Treatment of airway inflammation improves exercise pulmonary gas exchange and performance in asthmatic subjects

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Background: Asthma is an inflammatory disease of the airways that can lead to impaired arterial blood oxygenation during exercise.
Objective: We asked whether treatment of airway inflammation in asthmatic subjects would improve arterial blood gases during whole-body exercise.
Methods: By using a double-blind parallel-group design, 19 asthmatic subjects completed treadmill exercise to exhaustion on 2 occasions: (1) before and (2) after 6 weeks' treatment with an inhaled corticosteroid (ICS; n = 9) or placebo (n = 10).
Results: The ICS group had improved resting pulmonary function, decreased exercise-induced bronchospasm, and decreased postexercise sputum histamine during the posttreatment study compared with that during the pretreatment study. In the ICS group exercise Pa_{O_2} was significantly increased after treatment (84.8 to 93.8 mm Hg). Increased alveolar ventilation (arterial P_{CO_2} decreased from 36.9 to 34.1 mm Hg) accounted for 37% of the increased Pa_{O_2} and improved gas exchange efficiency (alveolar-to-arterial P_{O_2} difference decreased from 22.5 to 16.3 mm Hg) accounted for the remaining 63% of the increased Pa_{O_2} after treatment. In the ICS group exercise time to exhaustion was increased from 9.9 minutes during the pretreatment study to 14.8 minutes during the posttreatment study.
Conclusion: Treatment of airway inflammation in asthmatic subjects can improve arterial blood oxygenation during exercise by (1) improving airway function, thereby allowing increased alveolar ventilation during exercise, and (2) improving the efficiency of alveolar-to-arterial blood O_2 exchange.
Clinical implications: In asthmatic patients ICSs not only attenuate exercise-induced bronchospasm but also improve arterial blood oxygenation during exercise. (J Allergy Clin Immunol 2007;120:39-47.)

Key words: *Airway inflammation, arterial blood gases, asthma, exercise, exercise-induced bronchospasm, flow-volume loop, inhaled corticosteroids, pulmonary gas exchange, pulmonary function, pulmonary mechanics*

Inflammation of the airway tree is a principal feature of bronchial asthma.[1] As a consequence of this airway inflammation, pulmonary gas exchange and arterial blood gas status during exercise might be compromised in asthmatic subjects. A heterogeneous ventilation distribution as a result of bronchial smooth muscle contraction, mucosal edema, luminal mucus and fluid accumulation, and small airways closure will worsen the mismatch between alveolar ventilation and perfusion (V_A/Q). Indeed, lung imaging and the multiple inert gas elimination technique have shown greater than normal V_A/Q mismatch in asthmatic subjects at rest and after exercise.[2-4] Asthmatic subjects might also be disadvantaged during exercise because of increased propensity for developing constraints to ventilation. This is because many asthmatic subjects have narrowed airways and a reduced maximal flow-volume loop, which will increase their likelihood for experiencing expiratory flow limitation (EFL) during exercise. Indeed, we have recently shown significant EFL and an insufficient exercise hyperpnea in some asthmatic subjects with mild-to-moderate disease.[5]

We have previously shown that arterial blood gas status during whole-body exercise is compromised in habitually active subjects with mild-to-moderate asthma compared with their nonasthmatic counterparts.[5] The purpose of the present investigation was to determine whether treatment of airway inflammation in asthmatic subjects leads to improved arterial blood gas status during exercise. Arterial

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Abbreviations used

$AaDO_2$:	Alveolar-to-arterial blood oxygen pressure difference
EELV:	End-expiratory lung volume
EFL:	Expiratory flow limitation
eFVL:	Exercise tidal flow-volume loop
EIB:	Exercise-induced bronchospasm
$FEF_{50\%}$:	Forced expiratory flow at 50% of the forced vital capacity
FRC:	Functional residual capacity
FVC:	Forced vital capacity
ICS:	Inhaled corticosteroid
MFVL:	Maximal volitional flow-volume loop
Rrs 5 Hz:	Total respiratory resistance
Rrs 5-25 Hz:	Frequency dependence of resistance
Sao_2:	Arterial blood oxyhemoglobin saturation
TLC:	Total lung capacity
$\dot{V}A/Q$:	Alveolar ventilation-to-perfusion ratio
$\dot{V}E$:	Minute ventilation
$\dot{V}E$Cap:	Exercise ventilatory capacity
$\dot{V}O_{2max}$:	Maximal oxygen uptake

blood gases and their determinants were assessed during exhaustive endurance exercise in a group of subjects with mild-to-moderate asthma before and after 6 weeks of treatment with an inhaled corticosteroid (ICS) or placebo inhaler. We hypothesized that treatment with ICSs would reduce airway inflammation and improve lung function and that this would be related to improved arterial blood oxygenation during exercise after the treatment.

METHODS

See the Methods section in the Online Repository at www.jacionline.org for additional information.

Subject selection

This study was approved by the institutional review board at the University of Wisconsin–Madison, and informed consent was obtained in writing from all subjects.

Nonsmoking, habitually active subjects with a physician diagnosis of asthma underwent several screening sessions to determine eligibility for participation. All subjects were required to demonstrate one or more of the following criteria: (1) 12% or greater increase in FEV_1 after β-agonist inhalation; (2) 4 mg · mL^{-1} or less provocative concentration of methacholine causing a 20% decrease in FEV_1; (3) 2% or greater eosinophils in induced sputum; and (4) 10% or greater decrease in FEV_1 after an incremental treadmill exercise test to exhaustion. Detailed results from these screening studies have been reported previously.[5]

Medications

None of the subjects had taken any oral corticosteroids or ICSs for at least 3 months before the initial screening studies. Subjects were allowed to continue use of other medications during the course of the study but were instructed to abstain from using any short-acting β-agonists within 12 hours and any long-acting β-agonists, antihistamines, leukotriene modifiers, and sodium cromoglycate within 48 hours of each study. Subjects were also instructed to refrain from ingesting any food, beverages, or other products containing caffeine for at least 8 hours before all studies.

Lung function measurements

Forced vital capacity (FVC), FEV_1, and forced expiratory flow at 50% of FVC ($FEF_{50\%}$) measurements were completed in agreement with American Thoracic Society recommendations.[6] A body plethysmograph was used to measure functional residual capacity (FRC), and total lung capacity (TLC) was calculated as the sum of FRC and the inspiratory capacity. The forced oscillation technique (Jaeger) was used to determine total airway resistance (Rrs 5 Hz) and frequency dependence of resistance (Rrs 5-25 Hz).[7]

Airway inflammation measurements

Induced sputum was collected and processed as described previously.[8,9] Sputum supernatant and urine samples were analyzed for histamine and 9α, 11β-prostaglandin F_2, respectively, by using competitive enzyme immunoassay kits (Cayman Chemical Co, Ann Arbor, Mich). Exhaled nitric oxide was measured at a constant flow rate, as described previously.[10]

Exercise measurements

Samples of arterial blood were obtained from a radial artery catheter and analyzed for blood gas tensions (ABL-505; Radiometer, Copenhagen, Denmark), oxyhemoglobin saturation (OSM-3; Radiometer, Copenhagen, Denmark), and pH, as described previously.[7] Exercise ventilatory and breathing mechanics parameters, including end-expiratory lung volume (EELV) and EFL, were determined as described previously.[7,11]

Experimental design

Participants completed a randomized, placebo-controlled, double-blind, parallel-group design with one pretest and one posttest exercise study separated by a 6-week treatment period. After the pretreatment exercise study, subjects were randomly assigned to a placebo or ICS treatment group. Subjects in the ICS group inhaled 440 μg of fluticasone propionate (GlaxoSmithKline, Research Triangle Park, NC) twice daily (880 μg/d) for 6 weeks. For the placebo group, we used placebo inhalers (GlaxoWellcome, Inc, Research Triangle Park, NC) that consisted of propellants and lecithin (no active ingredients). Subjects in the placebo group used the inhaler twice daily for the same amount of time as the ICS group.

Subjects were provided detailed instructions, both verbally and in writing, regarding daily inhalation of the aerosol. To minimize intersubject variability of drug deposition in the airways, subjects were given a 150-mL spacer (Monaghan Medical Corp, Plattsburgh, NY) that generated a "whistle" sound if the flow rate exceeded recommended limits during inhalation. Subjects were also contacted regularly by telephone or e-mail to help ensure adherence to the dosing.

Protocol for exercise studies

After resting expired gas and arterial blood collection, a constant workload treadmill test to exhaustion was performed that elicited a metabolic rate approximating 90% of each subject's maximal O_2 consumption ($\dot{V}O_{2max}$). During the exercise test, arterial blood was collected every 2 minutes and also at exhaustion. Inspiratory capacity maneuvers were performed for placement of exercise tidal flow-volume loops (eFVLs) within the maximal volitional flow-volume loop (MFVL). Pulmonary function was assessed before and at 5, 10, and 20 minutes after exercise. Another exercise bout to exhaustion (performed at $\dot{V}O_{2max}$) was performed approximately 40 minutes after the constant workload bout; however, data from this bout are not presented. Urine samples were collected before exercise and 45 minutes after completion of the final exercise bout, and induced sputum was collected approximately 60 minutes after termination of exercise.