

## Use and safety of a shortened histamine challenge test in an occupational study

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*Use and safety of a shortened histamine challenge test in an occupational study. A.M. Kremer, T.M. Pal, M. Oldenziel, M. Kerkhof, J.G.R de Monchy, B. Rijcken. ©ERS Journals Ltd 1995.*

**ABSTRACT:** A shortened histamine challenge test was used in a study of occupational airway disease. We evaluated the safety, defined as the absence of a decrease in forced expiratory volume in one second (FEV<sub>1</sub>) of greater than 40%. The occurrence of complaints, the repeatability of test results, and the average amount of time saved were measured.

A standard protocol was used comprising 30 s tidal breathing with sequential doubling concentrations from 1 to 32 mg·ml<sup>-1</sup> histamine. Subjects with no indication of hyperresponsive airways started at 4 mg·ml<sup>-1</sup>. If the decrease in FEV<sub>1</sub> was <6%, a concentration step was skipped (fourfold increase in concentration). The test was terminated when the decrease in FEV<sub>1</sub> was at least 18%.

A total of 697 subjects performed a test. All subjects with a provocative concentration of histamine producing a 20% decrease in FEV<sub>1</sub> (PC<sub>20</sub>) value of ≤4 mg·ml<sup>-1</sup> (n=16) started at the lowest concentration. Six subjects reached a ≥20% decrease in FEV<sub>1</sub> (range 21–24%) after a fourfold increase in concentration. Five subjects had a decrease in FEV<sub>1</sub> of greater than 40%, and this decrease occurred after a doubling concentration. Cough, flushing, and chest tightness were noted in 18% of the subjects. In 56% of the tested subjects, the shortest provocation scheme (phosphate solution followed by 4, 16 and 32 mg·ml<sup>-1</sup> histamine) was applied, resulting in a time reduction of nearly 50% per test, and reducing the time needed to complete the study from 5 to 3 months. The shortened test was repeatable within one concentration difference.

We conclude that, in this occupational setting, the histamine challenge test can be shortened to save time without risk of excessive falls in FEV<sub>1</sub>.

*Eur Respir J., 1995, 8, 737-741.*

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Keywords: Airway responsiveness  
epidemiology  
histamine  
shortened challenge test

Received: November 26 1993  
Accepted after revision February 19 1995

Supported by Grant No. 88-32 of The Netherlands Asthma Fund.

Measuring airway responsiveness may be important in the investigation of effects of airborne exposure. However, challenge tests are time-consuming, and this can be a problem in an occupational setting when healthy workers participate in a study. The full protocol both of the 2 min tidal breathing method with sequential doubling concentrations from 0.03 to 8.00 mg·ml<sup>-1</sup> of the agonist (total of nine concentrations) and the dosimeter method with doubling sequential concentrations from 0.075 to 25 mg·ml<sup>-1</sup> of the agonist, inhaled at intervals of 5 min [1, 2] take at least 50 min to complete. The 30 s tidal breathing method, with doubling concentrations from 1 to 32 mg·ml<sup>-1</sup> (total of seven concentrations), inhaled at intervals of 2.5 min [3] takes about 20 min to complete.

In an occupational setting, we studied the relationship of airborne exposures, airway responsiveness and respiratory problems. Airway responsiveness was assessed by means of a histamine challenge test. To improve the acceptability of the test both for the participants and the management of the plant, we decided to apply a shorter

challenge test that was less time-consuming. There are various ways to achieve this: starting with a higher dose (or concentration) [4-6]; using fourfold increases in the inhaled doses [4, 7]; resuming doubling doses if a 10% fall in forced expiratory volume in one second (FEV<sub>1</sub>) occurs [8]; and decreasing the time between doses [7]. We followed the recommendations of the Societas Europae Physiologiae Clinicae Respiratoriae (SEPCR) Working Group [9] and of HARGREAVE *et al.* [10].

Applying shortened challenge tests may imply certain risks for the participants. A high starting dose may be followed by a considerable bronchoconstriction that might not have occurred at the regular low starting dose. In general, a sudden fall in FEV<sub>1</sub> in excess of 40% after the initial dose is to be avoided if possible. Such a degree of obstruction is likely to cause discomfort to the tested subject. Thus, subjects who are likely to have hyperresponsive airways should not be allowed to have the high starting dose. A subject might also experience such a severe obstruction if a fourfold increased dose is applied,

whereas a twofold increased dose would have caused a less severe obstruction. For this reason, shortened protocols resume doubling doses if a dose is followed by a decrease in FEV<sub>1</sub> of greater than 10%.

The purpose of the current report was to evaluate the safety of the shortened protocol applied by determining whether a fall in FEV<sub>1</sub> of >40% occurred after the high initial dose or after a fourfold doubling dose. In addition, we considered the occurrence of complaints, the repeatability of test results, and the average amount of time saved.

## Methods

Forced expirations after maximal inspiration were performed with a water-sealed spirometer. Three satisfactory manoeuvres were required of each subject, from which forced vital capacity (FVC) was reproducible within 5% with a maximum of 300 ml [11]. Measurements were corrected for body temperature, atmospheric pressure, and water saturation (BTPS). Aerosols were generated by a Wiesbaden Doppelinhalator. The nebulizers were calibrated at an output of 0.13 ml·min<sup>-1</sup>. The full 30 s tidal breathing protocol had a repeatability [12] comparable to other tests [13–15]. Subjects with a prechallenge FEV<sub>1</sub> of less than 80% predicted [9, 11], or daily medication for a pulmonary or a cardiovascular disease were not allowed to perform a challenge test. After pretest with phosphate solution, subjects inhaled sequential aerosols of histamine biphosphate in concentrations of 1, 2, 4, 8, 16 and 32 mg·ml<sup>-1</sup> at intervals of 2.5 min. The FEV<sub>1</sub> was measured at 30 and 90 s after each concentration. The test was terminated if there was a fall in FEV<sub>1</sub> of at least 20% from baseline, or if the highest concentration had been given. Subjects were asked not to take bronchodilators within 8 h, or antihistamine drugs within 72 h before the test.

The starting concentration of the short protocol was 4 mg·ml<sup>-1</sup> histamine. However, subjects had to commence at 1 mg·ml<sup>-1</sup> if they met one or more of the following criteria: reporting dyspnoea grade III (confirming the question whether they had "shortness of breath when walking with other people of their own age on level ground"), or ever wheeze, or ever asthma attacks, or a "history of allergy" (confirming the question "Have you ever had hay fever?" or "Do you get eye, nose, or respiratory symptoms when you are exposed to house dust, domestic animals or fungi?"); a fall in FEV<sub>1</sub> of at least 6% after phosphate solution. The next concentration was skipped when the fall in FEV<sub>1</sub> was less than 6%.

After a fall of FEV<sub>1</sub> of ≥6%, doubling concentrations were resumed. The test was terminated if the fall in FEV<sub>1</sub> was at least 18%, or if the highest histamine concentration had been given. Airway hyperresponsiveness was defined as a provocative concentration of histamine producing a 20% decrease in FEV<sub>1</sub> (PC<sub>20</sub>) of ≤32 mg·ml<sup>-1</sup>. When the test was terminated at an 18 or 19% decrease, a PC<sub>20</sub> value was estimated by loglinear extrapolation [9, 16].

Complaints during or after the test, such as flushing, chest tightness, coughing, not feeling well (shivering,

paleness and/or dizziness), hoarseness and throbbing headache were recorded. Only coughing that occurred independently of the spirometric manoeuvres performed and that was distressing for the participant, was considered as a side-effect of histamine challenge.

The study was approved by the Ethics Board of the Groningen University Hospital and Medical School. Written informed consent was obtained from all participants.

## Results

### Subjects and complaints

The short protocol was applied in an occupational health study in 1989 [17]. Of the 909 invited male workers, 790 subjects participated in the study. An acceptable pulmonary function test was obtained in 775 subjects. The variation coefficient of the FEV<sub>1</sub> was 2.5% (95% confidence interval 0.0–5.3%), thus meeting the 5% standard [18]. A challenge test was performed by 735 subjects. One or more complaints were reported by 125 subjects (17%) (table 1): 7.5% had flushing (n=55); 6.5% chest tightness (n=48); 2.7% cough (n=20). Seven subjects reported not feeling well (shivering, paleness and/or dizziness, in combination with cough, headache and/or chest tightness), four subjects had hoarseness and three subjects a throbbing headache. Coughing occurred mainly at 32 mg·ml<sup>-1</sup>, whereas "not feeling well" also occurred at lower concentrations of histamine (16 and 8 mg·ml<sup>-1</sup>).

No challenge test was performed in 55 subjects (table 2). Daily medication for cardiovascular disease (n=15) and a FEV<sub>1</sub> value of <80% of predicted (n=22) were the major reasons for exclusion. For various reasons, the challenge data of 38 subjects could not be used: the test had to be terminated because of not feeling well (n=6); coughing (n=7); or error in the procedure (n=3). Poor quality of the test caused an additional loss of data of 22 subjects.

### Specificity and sensitivity of selection criteria

A complete test of good quality was achieved in 697 subjects (n=790-55-38) and 440 of these started at 4 mg·ml<sup>-1</sup>. There were 257 subjects with ≥1 positive criteria, and these subjects started the test at 1 mg·ml<sup>-1</sup> histamine (table 3). If our selection criteria were sensitive,

Table 1. – Reported complaints during and after histamine challenge testing in 735 subjects

Complaint	
Flushing	55 (7.5)
Chest tightness	48 (6.5)
Cough	20 (2.7)
Not feeling well (shivering, paleness and/or dizziness)	7 (1.0)
Hoarseness	4 (0.5)
Throbbing headache	3 (0.4)

Data are presented as actual number and percentage in parenthesis.

Table 2. – Reasons for excluding subjects from analysis

No histamine challenge test (n=55)	
Exclusion criteria	
Daily medication for a lung disease	5
Daily medication for a cardiovascular disease	15
Lung disease	2
FEV <sub>1</sub> <80% of predicted value	22
Refused	2
Procedure error	1
Subjective complaints during spirometry	4
Miscellaneous reasons	4
Data histamine challenge test rejected (n=38)	
Incomplete data	
Had to stop, not feeling well	6
No FEV <sub>1</sub> manoeuvre because of cough	7
Procedure error	3
Poor quality of the test	22

FEV<sub>1</sub>: forced expiratory volume in one second

subjects with a PC<sub>20</sub> value of  $\leq 4$  mg·ml<sup>-1</sup> should have one or more of the selection criteria. This was indeed the case (table 2), so that the sensitivity of the selection criteria was 100%. However, the specificity of the selection criteria, this is the proportion of subjects with a PC<sub>20</sub> value of  $>4$  mg·ml<sup>-1</sup> (n=697–16) who had no positive criterion (n=440), was relatively low: 65% (440 out of 681). This means that 35% of these 681 subjects could have started the test at 4 mg·ml<sup>-1</sup>. To increase the specificity of the selection criteria, the presence of frequent wheeze (wheeze more than once a year) might have been chosen instead of ever wheeze. This would have reduced the number of subjects in whom the test had to be started at 1 mg·ml<sup>-1</sup> from 257 (37%) to 197 (28%), and increased the number of subjects with a PC<sub>20</sub> value of  $>4$  mg·ml<sup>-1</sup> who could have started the test at 4 mg·ml<sup>-1</sup>, resulting in a higher specificity (73%). However, one subject with a PC<sub>20</sub> value of 1.53 mg·ml<sup>-1</sup> (31% fall in FEV<sub>1</sub> at 2 mg·ml<sup>-1</sup>), would have started at 4 mg·ml<sup>-1</sup>, lowering the sensitivity to 94%. We did not use the presence of chronic cough, chronic phlegm and bronchitis episodes as additional criteria in the protocol for starting at 1 mg·ml<sup>-1</sup>. Including these symptoms as selection criteria would have excluded 308 subjects from starting at 4 mg·ml<sup>-1</sup> and decreased the specificity from 65 to 43%. The sensitivity could not improve by adding these criteria to the protocol because it was already 100%.

### Safety (% fall in FEV<sub>1</sub>)

The mean fall in FEV<sub>1</sub> for subjects with a PC<sub>20</sub>  $\leq 32$  mg·ml<sup>-1</sup> was 24.2% (range 18–50%) with a median of 23%. Twelve (7%) of the 164 subjects with a PC<sub>20</sub>  $\leq 32$  mg·ml<sup>-1</sup> had a  $\geq 18\%$  FEV<sub>1</sub> fall after a fourfold increase in concentration. Of these 12 subjects, six had a  $\geq 20\%$  fall in FEV<sub>1</sub> (range 21–24%). A fall in FEV<sub>1</sub> of  $\geq 30\%$  after doubling concentration occurred in 21 subjects, of whom five had a fall of  $\geq 40\%$  (range 40–50%). Of these subjects, one subject had a 31% FEV<sub>1</sub> fall at 1 mg·ml<sup>-1</sup> with a previous fall on phosphate solution of 16%. In 20 subjects the challenge test was terminated because a fall of 18 or 19% in FEV<sub>1</sub> had occurred.

In this population, in eight subjects a 6–10% fall in FEV<sub>1</sub> at  $\leq 8$  mg·ml<sup>-1</sup> was followed by a  $\geq 20\%$  fall (range 20–34%) after one doubling concentration. In another 39 subjects, a 6–10% fall in FEV<sub>1</sub> at  $\leq 8$  mg·ml<sup>-1</sup> histamine was followed by a  $\geq 20\%$  fall in FEV<sub>1</sub> after two doubling concentrations. Thus, if we had chosen to resume doubling doses if the fall in FEV<sub>1</sub> was greater than 10%, 14 (6+8) to 53 (6+8+39) of the hyperresponsive subjects (9–32%) might have had a  $\geq 20\%$  fall in FEV<sub>1</sub> after a fourfold increase in concentration.

### Time saved and repeatability

A full protocol required approximately 20 min to complete (baseline spirometry not included). Subjects who started their test at 4 mg·ml<sup>-1</sup> and skipped the next concentration had to perform four provocation manoeuvres: the phosphate solution, the 4, 16 and 32 mg·ml<sup>-1</sup>, and this challenge test took about 11 min. The minimal test time was obtained in 56% of the study population.

The repeatability of the short protocol was examined in 19 subjects with known airway responsiveness to histamine and who were not involved in the health survey study. The two tests were performed at the same time of the day with 1–3 days in between. After <sup>2</sup>log-transformation, the differences between the two PC<sub>20</sub> estimations of 18 subjects ranged from -1.23 to +0.67 doubling concentrations, with a mean of -0.08 (fig. 1). The repeatability, expressed as the 95% range for a single measurement to  $0.05(\text{SD})/\sqrt{2}$ , was  $\pm 0.85$  doubling concentrations [19]. For one subject, the difference could not be estimated (PC<sub>20</sub>  $>128$  mg·ml<sup>-1</sup> and 37.4 mg·ml<sup>-1</sup>).

Table 3. – Distribution of the selection criteria, to commence at 1 mg·ml<sup>-1</sup>, stratified by PC<sub>20</sub> values

Selection criterion	PC <sub>20</sub> values mg·ml <sup>-1</sup>					Total (n=697)
	$\leq 4$ (n=16)	$>4-8$ (n=13)	$>8-16$ (n=38)	$>16-32$ (n=97)	$>32$ (n=533)	
Dyspnoea grade $\geq$ III	1 (6)	2 (15)	2 (5)	3 (3)	8 (2)	16 (2)
Ever wheeze	12 (75)	7 (54)	19 (50)	33 (34)	105 (20)	176 (25)
Ever asthmatic attack	3 (19)	2 (15)	5 (13)	6 (6)	12 (2)	28 (4)
History of allergy	7 (44)	4 (31)	9 (24)	13 (13)	57 (11)	90 (13)
$\geq 6\%$ FEV <sub>1</sub> fall on phosphate solution	9 (56)	7 (54)	7 (18)	9 (9)	15 (3)	47 (7)
$\geq 1$ criteria positive	16 (100)	10 (77)	28 (74)	47 (48)	156 (29)	257 (37)
No criteria positive	-	3 (23)	10 (26)	50 (52)	377 (71)	440 (63)

Data are presented as actual number and percentage in parenthesis. FEV<sub>1</sub>: forced expiratory volume in one second; PC<sub>20</sub>: provocative concentration producing a 20% decrease in FEV<sub>1</sub>.

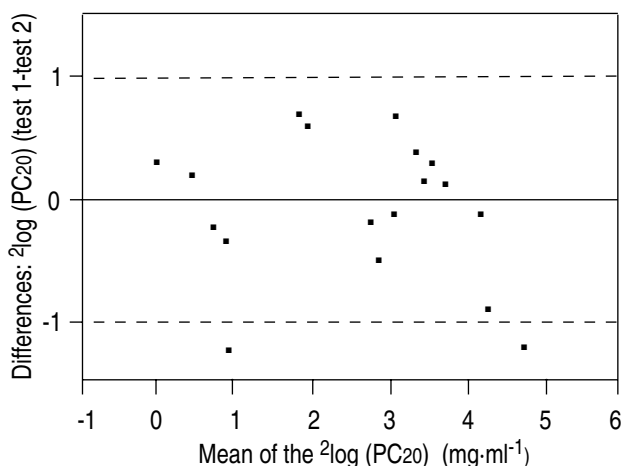


Fig. 1. — Repeatability of PC<sub>20</sub> measurements within 5 days in 18 subjects: differences in doubling concentration between the two PC<sub>20</sub> values against the average PC<sub>20</sub> value. PC<sub>20</sub>: provocative concentration of histamine producing a 20% decrease in forced expiratory volume in one second.

### Discussion

Using the short protocol, decreases in FEV<sub>1</sub> of 30% or more did not occur at the 4 mg·ml<sup>-1</sup> starting concentration, nor after a fourfold increase in concentration. All subjects with a PC<sub>20</sub> value of ≤4 mg·ml<sup>-1</sup> were identified by the selection criteria. A more severe bronchoconstriction was prevented in 20 subjects by stopping at 18% fall FEV<sub>1</sub>. The maximal reduction of time needed to complete a test was nearly 50%, and as much as 56% of the participants performed this maximally shortened test. Complaints were reported by 18% of the participants.

Although all hyperresponsive subjects were identified appropriately, the low specificity of the selection criteria of 65% resulted in a large proportion of the population that also had to start at 1 mg·ml<sup>-1</sup> histamine. The specificity may be higher when questions such as: "wheeze, more than once a year" (our questionnaire) or "wheeze in the last 12 months, even when one does not have a cold" (not in our questionnaire) are used, instead of: "ever wheeze". Chronic cough or phlegm and bronchitis periods did not provide additional information, confirming the results of others [20, 21].

Stopping at 18% fall in FEV<sub>1</sub> shortened the duration of the test and resulted in a less severe bronchoconstriction in 20 of the 164 hyperresponsive subjects (12%). The purpose of this was to avoid having workers with a severe bronchoconstriction who could tell fellow workers that the challenge test was distressing. Such stories can be a reason for the nonparticipation of other subjects in the plant. The perceived safety of a test also influences the participation in the follow-up study [6, 22]. Falls of more than 40% in FEV<sub>1</sub> occurred in five of the 697 subjects. However, this happened after the normal double increase in concentration.

PC<sub>20</sub> values estimated by a full and a shortened protocol may be different, due to a difference in the cumu-

lative dose of the inhaled histamine. Some investigators [7, 23] have found evidence to support a cumulative effect of histamine, whereas others have been unable to demonstrate this effect [16, 24]. TREMBLAY *et al.* [25] concluded that the cumulative effect of histamine might only be present once "significant bronchoconstriction" is reached. Differences between PC<sub>20</sub>, calculated on a noncumulative scale and on a cumulative scale, are within the repeatability range of the provocation test [25]. These findings, as well as recently published safety guidelines [26], support our decision to resume doubling concentrations when there was a 6% decrease of FEV<sub>1</sub>. In other studies, doubling doses were resumed after a fall of FEV<sub>1</sub> of greater than 10%, but doses were skipped only in subjects who were not at increased risk of responding [7, 13, 27]. To complete the evaluation of the short protocol, results should be compared to those from a standard full protocol, specifically with respect to subjects who started at 4 mg·ml<sup>-1</sup> and appeared to be hyperresponsive.

In the current study, subjects with an FEV<sub>1</sub> value of less than 80% predicted were not allowed to perform a challenge test [17]. Other investigators used an FEV<sub>1</sub> value of <60% [13, 27], <65% [28], or, <70% [29], and no problems were reported. This suggests that subjects with an FEV<sub>1</sub> of 70–80% predicted could be included, starting at 1 mg·ml<sup>-1</sup> histamine.

It took 3 months to complete our fieldwork. If we had used a full protocol of the 2 min tidal breathing method with sequential doubling concentrations from 0.03 to 8.00 mg·ml<sup>-1</sup> of the agonist (total of nine concentrations), or the dosimeter method with doubling sequential concentrations from 0.075 to 25 mg·ml<sup>-1</sup> of the agonist, inhaled at intervals of 5 min [1, 2], this would have taken 5 months. In subjects with nonresponsive airways, it took 11 min to perform the challenge test, which is similar to the short protocol of YAN and co-workers [7, 29]. This latter protocol seems to be well-tolerated, but no safety data have been published.

Histamine may cause more side-effects, such as flushing and throbbing headache, than methacholine [9]. In a study among 342 adults, HIGGINS *et al.* [22] found that histamine caused voice changes more often than methacholine, 21 *versus* 11%, whereas the occurrence of cough was similar with both agents, 30 and 34%. The symptoms of shivering, paleness and/or dizziness which occurred in a few subjects in our study, are most likely to be due to the repeated spirometric manoeuvres and not to the use of histamine. In addition to the side-effects during the test, some subjects reported that they had experienced symptoms, such as hoarseness and chest tightness, after they returned to work. This finding was also reported by HENDRICK *et al.* [6], who found in their study with methacholine challenge that 61 out of 222 workers had symptoms, such as cough, chest tightness or wheeze, that started within 6 h of testing. Participants should be informed about potential side-effects in advance [6].

We conclude that the shortened histamine challenge test is time saving in an occupational study and without risk of excessive bronchoconstriction.

**Acknowledgements:** The authors thank all the workers of the synthetic fibre plants who participated for their co-operation, the employees of the Occupational Health Department for their extra efforts, the members of the survey team, F. de Wolff and G. Swart, for their contribution, J. Veltman for help with statistics, and SensorMedics BV for the lung function apparatus.

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