Effects of Inhaled Albuterol and Ipratropium Bromide on Autonomic Control of the Cardiovascular System*

A. Joel Dagnone, BSc; and Joel L. Parlow, MD, MSc

Study objective: Systemic administration of β-agonist and anticholinergic drugs markedly impair normal autonomic heart rate control. The purpose of this study was to quantify and compare the effects of therapeutic doses of inhaled albuterol and ipratropium on autonomic control of the cardiovascular system.

Design: Randomized, double-blind, placebo-controlled, crossover design study.

Setting: Tertiary-care hospital.

Subjects: Twelve healthy male volunteers.

Interventions: Subjects self-administered four puffs through a spacer device from one of three identical inhalers containing albuterol (100 μg per puff), ipratropium (20 μg per puff), or placebo in three different testing sessions.

Measurements: ECG and noninvasive continuous BP traces were recorded at baseline and from 45 to 75 min after administration of the drug. Autonomic control of the cardiovascular system was quantified by analysis of spontaneous baroreflex sensitivity and power spectral analysis of heart rate variability.

Results: Neither albuterol nor ipratropium caused a significant alteration in baroreflex sensitivity, normalized low-power frequency, or normalized high-power frequency. No adverse effects were reported by subjects.

Conclusions: Inhalation of four puffs of albuterol (400 μg) or ipratropium (80 μg) does not alter the autonomic control of the cardiovascular system in young, healthy male subjects.

(CHEST 1997; 111:1514-18)

Key words: albuterol; baroreflex; bronchodilators; heart rate; heart rate variability; ipratropium bromide; parasympathetic nervous system; sympathetic nervous system

Abbreviations: BRS=baroreflex sensitivity; HRV=heart rate variability; PNS=parasympathetic nervous system; RR interval=time between two successive R waves of ECG (heart period); SNS=sympathetic nervous system

---

Albuterol (salbutamol), a β2-receptor agonist, and the anticholinergic ipratropium bromide are two commonly used drugs in the treatment of reactive airway disease. In addition to their local bronchodilating effects, inhaled albuterol and ipratropium are also capable of causing untoward systemic effects. The use of inhaled β2-agonists has 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.\(^3\)\(^4\) Past investigators have studied changes in heart rate and blood pressure (BP) to measure the cardiovascular effects of albuterol and ipratropium.\(^5\)\(^6\) However, these measures may be insensitive to the more subtle effects these drugs exert on the autonomic nervous system and its control over the cardiovascular system. Furthermore, heart rate and BP are influenced by changes in inherent autonomic nervous system activity, thus confounding the interpretation of the cardiovascular effects using these markers.\(^7\) Recently, a number of noninvasive methods have been developed to quantify the autonomic control of the cardiovascular system. Spontaneous baroreflex sensitivity (BRS) represents an index of beat-by-beat parasympathetic nervous system (PNS) control of heart rate.\(^5\)\(^9\) Spectral analysis of heart rate variability (HRV) allows the quantification of the...
relative influence of the PNS and sympathetic nervous system (SNS) input on the heart.\textsuperscript{10,11}

Impairment of autonomic control of heart rate is strongly associated with adverse outcome following episodes of myocardial ischemia or infarction.\textsuperscript{12-14} Since many patients with chronic obstructive lung disease have coexisting ischemic heart disease, preservation of autonomic control of the heart may be an important goal in the treatment of these patients during periods of stress, hypoxemia, and acidosis, which may accompany exacerbations of their pulmonary disease. Since systemic administration of \(\beta\)-agonist and anticholinergic drugs markedly impairs normal autonomic heart rate control,\textsuperscript{9,15} it would be important to determine whether inhalation of these agents causes a similar effect. The purpose of this study was to quantify and compare the effects of therapeutic doses of inhaled albuterol and ipratropium on autonomic control of the cardiovascular system.

\section*{Materials and Methods}

\subsection*{Subjects}

Following approval by the Queen's University Research Ethics Board, 12 healthy male volunteers, aged 18 to 27 years, were studied in a randomized, double-blind, placebo-controlled, crossover design study. A minimum sample size of 11 subjects was determined to be necessary to detect a decrease in BRS of 40% with a power of 0.80 and alpha error of 0.05. Subjects were excluded from the study if they had documented history, symptoms, or physical signs of respiratory or cardiovascular disease, diabetes, allergy to study drugs, or smoking, or had used any medications acting on the respiratory, cardiovascular, or nervous systems. Women were not studied owing to the variation in hormonal effects on the autonomic system during different times in the menstrual cycle.\textsuperscript{16} Written informed consent was obtained from all subjects. Testing was performed between 7 and 11:30 AM, with subjects having abstained from caffeine-containing beverages and alcohol for 12 h and having avoided strenuous exercise for 24 h prior to each study period.

\subsection*{Procedure}

Each volunteer attended three testing sessions separated by at least 48 h to eliminate the possibility of carryover effects from the previous test. Subjects were studied in a semireclining position in a quiet, dimly lit room. An instruction period preceded the first session to familiarize subjects with the use of inhalers. Subjects self-administered four puffs from one of three identical metered-dose inhalers, containing albuterol (100 \(\mu\)g per puff), ipratropium (20 \(\mu\)g per puff), or placebo. These doses are at the high end of the therapeutic range and have been shown to be clinically efficacious and equipotent.\textsuperscript{3,17,19} Single repeated puffs separated by 30 s were administered.\textsuperscript{20} A spacer device was used to maximize and standardize drug delivery to the lower airways as much as possible.\textsuperscript{21,22} The order of administration of test drugs was randomized and subjects were blinded to the test drug received. Subjects were questioned before and after each testing session to identify any side effects from the test drugs.

Oscillometric BP (Dinamap; Critikon; Petersboro, Ontario), peak expiratory flow (Mini-Wright Peak Flow Meter; Airmed; London), and respiratory rate were assessed prior to all interventions. Monitoring consisted of lead II ECG (Tektronix; Beaverton, Ore) and noninvasive continuous BP by the volume clamp method (Finapres 2300; Ohmeda; Englewood, Colo). Respiratory rate was paced by a metronome at each subject's natural respiratory rate with a minimum of 12 breaths/min.\textsuperscript{23} BP and ECG traces were recorded for 12 min at baseline, and for the period from 45 to 75 min after administration to reflect the time of peak serum levels and peak improvement in pulmonary function after albuterol and ipratropium.\textsuperscript{3,17,18,24} The data from 45 to 60 min (time 1) and 60 to 75 min (time 2) after drug administration were compared so as to ensure sampling during the period of peak effect.

\subsection*{Data Analysis}

Continuous ECG and BP traces were digitized by a 12-bit analog-digital converter at a sampling rate of 1,000 Hz (CIO DAS-16) and stored on computer. During digitization, systolic and diastolic BP and time between two successive R waves of ECG (RR intervals) were measured and recorded for every heart beat. Data for each study period were placed in coded files and analyzed by an investigator blinded as to study condition. Cardiac BRS was calculated using the spontaneous baroreflex method, which identifies series of spontaneously occurring increases and decreases in BP that are accompanied by appropriate baroreflex-mediated responses in RR interval. Detailed descriptions of the method have been published previously.\textsuperscript{9,25} For each of the hemodynamic recordings, the computer software selected all sequences of three or more successive heart beats in which there were concordant increases or decreases in systolic BP and RR intervals. The systolic pressure and RR interval points for these sequences were plotted on an x-y curve, and linear regression was applied to each of the sequences. An average regression slope of all sequences detected during each recording period was thereby calculated. This slope represents the cardiac BRS (ms/mm Hg) for any study condition and has been shown to correlate with values obtained by the vasoactive method.\textsuperscript{9}

Spectral analysis was carried out using methods published previously.\textsuperscript{10,26} For each study period, a time series of 512 consecutive RR intervals (representing approximately 8 to 10 min) was selected from stationary data free from artifact. A fast Fourier transformation was applied to the time series to generate a power spectral curve. This power spectrum describes the frequency distribution of the variability of RR intervals (heart rate) in units of ms\(^2\)/Hz. The absolute power of RR interval variability is calculated as the integration of the area under the curve over any given frequency range. Spectral power was calculated over the low (0 to 0.15) and high (0.15 to 0.50 Hz) frequency ranges. When normalized to total power (0 to 0.50 Hz), these values yield indicators of SNS and PNS influence on the heart, respectively.\textsuperscript{11,27}

Continuous data were analyzed statistically by repeated measures of variance on two factors (time and drug), with \(p<0.05\) considered significant.

Results

Baseline measures of BP, RR interval, respiratory rate, and peak flow were similar between study sessions, and there were no significant effects of either drug on these parameters (Table 1). The top
Table 1—Hemodynamic and Respiratory Values*

<table>
<thead>
<tr>
<th>Study Session</th>
<th>Placebo</th>
<th>Albuterol</th>
<th>Ipratropium</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>Drug</td>
<td>Baseline</td>
</tr>
<tr>
<td>Systolic BP, mm Hg</td>
<td>119±13</td>
<td>125±12</td>
<td>113±10</td>
</tr>
<tr>
<td>RR interval, ms</td>
<td>1,034±148</td>
<td>1,096±174</td>
<td>1,066±142</td>
</tr>
<tr>
<td>Respiratory rate, breaths/min</td>
<td>13±1</td>
<td>13±1</td>
<td>12±1</td>
</tr>
<tr>
<td>Peak flow, L/min</td>
<td>610±63</td>
<td>606±62</td>
<td>615±48</td>
</tr>
</tbody>
</table>

*Mean±SD; p>0.05 for all conditions.

panel of Figure 1 illustrates the mean spontaneous BRS for all 12 subjects. There was no statistical difference among the three different baseline measures. Neither albuterol nor ipratropium caused a significant alteration in BRS at either time 1 (45 to 60 min) or time 2 (60 to 75 min).

The middle and lower panels of Figure 1 represent high- and low-power activity of all 12 subjects, normalized to total power of HRV. There was no statistical difference between the baseline measures. Neither albuterol nor ipratropium caused a significant change in normalized low- or high-frequency power at either time 1 or time 2.

All subjects cooperated well and mastered the administration of the test drugs. No subjects reported adverse side effects such as palpitations, headache, or tremors.

**DISCUSSION**

The aim of this study was to evaluate and quantify the effects of two commonly used asthma drugs on autonomic nervous system control of the cardiovascular system. Previous studies have generally focused on gross heart rate and BP changes when examining the cardiovascular effects of these drugs. However, alterations in the balance of parasympathetic and sympathetic control of the heart rate may exist in the absence of gross effects on heart rate and BP. We have shown that inhalation of single, high therapeutic doses of albuterol or ipratropium does not result in significant impairment of PNS-mediated baroreflex control of heart rate. In addition, PNS and SNS modulation of heart rate were not altered. In addition, no unpleasant systemic effects were reported.

The importance of parasympathetic control of the heart has been elucidated by a number of different studies. Reduced parasympathetic activity is associated with arrhythmias and sudden cardiac death after episodes of myocardial ischemia. Diabetic patients with evidence of vagal impairment are at increased perioperative risk for cardiovascular instability. In animals with experimentally induced myocardial infarction, increased sympathetic activity and impairment of parasympathetic activity are associated with fatal arrhythmias during periods of myocardial ischemia. The association of sudden death from asthma with regular β2-agonist use raises concerns about the effects of these drugs on the cardiovascular and autonomic nervous systems. In individuals with cardiopulmonary disease, who characteristically exhibit preexisting decrease of PNS control, further impairment could make these individuals more vulnerable to stresses such as hypoxemia and acidosis, which might accompany exacerbations of their respiratory disease. Alternatively, these individuals may have already adapted to the decreased parasympathetic influence on their heart, making a further reduction in parasympathetic tone inconsequential.

Most previous studies examining the effects of albuterol and ipratropium on the cardiovascular system have focused on heart rate and BP changes, which may ignore the more subtle effects these drugs have on cardiovascular stability. IV and oral administration of both bronchodilators causes dose-dependent increases in heart rate, while large doses of albuterol (400 to 1,200 µg), but not ipratropium (up to 250 µg), administered via a metered-dose inhaler have been shown to cause tachycardia. One recent study examined the effect of ipratropium on respiratory sinus arrhythmia, a non-specific indicator of PNS modulation of heart rate, showing no effect in asthmatic subjects. These investigators used a low therapeutic dose of ipratropium (40 µg) without a spacer device. In addition, the subjects were not standardized with respect to their disease severity, and it has been shown that the amount of inhaled drug that reaches the terminal airways depends on the severity and type of respiratory disease, lung volumes, and utilization of a spacer device.

In the present study, the drug amounts administered were chosen to reflect the high end of recommended clinical doses and equipotency.

Larger doses of albuterol or ipratropium, such as those used in asthmatic exacerbations, might have produced significant changes in autonomic control of the heart.
In pilot studies conducted by the present authors, extremely high doses of inhaled albuterol (1.200 μg) resulted in an increase in heart rate and systolic BP, and decreased BRS and high-frequency HRV. No similar changes occurred when high doses of ipratropium (240 μg) were inhaled. The data sampling times (45 to 75 min) used in this study were chosen to reflect the peak serum level of the drug and the time of maximal bronchodilation. It is thus unlikely that data collection sooner following drug administration would have yielded different results. Healthy, young male volunteers were studied to elucidate pure drug effects without the difficulties in standardizing for confounding factors such as age, timing of menstrual cycle, severity of underlying disease, and concurrent drug use. Future studies are required to clarify the autonomic effects of these agents in other study populations, including women and pregnancy, the aged, and individuals with underlying respiratory and cardiovascular disease.

REFERENCES

1 Sussa S, Blais L, Ernst P. Patterns of increasing beta-agonist use and the risk of fatal or near-fatal asthma. Eur Respir J 1994; 7:1602-09

Figure 1. Spontaneous BRS (top panel) and normalized ratios of high and low power of HRV (middle and bottom panels) for placebo, albuterol, and ipratropium treatments. Data were collected at baseline, and at time 1 (45 to 60 min) and time 2 (60 to 75 min) after drug administration. Data are expressed as mean ± SEM, n = 12 subjects, p > 0.05 for all treatments vs respective baseline.