Shift work effects on serial PEF measurements for occupational asthma

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Background
Diurnal variation (DV) affects lung function but the changes are thought to be related to sleep patterns rather than time of day. When diagnosing occupational asthma (OA), serial peak expiratory flow (PEF) measurements are the recommended first line investigation, but could be confounded by shift work.

Aims
The aim of the study was to investigate the effects of shift work on PEF measurements used for diagnosing OA.

Methods
PEF records containing more than one shift pattern with ≥4 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. The mean area between curves (ABC) score, mean PEF DV and cross-shift PEF changes were calculated for each shift.

Results
Records from 123 workers with OA and 69 without OA satisfied inclusion criteria. In the OA group, PEF declined more on afternoon and night shifts than days (P < 0.001). The ABC score was lower in the OA group on night (P < 0.05) and afternoon shifts (P < 0.05) as compared with days, without significant differences in DV. Among those without OA, cross-shift PEF increased more on day shifts (mean + 25 l/min) than afternoon or night shifts (+1 l/min) (P < 0.001). The sensitivity for the ABC score and DV were good and similar across shifts, but specificity was reduced using DV (DV mean 39%; ABC 98%).

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 shifts; differences in DV have lower specificity.

Key words
Circadian variation; Oasys; occupational asthma; peak expiratory flow; shift work.

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 [1–6]. It has been suggested that circadian variation in lung function is related to sleep patterns rather than time of day [1], but on the other hand, there has been concern that it could affect diagnosis of occupational asthma (OA) based on serial peak expiratory flow (PEF) measurements.

Increased DV (measured by subtracting the lowest PEF from the highest PEF in a 24h cycle and expressing it as a percentage of the subject’s mean, maximum or predicted PEF) can be used for diagnosing asthma. Studies of healthy populations measuring PEF every 2h have shown a mean DV of 8.7% (calculated as % of mean) with an upper 95% confidence interval of 26.3% [4]. Often a cutoff point of 15% or 20% of DV is used for the asthma diagnosis, but the sensitivity has been
rather low [4–7]. Clark and Hetzel showed sleep to be the most important trigger for the diurnal changes [1]. It seems that 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 [8]. A healthy worker would, therefore, be expected to have an increase in PEF across a shift that starts relatively soon after waking from sleep. In occupational asthma, exposure to agents in the workplace influences these responses. 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 as compared with rest days can be analysed using a computer-based analysis, such as the Oasys program [9]. Oasys’ outputs include diurnal variation (which can be calculated separately for different shift types) and a PEF plot, where the mean of all exposed and unexposed readings taken every 2h are plotted separately for each shift pattern. The Oasys score has not been used to study the effects of shift work as it gives a whole record score rather than scoring shifts separately. The Area Between the Curves (ABC) score is the area between the work and rest PEF curves expressed in l/min/h (Figure 1) [10]. 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/afternoon shifts. A cutoff point of ≥15 l/min/h for the ABC score has a sensitivity of 69% and specificity of 100% for the diagnosis of OA in day shift workers as compared with OA diagnosis based on independent confirmatory tests [10]. Whether night or afternoon shifts show a different PEF response as compared with day shifts when using the ABC score for diagnosing OA is currently unknown.

The aim of this study was to investigate whether the PEF responses to occupational exposures are altered by shift work and whether the ABC score can be used across different shift types for diagnosing occupational asthma.

Methods

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 symptoms of OA starting after a latent interval and confirmed with an Oasys PEF score of ≥2.51 formed the OA group and those without work related asthmatic symptoms at the time of the record and an alternative diagnosis including an Oasys score <2.51 formed the non-OA group. Within the OA group, workers who also underwent other confirmatory testing (specific inhalation challenge test, 4-fold change in non-specific reactivity between periods of exposure and non-exposure or a positive specific IgE and a strong relevant occupational history) were analysed as a subgroup. 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 [11]. PEF records performed during respiratory tract infections, changes in asthma treatment or with known differences in exposure on each shift type were also excluded. In the analyses, readings on work days started with the first reading at work and continued to the last reading before work on the next day [12]. Only one record per worker was used and if more than one was available, the first by date was chosen.

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

The mean ABC score, 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 4h at work) from the pre-shift value (defined as the last recording available in the hour before starting work) and then calculating the mean value for each record [13]. Records were required to contain at least 3 workdays of acceptable readings per shift type for this analysis. A cutoff of ≥15 l/min/h for the ABC score and an increased DV on work days as compared with rest days were selected to indicate occupational asthma based on previous publications [14–16]. Differences between sleeping patterns, number of hours worked, number of days off before a shift and reaction type (grouped as immediate, late or flat/depressed reactions observed from the mean 2h PEF plot, Figure 1) were compared.

SPSS 15 was used for all statistical analyses. The chi-square test was used to investigate differences between OA and non-OA for males versus females, atopics versus non-atopics, current smokers versus non-smokers versus ex-smokers, methacholine reactors versus non-reactors and workers taking inhaled corticosteroids (ICS) versus those not taking ICS. The Mann–Whitney U-test was used for mean FEV1 and mean work diurnal variation differences between OA and non-OA groups as these data were not normally distributed and the independent samples t-test for age differences (normally distributed). For analysis of PEF outcomes by shift type, only average cross-shift changes for day and night shifts were normally distributed, therefore the paired samples t-test was used to compare two shift types. All other PEF response data were not normally distributed and therefore the Wilcoxon Signed Rank test was used to compare two shift types and the Friedman test for all three shift types. Sensitivity and specificity were used to assess the diagnostic usefulness of the ABC score and diurnal variation by shift type.
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 2 shows the stages according to which the exclusion of records took place. Thirty six of the 123 workers had a diagnosis of OA based on confirmatory tests independent from their PEF records. Table 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 4-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. For the OA group as a whole (n = 123), 83% of the workers 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%).

Table 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 (showing a larger difference between work and rest days), significant differences being observed between day versus night shifts (P < 0.05) and day versus afternoon shifts (P < 0.05). In the non-OA group, the ABC score was significantly higher on night shifts as compared with afternoon (P < 0.05). Cross-shift changes showed an increase in mean PEF during day shifts in the group without OA, with no change across afternoon or night shifts (P < 0.001 for day versus afternoons or nights). Those with OA showed significantly larger declines in cross-shift change on night and afternoon shifts as compared with day shifts (P < 0.001 for both).

Table 1. Demographics of the study population

<table>
<thead>
<tr>
<th></th>
<th>All workers with OA (n = 123)</th>
<th>OA workers with all 3 shift types (n = 14)</th>
<th>Workers with non-OA diagnoses (n = 69)</th>
<th>P (all workers with OA versus non-OA)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age (SD)</td>
<td>41.0 (9.9)</td>
<td>42.1 (10.0)</td>
<td>46.2 (9.5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>% males</td>
<td>85</td>
<td>100</td>
<td>78</td>
<td>NS</td>
</tr>
<tr>
<td>% atopics</td>
<td>59</td>
<td>54</td>
<td>48</td>
<td>NS</td>
</tr>
<tr>
<td>% current smokers</td>
<td>29</td>
<td>29</td>
<td>21</td>
<td>NS</td>
</tr>
<tr>
<td>% methacholine reactive</td>
<td>31</td>
<td>23</td>
<td>13</td>
<td>NS</td>
</tr>
<tr>
<td>% taking ICS</td>
<td>47</td>
<td>62</td>
<td>22</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Mean FEV1 % predicted (SD)</td>
<td>87.7 (19.4)</td>
<td>95.9 (19.6)</td>
<td>97.4 (23.3)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Mean diurnal PEF variation at work (SD)</td>
<td>15.5 (8.9)</td>
<td>17.2 (16.3)</td>
<td>10.9 (5.7)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

ICS, inhaled corticosteroids; OA, occupational asthma.
No significant differences in DV were seen among those with OA between any shifts. Among those without OA, DV was significantly higher in day shifts compared with night shifts ($P < 0.01$).

Analysis of workers independently confirmed to have OA as compared with those with a diagnosis based only on the Oasys score gave similar results; therefore only results for the OA group as a whole are given.

Although differences were found in ABC scores between days and afternoon or night shifts on average, not all workers had higher ABC scores on days as compared with 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 (immediate, late or flat/depressed reactions), 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 OA based on the ABC PEF score (applying a cutoff value of $>15$ l/min/h) and a larger DV on work days as compared with rest days (i.e. workday DV minus rest day DV being $>0$) are shown by the type of shift in Table 3. The sensitivity of both the ABC score and the increased DV on workdays as compared with rest days were good during each shift. Specificity was high for each shift using the ABC analysis, but low for increased DV on workdays.

### Discussion

We found that the ABC score showed larger differences between work and rest days on day shifts as compared with afternoon and night shifts in those with occupational asthma. We have previously recommended a cutoff point of 15 l/min/h for the diagnosis of OA [10], and this showed a good sensitivity and specificity for each shift pattern, including afternoon and night shifts. When using larger diurnal variation in PEF on work days as compared with rest days for diagnosing OA, there were no significant differences between shift types, the sensitivity being good, but the specificity low for all shifts. Cross-shift changes in PEF followed normal circadian patterns: those without occupational asthma showed an average increase in PEF across day shifts and no change across afternoon and night shifts; those with OA showed a small mean decline in PEF on day shifts (due to exposure blunting the spontaneous increase in PEF), which was significantly less than on night or afternoon shifts. The ABC score showed a sensitivity and specificity for the diagnosis of OA.

<table>
<thead>
<tr>
<th>Shift type</th>
<th>Mean ABC from waking score (SD)</th>
<th>Mean cross-shift change l/min (95% CI)</th>
<th>Mean diurnal variation % (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Records with day and night shifts (ABC/DV: all OA $n = 73$, non-OA = 27; cross-shift: all OA $n = 18$, non-OA = 53)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Day</td>
<td>44.8 (39.7) −0.6 (10.0) −10 (−26 to +7) +25 (15 to +35) 15.5 (9.9) 10.5 (6.4)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Night</td>
<td>39.6 (35.3) 1.5 (5.3) −40 (−51 to −28) +1 (−3 to +5) 16.0 (9.7) 8.5 (6.0)</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Records with day and afternoon shifts (all OA $n = 61$, non-OA = 52; cross-shift: all OA $n = 41$, non-OA = 34)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Day</td>
<td>36.8 (37.4) −2.7 (8.0) −6 (−23 to +10) +23 (14 to +32) 15.2 (9.0) 10.8 (5.5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Afternoon</td>
<td>32.1 (32.5) −2.4 (9.2) −40 (−59 to −21) +1 (−6 to +9) 16.1 (11.8) 10.7 (5.4)</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Records with afternoon and night shifts (all OA $n = 17$, non-OA = 10; cross-shift: all OA $n = 14$, non-OA=10)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Day</td>
<td>47.9 (50.9) −2.1 (6.3) −61 (−143 to +21) −3 (−9 to +3) 18.7 (18.9) 7.7 (5.2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Night</td>
<td>45.5 (57.7) 2.9 (3.2) −47 (−99 to +4) −3 (−10 to +4) 16.9 (14.1) 6.2 (3.6)</td>
<td>&lt;0.05</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Records with day, afternoon and night shifts (all OA $n = 14$, non-OA = 10; cross-shift: all OA $n = 9$, non-OA = 6)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Day</td>
<td>46.6 (62.9) 0.7 (7.0) −28 (−103 to +47) +19 (−6 to +33) 15.5 (14.1) 7.8 (3.5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Afternoon</td>
<td>46.0 (54.1) −2.1 (6.3) −76 (−167 to +15) +2 (−11 to +7) 19.3 (20.6) 7.7 (5.2)</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Night</td>
<td>42.8 (59.7) 2.9 (3.2) −64 (−124 to −3) +0.2 (−5 to +6) 17.5 (15.5) 6.2 (3.6)</td>
<td>&lt;0.05</td>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>

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 3.3).
OA of 79% and 99% for day shifts, 83% and 96% for night shifts, and 72% and 98% for afternoon shifts. The sensitivity and specificity of the ABC score is likely to have been increased by the requirement of a positive Oasys score for OA and a negative score for controls in this study. However, this should not invalidate the comparison between shift types, as the same definitions were used for each shift. The similar sensitivity for all shift patterns was supported by the analysis limited to workers who had an independently confirmed diagnosis of OA.

Many centres base their diagnosis of OA on differences in DV between work and rest days [14–16]. Some centres require a greater number of workdays to have a diurnal variation exceeding 20% as compared with rest periods. [15,16] Using a DV greater on workdays as compared with rest days showed a good sensitivity across all shifts (70–78%), but the specificity was very low. Diurnal variation may be below 20% in many workers with OA confirmed by specific inhalation challenge testing [13,15–17], but there is lack of research identifying the best cutoff point for the difference in DV between workdays and rest days for diagnosing OA. No previous studies have investigated differences in the ABC score or mean DV across shift types among workers with OA. In healthy working populations cross-shift changes in PEF have been shown to increase over day shifts and decrease over afternoon and night shifts, following normal circadian variation [18–21]. Our study shows similar findings. In a previous study we showed that workers with OA 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 OA [13].

The ABC score is calculated separately for each shift and uses mean 2 h readings from the recording period to identify PEF changes between work and rest in a similar way as in a specific challenge test. Conversely, the Oasys score uses a discriminant analysis to compare differences within each rest-work-rest and work-rest-work period, so this method provides a whole record score, without discrimination between shift types, and does not require any particular magnitude of a PEF difference to diagnose OA. A statistical comparison of measurements at the same time on work and rest days (time point analysis) is also available but confounded by different waking times on different shift patterns when clock time is used. These Oasys outputs each have different minimum data quantity requirements and are complementary, coping with different work patterns and frequencies of recording. When all scores (ABC, Oasys and time point) were required to be positive, previous work has shown a sensitivity of 56%, increasing to 89% if any one of them was positive [22].

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 OA group. For the OA group, methacholine reactivity testing was not always possible within 24 h of work exposure which may have reduced the number of methacholine reactors. Some would argue that without methacholine reactivity and increased DV, some of these workers do not have OA. However, all had latency and a relevant history of symptoms related to exposure, plus work-related changes on their PEF records. It is not possible to differentiate between irritant (with latency) and allergic reactions from PEF records [23]. As work exposure can reduce DV in those with OA (i.e. PEF increases less during the day), we believe that a DV within the normal range should not be used to exclude OA.

We did not have data on the levels of exposure for each shift type, which could have influenced the results.

### Table 3. Sensitivity and specificity of the ABC PEF score from waking time and increased diurnal variation on workdays as compared with rest days for diagnosing OA according to the shift type

<table>
<thead>
<tr>
<th>Shift type</th>
<th>Sensitivity (all OA workers)</th>
<th>Sensitivity (without independent validation of OA)</th>
<th>Sensitivity (independent OA diagnosis)</th>
<th>Specificity (non-OA)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Day</td>
<td>Aft</td>
<td>Night</td>
<td>Day</td>
</tr>
<tr>
<td>% with ABC score ≥15 l/min/h for OA (&lt;15 l/min/h for non-OA)</td>
<td>79</td>
<td>72</td>
<td>83</td>
<td>78</td>
</tr>
<tr>
<td>% with higher DV on work days as compared with rest days for OA (similar or lower DV on work days for non-OA)</td>
<td>76</td>
<td>70</td>
<td>78</td>
<td>77</td>
</tr>
</tbody>
</table>

Aft, afternoon shift.
Many night shift workers are on premises where the level of activity is reduced as compared with 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 but difficult to conduct.

In conclusion, the sensitivity and specificity of the ABC PEF score calculated from waking time are good for diagnosing OA and similar across all three shift types. A cutoff of 15 l/min/h for the ABC score is appropriate for all shift types. Cross-shift changes are significantly different between morning and afternoon or night shifts. A greater DV on workdays as compared with rest days has good sensitivity, but low specificity for all shift types.

Key points
- The area between curves (ABC) score based on serial peak expiratory flow recording used for separating occupational from non-occupational asthma has good sensitivity and specificity with a cut off of 15 l/min/h for day, afternoon and night shift working.
- In workers with occupational asthma the differences between peak expiratory flow on days at and away from work are smaller on afternoon and night shifts than day shifts.
- Cross-shift differences in peak expiratory flow are greater on night and afternoon shifts as compared with day shifts in workers with occupational asthma.

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Conflicts of interest
None declared.

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Why I became an occupational physician...

One year after qualifying in 1972 I was invited to join the staff of a large London church where I worked for 3 years keeping my stethoscope warm in part time General Practice. During that time I founded a Christian professional theatre company which ran for 7 years with a permanent theatre in central London and a touring element performing regularly at the Edinburgh Festival. In returning to medicine, I needed a nine-to-five job in order to continue managing the theatre. Occupational Medicine fitted the bill and although initially boring with routine medicals, a career full of fascination developed. Most companies seem to have been British (Petroleum, Airways and Broadcasting Corporation!)

The patient with the most dangerous job was Al Capone’s driver (before reasonable adjustments came in!).

The most intriguing study was hooking up the BBC Symphony Orchestra members with portable ECG’s in the Royal Festival Hall and matching the ECG output against the complexity of the score. A significant finding was an ergonomic one that the cellists had a marked tachycardia six bars before the trombones behind them were due to come in! The CMO Dr Ann Fingret introduced me to Steve Williams, the first organizational psychologist to develop a validated stress questionnaire assessment and thus my career-long interest in the psychology of the workplace was born.

The most scary moment was presenting to a paying public audience in Central Hall, Westminster, on workplace aspects of migraine.

I have enjoyed a rich variety of workplaces and some seriously helpful mentors. Belonging to a small speciality, I count myself fortunate to have been working with colleagues and friends who are prepared to pioneer unusual areas combining clinical and business expertise. Tropical disease training with British Airways has led to a global perspective with International SOS developing Occupational Health training in a worldwide context. The group (IAPOS) founded 35 years ago by Dr Stanley Browne, world famous leprologist who drew together Chief Medical Officers of global companies, Mission and NGO doctors and tropical disease specialists, has been a particular stimulation.

The need for people with good medical and managerial skills is as great as ever, particularly if they have the courage to make it fun as well. As a speciality we continue to need those who dare to be different and have the courage of their convictions.

Robert Willcox  
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