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Perception of dyspnea during exercise-induced bronchoconstriction

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Abstract After strenuous physical exercise, many subjects show a significant bronchoconstriction and report dyspnea. Despite this clinical condition being a commonly encountered situation during daily life, which may be responsible for substantial disability, there is little information on the relationship between the perception of dyspnea and exercise-induced bronchoconstriction (EIB) after a standardized exercise challenge. For these reasons, we evaluated 200 consecutive outpatients (median age 13 years, ranging from 5 to 56 years) referred to our laboratory to perform an exercise test out of suspicion of EIB. On exercise challenge, perception of dyspnea was rated on a modified bipolar Borg scale immediately before each FEV_1 measurement. Sixty-nine (35%) subjects had a positive exercise challenge, defined as a decrease of at least 20% in FEV_1 from baseline. Both the onset and the decay of dyspnea preceded those of bronchoconstriction. Overall, the rating of dyspnea in the laboratory was well related with the reports of exercise-related symptoms. Sumilarly, 36 of 77 (47%) asthmatics with a history of exertional symptoms and 24 of 65 patients (40%) without a history had a positive challenge. Asthmatics reporting exertional symptoms perceived a greater magnitude of dyspnea after exercise independently from the degree of bronchoconstriction. Overall, dyspnea was significantly, but loosely correlated to the magnitude of decrease in FEV_1, being also influenced by age, gender and BMI. Conclusions: We conclude that dyspnea recorded in the laboratory after exercise test is related to exertional symptoms reported during real life, but not completely related to EIB. The rating of dyspnea is a well-suited model to study naturally occurring exercise-induced dyspnea and a useful tool to enlarge the results of an exercise challenge.

Keywords asthma; dyspnea; exercise; perception; bronchoconstriction.

INTRODUCTION

Asthma is characterized by bronchial hypersensitivity to several triggers with recurrent attacks of bronchial obstruction and dyspnea. Exercise is one of the most common of these triggers (1). Many asthmatic subjects and some individuals without a history of asthma show a significant exercise-induced bronchoconstriction (EIB) after strenuous physical exercise.

Dyspnea and wheezing after exercise are the clinical (1) and epidemiological (2) hallmarks of EIB. Exercise-induced symptoms may be responsible for substantial disability, mainly in children due to their high level of physical activity. Dyspnea can succeed in limiting the level of physical activity and leading to a sedentary lifestyle, which, in turn, decreases fitness and exercise tolerance (3).

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Despite its widespread prevalence and clinical significance, very little information exists on the perception of dyspnea in EIB (4,5).

Turcotte *et al*. (4) have shown a relationship between breathlessness and EIB and, for a given level of bronchoconstriction, the perception of dyspnea did not seem to differ whether it was provoked by exercise, or histamine-or allergen challenge. However, this study comprised only eight subjects and may not have had sufficient power to detect differences. Rietveld *et al*. (5) did not accurately describe the time points after exercise challenge where lung function measurements and dyspnea ratings were performed, failing to establish a clear relationship between EIB and dyspnea. Killian and co-workers (6) have compared the perceived level of dyspnea on methacholine-induced bronchoconstriction with that reported during exercise in a large number of asthmatic subjects, concluding that subjects with higher magnitude rating of dyspnea on challenge also reported higher dyspnea during exercise. Unfortunately, these authors did not describe whether the perception of dyspnea during exercise was related to bronchoconstriction, so that the relevance of their findings to exercise-induced asthma (EIA) remains unclear. Indeed, other authors have suggested that dyspnea may vary depending on the trigger used to induce bronchoconstriction (7,8) or in naturally occurring asthma (9).

Due to these reasons, we report our observations on the relationship between dyspnea and bronchoconstriction in a large setting of outpatients undergoing exercise challenge for the suspicion of EIB.

MATERIALS AND METHODS

From 1995 to 1998, we analyzed 200 consecutive outpatients referred to our institution for exercise testing from family physicians, sport physicians or pulmonary specialists, who were able to perform a technically suitable exercise challenge and to rate the perceived intensity of their dyspnea after challenge, and had a baseline FEV_1 of at least 70% of the predicted value on the study day. The test was performed when patients were in stable state for at least 4 weeks prior to the study. All the subjects gave written informed consent to the study.

For each patient, we recorded clinical history, symptoms, use of tobacco and, when available, the results of allergen skin prick tests, using the clinical record including specific questions on EIA.

There were 138 males and 62 females. The mean age was 16.8 years, the median 13, and the range from 5 to 56 years. Smokers were 13% of the total. Baseline FEV_1 was $95 \pm 1\%$ ($M \pm SE$) of predicted. Body mass index (BMI) was 22.7 ± 0.6 kg m^{-2}. Skin-prick test was available for 152 subjects. Of these, 122 (80%) were found positive for at least one allergen (27 perennial allergens only, 32 seasonal allergens, 64 both, and 1 only to food allergen). Many subjects were untreated, whereas 48 had received the prescription of an inhaled corticosteroid and 115 of β_2-agonists. Before the challenge, long-acting β_2-agonists and theophylline derivatives were withheld for at least 24 h, antihistamines for 7 days, and all other treatments for 12 h. Subjects were also asked to refrain from physical exercise and to avoid beverages containing caffeine on the study day.

On the basis of patients' history recorded in the clinical chart, two doctors of us (PS and GC), without direct knowledge of the patients and blinded to the results of the exercise challenge, divided the enrolled subjects in four clinical groups. Asthmatic patients who clearly reported repeated episodes of dyspnea with cough or wheezing when running or practising sports were classified as having probable EIA. Asthmatic patients without any reported exercise-induced symptoms as asthma only (AO). Patients who reported exertional breathlessness without any history of asthma were classified as having exertion dyspnea (ED). Finally, patients who denied exercise-related symptoms and had no evidence of asthma were classified controls (C).

There were 77 patients in the EIA group, 65 in the AO group, 36 in the ED group and 22 in the C group. To restrict the analysis to patients in whom the diagnosis other than asthma could be excluded by objective measurements, the clinical records of asthmatic patients were screened for the presence of either documented bronchial hyperresponsiveness to methacholine ($PD_{20} <$ 400 μg), or reversible airway obstruction (FEV_1 improvement of at least 19% over baseline after salbutamol 0.2 mg), or wheezing at chest auscultation directly recorded by a physician of our center at any visit. According to these criteria, objective documentation of bronchoconstriction or bronchial hyperresponsiveness was found in 62 patients, 26 having AO and 36 EIA. However, the failure of finding such a objective documentation on the clinical records did not exclude a diagnosis of asthma, as patients could be free of symptoms at the time of testing, and both the methacholine challenge and the bronchodilation test were not routinely performed, unless specifically requested by the referring physician.

The exercise challenge test was performed according to a standardized protocol on a motor-driven treadmill (Runrace RHC1200, Technogym, Forlí, Italy) with a slope of 15%. Subjects always ran wearing a nose clip. During the first 2 min, the speed of the treadmill was gently increased until the subject reached 85% of the maximal predicted heart rate for age. The exercise was therefore continued for 8 min adjusting the speed to maintain the required heart rate. Heart rate was continuously recorded using a Sport Tester PE2000 electronic device (Polar Elektro, Kempele, Finland). We only included subjects able to develop a technically suitable challenge to provoke EIB in accordance to Haby *et al*. (10). One hundred and ninety-six subjects maintained the required heart rate during the exercise test, four others, where the heart rate was lower than prescribed, had an estimated oxygen consumption greater than 35 ml kg min^{-1}. The distance run by each enrolled subject was measured to provide, in conjunction with body weight, an indirect estimation of oxygen consumption (11). Due to an air-conditioning system, room temperature was constantly lower than 23°C and humidity less than 50% on the study days.

Spirometry was performed before the test, immediately after stopping (t=0), at 3, 6, 10, 15, 20 and 30 min after the end of exercise (mod. Altair 4000, Cosmed, Roma, Italy). The best of three maneuvers of acceptable quality were retained for analysis. Predicted lung function values were according to Quanjer *et al*. (12) and Zapletal *et al*. (13).

Immediately before each post-exercise spirometry, the subjects rated the perceived intensity of their dyspnea at each chosen time point by matching and marking it as they were in that moment on a modified bipolar transitional Borg scale (14), but always with reference to the pre-exercise condition. The numbers of the bipolar Borg scale ranged from −10 (maximal worsening) to +10 (maximal improvement), with a score of 0 indicating no change from baseline and were tagged to descriptive phrases, e.g. 0.5="very,very slight"; 2="slight"; 3="moderate"; 4="somewhat severe", etc. Subjects were not restricted to the use of whole numbers, scores between fixed intervals also being permitted. There was a different scale for each chosen time point; the scales were drawn as parallel 20 cm vertical lines on a single sheet of paper. The subjects were allowed to see the values scored at the previous time points, as suggested by Guyatt and co-workers (15). We anchored the extremes of the scale on general experience of the same perceiver, such as "the worst/best dyspnea which you have ever experienced". To the aim of minimizing the problem of confounding bias, immediately before the exercise challenge, each subject received a clear and standardized explanation on the use of the scale and that the studied perception was dyspnea, neither leg muscle fatigue, nor the awareness of increased ventilation, nor the sensation of dryness in throat.

The technicians supervising the exercise test and the spirometry were blinded to the dyspnea scale rating. None of the enrolled subjects had experience of dyspnea evaluation prior to this survey. The subjects were blinded to the results of their lung function testings.

Statistical analysis

The responses to the exercise challenge were initially scored as positive for a reduction in FEV_1 of 20% or more over baseline; doubtful ones, when the maximal decrease in FEV_1 was between 20 and 15% of baseline; and completely negative responses for a reduction in FEV_1 from baseline less than 15%. Since preliminary analysis, showed that the doubtful responses were equally distributed in the groups with or without asthma (see results), after a first description for subsequent analysis, all challenges with less than 20% decrease in FEV_1 were considered as negative responses. In patients who performed more than one exercise challenge during the study period, only the first one was selected for analysis.

The association between a positive exercise challenge and the different clinical groups was investigated using logistic regression. Differences between groups in continuous variables were investigated by ANOVA or by Student's t-test. The Spearman rank test was used to analyze the correlation between changes in FEV_1 and dyspnea score. Backward stepwise multiple regression analysis was used to investigate the correlation between the degree of dyspnea (the dependent variable) and other factors. These included the percent decrease in FEV_1 and in PEF from baseline, percent predicted FEV_1 at baseline, age, current smoking, and BMI. Probability to enter and to remove variables in the model was set to 0.1 and to 0.25, respectively. A level of $P<0.05$ for a two-tail test was considered significant. In addition to analyzing the data at each time point, we also examined the correlation between the maximum fall in FEV_1 and the minimum value of the dyspnea score over the entire period of observation after exercise.

All the analyses were performed using the statistical package Stata on a PC-compatible personal computer (Stata Corporation, College Station, TX, U.S.A.).

RESULTS

The distribution of the responses to the exercise challenge in terms of the maximal fall in FEV_1 from baseline according the clinical classification and some anthropometric characteristics of enrolled patients is reported in Table 1. We distinguished 69 positive (maximal fall in FEV_1 of at least 20% from baseline), 19 doubtful (maximal fall in FEV1 from 15 to 19% from baseline) and 112 negative responses. A positive response was clearly associated with the reports of either asthmatic features or exertional dyspnea, whereas the presence of a doubtful response was not associated to any clinical pattern. In the following text, the subjects with the maximal decrease in FEV_1 of less than 20% were therefore analyzed all together. Interestingly, the presence of a positive response in subjects with a clear history of EIA (47%) was not significantly more frequent than in asthmatics with less suggestive findings (40%). There was no difference in the percentage of patients reporting to use inhaled steroids between asthmatics in the AO or in the EIA group. There was no difference in the mean daily dose between subjects who used inhaled steroids in the AO or in the EIA group.

The time course of both FEV_1 and dyspnea score changes from baseline after exercise in subjects with positive or negative bronchial obstructive response is shown in Fig. 1. In subjects with a positive challenge, dyspnea preceded bronchoconstriction, and also reverted more quickly to baseline value. Only 4% of the subjects with a positive challenge reached the maximum fall in FEV_1 immediately after exercise, 39% at 3 min, 22% at 6 min, 17% at 10 min and 18% at later time points. By contrast, 39% of these subjects reported the worst dyspnea score immediately after exercise (by definition), but an appreciable worsening in the dyspnea score was observed shortly after exercise, which reverted to values above baseline afterwards. The group of patients with a negative challenge had no significant change in FEV_1 after exercise (by definition), but an appreciable decrease in the dyspnea score was observed shortly after exercise, which reverted to values above baseline afterwards.

A highly significant correlation ($P<0.001$ for all comparisons, Spearman rank test) was observed between

Table 1. Classification based on the history of enrolled patients recorded in the clinical chart in reference to some anthropometric data and the response to the exercise challenge

	Clinical classification			
	EIA, No (%)	AO	ED	C
Gender (males/females)	59/18	42/23	18/18	19/3
Mean age (± SD)	16 (± 10)	15 (± 9)	26 (± 13)	13 (± 7)
Mean BMI (± SD)	22 (±4)	21 (±4)	23 (±4)	19 (± 3)
Greatest fall in FEV_1 from baseline				
≤20%	36 (47%)	26 (40%)	7 (19%)	0 (0%)
≥15, <20%	6 (8%)	4 (6%)	5 (14%)	4 (18%)
< 15%	6 (8%)	35 (54%)	24 (67%)	18 (82%)

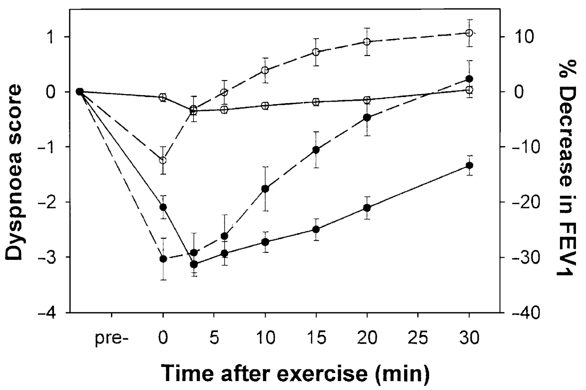

Fig. 1. Changes from baseline in both FEV_1 (right axis, solid lines) and dyspnea score (left axis, dashed lines) after exercise for subjects with either a positive (closed symbols) or a negative (open symbols) response to exercise challenge. Bars indicate the mean ± SE.

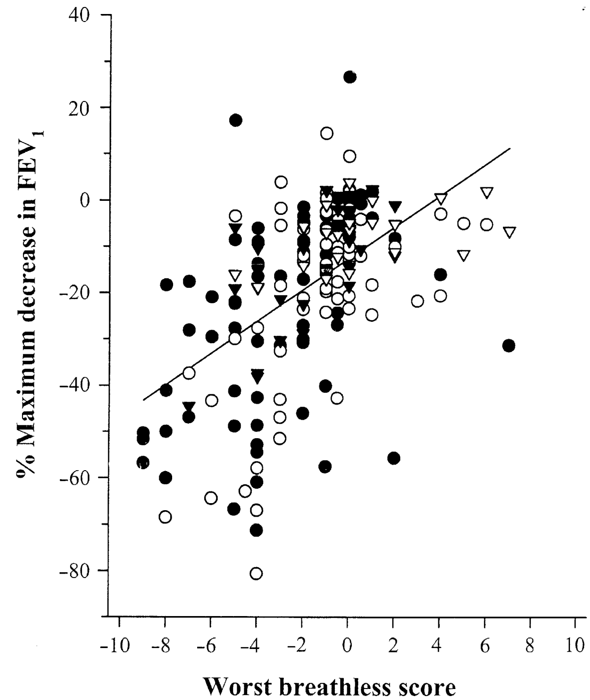

Fig. 2. Individual values of both the greatest fall in FEV_1 and the maximum worsening in dyspnea score from baseline after exercise challenge. Closed circles: asthmatic patients with exertional symptoms (EIA Group); open circles: asthmatic patients without any exercise-induced symptoms (AO Group); closed triangles: patients with ED, but without any asthma-like features (ED group); open triangles: subjects not reporting any symptom (C group). Also reported in each panel is the univariate regression line computed on all the data points in the plot and the Spearman rank correlation rho between FEV_1 and dyspnea score.

the maximum fall in FEV_1 and greatest worsening in dyspnea score, as shown in Fig. 2. However, when the analysis was performed pairing data of FEV_1 and dyspnea recorded at the same time points, the correlation coefficient was rather small, although statistically significant, immediately after exercise, increased to slightly higher values between 3 and 10 min, to decrease again at subsequent time points.

The determinants of the degree of exercise-induced dyspnea at different time points, as identified by stepwise multiple regression analysis, are reported in Table 2. This analysis was restricted to patients with symptoms of asthma (with or without exercise-induced dyspnea) to ensure a more homogeneous group of patients. However, similar results were obtained when the analysis was repeated on the whole set of patients. The degree of dyspnea was correlated with the decrease in FEV_1 and with increasing age at all time points up to 20 min after exercise, and the percentage of variability explained by the regression model, expressed by the R-squared value, was maximal at the points of the greatest fall in FEV_1 (41%). Female gender and an increased BMI ware also loosely correlated with dyspnea, the latter notably only immediately after exercise. Percent predicted FEV_1 at baseline, smoking, and changes in PEF never entered in the model. Remarkably, however, a history of symptoms after exercise was highly significantly associated with a greater degree of dyspnea at all time points, even after

Table 2. Correlation coefficients of factors associated with perceived dyspnea at different times after exercise (stepwise regression analysis)

Time (min)	R-Squared	Change in FEV_1	Age	Female sex	BMI	EIA group
0	0.27	0.078***	−0.062*	0.9	−0.08	−0.90*
3	0.34	0.068***	−0.063*		−0.08	−1.21***
6	0.31	0.071***	−0.063**			−0.96*
10	0.25	0.070***	−0.069***	0.63		−0.53
15	0.17	0.046***	−0.079***	0.64		
20	0.12	0.032*	−0.089***			
30	0.07		−0,078***			
Maximum decrease[a], all subjects	0.41	0.071***	−0.080***	0.74		−1.47***
Maximum decrease[a], subjects with confirmed asthma	0.39	0.052***	−0.083***			−1.72***

[a]Maximum decrease in FEV_1 *vs.* maximum worsening in dyspnea at any time after exercise challenge.
*$P<0.05$; **$P<0.01$; ***$P<0.005$.

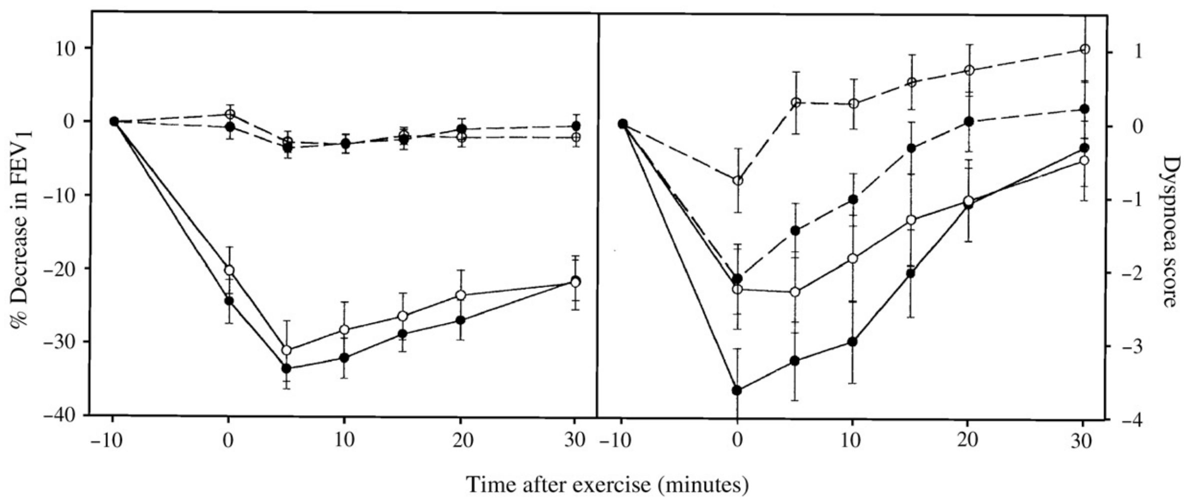

Fig 3. Changes in FEV_1 (left panel) and in dyspnea score (right panel) after exercise in subjects with positive (solid lines) or negative (dashed lines) response to exercise challenge and with (closed symbols) or without (open symbols) symptoms suggestive of exercise-induced bronchoconstriction. Bars indicate the mean ± SE.

adjustment for all these factors. Accordingly, when univariate linear regression analysis between the greatest fall in FEV_1 and the minimum dyspnea score was separately computed in asthmatic patients with or without a report of exercise-related symptoms, we found that the slopes were very similar (M ± SE; EIA −0.073 ± 0.014; AO −0.064 ± 0.015), although the intercepts were markedly different (EIA −2.21 ± 0.43; AO −0.71 ± 0.41). Furthermore, substantially similar results were obtained when the analysis was restricted to subjects with a known objective parameter of asthma, such as expiratory wheezing on chest auscultation, reversible airway obstruction, or hyperresponsiveness to methacholine.

In Fig. 3, we reported the change in FEV_1 (left panel) and in dyspnea score (right panel) after exercise challenge for the four groups of subjects with or without exertional symptoms and with or without asthma. Subjects with a positive response to exercise showed similar bronchoconstriction, regardless of the presence or the absence of a report of exercise-related symptoms. Similarly, no differences are observed in FEV_1 in subjects with negative challenge. By contrast, among subjects with a positive challenge those ones with a history of exertional symptoms showed significantly more dyspnea than those without. In fact, the greatest change in dyspnea score was −4.1 ± 0.5 in the EIA group and −2.4 ± 0.6 in the AO group ($p<0.05$). Surprisingly, also among subjects with a negative exercise challenge, those with a history of exercise-induced disturbances had more dyspnea than those without, despite the lack of bronchoconstriction in both groups. The greatest change in dyspnea score was −1.5 ± 0.3 in the ED group and −0.5 ± 0.4 in the C group ($P<0.05$).

DISCUSSION

Our survey confirms the previous limited studies indicating that dyspnea is loosely, but significantly correlated with EIB (4,5). This relationship is looser at the beginning and at the end of the EIB, due to a decoupling in the time course of exercise-induced dyspnea and bronchoconstriction, as dyspnea peaked and recovered before the decrease in FEV1. The early appearance of dyspnea might be related to irritative/inflammatory phenomena preceding EIB, such as the release of tachykinins (16). On the other hand, the shorter duration of dyspnea with respect to the bronchial obstruction could be due to the perception of ongoing resolution of bronchoconstrictor response or temporal adaptation (14). Overall, we found that the relationship between the decrease in FEV1 and the perception of dyspnea was relatively loose, as the latter was also influenced by age, gender, BMI, and, possibly, other variables that we did not record in this study, such as psychological condition and fitness. Likewise, our findings show that the perception of dyspnea can occur even independently from bronchoconstriction. This is particularly evident looking at subjects with a negative challenge who reported dyspnea without any significant bronchoconstriction. Accordingly, stepwise regression analysis shows that the report of typical symptoms is significantly correlated to the perception of dyspnea, particularly at the earliest time points after exercise, independently from the degree of bronchoconstriction. Fatigue is widely recognized as a cause of exercise limitation different from dyspnea and there is a considerable overlap on the report of these symptoms (17). It is possible that the inclusion of a measure of fatigue might have accounted for part of dyspnea not explained by bronchoconstriction, improving the accuracy of our statistical model and we suggest that future studies addressing this issue will include the recording of exercise-induced fatigue. However, our challenge was not limited by fatigue and our subjects were clearly instructed to rate the perceived intensity of dyspnea, so that we think that the validity of our data is not diminished by this absence. Other conditions which might explain for some patients the perception of dyspnea regardless of bronchoconstriction are the occurrence of a vocal cord dysfunction (18) and a "functional breathing disorder" (19). The latter has been described for a group of subjects reporting symptoms very similar to EIA, but failing to show clinical features of asthma and with a negative exercise challenge (20). However, we think that it is unlikely that the occasional presence of some of these subjects at least in the EIA group with a negative response to the exercise challenge has biased our results. This is confirmed by the fact that we have obtained virtually identical results when the analysis was repeated after exclusion of all the asthmatic subjects for whom we had no objective documentation of asthma or bronchial hyperresponsiveness, thus reducing the chance of including non-asthmatic patients in the analysis. Therefore, whatever the factor associated to non-EIB-related exertional dyspnea, it has to be present in a subgroup of asthmatics.

A standardized exercise challenge is known to have a good sensitivity to evaluate bronchial responsiveness (10). Our findings confirm these remarks, because none of the asthmatic subjects failing to report exercise-induced symptoms showed an unambiguous positive response to the exercise test, whereas the challenge could also identify the asthmatic nature of exercise-induced symptoms reported without any clinical features suggestive of asthma, such as cough or wheeze.

We did not find any significant difference in the occurrence of a positive response between asthmatic subjects with or without report of exertional dyspnea. It has to be remembered that most of our subjects were referred to us for investigation of a suspicion of EIB and we classified them retrospectively on the basis of their reports. It may be that, for some subjects not reporting asthmatic symptoms, these had been observed by a third person, such as a physician, a parent, or a teacher. However, direct report by the patient is known to be mostly reliable, including the pediatric setting (21–23). Likewise, this is not surprising, because it is know since many years that asthmatic subjects are not very good in judging naturally occurring changes in bronchial tone (9,24) and the perception of dyspnea may vary largely, so that, for a given degree of bronchial obstruction, some patients show a hypoperception, or under-reporting the importance of their symptoms, as well as others disproportionately over-perceive their level of dyspnea (14,25). This is confirmed by our findings that asthmatic patients with a history of exercise-induced symptoms rated a greater magnitude of dyspnea for the same reduction in FEV_1 than those without any report. Nevertheless, it is interesting to note that the perception of exercise-induced dyspnea in the laboratory was related with the report of exercise-induced symptoms in real life.

We think that our survey has an adequate study design to evaluate the relationship between exercise-induced dyspnea and EIB. The method of execution for the exercise challenge was in accordance with Haby *et al.* (10). Due to an air-conditioning system, the indoor temperature and humidity were also adequate for a suitable exercise challenge (1). Due to its subjective nature, the rating of dyspnea appears to be variable. However, it is known that, under standardized conditions, the averaged results across large groups of subjects are reliable in isolating factors contributing to dyspnea (26). The Borg scale has been used since many years for the assessment of exercise-induced dyspnea (27). In our study, we used a modified bipolar Borg scale, because, after exercise, many healthy subjects can show an improvement in FEV_1 (28). This choice has been supported by our results, being not uncommon that subjects reported an improvement of their breath after exercise. Likewise, dyspnea has already been rated using a bipolar scale in asthmatic subjects (29). As suggested by Rietveld *et al*. (5), our subjects were always blinded to the results of lung function testings for avoiding any influence on dyspnea ratings.

We conclude that, although a history of exercise-induced symptoms is the clue to identify EIB, it always requires the execution of an exercise challenge for it to be confirmed, because exertional symptoms are poorly predictive of EIB. Our results show that the exercise challenge is also useful to detect EIB in asthmatic subjects failing to perceive or report exertional symptoms. On the other hand, our findings show that dyspnea is loosely, but significantly related to EIB. We suggest that the simultaneous rating of dyspnea to each spirometry measurement on exercise test is a well-suited model to study naturally occurring exercise-induced dyspnea and to improve its clinical usefulness of challenge, giving an evaluation of mastering daily life physical activities.

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