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Short-term cardiovascular and autonomic effects of inhaled salbutamol

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ABSTRACT

Asthma independently increases the risk of developing cardiovascular disease. As inhaled β-agonists have systemic cardiovascular effects, and elevations in arterial stiffness and sympathetic nerve activity are associated with increased cardiovascular morbidity/mortality, this study examines the effect of salbutamol use on pulse wave velocity (PWV) and muscle sympathetic nervous activity (MSNA). Healthy men and women (26.2 ± 1.5years) were recruited for: Day 1: 4 inhalations of placebo followed by 4 inhalations of salbutamol (4 × 100 μg); Day 2: placebo only; Day 3: carotid-femoral PWV measurements before/after placebo/salbutamol. Heart rate (HR), mean arterial pressure (MAP), and carotid-radial PWV were obtained on Day 1 and 2. MSNA was obtained on Day 1. Salbutamol increased HR and total MSNA (Baseline1: 2.8 ± 2.8 au; Placebo: 2.4 ± 2.1 au; Baseline2: 2.7 ± 3.0 au; Salbutamol: 3.3 ± 2.9 au; $p = 0.05$), with no changes in MAP or PWV. There were no effects of placebo on HR, MSNA, or PWV. Acute salbutamol use increases sympathetic activity suggesting that salbutamol could contribute to cardiovascular morbidity/mortality in individuals using inhaled β-agonists.

1. Introduction

Asthma is associated with increased cardiovascular morbidity and mortality (Iribarren et al., 2004), including a 1.40-fold increased risk of coronary heart disease and a 2.14-fold increased risk of heart failure (Iribarren et al., 2012). The reason for this increased cardiovascular risk is currently unknown; however, it has been speculated to be a result of chronic inflammatory changes, as well as common comorbidities shared by asthmatic patients and those with coronary heart disease (Iribarren et al., 2012). Since the 1990s, some studies have suggested that the use of β-agonists represents an independent cardiovascular risk factor (Appleton et al., 2009; Spitzer et al., 1992). Different mechanisms have been proposed to explain the increased cardiovascular risk with β-agonists including: (i) pro-arrythmogenic effects from hypokalemia or prolonged QT interval; (ii) shortened diastole induced by the increase of heart rate (i.e. less myocardial perfusion); (iii) increased sympathetic outflow (as evaluated by indices of heart rate variability (HRV) or plasma norepinephrine) (Cekici et al., 2009; Iribarren et al., 2012; Sears, 2002; Snyder et al., 2011). Indeed, chronically elevated sympathetic nerve activity is associated with cardiovascular deterioration (Middlekauff and Mark, 1998; Zucker et al., 2001) and is related to decreased survival in heart failure (Barretto et al., 2009) and chronic obstructive pulmonary disease (Andreas et al., 2014).

Recently we compared young asthmatics to fitness and physical activity-matched non-asthmatics, and found that both groups had similar levels of systemic inflammation and vascular function; however, arterial stiffness was increased in the asthmatics (Moore et al., 2015). As arterial stiffness and vascular remodelling can be influenced by elevations in sympathetic activity, it may be that β-agonists influence vascular stiffness by their effect on sympathetic outflow. Many studies have described the cardiovascular effects of β-agonist use, in particular an increase of heart rate and/or a decrease of peripheral vascular resistance (Beloka et al., 2011; Cekici et al., 2009; Snyder et al., 2011; Tahvanainen et al., 2009). However, the effects on blood pressure and autonomic balance may depend on the medication, dose and/or the method of administration. For example, an intravenous infusion of salbutamol (10 μg/min) increased systolic blood pressure (Beloka et al., 2011) whereas inhaled albuterol/salbutamol did not affect blood

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pressure (Cekici et al., 2009; Snyder et al., 2011; Tahvanainen et al., 2009). Similarly, there are conflicting results concerning the effects of β-agonists on autonomic balance. Inhaled albuterol (400 μg) was found to have no effect on spontaneous baroreceptor sensitivity or HRV (Dagnone and Parlow, 1997) suggesting no autonomic effect; however, when the dose of albuterol increased to 2.5 mg, higher sympathetic activity indices were observed (Snyder et al., 2011). Further, intravenous salbutamol (10 μg/min) did not lead to a change in muscle sympathetic nerve activity (MSNA) (Beloka et al., 2011), yet when salbutamol was inhaled (200–600 μg) there was a shift in HRV suggesting increased sympathetic activity (Cekici et al., 2009; Jartti et al., 1997).

Despite the evidence that asthma and β-agonist use are associated with increased cardiovascular morbidity/mortality, and that elevations in sympathetic output may play a role, there is a dearth of research examining the effect of a therapeutic dose of an inhaled β-agonist on MSNA—the 'gold-standard' technique to quantify sympathetic outflow. Accordingly, we sought to examine the MSNA response to a therapeutic dose of inhaled β-agonist (400 μg salbutamol). As increased MSNA could lead to an increase in arterial stiffness (which by itself is associated with increased cardiovascular morbidity/mortality (van Sloten et al., 2014)), a secondary aim was thus to examine the effects of inhaled β-agonist on arterial stiffness. We hypothesized that inhaled salbutamol (4 × 100 μg over 15 min) would increase MSNA and pulse wave velocity (PWV; a marker of peripheral arterial stiffness) in young healthy participants. This increase in sympathetic activity could be a contributing mechanism behind greater cardiovascular risk in asthmatics that use β-agonists as part of their mainstay treatment.

2. Materials and methods

2.1. Ethical approval

This study was approved by the University of Alberta Health Research Ethics Board (Biomedical Panel; Pro00029773). Participants were recruited from the University of Alberta and the general population. Each participant provided written, informed consent.

2.2. Participant description

Twelve healthy men (n = 7) and women (n = 5) were initially recruited (age: 26.3 ± 4.8 years, height: 173.5 ± 8.9 cm, weight: 72.7 ± 16.7 kg, and BMI: 24.0 ± 4.6 kg/m^2). In a secondary study to examine femoral arterial stiffness, seven healthy men (n = 4) and women (n = 3) were recruited (age: 20.7 ± 2.0 years, height: 171.9 ± 10.5 cm, weight: 72.0 ± 15.4 kg, BMI: 24.1 ± 3.2 kg/m^2). All subjects were free from known cardiovascular and pulmonary disease, and none were taking any acute or chronic medication (2 women were taking non-cyclic hormonal birth control). Subjects were asked to refrain from heavy exercise, alcohol and caffeine for 12 h prior to the study.

2.3. Study 1 protocol

Participants came to the lab for two trials on two separate testing days, and were blinded to the order of placebo or drug administration. MSNA was measured on the drug administration day only as we did not anticipate a change in resting MSNA on the placebo day as previous work has shown that 15 min of supine rest does not affect MSNA (Houssiere et al., 2006), and that MSNA is consistent in tests that run over an hour (Kamiya et al., 2009). Further, between-day comparisons of MSNA burst amplitude and therefore total MSNA are difficult because of the variability of needle placement. The search for acceptable MSNA signals took up to 60 min immediately followed by a 10 min resting period.

2.3.1. Drug administration testing day

Trial 1. The first trial consisted of 4 inhalations of placebo over 25 min as follows: (1) 5 min of resting cardiovascular measurements and 2 min of carotid-radial tonometry data were obtained, (2) two inhalations of placebo (Placebo inhalation aerosol, GlaxoSmithKline, Mississauga, Canada) were administered via a spacer device (ProChamber, Respironics, Parsippany, USA) using the standard protocol of an inhalation followed by a 10 s breath-hold (Ventolin® HFA Patient Information, GlaxoSmithKline, Mississauga, Canada) with 50 s separating each inhalation, (3) 5 min of cardiovascular measurements and 2 min of carotid-radial tonometry data were again obtained (data not shown), (4) another two inhalations of placebo, and (5) a final 5 min of cardiovascular measurements, and 2 min of carotid-radial tonometry. The trial finished with a 5 min rest period with no data collected.

Trial 2. The second trial repeated the above protocol but 4 × 100 μg inhalations of salbutamol were administered over 25 min rather than placebo. 100–400 μg (up to four times daily) is the recommended dose for prevention of bronchospasm, and a measureable effect on airway conductance is observed within 15 min (Palminteri and Kaik, 1983).

2.3.2. Time-control testing day

On a second day, the identical protocol was used (as above); however, only placebo medication was given during both trials and no MSNA data were obtained.

2.4. Study 2 protocol

As we were unable to obtain carotid-femoral pulse wave velocity and MSNA simultaneously, a secondary study was conducted on a separate group of participants. On two separate days (order randomized), carotid-radial and carotid-femoral pulse wave velocity data were obtained at rest while supine, and 15 min after the administration of either 400 μg salbutamol (4 × 100 μg inhalations) or placebo (4 inhalations).

2.5. Cardiorespiratory measurements

All data were collected in the supine position. Pulse wave velocity (PWV), heart rate (HR), and beat to beat blood pressure were recorded and integrated by a Powerlab data acquisition system using LabChart 7.3 Pro software (Powerlab 16/30; ADInstruments, Australia). Heart rate was determined using a single-lead ECG (BioAmp; ADInstruments, Australia), and beat-by-beat blood pressure was determined using finger photoplethysmography (Finometer Midi, Amsterdam, Netherlands). Blood pressure was calibrated at regular intervals using a manual measurement.

Pulse waves were gathered simultaneously from the carotid and radial arteries using applanation tonometry (Mikro-tip Catheter Transducers model SPT-301, Millar Instruments, Inc., Houston, USA). During the primary study, carotid-radial PWV was determined in lieu of carotid-femoral PWV due to the necessity of keeping the leg still during MSNA data collection. For the secondary study, PWV was determined from the carotid and radial arteries and then from the carotid and femoral arteries. PWV was calculated as $PWV = D\,Dt^{-1}$, where D = distance (m) between sites and Δt = time difference(s) between pulse waves using the foot-to-foot method (Laurent et al., 2006). Distance was measured on the surface of the body beginning at the sternal notch and extending to the recording sites of the carotid and radial arteries (Laurent et al., 2006). Mean