We are IntechOpen, the world’s leading publisher of Open Access books
Built by scientists, for scientists

6,500
Open access books available

177,000
International authors and editors

195M
Downloads

154
Countries delivered to

TOP 1%
Our authors are among the most cited scientists

12.2%
Contributors from top 500 universities

WEB OF SCIENCE™
Selection of our books indexed in the Book Citation Index in Web of Science™ Core Collection (BKCI)

Interested in publishing with us?
Contact book.department@intechopen.com

Numbers displayed above are based on latest data collected.
For more information visit www.intechopen.com
Chapter

Autonomic Neuroregulation in the Larynx and Its Clinical Implication

Syahrial M. Hutauruk, Elvie Zulka Kautzia Rachmawati and Khoirul Anam

Abstract

The central nervous system controls autonomic function through interconnected areas distributed throughout the neural axis known as central autonomic network (CAN). Central nervous systems are organized and control functions of the body and secretion of brain neurotransmitter. The autonomic nervous system includes all regions controlling autonomic, unconscious, and involuntary functions in body homeostasis. Vagal nerve is the longest and most complex nerve of the autonomic nervous system and plays a role in regulating innervation in the larynx. Altered vagal nerve activity caused by impaired autonomic regulation was thought to be responsible for clinical entities related to laryngology diseases, such as laryngopharyngeal reflux (LPR), sleep-disordered breathing (SDB), chronic cough (CC), and vocal cord dysfunction (VCD). This chapter reviews the pathogenesis and clinical findings of laryngeal disease related to autonomic nerve dysfunction.

Keywords: autonomic nerve dysfunction, vagal nerve, laryngopharyngeal reflux, sleep-disordered breathing, chronic cough, vocal cord dysfunction

1. Introduction

The central nervous system controls autonomic function in several areas. These areas are interconnected and then distributed throughout the neuroaxis. The area is called the central autonomous network (CAN); they control many other functions, of which the tasks of arousal and respiration are included [1]. One of the main outputs of this integrated network is mediated by preganglionic sympathetic and parasympathetic nerves. Hierarchically, the central autonomous control area has been arranged. The delivery of interoceptive information to the forebrain and the mediation of the cardiovascular, respiratory, gastrointestinal, and micturition reflex systems are regulated by the medullary and lower pons areas. The solitary tract nucleus (NTS), the reticular formation of the rostral ventrolateral medulla (VLM), rostral ventromedial medulla (RVMM), including the caudal raphe nucleus, medullary respiratory group, parabrachial nucleus (PB), and pelvic organ stimulation center (Barrington Nucleus) belong to this area [1, 2].
Autonomic control by modulating pain, response to stress, behavioral stimuli, and motor responses is integrated by areas in the upper pons and midbrain. These areas include the periaqueductal gray (PAG), the pedunculopontine tegmental nucleus/ pedunculopontine nucleus (PPT/PPN), and the locus coeruleus (LC) [3]. The hypothalamus takes over the generators of integrated autonomic, endocrine, and behavioral response patterns. This is done to ensure homeostasis and adaptation of the body to the environment. Hypothalamic autonomic output mainly comes from the paraventricular nucleus (PVH), dorsomedial nucleus (DMH), and lateral hypothalamic regions, including the orexin-synthesizing group of neurons (Orx, also known as hypocretin, Hcrt). The midcingulate cortex, anterior insular cortex, and amygdala are core areas of the telencephalon that control autonomic functions. Although the functional anatomy of the central control of autonomic function has been best characterized in experimental animals, several functional neuroimaging studies show that many of the same areas are activated during autonomic responses in humans [3, 4].

Autonomic functions are controlled by areas of the brain whose input is received and integrated from four main sources: interoceptive, humoral, limbic, and circadian. Spinal afferents relay information about interoceptive input from visceral, pain, and thermal receptors via ascending projections to lamina I of the dorsal horn or via cranial nerve afferents relayed in the NTS. The central autonomic regions, directly or indirectly, are reached by humoral signals from blood (such as glucose or cytokine levels) or cerebrospinal fluid (CSF, such as pH) via the circumventricular sensory organs. It is also the main neurotransmitter (sometimes along with the inhibitory amino acid glycine) of the circuits that control respiration and the sleep-wake cycle [5]. Autonomic, respiratory, and arousal circuits are modulated in state-dependent function by cholinergic, monoaminergic, and peptidergic influences from the brainstem, basal forebrain, hypothalamus, and local interactions mediated by local interactions by nitric oxide (NO), purines, endocannabinoids, and other signals [5, 6].

Sympathetic neurons and parasympathetic preganglionic neurons are the final effectors of the control center for autonomic function and are cholinergic. These neurons stimulate the excitatory signal of autonomic ganglia and enteric neurons through ganglion-type nicotinic receptors. Sympathetic preganglionic neurons are in the thoracolumbar spinal cord in segments T1 to L2, primarily in lamina VII, which forms the intermediolateral column (IML) and forms separate functional units that are selectively activated in response to different stimuli [5]. Sympathetic output is critical for maintaining blood pressure, local regulation of blood flow, thermoregulation, and response to exercise and internal or external stressors [5, 6]. Preganglionic sympathetic axons terminate in the paravertebral, prevertebral, terminal ganglia, and the adrenal medulla [6]. Norepinephrine is the main neurotransmitter in postganglionic sympathetic neurons. Except for the postganglionic sympathetic nerves, which innervate the sweat glands, they are cholinergic nerves and vasodilators in muscles and coronary arteries. From a functional point of view, the parasympathetic output can be further subdivided into outputs to cranial effectors via cranial nerves III, VII, and IX, output to the thoracic and abdominal viscera mediated by the vagus nerve (cranial nerve X), and outputs from the pelvic organs (bladder, rectum, and sexual organs) from sacral preganglionic neurons [4, 6]. Organ-specific reflexes are mediated by sympathetic output. Acetylcholine is the main neurotransmitter of the most parasympathetic ganglion and enteric nervous system (ENS) neurons. Noncholinergic neurons also mediate parasympathetic output, releasing NO and vasoactive intestinal polypeptide (VIP) [6].
2. Autonomic innervation in the larynx

Two conventionally divided subtypes of the autonomic nervous system (ANS), the sympathetic and parasympathetic nervous systems, are defined as peripheral efferent fibers. Recent studies have revealed the presence of general visceral afferent fibers. The autonomic innervation of the larynx had been veiled; however, recent studies have identified the autonomic nerve fibers in the larynx and illuminated the distribution of autonomic innervation [5, 6].

The postganglionic neurons of the laryngeal sympathetic nervous system have their cell body mainly in the superior cervical ganglion. The preganglionic neurons originate in the gray matter of the upper thoracic spinal cord. Sympathetic innervation of the larynx had been considered to be innervated along with superior or inferior laryngeal arteries and veins [6]. However, study by Hisa et al. [7] using the Falck-Hillarp method revealed that sympathetic innervation of the canine larynx is distributed via the superior laryngeal nerve and inferior laryngeal nerve. Hisa et al. [7] also revealed the detailed distribution of sympathetic nerve fibers in the laryngeal arteries and glands in the supraglottic, glottis, and subglottic using the Falck-Hillarp method and tyrosine hydroxylase (TH) immunohistochemistry. Tanaka et al. [8] describe that TH-immunoreactive nerve fibers were located in the vicinity of the basal lamina, but they never terminated or penetrated the basal lamina. Recent studies also revealed that there is a specific distribution of adrenergic neurons and noradrenergic nerve fibers in the larynx. Adrenergic fibers with fluorescent varicosities were observed around the base of the acini, blood vessels around intrinsic laryngeal muscles, gland cells, and myoepithelial cells in the submucosal gland region [8].

Many noradrenergic nerve fibers are contained in the superior laryngeal nerve and the recurrent laryngeal nerve. The supraglottic and subglottic submucosal glands received the noradrenergic nerve fibers from the internal branch of the superior laryngeal nerve and the recurrent laryngeal nerve, respectively [7]. The external branch of superior laryngeal nerve supplies noradrenergic fibers to the cricothyroid muscle, while other intrinsic muscles received noradrenergic fibers from the internal branch of the superior laryngeal nerve and the recurrent laryngeal nerve. The noradrenergic nerve fibers in the superior laryngeal nerve originated from the superior cervical ganglion. Noradrenergic nerve fibers are contained in the recurrent laryngeal nerve. Noradrenergic nerve fibers originate from the middle cervical ganglion and superior cervical ganglion via the vagus nerve [7, 9].

The parasympathetic nervous system plays a major role in the motor control of mucus secretion in the larynx. The cell body of the postganglionic neuron is present in the intralaryngeal ganglion [9]. As Yoshida et al. [10] describe, intralaryngeal ganglionic neurons have cholinergic nature and innervate vessels and glands. The cell body of the preganglionic neuron is in the dorsal nucleus of the vagal nerve. It projects the nerve fiber to the larynx via the vagal nerve and superior or inferior laryngeal nerve. ACh is the transmitter of motor neurons, pre- and postganglionic nerve fibers of parasympathetic nerves, and some of the sympathetic nerves [9, 10].

3. Heart rate variability analysis and autonomic nerve dysfunction

Heart rate (HR) is controlled by the autonomic nervous system. Changes in sympathetic and parasympathetic nervous system activity result in beat-by-beat variations in heart rate; therefore, these variations reflect autonomic nervous system
activity. Heart rate variability (HRV) is pathological, like ischemic heart disease, and decreased variability predicts poorer outcomes. Heart rate variability (HRV) is the result of the interaction between the autonomic nervous system (ANS) and sinoatrial node (SAN) activity; experts then assume that HRV is a surrogate marker for autonomic nerve dysfunction [11]. Heart rate variability (HRV) is the fluctuation in the time interval between adjacent heartbeats. HRV is thought to reflect the heart’s ability to adapt to changing circumstances by detecting and rapidly responding to unpredictable stimuli. HRV measures neurocardiac function produced by heart-brain interactions and a dynamic nonlinear autonomic nervous system activity. HRV is an emergent response from interconnected regulatory systems working at various time scales that aids individuals in adapting to environmental and psychological stresses.

Autonomic balance, blood pressure, gas exchange, intestinal motility, heart, rhythm, and vascular tone are all regulated by HRV (which refers to the diameter of blood vessels that regulate blood pressure) [11–13]. A healthy heart is not a metronome. Healthy heart oscillations are complex and nonlinear. The nonlinear system variability provides the flexibility to quickly adapt to an uncertain and changing environment. Optimal HRV status is always associated with health and self-regulation capacity, as well as adaptability or resilience of an individual. Higher levels of HRV, mediated by the vagal nerve at rest, were strongly associated with the performance of executive functions such as attention and emotional processing by the prefrontal cortex. The processing of afferent information by the intrinsic cardiac nervous system can modulate frontocortical activity and influence human executive and cognitive functions at higher levels [11].

HRV analysis is one of the modalities that can be used to assess overall cardiac health, especially with regard to the state of the autonomic nervous system, which is responsible for regulating heart activity and rhythm. HRV refers to the variation of the pulse interval or is related to the response to instantaneous changes in heart rate. Normal variability in heart rate is modulated by the autonomic nervous regulation of the heart and circulatory system. The balance mechanism of the sympathetic nervous system and the parasympathetic nervous system branch of the autonomic nervous system then control the heart rate. Increased sympathetic or reduced parasympathetic activity will cause accelerated cardiac activity; conversely, low sympathetic activity or high parasympathetic activity can cause cardiac deceleration. The degree of variability in heart rate can provide information about the function of neural control of heart rate and the ability of the heart to respond to changing conditions [11–13].

The classic measurement of HRV can be calculated from the electrocardiogram (ECG) i.e., at R-R intervals and consensus guidelines regarding appropriate indicators are available. Arroyo-Carmona et al. [12] used the R-R time series on several ECG studies to determine HRV. An ECG is a recording of the electrical activity in heart tissue, each of which is represented by different waves of different amplitude and duration. The morphology of the ECG is the result of the activities of the autonomic nerve system (ANS) and SAN and can be classified into two groups: positive deflection and negative deflection. This classic R-R measurement has been abandoned, considering that if it is analyzed in detail, the R-R distance will most likely indeed be a difference. Experts think that it can be influenced by the physiological regulation of baroreceptors and mechanosensory receptors in the cardiovascular system. Recent studies reveal that SAN also has its own variability; it is very important to separately evaluate the correlation of the two oscillators to use HRV to be a better surrogate marker for disease evaluation and even to describe physiological conditions such as aging and behavior [11, 14].
HRV can be measured by pulse photoplethysmography (PPG) method with finger plethysmogram (FPG). Measurement only takes about 20 minutes. The research of Lu et al. [11] has proven that although the PPG method has a quick process, it has been shown to produce results similar to Holter ECG measurements. Lu et al. [11] found a very strong correlation value ($r = 0.99$) and significant ($p < 0.000$) between PPG examination and Holter's ECG in both the frequency and time domains through linear regression analysis. Standard deviation normal to normal (SDNN) parameters and the low frequency/high frequency (LF/HF) ratio have also been shown to have fairly good sensitivity and specificity values (>82%) in detecting vagal autonomic disorders [11]. This HRV measurement method generally has three examination domains: frequency domain, time domain, and measurement aspects. The time-domain index on HRV will calculate the amount of variability in the interbeat interval (IBI) measurement, which is the period of time between successive heartbeats. The frequency-domain index divides the absolute or relative power distribution into four frequencies. Heart rate (HR) oscillations are classified as ultralow frequency (ULF), very low frequency (VLF), low frequency (LF), and high frequency (HF) by the Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology [11–14].

### 4. Autonomic neuroregulation and its clinical implication in laryngology

Vagal nerve is the longest nerve of the autonomic nervous system and is one of the most important nerves in the body. Altered vagal nerve activity caused by impaired autonomic regulation was thought to be responsible for several clinical entities related to laryngology diseases, such as laryngopharyngeal reflux (LPR), sleep-disordered breathing (SDB), chronic cough (CC), and vocal cord dysfunction (VCD) [15].

Esophageal sphincter and gastrointestinal tract are innervated by the vagal nerve; therefore, deteriorated vagal nerve function may be an important factor in LPR regarding the incompetence of esophageal sphincter. Chronic inflammation in the larynx is also thought to be responsible in the occurrence of vagal neuropathy, a condition where laryngeal mucosa is in the hyposensitive and hypersensitive state simultaneously. This mechanism is thought to contribute in the pathogenesis of CC and VCD. Since CAN also plays an important role in regulating sleep-wake cycle, it is known that hypoxia and apnea during sleep will alter the neural modulation in the CAN through some neurotransmitters. These theories have supported the evidence on where autonomic nerve dysfunction could contribute in several laryngology diseases and SDB [1, 9, 15].

#### 4.1 Laryngopharyngeal reflux (LPR)

LPR is an inflammatory condition of the upper gastrointestinal tract associated with the direct and indirect effects of the retrograde flow of gastroduodenal contents, which can cause morphological changes in the upper aerodigestive tract. LPR causes many laryngeal diseases. Reflux laryngitis, subglottic stenosis, granulomas, laryngeal carcinoma, contact ulcers, and vocal cord nodules are caused by LPR. Because the signs and symptoms of LPR are nonspecific and may be manifestations of other etiologies, e.g., infection, voice abuse, allergies, smoking, inhalation of irritants, alcoholism, and nonpathological changes, patients with LPR may experience prolonged and generalized suffering if their physician is unable to make a diagnosis [16, 17].
Coughing, hoarseness, and globus pharyngeus (a lump sensation in the throat) are the most prevalent symptoms. Hoarseness is a symptom that usually starts in the morning and improves over the day. Belafsky et al. [18] created the reflux symptom index (RSI), a nine-item questionnaire that can be completed in less than 1 minute for symptom assessment in patients with reflux illness. One of the challenges in diagnosing LPR is that the symptoms of the disease are less specific to confirm LPR, and thus, it is necessary to exclude other causative agents. In fact, there are still several studies showing an unrelated correlation between LPR symptoms, laryngeal findings, and findings from hypopharyngeal pH monitoring [18].

Belafsky et al. [19] developed the RFS, which includes an eight-item reflux clinical severity scale based on laryngoscopy findings. Subglottic edema, ventricular obliteration, erythema/hyperemia, vocal cord edema, widespread laryngeal edema, posterior commissure hypertrophy, granulomas, and thick endolaryngeal edema were all evaluated and graded on a scale of 0–4. According to Belafsky et al., a practitioner can be 95% certain that a patient has LPR. The common findings of LPR are posterior commissure hypertrophy, subglottic edema, inflammation of the larynx or arytenoids, and the presence of thick endolaryngeal mucus [19].

LPR and gastroesophageal reflux disease (GERD) are considered as a continuum of similar basic pathophysiological mechanisms with some overlapping symptoms. The long-standing controversial differences between the two diseases still exist today. Most patients with throat complaints related to LPR deny the classic symptoms of GERD, especially heartburn. On the other hand, many LPR patients report no endoscopic findings of esophagitis, and the severity of esophagitis based on endoscopic examination is not related to the level of symptoms and signs of LPR. LPR and GERD are disease entities that are both caused by the retrograde flow of gastric contents, but the pathogenesis of these two conditions is different even though they are interrelated. The lower esophageal sphincter (LES) and gastrointestinal tract are innervated by the vagal nerve, and the pathogenesis of GERD itself mainly involves the presence of lesions in LES. According to research, the vagal nerve regulates the parasympathetic regulation of the gastrointestinal system. The malfunction of the LES and the transiently increased relaxation of the lower esophageal sphincter seen in GERD, which results in an increased amount of gastric acid going back into the esophagus, appear to be caused by decreased vagal nerve activity induced by inadequate autonomic regulation [18, 20, 21].

It is also known that there is a relationship between gastrointestinal symptoms and the incidence of cardiac dysrhythmias, as one of the disorders of the autonomic system in GERD patients. This phenomenon has been described as a gastrocardiac syndrome. The severity of esophageal inflammation is not related to the dysfunction of the autonomic nervous system itself, given that the presence of vagal dysfunction has been observed in those with or without severe esophageal inflammation. Several studies have suggested that this parasympathetic dysfunction is not only a consequence of esophageal inflammation, but also a major factor in the etiopathogenesis of GERD. Disturbances in autonomic nervous system activity affect the temporary contraction and relaxation of LES, which then causes GERD and affects its severity [15, 16, 22].

Decreased vagal nerve activity, caused by impaired autonomic regulation, appears to be responsible for the dysfunction of LES and the increased transient lower esophageal sphincter relaxation (TLESR) seen in GERD, which results in the increased volume of gastric acid reflux to the esophagus. The exact stimulus and mechanism underlying TLESR are still debatable, although it is currently thought...
that TLESR and experimentally induced relaxation of the LES are controlled by neural feedback involving the vagal nerve. The TLESR is triggered by the nerve stimulation of the pharynx, and the relaxation of the LES is triggered by the stimulation of the superior laryngeal and vagal nerves. In addition, gastric distention can also trigger TLESR, but is then inhibited or controlled by vagal efferent and vagal afferent pathways. Most of the sensory neurons that innervate the LES are integrated in the vagal nodular ganglion. There are two things to note before concluding that TLESR is mediated by the vagal pathway. The first is related to vagal efferent fibers that modulate the occurrence of TLESR and the relaxation of the LES; it is still not known whether these two processes are mediated by the same fibers. Second, nonvagal pathways also contribute to the control of the LES. Experimental studies in experimental animals have shown that there is a contribution from spinal afferent innervation in cats, and the relaxation of the LES has also been shown to involve the vagospinal pathway in ferrets. In general, the published literature is consistent with the motion that LES regulation is primarily based on vagal afferent - vagal efferent (vagovagal) reflex mechanisms [15, 16].

In 1980, Heatley et al. [16] studied vagal nerve activity in GERD patients by observing changes in pulse rate variability during deep breathing and found that a quarter of these patients had distinct vagal nerve dysfunction, suggesting that vagal nerve dysfunction was the cause of GERD in these patients. The Cunningham et al.'s study [15] first demonstrated a high prevalence of autonomic nerve dysfunction among patients with esophagitis diagnosed by endoscopy or abnormal outpatient pH recordings. Abnormalities in parasympathetic tone may cause delayed esophageal transit and abnormal peristalsis. The study by Lee et al. [23] found that autonomic tone was lower in patients with endoscopically confirmed (even asymptomatic) esophagitis compared with patients with nonerosive esophagitis (nonerosive reflux disease—NERD). Dobrek et al. [24] used heart rate variability (HRV) to measure the strength of high frequency (HF) and low frequency (LF) and found that the GERD group scores significantly lower than the control group at rest. In addition, Lee et al. [23] also found that compared with patients with nonerosive reflux disease (NERD), patients with esophagitis (even without symptoms) had lower autonomic nerve function (lower LF and HF strength). Chen et al. [21] found that HF strength was significantly lower in patients with erosive esophagitis (ERD) compared to NERD patients and the control group, but LF% and LF/HF ratio were significantly lower in patients with NERD than in ERD patients and the control group.

The study of Wang et al. [22] showed that patients with LPR mainly had autonomic dysfunction with relatively worsening vagal nerve function and better sympathetic nerve function. The digestive system is regulated by the autonomic nervous system. Therefore, autonomic dysfunction may lead to an abnormal regulation of gastric peristalsis and upper esophageal sphincter (UES) and LES function, making laryngopharyngeal reflux a risk factor for autonomic dysfunction. Patients with LPR had a significant negative correlation between the strength of HF with RSI and RFS. Higher symptoms and physical scores were associated with worsening vagus nerve function, suggesting that vagal nerve dysfunction is involved in LPR development. Longer disease duration in patients with LPR was associated with lower vagal nerve function, as demonstrated by the analysis of autonomic nerve dysfunction and disease duration. These findings suggest that restoring autonomic nerve function during LPR treatment is critical [16, 22].

Wang et al. [22] also showed that autonomic nerve dysfunction is correlated with LPR, and effective treatment needs to be explored. Research by Hu et al. [25]
confirmed that patients with anxiety and depression had marked autonomic nervous dysfunction and significantly improved after being treated for anxiety and depression. Chen et al. [26] concluded that a decrease in HRV can be used as a psychophysiological biomarker in patients with depressive disorders, and even a very significant decrease in HRV was found in a population of subjects with mixed anxiety and depression disorders. Our observations in outpatient care also observed that some patients with LPR showed signs of mild anxiety and depression [16, 22, 25, 26].

LPR is an inflammatory condition in the upper gastrointestinal tract associated with the direct and indirect effects of exposure to reflux of gastroduodenal contents and can cause morphological changes in the upper aerodigestive tract. The etiology of this disease is multifactorial, the diagnosis is still a challenge in itself, and the pathogenesis aspect has not been conclusively explained. This has an impact on the management of patients and the burden of health financing. Autonomic nerve dysfunction is thought to play a role in the occurrence of LPR. It is known that decreased vagal nerve activity caused by autonomic dysregulation is responsible for GERD, but whether the same pathomechanism associated with autonomic dysfunction occurs in LPR requires further research [25, 27].

4.2 Sleep-disordered breathing (SDB)

Obstructive sleep apnea (OSA) is characterized by an episodic collapse of the upper airway during sleep, resulting in the periodic reduction or pause in ventilation and hypoxia, hypercapnia, or awakening from sleep. The prevalence in the general population is estimated to be 3% in women and 10% in men with ages ranging from 30 to 49 years [28, 29]. Overnight polysomnography is required to document the frequency of respiratory events, apnea, and hypopnea during sleep in OSA diagnosis. Obstructive apnea is the complete (>90%) or nearly complete cessation of airflow for more than 10 seconds during sleep despite ventilation efforts. Hypopnea is a decrease in airflow of at least 30% followed by a decrease in oxygen saturation of at least 3% or awakening from sleep. The apnea-hypopnea index (AHI) was defined as the number of apneas and hypopneas per hour of sleep. OSA criteria are the occurrence of AHI at least five events per hour. Therefore, traditionally, AHI is categorized based on the number of events per hour. AHI in the mild category is 5–15 AHI events per hour, while the severe category is more than 30 events per hour [28–31].

Events in which 15 or more AHIs per hour were associated with a decrease in psychomotor speed are equivalent to 5 years of aging. The higher the AHI, the lower the subjective quality of life. Untreated OSA triples the risk of motor accidents compared to the general population. Most importantly, OSA was associated with an increased risk of cardiovascular disease, particularly stroke, hypertension, heart failure, and coronary artery disease, even after adjustment for body mass index (BMI) and other risk factors. In addition, OSA patients also tend to increase the risk of heart arrhythmias, including atrioventricular block, ventricular tachycardia, and sinus bradycardia [29–31].

In healthy individuals, hypoxia (i.e., decreased oxygen levels with an arterial pO2 of less than 60 mmHg) causes chemoreceptor activation and triggers tachycardia and an increase in blood pressure. Hypoxia and hypercapnia increase the incidence of hyperventilation (resulting in an increased distribution of oxygen to the peripheral blood), and increased sympathetic efferent activity resulting in vasoconstriction to redistribute oxygenated blood flow. Baroreflex activation in healthy individuals
eliminates the increase (reduction) in sympathetic activity caused by hypoxia, which can lead to vagal activation and bradycardia [29, 32, 33].

Convergent evidence obtained from studies with neuromuscular sympathetic nerve activity, plasma catecholamine levels, and analyses of heart rate variability suggests that in patients with OSA, hypoxia and apnea trigger a cascade of excitability that results in an acute elevation of efferent sympathetic activity during sleep when maintained over a prolonged period of time. Over time, it can induce the chronic sustained elevation of the sympathetic outflow regulatory point during wakefulness. This has implications for a higher risk of chronic hypertension, coronary artery disease, and cerebrovascular disease. Excessive sympathetic outflow, in turn, causes baroreflex-mediated cardiovagal efferent activity and bradycardia, atrioventricular block, and ventricular tachycardia, potentially resulting in sudden cardiac death. The incidence of arousal during obstructive apnea is associated with sleep fragmentation and further sympathetic efferent activity, leading to peripheral vasoconstriction and sudden increases in systolic and diastolic blood pressure and heart rate [29, 32, 33].

Upper airway collapse during sleep resulting in obstructive apnea causes changes in intrathoracic pressure resulting in myocardial stretching of the heart chambers and changes in the transmural pressure gradient, particularly affecting the atria. It can also cause atrial fibrillation and other arrhythmias. In addition to hypoxia and apnea, other mechanisms may be associated with sympathetic efferent overactivity that develops in OSA patients. Obesity, apart from mechanically obstructing the airway and causing OSA, is also responsible for increasing sympathetic afferent activity through mechanisms of leptin, insulin, angiotensin, and cytokines. On the other hand, many OSA patients are not obese. Studies with animal models have confirmed carotid chemoreceptor hypersensitivity due to intermittent hypoxia that contributes to the pathogenesis of OSA in humans. Overactivation of the nucleus in the CNS induces neural changes that increase excitatory impulses to the rostral ventrolateral medulla and maintain high sympathetic tone independently of peripheral sensory signals [32–34].

During sleep, the frequency of TLESR decreases because the stimulus is thought to be associated with gastric distension. During a person’s sleep, there is no eating or chewing process, resulting in a reduction in saliva production and a decrease in neuromuscular coordination activity in the swallowing process; this will have implications for the lengthening of the esophageal clearance so that there will be a longer contact between the irritant refluxate and the esophageal mucosa (prolonged contact). This phenomenon then underlies a new entity called sleep-related GERD. Although the frequency of TLESR decreases during sleep, transient relaxation has been observed to occur during cortical arousals in patients with sleep-disordered breathing (SDB). These findings also corroborate the results of Gottesmann’s study regarding the association of sleep disorders with the incidence of autonomic dysfunction through the modulation of the neurotransmitter gamma aminobutyric acid (GABA). Gottesmann found that TLESR is vagal mediated and can be inhibited by GABA-b. Lang et al. found another reflex pathway involved in the occurrence of TLESR when the patient was not in the process of swallowing, namely through the esophageal distention reflex (EDR) [22, 25, 27].

This EDR consists of several subtypes of pathways that can be evoked through pressure inflation-related stimuli (slow air and rapid air stimulation) instead of volume on mechanoreceptors in the mucous or muscular layers of the pharynx, larynx, and esophagus. In the slow air distention pathway, a secondary peristaltic reflex (2P) will occur, which then stimulates the esphago-UES contraction reflex.
(EUCR); this pathway will certainly play a role in preventing reflux episodes from occurring. Meanwhile, through the rapid air distention pathway, four other reflex pathways [esophago-UES relaxation reflex (EUSR), esophago-glottal closure reflex (EGCR), esophago-esophageal contraction reflex (EECR), and esophago-hyoid distraction reflex (EHDR)] will be activated and strongly suspected to play a role in the occurrence of belching. Lang et al. also found that all of these EDR subtypes were modulated by vagal afferents and could be inhibited by GABA-b, in accordance with Gottesmann’s findings. Experimental studies conducted on cats by Hornby showed that not only GABAb was involved, microinjection of GABAa antagonists into the dorsal vagus motor resulted in a 71% decrease in sphincter pressure. This proves that the neurotransmitter GABAa also plays a role in the transient relaxation of the esophageal sphincter [25, 27, 35].

Sleep disturbances in GERD patients have been shown to induce changes in visceral perception and pain threshold. This investigation showed that in GERD patients with sleep disturbances documented by actigraphy, acid-infusion-induced chest pain was markedly exacerbated after three nights of sleep deprivation. These functions are modulated by afferent branches of the vagus nerve. Gottesmann also found that low levels of GABA in the CNS will affect a person’s sleep quality. This would have implications for decreasing slow waved sleep and increasing paradoxical sleep (fragmentation and arousals) [35]. These observations prompted Chen and Orr to conduct a study to test the hypothesis that changes in autonomic function play a role in the pathogenesis of GERD. They achieved it by using spectral analysis of heart rate variability during their study’s esophageal infusion of 0.1 N hydrochloric acid. This study proves that the infusion of water and acid can cause a decrease in vagal tone in GERD patients compared to normal [36–38].

4.3 Chronic cough (CC)

Cough is the most common complaint of patient admitting to hospital. In the United States, as many as 27–30 million cases of cough are found in primary care each year [39]. Chronic cough is estimated to occur in 10–20% of the general population, and an important cause of morbidity in 3–40% of the population [39, 40]. The coughing process consists of a complex process; there are: (1) afferent pathways: sensory nerve fibers (branches of the vagus nerve) located in the ciliated epithelium of the upper airway; (2) central pathway (cough center): a central coordinating region for coughing that located in the upper brain stem and pons; and (3) efferent pathway: stimuli from the cough center travel to the diaphragm, abdominal wall, and muscles via the vagus, phrenic, and spinal motor nerves. The nucleus retroambigualis of the phrenic and spinal motor nerves transmits these stimuli to the inspiratory and expiratory muscles, while the ambiguous nucleus of the laryngeal branches of the vagus nerve transmits to the larynx [40]. Coughing is a physiological reaction of the body that can produce intrathoracic pressure up to 300 mmHg and particle velocities of up to 800 kilometers/hour. While these pressures and velocities are important on mucus clearance, they are also responsible for many of the complications such as exhaustion, insomnia, headache, dizziness, musculoskeletal pain, hoarseness, excessive perspiration, urinary and fecal incontinence, to rib fractures [41]. Based on cough duration, it is classified into three subtypes: acute (less than 3 weeks, usually due to viral upper respiratory tract infection), subacute (3–8 weeks), and chronic (more than 8 weeks) [39, 40]. Chronic cough is often associated with smoking. Chronic smokers are three times more likely to have a chronic cough than nonsmokers [41]. Chronic coughs
are more difficult to diagnose and require an examination by a specialist for further evaluation.

Sensory neuropathy or autonomic dysfunction of the laryngeal branch of the vagus nerve can also lead a chronic cough manifestation. The autonomic dysfunction of the vagus nerve puts the laryngeal mucosa in a hyposensitive and hypersensitive state. The most common cause of this symptom is laryngopharyngeal reflux (LPR) [42]. Another etiology of neuropathy is viral infection, especially in the upper respiratory tract. However, it is very difficult for the clinician to determine the etiology because of the atypical clinical symptoms and limited diagnostic modalities. Cough can be mediated by the detection of irritant stimuli in the airway by vagal sensory nerve fibers leading to cough induction via the brainstem without any conscious control or regulation. In neurogenic cough, there was an increase of cough reflex at brainstem level or central sensitization [39, 43].

Because of its neurogenic pain-like characteristic, some of the neuromodulator treatments were considered as a potential therapeutic option for neuropathy cough therapy. Neuromodulator therapy such as gabapentin, pregabalin, and amitriptyline, along with other agents such as baclofen and tramadol [44]. The study by Lee and Woo [45] examined 28 patients with suspected recurrent/superior laryngeal nerve neuropathy. All patients were given gabapentin therapy, with an initial dose of 100 mg/day, which then gradually increased to a maximum of 900 mg/day for 4 weeks. Overall, 68% of patient showed improvement of cough complaints and sensory neuropathy after therapy, especially in the group with clear signs of motor neuropathy.

Chronic cough due to post viral vagal neuropathy is one of the conditions that become the differential diagnosis in cases with unclear etiology. This type of cough is included in the neurogenic cough and is one of the symptoms of laryngeal hypersensitivity syndrome. This theory was originally stated by Morrison et al. [43], who said that irritable larynx syndrome (ILS) is an individual response against changes in the central nervous system that cause the sensorimotor pathways to be in a hyperexcitable state. These changes are thought to have a multifactorial etiology, but the most common are reflux. However, more than one-third of the patients in this study have had a history of upper respiratory tract infection before the onset of symptoms. Neural plasticity processes that occur as a result of postinfectious nerve injury can inactivate initial afferent nerves from central neurons and then create new pathways or reactivate old synapses. An afferent stimulus will produce a different response due to changes in the expression of ion channels and other receptor, including TRPV-1, which has an important role in regulating nervous excitability by chemical stimuli [44].

4.4 Paradoxical vocal cord movement

Paradoxical vocal cord movement (PVCM) is a laryngeal disorder, an inappropriate adduction of the vocal cords during inhalation and sometimes exhalation that affects respiratory function and serves as a mimicker of asthma. Vocal cord dysfunction can be difficult to treat as the condition is often underpredicted and misdiagnosed as asthma or other airway disorder and causing inappropriate treatment [46].

The vocal cords normally open (abduction) into a V opening, called the glottic chink during inspiration and close (adduction) into a narrower V shape during expiration. The contraction of the posterior cricoarytenoid muscle allows the outward rotation of the arytenoid on the cricoid cartilage opening the airway
during inspiration. Passive relaxation of the posterior cricoarytenoid muscle during expiration, causing adduction of the vocal cords and close the laryngeal airway, with thyroarytenoid muscle movement supports and provides positive pressure at the end of expiration and prevents bronchial collapse [46, 47], while the lateral cricoarytenoid muscle allows inward rotation of the arytenoid on the cricoid cartilage, closing the laryngeal airway during deglutition, vocalization, and expiration.

The term of PVCM is laryngeal dyskinesia when there is adduction of the vocal cords during inspiration, thereby restricting the airway opening leading to episodic dyspnoea, wheezing and/or stridor, so that it is usually mistaken for asthma. Direct visualization by using laryngoscopy of the vocal cords while the patient is having symptoms is the gold standard for diagnosing PVCM [46]. The etiology of PVCM is unclear but has been hypothesized triggered by a psychological, neurological, or physiological component. Laryngopharyngeal reflux, GERD, croup disease, or exposure to toxic inhalants were suspected as PVCM triggers [47]. In a study by George et al. [48], from 27 patients diagnosed with PVCM, 66% of the patient also have LPR, which was found through flexible fiber laryngoscopy examination. Another finding on examination is that there was a presence of posterior laryngitis and cobblestone on the posterior pharyngeal wall.

PVCM is defined as voice disorder in the absence of organic pathology and suspected have association with autonomic nervous system (ANS) function. Study of Helou et al. [49] found that laryngeal muscle activity, an intrinsic laryngeal muscle (ILM), was increased with activation of the autonomic nervous system due to the presence of acute stress. This study showed that participant’s heart rate and blood pressure measures are significantly increased during the exposure of the stress, which represents the activity of autonomic nerve. ILM activity observed was elevated followed by the increase of heart rate and blood pressure due to the stimuli from afferent nerve of the stress. The larynx receives both sympathetic and parasympathetic innervation, which human laryngeal muscle exhibits a response due to ANS activation [49]. Exposure to acids and irritants in the laryngeal area were suspected causes PVCM incidence. Vocal cord dysfunction may be caused by laryngeal hyperresponsiveness, initiated by an initial inflammatory insult and resulting in altered autonomic balance. Inflammatory and irritant stimuli can have tendency to laryngeal narrowing due to laryngeal hyperresponsiveness which will contribute to wheezy breathlessness [50].

A study of Morrison et al. [43] stated that irritable larynx syndrome (ILS) is caused by chronic reflux stimulation. In ILS, a process called neural plasticity causes changes in neuronal control of the larynx and other structures due to exposure to irritants. It causes changes in the neuronal control of the larynx and surrounding structures due to exposure to irritants. This explains the changes in the central nervous reaction to certain stimuli. In PVCM, neural plasticity is a response to an irritating process that makes the afferent input work incorrectly and then forms a new connection of the dendrites resulting in inappropriate afferent input response, such as the laryngeal adductor reflex (LAR) [43, 51].

The LAR is also called the glottal closure reflex, which is a protective mechanism of the larynx to prevent material entering the upper respiratory system. The muscle that plays a role in this mechanism is the thyroarytenoid muscle, which responds to mechanical stimuli and chemical irritants in the laryngeal mucosa. LAR is mediated by the brain stem, which is an involuntary reflex innervated by the internal branch of the superior laryngeal nerve as an afferent and the recurrent laryngeal nerve as an efferent component [51]. In patients with LAR disorder, laryngeal hypersensitivity, chronic cough, and vocal cord dysfunction also might be found [43].
Episodes of PCVM can be triggered by the irritation of the laryngeal mucosa, as in tobacco abuse, allergic laryngitis, viral illness, and untreated sleep apnea, making treatment more difficult. Irritation of the vocal cords can be directly caused by rhinosinusitis and the resulting postnasal drip. However, inflammation can also occur indirectly due to the release of inflammatory mediators [47]. Patients with PVCM usually present with shortness of breath (stridor or wheezing) that appears suddenly and worsens rapidly to apnea and aphonia. Complaints appear for a few seconds but can continue for several minutes before disappearing. Attacks can occur at any time, even during sleep. Complaints of wheezing are usually more common during inspiration than expiration [46, 47].

In acute attacks, patients with PVCM can show signs such as upper airway obstruction, namely shortness of breath, stridor, respiratory muscle retraction, difficulty in speaking, and anxiety and even loss of consciousness. Some typical symptoms such as a feeling of suffocation in the neck or throat, more difficult to inhale than exhale, partial response or no response to inhalation [47]. At the time of an acute attack, patients with PVCM may show signs such as upper airway obstruction, namely shortness of breath, stridor, respiratory muscle retraction, difficulty in speaking, and anxiety and even loss of consciousness [52]. Auscultation should be performed on the neck and lungs to exclude lower respiratory disorders, i.e., asthma and other pulmonary diseases. On auscultation of the neck, wheezing or stridor will be found, especially during inspiration [53].

The diagnosis of PVCM requires flexible fiber-optic laryngoscopy as the gold standard, and vocal cord movement is observed when breathing. Typical findings in PVCM are paradoxical movement of the vocal cords, adduction on inspiration, and narrowing of the glottis during acute attacks. Complete adduction of the vocal cords during inspiration with or without formation of a small posterior diamond shaped, known as posterior chink, is the pathognomonic of PVCM. These findings may also be present during expiration [47, 53]. The differential diagnosis of PVCM is laryngeal edema, vocal cord paresis, laryngeal or tracheal neoplasms, subglottic stenosis, aspiration of foreign bodies, laryngomalacia or tracheomalacia, laryngeal granulomas, and laryngeal spasm [54].

Management of PVCM requires a multidisciplinary approach. Mentally supporting the patient or reassurance can reduce symptoms significantly. The patient is directed to inhale slowly through the nose and exhale through the mouth [46, 55]. There is no standard pharmacologic management of PVCM besides that used to control comorbid conditions. Medical therapy such as benzodiazepines can also be given to patients with PVCM who have an acute attack. The management of chronic PVCM through breathing exercises, supportive counseling, can be effective. Laryngeal control therapy (LCT) given by a speech pathologist can reduce symptoms in the long term [55]. Proton pump inhibitor therapy and lifestyle modifications can also be given to patients with PVCM associated with an irritated larynx due to gastric acid reflux. The recommended PPI that can be given is omeprazole 20 mg or lansoprazole 30 mg 2 times per day for 3–6 months or for child dose of 1 mg/kg/time given two times per day [55].

5. Conclusions

Altered vagal nerve activity caused by impaired autonomic regulation may appear to play a role in the pathogenesis of laryngeal clinical manifestation and have an
impact in person’s quality of life. This often leads to high economic and social burdens on patients due to delay in diagnosis, numerous tertiary care referrals, and lack of effective medications. The degree of dysfunction may have correlation with disease severity. Impaired autonomic regulation in the larynx was thought to be responsible for clinical entities, such as laryngopharyngeal reflux (LPR), sleep-disordered breathing (SDB), chronic cough (CC), and paradoxical vocal cord movement (PVCM). Treating the underlying specific conditions and symptoms are needed, and research with a large series of subjects and application of autonomic modulation as a therapeutic target is recommended in the future.
References


Updates on Laryngology


[26] Chen LF, Chang CC, Tzeng NS. Depression, anxiety, and heart rate variability: A case-control study in Taiwan. Journal of Medical Sciences. 2014;34:9


[42] Pacheco A, Cobeta I. Refractory chronic cough, or the need to focus on the relationship between the larynx and the esophagus. Cough. 2013;9(1):1-7


[55] Holley D, Mendez A, Donald C. Paroxysmal laryngospasm: Episodic closure of the upper airway. JAAPA. 2019;32(2):31-34. DOI: 10.1097/01.JAA.0000552724.72939.4c