Until recently, therapeutic-use exemptions have been requested to justify the need for some asthma medications (inhaled corticosteroids [ICS] and β₂-agonists) in elite athletes.¹ ¹ These exemptions are regulated by the World Anti-Doping Agency (WADA) and the International Olympic Committee—Medical Commission (IOC-MC). Because a poor correlation has been observed between asthma symptoms and postexercise bronchoconstriction in certain athletes,³ ⁴ these agencies require the demonstration of a bronchial provocative challenge to confirm the diagnosis of asthma or exercise-induced bronchoconstriction (EIB) in international-level athletes.⁵ ⁶

The WADA and IOC-MC consider eucapnic voluntary hyperpnea (EVH) the best method to confirm EIB, but methacholine challenge is also accepted and widely used as a test for asthma. About 30% of the requests for β₂-agonist use at the 2004 Athens Olympic Games were based on the methacholine challenge.⁵ ⁶ Although EVH is an indirect challenge acting as a surrogate of exercise inducing the release of inflammatory mediators considered responsible for EIB,
methacholine challenge acts directly on the airway smooth muscle and mainly reflects airway responsiveness related to airway structural elements.

Some features remain to be clarified in regard to the diagnosis of airway hyperresponsiveness (AHR) and EIB using methacholine or EVH challenge. Particular attention should be paid to the choices of the cutoff defining AHR to methacholine, and of the selection of the FEV₁ post-EVH test to calculate the maximum decrease in FEV₁. These methodologic aspects may have an impact on the prevalence of AHR in athletes. Previous reports suggested that a methacholine provocative concentration inducing a 20% decrease in the FEV₁ (PC₂₀) ≤ 16 mg/mL indicates the presence of very mild or borderline AHR in the general population.⁷,⁸ Respiratory symptoms in subjects with a PC₂₀ between 4 and 16 mg/mL may thus be due to asthma. A methacholine challenge cutoff for AHR such as a PC₂₀ ≤ 4 mg/mL, as suggested by the WADA and IOC-MC for athletes not taking ICS or taking ICS for less than 1 month, may underestimate the prevalence of EIB in symptomatic athletes not taking ICS with a PC₂₀ between 4 and 16 mg/mL. Furthermore, when calculating the maximal post-EVH FEV₁ decrease, two methodologies have been used. This methodologic difference may have an impact on the prevalence of EIB, although this remains to be determined.

We first aimed to determine the prevalence of a positive diagnosis for AHR and/or EIB in swimmers and winter sport athletes, according to the last WADA and IOC-MC recommendations. Second, we aimed to assess the report of exercise-induced respiratory symptoms in relation to the results of bronchial challenges in those subjects. Third, we examined the impact of two methacholine challenge cutoffs on the prevalence of AHR in these two groups of athletes and in controls in comparison with response to EVH. Finally, we assessed the impact of choosing the highest vs the lowest post-EVH FEV₁ values on the prevalence of positive EIB diagnosis.

Materials and Methods

Study Subjects

Swimmers, winter sport athletes, and nonathlete controls were recruited. Athletes and controls had to be nonsmokers, nonobese, and free of any disease that may interfere with the study. Controls taking asthma medication were excluded. To be included, swimmers and winter sport athletes had to be active competitors and train at least 10 h per week in a chlorinated swimming pool and outside in winter, respectively. Winter sport athletes were not exposed to chlorinated environments and all athletes performed the respiratory tests out of pollen season and during their training period, in fall or winter. Controls had to be nonasthmatic and take part in physical activities for <6 h per week. They were matched for age (±5 years) and sex with swimmers and winter sport athletes. No control was involved in a competitive sport or an outdoor winter sport activity, or was exposed to a chlorinated environment. All subjects gave their written informed consent. The study protocol was approved by our institutional ethics committee and was registered at www.clinicaltrials.gov (NCT 00086491 and NCT 00086452).

Study Design

Each set of the tests was performed at least 14 h after the last training session for all athletes. A physical examination and allergy skin-prick tests were done, and a questionnaire on current health status and training was administered. EVH and methacholine challenges were performed consecutively after recovery of expiratory flows within 10% of baseline.

Allergies

Atopic status was determined by skin-prick tests with common airborne allergens, including animal danders, house-dust mite, mixed trees, mixed grasses, pollens, and molds. The presence of atopy was defined as at least one positive (>3-mm mean wheal diameter at 10 min) response to allergens in the presence of a negative saline control and a positive skin response to histamine.

Baseline Spirometry

Spirometry was carried out according to the American Thoracic Society specifications.² Predicted spirometric values were defined according to Knudson et al.¹⁰ Three reproducible measurements of FEV₁ were obtained.

Eucapnic Voluntary Hyperpnea Challenge

The EVH challenge was performed according to the method described by Anderson and Brannan.¹¹ Briefly, subjects inhaled a dry-air mixture containing 5% CO₂ at room temperature for 6 min. The target ventilation was 30 × FEV₁. FEV₁ was measured before the test and at 3, 5, 10, 15, 20, 25, and 30 min after EVH. At each time interval, FEV₁ was measured twice, and if there was a >10% difference between the FEV₁ at each attempt, a third FEV₁ was performed. We used both the lowest and the highest of the two reproducible measurements after the test to calculate the lowest post-challenge value (therefore generating two sets of data), to verify the impact of these different methods to calculate the maximal decrease in FEV₁. In keeping with IOC recommendations, we used the higher of the two reproducible values to discuss the prevalence of EIB to EVH, as previously suggested.¹²

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Subjects had a diagnosis of EIB when a decrease in FEV$_1$ $\geq 10\%$ from baseline was recorded and sustained over 5 min after EVH. After the EVH challenge was performed, FEV$_1$ had to return to at least 90% of baseline before the methacholine challenge was done; this usually took between 30 and 60 min.

Methacholine Challenge

AHR to methacholine was measured using the tidal-breathing method. After baseline measurements of FEV$_1$ and FVC, each subject inhaled saline (0.9%) followed by doubling concentrations of methacholine between 0.03 and 128 mg/mL to obtain a 20% decrease in FEV$_1$. Methacholine aerosols were generated by a Wright nebulizer with an output of 0.13 mL/min and were inhaled for 2 min at 5-min intervals. FEV$_1$ was measured 30 and 90 s after each inhalation and every 2 minutes until it started to increase. An acceptable-quality FEV$_1$ was obtained at each time point; otherwise the FEV$_1$ maneuver was repeated. AHR was defined as a PC$_{20}$ $\leq$ 4 mg/mL, according to the WADA and IOC-MC guidelines, and for athletes taking ICS for at least 1 month, a positive response is a PC$_{20}$ of $\leq$ 16 mg/mL. The impact of a methacholine challenge PC$_{20}$ cutoff $\leq$ 16 mg/mL on the prevalence of AHR was also studied and compared with EVH.

Questionnaire

A questionnaire regarding past and current respiratory conditions and exercise-induced respiratory symptoms (wheezing, cough, phlegm production, and chest tightness), family history of asthma and allergies, and training and sport habits was administered. We used a questionnaire translated and adapted from the European Community Health Survey, as previously described.

Statistical Analysis

Data were expressed as mean $\pm$ SD or percentage values. Analysis of variance was used to compare the three groups. Subjects with a PC$_{20}$ $>$ 128 mg/mL were assigned a PC$_{20}$ of 128 mg/mL for statistical analysis. Statistical results from this parameter were expressed with the log-transformed values. Post hoc comparisons were performed using the Tukey/Kramer technique. Contingency tables were used to compare the prevalence of AHR or EIB in all three groups and the prevalence of exercise-induced symptoms in the two groups of athletes. The results were considered significant at $P$ values $\leq .05$. Data were analyzed using the statistical package program SAS, version 9.1.3 (SAS Institute Inc.; Cary, NC).

Results

Subjects’ Characteristics

The characteristics of the subjects included in the study are presented in Table 1. Swimmers (11 synchronized swimmers, 32 swimmers, and two divers) and winter sport athletes (seven biathletes, 22 cross-country skiers, and 16 speed-skaters training outdoors) were competing at national to Olympic levels. Eleven percent of swimmers and 9% of winter sport athletes had asthma diagnosed during their childhood before beginning their sport career. All athletes taking ICS for $> 1$ month had also been prescribed short-acting $\beta_2$-agonists on demand, except for one swimmer, who used a long-acting $\beta_2$-agonist (formoterol).

Prevalence of AHR and/or EIB According to Sport Authorities’ Criteria

One swimmer withdrew from the study without performing the EVH challenge. Five swimmers, four winter sport athletes, and three controls were considered negative to EVH because they reached a decrease in FEV$_1$ of at least 10% at one time point only, as well as one subject in each group who reached a 10% decrease at two nonconsecutive time points. All subjects with a positive EVH had an FEV$_1$ decrease of at least 10% for a sustained 5 min. When considering the highest of the two reproducible measurements after the test to calculate the lowest post-EVH value and obtain the maximal decrease in FEV$_1$, the prevalence of EIB on EVH or AHR (as defined by a methacholine challenge PC$_{20}$ $\leq$ 4 mg/mL or $\leq$ 16 mg/mL in athletes on ICS) was significantly higher in swimmers compared with winter sport athletes and controls (60% vs 29% and 17%, respectively) ($P < .005$) (Table 2).

When considering the lowest of the two reproducible measurements at each time point after EVH to calculate the lowest post-EVH value and obtain the maximal decrease in FEV$_1$, the prevalence of EIB to EVH was significantly higher in the three groups compared with the prevalence previously used when considering the higher of the two reproducible measurements ($P < .05$). Using this former method of calculation, the prevalences of EIB to EVH were 75% in swimmers, 40% in winter sport athletes, and 33% in controls. The prevalence remained significantly higher in swimmers compared with controls ($P < .05$). According to the WADA and IOC-MC criteria, the prevalence of EIB assessed with EVH using this method

### Table 1—Subject Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Swimmers (n = 45)</th>
<th>Winter Sport Athletes (n = 45)</th>
<th>Control Subjects (n = 30)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Men</td>
<td>13 (29)</td>
<td>26 (58)</td>
<td>14 (47)</td>
</tr>
<tr>
<td>Age, y</td>
<td>20 $\pm$ 4</td>
<td>18 $\pm$ 2</td>
<td>21 $\pm$ 2</td>
</tr>
<tr>
<td>BMI, kg/m$^2$</td>
<td>21 $\pm$ 2</td>
<td>22 $\pm$ 2</td>
<td>21 $\pm$ 3</td>
</tr>
<tr>
<td>Atopy</td>
<td>34 (76)</td>
<td>33 (73)</td>
<td>23 (77)</td>
</tr>
<tr>
<td>Years of training</td>
<td>12 $\pm$ 4$^{a,b}$</td>
<td>9 $\pm$ 4$^{a}$</td>
<td>4 $\pm$ 3</td>
</tr>
<tr>
<td>Hours of training per week</td>
<td>28 $\pm$ 8$^{a,b}$</td>
<td>15 $\pm$ 7$^{a}$</td>
<td>3 $\pm$ 3</td>
</tr>
<tr>
<td>Physician-diagnosed asthma</td>
<td>11 (24)</td>
<td>13 (29)</td>
<td>...</td>
</tr>
<tr>
<td>Current inhaled $\beta_2$-agonists</td>
<td>5 (11)</td>
<td>10 (22)</td>
<td>0</td>
</tr>
<tr>
<td>Current ICS</td>
<td>2 (4)</td>
<td>6 (13)</td>
<td>0</td>
</tr>
<tr>
<td>FEV$_1$, % predicted</td>
<td>119 $\pm$ 16$^{b}$</td>
<td>109 $\pm$ 10</td>
<td>105 $\pm$ 14</td>
</tr>
<tr>
<td>FVC, % predicted</td>
<td>133 $\pm$ 16$^{b}$</td>
<td>116 $\pm$ 13</td>
<td>112 $\pm$ 14</td>
</tr>
</tbody>
</table>

All values are expressed as means $\pm$ SD or No. (%). ICS = inhaled corticosteroids.

*P < .001 compared with control subjects.
*P < .001 compared with winter sport athletes.
and/or methacholine challenge (PC_{20} ≤ 4 mg/mL) remained significantly higher in swimmers compared with winter sport athletes and controls (82% vs 47% and 33%, respectively) (P < .0001).

There was a negative correlation between the methacholine challenge PC_{20} and the lowest FEV_1 value observed after the EVH test in swimmers, winter sport athletes, and in the entire population, whatever the reproducible measurement chosen at each time point after EVH to calculate the lowest post-EVH value (the lowest or highest) (Fig 1). In the whole group of athletes, the correlation between methacholine challenge PC_{20} and the lowest FEV_1 value observed after the EVH test was r = −0.50, P < .0001.

Prevalence of Exercise-Induced Respiratory Symptoms

Because most controls performed only occasional physical activity, we only report this group’s exercise-induced respiratory symptoms for descriptive purposes (Table 2). Fifty-three percent of swimmers and 71% of winter sport athletes reported having exercise-induced symptoms during the previous 12 months (Table 2). Cough was the only symptom that was significantly more frequently reported in winter sport athletes than in swimmers (P < .005).

The prevalence of symptomatic AHR and/or EIB was not significantly different between the two groups of subjects (P = .16). Asymptomatic AHR and/or EIB was significantly higher in swimmers compared with winter sport athletes (P < .05) (Fig 2). However, among athletes without a diagnosis of AHR and/or EIB, winter sport athletes reported exercise-induced respiratory symptoms more often than swimmers (P < .01).

Prevalence of AHR According to Various Methacholine Challenge PC_{20} Cutoffs

Swimmers had a significantly higher prevalence of AHR than winter sport athletes and controls for the two methacholine challenge cutoffs (P < .0001) (Table 2). The distribution of athletes positive to EVH and methacholine challenge according to the chosen cutoff is represented in Figure 3.
Furthermore, among athletes with a methacholine challenge PC\textsubscript{20} between 4 and 16 mg/mL, all winter sports athletes and 43% of swimmers were symptomatic, whereas 36% of swimmers, 50% of winter sport athletes, and 25% of controls had a positive EVH test (using the highest of two reproducible FEV\textsubscript{1} post-EVH) suggesting a diagnosis of EIB. Our observations raise the following questions: (1) Should a systematic screening for EIB be done in athletes, especially swimmers? (2) Should athletes with a methacholine challenge PC\textsubscript{20} between 4 and 16 mg/mL with exercise-induced symptoms be considered to have asthma? Furthermore, this study stresses the need to specify the method used to calculate response to EVH to allow adequate comparison of the results with other studies.

Using the highest value among two reproducible values at each time point to calculate the maximal FEV\textsubscript{1} decrease after EVH, we found 39% of swimmers having EIB on EVH and 47% having AHR according to the WADA criteria of a methacholine challenge PC\textsubscript{20} between 4 mg/mL or \leq 16 mg/mL for athletes taking ICS for at least 1 month. These rates corroborate the results other investigators have reported in swimmers.\textsuperscript{15-17} Pedersen et al\textsuperscript{18} found a similar prevalence of EIB of 31% in nonallergic female swimmers, and Castricum et al\textsuperscript{17} reported a prevalence of 50% of EIB to EVH in elite swimmers, without previously diagnosed asthma. It is interesting to note that despite the high prevalence of atopy in our subjects and the inclusion of subjects previously diagnosed with asthma we did not observe an increased prevalence of EIB compared with previous reports.

**Discussion**

Using the IOC-MC criteria, we found that 60% of swimmers and 29% of winter sport athletes had AHR or EIB, and therefore could be allowed to use certain types of asthma medication. Interestingly, our study underlines that the elite swimmer population is characterized by a high prevalence of symptomatic and asymptomatic AHR and/or EIB, whereas winter sport athletes often report exercise-induced cough but with a prevalence of AHR and/or EIB similar to controls. Furthermore, among athletes with a methacholine challenge PC\textsubscript{20} between 4 and 16 mg/mL, all winter sports athletes and 43% of swimmers were symptomatic, whereas 36% of swimmers, 50% of winter sport athletes, and 25% of controls had a positive EVH test (using the highest of two reproducible FEV\textsubscript{1} post-EVH) suggesting a diagnosis of EIB. Our observations raise the following questions: (1) Should a systematic screening for EIB be done in athletes, especially swimmers? (2) Should athletes with a methacholine challenge PC\textsubscript{20} between 4 and 16 mg/mL with exercise-induced symptoms be considered to have asthma? Furthermore, this study stresses the need to specify the method used to calculate response to EVH to allow adequate comparison of the results with other studies.

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In our study, the prevalence of EIB in swimmers was significantly higher compared with controls. We may wonder if EVH is too sensitive for swimmers or does not reflect swimming-induced bronchoconstriction. The absence of reported exercise-induced respiratory symptoms in swimmers may be due to a lack of bronchoconstriction during swimming, possibly related to the protective effect of warm and humid ambient air \(^{19}\) or to the bronchoprotective role of CO\(_2\) during swimming, as it has been previously hypothesized by Donnelly.\(^{20}\) A positive diagnosis of EIB to EVH in swimmers could reflect the damage to the airway epithelium provoked by chlorine derivatives exposure, but its clinical significance remains to be examined.\(^{21}\) Further studies are therefore needed to confirm the above hypothesis, which is supported by a study showing that 55% of the swimmers evaluated had a positive EVH, whereas only 3% of those had EIB after swimming.\(^{17}\)

In our study, winter sport athletes had a prevalence of 24% of EIB to EVH, similar to controls and to the overall prevalence found in athletes.\(^{4}\) Interestingly, 44% of winter sport athletes reported exercise-induced symptoms but had no AHR. We also observed that all winter sport athletes with a PC\(_{20}\) between 4 and 16 mg/mL reported exercise-induced respiratory symptoms, compared with 67% in those with a PC\(_{20}\) \(\leq\) 4 mg/mL and 60% in those with a PC\(_{20}\) > 16 mg/mL. The discrepancy between the prevalence of AHR and reported exercise-induced symptoms has been documented by Rundell et al\(^{4}\) and is often attributed to a poor perception of airway dysfunction by athletes. Others have observed that cold-air inhalation can induce respiratory symptoms in the absence of asthma or AHR.\(^{12,22}\) It has also been shown that hyperventilation with cold or dry air resulted in cough when high ventilatory rates were reached, without requiring underlying AHR.\(^{23}\) Thus, exercise-induced symptoms, particularly cough, may simply result from the cooling and drying of the airways and the concomitant release of inflammatory mediators, especially in winter sport athletes. Mechanical stress may also be implicated, resulting in the deformation of airway receptors, followed by the release of mediators such as prostaglandins from the bronchi, stimulation of airway C-fibers, and finally induction of cough.\(^{24}\)

With regard to the method used to calculate the response to EVH, we may consider that when the FEV\(_1\) is changing rapidly, the lowest value of each measurement could reflect the maximal response if the expiratory maneuver is of good quality. With regard to methacholine, we did use the lowest value, but it has been shown that using the highest or lowest value at each postdosing time point does not significantly change the results.\(^{24}\) However, according to our present analysis, using the highest or lowest value of FEV\(_1\) at each time point posttest to estimate the maximal decrease in this parameter makes a difference in the determination of prevalence of EIB to EVH test.

We found that either 39% or 75% of swimmers had a positive response to EVH according to the methods used. The choice of the FEV\(_1\) among two reproducible measures (the highest or the lowest) at each time point after EVH is often not mentioned in the methods section of current reports and guidelines, but different methodologies may have been used. This stresses the need for standardization of the methods, and we suggest the use of the highest of the reproducible measures done at each time point post-EVH to determine such response. The prevalence of EIB to EVH may be overestimated when selecting the lowest of these posttest values, and to our knowledge, standardization of this test has been done using the highest value.

Because 24% of swimmers with AHR or EIB were asymptomatic, our study raises the question of a systematic screening for EIB in athletes, especially swimmers. Furthermore, the significance of a methacholine PC\(_{20}\) between 4 and 16 mg/mL in athletes needs to be further studied to determine if there is a necessity to increase the cutoff value for future international events, although the significance of such PC\(_{20}\) may differ from one category of athletes to another. In this regard, bronchial provocation challenge should be done in symptomatic winter sport athletes to avoid the opposite problem of overdiagnosing EIB. The significance of a positive EVH challenge should also be studied in swimmers.

Acknowledgments

Authors contributions: Dr Bougault: contributed to conceiving the study, performing the tests, coordinating the study, drafting the manuscript, and reading and approving the final manuscript.

Dr Turmel: contributed to conceiving the study, performing the tests, and reading and approving the final manuscript.

Dr Boulet: contributed as the main investigator of the study; he helped with the conception of the study, performed the medical examination of all subjects, helped to draft the manuscript, and read and approved the final manuscript.

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and as co-leader of the Therapeutics Theme of the Canadian AllerGen Network of Centers of Excellence. He holds the Laval University Chair on Knowledge Transfer, Prevention and Education in Respiratory and Cardiovascular Health, and is a Member of the asthma committee of the World Allergy Organisation. Drs Bougault and Turmel have reported no conflicts.

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