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Dynamic hyperinflation in patients with asthma and exercise-induced bronchoconstriction

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A R T I C L E   I N F O

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A B S T R A C T

Background: Little is known about the behavior of operative lung volumes during exercise in patients with asthma and exercise-induced bronchoconstriction (EIB).

Objectives: To compare the presence of dynamic hyperinflation (DH) in patients with mild asthma with and without EIB and in healthy individuals and to relate the changes in end-expiratory lung volume (EELV) with postexercise airflow reduction.

Methods: A total of 122 consecutive stable patients (>12 years of age) with mild asthma and 38 controls were studied. Baseline lung volumes were measured, and all patients performed an exercise bronchial challenge. At each minute of exercise, EELV and end-inspiratory lung volume (EILV) were estimated from inspiratory capacity measurements to align the tidal breathing flow-volume loops to within the maximal expiratory curve.

Results: DH was more frequent in patients with asthma and EIB (76%) than in patients with asthma but without EIB (11%) or controls (18%). The EELV increased in patients with asthma and EIB and decreased in patients with asthma without EIB and controls during exercise. In the patients with asthma, the decrease in forced expiratory volume in 1 second after the exercise challenge correlated with age ($r = -0.179$, $P = .05$), baseline forced vital capacity ($r = 0.255$, $P = .005$), EELV increase ($r = 0.447$, $P < .001$), and EILV increase ($r = 0.246$, $P = .007$). Age, baseline forced vital capacity, and magnitude of DH were retained as independent predictors of EIB intensity.

Conclusion: In patients with asthma and EIB, the development of DH is very frequent and related to the intensity of postexercise bronchoconstriction. This finding could implicate DH in the development of EIB.

Introduction

Exercise-induced bronchoconstriction (EIB), a transient narrowing of the lower airways that occurs after vigorous exercise, is a frequent manifestation in patients with asthma.[1–3] Classically, the development of EIB has been attributed to a dual mechanism. The evaporative loss of water associated with hyperventilation leads to a transient increase in osmolarity of the airway surface fluid, which causes inflammatory cells to release mediators of bronchoconstriction.[2,4] On the other hand, the reactive hyperemia of the bronchial circulation after exercise and the subsequent edema of the airway wall may also precipitate or enhance airway narrowing.[3–6]

Until now, most research about the pathogenic mechanisms of this functional disorder has been focused on the bronchoconstriction developed after exercise.[7] However, it has been proposed that the ventilatory strategy adopted during exercise might have consequences on postexercise bronchoconstriction.[2,3,8,9] In fact, even though maximal airway narrowing usually occurs 5 to 12 minutes after 6 to 8 minutes of vigorous exercise, flow rates can start to decrease during exercise.[10,11]

Although the prevalence of expiratory flow limitation at rest is very low in patients with mild asthma,[12] these patients exhibit tidal

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expiratory flow limitation during exercise.[13] Given the increased ventilatory demands induced by exercise, if patients with asthma and EIB experience a more pronounced expiratory flow limitation during exercise, their respiratory system must operate at higher lung volumes to ensure adequate ventilatory response. In this case, an increase in end-expiratory lung volume (EELV) during exercise could reflect the presence of dynamic hyperinflation before the development of postexercise airway narrowing.

The term *dynamic hyperinflation* refers to the temporary increase during exercise in operating lung volumes above their resting value, reflecting that a new breath begins before the lung has reached the static equilibrium volume. Although this abnormal response to exercise has been extensively analyzed as a determinant of breathlessness and exercise intolerance in patients with chronic obstructive pulmonary disease,[14] it is not exclusive of this disease. Interestingly, dynamic hyperinflation has been reported during methacholine-induced bronchoconstriction in patients with stable asthma.[15] In patients with mild to severe asthma, a forced expiratory volume in 1 second (FEV_1) decrease of 25% during methacholine challenge tests was associated with significant dynamic hyperinflation,[15] reflecting compromised lung emptying and air trapping during tidal breathing.[16] Moreover, in obese individuals with asthma, dynamic hyperinflation in response to acute bronchoconstriction is greater with increasing body mass index,[17] which provides evidence that obesity might contribute to increased dynamic hyperinflation during acute bronchoconstriction. However, to our knowledge, no studies have explored the correlation between changes in operative lung volumes during exercise and postexercise bronchoconstriction in patients with asthma without airflow limitation at rest.

In this prospective study, we hypothesized that the development of dynamic hyperinflation during the exercise challenge is previous to the occurrence of EIB. Our aim was to explore the presence of dynamic hyperinflation in patients with mild asthma with and without EIB and in healthy individuals and to correlate the EELV change with postexercise airflow reduction.

Methods

Study Participants

A total of 122 consecutive patients with mild asthma were recruited from the asthma clinic at the Hospital Universitario La Paz (Madrid, Spain). All patients were older than 12 years and met the Global Initiative for Asthma criteria for a diagnosis of asthma,[18] and no clinical or laboratory evidence of any other cardiorespiratory disease was present. Thirty-eight healthy individuals were recruited as a control group; they were asymptomatic, had normal pulmonary function, and had negative methacholine bronchial challenge results.

All participants were in stable clinical condition and had had no changes in respiratory medications within the 6 weeks before testing. Patients with asthma were asked to withhold their short- and long-acting bronchodilators for 8 and 24 hours before the test, respectively. None of the patients had used inhaled corticosteroids in the 3 months before recruitment. The study was approved by the local ethics committee (CEIC Hospital Universitario La Paz), and all participants or their representatives gave their written informed consent.

Measurements

All determinations were performed by an investigator who was masked to the patients' characteristics. A baseline spirometry was performed before the challenge in accordance with current recommendations[19] and using a pneumotachograph spirometer (MasterScope, Jaeger, Würzburg, Germany). Body plethysmography was conducted with a MasterLab body 6.0 system (Jaeger) according to current recommendations.[20] The values were expressed as a percentage of the predicted normal.[21]

The exercise challenge was performed according to American Thoracic Society recommendations[22] with a bicycle ergometer (Ergobex, Bexen, Madrid, Spain). The protocol used for the exercise challenge was based on that of Anderson et al.[23] The work intensity was selected for each participant to achieve a minute ventilation between 40% and 60% of his or her predicted maximal voluntary ventilation ($35 \times FEV_1$ predicted) for 6 minutes. With the aid of an air-conditioning apparatus, the exercise laboratory temperature and relative humidity were kept from 20°C to 22°C and 50% to 55%, respectively. The participant wore a face mask covering the nose and mouth together with a nose clip to ensure mouth breathing of dry air alone. Minute ventilation rates during exercise (V_E) were measured by means of a pneumotachograph (Oxycon Alpha, Jaeger). At every minute during exercise, V_E values were calculated from 10-second means of the breath-by-breath data. Standard spirometry measurements were obtained before and 1, 3, 5, 10, 15, 20, and 30 minutes after cessation of exercise. EIB was defined as a decrease in FEV_1 of more than 10% after exercise.[23]

Assuming that total lung capacity did not change during exercise,[24] changes in inspiratory capacity (IC) were used to assess the level of dynamic hyperinflation. At least 2 reproducible IC maneuvers were obtained at rest and every minute during exercise (Oxycon Alpha, Jaeger). If efforts appeared submaximal or if anticipatory changes in breathing pattern occurred immediately preceding a maneuver, then the IC was not accepted.[25] Changes in end-inspiratory lung volume (EILV) were reflected by changes in inspiratory reserve volume, which was derived by subtracting tidal volume from the coinciding IC. Before exercise testing, the IC maneuvers were explained and then practiced by the patients until consistently reproducible values (difference <10%) were obtained. Patients were specifically instructed after the verbal signal and at the end of the next normal breath out to continue the next breath until the lungs were full and then to try to make an extra effort to fill them up even more. They were asked to do this fairly quickly to not interrupt breathing for very long. The maneuver ended with a normal, unforced exhalation. After the training phase, less than 15% of IC maneuvers were rejected and repeated.

The patient was considered to have developed dynamic hyperinflation when the slope of linear regression of the EELV as a function of time was higher than zero. In addition, the difference among the last EELV measurement, near end exercise, and the resting value was computed.

Statistical Analysis

Values are expressed as means (SD) or percentage. The comparisons between the groups were performed by means of the analysis of variance with Bonferroni post hoc tests, whereas the χ^2 test was used for evaluating frequencies. Associations between variables were determined by Pearson correlation analysis. Significant contributors to the intensity of EIB were introduced in a stepwise multiple linear regression analysis. In this model, predictor variables were retained only if their addition significantly improved ($P < .05$) the fraction of explained variability (r^2). Other aspects explored included residual SD, changes in the distribution of the residuals, and the homogeneity of the variance over the predictors. These analyses were performed using the SPSS statistical software, version 11.0 (SPSS Inc, Chicago, Illinois). In all cases, $P < .05$ was considered significant.[26]

Results

Forty-one patients with asthma had positive response to the exercise bronchial challenge, whereas EIB was not identified in the