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Seasonal changes influence the improvement in asthma symptoms by exercise training in subjects with asthma

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**Seasonal changes influence the improvement in asthma symptoms by exercise
training in subjects with asthma**

Running head: Seasonal change and asthma symptoms after exercise

Keywords: seasonal variations, pulmonary rehabilitation, health-related quality of life, oxygen consumption, clinical control.

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ABSTRACT

Objective: To investigate whether patients with moderate to severe asthma who commence an exercise training program in winter or summer show differences in exercise capacity, health-related quality of life (HRQoL) and asthma symptoms.

Methods: Forty-two consecutive subjects visiting the outpatient clinic were enrolled in the 17-week rehabilitation program. One group of patients received the intervention from summer to winter (SWG, n = 21), and the other group participated from winter to summer (WSG, n = 21). Before and after the exercise training program, all patients were evaluated by cardiopulmonary exercise test, pulmonary function test, quality of life questionnaire and a daily diary that evaluated clinical asthma symptoms. **Results:**

After the training period, both groups improved similarly in health-related quality of life (HRQoL) and aerobic capacity. The WSG patients had a greater increase than those in the SWG in asthma symptom-free days ($p < 0.05$, Table 2). **Conclusions:** Our results indicate that seasonal variations affect the improvement in asthma symptoms after an exercise training program but have no effect on health-related quality of life, exercise capacity or pulmonary function.

Keywords: seasonal variations, asthma, pulmonary rehabilitation.

INTRODUCTION

Asthma is a disease defined by a history of respiratory symptoms such as wheezing, shortness of breath, chest tightness and cough that vary over time and in intensity and by variable expiratory airflow limitation [1]. Asthma treatment aims to control respiratory symptoms, ensure the patient can participate in normal activities, prevent asthma exacerbations and provide a patient with a good health-related quality of life (HRQoL) [1].

Currently, exercise training has been proposed as an adjunctive asthma treatment because it improves HRQoL, physical capacity and clinical control in subjects with moderate and severe asthma [2-8]. The average length of exercise training programs ranges from 3 to 6 months [9], and during this period, the patient is exposed to seasonal variations that can affect clinical and physiological exercise responses. There is strong evidence that seasonal variations significantly influence clinical endpoints in asthma such as increased airway hyperresponsiveness [10], exercise-induced bronchospasm [11], exacerbations and hospitalizations [12]. Lower temperature and humidity, increased air pollution levels, and contact with infectious agents and aeroallergens, especially in the winter, are factors that trigger asthma attacks related to seasonal variations [13-15].

In subjects with chronic obstructive pulmonary disease (COPD), the improvement in physical activity following pulmonary rehabilitation is influenced by season variations [16]. For instance, patients who began the pulmonary rehabilitation program in the winter achieved a greater improvement in physical activity than those who started in the summer [16]. An understanding of seasonal influences on the outcomes of a

training program is important because such factors can interfere with the patient's performance; however, to the best of our knowledge, this understanding remains poor in the context of patients with asthma. Thus, we hypothesized that outpatients with asthma who have finished exercise training in the Winter would have lower improvement in the outcomes than those finishing in the Summer. Thus, the aim of the present study was to investigate whether individuals with moderate or severe asthma who finished an exercise training program in winter or summer show different responses in exercise capacity, HRQoL or asthma symptoms.

METHODS

Subjects

Forty-two consecutive subjects visiting the outpatient clinic entered the study. Subjects of both genders with moderate or severe persistent asthma aged between 20 and 59 years were enrolled in the pulmonary rehabilitation program. Asthma diagnosis was based on the Global Initiative for Asthma [1], and patients had been under medical treatment for at least 6 months and were considered clinically stable (i.e., without exacerbations or changes in medication for at least 30 days). Patients diagnosed with cardiovascular, pulmonary, or musculoskeletal diseases that would impair exercise training were excluded from the study. The Ethics Review Board approved the study (protocol number 0121/10), and all patients signed an informed consent.

Seasonal conditions during the study intervention

The study was performed in São Paulo city, a megalopolis with 12 million habitants located in Southern Brazil, where the Winter begins in June and the Summer begins in December. São Paulo's Winter is characterized by an average temperature of 15°C

(ranging from 10°C to 22°C), low humidity, limited rains, a higher frequency of thermal inversions, the highest levels of air pollution and a significant increase in respiratory symptoms [17].

Experimental design

This observational study was performed between two medical regular visits. Before and after the pulmonary rehabilitation, all patients were evaluated by a health-related quality of life questionnaire, cardiopulmonary exercise testing, daily diary to evaluate asthma clinical symptoms, Fractional exhaled nitric oxide (FeNO) and pulmonary function test. The rehabilitation program had a duration of 17 weeks, divided into two weeks of assessment, one week of an educational program, 12 weeks of aerobic training and 2 weeks of reevaluation. One group of patients received the intervention from mid-February to mid-June (Summer-Winter group (SWG), n = 21), and another participated from mid-July to mid-November (Winter-Summer group (WSG), n = 21). During pulmonary rehabilitation, the prescribed medications remained unchanged and patients in both groups completed all sessions.

Assessments:

Health-related quality of life:

It was evaluated using the quality of life for asthma questionnaire (EPM), which was translated into and validated in Portuguese. The questionnaire has four domains [18]: i) physical limitations due to asthma symptoms; ii) frequency of symptoms; iii) socioeconomic limitations; and iv) psychosocial limitations. The questionnaire scores are presented as a percentage (the highest value, 100%); lower scores indicate a better quality of life, while higher scores indicate a poorer quality of life.

Cardiopulmonary exercise testing:

The test was performed on a treadmill coupled to a digital computer containing the assessment exercise program (Sensormedics, Vmax 229, CA, USA) responsible for performing the breath-by-breath analysis of metabolic, ventilatory and cardiovascular system parameters according to the modified Balke protocol [19]. A bronchodilator (200 µg of salbutamol) was administered 15 min before cardiopulmonary exercise testing to allow patients to achieve maximal oxygen consumption.

Clinical asthma symptoms:

Asthma symptoms were quantified by a daily diary of cough, diurnal or nocturnal dyspnea, wheezing, and use of relief medication. A free-day of asthma symptoms was considered when the patient did not report any symptoms. All patients were familiarized with the diary during the 30 days before the study, and the patients filled out the diary during the follow-up period. Symptom-free days were quantified monthly [4,5].

Fractional exhaled nitric oxide (FeNO)

All measurements were determined by chemiluminescence (Sievers 280 NOA; Sievers Instruments, Boulder, CO) in accordance with the ATS recommendation [20].

Pulmonary function:

Spirometry was performed according to the technical procedures, and the criteria for acceptability and reproducibility were recommended by the American Thoracic Society [21] (Sensor Medics 229; Sensor-Medics Corp., Yorba Linda, CA). Predicted normal values were proposed by Pereira et al. [22] (2007).

Interventions

Education program:

The educational program consisted of 2 classes (once a week) with a total duration of 4 hours; this program aimed to educate patients about asthma and its clinical management. The topics discussed included asthma pathophysiology, asthma diagnosis and treatment, environmental control, disease control using the daily diary, proper medication use and daily peak expiratory flow measurements. In addition, educational videos on these issues were used [4,5].

Aerobic training program:

All subjects performed the aerobic training program twice a week for 12 weeks using an indoor treadmill (*Imbramed Export Plus*, Brasil), and each 35-minute aerobic training session consisted of 5 minutes of warm-up, 25 minutes of aerobic training and 5 minutes of cool-down. The heart rate (HR) and the level of breathing discomfort were monitored. In the first two weeks, the intensity in the beginning of the program corresponded to 60% of VO_2max obtained by cardiopulmonary exercise testing and was monitored by heart rate (HR). After two weeks of adaptation, the aerobic training intensity was increased to 70% VO_2max [4,5]. If patients maintained this intensity for two consecutive exercise sessions without symptoms, the exercise intensity was increased by 5% of HR (until 80% of maximal heart rate was reached) by changing treadmill speed or grade. 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.

STATISTICAL ANALYSIS

Using a standard 2 group design with equal variance and setting the power at 0.8 with $\alpha = 0.05$ and two-sided hypothesis testing, a decrease in symptom-free days of 8.6 days (SD 7.5) [4] would require a sample size of 18/group for a total sample of 36 subjects. Normality was evaluated using the Kolmogorov-Smirnov test, and data are presented as the mean $\pm$ standard deviation (SD). Baseline values and differences between the mean changes in the groups were compared by Student's *t*-test. The intra-group comparison (pre vs. post treatment) was performed using the paired *t*-test. The Fisher exact test was used to evaluate categorical variables. The significance level was set at 5% for all variables. All analyses were performed with statistical software (SigmaStat 3.5, Systat Software Inc.).

RESULTS

Before aerobic training, the groups were similar with respect to gender, age, body mass index (BMI), daily dosage of corticosteroids, pulmonary function, aerobic capacity, health-related quality of life and asthma symptom-free days (Tables 1 and 2).

After the training period, both groups improved similarly in HRQoL (percentage improvement 32.2% in SWG vs 39.8% in WSG, effect size 0.416, $p = 0.18$, Table 2) and aerobic capacity (percentage improvement 15.1% SWG vs 11.3% in WSG, effect size 0.27, $p = 0.36$, Table 2). The two groups also had more days free of asthma symptoms ($p < 0.05$, Table 2), but the group that trained during the winter-summer period (WSG) showed a greater increase in symptom-free days than the summer-winter group (percentage improvement 22.2% SWG vs 66.6% in WSG, effect size 0.69, $p = 0.02$, Table 2). It was also observed that the improvement in the number of free-day asthma symptoms in both groups was negatively associated with the number of free-day

asthma symptoms at baseline ($r = -0.45$; $p < 0.001$). Fractional exhaled nitric oxide decreased in only the winter-summer group ($p = 0.003$), and there was no difference between the groups (percentage improvement 11.1% SWG vs 20.5% in WSG, effect size 0.36, $p = 0.23$). There was no improvement in lung function in either group (Table 2).

DISCUSSION

The results of the present study demonstrate that seasonal variations influence the improvement in asthma symptoms after subjects with moderate and severe asthma participate in a physical training program. However, such variations do not influence the improvement in the HRQoL and the maximal aerobic capacity. Additionally, no differences were identified between variables at baseline, independent of seasonality.

As highlighted in clinical guidelines, the reduction of asthma symptoms is the major goal in asthma management and an indicator of overall disease control [1]. Daily diary has been recommended as an outcome for cost-effectiveness evaluation in asthma therapies [23], and the improvement of the free-days of asthma symptoms is associated with the increase in aerobic capacity (VO_{2peak}) [4]. Previous studies have demonstrated that exercise training improves asthma symptoms and the HRQoL of subjects with asthma [4,5,24]. Our results reinforce the concept that exercise has an important role as an adjuvant in the treatment of patients with asthma. However, we observed a greater increase in asthma symptom-free days among patients who finished the program in the summer (WSG) than among those who finished in the Winter (SWG). We hypothesize two main reasons for the difference observed in the response to exercise training based on seasonal variations. One, patients who began the exercise program in the Summer

(SWG) had fewer asthma symptom-free days than those who began training in the Winter (WSG) (13 vs. 16 days, respectively). Consequently, patients in the WSG had a greater chance than those in the SWG to improve the number of asthma symptom-free days. Two, the improvement in symptoms may have been attenuated in patients who completed the training program in the winter due to worsening weather conditions. In our opinion, this latter explanation is the most likely. Although this study was performed in Brazil, which is considered a tropical country, our hospital is located in São Paulo, a city located in the Southern region of the country, and diurnal temperature range of 10 degrees Celsius. In addition, São Paulo is a megalopolis with 12 million habitants, and the air pollution reaches the highest concentration in the Winter. Social factors such as housing conditions and lack of thermal insulation, which are common issues in development countries, might also increase the seasonal effect of winter [17]. The combination of lower temperature and increased levels of air pollution is likely to induce airway hyperresponsiveness [10], exercise-induced bronchospasm [11] and asthma exacerbations [12].

Previous studies have investigated the influence of season on pulmonary rehabilitation outcomes for patients with COPD [16]; however, to the best of our knowledge, this study is the first to evaluate the influence of seasonality on asthma patients. In the COPD study, patients who finished the PR in summer had a greater increase in physical activity than those who finished in the winter. However, seasonality did not influence health-related quality of life and physical capacity after pulmonary rehabilitation. In our study, asthma patients improved their functional capacity and HRQoL regardless of changes in season. These results may indicate that improvements in exercise capacity

and psychosocial morbidity after pulmonary rehabilitation are less affected by seasonal variations in subjects with asthma.

Health-related quality of life improved by an average of 36% in both groups. A similar improvement was previously observed by Mendes et al. [4] (33%) and Gonçalves et al. [25] (35%) using a specific asthma HRQoL questionnaire (EPM-Paulista). Other studies using the asthma quality of life questionnaire (AQLQ) have shown an improvement of approximately 15% [2,26,27]. We also showed an increase in maximum aerobic capacity of $3.3 \text{ mL O}_2 \cdot \text{kg} \cdot \text{min}^{-1}$ in both groups (10% mean improvement), and this result is in agreement with the meta-analysis of Carson et al. [8]. Taken together, our data reinforce the relevance of aerobic training in patients with asthma.

Certain limitations need to be addressed. First, differences in the geographical and climatic characteristics may vary the level of exposure to asthma triggers. Then, future studies may be required to confirm our results in countries where either changes between seasons or exposure to asthma triggers present greater differences. Second, our rehabilitation program was 17 weeks long [9], starting in the end of one season and ending in the beginning of the other season (either Winter or Summer). Thus, differences between the initial and final evaluations may have been more pronounced. Third, we selected only two training periods because climatic variations in São Paulo city are more clearly defined between winter and summer, and the incidence of respiratory problems in this population is higher in Winter [28].

CONCLUSION

Our results indicate that seasonal variation influence the improvement in asthma symptoms after a physical training program but did not have effect on health-related quality of life or maximal aerobic capacity. The difference was clinically relevant and should be considered in the preparation and evaluation of physical training programs.

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Declaration of interest:

The authors of the present study do not have any conflicts of interest and there are not any relationships with companies/organizations whose products or services may be discussed in this article.

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TABLES

Table 1 – Baseline values in the summer and winter seasonal groups

	SWG (n=21)	WSG (n=21)	p-value
Anthropometric data			
Gender (female/male) ^a	16/5	18/3	0.46
Age (years) ^b	38 (8.1)	35.4 (8.5)	0.26
BMI (kg.m ⁻²) ^b	24.1 (3.5)	25.3 (3.2)	0.23
Medication			
Budesonide dosage (µg.d ⁻¹) ^b	724.0 (449.0)	761.0 (472.0)	0.86
Long-acting β ₂ agonists, µg.day ⁻¹	28.0 (22.3)	28.5 (21.2)	0.94
Onset of asthma in childhood ^a , n (%)	17 (83)	18 (87)	0.67
IgE, IU.mL ^{-1b} ; median (25 th -75 th)	442.0 (165-1343)	446.5 (74-1677)	0.80
Exacerbations in the last 12 months ^b ; n° events/patients	1.6	1.1	0.57
Pulmonary function			
FEV ₁ (L) ^b ;	2.2 (0.53)	2.2 (0.61)	0.77
(% predicted) ^b ;	80.0 (17.0)	79.1(22.0)	0.47
FEV ₁ /FVC;	71.5 (10.5)	72.0 (11.0)	0.91

Legend: Data are presented as means ± standard deviations (SDs) unless otherwise stated. CVF, forced vital capacity; FEV₁, forced expired volume in the first second; IgE, immunoglobulin E; kg.m⁻², kilograms per meter square; µg, micrograms; 25th-75th: percentile 25% -75%.

^a Fisher's exact test.

^b Unpaired t-test

Table 2. Comparison of asthma symptoms, HRQoL, aerobic capacity, pulmonary function and FeNO within the group and between groups.

	SWG (n=21)			WSG (n=21)			Between groups	
	Baseline	After training	within-group difference	Baseline	After training	within-group difference	Mean difference of mean change	p-value
Asthma symptom-free days	16.2 (9.3)	19.8 (9.2)	3.6 (7.52) ^b	13.3 (6.1)	22.1 (7.3)	8.8 (7.48) ^a	5.2 (10.0) ^c	0.02
HRQoL	57.1 (15.0)	38.7 (12.5)	-18.4 (14.30) ^a	59.0 (20.5)	35.5 (14.5)	-23.5 (9.84) ^a	-5.1 (21.2)	0.18
Aerobic Capacity								
VO _{2max} (mLO ₂ .kg.min ⁻¹)	24.4 (5.4)	28.8 (5.2)	3.7 (3.00) ^a	25.6 (4.9)	28.5 (3.9)	2.9 (2.93) ^a	-0.8 (3.4)	0.36
% predicted	79.2 (16.2)	91.1 (14.3)	11.8 (9.51) ^a	83.2 (17.5)	92.5 (15.6)	9.2 (9.07) ^a	-2.3 (10.6)	0.36
FeNO	42.2 (17.0)	37.5 (19.6)	-4.7 (15.8)	49.1 (17.5)	38.9 (23.7)	-10.1 (13.5) ^a	-5.4 (20.1)	0.23
Pulmonary Function								
FEV ₁ (L) ^b	2.2 (0.5)	2.2 (0.6)	0.0 (0.3)	2.2 (0.6)	2.2 (0.6)	0.0 (0.3)	0.0 (0.4)	0.77
% predicted ^b	79.8 (17.0)	79.4 (18.4)	-0.4 (5.9)	79.1 (22.0)	81.2 (23.7)	2.0 (9.2)	2.5 (10.6)	0.30
FEV ₁ /CVF	71.5 (10.6)	69.5 (10.9)	-2.1 (5.7)	71.9 (11.0)	73.0 (10.7)	1.0 (5.4)	3.1 (7.4)	0.08

Legend: Data are presented as the mean and standard deviation (SD). FeNO = fractional exhaled nitric oxide; HRQoL = health-related quality of life; VO_{2max} = maximal oxygen consumption.

^a p<0.001, paired t-test (baseline vs after training).

^b p<0.05, paired t-test (baseline vs after training).

^c p<0.05, unpaired test (mean difference of mean change).