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Eucapnic Voluntary Hyperventilation as a Bronchoprovocation Technique*
Comparison With Methacholine Inhalation in Asthmatics

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Methacholine inhalation challenge (MIC) is probably the most widely used and best standardized test for nonspecific bronchoprovocation challenge (BPC). There has been increasing interest in developing "physical" stimuli such as eucapnic voluntary hyperventilation (EVH) with dry gas to assess airway hyperreactivity (AHR), because of inherent problems with using a pharmacologic agent in epidemiologic surveys. To our knowledge, no studies exist that compare MIC with EVH in known asthmatics. We conducted a prospective, randomized, crossover trial with a group of subjects (n = 16) who met the American Thoracic Society definition of asthma with these objectives: (1) to compare the sensitivity of EVH with MIC; (2) to compare the quantitative response of one test with the response to the other challenge; and (3) to correlate the response of both tests with symptoms, serum IgE levels, and serum eosinophil counts. We found that (1) EVH was positive in 75 percent of cases and MIC was positive in 81 percent of cases; one subject reacted to EVH but not to MIC and vice-versa. (2) The quantitative response to one test correlated with the response to the other test (r = 0.60, p = 0.01). (3) There was a correlation between severity of asthma symptoms and the response to EVH (r = 0.62; p = 0.01), but not to MIC. (4) Response to MIC (log PD20), but not EVH, correlated with serum IgE level (r = -0.53, p = 0.04). We suggest that EVH may be used for the initial assessment of AHR in the evaluation of asthma. Eucapnic voluntary hyperventilation is a sensitive measure of AHR and it correlates well with symptoms. Furthermore, though these points were not addressed in our study, it is more physiologic than MIC, and it is easy and less expensive to perform. (Chest 1994; 105: 667-72)

The definition of asthma that is most widely used today is that proposed by the American Thoracic Society (ATS) in 1962: "Asthma is a disease characterized by an increased responsiveness of the trachea and bronchi to various stimuli and manifested by a widespread narrowing of the airway that changes in severity either spontaneously or as a result of therapy."1 This definition has been the basis for the majority of clinical studies on asthma since that time. Recently, the National Asthma Education Program further refined the definition of asthma as follows: "Asthma is a lung disease with the following characteristics: (1) Airway obstruction (or airway narrowing) that is reversible (but not completely so in some patients) either spontaneously or with treatment; (2) Airway inflammation; (3) Airway hyperresponsiveness to a variety of stimuli."2

Regardless of which definition is used, airway hyperreactivity (AHR) is fundamental to the pathophysiology of asthma. In patients suspected of having asthma, the demonstration of AHR has been shown to be diagnostically of greater predictive value than findings on history, physical examination, and routine spirometry.3 Many stimuli, including pharmacologic agents (eg, histamine or methacholine [Mch]), chemical agents (eg, environmental irritants), allergens, and physical agents (eg, isocapnic hyperventilation with cold dry air, exercise, osmotic stimuli) have been used to evaluate the degree of AHR in patients suspected of having asthma.4,5 Though there is no clear gold standard, Mch (betamethanol analogue of acetylcholine) has become the most widely used test in the United States for the identification of typical, occult, or cough variant asthma.6,7 It is the only bronchoconstrictor approved by the Food and Drug Administration for bronchial

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AHR = airway hyperreactivity; ATS = American Thoracic Society; BPC = bronchoprovocation challenge; BU = breath units; EVH = eucapnic voluntary hyperventilation; IHCDA = isocapnic hyperventilation with cold, dry air; Mch = methacholine; MIC = methacholine inhalation challenge
inhalation challenge. As Mch is a pharmacologic agent, questions have been raised regarding its utility in epidemiologic studies. In addition, methacholine inhalation challenge (MIC) appears to have a high incidence of false-positive studies, in that some people with disease processes other than asthma (eg, COPD, cystic fibrosis, and atopy) have positive tests. Consequently, increasing attention has been focused on developing and standardizing "physical" stimuli as techniques to assess AHR with the expectation that these methods may be more specific for diagnosing asthma.

Exercise-induced bronchospasm has been shown by many investigators to be related to the level of respiratory heat and/or water loss. It has been suggested that dry or cold air hyperventilation could be substituted for exercise or inhalational challenge tests to diagnose AHR/asthma. Much has been published in the literature in the last 15 years regarding isocapnic hyperventilation with cold dry air (IHCDA) and its comparison with MIC. Eucapnic voluntary hyperventilation (EVH) is a relatively recently described technique that is technically much simpler to perform than IHCDA. To our knowledge, no studies have been done that compare EVH with MIC in known asthmatics. The purpose of this project was to compare the response to EVH with the response to MIC in asthmatic subjects, and further to correlate the results of these challenges with symptoms and certain laboratory tests for atopy (IgE level and total eosinophil count).

MATERIALS AND METHODS

Subject Population

Study subjects were identified by reviewing pulmonary clinic records, as well as by examining new referrals to the clinic. In order to meet our entry criteria to be labeled as "asthmatic," subjects had to meet the definition proposed by the ATS as previously mentioned. That is to say, they must have had clinical and/or physiologic evidence of reversible airway obstruction at some point, without any other obvious cause (eg, reactive airways disease after an upper respiratory tract infection). They also needed to have experienced symptoms (or required treatment) for at least 6 months in order to exclude patients with transient reactive airways disease.

Evaluations

During the first day of testing, each subject was randomized to undergo a bronchoprovocation challenge with either EVH or MIC. For the EVH challenge, subjects breathed compressed gas containing 5 percent CO2 at a target minute ventilation of 30 times their baseline FEV1, for 6 min. The inspired gas flow was set with a rotameter, and the gas was passed through a 3.5-L meterologic balloon. Subjects achieved target minute ventilation by adjusting their respirations so as to keep the balloon half full; minute ventilation was not otherwise quantified. Spirometry was performed before hyperventilation and then repeated immediately after and at 5, 10, and 20 min following challenge. The lowest value of FEV1 observed postchallenge was used to calculate the percentage fall in FEV1. Based on previous reports using both cold air and dry, ambient air, a positive test was defined as a decline in FEV1 postchallenge of at least 10 percent. This value was chosen as the criteria for FEV1 postchallenge because it was to provide the specificity of the test but decrease sensitivity considerably. The nebulized dosimeter method as described by Rosenthal was used to perform the MIC challenge. Following baseline spirometry, subjects were given up to five successive inhalations of increasing concentrations of Mch. Spirometry was done within 5 min of each dose sequence until the target fall in FEV1 (defined as a 20 percent decline compared to baseline) was achieved or until all doses were given.

The second day of testing was done at least 6 but not more than 16 days after the first test with the subject receiving the "cross-over" challenge. This time period was chosen to ensure that the effects of the first test would have no impact on the results on the second test, as well as to minimize any variables that may arise with a longer delay between tests. All studies were done between 8 AM and 10 AM to minimize the effect of diurnal variation on spirometry. Subjects were required to have a baseline FEV1 of greater than 60 percent predicted prior to undergoing any challenge. They were asked not to consume caffeine-containing beverages or foods for 24 h and not eat within 2 h prior to testing. They were also asked not to take theophylline preparations or use inhaled corticosteroids or cromolyn for 24 h, and not to use inhaled b-agonist inhalers for at least 12 h prior to testing. After the first day of testing, subjects were to resume their usual medication regimen until they needed to make the appropriate changes in preparation for the second day of testing.

Subjects also completed a pulmonary questionnaire (available on request). Questions focused on a history of atopy or exercise-induced symptoms, smoking history, and current treatment regimen. Subjects were also asked to grade the severity of each of their average daily symptoms (including chest tightness, wheezing, breathlessness, and cough) on a scale of zero (no symptoms) to five (intolerable/incapacitating). Serum immunoglobulin E levels and total eosinophil counts (calculated as percent of eosinophils observed by manual differential multiplied by the total WBC) were obtained on the first day of testing. Serum caffeine levels and serum theophylline levels were obtained on both days of testing in order to assess compliance with abstention and to identify possible covariables of AHR.

Statistical Analyses

All descriptive statistics are presented as arithmetic means ± the standard error of the mean (SEM). The primary response variable for the MIC was the PD20 (dose of Mch necessary to provoke a decline in FEV1 ≥ 20 percent compared with pretest value). The primary response variable for the EVH test was the percentage decline (as compared with baseline) of FEV1 postchallenge. A positive test result for MIC was defined as a PD20 ≤ 188.9 breath units (BU). A positive test result for EVH was defined as a drop in FEV1 ≥ 10 percent postchallenge. Correlations between MIC (PD20) and various parameters were evaluated using the logarithm of the PD20. An overall symptom score was calculated for each subject based on the sum of the scores given to each of the four individual symptoms. Associations among total symptom score, immunoglobulin E levels, and eosinophil count, logPD20, and percentage decline of FEV1 (following EVH) were examined using Pearson's correlation coefficient.

RESULTS

Descriptive Statistics

Descriptive statistics for the study population are presented in Table 1 (data expressed as arithmetic
Table 1 — Descriptive Statistics

<table>
<thead>
<tr>
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<th>Mean (± SEM)</th>
<th>Range</th>
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<tr>
<td>Age, yr</td>
<td>41.2 (3.7)</td>
<td>23-74</td>
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<tr>
<td>Sex, M/F</td>
<td>12/4</td>
<td></td>
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<tr>
<td>FVC, L</td>
<td>4.56 (0.4)</td>
<td>1.91-6.63</td>
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<tr>
<td>% Pred</td>
<td>94.80 (5.4)</td>
<td>63.5-139.0</td>
</tr>
<tr>
<td>FEV₁, L</td>
<td>3.16 (0.3)</td>
<td>1.54-2.98</td>
</tr>
<tr>
<td>% Pred</td>
<td>85.71 (4.8)</td>
<td>61.3-126.5</td>
</tr>
<tr>
<td>IgE, IU/(nl &lt;180)</td>
<td>95.84 (19.9)</td>
<td>5.1-266.4</td>
</tr>
<tr>
<td>Eosinophils, mm³ (nl &lt;350)</td>
<td>241.2 (48.7)</td>
<td>30.0-650.0</td>
</tr>
<tr>
<td>Total symptom score</td>
<td>4.4 (1.1)</td>
<td>0-16</td>
</tr>
<tr>
<td>Days between tests</td>
<td>7.94 (2.4)</td>
<td>6-14</td>
</tr>
</tbody>
</table>

percent) admitted to worsening of their symptoms upon exercise. The subjects were only mildly obstructed prechallenge and there was no difference in baseline spirometry between the first and second days of testing (paired t test: FVC p = 0.44, FEV₁ p = 0.48). The maximum response to EVH in terms of decline in FEV₁ was noted immediately postchallenge in 4 subjects (25 percent), 5 min postchallenge in 8 subjects (50 percent), 10 min postchallenge in 3 subjects (18.8 percent), and 20 min postchallenge in 1 subject (6.2 percent).

Twelve subjects (75 percent) were taking varying doses of inhaled corticosteroids and ten (62.5 percent) were taking inhaled β-agonists on either a regular or an as needed basis. One subject was receiving inhaled cromolyn. Three people were receiving no medication at the time of the study, and two were taking oral theophylline preparations. Serum theophylline levels in all subjects were <2.5 μg/ml with the exception of one subject who had a level of 2.6 μg/ml on the first day of testing. Serum caffeine levels were measured in 14 subjects (87.5 percent) on day 1 and in 12 (75 percent) on day 2.

Table 2 — Individual Responses to EVH and MIC*

<table>
<thead>
<tr>
<th>Subject</th>
<th>EVH (% Fall in FEV₁)</th>
<th>MIC (PD20 in BU)</th>
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<tr>
<td>1</td>
<td>0.00</td>
<td>&gt;188.88</td>
</tr>
<tr>
<td>2</td>
<td>0.36</td>
<td>56.94</td>
</tr>
<tr>
<td>3</td>
<td>1.68</td>
<td>&gt;188.88</td>
</tr>
<tr>
<td>4</td>
<td>7.85</td>
<td>180.57</td>
</tr>
<tr>
<td>5</td>
<td>12.35</td>
<td>5.30</td>
</tr>
<tr>
<td>6</td>
<td>12.53</td>
<td>&gt;188.88</td>
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<tr>
<td>7</td>
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<tr>
<td>12</td>
<td>23.87</td>
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<tr>
<td>13</td>
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<tr>
<td>14</td>
<td>44.56</td>
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<tr>
<td>15</td>
<td>51.31</td>
<td>0.04</td>
</tr>
<tr>
<td>16</td>
<td>51.48</td>
<td>0.11</td>
</tr>
</tbody>
</table>

*Note: ranked by degree of response to EVH. Negative test results in italics.

Only two subjects on day 1 and one subject on day 2 had detectable levels of caffeine; the highest level being 1.5 mg/L. A previous study in our laboratory has shown an insignificant effect on bronchoprovocation from such a low level.12

Sensitivity Data

Using the definitions for a positive test result as previously described, 12 subjects (75 percent) had a positive EVH test and 13 (81.2 percent) had a positive MIC. Each subject's quantitative response to both methods of BPC are presented in Table 2. One subject's response to both studies was marginal, in that his FEV₁ fell 7.85 percent after EVH (abnormal, but not "positive"), and his PD20 was 180.6 BU (positive test = PD20 ≤ 188.9 BU). One subject had a positive EVH (FEV₁ fell 12.5 percent) and a negative MIC, and an additional subject had a positive MIC (PD20 of 56.9 BU) and a negative EVH. Two of the subjects had negative results to both challenges.

Correlations

The quantitative response to MIC correlated with the quantitative response to EVH (Fig 1: r = -0.60, p = 0.01). The EVH response correlated with overall symptom score (Fig 2: r = 0.62, p = 0.01), but MIC response did not (r = -0.29, p = 0.27). Serum IgE levels correlated with response to MIC (Fig 3: r = -0.53, p = 0.04) but not with EVH (r = 0.24, p = 0.38). Serum eosinophil count may have been weakly correlated with MIC response (r = -0.41, p = 0.16) but not with EVH (r = 0.26, p = 0.39).

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and asthmatic subjects in their responsiveness to the challenge. The greatest postchallenge decline in FEV₁ in any normal subject was 4 percent, whereas the least postchallenge decline in any asthmatic subject was 9 percent. O’Byrne et al,¹⁵ using cutoffs to define a “positive” challenge as a 10 percent decline in postchallenge FEV₁ for IHCDA and 20 percent decline in the same parameter for MIC, demonstrated a close linear correlation between the provocative dose of minute ventilation and the provocative concentration of Mch required to cause bronchoconstriction. They concluded that either IHCDA or MIC was a suitable stimulus for assessing nonspecific AHR, as have several other studies.⁷,¹⁴,¹⁵ Filuk et al¹⁸ found that several subjects suspected of having asthma had positive responses to IHCDA but not MIC; the converse was also true. They concluded that a negative response to either test should not be used to conclusively exclude the diagnosis of asthma.

Cumbersome to perform, widespread use of IHCDA has been limited because large volumes of air must be dried by cooling to as low as −20°C, and isocapnia must be ensured by monitoring end-tidal CO₂ and adding CO₂ continuously to the inspired air.¹⁶ Phillips et al¹⁷,¹⁸ demonstrated that when a dry gas mixture containing 4.9 percent CO₂ was breathed, near normal alveolar CO₂ was maintained over a wide range of voluntary hyperventilation. They also revealed that it was not necessary to cool the inspired air to provoke a bronchospastic response. Thus, the technique of EVH that they described is greatly simplified as compared with IHCDA. Despite these simplifications, there have been few studies done evaluating its applications, and it remains an infrequently used broncho-provocation technique.

From our institution, several studies on various aspects of EVH have been completed. Duffy and Phillips¹² showed that caffeine consumption decreases the response to EVH. In addition, Roach et al¹⁹ demonstrated that pyridostigmine has no significant effect on AHR as measured by EVH,¹⁹ and Argyros et al²⁰ proved that respiratory water loss (and not heat loss) correlated with bronchoconstriction after EVH. Recently, Eliasson et al²¹ demonstrated that in a group of patients who had symptoms consistent with exercise-induced bronchoconstriction there was a correlation between the response to EVH and to MIC (r = 0.56, p < 0.001). In the study of Eliasson et al, as in ours (and that reported by Filuk et al),¹³ some people reacted to EVH but not MIC and vice-versa.

We also investigated the relationship between serum total IgE levels and peripheral eosinophilia (nonspecific markers of allergic airway inflamma-

**FIGURE 2.** Correlation between overall symptom score and response to EVH.

**FIGURE 3.** Correlation between serum IgE level and response to MIC.
tion)\textsuperscript{22} and the response to EVH and MIC. Although the majority of subjects reported a history of atopic symptoms, the mean IgE level in the group was only 95.8 IU/ml, and only two subjects had elevated IgE levels (> 180 IU/ml). In addition, the mean eosinophil count (measured in 13 subjects) was 241.2/95.8 IU/ml, and only two subjects had elevated IgE levels (≥ 350 mm\(^3\)). Despite this, we still observed a correlation between IgE level and response to MIC and a trend toward a weak correlation between eosinophil count and MIC.

Annesi et al\textsuperscript{23} found that IgE level was not associated with the PD20 to Mch. Others have shown no association between IgE level and AHR as measured by histamine inhalation challenge.\textsuperscript{24} These conclusions are in contrast to other investigations that have demonstrated a relationship between the severity of atopy and AHR\textsuperscript{25} and between IgE levels and the slope of the dose-response curve to MIC.\textsuperscript{22} As the presence of asthma is closely linked to both severity of atopy and AHR\textsuperscript{25} and between IgE levels and quantitative response to MIC and EYH was also assessed. We noted a correlation (r = 0.60), and variable individual responses to both tests provide indirect evidence that the two challenges provoke bronchoconstriction at least in part through different mechanisms.

It is well known that people with diseases other than asthma may react to either histamine inhalation challenge or MIC.\textsuperscript{26-30} In a recent study, 27 percent of patients with allergic rhinitis and 22 percent of patients with chronic bronchitis had a positive MIC.\textsuperscript{26} It was also noted that a marked overlap existed between the degree of AHR associated with asthma and that noted with the other illnesses. Ramsdale et al\textsuperscript{30} performed MIC and IHCDCA on 27 subjects with a history of smoking, chronic bronchitis, and some degree of baseline airway obstruction. Nineteen of these individuals had a positive MIC in the asthmatic range (PC20 < 8 mg/ml), but only three developed bronchoconstriction in response to IHCDCA.\textsuperscript{30} Other studies of IHCDCA have shown no overlap at all between the response of normal subjects and those with asthma.\textsuperscript{9} These studies suggest that IHCDCA is a highly specific means of diagnosing asthma. O’Byrne et al\textsuperscript{35} have speculated that IHCDCA may be more specific for the diagnosis of asthma than tests involving inhaled chemical bronchoconstrictors. Though our study was not designed to evaluate the specificity of EVH in a spectrum of patients with respiratory complaints, we speculate that the physiologic basis of this test, as in IHCDCA, would translate into improved specificity for the diagnosis of asthma.

The relationship between severity of symptoms and quantitative response to MIC and EVH was also assessed. We noted a correlation (r = 0.62) between symptom score and response to EVH, but not to MIC. The absence of this relationship for MIC was largely due to the response of one patient (subject 14, Table 2) who responded dramatically to EVH but only mildly to MIC. There are several studies in the literature that comment on the association between AHR as measured by MIC or histamine inhalation challenge and the presence of respiratory symptoms.\textsuperscript{24,31-35} Most of these studies\textsuperscript{24,31-35} have noted an association between AHR and symptoms, but the relationship is weak. Pattemore et al\textsuperscript{35} noted that the severity of AHR tended to increase with wheezing frequency, but all grades of severity were noted for any given frequency of wheeze. Josephs et al\textsuperscript{34} found that individual PD20 measurements were not consistently related to current asthma severity, and Chhabra et al\textsuperscript{35} also found no correlation between the clinical severity of asthma and the degree of AHR. We are unaware of any other studies that have specifically addressed this question using EVH or IHCDCA to assess AHR; though our severity of asthma scale remains to be validated, our work suggests that the response to EVH is related to the severity of symptoms.

Our study showed that EVH is a useful means of detecting AHR and confirming the diagnosis of asthma, with a sensitivity similar to that of MIC. Twelve of our 16 subjects had a positive EVH test, and 13 had a positive MIC. Of the two subjects who had negative responses to both tests, one subject was receiving no medications, had normal baseline spirometry, and had been asymptomatic for an extended period of time. Clearly his asthma—if he truly had asthma—was mild. The other subject was taking 16 puffs a day of a corticosteroid inhaler and 12 puffs a day of a cromolyn inhaler; it is very likely that his response to BPC was attenuated by this intense regimen.

In summary, the sensitivity of EVH approximated that of MIC in detecting AHR subjects with a history of asthma; studies on a larger population (including normal subjects) need to be performed to confirm this and to test whether its specificity

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result more often with EVH. We believe that EVH should be used initially as the method of choice for BPC because it is a sensitive measure of detecting AHR and the quantitative response to EVH correlates well with the severity of symptoms. In addition, though our study did not directly assess these issues, EVH is based on a more physiologic response than MIC and is probably more specific for the diagnosis of asthma. Also, EVH is easy, quick, and inexpensive to perform.

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