



ORIGINAL ARTICLE

Aerobic training decreases bronchial hyperresponsiveness and systemic inflammation in patients with moderate or severe asthma: a randomised controlled trial

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► Additional material is published online only. To view please visit the journal online (<http://dx.doi.org/10.1136/thoraxjnl-2014-206070>).

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Received 22 July 2014
Revised 3 February 2015
Accepted 1 April 2015
Published Online First
10 June 2015



CrossMark

To cite: França-Pinto A, Mendes FAR, de Carvalho-Pinto RM, et al. *Thorax* 2015;**70**:732–739.

ABSTRACT

Background The benefits of aerobic training for the main features of asthma, such as bronchial hyperresponsiveness (BHR) and inflammation, are poorly understood. We investigated the effects of aerobic training on BHR (primary outcome), serum inflammatory cytokines (secondary outcome), clinical control and asthma quality of life (Asthma Quality of Life Questionnaire (AQLQ)) (tertiary outcomes).

Methods Fifty-eight patients were randomly assigned to either the control group (CG) or the aerobic training group (TG). Patients in the CG (educational programme +breathing exercises (*sham*)) and the TG (same as the CG+aerobic training) were followed for 3 months. BHR, serum cytokine, clinical control, AQLQ, induced sputum and fractional exhaled nitric oxide (FeNO) were evaluated before and after the intervention.

Results After 12 weeks, 43 patients (21 CG/22 TG) completed the study and were analysed. The TG improved in BHR by 1 doubling dose (dd) (95% CI 0.3 to 1.7 dd), and they experienced reduced interleukin 6 (IL-6) and monocyte chemoattractant protein 1 (MCP-1) and improved AQLQ and asthma exacerbation ($p<0.05$). No effects were seen for IL-5, IL-8, IL-10, sputum cellularity, FeNO or Asthma Control Questionnaire 7 (ACQ-7; $p>0.05$). A within-group difference was found in the ACQ-6 for patients with non-well-controlled asthma and in sputum eosinophil and FeNO in patients in the TG who had worse airway inflammation.

Conclusions Aerobic training reduced BHR and serum proinflammatory cytokines and improved quality of life and asthma exacerbation in patients with moderate or severe asthma. These results suggest that adding exercise as an adjunct therapy to pharmacological treatment could improve the main features of asthma.

Trial registration number NCT02033122.

INTRODUCTION

Asthma, defined as a chronic inflammatory disorder of the airways, is characterised by airway obstruction and bronchial hyperresponsiveness (BHR) and is associated with recurrent episodes of wheezing, breathlessness, chest tightness and coughing.¹ Asthma symptoms experienced during daily

Key messages

What is the key question?

- Does aerobic exercise improve bronchial hyperresponsiveness and airway and systemic inflammation in patients with moderate or severe asthma?

What is the bottom line?

- Improvements in aerobic fitness reduced bronchial hyperresponsiveness in one doubling dose of histamine and reduced systemic inflammation in patients with moderate or severe asthma under optimal medical treatment, suggesting that this therapy is an important adjuvant in asthma treatment.

Why read on?

- This randomised and controlled trial provides the first evidence, obtained using a gold-standard method, that improvement in aerobic exercise reduces bronchial hyperresponsiveness and systemic inflammation.

physical activities or the fear of triggering asthma may keep patients with asthma from engaging in physical exercise,² which often leads to a detrimental health cycle and an aversion to exercise, and reduces activity in daily life and physical fitness.^{3–4} Interestingly, a low level of physical activity has been strongly and independently associated with increased BHR in patients with asthma.⁵

However, exercise training has been proposed as an adjunctive therapy in asthma treatment because it improves physical fitness, health-related quality of life (HRQoL)⁶ and asthma symptoms,⁷ and because it reduces corticosteroid consumption.⁸ However, the effects of exercise training on BHR remain controversial. Two recent systematic reviews evaluated the effects of aerobic training on BHR and reported either no benefit⁹ or only a trend towards lower BHR after exercise training.¹⁰



The lack of evidence observed in these reviews is explained by the great diversity in patient disease severity, clinical control status and medication management. In addition, BHR in these studies^{9–10} was not properly evaluated using a doubling dose, which is the gold-standard method recommended by current guidelines and has been widely used in clinical trials.¹¹ As a consequence, both meta-analyses recommended performing well designed trials using standardised tools and more detailed sample characterisation to investigate the potential benefits of regular exercise on BHR in patients with asthma.

Although the effect of aerobic training on BHR in patients with asthma remains poorly understood, studies in asthma animal models have demonstrated that exercise training reduces airway responsiveness and inflammation.^{12–13} Three potential mechanisms have been proposed: reductions in expression of the T helper 2 (Th2) cytokines interleukin (IL)-4, IL-5 and IL-13,^{13–16} reductions in the chemokines monocyte chemoattractant protein (MCP)¹⁶ and keratinocyte chemoattractant (KC; murine homologue to human IL-8)¹⁵ and increases in the anti-inflammatory cytokine IL-10.^{13–16} To the best of our knowledge, no previous study has investigated such mechanisms in patients with asthma. Given that BHR and inflammation are characteristic features of asthma and given that exercise has systemic anti-inflammatory effects,¹⁷ the aim of the present study was to investigate the effects of aerobic training on BHR (primary aim) and serum inflammatory cytokines (secondary aim). In addition, clinical control, asthma quality of life and airway inflammation were evaluated (tertiary outcomes).

METHODS

Detailed study methods are provided in the online supplementary appendix.

Subjects

Outpatients with moderate or severe persistent asthma, aged between 20 and 59 years, were recruited from a University Hospital. The Ethics Review Board of the Clinical Hospital approved the study (protocol 0121/10). All patients signed an informed consent form and the trial was registered at ClinicalTrials.gov (NCT02033122). Asthma was diagnosed according to the Global Initiative for Asthma,¹ and disease severity was determined by combining the current level of symptoms, pulmonary function and maintenance treatment.¹⁸ The patients were managed under optimal medical treatment, monitored by pulmonologists for at least 6 months and considered clinically stable (without exacerbations or changes in medication for at least 30 days).

Patients who met the following criteria were excluded: cardiovascular, musculoskeletal or other chronic lung diseases; current participation in a moderate or vigorous exercise programme; and current smokers or ex-smokers.

Experimental design

This was a randomised, controlled and single-blinded trial that included an intervention of an aerobic training programme. The study was performed between two medical visits, and during the intervention period, the pharmacotherapy was maintained. Before and after the intervention, BHR, serum levels of cytokines, total immunoglobulin E (IgE), induced sputum, fractional exhaled nitric oxide (FeNO), clinical control (exacerbation, diary of daily symptoms and Asthma Control Questionnaire (ACQ)), Asthma Quality of Life Questionnaire (AQLQ), pulmonary function and exercise capacity were assessed.

After the baseline evaluation, the eligible patients were randomly assigned following simple randomisation procedures (drawing of a sealed opaque envelope containing group code control group (CG) or training group (TG)) by a researcher not involved in the study. The CG patients were subjected to a breathing exercise programme (sham intervention), and the TG patients were subjected to the same breathing exercise programme and an aerobic exercise training programme. Both groups also underwent a 4 h educational programme. All patients completed the 24 treatment sessions, after which they were reevaluated.

Interventions

Breathing exercise programme

Both groups completed a yoga breathing exercise programme twice a week for 12 weeks.^{6–7} Each session lasted 30 min and was supervised by a physiotherapist. Breathing exercises were included as a sham intervention in the CG to prevent differences in the number of hospital visits and to reduce possible differences in the amount of attention between groups but not to induce benefits in patients with asthma.^{6–7}

Aerobic training programme

All subjects from the TG completed the aerobic training programme twice a week for 12 weeks on an indoor treadmill. Each aerobic training session lasted 35 min and was divided into 5 min of warm-up, 25 min of aerobic training and 5 min of cool-down.⁶ At the end of the programme, all the subjects were performing vigorous training, based on the anaerobic threshold (AnT) and the respiratory compensation point.

Assessments

Bronchial hyperresponsiveness

A bronchial provocation test with histamine was conducted according to American Thoracic Society (ATS) guidelines.¹⁹ The test was considered positive when the histamine concentration promoted a decrease $\geq 20\%$ in forced expiratory volume in 1 s (FEV₁, PC₂₀).

Serum cytokines and total IgE

The cytometric bead array method (BD Biosciences, San Jose, California, USA) was used to analyse the levels of IL-4, IL-5, IL-6, IL-10, tumour necrosis factor (TNF)- α , IL-12p70, IL-8/CXCL8, MCP-1/CCL2 and RANTES/CCL5. Total serum IgE was measured by nephelometry using commercially available kits (Dade Behring/Siemens, Deerfield, Illinois, USA).

Fractional exhaled nitric oxide

All measurements were determined by chemiluminescence (Sievers 280) in accordance with the ATS recommendations.²⁰ FeNO values were considered elevated at >26 ppb.²¹

Induced sputum

Sputum was collected and processed using a standard method.²² Eosinophil values were considered elevated at $>3\%$.²³

Asthma symptoms and exacerbation

Asthma symptoms and exacerbation were evaluated using a daily diary of symptoms as previously reported.^{6–7} A day was considered free of asthma symptoms when the patient did not report any symptoms, and these days were totalled monthly. Asthma exacerbation was defined as an increase in symptoms associated with at least one of the following criteria: use of rescue medication ≥ 4 puffs per 24 h during a 48 h period, need

for systemic corticosteroids, unscheduled medical appointment, visit to an emergency room or hospitalisation.

Asthma control questionnaire

The ACQ-7 consists of seven questions related to asthma symptoms, use of short-acting β_2 agonists and FEV₁ in the percent of predicted values. The ACQ-6 is the same as the ACQ-7 without the question related to FEV₁.²⁴

Asthma quality of life

Asthma quality of life was assessed using the AQLQ,²⁵ which has four domains: activity limitations, symptoms, emotional function and environmental stimuli. A higher AQLQ score indicates a better quality of life.²⁵

Cardiopulmonary exercise test and pulmonary function

The test was performed on a treadmill with a ramp protocol, as recommended by the American College of Cardiology/American Heart Association.²⁶ Pulmonary function testing was performed according to the current ATS/European Respiratory Society guidelines.²⁷

Atopy

Patients were considered atopic if they presented a clinical history suggestive of respiratory allergy and specific IgE antibodies in the following tests: in vivo (skin prick test) and/or in vitro (Phadiatop test).

Statistical analysis

A sample size of 34 patients (17 in each group) was estimated to provide 80% power to detect a 1 doubling-dilution shift in histamine PC₂₀ value (minimal clinical difference), assuming a 1.0 within-patient SD in doubling-dilution shift and an α of 0.05 (two tailed).²⁸ PC₂₀ histamine changes were expressed in terms of doubling dose (dd) concentrations, calculated as $\Delta \log PC_{20}/\log 2$,²⁸ and Student's t test was used to compare groups. ACQ, AQLQ, aerobic capacity and pulmonary function were summarised using means and SDs, and differences between the CG and TG were compared using Student's unpaired t test. Sputum cell counting, FeNO, cytokine concentrations and total IgE were summarised using medians and IQRs (25% and 75%), and differences between the CG and TG were compared using the unpaired Mann-Whitney U test. The proportion of patients experiencing exacerbations between the TG and placebo CG were compared by

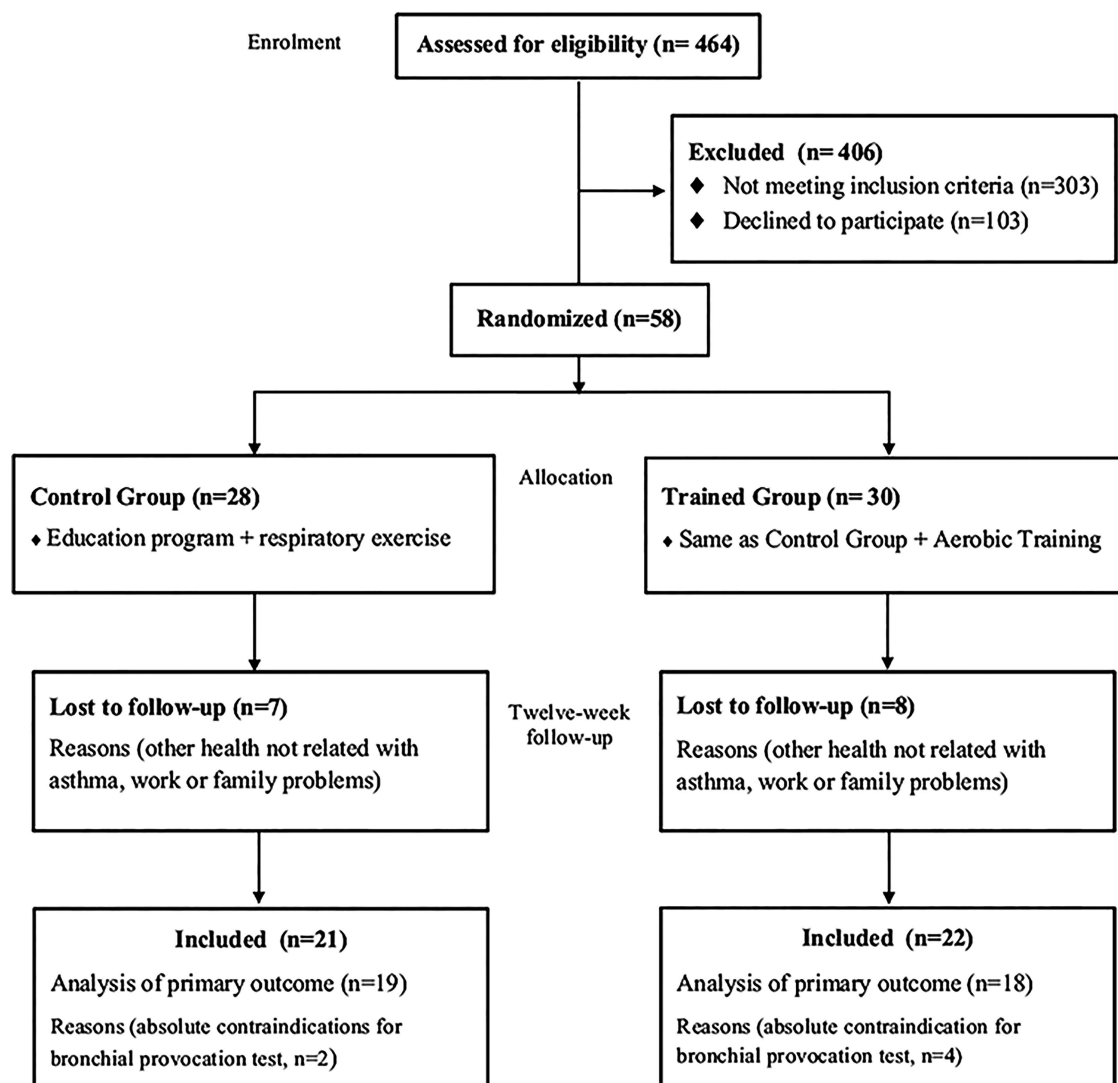


Figure 1 Flow of participants through the study (CONSORT diagram). CG, control group; TG, training group.

Table 1 Baseline characteristics of patients with asthma

Patient characteristics	Control group (n=21)	Training group (n=22)
Anthropometric data		
Sex (F/M)	17/4	17/5
Age, years old; mean (SD)	44 (9)	40 (11)
BMI, kg/m ² ; mean (SD)	26.4 (4.3)	26.5 (4.2)
Medication		
Budesonide dosage, µg/day; mean (SD)	804 (370)	909 (594)
Long-acting β ₂ agonists, µg/day; mean (SD)	34.5 (32.1)	26.7 (17.7)
Onset of asthma in childhood, n (%)	12 (57)	17 (77)
IgE, IU/mL; median (25th–75th)	289.0 (57–877)	451.5 (151–1183)
Atopy, n (%)	15 (71.4)	20 (91.0)
BHR, PC ₂₀ , mg/mL; median (25th–75th)	0.5 (0.3–1.7)	0.3 (0.2–0.5)
Eosinophils, %; median (25th–75th)	6.1 (9)	10.1 (12)
FeNO, ppb; median (25th–75th)	26.7 (22.5–38.9)	32.0 (21.1–44.8)
ACQ-7, score; mean (SD)	1.6 (0.9)	1.4 (1.2)
Exacerbations in the last 12 months; no. events/patients	1.9	1.2
AQLQ, total score; mean (SD)	4.2 (1.1)	4.6 (1.4)
Aerobic capacity, VO _{2max} , mL/kg/min; mean (SD)	25.5 (5.9)	27.0 (4.3)
Pulmonary function		
FEV ₁ , %; mean (SD)	66.3 (19.0)	69.0 (21.0)
FEV ₁ /FVC, %; mean (SD)	72.2 (10.0)	73.0 (10.5)

Data are presented as mean±SD unless otherwise stated.

ACQ-7, Asthma Control Questionnaire; AQLQ, Asthma Quality of Life Questionnaire; BHR, bronchial hyperresponsiveness; BMI, body mass index; FeNO, fractional exhaled nitric oxide; FEV₁, forced expiratory volume in 1 s; FVC, forced vital capacity; IgE, immunoglobulin E; PC₂₀, provocation concentration of histamine causing a 20% decrease in FEV₁; ppb, parts per billion; VO_{2max}, maximal oxygen consumption.

2×2 contingency tables using the χ^2 test. Within-group differences were compared by the paired t test. The level of significance was set at 5% ($p < 0.05$) for all the tests. The statistical analysis was blinded to the treatment allocation and was performed using statistical software (SigmaStat 3.5, Systat Software Inc).

RESULTS

A total of 464 subjects were assessed for eligibility: 303 were excluded, 103 refused to participate and 58 patients were randomised into two groups. Forty-three patients completed the study and were analysed (21 CG/22 TG) (figure 1). Both groups had similar baseline characteristics (table 1).

Bronchial hyperresponsiveness

Six patients (2 CG, 4 TG) were not able to perform the bronchial provocation test because they had FEV₁ < 1.0 L after medication was withdrawn for 12 h during the initial evaluation. At baseline, two patients were classified as borderline, five were classified as mildly hyperresponsive and 29 were classified as moderately to severely hyperresponsive. After the intervention, the BHR decreased in the TG (n=18), with an increment in PC₂₀ of 1 dd (95% CI 0.3 to 1.7 dd), and did not change in the CG (n=19) (0.06 dd; 95% CI -0.6 to 0.7 dd) ($p = 0.039$; figure 2).

Cytokine and chemokine levels and total IgE

The CG and TG had similar baseline levels of cytokines (IL-5, IL-6, IL-8 and IL-10), but MCP-1 was higher in the TG ($p = 0.002$) (table 2). There were significant reductions in IL-6 ($p = 0.042$) and MCP-1 ($p = 0.045$) in the TG compared with

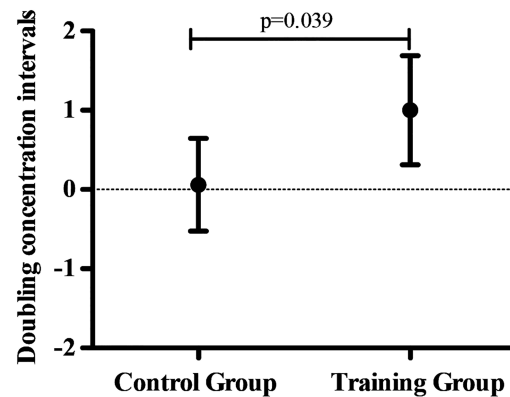


Figure 2 Effect of aerobic training exercise on bronchial hyperresponsiveness in patients with asthma (control group, CG, n=18; training group, TG, n=18). Data are presented as means and 95% CIs of the doubling dose concentration.

the CG (table 2). IL-8 was decreased in the TG, but the differences between groups were not significant ($p = 0.055$). IL-5, IL-10 and IgE did not significantly change ($p > 0.05$) (table 2). IL-4, TNF- α and RANTES were outside the limit of detection of the assay and could not be analysed.

Clinical asthma control

The number of days free of asthma symptoms increased in the TG after the intervention ($p = 0.042$), with no difference between the groups ($p = 0.987$, table 3). The frequency of exacerbations during treatment was lower in the TG compared with the CG (0.6 vs 1.5 exacerbations/patient; $p = 0.021$). According to ACQ-7 before intervention, 12 patients were classified as having controlled asthma (< 0.75), 12 partially controlled (0.75–1.5) and 19 uncontrolled (> 1.5). TG patients with non-well-controlled asthma (ACQ-6 > 0.75 points, n=14) presented an improvement after aerobic training ($p = 0.001$), with no differences between the groups ($p = 0.248$, figure 3D). The same analysis using the ACQ-7 demonstrated no difference within or between the groups ($p = 0.785$) (figure 3C).

Asthma quality of life questionnaire

Between-group differences were observed in the activity limitation ($p = 0.009$) domains and in the AQLQ total score ($p = 0.034$) in favour of the TG (table 3). Significant within-group improvement in the emotional function domain was seen in the TG ($p = 0.005$), with no difference between the groups ($p = 0.084$, table 3). Fifteen patients (68%) from the TG showed a clinically significant improvement in AQLQ total score (≥ 0.5 points). The TG presented a linear relationship between improvements in the ACQ-7 and AQLQ ($r = -0.74$, $p < 0.001$).

Induced sputum cellularity and FeNO

The intervention did not induce a significant change in either sputum cellularity ($p = 0.648$) or FeNO in either group ($p = 0.397$) (table 3). Patients from the TG with increased eosinophilic inflammation ($> 3\%$, n=13) or FeNO (> 26.0 ppb, n=12) at baseline presented a significant reduction in these values ($p = 0.015$ and 0.019 , respectively), but the differences between the groups were not significant ($p = 0.533$ and 0.452 , respectively; figures 3A, B). Eight patients in the CG and 9 in the TG presented increased eosinophilic inflammation and FeNO. The TG presented a linear relationship between baseline eosinophil counts and reduction after exercise training (in delta,

Table 2 Within-group comparison and between-group comparison for cytokine levels and total IgE in patients with asthma

Outcomes	Control group (n=21)			Training group (n=22)			Treatment effect	
	Before	Mean (95% CI) within-group difference	p Value time	Before	Mean (95% CI) within-group difference	p Value time	Mean (95% CI) between-group difference	p Value treatment
IL-5 (fg/mL)	129.2 (80.1 to 205.3)	46.8 (−3.3 to 95.6)	0.066	155.5 (87.4, −170.3)	2.0 (−21.2 to 25.1)	0.862	−19.4 (−53.3 to 14.4)	0.252
IL-6 (fg/mL)	298.2 (162.8 to 633.9)	67.6 (−186.7 to 322.0)	0.585	258.7 (214.5 to 467.6)	212.6 (83.0 to 341.7)	0.003	207.1 (7.7 to 406.1)	0.042
IL-8 (fg/mL)	1713.9 (1392 to 1858)	51.7 (−185.9 to 289.6)	0.655	1564.0 (1115 to 1941)	318.8 (76.0 to 561.6)	0.013	127.3 (−5.4 to 508.6)	0.055
IL-10 (fg/mL)	100.7 (1.0 to 166.7)	21.3 (−16.4 to 58.9)	0.253	95.4 (1.0 to 123.9)	17.6 (−16.3 to 51.5)	0.291	10.7 (−39.1 to 60.5)	0.667
MCP-1 (pg/mL)	14.1 (4.5 to 19.3)	0.5 (−2.8 to 3.9)	0.743	20.6 (17.1 to 26.7)	4.5 (−0.4 to 9.0)	0.052	−5.3 (−10.5 to −0.1)	0.045
IgE (IU/mL)	289.0 (60.5 to 878.5)	65.4 (−133.3 to 264.1)	0.500	360.5 (78.5 to 993.2)	−238.5 (−1066.3 to 589.4)	0.555	−280.4 (−1144 to 583.7)	0.516

Values are presented as medians and (25th–75th) percentiles. fg, femtogram; IgE, immunoglobulin E; IL, interleukin; MCP-1, monocyte chemoattractant protein 1; pg, picogram.

Δ final–initial) ($r=-0.51$; $p=0.012$). Similar results were observed in FeNO levels ($r=-0.61$; $p=0.008$).

Maximal aerobic capacity and pulmonary function

TG patients experienced increased maximal oxygen consumption (VO_2max) ($p=0.019$) and aerobic power ($p=0.029$) compared with CG patients (table 3 and see online supplementary appendix table S1). No changes in spirometry were observed in either group ($p>0.05$) (table 3 and see online supplementary appendix table S2).

DISCUSSION

The results of the current study demonstrate that a 12-week aerobic training programme reduces BHR and serum proinflammatory cytokines and improves quality of life and asthma exacerbation in adults with moderate to severe persistent asthma. In addition, it seems that aerobic training reduces sputum eosinophils and FeNO in patients with higher inflammation and improves clinical control in patients with worse asthma control.

We are aware of only two randomised controlled trials that evaluated the effect of exercise training on BHR in adults with asthma, and their results are controversial.^{29,30} Arandelovic *et al*²⁹ found a significant improvement in histamine PC_{20} after 6 months of swimming training in patients with mild asthma who were treated with low doses of medication and had normal baseline pulmonary function. In contrast, Cochrane and Clark³⁰ reported no change in histamine PC_{20} after 3 months of land aerobic training in patients with mild or moderate asthma using a higher dose of medication and with worse baseline pulmonary function. The discrepancy between these studies may have been multifactorial and depends on patient characteristics (disease severity, atopy, pharmacotherapy), exercise training programme (duration and intensity), and methodology of BHR analysis. The current study introduces several aspects that merit consideration and certainly add information to explain the effect of aerobic training on asthma pathophysiology for several reasons: this is the first study to observe a clinically significant increase of one doubling concentration in BHR, the proper methodology according the guideline;¹¹ the benefit to BHR observed in our study may be explained only by the aerobic training because our patients were under proper medical treatment, in accordance with the recommended guidelines;¹ we have studied patients with moderate to severe asthma, who often have a greater degree of BHR;³¹ and finally, in our study the patients' clinical characteristics were thoroughly assessed, and the training programme was carefully monitored. These data strongly suggest that the observed effect in the BHR was relevant and was a direct result of the aerobic training.

By definition, BHR in asthma is associated with ongoing airway inflammation, and experimental studies in asthma animal models from our group and other groups have systematically

shown that exercise reduces airway inflammation and remodeling.^{13–16} These effects seem to occur due to decreases in Th2 cytokines (IL-4, IL-5 and IL-13)^{13–16} and chemokines (MCP-1 and IL-8),^{13,16} and increases in the expression of the anti-inflammatory cytokine IL-10.^{13,16} In the present study, we investigated these mechanisms and observed that aerobic training reduced serum proinflammatory mediators IL-6 and MCP-1; unlike the results in asthma animal models, we did not observe any effect on IL-5, IL-10 and IL-8. Although it is not possible to establish a direct association among the reduction of BHR and IL-6, and MCP-1 observed in our study, there is enough evidence in the literature demonstrating the importance of these cytokines in airway inflammation and BHR in asthma.³² Additionally, we observed a within-group reduction in sputum eosinophil and FeNO in patients in the TG with worse airway inflammation, and that improvement was correlated with the baseline values, in agreement with previous findings from our group. This suggests that the benefits of aerobic training were associated with baseline airway inflammation.⁷ Interestingly, a recent study also observed a reduction in serum IL-6 and sputum eosinophils and neutrophils in obese patients with asthma submitted to exercise training and dietary changes. Taken together, these results indicate that exercise may have an anti-inflammatory effect in distinct asthma phenotypes.³³

We also observed that aerobic training improved clinical control by reducing exacerbations in TG compared with CG. However, the ACQ-7 was not different between groups. Turner *et al*³⁴ and Dogra *et al*³⁵ also observed that aerobic training does not modify clinical control as evaluated by the ACQ-7; however, Dogra *et al*³⁵ observed an improvement in patients with partially controlled asthma using the ACQ-6 (ACQ-7 without the FEV₁ question). Similarly, significant within-group improvements in ACQ-6 were found in patients with non-well-controlled asthma from the TG, demonstrating that the improvement in the ACQ with aerobic training seems to be better quantified by using the ACQ-6 rather than the ACQ-7. These results may be explained by the widely known fact that aerobic training does not improve lung function.⁴ We also showed an average improvement in AQLQ score of 0.8 in the TG that is similar to the improvement observed by Turner *et al*³⁴ (0.8) and Dogra *et al*³⁵ (1.0), thereby confirming the importance of regular exercise to improve health-related quality of life, even in patients with asthma undergoing clinical treatment.

Certain limitations need to be addressed when interpreting our results. We evaluated the serum cytokine levels, which may not necessarily reflect airway inflammation; however, it has been extensively demonstrated that the effects of exercise training are more pronounced in the systemic immune response.¹⁷ In addition, the strict inclusion criteria used in our study limit the external validity of our findings; however, this was an important feature of the

Table 3 Within-group and between-group comparison for induced sputum cellularity, FeNO, clinical control, health-related quality of life, aerobic capacity and pulmonary function of patients with asthma

Outcomes	Control group (n=21)			Training group (n=22)			Treatment effect	
	Before	Mean (95% CI) within-group difference	p Value time	Before	Mean (95% CI) within-group difference	p Value time	Mean (95% CI) between-group difference	p Value treatment
Clinical Control								
Asthma symptom-free days	15.3 (11.0)	−2.5 (6.2 to 1.2)	0.180	12.0 (11.2)	−4.3 (−8.4 to −0.2)	0.042	0.1 (−7.2 to 7.3)	0.987
ACQ-7	1.6 (0.9)	0.1 (−2.1 to 0.5)	0.395	1.4 (1.2)	0.2 (−0.2 to 0.5)	0.267	0.2 (−0.3 to 0.7)	0.457
ACQ-6	1.5 (1.0)	0.1 (−2.8 to 0.6)	0.502	1.2 (1.2)	0.2 (−0.2 to −0.6)	0.236	0.3 (0.3 to 0.8)	0.327
AQLQ								
Overall	4.2 (1.1)	−0.3 (−0.8 to 0.2)	0.259	4.6 (1.4)	−0.7 (−1.9 to 0.2)	0.005	−0.9 (−1.7 to −0.1)	0.034
Activity limitation domain	3.8 (0.9)	−0.2 (−0.8 to 0.4)	0.433	4.3 (1.3)	−0.8 (−1.2 to −0.3)	0.002	−1.1 (−1.8 to −0.3)	0.009
Symptoms domain	4.8 (1.5)	−0.2 (−0.9 to 0.4)	0.469	5.1 (1.5)	−0.6 (−1.1 to 0.0)	0.053	−0.7 (−1.5 to 0.1)	0.091
Emotional function domain	4.1 (1.9)	−0.6 (−1.6 to 0.4)	0.250	4.6 (1.8)	−1.0 (−1.6 to −0.3)	0.005	−0.9 (−2.0 to 0.1)	0.084
Environmental stimuli domain	3.7 (1.8)	−0.5 (−1.5 to 0.6)	0.359	4.5 (2.0)	−0.6 (−1.3 to 0.2)	0.118	−0.9 (−2.0 to 0.3)	0.140
Induced sputum								
Total cell (10 ⁶ /mL) median (25th–75th)	0.9 (0.1–1.4)	−0.8 (−1.5 to 0.2)	0.055	0.8 (0.4 to 1.6)	0.2 (−0.44 to 0.77)	0.583	0.6 (−0.6 to 1.7)	0.333
Eosinophils (%) median (25th–75th)	6.1 (0.25–14.9)	−7.9 (−17.7 to 1.8)	0.106	10.1 (1.6 to 21.9)	−0.6 (−8.8 to 7.6)	0.881	−8.8 (−2.0 to 0.3)	0.648
Neutrophils (%) median (25th–75th)	33.8 (22.1–66.2)	3.4 (−6.9 to 13.7)	0.500	37.4 (16.7 to 57.5)	1.6 (−12.6 to 15.7)	0.821	1.7 (−13.1 to 16.6)	0.816
Lymphocytes (%) median (25th–75th)	0.0 (0.0–0.1)	0.9 (−2.7 to 4.4)	0.620	0.0 (0.0 to 0.8)	−1.2 (−2.9 to 0.4)	0.137	−1.0 (−2.8 to 0.7)	0.251
Macrophages (%) median (25th–75th)	40.5 (11.1–73.1)	1.4 (−9.8 to 12.5)	0.799	43.4 (25.7 to 65.2)	−0.9 (−16.1 to 14.4)	0.907	−6.7 (−22.7 to 9.2)	0.248
FeNO (ppb) median (25th–75th)	26.7 (22.5–38.9)	−5.9 (−5.8 to 4.6)	0.815	32.0 (21.1 to 44.8)	4.5 (−0.7 to 9.7)	0.087	4.4 (−5.9 to 14.7)	0.397
Exercise capacity								
Aerobic capacity (VO _{2max} mL/kg/min)	25.5 (5.9)	2.4 (−0.2 to 4.5)	0.053	27.0 (4.2)	−1.0 (−2.4 to 0.5)	0.182	−4.8 (−8.9 to −0.8)	0.019
Maximal workload (watts)	202.8 (67.3)	−3.3 (−25.4 to 18.9)	0.762	190.3 (32.3)	−57.1 (−73.1 to −41.1)	<0.001	−44.1 (−83.4 to −4.8)	0.029
Pulmonary function								
FEV ₁ (L)	2.00 (0.7)	−0.1 (−0.2 to 0.1)	0.471	2.1 (0.76)	0.00 (−0.1 to 0.1)	0.952	−0.0 (−0.5 to 0.4)	0.930
FEV ₁ % predicted	66.3 (19.0)	−2.3 (−8.6 to 3.9)	0.447	69.0 (21.0)	−1.1 (−4.8 to 2.6)	0.546	2.5 (−11.5 to 16.5)	0.721

Data are means (SDs) unless otherwise stated.

ACQ, Asthma Control Questionnaire; AQLQ, Asthma Quality of Life Questionnaire; FeNO, fractional exhaled nitric oxide.

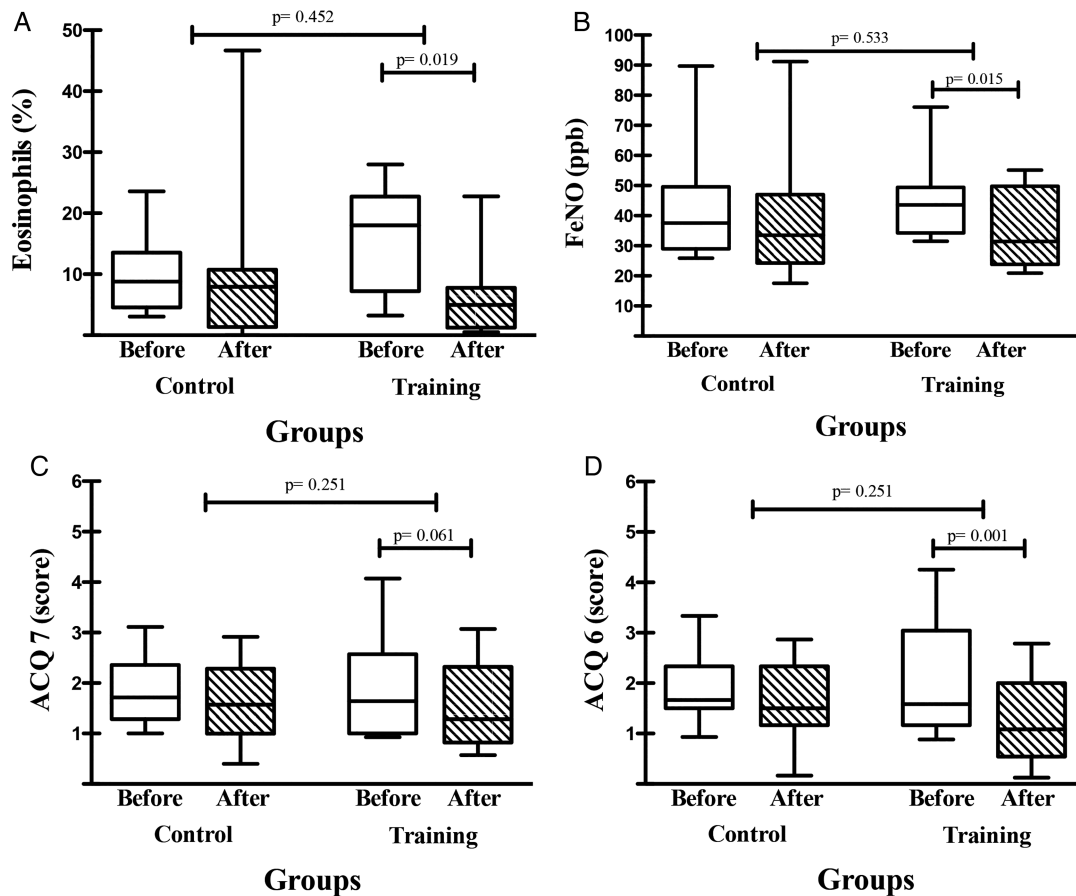


Figure 3 Subgroup analysis: (A) Percentage of eosinophils in induced sputum $>3\%$ (control group, CG, $n=9$; training group, TG, $n=13$). (B) Fractional exhaled nitric oxide >26 ppb (CG, $n=12$; TG, $n=12$). (C) ACQ-7 >0.75 (CG, $n=17$; TG, $n=14$). (D) ACQ-6 >0.75 (CG, $n=14$; TG, $n=12$). ACQ, Asthma Control Questionnaire. Boxes represent the 25th to 75th percentiles, the lines inside the boxes represent the median values, and the bars represent the 10th and 90th percentiles.

study design to reduce variability within the sample for the main outcome (BHR). Finally, for subgroup analysis, significant between-group differences following treatment could not be demonstrated, probably due to the reduced number of individuals, because the sample size was not primarily to evaluate these secondary outcomes. Although, it is well known that the key outcome in a clinical trial is the difference between the intervention and CGs, we consider that this within-group difference in the TG was clinically relevant for identifying patients who respond to physical training. As a consequence, this information should subsidise future studies aiming to evaluate differences between treatments to determine the impact of exercise on clinical control and airway inflammation.

In conclusion, our results demonstrate that aerobic training reduces BHR, systemic inflammation and exacerbations and improved quality of life in adults with moderate to severe persistent asthma. In addition, we showed that patients with higher inflammation and lower asthma control obtained greater benefits. These findings suggest that adding exercise as an adjunct therapy to pharmacotherapy can improve the main features of asthma pathophysiology.

Acknowledgements The authors would like to acknowledge: Dr Júlia M D Greve and the exercise physiologist Paulo R Santos-Silva (Institute of Orthopedics and Traumatology, Clinics Hospital, School of Medicine, University of São Paulo, São Paulo, Brazil) for their support and blinded analysis of the cardiopulmonary exercise testing; Professor Maria N Sato and PhD student Luanda M S Oliveira (Laboratory of Dermatology and Immunodeficiencies, Department of Dermatology, Medical School, University of São Paulo, São Paulo, Brazil) for conducting the blood sample analysis; and Professor Clarice Tanaka (Department of Physical Therapy, School of Medicine,

University of São Paulo, São Paulo, Brazil) for her technical support. The authors would also like to acknowledge the American Thoracic Society (ATS) and the Methods in Epidemiologic, Clinical and Operations Research (MECOR) Program for their assistance in the development of research skills in Latin America.

Contributors AF-P: study concept and design, recruitment of patients, manuscript writing and review, data acquisition and results interpretation; FARM (principal contributor guarantor): study concept and design, recruitment of patients, manuscript writing and review; data acquisition; results interpretation and statistical analysis; RMdC-P: patient's medical treatment and manuscript review; RCA: bronchial provocation test support, blinded outcome assessment and manuscript review; AC and RS: study concept and design, results interpretation and manuscript review; BMS-R: blinded outcome assessment, cytospin reading, FeNO analysis, and manuscript review; JK: project supervision and manuscript review; MAM: project supervision, study concept and design and manuscript review; PG-B: project supervision, study concept and design, manuscript review and results interpretation; CRFC: study concept and design, project supervision, results interpretation, overall study coordination, and manuscript writing and review. All the authors have read and approved the final version of the manuscript.

Funding The study was supported by the São Paulo Research Foundation (FAPESP; Grants 2009/53904-9 and 2009/53817-9) and Ministério da Ciência, Tecnologia e Inovação—Conselho Nacional de Pesquisa (CNPq Grants 305987/2010-0).

Competing interests None declared.

Patient consent Obtained.

Ethics approval Clinical Hospital (protocol 0121/10).

Provenance and peer review Not commissioned; externally peer reviewed.

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Supplementary Appendix

This appendix has been provided by the authors to provide readers with additional information about the authors' work.

Supplement to: França-Pinto A, Mendes FAR, Carvalho-Pinto R, Agondi RC, Cukier A, Stelmach R, Saraiva-Romanholo BM, Kalil J, Martins MA, Giavina-Bianchi P, Carvalho CRF. **Aerobic training decreases bronchial hyperresponsiveness and systemic inflammation in patients with moderate or severe asthma: a randomized controlled trial**

Supplementary Appendix

This supplementary material section has been provided by the authors to provide readers with additional information about the methods and results.

The components in this Supplementary Material document are as follows:

1. Methods

- a) Experimental design*

- b) Interventions*

- c) Assessments*

2. Results

3. Table S1

4. Table S2

5. References for Supplement

Online publication Supplementary Material for **Aerobic training decreases bronchial hyperresponsiveness and systemic inflammation in patients with moderate or severe asthma: a randomized controlled trial**

METHODS

Experimental design

All patients underwent the baseline assessment and performed all the tests in the following sequence: during week 1, the asthma control questionnaire (ACQ) and asthma quality of life questionnaire (AQLQ) were administered, and the patients received a daily diary for symptoms and underwent pulmonary function testing; during week 2, induced sputum and fractional exhaled nitric oxide (FeNO) were collected; during week 3, a maximal aerobic exercise test was performed, and a blood sample was collected; and during week 4, bronchial hyperresponsiveness was assessed. Persons involved in data collection were blinded to the group allocation. After completing the 24 treatment sessions, the patients were re-evaluated following the same sequence as the baseline assessment. All patients were clinically stable (i.e., at least 30 days without exacerbation) at baseline and re-evaluation. In addition, the patients were asked to refrain from vigorous exercise 24 h before all assessments.

Interventions

Education program

Both groups completed an educational program consisting of 2 classes, lasting 2 hours each, during week 4. The topics discussed included asthma pathophysiology, diagnosis and treatment, environmental control, disease control using the daily diary, proper medication use and daily peak expiratory flow measurements.[1]

Breathing exercise program

Both groups completed a breathing exercise program twice a week for 12 weeks. Each session consisted of 30 minutes of yoga breathing exercises, including Kapalabhati (fast expiratory breathing exercise followed by passive inhalation), Uddhiyana (full exhalation followed by

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).[2, 3] Each exercise was executed in sets of 3, lasting 2 minutes each, followed by 1 minute of rest. For the TG patients, breathing exercise sessions were performed before the aerobic training sessions.

Aerobic training program

The aerobic training was initially performed at the heart rate (HR) corresponding to one-third of the difference between the anaerobic threshold (AnT) and the respiratory compensation point (RCP) ($HR_{AnT} + 33\% \times [HR_{RCP} - HR_{AnT}]$) obtained from cardiopulmonary exercise testing (see below). After two weeks of the adaptation, the exercise intensity was increased to two-thirds of the difference between the AnT and the RCP ($HR_{AnT} + 66\% \times [HR_{RCP} - HR_{AnT}]$).[4] If a patient maintained this intensity for 2 consecutive exercise sessions without symptoms, the exercise intensity was increased by 5% of HR (until 85% of patient's maximal heart rate was achieved) by increasing either the treadmill speed or the inclination. The use of salbutamol (200 µg) before an exercise session was recommended only if the peak expiratory flow was <70% of the patient's best value. Peak expiratory flow and asthma symptoms were monitored at the end of every exercise session.

Assessments

Bronchial hyperresponsiveness

The bronchial provocation test was conducted according to American Thoracic Society (ATS) guidelines.[5] Patients inhaled increasing concentrations of histamine in the following sequence: 0.0625 mg/mL, 0.25 mg/mL, 1.0 mg/mL, 4.0 mg/mL and 16.0 mg/mL using the dosimeter method (DeVilbiss 646 nebulizer, DeVilbiss Health Care, Somerset, PA, USA).

This method consists of 5 deep inhalations from each concentration, starting at functional residual capacity and holding the breath (near total lung capacity) for 5 seconds. Forced expiratory volume in the first second (FEV₁) was measured 30 and 90 seconds after the inhalations. The test is considered positive when the histamine concentration promotes a decrease $\geq 20\%$ in FEV₁ (PC₂₀) in relation to the post-saline value or when the maximum concentration is reached (16 mg/mL). We followed the criteria of absolute and relative contraindications recommended by the ATS guidelines.[5] One double dose of concentration is considered an important clinical improvement.[6, 7]

Serum cytokines and total IgE

Plasma levels of inflammatory mediators were evaluated before and after 3 months of intervention. The patients were instructed to fast for 8 hours and not to drink alcohol or caffeine for 12 hours preceding the blood collection. Venous blood samples were centrifuged, and the supernatants were frozen in aliquots at -80 °C and analyzed at the end of the study. The cytometric bead array method (BD Biosciences, San Jose, CA, USA) was used to analyze the levels of IL-4, IL-5, IL-6, IL-8, IL-10, tumor necrosis factor (TNF)- α , IL-12p70, IL-8/CXCL8, monocyte chemotactic protein-1 (MCP-1/CCL2) and RANTES/CCL5. Samples were analyzed in a flow cytometer (LSR, model Fortessa) using FACSDiva™ software (both from BD Biosciences). The assay was performed according to the manufacturer's protocol; the detection limits for each interleukin or chemokine were as follows: IL-4 (144.4 fg/mL), IL-5 (67.8 fg/mL), IL-6 (68.4 fg/mL), IL-8/CXCL8 (0.2 pg/mL), IL-10 (13.7 fg/mL), TNF- α (67.3 fg/mL), IL-12p70 (12.6 fg/mL), MCP-1/CCL2 (2.7 pg/mL) and RANTES/CCL5, IL-8 (69.9 fg/mL). Total serum IgE was measured by nephelometry and commercially available kits (Dade Behring/Siemens, Deerfield, USA). The cut-off value for elevated IgE was set at 100 IU/mL.

Fractional exhaled nitric oxide (FeNO)

FeNO was collected offline, and the evaluation was made before spirometry. The patients were advised to blow into a Mylar bag, with a breath pressure of 12 cmH₂O, monitored by the pressure gauge, reaching a flow rate of 200 mL/s. All measurements were determined by chemiluminescence (Sievers 280) in accordance with the ATS recommendations.[8] This procedure and analysis were performed by a blinded investigator.

Induced sputum

After each patient was pre-medicated with 400 µg salbutamol, 3% hypertonic saline inhalation was administered using an ultrasonic nebulizer for 15 minutes.[9] The patients were asked to blow their nose, rinse their mouth with water and swallow the water to reduce contamination of the sputum specimen with post-nasal drip or saliva. Sputum samples were visually separated from saliva, the aliquot was treated with 0.1% dithiothreitol (Sigma-Aldrich, SP, Brazil), and the mixture was briefly stirred with a vortex mixer. Total cell counting was performed with a hemocytometer;[10, 11] the cell suspensions were adjusted to $1.0 \times 10^6/\text{mL}$. [12] The sputum was processed using the cytopspin method, and the 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.

Asthma symptoms and exacerbation

Asthma symptoms and exacerbation were evaluated using a daily diary of symptoms according to previous methods.[3, 13] A daily diary was used to record asthma symptoms, such as cough, diurnal and nocturnal dyspnea, wheezing and use of relief medications. All

patients received the diary on the first day of assessment and filled it out 30 days before intervention and every month during intervention.

Asthma Control Questionnaire

ACQ-7, a standardized tool for assessing clinical control in asthmatic patients, consists of 7 questions: 5 questions related to asthma symptoms (daytime and nighttime symptoms, activity limitations, dyspnea, wheezing); one question related to the use of short-acting β_2 agonists, such as rescue medication; and one question related to FEV₁ before bronchodilator in the percent of predicted values. The ACQ score is the average of the 7 items obtained over a 7-day period and ranges from 0 to 7.[14] The patients were classified based on ACQ-7 score as having controlled asthma (<0.75), partially controlled asthma (0.75-1.5) or uncontrolled asthma (>1.5).[15] A minimum clinically important difference is 0.5 on a 7-point scale.[16]

Asthma quality of life

The total score was obtained using the average score of the 32 questions.[17] A higher AQLQ score indicates a better quality of life. A minimum clinically important difference is 0.5 on a 7-point scale.[18]

Cardiopulmonary exercise test

This test was performed on a treadmill (h/p/cosmos®, Pulsar, Nussdorf-Traunstein, Germany) using a ramp protocol with fixed speed and increments of 2% inclination every minute. Pulmonary gas exchange was measured using a breath-by-breath automated gas analysis system (CPX/D) with a disposable pneumotach flowmeter (CPX/D, Medgraphics®, USA). Heart rate, blood pressure and subject perception of effort were assessed throughout the test; 200 µg of salbutamol was used 15 min before the test to allow patients to reach maximum

oxygen consumption. All asthmatic subjects achieved physical exhaustion as determined by the following criteria: reaching the plateau or peak VO_2 independent of the increased workload; reaching the maximum predicted heart rate ($\pm 5\%$); or a respiratory coefficient ≥ 1.10 with the subject unable to maintain the speed test. The anaerobic threshold (AnT) was determined using the following combination of factors: (i) loss of linearity between VCO_2 and VO_2 and (ii) the point at which the ventilatory equivalent for oxygen (VE/VO_2) and the final expiratory pressure oxygen ($\text{P}_{\text{ET}}\text{O}_2$) reached their lowest value before their increase during the test that was associated with an increased respiratory exchange ratio (RER) and an abrupt increase in the pulmonary ventilation.[19, 20] The respiratory compensation point (RCP) was defined as the point where the VE began to change out of proportion to VCO_2 ; that is, a systematic increase in VE/VCO_2 with a consequent decline in final expiratory carbon dioxide ($\text{P}_{\text{ET}}\text{CO}_2$). A blinded exercise physiologist expert performed the analysis. The mechanical power load was calculated for each subject from the following equation: power (watts) = weight (kg) \times $9.81 \times \sin$ of the angle of inclination \times speed (meters/second).[21]

Pulmonary function

The following variables were recorded: forced vital capacity (FVC, in liters); forced expiratory volume in the 1st second (FEV_1 , in liters); and FEV_1/FVC ratio. The percentage off the predicted normal values were calculated for the Brazilian population.[22]

Atopy

Patients were considered atopic if they presented a clinical history suggestive of respiratory allergy and specific IgE antibodies on the following tests: *in vivo* (skin prick test) and *in vitro* (Phadiatop test). The skin prick test was performed using 5 classes of 9 common aeroallergens: house dust mites (*Dermatophagoides pteronyssinus* and *Blomia tropicalis*),

animal dander (*Felis domesticus* and *Canis familiaris*), pollens (*Lolium perenne*), molds (*Aspergillus fumigatus* and *Penicillium notatum*) and cockroach (*Blattella germanica* and *Periplaneta americana*). The allergens were supplied by Asac pharma (Sao Paulo, Brazil), and the test was considered positive in the presence of a mean wheal diameter 3 mm greater than the negative control. The Phadiatop test was used to determine atopic status using the fluoroenzymeimmunoassay (FEIA) method. It was performed on the ImmunoCAP system according to the manufacturer's instructions (Phadia AB – Sweden). The test was considered positive (atopic) when the IgE concentrations ≥ 0.35 KU/L.

RESULTS

A total of 464 subjects were assessed for eligibility: 406 were excluded, 103 refused to participate and 58 patients were randomized into 2 groups. Fifteen patients (7 CG/8 TG) withdrew from the study: 3 patients withdrew because of health problems not related to asthma (cataract surgery, renal or cardiovascular disease), 10 because of scheduling difficulties related to work and 2 for personal reasons. Therefore, 43 patients completed the study and were analyzed (21 GC / 22 GT). All patients used moderate- to high-dose corticosteroids, and both groups used β_2 agonists as rescue medication. Before treatment, 29 patients (67.4%) did not present airway obstruction, 8 patients (18.6%) had mild obstruction and 6 patients (14.0%) had moderate obstruction.

During the first two weeks, the patients trained at 65% of maximal HR. By the 3th to 8th weeks, the patients trained at approximately 75% of HRmax. During the last 4 weeks, 95% of the patients trained at 85% of HRmax.

TABLE S1 – Within-group comparison and between-group comparison for cardiopulmonary exercise testing in asthmatic patients before and after the intervention

Outcomes	Control Group (n=21)			Training Group (n=22)			Treatment effect	
	Before	Mean (95% CI) within-group difference	p-value time	Before	Mean (95% CI) within-group difference	p-value time	Mean (95% CI) between-group difference	p-value treatment
Maximal Aerobic Capacity								
VO ₂ (mLO ₂ .kg ⁻¹ .min ⁻¹)	25.5 (5.9)	2.2 (-0.2-4.5)	0.053	27.0±4.2	-0.97 (-2.43-0.49)	0.182	-4.84 (-8.86- -0.82)	0.019
Power (W)	202.8 (67.3)	-3.3 (-25.4-18.9)	0.762	190.3±32.3	-57.07 (-73.08- -41.07)	<0.001	-44.08 (-83.37- -4.80)	0.029
RCP								
VO ₂ (mLO ₂ .kg ⁻¹ .min ⁻¹)	21.0 (3.8)	1.3 (0.3-2.3)	0.045	22.6±3.6	-0.56 (-2.29-1.16)	0.502	-3.51 (-6.99- -0.45)	0.017
Power (W)	124.8 (50.1)	0.5 (-16.2-40.5)	0.965	115.5±32.1	-32.14 (-54.08- -10.20)	0.006	52.68 (13.44-91.90)	0.010
Anaerobic Threshold								
VO ₂ (mLO ₂ .kg ⁻¹ .min ⁻¹)	17.8 (3.9)	1.9 (0.5-3.4)	0.011	18.7±3.1	-0.01 (-2.00-1.98)	0.993	-3.11 (-5.40- -0.82)	0.009
Power (W)	76.2 (33.6)	6.0 (-15.3-27.3)	0.560	65.5±32.3	-57.80 (-69.08- -46.52)	<0.001	4.82 (-22.95-32.58)	0.728

Values are presented as the means and (standard deviations). VO₂, oxygen consumption; RCP, respiratory compensation point.

TABLE S2 – Within-group comparison and between-group comparison for pulmonary function in asthmatic patients before and after the intervention

Outcomes	Control Group (n=21)			Training Group (n=22)			Treatment effect	
	Before	Mean (95% CI) within-group difference	p-value	Before	Mean (95% CI) within-group difference	p-value	Mean (95% CI) between-group difference	p-value
FEV ₁ , L	2.00 (0.7)	-0.1 (-0.2-0.1)	0.471	2.1 (0.8)	0.0 (-0.1-0.1)	0.952	-0.0 (-0.5-0.4)	0.930
% predicted	66.3 (19.0)	-2.3 (-8.6-3.9)	0.447	69.0 (21.0)	-1.1 (-4.8-2.6)	0.546	2.5 (-11.5-16.5)	0.721
FVC, L	2.7 (0.9)	-0.0 (-0.1-0.1)	0.640	2.8 (0.9)	-0.01 (-0.1-0.1)	0.800	-0.1 (-0.6-0.4)	0.762
% predicted	77.0 (18.0)	-1.0 (-4.4-2.3)	0.525	78.2 (17.6)	-1.9 (-4.5-0.7)	0.148	1.2 (-11.8-12.4)	0.961
FEV ₁ /FVC	72.2 (10.0)	-0.2 (-0.5-0.0)	0.432	73.0 (10.5)	0.0 (-0.0-0.0)	0.769	-0.0 (-0.1- 0.1)	0.659
FEF _{25-75%} , L.s ⁻¹	1.6 (0.7)	-0.1 (-0.4-0.2)	0.550	1.7 (0.9)	0.0 (-0.2-0.2)	0.942	-0.0 (-0.6-0.6)	0.963
% predicted	51.0 (23.2)	-2.6 (-13.0-7.6)	0.595	54.5 (33.0)	0.1 (-5.1-5.4)	0.958	3.6 (-11.4-18.6)	0.633

Values are presented as the means (standard deviations). FEV₁, forced expired volume in the first second; FVC, forced vital capacity; FEF_{25-75%}, mean forced expiratory flow (FEF) between 25% and 75% of FVC; L.s⁻¹, liters per second.

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PRESS RELEASE

Aerobic exercise seems to curb asthma severity and improves quality of life

It should be routinely added to drug treatment of moderate to severe asthma, suggest researchers

Aerobic exercise seems to curb the severity of asthma symptoms and improves quality of life, finds a small study published online in the journal **Thorax**.

It should be routinely added to the drug treatment of moderate to severe asthma, suggest the researchers, who point out that people with asthma often avoid exercise for fear of triggering symptoms.

Exercise has been recommended in the past for asthma patients, because it improves physical fitness, overall quality of life, and reduces the need for inhalers. But it has not been clear whether the pros outweigh the cons.

The researchers therefore compared the impact of aerobic training and breathing exercises on the severity of symptoms in 58 people with moderate to severe asthma.

All the participants, who were aged between 20 and 59, were randomly assigned to either a 30 minute yoga breathing exercise twice a week for 12 weeks, or the breathing exercise plus a 35 minute indoor treadmill session twice weekly for 3 months.

Their bronchial hyperresponsiveness, or BHR for short, was tested at the beginning and end of the three month monitoring period. BHR indicates the speed of airway constriction and inflammation, a hallmark of asthma.

Levels of proteins (cytokines) generated during the inflammatory response and of IgE, an antibody produced by the body to tackle potentially harmful substances or antigens, were also assessed before and after the trial.

Participants were asked to keep a symptom diary and record their use of inhalers, any unscheduled medical consultations, requirement for emergency care, or hospital admission prompted by their asthma. And they filled in a validated quality of life questionnaire for asthma.

Forty three people (21 in the breathing group and 22 in the breathing plus aerobic exercise group) completed the study.

At the start of the study, among those who were able to take the BHR test, two people were classified as borderline hyperresponsive; five were classified as mildly hyperresponsive; and 29 were deemed to be moderately to severely hyperresponsive.

At the end of the study, BHR had fallen in those in the aerobic exercise group in one doubling dose of histamine, which means they were able to tolerate twice the level of trigger factor before symptoms developed. But BHR did not change in those just given the breathing exercises.

Levels of some cytokines also fell significantly among those in the aerobic exercise group, while the number of symptom free days increased. And bouts of worsening symptoms were fewer than in the breathing group.

Quality of life score rose significantly in 15 people in the aerobic exercise group, while maximum oxygen intake and aerobic power increased.

The effects were most noticeable in those with higher levels of systemic inflammation and poorer symptom control to begin with.

"These results suggest that adding exercise as an adjunct therapy to pharmacological treatment could improve the main features of asthma," conclude the researchers.

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About the journal:

Thorax is one of more than 50 specialist journals published by BMJ. The title is co-owned with the British Thoracic Society. <http://thorax.bmj.com>

Aerobic training decreases bronchial hyperresponsiveness and systemic inflammation in patients with moderate or severe asthma: a randomized controlled trial

O treinamento aeróbio reduz a hiperresponsividade brônquica e inflamação sistêmica em pacientes com asma moderada ou grave: um estudo clínico controlado e randomizado

RESUMO

Introdução: Os benefícios do treinamento aeróbico para as principais características da asma, como hiperresponsividade brônquica (HRB) e inflamação, são pouco compreendidos. Foram investigados os efeitos do treinamento aeróbio sobre HRB (desfecho primário), citocinas inflamatórias séricas (desfecho secundário), controle clínico, qualidade de vida (AQLQ) e inflamação das vias aéreas (desfecho terciários).

Métodos: Foram estudadas cinquenta e oito pacientes, aleatorizados em grupo controle (GC) ou grupo de treinamento aeróbio (GT), entre duas visitas médicas e sem mudanças na medicação. Os pacientes do GC (programa educacional + exercícios de respiração [sham]) e GT (mesmo que o controle + treinamento aeróbio) foram acompanhados durante 3 meses. HRB, os níveis séricos de citocinas, escarro induzido, fração exalada de óxido nítrico (FeNO), controle clínico e AQLQ foram avaliados antes e após a intervenção.

Resultados: Após 12 semanas, 43 pacientes (21 CG / 22 TG) completaram o estudo e foram analisadas. Os pacientes do GT melhoraram a HRB em uma dupla dose (dd) (95% IC, 0,3-1,7 dd), reduziram IL-6 e MCP-1 no plasma e melhoraram AQLQ e a exacerbação na asma ($p < 0,05$). Não foram observados efeitos na IL-5, IL-8, IL-10, celularidade do escarro, FeNO e ACQ-7 ($p > 0,05$). Melhora intra-grupo foi encontrado no ACQ-6 para pacientes com asma não totalmente controlada e no eosinófilo do escarro e FeNO em pacientes do GT que tinham maior inflamação das vias aéreas.

Conclusão: O treinamento aeróbico reduziu a HRB e citocinas pró-inflamatórias no plasma, melhorou qualidade de vida e reduziu exacerbação da asma em pacientes com asma moderada ou grave. Estes resultados sugerem que a adição de exercício como terapia adjuvante ao tratamento farmacológico pode melhorar as características principais da asma.

Número de registo de avaliação: NCT-02033122.