



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

Marcelo José Chateaubriand do Nascimento Silva Filho, PT, MSc^{*}; Adriana Vellozo Gonçalves, MD^{*}; Marcelo Tavares Viana, PE, PhD^{*}; Décio Medeiros Peixoto, MD, PhD[†]; Emanuel Sávio Cavalcanti Sarinho, MD, PhD[‡]; and José Ângelo Rizzo, MD, PhD[‡]

^{*} Health Sciences Postgraduate Course, Universidade Federal de Pernambuco, Recife, Pernambuco, Brazil

[†] Departments of Pediatrics and Allergy, Hospital das Clínicas, Universidade Federal de Pernambuco, Recife, Pernambuco, Brazil

[‡] Departments of Pneumology and Allergy, Hospital das Clínicas, Universidade Federal de Pernambuco, Recife, Pernambuco, Brazil

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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 (FEV₁) 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 FEV₁ determination followed by TR for 8 minutes or EVH for 6 minutes on consecutive days. The first challenge was chosen at random. Serial FEV₁ 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 FEV₁ 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 FEV₁ 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 FEV₁ response to the EVH challenge has to be properly evaluated to better understand its role in EIB diagnosis.

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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 (FEV₁) 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

Reprints: José Ângelo Rizzo, MD, PhD, Rua de Apipucos 235/1901, CEP 52071-000, Apipucos, Recife, PE, Brazil; E-mail: josearizzo@gmail.com.

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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 FEV₁ 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 FEV₁ 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 O₂ saturation (Nonin Onix, Minneapolis, Minnesota) measurements had been taken, patients underwent basal FEV₁ 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 FEV₁ 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 FEV₁ 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; Ecafex, 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% CO₂, 21% O₂, and 74% N₂ 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 FEV₁ 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 FEV₁ 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 FEV₁ 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 FEV₁ lower than 60% of the

Table 1

Participants' baseline characteristics (n = 34)

Boys/girls	19/15
Age (y), mean $\pm$ SD	11.9 $\pm$ 2.4
Weight (kg), mean $\pm$ SD	49.0 $\pm$ 10.8
BMI (kg/m ²), mean $\pm$ SD	21.2 $\pm$ 3.9
ACT ^a , mean $\pm$ SD	21.5 $\pm$ 2.7
Basal FEV ₁ (% predicted), mean $\pm$ SD	91.2 $\pm$ 14.5

Abbreviations: ACT, Asthma Control Test; BMI, body mass index; FEV₁, forced expiratory volume in 1 second.

^aACT limits 17 to 25.

predicted value. None were excluded because of an incapacity to perform acceptable expiratory maneuvers for the FEV₁ measurements or to execute the TR or EVH protocol. Patients' general data are presented in Table 1. There was no difference in mean baseline FEV₁ values expressed as a percentage of predicted between challenge days (TR, mean $\pm$ SD FEV₁ 92.9 $\pm$ 15.6%, 95% confidence interval 98.4–87.6%; EVH, FEV₁ 88.3 $\pm$ 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 $\pm$ 1.4°C and 56.9 $\pm$ 4.4% (absolute humidity $\sim$ 10.9 g of H₂O/m³) on the TR day.

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 FEV₁ 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 FEV₁ decrease within the same interval ($P = .28$; Fig 1). For the 2 tests, the greatest FEV₁ decrease was observed between minutes 3 and 15 in 95% of the challenges. In those patients in whom the FEV₁ decrease persisted to minute 30 after the challenge (10 subjects after TR and 7 after EVH), 400 μ g of albuterol was administered by inhalation, with complete reversal in all cases. FEV₁ 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 FEV₁ expressed as a percentage of the predicted value and the magnitude of the decrease in FEV₁ after TR ($R^2 = 0.01$) or EVH ($R^2 = 0.003$).

The limits of agreement in FEV₁ 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 $\pm$ 3% vs 91 $\pm$ 2%, $P = .79$).

Mean ventilation rates achieved by patients with and without an FEV₁ decrease of at least 10% after EVH (EVH⁺ and EVH⁻, respectively) showed no differences (35.2 $\pm$ 8.8 L/min⁻¹ and 38.6 $\pm$ 8.6 L/min⁻¹, $P = .27$). For target ventilation levels as a multiple of basal FEV₁, mean values achieved by EVH⁺ individuals were 17.3 $\pm$ 2.8 and by EVH⁻ values were 15.9 $\pm$ 2.0 ($P = .1$). In the EVH⁺ group, only 4 patients achieved a ventilatory rate of 21 times the basal FEV₁, 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 $\pm$ 2.5 vs 21.9 $\pm$ 1.9 points, $P = .77$) or after EVH (21.6 $\pm$ 2.2 vs 21.8 $\pm$ 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

Table 2
Comparative challenge results^a

EVH	Treadmill running		Total
	Positive	Negative	
Positive	13	4	17
Negative	6	11	17
Total	19	15	34

Abbreviation: EVH, eucapnic voluntary hyperventilation.

^aA positive response was a decrease in forced expiratory volume in 1 second of at least 10% from basal values at 2 moments. A negative response was a decrease in forced expiratory volume in 1 second lower than 10% from basal values. Overall agreement was 71%. Proportionate positive agreement was 72%, and proportionate negative agreement was 69% (Cohen $\kappa = 0.412$, $P = .016$).

diagnosis in an adolescent asthmatic population. After TR the observed EIB prevalence in the studied population was 56% (19 children), somewhat higher than that found in other studies of Brazilian patients with asthma of the same age (33% to 52%).^{17,18} After EVH, 50% (17 with asthma) had a positive challenge result. The agreement between the responses measured by the 2 bronchial challenge methods was 71%, but the Cohen κ coefficient used to measure chance-corrected nominal scale agreement was only moderate ($\kappa = 0.412$).¹⁹ Furthermore, the limits of agreement in FEV₁ change as a percentage of basal values after the 2 challenges were very wide (+19.8% to -19.6%).

One important reason for these findings might be the inherent variability of the response to the challenge methods at different occasions. This supposition is corroborated by the findings of Anderson et al²⁰ and Argyros et al.⁷ Anderson et al evaluated the reproducibility of FEV₁ changes after exercise (running on a motorized treadmill while breathing dry air) at 2 occasions in 373 individuals with mild asthma symptoms. They found a positive response (FEV₁ decrease $\geq 10\%$ after the challenge) for the 2 tests in 72 subjects (19%) and for only 1 of the 2 tests in 89 subjects (24%), with an overall agreement of 76.1%. In a smaller population of 16 adult patients with asthma, Argyros et al¹⁷ reported an agreement of 75% in FEV₁ response between the 2 EVH challenges, but this needs to be confirmed in a larger population.

This study followed the stricter recommendations of Weiler et al¹³ and considered positive only those test results that showed a

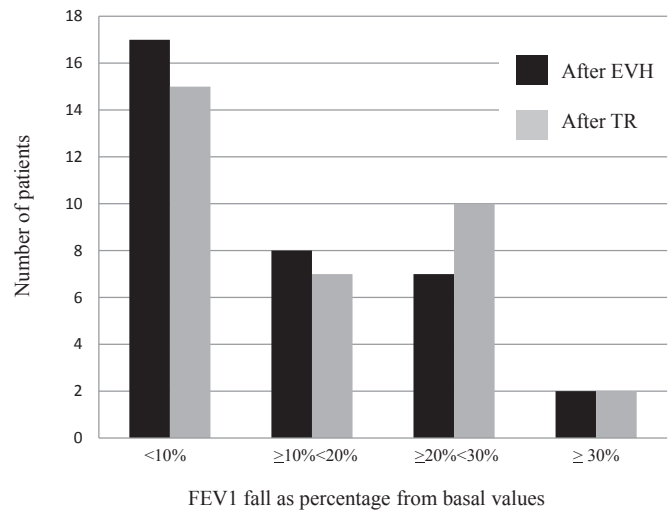


Figure 2. Distribution of decrease in forced expiratory volume in 1 second (FEV₁) as a percentage of basal values after eucapnic voluntary hyperventilation (EVH) and treadmill running (TR).

decrease in FEV₁ of at least 10% below basal values at at least 2 consecutive evaluation moments after each challenge. Although adding some specificity to bronchial provocation tests, this has not been adopted by the international guidelines that recommend that the test result be considered positive if a decrease in FEV₁ of at least 10% is observed at any moment.⁵ By this last criterion, 20 patients (59%) would have shown a positive response after TR and 22 (65%) after EVH. Therefore, although adding some sensitivity, this criterion for a positive FEV₁ response would not have changed the level of concordance between the 2 methods (68% general agreement, Cohen $\kappa = 0.504$). Moreover, if more stringent criteria for a positive FEV₁ response, such as a decrease of at least 15% from baseline, had been used,²¹ then the concordance between tests would have not changed significantly (71% general agreement, $\kappa = 0.531$).

In athletes without asthma, an EVH challenge is considered effective if a minute ventilation rate of 30 times the basal FEV₁ is achieved during the hyperventilation maneuvers. In individuals with an established diagnosis of asthma, the recommended minimum valid threshold is 21 times to avoid the possibility of severe

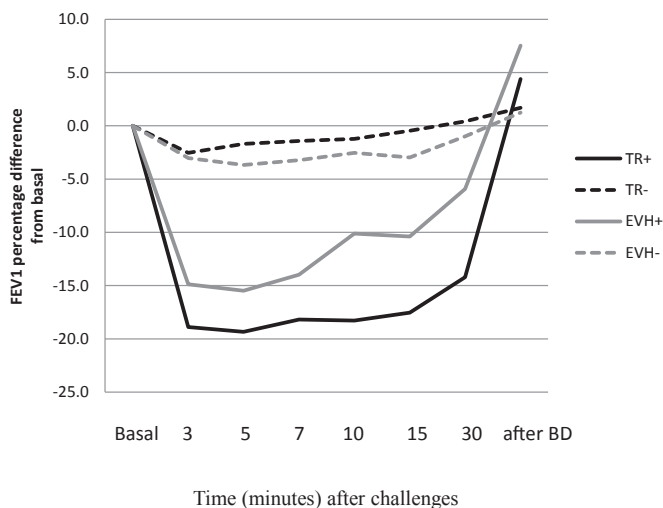


Figure 1. Variation of forced expiratory volume in 1 second (FEV₁) as a percentage from basal values after TR and EVH. BD, bronchodilator; EVH⁺, positive response to eucapnic voluntary hyperventilation; EVH⁻, negative response to eucapnic voluntary hyperventilation; TR⁺, positive response to treadmill running; TR⁻, negative response to treadmill running.

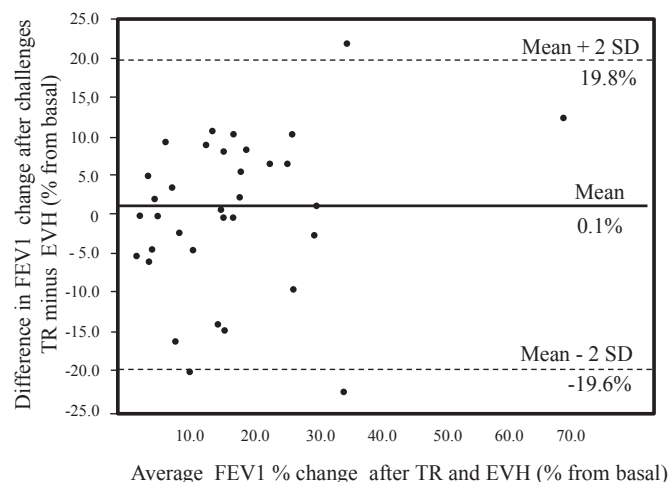


Figure 3. Limits of agreement. Bland–Altman plot of differences against changes in the mean of forced expiratory volume in 1 second (FEV₁) after treadmill running (TR) and eucapnic voluntary hyperventilation (EVH; percentage of basal values). Mean difference $\pm$ 2 SD is indicated.

decreases in FEV₁.^{5,14} This threshold was achieved by only 4 of the present patients despite the examiners actively coaching the patients to reach this target. The authors did not identify a cause for this and can only speculate about the influence of these patients' youth. However, there were no significant differences in mean ventilation rates in patients with vs without a positive response to EVH, and even a patient with a ventilation rate 12.1 times the basal FEV₁ showed a positive bronchial EVH response (14.7% decrease from basal value).

In children 9 to 17 years of age, the decrease in FEV₁ was found to be highly dependent on exercise load.²² It is noteworthy that the mean heart rate achieved by the present patients with asthma during the TR was above 90% the calculated maximum heart rate.

In a retrospective study evaluating the clinical utility of EVH for EIB diagnosis, Brummel et al⁹ did not observe differences in the proportions of individuals with a FEV₁ decrease of at least 10% between those who achieved a ventilation rate of at least 60% of the maximum voluntary ventilation (≈ 21 times FEV₁) and those with lower rates. In children with asthma, a target ventilatory rate of 40% of the maximum voluntary ventilation (≈ 14 times basal FEV₁) for the EVH test might be adequate. There are no data in the literature to support this hypothesis and more studies are required to elucidate this issue.

It is noteworthy that no patient required rescue medication for severe symptomatic bronchospasm after the EVH challenge (only 3 had a FEV₁ decrease $>30\%$). For this reason, the authors consider this challenge safe and without greater technical executional difficulties, although this might not be so in younger children.² However, safety recommendations and equipment must be available, as with any bronchial challenge.⁵

A retrospective study involving 131 patients compared EVH with a methacholine challenge for the detection of EIB. Based at a US Army medical center, Holley et al²³ investigated exercise-associated respiratory complaints (40 patients with asthma) and concluded that the 2 tests were complementary. However, EVH showed a greater sensitivity (positive in 32 patients) than methacholine (positive in 11 patients) and 26 patients with a positive response to EVH had a negative response to methacholine. This finding and those by Anderson et al²⁰ indicate that no single test can be considered the gold standard for EIB diagnosis.

Most of the present patients had well-controlled asthma (ACT score ≥ 20 points), but asthma was not well-controlled in 8 (ACT score ≤ 19). In 5 of these patients, the TR and EVH challenge results were concordant (positive and negative in the 2 tests in 4 patients and 1 patient, respectively). Asthma control status based on ACT score had no influence on the overall agreement results. Patients with severe and poorly or not well-controlled asthma more often have exercise-related respiratory symptoms and/or EIB diagnosis than those with well-controlled disease.^{24,25} For these patients, inhaled steroids are considered the most effective anti-inflammatory drugs,⁵ but in many patients their long-term use significantly attenuates but does not abolish exercise-related respiratory symptoms or EIB. Thus, patients with these complaints despite appropriate treatment and disease control should be objectively evaluated to implement an adequate preventive treatment or, excluding other possible causes, to assure patients and their parents that the symptoms are not due to worsening of asthma during exercise.⁴

A meta-analysis evaluating the accuracy of EVH to diagnose EIB compared with standard exercise challenge testing concluded that higher-quality studies are needed before this method can be confirmed as an alternative to exercise tests.²⁶ By the same criteria adopted in this meta-analysis that considered exercise testing the gold standard, the present results showed a sensitivity of 68% and a specificity 73% for EIB diagnosis, although, as discussed previously, owing to its inherent variability in FEV₁ response to duplicate

challenges,²⁰ exercise tests cannot be considered the gold standard for EIB diagnosis. Instead, the limitations and inherent variability of the 2 methods must be understood and taken into consideration in daily clinical practice or in diagnostic or therapeutic studies. For a more solid conclusion about a comparison between these methods, studies should use duplicate challenges.

The present results show that bronchial challenge with EVH is simple and safe to perform and requires no sophisticated equipment. Some aspects still need to be elucidated such as its repeatability and the minimum ventilation rate to be achieved for the EVH test to be considered valid. Although a positive EVH test result is consistent with a diagnosis of EIB, it must be interpreted in the appropriate clinical context.¹³ However, in individuals who do not show an FEV₁ decrease of at least 10% after the TR or EVH challenge, or for whom the decrease occurs at just 1 post-challenge evaluation moment, the test should be repeated for this diagnosis to be excluded.

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