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**Effect of Brief Exercise on Airway Blood Flow in Subjects With and Without Asthma**

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##### ABSTRACT

**Mendes ES, Lit L, Horvath G, Rebolledo P, Wanner A**. Effect of Brief Exercise on Airway Blood Flow in Subjects With and Without Asthma. **JEPonline** 2012;15(5):10-17. Exercise-related hyperventilation is associated with cooling and drying of the airway mucosa. A compensatory increase in the blood perfusion of the airway (Qaw) theoretically could counteract this effect. Subjects with asthma have been shown to have a blunted endothelium-dependent vasodilation in their airway, and this could attenuate their Qaw response to exercise. We measured the Qaw response to a 5-min exercise challenge in 15 subjects with mild asthma and 10 controls. Baseline mean(±SE) Qaw was 39.6±3.5 µl·min-1·ml-1 in asthmatics and 37.7±4.1 µl·min-1·ml-1 in controls (P=NS), but asthmatics had a blunted vasodilator response to inhaled albuterol (consistent with endothelial dysfunction). Mean Qaw increased significantly in both groups after exercise, reaching a peak of 48±14% at 15 min in asthmatics and 35±10% at 60 min in controls, respectively (P=NS between the groups). In the asthmatics, mean Qaw returned to baseline level by 30 min, whereas in the non-asthmatics, mean Qaw remained high through the 90 min measurement point. Since mean arterial pressure, the driving pressure for Qaw, did not change after exercise in either group, the increase in Qaw reflected local vasodilation in the airway. Thus, brief exercise led to a transient increase in the blood perfusion of the airway without a difference between asthmatics and controls, despite the presence of a blunted endothelium-dependent vasodilation in asthmatics. This suggests that the exercise-related increase in Qaw was not endothelium dependent.

**Key Words:** Exercise, Asthma, Airway Blood Flow

**INTRODUCTION**

Exercise-dependent and independent hyperventilation is associated with cooling and drying of the airway mucosa (2,7). A compensatory increase in the blood perfusion of the mucosa theoretically could counteract this effect. In healthy subjects, airway mucosal microvascular blood flow (Qaw) has been reported to increase during and after exercise and eucapnic hyperventilation with frigid air (6,9).

However, the airway vascular response to exercise has not been examined in subjects with asthma.

We have shown that endothelium-dependent vasodilation is blunted in asthmatic subjects, which is consistent with endothelial dysfunction (3,8,12). This raised the possibility of an abnormal airway vascular response to exercise in asthmatics that could influence the cooling and drying of the airway mucosa, the presumed trigger for exercise-induced respiratory symptoms (10). Thus, the purpose of this study was to determine the magnitude and time course of the Qaw response to exercise in subjects with and without asthma to test the hypothesis that asthmatics have an attenuated Qaw response.

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###### METHODS

**Subjects**

Fifteen non-smokers with physician diagnosed asthma and 10 non-asthmatic and non-smokers participated in this study. All asthmatic subjects had mild intermittent asthma (14), and none was using controller medication within a month prior to the study. Their asthma management consisted of on demand short acting β2-adrenergic agonists. All subjects were free of cardiovascular disease, and they were not taking vasoactive drugs. No subject reported a respiratory infection during the 4 weeks preceding the study. The University of Miami Institutional Review Board approved the study, and the subjects gave informed consent. They received financial remuneration for their participation

**Procedures**

***Airway Blood Flow (Qaw):*** We measured Qaw with a previously validated soluble inert gas uptake method (13,15) that is based on quantifying the disappearance of the soluble gas dimethylether (DME) from the anatomical dead space. Briefly, the method involves inhaling 500 ml of a gas mixture containing 10% DME and 90% nitrogen, followed by a breath hold (5 sec or 15 sec) and subsequent exhalation while the instantaneous concentrations of DME and nitrogen are recorded along with the expired volume. The nitrogen signal is used to delineate the anatomical dead space segment in the expired gas. From the difference in the concentration of DME coming from the dead space after the 5 sec or 15 sec breath hold (ΔFDME), the virtual anatomical dead space volume (VD), the solubility coefficient of DME in blood (α), and the mean DME concentration in the dead space gas (FDME), Qaw was then calculated according to the Fick’s principle: Qaw = (ΔFDME.VD) / (α.FDME). Since Qaw is normalized for VD, VD cancels out. It does not have to be measured. Qaw is expressed in units of µl·min-1·ml-1.

Blood pressure (BP), heart rate (HR), and arterial O2 saturation by pulse oximetrywere determined at every Qaw measurement point. The airway circulation is derived from the aorta, and the perfusion pressure for Qaw is the mean systemic arterial pressure. Since we were interested in the local regulation of Qaw independent of perfusion pressure, we calculated mean systemic arterial pressure (diastolic pressure plus 1/3 of the pulse pressure) to correct for its effect on Qaw.

***Spirometry:*** For spirometry (FEV1, FVC, and FEV1/FVC), the tracing with the highest FVC of three forced vital capacity maneuvers was analyzed. Predicted normal values were taken from Crapo et al. (5). The values were expressed in absolute values and percent of predicted.

***Exercise Challenge:*** The exercise challenge was performed on a treadmill. Heart rate was monitored with an electrocardiogram. The workload was gradually augmented by increasing the speed and/or grade until 85% of predicted maximal HR was achieved. The subjects were then asked to continue exercise at that workload for 5 min (1).

***Protocol:*** There were two visits to the laboratory separated by at least 48 hr. The subjects were asked to abstain from ingesting alcohol the night before the visit and not to drink coffee or caffeinated beverages in the morning before the test. They were also told to refrain from strenuous exercise and the asthmatics were asked to not use albuterol for 12 hrs before the study. On visit 1, the subjects underwent a physical examination to ensure good general health. They had a Qaw measurement and performed spirometry before and 15 min after inhaling 180 µg albuterol from a MDI using a spacer. On visit 2, the subjects performed the exercise protocol. The beginning of the exercise challenge was designated time zero. Qaw, FEV1, BP, HR, and O2 saturation were measured at –15 min, 5 min, 15 min, 30 min, 60 min, and 90 min. The 5 min measurement was started with Qaw, 1-2 min after termination of the 5 min exercise.

**Statistical Analyses**

Data were analyzed using JMP for Macintosh, version 4.0 (SAS Institute Inc. Cary, NC). A t-test was used to assess the effect of inhaled albuterol on Qaw and FEV1. ANOVA was used to determine the significance of exercise-induced changes of several parameters over time with a post-test analysis. A P-value of ≤0.05 was considered significant.

RESULTS

The subjects’ demographic and baseline physiologic data are shown in Table 1. None of the subjects had airflow obstruction at visit 1 and the hemodynamic parameters were within the normal range. The pre-albuterol mean Qaw values were 39.6±3.5 µl·min-1·ml-1 in the asthmatic subjects and 37.7±4.1 in the non-asthmatic subjects (P=NS). Albuterol increased mean Qaw by 9.7±1.5% in the asthmatics (P=NS) and by 47.9±13.8% in the non-asthmatic controls P≤0.05 between the two groups) (Table 2). The corresponding changes in mean FEV1 were not significant.

|  |  |  |
| --- | --- | --- |
|  | **Asthma** | **Controls** |
| **N** |  15  |  10  |
| **Gender**  |  10F/5M |  8F/2M |
| **Age** (yr)  |  38 (18-54) |  30 (24-42) |
| **FEV1** (L) |  3.95 ± 0.21 |  4.19 ± 0.17 |
| **FEV1**(% predicted) |  104 ± 2 |  103 ± 2  |
| **Qaw** (ml·min-1·ml-1) |  39.6 ± 3.5    |  37.7 ± 4.1 |
| **Systolic blood pressure** (mmHg) |  108 ± 1  |   115 ± 2 |
| **Diastolic blood pressure** (mmHg) |  68 ± 1 |  70 ± 1 |
| **Mean blood pressure** (mmHg)  |  81 ± 2 |  86 ± 2 |
| **Qaw /mean blood pressure** (ml·min-1·ml-1·mmHg-1) |  0.46 ± 0.03 |  0.43 ± 0.04 |
| **Heart rate** (beats·min-1)  |  69 ± 1 |  73 ± 1 |

**Table 1**. **Demographics and Baseline Physiological Data Measured during Visit 1.**

**Table 2**. **Effect of Albuterol on Qawand FEV1**

|  |  |  |
| --- | --- | --- |
| **Asthma Controls** |  | ***Controls*** |
|  |
| Change in Qaw (%) 9.7 ± 1.5\* 47.9 ± 13.8 |
| Change in FEV1  (%) 6.1 ± 1.1 3.6 ± 1.0 |

 Mean ± SE. \*P≤0.05 vs. control

The time-course for mean Qaw and HR from 15 min before to 90 min after the beginning of the 5 min exercise challenge are shown in Figure 1 for the asthmatic and controls. Mean Qaw increased significantly in both groups after exercise, reaching a peak of 48±14% at 15 min in the asthmatics and 35±10% at 60 min in the controls, respectively (P=NS between the groups). In the asthmatics, mean Qaw returned to the baseline level by 30 min, whereas in the non-asthmatics, mean Qaw remained elevated throughout the 90 min measurement point.



**Figure 1.** **Time course of hemodynamic parameters after exercise in 15 asthmatic subjects and 10 healthy controls.** Baseline values are pre-exercise. The values at all other time points are after termination of exercise. Values are expressed as mean ± SE . \*P≤0.05 vs. baseline.

Mean HR increased similarly in both groups with a peak at 5 min after the start of exercise (P≤0.05 for both). The post-exercise mean HR increase peaked before the peak increase in mean Qaw in both groups. Mean HR gradually decreased subsequently in both groups, although mean Qaw remained elevated in the controls. This suggests that Qaw was locally regulated after exercise. Mean systemic arterial pressure (perfusion pressure for the airway circulation) did not change throughout the observation period. This indicates that the increase in Qaw reflected local vasodilation. There were no significant changes in mean FEV1 from before to any measurement point after exercise in either group (Figure 2).



**Figure 2. Time course of mean FEV1 after exercise in 15 asthmatic subjects and 10 healthy controls.** Baseline values are pre-exercise. The values at all other time points are after termination of exercise. Values are expressed as mean ± SE. There were no significant changes in either group after exercise.

DISCUSSION

This is the first reported study of airway blood flow responses to exercise in subjects with asthma. The results showed that Qaw is increased after exercise by the same magnitude in asthmatic and non-asthmatic subjects, but that the increase tends to be of longer duration in the latter. Since the increase in Qaw was not associated with an increase in mean systemic arterial pressure, we believe that exercise induced vasodilation in the airway circulation and that the increase in Qaw was not merely a consequence of the exercise-associated increase in cardiac output (9). We were not able to measure Qaw during exercise and therefore were not able to determine the onset of Qaw ‘s increase. However, Morris et al. (9) reported that mean Qaw was already increased between 3 and 5 min into a 10 min exercise period in healthy subjects, and it is likely that the same was present in our asthmatic and non-asthmatic subjects.

In our subjects, who exercised for 5 min, the increase in Qaw was of longer duration than in the subjects studied by Morris et al. (9). We have no explanation for this discrepancy as a similar method was used to determine Qaw in the two studies. The exercise protocol in the study of Morris et al. (9) involved exercising for 10 min and at a higher load than in the present investigation. However, it is difficult to speculate how this would influence the duration of the exercise-induced increase in Qaw.

The magnitude of exercise-induced vasodilation in the airway was not greater in the asthmatic subjects in our study, and there was even a tendency for a longer lasting vasodilation in the non-asthmatic subjects. Most inflammatory mediators that are locally released in the airway of asthmatic subjects are vasodilators (4,10,16) and one, therefore, would have expected a greater and longer lasting vasodilation in the asthmatic than non-asthmatic subjects. Vascular tone is also regulated by endothelial NOS. We and others previously have shown that patients with asthma have a blunted vasodilator response in the airway to inhaled β2-adrenergic agonists (i.e., vasodilators that are known to activate eNOS in vascular endothelium), thereby causing NO related vascular smooth muscle relaxation. This finding, confirmed in the present study, is consistent with the presence of endothelial dysfunction (3,8,11). It is possible that in the asthmatic subjects the endothelial dysfunction masked the vasodilatory actions of inflammatory mediators that may have been released during exercise.

The magnitude of exercise-induced increase of Qaw, both in the asthmatic and non-asthmatic subjects was considerably less than the previously shown increase of Qaw during and after eucapnic hyperventilation with frigid air in healthy subjects (6). The difference may be due to differences in the thermal stress between the two types of challenge. Although we used a previously reported exercise challenge that has been reported to induce bronchoconstriction in asthmatics (3), mean FEV1 failed to change after exercise in our asthmatic subjects. Also, there was no correlation between the post-exercise change in FEV1 and Qaw. One might argue that the magnitude of the exercise-induced decrease in FEV1 would be inversely related to the increase in Qaw as the vascular clearance of locally released spasmogens would increase with the increase in Qaw. Perhaps such a relationship would have emerged in subjects with a strong history of exercise-induced bronchoconstriction or a more vigorous exercise protocol.

### **CONCLUSIONS**

Our study showed for the first time that airway blood flow is similarly increased after exercise in subjects with mild intermittent asthma and non-asthmatic controls, and that the blood flow response is due to local vasodilation in the airway. The asthmatic subjects had impaired endothelium-dependent vasodilation, suggesting that the exercise-induced vasodilation was not mediated by the endothelium. Other, as yet unknown mechanisms must have been involved.

The DME uptake technique used in the present investigation captures blood flow in the mucosa (13), the proposed site in the airway where drying and cooling occurs during exercise-associated hyperventilation. The exercise-induced increase in airway mucosal perfusion may attenuate mucosal cooling and drying. This compensatory vasodilator response seems to be preserved in mild asthmatics.

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