Effects of exercise training on airway closure in asthmatics

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AIRWAY HYPERRESPONSIVENESS (AHR) is a cardinal feature of asthma, defined as an increase in the ease and degree of airway narrowing in response to external stimuli. AHR is associated with several clinical outcomes, such as increased decline in lung function (23, 16) and dyspnea perception (14, 21), and has been proposed as an additional variable to consider in optimizing the long-term management of asthma. The potential mechanisms underlying the phenomenon of AHR in asthmatics are still a matter of debate and include abnormalities in airway smooth muscle (ASM) contractility (6), airway inflammation, and remodeling (12). Deep inspirations (DI) have also been shown to modulate the degree of AHR (20, 24). In healthy subjects, substantial bronchoconstriction is induced by inhaled methacholine (Mch) when DIs are prohibited (9), because of the absence of the bronchoprotective and bronchodilatory beneficial effects of lung inflation. Avoidance of DI is, therefore, a sensitive bronchoprovocation challenge test to assess airway smooth muscle response to spasmogens.

The rationale of the current study lies in our previous findings (26): in 2005, we demonstrated that airway responsiveness to single-dose Mch challenge in the absence of deep inspirations was greatly attenuated in nonasthmatic habitual runners compared with sedentary runners. Since endurance training appeared to accentuate the airway resistance to spasmsogens, we decided to longitudinally explore whether a course of intensive exercise training would induce a condition of hypersensitivity in sedentary normal subjects. Our hypothesis was confirmed by the finding that a short course of training significantly reduced the airway response to Mch in the absence of deep inspirations in healthy subjects (27). A replicative study on asthmatics population was therefore strongly advocated (5).

A body of evidence suggests that exercise may positively influence AHR to various extents (9, 26, 29), suggesting a possible therapeutic role of exercise in asthmatic patients (5). The current prospective “proof of concept” study was designed to test the hypothesis that a short course of intensive physical training may reduce AHR in mild asthma. We therefore repeated in asthmatics the same protocol already used in our previous study in healthy subjects (27).

MATERIALS AND METHODS

Subjects. We recruited individuals attending the Pulmonary and the Allergy Outpatient Clinics of the Institute of Respiratory Diseases of the University of Palermo, Palermo, Italy and who had received the diagnosis of asthma by a pulmonologist, in accordance with the Global Initiative for Asthma (GINA) guidelines (35). All subjects were mild asthmatics and skin test positive to at least one aeroallergen. No subject was a former or current smoker or reported upper respiratory infections in the 4 wk preceding enrolment. All subjects had a sedentary lifestyle, with physical activity defined as modest (<2 h/wk in the previous 6 mo). Three subjects who were under inhaled corticosteroids and/or leukotriene receptor antagonists were asked to refrain from taking the medications for 3 wk before and throughout the study. All subjects were allowed to use rescue medication as needed (short-acting-agonists) except in the 12 h before each evaluation. In the days when tests were performed, exercise, as well as coffee or tea, was not allowed in the morning. The study was approved by the Local Ethics Committee, and all subjects gave written informed consent.

Study design. The protocol of the study has been previously described (27). At the pretraining evaluation (week 0), modified spirometry was first conducted followed by determination of airway responsiveness to Mch in the absence of DIs. The same protocol was repeated at week 5 (mid-training) and 10 (end of training), as well as 4 to 6 wk after the end of the training program (recovery). During the...
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recovery period, subjects were asked not to engage in any training activity. The five subjects that served as controls underwent the same tests at week 0 and 10.

Training program. Indoor rowing training consisted of two to three sessions per week for 10 wk (total 28 sessions), as previously described (27). Each session included a warm-up period for 20 min (running and stretching) and a specific training on rowing ergometer (Concept II, Morrisville, VT) for 40–70 min. To document power output, strokes, and mean maximal speed for each individual, a 1,000-m all-out rowing test was first performed after a 20-min warm-up. Based on the performance, watt per stroke, and strokes per minute recorded in the 1,000-m all-out test, a certified European rowing coach created personalized training programs. At week 0, 5, and 10, 1,000- and 2,000-m all-out rowing tests were performed to evaluate performance and reassess the individualized workload. The 10-wk training program included 20% of all training time at maximal power output, 10% of all training time at 75–90% of maximal power output, and 70% of all training time at 60–65% of maximal power output. All sessions were supervised by a certified training instructor and a pulmonologist.

Pretraining clinical evaluation. At the beginning of the study and before the training program began, each subject underwent clinical and functional evaluations that included conventional spirometry and conventional Mch bronchoprovocation (Biomedin; Padua, Italy). Measurements were made in accordance to the guidelines proposed by the American Thoracic Society/European Respiratory Society (ATS/ERS) Task Force (20). All subjects had mild-moderate AHR, except two individuals with severe degree of responsiveness under conventional bronchoprovocation tests [a 20% FEV1 decrease in forced expiratory volume in 1 s (PD20FEV1): 897 mcg, range: 43–1,248 mcg].

Assessment of airway responsiveness in the absence of DI. To evaluate airway responsiveness in the absence of DI, we employed a single-dose Mch bronchoprovocation procedure as previously described (27). At baseline, three acceptable, modified (see below) spirometric maneuvers were obtained. Subjects were then instructed to avoid DIs for 20 min and were observed for compliance during this period. Thereafter, subjects inhaled a single Mch dose with five tidal breaths and, after 3 min of no DIs, a single modified spirometry was repeated. This consisted of a slow expiratory maneuver from tidal volume to maximal expiration, immediately followed by maximal inspiration to calculate the inspiratory vital capacity (IVC), which would reflect changes in residual volume (RV), assuming that total lung capacity remains stable (13). Figure 1 describes the spirometric maneuver employed to calculate IVC. IVC was chosen as the primary outcome of the Mch provocation, because it offers the advantage of not being affected by a preceding deep inspiration, as FEV1 does. The usage of IVC does not eliminate our ability to also measure FEV1 and forced vital capacity since a maximal maneuver always follows the partial one. The Mch-induced effect on IVC is recorded as the percent difference between the post-Mch IVC and the best IVC from the three baseline, modified spirometric measurements.

The dose of Mch used in the pretraining bronchoprovocation was individualized as the inhaled dose of spasmogen attaining ≥15% reduction in IVC from baseline and was determined for each subject by a series of increasing single-dose Mch bronchoprovocations carried out earlier, in the absence of deep breaths. If the first dose was ineffective, the test was repeated with a higher dose and, if needed, with increasing doses. These single-dose Mch bronchoprovocations were repeated on the same day (≥2 h apart) if the preceding provocation reduced IVC by <5% from baseline or on the following day if IVC had dropped by >5%. The dose of Mch that was used for the single-dose challenge in the pretraining bronchoprovocation was used in all subsequent bronchoprovocations.

Statistical analysis. Data are reported as means ± SD. Different time points and experimental conditions were compared by ANOVA; the Bonferroni test was used for post hoc comparisons. Nonparametric tests were used for non-normally distributed variables. The statistical package we employed was StatView 5.0.1 (Abacus Concepts, Berkeley, CA). Statistical significance was accepted at P < 0.05.

RESULTS

We enrolled 15 mild asthmatics (male/female: 4/11; mean age ± SD: 24 ± 2.5 yr) with normal lung function (FEV1% predicted: 101 ± 7.1%; FEV1/VC: 0.87 ± 0.7) who were randomly divided into two groups in a 2:1 ratio; the first group underwent the training program (active group), whereas the second one served as control group. One subject from the active group abandoned the study immediately after screening for personal reasons. The demographic and lung function characteristics of the study subjects are reported in Table 1.

Training. On average, subjects attended 23.7 ± 3.9 training sessions, corresponding to 85% of total protocol. Mean power output during the 1,000-m test was 123 ± 63 W/stroke at week 0, 137 ± 53 W/stroke at 5 wk, and 148 ± 66 W/stroke at 10 wk of training (P = 0.02); similarly, mean power output in the 2,000-m test increased from 118 ± 52 to 131 ± 54 W/stroke.

Fig. 1. Single-dose methacholine bronchoprovocation protocol. Insert: modified spirometric maneuver that was used in the study. This consists of a slow expiration (A) immediately followed by a maximal inspiration (B). Inspiratory vital capacity (IVC) is the volume from the end of the partial expiratory maneuver to the end of the maximal inspiratory maneuver and represents the primary outcome of the methacholine provocation. Forced expiratory volume in 1 s (FEV1) and forced vital capacity (FVC) are measured from the maximal expiratory maneuver (C). DI, deep inspiration; SD Mch, single-dose methacholine; A: partial slow expiratory maneuver; B: maximal forced inspiratory maneuver; C: maximal forced expiratory maneuver.
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Table 1. Demographic and lung function characteristics of the study subjects

<table>
<thead>
<tr>
<th></th>
<th>Active Group</th>
<th>Control Group</th>
<th>P Value</th>
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<tbody>
<tr>
<td>Male/Female</td>
<td>3/6</td>
<td>1/4</td>
<td></td>
</tr>
<tr>
<td>Age, yr</td>
<td>24 ± 1.1</td>
<td>26 ± 3.2</td>
<td>0.71</td>
</tr>
<tr>
<td>FEV1, %predicted</td>
<td>100 ± 7.4</td>
<td>102 ± 7.6</td>
<td>0.57</td>
</tr>
<tr>
<td>FEV1/VC</td>
<td>0.90 ± 0.7</td>
<td>0.83 ± 0.6</td>
<td>0.06</td>
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</table>

Values are means ± SE. FEV1, forced expiratory volume in 1 s; VC, vital capacity.

from week 0 to 10 (P = 0.03). This improvement in performance confirmed the effectiveness of the training program.

One subject had used salbutamol weekly before the study and three individuals twice in the last month. None of the study subjects developed exercise-induced bronchospasm during the training sessions. In addition, none of them needed to use short-acting β2-agonists during the exercise sessions. Only two subjects (who had been asked to discontinue the inhaled corticosteroids before the beginning of the study) reported to have occasionally used salbutamol in the first 5 wk of the study (less than once/weekly). None of the four asthmatics who needed rescue medications before the study used it during the training program.

Airway responsiveness. Spirometry at rest was unaffected by exercise training: FEV1 was 3.72 ± 0.86 and 3.61 ± 0.83 liters (P = 0.78) before and at the end of training, respectively; corresponding values for VC were 4.22 ± 1.23 and 4.30 ± 1.10 liters (P = 0.89). The median Mch dose used for the tests in the absence of DI was 463 mcg (range: 21–939 mcg) in the active group and 321 mcg (range: 21–626 mcg) in untrained controls (P = 0.42). At the pretraining evaluation, the percent reduction in IVC after inhalation of Mch in the absence of DI was 22 ± 10% in the active group and 21 ± 20% in controls (P = 0.27). During the same evaluation, FEV1 decreased by 23 ± 12% in the active group and 34 ± 14% in untrained controls (P = 0.17).

In the active group, the Mch-induced reduction in IVC almost halved (13 ± 11%, P = 0.03) at week 5 (mid training) compared with the pretraining provocation and further decreased (11 ± 8%, P = 0.01) at week 10 (end of training). Individual data points for percent reduction in IVC during training are shown in Figure 2 (ANOVA for repeated measures: P = 0.028). The Mch-induced reduction in FEV1 did not change at the three time points (23 ± 12% at week 0, 19 ± 15% at week 5, and 21 ± 13% at week 10; ANOVA: P = 0.69).

In untrained controls, the Mch-induced reduction in IVC remained unchanged after 10 wk (%reduction IVC at week 10: 29 ± 14%, P = 0.28). An intriguing finding was noticed during the recovery phase that followed the training program. The results did not differ from those obtained at the end of the training program: the percent fall in IVC at recovery was 13 ± 8%, (P = 0.66 vs. end of training), meaning that the reduction in responsiveness was maintained during the recovery period.

Changes in the airway response to Mch at each step of the protocol are described in Table 2.

**DISCUSSION**

This study was designed to further test the hypothesis that a short course of intensive physical training can modulate the airway responses to bronchoconstrictors in individuals with asthma. Our results clearly show that airway responsiveness to Mch in the absence of DIs decreases with exercise training in mild untreated asthmatics. In addition, the attenuation of the Mch-induced reduction in IVC persisted for ≥ 1 mo after training cessation. The current findings demonstrate a beneficial role of exercise in reducing the degree of AHR in mild asthmatics, opening a new area of intervention in the management of asthma.

Epidemiologic and experimental data from the general population give support to the concept that habitual exercise may decrease airway responsiveness. A recent epidemiologic study (29) reported an inverse relationship between level of habitual physical activity and prevalence of AHR in the general population. Freedman et al. (9) showed that exercise decreased airway resistance induced by Mch inhalation in healthy subjects. More recently, Rosenkranz et al. (25), demonstrated that in sedentary nonasthmatic preschool children, 8 wk of high-intensity running training reduced airway responsiveness after exercise or eucapnic voluntary hyperventilation. In a randomized study performed in children with mild asthma to assess the effects of aerobic training for 12 wk alone or in combination with montelukast on airway responsiveness to Mch (1), we came across the observation that exercise training was associated with improved AHR in both groups, thus suggesting a potential protective role of exercise against spasmodgens. The findings of the current study confirm and extend this observation.

Airway inflammation and chronic airway wall remodeling are widely accepted as being implicated in the pathogenesis of asthmatic bronchitis.

Table 2. Changes in the airway response to Mch at each step of the protocol

<table>
<thead>
<tr>
<th></th>
<th>Week 0</th>
<th>Week 5</th>
<th>Week 10</th>
<th>Postrecovery</th>
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<tbody>
<tr>
<td>Active group</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Reduction in IVC, %from basal</td>
<td>22 ± 10</td>
<td>13 ± 11*</td>
<td>11 ± 8*</td>
<td>13 ± 8</td>
</tr>
<tr>
<td>Reduction in FEV1, %from basal</td>
<td>23 ± 12</td>
<td>19 ± 15</td>
<td>21 ± 13</td>
<td>22 ± 13</td>
</tr>
<tr>
<td>Control group</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reduction in IVC, %from basal</td>
<td>21 ± 20</td>
<td>-</td>
<td>29 ± 14</td>
<td></td>
</tr>
<tr>
<td>Reduction in FEV1, %from basal</td>
<td>34 ± 14</td>
<td>-</td>
<td>33 ± 19</td>
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Values are means ± SE. IVC, inspiratory vital capacity. *P < 0.05.

![Fig. 2. Individual data for methacholine-induced %reduction in IVC from baseline obtained at pretraining and after 5 and 10 wk of exercise training. #P = 0.03, week 5 vs. pretraining; $P = 0.01, week 10 vs. pretraining.](http://jap.physiology.org/Downloads/a220505d834246)
AHR (2, 11, 12, 15). The inflammatory condition of the airways could induce changes in the contractile behavior of the ASM, as well as in the context of the airway wall components (8). However, the association between airway inflammation (cells and/or mediators) and AHR is far from being established (4). In this regard, it cannot be excluded that exercise lowered the airway response to spasmogen by reducing the level of airway inflammation in our asthmatics. A number of studies have demonstrated the beneficial effects of aerobic exercise in chronic allergic airway inflammation. Regular aerobic exercise performed at low or moderate intensity decreased eosinophilic and lymphocytic inflammation and Th-2 immune response in a murine model of allergic asthma (10, 11, 18, 24, 32–34). In our previous study in nonasthmatics (27), we failed to demonstrate an association between changes in inflammatory cells and airway responsiveness; however, a significant decrease in bronchial epithelial cells in sputum after training was detected, which could suggest the loss of a protective effect of this cell line against spasmogens. In the current study, we did not measure markers of inflammation: therefore, we cannot confirm (or exclude) that the beneficial effect of exercise could be mediated by changes in the inflammatory pattern of the airways. Also, we do not have information on markers of oxidative stress or changes in the nutrition habit, which could have affected the results. The link between AHR and bronchial inflammation might also be mediated by mechanical alterations of the respiratory system induced by the inflammatory changes (3, 28). In our study, spirometric outcomes did not change after training, making it unlikely that the observed changes in airway responsiveness are causally linked to changes in lung volumes. We favor the hypothesis that the intensive lung excursions associated with exercise result in ASM stretch and may induce persistent functional changes leading to reduction in smooth muscle contractility. The findings from the study of McClean et al. (19) support this hypothesis. In sheep that were chronically subjected to breathing at low lung volumes using a corset for 4 wk, the contractile apparatus of the ASM cells may be altered. The finding of an alteration in the contractile properties of ASM with chronic lung volume reduction provides a theoretical basis for the change in airway responsiveness that are observed with repetitive lung inflations. In this context, the lengthening or stretching of ASM that occurs during a DI may reorganize the contractile apparatus of the ASM cells and reduce airway responsiveness. This has been clearly shown by in vitro studies (7, 15, 30), although recent studies (17) showed only modest effects of oscillations of physiologically relevant amplitudes applied to the airway on the ability to modulate airway responsiveness. As stated by the authors (17), a gap exists in translating cellular level hypotheses from isolated ASM studies to actual AHR in vivo, which could perhaps explain why exercise did not attenuate the reduction in FEV\textsubscript{1}. If DIs are prevented, the muscle is not lengthened intermittently, and, as a result, the muscle shortens more. In this regard, Freeman et al. (9) were able to demonstrate that the reversal of bronchoconstriction was not related to exercise per se but to increased ventilation. Stirling et al. (31) found that, in asthmatic individuals, the airway response to histamine was attenuated by exercise, and this effect was not mediated by release of catecholamines.

An interesting finding from the current study is the different response to exercise in terms of attenuation of IVC and FEV\textsubscript{1} reductions in the absence of DI. The attenuation of the Mech-induced reduction in IVC, and not in FEV\textsubscript{1}, after the training program indicates that the beneficial effect of exercise is such that it prevents (or attenuates) airway closure more than large airway narrowing. Since the IVC depends on the RV that is reached, changes in IVC reflect those in RV. Thus the effect of exercise appears to act mostly at the level of peripheral airways, which are by definition more prone to distend following the deep inspiratory maneuvers. This is not surprising, given that the radial traction following lung inflations acts mostly at the level of peripheral airways, which are more distensible (2). In this respect, an interesting hypothesis is the enhanced production of surfactant stimulated by the repetitive lung inflation maneuvers (22), which would favor the relief of airway closure. On the other hand, the lack of improvement when FEV\textsubscript{1} is measured could be explained by the fact that this spirometric variable results from phenomena that involve both the small and the large airways, the latter being more resistant to the distending effect of DI. Finally, we cannot exclude that the different response of IVC and FEV\textsubscript{1} to exercise is only apparent; in other words, since IVC is not affected by a preceding lung inflation maneuver, as FEV\textsubscript{1} does, it could simply be a more sensitive parameter to detect changes in reactivity. Additional studies in larger samples of study groups are needed to clarify this issue.

These results may have clinical implications. Any factor reducing AHR theoretically would delay the occurrence of asthmatic symptoms or slow the lung function decline. In this scenario, regular physical exercise becomes of increasing importance. The findings of our study, together with those from our previous observation in asthmatic children (1) strongly indicate that exercise per se may reduce the degree of airway response to spasmogen, which is one of the major goals of asthma management. The clinical implication is highlighted by the fact that, although it did not represent an outcome of the study, the use of rescue medications was limited to very few subjects and decreased with the length of the exercise training program. Whether the observed effect of training on AHR might be specifically associated with rowing is an interesting topic for further work. We cannot predict whether another modality of exercise would yield similar results. However, we (26) have already demonstrated that amateur runners show reduced AHR assessed with the identical protocol. We suspect that long-lasting exercise, irrespective of specific characteristics, is the main determinant of changes in airway responsiveness. In addition, our observations imply that a sedentary lifestyle may favor development of airways hyperresponsiveness, in agreement with recent epidemiological data (29).

In conclusion, we have found that a 10-wk course of exercise training results in ~50% attenuation of AHR in the absence of deep inspirations in untreated mild asthmatics. As stated by Chapman et al. (5), reducing airway responsiveness with such a short exercise program provides the potential to dramatically affect the progression of asymptomatic AHR to asthma.

**ACKNOWLEDGMENTS**

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DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the author(s).

AUTHOR CONTRIBUTIONS


REFERENCES