Dyspnea Perception During Induced Bronchoconstriction Is Complicated by the Inhaled Methacholine in Children With Clinical Asthma

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Dyspnea Perception During Induced Bronchoconstriction Is Complicated by the Inhaled Methacholine in Children With Clinical Asthma

Directed by Professor Myung Hyun Sohn

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ABSTRACT

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Purpose

Dyspnea is not widely utilized as an indicator of asthma provocation despite its universal presentation. We hypothesized that dyspnea severity was proportionate with the lung function decline, methacholine dose-step, and the degree of bronchial hyperresponsiveness (BHR).

Methods

We retrospectively analyzed 73 children's bronchial provocation test data with an assessment of dyspnea at every dose-step. Dyspnea severity was scored using a modified Borg (mBorg) scale. A linear mixed effect analysis was performed to evaluate the relationship between the mBorg scale, the percentage fall in the forced expiratory volume in 1 second (FEV_1) (ΔFEV_1%), the methacholine dose-step, and the degree of BHR (BHR grade).

Results

Subjects were divided into 5 BHR groups based on their last methacholine dose-steps. The mBorg scores did not differ significantly among BHR groups (P=0.596, Kruskal-Wallis test). The linear mixed effect analysis showed that ΔFEV_1% was affected by the methacholine dose-step (P<0.001) and BHR grade (P<0.001). The mBorg score was affected by the dose-step (P<0.001) and BHR grade (P=0.019). We

developed a model to predict the mBorg score and found that it was affected by the methacholine dose-step and $\Delta FEV_1\%$, elevating it by a score of 0.039 ($\chi 2$ [1]=21.06, P<0.001) and 0.327 ($\chi 2$ [1]=47.45, P<0.001), respectively. A significant interaction was observed between the methacholine dose-step and $\Delta FEV_1\%$ ($\chi 2$ [1]=16.20, P<0.001).

Conclusions

In asthmatic children, inhaled methacholine, as well as the degree of BHR and lung function decline, may affect dyspnea perception during the bronchial provocation test. If we wish to draw meaningful information from dyspnea perception, we have to consider various complicating factors underlying it.

Key words: asthma, bronchial provocation test, child, dyspnea, methacholine

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I. INTRODUCTION

Dyspnea is an unpleasant sensation of labored or difficult breathing.[1] It is one of the cardinal symptoms of asthma, along with cough, wheezing, and chest tightness. Furthermore, among asthmatic patients who visited the emergency department because of increased symptom severity, dyspnea was the most commonly reported complaint.[2] Recurrent episodes of dyspnea or other relevant symptoms indicating airway obstruction are essential for the diagnosis of asthma, as well as the exclusion of other possible causes.[3]

The bronchial provocation test is indicated to replicate asthma presentation by stimulating bronchial contraction. By gradually increasing the stimulus, we can verify the presence of bronchial hyperresponsiveness (BHR), which is a fall in the forced expiratory volume in 1 second (FEV_1) beyond a certain threshold in asthmatic subjects.[4, 5] In general, the amount of stimulus that can lead to a >20% bronchial obstruction is regarded as an indicator of BHR.[6] In young children, bronchial obstruction can be assessed using the relevant physical findings,

typically the emergence of wheezing or desaturation. However, dyspnea is not widely utilized as an indicator of asthma provocation despite its universal presentation. Additionally, it is controversial whether the degree of dyspnea is proportionate with lung function decline, or whether the relationship varies according to the degree of BHR (BHR grade).[7, 8, 9]

In this study, we intended to explore the clinical significance of dyspnea during induced bronchoconstriction. We measured changes in the severity of dyspnea during bronchial provocation tests in children with asthma and evaluated their association with lung function reduction. We aimed to verify whether dyspnea perception correlates with lung function decline and whether there are other variables that affect dyspnea perception.

II. MATERIALS AND METHODS

1. Subjects

We retrospectively analyzed deidentified data from another study that evaluated the relationship between a modified Borg (mBorg) scale and the pictogram-based dyspnea scale during induced bronchoconstriction in children with clinical asthma.[10] (approval No. H-1302-019-462) The study recruited 73 asthmatic children, aged ≥6 years, who visited the allergy clinic in our institute. All subjects had a history of clinical asthma, such as chronic cough, episodic dyspnea, and/or wheezing within the past year. Patients with a history of near-fatal asthma, major exacerbations necessitating the use of systemic corticosteroids, or serious respiratory diseases other than asthma, such as bronchopulmonary dysplasia or bronchiectasis, were excluded from the study. This analysis was approved by the Institutional Ethics Committee of the Seoul National University Hospital/Seoul National University College of Medicine (approval No. H-1704-112-847) and the requirement for consent was waived.

2. Pulmonary function test and bronchial provocation test

Forced vital capacity (FVC) and FEV_1 were measured via forced expiratory maneuvers according to standards that met the American Thoracic Society (ATS) criteria[11] using a spirometer (MicroPlus; CareFusion, Basingstoke, UK). All subjects were requested to stop taking inhaled corticosteroids and leukotriene receptor antagonists for 2 weeks, antihistamines for 1 week, bronchodilators and other medications for 48 hours, and short-acting β2-agonists for 8 hours before the tests. None of our subjects had any symptoms of upper respiratory tract infections in the 2 weeks preceding the tests. Before we proceeded to perform the bronchial challenges, the patients were trained to conduct spirometry in a reproducible way (i.e., a coefficient of variation of FEV_1 in 3 consecutive flow-volume curves of <5%), and they were required to have an FEV_1 of at least 70% of the predicted value.

The bronchial provocation test was carried out according to the ATS guidelines.[6] Fresh solutions of methacholine chloride (Sigma-Aldrich, St. Louis, MO, USA) were prepared in buffered saline solution at concentrations of 0.625, 2.5, 5, 25, and 100 mg/mL. We could not apply Provocholine® (methacholine chloride USP; Methapharm Inc., Ontario, Canada) because it was commercially unavailable in our country during the study period. First, the subjects were instructed to inhale a dose of 0.9% saline 5 times. After a 2-minute interval, we assessed the subjects' dyspnea and FEV_1, and recorded these measurements as the baseline readings. These measurements were then repeated 2 minutes after 5 inhalations of doses of 0.625, 2.5, 5, 25, and 100 mg/mL methacholine. The test was terminated if FEV_1 showed a decrease of more than 20% compared to the baseline value, or if FEV_1 did not decrease by more than 20% at the last dose-step. For subjects who exhibited a percentage fall in the FEV_1 from baseline ($\Delta FEV_1\%$) of $\geq$20%, the provocative concentration of methacholine causing the $\Delta FEV_1\%$ of 20% (PC_{20}) was calculated by interpolation from a log-linear graph.

3. Assessment of dyspnea perception

During the bronchial challenges, the severity of perceived dyspnea was assessed by the mBorg scale[12] and the pediatric dyspnea scale (PDS).[13] The Borg scale is a vertical list with labeled categories (0-10) describing increasing intensities of dyspnea (0 “nothing at all” and 10 “maximal”). We used a modified version of the Borg scale that was translated into the Korean language. Because the Korean version of the mBorg scale has previously been validated but the PDS has not, we selected the mBorg scale to assess the relationship with lung function parameters. Prior to the bronchial provocation, we explained the mBorg scale to the participants and gave them time to familiarize themselves with the scale. Before FEV_1 measurement on each dose-step, we asked the children “How severe was your breathlessness after this inhalation?” We did not remind subjects of their dyspnea scores in the previous step. Throughout the provocation test, the subjects were blinded to their lung function results.

4. Statistical analysis

The R statistical software (version 3.3.2; R Project for Statistical Computing, Vienna, Austria), are used for data analysis. Continuous variables, such as age, height, weight, FEV_1, and $\Delta FEV_1\%$ were presented as the mean±standard deviation. Dyspnea scores are presented as the median and the interquartile range. The Kruskal-Wallis test was utilized to assess the group difference in the medians of the last dose-step mBorg scores; the trend of these scores across the BHR groups was examined by the Jonckheere-Terpstra test.[14] A linear mixed model analysis[15] was performed to evaluate the relationship among the mBorg, $\Delta FEV_1\%$, methacholine dose-step, and BHR grade. P values were obtained using a likelihood ratio test of the full model with the effect in question against the model without the effect in question. The significance level was statistically significant when a P value was less than 0.05.

III. RESULTS

A total of 73 asthmatic children underwent the methacholine provocation test. Table presents their baseline characteristics, including the profile of BHR grades and mBorg scores. The mean age of the participants was 10.8 years (48% [35/73] of them aged <10 years) and 56.2% were male. Forty-three subjects (43/73, 58.9%) presented significant bronchoconstriction, defined as a $\Delta FEV_1\% \geq 20\%$ on any dose-step. Thirty children had a $\Delta FEV_1\%$ of <20% even after undergoing the final dose-step of the bronchial challenges. If we define BHR as the PC_{20} <16 mg/mL, 28 subjects (28/73, 38.4%) had BHR. We then assigned a BHR grade to all the subjects, based on the dose-step that they reached during the test (Table). This classification was performed as follows: group I (n=6) with $\Delta FEV_1\% > 20\%$ at the first dose-step, indicating severe BHR; group II (n=4) with $\Delta FEV_1\% > 20\%$ at the second dose-step; and similarly, for groups III (n=5) and IV (n=18). Group V (n=40) consisted of those subjects whose $\Delta FEV_1\%$ remained <20% after the fourth dose-step and ended up receiving the final dose-step.

There was no significant difference in the median last dose-step mBorg scores between subjects who had BHR and those who did not (*P*=0.272), neither was there a significant difference among the 5 BHR groups (*P*=0.596). The median of last dose-step mBorg scores increased from 2 to 4 as the group number increased from I to IV (Table), whereas the trend was not statistically significant, even when we confined the analysis to subjects in groupd I to IV, i.e., those who exhibited significant bronchoconstriction at methacholine concentrations <25 mg/mL (n=33, P=0.405, Jonckheere-Terpstra test).

Table 1. Characteristic of study subjects

Table 1. Characteristics of study subjects	
Characteristic	No./total No. (%)
Sex, No. (%)	
Male	41/73 (56.1)

Height ± SD (cm)	142.1 ± 16.3
Age ± SD (years)	10.8 ± 3.3
< 10	35/73 (48.0)
≥ 10 and < 13	19/73 (26.0)
≥ 13	19/73 (26.0)
Controller, numbers (%)	
None	51/73 (69.9)
LTRA	10/73 (13.7)
ICS	9/73 (12.3)
ICS/LABA combination	3/73 (4.1)
BHR, No. (%)	
PC_{20} <16 mg/mL	28/73 (38.4)
PC_{20} ≥16 mg/mL, and < 100 mg/mL	15/73 (20.5)
PC_{20} ≥100 mg/mL	30/73 (41.1)
BHR grade, No. (%)	
I (PC_{20} <0.6mg/mL)	6/73 (8.2)
II (0.6 mg/mL ≤ PC_{20} <2.5 mg/mL)	4/73 (5.5)
III (2.5 mg/mL ≤ PC_{20} <5.0 mg/mL)	5/73 (6.8)
IV (5.0 mg/mL ≤ PC_{20} <24.0 mg/mL)	18/73 (24.7)
V (24.0 mg/mL ≤ PC_{20})	40/73 (54.8)
Last dose-step mBorg score, median (range)*	
BHR (PC_{20} <16 mg/mL)	3.0 (0-7.0)
Non-BHR (PC_{20} ≥16 mg/mL)	3.0 (0-5.0)
	P = 0.272
Last dose-step mBorg score, median (range)†	
I (PC_{20} <0.6mg/mL)	2.0 (0.0- 5.0)
II (0.6 mg/mL ≤ PC_{20} <2.5 mg/mL)	3.0 (3.0- 4.0)
III (2.5 mg/mL ≤ PC_{20} <5.0 mg/mL)	3.0 (3.0- 5.0)
IV (5.0 mg/mL ≤ PC_{20} <24.0 mg/mL)	4.0 (0.0- 7.0)
V (24.0 mg/mL ≤ PC_{20})	3.0 (0.0- 5.0)

SD, standard deviation; LTRA, leukotriene receptor antagonist; ICS, inhaled corticosteroid; LABA, long-acting beta agonist; BHR, bronchial hyperresponsiveness.

*Analysis of difference in scores between those who have BHR and those who did not

†Analysis of difference in scores among the five BHR groups

Fig. 1 depicts the changes in ΔFEV_1% across dose-steps with regard to the subjects' BHR group. The linear mixed effect analysis showed that the methacholine dose-step affected ΔFEV_1% ($\chi 2$ [1]=233.48, P<0.001), increasing

by 3.90±0.21 (standard error). The BHR grades also affected $\Delta FEV_1\%$ ($\chi 2$ [1]=96.47, P<0.001), decreasing by -4.87±0.40.

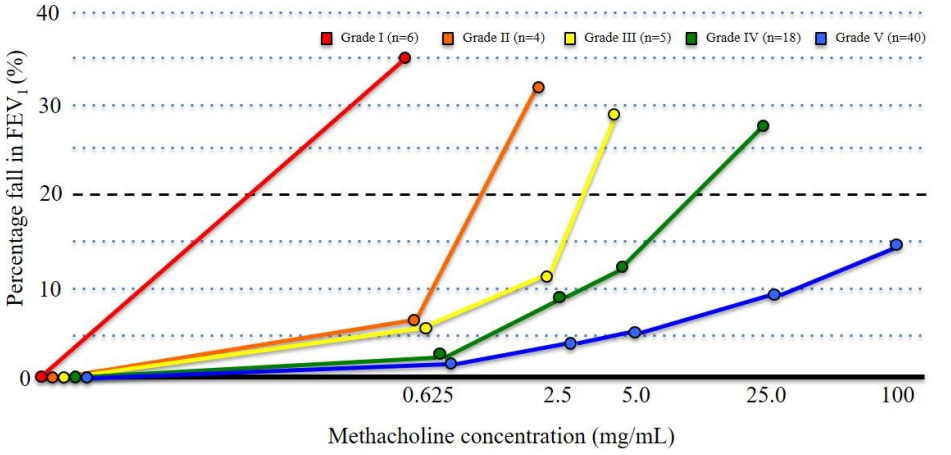

Fig. 1. Graph of the changes in FEV_1 according to BHR grade by increasing dose-step. The linear mixed effect analysis showed that the methacholine dose-step affected deltaFEV$_1$%. The BHR grades also affected deltaFEV$_1$%. FEV_1, forced expiratory volume in 1 second; BHR, bronchial hyperresponsiveness; deltaFEV$_1$%, percentage fall in FEV_1

The changes in mBorg scores for increasing dose-steps with regard to the subjects' BHR group are shown in Fig. 2. Except for one point (BHR group IV at a methacholine concentration of 2.5 mg/mL), the median mBorg score increased with the dose-steps in all BHR groups. For a given dose-step, the median mBorg score decreased when the BHR group number increased. The linear mixed effect analysis showed that the methacholine dose-step affected the mBorg scores ($\chi 2$ [1]= 162.88, P<0.001), increasing by 0.480±0.033 (standard error). The BHR grades also affected the mBorg scores ($\chi 2$ [1]=5.43, P=0.020), decreasing by -0.252±0.106.

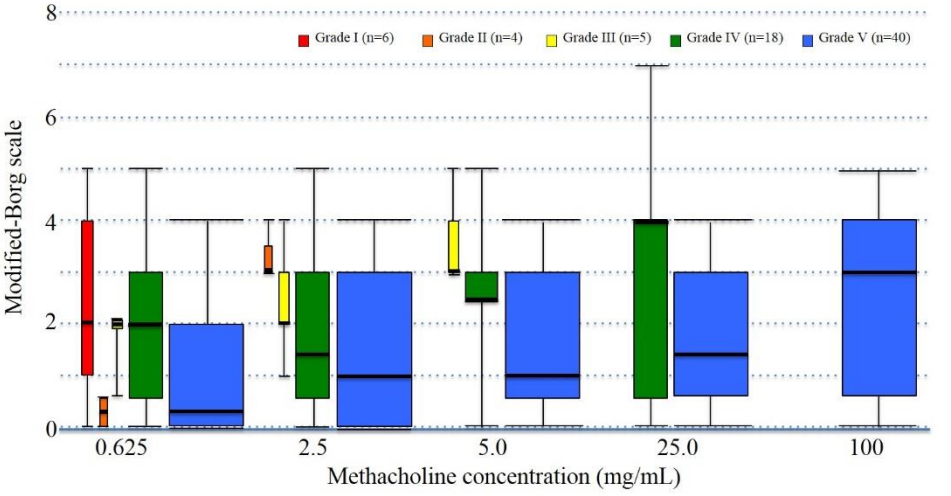

Fig. 2. Distribution of the median mBorg scores in each BHR group during the methacholine provocation test. Except for one point (the BHR grade IV at a methacholine concentration of 2.5 mg/mL), the median mBorg score increased with higher dose-steps in all BHR groups. BHR, bronchial hyperresponsiveness

Fig. 3 presents the distribution of mBorg scores according to $\Delta FEV_1\%$ by methacholine dose-steps. When we developed a model to predict mBorg scores by $\Delta FEV_1\%$, dose-step, and BHR grades, we found that the $\Delta FEV_1\%$ and methacholine dose-step affected the mBorg score, elevating it by 0.039 ($\Delta FEV_1\%$, $\chi 2$ [1]=21.06, P<0.001) and 0.327 (methacholine dose-step, $\chi 2$ [1]=47.45, P<0.001), respectively. BHR grades, however, did not show a significant contribution ($\chi 2$ [1]=0.315, P=0.574). A significant interaction was observed between the methacholine dose step and $\Delta FEV_1\%$ ($\chi 2$ [1]=16.20, P<0.001).

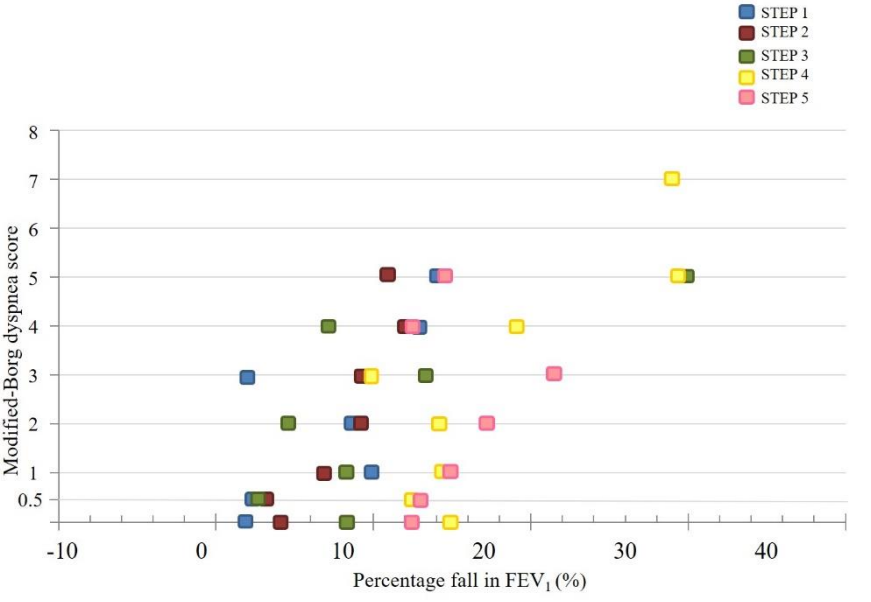

Fig. 3. Modified Borg score distribution plotted by the mean value of deltaFEV$_1$% according to dose step. A significant interaction was observed between the methacholine dose step and deltaFEV$_1$%. deltaFEV$_1$%, percentage fall in FEV$_1$

IV. DISCUSSION

When assessing the degree of dyspnea in asthmatic children during induced bronchoconstriction, we noticed a trend of decreasing lung function and increasing degrees of dyspnea as the dose-steps increased. We also observed that the trend was more evident when children had more severe BHR. It was a universal finding that subjects perceived more severe dyspnea as their lung function became worse, regardless of BHR status. One interesting finding was that the dose-step was independently associated with dyspnea perception. This study was the first to evaluate the complex relationships among dyspnea perception, lung function decrease, degree of BHR, and methacholine dose-step

during the provocation test in children with clinical asthma.

Asthmatic children specifically present with dyspnea, wheezy breathing, and lung function decline when exposed to bronchial stimulants. The latter 2 items have been widely used to assess BHR;[6, 16] however, dyspnea is seldom utilized as a means to assess BHR. This may be because dyspnea perception is multidimensional and difficult to score by a single scale, too obscure to verify via replication, or too subjective to allow for precise comparisons between subjects.[17] Tosca et al.[18] evaluated the degree of dyspnea in asthmatic children and reported that dyspnea assessed by the visual analog scale (VAS) in real life differs according to airway obstruction defined by FEV_1 values <80% of the predicted values. Ciprandi et al.[19] suggested a VAS score of $\geq$6 as a reliable cutoff for subjects who perceive asthma symptoms in adult asthmatics. These studies consistently show that subjects with poorer lung function exhibit a higher degree of dyspnea, which was in accordance with the findings in the present study. However, these studies did not give any information on the subjects' inherent BHR, which we assessed during the bronchial provocation test.

Regarding dyspnea measured during induced bronchoconstriction, most studies have focused only on the dyspnea perception score at a 20% decrease in FEV_1 relative to baseline (PS_{20}).[20, 21, 22] As an index of the awareness of asthma symptoms, PS_{20} is useful in differentiating between hypo-, normo-, or hyper-perceivers. Identifying children's perceiving patterns can help precisely interpret the level of control and prescribe appropriate controller medications.[21] However, PS_{20} does not cover subjects with BHR-negative clinical asthma whose PS_{20} cannot be calculated and it does not contain information on each subject's degree of BHR. Nuijsink et al.[22] calculated the Borg slope by plotting each subject's Borg scores against their fall in FEV_1. The Borg slope presented good associations with the baseline lung function and the cumulative dose of bronchial stimulant causing a 20% fall in FEV_1. These studies consistently found that BHR correlates with symptom perception, in other words, children with more severe

BHR would perceive their dyspnea as less severe.

In the present study, we focused on the multi-dimensional aspect of dyspnea. When we confined the analysis to subjects with BHR-negative clinical asthma, the median dyspnea score ranged from 0.5 to 3, although these subjects had no significant lung function decline. Moreover, they presented a trend of increasing dyspnea in accordance with increasing dose-steps. Because an increase in dose-step involves exposure to more stimulant for a longer time, the increasing dose-steps themselves may have affected the subjects psychologically, or the bronchial stimulant inhaled during the challenge tests may have caused unpleasant feelings in the asthmatic children. Therefore, we speculated that the increase in dose along with the longer duration of exposure may have confounded their dyspnea perception and even reversed the dyspnea perception related to BHR. Indeed, when we divided the subjects according to their BHR grades, we found a trend of more severe dyspnea perception corresponding to more severe BHR, which is the opposite of previous findings. This discrepancy points toward the complexity of dyspnea perception, which is the sum of various factors, such as lung function decline, amount of inhaled stimulant, and subjects' degree of BHR at the time of bronchial constriction.

Among various indices of dyspnea, we selected the mBorg scale because it was widely used in assessing PS_{20} in previous studies.[21, 22, 23, 24] However, the Borg scale was not invented specifically for asthmatic subjects, but rather intended for assessing fatigue by any cause. Furthermore, pediatric patients might not fully understand the difference in degrees of dyspnea when it is expressed in words rather than through the VAS.[25, 26, 27] Moreover, it is still unclear whether children are impaired in this complex process of cognition, interpretation, and scoring, and, if yes, how much they are impaired.

The present study is a re-analysis of data from another study that aimed to validate a dyspnea scale complemented by pictograms.[10] Unfortunately, we did

not collect information on clinical severity or the duration of asthma symptoms when enrolling subjects in the initial study. This would have allowed us to estimate the proportion of chronic severe asthmatics, which may have influenced the association between the bronchoconstriction and dyspnea perception. Moreover, the season of bronchial challenges or the time elapsed since the subjects' last exacerbation may have influenced their asthma control status and affected the relationship between dyspnea and the other pulmonary function parameters.[28, 29] Children with severe persistent asthma typically have blunted dyspnea perception due to their declined lung function.[8, 22, 30]

In this study, we investigated dyspnea intentionally induced by a nonspecific and direct stimulus. In reality, dyspnea perceived during asthma exacerbation might originate from different sources. Therefore, the generalizability of our findings to asthmatic children experiencing natural exacerbation is limited. However, our findings do suggest that PS_{20} values are insufficient for categorizing asthmatic subjects; clinicians should take into account the degree of BHR. Further studies on this topic should adopt an exercise challenge test rather than a methacholine test, because such graded challenges cannot be free from the psychological issues that accompany repeated procedures. More clinical information, including the asthma duration, clinical severity, and other demographic variables, would also be helpful to adjust for confounding factors.

V. CONCLUSION

In conclusion, the evaluation of dyspnea perceived during induced bronchoconstriction is complex. In asthmatic children, inhaled methacholine, as well as the degree of BHR and lung function decline, may affect dyspnea perception during the bronchial provocation test. Contrary to previous findings, more severe BHR presents as more severe dyspnea when the effect of the methacholine inhaled during the increased dose-steps is considered. If we wish to draw meaningful information from an assessment of dyspnea perception, we

have to consider various complicating factors underlying it.

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ABSTRACT(IN KOREAN)

소아 천식 환자에서 기관지 유발 검사 중 흡입하는 메타콜린이 호흡 곤란 인지에 미치는 영향

<지도교수 손 명 현>

연세대학교 대학원 의학과

최 윤 정

목적

천식 환자에서 호흡 곤란은 질병의 진단, 조절 및 치료에 대한 반응을 평가하는 도구로서 이용된다. 본 연구는 소아 천식 환자에서 기관지 유발 검사 중 발생하는 호흡 곤란의 임상적 의미와 그 유용성을 확인하고자 한다.

방법

기관지 유발 검사와 함께 호흡 곤란 점수 평가를 시행한 73명의 6세 이상 임상적 소아 천식 환자를 대상으로 하였다. 연구 대상에 해당하는 소아가 메타콜린 유발 검사를 시행 할 때, 각 단계별로 폐 기능 평가를 하기 전 호흡 곤란 점수를 물어보아 폐 기능 검사 결과와 함께 기록하였다. 메타콜린 용량 단계, 기관지 과민성의 정도에 따른 폐 기능 감소(ΔFEV_1%)와 호흡 곤란 점수(mBorg 점수)의 변화 양상을 확인하고 비교하였다. 반복 측정을 시행하는 검사로서 선형 혼합 효과 분석(linear mixed model)을 적용하여 유효성을 평가하였다.

결과

대상자들의 마지막 메타콜린 흡입 단계를 기준으로, 총 5 개의 기관지 과민성 군으로 나누어 분석을 시행하였다. mBorg 점수는

5개 기관지 과민성 군 간에 유의한 차이가 없었다(P = 0.596, Kruskal-Wallis test). 선형 혼합 효과 분석을 통해 ΔFEV_1%가 메타콜린 용량 단계(P <0.001)와 기관지 과민성 정도(P <0.001)에 의해 영향을 받음을 확인하였다. mBorg 점수도 용량 단계(P <0.001)와 기관지 과민성 정도(P = 0.019)에 의해 영향을 받았다. mBorg 점수를 예측하는 통계 모델을 이용하여 분석한 결과, 메타콜린 용량 단계가 증가할수록 mBorg 점수가 0.039 (χ^2 [1] = 21.06, P <0.001) 증가하며, ΔFEV_1%가 증가할 때는 호흡 곤란 점수가 0.327 (χ^2 [1]] = 47.45, P <0.001) 증가하였다. 메타콜린 용량 단계와 폐 기능 감소가 호흡 곤란 점수에 미치는 영향을 통계적으로 확인할 수 있었다. 메타콜린 용량 단계와 ΔFEV_1% 사이에서도 유의한 상호 작용이 관찰되었다 (χ^2 [1] = 16.20, P <0.001).

결론
소아 천식 환자가 흡입한 메타콜린과 환자의 기관지 과민성, 폐 기능 저하 정도는 기관지 유발 검사 중 발생하는 호흡 곤란에 영향을 줄 수 있다. 호흡 곤란 인지에 대한 의미 있는 정보를 얻고자 한다면, 호흡 곤란의 원인이 되는 여러 가지 복잡한 요인을 고려해야한다.

핵심되는 말: 천식, 기관지 유발 검사, 소아, 호흡 곤란, 메타콜린