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Self-reported Symptoms after Induced and Inhibited Bronchoconstriction in Athletes

ANDREW J. SIMPSON, LEE M. ROMER, and PASCALE KIPPELEN

Centre for Sports Medicine and Human Performance, Department of Life Sciences, Brunel University London, UNITED KINGDOM

ABSTRACT

SIMPSON, A. J., L. M. ROMER, and P. KIPPELEN. Self-reported Symptoms after Induced and Inhibited Bronchoconstriction in Athletes. *Med. Sci. Sports Exerc.*, Vol. 47, No. 10, pp. 2005–2013, 2015. **Purpose**: A change in the perception of respiratory symptoms after treatment with inhaled beta2 agonists is often used to aid diagnosis of exercise-induced bronchoconstriction (EIB). Our aim was to test the association between subjective ratings of respiratory symptoms and changes in airway caliber after induced and inhibited bronchoconstriction in athletes with EIB. **Methods**: Eighty-five athletes with diagnosed or suspected EIB performed a eucapnic voluntary hyperpnea (EVH) challenge with dry air. Of the 45 athletes with hyperpnea-induced bronchoconstriction [i.e., post-EVH fall in forced expiratory volume in 1 s (FEV_1) ≥10%, EVH^-], 36 were randomized in a double-blind, placebo-controlled, crossover study. Terbutaline (0.5 mg) or placebo was administered by inhalation 15 min before EVH. Spirometry (for FEV_1) was performed before and after EVH, and respiratory symptoms were recorded 15 min after EVH on visual analog scales. **Results**: Terbutaline inhibited bronchoconstriction (i.e., maximal fall in FEV_1 <10% after EVH) in 83% of the EVH-positive athletes, with an average degree of bronchoprotection of 53% (95% confidence interval [CI], 45% to 62%). Terbutaline reduced group mean symptom scores ($P < 0.01$), but the degree of bronchoprotection did not correlate with individual differences in symptom scores between terbutaline and placebo. Of the 29 athletes who had less than 10% FEV_1 fall after EVH in the terbutaline condition, almost half (48%) rated at least one respiratory symptom higher under terbutaline, and more than one quarter (28%) had a higher total symptom score under terbutaline. **Conclusion**: Self-reports of respiratory symptoms in conditions of induced and inhibited bronchoconstriction do not correlate with changes in airway caliber in athletes with EIB. Therefore, subjective ratings of respiratory symptoms after treatment with inhaled beta2 agonists should not be used as the sole diagnostic tool for EIB in athletes. **Key Words:** EXERCISE-INDUCED BRONCHOCONSTRICTION, ASTHMA, INHALED BETA2 AGONIST, TERBUTALINE, SPORT

Athletes frequently report respiratory symptoms on exertion, with almost a third of recreational roadrunners (29) and more than 70% of elite athletes—whether summer athletes (17), swimmers (35), or winter athletes (7)—reporting cough, wheeze, breathlessness, chest tightness, and/or mucus hypersecretion during or shortly after exercise. In a significant number of athletes, respiratory symptoms may arise from local release of inflammatory mediators (such as prostaglandins or leukotrienes) after dehydration of the airway surface lining in response to exercise hyperpnea and from ensuing narrowing of the airways (3). High prevalence of exercise-induced bronchoconstriction (EIB) has been reported in regular exercisers (21,23) and elite athletes (9). In approximately half of athletes, however, EIB does not explain the occurrence of symptoms (31). Hence, self-reported respiratory symptoms have been shown to have poor sensitivity and poor specificity for the diagnosis of EIB in athletes (17,31).

Despite the poor predictive value of respiratory symptoms in the diagnosis of EIB in athletes, health care providers rely heavily on symptoms for diagnosis (18,26). A change in the perception of respiratory symptoms after treatment with bronchodilator drugs, such as inhaled beta2 agonists, is used routinely to aid diagnosis of EIB. In the USA, most (78%) of family physicians and almost half of pulmonologists start empiric treatment with short-acting bronchodilators before exercise when EIB is suspected in an athlete (26). This symptom-based approach may explain the high rate of underdiagnosis and overdiagnosis of EIB reported in recreational (21,23) and elite athletes (4,12,24), and may contribute to inappropriate use of asthma medication (1).

The primary aim of the current study was to test the association between subjective ratings of respiratory symptoms

Address for correspondence: Pascale Kippelen, Ph.D., Centre for Sports Medicine and Human Performance, Department of Life Sciences, Brunel University London, Kingston Lane, Uxbridge, Middlesex, UB8 3PH, UK; E-mail: pascale.kippelen@brunel.ac.uk.

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and changes in airway caliber after induced and inhibited bronchoconstriction in athletes with EIB. Our primary hypothesis was that perception scores for respiratory symptoms would not correlate with the change in airway caliber induced by dry air hyperpnea with and without prophylactic administration of a single therapeutic dose of the inhaled bronchodilator terbutaline. The secondary aim was to determine whether subjective ratings of respiratory symptoms after bronchial provocation challenge could differentiate athletes with EIB and those without EIB. Our secondary hypothesis was that self-report of respiratory symptoms would neither identify nor exclude the presence of hyperpnea-induced bronchoconstriction in athletes.

MATERIALS AND METHODS

Participants

Participants were recruited from the Brunel University community and from local sports clubs. Eligible participants were male or female athletes, age 18 to 55 yr, trained regularly, and had a prior medical diagnosis of asthma and/or EIB or had suspected EIB (i.e., self-report of respiratory symptoms on exertion). Exclusion criteria were: baseline forced expiratory volume in 1 s (FEV_1) 65% or less than predicted, chest or upper respiratory tract infection in the 4 wk before testing; smoking; pregnancy; current "severe persistent asthma" [according to GINA classification (16)]; anaphylaxis; and any medical condition other than asthma or EIB.

The participants were requested to refrain from caffeine- or alcohol-containing drinks on the day of the study, to refrain from exercise within 4 h, and to avoid use of asthma medication for an appropriate period, i.e., 8 h for short-acting inhaled beta2 agonists, 12 h for inhaled corticosteroids and ipratropium bromide, 24 h for inhaled long-acting beta2 agonists (alone or in combination with an inhaled corticosteroid), 72 h for antihistamines, and 4 d for leukotriene receptor antagonists.

All participants provided written informed consent ahead of enrolment. Ethical approval was granted by the National Health Service Research Ethics Committee (ref #10/H0716/30).

Study Design

The study included two parts. Part 1 served as the screening visit (i.e., identification of athletes with EIB) and helped to address our secondary aim, based on the cross-sectional analysis of self-reported respiratory symptoms in athletes with and without EIB. Part 2 was designed to address our primary aim; it used a randomized, double-blind, placebo-controlled crossover design, with analysis of self-reported respiratory symptoms and airway caliber (via spirometry) after bronchial provocation with dry air in athletes with EIB premedicated with a short-acting beta2 agonist or placebo. The study was conducted at the Centre for Sports Medicine and Human Performance, Brunel University London, UK, from November 2010 to October 2012.

Part 1. Eligible participants performed a standardized eucapnic voluntary hyperpnea (EVH) test (2). Briefly, the participants were asked to breathe for 8 min while connected to a commercially available system (EucapSys, SMTEC, Nyon, Switzerland) that delivered a dry gas mixture of 21% O_2, 5% CO_2, and balance N_2 and provided the participants with visual feedback of their ventilation. Target ventilation was set at 30 times baseline FEV_1 [i.e., 85% of predicted maximal voluntary ventilation (MVV)]; the minimum threshold was set at 60% MVV (2). Before, and at regular intervals after EVH (2, 5, 10, 15, and 20 min), forced vital capacity maneuvers were performed on a spirometer (MicroLoop, Micromedical, Kent, UK) according to ATS/ERS recommendations (22). Predicted values were calculated using the equations of Quanjer et al. (27). Participants who complained about severe respiratory distress after EVH were administered 400 μg salbutamol via a spacer. All of the other participants recovered spontaneously. At 15 min after EVH, or immediately before drug administration (for those with severe respiratory distress), the participants rated their respiratory symptoms (i.e., cough, wheeze, chest tightness, and mucus secretion) on visual analog scales.

Part 2. Part of the methodology and spirometry data collected for the second part of this study has been published elsewhere to address a separate research question (33). Athletes with confirmed EIB (i.e., maximum fall in FEV_1 $\geq$10% after EVH in Part 1) were invited to return for Part 2. Briefly, an EVH test was performed at the same time of day (between 8:00 and 11:00 a.m.) on 2 d separated by at least 72 h. The order of treatment was randomly assigned with the use of a computerized random number generator. The participants and the experimenters were blinded to the order of the treatment conditions. A single therapeutic dose of 0.5 mg of the beta2 agonist terbutaline (Bricanyl Turbohaler, Astra Zeneca, London, UK) or a placebo was administered by inhalation 15 min before EVH. An empty demonstration Turbohaler was used for administration of the placebo. On both occasions, the participants were instructed to take one deep, hard inhalation and to hold their breath for 10 s. As for Part 1, the target ventilation for the EVH challenge was set at 85% predicted MVV. To standardize for the level of ventilation between conditions, the average ventilation achieved during the EVH challenge at the first visit was used as the target ventilation for the EVH challenge at the second visit. Recovery from the EVH test was spontaneous for all participants. Forced vital capacity maneuvers were performed at rest (before treatment administration), 10 min after treatment (taken as baseline), and at 2, 5, 10, 15, 20, 30, and 60 min recovery. Respiratory symptoms were recorded on visual analog scales at 15-min recovery.

Outcome Measures

The primary outcome measures were the maximum fall in FEV_1 after EVH and the respiratory symptom scores. Forced expiratory volume in 1 s was recorded at least three times before EVH and in duplicate after EVH. In cases where maneuvers were not reproducible (i.e., FEV_1 varied by >150 mL),

additional maneuvers were conducted (up to eight before EVH and up to four after EVH). The best reproducible FEV_1 was kept for analysis. The maximum fall in FEV_1 after EVH was calculated as the difference between baseline FEV_1 minus the lowest postchallenge FEV_1, divided by baseline FEV_1, and expressed as a percentage. The degree of bronchoprotection afforded by terbutaline was calculated by subtracting the maximum fall in FEV_1 on the drug treatment day from the maximum fall in FEV_1 on the placebo day, and expressing it as a percentage of the placebo. Bronchoconstriction was considered to be inhibited when the maximum FEV_1 fall after EVH in the terbutaline condition was less than 10% from baseline. Respiratory symptoms were assessed via a 10-cm visual analog scale (with "0" signifying completely free of the symptom and "10" the worst participants could envisage feeling) and were measured to the nearest 0.1 cm. The participants were instructed to rate their symptoms as the worst they felt during the EVH challenge or in the first 15 min after completion of the challenge. Cough, wheeze, chest tightness, and mucus secretion were individually recorded. For each participant, an overall respiratory symptom score was computed by adding scores of the four individual symptoms. Delta values were calculated as the difference between symptom scores under terbutaline minus symptom scores under placebo (with a negative delta value indicating an improved respiratory symptom score under terbutaline).

Statistical Analyses

A Shapiro–Wilk test was conducted on all study variables to identify the ones following a normal distribution. For Part 1, participants with a positive and negative response to EVH (using a 10% fall in FEV_1 as threshold value) were compared for baseline characteristics, maximum fall in FEV_1 after EVH, and respiratory symptom scores using unpaired *t*-tests, the Mann–Whitney *U*, or chi-square as appropriate. Pearson or Spearman correlation coefficients were computed for the maximum fall in FEV_1 after EVH *versus* the severity of reported respiratory symptoms. For Part 2, paired *t*-tests, Wilcoxon tests, and Pearson (or Spearman) correlation tests were conducted to evaluate the effect of the treatment on post-EVH maximum fall in FEV_1 and respiratory symptom scores. Statistical analyses were performed using SPSS 18.02 for Windows (SPSS, Chicago, IL). The level of significance was set at $P < 0.05$.

RESULTS

Part 1

Participants. Ninety-three participants were initially recruited for the study; five declined to participate and one was excluded based on anphylaxis (Fig. 1). One participant had an underlying diagnosis of Crohn disease; however, at the time of the study, he was asymptomatic and was not undergoing treatment for this condition. An EVH test was therefore carried out on 87 athletes. Of the 87 EVH tests, 85 were judged technically acceptable and were subsequently analyzed. The two participants who were excluded did not reach the minimum required ventilation threshold (i.e., 60% predicted MVV) owing to a gag reflex or severe cough (the latter leading to early termination of the test).

Baseline demographics and clinical and training characteristics of the 85 participants are presented in Table 1. All but six of the participants were regular competitors; 66 took part in local sporting events and 13 competed in national and/or international events. Forty-two participants trained in endurance-based sports (running, 21; rowing, 12; cycling, 6; and triathlon, 3), 30 in team sports (football, 13; rugby, 9; netball, 4; hockey, 3; and cricket, 1), 10 in athletics (sprinting, 8; middle-distance running, 1; and throwing, 1), 2 in racquet sports (squash, 1; and tennis, 1) and one in combat sport (Thai boxing).

All 85 participants reported current respiratory symptoms with exercise. Sixty-six (78%) had a previous medical diagnosis of asthma and/or EIB; in 44 of these (56%), the diagnosis was made during childhood. In participants without childhood asthma or EIB, the mean ± SD age of onset of respiratory symptoms was 25 ± 9 yr. At the time of the study, 22 athletes were prescribed salbutamol alone and 22 were prescribed inhaled corticosteroids alongside inhaled beta2 agonist(s). Six athletes were under fixed combination therapy (including one who was prescribed a leukotriene receptor antagonist as add-on therapy). No significant differences were noticed between athletes positive or negative for EVH for anthropometric and training characteristics.

Pulmonary function in EVH-positive athletes versus EVH-negative athletes. Forty-five athletes (53%) had a 10% or greater fall in FEV_1 after EVH. The maximal fall in FEV_1 in EVH-positive athletes ranged from 10% to 50%, with the fall in FEV_1 significantly greater compared to the EVH-negative group ($P < 0.001$; Table 2). In seven (15%) of the athletes classified EVH-positive, the fall in FEV_1 was only transient (i.e., sustained for <5 min). During the EVH test, the participants reached a mean ± SD ventilation of 101 ± 21 $L \cdot min^{-1}$, corresponding to 75% ± 8% of predicted MVV. The level of ventilation reached by the EVH-positive participants did not differ significantly to the level reached by those EVH-negative (Table 2).

Baseline spirometry revealed significant between-group differences, with lower FEV_1/FVC (Δ, 4.5%; 95% confidence interval [CI], 1.4% to 7.7%; $P = 0.006$), absolute forced expiratory flow between 25% and 75% of FVC ($FEF_{25–75}$) (Δ, 0.42 $L \cdot s^{-1}$; 95% CI, 0.18 to 0.83 $L \cdot s^{-1}$; $P = 0.041$) and % predicted $FEF_{25–75}$ (Δ, 11.3%; 95% CI, 3.1% to 19.5%; $P = 0.008$) in the EVH-positive group. Analysis of categorical variables revealed that women were less represented in the EVH-positive group ($\chi^2(1) = 4.95$; $P = 0.030$), whereas athletes with a previous medical diagnosis of asthma and/or EIB ($\chi^2(1) = 6.96$; $P = 0.010$), those with childhood asthma and/or EIB ($\chi^2(1) = 6.16$; $P = 0.017$), and those prescribed inhaled corticosteroids plus beta2 agonists ($\chi^2(1) = 4.66$; $P = 0.046$) were more represented in the EVH-positive group (Table 1).

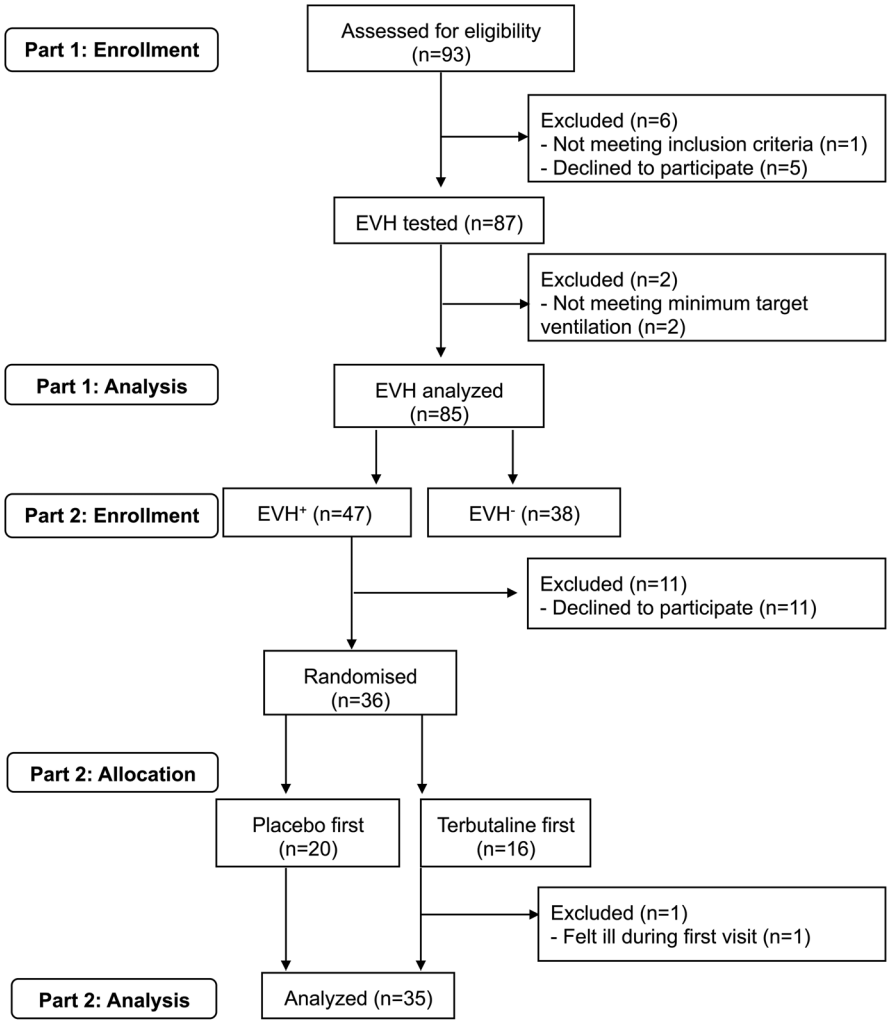

FIGURE 1—Flow diagram of the progress through the two parts of the study.

Correlation analysis revealed that baseline percent predicted FEV_1, PEF, and $FEF_{25–75}$ values were weakly associated with the maximal % fall in FEV_1 after EVH: $r_s = -0.22$, $P = 0.039$; $r_s = -0.24$, $P = 0.027$; and $r_s = -0.40$; $P < 0.001$, respectively.

Respiratory symptoms in EVH-positive athletes versus EVH-negative athletes. Wheeze was the only symptom that significantly differed between the groups, with the EVH-positive athletes rating significantly higher scores than the EVH-negative athletes ($P < 0.001$; Table 2). When symptom scores were pooled, the total score was significantly greater in the EVH-positive athletes ($P = 0.015$; Table 2). Moderate positive correlations were noted between the maximum fall in FEV_1 after EVH and wheeze ($r_s = 0.51$; $P < 0.001$) and total symptom scores ($r_s = 0.32$; $P = 0.003$). Cough, chest tightness, and mucus secretion were not significantly related to the maximum fall in FEV_1 after EVH. A weak negative correlation was noted between baseline % predicted $FEF_{25–75}$ and the rating of wheeze after EVH ($r_s = -0.24$; $P = 0.027$). No other significant correlation was found between baseline pulmonary function parameters and symptoms scores.

Part 2

Participants. Of the 45 participants eligible for Part 2, 11 (24%) declined to return (Fig. 1). Two athletes with a borderline response to EVH (i.e., 8%–9% fall in FEV_1 after EVH) were invited to return for Part 2. In total, therefore, 36 athletes were randomized. Athletes who returned did not differ significantly from those who did not return for: baseline demographics, clinical and training characteristics, airway response to EVH, and reported respiratory symptoms after EVH (data not shown). Except for one of the "borderline" participants, who felt ill after EVH in the terbutaline condition, all other randomized participants completed the two arms of the study.

Effect of terbutaline on pulmonary function in EVH-positive athletes. At rest, terbutaline had a significant bronchodilator effect, inducing an increase in FEV_1 of

TABLE 1. Baseline demographics and clinical and training characteristics of the participants.

	All (n = 85)	EVH$^-$ (n = 40)	EVH$^+$ (n = 45)
Age, yr	26 ± 9	26 ± 9	26 ± 10
Sex (females)	36 (42%)	22 (55%)	14 (31%)*
Height, cm	174 ± 8	173 ± 9	176 ± 8
Body mass, kg	74.6 ± 13.6	73.4 ± 14.8	75.7 ± 12.5
Medical diagnosis of asthma/EIB	66 (78%)	26 (65%)	40 (89%)*
Childhood asthma/EIB	44 (52%)	15 (38%)	29 (64%)*
Family asthma	45 (53%)	18 (45%)	27 (60%)
SABA only	22 (26%)	8 (20%)	14 (31%)
SABA + ICS	22 (26%)	6 (15%)	16 (36%)*
Reported allergies	53 (62%)	24 (60%)	29 (64%)
FVC, L	4.89 ± 0.99	4.72 ± 0.98	5.04 ± 0.98
FVC, % pred.	106 ± 11	106 ± 12	106 ± 10
FEV_1, L	3.87 ± 0.71	3.86 ± 0.73	3.88 ± 0.70
FEV_1, % pred.	99 ± 11	102 ± 10	97 ± 11
FEV_1/FVC, %	80 ± 8	82 ± 6	78 ± 9**
FEF_{25-75}, L·s^{-1}	3.65 ± 0.96	3.88 ± 0.87	3.46 ± 1.00*
FEF_{25-75}, % pred.	81 ± 20	87 ± 15	76 ± 23**
PEF, L·s^{-1}	8.41 ± 1.56	8.38 ± 1.76	8.44 ± 1.38
PEF, % pred.	96 ± 13	99 ± 15	94 ± 10
Training, h·wk^{-1}	9 ± 6	11 ± 7	8 ± 4
Training, yr	8 ± 6	8 ± 5	9 ± 6

Values are presented as mean ± SD (or n [%]).
*P < 0.05, **P < 0.01 indicate significantly different from EVH$^-$.
EVH$^-$, athletes with less than 10% fall in FEV_1 after EVH of dry air; EVH$^+$, athletes with 10% or greater fall in FEV_1 after EVH of dry air; FEV_1, forced expiratory volume in 1 sec; FEF_{25-75}, forced expiratory flow between 25% and 75% of FVC; FVC, forced vital capacity; ICS, inhaled corticosteroid; PEF, peak expiratory flow; SABA, inhaled short-acting beta2 agonist; % pred., % of predicted value (27).

194 mL (95% CI, 149–240 mL; P < 0.001) or 5% (95% CI, 4%–6%). No such bronchodilator effect was noticed after administration of the placebo: ΔFEV_1 was −7 mL (95% CI, −40 to 27 mL; P = 0.695) or 0% (95% CI, −1% to 1%). During the EVH test, ventilation was slightly (Δ,1.3 L·min^{-1}; 95% CI, 0.3–2.4 L·min^{-1}), but significantly (P = 0.015), increased in the terbutaline condition (Table 3).

In the placebo condition, all but one athlete had a 10% or greater fall in FEV_1 after EVH, with the peak fall in FEV_1 occurring within the first 15 min of recovery in all participants. The only athlete with a negative response had an 8% fall, which was close to the 10% fall noted for that participant in Part 1. Terbutaline inhibited hyperpnea-induced bronchoconstriction in 83% of athletes, with a mean degree of bronchoprotection of 53% (95% CI, 45%–62%). The six athletes who remained positive to EVH in the terbutaline condition had a maximum fall in FEV_1 of 16% (95% CI, 11%–21%). Overall, the maximum fall in FEV_1 after EVH was significantly reduced in the terbutaline condition (P < 0.001; Table 3). There was no significant correlation between the maximum fall in FEV_1 and the level of ventilation achieved by athletes during the EVH test in either the placebo or the terbutaline condition (P > 0.05).

Association between pulmonary function values and respiratory symptoms after induced and inhibited bronchoconstriction in EVH-positive athletes. Although terbutaline reduced group mean symptom scores (Table 3), the degree of bronchoprotection afforded by terbutaline did not correlate with individual differences in symptom scores between the terbutaline and placebo conditions (Fig. 2A–D). Furthermore, of the 29 athletes who had less than 10% fall in FEV_1 after EVH, 14 (48%) rated at least one respiratory symptom higher in the terbutaline condition (Fig. 3A–D). Finally, more than one quarter of these athletes (28%) had a higher total symptom score under terbutaline.

DISCUSSION

Respiratory symptoms are often the basis for the diagnosis and treatment of EIB. Our data suggest that group mean scores for perceived respiratory symptoms (including cough, wheeze, chest tightness, and mucus secretion) are reduced when hyperpnea-induced bronchoconstriction is at least partly inhibited by prophylactic administration of the bronchodilator agent terbutaline in symptomatic athletes with

TABLE 2. Airway response and self-reported respiratory symptoms after 8 min of EVH of dry air in symptomatic athletes positive (EVH$^+$) or negative (EVH$^-$) for exercise-induced bronchoconstriction (EIB).

	EVH$^-$ (n = 40)	EVH$^+$ (n = 45)	Difference: EVH$^+$ − EVH$^-$ (95% CI)
Achieved $\dot{V}E$, L·min^{-1}	99 ± 21	103 ± 20	3 (−6 to 12)
Achieved $\dot{V}E$, % pred. MVV	74 ± 8	76 ± 8	2 (−1 to 5)
Max fall in FEV_1 after EVH, %	6 ± 2	19 ± 11***	13 (10 to 17)
Cough, cm	5.8 ± 2.7	5.9 ± 2.2	0.0 (−1.0 to 1.1)
Wheeze, cm	3.5 ± 2.5	6.4 ± 1.6***	2.9 (2.0 to 3.8)
Chest tightness, cm	4.1 ± 2.5	5.0 ± 2.6	0.8 (−0.3 to 1.9)
Mucus secretion, cm	5.3 ± 2.7	5.0 ± 2.6	−0.3 (−1.4 to 0.9)
Total symptoms score, cm	18.8 ± 6.9	22.2 ± 5.9*	3.4 (0.7 to 6.2)

Values are presented as mean ± SD (or 95% CI).
*P < 0.05 and ***P < 0.001 indicate significantly different from EVH$^-$.
$\dot{V}E$, minute ventilation; % pred. MVV, percentage of predicted maximal voluntary ventilation.

TABLE 3. Airway response and reported respiratory symptoms after 8 min of EVH of dry air in symptomatic athletes with EIB premedicated with either 0.5 mg of terbutaline or a placebo.

	Placebo (n = 35)	Terbutaline (n = 35)	Difference: Terbutaline – Placebo (95% CI)
Achieved $\dot{V}E$, L·min^{-1}	104 ± 21	105 ± 21*	1.3 (0.3 to 2.4)
Achieved $\dot{V}E$, % pred. MVV	80 ± 7	82 ± 8**	2.2 (0.8 to 3.6)
Max fall in FEV_1 after EVH, %	16 ± 7	7 ± 5***	−8.8 (−6.1 to −11.4)
Cough, cm	5.5 ± 2.0	3.9 ± 2.7**	−1.7 (−0.8 to −2.6)
Wheeze, cm	5.4 ± 2.1	4.2 ± 2.2**	−1.2 (−0.5 to −2.0)
Chest tightness, cm	5.1 ± 2.2	3.8 ± 2.7**	−1.3 (−0.5 to −2.1)
Mucus secretion, cm	5.0 ± 2.5	3.9 ± 2.5**	−1.1 (−0.4 to −1.8)
Total symptoms score, cm	21.1 ± 7.4	15.8 ± 8.3***	−5.3 (−2.8 to −7.8)

Values are presented as mean ± SD (or 95% CI).
*$P < 0.05$, **$P < 0.01$, and ***$P < 0.001$ indicate significantly different from placebo.

EIB. However, at an individual level, perception scores for respiratory symptoms did not correlate with the changes in airway caliber induced by dry air hyperpnea with and without premedication with 0.5 mg of inhaled terbutaline. Wheeze during EVH challenge was the only respiratory symptom (of the four tested) that differentiated athletes positive compared to those negative to EVH (with higher scores reported by EVH-positive athletes). Therefore, there is a caveat in systematically prescribing inhaled beta2 agonists to athletes reporting respiratory symptoms on exertion and in relying on self-reported symptoms to assess the efficacy of bronchodilator treatment for EIB prevention.

The novelty of this work resides in the conjoint assessment of a change in airway caliber (measured by FEV_1) and in subjective ratings of respiratory symptoms in a condition of induced bronchoconstriction versus a condition of at least partly inhibited bronchoconstriction in athletes with EIB. In the past, the link between self-reported respiratory symptoms and airway caliber has only ever been assessed in athletes after induced bronchoconstriction, using either exercise (31,32,36) or its surrogates, e.g., EVH (7,17,36) or mannitol (36). These studies have consistently shown respiratory symptoms to be poor predictors of EIB. In our group of athletes, all of whom reported respiratory symptoms on

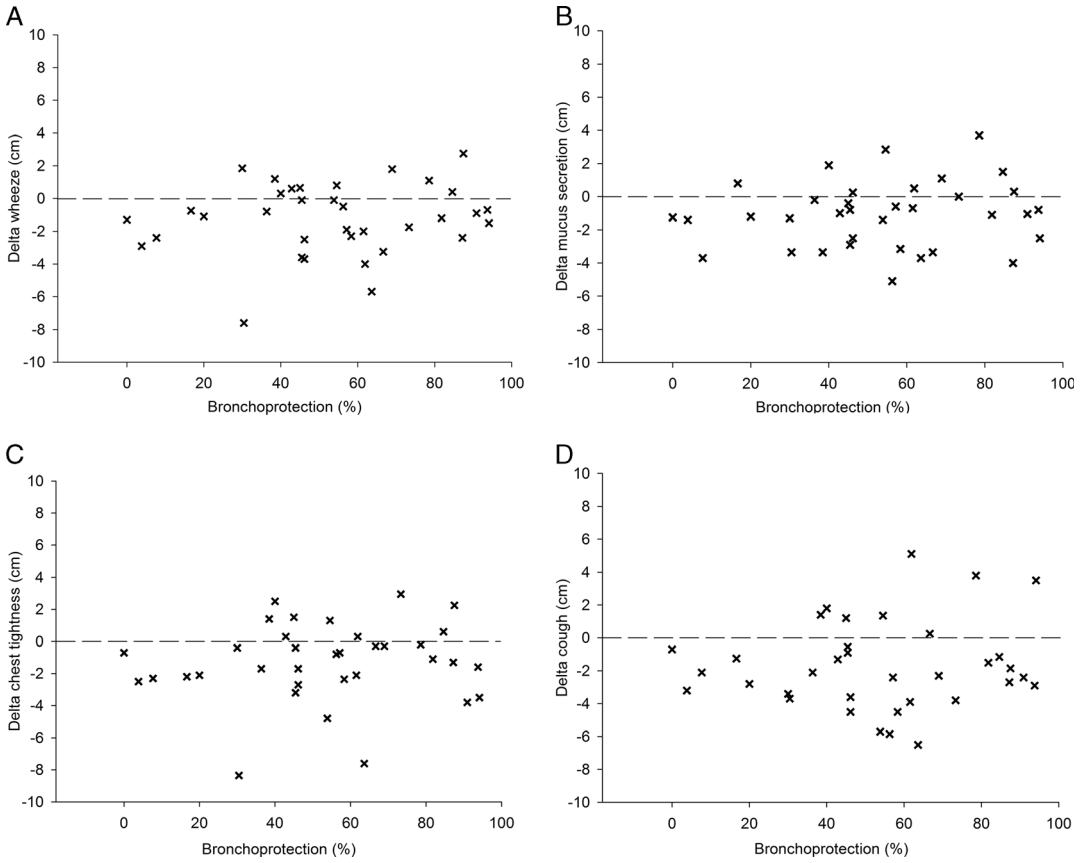

FIGURE 2—Absence of correlation between the change in respiratory symptoms (A, wheeze; B, mucus secretion; C, chest tightness; D, cough) and the degree of bronchoprotection afforded by terbutaline after EVH of dry air in 35 symptomatic athletes with EIB. Zero percent bronchoprotection: similar fall in FEV_1 after EVH with terbutaline and placebo; 100% bronchoprotection: no fall in FEV_1 after EVH with terbutaline; delta values were calculated as the difference between symptom scores under terbutaline minus symptom scores under placebo (with a negative delta value indicating an improved respiratory symptom score under terbutaline).

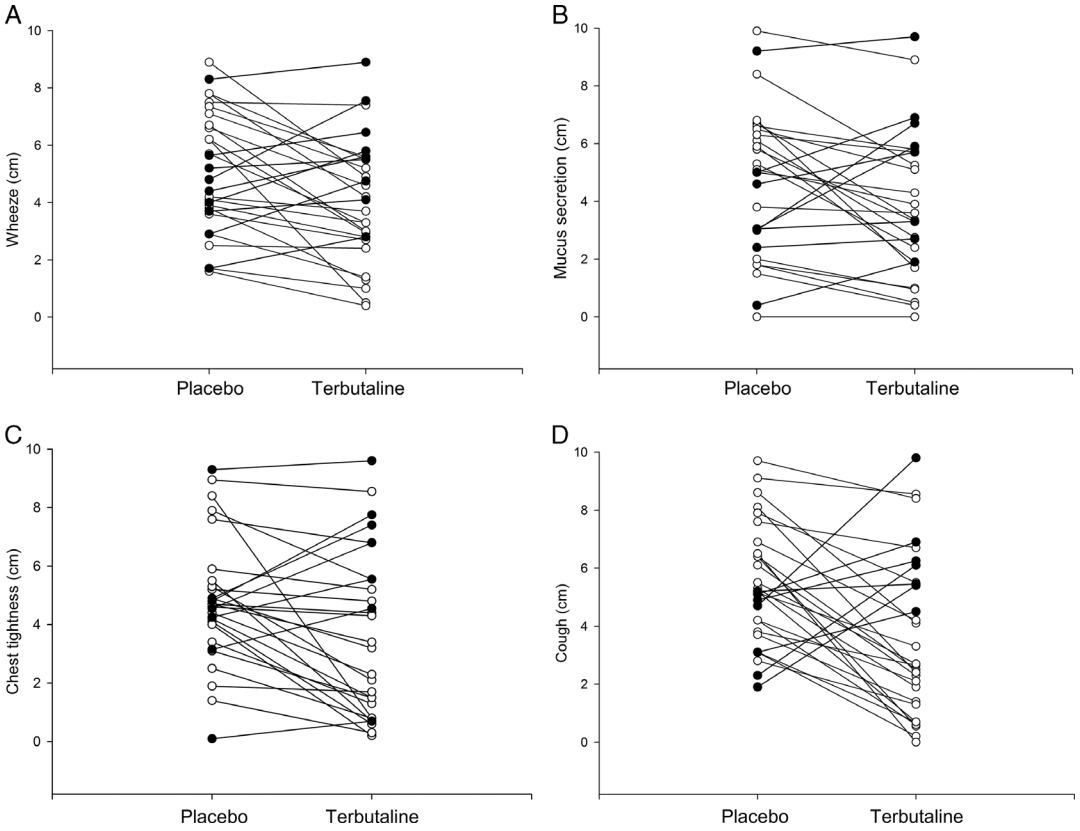

FIGURE 3—Individual ratings of respiratory symptoms (A, wheeze; B, mucus secretion; C, chest tightness; D, cough) after treatment with 0.5 mg terbutaline or placebo in 29 symptomatic athletes positive to EVH under placebo but negative under terbutaline. Closed circles represent athletes who scored symptoms higher under terbutaline (A, *n* = 9; B, *n* = 8; C, *n* = 7; D, *n* = 7).

exertion, only approximately half was positive for EIB when diagnosis with pulmonary function testing using a bronchial provocation challenge with dry air was used (53% if a 10% threshold in FEV_1 fall post-EVH was used and 45% if a sustained FEV_1 fall was considered). Although prophylactic administration of terbutaline reduced group mean respiratory symptoms scores after EVH, the difference in symptom scores between the active drug and placebo conditions did not correlate with the degree of bronchoprotection afforded by terbutaline. Furthermore, of the athletes with less than 10% fall in FEV_1 after EVH after inhalation of terbutaline, almost half rated at least one respiratory symptom higher compared to placebo (i.e., when significant bronchoconstriction occurred). This highlights a disconnection between objective changes of airway caliber and self-report of respiratory symptoms in athletes, and confirms our secondary hypothesis that symptoms alone cannot be used to identify or exclude the presence of bronchoconstriction in athletes.

In the current study, the only symptom that significantly differed between EVH-positive and EVH-negative and that positively correlated with the maximum fall in FEV_1 after EVH was wheeze. This somewhat contradicts the findings of Rundell et al. (31), which showed no association between the reporting of wheeze during usual training and the bronchial response to a sport/environment-specific field exercise challenge test. However, the same authors (32) found, in a different athletic population (i.e., elite women ice hockey players), that the presence of cough (not wheeze, chest tightness, or excess mucus) was significantly related to EIB (when EIB was assessed through a skating challenge in cold/dry air). Furthermore, using EVH as a surrogate for exercise, Holzer et al. (17) found in elite summer-sport athletes that wheeze had one of the highest positive predictive values for EIB (71%). More recently, Couillard et al. (11) showed that airway hyper-responsiveness to EVH and/or methacholine was associated with an increased perception of wheeze after EVH in competitive athletes (endurance athletes, swimmers, and winter athletes). Together, these results suggest that no single respiratory symptom can be used to accurately detect EIB in athletes, and that the mode of bronchoprovocation as well as the choice of the study population may influence the relationship between self-reported symptoms and the severity of induced bronchoconstriction.

The reporting of respiratory symptoms during and/or shortly after exercise, independent of airway narrowing, is not specific to athletic populations. Symptoms that mimic EIB have been reported in patients with exercise-induced dyspnea in the absence of bronchoconstriction when exercise was performed in the cold (37). Cold air and dry air are known to directly trigger cough and glandular secretion through sensory C-fibers (15) and submucosal gland cell

activation (14), respectively. The large thermal and osmotic stress placed upon the airways during exercise or dry air hyperpnea (as used in the current study) may therefore explain the frequent reporting of cough and mucus hypersecretion by athletes.

Exercise may also initiate a cough reflex and mucus hypersecretion indirectly, i.e., via an inflammatory response and/or injury to the airway epithelium. Hyperpnea of dry air has been shown to cause release of the inflammatory mediator prostaglandins, both in athletes with EIB and those without EIB (19). The excitability of nociceptive C-fiber afferents in the lungs increases in the presence of inflammatory mediators, such as prostaglandins and leukotrienes (20,25). Furthermore, acute exercise (5,10) and dry air hyperpnea (6,33) have been shown to perturb the integrity of the airway epithelium. Injury to the airway epithelium would expose sensory nerve endings to noxious agents (such as air pollutants and allergens) and may trigger a neurogenic inflammation (28). In swimmers (7), runners (29), and ice-arena athletes (32)—all of whom are frequently exposed to noxious airborne agents (e.g., chlorine derivatives and exhaust gas from cars or from fossil-fueled ice-resurfacing machines)—high prevalence of respiratory symptoms and pulmonary dysfunction has consistently been reported. That hyperpnea of dry air may stimulate cough and mucus hypersecretion independently of a change in airway caliber may explain why wheeze, which is more directly linked to airflow limitation (34), differentiated better EVH-positive athletes from EVH-negative athletes in Part 1 of this study.

Our intervention was highly successful in that inhalation of the single therapeutic dose of 0.5 mg of terbutaline inhibited bronchoconstriction (i.e., <10% fall in FEV_1 after EVH) in 83% of the athletes. Whereas many reports have focused solely on the link between self-report of respiratory symptoms by athletes and airway response to bronchoprovocation (7,11,17,31,32,36), the inclusion of a terbutaline arm in our study design provides novel practical information for physicians; that is, changes in self-reported respiratory symptoms after prophylactic usage of inhaled beta2 agonists before exercise should not be relied on for the detection and management of EIB in athletes. However, it should be acknowledged that the prophylactic effect of terbutaline on self-reported respiratory symptoms was only assessed on a single occasion. Yet, in daily practice, health care providers may give athletes several weeks to assess whether the medication has any perceived benefits.

Owing to its high sensitivity (13,30), EVH of dry air is the recommended bronchial provocation test for EIB diagnosis in elite athletes (2). Therefore, EVH was preferred to exercise challenge in the current study. One potential limitation, however, is that we were not in a position to assess the origin of the respiratory symptoms in the group of athletes negative to EVH. Recent evidence suggests that exercise-induced laryngeal obstruction is a common differential diagnosis in symptomatic athletes (24). Alternative causes for unexplained respiratory symptoms in athletes include rhinitis, recurrent upper respiratory tract infection, gastroesophageal reflux disease, and hyperventilation syndrome (8).

CONCLUSION

Our aim was to further characterize the subjective perception of bronchoconstriction in athletes. In Part 1, we compared post-EVH reports of respiratory symptoms in athletes positive and negative for EIB. In Part 2, we used a novel study design in which athletes with EIB were premedicated with either a bronchodilator (i.e., 0.5 mg terbutaline) or a placebo ahead of a bronchial provocation test with dry air. Of the four symptoms commonly associated with EIB (i.e., cough, wheeze, chest tightness, and mucus secretion), wheeze was the only one that significantly differed after dry air challenge between athletes positive to EVH and those negative to EVH. Furthermore, there was no evidence of a relationship between the degree of bronchoprotection afforded by terbutaline and differences in respiratory symptom scores between the terbutaline and placebo conditions. Therefore, health care providers should not rely solely on changes in subjective ratings of respiratory symptoms after prescription of inhaled beta2 agonists when posing a diagnosis of EIB in athletes. This reinforces the need for objective evidence of EIB for effective diagnosis and management of EIB in athletes (17,31).

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