Comparison of the effects of ipratropium bromide and salbutamol on autonomic heart rate control

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Abstract Aims B2-agonists and anticholinergic drugs may alter cardiac autonomic modulation. The aim of this study was to investigate the effects of inhaled salbutamol and ipratropium bromide on heart rate variability (HRV).

Methods and results A randomized, double-blind, crossover design study was conducted on 13 healthy volunteers. Salbutamol, ipratropium or placebo was administered in three different testing sessions. Time domain parameters; mean R–R interval (mean-RR), the standard deviation of R–R interval (SDNN) and the root mean square of successive R–R interval differences (RMSSD) and power spectral analysis of HRV were assessed in the supine position and during handgrip exercise before and after taking each drug. In time domain analyses, ipratropium administration resulted in a reduced mean-RR, SDNN and RMSSD during handgrip exercise compared with baseline values (775 ± 30 ms vs. 748 ± 21 ms, P < 0.05; 57 ± 5 ms vs. 50 ± 5 ms, P < 0.05; 30 ± 2 ms vs. 26 ± 2 ms, P < 0.01, respectively). This effect was not detected with salbutamol or placebo administration. In frequency domain analyses, salbutamol but not ipratropium and placebo inhalation increased high frequency power/total power during handgrip exercise compared with baseline (0.09 ± 0.02 vs. 0.12 ± 0.02, P < 0.05).

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Conclusion  Ipratropium inhalation may alter autonomic control of the heart rate in therapeutic doses during mild sympathetic stimulation in healthy subjects, while salbutamol does not show these effects. © 2004 The European Society of Cardiology. Published by Elsevier Ltd. All rights reserved.

Introduction

Inhaled short acting B₂-adrenergic agonist salbutamol and anticholinergic ipratropium are drugs widely used in the treatment of reactive airway disease. However, during the course of therapy with these drugs, several cardiac adverse effects including tachycardia, tremor, palpitation, arrhythmias have been reported [1–4]. Few studies have focused on the effects of these drugs on cardiac autonomic function that may be related to these side effects [5–8]. Head to head comparison of the effects of these two agents on autonomic modulation showed that both drugs did not alter autonomic function at rest [9]. However, to date, the effects of salbutamol and ipratropium bromide on HRV have not been studied, comparatively by adding a manoeuvre such as mild exercise. It is known that heart rate and HRV parameters change under different conditions such as upright position, mental stress and exercise that induce sympathetic stimulation and, thus, they have been used to detect autonomic alteration. Therefore, the aim of this study was to investigate and compare effects of salbutamol and ipratropium on cardiac autonomic function both at rest and during mild exercise.

Materials and methods

Subjects

Thirteen healthy male volunteers, mean age 26 ± 2 years (range 23–28 years), were studied in a randomized, double-blind, placebo-controlled, crossover design study. Subjects with coronary artery disease, respiratory, neurological or any other systemic disorder that might influence autonomic function, allergy to the drugs, history of smoking and diabetes mellitus were excluded from the study. All participants were asked to refrain from alcohol and caffeine-containing beverage and strenuous exercise for 24 h prior to each study session.

Study design

All subjects having had a light breakfast after an overnight period of fasting were taken to a quiet, dimly lit room maintained at 22–24 °C. The studies were performed between 09:00 am and 12:00 noon to avoid circadian variation in HRV parameters. An instruction period preceded the first session to familiarize subjects with the use of inhalers. All participants underwent spirometric pulmonary function tests (Spirobank, MIR, Italy) before taking each drug and just after the study was completed to detect whether the drugs were absorbed sufficiently. All participants were taken to the test room and rested in the supine position for at least 15 min on a comfortable bed to stabilize heart rate. After this resting period, HRV parameters were calculated from the continuous electrocardiographic (ECG) records taken in the supine position for 5 min and during handgrip exercise in the sitting position at 5 min intervals. Participants performed isometric handgrip exercise at 25% of their predetermined maximum voluntary capacity by 45 s contraction and 15 s rest per minute using a Jamar hydraulic hand dynamometer (Sammons Preston, Canada). After baseline data were obtained, subjects self-administered two puffs from one of the three identical metered-dose inhalers, containing salbutamol (100 µg), ipratropium (20 µg) or placebo. All subjects directly inhaled the drug after full expiration and then held their breath for 10 s. During inhalation, a spacer device was used to maximize and standardize drug delivery to the lower airways as much as possible. The order of administration of test drugs was randomized and subjects were blinded to the test drug received. Forty-five minutes later, the participants once again underwent the same procedures described above. Blood pressure measurements were obtained from the left arm supported at heart level by a trained physician using a sphygmomanometer prior to and after each period. Previously, it has been shown that the duration of action is nearly 6 h (for ipratropium) and 10 h (for salbutamol), and half lives of both the drugs are about 3.5 h [10,11]. Therefore, all participants attended three testing sessions separated by at least 72 h to eliminate the possibility of carryover effects from the previous test for each study drug.

HRV analysis

Heart rate variability (HRV) analysis is a useful noninvasive method, especially in detecting
diabetic neuropathy and risk stratification after myocardial infarction [12]. It has also been used for assessing numerous cardiac and noncardiac disorders. Time domain indices and spectral components of HRV allow the quantifications of autonomic nervous system control of the heart. It is well known that mental stress and some manoeuvres such as orthostatic change may easily affect the reliability of this method and may be its main limitation. However, HRV analysis may reveal subtle alteration in cardiac autonomic modulation and end organ responses to complex neuronal reflexes [13].

In our study to test cardiac autonomic functions, HRV analysis was used and to overcome the limitations of the method, the study was performed in three sessions and in a randomized, double-blind and crossover fashion. For HRV analysis, ECG data were fed into a personal computer and digitized via an analogue-to-digital conversion board (PC-ECG 1200, Norav Medical Ltd, Israel). All records were visually examined and manually over-read to verify beat classification. Abnormal beats and areas of artifact were automatically and manually identified and excluded. HRV analysis was performed using Heart Rate Variability Software (version 4.2.0, Norav Medical Ltd, Israel). Both time and frequency domain analyses were performed. For the time domain, mean R–R interval (mean-RR), the standard deviation of R–R interval (SDNN) and the root mean square of successive R–R interval differences (RMSSD) were measured. For the frequency domain analysis, power spectral analysis based on a Fast Fourier transformation algorithm was used. Three components of power spectrum were computed following bandwidths: high frequency (HF) (0.15–0.4 Hz), low frequency (LF) (0.04–0.15 Hz) and very low frequency (VLF) (0.003–0.04 Hz). The LF/HF ratio, LF/total power and HF/total power were also calculated.

### Statistical analysis

Data are presented as mean ± SEM. Non-parametric continuous variables were analyzed with Wilcoxon signed rank test. A P-value <0.05 was considered as statistically significant.

### Results

All participants tolerated the study well although they inhaled two puffs from each drug containing salbutamol (100 μg) and ipratropium (20 μg), which are routinely used doses and no adverse side effects such as palpitation, tremor, headache and rhythm disturbance were observed. There were no statistically significant differences in all baseline HRV parameters obtained before each drug administration (P > 0.05).

Ipratropium administration resulted in a significant decrease in mean-RR, SDNN and RMSSD obtained during handgrip exercise compared with their baseline values (P < 0.05 for heart rate and SDNN, P < 0.01 for RMSSD), while it did not change HRV parameters during supine position. These kinds of effects were not observed with salbutamol or placebo.

In frequency domain parameters, salbutamol but not placebo or ipratropium administration resulted in an increase in HF/total power

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Time and frequency domain parameters during handgrip exercise before and after drug administration</th>
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<tbody>
<tr>
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<td>Ipratropium Pre-drug</td>
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<tr>
<td>Mean-RR</td>
<td>775 ± 30</td>
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<tr>
<td>SDNN</td>
<td>57 ± 5</td>
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<tr>
<td>RMSSD</td>
<td>30 ± 2</td>
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<td>LF</td>
<td>212 ± 23</td>
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<td>HF</td>
<td>71 ± 12</td>
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<tr>
<td>LF/total power</td>
<td>0.36 ± 0.03</td>
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<tr>
<td>HF/Total power</td>
<td>0.12 ± 0.02</td>
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<tr>
<td>LF/HF ratio</td>
<td>4.03 ± 0.88</td>
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*P < 0.05; **P < 0.01 compared with pre-drug values.
compared with baseline values during handgrip exercise ($P < 0.05$). There were no differences with respect to other frequency domain parameters amongst the drugs. The results of time and frequency domain parameters of HRV during handgrip exercise after each drug administration are shown in Table 1.

**Discussion**

The principal findings of the present study are that: (1) inhalation of a single dose of ipratropium decreases parasympathetic modulation of heart rate in healthy men, (2) this decrease in parasympathetic modulation of the heart occurs during mild exercise but not at rest, (3) salbutamol did not affect HRV parameters both at rest and during exercise (Fig. 1).

Anticholinergic and $\beta_2$-adrenergic agents are widely used as a bronchodilator therapy in treatment of patients with respiratory system disorders. However, their systemic adverse effects associated with the autonomic nervous system are well known. Inhaled $\beta_2$-agonists have been associated with tachycardia, tremor, arrhythmias, and increased risk of death from asthma [1,2]. Similarly, the use of high doses of inhaled ipratropium has been associated with tachycardia and headache, suggesting a degree of systemic absorption [3,4]. Most of the previous studies analyzing the effects of salbutamol and ipratropium on the cardiovascular system have focused on the heart rate and blood pressure changes, which may have led to omission of the more subtle effects of these drugs on cardiovascular stability. Systemic administration of $\beta_2$-agonists and anticholinergic drugs have been shown to impair normal autonomic heart rate control [14,15]. However, the effect of the inhaled form of these drugs on cardiac autonomic function has not been well defined. Different results have been reported regarding the effect of these drugs on heart rate variability. In a study examining the effect of ipratropium on respiratory sinus arrhythmia, a non-specific indicator of parasympathetic modulation of heart rate, it has been shown to have no effect on asthmatic subjects [5]. Jartti and coworkers [6] showed that acute salbutamol inhalation decreased parasympathetic drive and increased sympathetic modulation of the cardiovascular autonomic balance. Two-week salbutamol treatment increased baseline LF variability and LF/HF variability ratio of ECG R–R intervals when compared with placebo. In our study, the failure to

**Figure 1** RMSSD, which illustrates parasympathetic modulation, significantly decreased after ipratropium inhalation (a) but not salbutamol (b) and placebo (c) during handgrip exercise.
observe any increase in LF/HF ratio after salbutamol inhalation might have resulted from the single dose use of the drug. Eryonucu and coworkers [7], comparing the effect of salbutamol and terbutaline on heart rate variability, showed that these two drugs produced similar effects on heart rate variability and increased sympathetic modulation of the cardiac autonomic activity. In our study, salbutamol inhalation did not change LF/HF ratio. We conducted the study on healthy subjects and compared with placebo, whereas Eryonucu and coworkers [8] performed their study on adult asthmatic patients and did not compare the two drugs with placebo. In addition, since it is well known that circadian rhythm of neural cardiac regulation assessed by HRV is altered in patients with bronchial asthma, the disease might have itself altered autonomic function [16].

In accordance with our findings, Rossinen and coworkers [8] showed that the commonly used doses of inhaled or nebulized salbutamol induced no acute myocardial ischaemia, arrhythmia or changes in HRV. To the best of our knowledge, our study is the first suggesting that inhaled ipratropium but not salbutamol attenuates parasympathetic modulation of the heart. Previously, Dagnone and Parlow [9] suggested that inhaled salbutamol and ipratropium do not alter autonomic control of the cardiovascular system in young healthy male subjects. However, in this study, only measurement of baroreflex sensitivity and power spectral analysis was done. In addition, time domain parameters of HRV especially RMSSD, which illustrates parasympathetic activity, and SDNN, which illustrates overall HRV were not studied. Furthermore, the changes on exercise were not tested. In our study, after ipratropium inhalation mean-RR, RMSSD and SDNN decreased during handgrip exercise but not at rest (supine). This observation suggests that decreased parasympathetic modulation induced by ipratropium may only be apparent when combined with sympathetic stimulation. Ipratropium rendered the subjects unable adequately to augment their parasympathetic drives, which may counterbalance sympathetic stimulation. This may explain why Dagnone and Parlow [9] could not demonstrate any significant change in HRV parameters with the use of these drugs in the supine position.

In this study, we could not observe changes in absolute powers of LF, HF, and LF/HF ratio that reflect sympathovagal balance with both ipratropium and salbutamol inhalation. However, we observed that during handgrip exercise HF/total power ratio increased with salbutamol inhalation but not ipratropium. In accordance with the findings of time domain analysis, increased HF/total power ratio seen with salbutamol inhalation but not with ipratropium supports the consideration that ipratropium attenuates the parasympathetic drive, which may counterbalance sympathetic stimulation during handgrip exercise.

In our study, the reason why ipratropium did affect time domain parameters rather than frequency parameters might have resulted from the breathing rate. Because it is well known that a controlled breathing rate is needed for a reliable assessment of cardiac vagal outflow in spectral analysis, and the time domain measure RMSSD is not affected by changes in the breathing rate [17]. These findings suggest that RMSSD is more suitable for the measurement of cardiac vagal outflow during ‘free-running’ ambulatory conditions. In our study, controlled breathing was not performed and possible effects of these drugs on respiratory mechanics may explain why ipratropium altered time domain but not frequency domain parameters.

The importance of parasympathetic control of the heart has been elicited by a number of different studies. Reduced parasympathetic activity is associated with arrhythmias and sudden cardiac death after an episode of myocardial ischaemia [18,19]. Individuals with cardiopulmonary disease exhibiting a decrease in parasympathetic control [20] and the patients with hypoxaemic COPD may have subclinical autonomic neuropathy and prolonged electrocardiographic corrected QT interval [21]. Further reduction in parasympathetic tone with inhaled ipratropium may make these patients prone to arrhythmias.

**Study limitations**

The present study included not only a small number of healthy volunteers but also short-term records were obtained. Therefore, our results do not reflect the overall effects of these drugs on cardiac autonomic function and the results may not be completely generalized to all patients with respiratory diseases. Furthermore, it is not clear that the observed changes are permanent or whether autonomic cardiac function returns to normal some time after inhalation. In addition, the study was planned only for comparison of the two drugs but not for drug interaction and the difference between the study drugs was evident only in time domain parameters. Therefore, our results should be interpreted with caution.
Conclusion

Ipratropium inhalation may alter autonomic control of the heart rate in therapeutic doses during mild sympathetic stimulation in healthy subjects, while salbutamol does not show these effects. However, the association between impaired cardiac autonomic control resulting from ipratropium use and cardiovascular events needs to be confirmed by larger scale studies.

References