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Association between laryngopharyngeal reflux disease and autonomic nerve dysfunction

A. Min Wang[1] · Gang Wang[1] · Ning Huang[1] · Yan Yan Zheng[1] · Fan Yang[1] · Xia Qiu[1] · Xian Ming Chen[1]

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Abstract

Purpose To assess autonomic nerve function in patients with laryngopharyngeal reflux disease (LPRD) and determine the correlation between LPRD and autonomic nerve dysfunction.

Methods Patients with suspected LPRD who visited our outpatient department were assessed using the reflux symptom index (RSI) and reflux finding score (RFS) scales. Eighty-one suspected LPRD patients with RSI > 13 and RFS > 7 were examined using 5-min short-range heart rate variability, and all were given proton pump inhibitor diagnostic treatment.

Results The root mean square of successive R–R intervals, high-frequency (HF) power, standardized HF, and HF % were significantly lower in the case group than in the control group ($p < 0.05$); however, the low frequency (LF)/HF ratio was significantly higher in the case group ($p < 0.05$). There were no significant differences in the standard deviation of the average normal-to-normal interval, total power, LF power, and LF % between the two groups ($p > 0.05$). RSI, RFS, and disease duration were negatively correlated with HF power ($r = -0.89$, -0.77, and -0.315, respectively; $p < 0.05$). The LF/HF ratio and disease duration were positively correlated ($r = 0.315$, $p < 0.05$).

Conclusions Autonomic nerve dysfunction was observed in our patients with LPRD. LPRD severity was significantly correlated with autonomic nerve dysfunction and negatively correlated with vagal nerve function.

Keywords Laryngopharyngeal reflux disease · Autonomic nerve function · Heart rate variability · Reflux symptom index · Reflux finding score

Introduction

Laryngopharyngeal reflux disease (LPRD) is a common otolaryngologic disease. In recent years, with the changes in modern lifestyle and dietary habits, the prevalence of LPRD has shown marked increase. However, its pathogenesis remains unclear. Many clinical studies have shown that LPRD is caused by multiple factors. Although LPRD and gastroesophageal reflux disease (GERD) are caused by the reflux of gastric contents, the pathogeneses of these conditions differ [1]. The lower esophageal sphincter (LES) and gastrointestinal tract are innervated by the vagus nerve, and the pathogenesis of GERD mainly involves LES lesions. Therefore, deteriorated vagal nerve function may be an important factor in the pathogenesis of GERD [2–6]. In LPRD, an important antireflux barrier is the upper esophageal sphincter (UES), which is also controlled by the vagus nerve. However, it remains unclear whether autonomic nerve dysfunction also plays a role in the pathogenesis of LPRD.

Therefore, in this study, we aimed to assess autonomic nerve function in patients with LPRD and to evaluate the relationship between LPRD and autonomic nerve dysfunction.

Materials and methods

Patient selection

Patients with suspected LPRD who visited our department of otolaryngology from May 2017 to December 2017 were included. The inclusion criteria [2] included the following:

A. Min Wang and Gang Wang contributed equally to this work.

✉ Xian Ming Chen
fzchxming@sina.com

[1] Department of Otorhinolaryngology Head and Neck Surgery, 900 Hospital of the Joint Logistics Team, Fuzhou 350025, China

age, 18–60 years; RSI > 13; RFS > 7; duration of effective proton pump inhibitor therapy, ≥ 8 weeks; and duration of diagnosis in newly diagnosed patients, > 3 months. The exclusion criteria were (1) the presence of diabetes, hypertension, malignant tumor, respiratory disease, endocrine disease, heart disease, arrhythmia, cardiac chest pain, recent episode of stroke, upper gastrointestinal disease, or other serious systemic diseases and upper abdominal surgery; (2) recent use of drugs that can affect vagal nerve function, such as cholinergic agonists or antagonists, antisecretory drugs, adrenergic agonists or antagonists, antipsychotics, immunomodulators, antiemetics or drugs that promote gastric motility, and prostaglandin analogs; (3) long-term smoking or alcohol abuse and consumption of caffeinated or alcoholic beverages 24 h before the experiment; and (4) menstruation, pregnancy, or lactation. Based on these exclusion criteria, a total of 53 patients were included in this study as the case group.

The control group comprised randomly selected healthy individuals from the physical examination center of our hospital. The inclusion criteria for this group were as follows: age, 18–60 years; RSI < 13; RFS < 7; no history of throat, respiratory system, digestive system, and cardiovascular system disease or other major diseases; no long-term history of alcohol and tobacco use; and no obvious abnormalities in physical examination indicators. Accordingly, a total of 55 individuals were included in this group. This study was approved by the Ethics Committee of our hospital.

RSI and RFS

RSI and RFS were calculated for all patients with suspected LPRD in the outpatient department, and all scores were completed and statistically analyzed by the same researcher [3, 8–10]. RSI > 13 and/or RFS > 7 were used to identify patients with suspected LPRD.

Assessment of autonomic nerve function

Short-term heart rate variability (HRV) analysis was performed for 81 patients with suspected LPRD and the controls. A DiCare m1CP Micro Ambulatory electrocardiogram (ECG) recorder was used to record the V5-lead ECG of the subjects in a static state for 5 min, and the sinus rhythm was automatically detected for HRV analysis. Further, the Kubios HRV version 2.1 analysis software was used to analyze the HRV time-domain and frequency-domain values. Time-domain indicators included the standard deviation of the average normal-to-normal interval (SDNN) and root mean square of successive R–R interval (RMSSD), whereas frequency-domain indicators included total power (TP) of 0.00–0.40 Hz, low-frequency (LF) power of 0.04–0.15 Hz, high-frequency (HF) power of 0.15–0.40 Hz, standardized LF (LFnu), standardized HF (HFnu), ratio of LF power to TP (LF %), ratio of HF power to TP (HF %), and ratio of LF power to HF power (LF/HF). RMSSD, HF power, HF %, and HFnu mainly reflect vagal nerve function, whereas SDNN and TP mainly reflect the activities of the total autonomic nervous system (sympathetic and vagal nerve activities). LF power is affected by sympathetic and vagus nerves, but sympathetic nerve function is dominant. Further, the LF/HF ratio reflects sympathovagal balance.

Treatment

All 81 patients with suspected LPRD were treated with proton pump inhibitor diagnostic treatment including 20 mg/bid esomeprazole combined with 5 mg/tid mosapride for ≥ 8 weeks consumed 0.5 h before dinner. The patients were advised to control their eating habits and adjust their lifestyle habits such as raising their head while sleeping at night, eating less sweets, avoiding overeating, consuming a low amount of high-fat diet, avoiding midnight eating, and avoiding alcohol. The treatment was considered effective based on the basic disappearance of symptoms or their improvement by > 50% or RSI ≤ 13 and a final diagnosis of LPRD [7].

Statistical analysis

All data were statistically analyzed using the SPSS 23.0 statistical software. The measurement data are expressed as mean ± SD. Enumeration data (expressed as rate) were examined using the Shapiro–Wilk test, and graphical examinations were used to test the normality of data. The measurement data conforming to a normal distribution were tested by the two-sample t test. The enumeration data were analyzed using χ^2 test. All differences associated with a chance probability of ≤ 0.05 were considered statistically significant. Correlation analysis was achieved by performing the Pearson's correlation test; correlation coefficient r values > 0 indicate a positive correlation and r values < 0 indicate a negative correlation.

Results

A total of 53 patients were finally included in the case group (26 males and 27 females) and 55 patients in the control group (27 males and 28 females). The sociodemographic characteristics of the two groups are summarized in Table 1.

RMSSD, HF power, HFnu, and HF % representing vagal nerve function were significantly lower in the case group than in the control group ($p < 0.05$). The LF/HF ratio, which represents sympathetic–vagal balance, was significantly higher in the case group than in the control

Table 1 Age, sex, and score of the patients of the two groups

Grouping	Case group	Control group	χ^2 or t	p value
Age (years)	39.87 ± 10.45	38.62 ± 10.16	0.630	0.530
Sex			0.000	0.997
Male	49.06%	49.09%		
Female	50.94%	50.91%		
RSI	18.60 ± 3.15	2.01 ± 1.55	34.570	0.000**
RFS	10.74 ± 1.70	3.93 ± 1.30	23.296	0.000**

RSI reflux symptom index, *RFS* reflux finding score

χ^2: χ^2 test value

t: t test value

**$p < 0.01$

group ($p < 0.05$); however, differences in terms of SDNN, TP, LF power, and LF % between the two groups were not significant ($p > 0.05$). The specific values of these parameters are shown in Table 2. Taken together, these results indicate that the case group exhibited autonomic nerve dysfunction characterized by a relative deterioration of vagal nerve function and improvement of sympathetic nerve function.

The results of the correlation analysis between the HRV parameters and RSI, RFS, and disease duration in the case group are presented in Table 3. HF power, which represents vagal nerve function, was negatively correlated with RSI, RFS, and disease duration. Further, HFnu was negatively correlated with disease duration; LFnu and the LF/HF ratio, which represent sympathetic–vagal balance, were positively correlated with disease duration. There were no significant correlations between other HRV parameters and RSI, RFS, and disease duration.

Table 2 Statistical comparison of heart rate variability parameters between the two groups

Grouping	Case	Control	t	p value
RMSSD	41.10 ± 10.90	45.91 ± 12.97	−2.082	0.040*
SDNN	57.83 ± 10.41	59.05 ± 13.37	−0.524	0.601
TP	2773.13 ± 997.26	3005.16 ± 1039.46	−1.183	0.239
LF power	1197.47 ± 776.53	1289.62 ± 901.37	−0.568	0.571
HF power	638.25 ± 283.10	803.15 ± 218.09	−3.398	0.001**
LF %	40.34 ± 15.67	39.81 ± 14.53	0.184	0.085
HF %	23.04 ± 9.32	28.18 ± 8.27	−3.033	0.003**
LFnu	63.02 ± 10.72	57.32 ± 11.87	2.616	0.010*
HFnu	36.98 ± 10.72	42.68 ± 11.87	−2.616	0.010*
LF/HF	1.99 ± 1.08	1.57 ± 0.93	2.137	0.035*

t *t* test value, *RMSSD* root mean square of successive R–R interval, *SDNN* standard deviation of the average normal-to-normal interval, *TP* total power, *LF power* low-frequency power, *HF power* high-frequency power, *LF %* ratio of LF power to TP, *HF %* ratio of HF power to TP, *LFnu* standardized LF, *HFnu* standardized HF, *LF/HF* ratio of LF power to HF power

*$p < 0.05$, **$p < 0.01$

Table 3 Correlation between HRV and RSI, RFS, and disease duration

Grouping	RSI		RFS		Disease duration	
	r	p value	r	p value	r	p value
RMSSD	−0.116	0.409	−0.158	0.258	−0.142	0.311
SDNN	−0.125	0.371	0.158	0.259	−0.144	0.305
TP	−0.558	0.000**	−0.562	0.000**	−0.003	0.980
LF power	−0.482	0.000**	−0.403	0.003**	0.069	0.623
HF power	−0.888	0.000**	−0.768	0.000**	−0.315	0.022*
LFnu	0.169	0.227	0.125	0.373	0.275	0.046*
HFnu	−0.169	0.227	−0.125	0.373	−0.275	0.046*
LF/HF	0.153	0.275	0.184	0.187	0.315	0.021*

RMSSD root mean square of successive R–R interval, *SDNN* standard deviation of the average normal-to-normal interval, *TP* total power, *LF power* low-frequency power, *HF power* high-frequency power, *LFnu* standardized LF, *HFnu* standardized HF, *LF/HF* ratio of LF power to HF power, *RSI* reflux symptom index, *RFS* reflux finding score

*$p < 0.05$; **$p < 0.01$

Discussion

In 1980, Heatley et al. studied vagal nerve activity in patients with GERD by observing the change in pulse variability during deep breathing and found that one quarter of these patients had impaired efferent vagal nerve function, which suggested that the impaired efferent function of the vagus nerve is the cause of GERD in some patients [11]. In 1991, Cunningham et al. used cardiovascular reflex test methods, e.g., they studied high incidence of patients with GERD and autonomic nerve dysfunction (21/48, 44%), mainly for vagal nerve abnormalities and found that LES competence, delayed gastric emptying, and increase in the frequency of transient LES relaxation may have been caused by lower vagal nerve tension [12]. Dobrek et al. used HRV to measure HF and LF powers and found that the score of their GERD group was significantly lower than that of their control group at rest [2]. Moreover, Lee et al. found that compared with patients with non-erosive reflux disease (NERD), patients with esophagitis (even without symptoms) have lower autonomic nerve function (LF and HF powers were lower) [13]. Chen et al. found that HF power was significantly lower in patients with erosive esophagitis (ERD) than in those with NERD and control group patients but LF % and the LF/HF ratio were significantly lower in patients with NERD than in those with ERD and control group patients [4]. Djeddi et al. conducted a study on 19 neonates with suspected GERD by performing 12-h synchronized polysomnography and esophageal multi-channel impedance–pH monitoring and compared the changes in the HRV parameters during the resting period and early stages of reflux. The results showed that parasympathetic nerve function (RMSSD, HF power, and HFnu) prior to the events involved in gastroesophageal reflux reduction, which led to the reverse flow before the change in autonomic nerve function, was one of the mechanisms of reflux in the neonates [15]. All mentioned studies confirmed that patients with GERD have autonomic nerve dysfunction, which is mainly related to abnormal vagal nerve function. However, whether vagal nerve dysfunction has an important role in the pathogenesis of LPRD has not been answered in the relevant literature.

In the present study, we found that patients with LPRD also had autonomic nerve dysfunction, with HF reduction being the main feature, which was consistent with the results reported by Dobrek, Lee, and Chen et al. [2, 13, 14]. However, the LF/HF ratio and LFnu were significantly higher in the case group than in the control group, which was inconsistent with the results of the former studies. These findings suggest that autonomic nerve dysfunction is involved in the pathogeneses of LPRD and GERD, but the underlying mechanism is different. Huang et al. demonstrated autonomic nerve dysfunction in patients with LPRD [16]. On the basis of this information, we selected a short-term (5 min) HRV analysis to increase patient compliance, increase sample size, and increase the time-domain indicators RMSSD and SDNN and the frequency-domain indicator TP. The analysis indicated that patients with LPRD mainly have autonomic nerve dysfunction with relatively deteriorated vagal nerve function and improved sympathetic nerve function. The gastrointestinal system is regulated by the autonomic nervous system. Therefore, the dysfunctionality of the autonomic nervous system can cause abnormal regulation of gastric peristalsis and UES and LES functions, making laryngopharyngeal reflux a risk factor for LPRD. Subsequently, we performed correlation analysis and found that significant negative correlations were present between HF power and RSI and RFS in patients with LPRD. Deteriorated vagal nerve function corresponded to higher symptom and physical scores, which suggest that vagal nerve dysfunction is involved in the development of LPRD. The analyses of autonomic nerve dysfunction and disease duration showed that longer disease duration in patients with LPRD is associated with lower vagal nerve function. These findings suggest that the recovery of autonomic nerve function during the treatment of LPRD is important.

This study also showed that autonomic nerve dysfunction is correlated with LPRD, and an effective treatment for it needs to be explored. In a study by Hu et al., it was confirmed that patients with anxiety and depression have marked autonomic nerve dysfunction, which significantly improved after anxiety and depression were treated [17]. During clinical case collection, we observed that some patients with LPRD exhibited signs of mild anxiety and depression. Therefore, in future studies, we will aim to determine if improvement in anxiety and depression before treating LPRD can increase the cure rate of LPRD.

Conclusions

Autonomic nerve dysfunction was found to be a factor involved in the development of LPRD, and the degree of dysfunction is significantly correlated with disease severity, suggesting that attention should be given to the recovery of autonomic nerve function during treatment of the disease. Combined treatment for autonomic nerve dysfunction may be a boon for patients with refractory LPRD.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the hospital's Ethics Committee (900 Hospital of the Joint Logistics Team, Number: 2016035) and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

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