Original Article

Effects of Aerobic Training versus Breathing Exercises on Asthma Control: A Randomized Trial

Karen B. Evaristo, MSc[a], Felipe Augusto Rodrigues Mendes, PhD[a,b], Milene G. Saccomani, PhD[a], Alberto Cukier, PhD[c], Regina M. Carvalho-Pinto, PhD[c], Marcos R. Rodrigues, MSc[d], Danilo F. Santaella, PhD[d], Beatriz M. Saraiva-Romanholo, PhD[e,f], Milton A. Martins, PhD[d], and Celso R.F. Carvalho, PhD[a] *São Paulo, Brazil*

What is already known about this topic? There is evidence suggesting that both breathing exercises and aerobic training are appropriate adjuvant therapies to improve asthma control.

What does this article add to our knowledge? This is the first study to compare the effects of these 2 non-pharmacological treatments for asthma control with a higher level of evidence.

How does this study impact the current management guidelines? Aerobic training and breathing exercises induce similar effects in asthma control, psychological distress, and airway inflammation; however, participants in the aerobic training were 2.6 times more likely to experience clinical improvement (Asthma Control Questionnaire >0.5) after 3-month follow-up.

BACKGROUND: Aerobic training and breathing exercises are interventions that improve asthma control. However, the outcomes of these 2 interventions have not been compared.
OBJECTIVE: To compare the effects of aerobic training versus breathing exercises on clinical control (primary outcome), quality of life, exercise capacity, and airway inflammation in outpatients with moderate-to-severe asthma.
METHODS: Fifty-four asthmatics were randomized into either the aerobic training group (AG, n = 29) or the breathing exercise group (BG, n = 25). Both interventions lasted for 24 sessions (2/week, 40 minutes/session). Asthma clinical control (Asthma Control Questionnaire [ACQ]), quality of life (Asthma Quality of Life Questionnaire), asthma symptom-free days (ASFD), airway inflammation, exercise capacity, psychological distress (Hospital Anxiety and Depression Scale), daily-life physical activity (DLPA), and pulmonary function were evaluated before, immediately after, and 3 months after the intervention.
RESULTS: Both interventions presented similar results regarding the ACQ score, psychological distress, ASFD, DLPA, and airway inflammation ($P > .05$). However, participants in the AG were 2.6 times more likely to experience clinical improvement at the 3-month follow-up than participants in the BG ($P = .02$). A greater proportion of participants in the AG also presented a reduction in the number of days without rescue medication use compared with BG (34% vs 8%; $P = .04$).
CONCLUSIONS: Outpatients with moderate-to-severe asthma who participated in aerobic training or breathing exercise programs presented similar results in asthma control, quality of life, asthma symptoms, psychological distress, physical activity, and airway inflammation. However, a greater proportion of participants in the AG presented improvement in asthma control and reduced use of rescue medication. **(J Allergy Clin Immunol Pract 2020;■:■-■)**

Key words: *Pulmonary rehabilitation; Persistent asthma; Symptoms; Clinical control; Quality of life; Airway inflammation; Asthma guidelines*

Asthma is a chronic disease defined as reversible airflow obstruction, inflammation, and hyperresponsiveness to different stimuli and characterized by wheezing, breathlessness, chest tightness, and coughing.[1] These symptoms reduce patients' quality of life and restrict daily-life physical activity (DLPA).[2] Subjects with asthma also present higher levels of anxiety and

[a]Department of Physical Therapy, School of Medicine, University of São Paulo, São Paulo, Brazil
[b]Department of Physical Therapy, Universidade Ibirapuera, São Paulo, Brazil
[c]Department of Pulmonary Division (InCor), School of Medicine, University of São Paulo, São Paulo, Brazil
[d]Department of Sports, School of Medicine, University of São Paulo, São Paulo, Brazil
[e]Department of Medicine, School of Medicine, University of São Paulo, São Paulo, Brazil
[f]Department of Physical Therapy, University City of Sao Paulo (UNICID), São Paulo, Brazil
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Corresponding author: Celso R.F. Carvalho, PhD, Department of Medicine, School of Medicine, University of Sao Paulo, Av. Dr. Arnaldo 455, Room 1210, Postal Code 01246-903, São Paulo, Brazil. E-mail: cscarval@usp.br.
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Abbreviations used
ACQ- Asthma Control Questionnaire
AG- Aerobic training group
AQLQ- Asthma Quality of Life Questionnaire
BG- Breathing group
BHR- Bronchial hyperresponsiveness
CI- Confidence interval
DLPA- Daily-life physical activity
HADS- Hospital Anxiety and Depression Scale
HR- Heart rate
HRQoL- Health-related quality of life
ISWT- Incremental shuttle walking test
LMM- Linear mixed model
MCID- Minimal clinically important difference
NNT- Number needed to treat
RCT- Randomized controlled trial
RR- Relative risk

depression, which may reduce adherence to medication[3] and clinical control.[4] Such control is essential to avoid a patient's impairment and reduce the risk of exacerbation and is centered on the amount of medication (controllers and relievers) required to avoid symptoms.

Aerobic[5] training and breathing[6] exercises are nonpharmacological interventions that improve asthma control and have been considered important adjuvants for medical treatment.[1] Both exercises have been widely used and are low cost, easy to apply, and safe. Aerobic training reduces corticosteroid consumption,[7] psychosocial distress,[8] and dyspnea and asthma symptoms[5] in addition to improving health-related quality of life (HRQoL),[9-11] aerobic capacity,[5] and clinical control.[9,10] There is evidence that breathing exercises also provide benefits, such as improvement in HRQoL[12-14] and reduction of anxiety and depression,[12,13] asthma symptoms,[12,15] the use of relief medication,[16] episodes of exacerbation, and airway hyperresponsiveness.[17] However, the benefits of these 2 types of exercises as interventions for asthma control have not yet been compared.

In the present study, we aimed to compare the effects of aerobic training and breathing exercises on clinical control (primary outcome) and airway inflammation (secondary outcome) in outpatients with persistent moderate-to-severe asthma.

METHODS

More details on the patient inclusion criteria, study design, randomization, interventions, outcome assessments, and statistical analysis are available in the Methods section of the Online Repository at www.jaci-inpractice.org.

Patients

Fifty-four outpatients with moderate-to-severe persistent asthma (aged 30-65 years) were recruited from the University Hospital during a regular medical visit. All volunteers gave their written informed consent. Asthma was diagnosed according to the Global Initiative for Asthma.[1]

Study design

The study was a prospective and randomized controlled trial (RCT) with 2 arms that compared nonpharmacological interventions (breathing exercises vs aerobic training) and was conducted between 2 medical consultations to avoid changes in medication during the interventions. All patients were advised to maintain their medications during the study.

Randomization. The eligible participants were randomly allocated to one of the following groups: aerobic training (AG, n = 25) or breathing (BG, n = 29). A simple randomization sequence was computer-generated by an investigator who was not directly involved with the recruitment, assessment, or treatment of the patients. Each patient's allocation was concealed using sequential numbering that was sealed and placed in opaque envelopes. The randomization process was performed after the baseline measurements.

Interventions

Educational program. This program consisted of two 2-hour classes/week for 2 weeks.[8] Presentations and group discussions included information on asthma physiopathology, medication skills, self-monitoring techniques, and environmental control.[1]

Aerobic training program. The program was performed with an indoor treadmill (Imbramed Export Plus, Brazil), and every session lasted 40 minutes, consisting of 5 minutes of warm-up, 30 minutes of aerobic training, and 5 minutes of cool-down. Aerobic training was initiated at 60% of heart rate (HR) recovery obtained by the Karvonen equation: $HR_{training} = HR_{rest} + 0.6(HR_{maximal} - HR_{rest})$.

Breathing exercise program. This program was based on the Pranayama Yoga breathing technique, which was developed by 2 senior yoga instructors (MRR and DFS). Breathing exercises aimed to stimulate nasal and diaphragmatic breathing, to increase expiratory time, to slow respiratory flow, and to regulate breathing rhythm.[18]

Outcome assessments. The primary outcome was clinical improvement of the Asthma Control Questionnaire 6 (ACQ6) scores.[19] Asthma symptoms and exacerbation were evaluated using a daily diary of symptoms as previously reported.[8,10] Sputum was collected and processed using a standard method.[20] Maximal exercise capacity was assessed by the incremental shuttle walking test (ISWT).[21] The Asthma Quality of Life Questionnaire (AQLQ)[22] and Hospital Anxiety and Depression Scale (HADS)[23] were used to estimate the quality of life and psychological distress. DLPA was quantified using an accelerometer (Power Walker SW 610, Japan),[24] and the spirometry test was performed following the American Thoracic Society/European Respiratory Society protocol[25] (Sensormedics Vmax 229, Yorba Linda, Calif). All outcomes were evaluated before and after the interventions. The ACQ, AQLQ, and HADS were also evaluated in a 3-month postintervention follow-up.

Statistical analysis

A sample size of 48 patients was calculated based on the minimal clinically important difference (MCID) in the ACQ score between the groups (0.5 ± 0.72, mean ± standard deviation)9 and considering a power of 80% and a 5% level of significance. The sample size was increased to 54 patients considering a 20% dropout rate. Analyses were preceded by multiple imputation analyses based on 100 imputed versions obtained via predictive mean matching. A linear mixed model (LMM) was used to test the significance of the effect of group, time, and their interaction over the course of the study. For all measures, a group-by-time interaction effect was tested using a full-factorial model. In all models, the subjects were considered random effects to account for within-subject correlations over time.

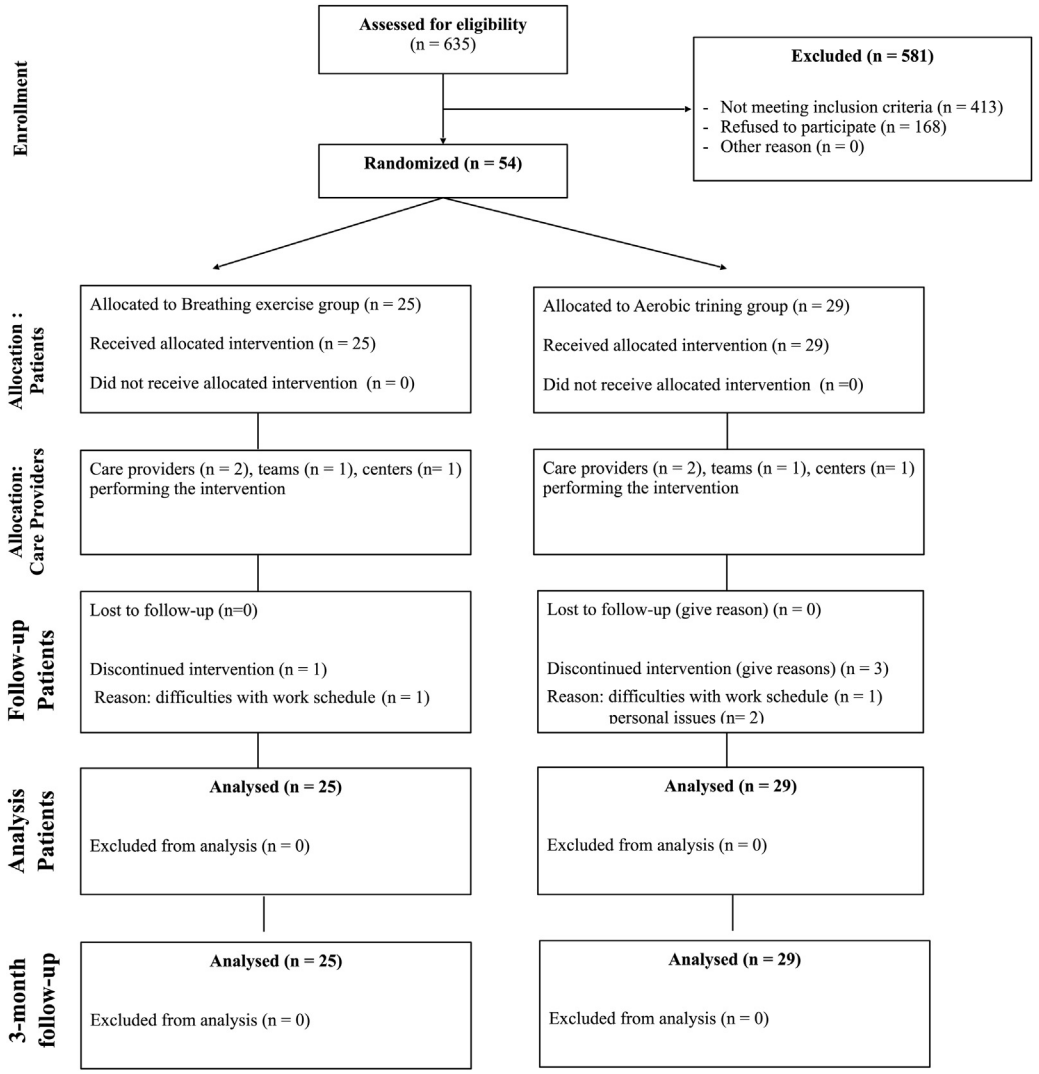

FIGURE 1. Flowchart of the participants through the study (CONSORT diagram).[27]

Group was used as a fixed factor, and time was used as a repeated measure. *Post hoc* comparisons were performed to determine the significance of the differences of the means and the Bonferroni method was used to adjust the *P* value obtained from the multiple comparisons.[26] Asthma symptom-free days (count data) were analyzed with a generalized linear model (generalized estimation equations) with the adequacy of the data determined by the negative binomial distribution. The threshold for statistical significance was set at 5%, and the Satterthwaite approximation was used to compute the degrees of freedom in the denominator of the LMM. The relative risk (RR) and number needed to treat (NNT) were used to evaluate the clinically important differences in the outcomes of the participants in the AG and BG. Data were analyzed using the Statistical Package for the Social Sciences (SPSS) (IBM, New York, NY).

RESULTS

More details on the patients and baseline characteristics, the HADS, the induced sputum, and the DLPA are available in the Results section of the Online Repository at www.jaci-inpractice.org.

Patients and baseline characteristics

A flow diagram of the study is presented in Figure 1. Both groups had similar demographic and clinical characteristics at baseline (Table I). No study-related adverse events were observed during or after the interventions. Ten patients in the AG (35%) and 6 patients (24%) in the BG reported asthma exacerbation during the study (non–study-related adverse events), and there was no significant difference between the groups ($P = .31$, χ^2).

Primary outcome

Clinical asthma control. The results show a significant effect for the "Treatment × Time" interaction ($P = .004$) and a main effect for "Time" ($P = .001$). The main effect for group was not significant ($P = .5$). Specifically, the "Treatment × Time" interaction was explored to check the group differences over time and the time differences within groups. No significant differences were observed between the groups after the

TABLE I. Baseline demographic and clinical characteristics in the breathing exercise and aerobic training groups

	Breathing exercise group (n = 25)	Aerobic training group (n = 29)	*P* value
Anthropometric data			
Sex, F/M	17/8	22/7	.41*
Age (y), mean (SD)	50.6 (9.2)	49.8 (9.7)	.95†
BMI (kg/m2), mean (SD)	27.5 (4.7)	28.4 (3.2)	.63†
Bronchodilator responders, n (%)	3 (12)	9 (31)	.10*
Budesonide dosage (μg/day), mean (SD)	774 (278)	869 (330)	.92†
Lung function			
FEV1 (L), mean (SD)	1.87 (0.5)	1.88 (0.6)	.39†
% of predicted, mean (SD)	70.2 (16.6)	72.7 (18.4)	.44†
FVC (L)	2.7 (0.8)	2.6 (1.0)	.67†
% of predicted, mean (SD)	84.7 (18.8)	83.9 (19.7)	.88†
FEV1/FVC, mean (SD)	0.67 (0.2)	0.71 (0.08)	.99†
Clinical control			
ACQ7 score, mean (SD)	2.11 (0.92)	2.31 (1.22)	.20†
Control level			
Uncontrolled, n (%)	21 (72)	17 (68)	.94*
Partially controlled, n (%)	7 (24)	7 (28)	
Controlled, n (%)	1 (4)	1 (4)	
Monthly symptom-free days, mean (SD)	6 (7.58)	8 (8.76)	.50†
No. of days/months of rescue medication use, mean (SD)	14.4 (10.7)	10.8 (11.4)	.26
Health-related quality of life			
AQLQ total score, mean (SD)	4.06 (1.14)	3.63 (1.47)	.28†
Cellularity in sputum			
Total number (105 × mL−1)	9.4 (7.5)	9.3 (6.9)	.21†
Differential cell counting (%)			
Neutrophils, median (95% CI)	48.0 (38.3-57.4)	54.7 (38.6-61.4)	.94†
Eosinophils, median (95% CI)	2.1 (0.3-3.7)	1.2 (0.1-2.6)	.60†
Macrophages, median (95% CI)	43.9 (34.7-53.1)	35.7 (24.0-47.4)	.08†
Lymphocytes, median (95% CI)	0.0 (0.1-0.6)	0.0 (0.1-1.0)	.50†
Maximal exercise capacity			
Distance ISWT (m), mean (SD)	341.8 (96.1)	360.4 (103.9)	.52†

ACQ7, Asthma Control Questionnaire 7; *AQLQ*, Asthma Quality of Life Questionnaire; *BMI*, body mass index; *CI*, confidence interval; *FEV1*, forced expiratory volume in the 1st second; *FVC*, forced vital capacity; *ISWT*, Incremental shuttle walk test.
Data are presented as means ± standard deviations (SDs) unless otherwise stated.
Uncontrolled asthma, ACQ ≥ 1.5; partially controlled, ACQ 0.76-1.49; controlled, ACQ ≤ 0.75.
**P* value from the χ^2 test.
†*P* value from the Mann-Whitney *U* test.

intervention (adjusted mean difference, −0.1; 95% confidence interval [CI], −0.59 to 0.38; $P = .68$) or after 3 months of follow-up (adjusted mean difference, −0.38; 95% CI, −0.86 to 0.11; $P = .13$) (Figure 2). The AG presented a decrease in the ACQ6 score from 2.0 (95% CI, 1.6-2.3) at the baseline to 1.3 (95% CI, 0.9-1.6) after the intervention and to 1.2 (95% CI, 0.8-1.5) at the 3-month follow-up ($P < .001$ for both after the intervention and at the 3-month follow-up vs the baseline). The BG presented no significant change in the ACQ6 score comparing the baseline score of 1.7 (95% CI, 1.2-2.0) with 1.5 (95% CI, 1.0-1.8; $P = .71$ vs baseline) after the intervention and 1.7 (95% CI, 1.4-2.2; $P = 1.00$ vs baseline) at the 3-month follow-up. Fifty-eight percent of participants from the AG (n = 17) and 32% in the BG (n = 8) showed a clinically significant improvement in the ACQ6 score (≥0.5 points) after intervention (RR, 1.8; 95% CI, 1-4.1; $P = .06$), and the NNT was 4. After 3 months of follow-up, 52% (n = 15) of the participants from the AG and 20% (n = 5) from the BG maintained their improvement (RR, 2.6; 95% CI, 1.2-10; $P = .02$), and the NNT was 4.

Secondary outcomes

Asthma symptoms. The results show a main effect for "Time" ($P = .003$), and there was no difference between the groups ($P = .69$) or for the interaction ($P = .25$). The number of days with rescue medication use was reduced by 34% in the AG from 14.3 (95% CI, 10.1-18.3) to 9.5 days (95% CI, 5.6-13.4) after intervention and by 6% in the BG from 12.2 (95% CI, 7.6-16.6 days) to 11.5 days (95% CI, 6.8-16.4 days) (Figure 3). After the intervention, 34% (n = 10) of the participants from the AG and 8% (n = 2) from the BG showed a reduction in the number of days with rescue medication use of more than 5 days (RR, 4.3; 95% CI, 1.04-17.8; $P = .04$), and the NNT was 4.

Health-related quality of life. The "Treatment × Time" interaction was not statistically significant for the total score, nor

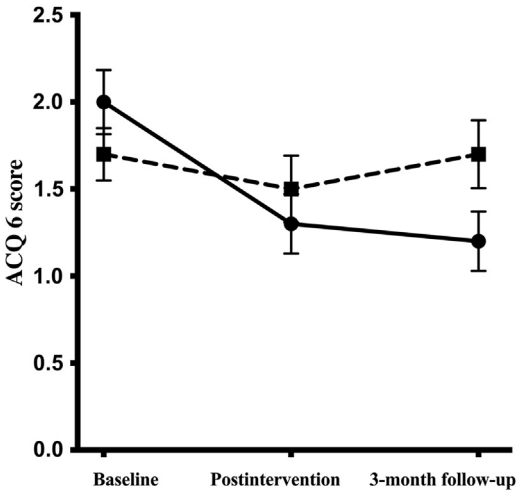

FIGURE 2. Effects of aerobic training (solid line) and breathing exercises (dashed line) on the Asthma Control Questionnaire 6 (ACQ6) score after intervention and after the 3-month follow-up. Data are presented as the least-squares means and standard error.

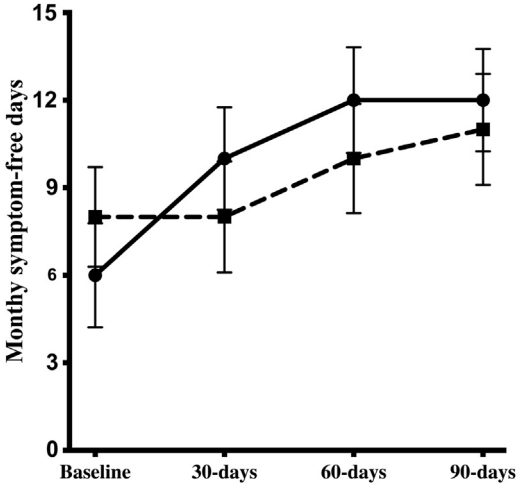

FIGURE 3. Effects of aerobic training (solid line) and breathing exercises (dashed line) on the monthly symptom-free days at 30, 60, and 90 days during the intervention. Data are presented as the least-squares means and standard error.

was the main effect for "Group" (Table II). In contrast, a main effect was observed for "Time" for all results, including the domains (symptom, activity limitation, environmental stimulus, emotional domains domain) (Table II). The activity limitation domain had a significant effect for the "Treatment × Time" interaction in favor BG ($P = .018$; Table II). After the intervention, 62% (n = 18) of the participants from the AG and 44% (n = 11) from the BG showed a clinically significant improvement in the total AQLQ score (≥0.5 points) after the intervention (RR, 1.6; 95% CI, 0.86-2.6; $P = .18$), and the NNT was 6. After 3 months of follow-up, 62% (n = 18) of the participants from the AG and 36% (n = 9) from the BG maintained their improvement (RR, 1.6; 95% CI, 0.99-3.6; $P = .15$), and the NNT was 4.

Induced sputum cellularity. There was no effect for "Time" ($P = .118$), Group ($P = .924$), or the "Treatment × Time" interaction ($P = .086$). The adjusted mean difference in the eosinophils between the AG and the BG was −0.67% (95% CI, 2.9%-1.5%) after the intervention.

Incremental shuttle walking test. The results show significant interaction ($P = .042$) and time ($P < .01$) effects; however, there was no significant group effect ($P = .98$). The adjusted mean difference in the walking distance between the AG and the BG was 17 m after the intervention. The AG had a mean improvement in the ISWT distance of 90.2 (95% CI, 65.0-115.5), and the BG had a mean improvement of 73.0 (95% CI, 36.9-109.2) (Figure 4).

Hospital Anxiety and Depression Scale. The results show a main effect for "Time" ($P < .001$), and there was no difference between the "Groups" or for the "Treatment × Time" interaction for the HADS anxiety and depression symptoms (Table II).

Daily-life physical activity. After interventions, no main effect was observed either for "Time," "Group," or for the "Treatment × Time" interaction ($P > .05$).

Magnitude of the interventions

Figure 5 shows the effect size (baseline to postintervention) for each outcome in both groups. Effect size was evaluated between baseline and postintervention. Patients in the BG had small-to-moderate effect sizes for all outcomes, whereas patients in the AG had moderate-to-large effect sizes (Figure 5). The asthma symptom-free days and the ISWT had lower and higher effects, respectively. Finally, the ACQ6 had the largest discrepancy in the effect between groups (Figure 5).

DISCUSSION

Our results demonstrate that aerobic training and breathing exercise resulted in a similar effect in asthma control evaluated by the ACQ score; however, when the improvement in asthma control was evaluated individually, aerobic training induced a longer-lasting benefit than breathing exercises and a greater reduction in rescue medication use. There were no differences between groups for the other outcomes, such as HRQoL, asthma symptom-free days, psychological distress, and DLPA and airway inflammation.

Primary outcome

Previous RCTs have shown that breathing exercises[30,31] and aerobic training[10,32] are appropriate adjuvant therapies to improve asthma control. However, the effect of breathing exercises on asthma control assessed by the ACQ score was evaluated in only 2 RCTs, and its benefits remain controversial.[13,14] Bruton et al,[14] in a recent and well-designed study, showed that physiotherapy mainly focusing on breathing exercises does not improve asthma control assessed by the ACQ score. The effect of exercise training on the ACQ score was evaluated in 4 RCTs,[10,11,32,33] and 3 trials demonstrated that exercise training improved the ACQ score.[10,32,33] Our results showed that there were no differences in the ACQ score between the AG and BG; however, the AG participants were 2.6 times more likely to experience clinical improvement than the BG participants at the 3-month follow-up. Our results suggest that at the group level,

TABLE II. Comparison of healthy-related quality of life and psychosocial symptoms between aerobic and breathing training

		Time period			*P* values		
Outcome	Groups	Baseline	After	Follow-up	"Group × Time"	"Time"	"Group"
AQLQ							
Activity limitation	AG	3.5 (1.1)	4.6 (1.0)	4.2 (1.3)	.018	.001	.600
	BG	4.0 (1.0)	4.1 (1.2)	4.8 (1.7)			
Symptoms	AG	4.3 (1.4)	5.0 (1.3)	5.3 (1.5)	.241	.001	.154
	BG	4.2 (1.3)	4.6 (1.5)	4.5 (1.5)			
Emotional function	AG	4.0 (1.5)	4.6 (1.7)	4.9 (1.2)	.614	<.001	.481
	BG	4.2 (1.4)	4.5 (1.6)	4.9 (1.3)			
Environmental stimuli	AG	3.5 (1.7)	4.4 (1.4)	4.9 (1.9)	.181	.038	.666
	BG	4.2 (1.6)	4.6 (1.5)	4.3 (1.4)			
AQLQ	AG	3.9 (1.1)	4.7 (1.0)	4.7 (1.0)	.468	<.001	.909
	BG	4.2 (1.0)	4.5 (1.3)	4.6 (1.2)			
HAD anxiety	AG	8.7 (3.9)	7.7 (3.6)	7.1 (3.4)	.443	<.001	.948
	BG	8.6 (4.6)	7.2 (4.4)	7.3 (3.9)			
HAD depression	AG	7.2 (3.8)	5.7 (4.3)	5.7 (3.5)	.877	<.001	.383
	BG	8.3 (4.4)	6.2 (3.9)	6.4 (4.8)			

AQLQ, Asthma Quality of Life Questionnaire; *HAD*, Hospital Anxiety and Depression.
Health-related quality of life and psychological distress at baseline, after intervention, and 3-month follow-up for aerobic training (AG) and breathing exercise (BG) groups. Data are presented as mean (standard deviation). *P* values from the main effects linear mixed models.

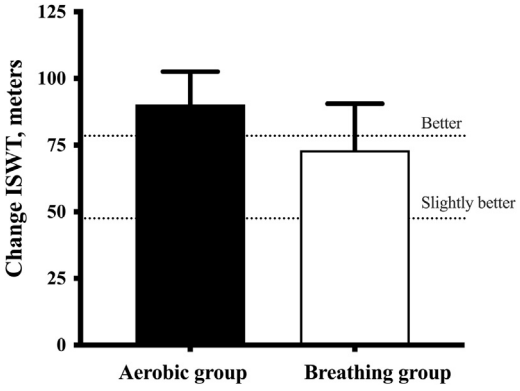

FIGURE 4. Effects of aerobic training (black bar) and breathing exercises (white bar) on the incremental shuttle walk test (ISWT) after the intervention (in meters). Data are presented as the mean change and standard error. Dotted lines represent a significant improvement of >78.7 m and a slight improvement of >47.5 m.[28]

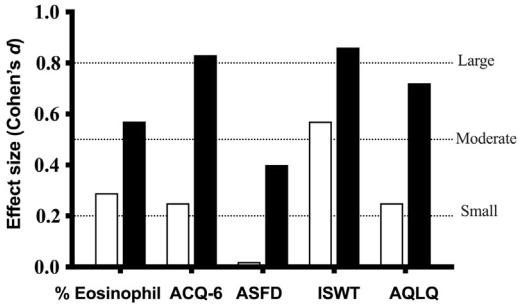

FIGURE 5. Effect size in the breathing exercises (white bars) and aerobic training (black bars) after intervention for eosinophil percentage. The dotted lines represent small (<0.2), medium (>0.2 and <0.5), and large (>0.8) effects.[29] The effect size was evaluated between baseline and postintervention. *ACQ6*, Asthma Control Questionnaire 6; *AQLQ*, Asthma Quality of Life Questionnaire; *ASFD*, asthma symptom-free days; *ISWT*, incremental shuttle walk test.

both aerobic training and breathing exercises induced a similar decrease in ACQ score; however, when the improvement in asthma control was evaluated individually, aerobic training induced a longer-lasting benefit than breathing exercises. These results suggest that further studies are required to comprehend which intervention results in a better response and long-term effect.

We hypothesize that aerobic training improves asthma control either by increasing aerobic capacity[5] and/or by reducing bronchial hyperresponsiveness (BHR)[10] because both are associated with better asthma control.[8,34] Breathing exercise could also reduce BHR, as reported by Manocha et al.[17] Breathing exercises are performed using different breathing patterns, and these changes in lung volume seem to relax the smooth muscle in the airway and improve the BHR. For instance, in asthma animal models, the airway resistance is reduced when the animals are ventilated with a greater tidal volume and lower breathing frequency in comparison with those animals ventilated with a smaller tidal volume and higher breathing frequency.[35] However, this hypothesis remains to be confirmed in humans after a breathing exercise program. In fact, 2 other studies did not show any effect of breathing exercises on BHR.[13,16]

Secondary outcomes

Asthma symptom-free days were similar between the AG and BG groups over the course of the study. The effect of exercise training on asthma symptom-free days in adults was assessed in 6 RCTs,[8,10,36-39] and 5 trials demonstrated that exercise training improved symptom-free days.[8,36-39] The effect of breathing exercises on asthma symptoms seems to depend on the technique.

Cooper et al[30] compared 2 breathing techniques and suggested that only the Buteyko technique produced a reduction in asthma symptoms. Ritz et al[40] observed a significant improvement after breathing exercises guided by capnometry, whereas Manocha et al[17] did not show any improvement in asthma symptoms in patients who performed yoga breathing exercises. Our results also demonstrate that a greater proportion of participants in the aerobic training group presented a reduction in the number of days without the use of rescue medication compared with those in the breathing exercises (34% vs 8%, respectively). Our results are supported by previous studies demonstrating that aerobic training reduced the consumption of rescue medication.[41] Contrary to our results, Slader et al[16] observed that breathing exercises reduced the number of days of rescue medication use by 86%. A possible explanation for this difference between our findings and those of Slader et al[16] is that in our study, the reduction was reported spontaneously, whereas in the study by Slader et al,[16] the participants were instructed to use breathing exercises before using rescue medication whenever they presented asthma symptoms.

Aerobic training and breathing exercises showed similar results in the total HRQoL. Previous studies have demonstrated that aerobic training[8,10,32] and breathing exercises[13-15] both have a positive impact on the HRQoL in asthmatic patients. Recently, Bruton et al[14] performed a very well-designed study with a large sample size and demonstrated that the HRQoL was the only outcome that had a significant effect after breathing exercise, even after 6 months of the intervention. The authors also demonstrated that 64% of patients in a face-to-face group exceeded the MCID for AQLQ score. Our results showed that 65% in the AG and 42% in the BG had significant clinical improvements with an average AQLQ score improvement of 0.8 and 0.6, respectively. These results may suggest that, on average, participants in both groups had clinically relevant improvements in quality of life during the study period.

The effects of nonpharmacological interventions on airway and systemic inflammation are still not well understood. There is evidence suggesting that aerobic training reduces airway eosinophil numbers[38] and inflammatory blood cytokine levels in adult asthmatics[10,32]; however, no effect was observed on blood eosinophilia in asthmatic children.[42] Thomas et al[13] evaluated the effects of breathing exercises on airway inflammation and did not show benefits. Our results showed no effects on sputum eosinophils in either group. However, it is important to note that the patients in our study presented normal mean values for sputum eosinophils.

Our results demonstrated that aerobic group had greater improvement in the ISWT than the breathing group over the course of the study. The AG had an improvement in ISWT distance greater than the limit for "better" (>78.7 m), whereas the BG improved to the limit for "slightly better" (>47.5 m).[28] Therefore, on average, both groups exceeded the MCID after the intervention.[43] This increase in exercise capacity after a breathing exercise program has never been previously shown. A possible explanation for this finding may rely on the fact that breathing exercises can improve a patient's ventilatory control and confidence in performing physical activities. We also observed that the DLPA did not differ significantly after the intervention between groups. However, patients in both groups increased their capacity by approximately 2000 steps after the interventions, reaching 10,000 steps, which is the recommended number for the general population to be considered physically active and to obtain health benefits.[44]

No difference between groups was observed in anxiety and depression symptoms. Only the depression domain exceeded the MCID of 1.5 points for both groups. In addition, previous studies with asthmatic subjects have demonstrated improvement in psychosocial symptoms in participants engaging in either aerobic training[8,10] or breathing exercise programmes[13,15] compared with the symptoms of controls. Finally, we compared the impacts of the interventions and observed that patients participating in aerobic training seemed to obtain a greater effect (from moderate to large) than patients in the breathing exercise program (from none to moderate). The present study is the first to compare these 2 interventions, and the results must be interpreted with caution. However, the comparison of the effect sizes shows the intervention's magnitude and provides a piece of complementary information that may help a clinician advise patients based on evidence.

Limitations

Our study has limitations. First, we developed a specific Pranayama breathing exercise, and our results cannot be compared with those of other studies that have used yoga or other groups of Pranayama breathing exercises. However, the sequence of exercises was developed by 2 senior yoga instructors (with >15 years of experience). In addition, our program aimed to stimulate nasal and diaphragmatic breathing, to increase expiratory time and to slow respiratory flow, as is recommended by other breathing exercises techniques, such as the Buteyko and Papworth techniques.[12,15,30] In addition, the sequence of exercises has been properly described.[18] Second, ISWT is not the gold standard to assess exercise capacity and has never been demonstrated to be sensitive in evaluating exercise training in subjects with asthma. However, this maximal incremental and standardized test was developed for patients with obstructive lung diseases, and the walked distance during the test has a good linear correlation with peak VO2.[45] Third, the conclusions of this study seem to be useful only for subjects with moderate-to-severe asthma without other comorbidities. On the other hand, the literature has shown that most excluded patients (elderly individuals, obese individuals, and those with cardiovascular disease) can also benefit from either exercise training or breathing exercise. Finally, although the results of some outcomes showed greater improvement than the MCID, these results need to be interpreted with caution because of the absence of a usual care or sham group. On the other hand, the effect size analysis suggests that these results may have clinical relevance.

CONCLUSION

Outpatients with moderate-to-severe asthma who participated either in aerobic training or breathing exercise programs presented similar results regarding asthma control, HRQoL, asthma symptom-free days, psychological distress, DLPA, and airway inflammation. However, a greater proportion of participants in the aerobic training presented a longer-lasting clinical control and reduced use of rescue medication than the breathing exercises. These results are relevant in clinical practice to support the benefits from nonpharmacological interventions.

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ONLINE REPOSITORY

METHODS

The study was approved by the Hospital Research Ethics Committee and registered in the clinicaltrials.gov database (NCT02065258).

Patients

The inclusion criteria were as follows: both sexes, person with body mass index (BMI) <35 kg/m^2, sedentary (<60 minutes of physical activity/week during leisure time), under medical treatment for at least 6 months, and clinically stable (ie, no crises or changes in medication for ≥30 days). The exclusion criteria were as follows: tobacco history >10 packs/year; other lung diseases or uncontrolled hypertension; and diabetes and musculoskeletal impairment affecting the patient's ability to perform the exercises.

Study design

The patients completed a 4-hour educational program and were randomly assigned with concealed allocation into either the breathing (BG) or aerobic training (AG) groups. Both interventions consisted of 24 face-to-face sessions (twice a week, 40 minutes/session) in a 3-month period; these sessions were performed in groups with 4 to 7 participants under the supervision of 1 therapist in the hospital. If a participant could not attend a session, the session was rescheduled for the same or the next week. In every session, exercise intensity, symptoms, peak flow values, and exercise adherence were recorded. The interventions were administered by 2 licensed therapists experienced in aerobic training and breathing exercises. Breathing Pranayama exercises were developed by 2 experienced yoga trainers (MRR and DFS), and the therapists underwent a 6-month intensive training program, including the teaching of the exercise and yoga philosophy. In addition, the yoga trainers also supervised the training sessions and the patient's progress every 2 weeks to assure the correct breathing exercise performance. Study-related adverse events were when the participant experienced an acute attack during or immediately after the session or had an orthopedic lesion or articular pain. Exacerbations related to allergen exposure or a respiratory infection were considered non—study-related adverse events.

The outcomes evaluated before and after the interventions were as follows: Asthma Control (ACQ) and Quality of Life (AQLQ) (via questionnaires); asthma diary; airway inflammation (sputum induction); spirometry; the incremental shuttle walking test (ISWT); Hospital Anxiety and Depression Scale (HADS); and daily-life physical activity (DLPA). ACQ, AQLQ, and HADS were also evaluated at a 3-month postintervention follow-up. All outcomes were assessed in a blinded manner by an investigator who was not involved in the study.

Randomization

The eligible participants were randomly allocated to one of the following groups: aerobic training (AG, n = 25) or breathing (BG, n = 29). Using Microsoft Excel, a simple randomization sequence was computer-generated by an investigator who was not directly involved with the recruitment, assessment, or treatment of the patients. Each patient's allocation was concealed using sequential numbering that was sealed and placed in opaque envelopes. The randomization process was performed after the baseline measurements.

Interventions

Aerobic training program. The maximal heart rate (HR) was estimated according to Tanaka's equation (208 − (0.7*age)).[E1] Exercise intensity was increased by 5% of the HR (up to a maximum of 80% HR recovery) if the patient participated in 2 consecutive exercise sessions without symptoms. Before and after every session, patients performed a peak expiratory flow measurement. The patient was advised to use the rescue dose of the prescribed bronchodilator if the peak flow was <70% of the patient's maximal value.

Breathing exercise program. The exercises were divided into 3 progressive phases.[E2] The first phase aimed to improve the control of diaphragmatic breathing; the second phase aimed to improve breathing control by changing the inspiratory and expiratory duration (1:1 to 1:4) according to the patient's capacity and comfort. The third phase combined the exercises from phases 1 and 2. The exercise protocol has been described in detail elsewhere.[E2]

Outcome assessments

Asthma Control Questionnaire 7. This questionnaire was composed of questions related to asthma symptoms, the use of short-acting β2-agonists, and 1st second forced expiratory volume (FEV_1) as a percentage of predicted values. The ACQ6 (ACQ7 without the question related to FEV_1) was calculated[E3] and used as the primary endpoint because pulmonary function (FEV_1) does not change with aerobic training[E4] or breathing exercise.[E5] An ACQ score <1.5 is considered to indicate controlled asthma, whereas a score ≥1.5 is considered to indicate poorly controlled asthma.[E4] A reduction of 0.5 after an intervention is considered clinically significant.[E6]

Clinical asthma symptoms. The patients were advised to complete a diary detailing the following asthma symptoms: cough, dyspnea, wheezing, quantified clinical asthma symptoms, and use of relief medication.[E7] A 5-day reduction in relief medication use after the intervention was considered clinically significant.[E8]

Airway inflammation. Patients inhaled 400 μg of salbutamol followed by a 3% hypertonic saline solution for 15 minutes using an ultrasonic nebulizer with an output of 2.4 mL/min.[E9] Differential cell counts were classified as eosinophils, lymphocytes, neutrophils, and macrophages based on cell morphology by a single-blinded investigator. Eosinophil values were considered elevated at >3%.[E10]

Maximal exercise capacity. Maximal exercise capacity was assessed by the ISWT.[E11] A change in distance of 47.5 m has been described as associated with feeling "slightly better," whereas a change of 78.7 m has been associated with feeling "better."[E12] The level of clinical significance for the ISWT is 48 m.[E13]

Asthma Quality of Life Questionnaire. This questionnaire has 4 domains: physical limitations, frequency of symptoms, socioeconomic factors, and psychosocial factors. Higher AQLQ scores indicate better quality of life, and an increase of 0.5 is considered clinically significant.[E14]

Hospital Anxiety and Depression Scale. The HADS has 14 items divided into 2 subscales (7 for anxiety and 7 for depression). For each item, there are 4 alternatives, with scores ranging from 0 to 3.[E15] A reduction of 1.5 after an intervention is considered clinically significant.[E16]

Daily-life physical activity. DLPA was quantified using an accelerometer (Power Walker SW 610, Japan).[E17] The assessment was performed over a period of 7 days, and DLPA was quantified before and after the interventions. The accelerometer automatically recorded the total number of steps during the 7 days. The first and the last day were disregarded, and the average number of steps performed during the remaining 5-day period was used.[E17]

Pulmonary function. The spirometry test was performed before and after inhalation of 400 μg of salbutamol, following the ATS/ERS protocol[E18] (Sensormedics Vmax 229, CA). The predicted normal values were those proposed by Pereira et al.[E19]

Statistical analysis

The distributions of ACQ6, AQLQ, ISWT, and pulmonary function were roughly normal, and the results were summarized using means and standard deviations. The eosinophil cell counts had a nonparametric distribution and were presented using the geometric mean and 95% confidence interval (CI). The analysis of sputum cellularity included only participants who provided an adequate sputum sample at baseline (79%). The success of randomization was assessed by comparing the baseline characteristics of the study groups using independent sample *t*-tests and the χ^2 test. The between-group differences were calculated using linear mixed models. Group (aerobic vs breathing training), time (baseline, postintervention, and 3-month follow-up, treated as categorical variables), and their interaction (group and time) were included in the model as fixed factors. Random intercepts were included at the participant level. Afterward, *post hoc* testing and correction for pairwise comparisons were carried out. Bonferroni adjustment for multiple comparisons was applied. Asthma symptom-free days (count data) were analyzed with a generalized linear model (generalized estimation equations) with the adequacy of the data determined by the negative binomial distribution.

The relative risk (RR) refers to the percentage of the participants in the AG with clinically meaningful outcomes versus the percentage of the participants in the BG with clinically meaningful outcomes. The number needed to treat was defined as the number of participants who needed to be treated in the AG versus BG for 1 participant to exhibit significant clinical improvement.

RESULTS

Patients and baseline characteristics

In total, 635 outpatients with moderate-to-severe asthma were evaluated for eligibility, of whom 168 refused to participate and 413 patients did not meet the inclusion criteria: >65 years (n = 121), obese (BMI > 35 kg/m^2) (n = 79), cardiovascular disease (n = 56), type 2 diabetes (n = 29), musculoskeletal disabilities (n = 21), regular exercise (n = 18), psychiatric disorder (n = 25), exacerbation in the previous 30 days (n = 23), cancer (n = 19), other pulmonary disease (n = 17), and pregnancy (n = 5). Fifty-four patients met the inclusion criteria and were randomized. Four participants (1 BG and 3 AG) withdrew before completing the intervention because of difficulties with work schedule (1 BG and 1 AG) or personal issues (2 AG). Fifty patients (92%) completed the 24 treatment sessions (24 in the BG and 26 in the AG). All patients maintained a similar bronchodilator and corticosteroid dosage throughout the study.

Health-related quality of life

We used the 50th percentile to dichotomize the AQLQ score, and 58% (n = 17) of the participants from the AG and 60% (n = 15) from the BG had AQLQ scores higher than the 50th percentile at baseline, with no difference between groups (P = .91, χ^2 test).

Asthma symptoms

In the AG, the number of asthma symptom-free days at baseline was 6 days (95% CI, 2.7-9.7 days); after 30 days, it was 10 days (95% CI, 6.2-13.5 days); after 60 days, it was 12 days (95% CI, 8.5-15.7 days); and after 90 days, it was 12 days (95% CI, 8.4-15.6 days). In the BG, the number of asthma symptom-free days at baseline was 8 days (95% CI, 3.8-11.7 days); after 30 days, it was 8 days (95% CI, 3.6-11.6 days); after 60 days, it was 10 days (95% CI, 5.9-13.78 days); and after 90 days, it was 11 days (95% CI, 6.6-14.6 days).

Induced sputum cellularity

Adequate sputum samples were obtained from 79% of the participants (21 AG and 21 BG), and only 14% presented an eosinophil percentage >3% (5 AG and 1 BG). The mean within-group difference was 1.4% of eosinophils (95% CI, 0.2% to 2.8%) in the AG and 0.82% of eosinophils (95% CI, −1.3% to 1.1%) in the BG.

Hospital Anxiety and Depression Scale

There was a main effect for "time" (P = .001) but no effect for the "treatment × time" interaction (P > .05, Table II) and the HADS anxiety and depression subscales. In the AG, the HADS anxiety score was 8.7 (95% CI, 7.0-10.4) at baseline, 6.5 (95% CI, 4.5-8.2) after the intervention, and 5.0 (95% CI, 3.3-6.8) at 3 months of follow-up. In the BG, the HADS anxiety score was 8.2 (95% CI, 6.4-10.1) at baseline, 6.9 (95% CI, 5.1-8.8) after the intervention, and 5.3 (95% CI, 3.5-7.1) at 3 months of follow-up. In the AG, the HADS depression score was 7.2 (95% CI, 5.6-8.8) at baseline, 4.7 (95% CI, 3.0-6.3) after the intervention, and 4.0 (95% CI, 2.3-5.6) at 3 months of follow-up. In the BG, the HADS depression score was 7.9 (95% CI, 6.1-9.7) at baseline, 6.0 (95% CI, 4.2-7.8) after the intervention, and 4.5 (95% CI, 2.7-6.2) at 3 months of follow-up. After the intervention, 60% of the participants from the AG and 36% from the BG showed a clinically significant improvement in the total HADS anxiety score (≥1.5 points) (RR, 1.65; 95% CI, 0.87-3.12). After 3 months of follow-up, 50% of the participants from the AG and 33% from the BG maintained their improvement (RR, 2.0; 95% CI, 0.76-5.26; P = .16). After the intervention, 36% of the participants from the AG and 41% from the BG showed a clinically significant improvement in the total HAD depression score (≥1.5 points) after the intervention (RR, 0.88; 95% CI, 0.43-1.81; P = .73). After 3 months of follow-up, 28% of the participants from the AG and 37% from the BG maintained their improvement (RR, 0.74; 95% CI, 0.28-1.96; P = .55).

Incremental shuttle walking test

For participants in the AG, the mean ISWT distance improved from 342 m (95% CI, 302-382) at baseline to 429 m (95% CI, 389-470). In the breathing exercise group (BG), it improved from 360 at baseline to 412 (95% CI, 369-456) after the intervention.

Daily-life physical activity

The mean total number of daily steps increased from 9186 at the baseline (95% CI, 7926-10,446) to 11,192 steps after the intervention in the AG (95% CI, 9649-12,735) and from 8809 (95% CI, 7428-10,189) to 10,796 steps (95% CI, 9298-12,293) in the breathing exercise group.

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