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

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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 FEV₁ 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 (κ = 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 (κ = 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 FEV₁ 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. (CHEST 2005; 128:2435–2442)

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; FEF25–75% = forced expiratory flow between 25% and 75% of FVC; HR = heart rate; IWR = rapid-incremental work rate; MVV = maximum voluntary ventilation; Ve = minute ventilation; VO₂ = 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.⁹¹⁰ For this purpose, high-intensity constant work rate (CWR) tests are gener-
ally employed rather than rapid-incremental work rate (IWR) exercise protocols. 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.

However, asthmatic patients hyperventilate throughout progressive exercise, even during low-intensity work rates. In addition, they may present with an early lactic (anaerobic) threshold; 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, in whom EIB is a frequent cause. In this context, IWR is more useful than CWR since the former allows a better differentiation of pulmonary from cardiovascular causes of exercise intolerance. 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 FEV1 > 75% predicted). 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 contra-indication for exercise testing.

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 β2-adrenergics (n = 20), long-acting β2-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, 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). 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, FEV1, FEV1/FVC ratio, and forced expiratory flow between 25% and 75% of FVC (FEF25–75%). Values were compared with those predicted from Pereira et al for the adult Brazilian population. These regression equations consider age, gender and height. Maximum voluntary ventilation (MVV) was estimated by multiplying preexercise FEV1 by 37.5.

Exercise Tests: The exercise tests were performed on an electromagnetically braked cycle ergometer (CardiO2 Cycle; Medical Graphics Corporation; St. Paul, MN) with the subjects maintaining a pedaling frequency of 60 revolutions per minute (± SD). Pulmonary gas exchange and ventilatory variables were obtained from calibrated signals derived from rapidly responding gas analyzers and a pneumotachograph (CardiO2 System; Medical Graphics Corporation). The following variables were recorded breath-by-breath and expressed as 15-s mean: pulmonary oxygen uptake (Vo2, standard temperature and pressure, dry), pulmonary carbon dioxide output (standard temperature and pressure, dry), minute ventilation (Ve, body temperature and pressure, saturated), tidal volume, and respiratory rate. Heart rate (HR) was determined using the R-R interval from a
12-lead, on-line ECG. Subjects were also asked to rate “shortness of breath” and “leg effort” each minute in an alternating sequence using the 0 to 10 Borg category-ratio scale.\textsuperscript{19}

**CWR Protocol:** High-intensity CWR tests were performed according to the ATS/European Respiratory Society (ERS) guidelines\textsuperscript{9,10}. Briefly, a target work rate was calculated based on the expected submaximal $\dot{V}e/\dot{V}o_2$ and $\dot{V}o_2$/work rate relationships. In this protocol, the target work rate is reached after 3 min of exercise, in which progressively higher fractions of this work rate are imposed every minute (60%, 70%, and 90%). Subjects are asked to sustain the target power output for a minimum of 4 min and a maximum of 6 min. If a subject indicates that he/she will not be able to sustain the designed exercise load, this is rapidly reduced to the point that the subject can sustain, provided that the ventilation is maintained \textgreater 40% MVV for at least 4 min.

**IWR Protocol:** All tests were preceded by a 1-min baseline of “true” unloaded pedaling. A ramp-incremental protocol was performed.\textsuperscript{20} The power incrementation rate was individually selected to provide an exercise duration from 8 to 12 min. The rate of incrementation varied between subjects: 10 to 35 W/min in males and 10 to 20 W/min in females. Maximum effort was established if maximum HR was \textgreater 90% predicted and carbon dioxide output/\dot{V}o_2 values at peak exercise were \textless 1.15.\textsuperscript{21}

**Data Analysis**

The primary outcome for analysis was the degree of FEV\textsubscript{1} decline after exercise (preexercise – postexercise/preexercise values), as determined by its lowest value (nadir). In those subjects with positive EIB (FEV\textsubscript{1} decline >10% of baseline),\textsuperscript{9,10,22,23} we calculated the area under the curve (AUC) of postexercise FEV\textsubscript{1} (Fig 1). In addition, the ventilatory stress in response to the two exercise test formats was determined as the AUC of the total and intense ($\dot{V}e > 40\%$ MVV) pulmonary ventilation (Fig 1). Data are expressed in arbitrary area units (Microcal Origin 4.0; Microcal Software; Northampton, MA).

Data for which the distribution was Gaussian are reported as mean (SD). Differences in proportions were assessed by \chi\textsuperscript{2} tests; \kappa statistic was used to assess the degree of tests agreement in diagnosing EIB and to evaluate test-retest concordance\textsuperscript{24} (Table 2). The \kappa coefficient was used to categorize agreement into three broad levels: excellent (> 0.75), moderate (0.40 to 0.75), and
mild (0 to 0.39). A nonpaired Student t test was used to contrast physiologic responses between groups. Probability of type I error was established at 0.05 for all tests.

Results

Individual Test Performance for EIB Detection

Twenty-seven patients (46.5%) presented with EIB either after CWR or IWR testing. From these subjects, EIB was diagnosed in both tests in 21 subjects (κ = 0.78, p < 0.001, excellent agreement) [Table 3]. Of the six subjects in whom there was a discordance between test results, four subjects had EIB after CWR, but not IWR, and two subjects had EIB only after IWR. Assuming CWR as the criterion test, IWR presented with high sensitivity (84%), specificity (94%), positive predictive value (91.3%), negative predictive value (88.6%), and likelihood ratio for a positive result (14.0). Similar results were found when subjects were grouped by gender (data not shown).

We contrasted the clinical and functional responses between subjects who presented with or without EIB. EIB-positive patients showed a significantly lower baseline FEV₁ (87.3 ± 11.5% predicted vs 94.2 ± 13.2% predicted) and FEF25–75% (64.1 ± 20.5% predicted vs 76.8 ± 23.2% predicted) as compared with EIB-negative subjects, respectively (p < 0.05). There was a significant association between EIB and usage of bronchodilators and inhaled steroids (p < 0.05). In addition, the occurrence of EIB was higher in patients with a clinical history of chronic rhinitis (p < 0.01).

Physiologic Responses to Different Exercise Tests

We found a significant overestimation of the power output that patients could sustain during CWR according to the ATS/ERS formulae.9,10 Therefore, 50 of 58 patients did not tolerate the target work rate during a minimum of 4 min (see “Materials and Methods”); as shown in Figure 2, the actual exercise loads used in these tests were significantly lower than those initially calculated (96 ± 41 W vs 140 ± 53 W, respectively; p < 0.01).

As expected, several indexes of maximum physiologic stress were significantly higher at peak IWR than CWR (Table 4). Total exercise duration, however, did not differ between the two tests (p > 0.05). We also sought to evaluate potential differences on the ventilatory stress according to individual protocols. As shown in Table 4, the area under the intense ventilatory response (VE > 40% MVV), but not the total ventilation, was higher during CWR than IWR. In addition, VE was sustained > 40% MVV for a longer time during CWR as compared with IWR. However, a within-protocol analysis (ie, EIB-positive vs EIB-negative subjects in CWR and IWR) failed to show between-group differences on the ventilatory stress and the time under high ventilation.

Similarly, no between-test differences in the de-

Table 2—Test-Retest Reproducibility of EIB (Postexercise FEV₁ Decline > 10% From Baseline) After IWR and CWR Protocols

<table>
<thead>
<tr>
<th>Variables</th>
<th>CWR Protocol</th>
<th>IWR Protocol</th>
</tr>
</thead>
<tbody>
<tr>
<td>EIB Positive</td>
<td>EIB Negative</td>
<td>Total</td>
</tr>
<tr>
<td>Second Visit</td>
<td>First Visit</td>
<td></td>
</tr>
<tr>
<td>CWR protocol</td>
<td>EIB positive 7*</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>EIB negative 0</td>
<td>12*</td>
</tr>
<tr>
<td></td>
<td>Total 7</td>
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<tr>
<td>IWR protocol</td>
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<td>3</td>
</tr>
<tr>
<td></td>
<td>EIB negative 0</td>
<td>10†</td>
</tr>
<tr>
<td></td>
<td>Total 8</td>
<td>13</td>
</tr>
</tbody>
</table>

*κ statistic, 0.80.
†κ statistic, 0.72 (p < 0.001).

Table 3—Intertest Agreement on the Diagnosis of EIB (Postexercise FEV₁ Decline > 10% From Baseline)

<table>
<thead>
<tr>
<th>Variables</th>
<th>CWR Protocol</th>
<th>IWR Protocol</th>
</tr>
</thead>
<tbody>
<tr>
<td>EIB Positive</td>
<td>EIB Negative</td>
<td>Total</td>
</tr>
<tr>
<td>IWR protocol</td>
<td>EIB positive 21*</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>EIB negative 4</td>
<td>31*</td>
</tr>
<tr>
<td></td>
<td>Total 25</td>
<td>33</td>
</tr>
</tbody>
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*Significant agreement (κ = 0.78, p < 0.001).
gree of postexercise FEV₁ decline were found (Table 2). Therefore, we were unable to find a significant relationship between exercise ventilatory stress and the magnitude of EIB, independent of the test protocol (Fig 3).

Tests Reproducibility in Eliciting EIB

Twenty-one subjects, who were representative of the total population, repeated both exercise challenges. We found that reproducibility for EIB detection was very high after both tests (κ = 0.72 and 0.80, p < 0.001, for IWR and CWR tests, respectively). In addition, exercise-induced ventilation was similar between the first and the second tests, independent of the protocol (Fig 4).

Discussion

The present investigation examined the clinical role of IWR in eliciting postexercise bronchospasm
(FEV₁ decline > 10% baseline). Assuming a high-intensity CWR as the criterion test, we found that IWR presented with similar diagnostic performance and reproducibility as compared with CWR. Our results highlighted the appropriateness of serial postexercise spirometric measurements for the diagnosis of EIB in patients undergoing IWR cardiopulmonary exercise testing (CPET).

EIB a common clinical condition that contributes to a sedentary lifestyle, social isolation, and even disability. Symptoms alleviation is an important feature of most of the antiasthmatic medications, and there is a renewed interest in developing new therapeutic strategies for this condition. In this context, the guidelines on bronchial challenging tests of the ATS and the ERS have emphasized a potential advantage of CWR over IWR in eliciting EIB. The rationale to support this hypothesis is generally based on the theoretical assumption that during IWR a high intensity ventilatory response would not be sustained in order to induce a measurable degree of postexercise bronchoconstriction. Surprisingly, this assertion has not been formally tested in patients presenting with suspected EIB.

We found that the diagnosis performance of CWR and IWR were equivalent in patients with a clinical history suggestive of EIB (Table 3). Importantly, EIB-positive and EIB-negative subjects maintained high levels of ventilation (VE > 40% MVV) during similar timeframes in each individual protocol. In addition, no significant relationship was found between the total or intense ventilatory stresses with the magnitude of EIB, independent of the test format (Table 4). These results suggest that the ventilation/EIB relationship could not be explained by a simple linear dose-effect relationship. Alternatively, there seems to exist a “threshold ventilation intensity” that would be sufficiently high for triggering EIB. However, this threshold intensity should be attained over a relatively short time. In this context, Rundell et al found that even a 2-min exercise challenge that provoked a high ventilatory stress was as effective as longer tests in eliciting EIB. Interestingly, this timeframe was quite comparable with those found during IWR in the present study. Therefore, a rapid-incremental test lasting no longer than 12 min is likely to induce at least 2 min of high-intensity ventilation. Future studies, however, should address this issue by submitting the same subject to similar ventilatory stresses developed on different timeframes, for example, by using different ramp slopes.

In the present study, we assumed CWR as the criterion test. However, EIB was detected only after IWR testing in two patients. These data suggest that standard CWR testing may not constitute a true “gold standard” for the diagnosis of ventilation-induced bronchoconstriction. In fact, studies have demonstrated that isocapnic hyperventilation may be as useful as exercise in eliciting bronchoconstriction. Nevertheless, it should be recognized that voluntary hyperventilation is not always equivalent to exercise-induced hyperpnea as a bronchial challenge test. Future research is needed to assess the performance of IWR as compared to isocapnic hyperventilation.

Interestingly, the target work rate during CWR was found to be too high to be sustained for 4 to 6 min in most subjects (Fig 2). A possible explanation for this finding may be related to the use of a low Ve/VO₂ constant for the calculation of the target work rate according to the current guidelines. In fact, the slope of this relationship is significantly higher at exercise intensities performed above the lactate threshold, i.e., a lower VO₂ (and work rate) would be sufficient to produce the desired ventila-
tion during the high-intensity exercise challenges. Future revisions of the current guidelines are therefore warranted to establish more realistic estimates of the target power output for CWR tests.

It was not our objective to evaluate the role of the IWR test as an epidemiologic tool for the diagnosis of EIB. In fact, there are a number of simpler and more practical protocols for field evaluation of EIB.\(^{2,22,23}\) However, EIB is a frequent cause of unexplained dyspnea\(^ {24-26}\); most of these patients will eventually be submitted to CPET.\(^ {33,34}\) In this context, CPET is valuable in defining exercise intolerance and to separate cardiac vs pulmonary ventilatory causes of exercise limitation. Therefore, the present results add novel clinical value to IWR since post-IWR FEV\(_1\) measurements seems to be useful as post-CWR spirometry in diagnosing EIB. Future studies should be undertaken to evaluate whether this also holds true for subjects with unexplained dyspnea, ie, in those subjects in whom pretest prevalence is expected to be lower than in subjects with a typical history of EIB.

There are some important limitations in the present study. Subjects were evaluated during cycling exercise, a less asthmogenic activity than running.\(^ {9,35}\) However, it is reasonable to expect that this study limitation would diminish the sensitivity of both tests. Similar considerations may apply for the use of cold and/or dry air, two well-known triggers of EIB. In addition, we did not evaluate patients with severe EIB in whom test performance may be different.

In conclusion, our data demonstrate that IWR protocols (8 to 12 min in duration) can be as useful as standard CWR tests in eliciting EIB. Postexercise spirometry, therefore, should be performed after incremental CPETs when EIB is clinically suspected.

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