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Original Article

# Exercise-induced bronchoconstriction in children with asthma: An observational cohort study

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**KEYWORDS**
Exercise-induced broncho-constriction;
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Methacholine challenge

**Abstract** *Background/purpose:* The diagnosis of exercise-induced bronchoconstriction (EIB) was established by changes in lung function after exercise challenge. The prevalence of EIB and factors related to EIB were not fully described in children with asthma. The aim of this study was to investigate the prevalence and predictors of EIB in children with asthma.
*Methods:* A total of 149 children with physician-diagnosed asthma above 5 years of age underwent standardized treadmill exercise challenge for EIB and methacholine challenge for airway hyper-responsiveness from October 2015 to December 2016.
*Results:* EIB presented in 52.5% of children with asthma. Compared with children without EIB, there were more patients with atopic dermatitis in children with EIB ($p = 0.038$). Allergic to *Dermatohagoides pteronyssinus* and *Dermatophagoides farinae* were also found more in children with EIB ($p = 0.045$ and 0.048 respectively). Maximal decrease in forced expiratory volume in 1 s ($FEV_1$) were highest in patients who were most sensitive to methacholine provocation (provocation concentration causing 20% fall in FEV1 [$PC_{20}$] $\leq$ 1 mg/mL). Patients, who were more sensitive to methacholine challenge (with lower $PC_{20}$ levels), develop EIB with more decline in $FEV_1$ after exercise challenge ($p = 0.038$). Among patients with EIB, airflow limitation development in patient with methacholine-induced airway hyper-responsiveness

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was more abrupt and severe compared with patients without airway hyper-responsiveness ($p = 0.045$ and 0.033 respectively).
*Conclusion:* EIB presented in 52.5% of children with asthma. The more severe methacholine-induced hyper-responsiveness, the higher prevalence of EIB as well as the severity.


## Introduction

Exercise-induced respiratory symptoms are common, but the diagnosis of exercise-induced bronchoconstriction (EIB) was established by changes in lung function after exercise challenge.[1] Exercise-induced respiratory symptoms have a poor predictive value for bronchoconstriction,[2] so exercise challenge test is recommended to confirm EIB. Guidelines from the American Thoracic Society (ATS),[3] European Respiratory Society (ERS),[4] and recent clinical practice guidelines[5] suggested a standardized exercise challenge test to confirm EIB.

The prevalence of EIB were 10–20% of general population[6–8] and 40–90% of adolescents and adults with known asthma.[7,9,10] The prevalence of EIB, lung function changes after exercise challenge, and risk factors related to EIB were not fully described in children with asthma, especially young children. Exercise challenge test for EIB is costly and time-consuming, and may be difficult for young children. Identifying factors related to EIB may be valuable in clinical practice.

The aim of this study was to investigate the prevalence, bronchoconstriction profiles, and time pattern of EIB by using a standardized exercise challenge test in children with asthma in Taiwan. Another aim was to investigate factors related to the development of bronchoconstriction after exercise.

## Methods

### Ethical consideration

This research including planning and execution was approved by the Institutional Review Board (IRB No. 103-7068A3) of Chang Gung Medical Foundation. The written informed consent from the parents of study participants was obtained.

### Study subjects

A total of 187 children (aged 2–10 years) with physician-diagnosed asthma participated in this study from October 2015 to December 2016. Those patients attended to our out-patient department for regular follow-up. This included 150 patients who were above 5 years of age and able to perform pulmonary function test. One patient with bronchiectasis was excluded. Patients with excessive bronchodilator reversibility (improvement of forced expiratory volume in first second [FEV1] above 12% after simple bronchodilator test) or with features suggesting a diagnosis of asthma and fair response to asthma treatment were diagnosed as asthma. All participants were evaluated by a questionnaire about past history, family atopic history, and life styles, and an interview conducted by a pediatric allergist. Exercise-induced symptoms are surveyed by the questions including "Have you ever experience exercise-induced asthma symptoms during exercise?" and "did you experience exercise-induced asthma symptoms during exercise within 1 year?" The use of medications for asthma including inhaled corticosteroids (ICSs), short-acting $\beta_2$-agonists (SABAs), long-acting $\beta_2$-agonists (LABAs), and leukotriene receptor antagonists (LTRAs) in the past three months was recorded.

### Exercise challenge and methacholine challenge

The participants were instructed to withdraw SABAs, LABAs, ICSs, and LTRAs at 2 days, Chinese herbal medicine at 1 day before the test, and to avoid heavy meals, vigorous exercise 4 h before the test.[3,5] Baseline spirometry, standardized treadmill exercise challenge,[1] and methacholine challenge tests (MCT)[3] were performed based on American Thoracic Society/European Respiratory Society guidelines. All the pulmonary function and challenge tests were performed indoors with constant temperature (24–26 °C) and humidity (45–55%).

Pre-challenge baseline lung function test was documented as the best of three measurement (Spirolab II®, Medical International Research [MIR]; Rome, Italy) and expressed as percent of the predicted value, which was calculated by patient's age, gender, and body heights according to Taiwanese standard values.[11,12] Heart rate and oxygen oximeter were monitored continuously during the exercise test on the treadmill. The treadmill exercise challenge included 2–4 min of rapid increase in exercise intensity to achieve 90% of predicted maximal heart rate for 6 min. $FEV_1$ was measured at 1, 5, 10, 15, 20, and 30 min after exercise challenge. EIB was defined as the percent fall in FEV1 from baseline $\geq$10%, and was graded to mild ($\geq$10%, but $<$ 25%), moderate ($\geq$25%, but $<$ 50%), and severe ($\geq$50%) based on the ATS guidelines.[1]

Airway hyper-responsiveness to methacholine was also measured according to ATS guidelines.[3] Methacholine challenge was performed on another day within 2 weeks of treadmill exercise challenge test with a procedure using the dosimeter technique (KoKo® Dosimeter, nSpire Health; Longmont, USA) with controlled tidal breathing. Food and Drug Administration (FDA)-approved methacholine (Provocholine®) was used, and methacholine solution was prepared by a pharmacist using sterile technique at 5 concentrations: 0.0625, 0.25, 1, 4, 16 mg/mL. Baseline spirometry (Spirolab II®, Medical International Research [MIR]; Rome, Italy) was performed, and a target FEV1 that indicates a 20% fall in FEV1 was calculated (baseline FEV1 multiplied by 0.8). Using five breath dosimeter protocol,[3] patients inhaled methacholine solution at increasing concentrations (0.0625, 0.25, 1, 4, 16 mg/mL), until positive result demonstrated, or when the highest concentration of methacholine (16 mg/mL) was achieved. Methacholine challenge test result was defined as positive if provocation concentration causing 20% fall in FEV1 ($PC_{20}$) was less than 16 mg/mL. The severity of methacholine airway hyper-responsiveness was categorized into normal ($PC_{20} > 16$ mg/mL), borderline ($PC_{20} \leq 16$ mg/mL, but $> 4$ mg/mL), mild ($PC_{20} \leq 4$ mg/mL, but $> 1$ mg/mL), and moderate to severe ($PC_{20} \leq 1$ mg/mL) bronchial hyper-responsiveness.

## Atopy

Serum eosinophil cationic protein (ECP), serum levels of total IgE and IgE against specific aeroallergens (*Dermatohagoides pteronyssinus*, *Dermatophagoides farinae*, Blomia tropicalis, house dust, and cockeroch) were measured by ImmunoCAP® (Phadia, Uppsala, Sweden) within 1 year of the exercise challenge test. Children with total serum IgE $\geq$77.7 kU/L was defined as having atopy.[13] Aeroallergen sensitization was defined as specific IgE $\geq$0.35 kU/L.

## Statistical methods

All the data was analyzed by Statistical Package for Social Science (SPSS) software version 22 (SPSS Inc., Chicago, IL, USA). Continuous variables including body height, body weight, body mass index (BMI), ECP, serum total IgE, pulmonary function, $PC_{20}$, and decrement of $FEV_1$ in exercise challenge test were summarized as means and standard deviations (SD). Categorical variables including symptoms of exercise-induced dyspnea, history of atopic dermatitis, parental atopy, and asthma medications were summarized as numbers and percentages. Continuous variables were compared between patient groups by Student's *t*-tests. For categorical variables, the groups were compared by Pearson's chi-squared tests/Fisher's exact tests. Multivariable logistic regression was used to analysis independent risk factors for the development of EIB. One-way ANOVA was used to determine whether there are any statistically differences between two or more independent groups. Pearson's correlation was used to evaluate the relation between EIB and methacholine hyper-responsiveness. A *p* value of less than 0.05 was considered as statistical significance.

**Table 1** Clinical characteristics of subjects with and without a positive EIB test, N = 149.

| Clinical Features | EIB (+) N = 78 | EIB (−) N = 71 | *p*-value |
|---|---|---|---|
| Age (year) | 7.1 ± 1.7 | 6.7 ± 1.6 | 0.182 |
| Female | 29 (37.2%) | 21 (29.6%) | 0.386 |
| BH (cm) | 124.3 ± 11.6 | 122.6 ± 10.1 | 0.363 |
| BW (kg) | 26.4 ± 8.6 | 24.8 ± 6.7 | 0.225 |
| BMI ($kg/m^2$) | 16.7 ± 3.2 | 16.3 ± 2.7 | 0.351 |
| EIRS within 1yr | 25 (32.1%) | 16 (25.4%) | 0.262 |
| EIRS ever | 28 (39%) | 18 (29.5%) | 0.206 |
| **Atopy** | | | |
| ECP (ug/L) | 22.3 ± 19.4 | 18.3 ± 19.9 | 0.355 |
| Serum IgE (kU/L) | 916.0 ± 197.3 | 918.6 ± 127.4 | 0.989 |
| Atopy[a] | 66 (90.4%) | 65 (95.6%) | 0.329 |
| Atopic dermatitis | 44 (58.7%) | 30 (42.9%) | **0.038** |
| Allergic rhinitis | 75 (96.1%) | 68 (95.7%) | 0.811 |
| Parental atopy[a] | 59 (77.6%) | 53 (74.6%) | 0.702 |
| **Pulmonary function test** | | | |
| FVC (%)[b] | 88.1 ± 15.6 | 91.1 ± 14.1 | 0.228 |
| $FEV_1$ (%)[b] | 91.3 ± 16.2 | 94.8 ± 14.0 | 0.156 |
| $FEV_1$/FEV (%)[b] | 107.5 ± 8.5 | 107.5 ± 8.4 | 0.993 |
| PEF (%)[b] | 84.3 ± 31.2 | 86.0 ± 23.9 | 0.702 |
| $FEF_{25-75}$ (%)[b] | 100.9 ± 32.4 | 107.7 ± 31.8 | 0.201 |
| **Methacholine challenge test** | | | |
| Positive | 44 (61.1%) | 33 (50%) | **0.048** |
| $PC_{20}$ (mg/mL) | 8.9 ± 6.4 | 10.4 ± 6.0 | 0.152 |
| **Exercise challenge test** | | | |
| Decrement of $FEV_1$ (%) | 17.8 ± 7.7 | 3.2 ± 5.0 | <**0.005** |
| **Medication** | | | |
| LTRA | 22 (28.2%) | 14 (19.7%) | 0.438 |
| ICS | 3 (3.8%) | 2 (2.8%) | 1.000 |
| ICS/LABA | 56 (75.6%) | 58 (81.7%) | 0.427 |
| LTRA + ICS/LABA | 16 (20.5%) | 7 (9.9%) | 0.079 |

[a] Subjects' atopy was defined as total serum IgE $\geq$77.7 kU/L; Parental atopy was surveyed by questionnaires.
[b] Forced vital capacity (FVC), forced expiratory volume in 1 s (FEV1), peak expiratory flow (PEF), and forced expiratory flow at 25–75% of forced vital capacity ($FEF_{25-75}$) presented as percentage recorded at baseline before exercise challenge test.
Significant *p*-levels (below 0.05) are in bold.
Data are represented as number (percent) or means ± standard deviation. EIB (+) represented patients with positive results after exercise challenge test; EIB (−) represented patients with negative results after exercise challenge test.
BH, body height; BW, body weight; BMI, body mass index; EIRS, exercise-induced respiratory symptoms; ECP, eosinophi cationic protein; IgE, immunoglobulin E; $PC_{20}$, provocation concentration causing 20% fall in FEV1; LTRA, leukotriene receptor antagonist; ICS, inhaled corticosteroid; LABA, long-acting $\beta_2$-agonist.

## Results

### Profile, time pattern of bronchoconstriction, and risk factors in patients with EIB

The characteristics of all 149 participants (99 boys; age 6.9 ± 1.7) are listed in Table 1. Among the 149 participants, EIB presented in 78 (52.5%) of children with asthma, but 71 patients had negative EIB tests after exercise challenge. No significant difference was observed with regards to age, body height, body weight, body mass index, and patient-reported exercise-induced symptoms between two groups. Compared with children without EIB, there were more patients with atopic dermatitis in children with EIB ($p = 0.038$), but there was no difference among serum levels of ECP, total IgE, the prevalence of IgE sensitization, allergic rhinitis, and parental atopy. With respect to the baseline pulmonary function test, there was no difference among forced vital capacity (FVC), $FEV_1$, $FEV_1$/FVC, peak expiratory flow (PEF), forced expiratory flow at 25–75% of forced vital capacity ($FEF_{25-75}$) between two groups. With regards to the medication for asthma control, there was no difference among the medications used for asthma control, including LTRA, ICS, ICS/LABA, and LTRA plus ICS/LABA. About the life styles, including exposure to pet, second-hand smoke, and incense stick at home, there was no difference between two groups. ($p = 0.731$, 0.626, and 0.801 respectively).

Fig. 1 represents the distribution of the maximal decline of $FEV_1$ in all patients. Seventy-eight patients met the criterion of EIB that the percent fall in $FEV_1 \geq 10\%$ with a mean percent decline of 17.8 ± 7.7%. Sixty-four patients had mild EIB, fourteen patients had moderate EIB, but none had severe EIB. In seventy-one patients without EIB, the percent fall in $FEV_1$ was 3.6 ± 3.8%. Number of patients according to the time of maximal fall in $FEV_1$ after exercise challenge test is showed in Fig. 2. There were 47% (N = 70) of patients that had their maximal decline in $FEV_1$ at first minutes after exercise challenge. Most of the patients (88.6%, N = 132) showed the greatest decline in $FEV_1$ within 15 min after exercise challenge test.

## Relation between atopic sensitization and EIB

No difference was found among serum levels of ECP, total IgE, the prevalence of IgE sensitization and parental atopy, but there were more subjects with sensitization to *D. pteronyssinus* and *D. farinae* in EIB-positive group ($p = 0.045$ and 0.048 respectively; Table 2). There was no difference with respect of the prevalence of allergy to *Blomia tropicalis*, house dust, and cockroach between two groups.

## Methacholine-induced bronchial hyper-responsiveness and EIB

Bronchial hyper-responsiveness to methacholine ($PC_{20} <$ 16 mg/mL) was detected in 55.8% (N = 77) of our study projects. There were 24.6% of all patients having borderline and mild bronchial hyper-responsiveness, and 6.5% having moderate to severe bronchial hyper-responsiveness. 7 (Fig. 3-A). 45.9% of patients without methacholine-induced bronchial hyper-responsiveness had EIB. The prevalence of EIB was higher in patients with borderline, mild, and severe hyper-responsiveness (50.0%, 58.8%, and 77.8% respectively). Maximal decrease in $FEV_1$ was also highest in patients who were most sensitive to methacholine provocation ($PC_{20} \leq 1$ mg/mL; Fig. 3-B). The maximal percent decline in $FEV_1$ were 8.9 ± 8.5%, 10.9 ± 10.2%, 13.2 ± 11.3%, and 16.5 ± 11.8% in patient with normal, borderline, mild, and moderate to severe methacholine-induced bronchial hyper-responsiveness respectively. There was significant difference of the maximal percent decline in $FEV_1$ between patients with normal, borderline, mild, and moderate to severe bronchial hyper-responsiveness ($p = 0.07$).

$PC_{20}$ of methacholine challenge test was lowest in patient with moderate EIB, since there was not any patient with severe EIB in our study (Fig. 4). The means of $PC_{20}$ were 10.2 ± 6.1, 9.5 ± 6.4, and 6.8 ± 6.2 mg/mL in patient

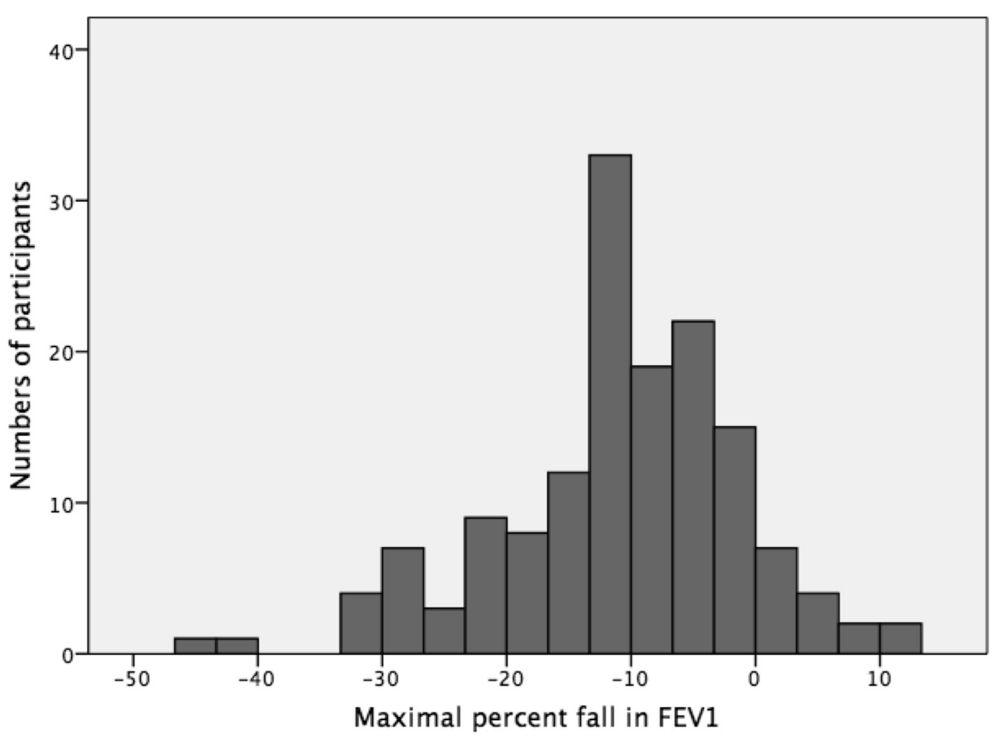


**Figure 1.** Distribution of the maximal percent fall in $FEV_1$ in all participants (N = 149). $FEV_1$, forced expiratory volume in 1 s.

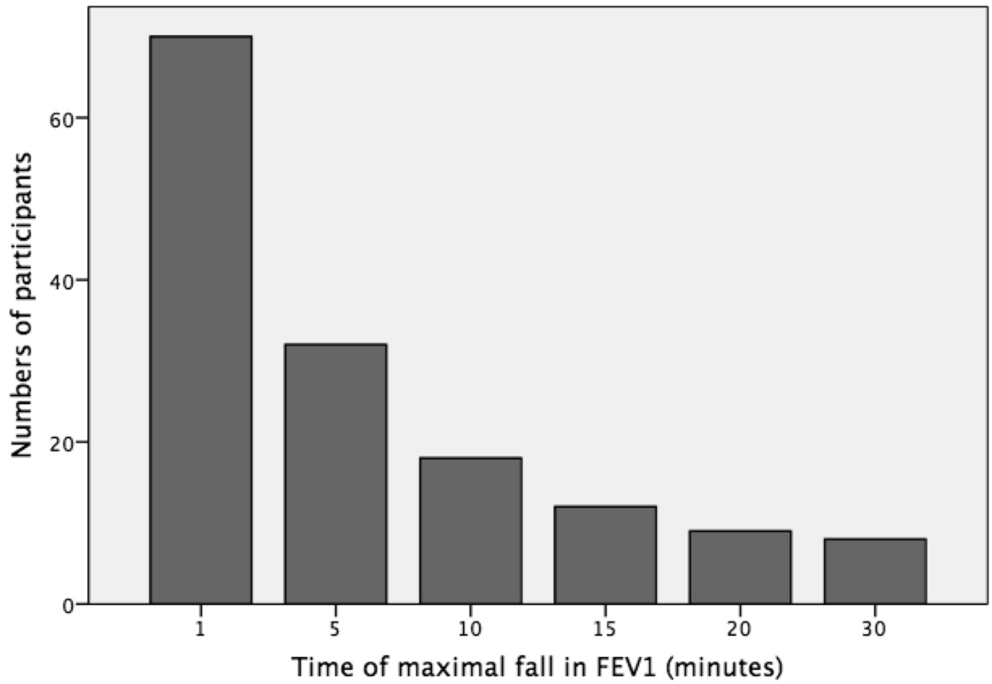


**Figure 2.** Numbers of participants according to the time of maximal fall in $FEV_1$ after exercise challenge test. $FEV_1$, forced expiratory volume in 1 s.

without EIB and with mild and moderate EIB respectively. However, the difference was not statistically significant between these three groups ($p = 0.174$).

Patients, who were more sensitive to methacholine challenge (with lower $PC_{20}$ levels), develop EIB with more decline in $FEV_1$ after exercise challenge. The correlation between methacholine-induced bronchial hyper-responsiveness and EIB was significant ($p = 0.038$; Fig. 5).

**Table 2** Positive rate and specific IgE levels of aeroallergen in patients with and without EIB.

| Aeroallergen | EIB (+) N = 78 | EIB (−) N = 71 | *p*-value |
|---|---|---|---|
| ***Dermatohagoides pteronyssinus*** | | | |
| Positive rate | 76 (97.4%) | 59 (83.1%) | **0.045** |
| Specific IgE (kU/L) | 62.6 ± 41.4 | 61.6 ± 39.1 | 0.895 |
| ***Dermatophagoides farinae*** | | | |
| Positive rate | 77 (98.7%) | 63 (88.7%) | **0.048** |
| Specific IgE (kU/L) | 59.5 ± 41.7 | 53.4 ± 39.1 | 0.381 |
| ***Blomia tropicalis*** | | | |
| Positive rate | 62 (79.4%) | 56 (78.9%) | 0.982 |
| Specific IgE (kU/L) | 15.2 ± 22.5 | 10.6 ± 13.7 | 0.151 |
| **House dust (Greer labs)** | | | |
| Positive rate | 63 (80.7%) | 56 (78.9%) | 0.833 |
| Specific IgE (kU/L) | 4.3 ± 5.6 | 3.2 ± 0.8 | 0.208 |
| **Cockroach** | | | |
| Positive rate | 22 (28.2%) | 18 (25.4%) | 0.701 |
| Specific IgE (kU/L) | 0.7 ± 1.6 | 0.7 ± 2.4 | 0.934 |

Significant *p*-levels (below 0.05) are in bold.
Data are represented as number (percent) or means ± standard deviation. EIB (+) represented patients with positive results after exercise challenge test; EIB (−) represented patients with negative results after exercise challenge test.

Among patients with EIB, airflow limitation development in patient with methacholine-induced bronchial hyper-responsiveness was relatively more abrupt and severe compared with patients without bronchial hyper-responsiveness (Table 3). The time of maximal decline in $FEV_1$ in patient with positive methacholine challenge test was shorter than the time in patient with normal airway hyper-responsiveness relatively ($3.4 \pm 4.1$ min and $5.1 \pm 5.0$ min respectively, $p = 0.045$). The maximal fall in $FEV_1$ in patients with positive methacholine challenge test was more than patient with negative results ($19.3 \pm 8.7\%$ and $15.0 \pm 6.2\%$, $p = 0.033$).

## Independent risk factors for EIB

Within out study, we've found that positive methacholine challenge test, history of atopic dermatitis, sensitization to *D. pteronyssinus* and *D. farinae* may be related to the development of EIB. However, only history of atopic dermatitis seemed to be an independent risk factors for EIB (95% confidence interval, 0.22–0.97, $p = 0.041$).

## Discussion

Previous studies have reported that the prevalence of EIB ranged from 40 to 90%,[7,9,10] whereas there are only 10–20% of general population presenting EIB after exercise.[6–8] The mean age of our study ($6.9 \pm 1.7$ years) was younger than previous studies, which were focusing on elder children, adolescents, or adults.[6,14–17] The prevalence of EIB was influenced by the temperature and humidity of inhaled air.[16,18] The average temperature and humidity were lower in Taiwan, where is in humid subtropical climate. A prevalence of exercise-induced bronchoconstriction of 52.5% in

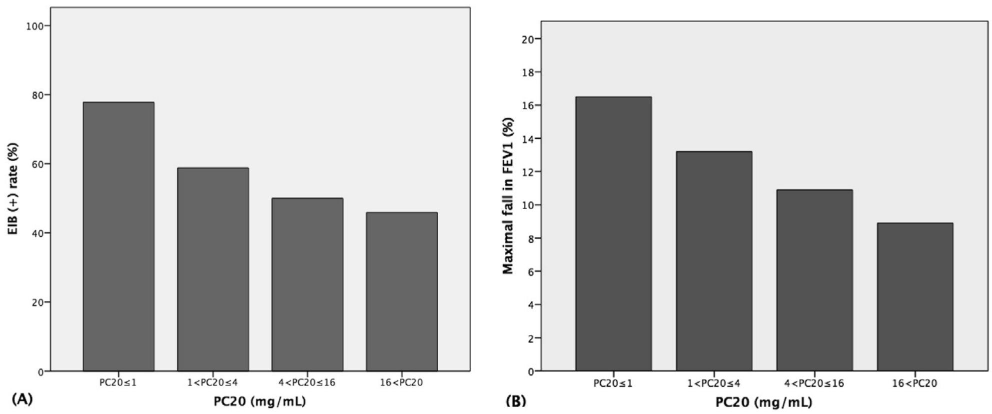


**Figure 3.** Positive rate and maximal fall in $FEV_1$ of exercise challenge test according to $PC_{20}$ of methacholine challenge test. $FEV_1$, forced expiratory volume in 1 s. $PC_{20}$, provocation concentration causing 20% fall in $FEV_1$.

children with asthma in Taiwan was found in present cross-sectional cohort study, and it was compatible with previous studies.

It has been previously reported that there was a larger proportion of female and a larger proportion of patients with exercise-induced symptoms, higher levels of IgE and ECP in subjects with exercise-induced bronchoconstriction.[15,16,19] Atopy were also known to influence the presence of EIB in previous study.[20] There was no difference of the percentage of patient with reported exercise-induced symptoms between patient with and without EIB. In our study, the mean age of our subjects was younger than previous studies, and most of the exercise-induced symptoms were reported by parents or care-giver who answered the questionnaires. There were more patients with higher serum levels of IgE, ECP, atopic sensitization, history of atopic dermatitis, and history of parental atopy in subjects with positive exercise challenge test, but the difference was only significant in history of atopic dermatitis between two groups. Atopy, and higher level of IgE, and higher rate of sensitization to house dust mites was reported to be related to EIB.[17,20] In our study, we found that there were more subjects with sensitization to

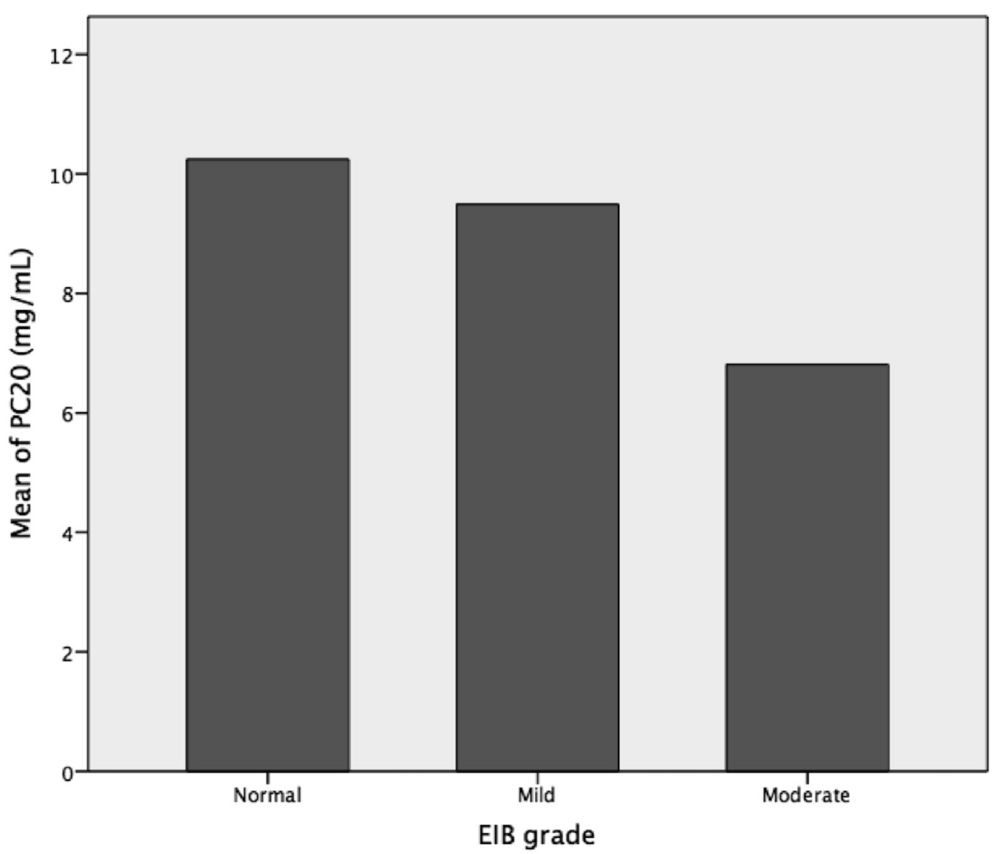


**Figure 4.** The mean of PC20 of methacholine challenge test according to the grading of EIB. FEV1, forced expiratory volume in 1 s. PC20, provocation concentration causing 20% fall in FEV1.

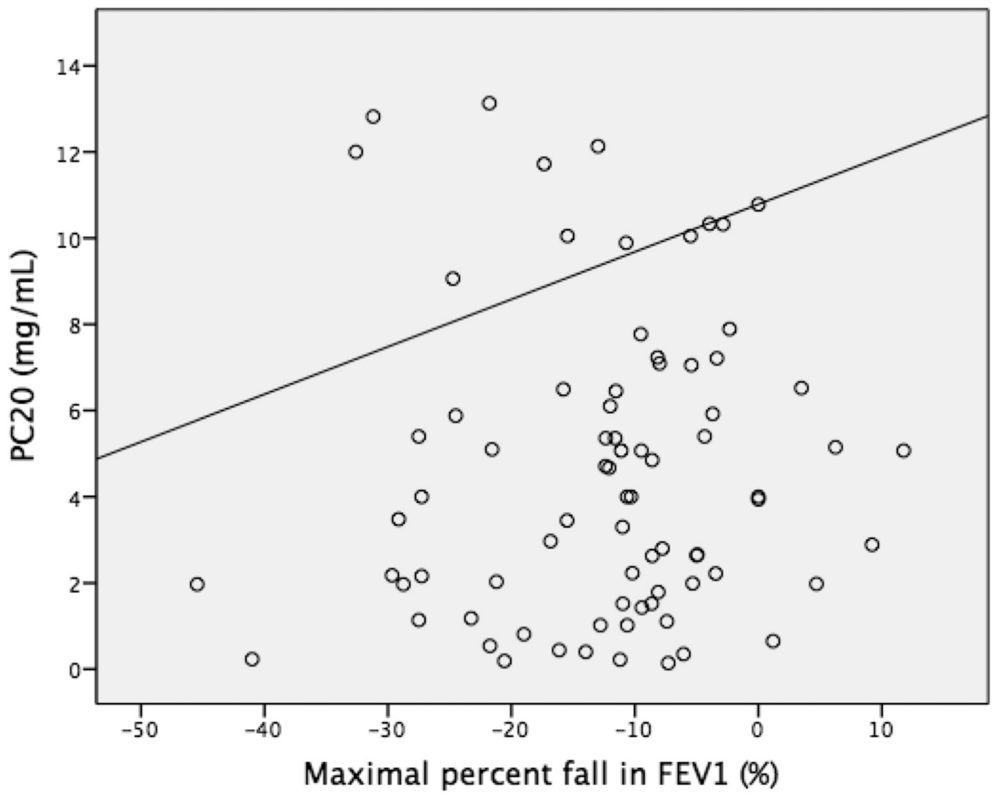


**Figure 5.** Relationship between maximal percent fall in FEV1 after exercise challenge test and PC20 of methacholine challenge test (Pearson correlation: r = 0.176; $p = 0.038$). FEV1, forced expiratory volume in 1 s. PC20, provocation concentration causing 20% fall in FEV1.

*D. pteronyssinus* and *D. farinae*, but there was no difference was found with respect to *B. tropicalis*, house dust, and cockroach. Further study may be needed to investigate the difference between species of aeroallergens.

It has been reported that lower baseline $FEV_1$, FVC, $FEV_1$/FVC, and lower levels of $PC_{20}$ were related to the presence of EIB.[15,16,21] Lower FEV1 and lower levels of $PC_{20}$ may reflect less control of asthma, which may be associated with the presence and severity of EIB.[21] However, there was no difference of medications for asthma control in present study.

With regards to the medication used for asthma control, we found that there was no difference between two groups. The results of previous studies showed that there were more patients under control with SABAs in EIB positive group,[6,15] and it may reflect a relatively poorer control of asthma. However, it remained controversial that whether medication for asthma control, including ICSs, LTRAs, and LABAs, would affect the development or severity of EIB or not.[6,15] The finding of non-significant difference of medication for asthma between two groups may reflect that the baseline condition was quite similar between patient with and without EIB. LTRA may improve EIB and recovery to baseline in some patients in one review.[22] Protection from EIB is apparent by 2 h after a single dose of LTRA.[23,24] However, LTRAs are not effective in all patients.[25] ICSs may also improve airway hyper-responsiveness and decrease the magnitude of EIB over weeks to months, but ICSs do not have an immediate protective effect on EIB.[26–28] These may explain that the difference was not statistically significant with regards to the medication used for asthma control. However, the compliance of medication use in our subjects should also be considered, and the impact could not be totally excluded.

In our study, most of the patients (88.6%, N = 132) showed the greatest decline in $FEV_1$ within 15 min after exercise challenge test. In previous studies, it has been reported that bronchoconstriction typically happened and reached peak within 10–15 min, but may be recovered completely within 30 min.[3,15] Our study showed similar time pattern of $FEV_1$ decline after exercise challenge. At first minutes, there were 47% (N = 70) of patients that had their maximal decline in $FEV_1$ after exercise challenge. This

**Table 3** The time and percentage of maximal decline in $FEV_1$ in patient with exercise-induced bronchoconstriction.

| | EIB (+) and MCT (+) | EIB (+) and MCT (−) | *p*-value |
|---|---|---|---|
| Time of maximal fall in $FEV_1$ (minute) | 3.4 ± 4.1 | 6.2 ± 5.0 | **0.045** |
| Maximal percent fall in $FEV_1$ (%) | 19.3 ± 8.7 | 13.0 ± 6.2 | **0.033** |

Significant *p*-levels (below 0.05) are in bold.
Data are represented as means ± standard deviation. EIB (+) represented patients with positive results after exercise challenge test; MCT (+) represented patients with positive results after methacholine challenge test; MCT (−) represented patients with negative results after methacholine challenge test; $FEV_1$, forced expiratory volume in 1 s.

result suggested pulmonary function test should be monitored for at least 30 min after exercise cessation.

Exercise is an indirect stimulus for the development of bronchoconstriction, and it was triggered by airway hyperosmolarity and airway cooling.[29–31] In contrast, methacholine caused airway limitation by directly simulating effector cells, such as airway smooth muscle cells, bronchial epithelial cells, and mucus-producing cells.[31] The mechanism and pathophysiology of airway limitation of these two stimuli are different, however, the bronchial hyper-responsiveness to exercise and methacholine were reported to be related in previous studies.[16,32,33] In our study, the positive rate of EIB was larger in patient with more hyper-responsiveness to methacholine. The positive rate of EIB was 77.8% and 58.8% in patients with moderate to severe and mild methacholine-induced airway hyper-responsiveness. Compared with patient with normal bronchial responsiveness, the decline of $FEV_1$ after exercise challenge was significantly lower than patients with mild and moderate to severe bronchial hyper-responsiveness ($p = 0.040$ and $p = 0.019$ respectively). The correlation between methacholine-induced bronchial hyper-responsiveness and EIB was also significant ($p = 0.038$). Patients with lower $PC_{20}$ level after methacholine provocation had more decline in $FEV_1$ after exercise challenge. Furthermore, our study suggested that the decline in $FEV_1$ was more abrupt and severe after exercise challenge in patient with positive methacholine provocation. In patients with asthma and advanced methacholine-induced airway hyper-responsiveness, more caution should be taken for breath pattern and symptoms after exercise. An exercise challenge test or further prophylactic medication may be needed in those patients.

In our study, baseline pulmonary function test, standardized treadmill exercise challenge,[1] and methacholine challenge tests (MCT)[3] were performed based on American Thoracic Society/European Respiratory Society guidelines. The patients' heart rates were monitored to make sure to reach the target heart rates during the exercise challenge, and the temperature and humidity of the place we performed pulmonary function and provocation tests was constant. The mean age of our study ($6.9 \pm 1.7$ years) was younger than previous studies.[6,14–17] The average temperature and humidity was higher than previous studies.[15,16] However, one of the limitation of our study is relatively small size of our study subjects. Furthermore, potential selection bias cannot be excluded. The average age of our study subjects was younger than previous studies,[6,14–17] and there was some patient could not cooperate with pulmonary function test and provocation test.

We concluded that exercise-induced bronchoconstriction presented in 52.5% of children with asthma. Patients, who were more sensitive to methacholine challenge (with lower $PC_{20}$ levels), developed exercise-induced bronchoconstriction with more decline in $FEV_1$ after exercise challenge.

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