Research Square

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Predictors of Exercise-Induced Bronchoconstriction in Subjects with Mild Asthma

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Research Article

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Abstract

Background: Physical effort is one of the natural stimuli capable of triggering airway obstruction in asthmatics, the so called exercise-induced bronchoconstriction in asthma (EIBa). This study was performed in subjects with mild persistent asthma suspected for EIBa, aiming to find predictors among functional parameters at rest and during exercise for developing EIBa.

Methods: In 20 subjects with mild asthma in stable conditions who reported respiratory symptoms on exertion in the past, measurements of baseline functional respiratory parameters and airways responsiveness by a methacholine challenge were obtained on the first day of the study after an adequate pharmacological washout. The day after, a maximal symptom-limited incremental cardiopulmonary exercise test (CPExT) was performed, with subsequent, repeated maneuvers of maximal full forced expiration to monitor the FEV_1 change at 1,3,5,7,10 and 15 minutes after the end of exercise for diagnosing EIBa.

Results: 19 subjects aged 27±5 years completed the two-days protocol. No functional parameters both at rest and during effort were useful to predict EIBa after stopping exercise that actually occurred in 12 individuals. In contrast to asthmatics without EIBa, in those with EIBa, however, mean Inspiratory Capacity (IC) did not increase with increasing ventilatory requirements during CPExT because 6 of them (50%) displayed dynamic pulmonary hyperinflation (DH) throughout the exercise, as documented by the progressive increase of end-expiratory lung volume. This subgroup of asthmatics with EIBa who in turn showed earlier and greater post-exercise FEV_1 fall had significantly lower forced mean expiratory flow between 25% and 75% of forced vital capacity ($FEF_{25-75\%}$) at rest ($p<0.05$) and higher airways responsiveness, expressed as $PD_{20}FEV_1$ ($p<0.05$).

Conclusions No functional respiratory parameters either at rest or during the effort seem to predict EIBa in mild asthmatics after maximal exercise test. In those with EIBa, however, a subgroup developed DH during exercise, and this was associated with baseline reduced forced expiratory flow-rates at lower lung volumes and higher airway hyperresponsiveness, suggesting a prominent small airways impairment.

Background

In patients suffering from bronchial asthma, physical exertion may acutely trigger airway obstruction leading to chest tightness, wheezing, dry cough, and dyspnea, that cease spontaneously with time or more quickly after treatment, namely bronchodilators with rapid onset of action (1).

This picture is now called exercise-induced bronchoconstriction in asthma (EIBa) (2), and although sometimes may be the prominent clinical manifestation of asthma, it is enough to impair lifestyle and quality of life, especially among children, teens, young adults, and athletes (1,3). A high prevalence of asthmatics can be affected by EIBa (4,5,6).

Usually, airflow obstruction occurs soon after the end of exercise mainly due to both osmotic and thermal mechanisms (2,7,8), but sometimes may develop during exercise, limiting the subjects' physical performance (9).

Adequate treatment of underlying airway inflammation and, if needed, pre-treatment with fast short-acting (rarely fast long-acting) beta-2 selective agonists, or leukotriene-receptor antagonists is effective to control and prevent this event (10).

It would be useful to have predictors of EIBa, mainly in asthmatic young people, in order to implement an adequate strategy to avoid bronchoconstriction after exercise or during it as much as possible.

The study aimed to identify, in subjects with persistent mild asthma suspected for EIBa, functional parameters, either at rest or during exercise, predictors of effort-related airflow obstruction.

Methods

Subjects

This prospective study was performed at the Respiratory Medicine Unit of Spedali Civili University-Hospital of Brescia, Italy, from July 2018 to February 2019. To be included in the study, the subjects had to be aged 18-40 years and never smokers, have had a diagnosis of mild persistent asthma, according to GINA guidelines (11), supported by clinical judgment and objective measurements of lung function, including a positive methacholine challenge test for airway hyperresponsiveness and stable conditions for at least 8 weeks under usual treatment. Asthmatic subjects with other respiratory diseases and medical comorbidities were excluded from the study. The participants were recruited only if, in the past, they reported or were reported to have episodes suspected for effort-related acute respiratory symptoms.

Study design

Functional respiratory tests

In the morning of the first day, after 8 hour washout from short-acting bronchodilators, 24 hour washout from long-acting bronchodilators, and 4 week washout from any inhaled corticosteroids (ICS) or oral anti-cysteinyl leukotrienes, each subject performed in the first day a spirometry (BIOMEDIN Instruments, Padua, Italy) wearing a nose clip and breathing through a flanged mouthpiece. Slow vital capacity (VC) and inspiratory capacity (IC) were measured twice using a bell spirometer at rest in sitting position. At least three acceptable and reproducible maximal full expiratory maneuvers were performed to measure forced vital capacity (FVC), maximal expiratory volume in the first second (FEV_1), and maximal forced expiratory flows ad different lung volumes.

Lung volumes were measured with a pressure-constant plethysmograph (BIOMEDIN Instruments, Padua, Italy). During the procedure, patients panted at a 0.7 Hertz frequency. Three acceptable tracings of mouth pressure versus box volume changes were averaged to achieve a final measurement of functional

residual capacity (FRC). Total lung capacity (TLC) and residual volume (RV) were computed subsequently. In each circumstance, the best values were collected for analysis. All tests were performed according to the ERS-ATS recommendations (12). Predicted values of lung function parameters were those proposed by the European Community for Coal and Steel (13).

In the late morning, each subject performed a challenge test for measuring nonspecific, direct airway responsiveness using doubling doses of methacholine inhaled by dosimeter (MEFAR, Brescia, Italy). The tests were stopped just after more than 20% reduction of FEV_1 from baseline (saline inhalation) to calculate airway sensitivity as $PD_{20}FEV_1$.

The second day, in the late morning, each subject underwent a symptom-limited, incremental cardiopulmonary exercise test by computer-driven cyclo-ergometer with ramping protocol (15 watts increment per minute) at a pedaling frequency of 50-60 per minute (CPExT). This protocol was able to achieve always 80-90 % of predicted maximum heart rate towards the end of the exercise and to maintain it for a few minutes. At rest and regular intervals of 2 minutes during exercise, the subjects were asked to inspire maximally toward total lung capacity (TLC) to obtain their inspiratory capacity (IC) that was measured off-line and expressed as % of TLC, at 33%, 66% and 99% of the peak workload.

At the end of the effort, repeated full forced expiratory maneuvers were requested to obtain maximal flow-volume curves for measuring FEV_1 at 1-3-5-7-10-15 minutes after stopping exercise. A FEV_1 fall greater than 10% of FEV_1 measured before starting exercise was considered as indicative of EIBa.

The study was performed in accordance with the Helsinki declaration and was approved by the local University-Hospital Ethic Committee. All participants signed written informed consent upon enrolling.

Statistics

Unless specified otherwise, data are expressed as the mean ± standard deviation. The comparisons of the functional variables between groups were performed according to the Student's unpaired t-test or the Mann-Whitney U test if the normal distribution could not be assumed. Statistical significance was accepted if $p \leq 0.05$. Statistical analyses were performed using Graph Pad Prism 6.0 (Graph Pad Software, La Jolla, CA) and SPSS 23.00 (IBM, Armonk, NY)

Results

Twenty asthmatic subjects were enrolled in the study. One subject refused CPExT and was excluded from the analysis. Among 19 subjects, 7 (32%) did not show EIBa with a $DFEV_1$ max from baseline (made equal to 100) amounting to 97±6% (absolute change -2.6±2.0%), while 12 (68%) had EIBa with a $DFEV_1$ max from baseline (made equal to 100) amounting to 85±6% (absolute change -16.2±6.7%)

Anthropometric and baseline functional data of the 19 patients of the study are shown in Table 1, all together and divided into 2 groups according to the presence or absence of EIBa. No significant

differences emerged between the 2 groups. The mean duration of asthma was 11±3 yr, with no significant difference between the two groups. All subjects were usually treated with inhaled corticosteroids that were withdrawn 4 weeks before the study and 7 with long-acting beta-2 agonists on top.

Mean data obtained at the peak of CPExT were presented in Table 2 with the IC values (as % TLC) at different prefixed percent levels of the maximal effort, again in all subjects, and divided into 2 groups with and without EIBa. Not significantly different values of the main variables of interest at peak exercise were found between the 2 groups. However, while the mean IC progressively increased throughout the exercise in asthmatics without EIBa, mean IC slightly decreased progressively in asthmatics with EIBa.

The end-inspiratory (EILV) and end-expiratory (EELV) lung volume changes during exercise were illustrated in Fig.1, panel a, and b for the non-EIBa and EIBa groups, respectively, indicating a possible exertional dynamic pulmonary hyperinflation (DH) at least in some asthmatics with EIBa.

In fact, looking at the individual measurements of IC during exercise in asthmatics with EIBa, 6 out of 12 (50%) displayed a marked EELV increase and IC decrease (EIBa subgroup 2), reflecting a noticeable DH, whereas the other 6 (EIBa subgroup 1) had a normal lung mechanics behavior during the effort, similar to that shown by the asthmatics without EIBa (Fig. 1, panel d and c).

The only different variable at peak of exercise between the two subgroups with EIBa was the respiratory rate, much higher in the EIBa subgroup 2 (41.3±6.5 vs. 33.3±6.4, $p<0.05$).

By comparing the lung function measurements at rest between these two subgroups of asthmatics with EIBa, the only different parameter resulted the maximal mean expiratory flow-rate between 25% and 75% of forced vital capacity ($FEF_{25-75\%}$), which was significantly reduced ($p<0.05$) in the subgroup with DH (EIA subgroup 2), suggesting a greater structural involvement (inflammation/remodeling) of the small airways in these subjects (Fig. 2,a). Interestingly, $PD_{20}FEV_1$ was markedly lower in this subgroup with DH (geometric mean 55 (33-261) mcg vs. 389 (101-683) mcg; $p<0.05$), partly explained by larger ventilation heterogeneity that is a marker of peripheral airway impairment (Fig. 2,b).

Finally, the post-exercise fall in FEV_1 was more rapid and pronounced in the EIBa with DH during exercise (EIBa subgroup 2) as compared with those with EIBa but without DH during exercise (EIBa subgroup 1) (Fig. 3).

No differences were found between the non-EIBa group and EIBa subgroup 1 concerning both baseline pulmonary function tests (including $FEF_{25-75\%}$) and parameters obtained during CPExT.

Discussion

The main findings of the study are the following. No functional parameter either at rest or during exercise was significantly different and able to distinguish in a population of subjects with mild persistent asthma

who would have had EIBa and who not. In contrast with asthmatics without EIBa, however, in those with EIBa, IC did not increase during exercise, and some of them (in our series 50%) developed DH during exercise with earlier FEV_1 fall after stopping it. This subgroup of asthmatics with EIBa with DH during exercise (subgroup 2) showed a significant reduction of $FEF_{25-75\%}$ at rest and higher airway responsiveness to methacholine, suggesting a more extensive structural and functional involvement of small airways.

We did not found any respiratory functional parameters at rest useful to predict the occurrence of exercise-induced bronchoconstriction in relatively young asthmatics with similar history and severity of disease (mild persistent asthma). Also during exercise, albeit patients developing EIBa had slightly lower mean peak values of workload and oxygen uptake, there were no significant differences in average between the two groups.

Asthmatics with EIBa, however, showed a distinct functional behavior during exercise characterized by the absence of EELV reduction (Fig. 1) with a subgroup developing DH, as witnessed by the progressive IC decrease, that was associated with significantly reduced forced expiratory flows at lower lung volumes at baseline and higher airway responsiveness.

In the presence of normal FEV_1 and FVC, reduced $FEF_{25-75\%}$ strongly suggests an increased up-stream resistance in these asthmatics' small airways that, favoring a larger ventilation heterogeneity, may in part explain the higher airway hyperresponsiveness we observed concurrently (14).

The baseline reduced expiratory flow reserve at lower lung volumes, corresponding to the tidal volume range, may promote tidal expiratory flow limitation (EFL) when the ventilatory requirements increase during exertion. This possibility was elegantly demonstrated by Kosmas and coworkers some years ago, using the negative expiratory pressure technique, in a large percentage of subjects suffering from asthma of different severity, from intermittent or mild to severe, but without EIBa, during symptom-limited incremental bicycle exercise test (15). Also in this study, asthmatics who developed EFL during exercise had a lower baseline $FEF_{25-75\%}$ and $FEF_{75\%}$ than those without EFL during exercise.

An increment of airway resistance throughout the exercise observed in some asthmatics (15,16), especially with EIBa (9, 17,18), can markedly increase this possibility.

In these circumstances breathing at higher operative lung volumes allows to escape tidal EFL or have minimal EFL and continue exercising but at the expense of progressive DH (19).

Therefore, these indices such as $FEF_{25-75\%}$ and $PD_{20}FEV_1$, easily obtained at rest, could explain why some asthmatics with EIBa may have symptoms also during effort linked to the development of DH that might limit their exercise tolerance and maximal performance because of its associated mechanical constraints.

In the future would be interesting by using FOT to measure parameters of respiratory system resistance (Rrs5-Rrs20 difference) and reactance (Xrs5 or AX), exploring small and peripheral airway mechanical properties to confirm this hypothesis in asthmatics suffering from EIBa, who begin to have symptoms also during effort (20).

Higher airway hyperresponsiveness (i.e., higher sensitivity as $PD_{20}FEV_1$) can ensue from a deeper epithelial damage associated with either greater airway inflammation or abnormal neurogenic control or both, and this condition may certainly induce a worse functional impairment of small airways. Concurrently, larger ventilation heterogeneity sustained by a marked small airway involvement might also explain a higher airway hyperresponsiveness (13). We cannot discriminate between these two different mechanisms that, however, could coexist in this subgroup of asthmatics with EIBa.

This study is limited by the relatively small number of subjects and possibly the choice of the exercise challenge that is less than optimal for induction of EIBa, but needful to measure the operational lung volumes dynamic changes. However, we were able to elicit EIBa in more than 65% of the subjects recruited for suspicious symptoms. Finally, we do not think that the absence of a matched control group could invalidate the meaning of our findings.

Conclusions

None of the routine functional parameters measured at rest and during exercise can distinguish among mild asthmatics those who will develop EIBa or not.

However, in some mild asthmatics with EIBa, dynamic hyperinflation can occur during exercise, likely limiting their exercise tolerance and performance. Such as unfavorable mechanical constraint is associated with significantly decreased forced mean flow rates at lower lung volumes at rest and higher airway hyper-responsiveness, suggesting a more profound involvement of small airways in these subjects. That may explain why some asthmatics with EIBa become symptomatic during effort and not only after stopping it.

List Of Abbreviations

EIBa = Exercise-induced bronchoconstriction in asthma

ICS = Inhaled corticosteroids

VC = Vital capacity

IC = Inspiratory capacity

FVC = Forced vital capacity

FEV1 = Maximal expiratory volume in the first second

FRC = Functional residual capacity

TLC = Total lung capacity

RV = Residual volume

CPExT = Cardiopulmonary exercise test

EILV = End-inspiratory lung volume

EELV = End-expiratory lung volume

DH = Dynamic hyperinflation

FEF25-75% = Expiratory flow-rate between 25% and 75% of forced vital capacity

Declarations

Ethics approval and consent to participate

The study was performed in accordance with the Helsinki declaration and was approved by the local University-Hospital Ethic Committee. All participants signed written informed consent upon enrolling.

Consent for publication

Not applicable

Availability of data and materials

All data generated or analyzed during this study are included in this published article.

Competing interests

The authors declare that they have no competing interests

Funding

Not applicable

Authors' contributions

CT and MS: Study design

MS, FS, FQ and LP: Data collection

LP, DB and FS: Data Analysis

All authors: Interpretation of results

CT: Initial draft

All authors: Review of the manuscript for intellectual content

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Tables

Table 1

Anthropometric and baseline functional respiratory parameters obtained for all asthmatic subjects and those divided according to the absence (non-EIBa) or presence (EIBa) of exercise-induced bronchoconstriction.

	All	non-EIBa	EIBa	p
Subjects (n)	19	7	12	ns
Sex (m-f)	9-10	5-2	4-8	ns
Age (yrs)	27±10	28±8	27±11	ns
Weight (kg)	68±11	72±13	66±10	ns
Height (m)	1.71±0.09	1.75±0.09	1.69±0.09	ns
BMI (kg/m²)	23±4	23±2	23±5	ns
VC (% pred)	108±8	107±8	109±9	ns
FVC (% pred)	109±8	110±8	108±9	ns
IC (% pred)	100±15	107±11	96±16	ns
FEV1 (% pred)	103±8	105±11	102±7	ns
FEV1 /VC (% pred)	96±7	97±6	95±8	ns
PEF (% pred)	96±13	101±13	94±12	ns
FEF 25-75 % (% pred)	83±20	88±22	79±19	ns
RV (% pred)	105±32	100±22	108±36	ns
FRC (% pred)	108±31	98±25	113±33	ns
TLC (% pred)	107±11	104±4	109±13	ns
RV/TLC (% pred)	96±21	94±21	97±22	ns
FRC/TLC (% pred)	100±21	91±19	105±21	ns

BMI = Body Mass Index; VC = Vital Capacity; FVC = Forced Vital Capacity; IC = Inspiratory Capacity; FEV1 = Forced Expiratory Volume in first second; FEV1/VC = Tiffeneau Index; PEF = Peak Expiratory Flow; FEF 25-75% = Forced mean Expiratory Flow-rates between 25% and 75% of FVC; RV = Residual Volume; FRC = Functional Respiratory Capacity; TLC = Total Lung Capacity;

Table 2

Parameters obtained during CPExT at peak of exercise and values of IC at rest (bas.) and at prefixed percentages of workload during exercise for all asthmatic subjects and those divided according to the absence (non-EIBa) or presence (EIBa) of exercise-induced bronchoconstriction.

	All	non-EIBa	EIBa	p
Work peak (% pred)	104±20	110±15	100±22	ns
VO2 peak (% pred)	99±13	104±15	96±11	ns
HR peak (% pred)	91±9	92±11	90±8	ns
VE peak (% pred)	53±10	53±12	52±9	ns
RR peak (br/min)	35±7	33±6	37±7	ns
Vt peak (L)	1.6±0.4	1.6±0.3	1.6± 0.5	ns
IC bas. (L)	3.0±0.5	3.2±0.7	2.9±0.5	ns
IC 33% Work peak (L)	3.0±0.5	3.3±0.7	2.9±0.4	ns
IC 66% Work peak (L)	3.0±0.6	3.3±0.8	2.9±0.4	ns
IC 99% Work peak (L)	3.1±0.7	3.5±0.9	2.8±0.4	ns

VO2 = Oxigen Consumption; HR = Heart Rate; VE = Minute Ventilation; RR = Respiratory Rate; Vt = Tidal Volume; IC = Inspiratory Capacity

Figures

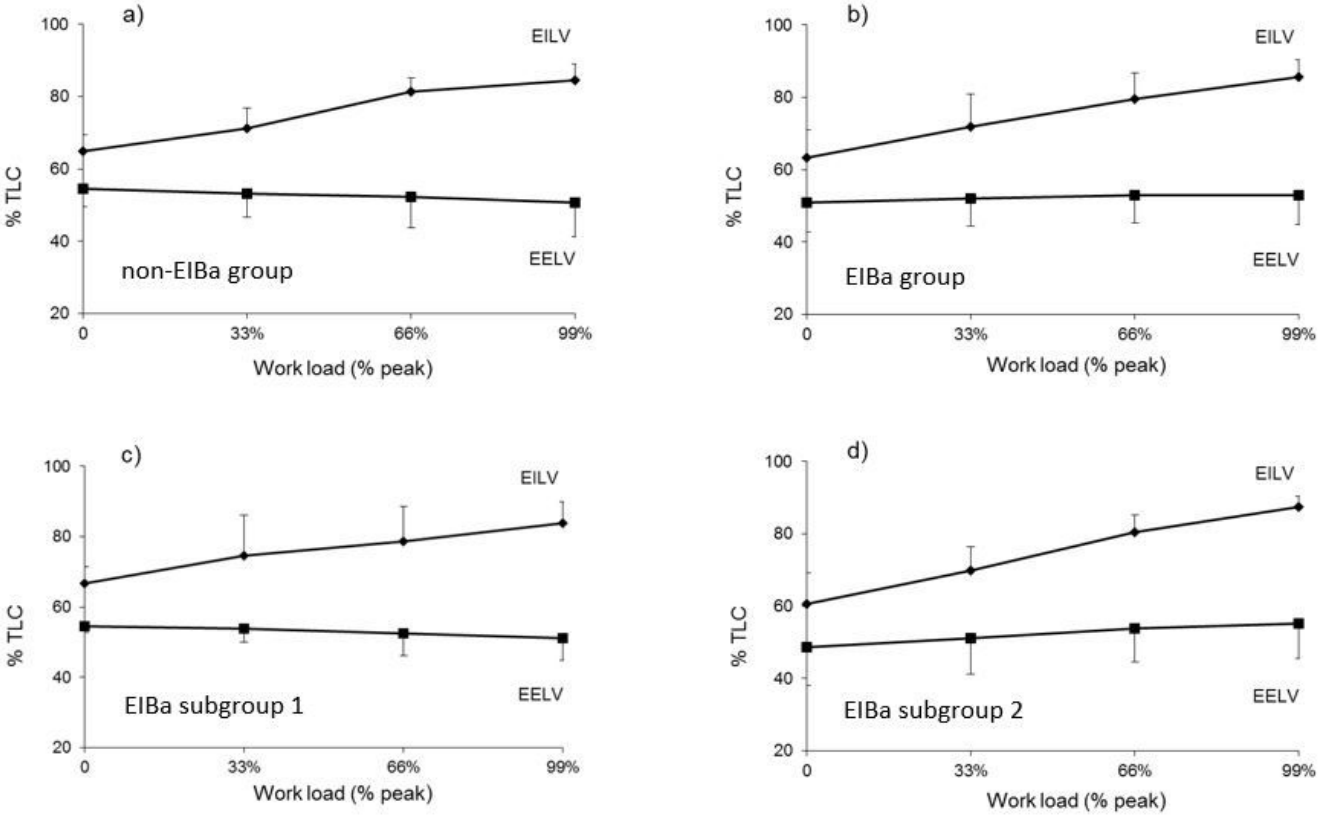
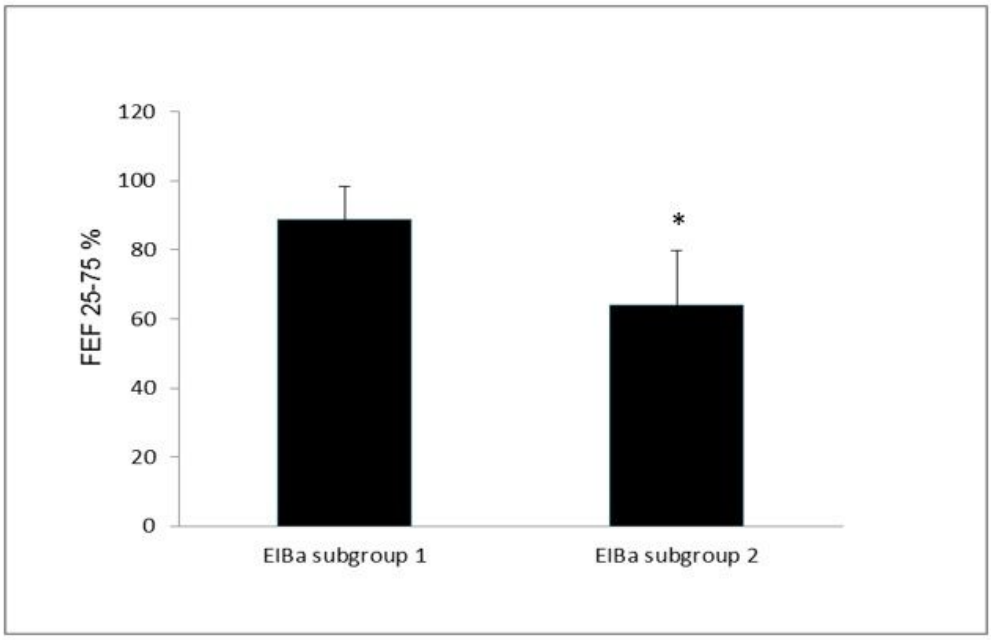


Figure 1

End-expiratory (EILV; squares) and end-inspiratory (EELV; diamonds) lung volume changes during exercise in asthmatics without EIBa (n = 7; panel a) and in asthmatics with EIBa (n = 12; panel b). EILV (squares) and EELV (diamonds) changes during exercise in asthmatics with EIBa without (n=6; panel c) and with (n=6; panel d) dynamic pulmonary hyperinflation.

Panel a)



Panel b)

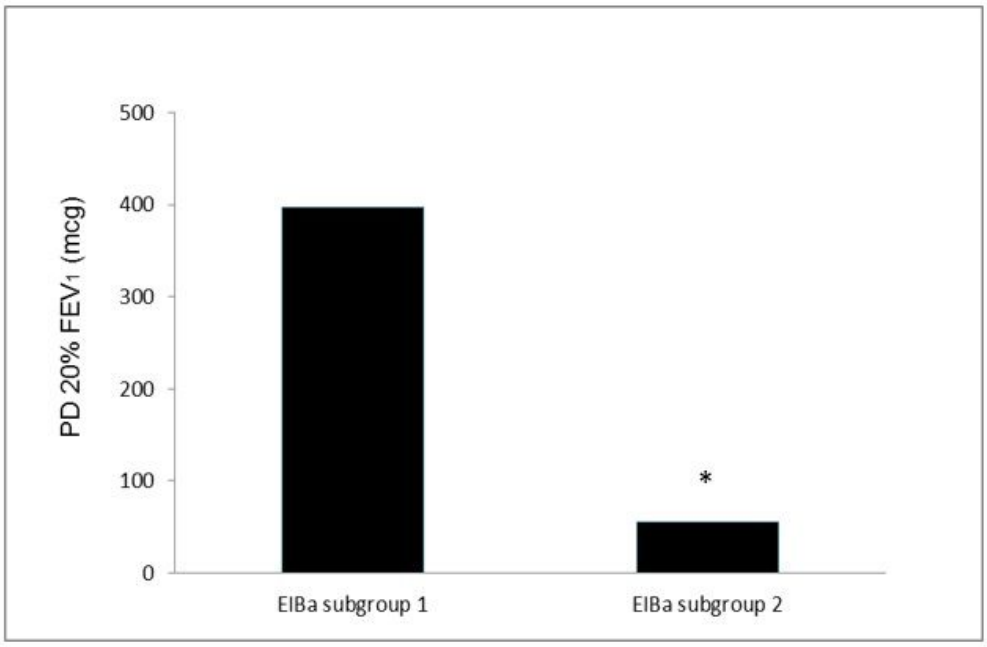


Figure 2

Mean Forced expiratory flow-rates between 25 and 75% of FVC (FEF25-75%) at rest in asthmatics with EIBa, without (subgroup 1) and with (subgroup 2) dynamic pulmonary hyperinflation during exertion (panel a) * $p<0.05$. Provocative dose of methacholine causing a 20% FEV1 fall from baseline (saline) FEV1 (PD20FEV1) in asthmatics with EIBa, without (subgroup 1) and with (subgroup 2) dynamic pulmonary hyperinflation during exertion (panel b) * $p<0.05$. Geometric mean.

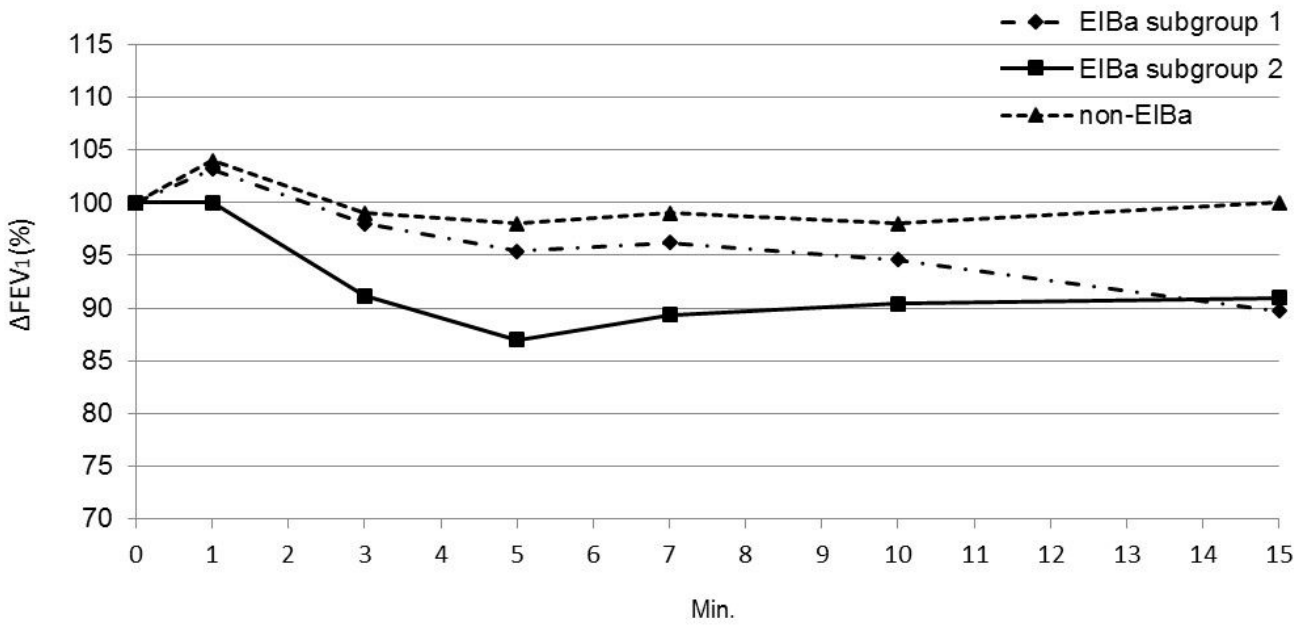


Figure 3

Changes of FEV1 after stopping exercise in asthmatics without EIA (n=7) and with EIBa, without (n=6; subgroup 1) and with (n=6; subgroup 2) dynamic pulmonary hyperinflation during exertion (DH). Asthmatics with EIBa and DH showed an earlier and more pronounced ΔFEV1 than asthmatics with EIBa but without DH.