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Effects of inhaled bronchodilators on lung function and cycling performance in female athletes with and without exercise-induced bronchoconstriction

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ABSTRACT

Objectives: Inhaled β_2-agonists may cause differential effects on lung function and athletic performance in female compared to male athletes. The objective of this study was to compare the effects of inhaled β_2-agonists on lung function and cycling performance between female athletes with and without exercise-induced bronchoconstriction and with previously published data on men.
Design: Double-blind crossover randomized controlled trial.
Methods: Twenty-one female athletes (6 with exercise-induced bronchoconstriction and 15 without exercise-induced bronchoconstriction) performed a simulated 10-km time-trial on a cycle ergometer 60 min after the inhalation of either 400 μg of salbutamol or placebo. Forced expiratory volume in 1 s, was measured immediately before and 30 min after inhalation. Performance was measured by mean power output over the duration of the time trial.
Results: After salbutamol inhalation, Forced expiratory volume in 1 s improved significantly in athletes with exercise-induced bronchoconstriction (M (SD) = 6.1% (47.6)) and athletes without exercise-induced bronchoconstriction (4.0% (3.1); $p \leq 0.02$). Mean power output was significantly decreased after salbutamol use (204 W (21)) compared to placebo (208 W (17); $p = 0.047$), regardless of airway hyperresponsiveness. Relative to placebo, salbutamol significantly increased mean oxygen consumption (46.9 mL kg^{-1} min^{-1} (5.9) vs. 44.8 mL kg^{-1} min^{-1} (4.0); $p = 0.049$) and significantly decreased cycling economy (72.8 W L^{-1} min^{-1} (6.8) vs. 76.4 W L^{-1} min^{-1} (4.3); $p = 0.01$).
Conclusions: The inhalation of salbutamol induced a significant increase in lung function in female athletes, but this increased lung function did not translate to improved exercise performance.

1. Introduction

Exercise-induced bronchoconstriction (EIB), the transient narrowing of the airways following exercise, affects many endurance athletes.[1] For example, 17% of cyclists competing at the 2004 and 2008 Olympics treated EIB-symptoms (e.g. coughing, chest tightness and dyspnea) with inhaled β_2-agonists (IBAs).[1] Inhaled β_2-agonists act on the adrenergic β_2-receptors, which are located primarily in the lungs but also in the heart and the skeletal muscles. In the lung, IBAs act as bronchodilators by inducing smooth muscle relaxation in the cells surrounding the airways.[2] In the heart and skeletal muscles, IBAs vasodilate the arteries; therefore increasing blood flow.

Interestingly, athletes treating their EIB-symptoms with IBAs have won a disproportionately greater percentage of individual Olympic medals compared to athletes without EIB.[1,3] Pluim et al.[4] and Kindermann[5] concluded in their meta-analyses that IBAs do not have a significant effect on endurance performance in athletes without EIB. In agreement with this conclusion, our research group recently demonstrated that despite a significant improvement in lung function following IBA use, cycling performance in trained male cyclists was not affected regardless of bronchial hypersensitivity.[6]

Despite the fact that sex-based anatomical differences in the airways and lungs cause differing respiratory responses to exercise in men and women, female athletes have been generally overlooked

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in the research on the effects of IBAs on athletic performance.[7,8] Dysanapsis refers to the altered relationship between airway size and lung volume.[9–11] When matched for lung size, women have smaller airway luminal areas and decreased conducting airway diameters compared to men.[12] Furthermore, women have smaller lung volumes, smaller maximal expiratory flow rates and decreased diffusion surfaces relative to men.[8,13] During heavy exercise, endurance-trained women were more likely to develop expiratory flow limitation (EFL) compared to endurance-trained men (90% vs. 43%, respectively).[14] In addition, the work required to breathe (i.e. work of breathing, WOB) was significantly greater during high-intensity cycling in female athletes compared to male athletes.[14]

Since, according to Poiseuille's law, airway diameter affects airflow by the fourth power, an IBA-induced bronchodilatory effect in women could lead to greater relative improvements in lung function and athletic performance compared to men. The primary aim of this study was to investigate the effects of IBAs on lung function and athletic performance in trained female endurance athletes with and without EIB. By adhering to the study design of our previous investigations on the effects of IBAs on cycling performance in male athletes,[6] we also aimed to compare the effects of IBAs between female and male athletes. We hypothesized that female athletes with EIB would demonstrate a significant bronchodilatory response to inhaled salbutamol, which would translate to improved ventilatory capacity and time-trial performance, while female athletes without EIB would not benefit from an ergogenic effect of inhaled salbutamol.

2. Methods

Twenty-seven female cyclists and triathletes, aged between 19 and 39 years, were screened. Athletes with a maximal oxygen consumption (VO_{2max}) $\geq 50\,mL\,kg^{-1}\,min^{-1}$ were included. All athletes had to have a racing history of at least one year and were participating in or training for races during the data collection. Participants were free of cardiopulmonary disease (excluding controlled asthma) and were not pregnant. The University of British Columbia Clinical Research Ethics Board provided ethical approval (H09-01154) conforming to the Declaration of Helsinki, and written informed consent was obtained from all subjects prior to data collection.

On the screening visit, bronchial hyper-responsiveness was assessed using a eucapnic voluntary hyperpnea (EVH) test.[15] Lung function was measured with spirometry[16] (TrueOne 2400; ParvoMedics, Sandy, UT, USA), and the highest forced expiratory volume in 1 s (FEV_1) from three maneuvers was used as baseline. Athletes then hyperventilated dry gas (5% CO_2) for 6 min and repeated spirometry at 3-, 5-, 15- and 20-min post-hyperventilation. A decrease in $FEV_1 \geq 10\%$ relative to baseline was classified as EVH+.[15] VO_{2max} was determined using a cycle ergometer (Velotron Dynafit Pro, RacerMate Inc., Seattle, WA, USA). The test began at 0 W, and work rate increased by $0.5\,W\,s^{-1}$ until cycling cadence was <60 rpm.

In this repeated-measures study design, each athlete performed two simulated 10-km time-trials, separated by a minimum of 3 and maximum of 14 days. Athletes were asked to withhold from β_2-agonists for at least 12 h prior to arrival but were allowed to continue corticosteroid treatments.

On the time-trial visits, the effect of each treatment on lung function was assessed by having athletes perform three FEV_1 maneuvers prior to, and 30-min after, inhalation of salbutamol or placebo (APOTEX Inc., Toronto, Canada). The treatments were delivered in a randomly assigned, double-blind manner. To assess metabolic parameters during time trials, athletes wore a facemask (Hans Rudolph; Shawnee, KS, USA) connected to a metabolic cart (ParvoMedics). A time-trial course (RacerMate Inc.) was displayed on a screen, with distance, cadence, and gearing information displayed throughout each time-trial. Every 2-km, athletes rated dyspnea and perceived exertion (RPE) for their legs on a 0–10 Borg-scale.[17] The main outcome variable was mean power output over the duration of the 10-km time-trial. Secondary outcome variables were cycling economy (ratio of mean power output and mean oxygen consumption (VO_2) maintained over the 10-km time-trial in $W\,L^{-1}\,min^{-1}$),[18] respiratory exchange ratio (RER), heart rate (HR), VO_2, minute ventilation (V_E), tidal volume (V_T), respiratory rate (rr), dyspnea and RPE. To assess for a possible time-effect of salbutamol on the outcome variables, these parameters were averaged for each 2-km interval.

All data are presented as means (SD). The effects of drug treatment and EVH status were tested with repeated-measures analysis of variance (ANOVA) tests. Post hoc analyses were performed using Tukey's HSD test. To compare the effects of salbutamol on lung function and time-trial performances between women and men (from a previously collected dataset with an identical protocol[6]), the percent change of all parameters between the salbutamol and the placebo time-trials were calculated and then analyzed using one-way ANOVA tests. Statistical analyses were completed using SPSS (IBM, Version 22.0, Armonk, NY, USA) and statistical significance was accepted when $p < 0.05$. Funding organizations were not involved in the data collection, analysis or interpretation.

3. Results

Of the 27 athletes screened, 21 met all inclusion criteria and were included in the study. Based on a positive EVH test, six athletes were classified as EVH+. The 15 EVH− athletes (M (SD) = 30 years (5)) were significantly older compared to the EVH+ athletes (24 years (4); $p = 0.027$). There were no differences between EVH+ and EVH− athletes in height, weight, fitness, and baseline spirometry (FVC = 4.8 L (0.6) or 120% (14) predicted; FEV_1 = 3.87 L (0.6) or 113% (14) predicted; FEV_1/FVC = 81% (6) or 94% (7) predicted). These data are more comprehensively reported in Table S1 in the supplemental online section.

By definition, EVH+ athletes showed a significantly greater drop in FEV_1 (16.3% (3.3)) after the EVH test compared to EVH− athletes (6.6% (1.8); $p < 0.001$). The bronchial hyper-responsiveness of all six EVH+ athletes was classified as mild (percent decrease in FEV_1 after EVH challenge ≥10% but <25%). Only two EVH+ athletes had previously been diagnosed with EIB: these athletes were treating their symptoms with daily inhalations of corticosteroids and IBAs on an as-needed basis. Two EVH+ athletes had no previous diagnosis of EIB but reported, prior to the EVH test, that they experienced difficulty breathing during high-intensity workouts. Two other EVH+ athletes did not report any respiratory symptoms when training and were not aware of their bronchial hypersensitivity. One EVH− athlete had childhood asthma but did not respond to the EVH test (percent decrease in FEV_1 = 6.6%).

Lung function, assessed by FEV_1, significantly improved 30 min after the inhalation of salbutamol (4.6% (4.7)) compared to 30 min post-placebo inhalation (−0.1% (2.8), $p = 0.002$). The bronchodilatory response to inhaled salbutamol did not differ statistically between EVH+ (6.1% (7.6)) and EVH− athletes (4.0% (3.1), $p > 0.05$).

The inhalation of 400 μg of salbutamol led to a significantly reduced 10-km time-trial performance in trained female athletes ($p = 0.047$), regardless of athletes' EVH status (see Fig. 1). Mean VO_2 during the time trial was significantly increased after the inhalation of salbutamol compared to placebo ($p = 0.049$). Consequently, cycling economy of the entire 10-km time-trial was significantly decreased following salbutamol compared to placebo ($p = 0.01$). The inhalation of salbutamol significantly reduced the respiratory

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