Assessment of the Long-Duration Effect of Inhaled Long-Acting Bronchodilator Salmeterol on Cardiac Autonomic Control in Adult Asthma Patients

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Abstract

The asthma patients usually received regular use of inhaled corticosteroid combined with long-acting β agonist (LABA) for their asthma control. The inhaled LABA achieved the bronchodilation effect through sympathetic activation in airways of asthma patients. These LABAs might have the cardiovascular effects such as palpitation, tachycardia and QTc prolongation. There are studies investigating the short-duration effect of LABA on cardiac autonomic control in asthma patients. However, the long-duration effect of inhaled LABA on cardiac autonomic control in adult asthma patients remains lacking. In this study, we explored the long-duration effect of inhaled bronchodilator Salmeterol (one kind of LABAs) on cardiac autonomic control with heart rate variability (HRV) analysis in adult asthma patients

.Serial resting, surface ECGs were recorded at different time intervals (from baseline to 180th min) after inhalation of Salmeterol in eligible adult asthma patients. Mean heart rate (mean RR), standard deviation of normal RR interval (SDNN), normalized low frequency band power (LFn), normalized high frequency band power (HFn) and the ratio LF/HF were obtained from analysis of heart rate variability (HRV) at these different time intervals.

Significant increase of LF/HF after inhalation of Salmeterol as compared with baseline time interval was noted. Significantly increased LFn and decreased HFn without significant change of LF/HF were also noted as compared with baseline interval. Besides, significantly increased mean RR and SDNN were also noted.

In this study, during the 3-hour duration after inhalation of Salmeterol in adult asthma patients, HRV analysis revealed that significant cardiac-sympathetic activation occurred at the 60th min, which precedes the maximal effect of bronchodilation occurred 2 to 4 hours after inhalation of Salmeterol.

1. Introduction

Asthma is a chronic inflammatory airway disease with increasing health problem worldwide. Exaggerated parasympathetic airway response to different stimuli such as cold air, exercise, allergen and inhaled methacholine could be one of the pathogenesis of asthma attack. Recent investigations also revealed some association between altered cardiac-autonomic control and asthma control [1, 2]. For the control of inflammation and relief of bonchospasm in asthma, the routine use of inhaled drugs containing corticosteroids combined with long-acting β agonists (LABAs) have been recommended [3].

The β agonists achieved the bronchodilatation effect via activation of the sympathetic β2 receptors on airway smooth muscles. However, the β agonists also have the effect of sympathetic activation on cardiovascular system. The patients may experience palpitation, hand tremor, tachycardia and QTc prolongation. For the above reasons, there are investigations revealed that increased mortality and morbidity in the patients with chronic airway diseases occurs after regular use of inhaled β agonists [4]. On the contradictory, regular use of LABAs seemed to have airway protection effect to improve asthma control [5].

Recently, heart rate variability study (HRV) has been widely applied to investigate the sympathovagal balance during diverse clinical conditions [6, 7]. Increased cardiac-sympathetic activity after inhalation of short-acting β agonists (SABAs) has been noted [8]. Besides, there is a study investigating the short dureation effect of inhaled LABA on cardiac-autonomic control in asthma patients. The study result revealed no significant change of sympathovagal balance during the short duration effect of inhaled LABA [9]. But the study of the long-duration effect of inhaled LABA on cardiac autonomic control in adult asthma remains lacking.

In this study, we aimed to explore the long-duration (3 hours) effect of inhaled bronchodilator Salmeterol (one

kind of LABA) on cardiac autonomic control with heart rate variability (HRV) analysis in adult asthma patients.

2. Methods

2.1. Subjects and study design

A cross-section clinical study was used and approved by the local institutional ethic committee. The subjects who were newly diagnosed asthma (American Thoracic Society criteria and GINA guideline) [10] and never received medicine for asthma control were recruited. The subjects with any of the following conditions such as: cardiovascular diseases, taking cardiovascular drugs, neurological diseases, psychiatric illness, diabetes or poor communication, were excluded from this study.

2.2. Experimental procedures

On the day of interview, the subjects were informed with the written consent and were briefed on the methodology of the study and the potential adverse effects of inhaled bronchodilator (Salmeterol). History and symptom review were recorded such as the family history of asthma, DM, hypertension, arrhythmia and atopy. Baseline pulmonary function was obtained before inhaled bronchodilator (Salmeterol) is given. Then the subjects were lying on the comfortable bed in a calm room. Serial ECGs (at least 5 min length) were recorded at the different time intervals (baseline, 0^{th}, 8^{th}, 20^{th}, 32^{th}, 45^{th}, 60^{th} and 180^{th} min after Salmeterol 25 μg 2 puffs).

2.3. Data acquisition

Data acquisition of ECG signal with sampling rate 250 Hz via A/D converter was performed and the data were stored in personal computer. Detection of peaks of R waves and R-R interval sequence calculation were also performed. The cardiac tachogram, which indicates the instantaneous R-R intervals along time axis, was obtained for the analysis of heart rate variability (HRV). We used the algorithm of fast Fourier transform (FFT) for analysis of heart rate variability. Spectral analysis of HRV provides a non-invasive tool for assessing the regulation of the autonomic system. The power of each spectrum in HRV is calculated at the different frequency bands. The low frequency band (LF) and the high frequency band (HF) are defined from 0.04 to 0.15 Hz, and from 0.15 to 0.40 Hz, respectively. The LF component of spectrum is influenced by the combined effect of sympathetic and parasympathetic activation. The HF component mainly reflects vagal activation and the. LF/HF ratio represents sympathovagal balance. On HRV study, mean RR interval, standard deviation of RR interval (SDNN), normalized low frequency power (LFn), normalized high frequency power (HFn), and LF/HF were obtained [7].

2.4. Statistical analysis

Statistical analysis was carried out by using SPSS 11.0.1 software (SPSS Inc., Chicago, USA). Data are presented as mean ± standard deviation. Wilcoxon signed-rank test was used for comparison between two continuous dependent variables. P value less than 0.05 is regarded as statistically significant

3. Results

Ten eligible subjects were enrolled into this study. The demographic data is shown in Table 1.

Table 1 demographic data in our study

Age (yrs)	40.8 ± 13.5
Gender (M/F)	5/5
Body weight (kg)	61.4 ± 12.0
Body height (cm)	163.6 ± 6.6
FEV1/FVC (%)	77.1 ± 8.6
FEV1 (L)	2.99 ± 0.85
PEF (L/min)	396 ± 102

Figure 1 reveals the fluctuation of frequency domain variables along time axis during 3 hours period after inhalation of Salmeterol. Significant elevation of LF/HF occurs at 60^{th} min after inhalation of Salmeterol as compared with baseline (3.18±3.89 vs 2.06±2.65; p= 0.028) (Figure1A). Significant increase of LFn occurs at 180^{th} min after inhalation of Salmeterol as compared with baseline (59.23±10.81 vs 50.45±16.29; p= 0.046) shown in Figure 1B. In the meanwhile, significant reduction of HFn is also noted at 180^{th} min interval as compared with baseline (35.14±12.48 vs 41.92±18.22; p=0.046) shown in Figure 1B.

Figure 2A and 2B show the fluctuation of time domain variables (mean RR and SDNN, respectively) along time axis during 3 hours period after inhalation of Salmeterol. Significantly increased mean RR (32^{th} min: 887.98±65.84 vs 845.05±108.33; p=0.017) and SDNN (32^{th} min: 52.54± 32.15 vs 45.20±35.35; p= 0.037. and 45^{th} min: 56.79±31.14 vs 45.20 ±35.35; p=0.028) after inhalation were noted.

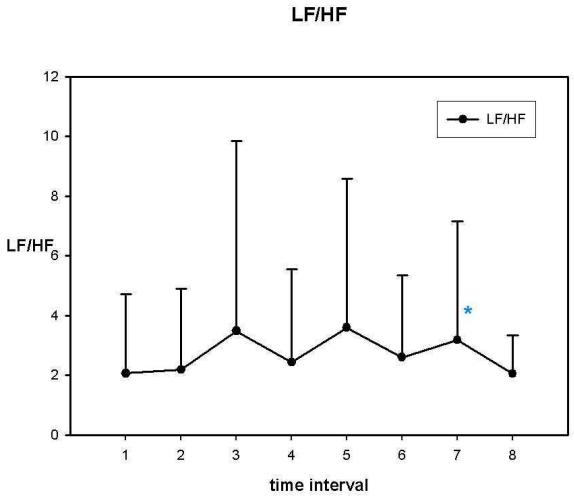

Figure 1A. LF/HF at different time intervals. Time interval 1: baseline , 2: 0 min, 3: 8th min, 4: 20th min, 5: 32th min, 6:45th min, 7: 60th min 8: 180th min after inhalation of Salmeterol.
*: P < 0.05 significant difference as compared with baseline

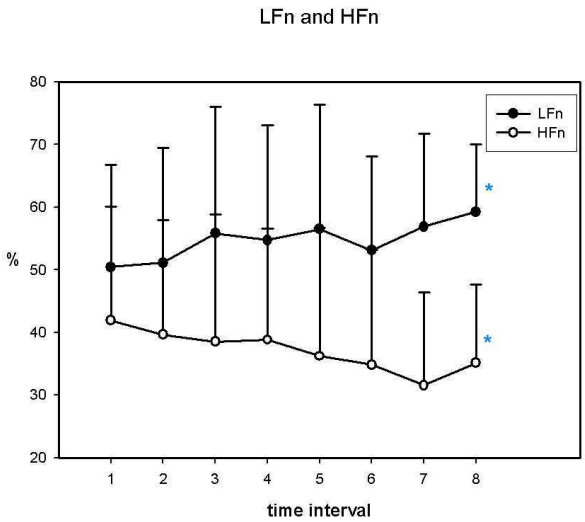

Figure 1B. LFn and HFn at different time intervals. Time interval 1: baseline, 2: 0 min, 3: 8th min, 4: 20th min, 5: 32th min, 6:45th min, 7: 60th min 8: 180th min after inhalation of Salmeterol.
*: P < 0.05 significant difference as compared with baseline.

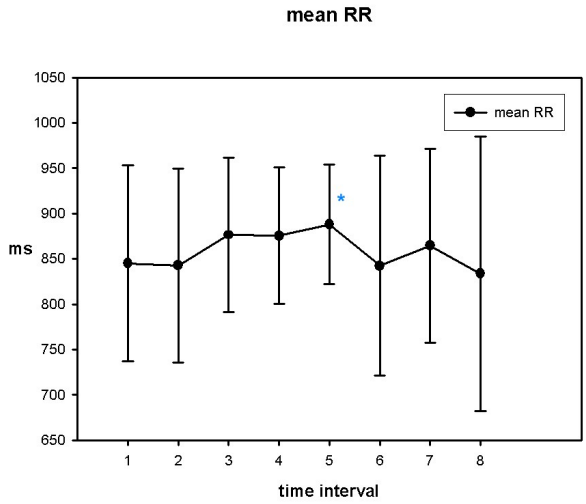

Figure 2A. mean RR at different time intervals.
Time interval 1: baseline, 2: 0 min, 3: 8th min, 4: 20th min, 5: 32th min, 6:45th min, 7: 60th min 8: 180th min after inhalation of Salmeterol.
*: P < 0.05 significant difference as compared with baseline.

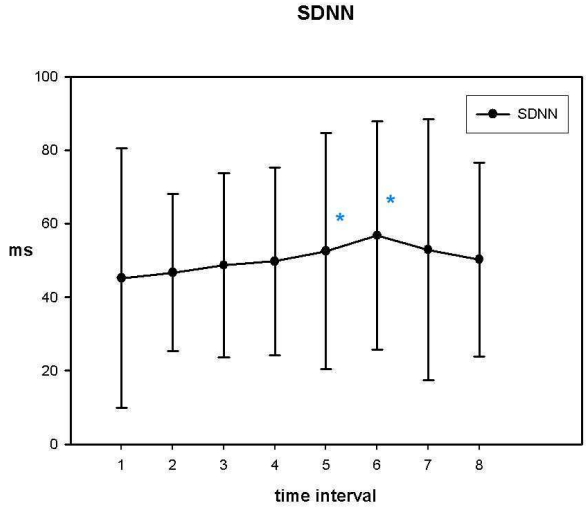

Figure 2B. SDNN at different time intervals.
Time interval 1: baseline, 2: 0 min, 3: 8th min, 4: 20th min, 5: 32th min, 6:45th min, 7: 60th min 8: 180th min after inhalation of Salmeterol.
*: P < 0.05 significant difference as compared with baseline.

4. Discussion and conclusions

The novel finding of our study is the significant increase in LF/HF around 60th min during 3-hour period after inhalation of Salmeterol with HRV analysis.

Previous investigation about the cardiovascular safety of long-term use of Salmeterol revealed no significant association with unfavourable change of cardiac function or increase in cardiovascular side effects [11]. Another study about LABA also revealed no significant change in HRV parameters [9]. Altered cardiovascular autonomic

response after Salmeterol treatment was also noted [12]. The possible explanation for these discrepancies may come from different study endpoints (arrhythmias and QTc vs HRV), different dosages of drug (30 vs 50 μg Salmeterol inhalation), different treatment regimens (daily use vs single use of Salmeterol) and different measured time intervals (30 min vs 180 min).

Another interesting finding of our study is the significant increase in LFn and simultaneous significant decrease in HFn at 180th min after inhalation of Salmeterol without significant LF/HF change at the same time. The interpretation of these findings about sympathovagal balance needs further investigation.

A decrease in RR interval is a measure of centrally mediated sympathetic activity and is influenced by respiration. Another parameter SDNN reflects an estimate of overall HRV. In our study, we found significant simultaneous increases in mean RR and in SDNN at 32th min after inhalation without significant elevation of LF/HF. These dissociative findings seem to be compatible with the previous investigation [13].

Small sample size is the main limitation of our study. Another limitation is lack of comparison with control group. Large sample size and case-control group study will be needed for further investigation on the cardiac-autonomic effect of LABA.

According to the literature, the maximal bronchodilation effect of Salmeterol which was mediated through sympathetic receptor activation in airways will occur about 2 to 4 hours after inhalation [14]. In our study, the significant cardiac-sympathetic activation (LF/HF) occurs about 1 hour after inhalation of Salmeterol. It seems to reflect the fact that the significant cardiac-sympathetic activation precedes the maximal respiratory-sympathetic activation after inhalation of Salmeterol.

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