

Autonomic function based on heart rate variability in children with laryngopharyngeal reflux

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Abstract

Background The pathophysiology of laryngopharyngeal reflux (LPR) is yet to be completely understood, but autonomic dysregulation may have a role in the opening of esophageal sphincters controlled by the parasympathetic nervous system, especially the vagal nerve. Autonomic dysregulation can be detected through heart rate variability (HRV). Currently, studies that identify autonomic nerve dysfunction through HRV in LPR patients are few, especially in the pediatric population.

Objective To identify autonomic nerve dysfunction in pediatric LPR patients with HRV components.

Methods This study involved 74 pediatric patients, 35 with LPR and 39 without LPR, from Dr. Cipto Mangunkusumo Hospital, Jakarta, from September 2023 to April 2024. Diagnostics for LPR included endoscopy and *Reflux Symptom and Sign Instrument* (RSSI) scoring, while measurement of autonomic nerve dysfunction was determined by HRV. The HRV was evaluated by standard deviation normal to normal (SDNN) assessment of the heart's interbeat interval (IBI) and low frequency/high frequency ratio (LF/HF).

Results Neither HRV measurement, SDNN or LF/HF, were significantly associated with autonomic nerve dysfunction in pediatric patients with LPR.

Conclusion Autonomic nerve dysfunction measured by HRV was not associated with LPR in pediatric patients. [Paediatr Indones. 2025;65:273-8; DOI: <https://doi.org/10.14238/pi65.4.2025.273-8>].

Keywords: *laryngopharyngeal reflux; Reflux Symptom and Sign Instrument (RSSI); autonomic nerve dysfunction; heart rate variability*

Laryngopharyngeal reflux (LPR) manifests as pathological mucosal inflammation of the upper respiratory tract involving reflux of gas and/or gastric and duodenal fluid.¹ The inflammatory reaction is caused by direct irritation from pepsin, trypsin, and other enzymatic molecules. Duodenal fluid also irritates the lower esophageal mucosa, stimulates chemoreceptors, and triggers the coughing reflex, throat clearing, and hypersecretion of laryngopharyngeal mucus.²

The most frequent complaints of LPR are foreign object sensation, stuffiness, hoarse voice, and mucus hypersecretion.³ The prevalence of each sign and symptom varies, but they are found in over 70% of LPR patients. These symptoms are not specific and can manifest in other respiratory tract diseases, making LPR difficult to diagnose based on clinical examinations alone. Additionally, the prevalence of these symptoms varies based on sex and age, with dysphonia being more common in women due to

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Submitted September 17, 2024. Accepted October 14, 2024.

anatomical, histological, and functional factors, for example.⁴

The pathophysiology of LPR is not yet fully understood. Other than pepsin, various enzymes play a role in mucosal inflammation. Stress and autonomic nerve dysfunction may also be involved in LPR. Autonomic nerve dysfunction can increase the frequency of lower esophageal sphincter (LES) and upper esophageal sphincter (UES) opening, along with other reflux events.⁵

Both the LES and gastrointestinal (GI) tract are innervated by the vagus nerve, and the pathogenesis of gastroesophageal reflux (GER) heavily involves LES lesion, as LES is an important anti-reflux barrier. As a result, disturbance in vagus nerve function can be an important factor in the incidence of GER.⁶

Vagus nerve function itself is part of the autonomic nervous system, as the vagus nerve is responsible for parasympathetic input to the viscera of the thorax and abdomen. Heart rate variability (HRV) is the variation of the intervals between each heartbeat, a physiological phenomenon associated with cardiovascular fitness and stress resiliency. The nucleus ambiguus, one of the vagal cell bodies, produces neurons that innervate the heart, the parasympathetic control of which can be studied with HRV. As the sympathetic nervous system controls contractility of the heart muscles and the parasympathetic nervous system promotes cardiac relaxation, both play a role in the heart's electrical conduction. HRV can indicate an imbalance of the autonomic nervous system through measuring both sympathetic and parasympathetic activities.⁶⁻⁸

Currently, few studies have identified autonomic nerve dysfunction in LPR patients, especially in the pediatric population, even though detection and proper management of LPR is particularly important for pediatric patients as the condition may hinder the growth and development in children.^{9,10} Wang *et al.*⁶ and Huang *et al.*⁷ reported that autonomic nerve dysfunction was found in adult LPR patients. Autonomic nerve dysfunction itself can be evaluated with dynamic cardiovascular reflex tests, measurement of heart rate variability, and direct catecholamine tests. Heart rate variability can be measured by linear and non-linear algorithms.¹¹ Our study was conducted to identify HRV analysis components in pediatric LPR patients with autonomic nerve dysfunction by

examining linear algorithms of HRV, which include analysis of time domain with standard deviation normal to normal (SDNN) interbeat interval (IBI) and analysis of frequency domain with low frequency/high frequency ratio (LF/HF).

Methods

Subjects were recruited from Dr. Cipto Mangunkusumo Hospital, Jakarta, from September 2023 to April 2024. Inclusion criteria were children aged 5 to 18 years who were chosen through consecutive sampling. Patients with previously known respiratory tract inflammation other than LPR were excluded.

Nasal endoscopy examination was done with an *Olympus Exera II CV-180™* flexible nasal endoscope and light source. Evaluation of LPR for all subjects was done using the Reflux Symptom and Sign Instrument (RSSI).¹² This scoring method is used for clinical scoring of LPR for children aged 5-18 years, and was validated by Rachmawati *et al.*¹² in 2016. The RSSI score evaluates three symptoms: throat clearing, troublesome cough, and choking, each of which are scored from 0 (none) to 5 (severe), along with two signs found in nasal endoscopy: vocal cord abnormalities (0=normal, 1=whitish patch, 2=Reinke edema, nodule, granulomas) and subglottic edema (0=none, 2=present). Clinical diagnosis of LPR can be declared positive with a total score of ≥ 5 .¹²

All subjects were assessed for autonomic nerve dysfunction by HRV analysis. Heart rate variability analysis was measured with a *Medicore HRV SA-3000P version 3*, using finger plethysmography and pulse photoplethysmography. Subjects were instructed to relax for 15-30 minutes before the procedure. A probe was attached to the subject's left index finger. Analysis started after the examiner previewed the heart rate variability. Once the subject's pulse wave and heart rate stabilized, recording began. Subjects must maintain their position without moving or speaking during the analysis. The result of HRV analysis shows the low frequency (LF)/high frequency (HF) oscillation ratio of heartbeats. High frequency oscillation represents parasympathetic activity, while low frequency oscillation represents overall autonomic activity, with the normal value for LF/HF ratio being in the range of 0.5-2.0. Higher values indicate

higher sympathetic activity, associated with anxiety and acute stress, while lower values indicate more parasympathetic activity.^{13,14}

Autonomic nervous activity was also recorded with time-domain HRV, which measures the variation of the heart's interbeat interval (IBI) using the statistical method standard deviation normal to normal (SDNN). The SDNN component is a time-domain measurement that detects abnormality in the interbeat interval of normal sinus rhythm, such as ectopic heartbeat, measured in milliseconds. Autonomic nerve dysfunction is indicated by SDNN <35.¹⁵

Data coding and analysis were done using SPSS version 27 software. Hypothesis testing was done with Mann-Whitney test due to abnormal data distribution. Multivariate analysis was done with logistic regression. Statistical significance was achieved in results with P values <0.05.

Results

Of 74 pediatric subjects, there were 35 with LPR and 39 without LPR (non-LPR control group). The mean ages were 12.0 (SD 3.43) years in the LPR group and 12.74 (SD 3.27) years in the control group. Demographic characteristics of subjects are shown in **Table 1**.

Throat clearing and troublesome coughing were the most frequent symptoms found in LPR subjects. Vocal cord abnormalities and subglottic edema were found in the majority of pediatric LPR patients: 94.3% and 82.9%. Details of RSSI score findings and comorbidities are shown in **Table 2**. The majority of LPR patients also had varying degrees of adenoid hypertrophy. Ear examination and tympanometry

revealed that over 60% of the LPR group had chronic otitis media and Eustachian tube dysfunction.

Autonomic nerve dysfunction was found in 44.7% of LPR subjects and 43.6% of the control group, showing no significant difference between the two groups (P>0.05). Results are shown in **Table 3**. In our study, heart rate variability analysis (both LF/HF and SDNN) results are shown in median (IQR) due to non-normal distribution based on Kolmogorov-Smirnoff test. Statistical analysis with Mann-Whitney test revealed no significant relationship between LPR and autonomic nerve dysfunction (P>0.05). Results are shown in **Table 4**.

Table 1. Demographic characteristics of LPR and non-LPR pediatric patients

Characteristics	LPR (n=35)	Non-PLR (n=39)
Sex, n		
Male	21	16
Female	14	23
Mean age (SD), years	12.0 (3.29)	12.74 (3.72)

Table 2. Clinical findings of laryngopharyngeal reflux patients

Clinical findings	(N=35)
RSSI component, n	
Throat clearing	26
Choking	6
Troublesome cough	25
Vocal node abnormalities	33
Whitish patch	3
Reinke edema, nodules, granuloma	29
Subglottic edema	29
Other comorbidities, n	
Adenoid hypertrophy	34
Grade 1	16
Grade 2	11
Grade 3	7
Chronic suppurative otitis media	23
Eustachian tube dysfunction	22

Table 3. Autonomic nerve dysfunction based on HRV findings in LPR and non-LPR groups

Variables	Autonomic nerve dysfunction	Normal autonomic nerve function	P value
LPR	16 (44.7)	19 (54.3)	0.854
Non-LPR	17 (43.6)	22 (56.4)	

Table 4. Analysis of LPR and autonomic nerve dysfunction based on HRV findings

Variables	LPR	Non-LPR	P value
Median LF/HF (IQR)	1.13 (1.82)	1.16 (1.45)	0.685
Median SDNN (IQR)	64.12 (33.24)	60.70 (49.6)	0.592

LF=low frequency; HF=high frequency; SDNN=standard deviation normal to normal

Discussion

Decreased parasympathetic activity and assessment of sympathetic activity can be done through evaluations of heartbeat oscillation ratio and interbeat interval of the heart.^{13,15} In our study, both LF/HF and SDNN measurements were used to evaluate for autonomic nerve dysfunction.

In our study, there was no significant difference of autonomic nerve dysfunction in the LPR and control groups, based on LF/HF ratio. Both groups had median LF/HF values in the normal range (0.5-2.0). This finding may have been due to both sympathetic and parasympathetic domination in autonomic nerve dysregulation playing a role in LPR incidence.^{6,7,16-18} Autonomic nerve dysfunction in the form of higher sympathetic activity, especially anxiety, is also linked with LPR incidence. A previous study reported that in HRV analysis, where HF represents parasympathetic activity and LF represents overall autonomic activity, lower HF percentage ($P=0.003$) and higher LF/HF ratio ($P=0.012$) were present in patients with gastroesophageal reflux disease (GERD), indicating poor autonomic modulation and higher sympathetic activity, often accompanied with anxiety in the LPR group. Higher sympathetic activity is closely linked in anxiety.⁷ Another study reported that the score of somatic anxiety is statistically higher in patients with LPR compared to control groups. *Reactive Strength Index* (RSI) score and *Beck Anxiety Inventory* score in LPR patients was significantly correlated ($\rho 0.286$; $P=0.021$).¹⁷ Higher LF/HF ratio shows that sympathetic activity is associated with acute stress, but a lower ratio signifies parasympathetic activity, which is associated with depression. Subjects in this study might have been experiencing acute stress during the examination, as children are highly anxious in hospital settings. Therefore, the median LF/HF ratio in the LPR group may have been in the normal range due to variability in parasympathetic/sympathetic activity dominance, both of which can contribute to LPR and GER.

Our results also showed no significant difference in autonomic nerve function between the LPR and control groups based on the SDNN component. This result may have been due to the use of SDNN as a parameter, a measurement much more specific as an indicator of autonomic nerve dysfunction, unlike

R-R variability as a parameter. The R-R variability is a wider concept that includes interbeat interval variability, while SDNN is more specific in quantifying normal-to-normal (NN) variability with the standard deviation of the NN interval. The word "R-R" refers to the interval between two consecutive R waves in an electrocardiogram (ECG). As such, SDNN is more significant and quantified in HRV analysis.¹³ A study used RR variability as an indicator of autonomic nerve dysfunction and observed that dysfunction was found in 44.4% of patients and only 7.9% of the control group ($P<0.001$), with lower RR variability in patients with GERD.⁹ A previous study also reported no significant difference of SDNN value in LPR patients and a healthy control group.¹⁵ There are several algorithms for determining the HRV measurement index, namely, (1) linear algorithms, including time domain and frequency domain; and (2) non-linear algorithms.^{11,19} Time-domain analysis such as LF/HF ratio represents the most straightforward analytical approach to assess HRV, whereby variation parameters in time curves are identified, including frequency distribution, standard deviation, and range of values. In this study, the frequency domain algorithm used is SDNN. In general, the frequency-domain method is preferred for interpreting physiological regulation in short HRV measurements, while the time domain method is preferred for analyzing results of HRV measurements ≥ 18 hours. The use of SDNN is often preferred over the LF/HF ratio in heart rate variability analysis because SDNN reflects the overall variability of RR intervals, including all frequencies, providing a comprehensive picture of autonomic nervous system health. In contrast, the LF/HF ratio is more specific and only describes the balance between sympathetic and parasympathetic activity, which can be influenced by various factors and does not always fully reflect overall cardiac variability.²⁰ In this study, neither SDNN component nor LF/HF ratio show significant difference of autonomic nerve dysfunction between LPR and non-LPR subjects.

Previous studies have shown that abnormal regulation of the autonomic nervous system can be observed in GER, a condition that shares similar pathophysiology with LPR. Wherein gastric reflux irritates the esophagus, the same fluids irritate the larynx and pharynx, resulting in LPR.^{6,7} The autonomic nervous system controls the GI tract.

Dysfunction in autonomic function influences esophageal peristaltic movement, LES function, and gastric motility. The vagal nerve is in control of parasympathetic activity in the GI tract. In GER, decreased vagal nerve activity leads to functional failure and increased transient relaxation of the LES, which in turn causes reflux of gastric fluid to the esophagus. Transient relaxation of the LES is a relaxation process not preceded by swallowing, but instead influenced by the vasovagal reflex, which can lead to reflux. This theory was supported by two studies which reported that administration of medicine to increase LES pressure did not increase LES tone.^{7,19} Refluxed fluids still directly cause inflammation to any area of contact, and UES relaxation allows these fluids to reach the larynx, hypopharynx, and nasopharynx. Transient relaxation of the LES is thought to have a significant role in pediatric LPR pathophysiology.^{7,19} Prolonged gastric emptying, decrease in LES competence, and increase in transient relaxation of the LES are results of parasympathetic dysfunction, which causes lower vagal nerve tone. Autonomic dysfunction in the form of lower vagal tone contributes to GER incidence, which in turn might increase the risk of LPR.^{6,7} Our study found that there was a high incidence of autonomic nerve dysfunction in all subjects overall. Among 74 subjects, 33 were found to have autonomic dysfunction through HRV analysis (44.6%). Autonomic nerve dysfunction is more prevalent in the pediatric population with sepsis, infections of the nervous system, and cardiometabolic syndromes, and is usually evaluated with dynamic tests instead of HRV analysis.^{21,22} The high incidence in our study may be tied to how HRV analysis is seldom studied in children, which means the parameters for autonomic dysfunction in HRV analysis for the pediatric population need further evaluation.

Both the SDNN and LF/HF ratio components in pediatric LPR patients were not found to be significantly different than non-LPR patients, showing that there was no association between autonomic nerve dysfunction and LPR in children. However, the strength of our study was that it is the first to analyze the incidence of autonomic nerve dysfunction and LPR in the pediatric population in Indonesia. The limitations of our study were that the study is a cross-sectional study and had a limitation of participants.

In conclusion, our study shows that LPR in

pediatric patients is not significantly associated with autonomic nerve dysfunction measured by HRV components. The association of LPR and autonomic nerve dysfunction should be studied more in the future through other ways of measurement.

Conflict of interest

None declared.

Funding acknowledgement

The authors received no specific grants from any funding agency in the public, commercial, or not-for-profit sectors.

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