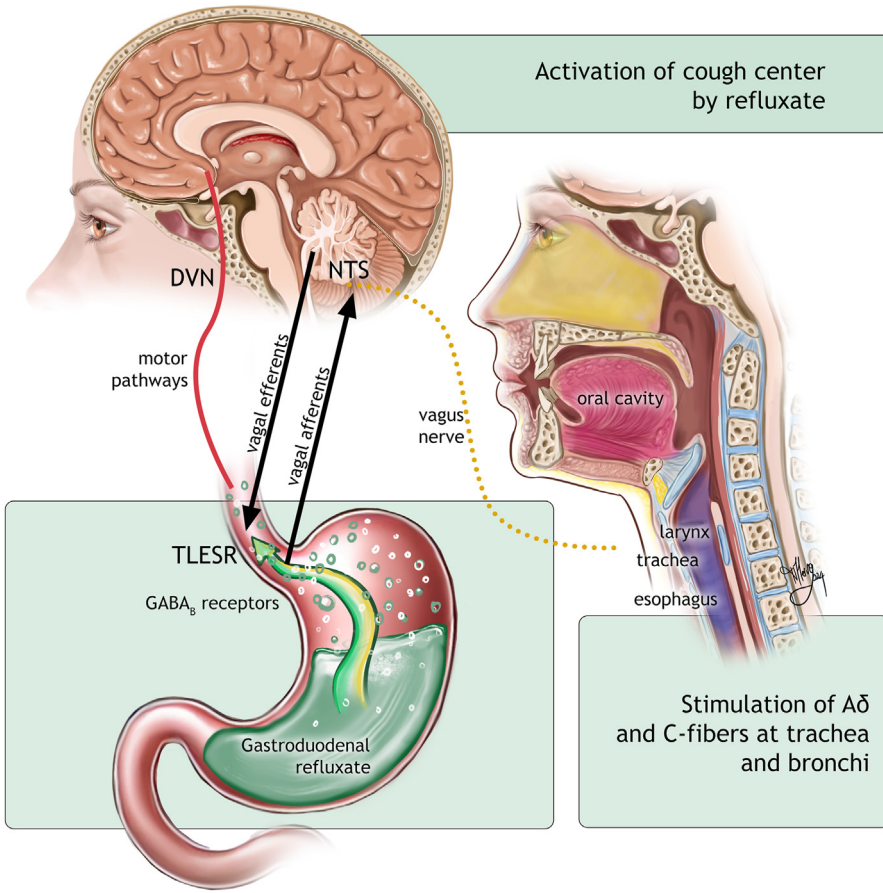

Fig. 1. Autonomic regulation of LPR.

be cleared by the upper esophagus, it may come into contact with highly sensitive laryngopharyngeal tissues for a longer period of time. Reflux of gastric contents into the esophagus triggers reflexes involving the UES and the esophageal body.[14] Vagal dysfunction may impair UES reflexes and contractility, allowing the refluxate to reach the sensitive upper airways. *Wang and colleagues* reported that vagal nerve dysfunction in LPR patients correlated with Reflux Symptom Index (RSI) and Reflux Finding Score (RFS) in LPR.[11] However, the reliability of RSI and RFS are limited as they overlook extra-laryngeal or other digestive symptoms.[14] A recent study compared baroreflex sensitivity in patients referred to gastroenterology for digestive symptoms (mostly GERD) and laryngology for aerodigestive complaints (half with painless throat symptoms). The findings introduced the *Overwhelmed Vagus Hypothesis*, suggesting reduced baroreflex sensitivity and diminished vagal control in patients with laryngopharyngeal symptoms compared to those with esophagogastric symptoms.[15]

Altered Reflex Mechanisms, Vagal Sensory Nerves, and Sensory Receptors

Cough is a common symptom of LPR, often associated with increased cough reflex sensitivity and neurogenic airway inflammation, which contribute to reflux-induced cough. Vagal sensory nerves innervating the airways and lungs and sensory nerves innervating the esophagus play an important role in the pathogenesis of cough related to LPR. Reflux theory and reflex theory have been proposed to explain the pathophysiology of cough in LPR. Reflux theory suggests that the backflow of gastric contents into the esophagus can directly stimulate cough receptors or increase mucus secretion in the lower respiratory tract through vagal reflexes thereby activating cough receptors.[16] Since the incidence of reflux episodes is relatively low and reflux theory is not used to elucidate the mechanism for nonacid reflux, reflex theory presents a better pathophysiological explanation.

Reflex theory, also known as esophageal-tracheobronchial reflex theory, indicates the stimulation of lower esophageal mucosal receptors by reflux material, then activation of the cough center leading to a bronchial cough reflex. Concurrently, the associated efferent nerve endings release neuropeptides such as substance P and calcitonin gene-related peptide (CGRP) via exocytosis. These neuropeptides can either trigger neurogenic inflammation or indirectly activate neuropeptide receptors on mast cells, resulting in the release of tryptase, histamine, prostaglandin E2, and other inflammatory mediators that ultimately stimulate cough receptors and inducing cough (**Fig. 2**).[16,17]

The study by *Sifrim and colleagues* that examined the relationship between cough and nonacid reflux showed that only 30% of cough episodes were associated with reflux and of these 29% had weakly acidic and 6% had alkaline reflux.[18] Another study reported a temporal association between cough and nonacid reflux in up to a quarter of patients with persistent CC despite PPI therapy.[19] Studies have demonstrated that the mechanisms of cough differ between acidic and nonacid reflux. Acid reflux activates chemical receptors known as transient receptor potential vanilloid type 1 (TRPV1) to excite the vagus nerve whereas nonacidic reflux activates mechanical stretch receptors through Aδ fibers to induce cough through esophageal-tracheobronchial reflex.[20,21]

A multicenter study from Taiwan examined patients with laryngeal symptoms, compared esophageal acid exposure and PPI response between isolated LPR patients (without typical reflux symptoms) and those with typical reflux symptoms. The isolated LPR group showed a lower response to esophageal acid perfusion test and fewer episodes of pharyngeal acid reflux compared to the group with typical reflux symptoms. Despite these differences, response to PPI therapy was similar in both groups. The authors suggested that esophageal hyposensitivity and altered

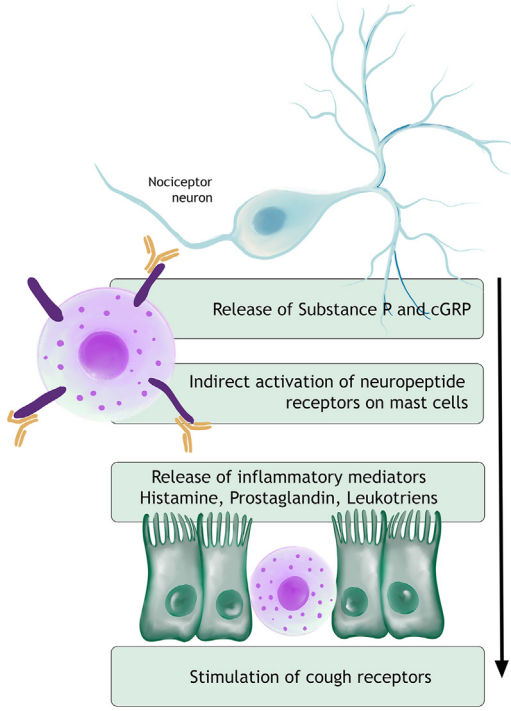

Fig. 2. Pathogenesis of neurogenic inflammation.

esophageal afferent signaling could explain the absence of typical reflux episodes in patients with isolated LPR.[22] Symptom generation in LPR appears to be complex, involving multiple pathways, with the role of vagal sensory nerves and sensory receptors requiring further exploration.

Functional Laryngeal Disorders

Functional laryngeal disorders often mimic LPR, complicating diagnosis and treatment due to overlapping symptoms. These disorders are characterized by persistent laryngeal symptoms such as cough, throat clearing, sore throat, without evidence of GERD or other underlying conditions. They are frequently linked to suspected laryngeal hypersensitivity, triggered by infections, aspiration, or comorbidities like asthma or chronic rhinosinusitis.[23] This hypersensitivity may explain the lack of response to PPI treatment in some presumed LPR cases and can coexist with LPR, influencing management strategies. Clinicians should consider laryngeal hypersensitivity in non-responders and prioritize developing validated assessment tools.

Stress may also play a significant role in LPR cases without an identified etiology. High stress levels can alter the sympathetic-vagal balance, increasing sympathetic activity, and potentially contributing to reflux episodes through transient LES relaxations. This effect is particularly relevant in LPR patients with stress-related globus sensation.[24]

THE ROLE OF ESOPHAGEAL DYSMOTILITY

Esophageal motor dysfunction may lead to impaired bolus or refluxate clearance. Studies that examined esophageal dysmotility in LPR are summarized in **Table 1**.

Table 1
Studies summarizing esophageal dysmotility in laryngopharyngeal reflux

Study, Ref, Year	Design	Diagnostic Method	Cohort	Aim	Result
Vardar et al,[25] 2013	Retrospective	HRM Ambulatory pH-monitoring	34 patients with CC 21 (62%): Negative reflux-cough SAP 13 (38%): Positive SAP 23: Healthy controls	Examine pharyngeal and esophageal motility in patients with CC with and without association to reflux events	*Average UES IRP* Higher in patients with cough compared to healthy controls *IEM* Higher in patients with reflux associated cough *LES pressures* Similar
Almansa et al,[26] 2015	Retrospective	HRIM 24-h MII-pH	32 patients with CC 32 patients with HB	Among patients with CC and HB; • Determine the prevalence of dysmotility, • Assess the relationship with total bolus/acid bolus exposure time and both swallowed bolus and reflux clearance time	*WPLBs* 34% of CC patients vs 12% of HB patients (P=.027) *Pathologic AET time* 81% of CC patients with WPLB vs 29% without WPLB (P = .011) WPLBs are directly related to impaired refluxate clearance
Benjamin et al,[5] 2017	Retrospective	HRM pH-monitoring (transnasal or 48-h wireless capsule)	n = 57 LPR n = 98 Typical GERD n = 65 LPR and GERD	Comparison of UES function esophageal function in LPR and GERD	*LPR group* Abnormal UES basal pressure (35%) UES-IRP normal *IEM* LPR: 15% Typical GERD: 20.7% LPR and GERD: 7.8% No abnormality is specific for LPR

Ding et al,[27] 2017	Observational	HRM	n = 22 (G-R) n = 20 (G-NR) n = 18 (NG-R) n = 20 (NG-NR)	Identification of HRM abnormalities Related factors associated to PPI refractory patients with globus	*Average resting and residual UES pressure* G-NR>NG-NR G-NR> NG-R *Average resting and residual UES pressure* *DCI* No difference
Bennett, et al,[28] 2018	Prospective	HRM pH-impedance testing off-PPI	218 patients Typical symptoms (n = 123) Atypical symptoms (n = 95)	Presence of long breaks Association of long breaks with symptoms and reflux metrics	*Long breaks* More common in patients with cough *Mean DCI* Similar in both groups Long breaks were associated with suboptimal treatment reflux
Sikavi et al,[6] 2021	Retrospective	RSI GERD Questionnaire 12-Item Short-Form Health Survey Combined hypopharyngeal-esophageal HEMII-pH	n = 194 LPR	Prevalence of coexisting esophageal dysmotility in LPR Association of dysmotility patterns with reflux parameters	Normal: 108 (55.7%) Abnormal HRM: 84 (43%) EM: 60 (31%) Major motility disorder: 26 (13.4%) No association of reflux burden and HRM findings
Sikavi et al,[29] 2021	Prospective	RSI GERD Questionnaire 12-Item Short-Form Health Survey Combined hypopharyngeal-esophageal HEMII-pH	138	Assess proximal esophageal contractility in LPR patients by PCI Examine the association with objective reflux metrics	PCI was independently associated with increased pharyngeal reflux

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Study, Ref, Year	Design	Diagnostic Method	Cohort	Aim	Result
Wu et al,[30] 2021	Prospective	HRIM RSI Chicago 3.0 UESII <1000 Ω over an observed time window of 15 s	N = 158 (101 LPR vs 57 healthy controls) Reflux, dysphagia, globus sensation	Relation of UESI and RSI	Lower UESII indicates poor bolus transit and related to RSI
Borges et al,[31] 2022	Retrospective	RSI HRM 24-h MII-pH	133 patients	To examine the association between abnormal HRM findings and RSI score in patients with suspected LPR symptoms.	*Mean RSI* IEM: 23.7 vs Normal: 18.6 (P = .01) Failed swallows independently predicted higher RSI

Abbreviations: DCI, distal contractile integral; G-NR, Globus-NonReflux; G-R, Globus-Reflux; HEMI-PH, Combined multichannel intraluminal impedance and pH-testing; IRP, integrated relaxation pressure; NG-R, nonglobus-reflux; UESII, upper esophageal sphincter integral; WPLB, weak peristalsis with large breaks.

Upper Esophageal Sphincter Abnormalities in Patients with Laryngopharyngeal Reflux

The proximal esophagus, composed of striated skeletal muscle, prevents gastric contents from reaching the upper respiratory tract. Motor abnormalities of the proximal esophagus and UES dysfunction may play a role in the development of LPR symptoms.

The availability of high-resolution manometry (HRM) with pressure sensors placed at 1-cm intervals in the hypopharynx and proximal esophagus has enabled detailed assessment of both esophageal and pharyngeal pressures in LPR patients. A small study comparing healthy individuals to those with LPR found that LPR patients exhibited impaired UES contractile reflexes and abnormal relaxation responses during simulated liquid reflux events.[32] *Vardar and colleagues* investigated the UES and esophageal motility in patients with CC and reflux and found an elevated residual relaxation pressure of UES in a small subset of patients with cough due to suspected LPR. This can lead to impaired clearance of pharyngeal contents or refluxate and thus stimulate cough.[25] A retrospective study examining UES abnormalities and HRM findings in patients with LPR and GERD revealed that one-third of the overall cohort exhibited abnormal UES pressure and relaxation. Notably, these abnormalities were not specific to either LPR or GERD.[5]

The relationship between globus sensation and UES abnormalities remains incompletely understood. Research has identified exaggerated respiration-associated variations in UES pressure and elevated residual pressures after swallowing in patients with globus.[33] Delayed pharyngeal clearance may also be responsible for symptoms of cough and globus. Interestingly, globus pharyngeus in the absence of LPR was found to be related to high UES pressure.[27]

Neverthless, clinical use of HRM in determining the UES functions is limited. High resolution impedance manometry (HRIM), integrated multiple impedance sensors detect the presence of air or liquid by measuring changes in electrical resistance. HRIM allows the simultaneous measurement of bolus transit and bolus clearance as they relate to esophageal pressures and may be a better diagnostic tool to identify the pharyngeal bolus flow and swallowing function.[34] Poor bolus transit of UES on HRIM was significantly associated with higher RSI score.[30] A large study including 138 LPR patients who underwent HRM and combined hypopharyngeal-esophageal multichannel intraluminal impedance-pH (HEMI-pH) testing assessed proximal esophageal contractility by using proximal contractile integral (PCI), found that decreased PCI on HRM was independently associated with an increase in pharyngeal reflux events, regardless of distal esophageal dysmotility. This finding highlights the role of impaired proximal esophageal contractile function in the development of pharyngeal reflux.[29]

Esophageal Motor Dysfunction

The impact of abnormal esophageal motor functions, such as ineffective esophageal motility (IEM) and large peristaltic breaks is well-documented in patients with typical GERD symptoms, and may be associated with severity of GERD.[35]

An early study of LPR patients who underwent conventional esophageal manometry and pH monitoring found no correlation between esophageal motility disorders and abnormal acid reflux.[8,36] However, HRM study by Vardar and colleagues found that CC patients whom had a positive symptom association probability (SAP) for reflux preceding cough showed a lower percentage of effective primary peristaltic contractions compared to those with a negative SAP.[25] Another study involving patients who

underwent both pH-impedance testing and HRM found that long peristaltic breaks were associated with cough as a presenting symptom. However, this association was not related reflux burden, symptom correlation, or other symptom metrics. Furthermore, the presence of long breaks was associated with suboptimal treatment response.[28] A later study, which used HRIM to examine the role of esophageal motility for increased reflux exposure in patients with CC revealed that weak peristalsis with breaks on HRIM were associated with increased acid exposure time (AET) and prolonged clearance of reflux, despite no differences in proximal extent of reflux events.[26] A retrospective cohort study involving 194 patients with LPR symptoms, referred for HRM and combined HEMI-pH testing, identified abnormal HRM findings in 43% of cases. IEM was the most common diagnosis, while major disorders of peristalsis or esophagogastric junction outflow obstruction were observed in 13% of patients. Those with esophageal dysmotility were more likely to report esophageal symptoms. Notably, reflux burden did not vary across different HRM findings.[6] A recent study reported positive correlation of ineffective swallows, particularly failed swallows, with higher RSI scores.[31] Underlying esophageal dysmotility may partly explain the lack of response to acid-suppressive therapy and anti-reflux surgery in LPR patients. Conversely, prolonged reflux symptoms may also be responsible for esophageal dysmotility, such as IEM.

Manometric findings are not specific to LPR and can also be observed in GERD. Although HRM is not recommended as a first-line diagnostic tool, it is frequently used in clinical practice to identify the LES before placing ambulatory pH/pH-impedance catheters.

IMPLICATIONS FOR TREATMENT

Understanding the neural-mediated pathophysiology of LPR can assist physicians in effective management of patients. Neuromodulators such as tricyclic antidepressants, serotonin reuptake inhibitors, and serotonin-norepinephrine reuptake inhibitors are commonly used to treat functional and laryngeal disorders associated with hypersensitivity, with CC being the well-studied example. In randomized-placebo controlled studies gabapentin and pregabalin have been shown to improve symptoms in patients with CC. Furthermore, pregabalin decreased the symptom severity in patients with CC, globus sensation, odynohonia, and or odynophagia.[37–39] In addition to medical treatment, cognitive behavioral therapy, speech, and breathing therapies focusing on the abdominal and oropharyngeal muscles have shown promising results in managing laryngeal hypersensitivity.[40] A novel therapy involving an external UES compression device, designed to reduce esophageal and UES responses to simulated reflux events, has demonstrated a treatment response rate of 29% to 55% in LPR patients, though further research is required to validate its efficacy.[41]

SUMMARY

The interplay between neural mechanisms and esophageal dysmotility plays a crucial role in the pathophysiology of LPR disease. Understanding these interactions is essential for effective management strategies to address both the physiologic and sensory aspects of the disease.

CLINICS CARE POINTS

- The lack of a diagnostic tool for LPR, combined with poor response to PPI therapy, poses a significant clinical challenge.

- Neural-mediated LPR should be considered in PPI-refractory patients, prompting physicians to explore neuromodulator treatments.
- Esophageal dysmotility may coexist with LPR; however, no concrete evidence supports it as either the cause or consequence of LPR.

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