Effects of Aerobic Training on Airway Inflammation in Asthmatic Patients

FELIPE AUGUSTO RODRIGUES MENDES¹, FRANCINE MARIA ALMEIDA², ALBERTO CUKIER³, RAFAEL STELMACH⁴, WILSON JACOB-FILHO⁴, MILTON A. MARTINS², and CELSO RICARDO FERNANDES CARVALHO¹

¹Department of Physical Therapy, School of Medicine, University of São Paulo, São Paulo, BRAZIL; ²Department of Medicine, School of Medicine, University of São Paulo, São Paulo, BRAZIL; ³Pulmonary Department, School of Medicine, University of São Paulo, São Paulo, BRAZIL; and ⁴Department of Geriatrics, School of Medicine, University of São Paulo, São Paulo, BRAZIL

ABSTRACT


Purpose: There is evidence suggesting that physical activity has anti-inflammatory effects in many chronic diseases; however, the role of exercise in airway inflammation in asthma is poorly understood. We aimed to evaluate the effects of an aerobic training program on eosinophil inflammation (primary aim) and nitric oxide (secondary aim) in patients with moderate or severe persistent asthma.

Methods: Sixty-eight patients randomly assigned to either control (CG) or aerobic training (TG) groups were studied during the period between medical consultations. Patients in the CG (educational program + breathing exercises; N = 34) and TG (educational program + breathing exercises + aerobic training; N = 34) were examined twice a week during a 3-month period. Before and after the intervention, patients underwent induced sputum, fractional exhaled nitric oxide (FeNO), pulmonary function, and cardiopulmonary exercise testing. Asthma symptom-free days were quantified monthly, and asthma exacerbation was monitored during 3 months of intervention.

Results: A t 3 months, decreases in the total and eosinophil cell counts in induced sputum (P = 0.004) and in the levels of FeNO (P = 0.009) were observed after intervention only in the TG. The number of asthma symptom-free days and V̇O₂max also significantly improved (P < 0.001), and lower asthma exacerbation occurred in the TG (P < 0.01). In addition, the TG presented a strong positive relationship between baseline FeNO and eosinophil counts as well as their improvement after training (r = 0.77 and r = 0.9, respectively).

Conclusions: Aerobic training reduces sputum eosinophil and FeNO in patients with moderate or severe asthma, and these benefits were more significant in subjects with higher levels of inflammation. These results suggest that aerobic training might be useful as an adjuvant therapy in asthmatic patients under optimized medical treatment.

Key Words: ASTHMA, EXERCISE, EOSINOPHILS, SPUTUM, NITRIC OXIDE, SYMPTOMS

Asthma is a chronic inflammatory disorder of the airways involving many cells and cellular elements. The chronic inflammation is associated with airway hyperresponsiveness that leads to recurrent episodes of wheezing, breathlessness, chest tightness, and coughing (10). The clinical treatment of the disease is centered on corticosteroids and bronchodilators to reduce airway inflammation, asthma symptoms, and limitations in daily life, physical activities, or exercise (10).

The effect of regular physical activity on the overall management of asthma has been previously considered, and there is evidence suggesting that an increase in exercise capacity improves psychosocial factors (14) as well as reduces exercise-induced bronchoconstriction (6) and corticosteroid consumption (6,17). Moreover, recent studies have also shown that asthmatic patients with higher exercise capacity present lower risk of exacerbation (7). Taken together, these results may suggest a possible role for physical activity in attenuation of allergic airway inflammation.

The anti-inflammatory effects of physical activity in healthy subjects and in many chronic diseases have previously been described (9,11,13); however, its role in allergic diseases such as asthma is poorly understood. Recent studies in experimental animal models of asthma have shown that aerobic training reduces eosinophil counts in the airways,
expression of allergic cytokines (IL-4, IL-5, and IL-13), and airway remodeling (30,27). In asthmatic patients, there are only two studies (16,4) evaluating the effect of aerobic training on inflammation, and the only observed effect was a reduction in the blood immunoglobulin E levels (16).

Therefore, the aim of the present study was to evaluate the effect of an aerobic training program on airway inflammation and asthma symptoms in patients with moderate or severe asthma.

METHODS

Patients

Sixty-eight patients (55 women and 13 men) with moderate or severe persistent asthma between 20 and 50 yr of age were recruited at a university hospital. Asthma diagnosis was based on the Global Initiative for Asthma (10). Patients were under medical treatment for at least 6 months and were considered clinically stable (i.e., no crises or changes in medication for at least 30 d). Patients diagnosed with cardiovascular, pulmonary, or musculoskeletal diseases that would impair exercise training were excluded from the study. The clinic’s hospital ethics committee approved the study, and patients signed informed consent forms. Some patients (26/68) participated simultaneously in a study that was recently published (14).

Experimental Design

The study was performed between two medical consultations to avoid changes in medication. Patients were randomized (by drawing lots) into control (CG; N = 34) or training (TG; N = 34; Fig. 1) groups. Both groups participated in a 4-h educational program and a breathing exercise program, but only the TG participated in an aerobic training program individually on the basis of V̇O₂max. Before and after the intervention, patients underwent induced sputum, fractional exhaled nitric oxide (FeNO), pulmonary function, and cardiopulmonary exercise testing. Asthma symptom-free days were quantified monthly. To prevent issues of compliance, the transport costs for every patient were covered by the researcher grants. Patients from both groups completed all 24 intervention sessions from either CG or TG.

Educational Program

Both groups completed an educational program that consisted of two classes (once a week), and each class lasted 2 h. The core activity was based on an educational videotape about the “ABC of Asthma,” including information about asthma pathophysiology, medication skills, self-monitoring techniques, and environmental control/avoidance strategies (10,14,24). Patients’ doubts were addressed during an interactive discussion.
Breathing Exercise Program

Both groups were taught yoga breathing exercises including Kapalabhati (fast expiratory breathing exercise followed by passive inhalation), Uddiyana (full exhalation followed by a forced inspiration performed without air inhalation (apnea)), and Agnisara (full exhalation followed by a sequence of retractions and protrusions of the abdominal wall in apnea) (14,29). A 30-min session was performed twice a week for 3 months, and every exercise was executed in sets of three with 2 min of exercise intercalated with 60 s of rest (14).

Aerobic Training Program

Subjects from the TG completed an aerobic training program for 30 min per session twice a week for 3 months in an indoor treadmill. Aerobic exercise was initiated at 60% of VO2max in the first 2 wk and then increased to 70% VO2max (14). After this increase, if the patient maintained two consecutive exercise sessions without symptoms, then exercise intensity was increased by 5% of cardiac frequency (until a maximal of 80% patient maximal cardiac frequency) by using either treadmill speed or grade. The use of salbutamol (200 µg) before an exercise session was recommended only if the peak expiratory flow (PEF) was <70% of the patient’s best value. The safety of aerobic training was monitored by quantifying PEF and asthma symptoms at the end of every exercise session.

Assessments

Induced sputum. After premedication with 400 µg of salbutamol, 3% of hypertonic saline was administered by inhalation over 15 min (20,21). The aerosol was generated by an ultrasonic nebulizer (Ultraneb 99; DeVilbiss, Somerset, PA) with an output of 2.4 mL·min⁻¹ and a mass median aerodynamic diameter of 4.5 µm as previously described (20). The subjects were asked to blow their nose and to rinse their mouth with water and swallow it to reduce contamination of the sputum specimen with postnasal drip and saliva. Sputum samples were visually separated from saliva with the help of an inverted microscope and divided into two aliquots. One part was spread over a glass slide before fixation and staining (19,25). The slide was air dried, fixed, and stained with Diff Quick (Sigma-Aldrich), and the mixture was briefly stirred with a vortex mixer (25). Total cell counts were performed with a hemocytometer (Neubauer chamber) (22), and the cell suspensions were adjusted to 1.0 × 10⁶ mL⁻¹ (8). Cells were classified as eosinophils, lymphocytes, neutrophils, macrophages, squamous cells, goblet, and ciliated cells on the basis of their morphology by a single-blinded investigator. The investigator who performed clinical tests had access to induced sputum data only at the end of the intervention program.

Fractional exhaled nitric oxide. Patients were advised to blow into a Mylar bag, keeping the expiratory pressure of 12 cm H₂O to avoid air contamination from the nasal cavity. Exhaled mouth air was diluted before being collected in the bag, and the expiratory pressure achieved by the individual was monitored by a manometer. All collected samples were mixed up to 10 s before the determination of NO concentration by chemiluminescence (Sievers 280 NOA; Sievers Instruments, Boulder, CO) and analyzed up to 24 h after sample collection as previously described (2). The equipment was calibrated before the start of each analysis.

Clinical asthma symptoms were quantified by a daily diary, including asthma symptoms such as cough, diurnal or nocturnal dyspnea, wheezing, and use of relief medication. A day free of asthma symptoms was considered when a patient did not report any symptoms. All patients were familiarized with the diary during the 30 d before the study. The diary was filled out during the follow-up period, and symptom-free days were quantified monthly. Visits to an emergency room and exacerbation of asthma symptoms were also monitored in the daily diary. Asthma exacerbation was defined as worsening of asthma symptoms requiring the use of short-acting β₂-agonist ≥4 extra puffs per day for a minimum of 48 h.

Spirometry was performed before and after the inhalation of 200 µg of salbutamol (Sensormedics 229; Sensor-Medics Corp., Yorba Linda, CA), and technical procedures were performed as recommended by the American Thoracic Society/European Respiratory Society (1). Predicted normal values were those proposed by Knudson et al. (12), and a 12% and a 200-mL increase in FEV₁ from baseline were characterized as a positive response to the bronchodilator.

Cardiopulmonary exercise testing was evaluated by a symptom-limited treadmill test on a digital computer-based exercise system (Sensormedics 229) with breath-by-breath analysis according to the Balke-modified protocol (26). A bronchodilator (200 µg of salbutamol) was used 15 min before cardiopulmonary exercise testing to allow patients to reach maximal oxygen consumption. Aerobic impairment was classified according to Cooper et al. (5).

Statistical Analysis

The sample size of 46 patients (23 each group) was calculated considering a decrease of 10% in eosinophil cell counts with a standard deviation of 12% as previously observed (15).

TABLE 1. Baseline anthropometric data, bronchodilator response, and corticosteroid consumption in patients with persistent asthma.

<table>
<thead>
<tr>
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<th>CG (n = 24)</th>
<th>TG (n = 27)</th>
<th>P</th>
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<tr>
<td>Anthropometric data</td>
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<tr>
<td>Gender (female/male)</td>
<td>18/6</td>
<td>24/3</td>
<td>NS</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>36.0 (22.0–47.5)</td>
<td>37.9 (25.7–47.4)</td>
<td>NS</td>
</tr>
<tr>
<td>BMI (kg·m⁻²)</td>
<td>26.8 (18.2–29)</td>
<td>24.5 (19.4–29.2)</td>
<td>NS</td>
</tr>
<tr>
<td>Bronchodilator responders</td>
<td>6 (27%)</td>
<td>3 (16%)</td>
<td>NS</td>
</tr>
<tr>
<td>Long-acting β₂-agonists (µg·d⁻¹)</td>
<td>24 (12–39)</td>
<td>24 (12–36)</td>
<td>NS</td>
</tr>
<tr>
<td>Budesonide dosage (µg·d⁻¹)</td>
<td>800 (400–1600)</td>
<td>800 (400–1200)</td>
<td>NS</td>
</tr>
</tbody>
</table>

Data are expressed as median (95% CI), except for gender and bronchodilator responders, which are presented as numbers of patients and percentages, n (%).

BMI, body mass index; NS, not statistically significant.

Chi-square test.

Mann–Whitney test.
and considering the average number of eosinophils observed in our patients with moderate and severe asthma (25). The statistical power normality was evaluated by using the Kolmogorov–Smirnov test, and data were presented as medians with a 95% confidence interval (CI). The Mann–Whitney test was used to compare nonparametric data (age, body mass index (BMI), and corticosteroid dosage), and the chi-square test was used to evaluate gender and bronchodilator response between groups at baseline. Induced sputum cellularity (primary outcomes), FeNO (secondary outcomes), and all other outcomes were assessed by a two-way repeated-measures ANOVA followed by a Holm–Sidak post hoc test. The Fisher test was used to evaluate emergency room visits and asthma exacerbation. The linear correlation analysis was evaluated by the Spearman test. The statistical significance level was set at 5% for all tests. Sigma Stat Software Package 3.5 was used for statistical analyses.

RESULTS

Seventeen patients (10 CG/7 TG) withdrew from the study because of health problems other than asthma, scheduling difficulties, or personal problems. Fifty-one patients completed the study (24 CG/27 TG). Before the study, both groups

![Figure 2](image2.png)

**FIGURE 2**—Percentages of cells in induced sputum before and after intervention. Eosinophils (A); total cells (B); macrophages (C); neutrophils (D). *P ≤ 0.05 compared with baseline and CG values (two-way repeated-measure ANOVA test). Boxes represent the 25th–75th percentiles, the line inside the boxes represents the median, and the bars represent the 10th and 90th percentiles.

![Figure 3](image3.png)

**FIGURE 3**—FeNO before and after the study. *P < 0.05 when compared with CG and baseline values (two-way repeated-measure ANOVA test).

![Figure 4](image4.png)

**FIGURE 4**—Asthma symptoms during the study period. Values are expressed as the mean number of symptom-free days per month with a 95% CI. Time points are as follows: 0 d, 1 month before intervention; 30 d, first month of intervention; 60 d, second month of intervention; 90 d, third month of intervention. *P < 0.05 when compared with baseline and CG values (two-way repeated-measure ANOVA test).
were similar in gender, age, BMI, daily doses of corticosteroids, and long-acting β2-agonists (P > 0.05; Table 1), induced sputum cellularity (P > 0.05; Fig. 2), FeNO (P > 0.05; Fig. 3), asthma symptoms (P > 0.05; Fig. 4), pulmonary function (P > 0.05; Table 2), and aerobic capacity (P > 0.05; Table 2). All patients were under budesonide and long-acting β2-agonists prescription (Table 1), and both groups maintained the same medication dosage throughout the intervention.

**Induced sputum cellularity.** After training, only the TG presented a reduction in eosinophil and total cells counts compared with the baseline and the CG values (Fig. 2). No changes were observed in macrophage, neutrophil, lymphocyte, and epithelial cell counts (squamous, goblet, and ciliated) between both groups after intervention (P > 0.05).

**The effect of training on FeNO.** Before intervention, patients from both groups presented, on average, a FeNO of 31.0 ppb (95% CI from 14.6 to 55.7), and 51% of the patients (12 CG/16 TG) presented increased levels of FeNO >30 ppb. After intervention, the TG presented a decrease in FeNO when compared with the baseline and the CG (Fig. 3; P = 0.009), and only 36% of patients from the TG (10/27) had FeNO >30 ppb. The CG did not present any change in the FeNO after intervention (P > 0.05).

**The effect of training on aerobic capacity and pulmonary function.** At baseline, 44% of the patients (22/51) presented VO₂max values <70% of predicted. After the study, only the TG showed an increase in VO₂max compared with the CG (P < 0.001; Table 2) without changes in pulmonary function (Table 2). A positive response to training (improvement in VO₂max ≥10%) was found in 24 patients (88%) who were considered “responders.” No patients presented a decrease in PEF ≥15% or an increase in asthma symptoms after each exercise session.

**Asthma symptoms.** At baseline, the TG presented 16 d-month⁻¹ (from 4.0 to 28.3) without asthma symptoms versus 14 d-month⁻¹ (from 5.2 to 24.7) for the CG (Fig. 4). The CG had similar numbers of days without asthma symptoms after 30, 60, and 90 d (P > 0.05). Nevertheless, the TG presented a significant increase in the number of days without asthma symptoms after 30 d (20.0 d, 95% CI from 4.0 to 28.2, P < 0.001), and this difference was maintained after 60 and 90 d of aerobic training (24 d each) compared with baseline and CG values (P < 0.001; Fig. 4). During the 3 months of intervention, the number of visits to the emergency room (4CG/1TG) and asthma exacerbations (7CG/1TG) was lower in the TG compared with the CG (P < 0.01).

**Linear relationship among outcomes.** The TG presented a strong linear relationship between the baseline eosinophil counts (r = 0.90, P < 0.001) and their reduction after exercise training (Δ initial–final). Similar results were observed in the FeNO levels (r = 0.76, P < 0.01). In addition, a negative linear relationship was observed between the baseline number of days without asthma symptoms and an increase in symptom-free days after aerobic training (Δ initial–final) (r = −0.58, P = 0.003).

**DISCUSSION**

The results of the present study demonstrate that adults with moderate or severe asthma who participated in an aerobic training program presented a decrease in eosinophil and total cell counts in the induced sputum as well as a reduction in FeNO levels and asthma symptoms. These benefits were significantly associated with baseline values, suggesting that the worse the airway inflammation and the asthma symptoms were, the greater the improvement induced by aerobic training.

**The effect of physical fitness on airway inflammation.** To the best of our knowledge, this study is the first to verify a reduction in airway inflammation after aerobic training in asthmatic patients. Although the anti-inflammatory effects of physical activity in healthy subjects and in many chronic diseases have previously been described (9,11,13), its role on asthma, an airway inflammatory disease, is poorly understood. Recent experimental studies in animal models of asthma from our group suggested that mice submitted to aerobic training presented decreases in the number of eosinophils, airway inflammation, and remodeling (27,30). In addition, those studies showed that these effects seem to occur in response to a decreased expression of Th2 cytokines (IL-4, IL-5, and IL-13) and NF-κB as well as an increased expression of anti-inflammatory cytokines IL-10 and IL-1ra.

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**TABLE 2. Pulmonary function and maximal aerobic capacity of adult asthmatic patients before and after the treatment program.**

<table>
<thead>
<tr>
<th>Pulmonary function</th>
<th>Before</th>
<th>After</th>
<th>Before</th>
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<th>P</th>
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<tbody>
<tr>
<td><strong>CG (n = 24)</strong></td>
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<tr>
<td>FEV₁ (L)</td>
<td>2.52 (1.3–3.2)</td>
<td>2.5 (1.3–3.5)</td>
<td>2.2 (1.2–3.2)</td>
<td>2.3 (1.0–3.4)</td>
<td>0.71</td>
</tr>
<tr>
<td>% predicted</td>
<td>85.5 (45.4–112.6)</td>
<td>84.4 (42.0–114.4)</td>
<td>79.9 (43.5–107.0)</td>
<td>79.6 (37.5–106.5)</td>
<td>0.89</td>
</tr>
<tr>
<td>FVC (L)</td>
<td>3.4 (2.3–4.3)</td>
<td>3.4 (2.4–4.60)</td>
<td>3.1 (1.9–4.1)</td>
<td>3.1 (2.4–4.3)</td>
<td>0.86</td>
</tr>
<tr>
<td>% predicted</td>
<td>90.0 (68.9–109.1)</td>
<td>92.1 (67.2–112.1)</td>
<td>94.0 (65.3–116.3)</td>
<td>96.2 (65.2–117.5)</td>
<td>0.83</td>
</tr>
<tr>
<td>FEV₁/FVC</td>
<td>69.0 (48.7–89.4)</td>
<td>67.9 (49.5–89.1)</td>
<td>71.7 (53.4–87.7)</td>
<td>69.9 (46.9–92.5)</td>
<td>0.62</td>
</tr>
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<td>FEF₂₅–₇₅% (L·s⁻¹)</td>
<td>1.7 (0.4–3.8)</td>
<td>1.4 (0.4–4.0)</td>
<td>1.8 (0.532–4.0)</td>
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<td>75.6 (57.6–99.5)</td>
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<td>&lt;0.001</td>
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<td>VO₂max (% predicted)</td>
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Data are expressed as median (95% CI). FEV₁, forced expired volume in the first second; FVC, forced vital capacity; FEF, forced expiratory flow.

* P < 0.05 when compared with the intragroup value before treatment using a two-way repeated-measure ANOVA test.
We are aware of only two studies aiming to evaluate the anti-inflammatory effects of aerobic training in asthmatics patients (4,16). Morreira et al. (16) evaluated the effect of aerobic training in 34 asthmatic children and did not observe changes on FeNO, blood eosinophils, eosinophil cationic protein, and C-reactive protein levels. In addition, they showed a reduction in total immunoglobulin E levels. Bonsignore et al. (4) evaluated the levels of FeNO in 50 children with mild persistent asthma and did not show a reduction in FeNO after aerobic training. The discrepancy between our findings and those previously obtained by Morreira et al. (16) and Bonsignore et al. (4) may be explained by exercise training, evaluated outcomes, and the patients’ disease severity. First, in our study, the intensity of exercise during aerobic training was monitored and graded by the cardiovascular response (heart rate), whereas in the studies of Morreira et al. (16) and Bonsignore et al. (4), the progression in exercise training was not precisely described. This difference may explain why the increase in maximal aerobic capacity observed in our patients was at a similar level to that described in a recent systematic review (4.8 vs 5.5 mL O₂·kg⁻¹·min⁻¹, respectively) (23). In contrast, Bonsignore et al. (4) only observed an increase in the submaximal capacity (anaerobic threshold), and Morreira et al. (16) did not evaluate such parameters.

Second, to evaluate asthma inflammation, we quantified sputum eosinophil counts and FeNO levels and observed a reduction in both parameters. Morreira et al. (16) evaluated asthma inflammation by quantifying blood eosinophils, which is considered less accurate than sputum eosinophils (20). In addition, Bonsignore et al. (4) did not evaluate eosinophil counts, and asthma inflammation was quantified only by measuring FeNO levels, which were not modified after aerobic training. Third, our patients had moderate and severe persistent asthma, whereas Bonsignore et al. (4) studied patients with a mild disease severity, and Morreira et al. (16) did not report the patients’ severities.

**Asthma symptoms and exacerbation.** There are few randomized and controlled trials investigating the effect of physical training on asthma symptoms (14,23,28) and exacerbation (7), and these issues remain controversial. Although those outcomes were not the main issue in our study, it is appropriate that they would be investigated simultaneously with airway inflammation because asthma symptoms and exacerbation are the main complaints in clinical practice. In our study, we observed that an improvement in aerobic capacity increased the number of asthma symptom-free days (Fig. 4) reported by the patients 30 d after the beginning of the exercise training program, and this was maintained until the end of the program. We also observed that patients from the TG had less asthma exacerbation and fewer visits in the emergency room than patients in the CG. Interestingly, a very recent study suggests that asthmatic women with higher physical activity levels present a reduced risk of exacerbation (7).

Subjectively, many asthmatic patients report a reduction in asthma symptoms after improvement in physical fitness, but the physiological basis of this perception has not been systematically investigated (23). The current hypothesis to explain the benefits of physical activity in patients with asthma is the decrease in minute ventilation, which reduces the perception of breathlessness (23). In our study, patients who participated in the aerobic training program presented an improvement in aerobic capacity and also a reduction in airway inflammation, which might suggest another hypothesis for the reduction in asthma symptoms because of exercise training. We did not observe any effect in patients that completed the yoga breathing exercises, and this may be because we used only three exercises without increasing the grade of difficulty. In the present study, our strategy was to follow-up with the CG twice a week, similar to the training group, to reduce any possible bias toward a better treatment between groups and not to compare yoga versus aerobic training. On the basis of our results, we cannot assume that yoga is ineffective for asthmatic patients.

It remains poorly understood which asthmatic patients benefit the most from exercise training. In our study, we observed that patients with higher baseline scores, even when they already received proper medical treatment, presented better improvement of asthma symptoms and airway inflammation. These results seem relevant to clinical prescription of exercise training in this population; that is, they suggest that aerobic training should be recommended to patients who continue to experience either asthma symptoms or airway inflammation even after adequate medication. In addition, our study also suggests that exercise training could be considered a safe procedure for these patients because none of them presented complications (increase in either asthma symptoms or decrease ≥15% of PEF) after any of the exercise sessions.

Certain limitations should be noted in our study. Our results may not be considered as representative of the entire population of patients with moderate or severe persistent asthma because we evaluated 42% (68 from 160 patients) of the patients assessed for eligibility in the study (Fig. 1). Furthermore, it is important to note that not all subjects from the aerobic training group showed improvement in the inflammatory markers. Most the patients (88%) were considered responders to aerobic training (improvement in VO₂max ≥10%): 80% of them presented a reduction in at least one inflammatory outcome (either eosinophil<3% [3] or FeNO<30 ppb [18]), and 16% presented a reduction in both parameters.

Second, although both groups completed 24 intervention sessions and received the same educational program, they were not exposed to a similar amount of attention during each intervention session (30 min CG vs 60 min TG). However, our experimental design is an improvement over previous studies where the CG only received usual care (23). Third, because there was no previous study evaluating the effect of aerobic training on airway inflammation, the sample size was calculated on the basis of the study of Minoguchi et al. (15), where the sputum eosinophil counts were similar to our patients (25). Fourth, pulmonary function
and cardiopulmonary tests were conducted by the same investigator in charge of aerobic training. However, sputum eosinophil counts and FeNO levels were determined by a blinded investigator. Finally, patients were followed for a short-term period, and further studies are required to understand long-term effects.

In conclusion, our results suggest that aerobic training reduces sputum eosinophil counts and FeNO levels in patients with moderate or severe asthma, and these benefits were more significant in subjects with higher levels of inflammation. These results suggest that aerobic training might be useful as an adjuvant therapy in asthmatic patients under optimized medical treatment.

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