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Exercise-induced bronchoconstriction diagnosis in asthmatic children: comparison of treadmill running and eucapnic voluntary hyperventilation challenges

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ABSTRACT

Background: Exercise-induced bronchoconstriction (EIB) occurs in up to 90% of young people with asthma and can be diagnosed using serial measurements of forced expiratory volume in 1 second (FEV_1) after standardized exercise, usually treadmill running (TR). Eucapnic voluntary hyperventilation (EVH) is a guideline-recommended alternative challenge for EIB diagnosis. The 2 methods have not been compared for EIB diagnosis in this population.
Objective: To compare 2 methods of EIB diagnosis in children and adolescents with asthma.
Methods: Thirty-four children 8 to 18 years of age attending the allergy clinic of the Hospital das Clínicas (Recife, Brazil) from September through December 2013 were examined. All underwent a basal FEV_1 determination followed by TR for 8 minutes or EVH for 6 minutes on consecutive days. The first challenge was chosen at random. Serial FEV_1 determinations were obtained at 3, 5, 7, 10, 15, and 30 minutes after the challenge and the test result was considered positive if at least 2 consecutive FEV_1 measurements decreased at least 10% below the basal value.
Results: Thirteen patients responded to the 2 challenges, 6 only after TR and 4 exclusively after EVH (agreement 71%, $\kappa = 0.41$). The 95% limits of agreement of FEV_1 decreasing after the challenges were widely spread (mean 0.1%, limits 19.8% to −19.6%).
Conclusion: The 2 tests cannot be used interchangeably and the reproducibility of the FEV_1 response to the EVH challenge has to be properly evaluated to better understand its role in EIB diagnosis.

Introduction

Exercise-induced bronchoconstriction (EIB) is the transient acute narrowing of the lower airways during or shortly after vigorous physical activity.[1,2] Its prevalence is estimated at 6% to 20% in the general pediatric population and 50% to 90% in children and adolescents with asthma.[2,3] In the latter group, EIB can lead to lower physical activity levels and impair psychomotor development, general physical conditioning, and quality of life.[2,3] For this reason, EIB needs to be diagnosed early and effectively.

Respiratory complaints, such as dyspnea, tightness of the chest, and coughing and wheezing, are frequently reported by people with asthma after vigorous exercise but even when encountered together are neither sensitive nor specific for the diagnosis of EIB.[2–4] Therefore, in adequately treated individuals with asthma and persistent exercise-associated complaints, objective tests are necessary for adequate EIB evaluation and the assessment of its severity.[5]

Free and treadmill running (TR) or pedaling on a stationary bike are exercise challenges usually used for EIB diagnosis. A post-exercise decrease of forced expiratory volume in 1 second (FEV_1) of at least 10% compared with the basal value is considered diagnostic.[1,5] Although TR is well standardized and widely used for EIB diagnosis in adults and children older 8 years, other challenge methods have been suggested as surrogates.[5] The most cited of these is eucapnic voluntary dry air hyperventilation (EVH), which could have some advantages over exercise challenges, such as better control over ventilation rates and easier execution.[2,5]

The EVH bronchial challenge technique was developed to evaluate EIB in US military recruits in the late 1970s and since then has

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been studied in elite athletes. In the present study, it was found to have greater sensitivity compared with TR.[3,6–8] However, although well standardized,[5] the clinical usefulness of EVH for the diagnosis of EIB in children and adolescents with asthma has not been established.[9] Thus, the aim of this study was to compare TR with EVH as a bronchial challenge for EIB diagnosis in this patient group.

Methods

This was a cross-sectional analytical study involving children 8 to 18 years old with asthma being treated at the outpatient clinic at the allergy and clinical immunology service of the Clinical Hospital of the Federal University of Pernambuco (Recife, Brazil). The project was approved by the institutional research ethics committee (registration number 399.888). Participation in the study was voluntary and a consent form was signed by all the parents or legal guardians and an assent form was signed by the subjects.

Asthma was diagnosed by an assistant specialist based on related symptoms and bronchodilator FEV_1 response, and the level of disease control during the previous 4 weeks was evaluated using the Asthma Control Test (ACT).[10] Selected patients did not have an asthma exacerbation or any respiratory infection complaints in the previous 4 weeks and had a basal FEV_1 value higher than 60% of the predicted value. Short- and long-acting β_2-agonists were interrupted at least 8 and 48 hours, respectively, before the tests.[11]

After height, weight, basal heart rate (FT1, Polar, Lake Success, New York), and peripheral O_2 saturation (Nonin Onix, Minneapolis, Minnesota) measurements had been taken, patients underwent basal FEV_1 measurements,[12] and then, after proper instruction, were asked to perform TR or the EVH maneuver, in a random order, with an interval of 24 hours between challenges. The FEV_1 was measured in duplicate 3, 5, 7, 10, 15, and 30 minutes after each challenge and the highest value was chosen to compare with basal values. A positive response was considered only if a decrease in FEV_1 of at least 10% from the pre-challenge value was observed at at least any 2 consecutive measurement time points after the challenge and the lower value was chosen for statistical analysis.[13]

For the exercise challenge, patients were instructed to run on the treadmill (EG700X; Ecafix, São Paulo, Brazil) without a ramp for 8 minutes. The first 2 minutes were for adaptation to reach 80% to 90% of maximum heart rate (220 minus age in years) and, for the last 6 minutes, the speed was adjusted to keep the heart rate between these limits.[11]

For the EVH, a 5% CO_2, 21% O_2, and 74% N_2 medical dry mixture (White Martins, Cabo de Santo Agostinho, Pernambuco, Brazil) was released through a rotameter into a flexible plastic reservoir and inhaled orally by the patients through a unidirectional low-resistance anesthesia plastic valve, with the nose clipped and the minute ventilation rate targeted at 21 times the patients' basal FEV_1 for 6 minutes as recommended for patients with known asthma.[14] Patients were coached to try to keep to this target and their minute ventilation was monitored by a digital ventilometer (Ventronic, Wampsville, New York).

Concordance analysis between challenge protocols was performed using the Cohen κ coefficient and positive and negative agreement proportions.[15] To compare the percentage of decrease in FEV_1 between the multiple moments of evaluation, a general linear model for longitudinal repeated measures was adopted with the Sidak test. To assess the agreement of change in FEV_1 between challenges, the limits of agreement were calculated and plotted according to the method of Bland and Altman.[16] In all cases, an α error probability was set at 5%.

Results

Forty-two patients were initially selected for the study. Of these, 8 were excluded because they had an FEV_1 lower than 60% of the predicted value. None were excluded because of an incapacity to perform acceptable expiratory maneuvers for the FEV_1 measurements or to execute the TR or EVH protocol. Patients' general data are presented in Table 1. There was no difference in mean baseline FEV_1 values expressed as a percentage of predicted between challenge days (TR, mean ± SD FEV_1 92.9 ± 15.6%, 95% confidence interval 98.4–87.6%; EVH, FEV_1 88.3 ± 15.4%, 95% confidence interval 93.8–83.1%; $P = .23$). Air temperature and relative humidity were not significantly different between days and were, respectively, 22.5 ± 1.4°C and 56.9 ± 4.4% (absolute humidity ~10.9 g of H_2O/m^3) on the TR day.

Table 1
Participants' baseline characteristics (n = 34)

Boys/girls	19/15
Age (y), mean ± SD	11.9 ± 2.4
Weight (kg), mean ± SD	49.0 ± 10.8
BMI (kg/m^2), mean ± SD	21.2 ± 3.9
ACT[a], mean ± SD	21.5 ± 2.7
Basal FEV_1 (% predicted), mean ± SD	91.2 ± 14.5

Abbreviations: ACT, Asthma Control Test; BMI, body mass index; FEV_1, forced expiratory volume in 1 second.
[a]ACT limits 17 to 25.

There were 19 subjects with positive challenge results after TR and 17 after EVH. Thirteen children had a positive response after the 2 challenges. In 6, the FEV_1 decrease was observed only after TR and in 4 the decrease was observed only after EVH ($\kappa = 0.412$, $P < .05$) and there was 71% concordance between the challenge methods (Table 2).

There were no differences between TR and EVH in the intensity of after-challenge FEV_1 decrease within the same interval ($P = .28$; Fig 1). For the 2 tests, the greatest FEV_1 decrease was observed between minutes 3 and 15 in 95% of the challenges. In those patients in whom the FEV_1 decrease persisted to minute 30 after the challenge (10 subjects after TR and 7 after EVH), 400 μg of albuterol was administered by inhalation, with complete reversal in all cases. FEV_1 decreased by more than 30% in 1 patient after EVH, in 1 after TR, and in 1 after EVH and TR, but without the need of albuterol inhalation for reversal before the end of the evaluation period (Fig 2). There was no correlation between baseline FEV_1 expressed as a percentage of the predicted value and the magnitude of the decrease in FEV_1 after TR ($R^2 = 0.01$) or EVH ($R^2 = 0.003$).

The limits of agreement in FEV_1 response after the 2 challenges were broad and are shown on Figure 3.

During TR, there was no difference between patients with and without EIB for mean heart rates as the percentage of the calculated maximum heart rate (91 ± 3% vs 91 ± 2%, $P = .79$).

Mean ventilation rates achieved by patients with and without an FEV_1 decrease of at least 10% after EVH (EVH^+ and EVH^-, respectively) showed no differences (35.2 ± 8.8 L/min^{-1} and 38.6 ± 8.6 L/min^{-1}, $P = .27$). For target ventilation levels as a multiple of basal FEV_1, mean values achieved by EVH^+ individuals were 17.3 ± 2.8 and by EVH^- values were 15.9 ± 2.0 ($P = .1$). In the EVH^+ group, only 4 patients achieved a ventilatory rate of 21 times the basal FEV_1, 5 reached 17 to 20.9, and in 8 the ventilatory rate was below 17. In the EVH^- group, the rates were, respectively, 0, 5, and 12 (χ^2 test, $P = .08$).

No differences were detected in the mean ACT scores of patients with and without positive challenge responses after TR (21.6 ± 2.5 vs 21.9 ± 1.9 points, $P = .77$) or after EVH (21.6 ± 2.2 vs 21.8 ± 2.0 points, $P = .83$).

Discussion

To the best of the authors' knowledge, this is the first study to compare TR with EVH as a bronchial challenge surrogate for EIB