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Autonomic Nerve Dysfunction in Patient with Laryngopharyngeal Reflux: The Study of Heart Rate Variability Finding, Risk of Having Sleep Disordered Breathing, and It's Inclination Towards Anxiety and Depression

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Abstract

Background: Altered vagal nerve activity caused by impaired autonomic regulation was thought to be responsible for esophageal sphincter dysfunction in Gastroesophageal Reflux Disease (GERD). Yet the role of Autonomic Nerve Dysfunction (AND) in the pathogenesis of Laryngopharyngeal Reflux (LPR) remains unclear. LPR and AND is also thought to be associated with other entities, such as anxiety-depression and Sleep-Disordered Breathing (SDB).

Aim: To determine the proportion and characteristics of AND based on Heart Rate Variability (HRV) analysis in patients with LPR and control group. Other risk factors that might contribute to the incidence of LPR and AND, such as the risk of SDB and anxiety-depression, were also assessed. Methods: Forty subjects were enrolled in the LPR group and 33 subjects as control. Fiberoptic laryngoscopy, HRV analysis, SDB risk assessment (ESS and PSQI questionnaire), and anxiety-depression status (HADS questionnaire) were performed on both groups.

Result: The difference in proportion of AND between LPR and the control group was significant (p=0.001). The proportion of AND in the LPR group was 71.4%. The difference in the risk of SDB based on ESS and PSQI was significant in the LPR group compared to control group ($p \leq 0.05$). The status of anxiety based on HADS in the LPR group was also significantly different compared to control (p=0.001).

Conclusion: The proportion of AND in the LPR group was greater than control. HRV findings were characterized by reduction of SDNN and LF/HF ratio, with the domination of parasympathetic properties. The risk of SDB and the inclination towards anxiety-depression were related to LPR and AND.

Keywords: Autonomic nerve dysfunction; Heart rate variability; HRV; LPR; SDB

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Introduction

Laryngopharyngeal Reflux (LPR) can be defined as an abnormal retrograde flow of gastric content into the laryngopharynx and upper aerodigestive tract. LPR is a common otolaryngologic disease; more than 10% of patients come to ENT specialists with LPR symptoms. The incidence of LPR in our hospital's outpatient clinic is estimated around 10% to 15%. Establishing a diagnosis of LPR can be challenging as symptoms can be nonspecific, lack of pathognomonic findings, and have similar clinical manifestations with other diseases. Therefore, LPR is often over-diagnosed and over-treated. It will not only affect the patient quality of life but also increase the health cost burden [1,2].

Pathogenesis of LPR has not been conclusively explained; with current mechanism proposed is transient relaxation of the upper esophageal sphincter regulated by the autonomic vagal nerve.

Altered vagal nerve activity caused by impaired autonomic regulation was thought to be responsible for lower esophageal sphincter dysfunction in Gastroesophageal Reflux Disease (GERD). The role of autonomic nerve dysfunction in the pathogenesis of LPR remains unclear. The association of LPR with autonomic nerve dysfunction is also thought to be associated with other clinical entities, such as anxiety-depression status and the incidence of sleep-disordered breathing [3-5].

A study by Floras et al. [6] revealed that there is a relationship between the incidence of Sleep-Disordered Breathing (SDB) and autonomic dysregulation. There is evidence obtained from studies of neuromuscular sympathetic nerve activity, catecholamine levels, and analysis of Heart Rate Variability (HRV), suggesting that in patients with obstructive sleep apnea, hypoxia and apnea trigger a cascade that increases efferent sympathetic activity during sleep, where the modulating center is at the nucleus of the solitary tract in the hypothalamus. Patients with anxiety and depression also suffer from reflux-related symptoms, which are often found in daily practice of otolaryngologists. Oyer et al. [7] proved that the population with LPR has a higher tendency to have anxiety based on higher Hospital Anxiety Depression Scale (HADS) score compared to the healthy population. Oyer et al. [7] showed that the prevalence of anxiety in patients with LPR reached 40% and only 6% in the control group [6-8].

Therefore, this study aimed to explore the role and evaluate the relationship between autonomic nerve dysfunction and LPR. We aimed to determine the proportion and characteristics of autonomic nerve dysfunction based on the HRV findings. Other risk factors that may contribute to the incidence of LPR and autonomic nerve dysfunction, such as the risk of having SDB and anxiety-depression status, were also assessed.

Materials and Methods

This was a comparative cross-sectional study that compares two HRV findings between LPR and non-LPR groups. This study has been approved by the Health Research Ethics Committee Universitas Indonesia and Dr. Cipto Mangunkusumo Hospital concerning the protection of human rights and welfare in medical research. Patients with suspected LPR who visited our otolaryngology outpatient clinic from August 2021 to October 2021 were enrolled using the consecutive sampling method. Informed written consent was obtained from all subjects prior to any procedure. The first group was the patient group (40 subjects) diagnosed with LPR, who had a Reflux Symptom Index (RSI) ≥ 13 and Reflux Finding Score (RFS) ≥ 7. The other group was the control group (33 subjects) without subjective symptoms (RSI<13). The RSI is a 0 to 5 point scale that grades the following symptoms: (1) excess throat mucus or postnasal drip, (2) throat clearing, (3) sensation of something sticking or a lump in the throat, (4) troublesome or annoying cough, (5) hoarseness or voice problems, (6) coughing after eating or lying down, (7) difficulty of swallowing, (8) breathing difficulties or choking spells, (9) heartburn, chest pain, indigestion, or stomach acid coming up [9]. While the RFS is an 8-item clinical severity scales for assessing laryngoscopic findings. Eight LPR-associated findings were rated on a scale from 0 to 4: Subglottic edema, vocal fold edema, ventricular obliteration, posterior commissure hypertrophy, erythema, diffuse laryngeal edema, granuloma, and thick endolaryngeal mucus. Based on the analysis by Belafsky et al. [9-10] one can be 95% certain has LPR with RSI greater than 13 and RFS greater than 7 [10]. Those who had body mass index >31 kg/m^2, history of neurological disorders, thyroid disorders, malignancy, history of trauma/surgery in the neck region, history of heart rhythm abnormality (arrhythmia), uncontrolled diabetes, and consuming systemic drugs that have a potential effect on the autonomic nervous system, such as; cholinergic agonist/antagonist, adrenergic agonist/antagonist, or antiemetics, and proton pump inhibitor within 2 weeks prior to examination were excluded. They also denied caffeine intake 24 h prior to the study.

All enrolled subjects were interviewed and asked to complete the Reflux Symptom Index (RSI) questionnaire based on their complaints. Subjects then underwent fiberoptic laryngoscopy examination, using Olympus Viscera 0TV-S7 video scope, to complete Reflux Finding Score (RFS) by another otolaryngologist blinded to the result of RSI (Examiner: EZKR or SYMH). Both the LPR and control group received the heart rate variability analysis using HRV Analyzer Medicore SA-3000P with Pulse Photoplethysmography (PPG) method. Assessment of autonomic nerve dysfunction was assessed by analyzing the HRV parameters which represent the time domain and frequency domain. SDNN (Standard Deviation Normal to Normal) was a parameter we used in the time domain analysis, while LF/HF (Low Frequency/High Frequency) ratio was a parameter that was commonly used to represent frequency domain analysis. Autonomic nerve dysfunction was defined if there was a reduction in SDNN (≤ 40) and/or deviation in the LF/HF ratio (≤ 0.5 for parasympathetic dominant subtype or ≥ 2.0 for sympathetic dominant subtype) [11].

The risk of having SDB and the anxiety-depression status were evaluated by Epworth Sleepiness Scale (ESS), Pittsburgh Sleep Quality Index (PSQI), and Hospital Anxiety Depression Scale (HADS) questionnaires. ESS is a subjective questionnaire measuring sleepiness based on the subject's complaints in the morning and afternoon (daytime sleepiness). This consists of eight questions with each question has a grading quantification from 0 to 3. Cut off value used for ESS was 8. PSQI is a subjective questionnaire that detects sleep disorder by measuring sleep quality in the last one month through the assessment of sleep quality, sleep latency, sleep duration, effective sleep duration in bed, sleep disturbances, consumption of sleeping pills, and impaired concentration in the morning and afternoon. The questionnaire consists of 17 questions with each question has a grading quantification from 0 to 3. Cut off value used for PSQI was 6. HADS is a questionnaire conducted using the self-assessment method as an instrument to detect anxiety and depression in an outpatient hospital setting. The questionnaire consists of 14 questions which were divided into seven subscales for anxiety and seven subscales for assessing depression. Cut off value used for this questionnaire was 8.

All data were statistically analyzed using the SPSS 23.0 statistical software. The quantitative data are expressed as mean ± SD or median (min-max) and categorical variables as percentages. Chi-square test or independent T-test were used to compare parametric variables and Mann-Whitney test or Fisher-Exact test was used for comparing nonparametric variables between the LPR and control group. A $p<0.05$ was considered statistically significant.

Results

The demographic characteristics of the patients are summarized in Table 1. A total of 73 subjects were included in this study, 19 men (26%) and 54 women (74%). The distribution of age between the two groups range from 23 to 60 years old, with the same median (31 years

Table 1: Demographic characteristics in LPR and control group.

Variable	LPR	Non LPR	p
Gender*			
Female	28 (70%)	26 (78.7%)	0.39
Male	12 (30%)	7 (21.1%)	
BMI**	23.52 (17.09 to 29.50)	22.38 (16.02 to 29.69)	0.38
BMI Category*			
≤ 18.5 kg/m^2	5 (12.5%)	3 (9.1%)	
18.5 to 22.9 kg/m^2	11 (27.5%)	17 (51.5%)	
23 to 24.9 kg/m^2	8 (20%)	2 (6.1%)	
25 to 30 kg/m^2	16 (40%)	11 (33.3%)	
Age (years)**	31 (21 to 60)	31 (25 to 45)	0.38
Age Category*			
<40 years	27(67.5%)	29(87.8%)	
≥ 40 years	13(32.5%)	4(12.2%)	

*Categorical data is presented in n (%) and analyzed using Chi-Square
**Numerical data with non-normal distribution presented in the median (min-max) were analyzed using the Mann-Whitney test

Table 2: Comparison of SDNN and LF/HF ratio in LPR and control group.

Variable	LPR	Non LPR	P
SDNN*	41.14 ± 15.39	46.88 ± 20.12	0.17
LF/HF**	0.57 (0.06 to 3.70)	1.04 (0.24 to 3.36)	0.15

*Numerical data with normal distribution presented in mean (SD) analyzed using independent T-test
**Numerical data with non-normal distribution presented in the median (min-max) analyzed using the Mann-Whitney test

old) in both the LPR group and non-reflux group. There were no statistical differences in age and sex between the two groups (p>0.05).

SDNN, as it was representing the basic function of autonomic neuroregulation, 11 were lower in the LPR group than the control group. The mean value in the LPR group was 41.14 ± 15.39, while in the control group was 46.88 ± 20.12. The median value of LF/HF ratio, which represents sympathetic–vagal balance,11 was also lower in the LPR group than the control group, 0.57 (0.06 to 3.70) and 1.04 (0.24 to 3.36) consecutively. However statistical analysis showed that there was no significant difference between two groups both in SDNN or LF/HF ratio (Table 2).

The incidence of autonomic nerve dysfunction was then assessed with HRV analysis in both the LPR group and control group using the categorization of SDNN and LF/HF ratio. A total of 30 subjects (71.4%) in the LPR group were found to have an autonomic nerve dysfunction, while in the control group was only 12 subjects (28.6%). Types of autonomic nerve dysfunction were also analyzed by interpreting LF/HF ratio. The most common type of autonomic nerve dysfunction in the LPR group was parasympathetic dominant (21 subjects), while the other 9 subjects were sympathetic dominant, and the remaining 10 subjects had balanced autonomic nerve functions (Table 3).

Analysis of Sleep-Disordered Breathing (SDB) was done using Epworth Sleepiness Scale (ESS) and Pittsburgh Sleep Quality Index (PSQI). The ESS and PSQI assessments were conducted on subjects both in LPR and control groups. It reveals that the median value of ESS and PSQI were greater in the LPR group compared to the control group (p ≤ 0.05) (Table 4).

Analysis with nominal categorization was carried out to identify

Table 3: Incidence of autonomic nerve dysfunction in LPR and control group.

Variable	LPR (n=40)	Non LPR (n=33)	p
Autonomic nerve dysfunction*			
Yes (n=42)	30 (71.4%)	12 (28.6%)	0.001
No (n=31)	10 (32.3%)	21 (67.7%)	
Type of autonomic			
dysfunction*	21 (72.4%)	8 (27.6%)	0.083
Parasympathetic dominant	9 (69.2%)	4 (30.8%)	
Sympathetic dominant			

*Categorical data is presented in n (%) and analyzed using Chi-Square

Table 4: ESS and PSQI value in LPR and control group.

Variable	LPR	Non LPR	p
ESS*	8.00 (1.00- to 24.00)	4.00 (0.00 to 17.00)	0
PSQI**	6.00 (1.00 to 14.00)	5.00 (2.00 to 9.00)	0

*Numerical data with normal distribution presented in mean (SD) analyzed using independent T-test
**Numerical data with non-normal distribution presented in the median (min-max) analyzed using the Mann-Whitney test

Table 5: LPR and SDB Based on ESS.

	SDB	Non SDB	p	OR (95% CI)
LPR	21 (52.5%)	19 (47.5%)	0.001*	6.18 (1.98 to 19.27)
Non LPR	5 (15.2%)	28 (84.8%)		
Total	26 (35.6%)	47 (64.4%)		

*Analyzed using Chi-Square

Table 6: Autonomic nerve dysfunction and SDB based on ESS.

	SDB	Non SDB	p	OR (95% CI)
Dysfunction	19 (45.2%)	23 (54.8%)	0.046*	2.83 (1.00 to 7.99)
Non-Dysfunction	7 (22.6%)	24 (77.4%)		
Total	26 (35.6%)	47 (64.4%)		

*Analyzed using Chi-Square

the proportion of daytime sleepiness and sleep impairment in LPR and control group. Statistics showed a significant difference in ESS variable between the LPR group compared to the control group (p=0.001) with OR 6.18 (CI 95% 1.98 to 19.27). These results conclude that LPR patients might have 6.18 times greater risk of experiencing daytime sleepiness as a manifestation of their SDB (Table 5). Correlation between ESS findings and the incidence of autonomic nerve dysfunction also showed a statistically significant difference between two groups (p=0.046) with OR 2.83 (CI 95% 1.01 to 7.99) (Table 6). These results conclude that the incidence of daytime sleepiness was statistically associated with the incidence of autonomic nerve dysfunction; patients with autonomic nerve dysfunction might have 2.83 times greater risk of experiencing daytime sleepiness.

A significant difference was also found in PSQI variable between LPR compared to the control group (p=0.001) with OR 8.66 (CI95% 2.96 to 25.37) (Table 7). These results revealed that LPR patients might have an 8.66 times greater risk of experiencing impaired sleep quality based on PSQI. PSQI findings were estimated to correlate with the incidence of autonomic nerve dysfunction as well, it showed a significant difference between two groups (p=0.042) with OR 2.67 (CI 95% 1.02 to 6.98) (Table 8). The analysis showed that the incidence of sleep impairment was significantly associated with the incidence of autonomic nerve dysfunction, and patients with autonomic nervous dysfunction had a 2.67 times greater risk of experiencing sleep impairment.

Table 7: LPR and sleep impairment based on PSQI.

	Sleep Impairment	Normal	P	OR (95% CI)
LPR	28 (70%)	12 (30%)	0.001*	
Non-LPR	7 (21.2%)	26 (78.8%)		8.66 (2.96 to 25.37)
Total	35 (47.9%)	38 (52.1%)		

*Analyzed using Chi-Square

Table 8: Autonomic nerve dysfunction and sleep impairment based on PSQI.

	Sleep Impairment	Normal	p	OR (95% CI)
Dysfunction	25 (59.5%)	17 (40.5%)	0.042*	2.67(1.02 to 6.98)
Non-Dysfunction	11 (35.5%)	20 (64.5%)		
Total	36 (49.3%)	37 (50.7%)		

*Analyzed using Chi-Square

Table 9: HADS score in LPR and control group.

Variable	LPR	Non LPR	p
HADS-Anxiety**	5.5 (0.00 to 18.00)	4.00 (0.00 to 9.00)	0.01
HADS-Depression**	2.5 (0.00 to 19.00)	2.00 (0.00 to 7.00)	0.06

Anxiety-depression trend analysis was carried out by assessing the anxiety and depression subscales in HADS questionnaire. The median value of the HADS-Anxiety Subscale in the LPR group was 5.5 (0.00 to 18.00) while in the control group was 4.00 (0.00 to 9.00). These results show that the median value of the HADS-Anxiety subscale in the LPR was greater than in the control group and statistically significant. Meanwhile, the median value of the HADS-Depression subscale did not show any significant difference between the LPR and control group (Table 7). Nominal categorization analysis was also conducted to identify the proportion of depression in the LPR and control group. A significant difference was found in both HADS subscales for anxiety and depression. These analyses showed that anxiety and depression may have a relationship with the incidence of LPR.

Discussion

The distribution of age between two groups in this study ranged from 23 to 60 years old, with a similar median of age (31 years) in both the LPR and control groups. A cohort study of Belafsky et al. [10] reported that the mean age of LPR patients was 40 ± 12 years. There was more female subject in the LPR group than male subject; however, the difference was not statistically significant. This was similar to Koufmann et al. [13] which stated that there was no significant difference in the LPR population based on gender, age, and country of residence.

The distribution of BMI ranged from 16.02 kg/m^2 to 30.07 kg/m^2 in both groups, however, it could be due to the exclusion of subjects who had BMI more than 31 kg/m^2. This limitation was used to minimize research bias related to BMI factors in the pathophysiology of LPR. Lechien et al. [14] reported that LPR occurred with more severe clinical symptoms in a group of obese patients. The most common reflux symptoms in obese patients are difficulty in swallowing, regurgitation, and heartburn. The existence of these three symptoms strengthens the hypothesis that LPR and GERD are more common in obese patients. The high prevalence of GERD in the obese group has been found in many studies regarding the relationship between central obesity, LES insufficiency, and the occurrence of TLESR [14].

Heatley et al. [15] firstly described the role of vagal nerve activity in patients with GERD by observing the change in heart rate variability during inspiration and expiration. This study found that one-quarter of these subjects had impaired vagal control function. In 1991, Cunningham et al. [16] found a high prevalence of autonomic nerve dysfunction among patients with reflux esophagitis through the assessment of ambulatory pH recordings. The delay in esophageal transit and abnormal peristaltic was probably caused by the tension abnormality of vagal tone. In line with Cunningham et al. [16] Lee et al. [17] found that the autonomic tone of patients with reflux esophagitis, even asymptomatic, was lower than patients in NERD (Non-Esophagitis Reflux Disease) group. Dobrek et al. [18], also reported that patients with GERD and NERD showed an abnormal resting HF and LF compared to healthy individuals in their HRV analysis. These studies above proved that the autonomic nervous system plays an important role in regulating the gastrointestinal system, dysfunction of autonomic nerve will lead to the impairment of esophageal peristaltic, esophageal sphincter function, and gastric motility. These findings also strengthen the hypothesis which stated that transient esophageal sphincter relaxation might be associated with autonomic nerve dysfunction and plays an important role in the occurrence of reflux [15-18].

Our study had successfully proven that the proportion of autonomic nerve dysfunction, which was assessed through the analysis of HRV, was found higher in LPR than in the control group. A total of 30 subjects (71.4%) in the LPR group experienced autonomic nerve dysfunction. Through the analysis of the LF/HF ratio, we found that the most common type of autonomic nerve dysfunction in the LPR group was parasympathetic dominant (72.4% of all LPR subjects). Hyper parasympathetic activity in patients with LPR might be associated with the incidence of transient esophageal sphincter relaxation since parasympathetic tone and GABA (Gama Amino Butyric Acid) have an inhibitory role in controlling sphincter relaxation. Dobrek et al. [18], Lee et al. [17], and Chen et al. [19] reported a reduction in SDNN and LF/HF ratio in the reflux group which is actually in line with our findings and most of the other studies. It could strengthen the hypothesis that autonomic nerve dysfunction also plays a role in the pathogenesis of LPR, not only GERD. Therefore, vagal autonomic dysfunction might also contribute to the abnormalities of esophageal peristaltic and the function of the esophageal sphincter [17-19].

The reduction of SDNN that we found in our LPR subjects and not statistically significant were similar with the findings of following studies by Lee et al. [17], Huang et al. [20], and Wang et al. [15] The insignificant finding of this variable might be due to the type of autonomic nerve dysfunction in both LPR and control group were varying in regards to the type of autonomic nerve domination. This could be used as a consideration in making a clinical decision regarding HRV interpretation, where the frequency domain appears to have a more consistent clinical correlation with autonomic reflux than time-domain parameter [15-20].

The risk of having SDB in this study was assessed using Epworth Sleepiness Scale (ESS) and Pittsburgh Sleep Quality Index (PSQI) questionnaires. Referring to Rosenthal [21] and Dolan [21] research findings who found out that sensitivity of ESS was up to 78% with cut-off values of 8 in identifying OSA based on the apnea-hypopnea incident. Eskizmiir [22] and Kezirian [22] stated that inflammation caused by reflux could cause dysfunction of negative intraluminal airway pressure and interfere laryngeal sensory reflexes, increasing upper airway collapsibility. Considering that the impairment of upper airway mucosal sensory receptors could induce changes in the neural control of pharyngeal dilator muscle, LPR episodes may contribute to

the progression of OSA severity [22]. Magliulo et al. [23] found that 45% of patients with OSA have LPR. This study found that patients with LPR tend to have higher ESS and PSQI scores than the control group.

Another study also found that the incidence of daytime sleepiness and impaired sleep quality was associated with the incidence of autonomic nerve dysfunction. Urbanik et al. [24] reported that the incidence of OSA could be a predictor for HRV reduction. This study used 24-h pH monitoring and found a significant association between low SDNN values with the incidence of OSA. Research also found that the dominant activity of the sympathetic nerve during sleep occurs in the REM and N2 sleep phase which was proved by the high LF/HF ratio in spectral analysis. SDNN findings were also found to have a negative correlation with an Apnea-Hypopnea Index (AHI) in PSG examination. The higher AHI values, the lower SDNN score [24]. Palma et al. [25] obtained evidence from their studies of neuromuscular sympathetic nerve activity, catecholamine levels, and analysis of HRV, suggesting that in patients with obstructive sleep apnea, hypoxia and apnea will trigger a cascade that increases efferent sympathetic activity during sleep. When it lasted over a while, it will induce chronic sustained elevation of sympathetic outflow regulatory points during wakefulness. This has implications for a higher risk of chronic hypertension, coronary artery disease, and cerebrovascular disease [25].

During sleep, human is not experiencing the process of eating or chewing, it will reduce the production of saliva and neuromuscular coordination. This will be lengthening the esophageal acid clearance process and result in prolonged contact between the irritant reflux and the esophageal mucosa. Although the incidence of TLESR decreased during sleep, it had been observed to occur during cortical arousals in patients with SDB. Gottesmann found an association between sleep impairment to the incidence of autonomic nerve dysfunction through the modulation of GABA [26]. It was believed that TLESR is vagal-mediated and could be inhibited by the activation of GABA-b receptors. Lang et al. [27] found another reflex pathway, namely Esophageal Distention Reflex (EDR), which is involved in the transient esophageal relaxation mechanism that could occur even when patient was not swallowing. Sleep impairment in patients with GERD had also been shown to induce changes in visceral perception and pain threshold. Schey et al. [28] in their study using actigraphy found that GERD patients with sleep impairment suffered from acid-induced chest pain after three nights of sleep deprivation [24]. Gottesman et al. [23] also emphasized that low levels of GABA in CNS will affect sleep quality. Those will have implications in reducing slow waved sleep and increasing paradoxical sleep (fragmentation and arousals) [26-28].

Categorization analysis comparing the proportion of anxiety and depression in the LPR and control group also showed a significant difference. These results were consistent with what was found in the studies of Cheung et al. [8] and Oyer et al. [7] that the prevalence of anxiety in LPR reached 40% and only 6% was found in the healthy control group. However, there was a different result in the study of Hoon Jo et al. [29], who found more episodes of depression in the reflux group through multivariate analysis. Researchers assumed that stress and anxiety were associated with vagal modulation impairment. Other studies also mention that those with lower HRV values had been shown to have anxiety or depressive disorders [6,7,29]. Whether or not mental status influences the LPR process has seldom been studied. As in our daily practice, conditions of anxiety are frequently observed in LPR patients. This was also shown in our study. However, whether it was the primary cause or secondary consequence of LPR cannot be proven at this time.

Although few studies have investigated the relationship between GERD and autonomic function, to the best of our knowledge this is the first study to identify the relationship between LPR, autonomic nerve dysfunction, risk of having SDB, and its inclination towards anxiety-depression. We had successfully found that autonomic nerve dysfunction might play a role in the pathomechanism of LPR. The limitation of this study is regarding the use of fiberoptic laryngoscopy for the diagnosis of LPR. Despite many debates regarding the use of MCII-pH monitoring in the diagnosis of LPR, this modality still remains the trusted gold standard for detecting reflux events. We did not use this modality considering the limitations of the tools in our institution and its high cost, as well as considering the validity and reliability of the RSI and RFS which were good enough to establish the diagnosis of LPR in several previous studies [9-10]. The assessment of SDB and anxiety-depression status in this study was also still limited to the subjective assessments, even though we have used measurement instruments that have been validated and were believed to have good reliability [12]. We did not use Polysomnography (PSG) to establish the diagnosis of OSA in our subjects. This is due to the unavailability of these tools in our institution and the high cost of accessing these examinations. Therefore, in this study, we emphasize more on the clinical phenotypes and/or the risk of developing SDB related to LPR and autonomic nerve dysfunction.

Conclusion

This study proved that the incidence of autonomic nerve dysfunction in the LPR group was higher and statistically significant compared to the control group. We discovered that HRV findings in the LPR group were characterized by the reduction of SDNN values and LF/HF ratio, with the domination of parasympathetic properties. This study also discovered that patients with LPR and autonomic nerve dysfunction have a greater risk of experiencing anxiety-depression and impaired sleep quality or SDB compared to the control group. Enrollment with a large series of subjects and application of autonomic modulation as a therapeutic target for patients with LPR is recommended in the future to expand this promising research.

References

1. Francis DO, Rymer JA, Slaughter JC, Choksi Y, Jiramongkolchai P, Ogbeide E, et al. High economic burden of caring for patients with suspected extra esophageal reflux. Am J Gastroenterol. 2013;108(6):905-11.
2. Ford CN. Evaluation and management of laryngopharyngeal reflux. JAMA. 2005;294(12):1534-40.
3. Krowicki ZK. Role of selected peptides in the vagal regulation of gastric motor and endocrine pancreatic function. J Physiol Pharmacol. 1996;47(3):399-409.
4. Dobrek L, Nowakowski M, Mazur M, Herman RM, Thor PJ. Disturbances of the parasympathetic branch of the autonomic nervous system in patients with Gastroesophageal Reflux Disease (GERD) estimated by short-term heart rate variability recordings. J Physiol Pharmacol. 2004;55(suppl 2):77-90.
5. Lee YC, Wang HP, Lin LY. Heart rate variability in patients with different manifestations of gastroesophageal reflux disease. Auton Neurosci. 2004;116(1-2):39-45.
6. Floras JS. Sympathetic nervous system in patients with sleep related

breathing disorders. Curr Hypertens Rev. 2016;12(1):18-26.

7. Oyer SL, Anderson LC, Halum SL. Influence of anxiety and depression on the predictive value of the reflux symptom index. Ann Otol Rhinol Laryngol. 2009;118(10):687-92.
8. Cheung TK, Lam PK, Wei WI. Quality of life in patients with laryngopharyngeal reflux. Digestion. 2009;79(1):52-7.
9. Belafsky PC, Postma GN, Koufman JA. Validity and reliability of the Reflux Symptom Index (RSI). J Voice. 2002;16(2):274-7.
10. Belafsky PC, Postma GN, Koufman JA. The validity and reliability of the reflux finding score (STR). Laryngoscope. 2001;111(8):1313-7.
11. Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology. Circulation. 1996;93(5):1043-65.
12. Groome M, Cotton JP, Borland M, McLeod S, Johnston DA, Dillon JF. Prevalence of laryngopharyngeal reflux in a population with gastroesophageal reflux. Laryngoscope. 2007;117(8):1424-8.
13. Koufman JA, Amin MR, Panetti M. Prevalence of reflux in 113 consecutive patients with laryngeal and voice disorders. Otolaryngol Head Neck Surg. 2000;123(4):385-8.
14. Lechien JR, Bobin F, Muls V, Saussez S, Hans S. Laryngopharyngeal reflux disease is more severe in obese patients: A prospective multicenter study. Laryngoscope. 2021;131(11):E2742-8.
15. Wang AM, Wang G, Huang N, Zheng YY, Yang F, Qiu X, et al. Association between laryngopharyngeal reflux disease and autonomic nerve dysfunction. Eur Arch Otorhinolaryngol. 2019;276(8):2283-7.
16. Cunningham KM, Horowitz M, Riddell PS. Relations among autonomic nerve dysfunction, oesophageal motility, and gastric emptying in gastro-oesophageal reflux disease. Gut. 1991;32(12):1436-40.
17. Lee YC, Wang HP, Lin LY. Heart rate variability in patients with different manifestations of gastroesophageal reflux disease. Auton Neurosci. 2004;116(1-2):39-45.
18. Dobrek L, Nowakowski M, Mazur M, Herman RM, Thor PJ. Disturbances of the parasympathetic branch of the autonomic nervous system in patients with Gastroesophageal Reflux Disease (GERD) estimated by short-term heart rate variability recordings. J Physiol Pharmacol. 2004;55(suppl 2):77-90.
19. Chen CL, Orr WC, Yang CC, Kuo TB. Cardiac autonomic regulation differentiates reflux disease with and without erosive esophagitis. Scand J Gastroenterol. 2006;41(9):1001-6.
20. Huang WJ, Shu CH, Chou KT, Wang YF, Hsu YB, Ho CY, et al. Evaluating the autonomic nervous system in patients with laryngopharyngeal reflux. Otolaryngol Head Neck Surg. 2013;148(6):997-1002.
21. Rosenthal LD, Dolan DC. The Epworth sleepiness scale in the identification of obstructive sleep apnea. J Nerv Ment Dis. 2008;196(5):429-31.
22. Eskiizmir G, Kezirian E. Is there a vicious cycle between obstructive sleep apnea and laryngopharyngeal reflux disease? Med Hypotheses. 2009;73(5):706-8.
23. Magliulo G, Iannella G, Polimeni A, De Vincentiis M, Meccariello G, Gulotta G, et al. Laryngopharyngeal reflux in obstructive sleep apnoea patients: Literature review and meta-analysis. Am J Otolaryngol. 2018;39(6):776-80.
24. Urbanik D, Gać P, Martynowicz H, Poręba M, Podgórski M, Negrusz-Kawecka M, et al. Obstructive sleep apnea as a predictor of reduced heart rate variability. Sleep Med. 2019;54:8-15.
25. Palma JA, Iriarte J, Fernandez S, Valencia M, Alegre M, Artieda J, et al. Characterizing the phenotypes of obstructive sleep apnea: Clinical, sleep, and autonomic features of obstructive sleep apnea with and without hypoxia. Clin Neurophysiol. 2014;125(9):1783-91.
26. Gottesmann C. GABA mechanisms and sleep. Neuroscience. 2002;111(2):231-9.
27. Lang IM, Medda BK, Shaker R. Mechanism of UES relaxation initiated by gastric air distension. Am J Physiol Gastrointest Liver Physiol. 2014;307(4):G452-8.
28. Schey R, Dickman R, Parthasarathy S, Quan SF, Wendel C, Merchant J, et al. Sleep deprivation is hyperalgesic in patients with gastroesophageal reflux disease. Gastroenterology. 2007;133(6):1787-95.
29. Joo YH, Song YS, Pae CU. Relationship between depression and laryngopharyngeal reflux. Psychiatry Investig. 2017;14(2):226-229.