Effects of Exercise Training and Montelukast in Children with Mild Asthma

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ABSTRACT

BONSIGNORE, M. R., S. LA GRUTTA, F. CIBELLA, N. SCICHILONE, G. CUTTITTA, A. INTERRANTE, M. MARCHESE, M. VECA, M. VIRZI', A. BONANNO, M. PROFITA, and G. MORICI. Effects of Exercise Training and Montelukast in Children with Mild Asthma. *Med. Sci. Sports Exerc.*, Vol. 40, No. 3, pp. 405–412, 2008. **Purpose:** Data from the general population suggest that habitual exercise decreases bronchial responsiveness, but the possible role of exercise in asthmatics is undefined. The leukotriene receptor antagonist montelukast decreases bronchial responsiveness and exercise-induced symptoms in asthmatic children. This randomized study in children with mild asthma evaluated the combined effects of aerobic training for 12 wk and montelukast or placebo on bronchial responsiveness (BHR) to methacholine, exercise-induced bronchoconstriction (EIB), inflammatory markers in exhaled breath condensate (EBC), and asthma exacerbations. **Methods:** Fifty children (mean age ± SD: 10.2 ± 2.4 yr) with mild stable asthma were randomly assigned to placebo ($N = 25$) or montelukast ($N = 25$). Before and after training, we assessed BHR and EIB and markers of airway inflammation—that is, exhaled nitric oxide (eNO), pH, and cysteinyl–leukotriene concentration—in EBC. **Results:** Training increased maximal workload and peak minute ventilation. After training, the methacholine dose causing a 20% fall in FEV_1 (PD_{20}) increased in both groups. A decreased slope of FEV_1 decline at increasing methacholine dose was found only in montelukast-treated children. EIB prevalence halved after training in both groups (EIB + children, placebo group: 10 pretraining, 4 posttraining; EIB + children, montelukast group: 8 pretraining, 5 posttraining; $P < 0.05$ by χ^2 on all children). Resting eNO was unaffected, whereas the pH of EBC decreased after training in both groups. Cysteinyl–leukotriene concentrations were low in most children at both times. During training, montelukast-treated children showed fewer asthma exacerbations compared with the same period of the previous year. **Conclusions:** In children with mild stable asthma, exercise training decreased bronchial responsiveness to methacholine. Montelukast also decreased bronchial reactivity (FEV_1 slope) and protected against exacerbations, suggesting a beneficial synergistic action of these two interventions in mild asthma. **Key Words:** AEROBIC EXERCISE, BRONCHIAL RESPONSIVENESS, METHACHOLINE, DEEP INSPIRATION, LEUKOTRIENES

Exercise training in asthma improves cardiopulmonary fitness and prevents exercise-induced bronchoconstriction (EIB) and respiratory symptoms (13,26,32). Training does not modify baseline spirometry in asthmatics (13,26,32), but its effects on bronchial responsiveness (BHR) and airway inflammation are largely unknown.

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Submitted for publication July 2007.
Accepted for publication October 2007.

0195-9131/08/4003-0405/0
MEDICINE & SCIENCE IN SPORTS & EXERCISE®

DOI: 10.1249/MSS.0b013e31815d9670

Low BHR to methacholine (MCh) has been shown in healthy, well-trained subjects (36). Inspiratory vital capacity after single-dose MCh in the absence of deep breaths fell significantly in sedentary controls but was unaffected in well-trained runners at rest; after a marathon race, the response to MCh further decreased (36), suggesting that repeated episodes of ventilation at high lung volumes might help to maintain a low BHR in athletes (26). Moreover, a recent study in the general population reported an inverse relationship between levels of habitual physical activity and prevalence of bronchial hyperresponsiveness (37). In asthmatic children, conflicting results have been obtained regarding the effect of training on BHR. Some studies found that the provocative dose of inhaled hypertonic saline, causing a 20% fall in FEV_1 (PD_{20}), increased after 4 wk of aerobic training (1), whereas others have shown that bronchial reactivity to MCh was higher in sedentary than in active subjects (29), suggesting that habitual

exercise may be associated with blunted bronchial reactivity also in asthmatics. Conversely, in children with mild to moderate asthma, hyperresponsiveness to histamine did not change after swimming training for 6 wk (27). In adult asthmatics, MCh PD_{20} was unchanged after 10 wk of training (12).

Experimental data suggest that exercise training might ''downregulate'' airway inflammation in both health and disease models, but this hypothesis has not been tested clinically. Studies in healthy human athletes and normal mice have shown increased inflammatory cell counts in the airways but no evidence of inflammatory activation after intense exercise (5) or training (9). In asthmatic mice, intensive training strikingly decreased airway inflammation (30).

An intriguing debate exists regarding the role of airway inflammation in the pathogenesis of EIB in asthma. Some studies have concluded that EIB did not show a clear relationship with airway inflammation (15,22), whereas recent data support a role of mediators such as cysteinyl–leukotrienes in EIB (7,8,21). The leukotriene receptor antagonist montelukast decreased EIB in asthmatic adults (21,25) and children (8,14,16,23,24), and inflammatory mediators in induced sputum (8,21). More recently, the clinical effects of montelukast in the reduction of BHR (19) and asthma exacerbations (4) have been demonstrated in preschool children.

In this randomized, placebo-controlled study, we hypothesized that aerobic training might improve BHR in children with mild stable asthma. In particular, we tested whether treatment with montelukast during training might be advantageous compared with training alone, because of its effects on EIB, airway inflammation, and exacerbations. To investigate the possible relationship between BHR and inflammation, noninvasive inflammatory markers (exhaled nitric oxide, pH, and concentration of cysteinyl–leukotrienes in exhaled breath condensate) were measured before and after training.

SUBJECTS AND METHODS

Fifty children (37 boys, 13 girls) were studied (Table 1). All children had mild stable asthma (i.e., symptoms less often than once a week) and were not on medications, except inhaled β2-agonists as needed for symptom relief. No patient reported use of inhaled or systemic corticosteroids or respiratory infections in the 4 wk before the study. Inclusion criteria were age 6–14 yr, previous diagnosis of asthma, positive skin test for *Dermatophagoides pteronyssinus*, and bronchial hyperresponsiveness (i.e., a decrease in $FEV_1 \geq 20\%$ of baseline at a cumulative MCh dose < 2250 μg). A positive history for exercise-induced symptoms was not required for enrollment.

Subjects were randomly allocated to placebo or montelukast group by computer-generated series and were unaware of treatment. Identical tablets were given to children in placebo and montelukast groups, with instructions to take one tablet per day during the 12 wk of training. The protocol was approved by the IRB of ARNAS, Palermo, and written informed consent was obtained by one or both parents. In addition, we met all the children participating in the protocol, informed them about the purpose of our work, and answered their questions about the project.

TABLE 1. Characteristics of the two groups.

	Placebo (*N* = 25)	Montelukast (*N* = 25)
M/F	17/8	20/5
Age (yr)	10.2 ± 2.0	10.2 ± 2.6
Body weight (BW, kg)	39.6 ± 9.9	37.6 ± 12.1
Height (cm)	138.6 ± 10.5	137.9 ± 13.0
BMI ($kg \cdot m^{-2}$)	20.4 ± 3.6	19.2 ± 3.4
Fat-free mass (% total BW)	77.2 ± 9.1	79.2 ± 8.3
Training sessions attended (*N*)	19.4 ± 7.0	17.5 ± 7.3

M/F, male/females. Other data are reported as means ± SD.

Training program and study design. The training program started at the same time for all children and lasted from mid-October to mid-January. Enrollment was done during the 2–3 wk immediately before the start of training. A dedicated class was organized in a gym center, and the program included four sessions per week of aerobic circuit training, each lasting 1 h. The children were asked to attend at least any two of the four weekly sessions. The intensity of training was gradually increased during the program. A certified training instructor and a pulmonologist supervised all sessions to ensure that the clinical condition was stable. Rescue medications were available during sessions.

Before training, the children underwent four visits a few days apart. On day 1, medical history, clinical examination, anthropometric measures and body composition, skin prick tests, and baseline spirometry were obtained. On day 2, exhaled nitric oxide (eNO) was measured, and oral and nasal exhaled breath condensate (EBC) and venous blood samples for complete blood cell counts and total IgE measurements were collected. On day 3, standard MCh challenge was performed in the morning. On day 4, an incremental exercise test was performed in early afternoon, with spirometry before and after the test. In the 2 wk after the end of training, the same protocol was repeated except for skin prick tests and blood samples (Fig. 1). All tests were done blindly with regard to the treatment group.

The number of asthma exacerbations during the training period was recorded and compared with the corresponding number in same period of the previous year, based on the records of the asthma outpatient clinic. Exacerbations were defined as episodes lasting three or more consecutive days requiring repeated use of β2-agonist, oral/inhaled corticosteroids during one or more days, or hospitalization for asthma. Exacerbations were defined as mild if they did not require a change in asthma treatment, or as moderate if they required the addition of rescue oral/inhaled corticosteroids or hospitalization.

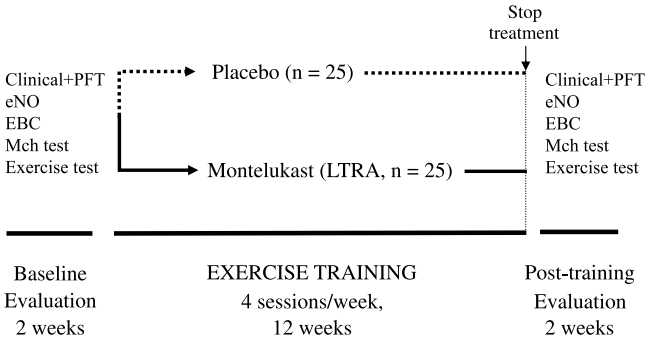

FIGURE 1—Summary of the study protocol.

Body composition. Body composition was measured at rest in the fasting state by the bioimpedance technique (STA/BIA Soft Tissue Analyzer/Bioelectrical Impedance Analyzer, Akern, Firenze, Italy) in 38 children (N = 19 per group) before training and in 45 children (placebo: N = 21, montelukast: N = 24) after training. The bioimpedance method has been validated in children (31). Fat-free mass was expressed as a percentage of total mass.

Spirometry, FeNO, and exhaled breath condensate. Spirometry was measured by a computerized water-sealed spirometer (Biomedin, Padua, Italy). Fractional eNO concentration was measured by chemiluminescence (Logan LR 2000, DASIBI, Italy) (3). Children inhaled NO-free air and exhaled through a dynamic flow restrictor with a target flow of 50 mL·s^{-1} for at least 6–7 s. Visual incentives provided feedback for flow-rate compliance.

For nasal and oral EBC samples, a condenser allowed for the noninvasive collection of nongaseous components of expiratory air (EcoScreen Jaeger, Wurzburg, Germany). For oral samples, patients wore a nose clip and breathed through a mouthpiece and a two-way nonrebreathing valve, which also served as a saliva trap, at a normal frequency and tidal volume for 20 min. Nasal EBC was collected according to Griese et al. (17) with minor modifications. After applying a nasal mask connected to the condenser equipment, children were asked to breathe through their noses, with their mouths closed. They washed their mouths before sample collection. All condensate samples (≥ 1 mL) were collected at −20°C, transferred to 1.5 mL of polypropylene tubes, and stored at −80°C until analysis. After deaeration/decarbonation of EBC samples by bubbling with argon (350 mL·min^{-1}) for 10 min (17), pH was measured within 5 min of EBC collection by a pH meter (Corning 240, Science Products Division, New York) with a 0–14 pH range. Cysteynil–leukotrienes were analyzed using a commercial ELISA kit according to the manufacturer's instructions (LTC4/D4/E4, Amersham, Pharmacia Biotech, UK; lower detection limit: 10 pg·mL^{-1}) (8).

BHR. Standard Mch challenge tests were performed using an ampoule-dosimeter (Mefar Elettromedicali, Brescia, Italy) delivering 5 μL of solution at each inspiratory effort (10). Lyophilized Mch chloride (Lofarma S.p.A, Milan, Italy) was reconstituted to 0.2% and 1.0% concentrations. After saline control, Mch was administered in doubling amounts, and FEV_1 was recorded 2 min after each Mch dose. The cumulative dose of Mch causing a 20% reduction of FEV_1 (PD_{20}) was computed. A PD_{20} lower than 2250 μg of Mch (equivalent to 11.50 mM of Mch) was considered a positive response (10).

Exercise stress test. Tests were performed under standard laboratory conditions (temperature: 21–22°C, humidity: 50%) on a motor-driven treadmill (PKMorgan Ltd, Gillingham, Kent, UK). Each child selected the preferred speed, which was kept constant during the test. Slope was increased by 2% every 2 min until exhaustion or attainment of maximal heart rate (220 − age in years). Load was expressed in watts (38). Breath-by-breath measurements were obtained by a metabolic cart (CPX, MedGraphics) during exercise and recovery. Peak oxygen consumption ($\dot{V}O_{2peak}$) and minute ventilation ($\dot{V}_{E\,peak}$) were calculated as the mean value in the last minute of exercise. Spirometry was performed at 10 and 20 min after exercise. EIB was defined as a postexercise ΔFEV_1 of −10% of baseline, occurring at either time point (10).

Statistics. Data were expressed as means ± SD, or median (range) in cases of nonnormally distributed variables. Paired comparisons were by t-test or Wilcoxon test. Analysis of variables according to group and pre- or posttraining status was by ANOVA. χ^2 test was used to compare frequencies (nominal variables). Relationships between variables were assessed by linear regression or Spearman rank correlation. In children who showed declines in FEV_1 < 20% at the posttraining MCh test, the arbitrary value of 4500 μg (i.e., twice the maximal dose) was used in analyses of PD_{20}. The value of 10 pg·mL^{-1} was used whenever cysteinyl–leukotriene concentrations in EBC samples were below the detection limit of the assay. A statistical package (Statview 5.01) was used for all analyses; significance was at $P < 0.05$ in all tests.

RESULTS

Placebo and montelukast groups were similar for age, gender ratio, body weight, height, body mass index, and fat-free mass (Table 1). No child was obese. The mean attendance of the training class was twice a week in both groups. No asthma attacks occurred during any training session.

Pretraining measurements. All children were asymptomatic at study entry. Table 2 illustrates the results of spirometry and MCh bronchoprovocation tests. Before training, most children had normal spirometry, whereas seven of them (five in the placebo and two in the montelukast group) showed evidence of mild airway obstruction. Before training, all children were hyperresponsive to MCh, without differences between groups in PD_{20} or in the slope of FEV_1 at increasing MCh doses (Table 2). The results of maximal exercise stress tests were

TABLE 2. Baseline spirometry, exhaled nitric oxide (NO), and methacholine bronchoprovocation test.

	Placebo		Montelukast	
	Pretraining	Posttraining	Pretraining	Posttraining
FVC, L (% pred)	2.22 ± 0.58 (96.1 ± 15.4)	2.47 ± 0.45 (103.9 ± 13.7)	2.25 ± 0.61 (98.2 ± 12.2)	2.38 ± 0.72 (99.6 ± 12.8)
FEV_1, L (% pred)	1.93 ± 0.43 (96.1±14.0)	2.03 ± 0.42 (97.8 ± 15.7)	1.92 ± 0.52 (96.9 ± 14.2)	2.05 ± 0.58 (95.9 ± 11.8)
FEV_1/FVC %	87.4 ± 8.2	84.4 ± 7.9	85.8 ± 8.0	85.2 ± 6.7
FEF_{25-75} ($L \cdot s^{-1}$)	2.25 ± 0.54	2.32 ± 0.66	2.23 ± 0.80	2.28 ± 0.59
Exhaled NO (ppb)	29.9 ± 24.2	31.0 ± 25.7	28.2 ± 21.3	25.1 ± 16.4
Methacholine PD_{20} mg (range)	0.410 (0.008–1.90)	0.681§ (0.004–4.50)	0.186 (0.004–1.93)	0.329§ (0.009–4.50)
FEV_1 slope; FEV_1 %pred/Mch dose, mg (range)	−43.6 (−1600/−7.8)	−28.2 (−5500/−2.5)	−105.2 (−5833/21.5)	−61.5* (−1151/−5.6)

Spirometric data are reported as means ± SD. PD_{20} and FEV_1 slope data are reported as median (range).
§ The value of 4500 μg of methacholine was used as PD_{20} for children (placebo: $N = 6$; montelukast: $N = 3$) who showed normal bronchial reactivity (i.e., $PD_{20} > 2250$ μg of methacholine) after training. PD_{20} increased significantly after training in both groups. Slope: * $P < 0.05$ pre- vs posttraining in the montelukast group (Wilcoxon test).

also similar in the two groups (Table 3). EIB, defined as postexercise 10% fall of FEV_1 (10), occurred before training in 18 children (8 placebo, 10 montelukast) (Fig. 2, upper panel).

Exhaled nitric oxide concentrations tended to be higher in EIB+ (37.9 ± 28.7 ppb) than in EIB− children (25.9 ± 21.1 ppb, $P = 0.10$, NS). The pH of oral EBC was in the normal range and was similar in EIB+ (8.14 ± 0.23) and EIB− (7.86 ± 0.56) children. The pH of nasal EBC was 8.00 ± 0.55 in the entire group of children, without differences between groups (Table 4). The mean cysteinyl–leukotriene concentration in oral EBC samples was 10.1 ± 0.7 $pg \cdot mL^{-1}$ in the entire group of children before training, without significant differences between groups (Table 4). In nasal EBC samples, cysteinyl–leukotriene concentrations were below the detection limit in all children (Table 4).

Posttraining measurements. Posttraining data were obtained in 48 children (24 placebo, 24 LTRA). In addition, exercise and MCh tests, respectively, could not be obtained in two children of the placebo group after training, for technical reasons. Body mass index, fat-free mass, and baseline spirometry (Table 2) did not change after training.

Training increased mean workload, oxygen consumption at anaerobic threshold, and minute ventilation and heart rate at peak exercise (Table 3). The increase in $\dot{V}O_{2peak}$ was largest in children with the lowest pretraining $\dot{V}O_{2peak}$ values ($r = -0.34$, $P < 0.05$). EIB was found in nine children (four on placebo, five on montelukast) after training (Fig. 2, lower panel). Changes in BHR were analyzed according to MCh PD_{20} and FEV_1 slope. After training, PD_{20} increased significantly in both groups ($P < 0.02$ by Wilcoxon test), with nine children (six on placebo, three on montelukast) showing normal BHR ($PD_{20} > 2250$ μg). There was a trend toward decreased slope of FEV_1, which had significant results only in the montelukast group ($P < 0.05$ by Wilcoxon test) (Fig. 3).

Exhaled NO concentrations were similar to pretraining values (Table 2) and in EIB+ and EIB− children (EIB+, 31.3 ± 17.1 ppb; EIB−, 25.6 ± 19.2, NS). No significant relationship was found between exhaled NO concentrations and postexercise falls in FEV_1 either before or after training. The pH of oral and nasal EBC decreased after training ($P < 0.001$ by ANOVA), without differences between placebo and montelukast groups (Table 4) or EIB + and EIB− children (data not shown). Mean cysteinyl–leukotriene concentrations in oral and nasal EBC showed a modest, nonsignificant trend to increase after training, both in the placebo and montelukast groups.

Relationship between EIB and BHR. Median MCh PD_{20} before training was 208 μg in the entire group; therefore, PD_{20} values below 200 μg were considered high BHR, and values between 200 and 2250 μg were considered mild BHR. Figure 4 summarizes the occurrence of EIB in both groups according to BHR. In pretraining measurements, half of the EIB+ children (6 out of 12) showed high BHR, whereas most EIB− children (20/32) showed mild BHR ($P < 0.05$ by χ^2 test). The same trend occurred after training, without differences between placebo and montelukast groups, with 2/21 EIB+ children in the mild BHR group, 6/16 EIB+ children in the high BHR

TABLE 3. Exercise stress test.

	Placebo		Montelukast	
	Pretraining	Posttraining	Pretraining	Posttraining
Test duration (min)	10.5 ± 3.2	13.4 ± 4.2	11.4 ± 3.1	13.7 ± 3.8
Load max ($W \cdot kg^{-1}$)	1.14 ± 0.38	1.38 ± 0.42*	1.33 ± 0.57§	1.63 ± 0.52§*
$\dot{V}O_{2peak}$ ($L \cdot min^{-1}$)	1.25 ± 0.39	1.35 ± 0.39	1.29 ± 0.49	1.37 ± 0.46
$\dot{V}O_{2peak}$ ($mL \cdot min^{-1} \cdot kg^{-1}$)	31.5 ± 6.0	32.0 ± 5.1	34.2 ± 6.4	33.9 ± 4.2
$\dot{V}O_2$ AT ($L \cdot min^{-1}$)	0.85 ± 0.67	1.16 ± 0.42**	1.01 ± 0.66	1.18 ± 0.51**
HR_{peak} (bpm)	189.6 ± 13.6	196.5 ± 10.2*	193.4 ± 14.7	199.9 ± 11.9*
$\dot{V}_{Epeak}$ ($L \cdot min^{-1}$)	41.1 ± 12.5	49.0 ± 13.5*	38.5 ± 16.5	46.4 ± 17.3*
Freq resp peak	58.4 ± 11.0	58.9 ± 8.5	54.2 ± 12.1	57.3 ± 12.8

Data are means ± SD.
* $P < 0.05$ vs baseline; § $P < 0.05$ vs corresponding value in placebo group; ** $P < 0.05$ between pre- and posttraining by ANOVA—not significant in placebo or montelukast group.

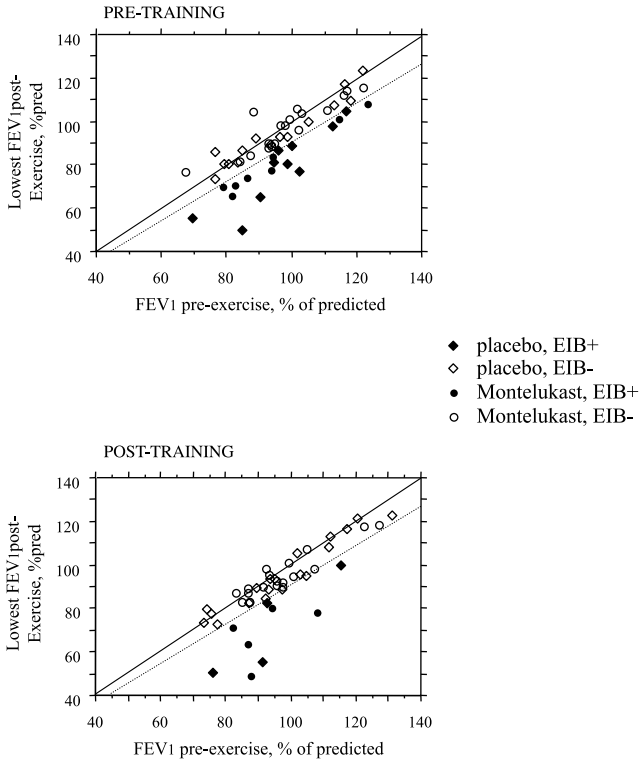

FIGURE 2—Exercise-induced bronchoconstriction before (*upper panel*) and after (*lower panel*) training. Baseline preexercise FEV_1 is reported in abscissa, whereas the lowest postexercise FEV_1 is reported in ordinate for each subject in both graphs. The *continuous line* is the line of identity; the *dotted line* indicates a 10% fall of FEV_1 below the baseline value.

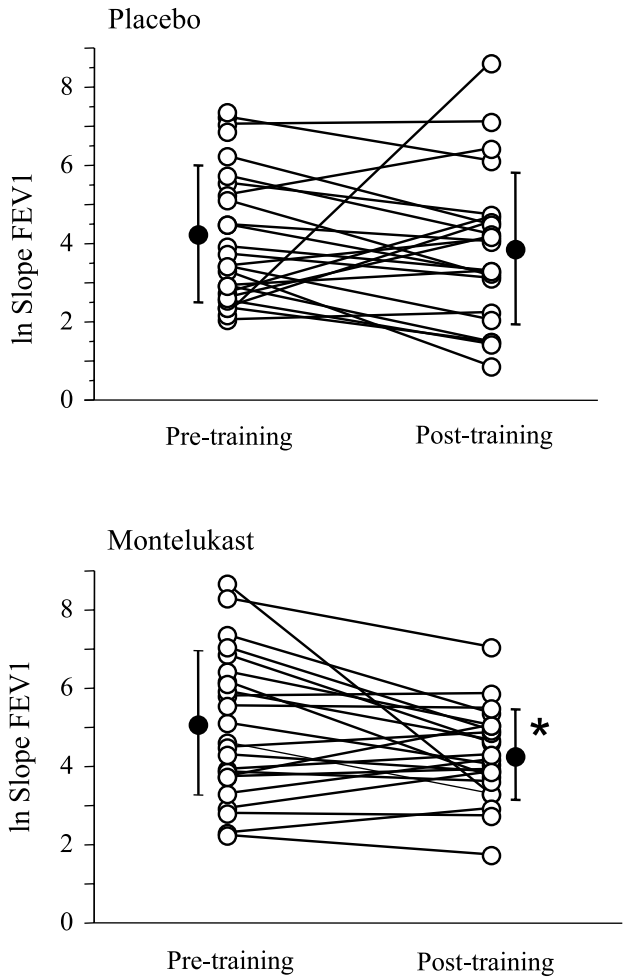

FIGURE 3—Changes in bronchial reactivity to methacholine estimated as changes in the slope: FEV_1/methacholine dose in placebo (*upper panel*) and montelukast (*lower panel*) groups. A significant decrease in FEV_1 slope was only observed in the active treatment group.

group, and only 1/9 EIB+ children in the normal PD_{20} range ($P = 0.10$).

Asthma exacerbations. Figure 5 reports the frequency of asthma exacerbations during training compared with the same period in the previous year. Occurrence of mild exacerbations (i.e., requiring no change in treatment) was unaffected by training in either group. Conversely, the frequency of moderate exacerbations (i.e., requiring addition of inhaled corticosteroids) decreased only in the montelukast group ($P < 0.05$, Wilcoxon test).

DISCUSSION

In children with mild, stable asthma, aerobic training for 12 wk was safe and improved maximal workload and $\dot{V}O_2$ at anaerobic threshold. Airway response to MCh and EIB decreased after training. Compared with placebo, montelukast treatment during training resulted in decreased slope of MCh-induced fall in FEV_1 and reduced frequency of moderate asthma exacerbations. Exhaled inflammatory markers were low and were little affected by training in both treatment arms. Our results indicate a clinically positive effect of exercise training in children with mild asthma, especially when associated with montelukast treatment. These data are in agreement with some epidemiological data suggesting a positive role of habitual exercise on BHR in both children and adults (29,37).

TABLE 4. Exhaled breath condensate pH and cysteinyl–leukotriene (Cys-LT) concentration.

	Placebo		Montelukast	
	Pretraining	Posttraining	Pretraining	Posttraining
Oral pH	7.83 ± 0.56	7.05 ± 0.55*	8.12 ± 0.30	6.87 ± 0.41*
Nasal pH	8.00 ± 0.63	6.58 ± 0.70*	7.99 ± 0.45	6.33 ± 0.66*
Oral Cys-LT ($pg \cdot mL^{-1}$)**	10.0 ± 0	20.0 ± 37.0	10.2 ± 1.1	13.3 ± 15.4
Nasal Cys-LT ($pg \cdot mL^{-1}$)**	10.0 ± 0	15.2 ± 18.5	10.0 ± 0	18.2 ± 27.8

* $P < 0.05$ vs pretraining.
** The lower limit of detection (10 $pg \cdot mL^{-1}$) was used in subjects with levels of Cys-LT concentration below the detection threshold.

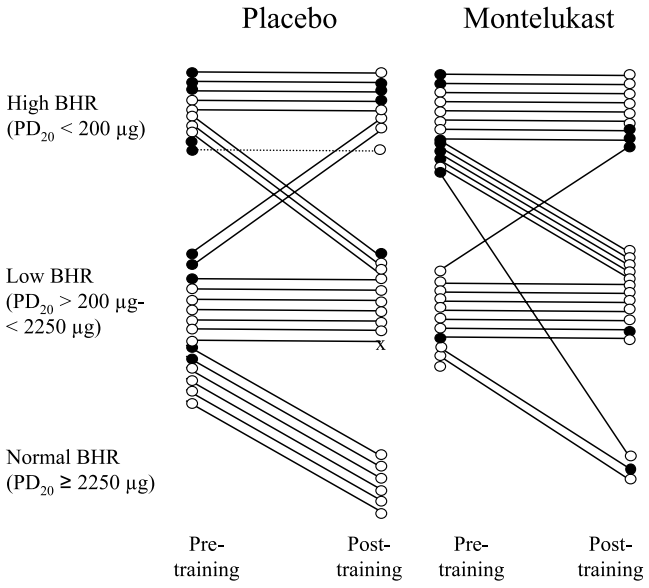

FIGURE 4—Changes in bronchial responsiveness and exercise-induced bronchoconstriction (EIB) after training in both groups. *Empty dots*, EIB−; *full dots*, EIB+. The x symbol indicates missing data for EIB. *Continuous lines* join pre- and posttraining individual points; the *dotted line* indicates missing data for bronchial responsiveness after training. Bronchial responsiveness was coded as high, low, and normal BHR (see text for details).

In our mildly asthmatic children, 12 wk of training decreased prevalence of EIB and increased peak oxygen consumption, especially in those children showing the lowest values before training. This result is similar to those of other studies in children with moderate to severe asthma, in which training increased peak oxygen consumption (13,28), particularly in the most unfit subjects (28). However, in children with more severe asthma, unchanged (28) or improved (13) EIB has been reported after short-term training.

Besides EIB, our study systematically assessed changes in BHR to MCh associated with training. A significant increase of PD_{20} to MCh occurred both in the placebo and montelukast groups, often coupled with decreased reactivity to exercise (Fig. 4). In addition, a significant decrease in bronchial reactivity (FEV_1 slope) to MCh occurred in the montelukast group (Fig. 3), suggesting decreased airway reactivity when the two interventions were combined. Montelukast treatment during exercise training was also clinically beneficial, because children under active treatment experienced fewer moderate asthma exacerbations compared with the placebo group, in line with previous clinical observations (11,16,24).

Our experimental design (i.e., posttraining measurements obtained in the 2 wk after interruption of drug treatment) may have underestimated the effect of the active treatment. Other limitations of our study were the limited sample size and the lack of untrained control arms. Despite these limitations, our study provides a comprehensive set of clinical and laboratory data, and it may yield some insight into training-induced modulation of BHR and noninvasive inflammatory markers in children with mild asthma.

The possible mechanism(s) involved in the modulation of BHR by exercise training deserve comment. In asthma, the magnitude of airway narrowing after the application of a constrictor stimulus results from the interaction of the intrinsic defect of the airway smooth muscle (ASM) (i.e., increased force generation and/or velocity of shortening) (18) and dynamic loads counteracting bronchoconstriction. Inspiration stretches the airway wall and ASM, thus altering its contractile state (14), whereas deep inflations further distend the airways because of the interdependence between airways and the surrounding parenchyma (18). Persistent bronchial hyperresponsiveness in asthmatics may depend on the attenuation, or complete loss, of the beneficial effects of deep inspirations. Repeated deep inspiration can reverse induced bronchoconstriction in healthy subjects (34) but not in adult asthmatics (35). Inflammatory and structural changes may contribute to uncouple the interdependence between airways and parenchyma, possibly accounting for the decreased effectiveness of lung inflation in asthma. We observed decreased BHR after training irrespective of treatment, and we speculate that this result might reflect an improved effect of lung inflation on asthmatic airways.

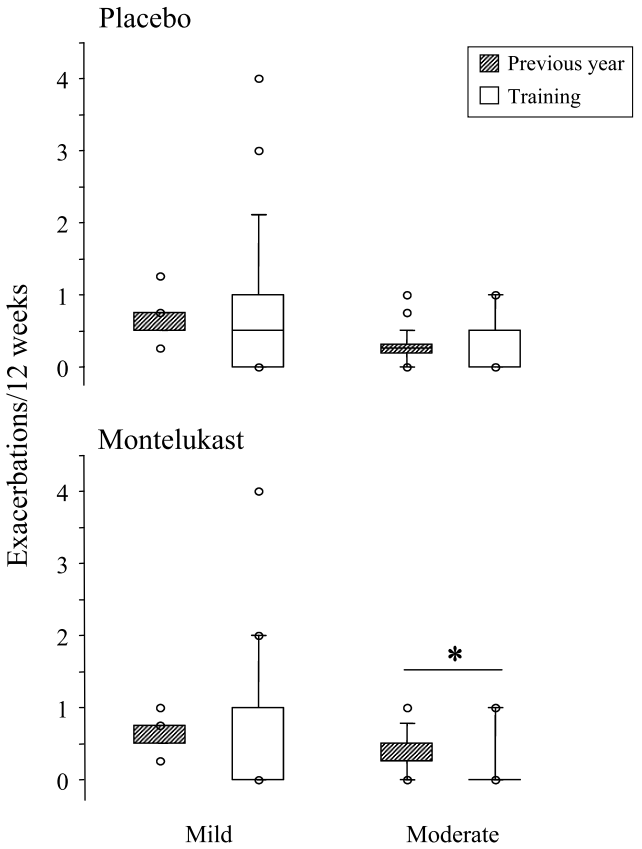

FIGURE 5—Montelukast treatment decreased the number of moderate asthma exacerbations during the training period compared with the same period of the previous year. Mild exacerbations were unchanged, both in placebo- and montelukast-treated children. * P < 0.05.

More specifically, repeated airway stretch associated with increased ventilation during regular training could modify the contractile apparatus of the ASM (14). Studies using high-resolution computed tomography have shown preserved airway distensibility after a single deep inspiration in mildly asthmatic adults (6). In asthmatic children, the few available studies on the effects of deep inspiration suggest a picture similar to that of asthmatic adults. Indeed, the effectiveness of deep inspiration to reverse MCh-induced (2) or spontaneous (33) bronchoconstriction was reduced in asthmatic compared with healthy children, especially when asthma was severe (2).

The inflammatory component of asthma may also be affected by exercise training. In a murine model of allergic asthma, training decreased the severity of airway inflammation (30). If such an effect occurred also in trained asthmatic children, it may contribute to decreased BHR. In normal mice undergoing endurance training, we found an influx of inflammatory cells and epithelial damage in small airways, but no evidence of inflammatory activation (9). Similarly, in marathon runners the increased number of inflammatory cells in large airways were not activated (5). In asthmatic children, however, training had mixed effects on exhaled markers of airway inflammation. The pH of EBC fell after training, whereas cysteinyl–leukotriene concentrations in EBC tended to increase, and exhaled NO did not change. Although these changes were small and were in agreement with the mild disease severity of our sample, a detailed analysis of airway cells and inflammatory markers is warranted, to assess the relationship between training and airway inflammation in asthmatic subjects. Increased bronchial epithelial cells and leukotriene concentrations in induced sputum have been reported in asthmatic subjects after acute exercise (21), but the effects of training were not assessed. We did not find higher exhaled NO levels in children with EIB compared with those without EIB at any time point; this finding is at variance with the data of Carraro and coworkers (8). Again, the mild severity of asthma in our sample might explain the different results between studies.

In summary, our study supports the hypothesis that aerobic training in asthmatic children may exert beneficial effects on BHR, especially when associated with montelukast treatment (26). On the basis of our previous data in healthy athletes (35), we propose that exercise training may improve asthma by acting on airway smooth muscle. This effect would be additive to other beneficial effects of training, such as increased peak oxygen consumption and decreased lactate production (20). Further studies are needed to assess whether the improvement seen in mild asthmatics also occurs in children with more severe asthma; in addition, longitudinal studies are necessary to confirm the role of physical exercise in modulating bronchial responsiveness.

We thank the children who participated in the study and their parents for their enthusiasm and patience shown during a time-consuming research protocol. We also thank Merck for providing the placebo and montelukast tablets, financial support for the gym class and instructor, and the commercial kits for leukotriene analysis in exhaled breath condensate samples. No author of this work had any competing interest with the topic of the reported research protocol.

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