Prevalence of Exercise-induced Bronchoconstriction in Japanese Medical Students

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Abstract

Objectives: Exercise-induced bronchoconstriction (EIB) is a transient acute airway narrowing that occurs as a result of exercise. Approximately 80% of individuals with asthma experience exercise-related symptoms (ERS). The prevalence of EIB in the general population without a known asthma diagnosis has been estimated to be approximately 5%–20%, but there is no consensus on this. There have been previous studies on asthma patients, infants and athletes, but few studies have investigated general students, particularly in Japan. The purpose of our study was to investigate the prevalence of EIB with screening questionnaires and laboratory exercise challenge tests in Japanese medical students.

Methods: This study included 233 potential participants. All participants completed an EIB screening questionnaire. The exercise protocol for the bicycle ergometer started at 25 W, and the participant remained in motion for 5 min in a multi-step load protocol that increased by 25 W per min. Spirometry was performed before and after all exercise challenge tests. The criterion for a positive test was a $\geq 10\%$ decrease in forced expiratory volume in 1 s (FEV₁) from the baseline measurement.

Results: Twenty-six of 217 students (12.0%) had a self-reported a history of ERS. However, only six students (2.8%) were EIB-positive on an objective test. Moreover, all six students had no history of asthma, ERS or EIB diagnosis.

Conclusions: Our data revealed EIB-positive participants in a generally healthy population. It is important that EIB diagnoses should not be made using only symptoms, a history of asthma, allergies or the baseline measurement of lung function. Objective tests should be used for the accurate diagnosis of EIB.

Key words

Asthma, exercise-induced bronchoconstriction, exercise test, spirometry, sports medicine

Introduction

Exercise is one factor in bronchoconstriction. Exercise-induced bronchoconstriction (EIB) is a transient acute narrowing of the airway that occurs as a result of exercise. Eighty percent^(1,2) of all individuals with chronic asthma experience exercise-related symptoms (ERS). EIB has also been shown to occur

in individuals without a known diagnosis of asthma, with a reported prevalence of up to 20%⁽³⁾. EIB may be the first indication of asthma or an indicator of poorly-controlled asthma⁽²⁾. Becker *et al.*⁽⁴⁾ reported that 61 deaths were identified as asthma deaths that occurred in close association with a sporting event or physical activity. These researchers also found that 49 of these 61 (81%) subjects were younger than 21

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years of age. Surprisingly, 6 of the 61 (10%) subjects had no known history of asthma. In Japan, 12 asthma deaths occurred at schools by 2009, and two of these were related to exercise⁵. Although the number of asthma deaths has significantly decreased in Japan, adolescent asthma still requires more careful control due to the multiple stresses characteristic of adolescence.

The prevalence of EIB in athletes is higher than that in the general population⁶⁻⁹. Athletes have more exposure to allergens and air pollutants because of the high intensity of their exercise and high ventilation rates^{8,10,11}. In 2009, a landmark national survey on EIB² was conducted that included subjects in both the general and asthma populations in the United States. By contrast, there have been few studies in the general population in Japan and particularly in Japanese adolescents.

The purpose of this study was to investigate the prevalence of EIB in Japanese medical students who were non-athletes using an exercise challenge test. We also investigated the relationship between EIB-positive participants and the history of asthma, history of ERS or allergy including rhinitis, atopic dermatitis, hay fever and allergies to food, animals, mites or house dust.

Materials and Methods

Participants

In this study, 233 students (148 males and 85 females) at the St. Marianna University School of Medicine were considered potential participants. The exclusion criteria included pregnancy, history of severe cardiovascular and pulmonary disease, recent upper-respiratory tract infection within the two previous weeks and an inability to perform the exercise challenge test. The study was conducted from September

through October 2015 during which the average air temperature was 23.9°C, and the average humidity was 49.6%.

Study design and protocol

All participation was voluntary. Written informed consent was obtained from all participants after an explanation of the study purpose and the potential risks of the study protocol. This study was approved in advance by the ethics committee at the St. Marianna University School of Medicine (approval no. 1945, 1976) and was registered in the UMIN Clinical Trials Registry, Japan (ID 000022869).

All participants completed a questionnaire to assess any history of asthma, any respiratory symptoms during and/or after exercise, any allergies and the type of sports played. We partially modified a questionnaire that had been used in previous studies¹². The history of asthma, ERS and allergy was self-reported. Participants were allowed to provide multiple answers in the sections on history of allergies and ERS symptoms.

The exercise protocol for the bicycle ergometer is shown in **Figure 1**. Participants started pedalling with a load of 25 W and continued for 5 min under a multi-step load protocol in which the load was increased by 25 W per min. The participants were instructed to maintain a rotational speed of 50 rpm. After the exercise, the participants rested for 3 min. During the exercise challenge test, we measured the participant's heart rate, blood pressure, electrocardiogram and the Borg Scale rating perceived exertion to maintain safety.

Spirometry was performed a few minutes before and immediately after performance of the exercise protocol according to the presiding physician's instructions. While standing with the nose clipped, the

Figure 1. Exercise protocol for the bicycle ergometer.

participants completed at least two forced maximal flow-volume manoeuvres. The following measurements were recorded for each manoeuvre: forced expiratory volume in 1 s (FEV₁), forced vital capacity (FVC), peak expiratory flow (PEF), maximal expiratory flow at 50% (MEF50) and maximal expiratory flow at 75% (MEF75). We used the following prediction formulas: FVC (L) = 0.042 × height (cm) – 0.024 × age – 1.785 for males and FVC (L) = 0.031 × height (cm) – 0.019 × age – 1.105 for females; FEV₁(L) = 0.036 × height (cm) – 0.028 × age – 1.178 for males and FEV₁(L) = 0.022 × height (cm) – 0.022 × age – 0.005 for females; MEF50 (L/sec) = 0.043 × height (cm) – 0.046 × age – 0.385 for males and MEF50 (L/sec) = 0.014 × height (cm) – 0.038 × age + 3.150 for females; and MEF75 (L/sec) = 0.021 × height (cm) – 0.031 × age – 0.073 for males and MEF75 (L/sec) = 0.003 × height (cm) – 0.025 × age + 2.155 for females¹³. Individual maximal flow-volume loops were analysed in accordance with the Japanese Respiratory Society guideline¹³ by two physicians.

Materials

The Spiro Sift SP-370 (Fukuda Denshi, Tokyo, Japan) was used to measure the pulmonary volumes and flow-volume loops. The exercise challenge tests were performed using an AEROBIKE 75XL II (COMBI WELLNESS, Tokyo, Japan), AEROBIKE 75XL III (COMBI WELLNESS) and Aerobic Exercise Ergometer STB-2400 (NIHON KOHDEN, Tokyo, Japan). Tango (SunTech Medical, Morrisville, NC, USA) was used to measure the heart rate and blood pressure. A TelePro Stand-Alone Patient Monitor WEP-4204 (NIHON KOHDEN, Tokyo, Japan) was used to record the ECG.

Criteria for a positive EIB result

The criterion for a positive test was a greater than 10% decrease in FEV₁ from the baseline measurement. A post-exercise decrease in FEV₁ was calculated using the formula {(baseline FEV₁ – post-exercise challenge FEV₁) / baseline FEV₁} × 100.

Measurements and statistical analysis

The participant demographics are presented in **Table 1**. The numbers and proportions were used to explain the prevalence of asthma, ERS and allergic diseases. Lung function measurements are expressed as the mean ± SD. The Shapiro-Wilk test was performed for all values. The paired *t*-test was used to

Table 1. Characteristics and Questionnaire Response Data.

Sex(male/female), n	141/76
Age, mean ± SD	21.9 ± 3.1
BMI, mean ± SD	21.7 ± 2.7
Resting HR, mean ± SD	85.3 ± 16.3
Max HR, mean ± SD	147.5 ± 19.6
%predicted Max HR, mean ± SD	74.5 ± 10.0
Smokers, n	15
Brinkman Index (mean ± SD)	45.8 ± 22.3
History of asthma, n (%)	38/217 (17.5)
From childhood, n	33
From adult, n	2
Unknown, n	3
Report ERS, n (%)	10/38 (26.3)
History of ERS, n (%)	26/217 (12.0)
Cough, n	10
Wheezing, n	16
Dyspnoea, n	11
Increased mucus, n	5
Chest tightness, n	3
Others, n	2
History of Allergy, n (%)	124/217 (57.1)
Rhinitis, n	54
Atopic dermatitis, n	19
Hay fever, n	72
Foods, n	14
Animals, Mites, n	13
House dust, n	9

Values are expressed as mean ± SD, counts (n) and frequency (approximately%).

SD; Standard Deviation, n; number, BMI; Body Mass Index, HR; Heart Rate, ERS; Exercise-Related Symptoms

compare the %FEV₁, %FVC, FEV₁/FVC%, %PEF, %MEF75 and MEF50/MEF75 values at baseline and post-exercise challenge. The Mann-Whitney U test, Kruskal-Wallis test, unpaired *t*-test and one-way analysis of variance (ANOVA) were used to compare the EIB-positive and EIB-negative participants. A *p* value < 0.05 was considered statistically significant for all analyses. All statistical analyses were performed using SPSS Statistics 20.0J software (IBM Japan, Tokyo, Japan).

Results

Sixteen participants were excluded from the analysis: three participants did not complete the exercise challenge test and spirometry, and 13 participants had an insufficient expiratory effort.

Six participants (2.8%) were EIB-positive, and none of them had a history of asthma or ERS. The

mean percent change from the baseline in FEV_1 was -12.82% in the EIB-positive participants and $+0.48\%$ in the EIB-negative ones. There were no significant differences in the baseline spirometry values between the EIB-positive and EIB-negative participants. However, the EIB-positive participants had a significant decrease after exercise in the $\%FEV_1$, $\%FVC$, $FEV_1/FVC\%$, $\%PEF$ and $\%MEF75$ values. The $MEF50/MEF75$ value increased by more than three (no significant difference) (**Table 2-A**). When the $MEF50/MEF75$ is 2 or more, it becomes a downward convex flow volume curve, and when it is 3 or more it is used as an index of air flow obstruction in the peripheral airway¹⁴⁾. Flow-volume curves of the EIB-positive participants are shown in **Figure 2-A, B**. Peak flow and $MEF75$ decreased after exercise compared to before exercise. The EIB-negative participants showed no significant differences in the $\%FEV_1$, $\%FVC$, $FEV_1/FVC\%$, $\%PEF$ and $\%MEF75$ values between the before and after exercise results (**Table 2-B**). From the questionnaire, 38 participants (17.5%) had a history of asthma, and 26 participants (12.0%) experienced ERS. Ten of 38 participants with a history of asthma (26.3%) experienced ERS. No significant changes between the before and after exercise challenge test values for $\%FEV_1$, $\%FVC$, $FEV_1/FVC\%$, $\%PEF$ and $\%MEF75$ were found in the participants with a history of asthma and ERS. The most frequent symptoms in ERS participants were wheezing, dyspnoea and coughing. However, none of these participants were determined to be EIB-positive (**Table 3**). One hundred twenty-four participants (57.1%) had self-reported allergic diseases. In the EIB-positive participants, two of the six participants had hay fever, one of the six had rhinitis, and one of the six had rhinitis and animal allergies (**Table 3**).

Discussion

The purpose of this study was to investigate the prevalence of EIB in Japanese medical students using an exercise challenge test. We found that 2.8% (6 of 216 students) had EIB; however, none of these students had a history of asthma, ERS or a diagnosis of

Table 2. The Results of Spirometry.

Table 2-A. The Results of Spirometry in EIB-positive Participants.

EIB-Positive Participants (n = 6)		
	Baseline	Post-exercise
$\%FEV_1$	100.9 ± 11.8	$87.9 \pm 9.6^*$
$\%FVC$	98.9 ± 12.7	$93.7 \pm 11.9^*$
$FEV_1/FVC\%$	90.4 ± 4.1	$83.4 \pm 6.9^*$
$\%PEF$	88.4 ± 5.6	$79.2 \pm 10.9^*$
$\%MEF75$	117.6 ± 28.8	$75.7 \pm 48.3^*$
$MEF50/MEF75$	1.7 ± 0.1	3.1 ± 0.4

All values are expressed as mean $\pm$ SD.

*Significant difference: $p < 0.05$

Table 2-B. The Results of Spirometry in EIB-negative Participants.

EIB-Negative Participants (n = 211)		
	Baseline	Post-exercise
$\%FEV_1$	93.7 ± 10.0	94.0 ± 10.1
$\%FVC$	94.8 ± 10.3	94.7 ± 10.3
$FEV_1/FVC\%$	88.5 ± 6.3	88.7 ± 6.6
$\%PEF$	96.4 ± 15.5	97.0 ± 13.8
$\%MEF75$	92.8 ± 29.7	94.9 ± 30.5
$MEF50/MEF75$	2.2 ± 0.6	2.1 ± 0.4

All values are expressed as mean $\pm$ SD.

*Significant difference: $p < 0.05$

Figure 2-A. EIB-positive participant's flow volume curve. $MEF75$ decreases after exercise compared to before exercise.

Figure 2-B. EIB-positive participant's flow volume curve. Peak flow decreases after exercise compared to before exercise.

Table 3. EIB-positive Participant Demographics.

	Sex	BMI	Smoking	Asthma	ERS	Allergy	Sports	Max HR	%predicted Max HR	%Fall in FEV ₁
1	Male	22.1	-	-	-	rhinitis, animals	-	137	70.6	-14.87
2	Male	22.1	-	-	-	rhinitis	-	167	84.3	-12.78
3	Male	22.1	-	-	-	-	soccer	118	59.0	-15.58
4	Female	22.9	-	-	-	hay fever	-	173	87.4	-10.13
5	Female	20.2	-	-	-	hay fever	table tennis	173	87.4	-13.02
6	Female	22.5	-	-	-	-	soft tennis	174	86.1	-10.53

Minus (-) indicated as no history of smoking, asthma, ERS, allergies and exercise habits.

EIB.

The prevalence of EIB in this study was lower than that in previous studies in college students or similar populations. Burnett *et al.*¹⁵⁾ reported a prevalence of 42.5% using an exercise challenge test in college athletes. Also, Parsons *et al.*¹⁶⁾ reported a prevalence of 39% using the Eucapnic Voluntary Hyperventilation (EVH) test in college athletes, whereas Molphy *et al.*¹⁷⁾ reported a prevalence of 13.2% using the EVH test in recreationally active individuals. Our exercise protocol consisted of a multi-step load applied over an exercise time of only 5 min. None of the participants, especially the females, could maintain the required rotational speed because of leg fatigue. Hence, the participants only achieved a heart rate of $74.5 \pm 10.0\%$ of the predicted maximum heart rate (Table 1). Our protocol may not completely provoke EIB because of load insufficiency. The American Thoracic Society (ATS) EIB clinical guidelines³⁾ have recommended breathing dry air with a nose clip in place while running or cycling at a load sufficient to raise the heart rate to 80%–90% of the predicted maximum or to increase the ventilation to 17.5–21 times FEV₁. Once this level of exercise is attained, the participants should continue to exercise at that high level for an additional 4–6 min³⁾. The FEV₁ is

usually measured at 5, 10, 15 and 30 min after exercise³⁾. This protocol met the consensus; however, it is not practical for use by a family doctor during daily medical examinations. In fact, among 148 athletes referred to an asthma clinic for evaluation, 24% had previously been diagnosed as having EIB, but only 8% had received prior objective testing for EIB¹⁸⁾. Hull *et al.*¹⁹⁾ reported that a quarter of family practitioners (23%) treated empirically based upon clinical features alone. In our study, it was noteworthy that the EIB-positive participants performed under a moderate exercise load. One student achieved a heart rate of 70.6% of the predicted maximum heart rate, and one student achieved 59.0% (Table 3). Two of the six EIB-positive participants could not achieve 80% of the predicted maximum heart rate in this study. Therefore, it may be possible to propose a lower and safer load protocol for the exercise challenge test.

Also, the differences in exercise testing may have influenced the detection power. The ATS EIB clinical guidelines³⁾ recommend laboratory exercise testing using a standardised exercise challenge performed on treadmill or bicycle. The ideal protocol with which to detect EIB involves a rapid increase in exercise intensity over approximately 2–4 minutes to achieve a high level of ventilation. This target is more

rapidly achieved with a running exercise than with a cycling exercise.

The mechanism of EIB has not been established; it has been proposed that airway cooling results from the air inspired during exercise, and the airway is re-warmed after exercise¹⁰. Thus, the key stimulus is airway dehydration as a result of increased ventilation, resulting in augmented osmolarity of the fluid lining the airway^{10,20}. These changes can lead to the release of mediators from airway inflammatory cells that promote airway smooth-muscle contraction and lead to airway oedema. Therefore, elite athletes have a high risk of EIB. Our study showed a lower prevalence of EIB in medical students compared with athletes, which may be associated with the lower ventilation rates in the students (average exercise time, 7.03 ± 4.02 h/week). Non-athletes have fewer opportunities for exposure to cold and dry air, air pollutants and allergens than athletes, which may result in reduced stimulation of the airway. It is thus possible that the risk for EIB in medical students is lower than that in athletes.

Three of the six participants participated in competitive sports (soccer, tennis and table tennis) (**Table 3**). A previous study on athletes reported that the prevalence of EIB in Olympic winter sport athletes was 15% in ice hockey athletes, 21% in figure skating athletes, 50% in cross-country skiing athletes and 17% in Nordic-combined athletes²¹. In high-level athletes, minute ventilation can reach 200 L/min¹⁰. Therefore, the prevalence of asthma can be higher in long-distance and endurance sports. An additional investigation of the athletes at the 2004 Athens Olympics and 2008 Beijing Olympics reported that the prevalence of EIB was much higher for endurance sports (24.9% in triathlon athletes and 17.2% in cycling athletes) than in those requiring little or no endurance (1.2% in weightlifting athletes and 1.5% in table tennis athletes)²². We were unable to identify the relationship between the type of sport and the prevalence of EIB in our medical students because of the low number of EIB-positive participants. We would like to consider this in future research.

The association between allergic disease (e.g., rhinitis or atopy dermatitis) and asthma was previously identified. It was reported that 70% of bronchial asthma patients had allergic rhinitis²³. Also, 25%–47.9%²⁴ of patients with atopic dermatitis and 5%–10%²⁵ of patients who had food allergies had asthma. Sallaoui *et al.*²⁶ reported that atopic dermatitis was a major risk factor for EIB in athletes. Also,

Minov *et al.*²⁷ reported that EIB was closely related to atopic dermatitis, a family history of asthma and a positive histamine challenge. Takeda *et al.*²⁸ reported that individuals who were allergic to mites tested EIB-positive after free-running for 12 min and mite-specific IgE antibodies were elevated in university students. Four of the six participants with EIB in the present study had some type of allergic disease; however, two of the six had no allergic diseases.

Couto *et al.*²⁹ proposed two distinct phenotypes of asthma in athletes: 'atopic asthma' and 'sports asthma'. The characteristics of 'atopic asthma' were the presence of allergic sensitisation, rhinitis and other allergic comorbidities and an increased FE_{NO}; the characteristics of 'sports asthma' were the presence of exercise-induced respiratory symptoms and bronchial hyperresponsiveness in the absence of allergic features. Therefore, specific training, training duration and environmental conditions may be associated with an increased risk of developing 'sports asthma'. In a mouse model, Tsukioka and Koya³⁰ reported that with longer exercise durations and longer periods of cold stimulation, there was a higher percentage of airway resistance, and the bronchial smooth muscle was thicker. From these findings, physicians should comprehensively use all information in diagnosis, including the history of asthma, ERS, allergic diathesis, family history, type and intensity of sports, types of training and competition environment and the results of objective tests.

Limitations

Our study has some limitations. First, the history of asthma and allergy was self-reported only. An asthma diagnosis should be established by a medical doctor according to the appropriate criteria. An allergy diagnosis should also be established by an objective test, such as a skin prick test or a blood test including specific IgE antibodies. Second, the participants in this study were from a single university. Third, we used three types of bicycle ergometer, so it is possible that the work rate may be different between the three ergometers.

Conclusion

In conclusion, the prevalence of EIB in college medical students was 2.8%. This value was lower than that in previous reports of studies in athletes or similar populations. All six participants with EIB had no history of asthma, ERS or a previous diagnosis of EIB. Therefore, it is important that EIB diagnoses

should not be made using only symptoms, a history of asthma, allergies or the baseline measurement of lung function. Objective tests should be used for the accurate diagnosis of EIB. Two of the six participants with EIB could not reach 80% of the predicted maximum heart rate. However, it may be possible to propose a lower and safer load protocol for exercise challenge tests.

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Conflict of Interest Statements

The authors have no conflicts of interest to declare.

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