Perception of respiratory symptoms after methacholine-induced bronchoconstriction in a general population

G. Devereux, D.J. Hendrick, S.C. Stenton


ABSTRACT: In an epidemiological study, methacholine-induced bronchoconstriction was used as a physical illustration of the sensations associated with asthma. The objective of this study was to assess whether familiarity with these sensations could be used as a measure of asthma prevalence.

Eight hundred and seventy six subjects aged 20–44 yrs completed a respiratory questionnaire and a measurement of airway responsiveness (the provocative dose of methacholine causing a 20% fall in forced expiratory volume in one second (PD20)). Subjects were asked about their perception of, familiarity with and description of the respiratory sensations experienced at the time of maximal bronchoconstriction.

The questionnaire-derived lifetime prevalences of wheeze, chest tightness and undue breathlessness were 43, 35 and 22% respectively. Asthma medication was used by 8% and the lifetime prevalence of diagnosed asthma was 12%. Quantifiable levels of airway responsiveness were measured in 34%, and airway responsiveness in the range considered to be consistent with untreated active asthma was present in 21%. Bronchoconstriction was perceived by 59%. Perception of bronchoconstriction was associated with the magnitude of bronchoconstriction, younger age, female sex and questionnaire-reported symptoms. Of subjects able to perceive bronchoconstriction, 58% reported previous experience of (familiarity with) the associated respiratory sensations. Familiarity with the sensations of bronchoconstriction was associated with questionnaire-reported symptoms, diagnosed asthma and increasing levels of airway responsiveness. There was poor agreement between the respiratory symptoms reported by questionnaire before the methacholine test and the words used to describe respiratory sensations induced by the test.

Familiarity with the sensations of methacholine-induced bronchoconstriction has all the appropriate associations of a measure of asthma prevalence and may be a useful adjunct to symptom questionnaires and airway responsiveness measurements in epidemiological studies. A sizeable number of subjects can be identified with intermediate levels of airway responsiveness, who are able to perceive bronchoconstriction and are familiar with the sensations associated with it, yet who are not recognized to suffer from asthma.


The identification of asthma in epidemiological studies is beset by a number of methodological problems [1, 2]. Respiratory symptom questionnaires are convenient to administer, but the data obtained are subjective and can be influenced by the presence of other cardiorespiratory disorders, the respondents' level of comprehension, memory, self image, concerns, smoking habit and psychological profile [3–6]. Records of an established clinical diagnosis of asthma depend on patients' willingness to report symptoms and physicians' interpretation of them, and can be influenced by sex, socioeconomic status and diagnostic fashion [7, 8]. Measurements of ventilatory function may not demonstrate airway obstruction, and when they do, they may not be able to distinguish an asthmatic cause from one attributable to other diseases [9, 10].

Measurements of airway responsiveness are objective and repeatable, and, within populations, correlate with other measures of asthma activity such as symptoms and use of medication [11–14]. However, high levels of airway responsiveness are not specific to asthma, and are found in other conditions associated with reduced ventilatory function. Furthermore, airway responsiveness measurements are unimodally distributed in the general population, and there is no clear level above which asthma can be said to be unequivocally present and below which it can be said to be absent [15, 16].

In a previous study of shipyard workers, it was noted that subjects with high levels of airway responsiveness did not report more respiratory symptoms on a questionnaire than those with low levels. However, when bronchoconstricted during a methacholine test, those with high levels of airway responsiveness were more likely to report previous experience of the associated sensations [17]. Airway responsiveness measurements, thus, appeared to be a better guide to previous experience of substantial bronchoconstriction (i.e. transitory decrements in forced expiratory volume in one second (FEV1) of at least 20%, signifying asthma), than the responses to the respiratory questionnaire.
From this study, it was postulated that using methacholine-induced bronchoconstriction as a physical illustration of an asthmatic reaction and recording subjects' familiarity with the associated sensations might be a useful adjunct in the identification of asthma in epidemiological settings, by aiding the interpretation of symptoms and airway-responsiveness measurements. The results of a further epidemiological study in which these techniques were used are now reported.

**Methods**

The study was part of an epidemiological investigation of respiratory symptoms and airway responsiveness in the north of England. The methodology and the primary results have been reported previously [18, 19]. In all, 608 males and 314 females, aged 20–44 yrs and randomly identified from respondents to a postal survey were studied. All participants gave written informed consent and the study was approved by the local Ethics Committees. All subjects answered an interviewer-administered questionnaire derived from that used in the study of shipyard workers and the European Respiratory Health Survey Questionnaire [17, 18]. Questions designed to identify asthma were:

1. Do you currently take medication for asthma?
2. Ever had asthma?
3. Have you ever had episodes of undue shortness of breath?
4. Have you ever had asthma?
5. Are you currently taking medication for asthma?

In total, 876 subjects underwent measurements of ventilatory function and airway responsiveness, which was quantified as the provocative dose of methacholine causing a 20% fall in FEV1 (PD20) using a locally developed dosimeter and protocol [20]. Following measurement of baseline FEV1, sequential cumulative doubling doses of methacholine were administered (dose range 3.125–6,400 µg) at five minute intervals until a >20% decrement in FEV1 from baseline was attained, or the maximum dose of 6,400 µg had been administered. The PD20 was quantified by linear interpolation from the dose-response plot. The ability to perceive bronchoconstriction was assessed at the end of the methacholine test, i.e. at a time when subjects were maximally bronchoconstricted, by asking: "Compared to before the methacholine test, does your chest now feel any different?" Subjects were asked 1) if they would describe any change in their respiratory sensations as "wheezing", "chest tightness" or "breathlessness", and 2) if they had ever experienced similar sensations previously, and, if so, under what circumstances?

Results were analysed using the STATA Release 3 statistical package (Computing Resource Center, Santa Monica, CA, USA). The majority of subjects with quantifiable levels of airway responsiveness (PD20 <6,400 µg) had similar falls in FEV1 in the range 20–25% from baseline, whereas those with unquantifiable levels (PD20 >6,400 µg) had FEV1 falls which were of smaller magnitude and distributed over a wider range (0–19.9%). The two groups were, therefore, examined separately. However, because several variables and associations were common to both groups, the results presented here are those of the two combined groups, with any differences highlighted.

**Results**

Basic anthropometric, clinical and airway responsiveness data are detailed in table 1. The mean±SD age of the 876 subjects was 34±7 yrs and 67% were males. The lifetime prevalence of wheeze reported on the questionnaire as chest tightness 35% and undue breathlessness 22%. The lifetime prevalence of diagnosed asthma was 12%, and 8% of subjects were currently using asthma medication. Quantifiable levels of airway responsiveness (PD20 <6,400 µg) were measured in 34%, and airway responsiveness in the range considered to be consistent with untreated active asthma (PD20 >1,000 µg) was present in 21% [21]. Symptoms, previous diagnosis of asthma and use of medication were all strongly associated with the level of airway responsiveness, as shown in figure 1.

A total of 818 (93%) subjects were asked if they perceived any difference in their respiratory sensations at the end of the methacholine test and of these, 59% (485) perceived some change. The question was inadvertently omitted for 58 subjects. The probability of perceiving bronchoconstriction was directly related to its magnitude, increasing by 13% for every 5% decrement in FEV1, as shown in figure 2 and table 2. In subjects with quantifiable levels of airway responsiveness (PD20 <6,400 µg and FEV1 decrement <20%) this association was highly significant (p<0.001). In those subjects with quantifiable levels of airway responsiveness (PD20 <6,400 µg) the association was not significant because of smaller numbers and because all these subjects had a FEV1 decrement ≥20%, a degree of bronchoconstriction which was perceived by almost everyone. Younger subjects and females were more

**Table 1.** Age, sex, symptom profile and presence or absence of diagnosed treated asthma for all subjects, and by level of airway responsiveness (as assessed by provocative dose of methacholine causing a 20% fall in forced expiratory volume in one second (PD20)).

<table>
<thead>
<tr>
<th>Group</th>
<th>Mean age yrs (95% CI)</th>
<th>PD20 &lt;1000 µg n=183 (20.8)</th>
<th>PD20 1000–64000 µg n=116 (13.2)</th>
<th>PD20 &gt;6400 µg n=577 (65.9)</th>
<th>All subjects n=876</th>
</tr>
</thead>
<tbody>
<tr>
<td>Males</td>
<td>32.8 (31.7–33.8)</td>
<td>33.4 (32.0–34.8)</td>
<td>33.8 (33.3–34.4)</td>
<td>33.6 (33.1–34.0)</td>
<td></td>
</tr>
<tr>
<td>Ever wheezed</td>
<td>97 (53.0)</td>
<td>67 (57.8)</td>
<td>423 (73.3)</td>
<td>587 (67.0)</td>
<td></td>
</tr>
<tr>
<td>Ever had chest tightness</td>
<td>140 (76.5)</td>
<td>57 (49.1)</td>
<td>182 (31.7)</td>
<td>379 (43)</td>
<td></td>
</tr>
<tr>
<td>Ever had asthma</td>
<td>109 (59.6)</td>
<td>50 (43.1)</td>
<td>146 (25.6)</td>
<td>305 (35.1)</td>
<td></td>
</tr>
<tr>
<td>Ever unduly short of breath</td>
<td>79 (43.2)</td>
<td>37 (31.9)</td>
<td>74 (12.9)</td>
<td>190 (21.7)</td>
<td></td>
</tr>
<tr>
<td>At least one symptom</td>
<td>150 (82.0)</td>
<td>75 (64.7)</td>
<td>259 (44.9)</td>
<td>484 (55.3)</td>
<td></td>
</tr>
<tr>
<td>Current using asthma med.</td>
<td>73 (39.9)</td>
<td>14 (12.1)</td>
<td>20 (3.5)</td>
<td>107 (12.2)</td>
<td></td>
</tr>
</tbody>
</table>

Percentages are shown in parenthesis. CI: confidence interval.
likely to perceive bronchoconstriction. Symptomatic subjects were more likely to perceive bronchoconstriction, but this association was only significant in subjects with unquantifiable levels of airway responsiveness (PD20 > 6,400 µg), probably because of the high (75%) overall prevalence of symptoms amongst those with quantifiable levels of airway responsiveness (PD20 = 6,400 µg), as shown in tables 1 and 2. There were no further independent significant associations with diagnosed asthma, use of medication or baseline ventilatory function.

Of the 485 subjects who were able to perceive bronchoconstriction, 280 (58%) reported that they had experienced a similar sensation in the past. This familiarity with bronchoconstriction was independently associated with the reporting of respiratory symptoms on the questionnaire, a diagnosis of asthma and level of airway responsiveness, as shown in figure 3 and table 3. Familiarity with bronchoconstriction was not associated with the magnitude of induced bronchoconstriction, age, sex or baseline FEV1 expressed either as an absolute value or as the percentage of the predicted value.

Subjects with a current or previous diagnosis of asthma were more likely to experience a 20% decrease in FEV1 and to be familiar with the associated sensations than subjects who had never had a diagnosis of asthma: 79% (79/100) versus 10% (71/718). There were 110 subjects with quantifiable levels of airway responsiveness (PD20 > 6,400 µg) who had never had a diagnosis of asthma, but who had the potential to attract such a diagnosis because they reported familiarity with the sensations of bronchoconstriction. When asked about similar previous episodes, 65 (59%) had experienced the sensations associated with substantial bronchoconstriction in the previous year and 35 (32%) had experienced such sensations on five or more occasions in the previous year.

Amongst those reporting familiarity with bronchoconstriction, the sensations associated with induced bronchoconstriction were described as "wheezing" in 62% of subjects, "chest tightness" in 89% and "breathlessness" in 56%. Two or more symptoms were reported by 72%. Subjects who perceived the sensations but denied previous experience of them used fewer descriptive terms (p<0.001), with 37% describing them as "wheezing", 35% as "breathlessness" and 83% as "chest tightness" and 44% reporting two or more symptoms.

There was surprisingly little agreement between the symptoms reported by the questionnaire and the symptoms used to describe the sensations associated with induced

Table 2. – Logistic regression analysis relating the probability of perceiving bronchoconstriction to the percentage of bronchoconstriction induced, age, sex and number of positive symptoms reported by questionnaire

<table>
<thead>
<tr>
<th></th>
<th>Odds ratio</th>
<th>95% CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Induced bronchoconstriction</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>% of baseline FEV1</td>
<td>1.13</td>
<td>1.11–1.16</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Age  yr⁻¹</td>
<td>0.97</td>
<td>0.94–0.99</td>
<td>0.01</td>
</tr>
<tr>
<td>Sex (females vs males)</td>
<td>1.73</td>
<td>1.18–2.55</td>
<td>0.005</td>
</tr>
<tr>
<td>One vs no symptoms</td>
<td>1.56</td>
<td>1.03–2.37</td>
<td>0.04</td>
</tr>
<tr>
<td>Two vs no symptoms</td>
<td>2.84</td>
<td>1.65–4.89</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Three vs no symptoms</td>
<td>3.09</td>
<td>1.65–5.78</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>
| Symptoms: "Ever wheezed", "ever had chest tightness" and "ever unduly short of breath". CI: confidence interval.

Subjects with a current or previous diagnosis of asthma were more likely to experience a 20% decrease in FEV1 and to be familiar with the associated sensations than subjects who had never had a diagnosis of asthma: 79% (79/100) versus 10% (71/718). There were 110 subjects with quantifiable levels of airway responsiveness (PD20 > 6,400 µg) who had never had a diagnosis of asthma, but who had the potential to attract such a diagnosis because they reported familiarity with the sensations of bronchoconstriction. When asked about similar previous episodes, 65 (59%) had experienced the sensations associated with substantial bronchoconstriction in the previous year and 35 (32%) had experienced such sensations on five or more occasions in the previous year.

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There was surprisingly little agreement between the symptoms reported by the questionnaire and the symptoms used to describe the sensations associated with induced
In this study, the ability to perceive bronchoconstriction was clearly related to its magnitude, with 71% of subjects experiencing a $10\%$ decrement in FEV1 being able to perceive it. This proportion is similar to that found by Brand et al. [25] who showed that 76% of their population were aware of a $10\%$ histamine-provoked decrement in FEV1. Bronchoconstriction beyond $20\%$ did not increase the proportion of subjects recognizing the sensation, suggesting that a small number of subjects have very poor perception. The ability to perceive bronchoconstriction was associated with the reporting of respiratory symptoms on the questionnaire, even amongst individuals with low levels of airway responsiveness, who experienced only small decrements in FEV1. This highlights the importance of individual variability in the awareness of respiratory sensations as an independent determinant of the recognition and reporting of respiratory illness. It also represents the corollary to the identification by Brand et al. [25] of a group of hyperresponsive subjects who were unable to identify bronchoconstriction, and who reported no asthmatic symptoms.

Females were more aware of a given degree of bronchoconstriction than males. Population studies suggest that after adjustment for baseline FEV1, there is no sex difference in the distribution of airway responsiveness. There is, however, a female predominance in the diagnosis of adult asthma. This has been attributed to diagnostic bias [26], but our data suggest that it might be a manifestation of a greater ability of females to perceive bronchoconstriction. Sex differences in the perception of respiratory sensations might also explain other phenomena such as the female predominance in reporting respiratory side-effects of angiotensin-converting enzyme-inhibitors in asthma. This has been attributed to diagnostic bias, but our data suggest that it might be a manifestation of a greater ability of females to perceive bronchoconstriction.

Just over half of those who were able to perceive bronchoconstriction were familiar with the associated sensations. Unlike the ability to perceive bronchoconstriction, the subjects’ familiarity with the sensations was independent of the magnitude of the bronchoconstriction induced. It was associated with the presence of respiratory symptoms on the questionnaire, a diagnosis of asthma and the degree of airway responsiveness, and these associations support its validity as a measure of asthma in epidemiological studies. It is clear, however, that a greater proportion of the population are familiar with bronchoconstriction than have clinically apparent asthma. Physiologically, asthma is quantitatively rather than qualitatively different from normality and so conventionally "nonasthmatic" subjects probably do experience significant degrees of bronchoconstriction from time to time in response to potent environmental stimuli [28]. Awareness of this bronchoconstriction is likely to explain, at least partly, the high prevalence of asthmatic symptoms reported in most epidemiological studies of young adults [4, 18, 29].

At high levels of airway responsiveness, i.e. PD20 $\geq$ 200 $\mu$g using our techniques, the majority of subjects perceive and recognize their marked bronchoconstriction, report their symptoms and receive a diagnosis of asthma. At intermediate levels of airway responsiveness, i.e. within the PD20 range 200–1,000 $\mu$g, only about 20% of subjects have a diagnosis of asthma. These subjects are no different from those without asthma in terms of airway physiology or their ability to perceive bronchoconstriction, with the majority of both diagnosed asthmatics (95%) and

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**Table 3.** Logistic regression analysis relating the probability of subject familiarity with the sensations of bronchoconstriction to questionnaire-reported symptoms, diagnosed asthma and the provocative dose of methacholine causing a 20% fall in forced expiratory volume in one second (PD20), in subjects perceiving bronchoconstriction.

<table>
<thead>
<tr>
<th>Odds ratio</th>
<th>95% CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>One vs no symptoms</td>
<td>4.61</td>
<td>2.69–7.91</td>
</tr>
<tr>
<td>Two vs no symptoms</td>
<td>16.3</td>
<td>8.28–32.1</td>
</tr>
<tr>
<td>Three vs no symptoms</td>
<td>39.6</td>
<td>12.9–121.4</td>
</tr>
<tr>
<td>Ever diagnosed asthmatic</td>
<td>7.24</td>
<td>1.55–33.8</td>
</tr>
<tr>
<td>PD20 $\geq$ 6400 $\mu$g vs $&lt;$ 6400 $\mu$g</td>
<td>2.20</td>
<td>1.37–3.54</td>
</tr>
</tbody>
</table>

Symptoms: "Ever wheezed", "ever had chest tightness" and "ever unduly short of breath". CI: confidence interval.
bronchial responsiveness (70%) reporting familiarity with bronchoconstriction. This suggests that willingness to report symptoms to a physician and willingness on the part of the physician to establish a diagnosis are important determinants of the probability of an individual being diagnosed as asthmatic. Numerical considerations suggest that subjects with intermediate levels of airway responsiveness are a potentially important group. The lifetime prevalence of diagnosed asthma in our study was 12%, but a further 7% had levels of airway responsiveness consistent with asthma and had previous experience of substantial bronchoconstriction, and so had the potential to attract a diagnosis of asthma. If changes in awareness and diagnostic criteria affect these subjects, then there is the potential for the apparent prevalence of asthma to increase by nearly 60%.

The language used to describe asthma is particularly important for epidemiological studies using symptom questionnaires. It is assumed that the responses to questionnaires reflect subjects' experience of bronchoconstriction. This is not necessarily so as the reporting of symptoms depends on psychological profiles [6], the setting in which the study takes place [21], respiratory diseases other than asthma, and probably, other factors. There was discordance between the terminology used to describe bronchoconstriction on the questionnaire and after the inhalation of methacholine in 27% of our study population. Questionnaire responses, therefore, do not necessarily give an accurate picture of the asthmatic sensations experienced by a group of subjects.

This study has demonstrated that recognition of induced bronchoconstriction has all the appropriate associations expected of a measure of asthma prevalence. In studies incorporating measurement of airway responsiveness, the perception of, and familiarity with, induced bronchoconstriction is simple to ascertain. Recording familiarity with bronchoconstriction may aid the interpretation of symptom questionnaires and airway responsiveness measurements and give a closer insight into the true prevalence of bronchoconstriction and asthma.

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3. Anderson HR, Bland JM, Peckham CS. Risk factors for asthma up to 16 years of age. Chest 1987; 91: 127S–130S.