The diagnosis of occupational asthma from timepoint differences in serial PEF measurements

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keywords
occupational asthma, peak expiratory flow, diagnosis, validation, Oasys

ABSTRACT

Background. The diagnosis of occupational asthma requires objective confirmation. Analysis of serial measurements of Peak Expiratory Flow (PEF) is usually the most convenient first step in the diagnostic process. We describe a new method of analysis originally developed to detect late asthmatic reactions following specific inhalation testing and have applied it to serial PEF measurements made over many days in the workplace, to supplement existing methods of PEF analysis.

Methods. 236 records from workers with independently diagnosed occupational asthma and 320 from asthmatic controls were available. The pooled standard deviation for rest day measurements was obtained from an analysis of variance by time. Work day PEF measurements were meaned into matching 2-hourly time segments. Timepoints with mean workday PEF statistically lower (at the Bonferroni adjusted 5% level) than the rest days were counted, after adjusting for the number of contributing measurements.

Results. A minimum of 4 timepoint comparisons were needed. Records with ≥2 timepoints significantly lower on workdays had a sensitivity of 67% and a specificity of 99% for the diagnosis of occupational asthma against independent diagnoses. Reducing the requirements to ≥1 non-waking timepoint difference increased sensitivity to 77% and reduced specificity to 93%. The analysis was only applicable to 43% of available records, mainly due to differences in waking times on work and rest days.

Conclusion. Timepoint analysis complements other validated methods of PEF analysis for the diagnosis of occupational asthma. It requires shorter records than required for the Oasys score and can identify smaller changes than other methods, but is dependent on low restday PEF variance.

INTRODUCTION

The diagnosis of OA has serious consequences for the affected worker, and the workplace. The diagnosis cannot be safely made from the history alone, which has around 45% false positives.[1;2] All guidelines recommend objective confirmation of the diagnosis with serial measurements of peak expiratory flow (PEF) analysed by a validated method being the most appropriate first step.[3] Once occupational asthma has developed, as in non-occupational asthma, many factors can influence the PEF, including sleep, treatment, exercise, respiratory infections, non-specific irritants and allergen exposures. The difficult part is to separate changes due to work, which are often delayed and cumulative, from those due to other confounding factors. The Oasys computer-based analysis of serial PEF measurements now has three analytical measurements; a discriminant analysis based on plots of daily maximum, mean and minimum PEF (the Oasys score)[4] with a sensitivity of 82% and specificity of 94% for high quality 4-week recordings (but only 70% and 82% respectively for 2-week records).[5] The difference between the mean PEF on workdays and restdays has an upper limit of normal of 16 litres/min,[6] and an analysis comparing the mean hourly PEF on workdays and restdays, the Area Between Curves (ABC) score (so far only validated for day shifts), has sensitivity 69% and specificity 100% for time from waking.[7] If occupational asthma exists, exposure to the cause at usual levels in the workplace must result in worsening asthma and a fall in PEF. There is a need to increase the sensitivity of analysis of serial PEF measurements, which must include the workplace signal for those with current occupational asthma, while reducing the length of records needed.

Specific inhalation testing is generally regarded as the gold standard for the diagnosis of occupational asthma, a positive test is usually defined as one or two measurements following exposure which are 15-20% below those following an appropriate control exposure. Stenton suggested that late asthmatic reactions following a challenge were not an all-or-none phenomenon, and could be identified by statistical methods. [8] They did an elegant series of experiments on 3 workers with occupational asthma to sodium isononanoyl oxybenzene sulphonate (SINOS), three asthmatic and three non-asthmatic controls. Dose-response studies were done with a total of 220 separate SINOS exposure days and 30 control days. They assumed that the variability in FEV_1 measurements was similar on 3 control days and that the standard deviations of 11 hourly measurements could be combined to produce a pooled standard deviation. Each hours FEV_1 measurement following exposure was compared with the mean hourly measurement made on the three control days with a Student's t-test using this pooled standard deviation and adjustments for multiple comparisons. They found that late reactions with FEV_1 falls between 5% and 8% were statistically significant in the three workers with SINOS sensitization. Using a $p<0.05$ for a single hours FEV_1 the false positive rate in the controls was 7%. If two consecutive hourly measurements were required to be below the lower boundary from the pooled control days, false positives were reduced to 1%.

We have tried to reproduce this method using measurements of PEF in the workplace from records collected initially for discriminant analysis using the Oasys software. Our measurements were from real life exposures, PEF measurements were unsupervised and only requested 2-hourly, but generally included many more exposure and control days than the Stenton method. Our aim was to see whether

relatively short-term drops in PEF could be identified which might supplement the other methods of PEF analysis used by Oasys that are weighted in favour of drops in mean daily PEF. We also specifically aimed to determine the sensitivity and specificity of the Stenton method when applied to serial workplace PEF measurements.

METHODS

Study Population

Records were selected from workers presenting to a specialist clinic with symptoms suggestive of occupational asthma who were asked to measure PEF 2-hourly from waking to sleeping for 4 weeks using a variety of PEF meters (with post recording linearization if measured on a non-linear meter). Most records were made on Clement Clarke Mini-Wright meters (where the worker transcribed the PEF results onto record cards), some on Ferraris Piko-1 logging meters, and a small number on other meters. 636 serial PEF records were available from workers investigated between 1980 and 2007 who had an independent diagnosis of occupational asthma or were an asthmatic control. These included (a) 316 serial PEF records from workers diagnosed as having occupational asthma based on independent clinical investigations of either specific inhalation challenge test, four-fold change in methacholine reactivity related to work exposure, or positive specific IgE plus a strong relevant history [occupational asthma positives] and (b) 320 records from patients diagnosed as asthmatics/occupational asthmatics but 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]. PEF measurements in occupational asthma negative records made between 9 am and 5 pm Monday to Friday were analysed as "at work" and compared with readings on Saturday and Sunday that were analysed as "off work". Atopics were defined as those having a positive skin prick test of ≥3mm compared with a saline control to a common non occupational environmental allergen.

Calculation of mean daily PEF

The mean PEF for each 2-hourly period from waking to sleeping was plotted separately for days away from work, and days on day shifts when there were at least 3 days of measurements for each data point. The mode waking time was calculated from all available days with PEF readings. Workers with a greater than 2 hour difference in mode waking time between work and rest days were excluded. Records with few daily readings were not excluded. Other exclusion criteria were records with evidence of upper respiratory tract infection and those with a treatment change or whose mean daily PEF increased or decreased by more than 5 litres/minute/day over the whole record.

Calculation of lower boundary for PEF on days away from work

The pooled standard deviation for all rest day measurements was obtained from an analysis of variance by time. All work day PEF measurements, starting with the first reading at work and continuing to the last reading before work on the next day, were meaned into 2-hourly time segments and tested by calculating a series of test statistics which identified whether the mean workday PEF at any particular time was statistically lower (at the 5% level) than the mean PEF for restdays at the same timepoint, after adjusting for the number of measurements included in each mean value, and the number of comparisons made. The test statistic for each 2-hour timepoint (Tj) $=(Pj-Qj)/s\sqrt{(1/m+1/n)}$ where Tj is the test statistic for 2-hourly timepoint j, Pj is the work day mean PEF at time j, Qj is the mean rest day PEF at time j, n is the number of rest days that contribute to a compared mean 2 hourly timepoint, m is the number of work days that contribute to a compared mean 2 hourly

timepoint and s is the pooled standard deviation. Each Tj was compared with the $0.95^{1/k}$ point of a Student's t distribution with k(n-1) degrees of freedom, k being the number of comparisons (the Bonferroni correction). The graphical equivalent is illustrated in figure 2 showing the mean values for rest day PEF measurements and the lower boundary given by $Pj - s\sqrt{(1/m+1/n)}tk(n-1)(0.95)^{1/k}$. The software within the Oasys program was used to perform the analysis. SPSS v15.0 was used for the demographic statistics.

The number of work day 2-hourly timepoints showing significant reductions compared with rest day measurements and the total number of timepoints available for comparison were recorded.

The records were also analysed using previous methods of analysis. The Oasys score is a discriminant analysis based on plots of daily maximum, mean and minimum PEF, a positive score is >2.5.[4] The Area Between Curves (ABC) score uses similar plots of the mean hourly PEF to the timepoint analysis, but interpolates missing times within the waking day, and calculates the area between the work and rest curves from waking; a positive record has a score ≥15 litres/min/hour.[7] The difference between the mean PEF on workdays and restdays has an upper limit of normal of 16 litres/min.[6] All methods use the day interpreter, which starts each “day” with the first reading at work, and continues to the last before work on the next day.[9]

RESULTS

316 records were identified from workers with an independent diagnosis of occupational asthma. After limiting the data to the first 2 records/worker, 236 remained. Ten were then removed for respiratory infections, and eight for excessive deterioration or improvement during the record. 34 records had <3 day shifts or <3 rest days and a further 83 had mode waking times >2 hours different on rest days from work days leaving 101 records for evaluation (43% of possible records). Workers woke up 65 minutes later on days off than on day shift days. This was reduced to 37 minutes after excluding patients with a > 2 hour mode difference.

The demographics of the workers and their PEF records selected are shown in table 1. The principal differences were in the occupational elements of the peak flow records. The control asthmatics were older (as many had previously been diagnosed with occupational asthma and were now unemployed), they had similar severity as measured by FEV_1 and need for treatment, and were somewhat less methacholine reactive in keeping with removal from exposure to the causative agent. The quality of the PEF record in terms of numbers of readings a day and the duration of the record was similar in both groups.

Table 1. Demographic data on workers and records included in the analysis.
SD = standard deviation, PEF = Peak Expiratory Flow, FEV_1 = Forced Expiratory Volume in 1 second, ABC = Area Between Curves. [7] The denominator is number of workers for the personal data and number of records for the peak flow data.

	Occupational asthma Positive (101 records from 84 workers)	**Occupational asthma Negative (188 records from 173 patients)**	**P value**
Mean age (SD)	46.1 (9.7)	51.1 (9.6)	<0.001
% males	49.2	60.1	0.136
% atopics	56.1	50.0	0.431
% current smokers	20.0	20.0	0.874
% methacholine reactive (<2000µg)	72.5	40.9	<0.005
% taking Inhaled Cortico Steroids	77.1	83.9	0.284
Mean FEV_1 % predicted (SD)	80.3 (27.0)	84.6 (22.4)	0.950
Mean diurnal PEF variation (SD)	23.4 (14.3)	16.8 (11.7)	0.116
Mean ABC from waking time (Litres/Min/Hour) (SD)	30.7 (32.3)	-0.4 (6.5)	<0.001
Mean number of rest days (SD)	14.2 (7.8)	13.9 (12.0)	0.816
Mean number of day shift days (SD)	16.4 (9.6)	15.1 (11.5)	0.087
Mean number of readings per day (SD)	7.1 (1.8)	6.7 (2.5)	0.135
Mean Oasys-2 score (SD)	3.0 (0.8)	1.3 (0.9)	<0.001
Mean work day-rest day PEF (SD)	27.9 (31.0)	-0.2 (5.8)	<0.001

Table 2 shows the causative agents for the occupational asthma group and the methods for independent confirmation of the diagnosis of occupational asthma. The group was weighted in favour of low molecular weight agents and work in engineering, reflecting the industry in the West Midlands, UK.

Table 2. Occupational asthma group, causes and method of independent diagnosis

NSBR = non-specific bronchial reactivity, a fourfold change was needed between work and rest periods for inclusion.

Causes		Occupational asthma group (%)
High Molecular Weight Agents		
	Total	21
	Latex	7
	Flour	5
	Enzymes	6
	Other	3
Low Molecular Weight Agents		
	Total	79
	Cleaning Agents	17
	Isocyanates	18
	Solder flux flume	8
	Metal working fluid	7
	Metals	5
	Adhesives	7
	Other	17
Methods of Independent Diagnosis		
Challenge Positive		59
Asthma + IgE +History alone		26
NSBR x 4 alone		15

Minimum data quantity

93/101 occupational asthma records and 162/188 of the control asthmatics had sufficient data on both work and rest days for comparison of at least 4 timepoints. Of these 77% of gold standard positives had ≥1 timepoint significantly worse on workdays and 67% had ≥2, 12% of the gold standard negatives had ≥1 timepoint significantly worse on the "work" days and 1% had ≥2. Further analysis was confined to those with data of at least 4 common timepoints.

Sensitivity and specificity with ≥4 timepoint comparisons available for analysis

67% of workers with occupational asthma had at least two significant timepoints with lower readings on work days, specificity was 99%. The requirement for only one significant time-point difference increased sensitivity and reduced specificity each by around 10%. Visual analysis of false positive records found significant differences for the waking reading alone was the most common reason for a false positive assessment, and was sometimes due to somewhat later waking times on rest days. A repeat analysis requiring only one significant timepoint difference excluding the waking reading increased the specificity from 88% to 93% for records with at least 4

timepoints for comparison and did not alter sensitivity at 77% (figure 1). If this is confined to one record per patient the sensitivity is 74%. The mean drop required for a timepoint to be significant was 23 l/m (sd 13) for the negative records and 29l/min (sd 21) for the positives. The higher value for the positives suggests the presence of carry over effects from exposed days to following rest days in the positive group.

Visual inspection of false negative records identified high variability on rest days as a common finding.

Comparison of the timepoint analysis with the Area Between Curves (ABC) and Oasys scores

These were done on all records that had at least 4 comparisons for the timepoint score. 27 records did not fulfill the quality criteria for an optimal Oasys score, which requires longer records. The quality requirements for the ABC and timepoint analysis are similar. The results are shown in figure 1. All methods of analysis were positive in 56% of the records from occupational asthmatics. The timepoint analysis increased the sensitivity above the other methods to 77%. There was some reduction of specificity to 93%.

DISCUSSION

We have treated serial measurements of PEF over many days in the workplace in a similar manner to the analysis of specific inhalation challenges, and shown that a statistical method designed to detect late asthmatic reactions has a sensitivity of 67% and a specificity of 99% when there were at least 2 timepoints with significant work day deterioration and at least four timepoints for comparison. The sensitivity increased to 77% if only one significant difference was required, at the expense of reducing specificity by about 10%. This could be reduced if the waking timepoint was excluded. Exclusion of records with confounding factors, particularly differences in waking times between work days and days off, made this analysis suitable for only 101/236 existing records from workers with independently diagnosed occupational asthma. This could be improved if records were collected with timepoint analysis in mind.

Changes in PEF due to circadian variation are seen in nearly all asthmatics, with a nadir around waking and an acrophase (the time at which the peak of a rhythm occurs) 4-12 hours later. Workplace exposure is superimposed on this. The present analysis is only for day shift work, as differences in waking time have major influences on across-shift changes in lung function.[10;11] Workers often wake later on days away from work confounding analysis, in the present study we required modal waking times to be within 2 hours on work and rest days, even with this requirement there was evidence that slightly later waking times on weekends increased waking PEF sufficiently to account for some false positive results in the control asthmatics.

It was assumed that the variability of work day PEF measurements were similar and that the standard deviations of the 2 hourly rest day PEF measurements could be combined to provide a pooled standard deviation. This method has been validated in the analysis of late asthmatic reactions following specific inhalation challenge testing.[8] The ability to detect significant differences between work and rest days requires a reasonably low variance for rest-day PEF. We excluded records with upper respiratory infections, when time off work (with infection) often shows reduced readings. We also excluded records which showed significant day-by-day increase or decreases in PEF, as may occur after starting (or stopping) prophylactic asthma treatments. The original Stenton method only used values on control days between 12:00 and 22:00. This excludes any morning dip and is likely to reduce the rest day variance. We have calculated our rest day variance on all available measurements throughout the 24 hours, which is likely to be more confounded by carry over effects. The finding of more than 5% positive timepoints in control subjects does suggest that the statistical method is underestimating variance at individual timepoints. Nevertheless the sensitivity and specificity of the results remains valid. Despite this the main reason for a negative test in those in whom the Oasys score was positive was increased variability in rest-day PEF readings. This is likely to be a limitation of this method of analysis.

Validating a new test requires a “gold standard” with which to make comparison. Our control asthmatic group were all asthmatic, providing many of the confounding factors seen in workers with occupational asthma, but were not at work (at least they said they were not at work). By constructing artificial work-periods from 9am to 5pm

Mondays to Fridays, many of the confounding exposures common to weekends were included. Most recognise specific inhalation testing as the gold standard for occupational asthma. However these may be falsely negative in up to 29% of those with genuine occupational asthma, and more than this if asthma has otherwise been confirmed.[12] We have been reluctant to do specific challenges when there is no evidence of any effect of usual work exposure from serial PEF measurements, as it is then very difficult to interpret the significance of any challenge positive results. Other recommended methods of validating occupational asthma include significant improvement in non-specific reactivity between periods at and away from work. These are less sensitive and specific than challenge testing,[1] but we have included this method of validation which is particularly useful for more severe occupational asthma where there are multiple and difficult to reproduce agents in the workplace, such as welding fume. The role of specific challenge is less clear in exposures to high molecular weight agents such as enzymes and rodent urine, where a good clinical history, the objective confirmation of asthma and the finding of specific IgE to the enzyme or rodent urine is usually considered enough to confirm the diagnosis.[13] As we do not usually perform specific challenges when the above data is clear, we have included them in the group with independently validated occupational asthma. The peak flow records themselves were not accessed when the independent diagnosis of occupational asthma was made.

The Oasys software provides summary plots of PEF data including the daily maximum, mean and minimum PEF, separated by work shift and exposure, and plots of the mean hourly PEF from waking (or by clock time) separated by exposures and shifts. This aids expert interpretation. However as not all experts agree on the diagnosis of occupational asthma from PEF plots,[14;15] reproducible methods of analysis are required. The original Oasys score, based on a discriminant analysis of work-rest-work complexes, or their counterpart rest-work-rest complexes, has a sensitivity of 82% and a specificity of 94% for 4-week records with at least 4 readings per day.[5] It requires longer periods of readings than other methods, but is tolerant of missing and mistimed readings. The ABC score requires at least 8 readings/day, but only 8 workdays and 3 restdays.[16] It has a sensitivity of 68% and a specificity of 91% using the same patient groups as the present study. None of the methods use diurnal variation or changes in diurnal variation in their calculations. Changes in diurnal variation between work and restdays discriminate poorly between those with and without occupational asthma and are not included in any of the validated methods of analysis.[11]

Most of the PEF readings used in the present study were made on manual meters and transcribed onto record cards by the worker. Several investigators have found significant discrepancies between hand transcribed and logged PEF readings.[17] Although some of the differences may be due to the logging meter software (such as overwriting readings made within one hour and incorrect setting of the logging meter clock), there is evidence of prefabrication for a significant proportion of readings. All the methods described above include any prefabricated readings, which we have found are usually recorded as average readings for the particular patient, rather than outliers, which would have a larger effect on interpretation.[18] The original Oasys score is tolerant of mistimed readings, however the ABC and timepoint analyses depend on accurate timings and should be considerably improved using datalogged recordings from reliable meters.

The diagnosis of occupational asthma from serial PEF measurements has been slow to gain widespread acceptance.[19] We hope that the addition of timepoint analysis, which is based on methods used for specific inhalation challenge testing, and its validation in the workplace, will help skeptics. Occupational asthma is currently widely under diagnosed, at least in part from the lack of specialist expertise. The analysis of serial PEF measurements is more sensitive and specific than any other externally validated method of diagnosis, including those based on non-specific reactivity,[1] and is suitable for use outside specialist centres. A positive analysis is the start of further investigation, it does not usually identify the cause of occupational asthma, but can be used to confirm successful relocation as its specificity is high.

Figure 1. Comparison of the timepoint analysis with previous methods of PEF analysis. For the Oasys score (from a discriminant analysis) an occupational asthma positive score was >2.5, and for the ABC (area between the curves) a positive score was ≥15 litres/min/hour. Timepoint analysis for ≥1 timepoint significantly worse on workdays, excluding the waking reading.

Figure 2

The lower boundary represents the level at each 2-hourly timepoint that must be crossed for a decrement in day shift PEF to be significant at the 5% level (grey line with square markers). It runs parallel to the mean rest day plot (black line with square markers). The dotted part of the lower boundary, where there are not enough rest readings for a comparison, is not used. The same applies to work days where there are not enough day shift readings. The black line with cross markers shows the mean PEF on work days that are below the grey line at 8.30-10.30 and 12.30-14.30. The number of readings contributing to each work and restday mean are recorded below the time. The lowest row of numbers shows the area between the mean rest and work day plots which are summed to produce the ABC score, here 6 litres/min/hour (a value ≥15 is needed for an ABC score to identify occupational asthma). The times at work have a shaded background. This lady worked with printing inks and laminates containing isocyanates. A second PEF record the next year showed larger work-related changes with a positive Oasys score of 3.0, and a positive ABC score of 19 litres/min/hour. Following removal from exposure all scores were negative when measurements made between 9 am and 5 pm Monday to Friday were analysed as “at work”.

CONFLICTS OF INTEREST
None declared.

FUNDING
PhD fellowship for Vicky Moore from the COLT Foundation.

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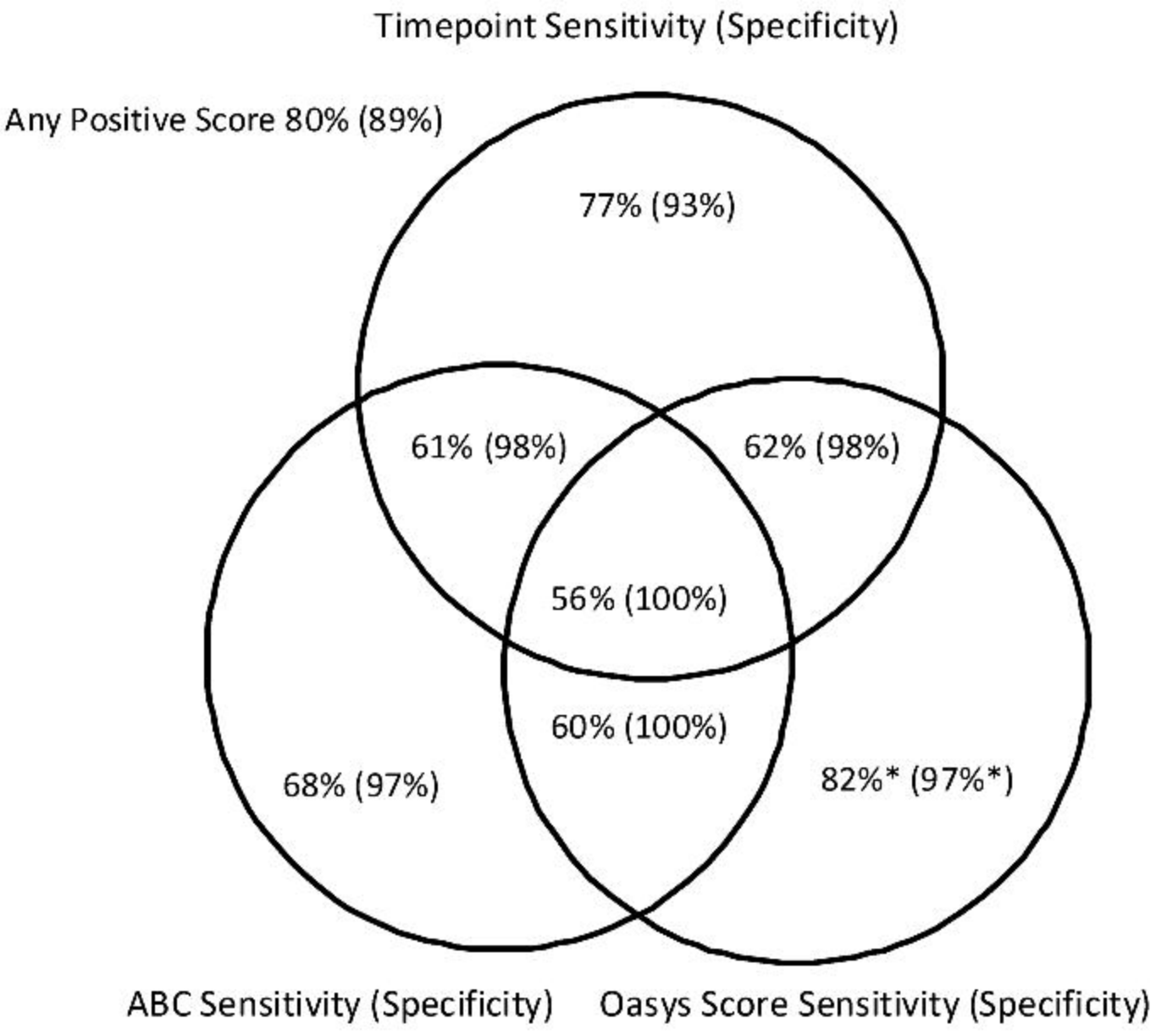
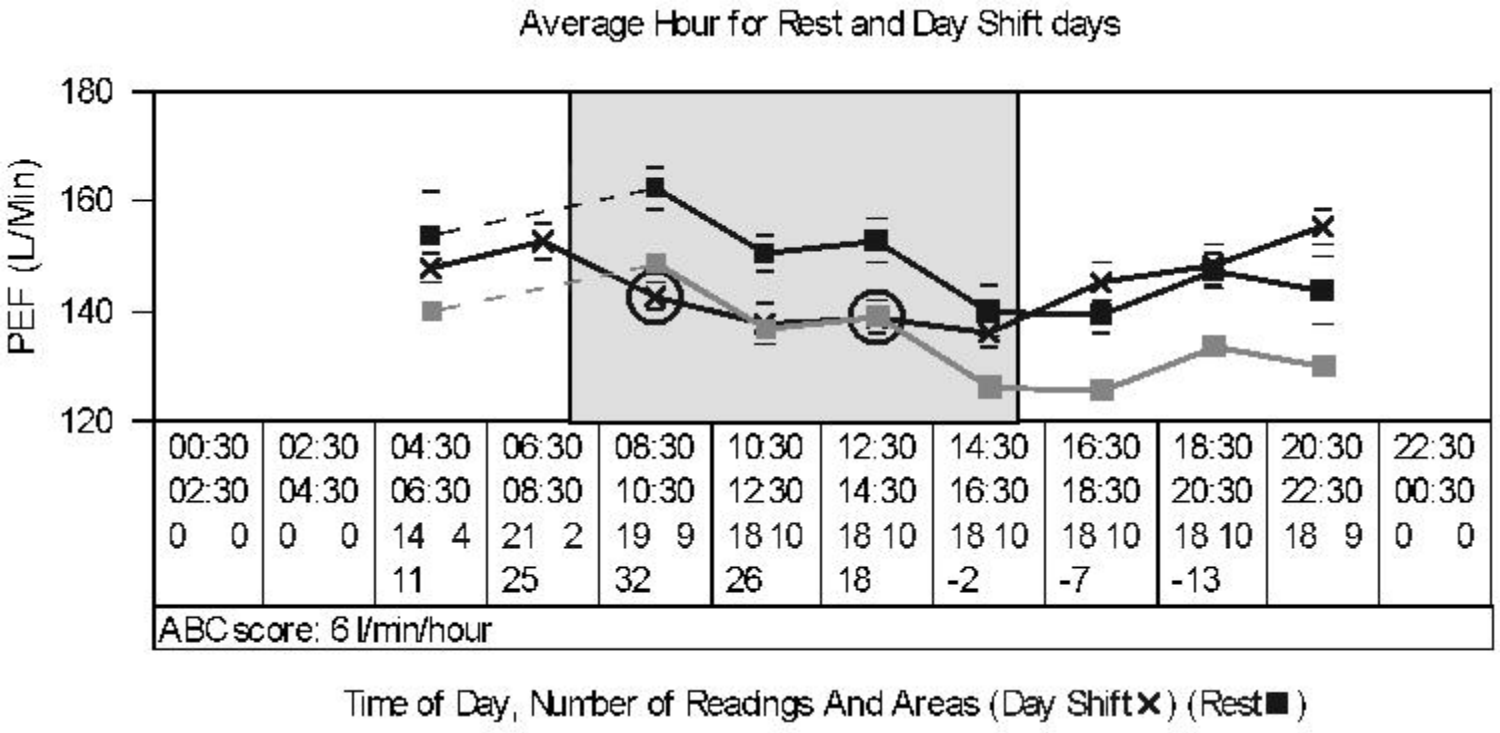


*These values are for records with optimal quality for analysis by Oasys only.
N= 66 (139)


Average Hour for Rest and Day Shift days
PEF (L/Min)
180
160
140
120
00:30 02:30 0 0
02:30 04:30 0 0
04:30 06:30 14 4 11
06:30 08:30 21 2 25
08:30 10:30 19 9 32
10:30 12:30 18 10 26
12:30 14:30 18 10 18
14:30 16:30 18 10 -2
16:30 18:30 18 10 -7
18:30 20:30 18 10 -13
20:30 22:30 18 9
22:30 00:30 0 0
ABC score: 6 l/min/hour
Time of Day, Number of Readings And Areas (Day Shift ×) (Rest ■)