

Cardiac Autonomic Imbalance in Children with Allergic Rhinitis

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The involvement of autonomic imbalance has been reported in the pathogenesis of hypersensitivity reactions. Allergic diseases are more frequent in children and some of predisposing factors may be changed according to the increasing age, but the involvement of autonomic imbalance has not been investigated in pediatric population. In this cross-sectional, case-control study, we evaluated the autonomic system by measuring heart rate variability (HRV) in pediatric patients with allergic rhinitis. Thirty-five pediatric patients with allergic rhinitis and 36 healthy children (mean age 11 ± 2.7 , and 12 ± 3 years, respectively) were enrolled in the study. Age and gender were not different between the groups. The diagnosis of allergic rhinitis was based on the history, symptoms, and skin prick tests. Participants with acute infection, nasal polyposis, bronchial asthma, and any other medical problems, assessed by history, physical examination and routine laboratory tests, were excluded. Twenty-four hour ambulatory electrocardiographic recordings were obtained, and the time domain and frequency domain indices of HRV were analyzed. We found significant increase in calculated HRV variables in children with allergic rhinitis compared to controls, which reflect parasympathetic tones, such as number of R-R intervals exceeding 50 ms, root mean square of successive differences between normal sinus R-R intervals, the percentage of difference between adjacent normal R-R intervals, and high frequency. These results indicate that HRV is increased, which implies sympathetic withdrawal and parasympathetic predominance. We propose that autonomic imbalance may be involved in the pathophysiology of allergic rhinitis in pediatric patients. ——— allergic rhinitis; cardiac autonomic functions; heart rate variability; power spectral analysis; time-domain analysis.

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Allergic rhinitis is a condition characterized by sneezing attacks, nasal discharge or blockage for more than an hour on most days for either a limited period of time or throughout the whole year (Skoner 2001). It is an important problem because of high prevalence, common co-morbid conditions, very low remission ratio. Allergic rhinitis is also considered as a risk factor for the development of asthma. Moreover, it significantly reduces quality of life, interferes with both attendance and performance at school and work, and results in a significant economic burden (Simons 1996; Blaiss 2004; Laforest et al. 2005; Vandenplas et al. 2008). Prevalence of allergic rhinitis is as high as 30% among adults and 40% among children. It is a global health problem and one of the most common chronic conditions in pediatric population (Berger 2001).

Although allergic rhinitis is defined as an inflammatory disorder of the upper airways, inflammation alone is insufficient to explain the chronic nature of the disease. It is widely accepted that allergic rhinitis is a multifactorial disorder, in which one of the most important causal component

is neurological involvement (Canning 2002). It has been found that central nervous system plays an important role in symptomology of hypersensitivity reactions, but the exact mechanism remains to be elucidated (Undem et al. 2000). One of the mechanisms for neural activity has been explained by changes in autonomic nervous system (ANS) activity (Mills and Widdicombe 1970; Baraniuk et al. 1994).

A recent study focused on the relationships between nasal ANS and central ANS maintaining cardiovascular hemodynamics revealed that the central ANS activities correlate with the nasal obstruction induced by the postural changes (Ko et al. 2008). It has been suggested that the central ANS, especially the sympathetic nervous system, is involved in the mechanism.

Heart rate variability (HRV), the degree of fluctuation of the beat-to-beat differences in cardiac rhythm, is known to be a reliable, noninvasive marker of autonomic nervous system activity (Malik and Camm 1990). Although there are some studies examining the association between HRV parameters and allergic diseases (Yokusoglu et al. 2007b),

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we could not find any report about this issue in pediatric patients. Most of these reports generally focused on the pathogenesis of bronchial asthma (Martin 1993; Lodi et al. 1997).

Allergic rhinitis is a multifactorial disease, in which the important several predisposing factors have some roles. As these factors change with increasing age, the pathophysiology of allergic rhinitis also may be changed and needs to be investigated in pediatric age group. Despite these facts, the pathophysiology of allergic rhinitis is less extensively investigated in children.

The purpose of this cross-sectional case-control study was to investigate HRV in pediatric patients with allergic rhinitis. We assessed the symptoms and time- and frequency-domain parameters of HRV with 24-hour ambulatory ECG monitoring in patients with allergic rhinitis. The results may have clinical implications with regard to the treatment of autonomic imbalance.

Material and Methods

Thirty-five (13 female, 22 male with a mean age of 11 ± 2.7 year) patients with a diagnosis of allergic rhinitis were enrolled in the study. All patients were symptomatic during the study period. We instructed all patients to stop drugs related to allergic rhinitis two weeks before Holter examination. Individuals with acute rhinosinusitis and nasal polyposis noted on nasal endoscopy were excluded. Gender and age matched 36 healthy subjects (14 female, 22 male, with a mean age of 12 ± 3 year) comprised the control group. Control subjects were chosen from those children admitted to pediatrics outpatient clinic for routine check-up. The ethics committee of Gulhane Military Medical School reviewed and approved the study protocol, and written informed consent was obtained from the curators of the participants.

Diagnosis of allergy

The diagnosis of allergic rhinitis was based on the history, symptoms, and skin prick test (SPT) results performed by an allergologist. The SPTs were performed according to a routine procedure. Fifty-six common aeroallergens with pollens found in the atmosphere, mites (*Dermatophagoides farinea* and *Dermatophagoides pteronyssinus*), molds and animal dander were used. SPTs were applied on the volar surface of the forearm by the same investigator. Negative (50% glycerin saline) and positive (0.1% histamine phosphate) controls were also performed. The skin tests examined at 10 min and the resulting wheal and flare was measured. A test was considered positive if the wheal was 3 mm larger in diameter than the negative control wheal. Drugs that depress the immediate type skin tests such as antihistamines or tricyclic antidepressants were discontinued 7 days prior to SPTs (Demoly et al. 1998). Patients with the suspicion of bronchial asthma according to history and respiratory function tests were not enrolled to the study.

Heart Rate Variability

Twenty-four-hour ambulatory electrocardiographic recordings were obtained from each subject with Rozinn RZ 152 digital holter recorder (Rozinn Electronics, Inc., Glendale, NY, USA). All the patients were told not to make any extraordinary changes in the normal course of their daily life. This was confirmed during the removal

of the device from each patient. Any medication was stopped at least two weeks prior to Holter ECG examination. The time-domain and frequency-domain parameters of heart rate variability were determined by the software of the same device. The time domain HRV parameters that measured in our study were the standard deviation of all normal sinus R-R intervals over 24 hours (SDNN), the standard deviation of all averaged normal sinus R-R intervals for each 5-minute segment in the 24-hour recordings (SDANN), root mean square of successive differences between normal sinus R-R intervals (RMSSD), the ratio of number of all R-R intervals to the height of histogram created by the charting all the RR intervals (HRV triangular index), number of R-R intervals exceeding 50 ms (SNN50 count), the percentage of difference between adjacent normal R-R intervals that are greater than 50 ms computed over the entire 24-hour ECG recording (PNN50).

Among them, RMSSD, SNN50, and PNN50 primarily reflect parasympathetically-mediated changes in heart rate (Kleiger et al. 1992). The other time-domain variables reflect a mixture of parasympathetic, sympathetic, and other physiologic influences. We used power spectral analysis of heart rate with the parameters of low frequency (LF: 0.04-0.15 Hz) which is related to baroreceptor control and is dually mediated by vagal and sympathetic systems, and high frequency (HF: 0.15-0.5 Hz) band reflects respiratory sinus arrhythmia and, thus, cardiac vagal activity (Akselrod et al. 1981; Pomeranz et al. 1985). Also the most indicative parameter of LF/HF is used for assessing the autonomic balance.

In addition to HRV variables, basic rhythm and associated problems such as atrial or ventricular arrhythmias were carefully evaluated.

Statistical Analysis

Continuous variables are expressed as mean \pm 1 standard deviation. We used percent values for categorical and nominal data. Normality tests of variables were assessed by one sample Kolmogorov-Smirnov test. Mann-Whitney *U* test was used for comparisons of variables in two groups because of non-normal data distribution, and one-way ANOVA test was used for comparing normally distributed variables. A *p* value below 0.05 was considered as significant.

Results

There was no statistically significant difference between the patient group and the control group in relation to age and gender. All subjects detected to be in sinus rhythm without episodes of sustained atrial or ventricular arrhythmias. The allergens that the patients showed sensitivity were house dust mites (6%), grass pollen (3%), tree pollen (23%), weed pollen (14%), cockroach (9%), molds (17%), dog (20%), cat (26%) and food (11%), and all the patients were symptomatic during the study period. Clinical characteristics of the patients are summarized in Table 1.

The statistical comparisons between the groups were shown in Table 2. The SDNN, SDANN, and HRV-triangular index were not different between the groups. However, the RMSSD, SNN50 count, and PNN50 values were significantly higher in the patients compared to the control group. While the difference in LF power between control and patient groups was not statistically significant, HF power was significantly higher and LF/HF ratio was

lower in patients than controls.

Discussion

This study showed that HRV parameters, which mainly reflect vagal tone, were increased in patients with allergic rhinitis. HRV parameters were found to be altered in various disorders, such as diabetic neuropathy (Bernardi et al. 1992), heart failure (Saul et al. 1988), preeclampsia (Yokusoglu et al. 2009), acute leukemias (Nevruz et al. 2007), depletion anemias (Yokusoglu et al. 2007a), fetal type Minamata disease (Oka et al. 2002), in preschool children with short nocturnal sleep (Sampei et al. 2006), prima-

ry nocturnal enuresis (Dundaroz et al. 2001; Unalacak et al. 2004), cardiac resynchronization therapy (Akyol et al. 2006) and during adrenocorticotrophic hormone replacement treatment in infants with West syndrome (Hattori et al. 2007).

Our study was performed on pediatric patients with allergic rhinitis. The main reason for choosing allergic rhinitis as the study group is the higher prevalence in the pediatric population. Neural involvement in allergic rhinitis has been investigated previously (Canning 2002; Ishman et al. 2007). Afferent nerves, derived from the trigeminal ganglion and postganglionic autonomic nerves, innervate the nose. These afferent nerves act as a regulator of air-conditioning function of the nose. Activation of nasal afferent nerves can also have profound effect on respiration, heart rate, blood pressure and airway caliber. Dysregulation of the nerves in the nose plays an integral role in the pathogenesis of allergic rhinitis, resulting in not only nasal, but also respiratory and cardiac changes. Shahabi et al. (2006) hypothesized that atopic diseases decrease sympathetic tone in all tissues except in the site of allergic reaction and secondary lymphoid organs via the cytokines which were secreted by T helper subtype 2 cells. Therefore, increased vagal activation indices of HRV as we detected can be explained by this mechanism.

There are a few studies about the HRV in patients with hypersensitivity reactions. In a study by Kazuma et al. (1997), HRV was studied in patients with asthmatic children. They have found that HRV is decreased in these patients. However, Ko et al. (2008) showed that total nasal airflow was significantly decreased and the total nasal airway resistance was significantly increased, and nasal airway changes were significantly correlated with central autonomic system responses in patients with allergic rhinitis.

Table 1. Demographic and Clinical Characteristics of Patients.

Characteristics	Patients (n = 35)
Mean age	11 ± 2.7 years
Gender	
Male	22 (63%)
Female	13 (37%)
Symptom duration	2.6 ± 1 year
Skin test results	
House dust mite	2 (6%)
Grass mixture	1 (3%)
Tree mixture	8 (23%)
Weed mixture	5 (14%)
Cockroach	3 (9%)
Mold mixture	6 (17%)
Dog	7 (20%)
Cat	9 (26%)
Food	4 (11%)

Table 2. Statistical comparison of HRV variables.

	Unit	Patient Group	Control Group	p value
SNN50 Count		21,778 ± 5,877	13,475 ± 6,322	0.012
RMSSD	ms	89 ± 45	47 ± 25	0.002
PNN50	%	33 ± 10	27 ± 7	0.048
HRV-Triangular Index		40 ± 9	39 ± 9	0.783
SDANN	ms	131 ± 45	127 ± 29	0.189
SDNN	ms	148 ± 36	143 ± 31	0.786
LF	n.u.	58 ± 5	57 ± 4	0.834
HF	n.u.	35 ± 5	27 ± 3	0.012
LF/HF		1.6 ± 0.3	2.2 ± 0.4	0.023

SNN50 count, number of R-R intervals exceeding 50 ms; RMSSD, root mean square of successive differences between normal sinus R-R intervals; PNN50, the percentage of difference between adjacent normal R-R intervals that are greater than 50 ms computed over the entire 24-hour ECG recording; HRV triangular index, the ratio of number of all R-R intervals to the height of histogram created by the charting all the RR intervals; SDANN, the standard deviation of all averaged normal sinus R-R intervals for each 5-minute segment in the 24-hour recordings; SDNN, the standard deviation of all normal sinus R-R intervals over 24 hours; LF, low frequency power; HF, high frequency power; n.u., normalized unit.

Different study populations and excluding asthmatic patients may explain the conflicting results. Generally, the HRV is decreased in higher heart rates, which is very common in both child population and beta-adrenergic agent-using patients. Another explanation might be the respiratory changes in asthmatic patients. Respiratory changes have influence on heart rate, thus might have affected the HRV. However, it must be also noted that asthmatic subjects have conflicting features about the autonomic balance. In a study by Kaliner et al. (1982), all allergic subjects showed abnormal beta-adrenergic hyporeactivity and cholinergic hypersensitivity, whereas allergic asthma was singularly associated with excessive alpha-adrenergic responsiveness.

Clinical implications: Increased vagal activation in allergic rhinitis may have some potential implications for clinical use. Anticholinergic drugs such as ipratropium, are frequently used in bronchial asthma. Their potential use in allergic rhinitis is also investigated in a few studies (Meltzer 1992; Kim et al. 2005). However, in some cases, ipratropium was found ineffective (Shusterman et al. 2002). For this reason it may be useful to know level of vagal activation in patients with allergic rhinitis resistant to anticholinergic therapy.

We found increases in HRV parameters which reflect parasympathetic tone in the patient group, although the HRV is accepted as abnormal if there is a decrease in the parameters. Therefore, ventricular arrhythmias are not expected to be increased in these patients. This expectation was also confirmed by the absence of arrhythmias during 24-hour ECG monitoring.

Limitations: We did not perform skin-prick test to the control group. Some of the participants might be allergic without any symptoms of allergy. However, we thought that being symptomatic may be of significance on cardiac autonomic functions.

In conclusion, the HRV is increased in patients with allergic rhinitis. This result implies sympathetic withdrawal and parasympathetic predominance in pediatric patients with allergic rhinitis. We propose that autonomic imbalance may be involved in the pathophysiology of allergic rhinitis in pediatric patients.

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