Clinical Role of Rapid-Incremental Tests in the Evaluation of Exercise-Induced Bronchoconstriction*

Marcelo B. De Fuccio, MD; Luiz E. Nery, MD, PhD; Carla Malaguti, PT, MSc; Sabrina Taguchi; Simone Dal Corso, PT, PhD; and J. Alberto Neder, MD, PhD

Study objective: To determine whether rapid-incremental work rate (IWR) testing would be as useful as standard high-intensity constant work rate (CWR) protocols in eliciting exercise-induced bronchoconstriction (EIB) in susceptible subjects.

Design and setting: A cross-sectional study performed in a clinical laboratory of a tertiary, university-based center.

Subjects and measurements: Fifty-eight subjects (32 males, age range, 9 to 45 years) with suspected EIB were submitted to CWR testing (American Thoracic Society/European Respiratory Society guidelines) and IWR testing on different days; 21 subjects repeated both tests within 4 weeks. Spirometric measurements were obtained 5, 10, 15, and 20 min after exercise; a FEV_1 decline > 10% defined EIB.

Results: Twenty-seven subjects presented with EIB either after CWR or IWR testing; 21 subjects had EIB in response to both protocols ($\kappa = 0.78$, excellent agreement; $p < 0.001$). Of the six subjects in whom discordant results were found, two had EIB only after IWR. Assuming CWR as the criterion test, IWR combined high positive and negative predictive values for EIB detection (91.3% and 88.6%, respectively). Tests reproducibility in eliciting EIB were similar ($\kappa = 0.80$ and 0.72 for CWR and IWR, respectively; $p < 0.001$). Total and intense (minute ventilation > 40% of maximum voluntary ventilation) ventilatory stresses did not differ between EIB-positive and EIB-negative subjects, independent of the test format. There were no significant between-test differences on FEV_1 decline in EIB-positive subjects (25.7 ± 10.8% vs 23.7 ± 10.0%, respectively; $p > 0.05$). Therefore, no correlation was found between exercise ventilatory response and the magnitude of EIB after either test ($p > 0.05$).

Conclusions: Rapid-incremental protocols (8 to 12 min in duration) can be as useful as high-intensity CWR tests in diagnosing EIB in susceptible subjects. Postexercise spirometry should be performed after incremental cardiopulmonary exercise testing when EIB is clinically suspected.

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Key words: asthma; bronchoprovocation; exercise-induced asthma; exercise tests

Abbreviations: ATS = American Thoracic Society; AUC = area under the curve; CPET = cardiopulmonary exercise testing; CWR = constant work rate; EIB = exercise-induced bronchoconstriction; ERS = European Respiratory Society; $FEF_{25-75\%}$ = forced expiratory flow between 25% and 75% of FVC; HR = heart rate; IWR = rapid-incremental work rate; MVV = maximum voluntary ventilation; $\dot{V}E$ = minute ventilation; $\dot{V}O_2$ = oxygen uptake

Exercise-induced bronchoconstriction (EIB) is a clinical condition in which intense, short-term physical exertion induces acute airway narrowing in susceptible subjects. EIB has been reported to occur to some degree in up to 80% of asthmatic patients.[1–3] Ventilation-related airway dehydration and changes in airway temperature or blood flow are thought to be associated with this phenomenon.[4–8]

Postexercise spirometric measurements are used for the diagnosis of EIB.[9,10] For this purpose, high-intensity constant work rate (CWR) tests are gener-

*From the Pulmonary Function and Clinical Exercise Physiology Unit, Division of Respiratory Diseases, Federal University of Sao Paulo, São Paulo, Brazil.

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Correspondence to: J. Alberto Neder, MD, PhD, Coordinator, Pulmonary Function and Clinical Exercise Physiology Unit, Respiratory Division, Department of Medicine, Federal University of Sao Paulo, Paulista School of Medicine, Rua Professor Francisco de Castro 54, Vila Clementino, CEP: 04020–050, Sao Paulo, Brazil; e-mail: albneder@pneumo.epm.br

ally employed rather than rapid-incremental work rate (IWR) exercise protocols.[11] This procedure is based on the assumption that, during IWR, a high ventilatory stress would be sustained for a timeframe insufficient to change airways temperature and/or humidity.[9]

However, asthmatic patients hyperventilate throughout progressive exercise, even during low-intensity work rates.[12] In addition, they may present with an early lactic (anaerobic) threshold[13]; this would provide another important source of ventilatory stimuli. Therefore, it is conceivable that IWR could elicit a sustained high ventilatory response in this patient population. This is a clinically relevant issue since maximal multistage exercise tests are the most common exercise protocols for the evaluation of dyspneic patients,[14] in whom EIB is a frequent cause.[15] In this context, IWR is more useful than CWR since the former allows a better differentiation of pulmonary from cardiovascular causes of exercise intolerance.[14] Surprisingly, no previous study has systematically compared the clinical performance of CWR vs IWR testing in diagnosing EIB. We therefore hypothesized that IWR protocols would be as useful as CWR tests for the diagnosis of EIB in patients with a clinical history suggestive of postexercise bronchoconstriction.

Materials and Methods

Subjects

The study group comprised 58 subjects (32 males, 26 females; Table 1) with a clinical history compatible with EIB, *ie*, breathlessness, chest tightness, and/or wheezing after physical exertion. In addition, resting spirometric values were required to be within the normal range (postbronchodilator $FEV_1 > 75\%$ predicted).[16] Subjects were referred from local chest physicians or were recruited by advertisement. Patients were excluded if they presented with a comorbid condition or if there was any contraindication for exercise testing.[15]

Table 1—*Population Characteristics According to Gender**

Characteristics	Gender: Male (n = 32)	Gender: Female (n = 26)
Age, yr	20.1 ± 10.1	20.5 ± 9.6
Weight, kg	62.0 ± 18.4†	53.2 ± 15.2
Height, m	1.65 ± 0.15‡	1.57 ± 0.09
Body mass index, kg/m^2	22.2 ± 3.7	21.2 ± 4.6
FVC, % predicted	101.2 ± 14.7	97.5 ± 10.4
FEV_1, % predicted	93.2 ± 13.1	88.2 ± 12.1
FEV_1/FVC, %	78.5 ± 7.4	79.1 ± 10.3
$FEF_{25-75\%}$, % predicted	71.8 ± 18.5	69.7 ± 27.4

*Data are presented as mean ± SD.
†$p < 0.05$.
‡$p < 0.01$.

In those subjects with a previous diagnosis of asthma (n = 46), the patients were required to be in a stable phase of the disease, with no change in medication usage in the last 3 months. Medications received included inhaled steroids (n = 23), short-acting β_2-adrenergics (n = 20), long-acting β_2-adrenergics (n = 13), anticholinergics (n = 1), and leukotriene modifiers (n = 1). Patients were instructed to refrain from use of the drugs before the exercise challenges according to published guidelines[9,10]; inhaled steroids, however, were maintained. No patient was receiving oral steroids or theophylline. Informed consent (as approved by the Institutional Medical Ethics Committee) was obtained from all subjects or, when appropriate, from their parents.

Study Design

This was a prospective, cross-sectional study. On different days, each subject was randomly assigned to CWR or IWR protocols with preexercise and postexercise spirometric evaluations. In order to determine the reproducibility of the two exercise formats for the diagnosis of EIB, a subgroup of patients repeated each test within 4 weeks (n = 21).

Tests were performed at the same time of day. Subjects and investigators were blinded to the results of the first exercise study. Air conditioning and active dehumidification were used to control room air conditions: temperature between 19°C and 24°C and air humidity < 60%. Care was taken for environmental conditions to be similar (within 2°C and 1%) between tests in the same subject.

Measurements

Spirometry: Spirometric tests were performed with a calibrated pneumotachograph (Pitot tube). Technical procedures, acceptability, and reproducibility criteria were those recommended by the American Thoracic Society (ATS).[17] The spirometric evaluations were performed before exercise and after exercise completion every 5 min for 30 min. Following this period, two puffs of inhaled salbutamol (400 μg via metered-dose inhaler) were administered before patient discharge. The subjects completed at least three acceptable maximal forced expiratory maneuvers before exercise and after bronchodilator; for the postexercise measurements, at least two maneuvers were obtained at each time point.

The following variables were recorded and expressed as body temperature, ambient pressure, saturated with water vapor conditions: FVC, FEV_1, FEV_1/FVC ratio, and forced expiratory flow between 25% and 75% of FVC ($FEF_{25-75\%}$). Values were compared with those predicted from Pereira et al[16] for the adult Brazilian population. These regression equations consider age, gender and height. Maximum voluntary ventilation (MVV) was estimated by multiplying preexercise FEV_1 by 37.5.[18]

Exercise Tests: The exercise tests were performed on an electromagnetically braked cycle ergometer (CardiO_2 Cycle; Medical Graphics Corporation; St. Paul, MN) with the subjects maintaining a pedaling frequency of 60 ± 5 revolutions per minute (± SD). Pulmonary gas exchange and ventilatory variables were obtained from calibrated signals derived from rapidly responding gas analyzers and a pneumotachograph (CardiO_2 System; Medical Graphics Corporation). The following variables were recorded breath-by-breath and expressed as 15-s mean: pulmonary oxygen uptake ($\dot{V}O_2$, standard temperature and pressure, dry), pulmonary carbon dioxide output (standard temperature and pressure, dry), minute ventilation ($\dot{V}E$, body temperature and pressure, saturated), tidal volume, and respiratory rate. Heart rate (HR) was determined using the R-R interval from a