Hypertonic saline challenge in an adult epidemiological survey

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Bronchial provocation tests using pharmacological agents such as methacholine or histamine are used in epidemiological studies to identify asthma despite recognition of limitations in specificity, positive predictive value and availability of reagents. Hypertonic saline (4.5%) bronchial challenge (HSBC), although less sensitive than pharmacological challenges, is reportedly highly specific in diagnosing current asthma. Added advantages are that reagents are cheap, stable and recognized by participants. Thus, HSBC may offer benefits over pharmacological tests in epidemiological surveys. This paper reports on the second field survey using the test, a study of 99 adults from the timber industry in Western Australia. The test is described and critically appraised as a practical epidemiological tool for assessing asthma prevalence. At a cutoff point of 20% FEV₁ fall, HSBC was positive in 8% of subjects, appeared specific for asthma, was safe, well-accepted and easy to use in the field.

Key words: Asthma; bronchial provocation tests; sputum; epidemiological methods.

INTRODUCTION

A diagnosis of asthma in occupational settings has often been made on the basis of clinical examination by a medical practitioner, questionnaire surveys and spirometry. This approach does not give an index of the underlying physiological abnormalities of asthma, i.e. airway hyperresponsiveness, and for this reason is inaccurate.¹ To overcome this problem The European Respiratory Society recommends the combination of airway hyperresponsiveness and recent wheezing (in the last year) as a definition of asthma for epidemiology.²

The most commonly used tests in the field have been inhalation of aerosols of methacholine and histamine. These pharmacological agents act directly on smooth muscle to cause contraction, and consequently are known as direct challenges. They are excellent tests for identifying airway hyperresponsiveness but their role in identifying current asthma in the random population has been questioned.³ The reason relates to the specificity of the challenge to identify current asthma and the subsequent high proportion of false positive results. For example, Enarson et al.³ found a sensitivity of 47%, specificity of 85% and positive predictive value of only 12% for methacholine challenge in identifying questionnaire-diagnosed asthma. They used a cutoff of PC_{20} (provocative concentration causing a 20% drop in FEV₁) of 8 mg/ml to identify subjects who had ever had asthma amongst a group of workers employed mainly in timber and grain industries. Similarly, using the same PC_{20} cutoff value, Cockcroft et al.⁴ recently reported a specificity of 93%, sensitivity of 100% and a positive predictive value of 29% for histamine in identifying current asthma in a random group of 500 college students.

There are other bronchial provocation tests that are thought to be more specific for asthma than direct challenges. These include cold air, exercise, distilled water and hyperosmolar saline. These tests are known as 'indirect challenges' and cause the airways to narrow by the endogenous release of mediators.⁵⁶⁷ Thus, both
cellular and neural pathways involved in the asthmatic response are tested with indirect challenges. It is for this reason they are considered to be more specific for asthma, while less sensitive for detecting bronchial hyperresponsiveness. Hypertonic saline bronchial challenge (HSBC) has an advantage over exercise testing in that it produces a dose-response curve while also identifying persons responsive to exercise and hyperventilation. Challenge with 4.5% NaCl is well established in hospital-based laboratories and recently the challenge has been used successfully in an epidemiological study of asthma in school children.

In the industrial setting, challenge with hyperosmolar saline appears to have some advantages over challenge with pharmacological agents. The equipment required for the test is easily obtained, sodium chloride BP is cheap, readily available for use in humans and the test is well tolerated. Salt is an easily recognized substance and not one perceived to be harmful, so higher rates of participation in the test might be expected. In laboratory-based populations the sensitivity of the challenge has been shown to be about 80% and the specificity 100%, using a cutoff point of ≥ 20% FEV1 fall for a positive test. In an epidemiological survey of school-children, using a cutoff point of ≥ 15% FEV1 fall, sensitivity and specificity of the test in identifying 'current wheeze' were 47% and 92% respectively, and the positive predictive value was 81%.

No serious adverse events have been reported using HSBC either in the laboratory or in the field. Cough is the only commonly reported side-effect. The maximum airway response occurs usually within 1–2 minutes following the last exposure to the aerosol and late reactions are very uncommon.

Because there are no reports of the use of HSBC in industrial surveys, and because of the potential advantages of the test, it was decided to investigate its use and acceptability in an industrial setting, on employees from work sites in the timber and particleboard industries of Western Australia. This paper addresses the practical aspects of using HSBC to detect airway hyperresponsiveness and assesses its use in epidemiological surveys.

**MATERIALS AND METHODS**

The study was a cross-sectional survey of 99 employees in six worksites of two timber industry companies in Western Australia. It included completion of a questionnaire, height measurement, baseline spirometry and the 4.5% saline bronchial challenge.

**Materials**

The materials necessary for performing the 4.5% saline bronchial challenge test, complying with the protocol of Smith and Anderson and the European Respiratory Society, are presented in Table 1.

**Questionnaire**

Self-administered questionnaire.

The questionnaire included questions on age, gender, medical conditions requiring intervention over a recent time period, respiratory symptoms, and smoking habits. Seven questions were taken from the International Union Against Tuberculosis and Lung Disease Questionnaire (IUAT Bronchial Symptoms Questionnaire, 1986), and most of these questions (except those on cough) have been shown to be associated with bronchial hyperresponsiveness to histamine. A series of questions designed to determine disease prevalence by asking the reasons for seeking interventions for recent health complaints were taken from the 1989–90 National Health Survey.

**Table 1. Equipment used for HSBC**

<table>
<thead>
<tr>
<th>Equipment required</th>
<th>Equipment used</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ultrasonic nebulisers</td>
<td>DeVilbiss 900 and DeVilbiss 2000. (De Vilbiss Health Care Inc, Somerset, PA, USA)</td>
</tr>
<tr>
<td>Large bore, non-rebreathing expiratory valves</td>
<td>Hans Rudolph 2700B with saliva trap (Kansas City Mo. USA)</td>
</tr>
<tr>
<td>35mm mouthpieces for the Hans Rudolph Valve</td>
<td>Vacumed (Ventura, CA, USA) part number 1001</td>
</tr>
<tr>
<td>Spirometers and mouthpieces</td>
<td>Vitalograph Alpha electronic, Vitalograph model S bellows. (Vitalograph Ltd, Buckingham, UK)</td>
</tr>
<tr>
<td>Spirometer calibrating syringe</td>
<td>Vitalograph 1 litre syringe (Cat 20.408)</td>
</tr>
<tr>
<td>Electronic balance, to 0.1g, max capacity &gt; 1kg</td>
<td>Sartorius PT1200 (Sartorius GmbH Goettingen Germany)</td>
</tr>
<tr>
<td>4.5% Sodium chloride solution</td>
<td>Sodium chloride BP, distilled water, beakers for weighing, 1 litre containers for storage</td>
</tr>
<tr>
<td>Bronchodilator</td>
<td>Salbutamol respirator solution 5mg/2.5ml, inhalers 100g/dose</td>
</tr>
<tr>
<td>Resuscitation equipment, including broncho- dilators, corticosteroids, oxygen supply with attachments for artificial respiration</td>
<td>Oxy-viva (CIGWELD, Melbourne, Australia) dexamethasone 8mg/ml injection, adrenaline 1mg/ml injection, 25 gauge hypodermic needles, 2 and 5ml syringes</td>
</tr>
<tr>
<td>Miscellaneous: electronic stopwatch, noseclips, hand calculator, towels and tissues†</td>
<td></td>
</tr>
</tbody>
</table>

* Two sets of equipment were used in the survey.
† Towels and tissues are important because the test provokes salivation.

Table 1. Equipment used for HSBC
Health Survey conducted by the Australian Bureau of Statistics.13

Administered questionnaire. In order to determine subject acceptance of the 4.5% saline bronchial challenge, participants were asked to record their reactions following the test in one of four categories. The categories were: (1) very uncomfortable (never again); (2) uncomfortable (not again unless I have to); (3) mildly uncomfortable (minor inconvenience to have it again) and (4) no problems.

METHODS

Selection and characteristics of participants

Eligibility for entry to the study was confined to employees from six worksites of two timber companies in Western Australia. Recruitment involved announcement of a 'health survey' by both management and employee-representative groups, a video demonstration of study procedures and distribution of a one-page information leaflet. On the back of this leaflet, recipients were asked whether they wished to participate in the study, and if they did, whether by completing a questionnaire only, or by full participation. From the list of volunteers, a sample from each worksite was chosen to participate in the study. The number of subjects in each sample depended on the rate of volunteering in the four small worksites (where all volunteers were included) or on the time constraints of the investigative team at the larger worksites (where random sampling of volunteers due at work occurred). The sample of 99 consisted of eight subjects from a chemical factory making formaldehyde-urea and melamine-urea for particleboard production, 11 from a pine sawmill, 35 from the main particleboard producing plant, 11 from a hardwood timber mill/processing centre, seven (no females) from a hardwood mill and 26 from a hardwood processing centre. There were six females. Mean age was 38 years (range 19–61). Ninety were employed as labourers, drivers of machinery or as plant operators. Nine were employed as tradesmen, para professionals and managers. Twenty-seven smoked, 32 were ex-smokers and 39 had never smoked.

Hyperosmolar 4.5% saline bronchial challenge

Current use and timing of medications were ascertained, with particular attention to asthma medications. Height was measured. The HSBC was performed using the techniques of Smith and Anderson9,12 which have been adopted by the European Respiratory Society.2 Exposures were for 0.5, 1, 2, 4 and 8 minutes. After each exposure the participant performed FEV1 on two occasions and the best was recorded. The procedure was stopped if FEV1 fell below 80% of baseline, if the subject requested cessation or after a total of 15.5 minutes exposure. Participants were observed for 20 minutes following the test. Those who recorded falls in FEV1 greater than 15% were administered inhaled bronchodilator (salbutamol 5mg) via nebuliser or 200μg via inhaler and observed until FEV1 improved to within 10% of baseline value. In the case of non-response to bronchodilator, further measures were taken at the discretion of the medical practitioner (see below). The test was deemed positive if the final FEV1 (following the 8 minute exposure or following cessation of the test) was 15% below baseline. This protocol differed from that of the European Respiratory Society in the following respects: medications were not requested to be withheld before the test, the test was not stopped after 15ml had been nebulised (although subjects who received <15ml and who did not have a fall in FEV1 > 15% were excluded from analysis), FEV1 measurements were performed 30–90 seconds following each exposure and bronchodilator was not given routinely at the completion of the test.

Data analysis

Statistical Analysis Software (SAS Institute Inc, Cary, NC, USA) was used. Falls in FEV1 > 15% and 20% of baseline recordings were determined and allocated to dichotomous variables, 'asth15' and 'asth20'. Cohen's kappa statistic15 was chosen as a measure of agreement between dichotomous responses to respiratory symptom questions and these variables. The statistic is the observed proportion of responses in agreement adjusted for expected chance agreement, and ranges from -1 to +1.18 Dose-response graphs were constructed for all subjects who were 'asth15' positive, and PD15 FEV1 values (the provoking dose of 4.5% saline required to cause a 15% FEV1 reduction) calculated by linear interpolation from these graphs. In addition to analyzing PD15, all data was analyzed using log dose-response ratios, calculated as log10 (per cent fall in FEV1 divided by total dose of 4.5% saline delivered in ml). In order to investigate relationships between a positive HSBC test and respiratory questionnaire responses, multiple logistic regression analysis (Proc Logistic—SAS) was performed using 'asth15' as the dependent variable and dichotomous responses to IUAT questions 1, 3, 7 and 11 (see Table 2) and the chronic bronchitis question 'have you brought up phlegm from your chest on most mornings for at least 3 months each year for the last 2 years?' A stepwise backward elimination procedure was used which eliminated the least significant variable and stopped when the residual χ² became significant at the 5% level. Gender and age were independent variables in a separate analysis with 'asth15' as the dependent variable. Multiple linear regression (Proc GLM—SAS) was used to analyze the same relationships for 'FEV1fall', the per cent fall in FEV1 from baseline value following the HSBC.
Table 2. Agreement between IUAT questions and 4.5% hyperosmolar bronchial challenge at 15% FEV₁ fall cutoff. Numbers in parentheses are results at 20% cutoff.

<table>
<thead>
<tr>
<th>Question</th>
<th>IUAT number</th>
<th>Positive HSBC</th>
<th>Kappa</th>
</tr>
</thead>
<tbody>
<tr>
<td>Have you ever had wheezing or whistling in your chest at any time in the last 12 months?</td>
<td>1</td>
<td>Yes</td>
<td>7 (5)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Have you at any time in the last 12 months had attacks of shortness of breath that come on during the day when you are not doing anything strenuous?</td>
<td>3</td>
<td>Yes</td>
<td>3 (3)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Have you, at any time in the last 12 months, been woken at night by an attack of coughing?</td>
<td>6</td>
<td>Yes</td>
<td>7 (2)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Do you usually cough first thing in the morning?</td>
<td>7</td>
<td>Yes</td>
<td>4 (1)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Do you usually bring up phlegm from your chest first thing in the morning?</td>
<td>8</td>
<td>Yes</td>
<td>3 (1)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Have you ever had an attack of asthma?</td>
<td>11</td>
<td>Yes</td>
<td>4 (4)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Have you had an attack of asthma at any time in the last 12 months?</td>
<td>12</td>
<td>Yes</td>
<td>4 (4)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Have you brought up phlegm from your chest on most mornings for at least 3 months each year for the last 2 years?</td>
<td>13</td>
<td>Yes</td>
<td>3 (1)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>National Health Survey asthma estimate</td>
<td></td>
<td>Yes</td>
<td>5 (5)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Have you feel you have problems with your breathing?</td>
<td></td>
<td>Yes</td>
<td>4 (3)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Have you at any time in the last 12 months felt chest tightness when you were not doing anything strenuous?</td>
<td>14</td>
<td>Yes</td>
<td>4 (3)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>No</td>
<td>No</td>
</tr>
</tbody>
</table>

* The IUAT number refers to the position of the question in the IUAT Bronchial Symptoms Questionnaire 1986.
† Positive 4.5% hypertonic Saline Challenge test is defined as > 15% reduction (or, in parentheses, > 20% reduction) in baseline FEV₁ during or following the test.
‡ Cohen’s Kappa Statistic (range -1 to +1) is a measure of agreement between question responses and saline challenge responses.

RESULTS

Rate of volunteering

Records are complete for only one of the two companies in the study. At this company, 107 employees were approached by receiving an information leaflet. Seventy agreed to full participation in the study, 12 wanted to answer the questionnaire only and 25 did not want to be involved.

4.5% hyperosmolar saline bronchial challenge

Ten subjects who underwent testing were excluded from analysis. Of these, six were excluded because nebuliser output was 1 ml/minute, and they had not developed a fall in FEV₁ at this lower output of saline and subsequent smaller saline dose. Two were excluded because of incomplete data on nebuliser output. One subject with previous asthma had inhaled salbutamol 5 minutes before the test and another could not use the spirometer in a reproducible way.

The results of per cent FEV₁ changes from baseline readings are plotted against the total dose of 4.5% saline delivered during the test for the 89 subjects in Figure 1. Fifteen subjects had a positive test when defined as FEV₁ fall greater than 15% of baseline, and...
seven at a fall of greater than 20%. The individual log
dose-response curves for the 15 subjects are presented
in Figure 2. The prevalence of positive tests was 16.9%
(95% CI 12.9–20.9). Ten of the fifteen had baseline
FEV₁ values > 80% predicted (mean 102.1%, SD
14.7%). The remaining five had mean FEV₁ 71.2%
(STD 6.6%) of predicted value. The median PD₁₅ FEV₁
value (dose of saline administered which caused a 15%
fall in FEV₁) was 15.64ml with a range of 0.32–28.78.
Nine of the fifteen had PD₁₅ values > 6.1ml and would
be considered mildly responsive. The other six had
moderately severe responses. The per cent fall of
FEV₁ from baseline at the end of the 4.5% saline
appeared mildly positively skewed with a mean fall of
6.8% (SD = 9.6) and median of 4.3% (range -10.5–
45.8).

‘Borderline’ responses (see Figure 1) were defined
as those who did not have a 15% fall in FEV₁ but who
had a dose response ratio (DRR = % FEV₁ fall/total
saline dose) in the same range as those with the 15%
fall. Higher DRR values indicate greater bronchial
hyperresponsiveness. Eight subjects with a fall in FEV₁
ranging from 9.15%–13.95% had log DRR values in
the range -0.3–0, and eight subjects with a fall in FEV₁
>15% also fell in that range. The distribution of log
dose response ratios is presented in Figure 3.

The present study did not inquire about former
wheeze, but found that the 95th percentile for per cent
fall in FEV₁ subjects who answered no to IUAT ques-
tion 1 about ‘current wheeze’ (“Have you ever had
wheezing or whistling in your chest at any time in the
last 12 months?”) was 16.9% and the 90th percentile
16.1%.

Figure 4 shows the effect on sensitivity, specificity
and positive predictive value of the test in diagnosing
'current wheeze' when the definition of a positive test is changed from an FEV₁ fall of 15% to other values. If 15% fall is the cutoff point, specificity was 0.88 (95% CI 0.79-0.96) sensitivity 0.28 (95% CI 0.10-0.46) and positive predictive value 47%. With 20% as the cutoff, prevalence was 7/89 (7.9%), specificity was 0.97 (95% CI 0.93-1.00), sensitivity 20% (95% CI 4.3-35.7) and positive predictive value 71%. Figure 5 stratifies subjects into classes indicating how much their FEV₁ fell and shows the proportion of respondents who reported 'current wheeze' in each class.

Comparison between self-administered question responses and hyperosmolar bronchial challenge responses

These comparisons, presented in Table 2, show that the question most in agreement with a positive hyperosmolar bronchial challenge is the question 'have you had an attack of asthma at any time in the last 12 months?' which is question 12 in the IUAT Bronchial Symptoms Questionnaire (1986). 'Have you ever had an attack of asthma?' and the National Health Survey questions asking about recent requirements for medical advice, treatment or medications were close behind. Other questions agreed poorly with the test.

The logistic regression analyses showed that only one of the four questions analyzed significantly predicted a positive HSBC at the 5% level. That question was 'have you ever had an attack of asthma?' (χ² = 7.15, 1 df, p = 0.0075). The same question was the only significant predictor of percentage FEV₁ fall following HSBC (f = 10.713, 85 at, p = 0.0015). Subjects who responded positively to the question had a mean percentage fall in FEV₁ of 17.6%, and those who did not had a mean percentage FEV₁ fall of 5.8%. Neither age nor gender were related to HSBC outcomes at less than p = 0.5.

Test safety and adverse reactions

Only one subject who recorded a fall in FEV₁ > 15% did not respond promptly (within 20 minutes) and adequately (to within 10% of baseline) to inhaled bronchodilator. He was Caucasian, lean, aged 47 and had smoked 20 unfiltered cigarettes per day since his late teens. He gave negative responses to questions from the questionnaire related to cough, shortness of breath, chest whistling and wheezing, chest tightness, asthma and the taking of medications. His baseline FEV₁ and FVC were 2.71 litres (predicted = 3.50) and 4.27 litres respectively. Following administration of 4.5% saline, his FEV₁ changed as follows: 0 min, 2.71; 1 min, 2.94; 2 min, 2.77; 4 min, 2.54 and 8 min, 1.87 litres. He noticed chest tightness and mild dyspnoea. Bronchodilator (5mg salbutamol) was given by nebuliser and his mild distress eased over 10 minutes. FEV₁ was recorded at 1.74 litres 20 minutes later. He was observed and his FEV₁ spontaneously improved to 3.42 litres three hours after the test. This value, being higher than his baseline reading, suggests that he had bronchoconstriction at the time of the test.

Bronchial hyperresponsiveness and smoking

No relationship between smoking status and a positive test was found. Five of 22 smokers, four of 29 ex-smokers and six of 37 never-smokers had positive responses to the challenge.

Subject acceptability of HSBC

Responses to the administered questionnaire showed that 65 reported 'no problems', 19 found it 'mildly uncomfortable', nobody found it 'uncomfortable' and only one person found the HSBC 'very uncomfortable'. This indicates a high level of acceptance. However, acceptance was less amongst those with a positive HSBC, since out of 12 recorded responses seven had 'no problems', four found it 'mildly uncomfortable' and one responded that the test was 'very uncomfortable'. He was a 50 year old ex-smoker with no previous history of asthma or breathing problems.

DISCUSSION

It has been demonstrated in this study that the 4.5% saline bronchial challenge test can be successfully used for measurements of bronchial responsiveness in industrial field settings. Sixty-five per cent of people approached using an information leaflet underwent the test. This percentage is less than the 81% participation Cockcroft et al. obtained for histamine challenge after telephoning students, although many other factors apart from the nature of the challenging agent would be expected to influence participation rates.

The data obtained in this study are consistent with results from previous published studies. Data of Anderson et al. on 180 healthy subjects referred for SCUBA diving examinations revealed that the distribution of per cent fall of FEV₁ from baseline at the end of the 4.5% saline challenge was mildly positively skewed with a mean of 7.2% (SD = 8.2) and median of 4.5% (range -7.7-47). The study of Riedler et al. recorded a median PD₁₅FEV₁ value of 11.75ml with range 0.24-40.4. Riedler et al. found that the 95th percentile for per cent fall in FEV₁ amongst children who did not report 'current wheeze' (a positive response to IUAT question 1, see Table 2) or 'former wheeze' ('have you ever had wheezing or whistling in the chest at any time in the past') was 15%, and the 90th percentile 13.4%. Riedler et al. also determined that the sensitivity and specificity of the 4.5% salt challenge for detecting current wheeze diagnosed by questionnaire (IUAT question 1) were 47% (95% CI 0.39-0.55) and 92% (95% CI 0.88-0.96).

Results from the present study amongst timber industry employees can be best compared to the study...
S. J. Rabone et al.: Hypertonic saline challenge

Table 3. Comparison of methacholine and hypertonic saline challenge results in detecting positive responses to the question 'have you ever had an attack of asthma?'

<table>
<thead>
<tr>
<th></th>
<th>4.5% saline challenge at 15% FEV₁ fall cutoff</th>
<th>4.5% saline challenge at (b) 20% FEV₁ fall cutoff</th>
<th>Methacholine challenge at PC₂₀ ≤ 8mg/ml cutoff</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n = 89*</td>
<td>n = 1,392*</td>
<td></td>
</tr>
<tr>
<td>Sensitivity</td>
<td>57 (20-94)†</td>
<td>57 (20-94)</td>
<td>47 (34-59)</td>
</tr>
<tr>
<td>Specificity</td>
<td>86 (79-94)</td>
<td>96 (92-100)</td>
<td>85 (83-87)</td>
</tr>
<tr>
<td>Positive predictive value</td>
<td>27 (4-49)</td>
<td>57 (20-94)</td>
<td>12 (8-16)</td>
</tr>
<tr>
<td>Negative predictive value</td>
<td>96 (91-100)</td>
<td>96 (92-100)</td>
<td>97 (92-98)</td>
</tr>
</tbody>
</table>

* number of subjects in the study
† 95% confidence interval

Figure 4. Sensitivity, specificity and positive predictive value of the 4.5% hyperosmolar challenge for diagnosing 'current wheeze' at different FEV₁ fall cutoff points. Ninety five per cent confidence limits of the sensitivity and specificity estimates are shown.

Figure 5. Per cent positive responses to IUT questions 1 and 12 for respondents grouped by %FEV₁ fall during 4.5% hypertonic saline challenge. The graph shows no increase in the proportion of positive responses below 19.8% FEV₁ fall.

of Enarson et al. of 1,392 workers (mainly timber and grain industries) using methacholine challenge, because a common questionnaire definition of asthma exists. The sensitivity, specificity, positive and negative predictive values of both the HSBC and the methacholine challenge in detecting positive responses to the questionnaire question 'have you ever had an attack of asthma?' are shown in Table 3. In this comparison, the HSBC at 20% FEV₁ fall cutoff has superior positive prediction and specificity whilst matching methacholine's sensitivity.

Departures from the protocol of Smith and Anderson deserve mention. A bronchodilator drug was not given routinely following the tests. The reasons for this were: that medical practitioners were present; that to give a pharmacologically active agent prophylactically seemed unnecessary in the absence of any fall in FEV₁ over the time of observation; and that FEV₁ is not expected to fall further 1 minute after test completion. How-

er these reasons do not consider subjects with current unsuspected bronchospasm undergoing the test. Bronchial hyperresponsiveness in these subjects may not be detected until administration of bronchodilator following the test reveals that their baseline FEV₁ has been underestimated. It is therefore recommended that bronchodilator be given following the challenge and the response measured.

Further FEV₁ fall following completion of the HSBC was demonstrated by one subject in the study. This is possibly of concern because previous information did not suggest that such a fall would occur. This man had undetected bronchospasm when commencing the test (because his baseline FEV₁ of 2.71 litres increased to 3.42 litres 3 hours after the test following administered bronchodilator) and had a positive test. The protocol of giving bronchodilator after the test, followed by checking FEV₁, left us alerted and prepared. He recovered; nevertheless, more research is required on larger numbers of people to document patterns of recovery.

The large variation in nebuliser output between tests performed over the standard 15.5 minutes is possibly of concern (see Figure 1), although it has been shown that few negative responses will change to positive by merely administering more saline, the rate of change of osmolarity in the airways being more important. Nebuliser output is recognized to vary with tidal volume and respiratory rate in children, and these
possibly accounted for part of the variation. Nevertheless, to minimize measurement error, weighing of the saline canister and tubing must be performed meticulously without loss of saline.

The definition of a positive test at a cutoff point of > 15% FEV₁ fall is arbitrary. The decision as to what cutoff point is appropriate will depend on the circumstances of the investigator, and the desirability for a sensitive or specific test. Whereas the necessity for an exact definition is acknowledged to enable practical usage of the test in epidemiological settings, the possible limitations of a cutoff point of 15% for population studies deserve consideration. Given that the data from this study come from a small group of subjects exposed to (possibly asthmagenic) wood dusts and may not generalize to other populations, they suggest that a cutoff point for a positive test which provides high specificity (see Figure 3 and Table 3) and which separates individuals who appear to react to inhaled saline differently (see Figures 1 and 4) lies above 15%. Figure 1 shows that responses of nine individuals (those with FEV₁ falls > 19%) appear separate from the rest. Separation of those with FEV₁ falls from 15–19% appears less clear. In epidemiological surveys there is usually responsibility to provide subjects with results and interpretation of procedures, and high specificity aids interpretation. The dose-response ratio, by considering the rate of saline administration, may offer some future advantages in defining cutoff points for the test. A cutoff of 20% FEV₁ fall in this study produced an asthma prevalence estimate of 7.9%, consistent with the estimate of participants (see Table 2). For the above reasons, a 20% cutoff point appears more appropriate for epidemiological surveys.

Responses to inhaled histamine have been quantified and classified by Cockcroft et al.¹ to provide predictions of current symptomatic asthma; for example, Cockcroft et al. state that a histamine challenge PC₂₀ below 2mg/ml is diagnostic of current symptomatic asthma and that a PC₂₀ greater than 8mg/ml virtually excludes current asthma. This type of information is of obvious use in interpreting results, and after appropriate research should become available for the HSBC. At that stage the best cutoff points for different applications will be apparent.

The equipment and expertise required to perform the HSBC are similar to those required for methacholine or histamine challenge; both procedures can be performed by one person in a non-laboratory setting. This study, in support of the study of Riedler et al., shows that the HSBC is safe, well-tolerated and produces results comparable to those obtained in laboratories.

Potential advantages of the indirect mechanism of action of HSBC in causing bronchoconstriction have not been demonstrated at this stage by a direct comparison between pharmacological challenge and HSBC. The differing methods of defining questionnaire-diagnosed asthma, of recruiting subjects into studies and of defining cutoff points have prevented accurate direct comparison between measures of bronchial responsiveness in the general population. The use of HSBC as an epidemiological tool for estimating asthma prevalence is uncertain, but given the difficulties normally involved in estimating asthma prevalence and the desirability to base such estimations on objective data, it is a measurement of bronchial hyperresponsiveness (amongst several) that warrants full investigation. Ideally, part of that investigation will involve a direct comparison between pharmacological challenge and the HSBC on the same subjects.

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