The development of Oasys-2; a system for the analysis of serial measurement of peak expiratory flow in workers with suspected occupational asthma

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Abstract

Background: Serial peak expiratory flow (PEF) measurement is usually the most appropriate first step in the confirmation of occupational asthma. Visual assessment of the plotted record is more sensitive and specific than statistical methods so far reported. The use of visual analysis is limited by lack of widespread expertise in the methods. A computer-assisted diagnostic aid (Oasys-2) has been developed which is based on a scoring system developed from visual analysis. This removes the requirement for an experienced interpreter and should lead to the more widespread use of the technique.

Methods: PEF records were collected from workers attending an occupational lung disease clinic for investigation of suspected occupational asthma and from workers participating in a study of respiratory symptoms in a postal sorting office. PEF records were divided into 2 development sets and 2 gold standard sets. The latter consisted of records from workers in which a final diagnosis had been reached by a method other than PEF recording. An experienced observer scored individual work and rest periods for the 2 development set PEF records; linear discriminant analysis was used to compare measurements taken from development set 1 records with visual scores. Two equations were produced which allowed prediction of scores for individual work or rest periods. The development set 2 was used to determine how these scores should be used to produce a whole record score. The first gold standard set was used to determine the whole record score which best separated those with and without occupational asthma. The second set determined the sensitivity and specificity of the chosen score.

Results: 268 PEF records were collected from 169 workers, these were divided into 2 development sets (81 and 60 records) and 2 gold standard sets (60 and 67 records). Linear discriminant analysis produced equations predicting the score for work periods incorporating 5 indices of PEF change, and one for rest periods using 7 indices. These equations correctly predicted the score for development set 1 work and rest periods on 61% of occasions (kappa 0.47). The whole record score for development set 2 records, after weighting for definite or definitely no occupational effect, correlated with the visual score (Correlation Coefficient 0.86). Comparison with Gold Standard Set

1 identified a cut off which proved to have a sensitivity of 75% and a specificity of 94% for an independent diagnosis of occupational asthma when applied to gold standards set 2.

Conclusion: These results suggest that the sensitivity and specificity of analysing PEF records for occupational asthma using Oasys-2 approaches that of visual analysis, but should be absolutely reproducible. Oasys-2's performance is more specific and approaches the sensitivity of other statistical methods of analysis. The evaluation on a large number of PEF records from workers exposed to different sensitising agents suggests that these result should be robust and should be repeatable in clinical practice.

Background

The diagnosis of occupational asthma can usually be suspected from the history. Confirmation of the diagnosis is important as the consequences for the worker, both in terms of health and livelihood, are considerable[1]. The most applicable currently available test is the serial measurement of PEF[2,3]. However, self measurement of PEF is not without its problems: there is a variable time delay between exposure and asthma, many meters are non-linear[4], workers vary in their ability to perform unsupervised recordings, and often show a learning effect at the start of a record. The meters may be incorrectly read and falsification of records is possible. Individuals with occupational asthma also develop asthma related to non-specific triggers, particularly exercise and respiratory infection. These changes, and the changes due to treatment, need to be differentiated from those due to work exposure.

Burge's original study divided the PEF record into work and rest periods, each period was then visually classified as showing work-related change or not [2,3]. A whole record subjective score was then produced as a percentage of work and rest periods in the record showing work-related changes. A cut off of 75% produced a specificity of 100% with a variable sensitivity ranging from 42 - 77% when compared to a final diagnosis based on re-exposure at work. Further work has shown this method to be reasonably reproducible between experienced interpreters[5]. A number of other authors have ascertained the sensitivity and specificity of visual interpretation of different PEF plot formats on worker groups exposed to a single agents and other groups exposed to a variety of agents. A summary of result are shown in Table 1.

Visual inspection of plotted PEF records has on the whole been found to be more sensitive and specific than statistical analysis. A summary of the results of other statistical analyses are shown in table 1. The problems with statistical analysis arise because improvement away from work may be progressive over several days resulting in some work days having higher PEF readings than rest days (Figure 1).

We describe the development and evaluation of a computer-based decision aid (Oasys-2) for use with PEF records. The aims were to develop a computer-assisted diagnostic aid for the identification of occupational asthma from serial PEF records plotted as daily maximum, mean and minimum and to evaluate the developed diagnostic aid to determine its sensitivity and specificity when applied to a wide range of PEF records taken by workers from different industries with and without occupational asthma

Method

PEF records used in the study were collected as previously described [2,3]. Workers were asked to measure PEF 2-hourly from waking to bed time, recording the best of 3 blows. If the highest two readings differed by more than 20 litres/min, then more readings were required. The minimum criteria required for a record to be included in this study was PEF readings over 2 work and 2 rest periods, with at least 4 readings per day. Records which contained PEF patterns which made the plot visually uninterpretable were excluded; these included drops in PEF associated with respiratory tract infection, and gradual improvements or deteriorations across the whole record. PEF records were collected sequentially from workers attending an occupational lung disease clinic with suspected occupational asthma and from a cross-sectional survey of respiratory symptoms in post office sorting workers. Four sets of PEF record were used: 2 development sets and 2 gold standard sets, the latter sets from workers on whom a final diagnosis had been made using methods unrelated to serial PEF measurements. These non-PEF methods included specific bronchial provocation testing; a clear history of asthmatic symptoms related to work exposure which improved away from work, supplemented with either significant levels of specific IgE to a relevant occupational allergen or a fourfold change in non-specific bronchial responsiveness between periods at and away from work. We also included workers in whom symptoms had been completely abolished by removal from exposure to the causative agent. Gold Standard negative records were supplemented by asymptomatic workers who had participated in the cross-sectional survey of respiratory symptoms in the post office, and workers who had a final diagnosis of occupational asthma, but were now relocated away from exposure to the causative agent.

The mean PEF value for each work "day" (starting with the first reading at work and continuing to the last reading before work the next day) was calculated and plotted with the maximum and minimum PEF for this period in the manner shown in Figure 1. Diurnal variation for each "day" expressed as percent predicted and the number of readings per day were also included on the plot. Fixed scale plots (1 cm = 20 l/min) of the PEF records in development set 1 were visually scored from 0 (no evidence of work-related effect) to 100 (definite work-related effect) for each consecutive period of work or rest "days". Fifty possible measurements, qualitatively felt to best describe change between consecutive work / rest periods, were entered into a linear discriminate analysis[6]. Measurements from work and rest periods were analysed separately. Linear dicriminant analysis determines which measurements are most predictive of the visual score, it works most efficiently when there are a small number of categorical scores. The visual scores were therefore divided into 4 group as follows: 1 = 0 (no effect of work), 2 = 1-49 (possible work effect), 3 = 50-99 (probable work effect) and 4 = 100 (definite work effect) based on what they signified to the scorer. The discriminate analysis also produces an equation to apply to the identified measurements to predict score group membership.

The equations were applied to development set 2 to evaluate them on a new set of PEF records which had been scored visually. A mean of the individual work and rest period scores was used, weighting score groups 1 and 4 by a factor of 2 to produce a whole record score. This was because the degree of certainty attached to a visual score of 1 (no effect of work) or 4 (definite work-related effect) was greater than that applied to a score of 2 (possible work effect) or 3 (probable work effect).

The equations and the technique for calculating a whole records score (together termed Oasys-2) were applied to first gold standard set, to determine the sensitivity and specificity of different whole record cut off scores for the presence or absence of a work-related effect as determined by the gold standard result.

The cut off point determined on the first gold standard set was then applied to whole record scores calculated for the second gold standard set to determine a final sensitivity and specificity for the presence of a work-related effect as determined by the gold standard result.

Results

Details of the 4 PEF sets used to develop and evaluate Oasys-2 are summarised in Table 2, a total of 268 records were used from 169 workers. In the cases of workers from whom more than one PEF records were used in the study, only 4 individuals PEF records appeared in both development and gold standard sets, however, these were completely different records seperated by long periods of time with different exposures. The mean duration of each PEF record was 26 - 37 days depending on the set; the mean number of work periods was 3.5 - 5.1 and rest periods 3.5 - 5.2 per record; the mean number of PEF readings per day in each group was 7.5 - 8.1, consistent with the instruction to perform 2 hourly PEF measurement whilst awake. All groups contained PEF records from workers exposed to a wide variety of agents with a mixture of workers taking no medication; inhaled bronchodilators alone and bronchodilators with inhaled steroids. Development set 1 was the largest, all types of PEF record were represented, including the most difficult type, those which were equivocal for the presence of a work-related effect (14%). Sixty four percent of the records were not thought to show a work-related effect. A similar distribution of PEF records was seen in development set 2 (10% equivocal, 62% no work-related effect). Both gold standard sets contained a relatively even distribution of records from workers with occupational asthma (45% and 48%). The methods used for independent diagnosis in the gold standard sets are shown in table 2.

Development set 1

From 81 PEF records 223 work and 246 rest periods were visually scored. Five measurements of PEF change for work periods and 7 for rest periods were identified by the linear discriminate analysis as being most predictive of the visual score group, these are shown in figures 2 and 3. The equations produced by the analysis are shown in the Appendix. Table 3 compares the score group attached to work and rest periods in development set 1 by visual analysis with that predicted by applying the equations. Seventy three percent of work periods were correctly predicted by the equation as group 1 (no effect of work) when compared to that given by visual analysis, 51% correctly predicted as group 2 (possible work-related effect), 55% correctly predicted as group 3 (probable work-related effect) and 55% correctly predicted as group 4 (definite work-related effect); 2 (4%) work periods were incorrectly predicted by more than 1 group but no work periods were incorrectly predicted by more than 2 groups. Eighteen (7%) rest periods were incorrectly predicted by more than 1 group and 1 (0.4%) rest period was incorrectly classified by more than 2 groups. The equation for rest periods appeared to produce more significant errors in score prediction compared with work periods. Over all the percent assigned to the correct score group by both equations was 61%. A moderate strength of agreement was suggested by a kappa of 0.47 for both work and rest periods. Considering any pattern in the prediction of an incorrect score: for work periods 21% of incorrect predictions were underscores and 18% over-scores; for rest periods 19% were underscores and 20% over-scores.

Development set 2

The results of the comparison of weighted whole record scores produced by visual analysis and Oasys-2 on the 60 test PEF records are shown in Figure 4. The figure shows a qualitatively good association between the 2 methods of analysis, the Pearson Correlation Coefficient was 0.86.

Gold Standard Evaluation 1

The sensitivity and specificity for different cut off scores when applied to the scores produced by applying Oasys-2 to PEF records from gold standard set 1 are shown in Figure 5. A cut off of greater or equal to a predicted score of 2.51 maximised sensitivity while maintaining a specificity of 100%. At this cut off, no PEF record was predicted as having occupational asthma when this was not thought to be the final diagnosis; 8 (30%) PEF records were predicted as not having occupational asthma when this was thought to be the final diagnosis.

Gold Standard Evaluation 2

The cut off of greater or equal to 2.51 was then applied to the Oasys-2 whole record scores from gold standard set 2 PEF records. Thirty two workers had an independent diagnosis of occupational asthma, which Oasys-2 correctly predicted in 24. The scores for the remainder were between 1.7 and 2.38. Thirty five records came from workers without occupational asthma, Oasys-2 scores exceeded 2.51 in two. The PEF records concerned both came from post office workers who gave no history of respiratory symptoms on questionnaire. Reviewing the 2 PEF records visually: one record showed diurnal variation of up to 30% and a definite work-related effect, this record scored 3.29; the other record showed low diurnal variation and small improvements in PEF away from work, this record scored 2.71. Further investigation of these 2 individuals is indicated. These results show a sensitivity of 75%, a specificity of 94%.

Discussion

Peak expiratory flow measurement is a technology available to nearly everybody, its use in the initial assessment of occupational asthma is therefore attractive both for the worker, who avoids hospital stays for specific bronchial provocation testing, and for doctors, as the costs and resources needed are far lower. If occupational asthma exists it should be possible to demonstrate changes in PEF related to occupational exposure. Several authors have shown that subjective assessment of plotted records is superior to statistical analysis[2,3,9,10] the main limiting factor is the expertise needed for reproducible subjective analysis, and the credibility of such a method. We have therefore tried to develop an assessment system which removes the subjectivity and non-reproducibility of expert assessed records. We have based the system, which we call Oasys-2 (because it is based on comparisons between two adjacent parts of the record), on the established method of serial PEF plotting[2,3] which accentuates the differences between days at and away from work. We have started by trying to reproduce the expert assessor, and then used the resulting scores on PEF records with independently made diagnoses. The final evaluation is therefore independent of the subjective assessments. The final evaluation has classified individuals as either having or not having occupational asthma. This classification is probably too simplistic, as some records were taken from workers who were only intermittently exposed, or who had been removed from direct exposure to the offending agent, where significant changes in PEF related to exposure may not necessarily be seen. Similarly some records were from workers taking large doses of inhaled corticosteroids, which would tend to mask any work-related effect[2,3]. The results presented suggest that the sensitivity and specificity of analysing PEF records for occupational asthma using Oasys-2 approaches that of visual analysis. The specificity of 94% is greater than that obtained in all but Burge's original work. The latter used PEF records from worker groups exposed to single agents. A sensitivity of 75% approaches that of other evaluations despite many of the worker taking inhaled corticosteroids. Oasys-2 is also more specific with approaching the sensitivity of other statistical methods of analysis.

Factors which reduce the sensitivity and specificity of analysis by Oasys-2 include the fact that it still relies on self recorded PEF which suffers from problems of poor technique and sometimes, when compensation is an issue, frank falsification. Analysis is also critically dependant on knowing when a worker is exposed to a sensitising agent, this is often difficult to assess particularly when exposure is intermittent. This can be sometimes be overcome by detailed record keeping by the worker, however, because of the nature of many sensitisers, the worker may be unaware when exposure has occurred. Oasys-2's formula are based on the opinion of an experienced interpreter who like any person has good and bad days and as such will not be totally reproducible. It is therefore likely that the development set 1 contained incorrectly scored work or rest periods which may have detracted from the performance of the linear discriminant analysis. Another factor which may affect assessment of sensitivity and specificity is the quality of gold standards. False negative and false positive bronchial provocation tests can occur. A number of workers seen on our own unit have made dramatic recoveries when removed from exposure because of positive PEF recording despite having a negative specific bronchial challenge. It is notoriously hard to reproduce exactly the conditions at work when performing specific bronchial challenges; consequently negative results do not always equate with the absence of occupational asthma. Similarly, if challenges are not correctly controlled, false positive results may be produced by either irritant levels being achieved or a worker wishing to create a positive result. Another problem specific to this evaluation was the choice of gold standard negative records. We rarely perform bronchial provocation tests in workers who are unlikely to have occupational asthma. This leaves workers with PEF records and negative specific bronchial challenge in short supply. In this evaluation we therefore used records from asymptomatic post office workers in whom we had no reason to suspect occupational asthma. A number of these records showed no evidence of asthma which may have served to assist Oasys-2 in correctly diagnosis them as not showing occupational asthma.

Despite these draw backs of PEF recording, visual analysis and evaluation of the results produced by Oasys-2 are encouraging. In clinical practise specificity is the most important index to evaluate in an investigation for occupational asthma, because of the clinical and financial implications of a diagnosis of occupational asthma[1]. A lower sensitivity is more easily tolerated as workers with false negative PEF's are likely to undergo further investigation if they have a good history of occupational asthma. The high specificity produced by Oasys-2 when applied to a large number of PEF records from workers exposed to different sensitising agents suggests that this is a useful diagnostic aid which can be used in clinical practise by Chest and Occupational Physicians. Oasys-2 is currently being made available to these Physicians for further evaluation in a more general clinical and occupational setting. Physicians will need to enter the data (by hand or downloading directly from electronic PEF meters), having excluded the poorest quality records, Oasys-2 will then produce a standard PEF plot (Figure 1) and a report with an overall score and conclusion. Oasys-2 is viewed as a prototype analysis system which may be improved in the future by the addition of refined analysis packages.

Occupational asthma remains a disease which is very substantially under-diagnosed[7], we hope that Oasys-2 will help make the diagnostic process easier. The demonstration of occupational asthma still leaves the problem of finding the specific cause, for which serial PEF measurements are not usually very helpful.

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Table 1: Summary of the results of previous evaluations of visual and statistical analysis

	Visual	analysis	Statistical	analysis	
Patient group exposure	**Sensitivity (%)**	**Specificity (%)**	**Sensitivity (%)**	**Specificity (%)**	**Author**
Isocyanate / Colophony	42 - 77	100	50-93	40-67	Burge et al[6,7]
Western Red Cedar	86	89	-	-	Cote et al[8].
Western Red Cedar	87	90	66-93	80-90	Cote et al[9]
Mixed Agents	81	74	44-76	14-78	Perrin et al[10]
Mixed Agents	-	-	72	53	Liss et al[11]

Table 2: Summary of Development Set 1, Development Set 2, Gold Standard 1 and Gold Standard 2 PEF sets

	Development Set 1	Development Set 2	Gold Standard 1	Gold Standard 2
Number of records	81	60	60	67
Isocyanate exposure	17%	21%	8%	3%
Oil mist exposure	15%	6%	0	9%
Metal exposure (Cr, Ni, Co)	10%	10%	8%	0
Flour exposure	4%	6%	0	4%
Colophony exposure	7%	6%	5%	7%
Epoxy resin exposure	4%	4%	0	9%
Glutaraldehyde exposure	0	0	7%	0
Wood dust exposure	0	6%	0	0
Post office dust exposure	0	0	38%	51%
Other exposures	43%	41%	34%	17%
Mean record duration (Days)	32	37	26	26
Mean readings per day	8.1	7.8	7.5	7.6
Mean number work periods	4.5	5.1	3.5	3.8
Mean number rest periods	4.5	5.2	3.5	3.7
Whole record opinion - visual interpretation:				
Occupational asthma	29 (36%)	23 (38%)	-	-
Equivocal	11 (14%)	6 (10%)	-	-
Asthma (not work-related)	26 (32%)	15(25%)	-	-
Normal / COPD	15 (18%)	16 (27%)	-	-
Independant diagnosis:				
Occupational asthma	-	-	27 (45%)	32 (48%)
No occupational asthma	-	-	33 (55%)	35 (52%)
Method of independant diagnosis:	-	-		
Specific challenge	-	-	14 (23%)	17 (25%)
Bronchial Hyperreactivity	-	-	8 (13%)	5 (8%)
Positive IgE RAST	-	-	4 (7%)	9 (13%)
Asymptomatic post office worker	-	-	24 (40%)	34 (51%)
Other	-	-	10 (17%)	2 (3%)

Table 3: Comparison of visual scores with scores predicted by Oasys-2 for the development set 1. Work periods (rest periods in brackets)

	Number of	Oasys-2 group score (%)			
Group assigned by expert	**complexes**	**1**	**2**	**3**	**4**
Group 1 (no occupational asthma)	84	61	21	2	0
	(104)	(66)	(35)	(3)	(0)
Group 2 (possible occupational asthma)	51	9	26	16	0
	(43)	(3)	(33)	(6)	(1)
Group 3 (probable occupational asthma	33	0	12	18	3
	(45)	(5)	(15)	(21)	(4)
Group 4 (occupational asthma)	55	0	8	17	30
	(54)	(1)	(9)	(14)	(30)

Figure 1: PEF plot

Two hourly serial PEF records performed on days at and away from work. The maximum, mean and minimum is plotted for each day. The mean is the mean of all the readings performed on that day. Days involving any period at work are shaded, different types of shading representing different work shifts. Diurnal variation as percent predicted (maximum PEF - minimum PEF / predicted PEF) and number of PEF readings per day are also shown.

Figure 2: PEF indices determined to be predictive of work-related change for work periods. (Lower case letters refer to point marked on the PEF plot)

mean of daily PEF means preceding (rest period) - maximum of daily PEF means (work period)

a - b

maximum of daily PEF means following (rest period) - mean of daily PEF maximums (work period)

c - d

mean of daily PEF means preceding (rest period) - mean of daily PEF means (work period)

a - e

minimum of daily PEF means preceding (rest period) - minimum of daily PEF means (work period)

f - g

mean of daily PEF maximums following (rest period) - mean of daily PEF maximums (work period)

h - d

Figure 3: PEF indices determined to be predictive of work-related change for rest periods. (Lower case letters refer to point marked on the PEF plot)

mean of daily PEF means (rest period) - maximum of daily PEF means preceding (work period)

a -b

mean of daily PEF means (rest period) - minimum of daily PEF means preceding (work period)

a - c

mean of daily PEF mean (rest period)- mean of daily PEF means preceding (work period)

a - d

mean of daily PEF minimums (rest period) - mean of daily PEF maximums preceding (work period)

e - f

mean of daily PEF means (rest period) - mean of daily PEF minimums preceding (work period)

a - g

mean of daily PEF minimums (rest period) - maximum of daily PEF means following (work period)

e - h

mean of daily PEF maximums (rest period) - mean of daily PEF maximums following (work period)

i - j

Figure 4: comparison of visual weighted whole record scores with Oasys-2 scores for the development set 2

Figure 5

Curve used to determine the cut off point for whole record score which maximises sensitivity while maintaining a specificity of 100%

Appendix

These equations allow a value to be calculated for each of the 4 score groups (1 = experienced interpreter score of 0, 2 = 1 to 49, 3 = 50 to 99 and 4 = 100). The group with the highest value is the group score predicted by the equation.

Equation produced by discriminate analysis for predicting work period scores

		Group Membership			
		Coefficients			
PEF Indices (measures on figure 2)		**1**	**2**	**3**	**4**
mean mean PEF preceding rest period - maximum mean PEF work period	multiply by	-0.129	-0.128	-0.124	-0.178
(a - b)		plus	plus	plus	plus
maximum mean PEF following rest period - mean maximum PEF work period	multiply by	0.034	0.020	-0.011	0.032
(c - d)		plus	plus	plus	plus
mean mean PEF preceding rest period - mean mean PEF work period	multiply by	0.109	0.130	0.176	0.327
(a - e)		plus	plus	plus	plus
minimum mean PEF preceding rest period - minimum mean PEF work period	multiply by	-0.030	0.001	0.001	-0.043
(f - g)		plus	plus	plus	plus
mean maximum PEF following rest period - mean maximum PEF work period	multiply by	-0.038	-0.018	0.003	0.003
(h - d)		plus	plus	plus	plus
Constant		-2.073	-2.107	-2.635	-4.901

Equation produced by discriminate analysis for predicting rest period scores

		Group Membership			
		Coefficients			
PEF Indices (measures on figure 3)		1	2	3	4
mean mean PEF rest period - maximum mean PEF preceding work period	multiply by	-0.068	-0.084	-0.030	-0.149
(a - b)		plus	plus	plus	plus
mean mean PEF rest period - minimum mean PEF preceding work period	multiply by	-0.043	-0.044	0.065	-0.057
(a - c)		plus	plus	plus	plus
mean mean PEF rest period - mean mean PEF preceding work period	multiply by	0.094	0.166	-0.025	0.361
(a - d)		plus	plus	plus	plus
mean minimum PEF rest period - mean maximum PEF preceding work period	multiply by	-0.037	-0.017	0.002	-0.036
(e - f)		plus	plus	plus	plus
mean mean PEF rest period - mean minimum PEF preceding work period	multiply by	0.013	0.008	0.032	0.012
(a - g)		plus	plus	plus	plus
mean minimum PEF rest period - maximum mean PEF following work period	multiply by	0.009	-0.009	-0.015	-0.002
(e - h)		plus	plus	plus	plus
mean maximum PEF rest period - mean maximum PEF following work period	multiply by	-0.017	0.004	0.056	0.021
(i - j)		plus	plus	plus	plus
(constant)		-2.925	-2.369	-3.489	-6.595

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