Aerobic conditioning and allergic pulmonary inflammation in mice. II. Effects on lung vascular and parenchymal inflammation and remodeling

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EXPERIMENTAL MODELS OF ALLERGIC asthma are characterized by the predominance of eosinophils, Th2 lymphocytes, increased secretion of Th2 cytokines, and also by structural changes known as lung remodeling (61, 66). These alterations are present in large and small airways, in the lung parenchyma, and also in the pulmonary arteries (30, 50, 52, 56, 54). Peripheral lung tissue inflammation and remodeling has also been associated with changes in tissue mechanics and with an increased response to bronchoconstrictor stimuli in experimental models of chronic allergic lung inflammation (66, 27). Although large and small airways and distal parenchyma inflammation and remodeling are well-established alterations in asthmatic patients, only few human studies have reported inflammatory and structural changes in pulmonary and bronchial arteries in patients that died of asthma (48, 16). Additionally, in asthmatic patients, small artery and lung parenchyma inflammation and remodeling have been related to asthma severity (4, 12, 58, 59).

Aerobic training has been recommended as an effective adjuvant treatment in the management of asthmatic patients (3, 6). The performance of aerobic training in asthmatic patients triggers several beneficial effects such as the improvement in physical fitness and ventilatory capacity and a decrease in asthma-related symptoms, exercise-induced bronchospasm, and daily use of inhaled steroids (7, 13, 36, 46). Aerobic training has been shown to modulate the immune response in healthy individuals; however, its effect depends on training intensity (42). In general, moderate training intensity improves the immune system, observed by the increased neutrophil and macrophage phagocytosis capacity and a reduction in reactive oxygen species production, whereas high-intensity exercise leads to opposite effects (8, 26, 65, 68). Aerobic exercise also has an important role in angiogenesis and reducing the vascular oxidative and remodeling process induced by cardiovascular disorders (5, 23, 64).

In previous studies, our and other groups have observed that low- and moderate-intensity aerobic exercise specifically decreases airway eosinophilic inflammation and remodeling (40, 41, 61). Recently, we demonstrated that low- and moderate-intensity aerobic training decreases airway inflammation and remodeling in an experimental model of chronic allergic lung inflammation in mice and that these effects are not mediated by interleukin (IL)-10 expression (61). Nuclear transcription factor-κB (NF-κB), a transcription factor that regulates the development of adaptive immunity in asthma, is correlated with increased Th2 cytokine expression and eosinophilic inflammation (25). Monocyte chemotactic protein 1 (MCP-1) is a chemokine that plays an important role in asthma, in the activation of the inflammatory cascade, bronchial hyperresponsiveness, and airway remodeling (47). However, the
effects of different intensities of aerobic exercise on the pulmonary NF-κB and MCP-1 expression are poorly understood. Insulin-like growth factor-I (IGF-I) also presents an increased pulmonary expression in experimental models of allergic lung inflammation, and its effects are linked with airway inflammation and remodeling, but the effects of aerobic exercise on these models remain unknown (33, 62).

Although few studies have investigated the effects of low- and moderate-intensity aerobic exercise on allergic immune responses, particularly on vascular and parenchymal inflammation, only Pastva et al. (40, 41) evaluated these pulmonary compartments. Therefore, this study evaluated the hypothesis that low and moderate aerobic exercise could decrease perivascular and parenchymal inflammation and vascular tissue remodeling in a mouse model of chronic allergic lung inflammation (61, 62). In the present study, we evaluated the vascular and parenchymal inflammation and remodeling in the same experimental animals used to explore airway changes (61, 62).

MATERIALS AND METHODS

This study was approved by the review board for human and animal studies of the School of Medicine at the University of Sao Paulo, protocol number 503/05. All animals in the study received humane care in compliance with the Guide for the Care and Use of Laboratory Animals (National Institutes of Health publication 85-23, revised 1985).

Animals and experimental groups. Our experimental protocol was described previously (1). Briefly, 48 male Balb/c mice (20–25 g) were divided in the following six groups (n = 8 each): nonsensitized and nontrained group (control group); nonsensitized and low-intensity aerobic training (Low group); nonsensitized and moderate-intensity aerobic training (Mod group); ovalbumin (OVA)-sensitized and nontrained (OVA group); OVA-sensitized and low-intensity aerobic training (OVA + Low group); and OVA-sensitized and moderate-intensity aerobic training (OVA + Mod group).

OVA sensitization. Balb/c mice were sensitized by an intraperitoneal injection of OVA (20 μg/mouse) adsorbed with aluminum hydroxide on days 0, 14, 28, and 42 or with saline solution, used as control in nonsensitized mice. After the first intraperitoneal OVA or saline injection (21 days), the mice were challenged with aerolized OVA (1%) or with saline solution three times a week until the 50th day (61, 62). The OVA aerosol was always performed between 1700 and 1800. Figure 1 shows the time line of the experimental protocol.

Aerobic training and exercise test. Animals were initially adapted to the treadmill for 3 days (15 min, 25% inclination, 0.2 km/h). After that, a maximal exercise capacity test was performed with a 5-min warm-up (25% inclination, 0.2 km/h) followed by an increase in treadmill speed (0.1 km/h every 2.5 min) until animal exhaustion, i.e., until they were not able to run even after 10 gentle mechanical stimuli. The test was repeated after 30 days (before death). Maximal aerobic capacity (100%) was established as the maximal speed reached by each animal. Mice were trained with low- or moderate-intensity exercise (respectively, 50 or 75% of maximal speed), 60 min/day, 5 days/wk during 4 wk. Aerobic conditioning started on the 1st day after OVA or saline inhalation (61). The exercise bout was performed always between 1000 and 1200 and OVA exposure was always performed between 1700 and 1800.

Anesthesia and death of animals. After the last day of inhalation (72 h), animals were anesthetized by an intramuscular injection of ketamine (50 mg/kg) and xylazine (40 mg/kg), tracheostomized, cannulated, and killed by exsanguination.

Lung histology, immunohistochemistry, and morphometry. All eight animals for each group were analyzed through histological and immunohistochemical technique. Lungs were fixed in formalin and embedded in paraffin. Thick (5 μm) sections were stained with hematoxylin and eosin for lung structure analysis, with Luna staining for detecting eosinophils (33, 61, 62), with Picrosirius for collagen fibers (27, 61, 62), and with Weigert’s Resorcin-Fuchsin with oxidation for elastic fibers (61, 62).

Immunohistochemistry was performed with the following antibodies: anti-IL-4, anti-IL-5, anti-interferon-γ (IFN-γ), anti-IL-2, anti-MCP-1, anti-NF-κB p65, anti-IGF-I (Santa Cruz), and anti-IL-10 (R&D Systems) through the biotin-streptavidin peroxidase method. With a 50-line and 100-point grid connected to the ocular of the microscope, the perivascular and parenchymal density of eosinophils, mononuclear cells, and IGF-I-positive cells and inflammatory IL-4, IL-5, IFN-γ, IL-2, MCP-1, NF-κB p65, and IL-10-positive cells were assessed using a point-counting technique (27, 61, 62). Counting was performed in 5 pulmonary arteries (in peribronchiolar space) and 15 alveolar parenchyma fields (area of alveolar septa, excluding areas of pulmonary capilar) in each animal at ×1,000 magnification, for a blinded investigator. The results were expressed as Cells per square millimeter (27, 61, 62). The perivascular edema index was established as the number of points hitting an edema area divided by the number of intercepts (lines of ocular grid) that crossed the arterial adventitia (53). The arterial muscle thickness index was assessed as the number of points hitting muscle areas divided by the number of intercepts that crossed the external limit of the muscular wall. The volume proportion of collagen and elastic fibers in the pulmonary artery was determined by dividing the number of points hitting the collagen or elastin by the number of points hitting the arterial area. In the alveolar tissue, the volume proportion of collagen and elastic fibers in the pulmonary artery was determined by multiplying the number of points hitting collagen or elastin by the total number of points hitting the alveolar septa. Results of volume proportion of collagen and elastin in the parenchyma and pulmonary artery were expressed as a percentage (27, 61, 62).

Statistical analysis. Parametric and nonparametric data are expressed as means ± SD or median ± 95% confidence interval, respectively. Comparisons between groups were carried out by two-way ANOVA followed by the Student-Newman-Keul’s post hoc test (parametric data) or by one-way analysis of variance on ranks followed by Dunn’s post hoc test (nonparametric data); the significance level was adjusted to 5% (P < 0.05).

RESULTS

Physical exercise capacity. Table 1 shows the initial time, final time, and the final less initial time reached in the physical test in all groups. All trained groups, regardless of the exercise intensity, presented an increase in physical exercise capacity when compared with the nontrained groups (control and OVA groups) (P < 0.001) and no difference was found among the trained groups (P > 0.05).

Perivascular and parenchyma inflammation. Figure 2, A–D, shows the perivascular and parenchyma density of eosinophils and mononuclear cells. Nonsensitized animals submitted to
In the perivascular edema when compared with the control group, and moderate-intensity exercise training did not present changes in the density of mononuclear cells. Additionally, low- and moderate-intensity exercise training led to an increased density of perivascular eosinophils when compared with all groups (P < 0.001). The OVA group also presented an increased perivascular density of IL-10 when compared with control, Low, and Mod groups (P < 0.001). The OVA group did not present changes in the perivascular density of IL-4, IL-5, IL-2, IFN-γ, MCP-1, IGF-I, IL-10, and NF-κB p65. Low and Mod groups did not present changes in the perivascular density of IL-4, IL-5, MCP-1, IGF-I, and NF-κB p65 positive cells when compared with all groups (P < 0.001). The OVA group also presented an increased perivascular density of IL-10 when compared with control, Low, and Mod groups (P < 0.001). The OVA group did not present changes in the perivascular density of IL-2 and IFN-γ (P < 0.05). OVA + Low and OVA + Mod groups presented a decreased perivascular density of IL-4, IL-5, MCP-1, IGF-I, and NF-κB p65 when compared with the OVA group (P < 0.001). OVA + Low and OVA + Mod groups did not present changes in the perivascular density of IL-2 and IFN-γ (P < 0.05). Figure 4, A–C, shows the representative photomicrographs of positive inflammatory cells to MCP-1 in control, OVA, and

### Table 1. Time in minutes reached in the initial, final, and difference between the final and initial physical tests in all experimental groups

<table>
<thead>
<tr>
<th>Group</th>
<th>Initial Test</th>
<th>Final Test</th>
<th>Final - Initial Test</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>33.3±2.7</td>
<td>35.2±3.8</td>
<td>1.9±4.24</td>
</tr>
<tr>
<td>Low</td>
<td>33.3±3.7</td>
<td>45.1±4.4</td>
<td>13.1±5.0*</td>
</tr>
<tr>
<td>Mod</td>
<td>35.2±5.7</td>
<td>49.6±7.1</td>
<td>12.7±4.8*</td>
</tr>
<tr>
<td>OVA</td>
<td>33.0±2.5</td>
<td>34.9±2.5</td>
<td>1.9±3.6</td>
</tr>
<tr>
<td>OVA + Low</td>
<td>36.1±4.8</td>
<td>47.6±5.6</td>
<td>11.3±3.0*</td>
</tr>
<tr>
<td>OVA + Mod</td>
<td>45.8±2.3</td>
<td>59.2±2.8</td>
<td>13.9±2.5*</td>
</tr>
</tbody>
</table>

Values are means ± SD; n = 8 mice/group. OVA, ovalbumin. *P < 0.001 compared with nontrained groups (control and OVA groups).

Low- or moderate-intensity training (Low and Mod groups, respectively) did not present changes in the perivascular density of eosinophils and mononuclear cells when compared with the control group (nonsensitized and nontrained). Low- and moderate (Mod)-intensity aerobic training led to an increased density of perivascular eosinophils when compared with all groups (P < 0.001) (OVA -5.58 ± 1.33 vs. control -3.73 ± 1.0 vs. Low -3.81 ± 0.8 vs. Mod -3.33 ± 1.44 vs. OVA + Low 2.82 ± 1.12 vs. OVA + Mod 3.77 ± 0.96). OVA + Low and OVA + Mod groups presented a decreased perivascular edema when compared with the OVA group (P < 0.001) (OVA -5.58 ± 1.33 vs. OVA + Low 2.82 ± 1.12 vs. OVA + Mod 3.77 ± 0.96).

**Perivascular expression of cytokines, chemokine, NF-κB p65, and IGF-I.** Figure 3, A–H, respectively shows the perivascular expression of positive inflammatory cells to IL-4, IL-5, IL-2, IFN-γ, MCP-1, IGF-I, IL-10, and NF-κB p65. Low and Mod groups did not present changes in the perivascular density on the expression of any investigated protein type by inflammatory cells. The OVA group presented increased perivascular density of IL-4, IL-5, MCP-1, IGF-I, and NF-κB p65 positive cells when compared with all groups (P < 0.001). OVA + Low and OVA + Mod groups did not present changes in the perivascular density of IL-4, IL-5, MCP-1, IGF-I, and NF-κB p65 when compared with the OVA group (P < 0.001). OVA + Low and OVA + Mod groups presented a decreased perivascular density of IL-10 when compared with control, Low, and Mod groups (P < 0.001). The OVA group did not present changes in the perivascular density of IL-2 and IFN-γ (P < 0.05). OVA + Low and OVA + Mod groups presented a decreased perivascular density of IL-4, IL-5, MCP-1, IGF-I, and NF-κB p65 when compared with the OVA group (P < 0.001). OVA + Low and OVA + Mod groups did not present changes in the perivascular density of IL-2 and IFN-γ (P < 0.05). Figure 4, A–C, shows the representative photomicrographs of positive inflammatory cells to MCP-1 in control, OVA, and

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**Fig. 2.** Box plots representing the perivascular density of eosinophils (A), mononuclear cells (B), and the parenchymal density of eosinophils (C) and mononuclear cells (D). Boxes show interquartile range, whiskers show range, and horizontal lines represent median values. A and C: *P < 0.001 when compared with all groups. B: *P < 0.01 when compared with control and low (Low)- and moderate (Mod)-intensity aerobic training groups. D: *P < 0.01 when compared with the control group.
OVA + Low groups at ×400 magnification. Figure 4D shows the representative photomicrographs of positive inflammatory cells to MCP-1 in OVA at ×1,000 magnification.

**Parenchymal expression of cytokines, chemokine, NF-κB p65, and IGF-I.** Figure 5, A–H, shows the parenchymal expression of positive inflammatory cells to IL-4, IL-5, IL-2, IFN-γ, MCP-1, IGF-I, IL-10, and NF-κB p65. Neither OVA-induced allergic inflammation nor exercise training changed the expression of IFN-γ and IGF-I in the parenchyma (P > 0.05). Low and Mod groups did not present changes in the parenchymal density of all outcomes (P > 0.05). The OVA group presented increased parenchymal density of IL-4, IL-5, MCP-1, and NF-κB p65 when compared with all groups (P < 0.001). The OVA group also presented increased parenchymal density of IL-10 when compared with control, Low, and Mod groups (P < 0.001). OVA + Low and OVA + Mod groups also presented an increased parenchymal density of IL-2 when compared with all groups (P < 0.01). OVA + Low and OVA + Mod groups also presented an increased parenchymal density of IL-10 when compared with all groups (P < 0.01).
Vascular and parenchymal remodeling. Figure 6 shows the volume proportion of collagen and elastic fibers and the smooth muscle thickness in the pulmonary artery. Low and Mod groups (nonsensitized animals submitted to low- or moderate-intensity aerobic training) did not present changes either in vascular collagen and elastic fiber content or in the artery smooth muscle thickness when compared with the control group (nonsensitized and nontrained, Fig. 6, A–C). The OVA group presented an increased arterial volume proportion of collagen and elastic fibers and in the smooth muscle thickness when compared with the other groups (P < 0.01, Fig. 6, A–C). Sensitized animals submitted to low- or moderate-intensity aerobic training (OVA + Low and OVA + Mod groups) presented a decrease in vascular collagen and elastic contents and smooth muscle thickness when compared with the OVA group (P < 0.01, Fig. 6, A–C). Figure 7, A–D, shows the representative photomicrographs of collagen fibers in the pulmonary artery in control, OVA, OVA + Low, and OVA + Mod groups. No changes were found in the volume proportion of collagen and elastic fibers in the alveolar parenchyma. Neither aerobic training nor OVA exposure modified the volume proportion of collagen and elastic fibers in the alveolar parenchyma.

DISCUSSION

The present study shows that aerobic training at low or moderate intensity decreases OVA-induced perivascular edema and increases density of eosinophils and also of positive inflammatory cells to IL-4, IL-5, MCP-1, NF-κB p65, and IGF-I in the perivascular and in the alveolar parenchyma compartments. Aerobic training also reduced OVA-induced vascular remodeling evaluated by smooth muscle thickness and collagen and elastic fiber contents. Therefore, our data present evidence supporting the extensive benefits of aerobic training to decrease chronic allergic lung inflammation.

The beneficial effects of aerobic training for asthmatic patients have been recognized by the American Association of Cardiovascular and Pulmonary Rehabilitation and the British Thorax Society (3, 6). These effects have been mainly attributed to an improvement in the ventilatory capacity and physical fitness as well as a decrease in dyspnea, exercise-induced bronchospasm severity, and use of corticosteroids (7, 13, 36, 46). These clinical benefits have also suggested a possible anti-inflammatory effect of aerobic training on asthma. Only few studies have investigated the anti-inflammatory effects of aerobic training on asthma, using an allergic murine model (40, 41, 61). In accordance with these studies, the anti-inflammatory effects of aerobic exercise could be attributed to decreased levels of IL-4, IL-5, IgE and also an increase in the anti-inflammatory cytokine IL-10 (40, 41, 61). Although these studies verified the leukocytes infiltration in the airways, they did not evaluate the remodeling in the pulmonary vessels and parenchyma, and only Pastva et al. (40) evaluated the perivascular infiltration by leucocytes (4, 12, 16, 27, 30, 48, 50, 52, 54, 56, 58, 59, 61, 66). In the present study, we observed that eosinophilic inflammation in the perivascular and parenchymal compartment was inhibited by aerobic conditioning, similarly to what was observed in the eosinophilic inflammation in the airways (61).

In healthy subjects, aerobic conditioning increases the Th1 response (8, 26, 42, 65, 68); however, its effect on the Th2 response is poorly understood. Postulated immune mechanisms underlying allergic disease suggest that, in the general population, allergy should be less common in individuals with improved Th1 response, since T lymphocytes would respond to antigen-presenting cells tending toward a Th1 subtype. We
then hypothesized that anti-inflammatory effect due to aerobic training in chronic allergic airway inflammation could be mediated by improved Th1 response and consequent reduced Th2 response (8, 26, 32, 42, 65, 68). However, in our experimental animal model, the OVA-induced increase in the expression of Th2 cytokines (IL-4 and IL-5) was reduced by aerobic training, although the expression of Th1 cytokines (IL-2 and IFN-γ) remained unchanged, suggesting that the anti-inflammatory effects of aerobic training in a murine model of lung allergic inflammation may occur due to a direct effect on the Th2 response. These results are in agreement to what we found in the previous study evaluating the airways (61). However, other pathways could be involved as possible mechanisms of anti-inflammatory effects of aerobic training.

First, we evaluated the effects of aerobic training on the anti-inflammatory cytokine IL-10. Some studies present that the effects of aerobic training on the immune system are mediated by increased release of IL-10 (34, 43, 55). Some recognized sources of IL-10 release during aerobic training are activated skeletal muscle and lymphocytes, as part of the anti-inflammatory effects of aerobic training in cardiovascular disease and type 2 diabetes (34, 43, 55). IL-10 also presents anti-inflammatory effects in experimental models of chronic allergic lung inflammation (14, 35). Recently, we demonstrated...
that, in the airways, aerobic exercise decreased Th2 cytokine expression, effects that seem mediated partially by exercise-increased IL-10 expression (61). As observed in the airway response, the results of the present study show that aerobic exercise training in sensitized animals increases the expression of IL-10 by inflammatory cells also in perivascular and alveolar parenchyma, reinforcing a possible mechanism of the exercise-induced decrease in allergic inflammation.

Second, we investigated the expression of the chemokine MCP-1. Chemokines present an important role in the physiopathology of asthma, such as activation of the inflammatory cascade, bronchial hyperresponsiveness, and airway remodeling (2, 22, 45, 51). In accordance with current literature, our mouse model of allergic lung inflammation presented an increased expression of MCP-1 by inflammatory cells, both in the pulmonary arteries and lung parenchyma (Figs. 3E and 5E).

It is possible that peribronchial and perivascular compartments communicate during the recruitment of cells in the lung inflammation process, and it is known that blood-bone cells such as eosinophils and neutrophils need to cross the vascular endothelium for an eventual transmigration to the injured sites (16, 37, 38, 39). The effects of aerobic conditioning on the vascular response have been extensively investigated except in the lung tissue (1, 23, 57). Aerobic training seems to exert its anti-inflammatory effects on diseases such as metabolic syndrome and cardiovascular disorders by reducing the levels of MCP-1 (1, 57). Our results show that aerobic exercise at low or moderate intensities reduces OVA-induced expression of MCP-1 in perivascular and parenchymal compartments, suggesting its involvement as a mechanism in the reduction of cellular migration to the perivascular and lung parenchyma compartments in this animal model.

At last, we investigated the expression of NF-κB p65. NF-κB is a major transcription factor that plays an essential role in the development of innate and adaptive immunity, and it is considered a major mediator of many genetic diseases such as asthma (25). NF-κB is activated in asthmatic patients and in animal models, and its activation has been related to an exacerbatory response due to allergens, ozone, particulate matters, and viral infection exposure, suggesting that NF-κB activation mediates Th2 cytokine synthesis and lung eosinophilic inflammation (17, 18, 20, 24, 25, 44). The levels of NF-κB in response to aerobic training in asthmatic patients have not been previously evaluated. In nonasthmatic patients, some studies demonstrate that high intense and exhaustive aerobic training increases NF-κB activation, effects that seem mediated by increased oxidative stress (11, 15, 60). An experimental study by Pastva et al. (4) demonstrated that aerobic training decreases NF-κB expression in the airways of OVA-sensitized animals. Our results demonstrated that aerobic training performed at either low or moderate intensities was capable of reducing the expression of NF-κB by inflammatory cells in the lung perivascular and alveolar parenchyma compartments (Figs. 3H and 5H). Therefore, we hypothesize that the suppression of NF-κB and MCP-1 followed by aerobic training together with aerobic training-increased expression of IL-10 could help to explain the anti-inflammatory effects of aerobic training in our model of chronic allergic lung inflammation.

The pulmonary remodeling in the asthmatic patients achieves mainly the airways, but some evidence shows that pulmonary vessels (16, 48) and parenchyma are also affected (4, 58, 59). The increased deposition of extracellular matrix in pulmonary vessels and parenchyma in asthma presents a significant clinical implication and has an important correlation with asthma severity, including airflow limitation and bronchial hyperresponsiveness (4, 16, 21, 31, 48, 49, 58, 59). Although there are differences between human asthma and murine models of asthma, we are aware that animals do not develop asthma and that there are several limitations in animal studies. However, many of the growing advances in the asthma pathophysiology and treatment are based on animal models (27, 30, 50, 52, 54, 56, 61, 66). For this purpose, we evaluated in the present study the distribution of collagen and elastic fibers in pulmonary artery and parenchyma and also the arterial smooth muscle thickness. In our animal model, no changes in collagen and elastic fiber contents were found in the lung parenchyma in all groups.

Fig. 6. Box plots representing the vascular collagen (A), elastic (B), and smooth muscle thickness index (C). A–C: *P < 0.01 when compared with all groups.

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In conclusion, we demonstrated that the vascular and parenchymal inflammation and remodeling in our experimental model of chronic allergic lung inflammation was substantially inhibited by aerobic conditioning. These effects seem to be mediated by the reduction of Th2 response, which might be explained by the increase of IL-10 and decreases of NF-kB, MCP-1, and IGF-I expression.

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chemokines MCP-1 and IL-8 in subjects with the metabolic syndrome. 