Bronchodilator response following methacholine-induced bronchoconstriction predicts acute asthma exacerbations

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ABSTRACT Methacholine bronchial provocation test provides the concentration of methacholine causing a 20% decrease in forced expiratory volume in 1 s (FEV₁) from baseline (PC₂₀). The dose-response slope (DRS), and other continuous indices of responsiveness (CIR; the percentage decline from the post-diluent baseline FEV₁ after the last dose of methacholine), and per cent recovery index (PRI; the percentage increase from the maximally reduced FEV₁ after bronchodilator inhalation) are alternative measures. The clinical relevance of these indices in predicting acute asthma exacerbations has not been fully evaluated.

In two prospective cohorts of childhood and elderly asthmatics, baseline PC₂₀, DRS, CIR and PRI were measured and evaluated as predictors of acute asthma exacerbations.

We found that PRI was significantly related to the presence of asthma exacerbations during the first year of follow-up in both cohorts of childhood ($p=0.025$) and elderly asthmatics ($p=0.003$). In addition, PRI showed a significant association with the total number of steroid bursts during 4.3 years of follow-up in the cohort of childhood asthmatics ($p=0.04$).

We demonstrated that PRI, an index of reversibility following methacholine-induced bronchoconstriction, was a good clinical predictor of acute exacerbations of asthma in both childhood and elderly asthmatics.

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Introduction

In clinical practice, the methacholine bronchial provocation test (MBPT) is widely used to measure airway hyperresponsiveness (AHR), which is one of the defining features of asthma [1]. When we interpret the results of MBPT, we usually focus only on the threshold causing a 20% decrease in forced expiratory volume in 1 s (FEV₁) from baseline (*i.e.* PC₂₀ or PD₂₀). However, MBPT provides us other metrics of AHR, such as dose–response slope (DRS; the per cent decline in FEV₁ per methacholine dose) [2, 3], the continuous index of responsiveness (CIR; the per cent decline from the post-diluent baseline FEV₁ after the last dose of methacholine) [3] and the per cent recovery index (PRI; the per cent increase from the maximally reduced FEV₁ after bronchodilator inhalation) [4]. DRS and CIR are indicators of airway responsiveness in the presence of a bronchoconstrictor and reflect the severity of response by assessing the intensity of bronchoconstriction [2, 3]. In stable asthma, the health-related quality of life is not related to the sensitivity index (PC₂₀) but rather to the reactivity index (DRS and CIR) [5]. PRI has been used to assess efficacy of anti-asthmatic drugs [6, 7]. However, the clinical implications of these other metrics of AHR have not been fully evaluated.

Asthmatics sometimes experience an acute deterioration of symptoms, termed an “exacerbation”. Even among asthmatics with controlled asthma, 43% had an unscheduled hospital visit, 10% had an emergency department visit and 3% had a hospitalisation in the past year [8]. The social and economic burden of asthma exacerbations remains considerable [9, 10]. Previously, we reported that pre-bronchodilator FEV₁ was negatively correlated with asthma exacerbation in asthmatic children [11]. Other physiological parameters that predict asthma exacerbations include forced expiratory flow between 25 and 75% of vital capacity in the setting of normal FEV₁ [12], peripheral airway impulse oscillometry [13] and peak expiratory flow rate [14]. However, there have been no reports comprehensively showing the role of indices obtained from MBPT in predicting asthma exacerbations.

The purpose of this study was to evaluate the clinical utility of measures (PC₂₀, DRS, CIR, and PRI) generated from MBPT in assessing the future risk of asthma exacerbations. For this, we investigated the relationship between baseline values of the MBPT indices and asthma exacerbations in two prospective cohorts composed of childhood and elderly asthmatics.

Methods

Each study was approved by the Institutional Review Board of the corresponding institution (Seoul National University Hospital, Seoul, Korea (number: 0812-045-266) and Brigham and Women's Hospital, Boston, MA, USA (number: 2004-P-000996) and informed consent was obtained from all study participants.

Study populations

The first cohort consisted of children from the Childhood Asthma Management Programme (CAMP) trial. CAMP demographics and study design have been described elsewhere [15, 16]. A total of 1041 children with mild-to-moderate asthma aged 5–12 years were enrolled; a positive MBPT test (PC₂₀ <12.5 mg·mL^{−1}) was an entry criteria for the CAMP trial. At baseline, the number of hospitalisations or emergency room visits in the past 12 months was measured. The children were randomised to budesonide, nedocromil or placebo and followed for a mean of 4.3 years. The total number of prednisone bursts and the total number of hospitalisations or emergency room visit during the study period were calculated. An acute exacerbation was defined if patients experienced one or more prednisone bursts, hospitalisations or emergency room visits.

The second cohort consisted of elderly asthmatics aged ≥65 years that were recruited from Seoul National University Hospital, Seoul and Bundang Seoul National University Hospital, Bundang, Korea. It was a subset of a prospective, observational multicentre cohort in Korea with the purpose of studying the natural history of asthma among elderly people [17]. History of a previous exacerbation (no *versus* yes) was assessed using a careful review of the medical records from 3 months before enrolment. Cognitive function was assessed using the Korean version of the Mini-Mental State Examination, and mood was assessed using the Korean version of the Geriatric Depression Scale Short Form. Proficiency in using inhaler devices was rated using a scoring system. After baseline evaluations, elderly adults with asthma who were enrolled were treated for 1 year with conventional medications based on the Global Initiative for Asthma guidelines [18]. Follow-up visits were scheduled every 3 months, and the occurrence of asthma exacerbations during the past 3 months was recorded at every visit. An asthma exacerbation was defined when one of the following criteria was satisfied: use of systemic corticosteroids for at least three successive days, asthma-specific unscheduled visits, and emergency department visits or hospitalisations.

Methacholine bronchial provocation test and index analysed

In the CAMP cohort, MBPT was carried out before randomisation using the method of 2 min of tidal breathing from a Wright nebuliser (Bayview Medical Supply, Baltimore, MD, USA) [19]. Children inhaled

incrementally doubling doses of methacholine from 0.098 to 12.5 mg·mL⁻¹ until there was a 20% fall from the post-saline FEV₁. Then a bronchodilator (two puffs of salbutamol) was administered and FEV₁ was measured 15 min after bronchodilator inhalation. In the elderly cohort, MBPT was carried out using the modified method described by CHAI *et al.* [20]. Concentrations of 1.25, 2.5, 6.25, and 12.5 mg·mL⁻¹ of methacholine were prepared by dilution with buffered saline. A Rosenthal–French dosimeter (Laboratory for Applied Immunology, Baltimore, MD, USA) was used to deliver the aerosol generated by a DeVilbiss 646 nebuliser (Medical Depot, Inc., Port Washington, NY, USA). Subjects inhaled five inspiratory capacity breaths of increasing concentrations of methacholine until FEV₁ fell by more than 20% of its baseline value. Then a bronchodilator (two puffs of salbutamol) was administered and FEV₁ was measured 15 min after bronchodilator inhalation.

Figure 1 shows how indices from the MBPT were calculated. PC₂₀ was calculated by interpolation from the last two concentrations. DRS, CIR and PRI were calculated as follows:

$$\text{DRS} = \frac{(\text{Post-diluent FEV}_1 - \text{FEV}_1 \text{ at the last dose of methacholine})}{(\text{Post-diluent FEV}_1 \times \text{Last methacholine dose})} \times 100$$

$$\text{CIR} = \frac{(\text{Post-diluent FEV}_1 - \text{FEV}_1 \text{ at the last dose of methacholine})}{\text{Post-diluent FEV}_1} \times 100$$

$$\text{PRI} = \frac{(\text{Post-bronchodilator FEV}_1 - \text{FEV}_1 \text{ at the last dose of methacholine})}{(\text{Post-diluent FEV}_1 - \text{FEV}_1 \text{ at the last dose of methacholine})} \times 100$$

All indices were natural log-transformed.

Statistical analysis

A regression analysis (with a logistic regression for the categorical variable and a linear regression for the continuous variable) was performed to evaluate the predictive roles of each index in both cohorts for exacerbations. In the CAMP cohort, age, sex (female *versus* male), body mass index (BMI) z-score, baseline FEV₁ % predicted, history of exacerbation during the previous 1 year (no *versus* yes), race (Caucasian *versus* African-American *versus* Hispanic-American *versus* Asian-American) and treatment group (placebo *versus* nedocromil *versus* inhaled corticosteroid) were included as covariates. The primary outcome was the presence of exacerbations within the first year (categorical variable). Secondary outcomes included per cent increase in FEV₁ from the baseline value 8 weeks after treatment, and cumulative number of hospitalisations

FIGURE 1 Indices generated from the methacholine bronchial provocation test. FEV₁: forced expiratory volume in 1 s; BD: bronchodilator; MCH: methacholine; PC₂₀: concentration of methacholine causing a 20% decrease in FEV₁ from baseline.

or emergency room visits at 4 years of follow-up (continuous variables). Covariates in the elderly asthma cohort included age, sex (female *versus* male), BMI, baseline FEV₁ % predicted, smoking status (no *versus* yes), history of exacerbation during previous 1 year (no *versus* yes), cognitive function, depression status and inhaler technique. As with CAMP, the primary outcome was the occurrence of exacerbations within 1 year after enrolment (categorical variable). A p-value of <0.05 was considered significant. All analyses were performed with R version 2.15.3 (www.r-project.org). R scripts can be found in the online supplementary material.

Results

Table 1 summarises the baseline characteristics of the childhood and the elderly asthmatics.

Cohort of childhood asthmatics

Pearson's correlation coefficients were measured to assess interdependency of indices generated from MBPT at baseline. High correlations were noted except between ln(PC₂₀) and ln(CIR) (table E1 and figure E1). To evaluate roles of each index in predicting clinical outcomes, regression models were constructed using age, sex, race, BMI z-score, FEV₁ predicted value, treatment group, history of past exacerbation and the four indices of responsiveness. Using the variance inflation factor, we evaluated the severity of multicollinearity in our models. The variance inflation factor enables us to measure how much the variance of an estimated regression coefficient is increased because of collinearity [21]. By removing ln(DRS) from our models we could obtain acceptable variance inflation factor values (<5) (table E2). Accordingly, ln(DRS) was excluded from the final model. The results of the regression analysis are presented in table 2. ln(PC₂₀) and ln(PRI) showed significant associations with incident exacerbations at 1 year. The odds ratio obtained from logistic regression analysis was 2.23 (95% CI 1.11–4.54). ln(PRI) also showed a significant association with cumulative numbers of steroid bursts at 4.3 years, but ln(PC₂₀) did not. There were no other associations between MBPT indices and any of the other clinical outcomes.

Cohort of elderly asthmatics

Unlike childhood asthmatics, high correlations were noted among all pairs of MBPT indices (table E1 and figure E1). After collinearity diagnostics, the final logistic regression model included age, sex, BMI, baseline FEV₁ % predicted, smoking status, history of exacerbation during the previous 1 year, cognitive function, depression status, ln(PC₂₀), ln(DRS), ln(CIR) and ln(PRI) (table E3). Among the indices generated from MBPT, only ln(PRI) was significantly associated with incident exacerbations at 1 year (table 3). The odds ratio obtained from logistic regression analysis was 59.88 (95% CI 4.65–1228.76). Figure 2 shows that the ln(PRI) of asthmatics who experienced an acute exacerbations during the first year

TABLE 1 Baseline characteristics

	Childhood asthmatics	Elderly asthmatics
Subjects n	736	145
Age years	8.9 [7.2–10.6]	68 [65–72]
Male sex	435 [59.1]	62 [42.7]
FEV₁ % predicted	93 [85–102]	75 [62–93]
BMI	0.47 [−0.21–1.28] [#]	23.8 [22.4–26.1] [¶]
Race		
Caucasian	495 [67.3]	0 [0]
African-American	109 [14.8]	0 [0]
Hispanic	68 [9.2]	0 [0]
Asian	64 [8.7]	145 [100]
Smoking (yes)	NA	46 [31.7]
History of exacerbation (yes)	228 [31.0]	18 [12.4]
Treatment group		
Inhaled corticosteroid	230 [31.3]	NA
Nedocromil	206 [28.0]	NA
Placebo	300 [40.7]	NA
Cognitive function score	NA	27 [24–29]
Depression score	NA	6 [3–10]
Inhaler technique score	NA	5 [5–6]

Data are presented as median [interquartile range] or n (%), unless otherwise stated. FEV₁: forced expiratory volume in 1 s; BMI: body mass index; NA: not applicable. [#]: z-score; [¶]: kg·m^{−2}.

TABLE 2 Relationships between the methacholine bronchial provocation test indices and clinical outcomes in the CAMP childhood asthmatics

	Experience of exacerbation at 1 year (no <i>versus</i> yes) [#]		FEV ₁ increase at 8 weeks [¶]		Cumulative number of events at 4 years			
	β coefficient	p-value	β coefficient	p-value	ER/hospital visit [¶]		Steroid burst [¶]	
					β coefficient	p-value	β coefficient	p-value
Age	−0.163	3.91×10^{−5}	−0.114	0.562	−0.040	0.185	−0.269	2.50×10^{−4}
Sex_male	0.050	0.755	0.665	0.416	−0.013	0.917	0.107	0.721
Race_African-American	−0.068	0.770	1.172	0.317	0.409	0.022	−0.016	0.970
Race_Hispanic	0.143	0.608	−0.301	0.830	0.138	0.520	0.564	0.278
Race_Asian	0.358	0.220	−1.280	0.370	0.180	0.408	0.755	0.153
BMI z-score	−0.078	0.308	−0.406	0.288	0.016	0.772	−0.453	1.41×10^{−3}
FEV ₁ % predicted	0.005	0.453	0.003	0.915	0.007	0.171	−0.011	0.359
Treat_nedocromil	−0.181	0.355	−0.071	0.942	−0.339	0.022	−1.224	7.26×10^{−4}
Treat_ICS	−0.926	9.63×10^{−7}	5.593	4.47×10^{−9}	−0.518	3.43×10^{−4}	−2.166	8.92×10^{−10}
History of acute exacerbation _yes	0.647	3.33×10^{−4}	−1.068	0.224	0.093	9.49×10^{−12}	1.710	1.86×10^{−7}
ln(PC20)	−0.216	7.99×10^{−3}	−0.008	0.984	−0.074	0.232	−0.178	0.236
ln(CIR)	−0.304	0.346	−0.136	0.933	0.259	0.297	0.310	0.605
ln(PRI)	0.803	0.025	1.147	0.515	0.373	0.232	1.341	0.039

CAMP: Childhood Asthma Management Programme; FEV₁: forced expiratory volume in 1 s; ER: emergency room; BMI: body mass index; ICS: inhaled corticosteroid; PC20: concentration of methacholine causing a 20% decrease in FEV₁ from baseline; CIR: continuous index of response; PRI: per cent recovery index. Data in bold indicates statistically significant results (p<0.05). #: Logistic regression analysis. A negative β coefficient means that the odds ratio is less than one. ¶: Linear regression analysis.

TABLE 3 Relationship between variables and acute exacerbations in the cohort of elderly asthmatics

	Experience of acute exacerbation at 1 year (no versus yes) [#]	
	β coefficient	p-value
Age	0.045	0.401
Sex_male	-1.175	0.179
BMI	-0.101	0.258
Smoking status_yes	1.651	0.043
FEV ₁ % predicted	-0.016	0.412
History of acute exacerbation_yes	1.549	0.091
Cognitive function	0.022	0.802
Depression	0.172	0.062
ln(PC ₂₀)	0.292	0.359
ln(DRS)	0.727	0.696
ln(CIR)	0.165	0.886
ln(PRI)	4.079	3.43×10⁻³

BMI: body mass index; FEV₁: forced expiratory volume in 1 s; PC₂₀: concentration of methacholine causing a 20% decrease in FEV₁ from baseline; DRS: dose-response slope; CIR: continuous index of response; PRI: per cent recovery index. Data in bold indicates statistically significant results ($p < 0.05$). #: Logistic regression analysis.

of follow-up was significantly higher when compared with ln(PRI) of those who did not in both cohorts of childhood and elderly asthmatics. Comparisons of the characteristics between the two groups in both cohorts are presented in table E4 and E5.

Discussion

MBPT is easy to perform and thus is widely used in clinical practice to diagnose asthma. In the present study, we evaluated the role of four measures (PC₂₀, DRS, CIR and PRI) obtained from MBPT in predicting future risk of asthma exacerbations. We found that PRI, the degree of response to bronchodilator after methacholine-induced bronchoconstriction, was significantly related to the occurrence of asthma exacerbations within 1 year of follow-up in two prospective cohorts of childhood and elderly asthmatics. In addition, PRI showed a significant association with the total number of steroid bursts within 4.3 years of follow-up in the cohort of childhood asthmatics. Of note, while PRI was a predictive marker of exacerbations in both children and elderly adults, the magnitude of effect was higher in the elderly adult cohort (OR 2.2 *versus* 59.9 for children *versus* adults, respectively), suggesting particular prognostic and therapeutic relevance in that cohort. Recently, it was reported that DRS showed clinical advantages over PC₂₀ for the

FIGURE 2 Comparison of the natural logarithm of per cent recovery index (ln(PRI)) between asthmatics who experienced acute exacerbations during the first year of follow-up and asthmatics who did not experience an acute exacerbation. a) Childhood asthmatics. b) Elderly asthmatics. The horizontal lines represent the median and boxes represent the interquartile range (IQR; Q1–Q3). Whiskers represent Q1–1.5×IQR (lower) and Q3+1.5×IQR (upper).

prediction of development of asthma, chronic obstructive pulmonary disease and allergic rhinitis in the general population [22]. Clinically, it seems that DRS may be more important in subjects without definite AHR defined by PC₂₀. However, in asthmatics, DRS was tightly correlated with PC₂₀ as our results showed and thus may have no more clinical relevance than PC₂₀. To the best of our knowledge, this is the first study to show a promising role for bronchodilator response following methacholine-induced bronchoconstriction in predicting asthma exacerbations.

Early reports showed that the degree of airway sensitivity and responsiveness to methacholine (PC₂₀, DRS and CIR in this study) could be markers of asthma severity [23–25]. It is natural to expect that asthmatics with increased airway sensitivity and responsiveness are more susceptible to bronchoconstriction when they are exposed to nonspecific stimuli. However, it was reported that inhaled corticosteroid treatment gradually decreased airway hypersensitivity and hyperresponsiveness [26, 27]. These findings suggested that airway sensitivity and responsiveness index measured at baseline could not predict future asthma exacerbations as long as proper medications were provided. HANCOX *et al.* [4] first introduced the challenge-rescue technique to assess bronchodilator response. Similar to the present study, they measured bronchodilator response after airway smooth muscle contraction induced by methacholine. PRI reflects the efficacy of bronchodilator medications in the environment causing maximal contraction of airway smooth muscle, as shown in the previous study [6, 7]. Airway smooth muscle of asthma patients was found to be abnormal in its functional properties and showed intrinsic heightened contractility independent of other structural cells and independent of the airway inflammatory milieu [28, 29]. At present, we cannot measure how much airway smooth muscle contraction contributes to AHR. Recent studies, which showed that anti-IgE or anti-interleukin-5 antibodies in addition to inhaled corticosteroids further improved inflammation but did not affect AHR, implied that a bronchodilator might have its own role in the management of asthma [30–32]. In addition, we observed that PRI was not associated with airway eosinophilic inflammation of elderly asthmatics (figure E2). Taken together, we may assume that sufficient bronchodilator treatment is important for the effective management of asthmatics with high PRI. In CAMP, ~5% of asthmatic children randomised to the inhaled corticosteroid arm showed consistent bronchodilator responses over the 4-year trial and they had more hospital visits and required more prednisone bursts [33]. It is possible that maintenance treatments of bronchodilator were essential in certain cases. Namely, asthmatic children with a high PRI should have been managed with maintenance treatments of bronchodilator, including a combination therapy with inhaled corticosteroid and long-acting β_2 -agonist, to reduce acute exacerbations. Another possible explanation is that asthmatic children with a high PRI might feel better symptomatic improvement compared with those with a low PRI when they used a short-acting β_2 -agonist as a reliever medication. Actually, we found a positive correlation with a borderline significance ($p=0.043$) between $\ln(\text{PRI})$ and the use of salbutamol (a short-acting β_2 -agonist) during the first 8 weeks of follow-up in the CAMP childhood asthmatics (figure E3). As noted previously, an effective bronchodilation through a short-acting β_2 -agonist therapy might mask symptoms of deteriorating asthma and lead to asthma exacerbations [34].

The elderly asthma cohort were treated with a combination of inhaled corticosteroid and bronchodilator (a long-acting β_2 -agonist) as recommended by the current guidelines [18]. Despite a long-acting β_2 -agonist therapy, a subset of this cohort continued to have an elevated PRI with very high likelihood of subsequent exacerbations (OR 59.88 (95% CI, 4.65–1228.76)). We postulate that a maintenance treatment of long-acting β_2 -agonist was not sufficient for elderly asthmatics with a high PRI. AHR was persistently observed even in the absence of airway inflammation following long-term use of ICS [35], which suggested that other pathophysiological factors, such as increased cholinergic and smooth muscle tone, might have a role in asthma [36, 37]. In accordance, tiotropium, a long-acting anti-cholinergic, as add-on to inhaled corticosteroid plus long-acting β_2 -agonist, was found to be associated with a reduction in the number of asthma exacerbations [38, 39]. Therefore, it was possible that intensive bronchodilator treatments including long-acting β_2 -agonists and long-acting anti-cholinergic agents would be needed for elderly asthmatics with high PRI.

The present study has notable strengths and weaknesses. The clinical relevancy of PRI was demonstrated in two populations at the extremes of age, that is, childhood and elderly asthmatics. As pulmonary function testing is known to be affected by age [40, 41], there may be concerns as to the accuracy of pulmonary function measurement in these extreme groups. However, preschool children and the elderly were capable of performing spirometry under the supervision of well-trained technicians [41–43]. Thus, the data in the present study are of high quality. A prospective study design of two cohorts is one of the strengths of the present study. However, we did not confirm that PRI is an invariant characteristic after long-term asthma treatments. If PRI improved after long-term asthma treatments, the clinical relevance of PRI measured at baseline in predicting asthma exacerbations would decrease as shown by a rise in the baseline PC₂₀. In addition, an ethnicity difference needs to be considered in generalising our observations. Most subjects in the childhood cohort were Caucasian or African-American, but the elderly cohort was entirely Asian. A difference in ethnicity introduces both possible environmental and genetic variation and

potentially alters the therapeutic efficacy of bronchodilators [44]. Finally, statistical issues need to be considered. The data used in the present study were gathered for another purpose and thus multiple testing was prone to type I errors. Bonferroni correction (multiplied by four (four comparable dependent variables)) effaced the significance of $\ln(\text{PRI})$. In addition, it has been reported that logistic regression analysis in studies with a small sample size overestimated odds ratios [45]. The high odds ratio in elderly asthmatics should be reassessed in another cohort.

In conclusion, we demonstrated that PRI, an index of bronchodilator response following methacholine-induced bronchoconstriction, was a good clinical factor for predicting acute asthma exacerbations in both childhood and elderly asthmatics. An intensive bronchodilator treatment including a long-acting anti-cholinergic agent may be necessary for asthmatics with a high PRI.

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CAMP credit roster

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