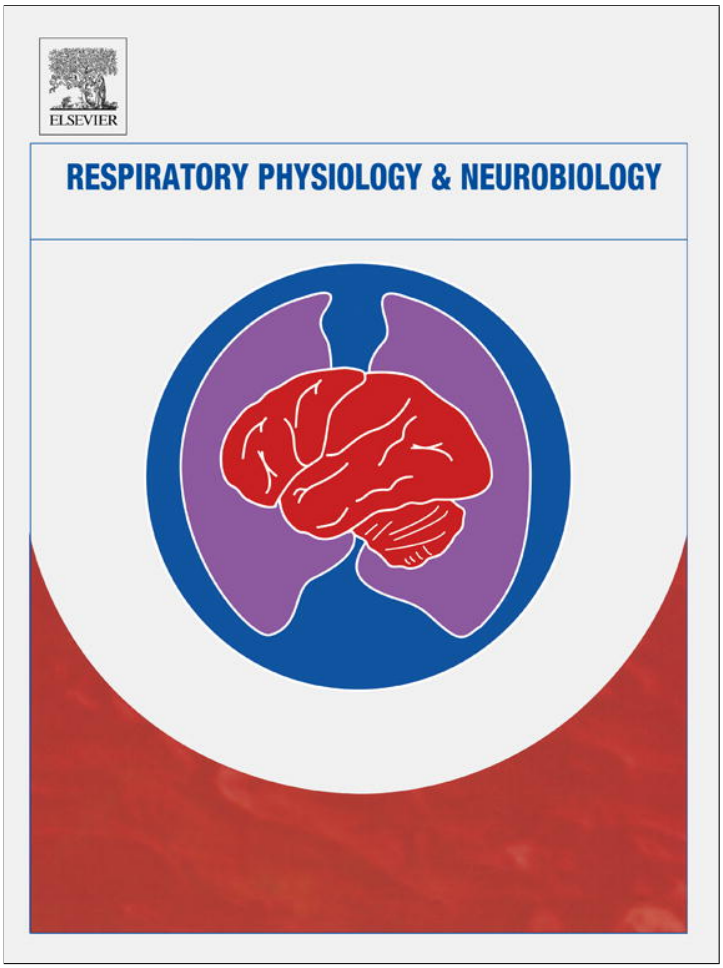

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Effects of aerobic exercise on chronic allergic airway inflammation and remodeling in guinea pigs

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ABSTRACT

We evaluated the effects of aerobic exercise (AE) on airway inflammation, exhaled nitric oxide levels (ENO), airway remodeling, and the expression of Th1, Th2 and regulatory cytokines in a guinea pig asthma model. Animals were divided into 4 groups: non-trained and non-sensitized (C), non-sensitized and AE (AE), ovalbumin-sensitized and non-trained (OVA), and OVA-sensitized and AE (OVA + AE). OVA inhalation was performed for 8 weeks, and AE was conducted for 6 weeks beginning in the 3rd week of OVA sensitization. Compared to the other groups, the OVA + AE group had a reduced density of eosinophils and lymphocytes, reduced expression of interleukin (IL)-4 and IL-13 and an increase in epithelium thickness ($p < 0.05$). AE did not modify airway remodeling or ENO in the sensitized groups ($p > 0.05$). Neither OVA nor AE resulted in differences in the expression of IL-2, IFN-γ, IL-10 or IL1-ra. Our results show that AE reduces the expression of Th2 cytokines and allergic airway inflammation and induces epithelium remodeling in sensitized guinea pigs.

1. Introduction

Asthma is defined as a chronic airway inflammatory disease (GINA, 2009) involving eosinophil infiltration, an event orchestrated by Th2 lymphocytes (Holgate, 2008). Classically, the Th2 pattern of T-cell activation and inflammation involves an augmentation in the production of pro-inflammatory cytokines such as interleukin (IL)-4, IL-5 and IL-13 (Feleszko et al., 2006). The increased Th2 profile in asthma is related to the release of different pro-inflammatory mediators; among them, nitric oxide has been well studied. Increased levels of ENO, which directly reflect the pulmonary production of NO, have already been demonstrated in asthmatic patients (Reid et al., 2003) and in animal models of asthma (Prado et al., 2005, 2006).

Aerobic exercise (AE) has been used as an important component of rehabilitation programs for asthmatic patients and results in reduced dyspnea (Ram et al., 2009), exercise-induced bronchospasm and corticosteroid consumption along with improved aerobic capacity and health-related quality of life (Fanelli et al., 2007; Mendes et al., 2010, 2011). Originally, the benefits of AE have been attributed to an increase in aerobic exercise capacity that raises the ventilatory threshold, thereby decreasing minute ventilation during exercise and the perception of breathlessness (Clark and Cochrane, 1999). However, over the last few years, experimental models of asthma have demonstrated that AE may reduce allergic airway inflammation and remodeling (Vieira et al., 2007; Silva et al., 2010).

Several studies have demonstrated that AE reduces allergic airway inflammation and remodeling and the Th2 response by decreasing NF-κB expression (Pastva et al., 2004; Vieira et al., 2008, 2011; Silva et al., 2010) and increasing the expression of the anti-inflammatory cytokine IL-10 (Vieira et al., 2007, 2008, 2011; Silva et al., 2010). However, these studies have two main criticisms: (i) AE was initiated at the same time as airway sensitization, which does not represent what occurs in asthmatic patients and (ii) mouse models of asthma using ovalbumin usually require peritoneal allergen sensitization to develop the Th2 allergic response, which provokes a systemic immune response with allergic inflammation predominantly in the lung vessels and parenchyma rather than in the airways, which occurs in the lungs of asthmatic individuals (Wenzel and Holgate, 2006).

Guinea pigs have been used in experimental models to evaluate allergic airway diseases such as asthma because they are

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rapidly sensitized to aerolized ovalbumin without the need for intraperitoneal injections. These results in an airway response to challenge similar to that of asthmatic phenotypes, including a robust bronchoconstriction that is lacking in other rodents (Bice et al., 2000; Wenzel and Holgate, 2006; Zosky and Sly, 2007). In addition, the pharmacological responses of guinea pig airways are very similar to those of humans in comparison to any other animal model (Ressmeyer et al., 2006).

Therefore, the aim of this study was to evaluate the effects of aerobic exercise on airway inflammation and remodeling in a model of chronic allergic airway inflammation in guinea pigs.

2. Methods

This study was approved by the review board for human and animal studies of the School of Medicine of the University of São Paulo (São Paulo, Brazil). All of the animals in the study received human care in compliance with the Guide for the Care and Use of Laboratory Animals (NHI publication 85-23, revised 1985).

2.1. Animals and study design

Thirty male Hartley guinea pigs (250–280 g) were divided into four groups: Control (non-exercised and non-sensitized; C group; $n = 7$); Aerobic Exercise (non-sensitized and aerobically exercised; AE group; $n = 7$); Ovalbumin (OVA-sensitized and non-exercised; OVA group; $n = 8$) and OVA + AE (sensitized and aerobically exercised; OVA + AE group; $n = 8$).

2.2. Sensitization protocol

Animals were placed in an acrylic box (30 cm × 15 cm × 20 cm) coupled to an ultrasonic nebulizer (Soniclear, SP, Brazil) and received seven sessions of OVA inhalation solution diluted in sterile saline (NaCl 0.9%). The Control and AE groups (non-sensitized) received the same number of inhalation sessions with sterile saline. All inhalation sessions lasted 15 min or until the animal displayed respiratory distress (sneezing, coryza, cough or retraction of the thoracic wall) as previously described. OVA inhalation was performed for 8 weeks (3×/week) with increasing concentrations (from 1 to 20 mg/ml) to avoid OVA tolerance (Tiberio et al., 1997).

2.3. Aerobic exercise training

Animals were initially adapted to the treadmill for 5 days (5 min, 8% inclination, 0.3 km/h). Next, a maximal exercise treadmill test was performed to establish the intensity of AE training (low intensity corresponded to 50% of the maximal speed). The maximal exercise treadmill test consisted of a 5-min warm-up (8% inclination, 0.3 km/h) followed by a gradual increase in treadmill speed (0.3 km/h every 3 min). The maximal exercise capacity was considered to be the maximal speed that animals were able to run after receiving 10 mechanical stimuli as previously described (Vieira et al., 2007). The speed of the AE was calculated as the average of the maximal speed achieved for each animal group in the maximal exercise treadmill test. AE was conducted on a treadmill (Imbramed®, RS, Brazil) for 6 weeks, beginning in the 3rd week of OVA inhalation; the sensitized animals continued to receive OVA inhalation during this period. Subsequently, the maximal treadmill exercise test was repeated to evaluate aerobic performance. The non-aerobically trained groups (Control and OVA) were not submitted to the AE protocol and were instead adapted to the treadmill for 3 days per week (8% inclination, 0.3 km/h, 5 min per session) until the last treadmill exercise test.

2.4. Measurement of exhaled nitric oxide (ENO)

Forty-eight hours after the last session of training and OVA or saline inhalation, all animals were anesthetized with sodium thiopental (170 mg/kg, i.p.), tracheostomized, and mechanically ventilated (60 breaths/min; 6 ml/kg of tidal volume) with a mechanical ventilator for small animals (Harvard, Rodent Ventilator Model 683, MA, USA) (Prado et al., 2005). Next, a sample of exhaled air was collected in a Mylar bag at the expiratory output valve for 5 min (Mehta et al., 1998; Ramos et al., 2010). ENO was measured by chemiluminescences using a rapidly responding analyzer (NOA 280; Sievers Instruments, CO, USA). The equipment was calibrated before each measurement with a certified 47 parts per billion (ppb) NO source (White Martins, SP, BRA). To avoid environmental contamination, a zero NO filter (Sievers Instruments) was attached to the inspiratory input. The results were expressed as parts of ENO per billion.

2.5. Histological and immunohistochemical analyses

After ENO collection, a 3-cm incision was made in the abdomen, and blood from the inferior cava vein was collected (5 ml). The animals were then exsanguinated by cutting the abdominal aorta. A positive end-expiratory pressure of 5 cmH_2O with 4% paraformaldehyde was applied through the cannulated trachea; the anterior chest wall was removed; and the lungs were removed *en bloc* and immediately immersed in 4% paraformaldehyde for 24 h. Next, sections were processed with paraffin embedding, and 5-μm slices were obtained and stained with hematoxylin and eosin for routine histological analysis and with Luna for eosinophil detection. Immunohistochemistry was also performed with anti-IL-4 (1:300), anti-IL-13 (1:150), anti-IL-2 (1:150), anti-IFN-γ (1:150), anti-IL-10 (1:50) and anti-IL-1ra (1:120) antibodies (Santa Cruz Biotechnology, Santa Cruz, CA, USA) using the biotin–streptavidin–peroxidase method (Vieira et al., 2007; Silva et al., 2010).

The peribronchial density of eosinophils, lymphocytes, and cells positive for IL-4, IL-13, IFN-γ, IL-2, IL-10 and IL-1ra was assessed by conventional morphometry using an ocular microscope with an integrating eyepiece with 100-point and 50 lines (point-counting technique) with a known area (10,000 μm^2) at 1000× magnification. Counting was performed in five non-cartilaginous airways per animal at 1000× magnification (Vieira et al., 2007). The results are expressed as cells per square millimeter.

The bronchoconstriction index (BI) was defined as the number of intercepts between the lines of the grid and the basal membrane divided by the square root of the number of points hitting the airway lumen ($BI = NI/\sqrt{L}$). NI = the number of intercepts that cross basal membrane, which is proportional to the perimeter of the airway; L = number of points hitting the airway lumen, which is proportional to the intraluminal area. BI was quantified in five non-cartilaginous airways per animal at 400× magnification (Sakae et al., 1994).

Airway smooth muscle area, airway epithelium thickness and edema were defined as the number of point hitting, respectively, in smooth muscle and epithelial cells and peribronchial edema. This value was divided by the number of intercepts that cross the basal membrane, which is proportional to the perimeter of the airway (Sakae et al., 1994; Vieira et al., 2007). Measurements were performed in five airways per animal at 1000× magnification.

Table 1
Exercise performance and immunoglobulin levels in studied groups.

Groups	Aerobic Treadmill Test (min)		Immunoglobulins (log)	
	Initial test	Final test	IgE	IgG1
C	18.1 ± 1.3	23.3 ± 1.7	0	0
AE	22.0 ± 2.1	38.5 ± 5.0*	0	0
OVA	14.7 ± 3.4	21.2 ± 3.2	2.9 ± 1.7**	5.7 ± 2.9**
OVA + AE	20.4 ± 2.0	40.5 ± 3.8*	2.7 ± 2.2**	4.8 ± 3.7**

Data are presented as mean ± SD. C = control group; AE = aerobic training group; OVA = sensitized and non-trained group; OVA + AE = sensitized and trained group.
* $p < 0.001$ as compared with initial test.
** $p < 0.001$ as compared with other groups.

2.6. Passive cutaneous anaphylaxis (PCA) for OVA-specific IgE and IgG_1

After blood collection from the cava vein, the samples were immediately centrifuged for 15 min (5 °C; 1000 rpm). Serum samples were stored at −70 °C until the assay was performed.

A PCA reaction was used to detect and estimate the levels of anaphylactic IgE and IgG1 OVA-specific antibodies as previously described (Ovary, 1964; Mota and Perini, 1970). Briefly, the back of a naïve guinea pig was shaved, and 0.1 ml of different serum dilutions was injected intradermally. Thirty naïve guinea pigs were used to evaluate the PCA, and the serum from each animal was included in the study ($n = 30$). After a long latent period of 48 h for IgE or a short period of 24 h for IgG1, the animals were challenged intravenously (i.v.) with 1 ml of a 0.5% solution of Evans blue in saline (0.9% NaCl) containing 1 mg of antigen (ovalbumin). The animals were euthanized 30 min after injection of the antigen, and the diameters of the blue spots on the inner surface of the flayed skin were measured. To detect the IgG1-type antibody, the serum was heated for 3 h at 56 °C to inactivate IgE activity; the heated serum was injected for PCA after a short latency period. The PCA titers were defined as the highest dilutions that gave an intradermal allergic reaction larger than 5 mm in diameter in triplicate tests (Ovary, 1964; Mota and Perini, 1970).

2.7. Statistical analysis

One-way analysis of variance (ANOVA) followed by a Student–Newman–Keuls post hoc test (parametric data) or ANOVA on ranks followed by Dunn's post hoc test (non-parametric data) were used to compare the different parameters between groups. The values were expressed as the mean ± SD for parametric data and as the median (variance) for non-parametric data. The level of significance was set at $p < 0.05$.

3. Results

3.1. Physical exercise capacity and PCA for OVA-specific IgE and IgG_1

Table 1 shows the maximal exercise capacity obtained in initial and final tests for each group before and after the AE protocol. Only animals from the trained groups (AE and OVA + AE groups) exhibited a significant increase in exercise capacity when compared with the animals in the non-trained groups (C and OVA) ($p < 0.001$; Table 1). The OVA and OVA + AE groups had increases in the OVA-specific IgE and IgG1 titers compared to the non-sensitized groups ($p < 0.001$; Table 1). However, AE did not have any effect on the OVA-specific IgE or IgG1 titers ($p > 0.05$).

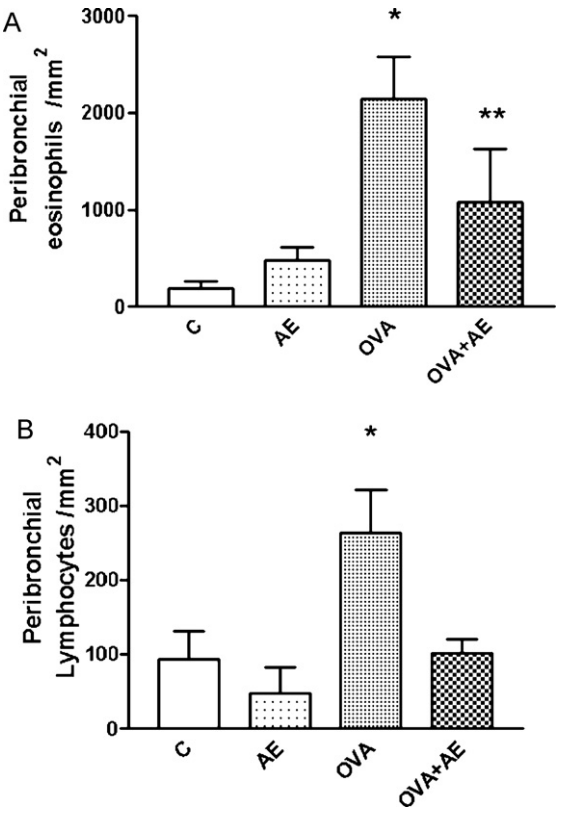

Fig. 1. Peribronchial counting of eosinophils (A) and lymphocytes (B). *$p < 0.001$ when compared with C, AE and OVA + AE and **$p < 0.01$ when compared with C and AE.

3.2. Lung tissue inflammation

OVA sensitization increased the density of eosinophil (Fig. 1A) and lymphocyte (Fig. 1B) migration to the peribronchial compartment compared to the non-sensitized groups (C and AE groups; $p < 0.001$). Importantly, AE training in the sensitized animals (OVA + AE group) resulted in a very significant decrease in the density of peribronchial eosinophils and lymphocytes ($p < 0.001$).

3.3. Expression of Th2 and Th1 Cytokines

The peribronchial density of cells positive for Th2 cytokines (IL-4 and IL-13) was increased in the OVA group compared to the non-sensitized groups ($p < 0.05$). AE training in the sensitized animals (OVA + AE group) resulted in a decrease in IL-13 (Fig. 2A) and IL-4 (Fig. 2B) compared to the OVA group. The expression of Th1 (IL-2 and IFN-γ) (Fig. 3A and B, respectively) and regulatory cytokines (IL-10 and IL-1ra) (Fig. 4A and B, respectively) remained unchanged by either OVA exposure or by exercise training; no differences were observed between the groups.

3.4. Exhaled nitric oxide (ENO)

Chronic OVA exposure increased the ENO levels compared to those in the non-sensitized groups ($p < 0.05$; Fig. 4C). However, AE did not change the ENO levels in either the sensitized or non-sensitized group ($p > 0.05$).

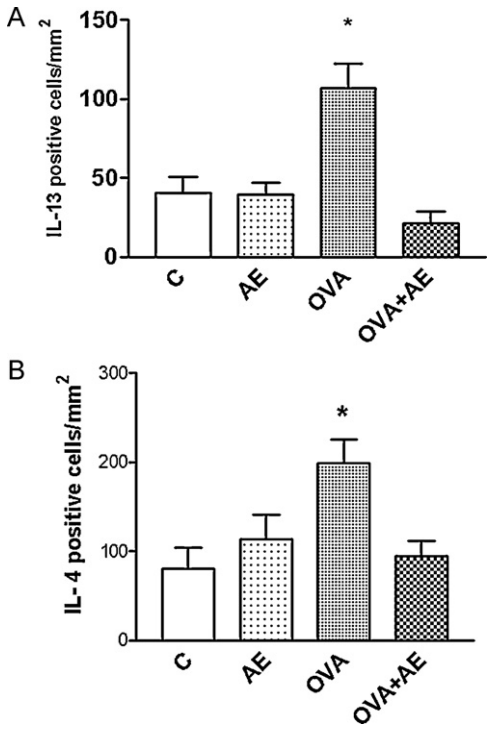

Fig. 2. Expression of IL-13 (A) and IL-4 (B) by the inflammatory cells. *$p < 0.001$ when compared with C, AE and OVA + AE.

3.5. Peribronchial edema, epithelium thickness, bronchoconstriction index and airway smooth muscle area

The animals exposed to OVA had higher values of peribronchial edema compared to the saline-exposed animals ($p < 0.01$). AE training in the animals exposed to OVA resulted in a reduced edema index at the same level as the non-sensitized groups (C and AE) (Fig. 5A). OVA sensitization also induced an increase in airway epithelium thickness (Fig. 5B), the bronchoconstriction index (Fig. 5C) and the smooth muscle area of the airway (Fig. 5D) ($p < 0.05$). AE training did not reduce the OVA-induced increase in the bronchoconstriction index (Fig. 5B; $p > 0.05$) or the airway smooth muscle thickness (Fig. 5D; $p > 0.05$). Interestingly, AE training in the sensitized animals (OVA + AE group) induced an increase in epithelium thickness compared to the values observed in the OVA group (Fig. 5B).

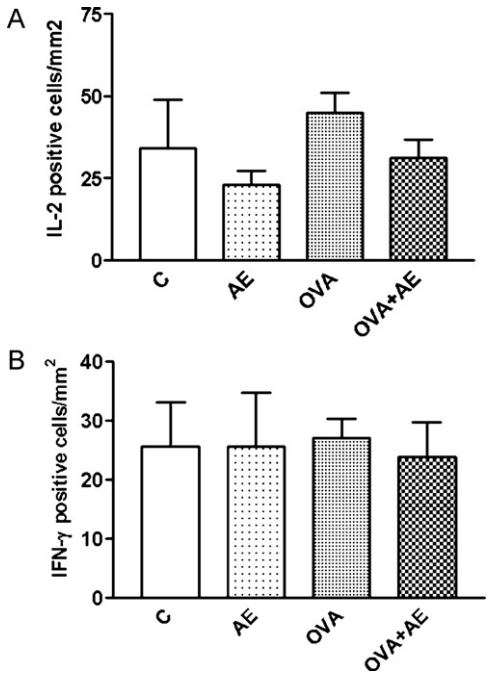

Fig. 3. Expression of IL-2 (A) and IFN-γ (B) by the inflammatory cells.

4. Discussion

In the present study, we showed that aerobic exercise (AE) training inhibited OVA-induced eosinophil and lymphocyte infiltration in airway walls as well as the expression of Th2 cytokines (IL-4 and IL-13) by inflammatory cells. In addition, AE reduced the amount of edema in the peribronchial area in OVA-sensitized animals. In contrast, AE in OVA-sensitized animals did not have any effect on the thickness of airway smooth muscle, the bronchoconstriction index or on the levels of exhaled nitric oxide (ENO). In addition, neither OVA sensitization nor AE had any effect on the expression of Th1 cytokines (IL-2 and IFN-γ).

Many benefits of AE for asthmatics have been described (Neder et al., 1999; Fanelli et al., 2007; Mendes et al., 2010); however, the physiopathological basis for such benefits remains poorly understood. Traditionally, the effect of AE on asthmatic patients has been attributed to a decrease in the ventilatory threshold (Satta, 2000; Ram et al., 2009); however, recent studies in murine models of asthma have suggested that AE might have a possible anti-inflammatory effect on chronic allergy airway inflammation (Pastva et al., 2004; Vieira et al., 2007, 2011; Silva et al., 2010).

Our group and others have shown some effects of AE on chronic allergic lung inflammation (Pastva et al., 2004; Vieira et al., 2007, 2008, 2011; Silva et al., 2010). However, many criticisms have been raised concerning the mouse model of asthma involving the use of ovalbumin. Wenzel and Holgate (2006) suggest that mouse models of asthma provide insights into immunologic processes but have shortcomings that continue to limit the understanding and treatment of human asthma. Several reasons are given as limitations: (i) mouse models of asthma require artificial intra-peritoneal allergen sensitization and adjunctive stimulation and provoke a systematic rather than a pulmonary allergic sensitization, which can even extend to include cardiovascular effects (Bice et al., 2000); (ii) the site of inflammation is mainly located in the parenchyma and the lung vascular vessels instead of the airways as occurs in human asthma (Wenzel and Holgate, 2006); and (iii) mice have lower levels of eosinophils in the airways following antigen challenge compared to guinea pigs and humans with asthma (Korsgren et al., 1997).

Our results showed that sensitized guinea pigs submitted to AE training had a reduction in eosinophil migration as well as in the migration of lymphocytes to the airways, which reinforced previous studies showing that AE reduces eosinophilic inflammation in mouse models of asthma (Pastva et al., 2004; Vieira et al., 2007). However, the reduction in lymphocyte migration to the airways following AE was previously unknown and is interesting because lymphocytes orchestrate eosinophilic migration. To better understand the effect of AE on reducing eosinophilic migration, we quantified the expression of Th2 cytokines. The results show that AE reversed the OVA-induced expression of IL-4 and IL-13, suggesting an important effect of AE on the pro-inflammatory cytokines involved in allergic airway inflammation. Despite the fact that AE has been shown to reduce IL-4 expression in mouse studies (Pastva et al., 2004; Vieira et al., 2007, 2008, 2011), this is the first study in guinea pigs to show that AE can also reduce the expression of IL-13. IL-13 is an important interleukin in the pathophysiology of asthma that modulates eosinophilic inflammation and mucus hypersecretion (Zhu et al., 1999). In addition, a

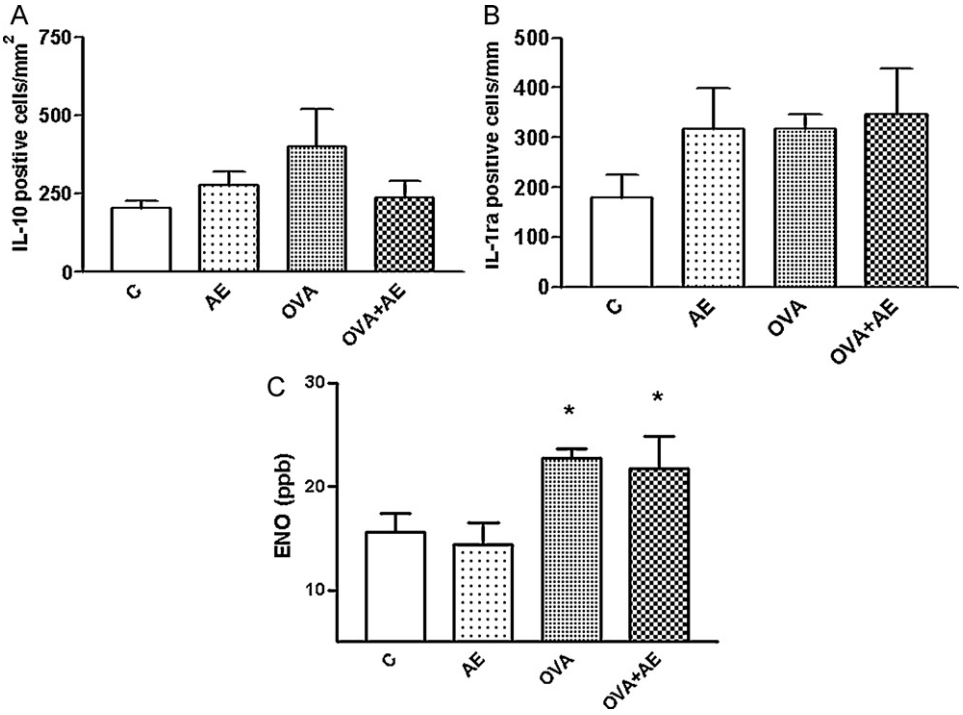

Fig. 4. Expression of IL-10 (A), IL-1ra (B) by the inflammatory cells and ENO levels (C). $^{*}p < 0.001$ when compared with C and AE groups; ppb: parts per billion.

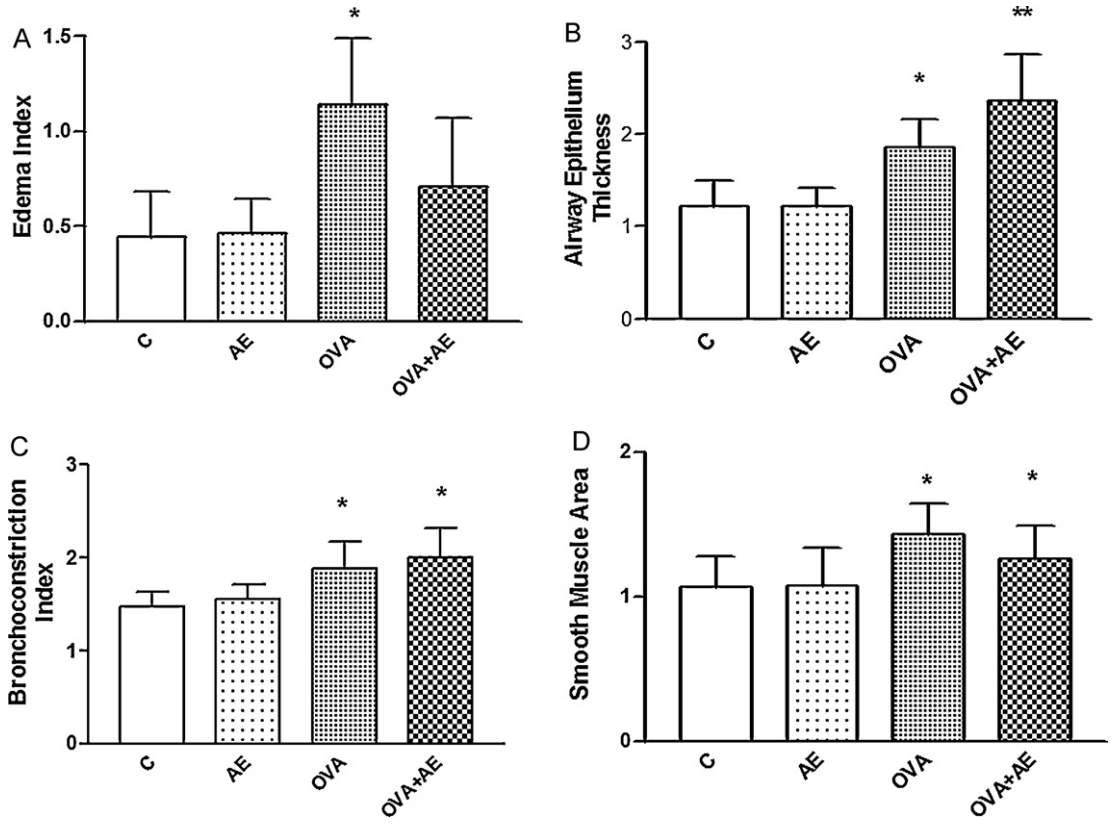

Fig. 5. Edema index (A), airway epithelium thickness (B), bronchoconstriction index (C) and airway smooth muscle area (D). $^{**}p < 0.05$ when compared with all other groups. $^{*}p < 0.01$ when compared with C and AE.

study by Willis-Karp et al. demonstrated that these pro-asthmatic effects of IL-13 are independent of IgE production (Wills-Karp et al., 1998). Interestingly, in our study, AE reduced eosinophilic inflammation but not OVA-induced IgE levels, suggesting that the anti-inflammatory effects of AE in a guinea pig model of asthma could be modulated by other factors not involving IgE production.

We quantified these mediators based on our knowledge of previous findings showing that AE improves the immunologic response by increasing levels of Th1 cytokines (Ray and Cohn, 2000) or the anti-inflammatory cytokine IL-10 (Nakagome et al., 2005). However, our results have shown that AE did not modify the expression of either Th1 cytokines (IL-2 and IFN-γ) or IL-10. Altogether, our results may suggest that AE acts directly on Th2 cytokine expression; however, the precise mechanism for such an effect needs to be evaluated in the near future.

Levels of exhaled nitric oxide (ENO) have been considered to be a marker of airway inflammation in asthmatic patients and are increased in asthmatic patients (Prieto et al., 2002). Suman and Beck (2002) suggested that the inhibition of NO synthesis slightly attenuates exercise-induced bronchoconstriction. Although we showed that OVA sensitization increased ENO to levels similar to those observed in another OVA-induced asthma model in guinea pigs (Prado et al., 2005), this increase was not reduced by AE, which suggests that the effect of AE was not mediated by NO in our guinea pig model of asthma.

Airway remodeling is an important feature of the asthmatic airway and seems to be a consequence of non-resolved inflammation as well as an imbalance in the healing and repair process (Irvin and Wenzel, 1995). Airway remodeling is characterized by epithelium desquamation, the increased deposition of extra-cellular matrix proteins on the airway wall and airway smooth muscle hypertrophy and hyperplasia (Larché et al., 2003). In our animal model, OVA exposure induced an increase in airway edema and bronchoconstriction as well as in the epithelium and smooth muscle. Although AE reduced airway edema, AE had no effect on airway smooth muscle or on bronchoconstriction. One limitation of our study is that we did not evaluate central (cartilaginous) airways that play an important role in the pulmonary mechanical changes secondary to antigen challenge in asthmatic patients and murine animal model of asthma. It is possible that the absence of reduction on airway smooth muscle and bronchoconstriction induced by exercise training may be due the fact that we have evaluated only peripheral and not central airways. In contrast, aerobic training induced a thickening of the airway epithelium. The effect on the airway epithelium observed in our study was previously reported by Chimenti et al. (2007), who demonstrated that aerobic training increases apoptosis and the proliferation rate of the airway epithelium independent of any previous inflammation.

Our results have also shown that AE did not reduce OVA-induced airway remodeling in our guinea pig model of asthma, contrary to other mouse studies from our group and others demonstrating the beneficial effects of AE on airway remodeling (Pastva et al., 2004; Vieira et al., 2007; Silva et al., 2010). It has been shown that the airway smooth muscle of guinea pigs most resembles that of humans because the airway smooth muscle has the following features: (i) it has similar mechanisms of contractile and relaxant agonists with similar potency and efficacy (Persson et al., 1997; Pack et al., 1984); (ii) it initiates reflex bronchospasm (Canning, 2006); and (iii) it is promptly sensitized to aerolized inhaled antigen and involves dramatic eosinophil and lymphocyte migration. In contrast to results from our own and other groups obtained using mouse models of asthma (Pastva et al., 2004; Vieira et al., 2007, 2011; Silva et al., 2010), our results may suggest that AE did not reverse OVA-induced airway remodeling. However, the discrepancies between the effects of AE in these animal models of asthma highlight the urgent need for human studies that investigate the effects of AE on airway remodeling in asthmatic individuals.

In conclusion, our study suggests that aerobic exercise decreases chronic allergic airway inflammation in guinea pigs by decreasing eosinophil and lymphocyte infiltration as well as the expression of Th2 cytokines but fails to reduce airway remodeling in this specific animal model of asthma.

Acknowledgements

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