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Comparison of the acute effects of salbutamol and terbutaline on heart rate variability in adult asthmatic patients

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Comparison of the acute effects of salbutamol and terbutaline on heart rate variability in adult asthmatic patients. B. Eryonucu, K. Uzun, N. Güler, M. Bilge. ©ERS Journals Ltd 2001.

ABSTRACT: This study investigated the effects of β_2-adrenergic agonist therapy on heart rate variability (HRV) in adult asthmatic patients by using frequency domain measures of HRV.

A randomized crossover design was used. Twenty adult patients with asthma were studied. All patients showed a mild-to-moderate decrease in baseline forced expiratory volume in one second. Any diseases that might have influenced the autonomic function were excluded. All patients had a complete physical examination and medical history that revealed no cardiovascular disease or medication. The study used 200 µg inhaled salbutamol and 500 µg inhaled terbutaline. HRV analysis was performed for each 5-min segment, 5 min before inhalation of the study drug and 5, 10, 15, 20, 25 and 30 min after inhalation. Total power (TP: <0.40 Hz), high-frequency power (HF: 0.15–0.40 Hz), low-frequency power (LF: 0.04–0.15 Hz) and LF/HF ratio were calculated.

The LF and LF/HF ratio increased and TP decreased at 5, 10, 15 and 20 min after the salbutamol and the terbutaline inhalation, HF did not change significantly after the salbutamol and terbutaline inhalation.

Acute salbutamol and terbutaline inhalation produce similar effects on heart rate variability and increase sympathetic modulation in the cardiac autonomic activity.
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In clinical cardiology, heart rate variability (HRV) is a valuable noninvasive tool for assessment of autonomic cardiovascular function. Indexes of the HRV reflect cardiac autonomic tone [1, 2]. Decreased HRV is associated with increased mortality and morbidity with various forms of heart disease including myocardial infarction, congestive heart failure and chronic mitral regurgitation [3–10].

The autonomic nervous function of asthmatic children was decreased in comparison to the normal subjects. Further, the autonomic nervous function of asthmatic patients, even in the normal condition in which the patient is free of an asthma attack, differs from that of normal children [11]. In addition, sympathetically mediated HRV (normalized low frequency power) was significantly lower in both asymptomatic and acute asthmatic patients compared to healthy controls. All these findings are consistent with altered sympathetic/parasympathetic regulation of heart rate in subjects with bronchial asthma [12].

Inhaled short acting β_2-adrenergic agonists are the most effective bronchodilator agents available for the treatment of asthma. Side-effects of β-agonists generally stem from activation of β_1-receptors. Cardiovascular effects include tachycardia, palpitation, dysrhythmias, exacerbation of myocardial ischemia, and hypo- or hypertension. These findings suggest that β_2-adrenergic agonists may interfere with autonomic cardiovascular function [13, 14].

Although the effects of salbutamol on HRV in asthmatic children have been established, the effects of β_2-adrenergic agonist therapy, such as salbutamol and terbutaline, on HRV in asthmatic adult patients have not been established [15]. The primary aim of this study was to assess the effect of β_2-adrenergic agonist therapy on HRV in patients with asthma by using frequency domain measures of HRV. In addition, evaluation of whether the effects of a salbutamol differed from those of terbutaline was undertaken.

Material and methods

Study subjects

Twenty patients (mean age 37±6 (range 28–47)) with newly diagnosed or known cases of bronchial asthma were studied. Asthmatic patients were selected consecutively according to the American Thoracic Society guidelines [16]. None of the patients had been receiving oral or inhaled asthma medication (β_2-agonists and corticosteroids) for the previous 2 months. All patients subjects showed mild-to-moderate decrease in baseline forced expiratory volume in one

second. Patients with diabetes mellitus, renal disorders or any diseases that might have influenced the autonomic function were excluded. All patients had a complete physical examination and medical history that revealed no cardiovascular disease or medication. Blood chemistry and urine tests were within normal ranges. Patients also had normal blood pressure, electrocardiography (ECG) and transthoracic echocardiography. The clinical characteristics of patients are shown in table 1. All patients gave informed consent to the study, which had been approved by the hospital ethical committee.

Study design

The study followed a randomized and crossover design. The patients were studied twice, 3 days apart. The studies were performed between 09.00 h and 12.00 h to avoid circadian variation of HRV parameters.

Study drug

The study used 200 μg inhaled salbutamol *via* pMDI (salbutamol aerosol, Ventolin, GlaxoWellcome, UK) and 500 μg inhaled terbutaline also *via* pMDI (terbutaline aerosol, Bricanyl, Astra, Sweden). The salbutamol dose was given by administering two 100 μg doses, while the terbutaline dose was given by administering two 250 μg doses. The subjects directly inhaled the drug without a spacer device after full expiration and then hold their breath for 10 s.

Holter monitoring and heart rate variability analysis

The ambulatory ECGs were recorded by a Del Mar Avionics 483 digicorder recorder (Irvine, CA, USA) 30 min before and 1 h after drug inhalation. All Holter recordings were obtained at supine rest. The subjects quietly breathed during the holter recordings. These recordings were analysed using computer software (Holter analysis system, Del Mar). All recordings were visually examined and manually over-read to verify beat classification. Abnormal beats and areas of artefact were automatically and manually identified and excluded from the analysis. All patients were in sinus rhythm throughout the recordings. The frequency domain analysis of HRV was performed by a fast Fourier transformation. HRV analysis was performed and mean heart rate (HR) calculated for 5 min before inhalation of the study drug and during 6 sequential, 5-min intervals starting after the inhalation of study drugs. The frequency domain variables (ms^2) considered in this analysis were: total power (TP: <0.4 Hz); high-frequency power (HF: 0.15 – 40 Hz); low-frequency power (LF: 0.04 – 0.15 Hz); and LF/HF ratio.

Table 1. – Patients characteristics

Characteristics	Value
Sex female/male	11/9
Age yr	37 ± 6
smoking history n	3
pH	7.38 ± 0.02
P_{CO_2} mmHg	41.5 ± 2.1
P_{O_2} mmHg	98 ± 2
FEV_1 % pred	67 ± 10
FEV_1/FVC	75 ± 9

Data are presented as absolute numbers or as mean ± SD. FEV_1: forced expiratory volume in one second; FVC: forced vital capacity.

Statistical analysis

Data are presented as mean ± SD. The normal distribution of the variables was evaluated using Kolmogorov-Smirnov tests. Measures of frequency domain indices of HRV were log transformed because they were not normally distributed. Data between the groups were compared with Chi-squared test or Fisher's exact test and unpaired two-tailed t-test. The changes of HRV parameters after inhalation of the study drugs were compared with repeated measures of the variance analysis. A two-tailed p-value <0.05 was considered significant.

Results

The changes of HRV parameters after inhalation of the study drugs are shown in table 2 and figures 1 – 3. The changes of HRV parameters after the salbutamol and terbutaline inhalation were similar in the two groups. The changes of HRV parameters in each 5 min segment in the salbutamol group were not statistically significantly different when compared to the same segment in the terbutaline group. HR, LF and LF/HF ratio increased and TP decreased at 5, 10, 15 and 20 min after both the salbutamol and terbutaline inhalation. The highest LF and LF/HF ratio values were observed 5 min after the salbutamol and terbutaline inhalation and the HF did not change significantly after the salbutamol and terbutaline inhalation.

Discussion

The presented findings show that both salbutamol and terbutaline have acute effects on autonomic cardiovascular function in asthmatic adult patients. The analysis of HRV showed that inhalation of salbutamol and terbutaline decreased TP and increased LF/HF and LF. The effects of salbutamol on HRV did not differ from those of terbutaline.

In previous studies, the asthmatic children had an increased parasympathetic drive and decreased sympathetic drive as compared to healthy children. The different autonomic nervous function of asthmatic children is related to the severity of the asthma [11, 17]. In addition, β_2-agonist medication increases sympathetic cardiovascular activity in asthmatic children [18]. Asthmatic children receiving fenoterol showed an

Table 2. – The changes of heart rate variability parameters after salbutamol and terbutaline inhalation

Time period min	Heart rate	TP	LF	HF	LF/HF	Heart rate	TP	LF	HF	LF/HF
	Terbutaline					Salbutamol				
Baseline	74±3	3.78±0.11	2.32±0.11	2.90±0.14	0.80±0.04	74±4	3.74±0.12	2.29±0.14	2.94±0.13	0.77±0.04
0–5	79±3¶	3.41±0.10¶	2.65±0.08¶	2.87±0.12	0.92±0.04¶	81±3¶	3.51±0.11¶	2.63±0.11¶	2.87±0.13	0.91±0.03¶
6–10	82±4¶	3.38±0.09+	2.75±0.08¶	2.91±0.13	0.95±0.06¶	84±4+	3.49±0.10¶	2.77±0.13¶	2.89±0.14	0.96±0.05+
11–15	85±4+	3.48±0.08¶	2.73±0.10¶	2.88±0.09	0.94±0.05¶	85±4+	3.42±0.14¶	2.74±0.12¶	2.86±0.15	0.95±0.03¶
16–20	82±2¶	3.53±0.10¶	2.68±0.09¶	2.83±0.10	0.93±0.03¶	84±3+	3.58±0.12¶	2.65±0.12¶	2.86±0.14	0.93±0.03¶
21–25	79±4	3.58±0.08	2.57±0.08	2.85±0.09	0.89±0.09	81±5¶	3.71±0.13	2.59±0.09	2.90±0.09	0.89±0.04
26–30	77±3	3.72±0.07	2.50±0.07	2.84±0.08	0.88±0.03	78±5	3.75±0.13	2.47±0.07	2.87±0.11	0.86±0.04

Heart rate variability parameters values are expressed as 10-base logarithmic values and given as mean±SD. TP: total power, HF: high-frequency power, LF: low-frequency power. ¶: $p<0.05$ *versus* baseline; +: $p<0.01$ *versus* baseline.

increased adrenergic drive [17]. In concurrence with the present findings, JARTTI *et al.* [19] found that the acute salbutamol inhalation decreased parasympathetic drive and increased sympathetic modulation in the cardiovascular autonomic balance. Two-week salbutamol treatment increased baseline LF variability and LF/HF variability ratio of ECG R-R intervals when compared to the placebo treatment. However, different results were obtained by ROSSINEN *et al.* [20] who reported the commonly used doses of inhaled or nebulized salbutamol induced no acute myocardial ischaemia, arrhythmias or changes in HRV as assessed by Holter monitoring of 24 patients with coronary artery disease and clinically stable asthma or chronic obstructive pulmonary disease. A 4-week salmeterol treatment increased baseline HR, LF/HF variability ratio of R-R intervals. This 4-week salmeterol treatment also decreased baseline HF variability of R-R intervals. As a response to the acute 600 μg of salbutamol, changes in HR and HF variability of R-R intervals were significantly smaller after 4 weeks salmeterol treatment [21].

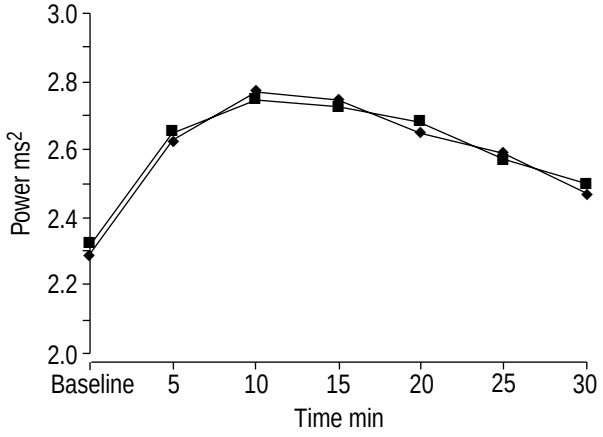

Fig. 1. – The changes of low frequency power components of heart rate variability after the salbutamol (◆) and terbutaline (■) inhalation. Values are expressed as 10-base logarithmic values and given as mean.

The cardiovascular actions of β-adrenergic agonists result from direct myocardial effects that increase the rate and force of contraction and from indirect rate effects that result from baroreceptor reflexes to peripheral dilation [13, 22–24]. In the present study, inhalation of β_2-adrenergic agonists caused an acute and statistically significant augmentation of LF and HR and decrease of TP, which is considered to reflect sympathetic activity. Thus, the observed β_2-adrenergic

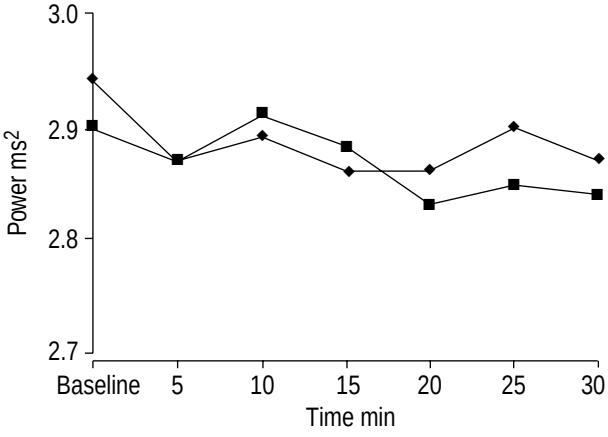

Fig. 2. – The changes of high frequency power components of heart rate variability after the salbutamol (◆) and terbutaline (■) inhalation. Values are expressed as 10-base logarithmic values and given as mean.

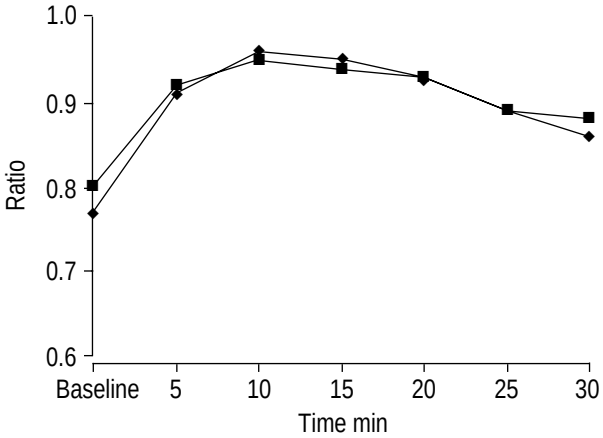

Fig. 3. – The changes of low frequency/high frequency power ratio components of heart rate variability after the salbutamol (◆) and terbutaline (■) inhalation.

agonist-induced changes of HRV may be due to increased β-receptor stimulation.

This study has some limitations. Respiration frequencies could not be determined simultaneously with the Holter monitoring. However, all subjects breathed quietly at rest during the Holter recordings. Thus, the effect of respiration on HRV was minimized. In addition, because study population consisted of patients who did not receive β_2-agonists for the previous 2 months, the results may be affected from receptor regulation in regular β_2-agonist use. Therefore, the results cannot be extrapolated to all asthmatic patients. The uncontrolled and unblind nature of this study was another limitation.

In conclusion, the present findings suggest that acute salbutamol and terbutaline inhalation elicited similar changes of heart rate variability and increased sympathetic modulation in the cardiac autonomic activity. Increased sympathetic activity may be implicated in the pathogenesis of a number of cardiovascular risk factors, including insulin resistance, hypertension, and the evolution of cardiovascular hypertrophy [25]. In addition, many recent studies have shown that patients with coronary artery disease and decreased vagal or increased sympathetic cardiac modulation, assessed by heart rate variability, have increased susceptibility to sudden coronary death, increased mortality and morbidity [26–28]. For these reasons, further studies are needed to evaluate the effects of salbutamol and terbutaline on cardiovascular autonomic activity and long-term cardiac mortality and morbidity in asthmatic patients with heart disease.

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