DEVELOPMENT AND VALIDATION OF A DIAGNOSTIC TOOL FOR OCCUPATIONAL ASTHMA BASED ON SERIAL LUNG FUNCTION MEASUREMENTS

BY

VICKY CLARE MOORE

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THESIS ABSTRACT

Serial peak expiratory flow measurements (PEF) are recommended as an initial investigation in the confirmation of occupational asthma. Plotting measurements in Oasys gives reproducible results and can be used by non-experts. I report a new analysis, the area between curves (ABC) score, which gives 72% sensitivity and 100% specificity using a cut off of 15 L/min/h. Two-hourly measurements of PEF require 8 work days and 3 rest days for sensitive and specific analysis. Serial PEF records with long periods off work (≥ 4 consecutive days) show improved sensitivity from 73% to 80%, implying that 7 more workers in every 100 would be diagnosed. In a comparison of forced expiratory volume in one second (FEV1) to PEF, PEF was more sensitive to diurnal changes than FEV1, although FEV1 was more reproducible. Exhaled breath nitric oxide (FE_{NO}) showed similar ABC scores between those with normal and raised $FE_{NO.}$ FE_{NO} was significantly correlated to methacholine reactivity. In shift workers, mean ABC scores were increased on morning shifts compared to nights, but the cut off of 15 L/min/h would be applicable across all shift types. The ABC score is a new robust method of confirming occupational asthma requiring shorter records than the Oasys score.

DEDICATION

For *Skipper*

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PUBLICATIONS ARISING FROM THIS THESIS

First author papers:

- Moore VC, Jaakkola MS, Burge CB, Robertson AS, Pantin CF, Vellore AD, Burge PS. A new diagnostic score for occupational asthma: the area between curves (ABC score) of peak expiratory flow on days at and away from work. *Chest* 2009;135:307-314.

- Moore VC, Jaakkola MS, Burge CB, Pantin CF, Robertson AS, Vellore AD, Burge PS. PEF analysis requiring shorter records for occupational asthma diagnosis**.** *Occupational Medicine* 2009;59:413-417.

- Moore VC, Jaakkola MS, Burge CBSG, Pantin CF, Robertson AS, Burge PS. Do long periods off work in PEF monitoring improve the sensitivity of occupational asthma diagnosis? *Occupational and Environmental Medicine* 2010; in press.

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- Moore VC, Jaakkola MS, Burge PS. A systematic review of serial peak expiratory flow measurements in the diagnosis of occupational asthma. *Annals of Respiratory Medicine* 2010;1:31-44.

Second author papers:

- Burge CBSG, Moore VC, Pantin CFA, Robertson AS, Burge P.S. The diagnosis of occupational asthma from timepoint differences in serial PEF measurements. *Thorax*. 2009;64:1032-1036.

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LIST OF ABBREVIATIONS

PEF	Peak expiratory flow
FEV_1	Forced expiratory volume in one second
FVC	Forced vital capacity
IgE	Immunoglobulin E
HMW	High molecular weight
LMW	Low molecular weight
SIC	Specific inhalation challenge
LCL(W)	Lower control limit at work
PB	Personal Best
SD	Standard deviation
RAST	Radioallergosorbant test
ELISA	Enzyme Linked ImmunoSorbent Assay
EAST	Enzyme-allergosorbent test
TDI	Toluene diisocyanate
HDI	Hexamethylene diisocyanate
MDI	Methylene diphenyl diisocyanate
FE_{NO}	Fractional exhaled nitric oxide
ICS	Inhaled corticosteroids
RTI	Respiratory tract infection
SWORD	Surveillance of Work Related and Occupational Respiratory Disease
PROPULSE	PROject PULmonaire SEntinelle
SORDSA	Surveillance of Work-related and Occupational Respiratory Diseases in South Africa
ONAP	Observatoire National des Asthmes Professionnels
NODS	Notifiable Occupational Disease System
SABRE	Surveillance of Australian workplace Based Respiratory Events
FROD	Finnish Register of Occupational Disease
ABC	Area between curves
WEI	Work effect index

ROC	Receiver operator characteristic
CI	Confidence interval
DV	Diurnal variation
COV	Coefficient of variation
ANOVA	Analysis of variance
PD_{20}	Dose of histamine or methacholine causing a 20% fall in FEV_1
BOHRF	British occupational health research foundation
SIGN	Scottish intercollegiate guidelines network
NSBR	Non-specific bronchial reactivity
PPB	Parts per billion

1. INTRODUCTION

Asthma is an inflammatory disease which affects the small airways in the lungs and is characterised by reversible airway narrowing, for example in response to allergens or non-specific stimuli. When a person has a response to a stimulus, active mediators such as histamine, leukotrienes and prostaglandins are released that act on surrounding tissues causing vasodilation, smooth muscle contraction, and inflammation. These lead to sputum production in the airways and to symptoms such as cough, shortness of breath and chest tightness. Stimuli can act non-specifically on the airways to cause a reaction, such as if histamine is inhaled or in other non-specific challenge tests, or by immunological mechanisms, such as immunoglobulin E (IgE) mediated responses. For some stimuli, we do not know the mechanism of action.

Clinically, asthma shows a variety of features and may be difficult to diagnose as there is no one gold standard definition and different guidelines suggest slightly different criteria that should be applied. Recent guidelines from the British Thoracic Society [1] tabulate features which increase the probability of having asthma and features that are linked to a lower probability. Those that increase the probability of asthma include symptoms such as wheeze, breathlessness, chest tightness and cough, particularly if these are worse at night or in the morning, occur when exposed to cold air or common allergens or when exercising. Other features such as atopy (reactions to common environmental allergens), obstructive spirometry (low FEV_1 [forced expiration in one second] or peak expiratory flow [PEF]) and the presence of sputum or blood eosinophilia also play a role. If obstructive spirometry is not present (particularly when the patient is asymptomatic) this

does not exclude asthma. These symptoms may however be present in other diseases therefore further lung function testing and investigations should be undertaken to exclude conditions such as chronic obstructive pulmonary disease (COPD). In adults, a clinical history should be taken to identify a possible cause of the asthma, including occupational exposures.

Occupational asthma accounts for approximately 9-20% of all adult asthma [2-4] and it is one of the most common occupational health issues. Several definitions for occupational asthma have been proposed, but presently there is no one internationally agreed definition. It is agreed that the causal agent should be specific to the workplace [5-11], but some original definitions also stated that there should be a sensitising mechanism [8;9;12]. However, specific IgE is only evident in a minority of cases of occupational asthma and occupational exposures can cause asthma by acute irritant exposures without immune sensitisation (often called reactive airways dysfunction syndrome, RADS), and perhaps even by less acute irritant mechanisms. More recently, evidence-based guidelines for the identification, management and prevention of occupational asthma have proposed two types of occupational asthma: 1) “hypersensitivity induced occupational asthma” in which the mechanism may or may not be known and the workers show a latent period between exposure and symptoms, and 2) “irritant induced occupational asthma” where the asthma is thought to be due to an irritant mechanism and a latent interval is not required [13]. This latter category includes RADS where a worker is exposed to high levels of an irritant agent and chronic asthma develops as a result. The difficult group from a diagnostic point of view are those who have had asthma previously and it reoccurs or those that have an increase in symptoms of current asthma due to occupational exposures without clear

latency. These workers are normally excluded from definitions of occupational asthma and other terms such as “work aggravated asthma” are used. [14]

An example of a group that could have an irritant-type of occupational asthma are winter sports athletes who are exposed to cold air for long periods. Cold air is generally considered to be an non-specific irritant stimuli, but it appears to cause asthma in some elite athletes such as cross-country skiers, ice hockey players, long distance runners and swimmers [15-20]. Larsson *et al* studied 42 elite skiers from cross country ski clubs in Sweden and 29 referents and found that 14 skiers had asthma compared to 1 control subject. None of the 14 had childhood asthma [20]. For those whose occupation is as a winter athlete or other cold air professions, this could potentially be a cause of occupational asthma.

The diagnosis given by a clinician affects the compensation that a worker can receive and should lead to removal from exposure to the causal occupational agent to achieve the best prognosis. In the UK, occupational asthma is compensated whereas work-aggravated asthma is not. Overall, if a suspicion of occupational asthma is raised, the current best practise is to refer the worker to a specialist clinic for further investigations [1]. There can however be a long delay between the first symptom and referral. This may make the diagnostic procedure more difficult, for example if the patient’s work tasks have changed before he/she is seen at the specialist clinic, and may also adversely affect their prognosis. It would be preferable to start the diagnostic tests immediately when the suspicion of occupational asthma has arisen, i.e. by the General Practitioner or Occupational Health Physician. Performing serial PEF measurements while the worker is at work and away

from work can be used as a first-line diagnostic test, and can easily be implemented in primary care. However, interpretation of the results of serial lung function recordings needs training and experience, which is why this is preferably done by a specialist. Developing diagnostic scores that can be computed automatically through software could achieve the diagnosis earlier and more reliably.

2. LITERATURE REVIEW

2.1. INVESTIGATIONS FOR OCCUPATIONAL ASTHMA DIAGNOSIS

2.1.1. Clinical history and questionnaires

The clinical history is one of the most important parts of occupational asthma diagnosis. It is essential to find out about a worker's current employment and their job immediately preceding the time that asthma symptoms started or worsened. The job title may not accurately identify a worker's exposure, for example there may also have been exposures from activities carried out by people working nearby, therefore a detailed description of the job tasks and the immediate work environment should be taken. The history should include current symptoms, onset of symptoms and work-relatedness. Factors relating to asthma including family history of any asthma or atopy, any childhood problems, and smoking history should be documented. This information can also be gathered in a questionnaire format which has been shown to have a high sensitivity (i.e. questionnaires can easily identify workers who have occupational asthma) but a low specificity (i.e. questionnaire information alone tends to produce a large amount of false positives) [1;21-23]. Venables *et al* designed a questionnaire for epidemiological asthma research, which asked nine questions to detect bronchial hyper-responsiveness. They found that either two or more or three or more symptoms appeared to be good indices of self reported asthma and bronchial hyper-responsiveness, or both, with a high sensitivity (65-91%) and specificity (85-96%) [24]. For occupational settings, the most important questions to add to general asthma questionnaires are "do your symptoms get better on days away from work" and "do your symptoms get better on holiday". It is important to ask this rather than whether the worker felt worse at work as many people have late reactions which do not begin until the work

shift has ended. Axon *et al* investigated this in a study of differences between occupational asthmatics and non-occupational asthmatics where significantly more occupational asthmatic subjects reported improvement on holiday but no differences were found for worsening of symptoms on work days [21]. Although these questions can be used as an aid in clinical settings, their use in large studies may introduce biases, as some subjects with occupational asthma may not be able to link their symptoms to being at or away from work (for example in long-term situations), whereas many subjects may report work-relatedness of symptoms that are linked to work due to reasons such as stress at work. Adults who have had asthma as a child but have had a symptom-free interval and are now exposed to an occupational sensitising agent should be treated as any other occupational asthmatic, suspecting that the occupational agent is causing the reoccurrence of symptoms and investigating it in the same way as someone with new onset asthma [1].

Questionnaires are widely used for studies into the prevalence of symptoms in workplaces due to their high sensitivity. Questionnaire information has been compared to exposure levels of various occupational agents to estimate exposure-response relationships [25-27]. Questionnaires have been shown to be useful tools for predicting occupational symptoms [28] with certain questions helping to identify occupational asthma when exposed to high molecular weight (HMW) agents [29]. In some cases, questionnaire data were used in conjunction with other objective measurements such as immunology or non-specific reactivity to attempt to decrease the number of false positives [30-32]. Questionnaires are widely used for health surveillance by occupational health departments but can sometimes underestimate the amount of disease and in some other cases overestimate it. They can also

prove to be unhelpful if there is not an appropriate plan on how to act upon the results [33;34].

The clinical history alone is not enough to confirm occupational asthma, as found by Malo *et al* who studied 162 workers referred to their clinic with a suspicion of occupational asthma. They performed a clinical assessment and gave patients a medical questionnaire including questions about symptoms and timing of them. They found symptoms alone did not provide a satisfactory differentiation between subjects with and without occupational asthma. The positive predictive value of a questionnaire diagnosis of occupational asthma was found to be low (63%) but the negative predictive value was higher at 83%. The presence or worsening of symptoms at work and improvement during weekends and holidays was not conclusively linked with occupational asthma [22]. Another study by Vandenplas *et al* found the clinical history to have a high sensitivity (87%) but low specificity (14%) in 45 workers who underwent specific inhalation challenge (SIC) testing [23]. In a meta analysis of all literature concerning clinical history versus SIC for the diagnosis of occupational asthma, Beach *et al* reported a pooled sensitivity of 93.6 to 95.1% (for high molecular weight, low molecular weight (LMW) or mixed agents) and pooled specificity of 32.3 to 68.9% [35]. Therefore for occupational asthma diagnosis, the clinical history and/or questionnaire information plays an important role in raising suspicion but should be followed by other tests for confirmation.

2.1.2. Serial lung function monitoring

Peak expiratory flow is defined as the maximum flow achieved during an expiration delivered with maximum force, starting from the level of maximum lung inflation [36].One

of the recommended ways of confirming a diagnosis of asthma is through serial PEF monitoring to see whether the PEF varies significantly over time [1]. The same applies to occupational asthma but rather than taking measurements for 2 weeks performing a minimum of 2 sets of measurements per day as is often recommended for diagnosing asthma in general [37], more extensive monitoring should be performed for occupational asthma diagnosis. In occupational asthma, it is not only changes in airway calibre that need to be identified but also whether there is a difference between when a person is at work and away from work. Serial PEF monitoring is currently recommended as a confirmatory test for occupational asthma by several guidelines [1;13;38]. Minimum data requirements for PEF monitoring in the diagnosis of occupational asthma have been suggested to be at least four readings per day, and 2 weeks at work and ≥ 10 days away from work [39-41]. When using a computer analysis system, such as Oasys [42], it has been shown that at least 3 complexes of data (approximately 3 weeks; one complex being either a rest-work-rest period or a work-rest-work period), 3 consecutive work days in any work period and 4 readings per day are required to give a sensitivity of 78% and specificity of 92% [43]. When the data were less than this amount, sensitivity fell to 64% and specificity to 83%. The number of readings per day has been found to be important by several authors as daily diurnal variation can be underestimated with too few readings [37;44;45]. Gannon *et al* concluded that at least 4 readings per day were required for an accurate estimate of diurnal variation [44] whereas D'Alonzo *et al* found that only 60 to 80% of the actual PEF variability is identified using four 8-hourly measurements, and 20 to 45% when using two measurements per day.

Although serial PEF monitoring is the classical measurement at work and at home for occupational asthma diagnosis, with the introduction of portable lung function meters, serial FEV_1 (forced expiration in one second) measurement is now possible. FEV_1 is achieved through the same manoeuvre as PEF, but is a volume measurement rather than a flow. The PEF is achieved earlier than the FEV_1, therefore the latter measure requires a longer expiration (with a minimum duration of 1 second). It has previously been shown that FEV_1 is a more sensitive measure for asthmatic changes than PEF [46] and it is generally the measure chosen for recordings of lung function in specific inhalation challenge testing, which is the gold standard for occupational asthma diagnosis. However, the FEV_1 manoeuvre is often harder to accomplish when unsupervised, as found by Leroyer *et al* who analysed PEF and FEV_1 measurements from 20 consecutive workers referred for possible occupational asthma and found the sensitivity and specificity to be lower when interpreting FEV_1. They concluded that unsupervised FEV_1 is less accurate than unsupervised PEF [47]. FEV_1 could therefore be less reliable when performing serial lung function at home and at work.

Fabrication of unsupervised readings performed at home and at work could be a limiting factor in this method of diagnostic confirmation. Malo *et al* studied 21 workers who were asked to record their PEF every 2 hours for a total of 4 weeks writing the times and values on paper without being aware that the meter was logging the results. They found that values corresponded precisely in 52% of readings and 71% were within an hour of the written time [48]. Anees *et al* completed a similar study and found that although some readings were falsified, the worker tended to invent a mean PEF value rather than a low value at work and high value away from work [49]. The more widespread use of these

logging meters is now possible due to the introduction of cheaper portable meters, therefore the problems of possible PEF fabrication can be removed (unless someone else blows into the meter).

When asking a worker to complete serial lung function measurements, the type of chart used to record the values should be considered. It is important that a chart containing boxes for information such as whether the person is at work or not, specific exposures encountered at work, the times the person is at work, the treatment they take and any symptoms they have and space to do 2-hourly measurements throughout the 24-hour period (particularly if a worker does shifts). This has been shown in a previous study of workers who completed PEFs on dedicated occupational asthma forms compared to graph-type forms often used for the diagnosis of non-occupational asthma, showing that the data quality was better using the former [50].

In the analysis of serial PEF measurements, consideration has to be given to confounding factors such as treatment and respiratory tract infections. If records are performed when there is a change in treatment or when a respiratory tract infection occurs, this is likely to influence the PEF and make it unusable for diagnosing occupational asthma. It is therefore important to keep asthmatic treatment the same (making sure the asthma is as stable as possible on the treatment), take measurements before beta-agonist treatment and record respiratory tract infections, as suggested in diagnostic guidelines [38].

2.1.2.1. FEV_1/PEF meters

Peak expiratory flow measurement has traditionally been performed on manual meters

such as the mini-Wright meter from Clement Clarke. The technology is simple using a displaced diaphragm against a spring. In 2004, these meters changed to have a linear scale rather than the previously used non-linear one. This has made interpretation easier as the non-linear measurements were found to over read up to 80L/min in the mid flow range (300-500L/min) and under read values greater than 600L/min [51]. Corrections for this inaccuracy eliminated the problem of underestimating diurnal variation [52], but with linear meters this problem has now resolved.

Many different types of portable meters are available such as the Vitalograph 2110 which uses a pneumotach, the N-spire Piko-1 which uses a coiled spring, the Micromedical MicroDL which uses a rotary turbine and the NDD Easyone which uses ultrasound technology. All of these devices measure flow directly and therefore calculate volume measurements (for FEV_1 and forced vital capacity, FVC, if they are capable of measuring the latter). As meters log both FEV_1 and PEF results, comparison of these measurements is possible.

2.1.2.2. Methods of analysing serial peak expiratory flow

Centres analyse serial PEF for the diagnosis of occupational asthma in different ways, leading to discrepancies in whether or not a record shows work-related changes. Methods can be statistical or non-statistical, hand plotted or computer generated. In Birmingham, UK (and many other occupational clinics around the world), computer based analysis by the Oasys 2 program is utilised [42].

2.1.2.3. Oasys

The Oasys (Occupational asthma system) program is a freely available computer based analysis for serial peak expiratory flow results. It was first developed in 1995 by Gannon *et al* [42] and was based on expert interpretation of hand plotted PEF records. It uses a discriminant analysis (non-statistical) to determine whether each work-rest-work period or rest-work-rest period (known as a complex) show occupational asthma. It allocates a score from 1 to 4 for each complex, 1 indicating that occupational asthma is unlikely, 2 for possible occupational asthma, 3 for probable occupational asthma and 4 for definite occupational asthma. All complex scores are then summated and divided by the number of complexes in the record to produce an overall score. The complexes scored as ones or fours are counted twice in the overall score so that the outcome is weighted to become more positive or negative. Records plotted in the Oasys program are day interpreted to produce the score. This means that PEF values are organised into exposed and non-exposed readings on a daily basis. For example, the first reading taken before work in the morning cannot be influenced by that work days exposure as it has not yet started, so the PEF value will be included in the previous day's analysis. The Oasys work effect index which is now more commonly known as the Oasys score, has been shown to have a sensitivity of 75% and specificity of 94% for the diagnosis of occupational asthma [42;53].

This original program, known as Oasys 2, required data to be hand entered. Oasys 2 is now being further developed and is able to import downloaded readings from most logging meters, analyse different working exposures separately and analyse FEV_1 measurements in addition to PEF. This updated version still produces an Oasys 2 score based on the same formulae as the original Oasys 2 program but the day interpreter has been updated. The

improved program is now known as Oasys Utilities although it is often commonly just referred to as the Oasys program.

2.1.2.4. Other analyses of peak expiratory flow

Several other methods of serial peak flow analysis have been suggested. In a study by Cote *et al* of 25 workers exposed to plicatic acid, qualitative serial PEF analysis (by 2 out of 3 physicians agreeing that work PEF was worse than rest PEF) was compared to quantitative methods (differences between work PEF and rest PEF being outside the 95% confidence interval for variations in PEF for 15 non-occupational asthmatics; and within day variability being greater on work days compared to rest days). Qualitative methods had a sensitivity of 87% and specificity of 90% compared to specific inhalation challenge. Of all the quantitative methods analysed, the difference in mean PEF between the maximum PEF on rest days and the minimum PEF on working days was the only one to have a slightly higher sensitivity (93%) than qualitative methods with similar specificity [54]. Perrin *et al* found a lower sensitivity (81%) and specificity (74%) using qualitative methods in 61 workers referred for occupational asthma [55].

Hayati *et al* investigated the use of the Shewhart control chart for use as an effective method to detect occupational asthma. The lower control limit at work control chart (LCL(W)) was compared to each subject's personal best (PB) value. It was shown that a LCL(W)<60% of the personal best value had a sensitivity of 85.7%, specificity of 87.5% compared to specific inhalation challenge [56]. In a further study by this group, the ratio of average daily PEF diurnal variation at work to the baseline average diurnal variation was investigated using the Shewart control chart method. A ratio of greater than 15% produced

a sensitivity of 94% and specificity of 61% [57]. In contrast, Ricciardi *et al* took a simple approach and analysed differences in mean PEF at work with iroko dust, at work with other woods and away from work in a study of 19 woodworkers. They showed a significant decrease in mean PEF in workers who had positive specific inhalation challenge tests [58]. The systematic review from Beach *et al* found few quality articles comparing serial lung function to SIC and reported a pooled sensitivity of 63.6-83.7% (LMW or mixed agents) and specificity of 77.2 to 90% [35]. These would have been from any type of analysis method.

Although qualitative analysis has been linked to high sensitivity and specificity, inter-observer agreement using this method can be low. In a study by Baldwin *et* al kappa values were 0.62 for diagnosing non-occupational asthma, possible occupational asthma, probable occupational asthma or definite occupational asthma between 7 experts. In Perrin's study, agreement was 78% between 3 experts from the same institution. Venables *et al* analysed agreement on 61 PEF records between four observers and found agreement occurred between all four observers in 69% of charts [59]. PEF records in 17 cork workers by Winck *et al* showed complete agreement between 3 observers in 70.6% of cases using visual inspection of mean daily values [60]. Turner *et al* used interclass correlations (ICC) to assess agreement between raters on the likelihood that 19 case histories with and without other investigative procedures showed occupational asthma. They found low agreement (ICC 0.12-0.54) between the 104 occupational/respiratory physicians. The addition of Oasys 2 scores ≥2.5 or non specific hyper-reactivity produced higher likelihood ratings [61]. Low levels of agreement between assessors indicate that computer based analysis

which performs the same way each time is likely to be more reliable for diagnosing occupational asthma.

2.1.2.5. Diurnal variation in peak expiratory flow

We all have natural daily variations in body functions which affect our biological systems. In the lungs, changes in airway calibre in response to these circadian rhythms is thought to be caused by complex interactions of inflammatory cells and mediators, hormone levels and vagal tone, all of which change during the night [62-65]. Changes in airway calibre have been shown to be present in both asthmatics and non-asthmatics, but are more pronounced in the former [66-71]. For non-asthmatic subjects, Hetzel and Clark showed that a low amplitude circadian rhythm in airway calibre (measured by the difference between the highest and lowest values in a 24-hour cycle and expressed as a percentage of the subjects mean PEF over the study period) can be demonstrated in the majority of normal subjects (65%) by measuring PEF. In the 76 normal subjects, whose lung function rhythm was not statistically significant, the computed estimates of the phase of their rhythms (using cosinor analysis) still showed a very similar distribution to that seen in the subjects with significant rhythmicity [66]. Others have demonstrated this phenomena in smaller numbers of subjects [67;68].

In asthmatics, these variations are more obvious and can therefore be used as a diagnostic aid. In Hetzel and Clark's study, the mean amplitude for the rhythmic normal subjects was 8.3% (standard deviation, SD of 5.2%) and for the asthmatics 50.9% (SD 41.7%) (this study was performed before the use of high dose inhaled corticosteroids for asthma treatment). The acrophase (time of highest PEF) occurred at similar times between

asthmatics and non-asthmatics, the majority being between 2pm and 10pm. The bathyphase (lowest point in the cycle) occurred between 2.40am and 5.15am for both asthmatics and non-asthmatics. The authors concluded that an amplitude of 20% of mean PEF would be unlikely to be exceeded by normal subjects and that this cut off could be used as a threshold for separating asthmatics from non-asthmatics [66]. Others have also demonstrated that a 20% or even 15% cut off is useful [59;70;71], although Higgins *et al* [69] found that using the upper 95% confidence interval of 26.3% amplitude % mean in a normal population showed considerable overlap with the asthmatics, many having amplitudes less than this.

In occupational asthma, diurnal variability has been found to be lower compared to other asthmatics in many studies [72-74]. For example, Revsbech and Anderson found median diurnal variability in asymptomatic workers to be 5.6% (inter-quartile range 3.7-7.5) and only 7.0% (inter-quartile range 5.2-10.7%) in those with work-related symptoms [72]. In a study by Hollander *et al* diurnal variability was 7.5% on days without animal contact compared to 5.9% on days with animal contact in those with asthmatic symptoms. In non-asthmatics, diurnal variability on days with animal contact was 5.1% [74]. The low diurnal variation in occupational asthmatics might be due to the fact that if a worker is exposed to an agent which is causing their PEF to fall at work, this will be superimposed on the natural circadian rhythm of their lung function and may act to simply just remove the normal increase in PEF which occurs during the day. The bathyphase part might also be affected as if the worker has left work by this time, their lung function may be overcoming the effects of the exposure and therefore the normal decline in PEF may not be seen. Randem *et al* showed that PEF variability at work was lower (13%) than on rest days

(18%) in a group of electronic workers. They also showed a decrease in the maximum PEF when exposed at work, with the acrophase occurring at an earlier time in the day compared to rest days [73]. Variability in sleep times when at work compared to weekends may also have had an impact on circadian rhythms.

Other studies have shown the opposite effect of an increase in diurnal variability of PEF on work days compared to rest days [54;75;76]. Chiry *et al* found that there was a significantly greater variability between days at work and rest days in workers diagnosed with either occupational asthma (19.8% vs 10.7%) or work exacerbated asthma (14.2% vs 10.6%) [75]. Lee *et al* reported a mean diurnal variation of 6.2% amongst polyurethane foam mixers which was significantly different to 4.3% seen in controls [76]. In Cote *et al's* study of different methods of PEF analysis, an increased within day variability on work days (mean 21%) compared to holidays (mean 12%) had a sensitivity of 86% and specificity of 80% against specific inhalation challenge [54].

With the timings of the acrophase and bathyphase found by Hetzel and Clark, this poses a question about whether the acrophase or amplitude % mean is altered in shift workers. In further studies by Clark and Hetzel, circadian variations of PEF in asthmatic shift workers was found to be related to sleep rather than solar time [77]. In a later publication, they showed that by waking asthmatic patients during the night, PEF cannot be improved [78]. Zock *et al* studied the influence of shift work on endotoxin-related acute peak flow changes and found that PEF decreased across afternoon and night shifts, but increased across morning shifts, although the differences were not statistically significant [79]. This suggests that circadian rhythm did not change after a change of work shift, with PEF

changes following normal circadian rhythm patterns regardless of what shift the person was working. In a further study by Milton *et al,* PEF changes during morning and night shifts were compared in fibreglass manufacturing workers. A larger number of night shift workers showed a ≥ 5% PEF change across a night shift compared to morning shifts [80]. Pasker and coworkers showed similar results in zinc oxide exposed and non-exposed workers where differences in across-shift lung function change were larger in the night shift, as compared with the day shift [81]. In a study by Nemery *et al*, FEV_1 (amongst other variables) was measured across 3 different shift types in a control group and a group of steelworkers exposed to strandcasting dust. They found no differences in morning shifts, but in afternoon and night shifts, FEV_1 significantly decreased in the casting group but not the controls [82].

2.1.3. Measures of Sensitisation

Measurements of specific immunoglobulin E (IgE) can be used to support a diagnosis of occupational asthma if used in conjunction with a relevant history of exposure to that particular substance and usually some form of physiological confirmation of asthma. It indicates sensitisation to a substance, for example a causal agent in occupational asthma. It can be measured repeatedly to see if levels change over time and it is useful in determining the response to relocation away from the agent.

Specific IgE can be identified by skin prick testing or by measuring serum specific IgE using the Radioallergosorbent test (RAST) [83], Enzyme Linked ImmunoSorbent Assay (ELISA) or Enzyme-allergosorbent test (EAST). The results of a RAST are usually classified from 0 to 4 to show the degree of sensitisation. For the skin prick test, a wheal

with a diameter ≥3 mm is usually taken as positive as long as there is no reaction to the negative control (saline) and there is a reaction to the positive control (histamine). Not all agents elicit an IgE reaction however, as it is dependent on the mechanism of allergy, and for many agents this is unknown. In occupational asthma, agents can be divided into high molecular weight (HMW) and low molecular weight (LMW) agents. The high molecular weight agents are often protein-derived and are capable of acting as complete antigens on their own. Low molecular weight agents are too small to be able to elicit an IgE response on their own, so they need to be conjugated with a carrier protein to act as an allergen. Specific IgE testing is therefore only useful in a small percentage of exposed workers. There are a few studies which assess the sensitivity and specificity of using specific IgE compared to specific inhalation challenge testing. Pezzini *et al* evaluated the sensitivity of specific IgE in 28 workers exposed to toluene diisocyante (TDI) and methylene diphenyl diisocyanate (MDI). They found a higher sensitivity in MDI exposed workers (83%) compared to TDI (27%) [84]. Tee *et al* also investigated specific IgE to isocyanates in 46 workers with asthma and a positive challenge test. They measured IgE by RAST for MDI, TDI and hexamethylene diisocyanate (HDI) and found that 28% had a RAST class of 2 or more, and 20% a class of 3 or more to one of the isocyanates tested. At a class of 3 or more, the RAST was 100% specific. The sensitivity of the test was also found to be best within 30 days of last exposure, consistent with the half-life of isocyanates [85]. Platinum salts have been widely investigated by Merget *et al* who found that skin prick tests were highly sensitive for occupational asthma diagnosis [86-88]. Other LMW agents such as exposure to reactive dyes have been studied by Park *et al* showing a sensitivity of 76.2% and specificity 91.4% for skin prick testing. This was higher than for specific IgE using ELISA in this group [89]. Combining all quality papers available regarding skin prick tests

versus SIC, Beach *et al* documented a pooled sensitivity of 72.9% and specificity of 86.2% for LMW agents using specific skin testing, whereas sensitivity was considerably reduced in those analysed through serum-specific IgE at 31.2% although specificity remained high at 88.9% [35]

Other groups have looked at the sensitivity and specificity of specific IgE for HMW agents against specific inhalation challenge. Vandenplas *et al* found that latex skin testing has a high sensitivity of 100%, but low specificity (21%) in 45 patients referred with possible occupational asthma to natural rubber latex [23]. Van Kampen *et al* have measured specific IgE in flour exposed workers. They found a sensitivity of 87% for wheat and rye flours and a specificity of 68% for wheat and 62% for rye when analysing serum specific IgE (using ImmunoCAP (type of RAST), with a cut-off point for a positive being $\geq$ 0.35kU/l) [90]. Baur *et al* performed SIC tests and measured specific IgE (using skin tests and EAST) in 9 workers exposed to anhydride dusts. Four had a positive SIC, 3 of which had positive specific IgE using EAST and 2 had positive skin tests [91]. Beach *et al* found an increased pooled sensitivity but lower specificity when analysing results for HMW, with skin testing being 80.6 and 59.6% respectively and serum-specific IgE 73.3 and 79.0% respectively [35]. Papers reporting results using a mixture of high and low molecular weight agents gave a pooled sensitivity of 63.0 to 85.1% (skin prick test or serum IgE) and specificity of 59.2-61.2%.

2.1.4. Non-specific reactivity measurements

Non-specific reactivity measurements, usually performed using histamine or methacholine, are used to aid asthma diagnosis as many asthmatics show hyper reactive airways. The test

is performed by inhaling the substance in doubling concentrations measuring lung function after each administration. There are several recognised protocols for this [92-95], but the outcome is essentially the same in all – a PD_{20} or PC_{20} or in Sovijarvi *et al's* protocol [93], a PD_{15} results. This stands for the provocative dose or concentration to cause a fall in FEV_1 by 20% or 15% in Sovijarvi *et al's* method. If given in a high enough dose, everyone would be expected to react to the substance administered, but dosage is usually curtailed due to systemic effects so it is not measurable in the majority of the normal population. When interpreting the results, a non-reaction at the highest dose is defined as normal bronchial responsiveness.

In occupational asthmatics, the non-specific reactivity measurement can be useful if carried out during a period of exposure to the likely causative agent and then repeated after at least a week away from exposure. It has been shown that a 3.2 fold decrease in reactivity when not exposed (the upper 95% confidence limit for the between day reproducibility of the test [96]) has a moderate sensitivity (48%) and specificity (64%) for diagnosing occupational asthma [55]. Burge *et al* also showed that after leaving exposure, reactivity measurements returned to normal in half of electronics workers studied who were exposed to colophony fumes [97]. In a study of workers previously exposed to HMW agents, Lemiere *et al* found that specific bronchial reactivity remained even if non-specific reactivity became normal [98].

There are many studies showing occupational asthmatics to have an increased reactivity when exposed [55;97-99], but there are also studies showing that normal non-specific reactivity (when exposed) also occurs in patients with proven occupational asthma

[22;30;31;87;100]. Baur *et al* showed that a combination of methacholine reactivity and a typical occupational case history had a sensitivity of 83%, 71%, 52% and specificity of 62%, 86%, 80% compared to specific inhalation challenge in 229 workers exposed to either latex, flour or isocyanates respectively [31]. Koskela *et al* found that a positive histamine reactivity test gave only 20% sensitivity in dairy farmers but a high specificity (94%), therefore showing that 80% had a normal non-specific reactivity despite a positive specific inhalation challenge [30]. Merget *et al* found no correlation between methacholine reactivity and specific reactivity to platinum salts [87]. Beach's meta analysis of a single positive non-specific reactivity measurement against SIC showed a pooled sensitivity of 66.7-83.7% and specificity of 48.4-63.9% (for HMW, LMW or mixed agents) [35].

2.1.5. Specific inhalation challenge testing

Specific inhalation challenge testing is considered to be the "gold standard" for occupational asthma diagnosis [101-103] and was first promoted by Pepys and colleagues for occupational exposures [104]. The test involves exposing the worker to a small amount of the likely causative agent(s) that they are exposed to in the workplace. It is usually performed in a dedicated laboratory and in a way that mimics the work exposure. For some allergens, solutions are available which can be nebulised (e.g. cow epithelium). There is generally a lack of standardised methods for some agents, yet the method used is likely to have an impact on the results. Lin *et al* compared two methods of challenge testing to workers exposed to red cedar. They found that a challenge using red cedar dust gave negative results in 3 workers who had a positive challenge by nebulised plicatic acid [105]. Three further workers were negative using either method.

Specific inhalation challenge testing is time consuming as with current methods only one allergen can be tested each day due to the occurrence of possible late reactions (anytime from 1 hour to 12 hours post exposure). The first day is usually a control (placebo) day using either another agent that the worker is exposed to but is unlikely to be the cause, or an agent which has similar (physical) properties to the active challenge agent so can be administered in the same way but is unlikely to be an allergen.

For exposures that are difficult to recreate in the laboratory setting e.g. welding or diesel fume exposure, a workplace challenge may be carried out instead. This would involve a specialist technician going to the workplace environment and carrying out measurements on site rather than in the laboratory. This may happen over 2 or more days, the first day possibly being in an area of the workplace without the suspected causative agent and the subsequent days being spent in the workers normal environment. The drawback of this type of testing though is that other exposures will also be present thereby the specific cause is not easily found as is the case with serial PEF measurements.

The sensitivity and specificity of specific inhalation challenge tests are difficult to assess as SIC is considered to be the gold standard so there is no recognised reference to compare with. It is likely that false negative tests occur, for example due to exposing to a lower dose than experienced at work, exposing the worker to the incorrect causal agent, exposing them by a different method to that taking place at work (if it cannot be reproduced easily in the laboratory) [106] or if there has been a long time since the worker was last exposed to the agent. A number of authors have found some workers to have a negative specific inhalation challenge when other tests for occupational asthma are positive [100;105;107-

109]. In a group of 99 workers who had negative specific inhalation challenges in the laboratory, Rioux *et al* carried out workplace challenges as there was either more than one suspected agent or the clinical history was highly suggestive of occupational asthma. They found that 22/99 had positive workplace challenge tests and a further 7 who were negative in the workplace and at the initial SIC became positive on a second SIC when exposed to a different agent [109]. Burge *et al* reported 2 workers who had negative specific challenge test to isocyanates, but had a physician final diagnosis of occupational asthma with one showing work-related changes on their PEF record [107]. Cartier *et al* investigated the results of serum specific IgE/IgG and SIC and found that 29/65 workers had positive challenges and 29/62 had serum specific IgE or IgG, 21 of whom had a positive SIC [108]. In a study of 113 workers exposed to Toluene diisocyanate, Moscato *et al* concluded that only 40.7% had isocyanate asthma (diagnosed through SIC), although all had work-related respiratory symptoms [100]. Serial PEF monitoring was not performed which might have indicated further affected workers. For workers who have less exposure, Paggiaro *et al* found that nine of sixteen workers with TDI induced asthma who had been removed from exposure, completely lost responsiveness to TDI on repeat specific challenge testing 48 months after the diagnosis [110]. In a study of workers previously exposed to high molecular weight agents, Lemiere *et al* showed that 5/16 workers had negative SIC tests after being unexposed for a mean of 5.7 years [98].

False positive reactions may also occur if too large a dose of an agent is given (irritant), or if a subject has severe non-specific bronchial reactivity [111].

2.1.6. Exhaled breath nitric oxide measurements

Nitric oxide is an endogenous messenger generated in the lower airways by enzymes of the nitric oxide synthatase family, although non-enzymatic synthesis and consumptive processes may also influence levels of nitric oxide in exhaled breath. It's role in lung disease is somewhat unclear as it has a diverse range of effects including non-adrenergic, non-cholinergic neurotransmission and vascular and non vascular smooth muscle relaxation [112]. In pathological situations nitric oxide is a pro-inflammatory mediator with immunomodulatory effects [112]. On the other hand, under physiological conditions nitric oxide acts as a weak mediator of smooth muscle relaxation and protects against airway hyper-responsiveness [113]. However, fractional exhaled nitric oxide concentration (FE_{NO}) has been found to be increased in patients with bronchial asthma [114] and has been shown to separate subjects with and without asthma [114-118]. FE_{NO} also correlates well with airway eosinophilia and with bronchial hyper-reactivity (responsiveness to methacholine/histamine) [15;119-127]. Thus, eosinophilic airway inflammation can be assessed non-invasively by measuring FE_{NO} concentration (FE_{NO}) [128]. With the availability of a range of commercial analysers, it has become possible to use FE_{NO} measurements routinely in the assessment of airway disease in the healthcare setting.

Exhaled nitric oxide is affected by several factors which include inhaled corticosteroid (ICS) use, smoking, respiratory tract infections, atopy, and height. A number of studies have shown that ICS use results in a fall in FE_{NO} levels in patients with mild asthma [129-135]. This data provides evidence that FE_{NO} measurements have a potentially important role in evaluating patients with airways disease. Smoking has been shown to lower FE_{NO} levels [136-138], whereas respiratory tract infections (RTIs) increase FE_{NO} [136;139-141].

Measurements during RTIs should therefore be ignored if analysing longitudinal data. Atopics have also been shown to have increased FE_{NO} levels compared to non-atopic subjects, irrespective of whether they have significant lower respiratory tract symptoms [125;126;142-144]. Height has been found to be positively correlated with FE_{NO}, and should be taken into account if comparing values between people [136;142]. In early nitric oxide analysers such as the Logan LR2000, the flow rate generally used was 250ml/second, whereas later models such as the Aerocrine Niox use lower flow rates of 50ml/second. Caution should therefore be exercised when comparing results of studies using these different flows, or a conversion equation used such as that suggested by Smith *et al* [145] who performed measurements at both flow rates and found that the equation: $2.866*10^{[\log_{10}(FE_{NO} @ 250ml/sec)/1.0883}$ can be used to convert between the two. Several studies have attempted to provide reference ranges for adults. In the study by Olin *et al* the interquartile range for FE_{NO} in healthy adults was 11.9–22.4 ppb [146]. In a later paper they suggested using the equation: $Ln(FE_{NO}) = 0.057 + 0.013$ x height (in centimetres) + 0.0088 x age (in years) to determine a reference value for healthy never smoking adults [147]. In Kharitonov *et al's* study of 30 healthy non-atopic adult subjects, the upper limit of normal (mean plus two standard deviations) was 33.1 ppb [148]. Taylor *et al* has suggested ranges for the management of asthma based on currently available data. If measured at 50mls/second, they propose that values of <25ppb are unlikely to show eosinophilic airway inflammation but may have a neutrophilic type asthma; in patients with values between 25ppb and 45ppb, eosinophilic inflammation may be present but is likely to be mild and at values >45ppb, there is likely to be significant eosinophilic inflammation. Changing treatment depending on the values has also been proposed [149].

2.2 FACTORS INFLUENCING DISEASE

2.2.1. Atopy

Atopy is defined as the presence of IgE antibodies in response to common environmental allergens such as grass, trees, cats, dogs, mites etc. It is usually investigated using skin prick testing with a positive response usually taken as a 3mm wheal with appropriate positive and negative controls as used in specific IgE skin testing described earlier. Atopy is regarded as a risk factor for asthma [150] and occupational asthma, although there is contradictory evidence for occupational asthma. Atopy has been shown to be a risk factor for the development of laboratory animal allergy in a number of studies [151-154]. Other allergens have also been shown to have an association. Cullinan *et al* reported an odds ratio of 1.59 for atopics associated with detergent enzyme sensitisation [155]. In a study of bakery workers, 75% of those sensitised to flour were atopic [156]. Zock *et a*l showed variable results comparing workers exposed to cleaning agents, high molecular weight agents and low molecular weight agents. They reported that atopics had an increased risk of asthma when exposed to HMW agents, but non-atopics were at an increased risk when exposed to cleaning agents or LMW gents [157]. Vedal *et al* have found no associations between bronchial hyper responsiveness and atopy in a longitudinal study of red cedar workers [158]. Similar results were shown in a group of siblings from 59 probands with atopic asthma [159].

2.2.2. Smoking

Current tobacco smoking has been found to have an impact on asthma in a number of studies [153;157;160-164]. Calverley *et al* studied a group of platinum refinery workers and showed that platinum salt sensitivity (defined by positive skin prick test) was

significantly associated with smoking [160]. In Zock *et al's* study of cleaners, workers exposed to HMW agents (including bakers, flour confectioners and other food processors) and workers exposed to LMW agents (including painters, hairdressers and metal workers); current smokers were at increased risk of current asthma in all occupations [157]. Cullinan *et al* showed an increase in chest symptoms in smokers and a strong association of positive skin tests to rat urinary allergens and current smoking [153]. Flood *et al* also found that a higher proportion of smokers were sensitised according to skin tests to detergent enzymes compared to non-smokers [161]. Specific IgE or immediate skin test response has been found to occur four or five times more frequently in smokers than non-smokers exposed to green coffee bean and ispaghula [162]. Smoking also increased the risk of asthma two fold in snow crab workers [163]. The mechanism of this effect is unknown, but may be related to injury of the respiratory mucosa.

2.2.3. Amount of exposure

Exposure levels of an agent in the workplace can often be difficult to quantify. Hygiene data can be collected for some agents, but even if exposures are below the recommended levels, sensitised individuals may still react. There are no evidence-based exposure limits for most sensitising agents even when considering the development of new asthma. Exposure-response relationships have been studied in a number of occupational settings. Many show that as exposure intensity increases, the amount of sensitised individuals also increases. Cullinan *et al* and Brant *et al* showed this in a group of bakery workers and enzyme detergent workers. Degree of exposure was defined by job title and sensitisation measured by specific IgE to detergent and bakery enzymes plus flour in the latter group [155;156;165]. Other researchers have shown this phenomenon in laboratory animal

workers where the frequency of positive skin tests to rat urinary allergen was increased with greater exposure, mostly showing a gradient effect [152-154;166]. The study by Hollander *et al* only showed the relationship in those exposed for four years or less [154]. In a group of platinum refinery workers, exposure was defined as high for those working in production areas and low for non-production services. Calverley *et al* found that workers were six times more at risk of becoming platinum salt sensitive if they worked in a high exposure job compared to low exposure [160].

2.3 CAUSATIVE AGENTS

The list of causative agents for occupational asthma is extremely long and covers almost all job categories. In the West Midlands, UK, the most commonly reported agent between 1991 and 2005 (inclusive) to the Shield database of occupational asthma notifications was isocyanates [167]. This is influenced by the fact that the car industry dominates in this area of the UK where isocyanates are used in the painting process and also in the foam for the car seats amongst other things. Other common agents have been metal working fluid, metals such as chrome and cobalt, latex and glutaraldehyde; the two latter agents being particularly important in healthcare workers, although they are now mostly substituted with alternatives. Latex has been largely removed from healthcare where it is widely known that it can cause asthma and skin symptoms, but more reports are coming from car garages and prisons [167].

For the UK as a whole, the SWORD (Surveillance of Work-related Occupational Respiratory Disease) scheme has a subsection for occupational asthma. A group of core respiratory physicians report to this scheme every month and others report around the year.

In 1999, their report also showed isocyanates to be the commonest cause, followed by latex, flour and grain, enzymes, laboratory animals and insects and cobalt [168]. Other schemes that also reported isocyanates as the commonest cause include PROPULSE (PROject PULmonaire SEntinelle) in Quebec which showed that the automotive, agricultural, wood and food industries were the most frequently notified for occupational asthma, making isocyanates, flour, wood dust farm animals, plastic, welding and fish/shellfish the highest suspected causal agents [169]; SORDSA (Surveillance of Work-related and Occupational Respiratory Diseases in South Africa) that reported isocyanates as the commonest cause followed by latex, with the healthcare industry being the most prominently reported workplace between 1997 and 1999 [170]; ONAP (Observatoire National des Asthmes Professionnels) in France which reported 21% of reports for occupational asthma from isocyanates exposure and 19% from flour between 2001 and 2002 [171]; and the Notifiable Occupational Disease System (NODS) in New Zealand which reported 24% of cases were due to isocyanates and 24% to aluminium smelting between 1996 and 1999 [172]. The SABRE (Surveillance of Australian workplace Based Respiratory Events) reported wood dusts as the most frequently reported agent for occupational asthma in the first 3.5 years of the scheme [173]. In Catalonia, Spain, a surveillance scheme was implemented in 2002 which identified isocyanates as the commonest notification followed by persulphates (hairdressers) and cleaning agents [174]. The Finnish Register of Occupational Disease (FROD) reports a slightly different group of common allergens due to the industries located there. In 2005, Piipari and Keskinen reported notifications to the scheme from 1986 to 2002 and found that animal epithelia was the most abundant problem (farmers) followed by flours and in more recent years, moulds and storage mites [175].

2.4 CONCLUSIONS

Each method of diagnosing occupational asthma has its own advantages and disadvantages. PEF monitoring appears to be a useful technique that has good sensitivity and specificity and has been recommended for use as a confirmatory test in occupational asthma by several guidelines [1;13;38]. However, improving interpretation of PEF results will make it more useful and could enable its use in primary care. The Oasys system appears to be the best alternative to visual expert analysis, and has been found to be more reproducible than expert opinion [176]. The development of this program is important as newer technologies emerge for lung function measurement. This will make serial PEF analysis even simpler to implement in any specialist and non-specialist centre and may serve to decrease missed diagnoses and improve worker prognosis if earlier diagnoses are made.

2.5 DEVELOPMENT OF OASYS

As discussed in the literature review, the Oasys program currently only has one scoring system for identifying whether workers have occupational asthma or not. There is another plot in Oasys based on mean 2-hourly PEF which plots work days and rest days separately. The graphs can be plotted by clock time or by time from waking up (figure 6.1.1 p50 and figure 6.2.1 p71) and were originally just pictorial for the expert to view. At the start of this thesis, it was decided that this plot could be used as an additional scoring system by utilising the area between the curves (ABC) of mean work day and mean rest day readings. The Oasys program was updated so that an area between curves score (ABC score) was calculated based on either the total area between the curves in each plot, or an area divided by the number of hours that make up the plot. It was not known whether this new system

would be as sensitive and specific as the Oasys score is, but it was thought that as this system calculates a magnitude of response to work exposures (rather than pattern recognition as with the Oasys score) it would be useful in different situations to the Oasys score, including when intermittent exposure is present.

3. AIMS OF THESIS

3.1. OVERALL AIM

To develop and validate a diagnostic score based on mean 2-hourly measurements of peak expiratory flow (PEF) during workdays and days away from work that would be sensitive and specific for occupational asthma.

3.2. SPECIFIC AIMS

1. To compare indices calculated from the mean 2-hourly PEF values within the Oasys program between cases of occupational asthma verified according to independent gold standard definitions and cases of non-occupational asthma to determine a cut-off score which best separates the groups, and to test the sensitivity and specificity of this cut off on an independent data set.

2. To determine the effect of the length of lung function monitoring and frequency of readings on the diagnostic ABC PEF score which is based on the 2-hourly PEF curves in Oasys to optimise patient compliance without compromising specificity and sensitivity.

3. To investigate whether PEF records containing a long period off work (at least 1 week) have an improved sensitivity over those with short periods off work for the diagnosis of occupational asthma when using the ABC PEF diagnostic score.

4. To study if serial forced expiratory volume in one second (FEV_1) measurements are more sensitive to asthmatic changes than PEF measurements and to investigate the reliability of 4 different PEF and FEV_1 logging meters used for these measurements.

5. To determine if exhaled breath nitric oxide, a simple measure of airway inflammation used in asthma monitoring relates to work-related changes in serial PEF measurements.

6. To study the effects of the type of shift worked on the diurnal PEF responses to occupational exposures and on the ABC PEF score in workers with occupational asthma.

7. To systematically review the use of serial PEF measurements in the diagnosis of occupational asthma.

4. OASYS UTILITIES SET UP

Oasys Utilities is an updated program from the original Oasys 2 program. The main difference is the how the serial PEF records are interpreted. At the beginning of this thesis, the interpreter within Oasys Utilities was programmed and used as described below for all research project analyses.

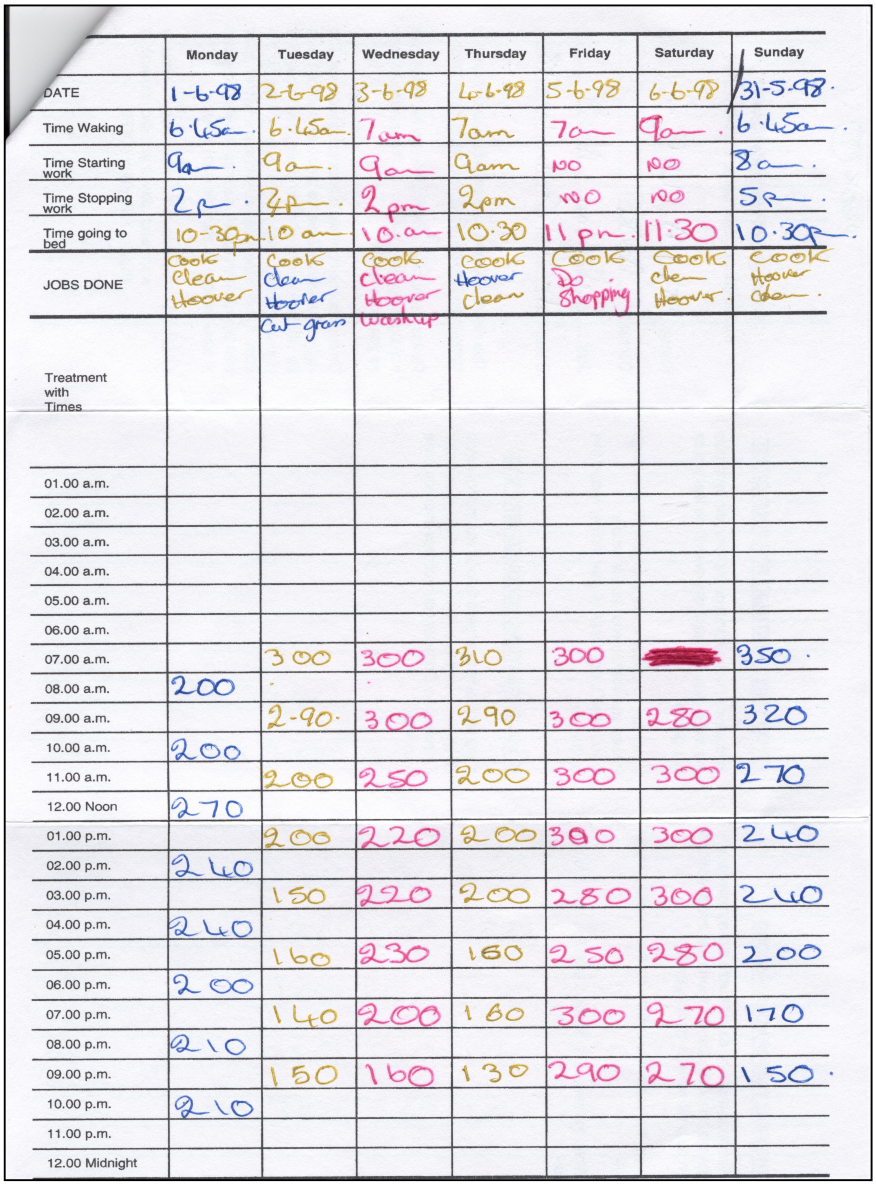
4.1. CREATION OF THE DAY INTERPRETER

Due to late and immediate reactions, Oasys has been programmed to compare readings at and away from work taking into account when the exposure took place. This is known as day interpretation. The primary aim of day interpretation is to create "days" in which all the peak flow readings are either during or following exposure or all non-exposed. Additionally each "day" must contain exactly one waking reading as this is one of the most important readings, often being the lowest for asthmatics if taken pre-treatment. The key concept is that a patient can experience the effects of exposure after being exposed but cannot possibly experience the effects before exposure has taken place. Hence a waking reading for a work "day" needs to be after the exposure, i.e. from the following day. This method of day interpretation was produced after discussion with experts who analysed a number of different PEF records and marked where the "day" should start and finish.

Figure 4.1 shows one week of a serial peak flow record. Electronic logging meters are capable of storing other spirometry measures (such as FEV_1) and record the precise time of the reading.

Figure 4.1. A hand written serial PEF record.

The section at the top shows the date, jobs, treatment and the times of waking up, starting work, finishing work and going to bed. The next section is where the worker records readings against the nearest hour.

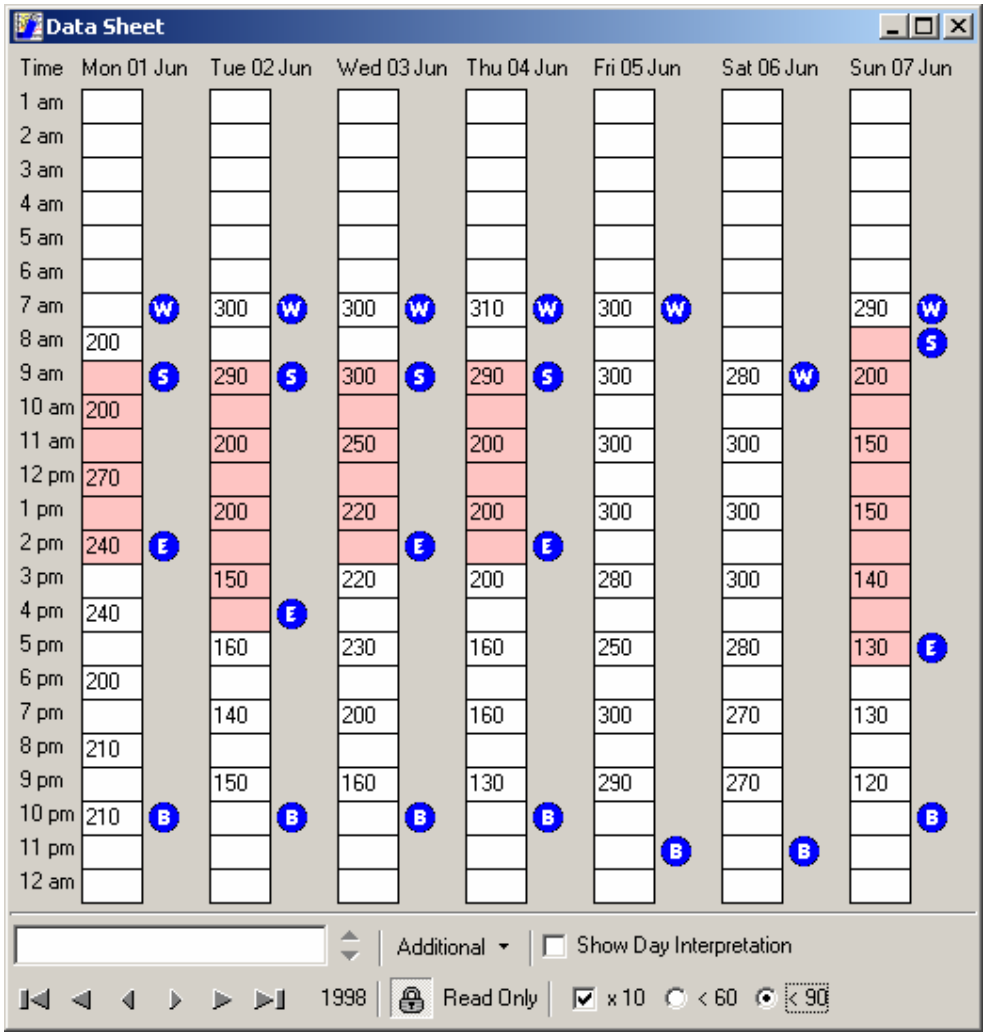


	Monday	Tuesday	Wednesday	Thursday	Friday	Saturday	Sunday
DATE	1-6-98	2-6-98	3-6-98	4-6-98	5-6-98	6-6-98	31-5-98
Time Waking	6.45a	6.45a	7am	7am	7am	9am	6.45a
Time Starting work	9a	9a	9am	9am	no	no	8a
Time Stopping work	2p	4p	2pm	2pm	no	no	5p
Time going to bed	10-30p	10 am	10.am	10.30	11 pm	11.30	10.30p
JOBS DONE	Cook Clean Hoover	Cook Clean Hoover Cut grass	Cook Clean Hoover Washup	Cook Hoover Clean	Cook Do Shopping	Cook Clean Hoover	Cook Hoover Clean
Treatment with Times							
01.00 a.m.							
02.00 a.m.							
03.00 a.m.							
04.00 a.m.							
05.00 a.m.							
06.00 a.m.							
07.00 a.m.		300	300	310	300	[illegible]	350
08.00 a.m.	200						
09.00 a.m.		2-90	300	290	300	280	320
10.00 a.m.	200						
11.00 a.m.		200	250	200	300	300	270
12.00 Noon	270						
01.00 p.m.		200	220	200	390	300	240
02.00 p.m.	240						
03.00 p.m.		150	220	200	280	300	240
04.00 p.m.	240						
05.00 p.m.		160	230	160	250	280	200
06.00 p.m.	200						
07.00 p.m.		140	200	160	300	270	170
08.00 p.m.	210						
09.00 p.m.		150	160	130	290	270	150
10.00 p.m.	210						
11.00 p.m.							
12.00 Midnight							

Figure 4.2. shows a screenshot of Oasys displaying the same data. The W, S, E and B's correspond to waking up, starting work, ending work and going to bed and are known as

events. The working ranges are coloured according to the type of work being done, which is always the same in this case.

Figure 4.2. A screen shot of the data from Figure 4.1. displayed in Oasys



4.1.1. Day interpreted "days"

The interpretation process defines a concept of day interpreted "days", which are the equivalent of 24 hour days. A day interpreted "day" must contain exactly one waking reading and may contain one or more periods at work, in which case the day interpreted

"day" must start with the first work period. There are only three types of day interpreted "days", rest, work and the special blank type. It is allowable for a day interpreted "day" to contain no peak flow readings. These will be called empty day interpreted "days", but note that they will still be working, resting or the special blank type.

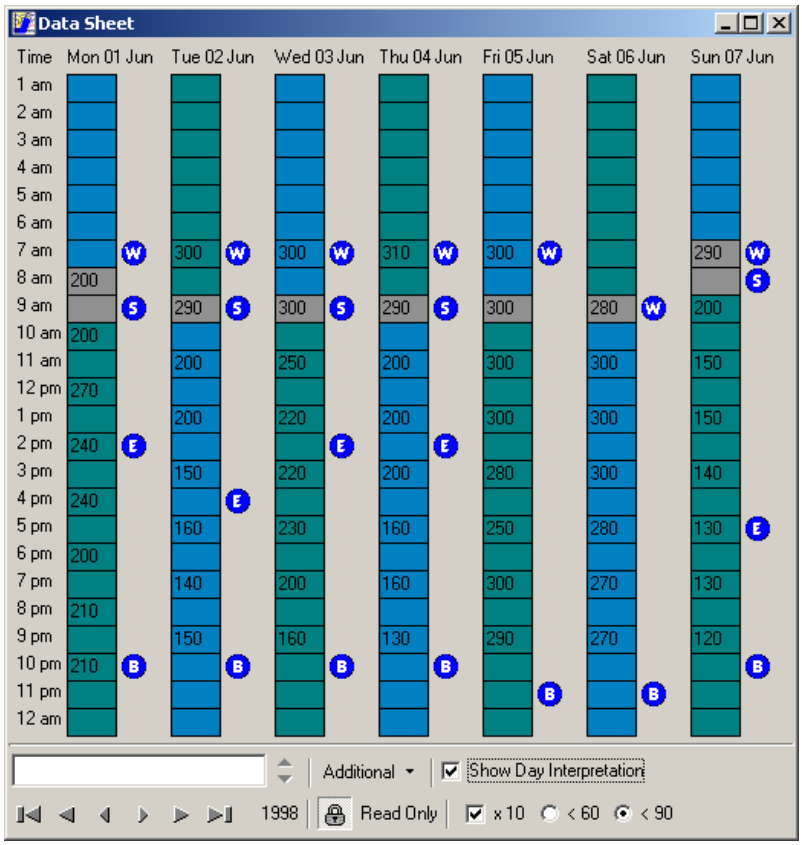
The day interpreted "days" are sorted by the start times. To ensure that all events remain in the day interpreted "days" (convenient for analysis and display) events are copied from the end of one day interpreted "day" to the end of the next one. The first day interpreted "day" includes all events from the start of the record. The last day interpreted "day" includes all events at the end of the record. Figure 4.3 shows a screenshot of Oasys showing the same data as before with the day interpreted "days" marked.

4.1.2. Waking readings

A waking reading is defined as the first reading up to and including 90 minutes after a waking event, regardless of any other events in that 90 minute period. For example if there is a reading 80 minutes after a waking event but also 10 minutes after a starting work event then that reading is still the waking reading, even though it was taken at work. A waking reading is said to be exposed or non-exposed. If the previous time that the patient was awake included a period at work then the waking reading is said to be exposed; otherwise it is said to be non-exposed. If it is not known what the patient was doing on the previous time awake then the exposure is said to be unknown.

Figure 4.3. A screen shot from Oasys once data has been day interpreted

Day interpreted "days" are alternately marked green and blue with grey marking the start and end. Where there is only one grey box the day interpreted "days" finish / start in the same hour but do not overlap. The first blue day interpreted "days" carries over from the previous week and the last green day interpreted "days" continues onto the next week.



4.1.3. Night shifts

When a worker goes on to a night shift following a rest period there is often a large time between waking up and going to work. The rules will make a rest day interpreted "day" out of this time if it is long enough (7½ hours long or more).

When a worker goes on to a night shift following a day shift, a rest day interpreted "day" will be created if it is 9½ hours long or more.

When a worker comes off a night shift there is usually a short period awake on that day, some of which may still be affected from the night shift exposure. A rest day interpreted "day" is created from the time when it is likely that readings are unaffected by exposure (24 hours after exposure began) until the worker returns to bed, but only if this time is long enough (3½ hours or more).

4.1.4. Work days in general

When a worker is working a constant shift for a number of days all readings are normally said to be exposed. Work day interpreted "days" are usually created from one time of starting work to the next (therefore incorporating the following day's waking reading if it was performed before that day's exposure).

4.1.5. Rest days

When a worker is resting for a number of days all readings are said to be non-exposed. Rest day interpreted "days" are created after a waking reading through to after the next waking reading.

4.1.6. First day readings

The exposure on the day before the first day of a peak flow record is not known. It is possible that an exposure on this day will have an affect on the peak flow readings on the first day. The interpretation assumes that all readings after the waking reading are not

affected by the previous day. In practice this is usually a good assumption for the following reasons:

- If the first day of the peak flow record is a work day then the readings are exposed anyway so exposure from the previous day is less relevant.
- The first day of a peak flow record is generally a Monday, which is a workday and usually precedes a Sunday off work (so no exposure on the previous day).
- If the previous day is a day shift then the effects of exposure are likely to be minimal.
- If the previous day is a night shift then this will encroach onto the first day and hence will be known.

4.2. CREATION OF THE 2-HOURLY PLOT BY TIME OF DAY

A graph of the average 2-hours by time of day for a serial peak flow record has been created, which plots the peak flow for rest and work (separately) "days" averaged into 2 hour segments over the 24 hour day (see figure 6.1.1, p50). It was decided that at least 3 readings are required to produce a worthwhile mean. Each line is drawn from the first segment where there are at least 3 readings to make up the mean to the last, any missing values are interpolated from the nearest neighbours.

The area differences shown for each time segment are calculated from one point to the next. These are calculated from the first segment where there are at least 3 readings to make up the work and rest means to the last. The total area difference is the sum of all the individual area differences. The total area difference per hour is the total area difference divided by the number of hours. This is done to standardise results and aid comparison between area differences calculated for different time spans.

4.3. 2-HOURLY PLOT BY TIME FROM WAKING

As comparing the average 2-hourly work and rest by time of day can be influenced by different waking times of work and rest days (usually later waking on rest days), an average 2-hourly plot by time from waking has also been produced (see figure 6.2.1, p71). This is plotted in a similar way to the average 2-hourly plot by time of day, but Rest and work "days" are averaged into 2 hour segments over the period that the worker stays awake: '00 – 02' averages readings taken within 2 hours of waking up and so on.

5. NARRATIVE: HOW THE RESEARCH PAPERS RELATE TO EACH OTHER

This thesis presents each specific aim as a separate research paper. The aim of the thesis, the initial aim was to create a new diagnostic score for occupational asthma from the 2-hourly plot of lung function in the Oasys program and to validate this new score and to investigate its performance in certain situations, such as shift work. At the time, the only scoring system available in Oasys was based on the maximum, minimum and mean daily plot which uses a discriminant analysis (rather than statistical methods) to produce a likelihood that the record shows occupational asthma. Although this score is sensitive (75%) and very specific (94%), it was hypothesized that by creating additional scoring systems, records showing occupational asthma that would be missed by the Oasys score (from the discriminant analysis) may be diagnosed by other methods of analysis.

The new Oasys program provides a 2-hourly plot of PEF which separates readings into those taken at work and those taken away from work, creating two curves. The plot was originally just a picture for expert interpretation. The first research project, therefore, created a new score (Area Between Curves, ABC score) from this plot and validated the cut off against serial PEF records from patients with occupational asthma according to gold standard diagnostic methods (i.e. those independently confirmed to have occupational asthma by other accepted tests) and comparing these to records performed while not at work (i.e. these records could not show occupational asthma). The results of this project can be found in chapter 6.1.

Once this new score had been created, the minimum data quantity requirement to keep the score sensitive and specific for the diagnosis of occupational asthma was determined. This information had been tested for the previous Oasys score but we did not know if the same minimum data quantity could be applied. A project was completed to determine these data amounts and the results are found in chapter 6.2.

In occupational asthma, there are different types of reactions to the occupational exposure: those that occur immediately on arriving at work (or immediately on being exposed to the causative agent) and those that can occur later, often starting after work has finished when back at home. The same principal can apply to recovery, with some workers getting better within an evening away from work and others requiring days to return back to a normal level. This analogy led to the third research paper which determined whether the sensitivity of serial PEF measurements used for the diagnosis of occupational asthma could be improved if workers took a week off work during their record. Equally, it was also important to know whether those without occupational asthma improved with a week off work in serial PEF monitoring. The results of this analysis can be found in chapter 6.3.

As serial PEF monitoring is completed on logging meters in many clinics nowadays, a project was undertaken to address whether some meters would be better than others for this purpose. Although serial PEF is generally the first measure used for occupational asthma diagnosis as it is easy to achieve, these digital meters also measure FEV_1 at the same time. FEV_1 has been suggested to be more sensitive for assessing small airway disease (asthma) and therefore this raised the question as to whether PEF or FEV_1 is more useful for

measuring asthmatic changes in serial monitoring. These questions were answered in chapter 6.4.

Asthma is characterised by airway inflammation. An indicator of it can now be measured easily in clinic by analysing exhaled breath nitric oxide. Previous work showed that there were two variants of occupational asthma: eosinophilic and non-eosinophilic (based on sputum eosinophilia). As sputum eosinophilia correlates strongly with exhaled nitric oxide, the question arose whether there would be two variants of occupational asthma that could be identified based on nitric oxide levels and whether the work related changes seen in their serial PEF monitoring would be different between the groups. The new ABC diagnostic score was chosen as a way to investigate asthmatic response to work exposure and compared between those with high nitric oxide levels and those with normal levels. The results are presented in chapter 6.5.

Another factor that could influence the analysis of serial PEF monitoring is whether workers have different responses depending on the type of shift they work. For example, asthma is usually worse at night due to natural circadian rhythms and therefore it leads to the question, are workers worse on night shifts compared to when they work day shifts? Differences between day and afternoon shifts could also occur which has been studied in chapter 6.6, again using the new diagnostic ABC score as the basis for defining PEF changes.

Throughout all of these projects, the literature available on these topics has been searched. It became apparent that there were no recent papers summarising all literature concerning

the use of serial PEFs in the diagnosis of occupational asthma. Guidelines have been produced informing us PEFs are useful and other diagnostic tests for occupational asthma have been evaluated systematically but there was a gap for serial PEFs. Thus a systematic review of the use of serial PEFs in the diagnosis of occupational asthma was carried out to synthesize all the recently published evidence including some of the work presented in this thesis. This review can be found in chapter 6.7.

6. RESEARCH PAPERS

6.1. A NEW DIAGNOSTIC SCORE FOR OCCUPATIONAL ASTHMA: THE AREA BETWEEN CURVES (ABC SCORE) OF PEAK EXPIRATORY FLOW ON DAYS AT AND AWAY FROM WORK

Moore VC, Jaakkola MS, Burge CB, Robertson AS, Pantin CF, Vellore AD, Burge PS. Chest 2009;135:307-314

6.1.1. Abstract

Evidence-based guidelines recommend serial peak expiratory flow (PEF) measurements on days at and away from work as the first step in the objective confirmation of occupational asthma. The aim of this study was to improve the diagnostic value of computer-based PEF analysis by calculating a score from the area between the curves (ABC) of PEF on days at and away from work in Oasys.

Mean 2-hourly PEFs were plotted separately for work days and rest days for 109 workers with occupational asthma and 117 control asthmatics. A score based on the ABC was computed from records containing ≥ 4 day shifts, ≥ 4 rest days and ≥ 6 readings per day. Patients were randomly divided into 2 datasets (analysis and test sets). Receiver operator characteristic (ROC) curve analysis determined a cut off point from Set 1 that best identified those with occupational asthma, which was then tested in Set 2.

Logistic regression analysis showed that all ABC PEF scores were significant predictors of occupational asthma, with the best being ABC per hour from waking (odds ratio= 11.9 per

10L/hour/min; 95% CI 10.8-13.1). ROC curve analysis showed that a difference of 15 l/min/hour provided a high specificity without compromising sensitivity for occupational asthma diagnosis. Analysis of dataset 2 confirmed a specificity of 100% and sensitivity of 72%.

The ABC PEF score is sensitive and specific for the diagnosis of occupational asthma and can be calculated from a shorter PEF surveillance than is needed for the current Oasys-2 work effect index.

6.1.2. Introduction

Occupational asthma is one of the most common occupational lung diseases in the UK [168], accounting for approximately 10-15% of all cases of adult asthma [3;13]. For those diagnosed with occupational asthma, it can mean serious consequences to health, loss of employment and financial loss [177;178]. An early diagnosis is important as removal from exposure to the causative agent within one year of initial symptoms is suggested to lead to a better prognosis [179-181]. Despite the poor specificity of a full medical history (even when taken by an expert [22]) around 60% of all respiratory and occupational physicians in the UK make decisions on diagnosis and future employment without any objective confirmation of the diagnosis [182]. Serial measurements of peak expiratory flow (PEF) on work and off-work days are recommended as the first objective method for confirming occupational asthma [13], since it is an inexpensive and non-invasive method and the technology is suitable for widespread implementation in non-specialist centres such as occupational health and primary care. It is currently recommended that PEF should be measured every 2 hours from waking to going to bed for the diagnosis of occupational

asthma, with measurements made on days at work and days away from work for a total of 4 weeks to ensure an acceptable sensitivity and specificity [13;39]. The measurements can then be analysed using a computer program, such as Oasys 2 (Occupational Asthma System). This system was originally developed by Gannon *et al* [42;53] and has been reported to have a sensitivity of 75% and specificity of 94% for the identification of work-related changes in peak flow (once a suspicion of occupational asthma has been raised) confirmed by unrelated objective tests. Oasys-2 currently has a scoring system (work effect index; WEI) which uses a discriminant analysis and scores "complexes" (comprised of either a work-rest-work period or a rest-work-rest period). It has been field tested and validated in a variety of situations [176;183;184]. The current diagnostic scoring system has been found to require a minimum of 3 complexes of data (approximately 3 weeks of PEF readings), 3 consecutive work days in any work period and at least 4 readings per day to produce a sensitivity of 78% and specificity of 92% [43].

The aim of this study was to improve the scoring system of PEF records by using an Oasys analysis that creates a new score utilising the area between rest and work day curves (ABC) from the average 2-hourly plot of PEF values. The average 2-hourly plot more closely represents the lung function changes used for diagnosis from specific inhalation challenge testing.

6.1.3. Methods

6.1.3.1. Computing the ABC PEF score by time of day

The average 2-hourly PEF plot is a graph in the Oasys program of the mean rest and work day PEF values plotted in 2-hourly segments according to the time of the day (in relation to

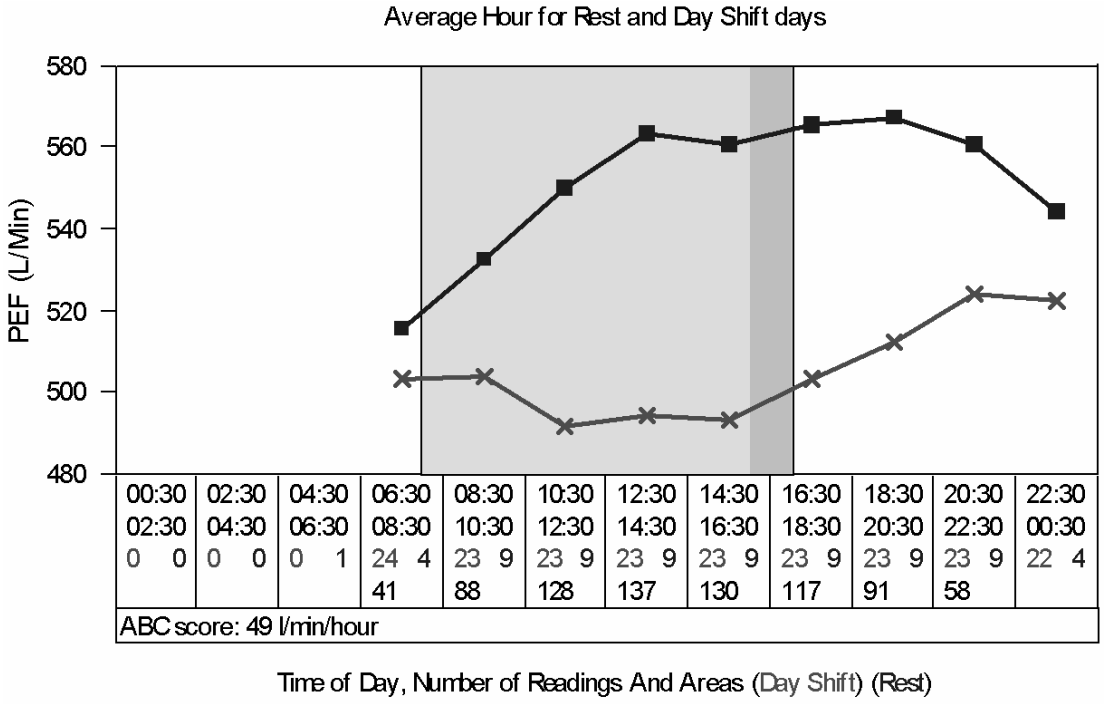
the 24-hour clock). It plots the mean of all work day readings taken between, for example, 06.30 – 08.30 as one data point, then all those taken between 08.30 – 10.30 as the next point and so on in 2-hourly segments throughout the 24 hours of the day. The rest day readings are then plotted in the same way in 2-hour segments (Figure 6.1.1). The points in the plot are linked so that 2 lines are formed (figure 6.1.1), one line for rest days and the other for work days. Each line is drawn from the first data point to the last. When at least 3 readings are available, the program is able to calculate the mean value for each segment, any missing values are interpolated from the values nearest in time. The area between the rest and the work day curves (ABC) is calculated in Oasys by subtracting the area under work days from the area under days off-work (rest days) in Litres/minute. The ABC score per hour is then the total area divided by the number of hours contributing to the calculation of the total area.

6.1.3.2. Computing average ABC PEF score by time from waking

As the average 2-hourly PEF plot can be influenced by different waking times on work and rest days (being usually later on rest days) because of the circadian rhythm of lung function, ABC scores can be calculated by plotting the data starting at waking time. This is plotted in a similar way to the ABC by clock time, but in this case, the first data point plotted is the mean of all work day readings taken 0 – 2 hours from waking up. The next data point is 2-4 hours from waking and so on. The programme then plots the rest days in the same way.

Figure 6.1.1. A 2-hourly plot of average PEF on rest days and work days from the Oasys program.

Mean PEF measurements taken between 06.30 and 08.30, 08.30-10.30, 10.30-12.30 and so on, are plotted from all work days and all rest days. The black upper line (square markers) shows the average peak flow for rest days in 2 hour segments according to the 24 hour clock. The grey lower line (cross markers) shows the same for work days. The grey area shows information about the times of starting and stopping work (mode, minimum and maximum). The legend shows the start and end of the 2 hour time segments, the number of readings used to calculate the work and rest day average PEFs, the area between the rest and work day curves (ABC) on the graph for each time segment and the ABC score. The ABC score in the record shown is 49 L/min/hr.



6.1.3.3. Study Population

A total of 389 serial peak flow records from workers diagnosed as having occupational asthma based on independent clinical investigations (labelled as occupational asthma positives) and 141 records from patients diagnosed as asthmatics/occupational asthmatics

who were not working during their serial PEF measurements (labelled as occupational asthma negatives) were available from a database at the Birmingham Chest Clinic, UK investigated between 1980 and 2007. Local ethics committee approval was obtained from the Birmingham East, North and Solihull committee and patient consent was not required for this study according to the UK system.

6.1.3.4. Occupational asthma positives

Occupational asthma positives were workers who had occupational asthma confirmed by means other than the serial PEF surveillance, i.e. positive specific bronchial challenge test, a fourfold change in methacholine reactivity at work and when away from exposure for at least 1 week, or specific IgE to an occupational exposure together with both a latent interval between first exposure to the causative agent and the onset of symptoms, regular deterioration with work exposure and improvement when away from exposure. Asthma during childhood with subsequent remission was not an excluding criterion.

6.1.3.5. Occupational asthma negatives

Occupational asthma negatives were patients with physician diagnosed non-occupational asthma or occupational asthmatics all of whom were not at work during the PEF measurements (i.e. could not have work-related changes in their PEFs because they did not have occupational exposures). Recordings made between 9am and 5pm Monday to Friday were analysed as “at work” (even when the subject was off work throughout the record) and compared with readings on Saturday and Sunday which were analysed as “off work”.

Occupational asthma positive and negative records were checked to exclude those performed during respiratory tract infections, changes in asthma treatment and those with a mean daily PEF increasing or decreasing constantly more than 5L/min/day over the surveillance period. Only PEF records containing a minimum of 4 day shifts, 4 rest days and 6 readings per day were used (for a minimum amount of data) and any rest periods longer than 3 days were removed as we did not want to include changes seen only after a long time away from exposure.

Records were then divided into 2 evaluation datasets: set 1 to determine a cut off score which gave the best combination of sensitivity and specificity based on ROC analysis and the highest specificity without compromising sensitivity (analysis set) and set 2 to test these scores (using different records to set 1 from occupational and non-occupational asthmatics) to ascertain the sensitivity and specificity gained when applying the cut off score identified (test set). The randomisation into these two datasets was achieved by ordering the records by Surname and assigning set 1 or 2 alternately.

Records were compared by analysing the mean WEI and mean ABC score in workers with occupational asthma.

6.1.3.6. Statistics

SPSS Version 15 was used for all analyses. The Chi-Square test was used to analyse differences between occupational asthma negative and positive groups in variables in a categorical format. The Mann Whitney U test was used when the outcome variable was continuous. Logistic regression was used to identify which ABC PEF score (total area by

clock time, area per hour by clock time, total area from waking time, area per hour from waking time) was the best predictor of occupational asthma by assessing each score individually in the regression model. The four area scores computed from the 2-hourly PEF plot were further analysed to find a cut off point using receiver operated characteristic (ROC) curve analysis. In the analysis of dataset 1, we identified 3 cut off scores which gave a high specificity while retaining good sensitivity and one score which was identified as the optimal for both sensitivity and specificity by the ROC analysis. These were further evaluated in the second dataset, computing the positive and negative predictive values for each cut off as well.

6.1.4. Results

After removal of patients who did not fulfil our inclusion criteria, the analysis dataset 1 included 55 occupational asthma positive patient records and 59 occupational asthma negative patient records. Test set 2 contained 54 occupational asthma positive patient records and 58 occupational asthma negative patient records. There were 84 workers (with 149 PEF records) who failed to fulfil the inclusion criteria in the occupational asthma positive group and 24 occupational asthma negatives. Those not included were similar in age (OA+ve: 43 v 43, p=0.776; OA-ve: 49 v 51, p=0.420), had a similar number of current smokers (OA+ve: 33% v 25% p=0.281; OA-ve: 38% v 21%, p=0.134), similar number of males (OA+ve: 69% v 60%, p=0.206; OA-ve:79% v 62%, p=0.116), similar number of atopics (OA+ve: 58% v 54%, p=0.585; OA-ve: 43% v 53%, p=0.609), similar number reactive to methacholine for OA+ve (68% v 71% p=0.686), different for OA-ve (80% v 42%, p=0.022), similar number taking steroids (OA+ve: 72% v 64%, p=0.223; OA-ve 82% v 84%, p=0.380), different PEF DV for OA+ve (18% v 23%, p=0.001), similar for OA-ve

(18% v 19%, p=0.618) and similar FEV_1 % predicted (OA+ve: 87% v 83%, p=0.552; OA-ve: 83% v 82%, p=0.946) to all the asthma positive/negative workers included.

Table 6.1.1. shows the distribution of the three diagnostic tests that were used as the independent validators for occupational asthma in both datasets 1 and 2. The distribution of tests was similar in both datasets.

Table 6.1.1. Diagnostic tests for occupational asthma used for independent validation

%	Set 1	Set 2
Specific Bronchial Challenge Test	60.0	64.8
4 fold change in methacholine reactivity	9.1	7.4
Specific IgE plus typical symptom history	30.9	27.8

Table 6.1.2. shows the agents identified as causal workplace exposures for occupational asthma in the 2 datasets. There was no significant difference in any of the four ABC scores between those exposed to high molecular weight agents and those exposed to low molecular weight agents (p=0.353 for ABC score from waking).

Table 6.1.2. Occupational exposures identified as causal agents for occupational asthma

%	Set 1	Set 2
High molecular weight agents	21.8	33.3
Low molecular weight agents	78.2	66.7
Latex	3.6	5.6
Flour	7.3	5.6
Isocyanates	14.5	5.6
Solder flux fume	5.5	7.4
Metal working fluid	10.9	7.4
Metals	7.3	13.0
Biological detergent enzymes	10.9	18.5
Cleaning agents	14.5	11.1
Adhesives	1.8	5.6
Other low molecular weight agents	23.6	16.7
Other high molecular weight agents	0	3.7

There were no significant differences in sex, atopy, smoking, or FEV_1 percent predicted between occupational asthma positives and occupational asthma negatives in either dataset (Table 6.1.3). Occupational asthma negatives were older than occupational asthma positives and were more likely to use inhaled corticosteroid treatment. Occupational asthma positives had more workers who were reactive to methacholine challenge, had larger diurnal PEF variability and higher ABC from waking time scores than occupational asthma negatives.

Table 6.1.3. Characteristics of occupational asthma negative and positive groups

	Set 1 OA+ve N=55	**Set 1 OA-ve N=59**	**P value**	**Set 2 OA+ve N=54**	**Set 2 OA-ve N=58**	**P value**
Mean age (SD)	43 (11.0)	51 (9.3)	<0.001^{+}	43 (10.0)	51 (9.3)	<0.001^{+}
% males	59	73	0.108$^{\#}$	61	52	0.342$^{\#}$
% atopics	44	49	0.619$^{\#}$	62	57	0.573$^{\#}$
% current smokers	32	22	0.306$^{\#}$	20	19	0.930$^{\#}$
% methacholine reactive*	74	42	0.003$^{\#}$	69	43	0.019$^{\#}$
% taking ICS	69	84	0.088$^{\#}$	59	83	0.010$^{\#}$
Mean FEV_1 % predicted (SD)	82 (22.4)	85 (20.7)	0.719^{+}	80 (23.0)	84 (24.3)	0.784^{+}
Mean diurnal PEF variation (SD)	23 (14.6)	23 (11.6)	0.112^{+}	21 (15.5)	18 (9.9)	0.016^{+}
Mean ABC from waking time score (SD)	27.8 (29.5)	0.5 (7.5)	<0.0001^{+}	34.9 (35.5)	0.0 (5.9)	<0.0001^{+}

OA – Occupational asthma
ICS – Inhaled corticosteroids
$^{\#}$ Analysed using Chi-square test
$^{+}$ Analysed using Mann Whitney U Test
* Methacholine reactivity was measured after workers had been exposed for ≥ 3 days in the occupational asthma positives

Table 6.1.3a shows that there were no differences between ABC from waking time and ABC by clock time scores and ICS use for records in set 1 or set 2.

Table 6.1.3a. Differences in ABC scores and ICS use for Set 1 and Set2.

	Set 1 OA+ve and OA-ve (n=114)				**Set 2 OA+ve and OA-ve (n=112)**			
	% No ICS	% ICS only	% ICS + LABA	P value	% No ICS	% ICS only	% ICS + LABA	P value
Mean ABC from waking time score (SD)	24.6 (39.9)	16.6 (25.9)	6.9 (17.0)	0.148	16.7 (31.1)	15.6 (29.4)	11.1 (23.6)	0.782
Mean ABC by clock time score (SD)	21.8 (37.4)	15.2 (25.1)	6.1 (16.2)	0.131	16.4 (28.2)	12.7 (28.0)	10.3 (21.9)	0.807

OA – Occupational asthma
ICS – Inhaled corticosteroids
LABA – Long acting beta agonist

The results from logistic regression analysis to identify which of the ABC PEF scores best predicted occupational asthma are shown in Table 6.1.4. The four scores from the average 2-hourly PEF plot (total area by clock time, area per hour by clock time, total area from waking time and area per hour from waking time) were analysed as predictors in set 1, adjusting for inhaled corticosteroid use, age, sex, smoking history, atopy and FEV_1 % predicted as covariates (i.e. possible confounders of the relation between the ABC PEF score and occupational asthma). Tables 6.1.4a-d show the regression models outputs from SPSS for each scoring system.

Table 6.1.4. Logistic Regression analysis of the four scoring systems from the average 2-hourly PEF plot in relation to occupational asthma

	Odds Ratio*	Lower 95% CI*	Upper 95% CI*	P value	R^2
ABC per hour from waking	11.9	10.8	13.1	<0.001	0.52
Total ABC from waking	10.1	10.1	10.2	<0.001	0.50
ABC per hour by clock time	11.9	10.8	13.1	0.001	0.50
Total ABC by clock time	10.1	10.1	10.2	<0.001	0.49

*per 10L/min/hr

Table 6.1.4a Regression model for ABC per hour from waking

		B	SE	Wald Statistic	P value	Odds ratio	95% CI for Odds ratio	
		Lower	Upper	Lower	Lower	Upper	Lower	Upper
Step 1(a)	sex	-1.467	.881	2.771	.096	.231	.041	1.297
	smoking	1.069	.995	1.152	.283	2.911	.414	20.483
	atopy	-.361	.832	.188	.665	.697	.136	3.560
	FEV_1 % predicted	-.003	.024	.014	.906	.997	.951	1.046
	steroids			1.713	.425			
	Steroids only	-.383	.938	.166	.684	.682	.108	4.292
	Steroids + LABA	-1.378	1.098	1.574	.210	.252	.029	2.170
	age	-.033	.047	.500	.480	.968	.883	1.060
	ABC per hour from waking	.171	.048	12.508	.000	1.187	1.079	1.305
	Constant	1.597	3.636	.193	.660	4.940		

a Variable(s) entered on step 1: ABC per hour from waking

Legend for tables 6.1.4a-d:

LABA: long acting beta 2 agonist

B: Represents the change in the outcome variable associated with a one-unit change in the predictor variable.

SE: Standard error

Wald statistic: indicates whether B is significantly different from zero and is therefore making a significant contribution to the outcome.

Table 6.1.4b Regression model for total ABC from waking

		B	SE	Wald Statistic	P value	Odds ratio	95% CI for Odds ratio	
		Lower	Upper	Lower	Lower	Upper	Lower	Upper
Step 1(a)	sex	-1.293	.850	2.318	.128	.274	.052	1.450
	smoking	.979	.964	1.032	.310	2.662	.402	17.608
	atopy	-.263	.795	.110	.741	.768	.162	3.654
	FEV_1 % predicted	-.006	.023	.069	.792	.994	.950	1.040
	steroids			1.467	.480			
	Steroids only	-.300	.914	.108	.743	.741	.124	4.441
	Steroids + LABA	-1.207	1.052	1.315	.251	.299	.038	2.353
	age	-.037	.044	.681	.409	.964	.884	1.052
	Total ABC from waking	.011	.003	13.160	.000	1.011	1.005	1.017
	Constant	1.916	3.476	.304	.581	6.793		

a Variable(s) entered on step 1: Total ABC from waking

Table 6.1.4c Regression model for ABC per hour by clock time

		B	SE	Wald Statistic	P value	Odds ratio	95% CI for Odds ratio	
		Lower	Upper	Lower	Lower	Upper	Lower	Upper
Step 1(a)	sex	-1.176	.851	1.912	.167	.308	.058	1.634
	smoking	1.004	.974	1.064	.302	2.730	.405	18.410
	atopy	-.283	.809	.122	.727	.754	.154	3.684
	FEV_1 % predicted	-.004	.024	.022	.882	.996	.951	1.044
	steroids			1.497	.473			
	Steroids only	-.405	.923	.193	.661	.667	.109	4.069
	Steroids + LABA	-1.233	1.039	1.408	.235	.292	.038	2.232
	age	-.043	.046	.880	.348	.958	.875	1.048
	ABC per hour by clock time	.172	.051	11.575	.001	1.188	1.076	1.311
	Constant	2.040	3.588	.323	.570	7.691		

a Variable(s) entered on step 1: ABC per hour by clock time

Table 6.1.4d Regression model for total ABC by clock time

		B	SE	Wald Statistic	P value	Odds ratio	95% CI for Odds ratio	
		Lower	Upper	Lower	Lower	Upper	Lower	Upper
Step 1(a)	Sex	-.987	.831	1.410	.235	.373	.073	1.900
	smoking	1.019	.957	1.133	.287	2.769	.425	18.059
	Atopy	-.260	.781	.111	.739	.771	.167	3.562
	FEV_1 % predicted	-.005	.023	.042	.837	.995	.952	1.041
	steroids			1.347	.510			
	Steroids only	-.362	.909	.159	.690	.696	.117	4.137
	Steroids + LABA	-1.123	1.002	1.256	.262	.325	.046	2.320
	Age	-.046	.044	1.101	.294	.955	.876	1.041
	Total ABC by clock time	.010	.003	12.161	.000	1.011	1.005	1.017
	Constant	2.201	3.472	.402	.526	9.034		

a Variable(s) entered on step 1: Total ABC by clock time.

This analysis identified that all scores were significant predictors for occupational asthma, explaining 49-52% of the variability, with the ABC per hour from waking score showing the highest odds ratio combined with the largest R^2. In an additional analysis of the ABC per hour from waking, methacholine reactivity was also adjusted for (due to the differences in occupational asthma positive and negative patients), which gave essentially similar findings, but increased the R^2 further to 0.58, with an odds ratio of 12.7 (95% CI 11.0-14.6).

In Set 1, ROC curve analysis showed the ABC per hour from waking time and the ABC per hour by clock time scores had the highest areas under the ROC curve (0.856; 95% CI; 0.779, 0.933 and 0.845; 95% CI 0.766, 0.924 respectively) (Figure 6.1.2). Table 6.1.5 shows results of sensitivity and specificity as well as positive predictive value and negative predictive value in datasets 1 and 2 using different cut off points of 1, 5.6, 10, 15 and 20

L/min/hr. The cut-off point of 5.6 gave the optimal combination of sensitivity and specificity in dataset 1 according to ROC analysis, whereas a cut off of 20, 15 or 10 L/min/hr gave a high specificity while retaining good sensitivity. The cut-off point of 1 L/min/hr was used to show how specificity was affected using such a small difference between rest and work PEF curves.

Figure 6.1.2. A ROC Curve analysis of the ABC per hour from waking up in Set 1, Area under the curve=0.856

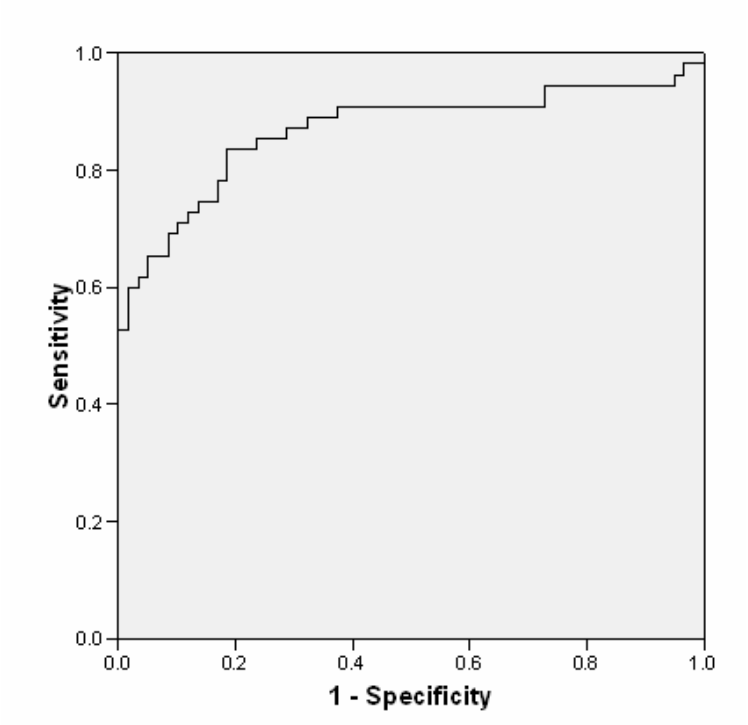


Table 6.1.5. Sensitivity and specificity for occupational asthma of different cut off points for the ABC score per hour plotted from waking time and ABC score per hour plotted by clock time

	Set 1: ABC per hour from waking		**Set 1: ABC per hour by clock time**		**Set 2: ABC per hour from waking**				**Set 2: ABC per hour by clock time**			
Cut off score (L/min/hr)	**Sens. (%)**	**Spec. (%)**	**Sens. (%)**	**Spec. (%)**	**Sens. (%)**	**Spec. (%)**	**PPV**	**NPV**	**Sens. (%)**	**Spec. (%)**	**PPV**	**NPV**
20	54.5	100	43.6	100	53.7	100	100	70.7	57.4	100	100	71.6
15	67.3	94.9	63.6	94.9	68.5	100	100	77.3	72.2	100	100	79.5
10	70.9	88.1	67.3	89.8	77.8	98.3	97.7	82.6	77.2	98.3	97.7	82.6
5.6	80.0	81.4	78.2	81.4	81.5	75.9	75.9	81.5	79.6	82.8	81.1	81.4
1	87.3	57.6	89.1	55.9	85.2	56.9	64.8	80.5	83.3	60.3	66.2	79.5

Sens.- sensitivity
Spec.- specificity
PPV - positive predictive value
NPV – negative predictive value

The Oasys 2 score (using the original work effect index cut off of ≥ 2.51) showed a sensitivity of 71% in set 1 and 74% in set 2 with a specificity of 83% in set 1 and 91% in Set 2. 3/109 records were positive for occupational asthma using the ABC analysis (using a cut off of 15L/min) and negative using the original work effect index; 11/109 had a negative ABC score and positive WEI. Table 6.1.6 compares the mean WEI and ABC score for occupational asthmatics.

Table 6.1.6. Comparison between Original work effect index (WEI) and ABC score for all records from workers with occupational asthma

	Mean WEI (SD)	**Mean ABC score (SD)**
+ve ABC score (n=71)	3.48 (0.50)	47.78 (29.12)
-ve ABC score (n=38)	2.12 (0.68)	0.90 (13.34)
+ve WEI (n=79)	3.46 (0.46)	43.15 (30.90)
-ve WEI (n=30)	1.81 (0.41)	0.59 (14.94)
+ve ABC score; -ve WEI (n=3)	2.23 (0.38)	18.30 (2.11)
-ve ABC score; +ve WEI (n=11)	3.00 (0.37)	6.48 (8.23)
+ve ABC score; +ve WEI (n=68)	3.54 (0.43)	49.08 (29.07)
-ve ABC score; -ve WEI (n=27)	1.76 (0.39)	-1.38 (14.45)

6.1.5. Discussion

This study has developed a new scoring system for occupational asthma from serial PEF measurements analysed by Oasys software utilising the average 2-hourly plot of PEF on days at and off work by clock time or time from waking up. We found that all scores investigated were significant predictors of occupational asthma and a score based on the area between off-work and work day curves (ABC) per hour from waking was the strongest predictor of occupational asthma in combination with explaining the largest proportion of variability (R^2). The analysis of different cut-off points for the score showed that with an ABC of 15 L/min/hour, 100% specificity is achieved, while the sensitivity is 68-72%. A score of 10 L/min/hour reduced specificity to 88-90% in set 1, while increasing sensitivity up to 78% with a specificity of 98% in Set 2. Compared to the currently used Oasys-2 work effect index (WEI) score (based on a discriminant analysis of the PEF on work and rest days utilising the maximum, minimum and mean daily plot), which has a sensitivity of 75% and specificity of 94% using a cut-off of 2.51 [42], the ABC per hour from waking score shows a slightly smaller sensitivity and better specificity using the cut-off score of 15L/min/hr. Four out of eleven occupational asthma positive records that were positive using the WEI and negative using the ABC score had an ABC score >10L/min/hr. Two out of three records scored positively by the ABC and negatively using the WEI had a WEI >2.0. This may indicate that the two scoring systems are useful for different types of records.

The ABC per hour from waking score was calculated from records containing at least 4 days shifts, 4 rest days and 6 readings per day. On analysis of minimum data quantity requirements for the current Oasys-2 work effect index, it was found that at least 3

complexes of data [42;53] (i.e. approximately 3 weeks of recording), 4 PEF readings per day for 75% of the record and 3 consecutive days in any work period are required to give a sensitivity of 78% and a specificity of 92% [43]. If the data quantity is any less, the sensitivity and specificity of the work effect index falls to 64% and 83% respectively. This means that when the data quantity needed for a sensitive and specific work effect index is not reached, the 2-hourly PEF plot can still give a reasonably sensitive and highly specific ABC score. This is an important improvement, as keeping PEF records for long time periods is usually an effort for patients, so this diagnostic score should improve patient compliance. The current analysis is confined to day shifts, so it is yet unknown how the type of shift could influence this new score.

6.1.5.1. Validity of methods and limitations of the study

Due to the feasibility issues, we were not able to perform specific bronchial challenge tests for all patients with suspicion of occupational asthma (considered currently as the best test to diagnose occupational asthma [13]), therefore we extended our independent validation for occupational asthma to include a diagnosis based on a 4-fold increase in methacholine reactivity related to occupational exposure or demonstration of specific IgE antibodies to a relevant occupational agent along with a typical medical history of occupational asthma. The latter criterion is not accepted by all specialists as a confirmatory test (when considered without serial PEFs). However, we found that the PEF diurnal variation and the ABC per hour PEF scores are similar in those diagnosed by specific bronchial challenge as those diagnosed by either of the other two methods. It also provides a diagnosis independent of any other lung function changes, as specific challenge tests are not usually performed in workers who do not demonstrate changes in their PEF surveillance during

usual work exposures. For this reason, we believe it could be used as a valid confirmation method for the purposes of our study.

Although other diagnostic investigations were used to confirm occupational asthma in all of the occupational asthma positive patients in this study, the peak flow record was available for the clinical diagnosis. Workers underwent confirmatory tests regardless of whether their peak flow record showed occupational asthma or not, therefore in some, further investigations confirmed the diagnosis even though the PEF record did not show clear occupational asthma changes when analysed using the methods available at the time. None of the occupational asthma positive patients in this study had a diagnosis based solely on their PEF record. This study investigates the ABC score against these other confirmatory tests, which would be sufficient on their own to diagnose occupational asthma without the PEF record.

Not all of our patients had non-specific reactivity to methacholine challenge, although they did have a physician diagnosis of either asthma or occupational asthma. A bigger proportion of those with occupational asthma had bronchial hyperresponsiveness compared to those with non-occupational asthma. Because of this, in an additional data analysis we adjusted for bronchial hyperresonsiveness in logistic regression and found that this did not change the results essentially, but that this model explained a higher percentage of the variability in occupational asthma.

Some interpreters may require increased diurnal variation to be present for a diagnosis of occupational asthma. The ABC score calculates the mean PEF at 2 hourly intervals

throughout the day for both work days and days off-work by either clock time or waking time. It therefore plots a curve of diurnal variation using means that are more stable than individual measurements. The score does not require the presence of an increased diurnal variation for analysis. We have found that some workers with occupational asthma do not show a higher diurnal variation than controls on their PEF record, even though the diagnosis has been made by specific bronchial challenge or from changes in methacholine reactivity (seen by the large standard deviation in table 6.1.3), therefore making diurnal variation a less useful method of analysis.

The current study excluded workers with work-exacerbated asthma, all in whom the mechanism was thought to be non-specific irritation and all without a latent interval. The diagnosis of occupational asthma was made with specific challenges with control exposures to exclude an irritant mechanism or specific IgE in >90%. Work exacerbated asthma is a term usually confined to those with asthma at the time of first exposure which deteriorates by non-specific mechanisms. Peak flow changes in work-exacerbated asthma (unusually defined as work-related symptoms and a negative specific challenge test) have been compared with occupational asthmatics, the changes in work-exacerbated asthma were smaller than in occupational asthma [75]. Workers with negative specific challenge tests were excluded in this paper.

The frequency of PEF measurements required for the diagnosis of occupational asthma is greater than needed to assess response to therapy. We have previously shown that 91% of workers are able to provide records with ≥ 4 readings/day (with the majority having more than 4) when specifically instructed [50]. Using readings made for other reasons may

produce less satisfactory results. In this study a cut off score was set up on those who had at least 6 readings per day, 4 work days and 4 rest days, but we will analyse the minimum data requirements for the ABC score in the future.

This study included real life records including any incorrectly measured or invented readings. The data quality checking identified individual readings >2 SD from the mean which were checked for transcription errors. The ability of the scoring system to be robust enough to cope with less than optimal data quality we believe is a strength of this new score.

Some workers need longer than 3 days to show improvement in PEF. As only a proportion of records included longer periods away from work, measurements made during 4 or more days away from work have been excluded so as not to influence the changes seen in the first 3 days. A separate analysis will be required to investigate the degree of improvement in PEF needed to diagnose occupational asthma from longer periods off work.

The workers included in this study were exposed to a wide variety of agents showing that the ABC score is likely to have general applicability. There was a paucity of workers with isolated immediate reactions to high molecular weight agents, although the inclusion of 17 workers with enzyme induced asthma confirmed with specific IgE represented such patients. We performed an analysis to investigate if there were ABC score differences between those exposed to high molecular weight agents and those to low molecular weight and found no differences in ABC score between these two groups.

6.1.5.2. Synthesis with previous knowledge

In comparison to other diagnostic tests used for occupational asthma, the sensitivity and specificity of the ABC per hour from waking score is similar or higher. For example, Dudek *et al* compared specific IgE to specific inhalation challenge with flour, grain, natural rubber latex and cotton, and found the sensitivity to be from 42.8 to 83.3%, and specificity from 57.1 to 81.5%, depending on the type of agent [185]. The sensitivity in relation to isocyanate challenges is slightly lower at 28-40%, but specificity remains high [85;186]. In a paper by Cote *et al*, methacholine reactivity and serial peak flows were compared (not analysed by Oasys) against specific challenge tests and for non-specific reactivity the sensitivity was 62% and specificity 78% [99]. Therefore, the ABC per hour from waking score seems to be a more specific test, even when a lower cut off is used to improve sensitivity.

6.1.6. Conclusions

The ABC score is a new scoring system based on mean PEF on days at and off work for diagnosing occupational asthma from serial PEF recordings, which can be calculated from shorter records than needed for the current Oasys scoring system. A score of 15 l/min/hr between rest and work days provides the highest specificity without compromising sensitivity and 5.6 L/min/hr provides an optimal combination of reasonable sensitivity and specificity based on ROC analysis. Even at 10L/min specificity remains high while sensitivity is improved. The ABC score is therefore a useful new diagnostic scoring system for occupational asthma and due to requiring smaller quantities of data it should improve compliance among workers with suspicion of occupational asthma.

6.2. PEF ANALYSIS REQUIRING SHORTER RECORDS FOR OCCUPATIONAL ASTHMA DIAGNOSIS

Moore VC, Jaakkola MS, Burge CB, Pantin CF, Robertson AS, Vellore AD, Burge PS. Occupational Medicine 2009;59:413-417

6.2.1. Abstract

The Oasys program plots serial peak expiratory flow (PEF) measurements and produces scores of the likelihood that the recordings demonstrate occupational asthma. We have previously shown that the area between the mean work day and rest day PEF curves, (the ABC score) has a sensitivity of 69% and specificity of 100% when plotted from waking time using a cut off score of 15 l/min/hour. This work investigates the minimum data requirements to maintain the sensitivity and specificity of the ABC score.

Methods: 196 sets of measurements from workers with occupational asthma confirmed by methods other than serial PEFs and 206 records from occupational and non-occupational asthmatics that were not at work at the time of PEF monitoring were analysed according to their mean number of readings per day. Measurements from work and rest days were sequentially removed separately and the ABC score calculated at each reduction. The sensitivity and specificity of the ABC score (using a cut off of 15l/min/hr) was calculated for each duration.

Results: 2-hourly measurements (~8 readings per day) with 8 work days and 3 rest days had 68% sensitivity and 91% specificity for occupational asthma diagnosis. As readings

decreased to ≤ 4 readings per day, ≥ 15 work days were required to provide a specificity above 90%.

Conclusion: To be sensitive and specific in the diagnosis of occupational asthma, the ABC score requires 2-hourly PEF measurements on 8 work days and 3 rest days. This is a short assessment period which should improve patient compliance.

6.2.2. Introduction

Serial peak expiratory flow (PEF) measurements are recommended as an initial investigation in diagnosing occupational asthma [13]. Analysis of these measurements is best performed by an expert or a computer program such as Oasys [13;42]. Oasys [42] is a program with various analysis outputs giving likelihood scores of a serial PEF record demonstrating occupational asthma. The original Oasys score that utilises the maximum, mean and minimum plot of PEF uses a discriminant analysis, this has been previously validated [53;176;184;187] and has been reported to have a sensitivity and specificity of 75% and 94% respectively. To produce an analysis with high diagnostic sensitivity and specificity, the Oasys score requires a minimum of 4 readings per day, 3 consecutive work days in any work period and approximately 3 weeks worth of readings (3 complexes, a feature of Oasys) [43]. Less data leads to reduced sensitivity and specificity.

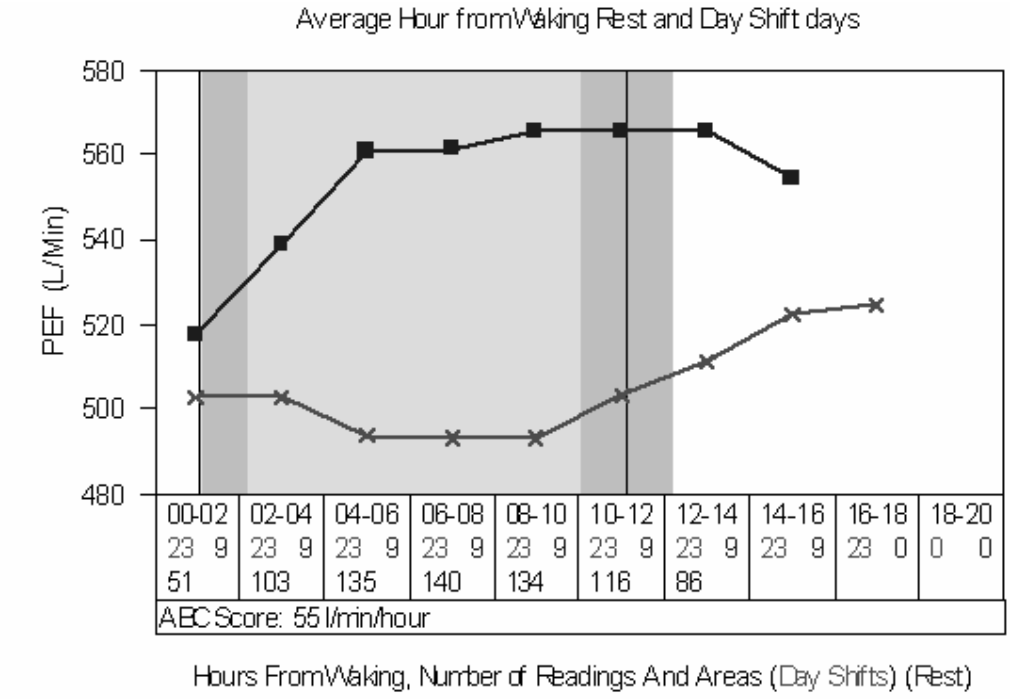
The new scoring system utilises the area between the rest and work day curves in the 2-hourly plot of mean PEF, producing an ABC score (Figure 6.2.1). The plot can be generated using either clock time or time from waking. In an initial study of day-shift workers, both the ABC score by clock time and the ABC score from waking had very

similar sensitivities and specificities [188], therefore only the ABC score plotted by waking time is being considered in this study. In this plot, the mean of rest day PEF values and that of work day PEF values are plotted in 2-hourly segments with the first data point representing the mean of all work or rest day readings taken 0 - 2 hours from waking. The next data point represents the mean of all work or rest day readings >2 - 4 hours from the time waking and so on. The area between the rest and the work day curves (ABC) is then calculated in Litres/minute and divided by the number of hours contributing to the plot to derive the ABC score; a minimum of 3 readings per data point is required.

The ABC score has recently been shown to have a sensitivity of 69% and specificity of 100% using a cut-off score of 15L/min/hour for the diagnosis of occupational asthma [188]. The minimum data requirements for maintaining this sensitivity and specificity are unknown. It is likely to need less data quantity compared to the score based on the daily maximum, mean and minimum plot, and therefore the minimum requirements may be more easily achieved by patients, which would increase the compliance.

Figure 6.2.1. A 2-hourly plot of average PEF on rest days and work days from the Oasys program.

Mean PEF measurements taken between 0 and 2, >2-4, >4-6 hours from waking and so on, are plotted based on all work days and all rest days. The black upper line (square markers) shows the average peak flow for rest days by 2 hour segments from 0 to 24 hours from waking. The grey lower line (cross markers) shows the same for work days. The grey area shows information about the times of starting and stopping work (mode, minimum and maximum). The legend shows the start and end of the 2 hour time segments, the number of readings used to calculate the work and rest day average PEFs, the area between the rest and work day curves (ABC) on the graph for each time segment and the total area between the lines. To calculate the ABC/hour score, the total area is divided by the number of hours for which there are measurements (in this case 16 hours). In this record it gives an ABC score of 55L/min/hr (shown on the plot).



6.2.3. Aims

To determine the effect of the number of work days, number of rest days and frequency of readings on the diagnostic sensitivity and specificity of the ABC score for occupational asthma based on the 2-hourly plot of serial PEF as calculated by the Oasys program.

6.2.4. Methods

A total of 712 serial PEF records were available from the database at the Birmingham Chest Clinic, UK from patients investigated between 1980 and 2007. These included (a) 389 serial PEF records from workers diagnosed as having occupational asthma based on independent clinical investigations of either specific bronchial challenge test (positive result defined as at least 15-20% fall in FEV_1 from baseline value in response to exposure to the occupational agent and no significant FEV_1 fall in response to exposure to the control agent), four-fold change in methacholine reactivity related to exposure, or positive specific IgE (positive result defined as $\geq$ 0.35 kU/l or $\geq$ 2.2% binding) plus a relevant history [occupational asthma positives] and (b) 323 records from patients diagnosed as asthmatics/occupational asthmatics who were not working during their serial PEF measurement period (to ensure that these records could not demonstrate work-related changes in PEF) [occupational asthma negatives]. Local ethics committee approval was obtained from the Birmingham East, North and Solihull committee.

To enable analysis by Oasys, PEF measurements in occupational asthma negative records made between 9am and 5pm from Monday to Friday were analysed as “at work” and compared with readings on Saturday and Sunday which were analysed as “off work”.

Occupational asthma positive and negative records were checked to exclude records performed during respiratory tract infections, changes in asthma treatment and those with a mean daily PEF increasing or decreasing more than 5L/min/day over the record. Any rest periods longer than 3 days were removed to exclude changes seen only after a long period away from exposure.

Records were grouped by their mean number of readings per day into four groups: ≥ 7.5 readings per day, ≥ 6.5 to <7.5, ≥ 4.5 to < 6.5 and ≤ 4.5 readings per day. Work days and rest days were then sequentially reduced as outlined below. Records were required to contain a minimum of 6 work days when analysing the rest day sensitivity and specificity (taken from an initial analysis of data reduction), and a minimum of 3 rest days when analysing workdays. Only 2 records were used from any 1 worker within each number of readings per day group. Where more than 2 records were available, the first two (by date) were taken.

Work days and rest days were removed individually from the end of the record in sequence. When works days were degraded, the number of rest days were left unchanged as in the original record and vice versa when rest days were degraded. After every step of data removal, the ABC score from waking (in L/min/hour) and the associated sensitivity and specificity of the score (using the pre-determined cut off of 15L/min/hr) was calculated. This process continued sequentially until data quantity reached a minimum of 3 days, as Oasys analysis could not be computed with fewer days.

SPSS 15 was used for all analyses. The Chi-Square test was used to look for differences in occupational asthma negative and positive groups with categorical data. Where outcome variables were expressed as continuous data and the predictors were categorical, the Mann Whitney U test was used.

6.2.5. Results

196 occupational asthma positive records from 124 workers and 206 occupational asthma negative records from 187 patients were available for analysis. Table 6.2.1 shows the diagnostic tests used to confirm occupational asthma positive workers and table 6.2.2 shows the demographics for occupational asthma positive and negative patients.

Table 6.2.1. Diagnostic tests for occupational asthma used for independent validation

	% **(n=124)**
Specific bronchial challenge test	59.7
4 fold change in methacholine reactivity	27.4
Specific IgE plus typical symptom history	12.9

Overall, a greater number of work days and rest days were required to maintain sensitivity and specificity as fewer readings per day were available. Table 6.2.3 shows the results. 2-hourly PEF records (≥ 7.5 readings per day) with 8 work days and cut down to only contain 3 rest days, showed a sensitivity of 68% and specificity of 91% for the diagnosis of

occupational asthma. When all available rest days were used (≥ 3 rest days), the sensitivity decreased to 62% and specificity remained similar at 92% (as shown in table 6.2.3).

Table 6.2.2. Demographics

	Occupational asthma Positive (n=124)	**Occupational asthma Negative (n=187)**	**P value**
Mean age (SD)	42.6 (9.7)	50.5 (9.1)	$<0.001^{+}$
% males	58.0	59.4	$>0.05^{\#}$
% atopics	57.0	51.5	$>0.05^{\#}$
% current smokers	19.8	20.7	$>0.05^{\#}$
% methacholine reactive	62.1	45.0	$<0.01^{\#}$
% taking ICS	73.1	82.9	$>0.05^{\#}$
Mean FEV_1 % predicted (SD)	84.2 (21.6)	84.8 (23.2)	$>0.05^{+}$
Mean PEF diurnal variation (SD) (OA positive n=196; OA negative n=206)	21.5 (13.7)	19.0 (28.7)	$<0.001^{+}$
Mean ABC from waking time score (SD) (OA positive n=196; OA negative n=206)	23.3 (32.4)	0.7 (7.6)	$<0.001^{+}$

* ICS- inhaled corticosteroids
# analysed using Chi-square test
+ analysed using Mann Whitney-U test

Table 6.2.3. Sensitivity and specificity for records according to reducing duration of PEF monitoring grouped by mean readings per day

	Mean readings per day (mode)															
Number of work or rest days	**≥ 7.5 (≥ 8)**				**≥ 6.5 to <7.5 (7)**				**≥ 4.5 to <6.5 (5 or 6)**				**<4.5 (≤ 4)**			
	Wse	Wsp	Rse	Rsp	Wse	Wsp	Rse	Rsp	Wse	Wsp	Rse	Rsp	Wse	Wsp	Rse	Rsp
All available	76	97	77	96	57	100	64	100	**58**	**97**	67	95	**59**	**97**	67	97
15	75	95			**64**	**100**			57	97			60	86		
10	66	94			55	95			39	89			54	86		
9	64	92			52	96			37	92			58	82		
8	**62**	**92**	77	95	57	96	47	100	34	89	**68**	**100**	60	81	60	96
7	62	89	75	95	59	96	60	100	33	89	56	95	56	78	59	96
6	65	87	81	97	60	96	67	100	28	89	58	97	57	78	55	91
5	64	83	75	96	56	93	**65**	**91**	36	82	54	100	59	78	**61**	**91**
4	65	84	72	93	52	93	52	88	34	77	55	100	59	71	64	89
3	62	82	**71**	**92**	47	89	48	94	40	72	46	100	55	77	57	90

Wse= work day sensitivity; Wsp=work day specificity; Rse=rest day sensitivity; Rsp=rest day specificity
Bold numbers highlight the number of rest days and work days required to keep the sensitivity at ≥ 60% (where possible) and specificity at ≥ 90%. Ranges of n: ≥ 8 readings: Wse=53-96, Wsp=97-111, Rse=66-119, Rsp=78-111; 7 readings: Wse=14-42, Wsp=10-29, Rse=19-24, Rsp=9-16; 5/6 readings: Wse=19-36, Wsp=34-37, Rse=20-33, Rsp=18-36; ≤ 4 readings: Wse=14-33, Wsp=35-44, Rse=15-22, Rsp=28-42.

6.2.6. Discussion

In this study of serial PEF monitoring on work days and rest days for diagnosing occupational asthma we have shown that records containing 8 work days, 3 rest days and ≥ 8 readings per day have a sensitivity of 68% and specificity of 91% when using the ABC score of 15 l/min/hr. The sensitivity could be increased further to 75% (reducing specificity to 86%) by using a cut off of 10 l/min/hr. This combination of sensitivity and specificity would still be better than pre and post shift measurements of PEF or change in non-specific reactivity [31;107;178;189]. Lesser data quantity reduces the sensitivity and specificity particularly when fewer readings per day are available. At the minimum data quantity requirement of 8 work days, 3 rest days and 8 readings per day, the ABC score is a useful addition to the analysis system. The system previously only gave a sensitive and specific Oasys score based on the maximum, mean and minimum daily plot for records containing approximately 3 weeks of readings (3 complexes), at least 3 consecutive work days in any work period and ≥ 4 readings per day [43]. The ABC score can also analyse records that do not contain consecutive work days, thereby making it more useful for workers with intermittent exposure.

The ABC score showed high specificity which mostly remained stable when rest days were reduced, but decreased when work days were reduced. This may be due to some workers not showing a consistent fall in peak flow on all days at work. Records with long rest periods have not been used in this analysis as many workers only have weekends off work (the exceptions being PEF monitoring at specific times of the year like factory shutdowns or holidays).

The sensitivity of the ABC score was significantly reduced when less than 7 readings per day were present, and higher numbers of work days and rest days were then required to maintain sensitivity and specificity acceptable for a diagnostic test. This is partly related to the fact that for calculating the ABC PEF score there is a requirement for ≥ 3 readings to be taken within the same 2 hour time period across the record for work and rest days. This is a particular problem for the important waking PEF measurements which are likely to vary in time. It would help if workers measured their PEF at consistent times of the day (from waking) to obtain an increased amount of analysable data.

The sensitivity of the ABC score may be further improved by including the analysis of records with a long period off work (these were not included in this analysis). However, as the ABC plots mean values, the first 3 days off work should be excluded in order to ensure that only the days showing improvement in PEF values are analysed (for those workers taking a long time to improve their PEF).

We used a method of grouping records by the number of readings per day that they contained. This enabled us to use real life measurements which are readily achievable in the clinical setting [43]. These records reflect the fact that subjects often make readings at inconsistent times on work and rest days, which may give less useful data compared to the ideal situation where subjects perform readings at consistent times.

We chose to reduce the record days starting from the end to reflect the real time situation where subjects get tired of recordings. Thus, this analysis does not necessarily apply to situations where there are gaps in the middle of the recording.

Although no other studies have looked at the data quantity requirements for the ABC PEF score calculated by the Oasys program, studies have assessed requirements for peak expiratory flow analysis in general. Malo *et al* assessed data requirements for peak flows plotted as a graph in four different ways analysed by 3 different readers and showed that 4 readings per day were adequate when carried out for at least 2 weeks at work and 2 weeks away from work, giving a sensitivity of 73% compared to positive specific bronchial challenge (agreement of at least 2 of 3 expert physicians) and specificity of 78% compared to negative specific bronchial challenge [40].

We have found that the Oasys score requires at least 3 complexes of data [42;53] (i.e. approximately 3 weeks of recording), 4 readings per day for 75% of the record and 3 consecutive days in any work period to give a sensitivity of 78% and a specificity of 92% [43]. If the data quantity is any less, the sensitivity and specificity of the Oasys score falls to 64% and 83% respectively. Achieving 3 consecutive work days in any work period is the commonest reason for failing these data quantity requirements [43]. In the PEF records used for sequential reduction in this study, the work and rest days were not required to be consecutive. Although all of the occupational asthma negative records contained at least 3 consecutive work days, 43% of the occupational asthma positives contained <3 consecutive work days in at least 1 work period before reduction. When the criteria for consecutive work

days was investigated, the sensitivity was 70% for those who had 3 consecutive work days and 68% for those with at least one period of less than 3 work days. This means that when the data quantity needed for a sensitive and specific Oasys score is not reached, the ABC score can still be a reasonably sensitive and highly specific diagnostic tool for occupational asthma.

6.2.7. Conclusion

Using an ABC PEF score of ≥ 15L/min/hr as the cut-off point, a sensitivity of 68% and specificity of 91% for occupational asthma diagnosis is achieved when the PEF record contains 8 work days, 3 rest days and at least 8 readings per day. When the mean number of readings per day is less than this, a greater number of work and rest days are required to maintain appropriate sensitivity and specificity. The ABC PEF score therefore requires a shorter serial PEF record for diagnosing occupational asthma compared to the original Oasys score, which should make the diagnosis of occupational asthma easier in workers finding it difficult to comply with the original requirements of longer record keeping.

6.3. DO LONG PERIODS OFF WORK IN PEF MONITORING IMPROVE THE SENSITIVITY OF OCCUPATIONAL ASTHMA DIAGNOSIS?

Moore VC, Jaakkola MS, Burge CBSG, Pantin CF, Robertson AS, Burge PS. Occupational and Environmental Medicine 2010;67:562-567

6.3.1. Abstract

Serial peak expiratory flow (PEF) monitoring is a useful confirmatory test for occupational asthma diagnosis. Many workers regularly have weekends off work, but this may not be long enough to see potential recovery in their PEF. This study investigates whether the inclusion of longer periods off work in PEF monitoring improves the sensitivity of occupational asthma diagnosis.

Serial PEF measurements from workers independently confirmed as having occupational asthma (occupational asthma positives) and measurements from workers not at work during their PEF record (occupational asthma negatives) containing previously defined minimum data amounts and at least one rest period with ≥ 7 consecutive days off work were analysed. Diagnostic sensitivity and specificity of the Area Between the Curves (ABC) score from waking time and Oasys score for occupational asthma were calculated for each record in 3 ways: 1) including only consecutive rest days 1-3 in any rest period 2) including only consecutive rest days from day 4 onwards in any rest period 3) including all available data. Records with changes in treatment or respiratory tract infections were excluded.

Analysing all available off work data (including long periods away from work of ≥ 7 days) increased the mean ABC score by 17% from 35.1 to 41.0 litres/min/hour (meaning a larger difference between rest and work day PEF values) (p=0.331) and the Oasys score from 3.2 to 3.3 (p=0.588). It improved the sensitivity of the ABC score for an occupational asthma diagnosis from 73 to 80% while maintaining specificity at 96%. The effect on the Oasys score using discriminant analysis was small (sensitivity changed from 85 to 88%). The degree of airflow obstruction (PEF % predicted) had no influence.

Sensitivity of PEF monitoring using the ABC score for the diagnosis of occupational asthma can be improved by having a longer period off work.

6.3.2. Introduction

Serial measurements of peak expiratory flow (PEF) remain the most cost effective confirmatory test in the diagnosis of occupational asthma and are recommended by several guidelines as an important initial confirmatory method, especially in occupational health, primary care and outpatient clinics [1;13;38]. Workers performing serial PEF measurements will often do so at a time when they only have weekends off work. However, recovery of PEF may take much longer than three days in some workers. Inclusion of longer periods off work may therefore improve the sensitivity of an occupational asthma diagnosis. The potential effect of such longer periods off work on the sensitivity and specificity of PEF monitoring has been unknown. Some specialist centres have encouraged workers to complete PEF measurements whilst having at least 1 week off work, [55;55] but in many countries such as the UK, this can usually only be achieved during workers annual leave holidays or during

factory shutdown periods without taking unpaid leave, making the records in a longer period off work an important consideration for the worker.

Serial PEF measurements can be analysed by computer based systems such as Oasys [42]. This system removes the problems encountered when there is variation in expert interpretations of the PEF patterns, which may lead to inconsistencies in diagnosis of occupational asthma [176]. Oasys computes several outputs, one of which utilises a plot of the maximum, mean and minimum daily PEF values and produces an Oasys score based on comparing each work-rest-work period and rest-work-rest period (complexes). This has been shown to have a sensitivity of 75% and specificity of 94% for the diagnosis of occupational asthma when using a cut off score of $\geq$ 2.51 [42;53]. The updated version of the Oasys program produces a new score from the plot of 2-hourly mean PEF measurements plotted separately for work and rest days and is based on the area between the work day and rest day curves. This score is known as the ABC score and has been shown to have a sensitivity of 69% and specificity of 100% using a cut off of $\geq$ 15 l/min/hr [188]. It requires shorter records (with more readings per day) than needed to maintain a similar sensitivity and specificity using the Oasys score [43;188;190]. The ABC score is a very suitable method for analysing PEF measurements carried out for 2 weeks at work and 2 weeks away from work as is sometimes recommended [38] whereas the Oasys score is often unsuitable in this situation. The initial analysis to identify the cut off point for the ABC score only considered records with $\leq$ 3 consecutive days off work in any rest period. The ABC plot can be generated according to either clock time or time from waking, but both of these ABC indices had a similar sensitivity and specificity; therefore only the ABC score by waking time is considered

here. It is not currently known whether having a longer period off work increases the sensitivity or reduces the specificity of the occupational asthma diagnosis based on the ABC score.

6.3.3. Aim

The aim of this study was to assess whether serial PEF measurements with only periods of ≤ 3 consecutive days off work in any rest period analysed, are less sensitive and/or more specific compared to serial PEF measurements that include only consecutive rest days from day 4 onwards in the analysis for the diagnosis of occupational asthma.

6.3.4. Methods

6.3.4.1. Study Population

A total of 133 serial PEF records with ≥ 7 consecutive days off work from workers diagnosed as having occupational asthma based on independent clinical investigations, i.e. specific bronchial challenge test, four-fold change in methacholine reactivity, or positive specific IgE combined with a strong relevant medical history [referred to as the occupational asthma positive group] were available from patients investigated at the Birmingham Chest Clinic, UK, between 1980 and 2007 after these patients had been referred for suspected occupational asthma. 117 records from patients diagnosed as asthmatics/occupational asthmatics who were not working during their serial PEF measurement period (to ensure that these records could not demonstrate work-related changes in PEF) [referred to as the occupational asthma negative group] were available from the same time period [188]. Ethics committee approval was

obtained from the Birmingham East, North and Solihull committee and patient consent was not required for this study.

6.3.4.2. Data analysis

To enable analysis by the Oasys program, PEF measurements in occupational asthma negative records (recoded while not being exposed to any occupational agents) made between 9am and 5pm from Monday to Friday were analysed as "at work" and compared with readings on Saturday and Sunday which were analysed as "off work". A week off work was chosen for each record of occupational asthma negatives using a random number generator from 1-3 (corresponding to the working weeks in the record) for the analyses of all measurements (inc, long period off work) and from consecutive rest day 4 onwards only.

Occupational asthma positive and negative records were excluded if they contained less than previously determined minimum data quantity for each score [43;190]. For the Oasys score minimum data requirements were ≥ 3 complexes (work-rest-work or rest-work-rest periods) with ≥ 3 consecutive workdays in any work period and ≥ 4 readings per day [43]. Only records with >8 day shifts were considered for the Oasys score to be comparable with minimum data requirements for the ABC score. For the ABC score, the minimum data quantity criteria were found to be dependent on the number of readings per day the record contained [190]. Therefore, records with a mean number of ≥ 7.5 readings per day required 8 work days and 3 rest days, those with a mean of ≥ 6.5 and <7.5 readings per day required ≥ 15 work days and 5 rest days and those with ≥ 4.5 but <6.5 per day required ≥ 15 work days and 8 rest days to maintain sensitivity above 60% and specificity above 90%.

PEF records performed during respiratory tract infections and changes in asthma treatment were excluded as these could have confounded the records. Only 1 record from any 1 worker was used in each set to ensure independency of observations.

Only scores for day shifts were considered for the ABC score as these are the only shift type that have been validated previously. Records were analysed in three ways: the first calculated scores for the records (ABC score and Oasys score) including rest days 1-3 only and removing consecutive rest days from day 4 onwards in any rest period (see figures 6.31 and 6.3.2a). The second removed rest days 1-3 in any rest period and only analysed consecutive rest days from day 4 onwards (see figure 6.3.1). The third analysed all available data (including the long period off work) (see figures 6.3.1 and 6.3.2b). The sensitivity and specificity at a cut off of ≥ 2.51 for the Oasys score and ≥ 15L/min/hr for the ABC score was calculated for each analysis and compared.

6.3.4.3. Statistical methods

SPSS 15 was used for all statistical analyses. The Chi-Square test was used to investigate differences in occupational asthma negative and positive groups with categorical data. Data were not normally distributed. Where outcome variables were expressed as continuous data and the predictors were categorical, the Mann Whitney U test or Kruskal Wallis test was used. An analysis of covariance was used when controlling for confounding factors. As the records of each individual were analysed in three ways, each individual served as his/her own control in the analysis comparing different durations of rest periods on diagnostic PEF scores.

Receiver operator characteristic (ROC) curves were used to determine the sensitivity and specificity of the different scores.

Figure 6.3.1. Maximum, mean and minimum PEF plotted by Oasys program from an occupational asthma positive worker exposed to cobalt (shown overleaf).

The top part of the chart shows the diurnal variation (DV) for each day. The middle of the chart shows the maximum, mean and minimum peak flow for each day. The black continuous line is the mean PEF, the upper line the maximum PEF and lower the minimum PEF for each day. The work periods are the shaded areas (diagonal back slash bars are morning shifts, diagonal forward slash bars are afternoon shifts) and the rest periods are blank areas. The horizontal lines containing numbers in this part of the chart are scores for the work-rest-work and rest-work-rest complexes (four complexes in total in this record). The bottom of the record shows the days and dates of the record. When analysing this record using consecutive rest days 1 to 3 only, days from 26th July to 14th August would be removed. For analysis using consecutive rest days from day 4 onwards in any rest period, the 19th July and 23rd to 25th July would be removed. The Oasys score of this record is 2.86 (probable occupational asthma). Using only rest days 1-3, the score changes to 1.80 (interpreted as unlikely to be occupational asthma) and using from consecutive rest day 4 onwards, the score becomes 4.0 (meaning definite occupational asthma). This worker had a four fold change in methacholine reactivity between when exposed and when away from exposure for at least 1 week.

Figure 6.3.1. Maximum, mean and minimum PEF plotted by Oasys program from an occupational asthma positive worker exposed to cobalt.

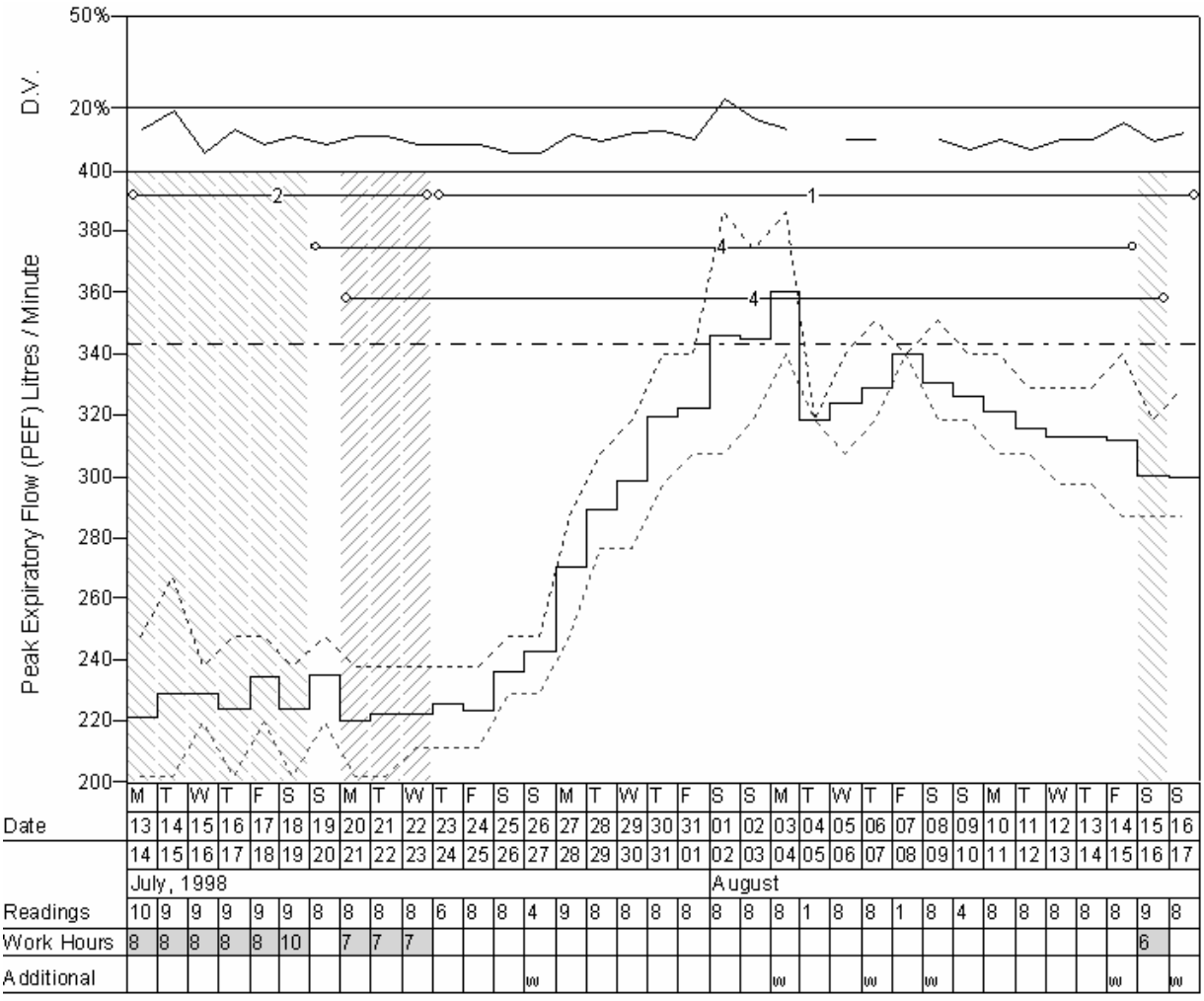


Figure 6.3.2.a A 2-hourly plot of the average PEF on rest days and work days analysed by the Oasys program for the same worker by analysing rest days 1 to 3 only.

Mean PEF measurements taken at the following times: 0 and 2, >2-4, >4-6 hours and so on from the waking time are plotted based on all work days and all rest days. The black upper line (square markers) shows the average peak flow for rest days by 2 hour segments from 0 to 24 hours from waking. The grey lower line (cross markers) shows the same for work days. The grey area shows information about the times of starting and stopping work (mode, minimum and maximum). The legend shows the start and end of the 2 hour time segments, the number of readings used to calculate the work and rest day average PEFs, the area between the rest and work day PEF curves (ABC) on the graph for each time segment and the total area between the lines. To calculate the ABC/hour score, the total area is divided by the number of hours for which there are measurements. This record gives an ABC score of 8L/min/hr (shown on the plot) (interpreted as not occupational asthma).

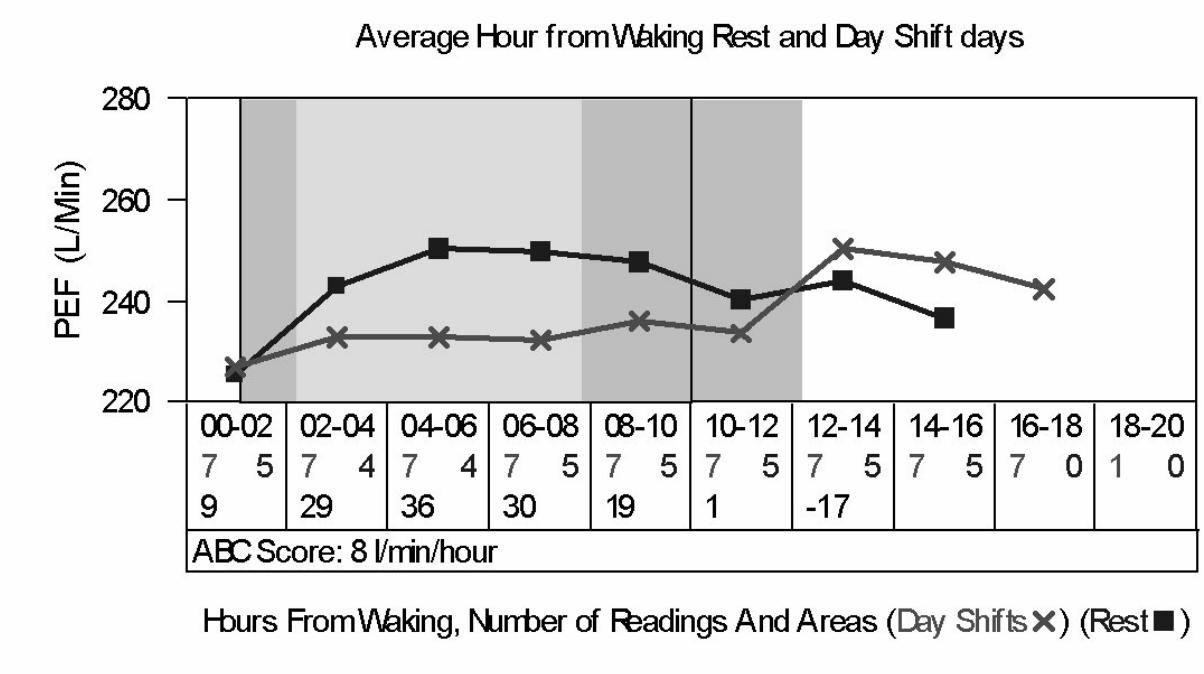
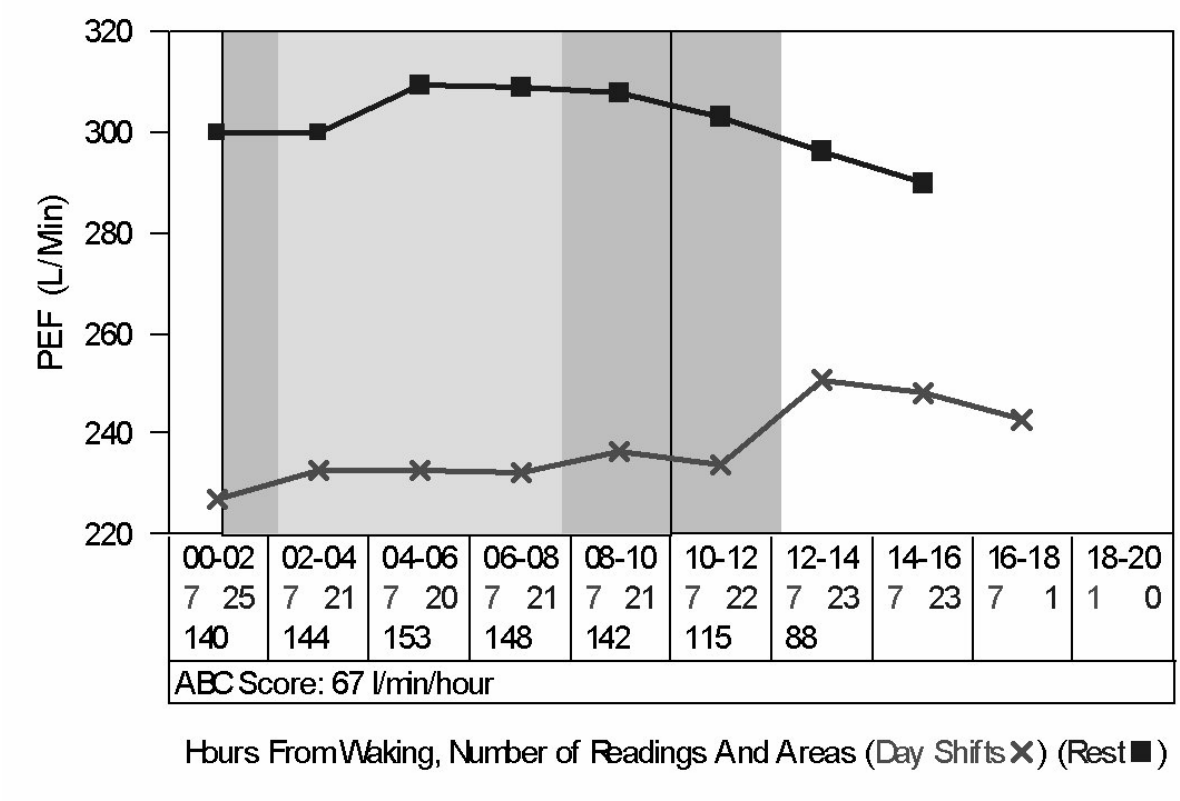


Figure 6.3.2.b The same worker's 2-hourly plot analysed using all available data.

The ABC score is now 67 l/min/hour (interpreted as definite occupational asthma). Using consecutive rest days from day 4 onwards gives an ABC score of 83 l/min/hour (definite occupational asthma).



6.3.5. Results

A total of 48 occupational asthma positive records and 104 occupational asthma negative records fulfilled all criteria including data quantity requirements for either score. For the ABC score, 45 occupational asthma positive records and 93 occupational asthma negative records satisfied all criteria and minimum data quantity and for the Oasys score, 36 occupational asthma positive records and 95 occupational asthma negative records satisfied all criteria,

including data quantity. 64.6% (31/48) of the occupational asthma positive workers were independently diagnosed through specific inhalation challenge testing, 6.3% by a fourfold change in methacholine reactivity (between periods at and away from work for at least 1 week) and 29.2% by specific IgE and a typical symptom history. The majority of workers were exposed to low molecular weight agents (79.2%).

Occupational asthma negatives were somewhat older than occupational asthma positives ($p<0.001$) and more were taking inhaled corticosteroids ($p=0.011$). There were no other significant differences in patient demographics between occupational asthma positives and negatives (Table 6.3.1).

Both the ABC score and Oasys score were significantly higher in occupational asthma positives compared to occupational asthma negatives when using all amounts of data (Table 6.3.2). Although the ABC score increased by 17% (showing a bigger difference between work and rest day PEF values) when the long off period was included or by 39% when only consecutive rest days from day 4 onwards were analysed, the differences were not statistically significant. ABC scores are represented graphically when analysing rest days 1-3 and consecutive rest day 4 onwards in Figure 6.3.3. The ABC score was useful for diagnosing occupational asthma when the analysis was restricted to including consecutive rest days from day 4 onwards, but due to a lack of a sufficient number of complexes (work-rest-work or rest-work-rest periods) Oasys scores could not be computed for most of the records in this latter analysis.

Table 6.3.1. Demographics of the study population

	Occupational asthma Positive (n=48)	**Occupational asthma Negative (n=104)**	**P value**
Mean age (SD)	44 (10.2)	51 (9.3)	<0.001[+]
% males	69.6	61.5	0.345[#]
% atopics	42.9	51.1	0.376[#]
% current smokers	14.3	20.6	0.308[#]
% methacholine reactive	55.3	42.7	0.199[#]
% taking ICS	64.1	84.3	0.011[#]
Mean FEV_1 % predicted (SD)	86.4 (26.8)	80.6 (24.3)	0.224[+]
Mean diurnal PEF variation (SD)	22.2 (13.5)	19.7 (13.2)	0.200[+]

* ICS- inhaled corticosteroids
[#] analysed using Chi-square test
[+] analysed using Mann Whitney-U test

Table 6.3.2. Differences between occupational asthma negatives and positives using records with and without long periods (≥7 consecutive days) off work

	Mean ABC score (SD)			**Mean Oasys score (SD)**		
	OA+ n=45	OA- n=93	p	OA+ n=36	OA- n=95	P
All available measurements (inc. long period off work)	41.0 (33.5)	0.4 (8.6)	<0.001	3.3 (0.7)	1.8 (0.6)	<0.001
≤ 3 consecutive rest days only in any rest period analysed	35.1 (31.2)	0.4 (8.1)	<0.001	3.2 (0.7)	1.9 (0.6)	<0.001
P value (all rest days compared to ≤ 3 consecutive rest days)	0.331	0.774	na	0.588	0.612	na
Consecutive rest days from 4 onwards in any rest period analysed	48.5 (42.3)	0.3 (12.0)	<0.001	na	na	na
P value (comparison of ≤ 3 consecutive rest days to consecutive rest day 4 onwards)	0.132	0.442	na	na	na	na

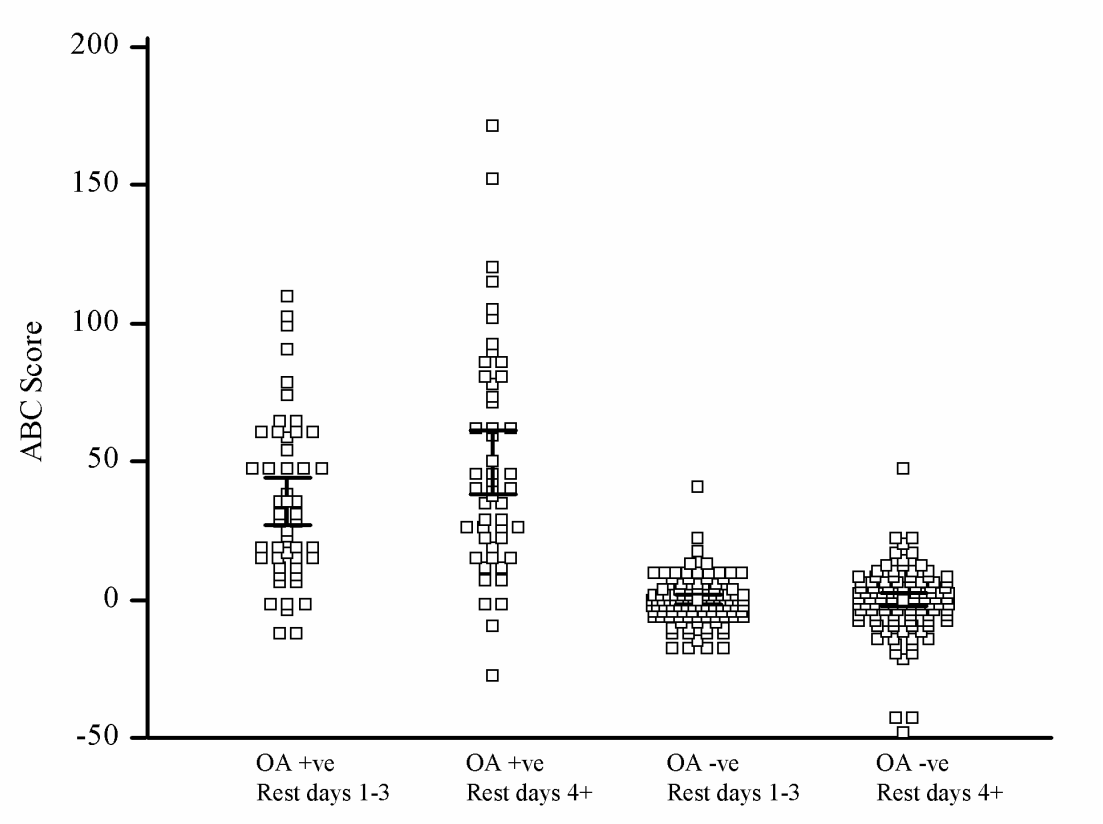
Table 6.3.3. shows the sensitivity and specificity of the Oasys score and the ABC score with respect to occupational asthma diagnosis (Oasys score ≥ 2.51; ABC score ≥ 15L/min/hour) for the three types of PEF record analyses. Analysis including longer periods off work (≥ 7 consecutive rest days) improved the sensitivity of the ABC score to 80% compared to the analysis that removed rest periods with ≥ 4 consecutive rest days showing a sensitivity of 73%. Specificity remained high at 96% when all data were used. No records that scored positively using rest days 1-3 became negative when including the long period off work.

Table 6.3.3. Sensitivity and specificity of Oasys score and ABC score for occupational asthma in records with and without long periods off work

	ABC score		**Oasys Score**	
	% sensitivity n=45	**% specificity** n=93	**% sensitivity** n=36	**% specificity** n=95
All available measurements	80	96	88	86
≤ 3 consecutive rest days only	73	98	85	90
Consecutive rest days from 4 onwards only	78	95	na	na

Figure 6.3.3. A scatter plot of ABC (by time from waking) scores grouped by analysis.

The plot is based on rest days 1-3 in any rest period and based on consecutive rest days from day 4 onwards in any rest period for the occupational asthma negative and positive records. The mean and 95% confidence intervals are also indicated on the plot.



Additional analyses were undertaken to investigate if the ABC score differs between occupational asthma positives with different levels of mean PEF, with the hypothesis that those with a low mean PEF level might need a longer period off work to recover. Thus, those with a mean percent predicted PEF of ≥ 60%, 70%, 80% and 100% predicted were compared with those with PEF <60%, 70, 80 and 100% predicted, analysing from

consecutive rest day 4 onwards only. Age, use of inhaled corticosteroids and smoking were controlled for by an analysis of covariance. There were no significant differences when using 60%, 70%, 80% or 100% as cut off point (p=0.885, p=0.515, p=0.472, p=0.744), suggesting that the influence of the duration of the rest period is not dependent of PEF level.

6.3.6. Discussion

We have shown that the ABC PEF score increases from 35.1 l/min/hr to 41.0 l/min/hr by including a long period off work in the monitoring period, but this was not a statistically significant improvement (p=0.331). The difference in the score between occupational asthma positives and negatives also increases. The Oasys score increased slightly when analysing all data including a long period off work, but not significantly so. This smaller effect on the Oasys score is likely to be explained by the way this score is computed using discriminant analysis [42;53] which does not require a particular amount of increase in the difference of PEF between work days and rest days. In contrast, the ABC score computes the difference in Litres per minute per hour between the mean work and rest day PEF curves plotted in 2-hourly periods (meaning 2-hourly mean PEF values) [188] and requires a difference of at least 15L/min/hr to achieve a sensitivity of 69% and specificity of 100% for the diagnosis of occupational asthma.

Sensitivity was improved for both scores in all analyses in this group of workers compared to previously published data [42;188] although specificity was slightly compromised. Including longer periods off work in the PEF record analysis improved the sensitivity of the ABC score for an occupational asthma diagnosis from 73 to 80%. Specificity was

robust, being >95% for the ABC score even when confining the rest day plot to start at consecutive day 4 away from work. Inclusion of longer rest periods had a lesser effect on the sensitivity of the Oasys score. The ABC score was more useful than the Oasys score in situations where there were fewer periods at and away from work. This is due to the Oasys score needing ≥ 3 complexes (rest-work-rest periods or work-rest-work periods) to meet minimum data quantity requirements for a good sensitivity and specificity. It therefore made the analysis of consecutive rest days from 4 onwards inapplicable to the Oasys score as 33 records meeting this minimum data quantity requirement for the Oasys score contained only 1 rest period with at least 7 consecutive rest days, leading to only one scorable complex. The ABC score does not have this minimum data requirement and can be used in situations where records have been completed for 2 weeks at work and 2 weeks away from work without compromising sensitivity and specificity of this score.

We found no differences in the ABC score for workers who had a mean PEF percent predicted ≥ 70% and those with a reduced PEF percent predicted of <70% (p=0.515). The workers with ≥ 70% predicted PEF had the largest ABC scores (49 l/min/hr versus 38 l/min/hr) suggesting that the influence of the duration of the rest period on the ABC PEF score is not restricted to workers with a low mean PEF level.

Although in many countries, such as the UK, PEF measurements during a week off work can only be achieved during workers' holidays, factory shutdown periods or by the worker taking unpaid leave, the extra 7 cases identified with this extended time off work may be worth the effort if occupational asthma is not diagnosed from recordings including weekends off alone.

6.3.6.1. Validity of methods and limitations of the study

We have utilised PEF records of workers whose occupational asthma was confirmed mainly through specific inhalation challenge testing (considered to be the gold standard for occupational asthma diagnosis), [13] but have also included workers who had at least four-fold change in non-specific reactivity between when exposed and after at least a week away from exposure, and workers with a positive specific IgE to a relevant occupational agent in combination with a strong typical work-related symptom history. Some may not agree with using this latter group, but we found no difference in their ABC or Oasys scores compared to the group with specific inhalation challenge test positive occupational asthma ($p=0.741$ and $p=0.582$ respectively). For this reason, we believe that this confirmation method can be used for the purposes of our study. Inclusion of this group extends the spectrum of workers to include the group for whom specific challenge tests are usually thought unnecessary and whose diagnosis of occupational asthma is clearly unrelated to their PEF recording at the time of diagnosis.

Not all of our occupational asthma positives and negatives had non-specific reactivity outside the normal range. Some centres consider non-specific reactivity to be a requirement for the diagnosis of asthma, but all our occupational asthma positive workers showed a latent interval before symptoms started and were exposed to levels of the agent that were below the level inducing irritant effects. In this study, 13/24 workers who had positive specific challenge tests had normal reactivity. Others have found similar results with regard to the relationship between specific and non specific reactivity [23;30;86;108].

Although the ABC score increased by including the long period off work, the difference was not significant. A power calculation revealed the requirement for a 28.1L/min/hour difference between analyses to show significance at 80% power.

6.3.6.2. Synthesis with previous knowledge

To our knowledge, no other studies have compared PEF records with long periods off work to those with only weekends or up to 3 consecutive days off at any one time. Some studies have requested that workers complete records for at least two weeks at work and two weeks away from work [40;55;191] with the idea that this could improve sensitivity to detect occupational asthma. For some workers, it seems to be important to investigate whether it takes longer than 3 days away from exposure for their PEF to recover, as we have shown here that such longer rest periods increase the sensitivity of the ABC PEF score, while maintaining high specificity. In this study, workers with a lower PEF level of predicted did not require a longer period off work to elicit a positive ABC score compared to those with normal PEF levels, so we were not able to identify any one group of workers whose diagnostics would benefit from such longer rest period.

6.3.7. Conclusion

The ABC score computed by the Oasys program to diagnose occupational asthma can be increased in those with occupational asthma by including a long period off work while monitoring PEF for diagnostic purposes. The sensitivity of the peak flow analysis by using the ABC score can also be improved in this way, identifying 7 more cases per hundred with independently diagnosed occupational asthma. Specificity was unchanged with inclusion of a long period off work.

6.4. SERIAL LUNG FUNCTION VARIABILITY USING FOUR PORTABLE LOGGING METERS

Moore VC, Parsons NR, Jaakkola MS, Burge CB, Pantin CF, Robertson AS, Burge PS. Journal of Asthma 2009;46:961-966.

6.4.1. Abstract

Portable lung function logging meters that allow measurement of peak expiratory flow (PEF) and forced expiratory volume in 1 second (FEV_1) are useful for the diagnosis and exclusion of asthma. The aim of this study was to investigate the within and between session variability of PEF and FEV_1 for four logging meters and to determine the sensitivity of meters to detect FEV_1 and PEF diurnal changes.

Methods: Thirteen assessors (all hospital staff members) were asked to record one week of 2-hourly PEF and FEV_1 measurements using four portable lung function meters. Within session variability of PEF and FEV_1 were compared for each meter using a coefficient of variation (COV). Between session variability was quantified using parameter estimates from a cosinor analysis which modelled diurnal change for both lung function measures and also allowed for variation in response for individual assessors between days.

Results: The mean within session COV for FEV_1 was consistently lower than that for PEF ($p < 0.001$). PEF showed a higher, but not significantly different ($p = 0.068$), sensitivity for detecting diurnal variation than FEV_1. PEF was also slightly more variable between days, but not significantly different than FEV_1 ($p = 0.409$). PEF and FEV_1 diurnal variability did

not differ between the four meters (p=0.154 and 0.882 respectively), but within session FEV_1 COV differed between meters (p=0.009).

Conclusion: PEF was marginally more sensitive to within day variability than FEV_1, but was less repeatable. Overall, differences between the four meters were small suggesting that all meters are clinically useful.

6.4.2. Introduction

Serial lung function measurements require high patient compliance, but are recommended by several guidelines as a useful confirmatory test for asthma and occupational asthma [1;13;38]. However, some workers have been shown to fabricate their readings [48]. Anees *et al* have shown that hand-recorded readings not logged by the meter, tended towards a mean value for that individual rather than showing work-related changes and therefore did not increase the likelihood of the record showing occupational asthma [49]. The introduction of portable lung function logging meters downloaded in clinic while the worker is present has mostly eliminated the fabrication problem. Logging meters do not just measure peak expiratory flow (PEF), as has been typically performed by the manual meters (e.g. mini-Wright), but also measure forced expiratory volume in one second (FEV_1) and sometimes forced vital capacity (FVC). It has previously been suggested that FEV_1 is a more sensitive measure for asthmatic changes than PEF [46;192] and the former is usually used in specific inhalation challenge testing, which is the gold standard confirmatory test for occupational asthma diagnosis. However, the FEV_1 manoeuvre may be harder to accomplish in the right way when unsupervised [47] and could therefore be less reliable when performing serial lung function measurements at home or at work. The

aim of this study was to investigate the variability of PEF and FEV_1, analyzing both the variability within a session of measurements and between all measurements. To add a further dimension, potential portable logging meter differences were also investigated by testing four different meters which operated in contrasting ways: (i) a metal spring (N-spire Piko-1) (ii) Fleisch pneumotachograph (Vitalograph Diary 2110), (iii) rotary turbine (Micromedical MicroDL) and (iv) ultrasound technology (NDD Easyone). The meters also differed significantly in price ranging from approximately £25 up to ~£1000 per unit.

6.4.3. Methods

Thirteen staff members with clinical and non-clinical jobs in a respiratory medicine department (hereafter referred to as 'assessors') were asked to measure their PEF and FEV_1, from the same manoeuvre, on four different meters: (i) N-spire Piko-1 meter, (ii) Vitalograph Diary 2110, (iii) Micromedical MicroDL and the (iv) NDD Easyone. They were instructed to do this at approximately two-hourly intervals from waking to sleeping for a total of one week per meter. The number of measurements made at each two-hourly interval depended on the meter used. For the Piko-1, the assessor made three measurements, aiming to get the highest two PEFs within 20L/min. If unsuccessful, they completed a fourth measurement. For the Diary 2110, the assessor made measurements until the machine required no further manoeuvres (between two and five measurements) and for the MicroDL the meter required three measurements in sequence before it switched off. The Easyone had programmed quality criteria but these were set for FVC manoeuvres which were not necessary for this study, therefore the same criteria as for the Piko-1 were used. Ethics committee approval was obtained from the Birmingham East, North and Solihull committee (reference number 06/Q2703/73).

Assessors were asked to write down each PEF and FEV_1 measurement made on the provided charts. The Piko-1 logged the highest measurements in each session and the MicroDL and Diary 2110 only logged the best measurements from acceptable blows in each session (highest measurement from those with a time to PEF >40ms and <300ms for the Diary 2110; back extrapolation volume <150ml and no second peak (indicating cough) for the MicroDL), therefore written readings and associated times were used for analyzing the data on these meters. The Easyone logged the best three values from all tests (when time to PEF was <120ms and back extrapolated volume <150ml or 5%, whichever was greater), therefore the downloaded meter readings and times were used for this meter instead of the written readings.

6.4.4. Statistical methods

6.4.4.1. Coefficient of variation

Within session variation (a session describes the group of measurements taken at each two-hourly interval, i.e. each set of 3-4 PEF/FEV_1 manoeuvres) was estimated by calculating the coefficient of variation (COV) for all measurements taken at each session. One-way analysis of variance (ANOVA) was used to assess differences in COV between meters, averaged across individual assessors and sessions for PEF and FEV_1. Post hoc comparisons were performed using the least significant difference test; tests were considered to provide evidence for a significant difference if p-values were less than 0.05 (5% significance level).

6.4.4.2. Cosinor models

To fully account for variations in lung function measurements between assessors and days and provide an unbiased analysis of between session variation, the daily time course (t hours in range 0 to 24) of the PEF data were modelled using a one-harmonic sinusoidal regression function (cosinor model), to account for natural diurnal variation. Models of this form were also used for diurnal variation in FEV_1 measurements, but arguments will be developed here using PEF only for simplicity. Separate models for diurnal variation in PEF (y_{ij}), of the form

$$y_{ij}(t) = (\beta_{0i} + b_{0j}) + \beta_{1i}\cos(k(t-\phi)) + \varepsilon_{ij}, \quad (1)$$

were fitted for each user, for meter $i = 1,2,3,4$ and day j. In equation (1), the terms, β_{0i}, β_{1i} and ϕ are model parameters that characterize the change in PEF during the course of a normal day for each assessor; the parameters β_{0i} and β_{1i} were allowed to vary between meters (fixed effects) for each user. The random effect terms b_{0j} are deviations in β_{0i} due to the day measurements were made (day 1,2,3, etc) and are assumed to be distributed Normally with mean 0 and variance τ^2, and ε_{ij} are independently distributed errors with mean 0 and variance σ^2. The constant $k = 2\pi/24$ transforms the hourly scale to a scale based on radians. The parameters are interpreted as follows; β_0 is the mean PEF level, β_1 is half the dynamic change in PEF during a day (half the amplitude) and ϕ indicates the time when the peak PEF occurs (acrophase).

Models were fitted using the nonlinear mixed effect models library (NLME), available as a package in the statistical software R (R Development Core Team, 2007). A range of

potential fixed and random effect models were tested, using appropriate likelihood ratio tests, for each assessor prior to the selection of the model expressed in equation (1). For all assessors, mean PEF level (β_0) varied significantly between meters, but for a number of assessors half the dynamic change in PEF (β_1) did not differ significantly between meters, therefore for these assessors a single fixed common parameter was fitted for all meters. The peak PEF time (ϕ) remained fixed across all meters for an individual assessor. Residual plots revealed no evidence to suggest that the model assumptions of Normally distributed errors were not valid.

The estimated variances (τ^2) of the daily deviations in mean PEF level (b_{0j}) for each assessor were used to compare the proportion of the variance in the daily baseline PEF or FEV_1 level that was accounted for by day-to-day variability, to the residual variance σ^2 for each assessor. The diurnal sensitivity of individual meters was analyzed by using the ratio of the dynamic change in PEF or FEV_1 during a day (β_1) to the mean PEF or FEV_1 level (β_0).

One-way analysis of variance (ANOVA) was used to assess differences in estimates of lung function parameters between meters, averaged across individual assessors for PEF and FEV_1. Post hoc comparisons were performed using the least significant difference test. Ratios were analyzed on a log-transformed scale as this considerably improved the normality assumptions required for ANOVA.

6.4.5. Results

6.4.5.1. Assessor demographics

Thirteen assessors completed measurements on all four meters. Their mean age was 39 years (SD 12.2), five had a clinical diagnosis of asthma, two were taking a constant dose of inhaled steroids throughout the PEF monitoring and none were current smokers. Their mean FEV_1 percent predicted was 102% (SD 11.5) and 1 had methacholine reactivity. The mean number of recording sessions per day was 5.1 (SD 1.05).

6.4.5.2. Within session variability

Estimates of COVs, shown in Table 6.4.1 for each meter, showed a low overall mean variability across assessors within each measurement session (COV in range 3-4%). FEV_1 within session variability, averaged across the four meters, was significantly lower than PEF within session variability ($p < 0.001$). Analysis of data for each meter separately indicated that COVs differed significantly between PEF and FEV_1 for Piko-1 and Easyone only ($p < 0.001$). Post hoc tests showed significant differences in FEV_1 COV between the Easyone and the Diary 2110 ($p = 0.003$), the Easyone and the MicroDL ($p = 0.016$) and the Piko-1 and Diary 2110 ($p = 0.028$). There were also small differences in PEF COV between the Easyone and Diary 2110 and Easyone and MicroDL ($p = 0.032$ for both).

Table 6.4.1. Estimates of within session coefficient of variation (%) for PEF and FEV_1 for meters (i) N-spire Piko-1 meter, (ii) Vitalograph Diary 2110, (iii) Micromedical MicroDL and (iv) NDD Easyone

	Meter				
Measure	**(i)**	**(ii)**	**(iii)**	**(iv)**	**p-value**†
PEF	3.98	3.89	3.91	4.41	0.102
FEV_1	3.47	3.96	3.80	3.27	0.009
p-value†	0.012	0.797	0.632	<0.001	

† p-values from ANOVA for comparing COV between meters and between PEF and FEV_1 measures

6.4.5.3. Between meter differences

Cosinor models of the form of equation (1) were fitted to the time course of data for each assessor for PEF and FEV_1 separately. Standard errors of the parameters were always less than 3% of the estimated parameters, indicating that the procedure was reliable. Mean estimates of the phase parameters (ϕ) across the thirteen assessors were, for both PEF and FEV_1, approximately 14.5, indicating that peak lung function occurred at around two thirty in the afternoon; estimates varied between ten in the morning and eight in the evening, dependent on the assessor. As an example of a typical assessor, fitted and raw data for assessor 1, plotted for the four meter types, are displayed in Figure 6.4.1 for PEF and Figure 6.4.2 for FEV_1. Analysis of variance of β_0 for PEF and FEV_1 across all assessors

showed no differences in either lung function measure between meters (p = 0.912 and p = 0.939, for PEF and FEV_1 respectively).

Figure 6.4.1. PEF data and fitted cosinor model curve for assessor 1 for meters (i) N-spire Piko-1 meter, (ii) Vitalograph Diary 2110, (iii) Micromedical MicroDL and (iv) NDD Easyone.

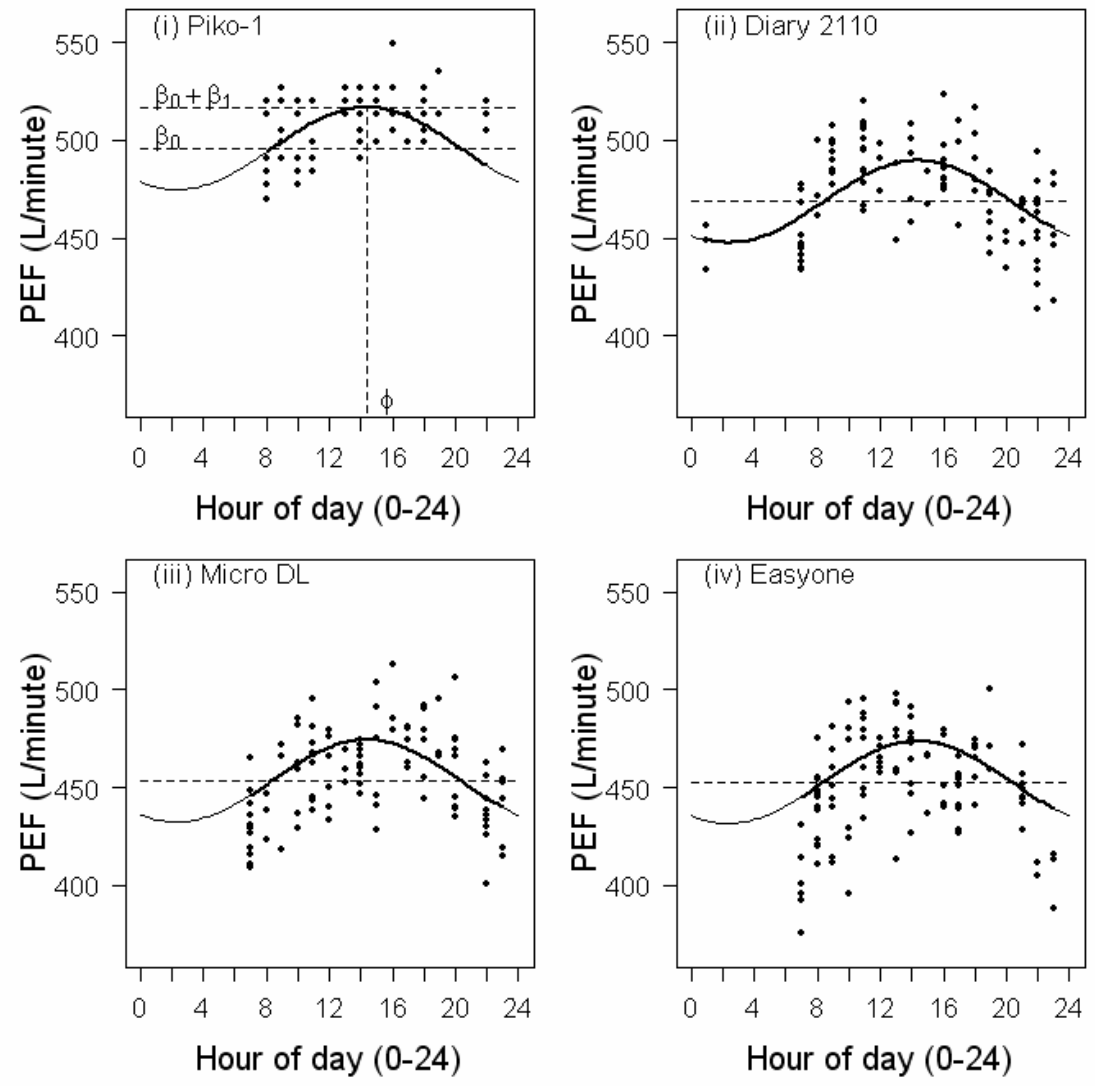
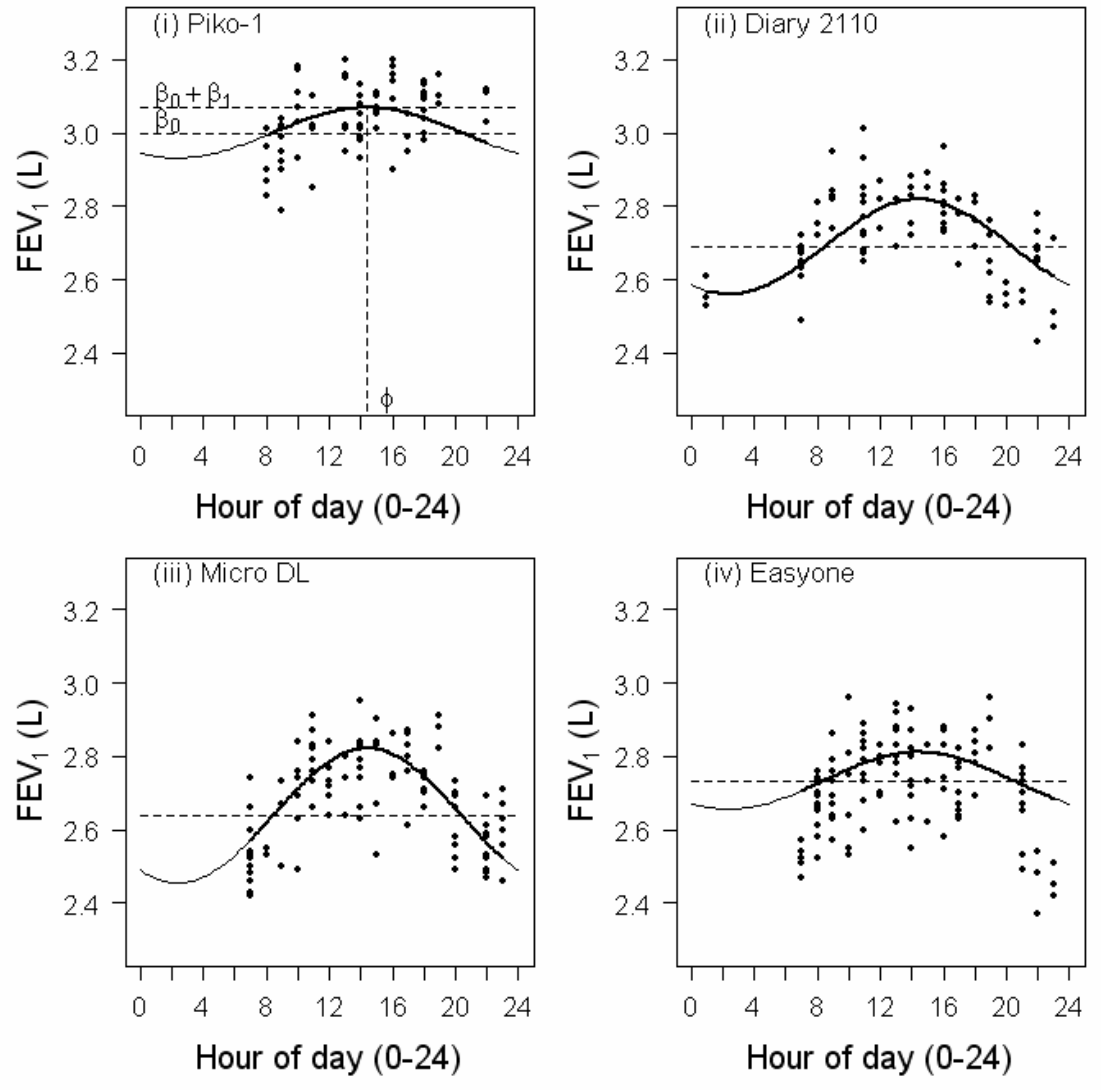


Figure 6.4.2. FEV_1 data and fitted cosinor model curve for assessor 1 for meters (i) N-spire Piko-1 meter, (ii) Vitalograph Diary 2110, (iii) Micromedical MicroDL and (iv) NDD Easyone.



6.4.5.4. Between Day Variability

The between day variability for both PEF and FEV_1 data, given by estimates of the ratio τ^2/σ^2 expressed as a percentage, was small for the majority of assessors (<5%). An ANOVA indicated that there was no evidence that mean between day variability differed significantly between PEF and FEV_1 ($p = 0.409$). However, there were considerable differences between assessors. For instance, assessors 7, 9 and 11 showed large between-day variability (~10%), particularly for PEF.

6.4.5.5. Sensitivity to detect diurnal variability

The sensitivity of the meter to detect diurnal variability, measured as the ratio of the dynamic change in PEF or FEV_1 during a day (β_1) to the mean PEF or FEV_1 level (β_0) expressed as a percentage, is summarized in Table 6.4.2. This shows mean values for each meter across all assessors. Overall, variation within a day was between 2 and 5% of the mean PEF or FEV_1 for each meter; although there was considerable variation between assessors. PEF was generally more sensitive in detecting diurnal changes than FEV_1, but this was not formally significant when analyzing all meters together ($p = 0.068$). However, when testing between individual meters it was clear that there were significant differences between PEF and FEV_1 for the piko-1 meter ($p = 0.026$) and the micro DL meter ($p = 0.017$); for both, PEF proved to be more sensitive to diurnal change than FEV_1. No significant differences were found between individual meters for PEF and FEV_1 separately. PEF and FEV_1 diurnal variability of all meters were similar between those diagnosed with asthma and those without asthma ($p = 0.468$ for PEF and $p = 0.202$ for FEV_1).

Table 6.4.2. Ratio of the dynamic change in PEF or FEV_1 during a day (β_1) to the mean PEF or FEV_1 level (β_0) expressed as a percentage (standard deviation shown in parentheses) for PEF and FEV_1 for meters (i) N-spire Piko-1 meter, (ii) Vitalograph Diary 2110, (iii) Micromedical MicroDL and (iv) NDD Easyone.

	Meter				
Measure	**(i)**	**(ii)**	**(iii)**	**(iv)**	**p-value**†
PEF	3.94 (2.94)	3.69 (5.90)	4.56 (3.75)	3.21 (2.11)	0.154
FEV_1	2.22 (0.88)	3.81 (5.71)	2.39 (1.73)	3.10 (3.10)	0.882
p-value†	0.026	0.548	0.017	0.363	

† p-values from ANOVA for comparing diurnal variation between meters and between PEF and FEV_1 measures

6.4.6. Discussion

We have shown that in general FEV_1 seems to be a less sensitive measure for identifying within day diurnal changes than PEF when measured serially by staff members of a respiratory medicine department. The difference between FEV_1 and PEF was significant for the Piko-1 ($p = 0.026$) and the Micro DL ($p = 0.017$) meters but no significant difference was observed for the Easyone and Diary 2110, the latter showing that FEV_1 was slightly more sensitive. The Micro DL showed the highest diurnal sensitivity for PEF and the Diary 2110 was the most sensitive for FEV_1, but there was no significant difference between individual meters for PEF and FEV_1 when analyzed separately by meter type.

Leyroyer *et al* (1998) described similar results when analyzing unsupervised FEV_1 measurements compared to PEF and showed that serial FEV_1 was less sensitive than serial PEF for diagnosing occupational asthma [47].

Five of the assessors had previously been diagnosed with asthma, but they showed no difference in diurnal variability when compared to the non-asthmatic assessor group. Assessor 9 showed a very high diurnal variability when using the Diary 2110 meter (22.7% for PEF and 22.4% for FEV_1). It was not clear why this was the case. However, we can speculate that it may have been due to the meter accepting only 2 measurements (using the meter's programmed quality criteria) making it much less easy to control; although none of the other assessors found this to be a problem for this meter. The opposite occurred for assessor 6 who had very low diurnal sensitivity when using meter 2 (0.13%) that may have been due to the very high PEF level for this individual which was at the top of the meter's range.

ANOVA of mean PEF and FEV_1 from the fitted models (β_0) showed that they did not differ significantly between meters ($p = 0.912$ and $p = 0.939$); despite there being a 43L/min difference in mean β_0 for PEF between the Diary 2110 and Micro DL. This suggests that although these meters measure flow in different ways (from which volume is calculated), they all provide equivalent estimates of lung function when averaged across a representative sample of individuals from the wider population of users. However, within an individual, there was up to a 233L/min difference between the highest and lowest estimates of β_0 between certain combinations of pairs of meters. Highest and lowest values were not consistently observed between the same pairs of meters for all assessors, hence

overall there was no statistically significant difference when data from all assessors were pooled. In contrast to our study, Keskinen *et al* (1996) found consistently lower results from the Wright PEF meter compared to the microplus pocket spirometer for PEF. However, when they compared FEV_1 on the micro plus spirometer to FEV_1 on the Vitalograph wedge bellows, they found a good correlation between the two [190]; although for our analysis β_0 value was not a simple mean of the PEF data, but rather a corrected estimate from a cosinor model, the principles are similar.

For within session variation, both FEV_1 and PEF showed low variability overall, but FEV_1 was found to be the most repeatable measure, particularly for the Piko-1 and Easyone. In a study by Hegewald *et al* (2007), PEF within session variability was also reported as being higher than FEV_1 within session variability [193]. We also found FEV_1 COV to be significantly different between meters ($p = 0.009$) whereas PEF COV was similar across all meter types. The highest FEV_1 COV was found with the Diary 2110 which had predetermined quality criteria set in the meter based on PEF which may have led to less repeatable FEV_1 measurements. The lowest FEV_1 COV was for the Easyone which may have been be due to the unit saving only the best three measurements, even if more were performed by the user, leading to lower variation.

We have also shown that between day variability was generally low, typically < 5%, for both FEV_1 and PEF. The assessors carried out their measurements on days at and away from work and were not known to have any work related symptoms or associated lung function problems. Assessors were selected to represent a typical panel of routine users of the meters. Assessors were familiar with the use of meters for serial PEF measurements for

assessing occupational and non-occupational asthma, but most had no previous experience of using the meters. The assessor who had the largest between day variability was the least experienced, this may have been the reason why their readings proved to be less consistent between days than the other assessors. This assessor was not asthmatic. In occupational and non occupational asthma, between day variability may be important if individuals are exposed to a trigger for their asthma on days when the highest diurnal variability was observed. Otherwise, in people showing increased between day variability, a repeat record with additional training may prove to be useful.

A coefficient of variation was used to measure the repeatability of FEV_1 and PEF within a set of measurements (session), as has been reported by others [194]. For between session variability, it is well known that the time of day readings are made has a large effect on lung function [66;68-71], simply averaging data by day and assessor and testing using ANOVA would provide a biased analysis. A more complex calculation was therefore undertaken using cosinor analysis to model the diurnal change, which is the recognised method of analysis for biological systems with circadian variation [195].

A drawback of this study is that we have not taken into account the activity of each individual on each day; e.g. whether work days were different to rest days or whether exercising affected the results. This information was not recorded by the assessors, so it is not possible to analyse this factor any further. However, there is no reason to believe in principle that work days should be any different to rest days in a group of individuals without a diagnosis of occupational asthma and without work-related respiratory symptoms.

Another factor that could potentially affect the interpretation of the results presented here is the frequency of recording; despite clear instructions not all assessors took measurements every 2 hours. Some individuals managed to achieve this on some days, but were rather intermittent on others. Clearly, if measurements had been made at precise times by each individual over the full cycle of 24 hours, some of the noise might have been removed from the model. However, this was a pragmatic trial and as such the observed data are a typical representation of patient measurement patterns in real life and clearly highlight the difficulty in achieving a fixed measurement protocol when using a population of real patients. A minimum of four measurements were achieved on all days of recording by all assessors, which Malo *et al* (1993) and Gannon *et al* (1998) [40;44] reported as providing sufficient data for interpreting diurnal variability.

6.4.7. Conclusion

PEF appears to be a more sensitive measure than FEV_1 for assessing within day diurnal changes. FEV_1 is more reproducible within a measurement session when performed by clinical and non-clinical staff members in a respiratory department. No one meter was more reproducible than another for PEF, and only within session variance differed between meters for FEV_1, showing that even the most basic meters are useful. With cheap, portable meters that measure both FEV_1 and PEF now available, their use in the diagnosis of occupational asthma is recommended, but reproducibility of measurements by patients should also be established in future studies.

6.5. TWO VARIANTS OF OCCUPATIONAL ASTHMA SEPARABLE BY EXHALED BREATH NITRIC OXIDE LEVEL

Moore VC, Anees W, Jaakkola MS, Burge CBSG, Robertson AS, Burge PS.

Respiratory Medicine 2010; 104:873-879

6.5.1. Abstract

Exhaled nitric oxide (FE_{NO}) has been used as a marker of asthmatic inflammation in non-occupational asthma, but some asthmatics have a normal FE_{NO}. In this study we investigated whether, normal FE_{NO} variants have less reactivity in methacholine challenge and smaller peak expiratory flow (PEF) responses than high FE_{NO} variants in a group of occupational asthmatics.

Methods: We measured FE_{NO} and PD_{20} in methacholine challenge in 60 workers currently exposed to occupational agents, who were referred consecutively to a specialist occupational lung disease clinic and whose serial PEF records confirmed occupational asthma. Bronchial responsiveness (PD_{20} in methacholine challenge) and the degree of PEF change to occupational exposures, (measured by calculating diurnal variation and the area between curves score of the serial PEF record in Oasys), were compared between those with normal and raised FE_{NO}. Potential confounding factors such as smoking, atopy and inhaled corticosteroid use, were adjusted for.

Results: There was a significant correlation between FE_{NO} and bronchial hyperresponsiveness in methacholine challenge ($p=0.011$), after controlling for confounders. Reactivity to methacholine was significantly lower in the normal FE_{NO} group

compared to the raised FE_{NO} group (p=0.035). The two FE_{NO} variants did not differ significantly according to the causal agent, the magnitude of the response in PEF to the asthmagen at work, or diurnal variation.

Conclusions: Occupational asthma patients present as two different variants based on FE_{NO}. The group with normal FE_{NO} have less reactivity in methacholine challenge, while the PEF changes in relation to work are similar.

6.5.2. Introduction

Measurement of exhaled breath nitric oxide (FE_{NO}) has been promoted as a measure of airway inflammation in asthma [115;120;121;196]. It has been shown to be correlated with sputum eosinophilia and non specific reactivity in asthmatics [15;119-127] but has the advantages of being less invasive for the patient and less labour intensive for the clinician. However, some symptomatic asthmatics have been reported to have normal levels of FE_{NO} [15;123;197;198] even when factors such as inhaled corticosteroid therapy and smoking have been accounted for. In the diagnosis of occupational asthma, one of the best first line investigations for occupational asthma is serial peak expiratory flow (PEF) monitoring and is recommended by several guidelines [1;13]. It has previously been suggested previously that using changes in sputum eosinophil counts between periods of exposure and non-exposure increases the sensitivity and specificity of serial PEF measurement in the diagnosis of occupational asthma [199]. Specific inhalation challenge tests to occupational agents have resulted in a mean increase of exhaled nitric oxide levels [200-203]. However, some workers with positive challenges have not showed changes. We have previously found a strong positive correlation between exhaled nitric oxide level and sputum

eosinophil count in workers with occupational asthma exposed to low molecular weight agents and a relationship between sputum eosinophilia and non specific reactivity [123]. The study suggested that workers can be separated into two variants, those with eosinophilic airways inflammation and those with non-eosinophilic inflammation and that they would also be separable by FE_{NO} due to the strong relationship between the two indices. The aim of this study was to investigate a prospective group of patients with occupational asthma to see whether our retrospective analysis could be confirmed with a prospective group, and whether there is a relationship between FE_{NO} phenotype (normal versus raised) and non-specific bronchial reactivity from methacholine challenge and whether the magnitude of PEF response to occupational exposure is related to FE_{NO}.

6.5.3. Methods

6.5.3.1. Study Population

Consecutive workers referred to the Occupational Lung Disease Clinic, Birmingham, UK between November 2001 and December 2004 were recruited who had performed an exhaled nitric oxide measurement (FE_{NO}), methacholine challenge test and serial PEF record while still exposed at work. Sixty subjects whose serial PEF measurements showed occupational asthma while exposed to the causative agent and who had a diagnosis of occupational asthma formed the study population. The study was approved by the East Birmingham Local Ethics Committee (reference 929).

6.5.3.2. Measurements

Workers were requested to record PEF every 2 hours from waking to going to bed on work days and days away from work for a total of 4 weeks. The best of 3 PEF readings were

recorded on each occasion, provided that the best 2 readings were within 20 l/min of each other. Records were plotted, linearised [51] (if recorded on a non-linear PEF meter) and analysed by the Oasys computer program [42]. Those with a work effect index score ≥ 2.51, (that was used as a cut-off point for definite occupational effect) [42] were included in this analysis.

Spirometry, FE_{NO} and non-specific bronchial reactivity in methacholine challenge were performed within 24 hours of work exposure after withholding treatment with long acting β-agonists for 24 hours (including combined steroid and long acting β-agonists inhalers), short-acting β-agonists for 6 hours and tiotropium for 36 hours as part of their routine clinic visit.

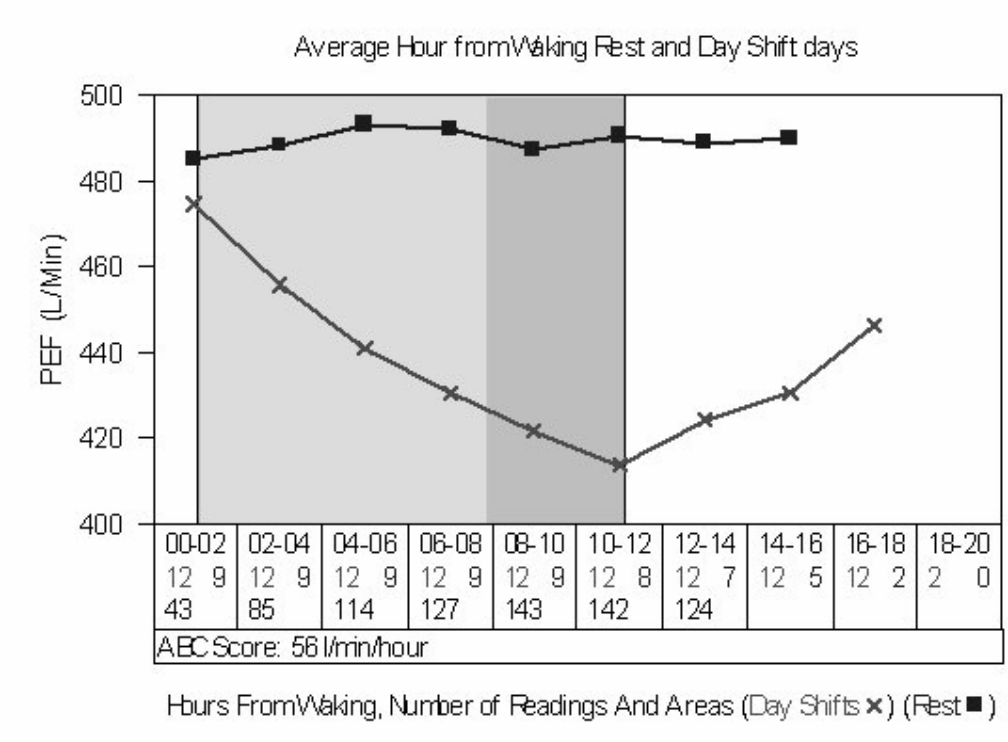
Spirometry was performed on either a wedge bellows Vitalograph spirometer or on the Jaeger pulmonary function system according to ERS/ATS standards [204]. Non-specific bronchial reactivity to methacholine was measured using the Yan technique [92]. FE_{NO} was measured during exhalation at 50ml/second using the Niox from Aerocrine, which requires values from two readings to be within 10% as recommended by the ATS/ERS [205] and performed before spirometry. The Oasys program [42] was used to calculate diurnal variation on days at and away from work and the area between curves (ABC) based on mean PEF on work days and days away from work (ABC score) plotted by waking time (Figure 6.5.1) [188].

Workers were split into normal and raised nitric oxide level groups based on an eosinophil cut off of 2.2% which was used in our previous study to separate eosinophilic and non

eosinophilic variants [123]. A cut off of 14.7ppb for smokers and 22.1ppb for non smokers (equivalent to < or ≥ 2.2% sputum eosinophilia) was selected from a regression analysis of all our previous combined measurements of sputum eosinophils and FE_{NO}. These values were then used to separate workers into those with normal FE_{NO} and those with raised FE_{NO} levels.

Figure 6.5.1. The ABC plot of a worker exposed to chrome from stainless steel welding.

He has normal methacholine reactivity (>4800mcg) and an FE_{NO} of 6.1ppb. The plot has a 56 L/min/hour difference between the mean curves of PEF on work and rest days. In the bottom panel, the first row of numbers is the time from waking in 2-hourly sections e.g. 00-02; 02-04 etc. The second row shows the number of readings used for the mean PEF curves in each 2-hourly section (left side shows work readings and right side shows rest readings). The third row shows the area between the curves for each 2-hourly section which are then used to calculate the ABC score which is in litres/min/hour. A score of ≥ 15 L/min/hr has a sensitivity of 69% and specificity of 100% for occupational asthma diagnosis [188].



Characteristics of the workers such as smoking history, atopy (defined as at least one positive skin prick test of ≥3mm wheal to a common environmental allergen using saline and histamine as negative and positive controls) and inhaled corticosteroid treatment were recorded. Inhaled corticosteroids were classified into groups according to the GINA (Global Inititaive for Asthma) guidelines [206] for analysis against $FE_{NO.}$

6.5.3.3. Statistical analysis

Data were analysed by using FE_{NO} as a continuous variable and also by grouping the workers into two variants based on their FE_{NO} level. Physiological data were not normally distributed, so reactivity to methacholine and nitric oxide levels were log transformed. Subjects who had a PD_{20} >4,800 μg (the highest dose used) in methacholine challenge had their percent fall in FEV_1 extrapolated to give a PD_{20} value. Differences in physiological parameters between groups were assessed using a Mann Whitney U test or Chi-square test for non-parametric data and either independent t-test or one way ANOVA for parametric data (age, FEV_1 percent predicted, ABC PEF score and log transformed reactivity to methacholine and nitric oxide). Multiple linear regression was used for controlling for variables potentially confounding the relation between FE_{NO} and bronchial hyperresponsiveness. Pearson correlation was used to compare reactivity to methacholine and nitric oxide levels when using both as continuous data. The Yates' continuity correction was used when at least one cell count was <5 when performing the Chi-square statistic. SPSS version 15 was used for all statistics.

6.5.4. Results

Workers had a mean age of 44 years and 83% were males. Mean FE_{NO} levels were similar

between atopics and non-atopics (p=0.521), males and females (p=0.183) and those with an FEV_1 percent predicted of <80% or >80% (p=0.547). There were eighteen workers at Step 4 of the GINA treatment pathway, eleven at step 3, eight at step 2 and twenty-three on inhaled short acting beta agonists only. There was no difference in log FE_{NO} between these groups (p=0.591). Current smokers had significantly lower nitric oxide levels (p=0.013) compared to ex or never smokers. Those who showed bronchial hyperresponsiveness in methacholine challenge had a significantly higher FE_{NO} (p=0.006). Table 6.5.1 shows statistical comparisons of characteristics and physiological parameters between raised and normal FE_{NO} groups, using the different cut-off points for smokers and ex or never smokers.

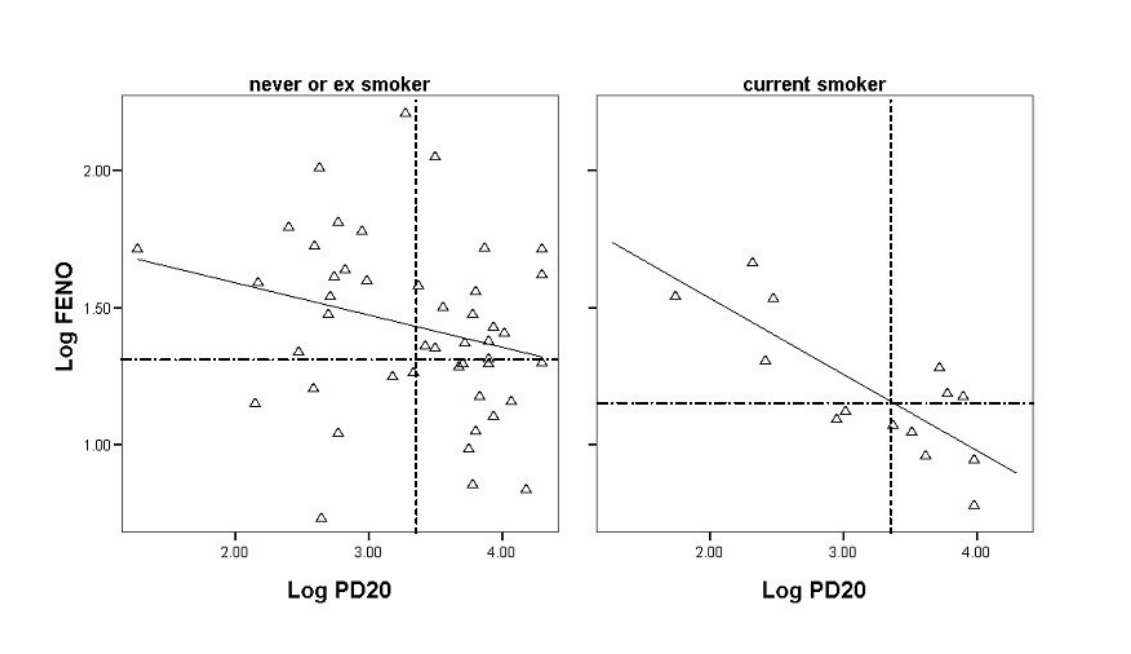
Table 6.5.1. Characteristics of the two variants of occupational asthma separated by FE_{NO} level and smoking

	Normal FE_{NO} (smokers <14.7ppb; never/ex <22.1ppb) n=25	**Raised FE_{NO}** (smokers ≥ 14.7ppb; never/ex ≥ 22.1ppb) n=35	**P value**
Mean Age (SD)	43.4 (9.7)	45.3 (10.1)	0.469
% Male	84.0	82.9	0.907
Mean FEV_1 % predicted (SD)	90.7 (21.8)	88.5 (18.1)	0.665
% Atopic	56.0	62.9	0.593
% using ICS	54.2	65.7	0.372
Mean ABC PEF Score (SD)	38.5 (23.9)	29.6 (24.9)	0.196
Mean PEF work diurnal variation (SD)	17.8 (9.4)	20.5 (12.4)	0.653
Mean PD20 in Methacholine challenge µg (SD)	5730 (4975)	3883 (5048)	0.035

There was a significant positive correlation between reactivity to methacholine and nitric oxide level when both were analysed as continuous data (Pearson correlation =-0.320; p=0.013). When controlling for smoking, inhaled corticosteroid use and atopy (the main determinants of nitric oxide levels) in multiple linear regression, there was still a significant relationship (R^2=0.221; p=0.009). Figure 6.5.2 shows the relationships split by current smokers and ex/ never smokers.

Figure 6.5.2. Scatter diagram of correlation between exhaled FE_{NO} and reactivity in methacholine challenge separated by smoking.

---------- indicates the cut off for normal methacholine reactivity
– – – – – – indicates the cut off separating normal and raised FE_{NO} levels



Correlations between nitric oxide level and ABC score (as a measure of PEF response) were analysed using multiple linear regression controlling for smoking, inhaled corticosteroid use and atopy. There was not a significant relationship (p=0.781). The ABC score was also compared between those with raised and normal FE_{NO} levels in a group of non-smokers who were not taking inhaled corticosteroids. The ABC score was similar (p=0.912). Diurnal variation in PEF was also similar between the two groups (p=0.653).

Workers were analysed for differences in the raised and normal nitric oxide groups according to causative agents (Table 6.5.2). There were no differences between those with raised and normal FE_{NO} for high versus low molecular weight agents (p =0.898).

Table 6.5.2. Causative occupational exposures by normal and raised FE_{NO} levels.

Type of occupational exposure	**Normal FE_{NO}** (smokers <14.7ppb; never/ex <22.1ppb) n=25	**Raised FE_{NO}** (smokers ≥ 14.7ppb; never/ex ≥ 22.1ppb) n=35	**P value**
Metals	9	11	0.711
Biocides	3	6	0.855
Metal-working fluid	1	5	0.383
Isocyanates	3	6	0.855
Adhesives	2	2	1.000
Plastics	0	1	1.000
Other low molecular weight agents	3	0	0.133
High molecular weight agents	4	4	0.898
Low molecular weight agents	21	31	

6.5.5. Discussion

In our study of 60 patients with occupational asthma confirmed by their PEF record, we found that occupational asthma patients can be divided into two variants by FE_{NO} level and that the group with raised FE_{NO} has significantly more reactivity in methacholine challenge. The two variants do not differ significantly according atopy, causative agents of

occupational asthma, inhaled steroid use, or FEV_1 percent predicted, indicating that these did not explain the relation between FE_{NO} and bronchial hyperresponsiveness. Both FE_{NO} groups were similar with respect to changes in PEF in response to occupational exposure, as small and large changes in mean PEF and low and high diurnal variation were seen equally in both normal and raised FE_{NO} groups.

Our results are compatible with others but our interpretation differs. Several groups have shown that the mean FE_{NO} increases with exposure in occupational settings, and that there is a relationship between FE_{NO} and non-specific bronchial reactivity in occupational and non-occupational groups [15;124-127;200-203]. Barbinova and Baur found that 52% of occupational asthmatics who had non-specific bronchial hyperresponsiveness had a >50% increase in FE_{NO} post specific inhalation challenge test compared to 20% with normal hyper-responsiveness [201]. The mean changes have however been driven by a subset who show changes, the subgroup without changes in FE_{NO} have not been analysed separately by others.

This study was designed as a follow on to the original Anees *et al* study [123]. The original observation was from a retrospective analysis, whereas the current paper is wholly prospective data. Following a retrospective analysis showing a relationship between FE_{NO} and non-specific bronchial reactivity, we started with the same hypothesis generated by our previous study hypothesis that there were two variants of occupational asthma separated by FE_{NO} values that were raised or within normal ranges while exposed, and hypothesised that the response to occupational exposures might differ. By analysing this prospective group, we have confirmed that the two variants differ in non-specific bronchial reactivity, but

have not found differences in either the agents responsible for the occupational asthma nor the responses seen in the workplace measured through serial PEFs. The results indicate that FE_{NO} can be used without the need to measure sputum eosinphilia, the former being a simple and cost effective clinical measurement and the latter a much more time-intensive process. There are centres around the world who believe that increased non-specific bronchial reactivity is essential for the diagnosis of occupational asthma. In our experience, normal non-specific reactivity is found in ~30% of workers currently exposed who have occupational asthma. The results therefore support the inclusion of workers with normal non-specific bronchial reactivity within the family of occupational asthma due to sensitisation. Our PEF response results agree with other studies that have also not shown any correlation between FE_{NO} and the magnitude of lung function (mainly FEV_1) in non-occupational asthma [125-127].

We think that these two variants of occupational asthma separable by the FE_{NO} level may be related to different types of inflammation in the airways, the raised FE_{NO} being related to eosinophilic inflammation and the normal FE_{NO} perhaps to neutrophilic or other types of inflammation, which has also been proposed by Taylor *et al* [149]. This hypothesis is supported by our previous finding that raised FE_{NO} was significantly correlated with sputum eosinophilia [123]. Others have also found a linkage between eosinophilia and raised nitric oxide levels [120-122]. If the magnitude of work-related changes in PEF was related to FE_{NO}, this may have indicated that those with large work-related changes had an eosinophilic type of inflammation whereas those with smaller changes could be predominately neutrophilic.We originally hypothesised that the occupational asthmatics with large changes in PEF related to work exposure were more likely to have a raised FE_{NO}

than the group with small changes; this however was not supported by our data. Whether these two variants of occupational asthma according to FE_{NO} level have implications for prognosis or treatment of the disease needs to be addressed in future studies. One of the factors relating to prognosis (FEV_1 % predicted) showed similar means for those with raised and normal FE_{NO} levels indicating that prognostic factors may only explain a small amount of the differences in the two variants. This outcome was significantly different in the original retrospective cohort, but other prognostic factors (length of symptomatic exposure and time from first exposure to disease onset) were similar between eosinophilic and non-eosinophilic groups.

A number of studies have shown that inhaled corticosteroid use results in a fall in FE_{NO} levels in patients with asthma [129-135;202]. As the group with a raised FE_{NO} were on more inhaled ICS than the normal group, we were unable to find a correlation between ICS use and FE_{NO}. A small number of patients may have been misclassified in the normal FE_{NO} group because of this. Workers taking combination inhalers (steroid and long acting beta agonists) would have withheld therapy for 36 hours prior to the clinic appointment for uncompromised non-specific reactivity measurements which may have led to higher FE_{NO} levels in this group. We also found that atopics and non atopics had similar FE_{NO} levels whereas other groups studying asthmatics have found a difference [125;126;142-144]. This may be due to the fact that our cohort is a group of occupational asthmatics which may be acting differently to general asthmatics.

6.5.5.1. Validity Issues

All workers in our study had PEF records showing a work-rest pattern compatible with

occupational asthma and Oasys score ≥ 2.51 (sensitivity of 75% and specificity of 94% for occupational asthma [42]). Workers were recruited consecutively and were currently exposed to the suspected occupational agent at the time of all investigations. There were 12 workers with normal FE_{NO} levels who had a normal reactivity to methacholine and an FEV_1 percent predicted >80%. Although some may regard these subjects as not having occupational asthma, all of them did fulfil the usual definitions of asthma requiring airflow obstruction which varies over short periods of time (here within 24 hours of occupational exposures) and their mean diurnal variation at work was 15%. All workers also had a clear, relevant symptom history compatible with occupational asthma and many were exposed to well known causative agents. In addition, 3 had positive specific inhalation challenge tests to the relevant occupational allergen.

Using a cut off for FE_{NO} may have its limitations, however we believe that by choosing a previously validated cut off based on sputum eosinophilia, this problem has been addressed. With a sample size increase, we may have seen more difference between groups, although looking at the data we feel this is unlikely.

6.5.6. Conclusions

We have identified two variants of occupational asthma which cannot be separated according to the degree of asthmatic reaction induced by workplace exposures or the agents that they are exposed to, but can be separated by measurement of exhaled nitric oxide whilst symptomatic. The group with raised FE_{NO} levels have greater reactivity to methacholine compared to those with normal FE_{NO}. This could reflect different types of

airway inflammation in these two groups. Whether they differ in prognosis remains a question to be addressed in future studies.

6.6. THE EFFECT OF SHIFT WORK ON OCCUPATIONAL ASTHMA DIAGNOSIS FROM SERIAL PEAK EXPIRATORY FLOW MEASUREMENTS

Moore VC, Jaakola MS, Burge CBSG, Pantin CF, Robertson AS, Burge PS. Sent to Occupational and Environmental Medicine July 2010.

6.6.1. Abstract

We investigated the effects of shift work on Peak Expiratory Flow (PEF) measurements used for diagnosing occupational asthma (OA).

Methods: PEF records containing more than one shift pattern with ≥ four days per shift were identified. OA diagnosis was based on an Oasys-2 score ≥2.51 and non-OA on having an alternative clinical diagnosis and Oasys-2 score <2.51. Records were excluded if they did not fulfil minimum data quantity for the Area Between Curves (ABC) PEF score, or contained factors potentially confounding the results. The mean ABC score, mean PEF diurnal variation (DV) and cross-shift PEF changes were calculated for each shift.

Results: Records from 123 workers with OA and 69 without OA satisfied the inclusion criteria. Among controls, cross-shift PEF increased more on day shifts (mean +25L/min) than afternoon or night shifts (+1L/min) ($p<0.001$); in the OA group PEF declined more on afternoon and nights than days ($p<0.001$). The ABC score was lower in the OA group on night ($p=0.028$) and afternoon shifts ($p=0.020$) compared to days, without significant differences in DV. The sensitivity and specificity for the ABC score was 79% and 99% for days, 83% and 98% for nights and 72% and 96% for afternoon shifts, respectively. An

increased DV on workdays compared to restdays showed similar sensitivity, but specificities were 26%, 48% and 42%, respectively.

Conclusions: PEF responses between work and rest show small differences according to shift type. The ABC score has a high sensitivity and specificity for all 3 shifts; differences in DV have lower specificity.

6.6.2. Introduction

Lung function is affected by natural circadian rhythm, as are other physiological functions of the human body. Diurnal variation (DV) in airway calibre has been shown to follow such rhythms in both asthmatics and non-asthmatics, with greater changes observed in asthmatics [66-71]. Increased diurnal variation (measured by subtracting the lowest peak expiratory flow (PEF) from the highest PEF in a 24-hour cycle and expressing it as a percentage of the subject's mean, maximum or predicted PEF) can be used for diagnosing asthma. However, using the mean or maximum PEF may not work well in those who have low PEF values. Studies of healthy populations measuring PEF 2-hourly have shown a mean DV of 8.7% (calculated as % of mean) with an upper 95% confidence interval of 26.3% [69]. Often a cut-off point of 15% or 20% of DV is used for the asthma diagnosis, but the sensitivity has been rather low [69-71;207]. The acrophase (i.e. the time of highest PEF) has been shown to occur at similar times in both asthmatics and non-asthmatics, in most cases between 2pm and 10pm. The bathyphase (i.e. lowest PEF in the diurnal cycle) occurs usually between 2.40am and 5.15am [66]. Clark and Hetzel showed sleep to be the most important trigger for the diurnal changes, which are little influenced by posture or treatment with corticosteroids or beta agonists. In shift workers, the diurnal changes in PEF

switch very fast, often with the first change from night to day sleeping, and this happens quicker than changes in cortisol or catecholamine rhythms [77]. A healthy worker would therefore be expected to have an increase in PEF across a shift which starts relatively soon after waking from sleep. In occupational asthma, exposure to agents in the workplace influences these responses. There may be a blunting effect on diurnal variation in some subjects as the worker's PEF fails to increase throughout the working day due to the effects of the occupational exposures. Alternatively, work day diurnal variation may be increased compared to days away from work particularly in those who have an immediate reaction to the exposure (leading to reduced PEF values during the work shift) and who recover within the same day. Differences in waking times in those doing shift work may produce different patterns of PEF. To our knowledge, no previous study has investigated the effects of shift work on serial PEF recordings used to diagnose occupational asthma.

PEF changes on workdays compared to rest days can be analysed using a computer-based analysis, such as the Oasys program [42]. Oasys outputs include diurnal variation (which can be calculated separately for different shift types) and a PEF plot, where the 2-hourly mean of all exposed and unexposed readings are plotted separately for each shift pattern. The Area Between the Curves (ABC) score is the area between the work and rest PEF curves expressed in litres/min/hour [188]. This is similar to the one produced from specific inhalation challenges, with the exception that the ABC curves are based on the mean PEF values of many days' exposure. The ABC score is best calculated when time is plotted from waking rather than by clock time, this allows for different waking times on night shifts. A cut-off point of $\geq$ 15 L/min/hour for the ABC score has a sensitivity of 69% and specificity of 100% for the diagnosis of OA in day shift workers compared with OA

diagnosis based on independent confirmatory tests [188]. Whether night or afternoon shifts show a different PEF response compared to day shifts when using the ABC score for diagnosing OA is currently unknown.

6.6.3. Aims

To investigate whether shift work pattern alters the PEF responses to occupational exposures or affects the use of the ABC score for diagnosing occupational asthma.

6.6.4. Methods

6.6.4.1. Study Population

Serial PEF records from patients who were investigated for suspected occupational asthma at the Birmingham Chest Clinic in Birmingham, UK between 1980 and 2008 were extracted: those with occupational asthma confirmed with an Oasys PEF score of ≥ 2.51 formed the occupational asthma (OA) group and those with an alternative diagnosis and an Oasys score <2.51 formed the non-occupational asthma (non OA) group. Records were required to have at least 4 days of each shift pattern. PEF records were excluded if they contained less than previously reported minimum data quantity for the ABC score, which is dependent on the number of readings per day; records with a mean of ≥ 7.5 readings per day had to include at least 8 work days and 3 rest days; proportionally more days are required with fewer readings/day [190]. PEF records performed during respiratory tract infections, changes in asthma treatment or with known differences in exposure on each shift type were also excluded. All records were "day interpreted" starting with the first reading at work and continuing to the last reading before work on the next day [53]. Only 1 record per worker was used and if more than one was available, the first by date was used.

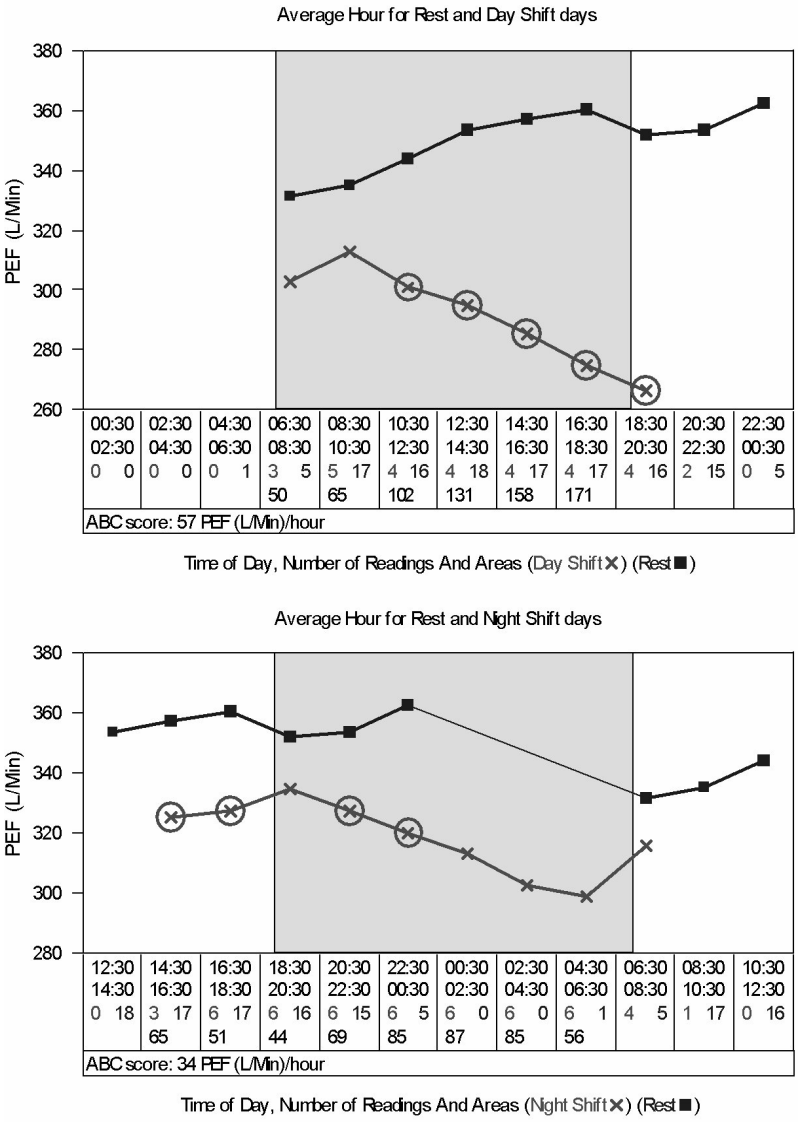
Ethics committee approval was obtained from the Birmingham East, North and Solihull committee.

6.6.4.2. Outcomes

The mean ABC score (Figure 6.6.1), mean workday diurnal variation (DV) as percent of predicted and the cross-shift change in PEF were analysed for each shift type. Cross-shift PEF change was calculated by subtracting the daily post-shift reading (taken as the last reading at work after a minimum of four hours at work) from the pre-shift value (defined as the last morning recording available in the hour before starting work) and then calculating the mean value for each record [208]. Records were required to contain at least 3 workdays of useable readings per shift type for this analysis. A cut off of ≥ 15L/min/hour for the ABC score and an increased DV on work days compared to rest days was selected to indicate occupational asthma based on previous publications [47;55;57]. To investigate factors potentially related to different PEF responses between shifts, the OA group was divided into three subgroups whose ABC score was >20% better, ≤20% worse to ≤20% better or >20% worse on nights as compared to day shifts. Differences between these groups in terms of working and sleeping patterns, asthma treatment, exposures, and reaction type (observed from the mean 2-hourly PEF plot, Figure 6.6.1.) were compared.

Figure 6.6.1. A 2-hourly plot of serial PEF measurements from an OA worker exposed to detergent enzymes who is worse on day shifts compared to night shifts.

The day shift plot (top) produces an ABC score of 57 L/min/hour and the night shift plot (below) an ABC score of 34L/min/hour. The line with square markers plots the mean rest day PEF readings every 2 hours from waking time. The line with cross markers plots the mean work day shift PEF values (top plot day shifts, bottom plot night shifts). The hours from waking time, number of readings contributing to the mean PEF plotted and the area between the curves (ABC) score are shown in the x-axis. The circles denote significant drops from the rest day values. The two vertical black lines at the edge of the grey area indicate the mode times of starting and ending work.



6.6.4.3. Statistical methods

SPSS 15 was used for all statistical analyses. PEF response data (except average cross shift changes for day and night shifts) was not normally distributed. The Chi-Square test was used to investigate differences in categorical data, Mann Whitney U or Kruskal Wallis for continuous non parametric data outcomes and independent samples t-test for continuous parametric data. For analysis of PEF outcomes by shift type, the Wilcoxon Signed Rank Test and Paired samples T-Test were used to compare two shift types and the Friedman Test comparing all three shift types. Age, number of sleeping hours and the difference in mean shift length (afternoon minus day shifts only) were normally distributed, therefore an analysis of variance (ANOVA) was used. Confidence intervals (CI) were calculated for the cross-shift changes.

6.6.5. Results

A total of 123 PEF records from shift workers fulfilled all criteria for the OA group and 69 for the non OA group. Figure 6.6.2 shows the stages according to which the exclusion of records took place. 36 of the 123 workers had a diagnosis of occupational asthma based on confirmatory tests independent from their PEF records. Table 6.6.1. shows the demographics of the shift workers. The non OA group contained patients with asthma, rhinitis, cough and chronic obstructive pulmonary disease diagnoses.

Thirty nine percent of the diagnoses of OA independent from PEF records were based on specific inhalation challenge testing, 14% on a four-fold change in methacholine reactivity at and away from work and 47% on specific IgE to a well known agent plus a strong relevant work-related symptom pattern. Most of the workers (83%) were exposed to low

molecular weight agents, the main agents being metals (24%), metal working fluid (22%) and isocyanates (14%). The most frequent high molecular weight agent was biological detergent enzymes (11%).

Figure 6.6.2. Diagram showing stages of excluding PEF records from the analysis

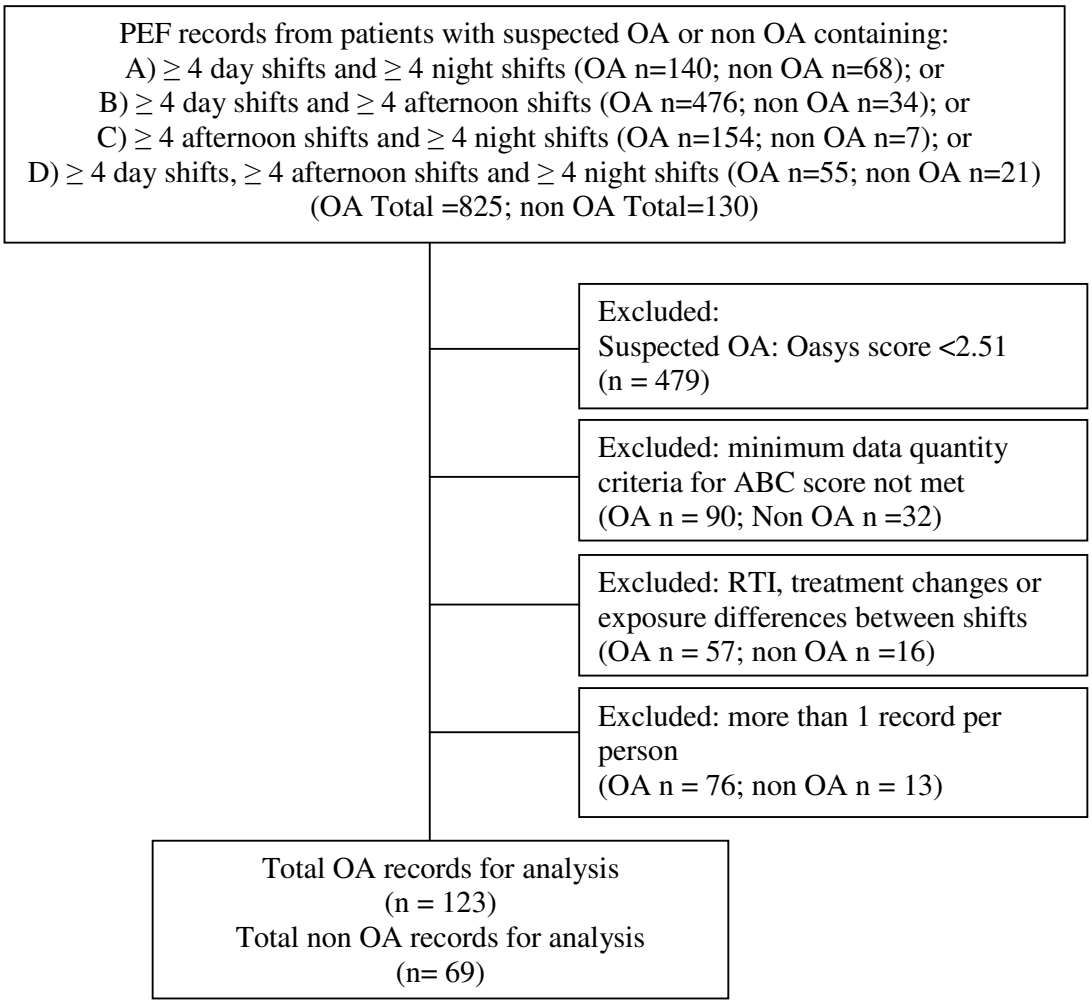


Table 6.6.1. Demographics of the study population

	All Workers with OA (n=123)	**OA workers with all 3 shift types (n=14)**	**A. Diagnosis of OA based on Oasys score (n=87)**	**B. Independent diagnosis of OA (n=36)**	**P (A vs B)**	**C. Workers with non-OA diagnoses (n=69)**	**P (All workers vs C)**
Mean age (SD)	41.0 (9.9)	42.1 (10.0)	42.2 (9.8)	38.2 (9.9)	0.002	46.2 (9.5)	0.001
% males	85.4	100	89.7	75.0	0.036	78.3	0.211
% atopics	59.3	53.8	55.4	68.6	0.184	48.1	0.290
% current smokers	28.9	28.6	24.4	40.0	0.228	20.5	0.571
% methacholine reactive	30.9	23.1	24.4	57.9	0.005	13.3	0.160
% taking ICS	46.6	61.5	46.9	45.7	0.905	22.0	0.006
Mean FEV_1 % predicted (SD)	87.7 (19.4)	95.9 (19.6)	89.4 (17.5)	81.4 (24.7)	0.083	97.4 (23.3)	0.011
Mean diurnal PEF variation at work (SD)	15.5 (8.9)	17.2 (16.3)	15.6 (9.1)	15.3 (8.3)	0.850	10.9 (5.7)	<0.001

ICS- inhaled corticosteroids
OA – occupational asthma

Table 6.6.2. shows the mean ABC scores calculated from waking time, the mean cross shift differences and the mean diurnal variation (DV) by work shift type. Among those with OA, the mean ABC scores were highest on day shifts, significant differences being observed between day vs. night shifts and day vs. afternoon shifts. In the non-OA group, the ABC score was higher on night shifts compared to afternoon and day shifts. Cross-shift changes showed an increase during day shifts in the group without occupational asthma, with no change across afternoon or night shifts. Those with occupational asthma showed significantly larger declines on night and afternoon shifts compared to day shifts.

No significant differences in DV were seen among those with OA between any shifts, although DV tended to be highest in afternoon shifts and lowest in day shifts. Among those without OA, DV was significantly higher in day shifts compared to night shifts.

Table 6.6.2. PEF responses according to day, afternoon and night shifts

		Mean ABC from waking score (SD)				Mean cross shift change L/min (95% CI)		Mean Diurnal variation % (SD)			
	Shift Type	All OA	A. Oasys score Dg	B. IDg	Non OA	All OA	Non OA	All OA	A. Oasys score Dg	B. IDg	Non OA
Records with day & night shifts (ABC/DV: All OA n=73, A. n=52, B. n=21, non OA=27; cross shift: All OA n=18, non OA=53)	Day	44.8 (39.7)	44.9 (42.0)	44.6 (34.2)	-0.6 (10.0)	-10 (-26 to +7)	+25 (+15 to +35)	15.5 (9.9)	15.3 (9.8)	16.0 (10.5)	10.5 (6.4)
	Night	39.6 (35.3)	38.5 (38.5)	42.2 (26.5)	1.5 (5.3)	-40 (-51 to -28)	+1 (-3 to +5)	16.0 (9.7)	15.9 (9.7)	16.4 (10.0)	8.5 (6.0)
	P	0.028	0.017	0.664	0.186	<0.001	<0.001	0.384	0.367	0.848	0.002
Records with day & afternoon shifts (All OA n=61, A. n=46, B. n=15, non OA=52; cross shift: All OA n=41, non OA=34)	Day	36.8 (37.4)	37.7 (41.5)	33.9 (20.7)	-2.7 (8.0)	-6 (-23 to +10)	+23 (+14 to +32)	15.2 (9.0)	15.7 (9.7)	13.7 (6.6)	10.8 (5.5)
	Afternoon	32.1 (32.5)	33.0 (35.0)	29.5 (24.1)	-2.4 (9.2)	-40 (-59 to -21)	+1 (-6 to +9)	16.1 (11.8)	17.3 (13.0)	12.2 (5.4)	10.7 (5.4)
	P	0.020	0.035	0.394	0.964	<0.001	<0.001	0.453	0.074	0.211	0.642
Records with afternoon & night shifts (All OA n=17 A. n=13, B.=4, non OA=10; cross shift: All OA n=14, non OA=10)	Afternoon	47.9 (50.9)	48.4 (55.4)	_	-2.1 (6.3)	-61 (-143 to +21)	-3 (-9 to +3)	18.7 (18.9)	20.4 (21.1)	_	7.7 (5.2)
	Night	45.5 (57.7)	45.0 (61.4)	_	2.9 (3.2)	-47 (-99 to +4)	-3 (-10 to +4)	16.9 (14.1)	18.8 (15.6)	_	6.2 (3.6)
	P	0.356	0.382	_	0.037	0.778	0.795	0.554	0.807	_	0.203
Records with day, afternoon & night shifts (All OA n=14, A. n=12, B. n=2, non OA=10; cross shift: All OA n=9, non OA=6)	Day	46.6 (62.9)	51.8 (67.8)	_	0.7 (7.0)	-28 (-103 to +47)	+19 (+6 to +33)	15.5 (14.1)	16.7 (15.0)	_	7.8 (3.5)
	Afternoon	46.0 (54.1)	49.5 (57.7)	_	-2.1 (6.3)	-76 (-167 to +15)	+2 (-11 to +7)	19.3 (20.6)	20.8 (22.0)	_	7.7 (5.2)
	Night	42.8 (59.7)	46.3 (63.9)	_	2.9 (3.2)	-64 (-124 to -3)	+0.2 (-5 to +6)	17.5 (15.5)	19.1 (16.2)	_	6.2 (3.6)
	P	0.145	0.338	_	0.273	0.015	0.031	0.319	0.558	_	0.122

IDg= Independent diagnosis: OA diagnosis based on independent confirmatory tests; Oasys score Dg: Oasys score diagnosis of OA
Mean rest day diurnal variation for all occupational asthma subjects (n=123) was 11.4 (SD 7.7) and for non occupational asthma subjects (n=69) 9.9 (SD 5.3). Gaps in table are due to too few data available.

Although differences were found in ABC scores between shifts on average, not all workers had higher ABC scores on days compared to afternoon or night shifts. Observed differences between shifts were not found to be related to the number of hours of sleep before each shift type, the PEF response type, the number of days off before each shift, the number of consecutive days worked per shift nor the mean hours worked per shift.

The sensitivity and specificity of the diagnosis of occupational asthma based on the ABC PEF score (applying a cut-off value of $\geq$ 15 L/min/h) and a larger diurnal variation on work days compared to rest days (i.e. workday DV-rest day DV>0) are shown by the type of shift in table 6.6.3. The sensitivity of both the ABC score and the increased DV on workdays compared to restdays were good during each shift. Specificity was high for each shift using the ABC analysis, but low for increased DV on workdays.

Table 6.6.3. Sensitivity and Specificity of the ABC PEF score from waking time and increased diurnal variation on workdays compared to restdays for diagnosing OA according to the shift type.

	Sensitivity All OA workers			**Sensitivity Oasys score diagnosis**			**Sensitivity Independent OA diagnosis**			**Specificity Non OA**		
Shift Type	**Day n=120**	**Aft n=64**	**Night n=76**	**Day n=86**	**Aft n=47**	**Night n=53**	**Day n=34**	**Aft n=17**	**Night n=23**	**Day n=69**	**Aft n=52**	**Night n=27**
% with ABC score ≥ 15 L/min/hr (<15 L/min/hr for non OA)	79.2	71.9	82.9	77.9	74.5	81.1	82.4	64.7	87.0	98.6	98.1	96.3
% with higher DV on work days compared to rest days (similar or lower DV on work days for non OA)	75.8	70.3	77.6	76.7	74.5	81.1	73.5	58.8	69.6	26.1	42.3	48.1

Aft = afternoons

6.6.6. Discussion

We found that cross shift changes in PEF followed normal circadian patterns: those without occupational asthma showed on average an increase in PEF across day shifts and no change across afternoon and night shifts. Among those with occupational asthma, the effects of exposures were superimposed on this rhythm. Thus, cross-shift falls due to occupational exposures were seen in PEF, but these were significantly less on day shifts compared to night and afternoon shifts. The effect of occupational exposure seemed to blunt the spontaneous increase in PEF on day shifts (seen in those without OA) resulting in a small mean decline in PEF. The findings on the ABC scores between shifts would be compatible with these observations, although larger differences between work and rest days were observed in day shifts compared to afternoon and night shifts. However, no significant differences were found in DV by the type of shift among those with OA.

The ABC score, using a previously reported cut off of 15 L/min/hour for day shifts [188], showed a sensitivity and specificity of 79% and 99% for day shifts, 83% and 96% for night shifts, and 72% and 98% for afternoon shifts when comparing to the diagnosis of OA that was based on a relevant medical history and the Oasys score (which is calculated by the discriminant analysis). The Oasys score has been shown to have a sensitivity of 75% and a specificity of 94% against an independent diagnosis of OA [42]. The sensitivity and specificity of the ABC score is likely to have been influenced by the inclusion criteria for OA used in this study. It was based on a positive Oasys PEF score and the controls were required to have a negative score, which is likely to have increased both the sensitivity and specificity of the ABC score. However, this should not invalidate the comparison between shift types, as the same definitions were used across the shifts. The results showed that the

ABC score with a cut off of 15 L/min/hour is suitable for all shift patterns. This was supported also by the analysis limited to workers who had an independently confirmed diagnosis of OA.

Using a DV of PEF greater on workdays compared to rest days also showed a good sensitivity across all shifts (70-78%), but the specificity was low. This probably reflects the lack of rigorous research identifying the best cut-off point for the difference in DV between workdays and rest days for diagnosing OA. More research is needed in the future, as many centres base their diagnosis of OA on DV patterns [47;55;57]. Some centres define OA based on a greater number of workdays with a diurnal variation exceeding 20% (as percent of the mean) compared to rest periods [47;55]. However, diurnal variation may be below 20% in many workers who show a positive specific inhalation challenge test [47;49;55;208].

We identified three PEF response types to occupational exposures based on patterns observed in the 2-hourly PEF plot in the Oasys output. These were grouped as immediate, late or flat/depressed reactions. The flat/depressed reaction group may still show increasing PEF across a day shift, but their diurnal variation is depressed compared to that seen on rest days and the late reaction group may show a decrease in PEF after the shift has ended. Both of these groups still show a work-related difference between day shift days and rest days, which would not be apparent from cross shift measurements. Those who were better, similar or worse on night shifts or afternoon shifts compared to day shifts showed no differences in the distribution of these PEF response types.

6.6.6.1. Synthesis with previous literature

No previous studies have investigated differences in the ABC PEF score or mean DV across shift types among workers with occupational asthma. In healthy working populations PEF has been shown to increase over day shifts and decrease over afternoon and night shifts, which follows normal circadian variation [79-82]. Zock *et al* showed such a pattern in endotoxin-exposed workers, but there were no statistically significant differences between the shift types [79]. Milton *et al* studied shift effects in fibreglass manufacturing workers and showed a larger number of workers having a ≥ 5% PEF change across night shifts compared to day shifts [80]. In a cross-shift study by Nemery *et al.*, FEV_1 (amongst other variables) showed similar day shift changes between steelworker and control groups, but in afternoon and night shifts FEV_1 significantly decreased in the casting group but not in the controls [82]. Our study shows similar findings with significantly smaller cross shift changes seen among OA workers in day shifts compared to afternoon and night shifts. In a previous study we showed that workers with occupational asthma often improve on day shifts; therefore even an extremely small decrease in PEF of 5 L/min between pre and post shift was enough to give a sensitivity of 50% and specificity of 91% for occupational asthma [208].

6.6.6.2. Validity issues of the methods and limitations of the study

Our study population consisted of workers who were being assessed for occupational asthma at the Birmingham Chest Clinic, UK, and who had work-related changes in their PEF according to their Oasys score. In these analyses comparing PEF changes across different types of shifts, workers served as their own controls, so personal characteristics did not confound the results. The Oasys score uses a discriminant analysis to determine

whether a record shows occupational asthma or not, i.e. it just compares whether there are differences within each rest-work-rest and work-rest-work period, so this method does not require any particular magnitude of a PEF difference to take place and it is independent of shift pattern.

A drawback of this study is the restricted number of patients in some parts of the analyses. The non OA control group were not all asthmatics and contained patients with rhinitis, cough and chronic obstructive pulmonary disease, who had lower diurnal variation, less methacholine reactivity and less inhaled corticosteroid use than the occupational asthma group. Another limitation of the study is that we did not have data on the levels of exposure for each shift type. Many night shift workers are on premises where the level of activity is reduced compared to the daytime, and some processes may not be working at all; on the other hand, supervision is often less and ventilation often reduced during night shifts which could lead to higher exposure. Workers were excluded from the analysis when our database suggested different jobs (with different exposures) on different shifts within a record. A prospective study recording all this information would be useful in the future.

6.6.7. Conclusions

Significant differences were observed in PEF responses between night and day shifts, and afternoon and day shifts in workers with occupational asthma. On average, the ABC PEF score is significantly smaller during night and to some extent during afternoon shifts compared to day shifts, but the sensitivity and specificity of the ABC score calculated from waking time are good and similar across all three shift types. A cut-off of 15 L/min/hour for the ABC score is appropriate for all shift types. Cross-shift differences follow normal

circadian rhythm, being greater on night and afternoon shifts compared to day shifts. Among those with occupational asthma, mean diurnal variation does not show any significant differences across shifts, but a greater DV on workdays compared to restdays has low specificity for all shift types.

6.7. A SYSTEMATIC REVIEW OF SERIAL PEAK EXPIRATORY FLOW MEASUREMENTS IN THE DIAGNOSIS OF OCCUPATIONAL ASTHMA

Moore VC, Jaakkola MS, Burge PS. Annals of Respiratory Medicine 2010; 1:31-44

6.7.1. Abstract

This paper systematically reviews literature on the application of serial peak expiratory flow (PEF) measurements in the diagnosis of occupational asthma and calculates summary estimates of the sensitivity, specificity and feasibility of serial PEFs.

Methods: Papers were searched for on the Medline database via the PubMed website (http://www.ncbi.nlm.nih.gov/sites/entrez) and on the Birmingham Chest Clinic departmental website (www.occupationalasthma.com) from 2004 until April 2009 using the search terms "Peak flow AND occupational asthma" and "Peak flow AND work related asthma". Abstracts were screened to select those justifying a full paper review. Papers used in the British Occupational Health Research Foundation (BOHRF) guidelines (current until June 2004) were also reviewed. Case studies and narrative reviews were excluded. Type of analysis, quality of paper, sensitivity and specificity of serial PEFs compared to reference tests and return rates were documented. Results were pooled from all studies to produce overall estimates.

Results: A total of 80 abstracts were reviewed, leading to 23 full papers for further review plus 15 papers from the 2004 BOHRF review. 7 papers were excluded (mostly for duplicate data) leaving 31 papers for inclusion. The pooled sensitivity of serial PEF

fulfilling minimum data quantity requirements for a diagnosis of occupational asthma was 82% (95% CI 76-90) and the pooled specificity 88% (95% CI 80-95). Return rates were similar between PEFs requested through workplace studies (85%) and those requested in a clinical setting (78%) with 61% being interpretable for a diagnosis of occupational asthma from either setting.

Conclusion: Based on a systematic literature search, serial PEF measurement is a feasible, sensitive and specific test for the diagnosis of occupational asthma, when potential sources of error are understood.

6.7.2. Introduction

Occupational asthma is asthma mainly caused by an agent in the workplace environment. According to population-based studies as much as 10-20% of adult asthma may be work-related [2-4]. When comparing this proportion to numbers of occupational asthma reported in registries [167;174;209-212], there seems to be a problem of under-diagnosing work-related asthma. Thus, more focus should be paid to methods that facilitate recognition and diagnosis of work-related asthma.

For a diagnosis of occupational asthma, it is important to establish a relationship objectively between the workplace exposure and asthma symptoms and signs. Physiologically, this can be achieved by monitoring airflow limitation in relation to occupational exposure(s). If there is an effect of a specific workplace exposure, airflow limitation should be more prominent on work days compared to days away from work (or days away from the causative agent). Airflow limitation can be measured by spirometry,

with peak expiratory flow (PEF) and/or forced expiratory volume in one second (FEV_1) being the most useful for observing changes in airway calibre. PEF is more a reflection of larger airways calibre, whereas FEV_1 reflects both the large and the small airways. It has been suggested previously that FEV_1 could be a more sensitive measure for asthmatic changes than PEF [46] and as a consequence of this, FEV_1 is usually used in specific inhalation challenge testing, which is the gold standard confirmatory test for diagnosing occupational asthma. However, the FEV_1 manoeuvre may be more difficult to accomplish reliably when unsupervised personally by health care personnel [47] and could therefore be less reproducible when performing unsupervised serial lung function measurements for diagnostic purposes at home and at work.

Serial PEF monitoring is currently recommended as a confirmatory test for occupational asthma by several guidelines [1;13;38], but not all diagnostic centres have agreed about its value. Previous reviews of diagnostic methods for occupational asthma have been published [35;38], but to our knowledge, this is the first systematic review of serial PEF measurements in diagnosing occupational asthma, with focus on feasibility, sensitivity and specificity of this method.

6.7.2.1. Work-related patterns of PEF

Work-relatedness of PEF values can be evaluated by assessing deterioration of mean values at work compared to mean values away from work [39;42;213] and/or by within day variability (i.e. diurnal variation) being larger during work days than rest days or being ≥ 20% for more work days than rest days [47;54;55;57]. Diurnal variability has been

calculated as [daily maximum PEF-daily minimum PEF] / mean daily PEF or predicted PEF or daily maximum PEF.

There are several patterns that can emerge from measuring PEF across work and rest days that are compatible with occupational asthma. These include immediate decreases in PEF (within an hour of arriving at work or being exposed to a specific exposure at work), delayed decreases in PEF (either starting later on in the working day or after leaving work), cumulative decreases in PEF over the working week (with PEF deteriorating further with each day at work), non-cumulative decreases (similar falls each day), and on rare occasions a tolerance developing to work exposure can be seen where PEF falls dramatically on the first day of exposure and becomes less as the working week progresses. Recovery usually shows two types of pattern, being either immediate or delayed. In the case of immediate recovery, workers make a full recovery within a few hours of leaving work, whereas with delayed recovery it may take several days to return to the individual's baseline values [39].

6.7.2.2. Plotting and Analysis of serial PEFs

Diagnostic centres around the world plot and analyse serial PEFs for the diagnosis of occupational asthma in different ways. Methods can be statistical or non-statistical, hand plotted or computer generated. For non-occupational asthma, graph-type charts are mostly used creating a line graph. This is useful when the aim is to evaluate asthma control, but may be harder to interpret occupational effect. Figure 6.7.1 shows a serial PEF record that has been plotted in this fashion for a worker exposed to oil mists. This type of line graph can be modified to show a line for the maximum and the minimum each day and labelling for days at work and days away from work (rest). Information on the diurnal variation each

day can also be shown and can be used in the assessment of an occupational effect. An example of this is shown in Figure 6.7.2 (data is from the same PEF record as Figure 6.7.1). Plotting can be "day interpreted" [53], with each work day starting with the first reading at work (rather than the waking reading) and finishing with the last reading before work on the following day. This is the preferred method as the first reading taken before work in the morning will be influenced by the previous day's exposure. Plotting can be done to create a maximum and minimum daily PEF with or without a mean PEF. Figure 6.7.3 shows the same PEF record as shown in Figures 6.7.1 and 6.7.2 plotted using a computer-based program known as Oasys (Occupational Asthma System). It is easier to see work-related deterioration in this record.

As with plotting, there are several ways to analyse serial PEF records. Records can be analysed visually by experts, they can undergo statistical analysis or other computer based analysis can be utilised. Features influencing expert interpretation include changes in mean daily PEF related to work exposure and the extent of changes in diurnal variation. Statistical analyses of PEF variability has shown significant differences between work and rest days in several studies [54;75;99]. However, the sensitivity and specificity of differences in diurnal variation analysed statistically is often not as high as expert evaluation or other computer-based analysis [39;42;47;54;55;57;188;213;214]. A further analysis utilises Shewart's control charts [56;57]. Two types of analysis have been suggested, the first compares the individual's lower limit on work days with their personal best on rest days (this method detects high diurnal variation rather than a work related decrease in PEF). The second compares diurnal variation on work days (in litres/min) with

diurnal variation on rest days. A 15% increase in workday variation constitutes a positive result. [42;43;53;188;215]. Neither method has been tested in prospective studies.

Figure 6.7.1 Serial plot of PEF measurements for a worker exposed to oil mists.

Working times have diagonal back slash bars (day shifts), times away from work are blank and times when the worker is asleep are block-grey. The highest PEF reading per measurement session (approximately 2-hourly) made throughout each day are plotted.

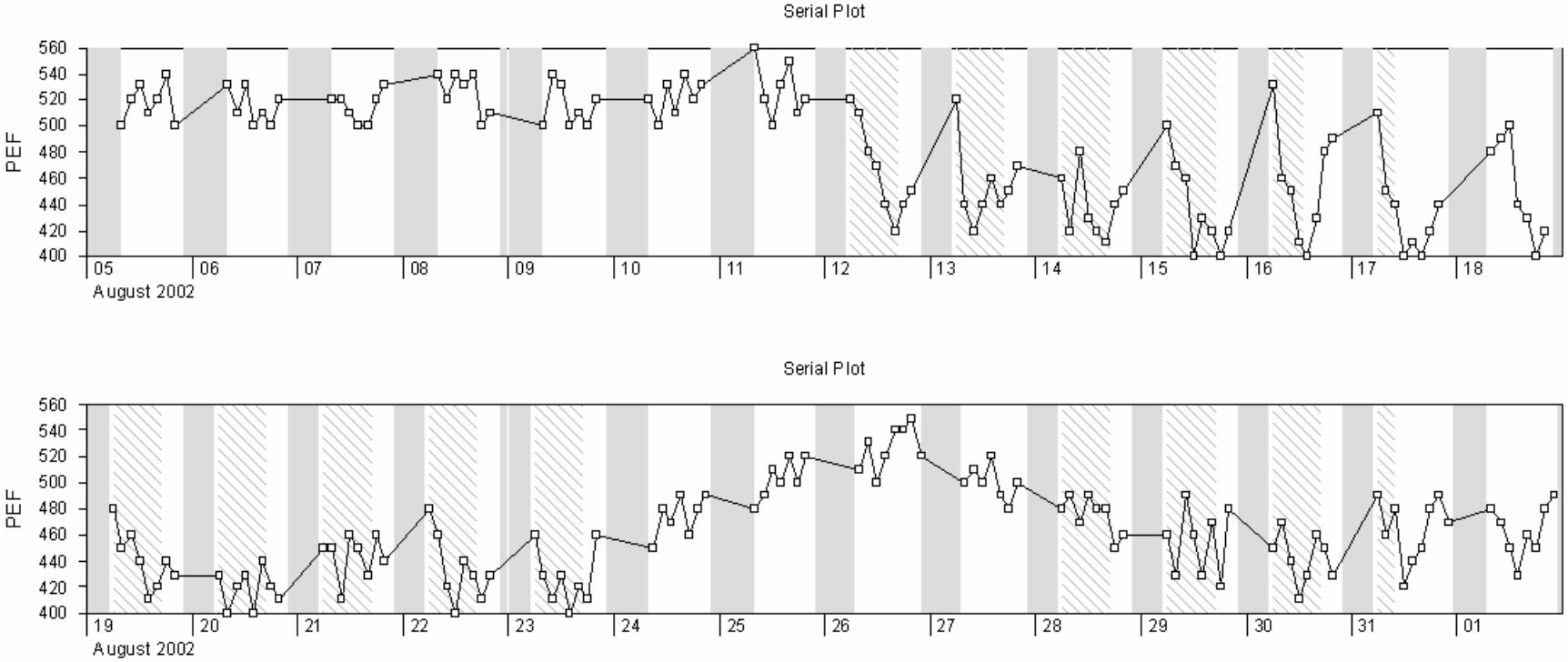


Figure 6.7.2. Quantitative analysis plot based on comparison of diurnal variation in PEF between work days and rest days. Plotted for the same worker as in Figure 6.7.1.

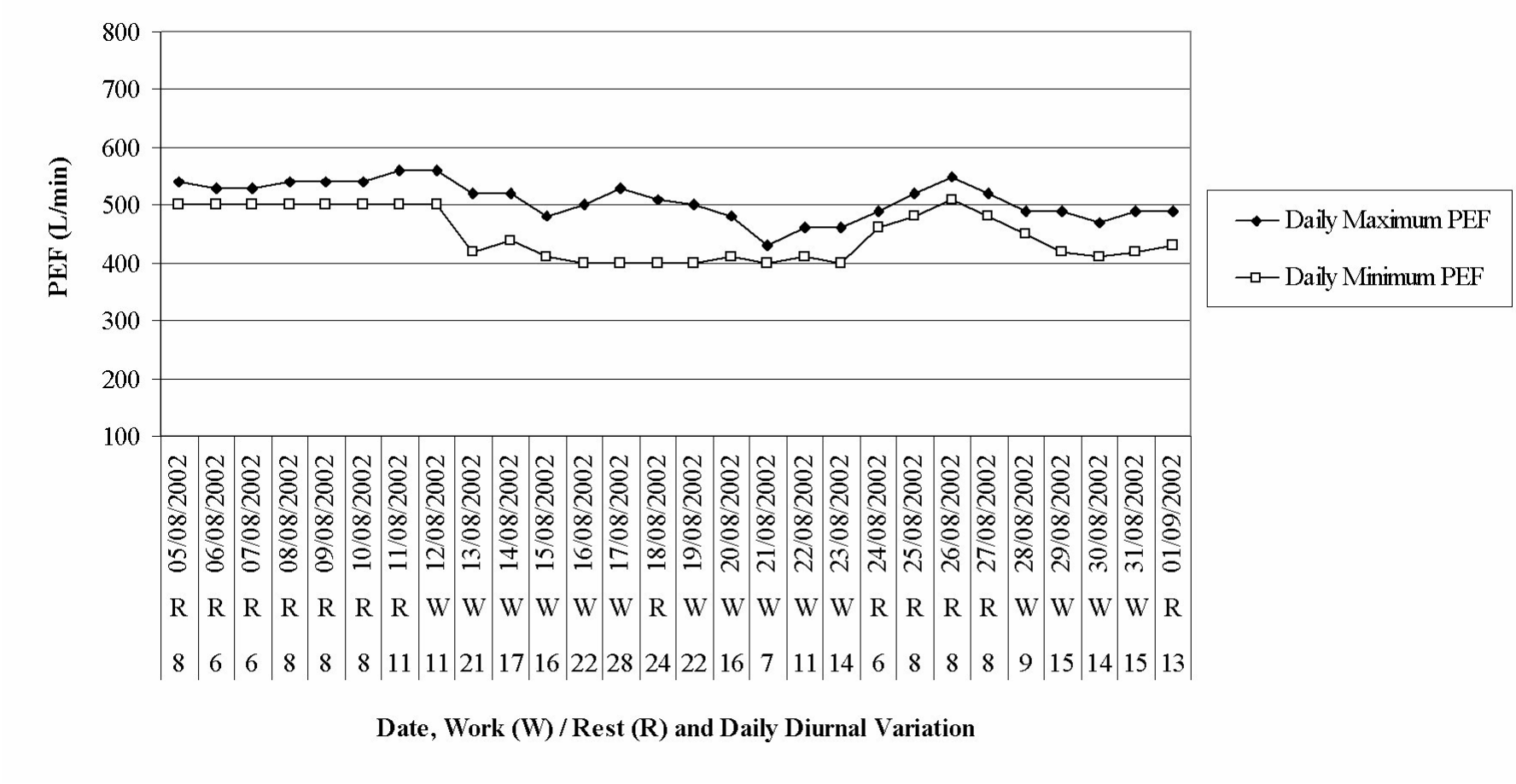
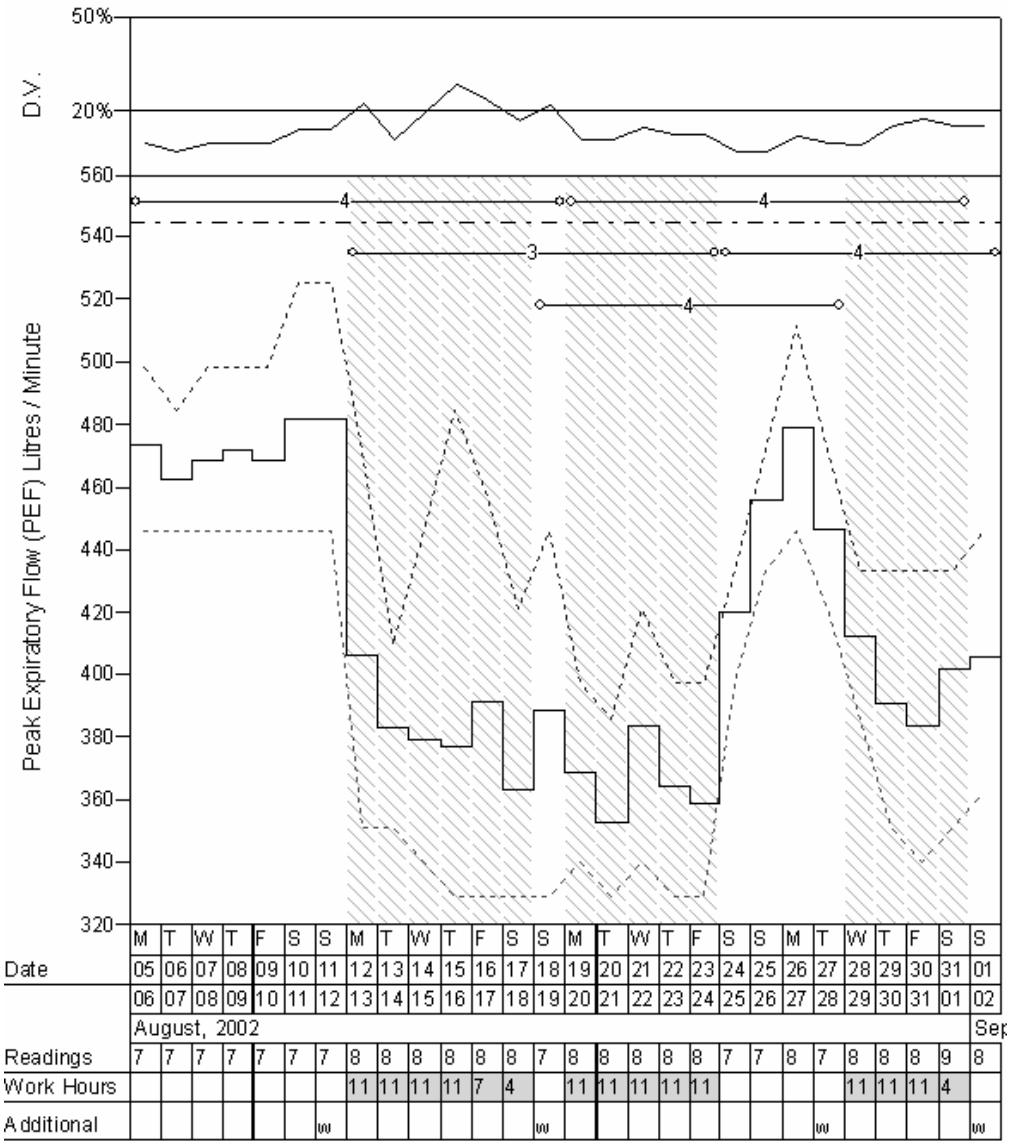


Figure 6.7.3. Maximum, mean and minimum PEF plot from the Oasys program for the same record as in Figure 6.7.1.

The top part of the chart shows the diurnal variation (DV) for each day. The middle of the chart shows the maximum, mean and minimum peak flow for each day. The black continuous line is the mean PEF, the upper line the maximum PEF and lower the minimum PEF for each day. The work periods are the shaded areas (diagonal back slash bars are day shifts) and the rest periods are blank areas. The horizontal lines containing numbers in this part of the chart are scores for the work-rest-work and rest-work-rest complexes (six complexes in total in this record). The bottom of the record shows the days and dates of the record. The Oasys score of this record is 3.89 (almost definite occupational asthma).



6.7.2.3. Oasys

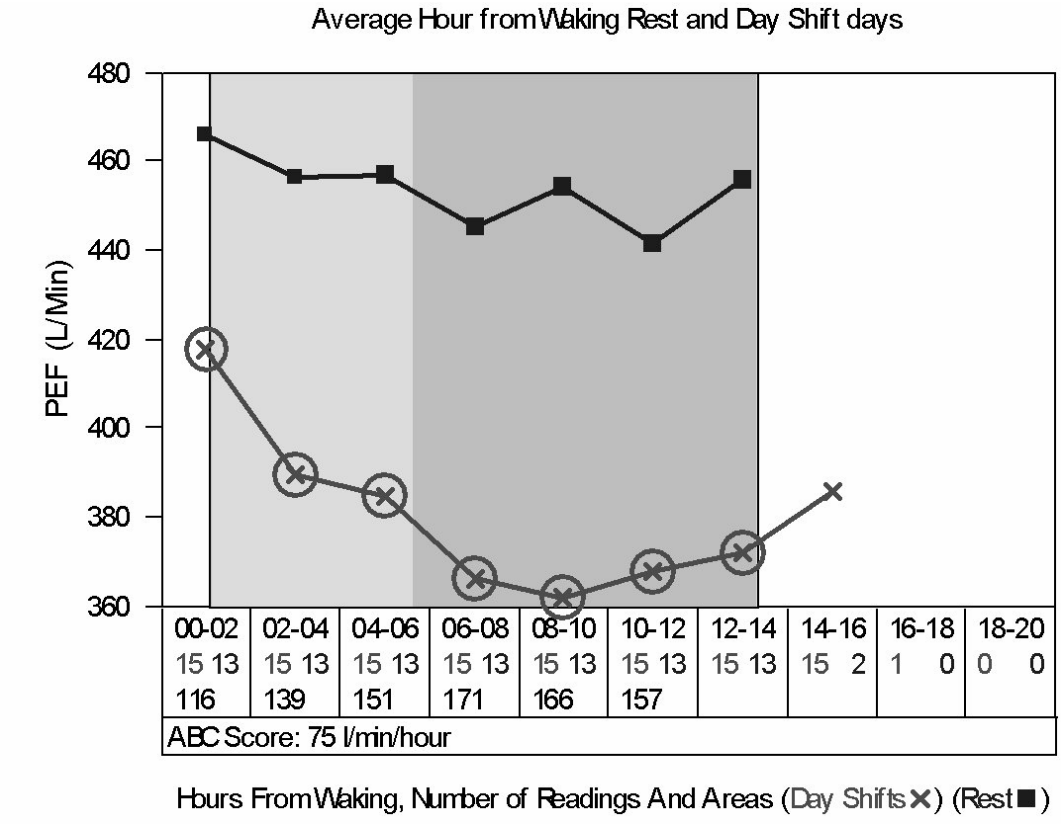
The Oasys 2 program is a freely available computer-based PEF analysis tool available from www.occupationalasthma.com. It was first developed in 1995 by Gannon *et al* [42] and was based on expert interpretation of hand plotted PEF records. It uses a discriminant analysis (non-statistical) to determine whether each work-rest-work period or rest-work-rest period (known as complexes) shows a pattern compatible with an occupational effect. In the updated version of Oasys, several other analyses have been developed such as the area between curves (ABC) score [188], timepoint analysis [215] and work-rest PEF score [49]. The ABC score utilises the 2-hourly plot of average lung function on rest days and work days and creates a score from the area between the mean work-day and mean rest-day curves plotted either by clock time or time from waking up [188]. Figure 6.7.4 shows this plot for the same worker as in figure 6.7.1. The timepoint analysis is a statistical method identifying measurements at a single timepoint which are below the 95% confidence interval for the mean rest-day measurements [215]. This has similarities with the first Shewart's chart method, but is less influenced by increased diurnal variation in occupational asthmatics compared with controls.

6.7.3. Aims

In this paper, all types of analysis method for serial PEFs have been included. The aims of this article are to systematically review studies published on serial PEF measurements used for the diagnosis of occupational asthma and to calculate summary estimates of the sensitivity and specificity and feasibility of serial PEF measurements for diagnosing occupational asthma in clinical and workplace settings.

Figure 6.7.4. A 2-hourly plot of the average PEF on rest days and work days analysed by the Oasys program for the same worker as in figure 6.7.1.

Mean PEF measurements taken at the following times: Between 0 and 2, >2-4, >4-6 hours and so on from the waking time are plotted based on all work days and all rest days. The black upper line (square markers) shows the average peak flow for rest days by 2 hour segments from 0 to 24 hours from waking. The grey lower line (cross markers) shows the same for work days. The circles relate to the timepoint analysis (significant drops). The grey area shows information about the times of starting and stopping work (mode, minimum and maximum). The legend shows the start and end of the 2 hour time segments, the number of readings used to calculate the work and rest day average PEFs, the area between the rest and work day PEF curves (ABC) on the graph for each time segment and the total area between the lines. To calculate the ABC/hour score, the total area is divided by the number of hours for which there are measurements. This record gives an ABC score of 75L/min/hr (shown on the plot) (interpreted as occupational asthma)



6.7.4. Methods

Articles published on serial PEFs as a diagnostic test for occupational asthma were systematically searched for from 2004 until April 2009 on the Medline database via the PubMed website (http://www.ncbi.nlm.nih.gov/sites/entrez) using the search terms "Peak flow AND occupational asthma" and "Peak flow AND work related asthma". The Birmingham Chest Clinic departmental website (www.occupationalasthma.com) was also searched using the same search terms. Abstracts were screened to select those that justified a full paper review. These included: 1. those that investigated serial peak flow/ FEV_1 measurements plus another confirmatory test for occupational asthma, 2. those that investigated the achievability of serial PEFs or FEV_1s in the clinical or workplace setting. Single case reports and narrative reviews were excluded. For the remaining abstracts, the full paper was obtained. In addition to these selected papers, the research articles used in the British Occupational Health Research Foundation (BOHRF) guidelines were also reviewed. The literature search for the BOHRF guidelines had been performed in a similar way, by systematically searching Medline and Embase from 1966 and 1974 respectively to the end of June 2004 [13].

Information on the country where the study took place, the year of the study, the reference confirmatory test, methodology and data needed for a quality assessment using Scottish Intercollegiate Guidelines Network (SIGN) methodology [216] and results on sensitivity, specificity, data quantity and return rates were recorded. Data were pooled to represent summary findings. For the pooled sensitivity and specificity, studies with more than one visual assessor were treated separately. For all other types of analyses (i.e. computer-based or quantitative), the index with the highest sensitivity and specificity being tested was

used. Pooled results were calculated using raw data from the studies. The total number of all those who were correctly identified as having occupational asthma were divided by the total number of reference test positives for sensitivity and the total number of those who were correctly identified as not having occupational asthma were divided by the total number of reference test negatives for specificity.

Oasys minimum data quantity criteria were used for computer-based analyses [43]; these require ≥ 4 readings per day, ≥ 3 consecutive workdays in any work period and ≥ 3 complexes (approximately 3 weeks) of data. For visual analysis the recommendations by Bright and Burge [213] and Malo [40] were used; these require 2 weeks at work and 2 weeks away from work with ≥ 4 readings per day. In the papers discussing Shewart's control charts, minimum data were taken as records that were usable for this method [56;57]. Records were deemed to be acceptable / interpretable based on the requirements defined by each study itself. That is, if records were able to be scored by any method and analysed to give a diagnostic outcome of whether they showed occupational asthma or not, they were considered to be acceptable or interpretable. If the study reported data for records failing to fulfil data quantity standards these were analysed separately [43].

Papers were reviewed applying quality criteria according to SIGN methodology for diagnostic studies which scores studies as ++, + or – according to how reliable the conclusions of the study were [216]. Only studies with ++ or + scores were included in pooled calculations.

6.7.5. Results

79 abstracts were found in the Medline (Pubmed) database search using the search terms "Peak flow AND occupational asthma" or "Peak flow AND work related asthma". One further abstract was found on the www.occupationalasthma.com database. The flow diagram in Figure 6.7.5 shows how papers were excluded leaving 31 articles, 17 of which were from this systematic review from 2004 until April 2009 and 14 papers from those used previously for the BOHRF 2004 guidelines.

Articles reviewed for the purpose of calculating the pooled sensitivity and specificity of diagnosis of occupational asthma based on serial PEF measurements are summarised in Table 6.7.1. Papers reviewed for the purpose of calculating the pooled return rates of serial PEF records and/or the numbers of acceptable/interpretable PEFs returned are summarised in Table 6.7.2.

Figure 6.7.5. Flow diagram of the selection process for inclusion of papers

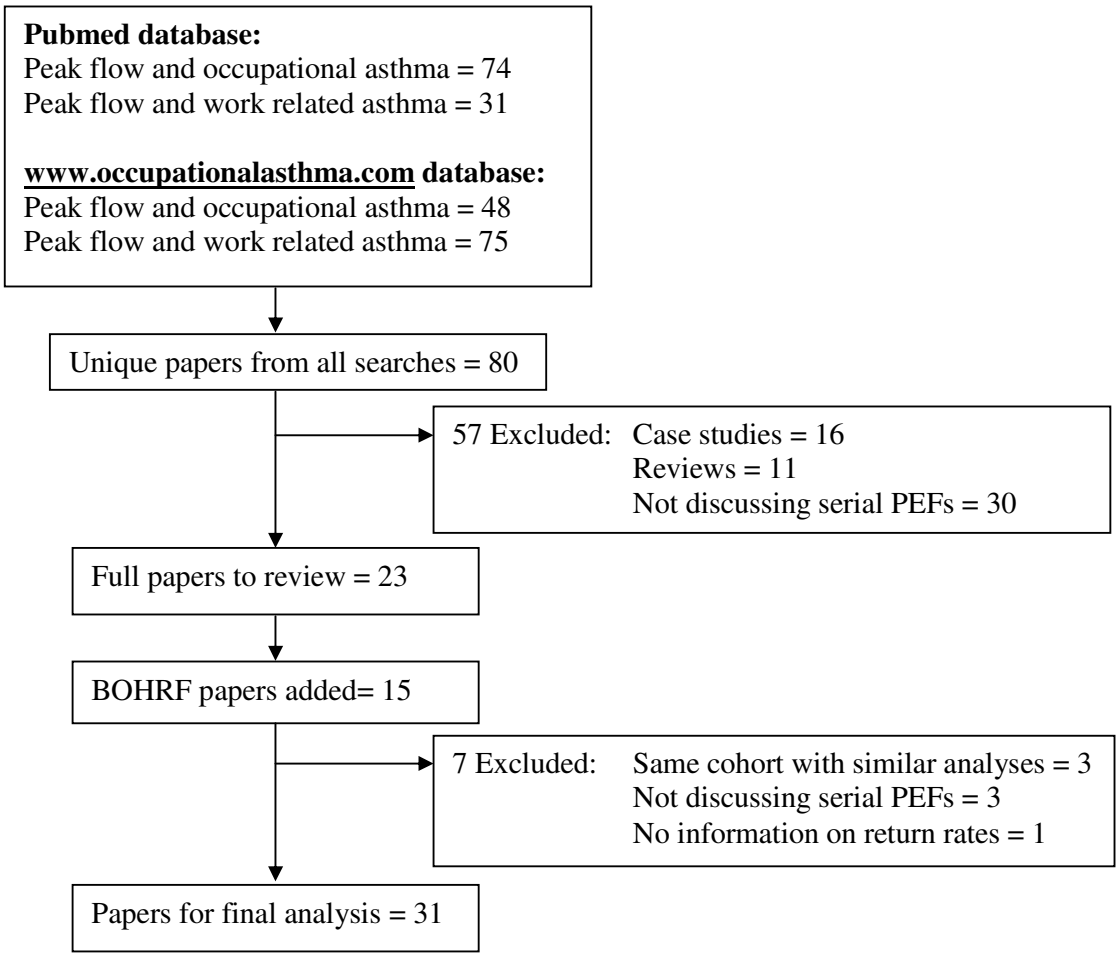


Table 6.7.1. Articles identified for sensitivity and specificity of the diagnosis of occupational asthma based on serial PEF measurements.

(SIC = specific inhalation challenge test, NSBR = significant improvement in non-specific bronchial reactivity away from work, IgE = Immunoglobulin E, Oasys 2 = discriminant analysis using the Oasys software, Oasys ABC = Area between the curves of work and rest day PEF 2-hourly plots using the Oasys software). Visual analysis is the opinion of an expert from a plotted PEF record, computer-based analysis are the results of Oasys 2 and Oasys ABC scores, Shewarts control chart is based on a statistical analysis which forms part of the Shewarts system, and quantitative analysis was mostly based on diurnal variation differences between work and rest day measurements. Those relying on differences in mean PEF on work and rest days are identified separately.

Author, Year	**Country**	**Included**	**Paper quality**	**PEF data quality**	**No. of subjects**	**Analysis type**	**Sensitivity %**	**Specificity %**	**Reference Test**
Girard [199] 2004	Canada	yes	++	Inadequate	49	Computer based Oasys 2 score and Visual	Oasys score: 34.8 Visual: 63.1 78.9 82.3 77.7 86.6	Oasys score: 65.2 Visual: 61.9 52.9 55.0 47.6 50.0	23 SIC +ve 26 SIC -ve
Hannu [217] 2007	Finland	yes	+	Unknown	9	Visual	83.3	na	SIC
Moore [188] 2009	UK	yes	++	Inadequate	112 (test set)	Computer based Oasys ABC score	72.2	100	54 SIC/ NSBR change/specific IgE +ve 58 asthmatics not at work
Hayati [56] 2006	USA	yes	+	Adequate	45	Other – Shewart's control chart	85.7	87.5	21 SIC +ve 24 SIC -ve
Chiry [75] 2007	Canada	No – same cohort as Girard paper							

		with same analyses							
Anees [43] 2004	UK	Yes	++	Presents adequate and inadequate data	122 (test set)	Computer based Oasys 2 score	78.1 (≥min data) 63.6 (< min data)	91.7 (≥min data) 83.3 (< min data)	74 SIC/ NSBR change/specific IgE +ve 60 asthmatics not at work
Kennedy [218] 2007	Canada	No – same cohort as Girard paper with same analyses.							
Munoz [219] 2004	Spain	Yes	+	Unknown	5	Visual	80		SIC
Hayati [57] 2008	USA/ Canada	Yes	+	Adequate	36	Other – Shewart's control chart (DV)	94 .4	61 .1	18 SIC +ve 18 SIC -ve
Park [208] 2009	UK	Yes	++	Adequate	40 (test set)	Computer based Oasys 2 score and other quantitative (mean PEF)	Oasys: 83.3 Other: 66.7	Oasys: 91 Other: 100	18 SIC +ve 22 asthmatics not at work
Cote [99] 1990	Canada	No – same cohort and analyses as 1993 Cote paper							
Cote [54] 1993	Canada	yes	++	Adequate	25	Visual and other quantitative (Max-min PEF)	Visual: 86.7 Other: 93.3	Visual: 90 Other: 90	15 SIC +ve 10 SIC -ve
Leroyer	Canada	Yes	++	Inadequate	20	Visual and other	Visual:	Visual:	11 SIC +ve

[47] 1998						quantitative (DV)	72.7 72.7 81.8 Other: 36.3	88.9 100 100 Other: 77.7	9 SIC -ve
Malo [40] 1993	Canada	Yes	++	Adequate	74	Visual	72	78	33 SIC +ve 41 SIC -ve
Bright [214] 2001	UK	Yes	++	Adequate	67 (test set)	Computer based Oasys 3 score and visual	Computer: 82 Visual: 100	Computer: 94 Visual: 93	35 SIC/ NSBR change/specific IgE +ve 32 asthmatics not at work or asymptomatic post office workers
Burge [39] 1982	UK	Yes	++	Inadequate	46	Visual	70	92	33 SIC +ve 13 no work effect after returning to work after a break or workers with OA not exposed
Liss [220] 1991	Canada	Yes	++	Inadequate	37	Visual	72	53	18 History plus NSBR change or NSBR <8 plus SPT or SIC 19 normals (NSBR >8 or SIC –ve)
Perrin [55] 1992	Canada	Yes	++	Inadequate	61	Visual and other quantitative (DV)	Visual: 81 Other: 60	Visual: 74 Other: 78	25 SIC +ve 36 SIC -ve
Gannon [42] 1996	UK	Yes	++	Adequate	67 (test set)	Computer based Oasys 2 score	75	94	35 SIC/ NSBR change/specific IgE +ve 32 asthmatics not at work or asymptomatic post office workers

Table 6.7.2 Articles showing return rates of serial PEF records, comparing records requested at workplace surveys and those requested following clinic referral

Author, Year	**Country**	**Included**	**Number of subjects**	**OA Clinic (1) or Workplace study (2)**	**% PEFs returned**	**% acceptable / interpretable PEFs returned**
Girard [199] 2004	Canada	yes	94	OA clinic	81	49
Hannu [217] 2007	Finland	yes	9	OA clinic	100	67
Medina-Ramón [221] 2006	Spain	yes	80	Workplace	64	46
Arbak [222] 2004	Turkey	yes	64	Workplace	100	na
Bolen [223] 2007	USA	yes	178	Workplace	76	53
Eifan [224] 2005	Turkey	yes	36	Workplace	78	61
Turgut [225] 2005	Turkey	yes	22	Workplace	95	na
Huggins [50] 2005	UK	yes	158 postal instructions 86 personal instructions	OA clinic	56 85	42 65
Sauni [226] 2009	Finland	yes	76	OA clinic	na	53
Minov [227] 2007	Macedonia	yes	5	Workplace	100	na

Robertson [32] 2007	UK	yes	191	Workplace	87	na
Hayati [56] 2006	USA	yes	48	OA clinic	na	94
Chiry [75] 2007	Canada	No – same cohort as Girard paper				
Munoz [219] 2004	Spain	yes	5	OA clinic	100	na
Hayati [57] 2008	USA/ Canada	yes	45	OA clinic	na	80
Cote [54] 1993	Canada	yes	29	OA clinic	100	86
Henneberger [228] 1991	USA	yes	26	Workplace	77	54
Hollander [74]1998	The Netherlands	yes	398	Workplace	90	52
Leroyer [47] 1998	Canada	yes	20	OA clinic	100	na
Malo [48] 1995	Canada	yes	21	OA clinic	na	71
Quirce [229] 1995	Canada	yes	17	OA clinic	76	65
Revsbech [72] 1989	Denmark	yes	139	Workplace	na	95
Redlich [230] 2001	USA	yes	75	Workplace	na	87
Liss [220] 1991	Canada	yes	78	OA clinic	na	64
Perrin [55] 1992	Canada	yes	61	OA clinic	100	72

Table 6.7.3. gives an overview of each article's country of origin and results of the pooled analyses. The majority of the articles were published from Canada (31%) and UK (25%), the rest of them being conducted in USA, Finland, Spain, and other European countries including Turkey. The pooled sensitivity from all studies was 75% and pooled specificity 79%. Two articles presented data for sensitivity only. When confined to PEF records fulfilling the minimum data quantity, the sensitivity was even better at 82% (95% CI 76-90), with specificity at 88% (95% CI 80-95). Visual analyses seemed to be slightly more sensitive (78%) than computer-based analysis (71%), but specificity was better with computer-based analysis (91%) vs. visual analysis (69%). Other quantitative methods of analysis gave a sensitivity of 74% and specificity of 82%.

The return rate of serial PEF recordings was good overall at 83%, with 61% containing interpretable and acceptable PEF data. The return rate was slightly better when requested in a workplace study (85%) as compared to an occupational respiratory clinic (78%), but the rate of interpretable and acceptable PEF data was similar between these two types of studies (62% vs. 61%, respectively).

Table 6.7.3. Overall results from the articles identified in the systematic search

Articles identified	**%**	**Confi-dence Interval**	**Likeli-hood ratio**	**Number of Studies**
Location				
Canada	31	-	na	8
UK	25	-	na	8
Turkey	10	-	na	3
Others	39	-	na	12
Articles including data on sensitivity of serial PEFs for independent diagnosis of OA	Sensitivity %			16
Pooled sensitivity	75	69-81	3.6	16
PEFs fulfilling minimum data quantity	82	76-90	6.8	8
PEFs not fulfilling minimum data quantity	69	61-78	2.5	7
Unknown data quantity	82	61-100	-	2
Computer-based analysis	71	54-85	7.9	6
Visual analysis	78	72-85	2.5	9
Other quantitative analyses	74	49-96	4.1	6
Articles including data on specificity of serial PEFs for independent diagnosis of OA	Specificity %			14
Pooled specificity	79	73-87	0.3	14
PEFs fulfilling minimum data quantity	88	80-95	0.2	8
PEFs not fulfilling minimum data quantity	72	65-85	0.4	7
Unknown data quantity	-	-	-	-
Computer-based analysis	91	78-99	0.3	6
Visual analysis	69	64-86	0.3	9
Other quantitative analyses	82	65-93	0.3	6
Reference confirmatory test	%			
Specific Inhalation Challenge (SIC)	74	-	na	11
Mixed (SIC, 4 fold change in NSBR, IgE)	26	-	na	5
Papers discussing feasibility of serial PEFs	Return rate %			24
Pooled return rates	83	80-94	na	17
Pooled return rates for interpretable/acceptable PEFs	61	58-74	na	19
Pooled return rates for PEFs requested through an Occupational Respiratory Clinic	78	77-100	na	8
Return rate for interpretable/acceptable PEFs	61	58-77	na	11
Pooled return rates for PEFs requested through a workplace study	85	76-95	na	9
Return rate for interpretable/acceptable PEFs	62	47-82	na	7

6.7.6. Discussion

This systematic review shows that serial PEF measurements are achievable, and have a good sensitivity and specificity for diagnosing occupational asthma. Acceptable and interpretable serial PEF recordings can be achieved by 61% of people asked to carry them out because of suspicion of occupational asthma. The pooled sensitivity and specificity of serial PEF recordings were 82% and 88%, respectively, when the minimum data requirements were satisfied.

The pooled return rate of PEF recordings was 83%. According to a previous study from the UK, return rates can be improved from 56% to 85% by giving personal instructions in an occupational clinic rather than sending instructions by post only [50]. Results are improved by using specialised record cards which require times of waking and going to sleep, and times of starting and stopping work. They provide better results than the standard asthmatic charts which simply graph PEF (often every 4 hours or less) [50], where details of times of working and sleeping are often missing. Workers seen in occupational clinics who are going through their diagnostic pathway yield similar return rates and acceptability to those who have taken part in specific work-based studies.

Visual analysis by an expert is the most sensitive method for deciding whether a PEF record shows a pattern compatible with occupational asthma or not, but it has been found to show only moderate repeatability within observers (kappa 0.47), which is reflected in lower specificity. Within observer agreement is further reduced when PEFs are of poorer quality [231;232]. Agreement between observers is moderate to high (Kappa values mostly from 0.6 to 1, but one study reported a kappa of 0.19), [40;47;55;176;199;220;231;232].

Computer-based interpretation overcomes observer disagreements; they have shown a slightly lower sensitivity (71%) but a better specificity (91%) compared to visual analysis (78% sensitivity and 69% specificity) for records with adequate quantity of data [42;43;214]. Computer-based interpretation can be used in any type of clinic, specialist or not, and usually does not require an expert to be present, as long as the interpreters are aware of potential sources of error in measurements. Analyses utilising methods such as the Shewart's control chart also display these attributes [56;57]. However, these methods have not been tested in prospective studies. Combining serial PEF records with induced sputum analysis improved sensitivity and specificity of the diagnosis of occupational asthma in one study which had an usually low sensitivity when using computer-based analysis [199]. Combining serial PEFs with non-specific bronchial reactivity measurements showed either no improvement to PEF recordings alone or an improvement in sensitivity and a decrease in specificity [55;99].

There are differences in opinion about the minimum diurnal variation and the magnitude of difference between mean PEF on work and rest days required for a diagnosis of occupational asthma [39;47;54;55;57;199;213]. Some centres require the diurnal variation in PEF to be >20% during work days at least in part of the record. Diurnal variation is increased in asthmatics and cut offs of 20% and 15% have been suggested previously [59;66]. In a population sample, the sensitivity of diurnal variation has been shown to be very low (32%) at a specificity of 90% for detecting asthma [233]. Many workers with occupational asthma show increased diurnal variation in PEF on workdays compared to days away from work, but this may not always be the case, as the acrophase (peak) PEF may be suppressed by work exposures, which would reduce work-day diurnal variation,

even if the values at work are lower. The magnitude of changes in PEF can be altered by treatment. The only papers that have assessed the effect of asthma medication on serial PEFs are from the 1980's and early 1990's when the PEF analysis methods were being developed. The changes seen in patients taking disodium cromoglycate or low dose inhaled steroids were smaller than those seen off treatment and initially led to reduced visual assessment scores [189]. Malo *et al* found little difference in the visual analysis of PEFs in patients using ICS compared to those using beta agonists alone [40] These studies preceded the use of long acting beta agonists and high dose inhaled steroids that are today used rather commonly in the treatment of asthma. Asthma treatments are likely to influence the methods based on numerical differences between work and rest periods more than those based on pattern recognition and discriminant analysis, although the latter are also likely to be influenced. Studies of non-occupational asthmatics and normal workers exposed to high levels of irritants have shown that 16L/min is the upper 95% confidence limit for differences in mean PEF between work and rest days in workers off treatment [49;208]. If PEF monitoring does not show a work-related effect while taking regular long-acting beta agonist or prophylactic asthma treatment, it is worth repeating the measurements off treatment or with minimal inhaled steroid medication required from the clinical point of view, if there is still a suspicion of occupational asthma based on symptom patterns. This is based on expert opinion and experience rather than on published studies.

When investigating sensitivity and specificity of a physiological test, a positive and negative reference test needs to be used. Specific inhalation challenge testing is most commonly used as the gold standard for occupational asthma, as this most closely represents a single exposure at work, thereby identifying a specific cause for occupational

asthma. Many studies use a positive result in a SIC as the positive reference standard and a negative SIC as the negative reference. However, this does have some drawbacks as false negative results may be obtained if the amount of exposure used in the specific challenge test was too small compared to real-life conditions, a wrong agent was chosen to be tested in SIC or if the exposure is difficult to reproduce in the laboratory conditions [109]. The latter may be the case if a mixture of occupational exposures is more relevant for developing occupational asthma than any single exposure alone. The opposite may also occur in that false positive results can be obtained if exposures in SIC are too high compared to real-life exposures and reach levels to which any general asthmatic would react.

Some authors use workplace challenge tests as the reference standard alongside specific challenge tests [40;75]. Workplace challenges allow supervision of exposures and lung function monitoring, but like serial PEF measurements do not usually identify the specific cause of the occupational asthma. Other authors have included tests such as changes in non-specific bronchial reactivity between a period of occupational exposure and a period of no such exposure (measured after at least 1 week away from work) and/or specific IgE to a relevant substance combined with a work-related symptom history as their reference standards [42;188;214;215;220]. The former has been shown to have a moderate sensitivity and specificity for occupational asthma diagnosis compared to SIC [55;99;234]. The latter is the only method that is exclusive from any lung function measurements. Specific IgE indicates sensitisation to a specific agent rather than disease, and validation of asthma is also required when it is used as a reference standard for occupational asthma. Such an approach has been validated for a limited number of agents [89;91;235;236]. In the current

review the reference test for occupational asthma was based on specific inhalation challenge test in 74% of the studies and a combination of SIC and other tests in 26% of the studies. The sensitivity of the studies with adequate PEF data using SIC vs. all methods were similar at 81% and 83% respectively. The corresponding specificity was 82% and 94%. It should be noted that Oasys score or Oasys ABC were used for all studies using the mixed method reference standards, so the high specificity reflects these methods.

6.7.6.1. Sources of error in PEF measurements

High sensitivity and specificity of PEF records has been found despite the many potential sources of error in PEF measurements, including suboptimal effort, fabricated measurements, variable asthma treatment and potential effects of other exposures that might affect airway calibre apart from workplace agents. Respiratory tract infections in particular may lower PEF independently of work exposures. To cause a systematic error in the interpretation of serial PEFs, i.e. to cause a bias, these factors need to be systematically different on work compared to rest days. Two potential errors need particular attention: the use of more bronchodilator treatment on workdays may mask work effects, and lower readings taken during sickness absence from respiratory infections may obscure improvement on rest days. It is important to try to keep asthma treatment the same during the entire period of serial PEF measurements, make measurements always before taking bronchodilating medication and record any respiratory tract infections occurring during the serial PEFs, as suggested in diagnostic guidelines [38]. These sources of error can be assessed by inspecting the record and removing the affected sections of serial PEFs from the final analysis of records.

Other potential sources of error that need to be taken into consideration include meter precision and meter/person accuracy. Recording reliability should be checked before interpretation; at least three measurements should have been carried out at each measurement session with the best two differing by less than 20 l/min. Fabrication should be suspected if all three measurements are exactly the same or the same results are recorded many times on each day [49]. Most often such fabrication is an attempt to compensate for forgotten recordings rather than to purposefully invent work-related changes. Errors related to fabrication can be eliminated using data-logging instruments (unless someone else has blown into the meter). However, there are still other issues as to whether the measurements are precise and accurate. The ways to improve these are to ensure that the meter conforms to certain standards, to understand how the meter logs the results and to train the patients so that they understand how to do their best readings and what to record on the chart. It should also be emphasized that the same meter should be used at work and away from work, as there are differences between individual meters. Differences between types of logging meters include that some models save only the highest of 3 measurements taken regardless of quality, while other models save only measurements that are deemed adequate based on pre-programmed quality criteria. Some models allow unlimited measurements within a session, while others only allow a set number of measurements. Some meters log every measurement session, whereas other meters will overwrite measurements taken within the hour. Getting the worker to write down as much information about their occupational and other exposures, exercise, and use of short-acting bronchodilators is the best way of trying to identify other factors that may affect the PEF recordings. Dedicated forms with space to write information on occupational and other exposures alongside working times, asthma treatment and

recordings of two-hourly measurements of PEF facilitate interpretation of serial PEFs [50]. Suitable forms are downloadable for example from http://www.occupationalasthma.com/resources/dataentryform.pdf.

6.7.6.2. Other issues related to serial PEFs in diagnosing occupational asthma

Serial measurements of PEF often involve the repeated exposure to an agent to which the worker is sensitised. It is not suitable to carry out such recordings in those who have a history of severe work-related reactions, and in these cases, carefully controlled specific challenge tests in hospital are preferable. Records should be made as early in the diagnostic process as possible, preferably when the suspicion of occupational asthma has been raised, and before exposures have been modified or the worker has been relocated. Because of this, serial PEF measurements should be started when first seen in primary care or occupational health departments. Serial PEFs can also be used to check the adequacy of relocation away from exposure to the causative agent after the diagnosis of occupational asthma has been made. The records are more sensitive if performed before asthma treatment is started [39]. Treatment may however be needed first if the asthma is severe or very variable.

PEF records cannot differentiate between reactions due to allergic or irritant or other mechanisms by which occupational exposures may have their effects. PEF records would be expected to show work-related changes in regular work-aggravated asthma for example due to exercise, sulphur dioxide or cold air. PEF records do not usually identify the specific cause for occupational asthma [75], but are better to identify reactions caused by a mixture of occupational exposures compared to SIC. They do not replace the need for

specific inhalation challenge testing, but do reduce the numbers for which these are required, as SIC need much more resources.

The question concerning the significance of specific challenge testing showing a positive result when there are no PEF changes seen from usual work exposures, or showing a negative result when there are obvious work-related changes in PEF warrants some further discussion. It should be remembered that the overall sensitivity of serial PEFs of 75% (including records of adequate and inadequate data quantity) means that the PEF recordings will not show diagnostic changes in 25% of workers who actually have occupational asthma. Non-diagnostic records may occur early in the disease when work-reactions are small or infrequent. Repeating the record after a few months (together with spirometry and NSBR) is the most appropriate next step. Records with high PEF variability are also difficult to interpret, but including periods at work with an intervening 1-2 week period away from work may then aid interpretation [237]. Alternatively the worker may be temporarily relocated away from exposure and comparisons then made between the two work periods with different occupational exposures. When serial PEF shows work-related changes, but SIC is negative, it should be remembered that the sensitivity of SIC is in reality also less than 100%; for example if the period between the last occupational exposure situation and the challenge testing is long, or when the SIC has been performed with a wrong agent or with a smaller amount of exposure than that encountered in real life. Another explanation may be that the work-related changes in PEF are due to nonspecific exposures at work rather than specific causal agents. However, if serial PEFs repeatedly show a pattern consistent with occupational asthma in the absence of any obvious non-specific exposures, the value of a single negative SIC should be questioned.

We think it is valid to pool the results from all papers assessed as being of adequate quality using the SIGN quality criteria. This is an accepted method and has been used in other systematic reviews [35]. Most studies used specific inhalation challenge testing as their reference standard and those that included four fold changes in NSBR, and/or a symptom history compatible with occupational asthma together with documentation of asthma and a positive IgE to a relevant allergen showed sensitivity and specificity similar to those validated by specific inhalation challenge testing within the same study [188;220]. We believe that the main differences in sensitivity and specificity between different studies relate to the quality of the PEF records. The improved effect related to good quality PEF records was shown in our results.

Summary estimates based on systematic reviews are always liable to publication bias, i.e. bias resulting from a tendency to publish positive studies more readily than negative results. However, there are centres in the world who believe that the results of SIC are more reliable for the diagnosis of occupational asthma than serial peak flow measurements which might bias the results in the other direction to those observed in this review [109]. Also, there is a difference between PEF records that are truly negative and the ones that are equivocal. However, the consistency of results between studies from different parts of the world, studies using different methods of PEF analysis and countries with different health and compensation schemes add confidence to the validity of our conclusions.

6.7.7. Conclusions

Serial peak expiratory flow measurements are a useful objective confirmatory test for a diagnosis of occupational asthma, when potential sources of error are understood. They can

be achieved by approximately two thirds of those asked to do them and have an overall sensitivity of 82% and specificity of 88% when minimum data quantity requirements for the method of analysis used are fulfilled. They do not usually identify the precise cause of the occupational asthma in an individual and complementary information of specific exposures are needed. They have been better validated against independent standards than any other method of occupational asthma diagnosis, including specific inhalation testing.

7. OVERALL DISCUSSION AND CONCLUSIONS

The data presented in this thesis strengthens the evidence that serial peak expiratory flow measurements should be used as the first line investigation in the confirmation of occupational asthma as has been recommended in recent guidelines [1;13;38]. Performing them is cheap and easy to achieve in most settings, including general practice surgeries, lung function departments, occupational health departments and specialist centres. They require a degree of patient effort and compliance and numbers returned with adequate data amounts for analysis are not always very high (mean rate 61%) as shown in chapter 6.7. Using the ABC score that requires a shorter duration of recording is likely to improve the usefulness and return rates of PEF recording in diagnosing occupational asthma. We have found that up to 85% of peak flows are returned when given out in person [50], with 59% of these fulfilling all data quantity requirements for the Oasys score. These numbers are now likely to be increased with the addition of the area between curves score (chapter 6.1) which requires shorter records than the Oasys score [188;190]. The Oasys score will capture those that have completed at least 3 weeks of readings with ≥ 4 readings per day and have at least 3 consecutive work days in any work period [43], whereas in chapter 6.2 we have shown that the ABC score works well even when exposure is intermittent and it requires a minimum of 8 readings per day but for a shorter period of 8 work days and 3 rest days (approximately 2 weeks). If there are less reading per day, more work and rest days are required [190].

Serial PEF measurements are not without their problems and confounding factors such as differences in treatment within the record (possibly less treatment on rest days compared to

work days or a change in dose/addition of a treatment), respiratory tract infections, exposure differences on certain days that may not be documented, suboptimal effort, fabricated measurements, meter precision and person accuracy need to be assessed. The sensitivity and specificity of PEF records found in this thesis include fabricated readings and possibly other sources of error where they have not been documented or are difficult to identify. It is important to keep asthma treatment the same during the PEF measurements and make measurements before taking bronchodilators, recording any respiratory tract infections, as suggested in diagnostic guidelines [38]. Workers should be asked to make at least three measurements at each measurement session with the best two differing by less than 20 l/min. It should also be emphasized that the same meter should be used at work and away from work. Getting the worker to write down as much information about exposures, exercise, and use of short-acting bronchodilators helps to identify factors that may affect the PEF recordings. Suitable forms for recording such information are downloadable for example from http://www.occupationalasthma.com/resources/dataentryform.pdf.

The ABC score has been set up to be highly specific, rather than taking the best overall sensitivity and specificity. This is due to the concerns that the investigators have about potential consequences of a diagnosis of occupational asthma i.e. unemployment and financial hardships [49]. The score was therefore set up to minimise false positive results. Our centre is a tertiary referral centre, therefore when workers come to our clinic, the suspicion of occupational asthma has already been raised meaning a higher specificity is more important in this situation. If serial PEFs are utilised in primary care however, choosing a lower cut off score (for example 5.6L/min which gives the best combined sensitivity and specificity) may be more useful. In contrast to the high specificity of the

ABC score using a 15 L/min/hr cut off, the use of questionnaires and medical histories are the opposite, being highly sensitive but unspecific [1;21-23]. When suspecting occupational asthma, this would be the tool used first, followed by serial PEFs to confirm the diagnosis. The data presented in this thesis shows the ABC score to have a sensitivity of 69% and specificity of 100% for occupational asthma when using a cut off of 15 L/min/hour [188]. The sensitivity of the ABC score can be further improved by including records with longer periods off work [238], as shown in chapter 6.3.

The sensitivity and specificity of the ABC score has been compared against "gold standard" independent validation tests. Those included are specific inhalation challenge (SIC) tests, a four-fold change in methacholine reactivity between periods of exposure and non-exposure and a positive specific IgE alongside a relevant strong occupational history. There are problems with all types of tests and no single test is a true "gold standard". The reasons for this are that false positive and false negative results may occur from SIC when too higher dose of allergen is administered or too small a dose/the wrong allergen is given. Those with negative challenge tests have been investigated with workplace challenge tests by Rioux *et al* who found that out of 99 workers who had a negative SIC, 22 went on to have positive workplace challenge tests [109]. The independence of this test from serial PEF recordings is also difficult as the majority of workers would need to show some work-related changes in serial monitoring before being sent for SIC (although there are some who are sent with a lack of PEF changes). In this thesis, work-related changes in PEF were analysed by the original Oasys score rather than the new ABC score. Specific IgE would usually be used in conjunction with serial PEF work-related changes, but to remain independent in our studies, we have combined it with an occupational history only. This

may lead to sensitised individuals who don't actually have asthmatic PEF changes being included in our studies. The non-specific reactivity changes have other problems in that it has a moderate sensitivity and specificity itself, so false positive workers could also be included. However, aside from these problems, there are no better tests for comparison which is why they are used by many research centres when comparing diagnostic methods.

Although the accepted method for assessing how well a diagnostic test performs is sensitivity and specificity calculations, these also have limitations. The values for sensitivity and specificity can be markedly changed by considering the prevalence of the disease in the population being screened. For example, our clinic will have a much higher prevalence of occupational asthma compared to if an entire workforce were screened. Sensitivity and specificity can be compared to positive predictive and negative predictive values which take prevalence into account which was calculated in chapter 6.1.

Other peak flow analysis programs have been created, but none have been prospectively validated and none are generally available, unlike Oasys (which is available from www.occupationalasthma.com). There is no published work on the sensitivity and specificity of scoring systems within the other programs. The systematic review in chapter 6.7 found that the other programs tend to plot results without giving diagnostic scores, giving some information about the peak flow records such as the mean diurnal variation on work days and rest days and plotting graphs of mean peak flow or best and worst PEF during work and rest periods. The clinician would then interpret these plots and outputs and decide whether the record is compatible with occupational asthma or not [39;40;47;54;55;199;217;219;220]. Agreement between observers has varied widely

however, with Kappa values mostly from 0.6 to 1, but one study reported a kappa of 0.19), [40;47;55;176;199;220;231;232]. There are other quantifying methods which can also be used such as Shewarts control charts, but these concentrate on changes in diurnal variation which is a very unspecific diagnostic method as shown in chapter 6.6 and also insensitive as shown by others [47;54-57]. Turner *et al's* study of agreement between occupational and respiratory physicians in the diagnosis of occupational asthma [61] based on history alone (phase 1) and then history plus other clinical investigations (phase 2) showed low agreement on whether workers had occupational asthma or not (interclass correlation range of 0.12 to 0.54 for all physicians). The addition of an Oasys score of >2.5 or the presence of non specific reactivity produced higher index ratings. The same cases were reviewed by a group of expert respiratory physicians previously and agreement showed a median kappa value of 0.26 [239]. The diagnosis of occupational asthma can be affected by the pretest probability of occupational asthma, as shown in Beach *et al's* paper [35] where the likelihood of diagnosing the disease from non-specific bronchial reactivity combined with either skin prick test of specific IgE decreases from approximately 90% with a pretest probability of 75% to around 40% when the pretest probability is 15%. The pretest probability in Turner *et al's* paper could have been low in some circumstances, therefore making a diagnosis more difficult. Using diagnostic scores, such as the new ABC PEF score and the earlier Oasys score should be done in combination with other clinical data, interpreters should have knowledge on interpreting such data and a unified approach for assessing whether investigations indicate occupational asthma or not are needed.

Serial PEF measurements do not find the specific cause of the occupational asthma. Further specialist tests such as specific inhalation challenge testing may be required for

this. SIC testing is time consuming as only one agent can be tested each day and therefore it is only performed on a small percentage of patients seen in clinic. To assess responses to occupational allergens in challenge tests, the change in forced expiration volume in one second (FEV_1) is the main measurement. This is because it is thought to be more sensitive to asthmatic change than PEF measurements [46;192]. However, PEFs are more easily achieved when performing unsupervised measurements, which is why they tend to be used for at work and at home serial measurements [47]. In our study of PEF versus FEV_1, using measurements made by departmental staff (chapter 6.4), we found that FEV_1 was a less sensitive measure than PEF for identifying within day diurnal changes. The differences between the four logging meters studied that measured PEF in different ways (turbine, pneumotachograph, colied spring and ultrasound) were small. When within session readings (sets of 2 or more readings) were analysed, there was less difference between consecutive blows for FEV_1 within a session while a larger variation was found between PEF measurements, but overall the variation in both measures was generally low. In a study by Hegewald *et al* PEF within session variability was also found to be higher than FEV_1 within session variability [193]. When analysing between meter differences, the coefficient of variation (COV) for FEV_1 was significantly different between meters ($p = 0.009$) whereas PEF COV was similar across all meter types. This study has only been completed in departmental staff who should produce more reproducible readings than a cohort of asthmatic patients/workers due to them understanding the readings, how to make the measurements and some how to use the meters. It would be useful to compare the results of this study with patient data to see if variability is much bigger in the latter group.

The agreement between written PEF/FEV_1 measurements and downloaded measurements from the logging meter were not assessed in our FEV_1 versus PEF meter study. However, fabrication of peak flows is an issue which is largely being overcome by the use of electronic devices. Malo *et al* [48] and Anees *et al* [49] have investigated PEF fabrication previously, with the Malo group finding that values corresponded precisely in 52% of readings and 71% were within an hour of the written time. Anees *et al* also found discrepancies, but concluded that fabricated values tend to regress to a mean rather than the worker aiming to give themselves disease. This suggests that there is a need to please the physician (by returning some values) rather than wanting a specific diagnosis. There are also differences between meters as to the values that they save. As some meters have programmed quality criteria in them, they do not always save the highest PEF/FEV_1 value which is what the worker may record. Fabrication or feadings needs to be taken into account when interpreting serial lung function measurements for the diagnosis of occupational asthma.

Asthma is an inflammatory disease of the airways and measures indicating such inflammation e.g. exhaled breath nitric oxide, can aid the diagnosis or monitoring of occupational asthma, or help with diagnosis and monitoring of asthma in general. In our study, we found that the amount of PEF fall at work (in response to exposure) did not correlate with having increased bronchial inflammation as monitored by average FE_{NO} levels (chapter 6.5). PEF response was assessed using the ABC score in Oasys along with diurnal variation which many physicians use for the diagnosis of asthma. The FE_{NO} did however positively correlate with non-specific bronchial reactivity. Several other researchers have also found that there is a relationship between FE_{NO} and non-specific

bronchial reactivity in occupational and non-occupational asthma [15;124-127;200-203]. Our PEF response results agree with other studies that have also not shown any correlation between FE_{NO} and the magnitude of lung function (mainly FEV_1) changes in non-occupational asthma [125-127].

As many changes in the body occur during sleep according to the normal circadian rhythm, some of which affect our breathing, the responses of those with occupational asthma who work on different shifts could be different depending on the shift type they are working. To address this question we assessed whether there were any differences in PEF responses between day shifts, afternoon shifts and night shifts. Only a few records had all 3 shifts types, but many had at least 2 shift types to compare. It was found that the mean ABC score was slightly increased on day shifts compared to afternoon and night shifts. However, in an analysis comparing those who were better, worse, or the same on day and night shifts, it was found that the differences were not always in the same direction for all workers. A cut off of 15 L/min/hour for the ABC score was shown to be appropriate for all shift types (this cut-off point was originally validated for day shifts, see chapter 6.6). The diurnal variation did not show any statistically significant changes across different shifts. The ABC score showed a high sensitivity and specificity across all 3 shift types, whereas changes in diurnal variation had good sensitivity but low specificity. Cross-shifts changes in PEF in workers with occupational asthma showed a mean decrease of 28 L/min in PEF when workers were on day shifts, a decrease of 76 L/min on afternoon shifts and 64 L/min on night shifts. Previous studies have mostly investigated cross shift changes in lung function for shift workers and haven't adjusted for time from waking, nor investigated changes in diurnal variation or other scores such as the ABC score. Others have found that

in working populations (although not workers with diagnosed occupational asthma) PEF increases over a day shift and decreases over afternoon and night shifts following normal circadian variation, similar to the findings in our non-occupational asthma group [79-82]. This study implies that shift work responses are superimposed on these normal circadian rhythms in occupational asthmatics, showing fewer declines on day shifts compared to afternoons or nights.

7.1. Conclusions

- The ABC score created during this thesis for diagnosing occupational asthma is robust across shift types.
- The ABC score has a good sensitivity and high specificity for occupational asthma diagnosis.
- The ABC score requires shorter records than earlier scores based on serial PEF measurements and can cope with intermittent exposure.
- The sensitivity of the ABC score improves with longer periods off work.
- PEF seems to work better at identifying diurnal responses than FEV_1 although FEV_1 shows less variability within a measurement session.
- PEF responses at work do not seem to correlate well with inflammatory markers such as exhaled breath nitric oxide. However, FE_{NO} does correlate well with non-specific bronchial reactivity.
- The use of serial PEFs in the diagnosis of occupational asthma has been widely investigated and is a useful confirmatory diagnostic test.

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