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# Testing bronchial hyper-responsiveness: provocation or peak expiratory flow variability?

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## SUMMARY

**Background.** Assessing bronchial hyper-responsiveness (BHR) is a main diagnostic criterion of asthma. Provocation testing is not readily available in general practice, but peak expiratory flow (PEF) is. Several guidelines promote the use of PEF variability as a diagnostic tool for BHR. This study tested the agreement between histamine challenge testing and PEF variability, and the consequences for diagnosing asthma

**Aim.** To investigate the possibility of assessing BHR by PEF variability, using a histamine provocation test as a reference.

**Method.** Subjects with signs or symptoms indicating asthma (persistent or recurrent respiratory symptoms or signs of reversible bronchial obstruction) ( $n = 323$ ) were studied. They had been identified in a population screening for asthma. A histamine provocation test and PEF variability were assessed over a three-week period. Asthma was defined as signs or symptoms together with a reversible airflow obstruction or BHR to the histamine challenge test. BHR was defined as a  $PC_{20}$  histamine of  $\leq 8$  mg/ml or a PEF variability of 15%. Overall correlation between  $PC_{20}$  and PEF variability was calculated using Spearman's rho. Furthermore, a decision tree was constructed to clarify the role of BHR in diagnosing asthma.

**Results.** Thirty-two patients had a reversibility in forced expiratory volume in 1 second ( $FEV_1$ ) of 9% predicted, 131 patients showed a  $PC_{20}$  of  $\leq 8$  and 11 patients had a PEF variability of 15%. Overall correlation was poor at only  $-0.27$  ( $P < 0.0001$ ). One hundred and fourteen of the 131 patients diagnosed as having asthma when the histamine challenge test was used were not diagnosed by PEF variability.

**Conclusion.** PEF variability cannot replace bronchial provocation testing in assessing BHR. This indicates that PEF variability and bronchial provocation do not measure the same aspects of BHR. If BHR testing is required in diagnosing asthma, a bronchial provocation test has to be used in general practice as well.

**Keywords:** asthma diagnosis, peak flow, bronchial hyper-responsiveness.

## Introduction

ASTHMA is a common disease in general practice, for which a pathognomonic test is lacking. At this moment, diagnosis of asthma by a general practitioner (GP) is based on a positive history of bronchial symptoms, atopic disease(s), occupational exposure to known sensitizing agents, and the findings at a physical examination.<sup>1-3</sup> GPs usually diagnose asthma on the basis of symptoms only, without the use of additional testing, such as spirometry or allergy testing. This may be one of the reasons that patients remain unrecognized — 'underdiagnosis' that leads to 'undertreatment' or a delay in treatment<sup>1,3</sup> — and might be an explanation for the increase in asthma morbidity.<sup>4,5</sup> As asthma is characterized by reversible airflow obstruction, BHR, and inflammation of the bronchial tubes, spirometry can confirm both the reversible airflow obstruction and the hyper-responsiveness.<sup>6</sup> Additional use of spirometry can facilitate the interpretation of symptoms and the identification of asthma from the commonly presented respiratory symptoms in general practice. Bronchial obstruction, one of the cornerstones of asthma diagnosis, is easy to assess. However, it might be absent at the time of testing.<sup>7</sup> Therefore, assessment of BHR is also proposed in the diagnosis of asthma.<sup>6,8</sup> Its assessment is considered to be a main diagnostic criterion<sup>2,9</sup> to distinguish between healthy subjects and subjects with respiratory diseases,<sup>10</sup> although there is conflicting evidence in this respect,<sup>11</sup> probably arising from variation in the population studied.<sup>10</sup>

BHR can be assessed by bronchial provocation testing or by measuring PEF variability.<sup>12-14</sup> This paper will focus on the value of PEF variability in assessing BHR. Chest physicians usually test BHR by a provocation test, not only as a diagnostic routine, but also as an indicator for adjusting or readjusting medication.<sup>9</sup> For the majority of asthma patients treated by GPs, BHR testing is quite an exception, as bronchial provocation would require easy access to a lung function laboratory. However, in general practice, PEF measurement has already established its place for measuring bronchial obstruction.<sup>7</sup> When the PEF is measured at least twice daily, the PEF variability, which reflects the degree of bronchial responsiveness, can be calculated as well.<sup>15</sup> This assessment requires only low technology: the five 'Ps' of patient, PEF meter, pocket calculator, pencil, and paper. In this way, adequate diagnosis of asthma might be within reach of general practice (Figure 1).

PEF variability measures the variation in airway calibre under everyday life or work conditions, and  $PC_{20}$  measures changes in bronchial calibre under standardized challenge. Several studies have been performed on the correlation between  $PC_{20}$  and PEF variability,<sup>12,16,17</sup> but there remains controversy over their findings. Asthma medication might interfere with both PEF and  $PC_{20}$  measurements,<sup>17</sup> and the use of medication might have been a factor interfering with the results of these studies. It was for this reason that we carried out a study on patients without a previous asthma diagnosis,<sup>18</sup> which has been described only once before in a random sample from a general practice population.<sup>19</sup> This study was carried out to determine if  $PC_{20}$  histamine can be replaced by PEF variability. It assessed histamine bronchial provocation testing and the PEF variability of subjects with signs or symptoms indicating asthma. Our hypothesis was that a peak

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flow variability of 15% is as successful in assessing BHR as PC<sub>20</sub> histamine. If true, mapping BHR in general practice would be possible this way.

## Method

### Design

In this explanatory study, PEF variability and PC<sub>20</sub> histamine were compared in 323 subjects reporting signs or symptoms of asthma in a population screening for asthma.<sup>18</sup>

### Subjects

Patients were recruited from a screening for asthma in an open population. A total of 1155 randomly selected subjects were screened. The selection procedure has been described extensively elsewhere.<sup>18</sup> In summary, all subjects were adults between 25 and 70 years old, recruited from the patients of 10 general practices. Included in this study were subjects with one or more of the signs or symptoms indicating asthma (Table 1).<sup>20</sup> Excluded were those who were unable to use a PEF device or to complete a diary.

### Asthma definition

To diagnose asthma, we used an adapted version of the algorithm of Sheffer *et al* (Figure 1).<sup>6</sup> All our subjects had a bronchoprovocation test and a three-week monitoring of their PEF. Asthma was defined as symptoms and a reversibility after bronchodilation with 800 mg of salbutamol of at least 9% predicted<sup>7</sup> or BHR, i.e. a PC<sub>20</sub> of  $\leq 8$  mg/ml.<sup>9</sup>

### Measurement scheme

All subjects eligible for study were visited and instructed at home by five trained investigators. After three weeks of measuring PEF twice a day, they were invited to a lung function laboratory.

### Questionnaire

Subjects were screened using an asthma questionnaire extended with questions of specific and non-specific BHR and smoking history.<sup>20</sup> Data were collected by five trained investigators.

### Diary and PEF measurement

All patients were visited at home and trained in how to perform and to use a mini-Wright peak flow meter, and how to register PEF in a diary. They recorded their PEF for three weeks, twice a day at the same time in the morning and in the evening. For analysis, the highest value of three measurements was taken. The diurnal PEF index was calculated as:<sup>21</sup>

In order to test for learning effects, the mean morning PEF values on days 1–7 were first compared with the mean morning val-

$$\text{PEF}_{\text{variability}} = \frac{\text{PEF}_{\text{highest}} - \text{PEF}_{\text{lowest}}}{\text{PEF}_{\text{mean}}} \times 100\%$$

ues on days 8–21. Since this showed no significant difference ( $P > 0.2$ , paired *t*-test), measurements for the total period of 21 days were used for analysis. For analysis, the mean diurnal PEF index was calculated by taking the arithmetic mean of 21 daily PEF variabilities.

### Spirometry

FVC and FEV<sub>1</sub> were assessed by means of an integrating flowmeter (Microspiro HI-298, Chest Corporation, Japan), according to the standards of the European Respiratory Society (ERS).<sup>9,22</sup> Reversibility was assessed 15 min after administration of 800 mg of salbutamol inhaled by means of a spacer, and expressed as percentage predicted.<sup>7,23,24</sup>

### Bronchial provocation testing

At the University Lung Center, Dekkerswald, lung function measurement was carried out during an exacerbation-free period. Twelve hours before lung function testing, no bronchodilator was used. Trained lung function technicians measured FVC, FEV<sub>1</sub>, and bronchial responsiveness to histamine (PC<sub>20</sub> histamine values) by means of the Microspiro HI-298 according to ERS standards.<sup>9</sup> Bronchial provocation with histamine (PC<sub>20</sub>) was assessed according to Cockcroft and Hargreave.<sup>10</sup> The provocative concentration of histamine causing a 20% fall in FEV<sub>1</sub> from the baseline value (PC<sub>20</sub>) was calculated by linear interpolation of the difference in FEV<sub>1</sub> versus <sup>2</sup>log PC<sub>20</sub>. Challenging started with saline and subsequent increases in histamine from a dose of 0.030 up to a concentration of 32 mg/ml.<sup>25</sup>

### Analysis

Overall correlation between PC<sub>20</sub> and PEF variability was calculated with Spearman's rho. Differences between groups were tested using Student's *t*-test or chi-square statistics as appropriate. As significance level,  $P \leq 0.05$  (two-tailed) was used.

In a second analysis, the diagnostic properties of PEF variability were compared with PC<sub>20</sub>. For this analysis, a decision tree was used. In the first step, all subjects were included with signs or symptoms. In the second step, reversible bronchial obstruction on testing was included. If subjects did meet this criterion, the diagnosis of 'asthma' was established, which concluded diagnostic testing. For all other subjects, BHR testing was introduced as the third step, and all subjects with a positive test result were considered asthmatic. This step was first analysed using the histamine challenge test result followed by diagnostic allocation when PEF replaced the histamine challenge. PEF-related classification was compared for correctness with the standard histamine challenge-based diagnosis.

To examine the influence of the cut-off point of PEF variability, a series of tables was produced to show the influence of the cut-off point of a PEF variability on the test characteristics (Table 2).

This study was approved by the ethics committee of the University Lung Center, Dekkerswald. All participants gave informed consent.

## Results

On screening, 529 subjects had signs or symptoms that could indicate asthma. Of these, 323 met the inclusion criteria and were willing to participate (Table 3). Non-participants ( $n = 206$ ) did not differ significantly in age, smoking habits or FEV<sub>1</sub>% predicted, but showed a lower reversibility of FEV<sub>1</sub> after bronchodilation (2.89% versus 4.05%,  $P = 0.002$ ) compared with the participants (Table 3). All 323 subjects were able to perform PEF measurement and to complete a diary. Five incomplete patient PEF diaries could not be evaluated and had to be excluded from the analysis. The overall correlation between PC<sub>20</sub> and PEF variability was  $-0.27$  ( $P < 0.0001$ ).

In the second part of the analysis, the decision tree was followed (Figure 2). In the first step, reversible bronchial obstruction of FEV<sub>1</sub> of 9% predicted was included, which was present

in 32 subjects, leading to the diagnosis 'asthma'. Analysis of BHR in this part of the tree is not further discussed, as its diagnostic testing in this group would be spurious.

The second step showed that, of the group of 291 patients with respiratory symptoms but without a reversible airflow obstruction, 111 had a PC<sub>20</sub> of  $\leq 8$  mg/ml leading to the diagnosis 'asthma'. The third step showed that, if a PEF variability of 15% was used for BHR instead of bronchial provocation testing, only nine of these 111 cases would have been diagnosed. Inclusion of PEF would have resulted in an overall frequency of

asthma of 0.13 (32 with a reversible airflow obstruction and nine with a PEF variability of 15% = 41/318) instead of 0.45 (143/318).

As shown in Table 2, the cut-off point of PEF variability influenced the test characteristics: with a variability of 4.56%, the discrimination between subjects diagnosed with 'asthma' on the basis of a PC<sub>20</sub> histamine of  $\leq 8$  mg/ml proved to be optimal, but a substantial number of cases would still have been incorrectly classified.

## Discussion

This study investigated the assessment of BHR in a general practice population of subjects with a risk of asthma using a histamine provocation test and PEF variability. It was concluded that the correlation between PC<sub>20</sub> histamine and PEF variability was low, and using PEF instead of PC<sub>20</sub> histamine did lead to a substantially lower diagnostic classification. Therefore, PEF could not be recommended as a substitute for the PC<sub>20</sub> histamine. So, our hypothesis that a PEF variability of 15% is as successful in assessing BHR as PC<sub>20</sub> histamine does not hold, and this implies that PEF variability cannot replace the PC<sub>20</sub> histamine provocation test. This requires a reconsideration of the diagnostic role of PEF, as advocated in various guidelines.<sup>1,9</sup>

Other studies have reported correlations between PEF and PC<sub>20</sub> histamine of  $-0.40$  to  $-0.50$ .<sup>12,17</sup> These studies were carried out with patients with an established diagnosis of asthma. For

**Table 1.** Questions used to determine subjects with a higher risk of asthma.<sup>21</sup>

Subjects were asked if they suffered from
- chronic cough on most days or nights in three consecutive months
- chronic phlegm production on most days or nights in three consecutive months
- more than one period of at least three weeks of cough or phlegm production in the previous three years
- dyspnoea when going upstairs or walking fast on level ground
- regular chest wheezing or whistling
- attacks of dyspnoea with wheezing (asthmatic attacks)
- 'allergic dyspnoea' after contact with dust, cats, dogs, etc.
- 'non-allergic dyspnoea' after exercise or contact with cold air, cigarette smoke, etc.

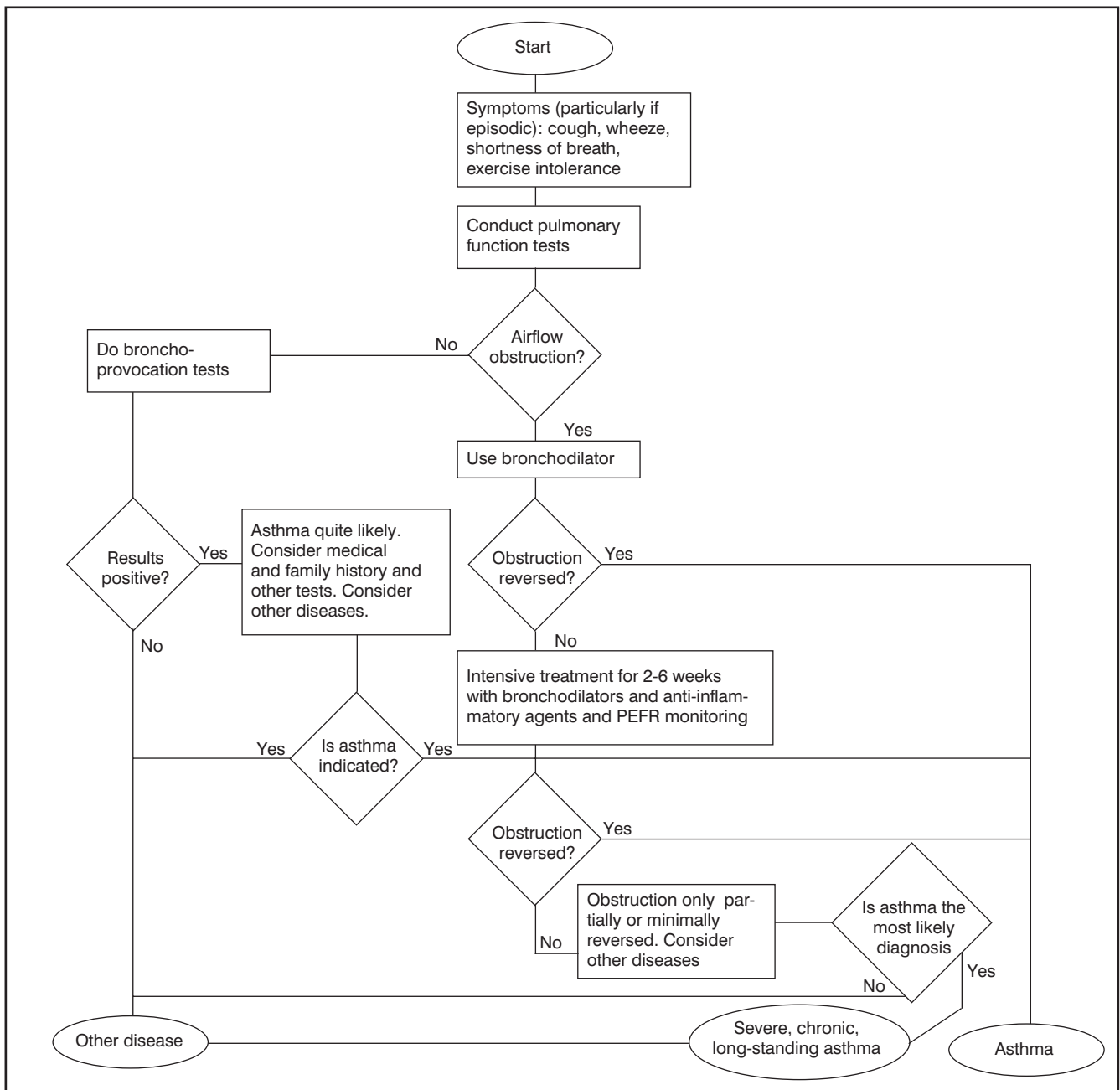
**Table 2.** Relation between PC<sub>20</sub> and PEF variability and test specifications using a cut off point of 5%, 10% and 15%.

	PC <sub>20</sub> 8 mg/ml	PC <sub>20</sub> > 8 mg/ml	Total
PEFR 5%	73	58	131
PEFR < 5%	57	130	187
PEFR 10%	18	8	26
PEFR < 10%	112	180	292
PEFR 15%	6	4	10
PEFR < 15%	124	184	308
Total	130	188	318
Test specifications			
PEFR	5%	10%	15%
Sensitivity	73/130 = 0.56	18/130 = 0.14	6/130 = 0.05
Specificity	130/188 = 0.69	180/188 = 0.96	184/188 = 0.97
PPV <sup>a</sup> for PEF	73/131 = 0.56	18/26 = 0.69	6/10 = 0.60
NPV <sup>b</sup> for PEF <	130/187 = 0.66	180/292 = 0.62	184/308 = 0.60

**Table 3.** Clinical characteristics.

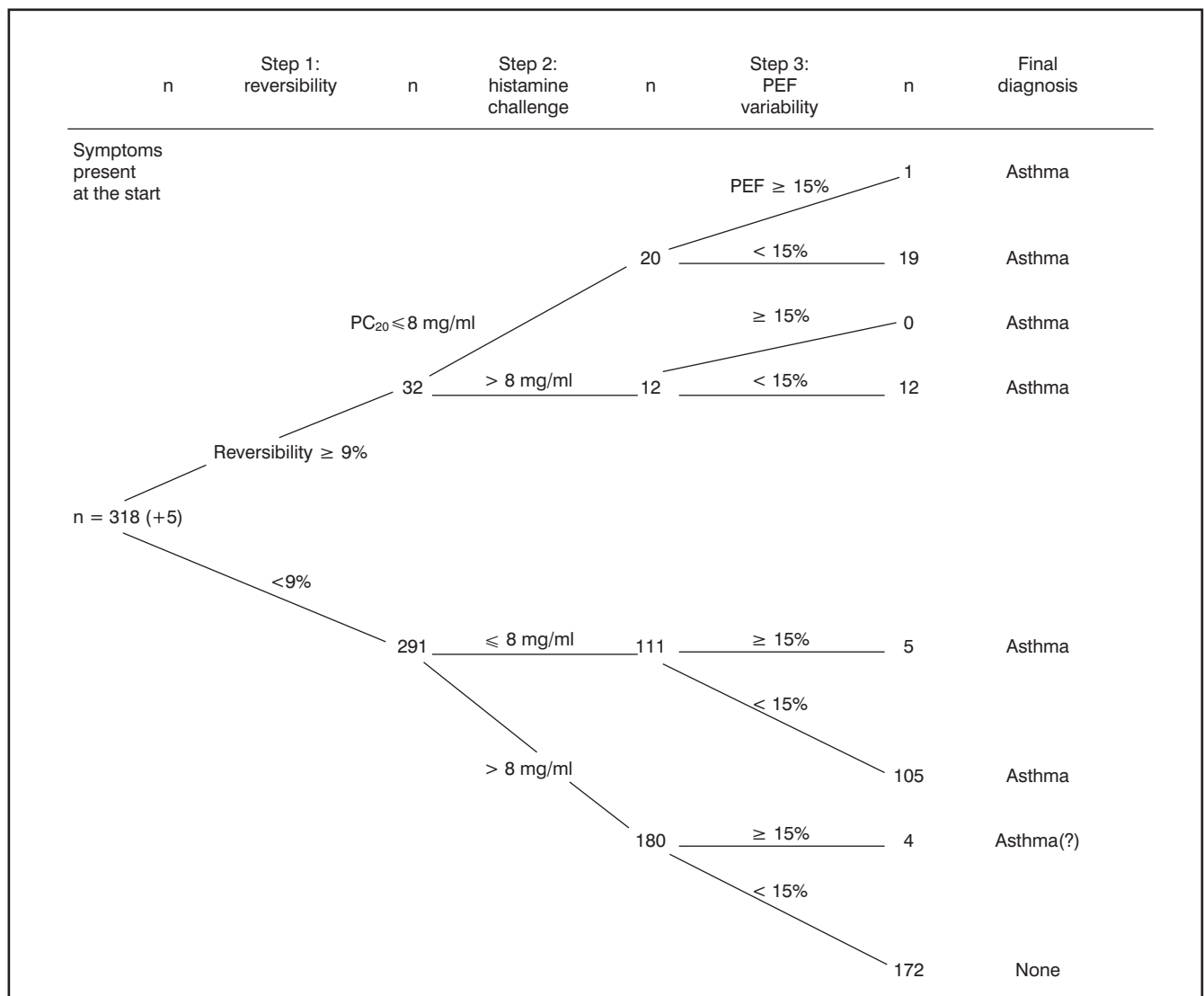
	Participants (n = 323)	Non-participants (n = 206)	P value
Male/female	135/188	73/133	NS
Age (years)	43±12	44±13	NS
FEV <sub>1</sub> (% predicted)	95±16	93±15	NS
FEV <sub>1</sub> (ml)	3154±800	3008±857	<0.05
Reversibility (% predicted)	4±5	3±4	<0.05
PC <sub>20</sub>	7.3	Not available	-
Smoking status			
(Ex)smokers/never smokers	129/194	96/110	0.131
Pack-years	8±10	10±11	0.183

Mean values ± SD except for PC<sub>20</sub> where the geometric mean is given of participants only.



**Figure 1.** Algorithm for diagnosing asthma. Asthma is characterized by reversible airflow obstruction and can often be diagnosed with complete certainty. However, when mixed signals are present clinically, one must consider other diseases that can also cause airflow obstruction. Sometimes, it may be impossible to distinguish among several possibilities or there may actually be coexisting diseases. This disclaimer is, in essence, true with any diagnosis. The general approach in diagnosing asthma is first to determine whether the patient has symptoms of cough, wheezing, shortness of breath or exercise intolerance. Do the symptoms appear to be episodic in nature? If so, a diagnosis of asthma should be strongly considered, and efforts should be made to demonstrate the reversibility of airflow obstruction after treatment using pulmonary function tests. If airflow obstruction is present but cannot be immediately reversed with an inhaled bronchodilator, it may be necessary to treat the patient aggressively with bronchodilators and anti-inflammatory agents for up to six weeks before deciding that airflow obstruction is truly irreversible. If the symptoms present suggest asthma but there is no evidence of airflow obstruction, a bronchoprovocation test should be performed. If the bronchial challenge is positive, then once again a diagnosis of asthma should be strongly considered. At the point of considering asthma strongly, one should consider other causes of reversible airflow obstruction, such as heart disease, the presence of foreign bodies in airways, and chronic obstructive pulmonary disease with a reversible component. If such diseases are present, and there are many to consider, one must try to determine whether this disease is predominant or whether asthma also coexists. When there is more than one disease present that can cause airflow obstruction, a conclusive diagnosis is difficult. Modifying factors that increase the probability of asthma include a personal or family history of asthma, hay fever or other allergies. It should be remembered at this point, however, that there are two ages of onset of asthma. Asthma that begins in childhood is almost always associated with a strong history of allergy and is likely to be atopic. One final consideration is that some patients with severe, longstanding and poorly treated asthma may develop irreversible airflow obstruction. These patients may still deserve a diagnosis of asthma if all other factors lead to that diagnosis, and if no other good cause for the airflow obstruction is found.





**Figure 2.** Decision tree starting with reversibility criterion followed by PC<sub>20</sub> criterion. Note that 5 PEF missing in the < 9% reversibility branch (see Results).

this group, the question as to whether PC<sub>20</sub> can be replaced by PEF variability as a diagnostic tool is less relevant. This question is particularly relevant for subjects with signs or symptoms suspicious of asthma but without an established diagnosis. Trigg *et al*<sup>19</sup> studied subjects from general practice with and without respiratory symptoms, and found figures similar to our results. A possible explanation of the low correlation might be the subclinical form of the disease in both Trigg *et al*'s study<sup>19</sup> and our population.

Another explanation is related to the method applied to express peak flow variation. We used the arithmetic mean of PEF measurements over a three-week period in our correlation, and this might disguise clinically relevant high PEF variability for only a few days. Therefore, the correlation between the number of days of a PEF variability of 15% and PC<sub>20</sub> histamine was also assessed. However, this did not essentially change the outcome ( $r = -0.26$ ). More frequent measurement, e.g. four times a day, would probably have increased the PEF variability,<sup>13</sup> but it is very unlikely that this would have increased the correlation substantially. From our analysis, it became clear that with a PEF variability of 15% the sensitivity is almost zero, and thus not

very applicable for use in everyday practice. A decrease in the PEF variability would increase the sensitivity, but then the values come so close to normal variability that the findings would lack any specificity.

BHR assessment generally refers to PC<sub>20</sub> histamine assessing BHR. When this is the case, PEF variability cannot replace this. The use of PEF measurements in general practice should be reserved for assessing reversibility.<sup>7</sup> The practical implication of this is that BHR testing would require access to a function laboratory. Although it is possible to perform a provocation test at the surgery,<sup>26</sup> testing in a laboratory setting is preferred for reasons of safety and technical quality of the test performance.

In conclusion, the results of this study suggest that PEF cannot replace PC<sub>20</sub> in testing BHR for the diagnosis of asthma. Where BHR is used as an inclusion criterion for asthma it should be tested by the PC<sub>20</sub>. This has consequences for the possibility of diagnosing asthma in primary care, where there is no easy access to a histamine challenge test.

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