

# Seasonal effect on exercise challenge tests for the diagnosis of exercise-induced bronchoconstriction

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## ABSTRACT

*Exercise challenge test (ECT) may help in the diagnosis of asthma. Asthma is season dependent (relative summer nadir). This study was designed to prospectively show that ECT sensitivity decreases when performed in summer and/or out of personal asthma season. We performed two ECTs in 49 patients with suspected asthma, at baseline and at least 6 months later. Test positivity was defined as a  $\geq 10\%$  drop of forced expiratory volume in 1 second after exercise. Patients were defined as having exercise-induced bronchoconstriction (EIB) if at least one of the two tests was positive. We analyzed the impact of season and of patient-reported asthma season on ECT sensitivity. We performed 21 ECTs in the summer and 77 in other seasons. Summer tests were positive in 14.3% of patients versus 33.8% in other seasons ( $p = 0.11$ ). In patients with confirmed EIB, the sensitivity (95% CI) of a summer test was 0.25 (0.007–0.57), compared with 0.76 (0.58–0.89) in other seasons. Tests performed out of personal asthma season were positive in 10.0% of tests compared with 37.1% of tests during personal asthma season ( $p = 0.007$ ). In patients with confirmed EIB, the sensitivity (95% CI) of a test performed out of asthma season was 0.27 (0.07–0.61), compared with 0.74 (0.55–0.87) during season. The sensitivity of ECT performed in the summer or outside of the personal asthma season is about one-third of ECT performed not in the summer or during personal asthma season. We suggest performing ECTs during personal asthma season and not in the summer if there is no asthma season known.*

(Allergy Asthma Proc 33:416–420, 2012; doi: 10.2500/aap.2012.33.3586)

The diagnosis of asthma is based on typical clinical signs and symptoms as well as on the presence of reversible airway obstruction. Challenge tests, such as the methacholine test or the exercise test, that detect airway hyperresponsiveness may assist in establishing the diagnosis.

The degree of airway hyperresponsiveness in asthmatic patients correlates with the severity of clinical symptoms.<sup>1,2</sup> It is known that asthma morbidity is season dependent, with a relative nadir during summertime.<sup>3,4</sup> Thus, one can anticipate that results of challenge testing may be season dependent, with lower sensitivity in summer.<sup>5</sup> The objective of this study was to prospectively test the hypothesis that the sensitivity of the exercise challenge test (ECT) is decreased when performed in summer and/or out of the “asthma season” of an individual. Hence, patients referred for an exercise test in our institution were asked to volunteer and repeat the study.

## METHODS

### Patients

The study group was composed of candidates for military recruitment. They were referred by army phy-

sicians to the pulmonary function tests laboratory at the Shaare Zedek Medical Center for an exercise test for evaluation of suspected asthma. All patients referred to us during a 19-month period were invited to participate in the study. Each patient was asked to come back for a new test 6 months after the first one. All candidates filled out a questionnaire containing information concerning known allergies, smoking status, controller treatment, presence of asthma symptoms (cough, shortness of breath, or wheeze) during the year, 3 and 1 month before the test, and symptoms of rhinitis during the previous month. In addition, they were asked to report the specific season(s) during which their asthma was more active. The patients were contacted 5 months after the first exercise test, and those who agreed to participate in the study were scheduled for a repeat test. We aimed to repeat the test 6 months after the first test. In some cases, tests were rescheduled several times before finally being performed; hence, the time interval between tests was not constant. After the second test, patients were asked to fill out a second questionnaire similar to the first one.

The study was approved by Shaare Zedek Medical Center Review Board (Helsinki committee), and all participants duly filled out and signed a written consent form.

### Exercise Testing

Only patients with a normal (80% or above) baseline forced expiratory volume in 1 second FEV<sub>1</sub> were

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tested. Patients were instructed not to take inhaled  $\beta_2$ -agonists, leukotriene antagonists, or anticholinergic agents for 48 hours before being tested but were allowed to use inhaled corticosteroids.<sup>6</sup> Patients who had any flu-like symptoms were rescheduled for testing at least 1 month after convalescence. The pulmonary function test room is located below ground level, with air supply *via* an air-condition system. Room temperature is set at 22–24°C, with relative humidity of 40–50%, without change throughout the year. Exercise testing was performed according to American Thoracic Society guidelines<sup>6</sup> for 6–8 minutes on a treadmill at a speed of 3.4–7.3 mph and at a slope of 10–15°, with maintenance of the heart rate at 80–90% of the predicted maximum for a minimum of 4 minutes. Spirometry was performed before exercise and at 1, 3, 6, 10, and 15 minutes after completion of the exercise. The exercise test result was considered positive if FEV<sub>1</sub> dropped  $\geq 10\%$  from baseline on any one of the postexercise spirometry evaluations.<sup>6,7</sup> All 98 tests were done by one of two trained technicians, using the same equipment under the same conditions including humidity and room temperature. A single author who was blinded to the patients' identity interpreted all of the tests. None of the patients had any adverse effects.

#### Data and Statistical Analysis

Summer was defined as the months of July through September as in our previous study.<sup>5</sup> The "personal asthma season" of each patient was defined as the self-reported period (or periods) associated with increased asthma symptoms.

Differences in the proportion of positive exercise test results in relation to different clinical parameters were assessed by  $\chi^2$ -test, by Fisher's exact test, or by Student's *t*-test as appropriate (PEPI Version 4.0 statistical software<sup>8</sup>).

The Vassar clinical calculator<sup>9</sup> was used for calculation of sensitivity and specificity of the tests performed at various seasons.

Results are expressed as mean  $\pm$  SD or percent (range). A value of  $p < 0.05$  was considered significant.

#### RESULTS

One hundred thirty-six patients filled out the first questionnaire, of whom 52 agreed to perform a second exercise test. Three patients were excluded: two because one of the two tests was considered technically unreliable, and one patient because of low baseline FEV<sub>1</sub> at the second encounter. The characteristics of the remaining 49 patients are summarized in Table 1.

Table 2 depicts the results of the first and second exercise tests. Briefly, 6 (12%) examinees had two positive tests, 17 (35%) had one positive and one negative test, and 26 (53%) had two negative tests. There were

Table 1 Patients' characteristics

|                                  |                 |
|----------------------------------|-----------------|
| Males (n, %)                     | 48 (98.0%)      |
| Mean age (yr) at first visit     | 17.7 $\pm$ 2.44 |
| Time interval between tests (mo) |                 |
| Mean $\pm$ SD                    | 14.1 $\pm$ 6    |
| Median, range                    | 13.2, 7.1–29.8  |
| BMI (kg/m <sup>2</sup> )         | 22.4 $\pm$ 3.43 |
| Smoking at first test (n, %)     | 7 (14.3%)       |

BMI = body mass index.

Table 2 Comparison of first and second exercise test

|             |          | First Test |          |
|-------------|----------|------------|----------|
|             |          | Positive   | Negative |
| Second test | Positive | 6          | 14       |
|             | Negative | 3          | 26       |

nearly twice as many positive tests in the second test than in the first one, but this difference was not statistically significant (Fisher's exact test,  $p = 0.13$ ).

Of the 98 tests performed in the 49 participants, 21 were done in the summer and 77 in other seasons. Of the tests performed in summer, 3 (14.3%) were positive compared with 26 (33.8%) of the tests performed in other seasons ( $p = 0.11$ ; Fig. 1a). When we analyzed only those patients who had at least one positive test ( $n = 23$ , 46 tests; Fig. 1 B), 12 tests were performed in the summer and 34 in other seasons. A minority (3 of 12, or 25%) of the tests performed in summer were positive, compared with a majority (26 of 34, or 76.5%) of the tests performed in other seasons. This difference was highly significant ( $p = 0.004$ ). If we define patients as having exercise-induced bronchospasm when at least one of the two tests was positive, the sensitivity (with 95% CI) of a test performed in summer was 0.25 (0.007–0.57) and its specificity was obviously 1, while the sensitivity of a test performed in other seasons was 0.76 (0.58–0.89), with a specificity of 1.

We then analyzed the tests in relation to the specific "asthma season" of each given participant. There were 62 tests performed during "asthma season," and 30 tests out of season. Data concerning personal asthma season of 3 patients (6 tests) were missing. As depicted in Fig. 2 A, of the 30 tests performed out of season, 3 (10%) were positive, compared with 23 (37.1%) of the 62 tests performed during the asthma season ( $p = 0.007$ ). When we analyzed only those patients who had at least one positive test ( $n = 21$ , 42 tests; Fig. 2 B) a minority (3 of 11, or 27.3%) of the tests performed out of asthma season were positive, compared with a majority (23 of 31, or 74.2%) of the tests performed during asthma season. This difference was highly significant

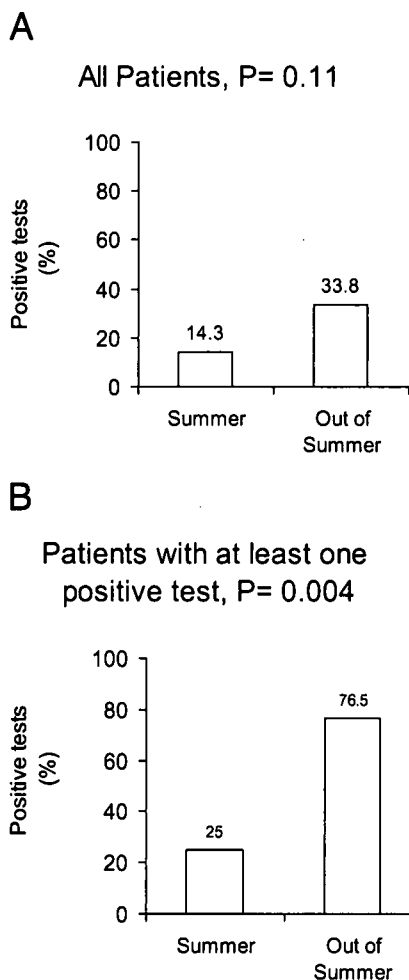


**Figure 1.** Percentage of positive tests in the summer compared with other seasons. (A) All patients. (B) Only patients with at least one positive test.

( $p = 0.01$ ). Using the aforementioned definition of exercise-induced bronchospasm, the sensitivity (with 95% CI) of a test performed out of asthma season was 0.27 (0.07–0.61), and its specificity was obviously 1, and the sensitivity of a test performed during asthma season was 0.74 (0.55–0.87), with a specificity of 1.

#### Additional Parameters and Results of Tests

In the group of patients with at least one positive exercise test, there was no correlation between test results and personal report of recent asthma or rhinitis, including asthma symptoms during the year before tests, asthma symptoms during last 3 months before tests, asthma symptoms during the month before tests, controller treatment, rhinitis in the month before tests, baseline FEV<sub>1</sub>, and baseline FEV<sub>1</sub>/forced vital capacity ratio (Table 3).

We also compared the group of patients who had two positive tests to the group of patients who had only one positive test. We found no difference in self-

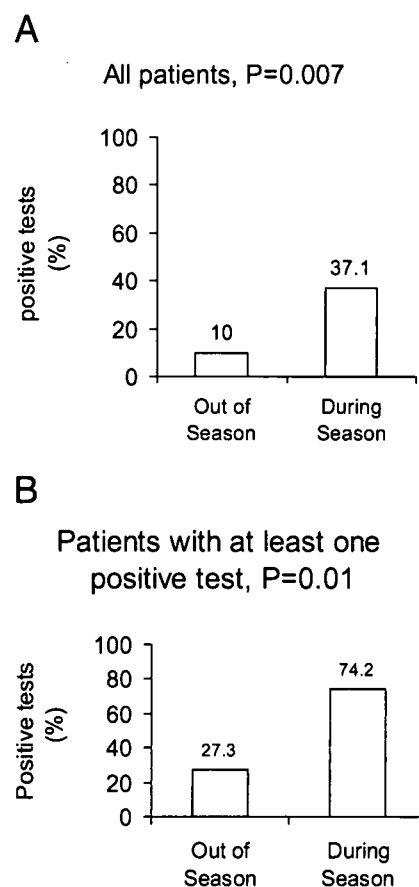


**Figure 2.** Percentage of positive tests during personal season and out of seasons. (A) All patients. (B) Only patients with at least one positive test.

reported recent asthma or rhinitis between the groups. However, the mean drop in FEV<sub>1</sub> postexercise (only positive tests) was significantly higher in patients who had two positive tests ( $34.5 \pm 19.5\%$ ) compared with patients with only one positive test ( $16.3 \pm 7.3\%$ ;  $p = 0.008$ ).

#### DISCUSSION

This study has prospectively shown that an ECT performed during periods of the year with lower asthma activity has a reduced sensitivity than those performed during a different period.

In a previous retrospective cross-sectional study,<sup>5</sup> we had shown that the percentage of positive exercise tests done in summer was less than one-half that of positive exercise tests done the rest of the year (12.9% versus 29.1%).

In the current, prospective study, we confirmed this finding, in 14.3% of the tests performed in summer were positive compared with 33.8% of those performed in other seasons. This difference did not reach the significance level ( $p = 0.11$ ) but the sample size ( $n = 49$ ) was much lower than that of the previous retrospective

Table 3 Clinical parameters in relation to exercise test results in patients with at least one positive test

| Test                                         | Positive  | Negative  | p Value |
|----------------------------------------------|-----------|-----------|---------|
| No. of tests                                 | 29        | 17        |         |
| Asthma symptoms during the year before test  | 16 (64%)  | 9 (60%)   | 1.0     |
| Asthma symptoms during 3 mo before test      | 13 (52%)  | 6 (40%)   | 0.53    |
| Asthma symptoms during the month before test | 8 (33.3%) | 2 (12.5%) | 0.26    |
| Controller treatment                         | 4 (15.4)  | 0 (0%)    | 0.14    |
| Rhinitis in the month before test            | 12 (46%)  | 8 (50%)   | 0.36    |
| Baseline FEV <sub>1</sub>                    | 92.2%     | 92.9%     | 0.8     |
| Baseline FEV <sub>1</sub> /FVC ratio         | 0.83      | 0.82      | 0.84    |

*In case of missing data, calculations of percentage were made out of available data.*

*FEV<sub>1</sub> = forced expiratory volume in 1 second; FVC = forced vital capacity.*

study ( $n = 532$ ), which might have introduced a type 2 error. However, when we analyzed only those patients who had at least one positive test, a minority (25%) of those performed in summer were positive, compared with a majority (76.5%) of the tests performed in other seasons, a difference that reached a high significance level ( $p = 0.004$ ). Thus, when exercise-induced bronchospasm was defined as at least one of the two tests being positive, the sensitivity of a test performed in summer was much lower than that of a test performed in other seasons (0.25 versus 0.76).

Furthermore, our findings, when related to the personal asthma season of the study participants, showed a striking effect of season on the results of the ECT. Indeed, only 10% of tests performed out of asthma season were positive, compared with 37.1% of those performed during asthma season. Moreover, when we analyzed only those patients who had at least one positive test, a minority (27.3%) of tests performed out of asthma season were positive, compared with a majority (74.2%) of the tests performed during the asthma season ( $p = 0.01$ ). Thus, when exercise-induced bronchospasm was defined as at least one of the two tests being positive, the sensitivity of a test performed out of season was much lower than that of a test performed in season (0.27 versus 0.74).

Exercise-induced bronchoconstriction (EIB) is a phenomenon of transient airway narrowing that occurs during or after physical exertion.<sup>10</sup> Exercise-related respiratory symptoms are frequent in both children and adults<sup>10-12</sup> and their prevalence is higher in children with more persistent asthma than those with intermittent asthma.<sup>13</sup> The mechanisms of EIB are related to markedly increased ventilation during exercise, which causes increased heat and water loss through respiration. Airway cooling and drying are thought to stimulate the release of inflammatory mediators, such as histamine and cysteinyl leukotrienes, which lead to bronchial constriction.<sup>6</sup> Hence, a positive response to an ECT is believed to reflect active airway inflammation.

Thus, we speculate that out of the personal asthma season or in summer, which is known to be a relatively "low season" of asthma,<sup>3,4</sup> there is a decrease in airway inflammation, and therefore the ECT is less likely to be positive. Consistent with this speculation, it has been shown that decreased airway inflammation induced by effective asthma therapy reduces the response to challenge tests<sup>14-16</sup> and minimizes the number and severity of EIB episodes.<sup>17</sup>

The influence of season on challenge test results is not restricted to indirect tests. Studies of methacholine challenge tests have shown a lower percentage of positive studies in summer<sup>18</sup> or during low allergic load periods<sup>1,2,19-21</sup> than in other seasons.

The difference between the first and second test results should not be explained only based on differences in the season in which they were performed. It was recently shown that the agreement between two exercise tests performed only a few days apart, under the same conditions, is only 76.1%.<sup>22</sup>

The differences between the first and second tests could not be explained by inhaled corticosteroid use, which is known to decrease the response to exercise testing<sup>19</sup> because all four patients who used this treatment (15.4% of patients with positive tests, data concerning three patients are missing) had a positive test while on treatment. Similarly, it could not be explained by increased level of aerobic fitness after army recruitment, because in most of the patients who had one positive and one negative test, the second test was the positive one.

In this relatively small study, we did not find a significant association between the self-reported asthma activity and the ECT results. We believe that the study was not structured to detect such a relationship.

Several other reports addressed the issue of the effect of season on the ECT.<sup>23-26</sup> These studies reported findings very similar to ours, because the challenge tests were more often positive in winter than in summer. However, in all of these studies, exercise was performed outdoors. In all but one<sup>25</sup> of the aforemen-

tioned reports, the temperature recorded outdoors was near zero or subzero and it is known that exposure to cold air is capable, in cold-sensitive individuals, to provoke acute bronchospasm.<sup>27,28</sup> Thus, cold air, rather than season, might have explained the results of the aforementioned studies. In the only study performed outdoors in a relatively warm environment in Ghana, 1.5% of 1095 students had a positive response to 6 minutes of outdoor free running during the wet season, compared with 3.1% in the dry season study. In the latter study, the increased humidity is probably the reason for the decreased proportion of positive tests during the wet season. It was shown that exercise-induced bronchospasm is reduced by one-half if performed in a humid environment.<sup>29</sup>

We conclude that the sensitivity of ECTs performed in summer or outside of personal asthma season is about one-third of the sensitivity of tests performed not in summer or not during personal asthma season. Although our study is limited by a relatively small sample size, we suggest that ECTs should be performed during the personal asthma season and preferably not in summer if there is no asthma season known.

## ACKNOWLEDGMENTS

The authors thank Sarit Koresh and Shoshi Hillel for their administrative help. They also thank Ahuva Tasama-Tewodaj and Ronit Hamami-Belisha for performing the exercise tests.

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