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Perception of Bronchoconstriction: A Complementary Disease Marker in Children with Asthma

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Introduction. Asthma guidelines use symptoms as the most important aspect of asthma control. Symptom perception varies widely between individuals. Over-perception as well as underperception of bronchoconstriction could have a negative effect on asthma management. We hypothesized that perception of bronchoconstriction in childhood asthma is not related to common measures of disease control. For that reason, we examined the clinical determinants of the perception of bronchoconstriction and the repeatability of perception measurements. *Patients and methods.* In school-age children with moderately severe atopic asthma, we measured the perception of bronchoconstriction (decrease in forced expiratory volume in 1 second (FEV_1)) during methacholine bronchoprovocation challenges. The perception of bronchoconstriction was assessed as the slope of the relation between FEV_1 and Borg score, and as the Borg score at a 20% decrease in FEV_1 from baseline during the provocation test (PS_{20}). Data from subjects who had a 20% or more decrease in FEV_1 ($n = 112$) were used for the analysis. Fifty-four children repeated the test after 3 months. Symptoms, use of rescue medication, and peak expiratory flows were scored in diaries during the 2 weeks before testing. *Results***.** Symptom perception was significantly better in children without ($PD_{20} > 1570$ μg, $n = 28$) than in children with airway hyperresponsiveness ($PD_{20} \leq 1570$ μg, $n = 112$), slope 0.22 versus 0.13 respectively ($p < .001$). Borg scores correlated with PD_{20} ($p = .01$), baseline FEV_1 (only for slope, $p = .04$), and use of rescue beta agonist ($p = .01$), but not with other aspects of asthma control. Repeatability of Borg scores was good (slope: $R = 0.59$, PS_{20}: $R = 0.52$). *Conclusion.* Poorer symptom perception in asthmatic children correlated with hyperresponsiveness, and was associated with lower baseline FEV_1 and less use of rescue bronchodilators. This suggests that the measurement of symptom perception should be taken into account in individual management plans for children with asthma.

Keywords airway hyperresponsiveness, Borg score, childhood asthma, methacholine challenge test, symptom perception

INTRODUCTION

Perception of bronchoconstriction is an important factor in asthma management. According to the GINA guidelines, the treatment of childhood asthma should be based on the level of control, which is largely estimated from reported symptoms and objective lung function measures (1). Inadequate perception of bronchoconstriction might therefore lead to under- or overtreatment. It has been shown that diminished perception of bronchoconstriction is related to more severe asthma and fatal asthma attacks in adults and children (2–7). Asthma medication and the duration of asthma seem to influence the adequacy of perception in asthmatics (3, 8–10). Although several studies examined the risk factors for poor perception in adult asthma patients, only a few studies have been performed in children. Baker et al. studied the perception of airway obstruction in 35 children with asthma, and found poor perception in approximately half of the children. They found no correlation

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with baseline FEV_1 or airway hyperresponsiveness (AHR) (11). In contrast, Motomura showed that children with severe AHR had a lower perception of bronchoconstriction than children with mild AHR (12). Results of repeated measurements of perception during exercise testing showed poor repeatability (13). The Borg score was developed to assess the perception of dyspnea and can be used during a bronchial provocation test to assess the perception of bronchoconstriction in a standardized way (14). The aim of this study was to define the clinical parameters that are risk factors for the poor perception of bronchoconstriction in children with stable, moderately severe atopic asthma. In addition, we examined whether the measurement of perception was repeatable.

METHODS

Patients

The present study was performed within the CATO (Children Asthma Therapy Optimal) study, a multi-center, double-blind, parallel-group randomized 2-year intervention trial. Details of this study have been published (15). Briefly, 210 children (6–16 y) with moderate atopic asthma were included, selected on the basis of symptom scores and/or presence of AHR. The subjects were recruited from 15 pediatric clinics, including 7 university hospitals, in the Netherlands. Every 3 months, children kept a symptom score diary for two weeks and underwent lung function and methacholine challenge tests. Medication was adjusted according to algorithms based on symptom score or on AHR and symptom score. All the children used fluticasone (range 100–1000 μg/d) and $n = 73$ used salmeterol (100 μg/d).

Design

Borg scores were measured at the time when a substantial part of the subjects had already completed the CATO study. For that reason, a Borg score was measured in 140 children. One hundred and twelve did reach a PD_{20} methacholine, and the data of those children were used for analysis. Fifty-four children repeated the test 3 months later.

Perception was expressed as the slope of the relation between changes in FEV_1 and Borg scores, and as the Borg score at a 20% fall in forced expiratory volume in 1 sec (PS_{20}). All parents and children >12 years gave written informed consent. The study was approved by the medical ethics committees of all participating hospitals.

Diary Cards

Twice daily, the subjects filled in a diary card during the 2 weeks before a clinic visit. Symptoms of asthma (cough, shortness of breath, and wheezing) during night and day were recorded on a 4-point scale (0 (=no symptoms) to 3 (=severe symptoms interfering with activity or sleep) and the use of salbutamol inhalations for rescue therapy was recorded. Symptoms were scored as the percentage of days in 2 weeks with at least 1 symptom recorded. Use of rescue medication was expressed as the percentage of days out of 2 weeks with at least 1 dose of salbutamol. Triplicate measurements of peak expiratory flow (PEF) were performed in the morning and evening, before medication. Diurnal PEF-variability was defined as the mean value of 2 weeks calculated from the highest minus the lowest daily value, divided by the mean (16).

Lung Function and AHR

The study medication was withheld for 36 hours and short-acting β-agonists for 8 hours prior to lung function and methacholine challenge testing. FEV_1 and forced vital capacity (FVC) were measured using a heated pneumotachograph. Values are reported as percentage of predicted. AHR was tested by methacholine challenge using a dosimeter (17). Nebulized methacholine bromide was given in doubling concentrations (0.076 mg/Ml–78.5 mg/mL). Three minutes after each inhalation, FEV_1 was measured. The provocation dose causing a 20% fall in FEV_1 from baseline (PD_{20}) was calculated by linear interpolation of the last two points of the log dose–response curve where FEV_1 had fallen below 20% of the baseline value. At the end of the challenge test, 800 μg of salbutamol was administered to reverse bronchoconstriction and FEV_1 was measured again.

Assessment of Perception of Dyspnea

During the challenge test, the severity of dyspnea was assessed by a Borg scale (14). The Borg scale is a vertical list with labeled categories: 0 (no breathlessness at all)—10 (most extreme breathlessness ever experienced). After each dose step of methacholine, the children were asked: "How severe is your breathlessness during and directly after this inhalation?" For each child, an individual "Borg slope" (derived from Borg scores plotted against % fall in FEV_1 from baseline) and the Borg score at 20% fall in FEV_1 (PS_{20}) (Figure 1) were calculated. During the test, the patient was blinded to the lung function response.

Statistical Analysis

All variables with a non-Gaussian distribution (symptom score, PEF-variability, and PD_{20}) were lognormalized.

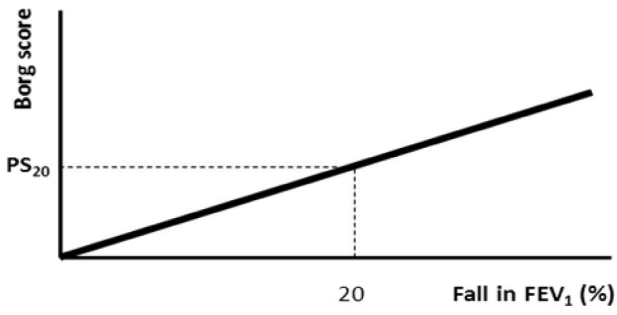

FIGURE 1.—Schematic representation of calculation of PS_{20}. The PS_{20} was found by linear interpolation of Borg scores (*vertical axis*) at the point where a 20% fall in FEV_1 during methacholine challenge was detected (*horizontal axis*).

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Data are given as medians (p10–p90). Borg slope was calculated for 28 subjects without AHR (PD_{20} > 1570 ug). Borg slope and PS_{20} were calculated for 112 subjects with a PD_{20} < 1570 μg. Borg slope was calculated by linear regression. PS_{20} was determined by interpolation of the last two perception scores, before and after the 20% fall in FEV_1. The relationship between Borg slopes and PS_{20} and asthma symptom scores, PEF-variability, usage of rescue medication, FEV_1 (%pred), PD_{20} methacholine, and age were calculated using Spearman's rank correlation coefficients. A two-sided *p*-value of <.05 was considered statistically significant.

RESULTS

We measured Borg scores in $n = 140$ children. Twenty-eight of them were not hyperresponsive (PD_{20} > 1570 μg). In these children, the median maximal fall in FEV_1 at bronchoprovocation testing was 14.6% (−17.7% to −3.6%). The median Borg slope was 0.22 (0.04–0.43). The baseline characteristics of all children with AHR are summarized in Table 1. At bronchoprovocation testing, the median maximal fall in FEV_1 from baseline was 23.0% (20.3–32.1). The median Borg score was 0 (0–2) before, and 4 (1–8) after methacholine challenge. After salbutamol, the median Borg score was 0.0 (0–2). The median Borg slope was 0.13 (0.04–0.26) and the median PS_{20} value was 3.5 (1.0–7.0). The age of the child, duration of asthma, the dose of inhaled corticosteroids, and the use of salmeterol did not correlate with the Borg slope or PS_{20}. Significant associations were present between baseline FEV_1 and Borg slope (Rs = 0.20, $p = .04$), between PD_{20} and Borg slope (Rs = 0.24, $p = .01$), and between PD_{20} and PS_{20} (Rs = 0.26, $p = .01$). A significant positive correlation existed between PS_{20} and the use of rescue salbutamol (Rs = 0.26, $p < .01$). No relation was found between the symptom severity or PEF-variability and Borg slope or PS_{20} (Table 2).

The correlation coefficients between Borg slope and PS_{20} was 0.82 ($p < .001$). There was good agreement between Borg slopes at the first and second occasion (R = 0.59, $p < .001$, $n = 54$) and PS_{20} (R = 0.52, $p < .001$, $n = 54$)(Figure 2).

TABLE 1.—Baseline characteristics of the study population.

Age (years)	11.8 [9.0–15.6]
Baseline FEV_1 (% predicted)	98 [79–116]
PD_{20} μg	154 [26–1022]
Symptom score (%)	20 [0–100]
Use of rescue medication (%)	0 [0–62]
PEF-variability (%)	4.7 [1.8–10.0]
Borg slope	0.13 [0.04–0.26]
PS_{20}	3.5 [1.0–7.0]

Notes: All data are median [10–90 percentile]. PD_{20}: provocative dose of methacholine causing a 20% fall in FEV_1 from baseline. Symptom score expressed as the percentage of days, out of 2 weeks, with at least one symptom recorded. Use of rescue medication expressed as the percentage of days, out of 2 weeks, with at least 1 dose of salbutamol. PEF-variability: highest PEF minus lowest PEF divided by the mean PEF. Borg slope: relation between change in FEV_1 (%) and Borg score. PS_{20}: Borg score at a 20% fall in FEV_1 from baseline.

TABLE 2.—Correlation of clinical markers of asthma control, lung function, and AHR versus Borg scores (slope and PS_{20}).

	Borg slope		PS_{20}	
	Rs	*p*	Rs	*p*
Diary card data				
Symptoms	−0.51	.60	0.11	.25
Salbutamol use	0.12	.20	**0.26**	**.01**
PEF-variability	0.00	.99	0.07	.18
Baseline FEV_1	**0.20**	**.04**	0.13	.18
PD_{20}	**0.24**	**.01**	**0.26**	**.01**

Notes: Data are Spearman rank correlation coefficients. Borg slope: relation between change in FEV_1 and Borg score. PS_{20}: Borg score at a 20% fall in FEV_1 from baseline. Symptom score: percentage of days, out of 2 weeks, with at least 1 symptom recorded. Use of rescue medication: the percentage of days, out of 2 weeks, with at least one dose of salbutamol. PEF-variability: highest PEF minus lowest PEF divided by the mean PEF. PD_{20}: provocative dose of methacholine causing a 20% fall in FEV_1 from baseline.

DISCUSSION

In this study, we examined symptom perception in relation to measures of asthma control in school-age children with moderately severe asthma. We aimed to identify risk factors for impaired symptom perception, as these could alert for undertreatment. Our results show that appropriate perception of bronchoconstriction is less likely in case of more severe AHR and lower baseline FEV_1, and we found a positive correlation between the perception and use of rescue medication. No relation was present between symptom scores and perception. Perception could be measured reproducibly.

Panditi et al. reported on the reproducibility of Borg ratings over time but this was only tested in a single population of asthmatic children during repeated exercise testing (13). The period between the consecutive tests in this study was 8 weeks. No significant correlation between the two Borg ratings over time was found. The authors of this study suggested that this could be due to the fact that confounders such as AHR were not analyzed. In our study, few factors appeared to be related to symptom perception, and these were AHR and baseline lung function. Conflicting data on the relation between AHR and perception have been reported in adults as well as in children with asthma. In a small group of 35 asthmatic children, poor perception was not associated with airway hyperreactivity (11). In contrast, in a large population of Japanese children, AHR was related to perception of bronchoconstriction, in agreement with our findings (12). The difference might be explained by sample size. Our finding suggests that children with more severe AHR would be at risk for undertreatment. This is in line with our previous finding that asthmatic children who have few symptoms in combination with more severe AHR are at risk for an unfavorable clinical course of their asthma, with more rapid decline in lung function compared to those who reported more symptoms (15). Also, low baseline lung function was correlated with lower symptom perception. In this line, Van Gent et al. recently reported that children with AHR without diagnosed asthma perceive induced bronchoconstriction less well than those with diagnosed asthma (18).

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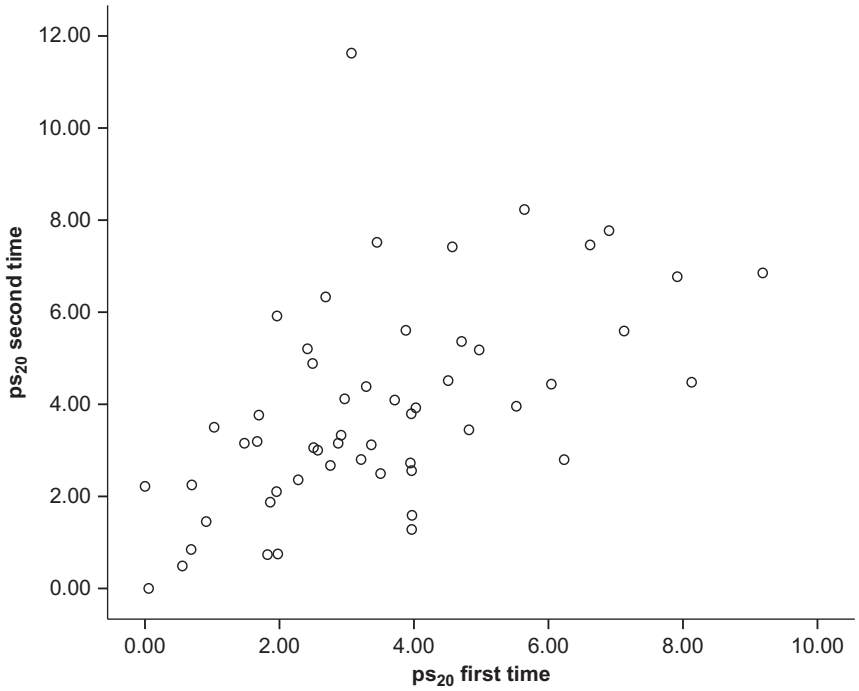

FIGURE 2.—Relation between Borg score at first and second occasion PS_{20}: Borg score at a 20% fall in FEV_1 from baseline.

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Concerning the relation between baseline lung function and AHR, conflicting data are reported in children as well as in adults (11, 19).

Interestingly, we found that low use of rescue medication was associated with lower symptom perception, in a dose-dependent manner. This supports earlier speculation that the underestimation of asthma symptoms predisposes to severe asthma attacks in adult asthmatics and children (3, 4, 6, 20).

We attempted to separate the sensitivity and dose–response characteristics of the Borg score. To that end, we analyzed the slope of the relation between FEV_1 and Borg score, and the scores at a given level of bronchoconstriction (PS_{20}). It appeared that both the ways of expressing symptom perception were closely correlated, so it seems analyzing one of the two would be sufficient. For ease of calculation, we would recommend the PS_{20}.

What are the clinical implications of our findings? Wide intersubject variability in the perception of changes of the airway diameter is reported in children and adults with asthma (11). Symptom perception is associated with functional morbidity, and poor perception with near-fatal asthma attacks (4–7, 21). In the present GINA guidelines, the level of asthma control does not involve a measure of symptom perception or hyperresponsiveness. We think that there is sufficient evidence that AHR is an important determinant of morbidity and future risk, and appears related to poor symptom perception (22). Hence, measurement of the perception of dyspnea provides potentially useful complementary information compared to common clinical disease markers. We propose that AHR should be assessed in settings where this is practically feasible to detect children at risk for more severe disease and undertreatment (15). Adding a Borg score to the routine protocol of such a bronchial challenge test could help to discover impaired symptom perception, and thereby allow improved asthma management.

In conclusion, we found that poor symptom perception in asthmatic children correlated with increased AHR, lower FEV_1, and was associated with less use of rescue bronchodilators. Perception was not related to other aspects of asthma control. This indicates that perception is a complementary disease marker in children with asthma. We propose that assessment of Borg scores could be a useful addition to routine bronchoprovocation testing in children.

DECLARATION OF INTEREST

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper. This study was initiated and designed by the investigators (CATO Study Group). GlaxoSmithKline donated study medication. Representatives of the company reviewed and commented on the protocol but made no other contributions to its design, conduct, interpretation, or presentation. The authors report no conflicts of interest.

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