The effects of air pollution and inhaled salbutamol on lung function and athletic performance in asthmatic and non-asthmatic athletes

Application for the CASEM Research Grant
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Conflict of Interests: None
Introduction

Overview of proposed study

Major Games in cities known for high levels of air pollution such as Athens 2004, Beijing 2008, and Delhi 2010 have raised concerns regarding athlete health and performance. At the upcoming Olympic Games in Rio de Janeiro (2016) and the Pan Am Games held in Toronto, ON, (2014), air pollution will also be a concern.

The detrimental effects of acute and chronic air pollution on cardiovascular and respiratory health are described in a large body of scientific literature. Ironically, athletes, who tend to follow a healthy lifestyle, are at a greater risk of cardiorespiratory symptoms and illnesses triggered by air pollution. Physical activity leads to the release of epinephrine (the fight-or-flight hormone). Epinephrine induces a widening of the airways to facilitate the increased ventilation required to sustain the physical demands placed by the exercise bout. Increased inhalation of polluted air through widened airways facilitates the travel of pollutants deeper into the bronchial tree, where they trigger responses such as coughing, wheezing and chest tightness. Ultimately, this air pollution exposure impairs lung function and athletic performance. The acute treatment of choice for these asthma-like symptoms is the inhalation β2-agonists (IBA), which mimic epinephrine. In addition to the natural bronchodilation due to the exercise-induced release of epinephrine, IBAs induce a further widening of the airways. Theoretically, inhaled β2-agonists relieve respiratory distress in the short-term, but IBAs may also increase the amount of pollutants traveling into deeper areas of the bronchial tree, where they can cause structural and functional damage in the long term. Thus, although IBA are routinely used in symptomatic athletes in high pollutant environments, there is no evidence that they help, and in fact a significant risk that they could affect health, performance or both. The purpose
of this study is to investigate the effects of IBA-use in the treatment of respiratory symptoms triggered by air pollution exposure on athletic performance and lung health in elite athletes.

Air pollution and respiratory symptoms in athletes

In Olympic athletes, asthma is the most common chronic health condition (prevalence: 8%), and endurance athletes are the most likely group of athletes to be diagnosed with exercise-induced asthma. Exercise-induced asthma (EIA) and exercise-induced bronchoconstriction (EIB) are the terms used to describe the transient narrowing of the airways that follows vigorous exercise. While EIA is used to describe symptoms and signs of asthma provoked by exercise, EIB describes the reduction in lung function after exercise (or an exercise test). Interestingly, the prevalence of EIB, asthma and low resting lung function is particularly high for athletes who train and compete in an environment with high particulate matter (PM) emissions, exceeding that of the non-athletes and the low-pollutant-exposed athlete. The cause of EIB is likely the thermal and osmotic consequences of water evaporation that results from humidifying large volumes of air in a short period of time, resulting in the release of inflammatory mediators, which causes the contraction of airway smooth muscle. The inhalation of air pollutants has been shown to act as an additional trigger for the release of inflammatory mediators from airway cells and to worsen the asthmatic response. Exercise leads to an increased deposition fraction (fraction of inhaled particles remaining in the lungs after inhalation) of PM. For example, the fractional deposition of PM with a diameter of 0.1 μm (PM$_{0.1}$) is increased 4.5-fold during mild exercise (mean ventilation rate of 38 Lmin$^{-1}$) compared to rest. For PM$_{2.5}$, it has been estimated that 9% of the inhaled pollutants are deposited in the lungs with 6% reaching the
alveolar region. Thus, exercise appears to act as a catalyst for the harmful effects of PM inhalation on cardiopulmonary health in the athlete.

**Air pollution and athletic performance**

The exposure to increased levels of air pollution has been shown to impair key parameters of athletic performance and athletic performance directly.\(^9,11-13\) For example, decreased work capacity and endothelial function, along with an elevated pulmonary arterial pressure were observed in a maximal 6-min cycle ergometer bout that immediately followed a 20-min high-PM exposure bout.\(^9\) Research performed in our laboratory showed a significantly attenuated exercise-induced bronchodilation (change in forced expiratory volume in 1 second, FEV\(_1\)) from baseline, and a significantly increased heart rate during a 20-km cycling time-trial following a 60-min exposure to high PM.\(^12\) Preliminary data from a second study in our laboratory show a significant increase in the perceived effort to breathe, and a significant increase in oxygen consumption (VO\(_2\)) in young healthy males when cycling at 50\% of maximum heart rate for 30 minutes in diesel exhaust (DE), compared to filtered air (FA). It is possible that the increased oxygen consumption was required to overcome respiratory distress, caused by the inhaled pollutants, to maintain the ventilation rates necessary for the required exercise bout.\(^26\)

**Air pollution and treatment of asthma symptoms in athletes**

At the 2004 (Athens) and 2008 (Beijing) Summer Olympics, an average of 24.9\% of the triathletes and 17.2\% of the cyclists were approved by the World Anti-Doping Agency (WADA) to use IBAs.\(^19\) Similarly to epinephrine, β\(_2\)-agonists act on adrenergic β\(_2\)-receptors that are primarily distributed in the lungs, but are also present in the heart and skeletal muscles.\(^15\) In the heart, β\(_2\)-agonists increase both heart rate and contractility. Due to its
vasodilating effects, β₂-agonists can also increase blood flow in the coronary and skeletal arteries.¹⁵

To treat asthma symptoms in polluted air, higher dosages of IBAs, taken in shorter intervals are needed.²⁷ An increase in dose and frequency of IBAs is critical, because of receptor down-regulation and desensitization.²⁸ When taken in polluted air by athletes, IBA may set a vicious cycle in motion. To this date, little is known about the damage air pollutants cause deep in the bronchial tree (where pollutants would not reach without the additional bronchodilating effect of IBA) and the downstream effects on athletic performance and cardiorespiratory health. It is likely that lung function and athletic performance will be further impaired and that respiratory symptoms will be aggravated. Higher doses of IBA may be required to treat these respiratory symptoms, as the removal of particles in mucus via coughing is more difficult from the smaller airways because of fewer mucus glands. These higher doses could further exacerbate respiratory symptoms, as described above. Thus the widely-used strategy of administering IBA in athletes training and competing in high pollution environments, is both untested, and potentially disadvantageous.

**Objectives, specific hypotheses of proposed research and practical implications of anticipated outcomes**

The purpose of the proposed study is to investigate the short-term effects of IBA treatment in elite athletes in response to asthma symptoms triggered by diesel exhaust (DE) on athletic performance and cardiorespiratory health. The proposed study is designed based on the following objectives and hypotheses:
**Objective 1:** To investigate the effects of short-duration DE-exposure on athletes’ respiratory function. We are especially interested in traditional spirometry measures (i.e. forced expiratory volume in one second (FEV$_1$), forced vital capacity (FVC), and the ratio of FEV$_1$/FVC) and newer respiratory measurement techniques (work of breathing (WOB) and expiratory flow limitation (EFL)) to assess lung health.

**Hypothesis 1:** There will be a decrease in lung function (decrease in: FEV$_1$, FVC, FEV$_1$/FVC; increase in: WOB and EFL) and an increase in respiratory symptoms in athletes when exposed to DE compared to clean, filtered air (FA).

**Objective 2:** To assess the immediate effects of IBA-use in the treatment of respiratory symptoms and impaired lung function due to air pollution exposure.

**Hypothesis 2:** Lung function (decreased: FEV$_1$, FVC, FEV$_1$/FVC; increased: WOB and EFL) will be improved and the prevalence of respiratory symptoms will be decreased immediately after IBA use in DE.

**Objective 3:** To assess the effects of IBA use in the treatment of respiratory symptoms and impaired lung function due to air pollution exposure after the cessation of exercise, up to 3 hours after the IBA-treatment.

**Hypothesis 3:** Lung function will be impaired (decreased: FEV$_1$, FVC, FEV$_1$/FVC; increased: WOB and EFL) and the prevalence of respiratory symptoms will be increased three hours after IBA-use in DE.
Project methodology

A randomized, double-blind, placebo-controlled, crossover design will be used. Athletes will be tested following IBA (inhalation of 200 μg of salbutamol) and placebo use (drug condition), while exercising or at rest (exercise condition), and in filtered air (FA) or polluted air (PA) (PM$_{2.5}$ of 300 μg/m$^3$; pollution condition). A level of PM$_{2.5}$ of 300 μg/m$^3$ corresponds to levels observed on high temperature, high humidity days in Rio de Janeiro. Each subject will visit the laboratory on five different occasions (see Figure 1).

Subjects

Fifteen non-asthmatic and fifteen asthmatic athletes (15 males and females each; n = 30), 19-40 years of age will be recruited for the study. Subjects will be excluded if they have any history of uncontrolled respiratory or cardiac disease.

Screening day

Eucapnic voluntary hyperpnea: To test for exercise-induced bronchoconstriction in all subjects, we will use the eucapnic voluntary hyperpnea test.$^{29}$ The highest FEV$_1$ value from the baseline spirometry will serve as the reference value. Subjects will be required to breathe dry air with added CO$_2$ (5%) at a high frequency and deep inhalations to provoke EIB. Subjects will ventilate 30 times their baseline FEV$_1$ volume for 6 min.$^{29}$ Subjects will repeat spirometry 3 min, 5 min, 15 min and 20 min post-hyperventilation. A decrease in FEV$_1$ of 10% or greater below the baseline value will be considered a positive EVH test.

Maximal Exercise Text: A graded exercise test with a step-protocol will be performed to measure peak oxygen consumption (VO$_{2peak}$) and peak heart rate (HR$_{peak}$) on a Velotron cycle ergometer. The test protocol for women and men will starting at a workload of 100
and 160 Watts, respectively, and resistance will increase by 30 Watts every 3 minutes until the subject reaches volitional exhaustion, a plateau in oxygen consumption, an RER ≥ 1.15, or a heart rate greater than their maximal predicted.

_Pulmonary function:_ Pulmonary function will be measured by spirometry following the guidelines of the American Thoracic Society. Spirometry will be assessed prior to exercise, immediately following exercise, 60 and 120 minutes following exercise. Standard measures of pulmonary function will be assessed, including FEV$_1$, FVC, and FEV$_1$/FVC.

**Test days II and III**

*Expiratory flow limitation (EFL) and work of breathing (WOB):* By assessing inspiratory and expiratory flow volumes and rates, we will be able to assess EFL and WOB. In addition to traditional spirometry, these are sensitive assessments of lung function that will provide us with a deeper insight into the effects of air pollution exposure on lung health in athletes. A reduction in WOB due to IBA use could reduce the oxygen cost for breathing, and thus possibly improve athletic performance. The work of breathing and EFL will be determined by taking the integral of an ensemble average of several tidal breaths to form the average trans-pulmonary pressure-tidal volume loop. Work of breathing for a single breath will then be multiplied by the frequency of breathing to determine the work done per minute by the respiratory muscles.

_Rest and exercise intervention:_ Prior to entering the Air Pollution Exposure Chamber (APEC), athletes’ lung functions will be assessed (spirometry, EFL and WOB, see Figure 2). Upon entering the APEC athletes will inhale a dose of salbutamol (200 μg) or placebo, which will be administered via a metered dose inhaler (MDI) connected to a spacer. During the 60-
A 60 min rest period after the drug treatment, resting measures will be collected (see Table 1). Athletes will start their graded exercise tests 60-min after the drug intervention. The exercise test will start at a resistance of 0 Watts. The resistance will then be increased by 30 Watts every 2.5-min until volitional exhaustion is reached. All exercise will be performed on a Velotron cycle ergometer. By controlling for exercise intensity during the graded exercise test, we will be able to compare WOB and EFL at a given exercise intensity to assess the effect of salbutamol.

**Table 1: Timing of parameters assessed prior, during and after the exercise test.**

<table>
<thead>
<tr>
<th>Timing of Parameter Assessment</th>
<th>Assessed Parameters</th>
</tr>
</thead>
<tbody>
<tr>
<td>• prior entering the APEC</td>
<td>• expiratory flow limitation (EFL)</td>
</tr>
<tr>
<td>• 15min after the IBA treatment</td>
<td>• work of breathing (WOB)</td>
</tr>
<tr>
<td>• 60min after the IBA treatment</td>
<td>• forced vital capacity (FVC)</td>
</tr>
<tr>
<td>• immediately after the completion of the graded exercise test (~ 30min)</td>
<td>• forced expired volume in 1s (FEV₁)</td>
</tr>
<tr>
<td>• 60 and 120min after completion of the exercise test (~ 150 and 210min)</td>
<td>• ratio of FEV₁/FVC (FEV₁/FVC)</td>
</tr>
</tbody>
</table>

Parameters continuously assessed during rest periods and during the exercise test:

- in APEC, post treatment (0min – 60min)
- during graded exercise test (60min- ~90min)
- post graded exercise test (~ 90min – 210min)

- heart rate (HR)
- oxygen consumption (VO₂)
- carbon dioxide consumption (VCO₂)
- oxygen saturation (SpO₂)
- minute ventilation (Vₑ)
- tidal volume (Vₗ)
- respiratory rate (RR)
- expiratory flow limitation (EFL)
- work of breathing (WOB)
- rating of perceived exertion for breathing and legs RPEB/RPEL
**Statistical considerations**

Data analysis will be completed using SPSS software (version 21.0). Two sets of analyses will be performed: those for the variables measured during exercise (for example: $HR, V_{E}, RR, HR, V_{t}$, and $VO_{2}$, EFL, WOB), and those for the pre- and post-testing variables (spirometry, WOB and EFL). The exercise data will be divided into the numbers of exercise-intensity stages ridden by each subject and compared among the eight conditions (DE-salbutamol-rest, DE-salbutamol-exercise, DE-placebo-rest, DE-placebo-exercise, FA-salbutamol-rest, FA-salbutamol-exercise, FA-placebo-rest, and FA-placebo-exercise) using repeated measures ANOVA. For the pre- and post-testing parameters, values will be compared at the 5 time-points (pre-treatment, 60min-post-treatment, immediately post-exercise, 60-min-post-exercise and 120 min-post exercise) among the eight conditions using repeated measures ANOVA. Significant main or interaction effects will be further analyzed using Tukey's HSD post-hoc tests. Significance will be set at $\alpha = 0.05$.

**Space, facilities and personnel support**

**Space:** All test days will take place in Dr. Carlsten's Air Pollution Exposure Laboratory (APEL). This 1000 square foot facility is located at the Chan-Yeung Center for Occupational and Environmental Respiratory Disease (CCOERD). It has the capacity to generate and monitor the particulate matter exposures proposed in this application.

**Equipment:** Exercise will be performed on a Racermate Velotron Pro cycle ergometer that is available at the APEL. We have a complete set-up of equipment for the EVH test, which can easily be transported to the APEL. We possess all of the equipment necessary to assess the described metabolic parameters and respiratory (spirometry, WOB and EFL) measurements. This includes $O_{2}$ analyzers, $CO_{2}$ analyzers and a pneumotach setup. All the
procedures outlined in this proposal have been performed in our laboratories, and thus we have the requisite ability and space to conduct this work.

**Personnel support:**

*Dr. Michael Koehle:* The principal investigator on this study will be Dr. Koehle, an Assistant Professor in the Division of Sports Medicine and the School of Kinesiology at the University of British Columbia. Dr. Koehle’s clinical work complements the proposed studies. Dr. Koehle served as the medical officer coordinating the medical teams for all Nordic events at the Vancouver 2010 Olympic Games, and has previously served as a physician on the medical team for other National and International Games. Working with such athletes has provided key real-world experience in elite athletic performance, athletes’ health and anti-doping issues.

*Dr. Christopher Carlsten:* Dr. Carlsten is an academic physician and associate professor at the Centre for Respiratory and Critical Care Medicine, Vancouver Coastal Health Research Institute and the UBC Division of Respiratory Medicine. Board certified in both, occupational and respiratory medicine, Dr. Carlsten is the director of the Chan-Yeung Center for Occupational and Environmental Respiratory Disease. His research interests include environmental respiratory disease, asthma and cardiovascular disease in relation to traffic-related air pollution, occupational lung disease, and the interplay between exercise and these conditions.

*Dr. Jordan Guenette:* Dr. Guenette is an assistant professor in the Department of Physical Therapy at the University of British Columbia. The aim of his research is to better understand the physiological factors that limit exercise tolerance and across the spectrum
of health and chronic lung disease. His prior research focused on the assessment of the mechanics of lung function during exercise in females. He has published widely in this area and is an expert with all the respiratory mechanics techniques to be used in the proposed study.

Relevance of the study to the field of Sport Medicine

Based on the findings of this study, the treatment of respiratory symptoms in elite athletes who are repeatedly exposed to air pollution during training and competition can be improved. Furthermore, strategies to prevent exacerbations of respiratory distress and a decrease in athletic performance will be developed, which could improve the long-term health and performance of athletes. High levels of air pollution are often present at competition venues, especially at major games such as Beijing, Delhi, Rio de Janeiro. Sport and Exercise Medicine Physicians involved in the care of athletes training and competing in these conditions would benefit from novel strategies to mitigate the adverse health and performance effects of polluted air.
Proposed budget

All anticipated costs are listed below. The expected final costs are estimated to be $38,500. A portion of these costs ($24,000) to be covered by an operating grant from the Natural Sciences and Engineering Research Council (NSERC), entitled Mechanisms of Environmental Stress on Human Performance.

Air Pollution Exposure Laboratory (APEL):
The Air Pollution Exposure Chamber (APEC) use in the APEL and technician cost ($100/hr):

30 participants, 4 visits of 2 hour duration/each: $24,000

Work of Breathing and Expiratory Flow Limitation Assessment:

30 esophageal catheters to determine WOB ($80/each): $2,400

Eucapnic Voluntary Hyperpnea Test:

Gas to assess asthma-status through EVH test: $800

Gas Tanks:

Calibration gas and compressed air for particulate matter and filtered air exposures in APEL: $1,500

Participant honoraria:

$200 for each participant for a total of 5 visits: $6,000

Spirometry:

Mouthpieces for asthma-test: 30 filters for $20 each: $600

Publication Costs: $700
References


### Appointment I: Medical Screening

- Informed consent
- Maximal exercise test
- Anthropometric measurement
- Pulmonary function test

### Appointment II-X Testing:

**Drug condition:** (A) inhalation of 200µg salbutamol; (B) inhalation of placebo

**Exercise condition:** (A) graded exercise test; (B) 60min sitting on chair (rest)

**Pollution condition:** (A) filtered air (FA); (B) PM$_{2.5}$ of 300µg/m$^3$ (DE)

*Randomly, double blind assigned, placebo controlled protocol (min. 72h apart, max. 12 weeks apart)*

<table>
<thead>
<tr>
<th>Pollution</th>
<th>Pollution</th>
<th>Filtered Air</th>
<th>Filtered Air</th>
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<tbody>
<tr>
<td>Rest/Cycling Salbutamol</td>
<td>Rest/Cycling Placebo</td>
<td>Rest/Cycling Salbutamol</td>
<td>Rest/Cycling Placebo</td>
</tr>
</tbody>
</table>

**Immediate post-testing after cycling**

Spirometry, WOB and EFL

**Delayed post-exercise testing (60 and 120 min after termination of cycling):**

Spirometry, WOB and EFL

*Figure 1: Randomized double-blind crossover study design of proposed research*
Figure 1: Timing of interventions on test days II and III.