Autonomic function in adults with allergic rhinitis and its association with disease severity and duration

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ABSTRACT

Background: The association between allergic rhinitis (AR) and the autonomic nervous system (ANS) has recently received substantial attention. However, no studies have assessed how the heart rate variability (HRV) parameters are associated with duration and disease severity in AR.

Objective: To compare the difference in autonomic conditions among individuals with AR of various durations and severities and healthy controls.

Methods: We divided individuals with AR into subgroups based on duration and severity of disease. Next, we measured HRV, and the results were compared among subgroups and healthy controls.

Results: High frequency (HF) and normalized high frequency (NHF) were significantly higher in the intermittent group than in the control group, whereas normalized low frequency (NLF) and the ratio of absolute LF to HF power (LF/HF) were significantly lower in the intermittent group than in the control group. Furthermore, NLF was significantly higher in the persistent group than in the intermittent group. HF and NHF were significantly higher in the mild group than in the control group, whereas NLF and LF/HF were significantly lower in the mild group than in the control group. The total nasal symptom and itchy nose scores were negatively correlated with NHF.

Conclusion: Our results indicate that patients with intermittent and mild AR have hypervagal activity and hyposympathetic activity, and the predominance lessens in patients with more persistent AR and severe symptoms. Further investigation of the mechanisms underlying the association between autonomic function and persistent and severe AR is needed.

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noninvasive and quantitative tool that can be used to evaluate the function of both the sympathetic and parasympathetic branches of the ANS (Fig 1). However, no studies have assessed how the HRV parameters are associated with duration and disease severity in AR. Therefore, the aims of this study were to compare ANS function among healthy controls and AR subgroups that were classified according to the ARIA guidelines and to investigate the influences of various clinical symptoms on ANS function in patients with AR.

Methods

Patients With AR

A total of 35 patients were recruited from the Department of Otorhinolaryngology at Kyung Hee University Hospital at Gangdong between March 12 and April 17, 2013. The inclusion criteria were as follows: (1) age older than 18 years; (2) presence of AR symptoms, such as clear nasal discharge, nasal obstruction, itchy nose, and sneezing; and (3) diagnosis of allergy using the skin prick test. The exclusion criteria were as follows: (1) presence of rhinosinusitis, nasal polyposis, or neoplasm on nasal endoscopy; (2) treatment using asthma medication or antihistamines within 2 weeks, corticosteroids within 1 month, or a nasal/oral decongestant or leukotriene receptor antagonist within 1 week; (3) presence of any disease known to affect HRV (eg, cardiovascular, endocrinologic, autoimmune, neurologic, or psychiatric disorder, including alcoholism and polytoxemia); (4) history of smoking; (5) anticholinergic, antidepressant, or contraceptive pill use for at least 4 weeks before the study; (6) use of hormone replacement therapy; or (7) pregnancy.

Written informed consent was obtained from all patients before enrollment. This study was approved by the Institutional Review Board of Kyung Hee University Hospital at Gangdong.

Healthy Controls

The control group comprised healthy people who were recruited from the Department of Sasang Constitutional Medicine, Kyung Hee University Korean Medicine Hospital, between November 2014 and March 2015. All participants were healthy, Korean individuals older than 18 years. They had undergone a general health checkup (recording of disease history, physical examination, vital signs, and chest radiography) and laboratory tests (measurement of complete blood cell count, total serum IgE, aspartate transaminase, alanine transaminase, blood urea nitrogen, creatinine, and erythrocyte sedimentation rate) and had no abnormal findings. The exclusion criteria were as follows: (1) presence of any disease known to affect HRV (eg, allergic, cardiovascular, endocrinologic, autoimmune, neurologic, or psychiatric disorders, including alcoholism and polytoxemia); (2) history of smoking in the 3 months before the study; and (3) pregnancy or lactation. After screening the healthy controls, we randomly extracted 32 individuals who were equally matched to the age and sex distributions of the AR group.

Skin Prick Test

The skin prick test was performed according to a routine procedure. Eleven common Aeroallergens (Dermatophagoides farinae, Dermatophagoides pteronyssinus, dog fur, cat fur, grass mixture, tree mixture, mugwort, ragweed, Alternaria tenuis, Aspergillus fumigatus, and cockroach) were used (Allergopharma GmbH & Co KG, Reinbeck, Germany). The skin prick test was performed on the volar surface of the forearm; negative (50% glycerin saline) and positive (0.1% histamine phosphate) controls were also used. The results were examined at 15 minutes, and the resultant wheals and flares were measured. A test result was considered positive if the diameter of the wheal was the same or larger than that of the positive control wheal. Skin prick tests were not performed on the healthy controls.

AR Subgroups and Evaluation of Nasal Symptoms

Patients with AR who met the inclusion criteria were classified, according to the ARIA criteria, as having either intermittent AR (IAR; <4 days per week or <4 weeks per year) or persistent AR (PAR; ≥4 days per week and ≥4 weeks per year); AR was also categorized as either mild (symptoms were present but did not interfere with quality of life) or moderate to severe (symptoms were serious enough to interfere with quality of life). Nasal symptoms (ie, rhinorrhea, nasal obstruction, itchy nose, and sneezing) were assessed using a 4-point Likert scale (0 indicating no symptoms; 1, mild; 2, moderate; and 3, severe). The total nasal symptom score (TNSS) was calculated as the sum of separate symptom scores and ranged from 0 to 12.

HRV Analysis

All patients with AR, as well as the healthy controls, were assessed using the same procedure and equipment. They removed any metal attachments from their bodies, were seated on comfortable chairs in a quiet room, and were asked to relax for 15 minutes. After the relaxation period, electrocardiography was performed for 5 minutes (SA-3000P, Medicore Inc, Seoul, Korea). Because HRV reflects the activity of the ANS on the sinus node, abnormal heartbeats and artifacts were excluded from the electrocardiographic recordings to obtain more reliable results. HRV was assessed on the basis of frequency domain measurements performed using fast Fourier transformation. All HRV parameters used in this study were logarithmically transformed to correct the skewness of distribution (Table 1).

Statistical Analysis

No report has compared autonomic function using HRV among AR subgroups that were classified according to ARIA guidelines. In a
The present study indicates the following: (1) adult patients with intermittent and mild AR have hyperparasympathetic activity and hypothesympathetic activity compared with healthy controls; (2) adult patients with persistent and severe AR have hypersympathetic activity compared with patients with intermittent and mild AR; and (3) the TNSS and itchy nose score are negatively correlated with parasympathetic nervous activity.

The association between the ANS and inflammatory diseases has been revealed in many studies. Parasympathetic nerves are major parts of the inflammatory reflexes that control innate immune responses. Decreased vagal activity disrupts the innate immune regulation, causing continual proinflammatory cytokine production.

Abbreviations: AR, allergic rhinitis; ANS, autonomic nervous system; HF, high frequency; HRV, heart rate variability; IAR, intermittent allergic rhinitis; LF, low frequency; LF/HF, ratio of absolute LF to HF power; NLF, normalized low frequency; NHF, normalized high frequency; PAR, persistent allergic rhinitis; TP, total power.
activity and excessive or chronic inflammation. Therefore, many inflammatory and autoimmune conditions are associated with decreased vagal tone.

On the other hand, vagal hyperactivity increases the release of nitric oxide, a substance that may enhance inflammation by altering the balance of TH cell types (TH1 and TH2). This may in turn lead to the proliferation of TH2 lymphocytes, which produce a cytokine profile that exacerbates allergic diseases.

In several previous clinical studies, patients with allergic diseases, including atopic dermatitis, atopic asthma, and AR, had vagal hyperactivity. When the nasal mucosa of patients with AR is exposed to allergens, symptoms such as rhinorrhea, sneezing, and itching begin within 30 minutes; this is called an immediate allergic reaction. The reaction is caused by the release of various chemical mediators, including histamine, prostaglandin, and leukotriene. Approximately 6 hours after the early phase, nasal congestion appears and slowly improves. This is called the late phase and is characterized by vasoconstriction and inflammatory cell infiltration in the nasal mucosa. Inflammatory cells destroy and subsequently reconstruct normal tissue of the nasal mucosa. As AR symptoms persist longer, this cycle occurs repeatedly and causes chronic nasal obstruction.

Both parasympathetic and sympathetic nerves can aggravate AR symptoms through different mechanisms. Parasympathetic nerves stimulate glands of the nasal mucosa and trigger allergic reactions. Accordingly, parasympathetic nerves can provoke nasal discharge, itching, and sneezing. Sympathetic nerves suppress erectile venous sinusoids in the nose; this causes vascular congestion and nasal obstruction.

In our study, as TNSS increased, the NHF parameter decreased. This means that as patients with AR develop more severe

![Figure 2. Comparison of normalized low frequency (NLF), normalized high frequency (NHF), high frequency (HF), and ratio of absolute LF to HF power (LF/HF) among the study groups. Controls vs IAR vs PAR (panel A, NLF and NHF; panel C, HF and LF/HF); Controls vs mild AR vs moderate to severe AR (panel B, NLF and NHF; panel D, HF and LF/HF); AR, allergic rhinitis; IAR, intermittent allergic rhinitis; PAR, persistent allergic rhinitis. Error bars indicate mean ± SD. *Significant differences between control and IAR groups; †IAR vs PAR groups; and ‡control vs mild AR groups (analysis of variance and the Tukey Honest Significant Difference post hoc test; P < .05).](https://example.com/figure2)

<table>
<thead>
<tr>
<th>Table 4</th>
<th>Comparison of HRV Parameters According to Severity (Control vs Mild AR vs Moderate to Severe ARs)†</th>
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<tbody>
<tr>
<td>HRV parameter</td>
<td>Controls (n = 32)</td>
</tr>
<tr>
<td>TP, ms²</td>
<td>6.63 (0.70)</td>
</tr>
<tr>
<td>LF, ms²</td>
<td>5.43 (0.79)</td>
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<tr>
<td>HF, ms²</td>
<td>4.73 (0.82)</td>
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<tr>
<td>NLF</td>
<td>35.83 (17.69)</td>
</tr>
<tr>
<td>NHF</td>
<td>2.92 (2.65)</td>
</tr>
<tr>
<td>LF/HF</td>
<td>0.00 (0.28)</td>
</tr>
</tbody>
</table>

Abbreviations: HF, high frequency; HRV, heart rate variability; LF, low frequency; LF/HF, ratio of absolute LF to HF power; NLF, normalized low frequency; NHF, normalized high frequency; TP, total power.

*Data are presented as mean (SD) (analysis of variance and Tukey honestly significant difference post hoc test).

Table 5 | Correlations Between Nasal Symptoms and HRV Parameters* |
<table>
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<tbody>
<tr>
<td>Symptom</td>
<td>TP, ms²</td>
<td>LF, ms²</td>
<td>HF, ms²</td>
<td>NLF</td>
</tr>
<tr>
<td>TNSS</td>
<td>0.00</td>
<td>0.28</td>
<td>0.33</td>
<td>0.33</td>
</tr>
<tr>
<td>Rhinorrhea</td>
<td>-0.18</td>
<td>0.17</td>
<td>0.11</td>
<td>0.30</td>
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<tr>
<td>Nasal obstruction</td>
<td>0.07</td>
<td>0.29</td>
<td>0.03</td>
<td>0.26</td>
</tr>
<tr>
<td>Itchy nose</td>
<td>0.17</td>
<td>0.22</td>
<td>0.05</td>
<td>0.32</td>
</tr>
<tr>
<td>Sneezing</td>
<td>0.00</td>
<td>0.12</td>
<td>0.10</td>
<td>0.06</td>
</tr>
</tbody>
</table>

Abbreviations: HF, high frequency; HF norm, normalized high frequency; HRV, heart rate variability; LF, low frequency; LF/HF, ratio of absolute LF to HF power; NLF, normalized low frequency; NHF, normalized high frequency; TP, total power.

*Data are Spearman correlation coefficients (r).

†P < .05.
symptoms, they tend to have a greater decrease in vagal activity and show predominance of sympathetic activity. Meanwhile, persistent nasal symptoms cause hypertrophy of nasal mucosa and nasal obstruction, and these symptoms are associated more with sympathetic activity.

On the basis of the mechanisms described above, we surmised that when AR duration is relatively short and symptoms are milder and more intermittent, nasal symptoms in the early phase (rhinorrhea, itching, and sneezing) predominate, and these symptoms are more associated with vagal activity. As symptoms persist longer and become more severe, nasal obstruction becomes more chronic, and this symptom is associated more with sympathetic nervous activity.

There is a limitation in our study. Although healthy controls were excluded for a history of allergic disease or an increase in total serum IgE, we did not perform confirmatory allergic testing, such as allergic skin tests.

To our knowledge, this was the first study to compare ANS function among patients with varying severities and durations of AR, as well as in healthy controls. Moreover, it was the first to investigate the association between the clinical features of AR and ANS function.

In conclusion, our study results indicate that parasympathetic nervous activity is predominant in patients with mild and intermittent AR and that this predominance lessens and sympathetic activity becomes predominant as the duration and severity increases. Further investigation of the mechanisms underlying the association between autonomic function and persistent and severe AR is needed.

References