Use of peak flow variability and methacholine responsiveness in predicting changes from pre-test diagnosis of asthma

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ABSTRACT: Asthma is usually diagnosed clinically. This study investigated how methacholine challenge and peak expiratory flow monitoring influenced change from a pretest clinical diagnosis.

Records of 132 patients referred with respiratory symptoms, who subsequently had reliable measurements of both airway responsiveness (provocative concentration of methacholine causing a 20% fall in forced expiratory volume in one second (FEV1 (PC20)) and peak expiratory flow variability (PEFV) were reviewed. Initial and final diagnoses for each patient were classified as: a) definite asthma; b) possible asthma; and c) definitely not asthma. The predictive value of PEFV and PC20 regarding overall change from pre- to post-test diagnosis, change from initial diagnosis of possible or definitely not asthma, and change from initial diagnosis of definite asthma, were tested by multiple logistic regression analysis. Odds ratios for PC20 were expressed per doubling dose, and for PEFV per 5% variability.

Clinical diagnosis of definite asthma and definitely not asthma were confirmed in 70% and 79% respectively. PC20, but not PEFV, predicted an overall change between pre- and post-test diagnosis. Both PC20 and PEFV independently predicted change to definite asthma. PEFV and interaction between PC20 and PEFV predicted a change in those whose initial diagnosis was definite asthma. Although both measurements showed a significant correlation, there was poor agreement between positive tests.

Both peak expiratory flow variability and provocative dose of methacholine causing a 20% fall in forced expiratory volume in one second influence diagnostic decision-making in patients with a high pre-test probability of asthma.
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There have been substantial advances over the past two decades in the understanding of the pathophysiological mechanisms [1] and the treatment of asthma [2]. However, there is still no consensus on a precise definition of this very common disease, for which there is no gold standard for diagnosis [3]. The clinical diagnosis of asthma is based on characteristic patterns of symptoms, and is supported by evidence of airway hyperresponsiveness, variable airflow limitation or response to treatment [4]. Airway hyperresponsiveness (AHR) is commonly assessed by bronchial provocation with methacholine or histamine [5], while variable airflow limitation is detected by observing spontaneous or treatment-related variability in forced expiratory volume in one second (FEV1) or in peak expiratory flow (PEF), expressed as amplitude per cent mean [6], low per cent best [7], or in other less common ways [8]. However, these objective measures do not always correlate strongly with each other [6] and may-measure different pathophysiological aspects of the disease [7–9]. In epidemiological studies, both AHR and PEF variability have low sensitivities and positive predictive values [10, 11], but relatively high negative predictive values for the diagnosis of asthma [10]. In clinical practice, both tests are used routinely and widely in the diagnosis and assessment of asthma [12, 13].

The usefulness of these tests, when applied together, in changing or influencing a pre-test clinical diagnosis or management decision is not known. In the present study, the authors examined how results of methacholine challenge testing and PEF monitoring influence the change from a pre-test clinical diagnosis to the final diagnosis.

Methods

This was a retrospective, single-centre, descriptive study. Medical records of patients referred to one physician at a university respiratory clinic between 1991–1997 for evaluation of respiratory symptoms considered suggestive of asthma, and who had measurements of both AHR and serial PEF ordered as part of their diagnostic work-up, were reviewed by an independent investigator (K. Parameswaran) who had not seen the patients earlier. The diagnosis of the physician at his first assessment of the patient, as recorded in the consultation letter dictated when they did not have the results of either investigation, was

coded as: a) definitely asthma (DA); b) possibly asthma (PA) (uncertain); and c) definitely not asthma (NA).

Methacholine tests were performed by the tidal breathing method of COCKCROFT *et al.* [5] and results expressed as provocative dose of methacholine causing a 20% fall in FEV_1 (PC_{20}) mg·mL^{-1} in noncumulative units. PC_{20} >16 mg·mL^{-1} (20% fall not achieved on final concentration) was recorded as 32 mg·mL^{-1}. PC_{20} <8 mg·mL^{-1} was considered indicative of airway hyperresponsiveness. Home peak flow recordings were performed using the procedure recommended by the European Respiratory Society [14] with a mini-Wright PEF meter (Clement Clarke International Ltd.; Armstrong Medical Industries of Canada, Scarborough, Ontario, Canada), usually for the 2 weeks preceding measurement of PC_{20}. All patients were given standardized instructions by a clinic nurse-educator regarding measuring and charting PEF. PEF was measured between 07:00–09:00 h and between 17:00–1900 h, before inhaling β_2-agonist if required. On each occasion, the best of three attempts was recorded. PEF variability (PEFV) was calculated as the difference between the lowest and highest PEF as a percentage of the highest PEF recorded during a 14 day period, effectively using the analysis of low percentage best [7]. PEFV >20% was considered indicative of variable airflow obstruction.

The PEF records and methacholine test results were scrutinized to select patients who performed both tests accurately and reliably. Patients were excluded if PEF recording was inadequate as defined by any one of the following criteria: a) PEF record for <2 days; b) <2 readings in one day; c) failure to chart PEF on a diary page; or d) if the physician had cause to suspect the credibility of the record. Patients were also excluded if they failed to return for a follow-up review, or if the results of PC_{20} or PEF monitoring were not available. The independent reviewer then coded the final recorded diagnosis of the physician as stated in the follow-up visit reports to the referring physician as: a) DA; b) PA (uncertain); and c) NA.

Analysis

The clinical and demographic characteristics were summarized using descriptive statistics (mean, standard deviation). PC_{20} values were log transformed (base 2) for analysis.

Possibilities for change, or no change, from the initial clinical diagnosis to the final diagnosis were considered in nine categories: 1) DA remaining DA (no change); 2) DA changing to PA; 3) DA changing to NA; 4) PA changing to DA; 5) PA remaining PA (no change); 6) PA changing to NA; 7) NA changing to DA; 8) NA changing to PA; 9) NA remaining NA (no change).

The ability of PC_{20} and PEFV (explanatory variables) to predict change ("1") or no change ("0") from pre-test to post-test diagnosis was analysed by multiple logistic regression analysis (back-ward elimination strategy based on likelihood ratio). The outcome variables were the groups in which there were changes and the groups in which there were no changes from pre- to post-test diagnosis.

Three analyses were performed to answer three different questions: 1) in patients referred to a tertiary referral centre with respiratory symptoms suggestive of asthma, what are the predictive values of PC_{20} and PEFV in influencing a change from pre-test to post-test diagnosis? The outcome variables were: a) the groups in which there was a change from pre-test to post-test diagnosis (groups 2, 3, 4, 6, 7, 8); and b) groups in which there was no change between pre-test and post-test diagnosis (groups 1, 5, 9); 2) In patients whose initial diagnosis was PA (uncertain) or NA, what are the predictive values of PC_{20} and PEFV in making a definite diagnosis of asthma, *i.e.* a change in diagnosis to that of definitely asthma? The outcome variables were: a) groups which changed to a final diagnosis of definite asthma *i.e.* the initial diagnosis was PA or NA and the final diagnosis was DA (groups 4, 7); and b) groups which did not change to a final diagnosis of DA, *i.e.* initial and final diagnoses remained as PA or NA (groups 5, 6, 8, 9); 3) in patients whose initial diagnosis was DA, what are the predictive values of PC_{20} and PEFV in predicting a change to PA or NA? The outcome variables were: a) groups in which the initial diagnosis was DA but the final diagnosis PA or NA (groups 2, 3); and b) group 1 where the initial and final diagnosis remained DA.

Since the independent (predictor) variables are both continuous, the odds ratios (OR) represent the ratio of probabilities of change of one unit magnitude in either PC_{20} or PEFV. The unit of change selected for PC_{20} was one doubling dose, and for PEFV it was 5%.

Correlation between PEFV and log PC_{20} was examined by Pearson's test. The agreement between the two measurements was assessed using Cohen's κ.

Results

Of 204 patients identified as having both tests ordered, 44 did not perform adequate PEF recording for analysis, 24 did not return for follow-up and 4 did not perform methacholine challenge. Of the remaining 132 patients with evaluable data, 51 were initially considered by the consultant physician to have DA, 67 PA and 14 NA. The pre-test diagnoses of DA and NA were confirmed by physician report after a second or subsequent visit in 38/51 (74%) and 11/14 (79%) respectively. Among the 67 patients who had an initial diagnosis of PA, only 7 (10%) remained with an indefinite diagnosis after the results of both tests were obtained. Table 1 provides the demographic and lung function data for patients in each group.

Figure 1 shows the final diagnoses of 51 patients whose pre-test clinical diagnosis was DA, according to values of PC_{20} (< and ≥8 mg·mL^{-1}) and PEFV (< and ≥20%). Figure 2 shows similar information for 67 patients whose initial diagnosis was PA, and figure 3 for 14 patients whose initial diagnosis was NA.

PC_{20}, but not PEFV predicted an over-all change from pre-test to post-test diagnosis (OR=1.35, 95% confidence interval (CI)=1.15, 1.58, coefficient β=0.3, constant= -0.6, sensitivity 83%, specificity 41%, p<0.0001). The OR of 1.35 is the chance for a change in diagnosis when the persons who are compared differ by one doubling dose in PC_{20}. For example, when comparing a person with a PC_{20} of 0.3 mg·mL^{-1} ($\log_2$= -1.74) with another with a PC_{20} of 32 mg·mL^{-1} ($\log_2$=5), the OR for change from the initial to a final diagnosis (in this case DA to NA) can be calculated to be 2.89, as follows:

Table 1. – Demographic and lung function data for all patients

Group	n	Age yrs	Sex F/M	FEV1 % pred	FEV1/VC %	FEV1 % revers.	PEFV % mean	PEFV ≥20% n	PEFV ≥20% %	PC20 mg·mL^{-1} median	PC20 ≤8 mg·mL^{-1} n	PC20 ≤8 mg·mL^{-1} %
Group 1	51	34.5±15.7	28/23	96.8±17.4	78.2±9.6	6.8±8.1	35.2±28.4	33	65	3.5 (0.02, 32)	35	69
1 (DA-DA)	38	35.8±16.6	20/18	95.1±17.6	76.5±8.9	8.4±8.1	39.8±30.5	29	76	1.3 (0.02, 32)	32	84
2 (DA-PA)	4	28.7±13.6	3/1	106.1±12.6	87.8±4.1	2.4±3.2	32.9±22.2	2	50	32 (3.5, 32)	1	25
3 (DA-NA)	9	34.8±14.9	5/4	100.0±18.2	80.4±11.1	4.6±6.4	16.6±8.0	2	22	32 (2.8, 32)	2	22
Group 2	67	42.2±18.8	42/25	97.0±16.2	79.9±8.4	4.5±6.5	22.7±16.0	29	43	32 (0.13, 32)	18	27
4 (PA-DA)	15	43.1±20.1	7/8	92.5±19.2	75.1±7.3	6.9±8.3	36.9±22.0	11	73	3.0 (0.13, 32)	11	73
5 (PA-PA)	7	46.8±20.1	5/2	100.6±19.0	83.3±9.7	5.5±7.8	31.6±16.6	5	71	32 (3.7, 32)	3	43
6 (PA-NA)	45	41.3±18.5	30.15	98.0±14.7	81.0±8.1	3.4±5.2	16.6±8.7	13	29	32 (3.7, 32)	4	9
Group 3	14	39.0±17.6	9/5	94.5±17.0	79.2±9.2	5.5±7.2	27.6±22.4	5	36	16 (0.3, 32)	4	29
7 (NA-DA)	3	35.7±17.6	2/1	83.2±27.3	65.3±9.7	14.9±4.6	49.4±10.0	3	100	0.3 (0.3, 5.0)	3	100
8 (NA-PA)	0	-	-	-	-	-	-	-	-	-	-	-
9 (NA-NA)	11	40.8±16.0	7/4	97.7±13.2	83.4±8.7	1.8±3.6	13.6±12.8	2	18	32 (4.0, 32)	1	9

Data are presented as mean±SD, except for the provocative concentration of methacholine which caused a 20% fall in forced expiratory volume in one second (FEV1) (PC20), which is expressed as the median with the minimum and maximum in parentheses. Group 1 - initial diagnosis: definite asthma (DA); Group 2 - initial diagnosis: possible asthma (PA); Group 3 - initial diagnosis: not asthma (NA). F: female; M: male; VC: vital capacity; revers.: reversibility; PEFV: peak expiratory flow variability.

$$OR = \frac{\text{Probability of PC20 } 32 \text{ mg·mL}^{-1}}{\text{Probability of PC20 } 0.3 \text{ mg·mL}^{-1}}$$

$$= \frac{\dfrac{1}{1 + e^{-(-c+(\beta\log_2 32))}}}{\dfrac{1}{1 + e^{-(-c+(\beta\log_2 0.3))}}}$$

$$= \frac{\dfrac{1}{1 + e^{-(-0.6+(0.3 \times 5))}}}{\dfrac{1}{1 + e^{-(-0.6+(0.3 \times -1.74))}}}$$

$$= 2.89,$$

where c is a constant and β is the coefficient for each variable derived from logistic regression analysis.

Both PC20 (OR=0.4, 95% CI=0.24–0.65) and PEFV (OR=1.37, 95% CI=1.04–1.79) were independent predictors of change in diagnosis to asthma in patients whose initial diagnosis was PA or NA (β for PC20= -0.9, β for PEFV=0.3, constant=0.3, sensitivity 61%, specificity 97%, p<0.0001).

PEFV (OR=0.30, 95% CI=0.11–0.84) and the interaction between PC20 and PEFV (OR=1.30, 95% CI=1.05–1.56) predicted a change in diagnosis in those whose initial diagnosis was DA (β for PEFV=-1.2, β for the interaction=0.23, constant=0.83, sensitivity 77%, specificity 89%, p=0.003). PC20 alone was not a predictor of change in this group.

Although PC20 and PEFV were well correlated (r= -0.5, p<0.01) and a comparable number of patients in each group had PC20 <8 mg·mL^{-1} and PEFV >20% (table 1), there was poor agreement between "positive" tests as defined by the cut-off-points selected (Cohen's κ 0.27, 95% CI 0.11–0.43).
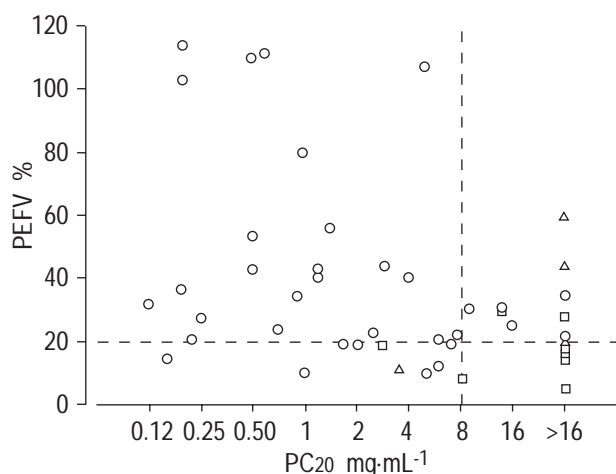

Fig. 1. – Scatter-plot of provocative dose of methacholine which causes a 20% fall in forced expiratory volume in one second (PC20) (log$_2$ scale) against peak expiratory flow variability (PEFV) of 51 patients with an initial diagnosis of definitely asthma, showing the final diagnosis. □ : not asthma; Δ : possible asthma; ○ : definite asthma. Horizontal dashed line represents 20% PEFV which is the upper limit of normal variability. The vertical dashed line represents the cut-off point for abnormal PC20, anything below this is abnormal.
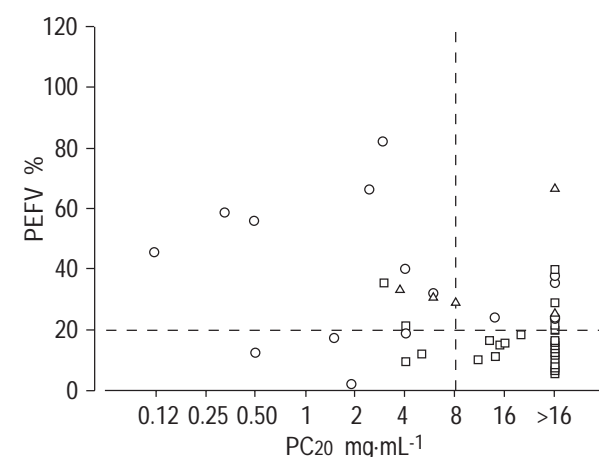

Fig. 2. – Scatter-plot of provocative dose of methacholine which causes a 20% fall in forced expiratory volume in one second (PC20) (log$_2$ scale) against peak expiratory flow variability (PEFV) of 67 patients with an initial diagnosis of possible asthma, showing the final diagnosis. □ : not asthma; Δ : possible asthma; ○ : definite asthma. Horizontal dashed line represents 20% PEFV which is the upper limit of normal variability. The vertical dashed line represents the cut-off point for abnormal PC20, anything below this is abnormal.
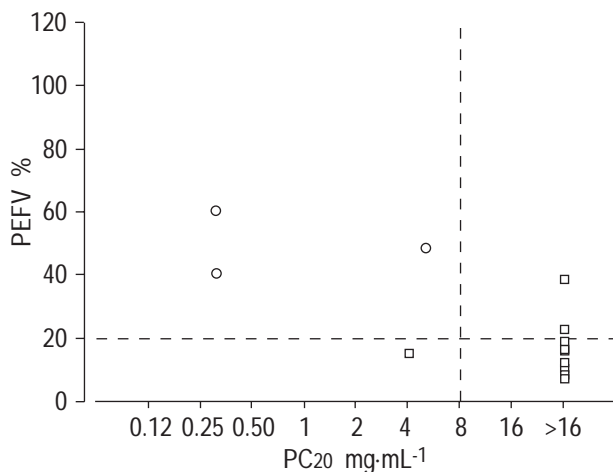
Fig. 3. – Scatter-plot of provocative dose of methacholine which causes a 20% fall in forced expiratory volume in one second (PC20) ($\log_2$ scale) against peak expiratory flow variability (PEFV) of 14 patients with an initial diagnosis of definitely not asthma, showing the final diagnosis. □ : not asthma; ○ : definite asthma. Horizontal dashed line represents 20% PEFV which is the upper limit of normal variability. The vertical dashed line represents the cut-off point for abnormal PC20, anything below this is abnormal.

Discussion

This retrospective study has shown the influence of both methacholine provocation test results (PC20) and PEFV (low per cent best) in confirming or negating an initial diagnosis of DA or NA. The results of methacholine challenge however, were more important than PEFV in predicting overall change of diagnosis in both directions.

The aim of the study was not to evaluate the measurement properties of either hyperresponsiveness to methacholine or PEFV as diagnostic tests for asthma, or the compliance of patients in making PEF measurements, but rather to observe how both tests when applied in conjunction with each other influence a change in pre-test to post-test diagnosis.

Various factors influence the making of a diagnosis, including the clinical presentation, the experience and judgement of the physician, the measurement properties of the diagnostic tests employed and response to treatment. The predictive value of a test refers to the post-test probability of disease after the test results are known, and depends on the sensitivity and specificity of the test and also on the prevalence of the disease (pre-test probability) in the population being tested. Used individually in the Odense School-children study [10], peak flow variability (analysed in that study as the average of the two lowest values as a percentage of the period mean) and methacholine responsiveness had positive predictive values of 45% and 72% respectively while both tests had negative predictive values of 75%, when the pre-test probability of asthma was high. However, currently there is no information on how results of these tests, when applied together, alter the diagnostic decision of the physician. The current study demonstrates that, when the direction of change is not considered, PC20 methacholine influences the overall change in diagnosis. However, when the direction of change is considered, both tests seem to influence decision-making.

In those patients in whom the physician had a high clinical index of suspicion of asthma before the results of the test were available, the result of PEFV was the primary confirmation of diagnosis (fig. 1). However, the decision was also influenced by the results of PC20 (the interaction between the two tests was significant). Hence the physician did not make the decision based solely on PC20 independent of the results of PEFV. For example, the physician would retain an initial diagnosis of asthma or change to a diagnosis of NA with extreme values of PEFV (for instance 50% or 4% respectively) irrespective of the results of PC20. If on the other hand, the PEFV was borderline, for example 20%, the physician would retain the diagnosis of asthma if the PC20 was low and change to a diagnosis of NA if the PC20 was high. In patients whose initial diagnosis was PA or NA, the change to a final diagnosis of asthma was influenced by both peak flow variability and methacholine airway responsiveness (figs. 2 and 3). In all, only 9 patients had a final diagnosis of DA, and 4 patients remained as uncertain, when both PC20 and PEFV were normal. Seven subjects had PC20 <8 mg·mL^{-1} but were not considered to have asthma: final diagnoses in these patients were cough from gastroesophageal reflux, post-viral bronchitis (3 subjects), cough from angiotensin converting enzyme inhibitor treatment, airway irritability with anxiety, and unrelated symptoms (present when PEF was normal).

The correlation observed in this study between PC20 methacholine and peak flow variability was less than that which has been previously reported [15]. This is related to the population studied, the use of bronchodilators and different methods of analysis in other studies. Measurements are more reliable when they are performed under the careful setting of a research study, whereas this retrospective study is a reflection of measurements in usual clinical practice in a tertiary referral centre. The use of bronchodilators was not considered in calculating PEFV in the current study, except that the highest value for PEF may well have been after the use of a bronchodilator. Post-bronchodilator PEFV has been shown to have better correlation with PC20, using the average of daily maximum and minimal values to define variability [15]. Co-interventions, including the use of nasal corticosteroids (n=8), long acting anti-histaminics (n=6) and allergen immunotherapy (n=1), may also have affected the results. The authors also observed poor agreement between "positive" tests defined by cut-off-points of 8 mg·mL^{-1} and 20% for PC20 methacholine and this method of analysing peak flow variability respectively, suggesting perhaps that a lower value of PEFV might be more useful in making a diagnosis of asthma [16].

The results of the study are subject to a number of limitations. The data was collected retrospectively from the referral practice of a single physician interested in asthma, hence increasing the pre-test probability of the disease and selection bias. The patients selected were those in whom both tests had been ordered. The physician did not request PC20 measurement in patients with moderate to severe airflow limitation (FEV1/vital capacity (VC) <65%) for safety reasons, even if a clinical diagnosis of asthma was entertained. Instead, these patients had their PEF monitored and FEV1 reversibility with a β-agonist measured to make a diagnosis of asthma. These factors introduce a selection bias towards subjects with a less certain diagnosis

of asthma. "Parallel testing" or applying multiple tests concurrently increase the sensitivity and therefore the negative predictive value for a given disease prevalence above those of each individual test, while lowering the specificity and positive predictive values. The maximum number of diagnostic shifts (n=45) was from a pre-test diagnosis of PA to a post-test diagnosis of NA (table 1), in keeping with the above observation. The addition of an extra measurement of disease activity, for example, measurement of eosinophils in sputum as a marker of airway inflammation, might increase the negative predictive value even higher.

In conclusion, it has been shown that both methacholine responsiveness and peak expiratory flow variability affect the decision making process of a physician in a tertiary referral centre, in making a diagnosis of asthma. This highlights the usefulness of both tests when used in conjunction, in evaluating patients with possible asthma.

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