Night-to-night variability of obstructive sleep apnoea

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Take home message

OSA is variable from night-to-night thus questioning single-night sleep studies for diagnosis and exclusion of OSA.

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Abstract

In current clinical practice, diagnosis and exclusion of obstructive sleep apnoea (OSA) is based on a single sleep study. The aim of this study was to assess night-to-night variability of OSA to evaluate the current practice.

77 patients previously diagnosed with OSA randomised to continuous positive airway pressure (CPAP) withdrawal within four trials performed nightly pulse oximetry over two weeks off CPAP. The main outcome of interest was the coefficient of variation (CV) of the oxygen desaturation index (ODI) as marker of night-to-night variability in OSA. OSA was categorised according to conventional thresholds using ODI (no OSA: <5/h, mild 5-15/h, moderate 15-30/h and severe OSA >30/h).

High night-to-night variability of OSA was evidenced by a CV of ODI of 31.1% (SD16.5). Differences in ODI >10/h between nights were found in 84.4% and shifts in OSA severity stages in 77.9% of patients. The probability of missing moderate OSA in a random night was up to 60%. Variability was higher in less severe OSA.

OSA shows a considerable night-to-night variability. Single-night diagnostic sleep studies are prone to misdiagnose OSA. Thus, treatment decisions should possibly be based on prolonged sleep studies, especially in less severe OSA or minimally-symptomatic patients.

Clinical trial registration

www.controlled-trials.com (ISRCTN 93153804, ISRCTN 73047833) and www.clinicaltrials.gov (NCT01332175 & NCT02050425).

Introduction

Obstructive sleep apnoea (OSA) is a common sleep-related breathing disorder with an estimated prevalence of symptomatic OSA of 2-4 % of the adult population in Western countries that has substantially increased during the last two decades and a considerable percentage of the population seems to be affected but not diagnosed [1-3].

As a disease entity, OSA is characterised by repetitive obstructions of the upper airway during sleep, resulting in apnoeas and hypopnoeas, causing oxygen desaturation, increased inspiratory effort, brief arousals and sleep disturbances [4, 5]. As a consequence, untreated patients suffer from daytime sleepiness, an increased risk of motor vehicle accidents, cardiovascular disease, and an impaired quality of life [5-7]. Currently, the gold-standard diagnostic test for OSA is in-laboratory polysomnography (PSG) [8]. This method has high diagnostic accuracy, but it is relatively costly, time-consuming and technically complex [9, 10]. Alternatively, in patients with a high pre-test probability for moderate-to-severe OSA based on clinical evaluation and no relevant comorbidity, portable home devices can be utilized with sufficient accuracy [9]. Also overnight pulse oximetry is an appealing method to diagnose OSA, because of its widespread availability and accurate estimation of OSA severity[11].

The current guidelines recommend a single full-night in-laboratory sleep study for diagnosis of OSA with a threshold >15 obstructive events/hour of sleep or >5 obstructive events/hour plus clinical symptoms to diagnose OSA [12]. Single testing requires high sensitivity of the test method and a stable disease of interest to warrant a low rate of false negative tests. The current guidelines presuppose that the number of obstructive events is consistent on consecutive nights. However, considerable variability on repeated measurements has been found [13, 14]. Especially in patients with mild OSA, night-to-night variability may lead to misdiagnosis, as there are often false negative sleep studies in such patients [15]. A factor proposed to be accountable for varying scores of the apnoea-hypopnoea-index (AHI) is the first night-effect due to a lower total sleep time, a reduction in quantity of rapid eye movement (REM) sleep, more intermittent wake time and longer REMs latency in the first night of in-laboratory polysomnography [16, 17]. However, studies observing more than two consecutive nights show sustained intra-individual alterations of OSA severity with only consistent mean values in the overall study population [18, 19]. As previous studies were limited by small study populations and study durations of only a few sequential nights, the aim of our study was to assess night-to-night variability of disease severity in patients with known OSA using nocturnal oximetry in an

accustomed environment over two weeks to assess the reliability of the current practice of diagnosing OSA based on sleep monitoring for one night only.

Methods

Trial Design and Intervention

Patients with OSA established on CPAP took part in one of four parallel-group randomised controlled continuous positive airway pressure (CPAP) withdrawal trials. They were randomly assigned to either continue therapeutic CPAP or to withdraw CPAP (subtherapeutic CPAP or non-therapeutic nasal expiratory positive airway pressure (EPAP) device) after a baseline in-laboratory sleep study on therapeutic CPAP [20-23]. Patients performed nightly pulse oximetry before returning for a follow-up in-laboratory sleep study at two weeks. For more detail please see online supplementary.

Randomisation and Blinding

Methods of randomisation and blinding have previously been reported [20-23].

Participants

197 patients previously diagnosed with OSA and effectively treated with CPAP participating in four randomised controlled CPAP-withdrawal trials [20-23] were randomly assigned to either continue therapeutic CPAP (n=88) or to withdraw CPAP (n=109) by either a sham-CPAP-device (60%) or an ineffective nasal EPAP-device (40%) depending on the specific protocol. The difference in the participant numbers between the two arms is due to three treatment groups (two of which correspond to a CPAP therapy withdrawal) in one of the original trials [21]. Patients allocated to CPAP-withdrawal and thus having a recurrence of OSA were analysed. Eligibility criteria are given in the online supplementary.

Outcomes

The main outcome of interest was the coefficient of variation (CV) of the oxygen desaturation index (≥4% dips/hour) as measure of variability of OSA severity during two weeks of CPAP-withdrawal.

Other outcomes of interest were the change in OSA severity categories according to conventional ODI-thresholds (no OSA: <5/h, mild OSA: 5-15/h, moderate OSA: 15-30/h, severe OSA: >30/h) between different nights, maximal differences in ODI between nights, probability of misdiagnosis of OSA, potential predictors of night-to-night variability of OSA, and the CV of the pulse rise-index

(>6/min) as a marker of arousals. The first night of CPAP-withdrawal was excluded from the analysis, taking into account the time needed for a complete recurrence of OSA [20].

Measurements

Nightly pulse oximetry was performed using a wrist-worn finger pulse oximeter (Pulsox-300i, Konica-Minolta-Sensing Inc, Osaka, Japan) or ResLink (ResMed-Corp, San Diego, CA, USA) at home. Patients were instructed to activate the pulse oximeter together with the sham-device for OSA treatment at the time of going to sleep each night of the two-week study period. For further details see online supplementary.

Statistical Methods

Results are shown as mean with standard deviation unless otherwise stated. The coefficient of variation (CV) of the ODI from day two to day thirteen of CPAP withdrawal was calculated in each participant. Patients were categorized as having no (ODI <5/h), mild (≥5/h ODI <15/h), moderate (≥15/h ODI <30/h), or severe OSA (ODI ≥30/h) depending on their mean, highest and lowest ODI during the study period.

Univariate and multivariate regression analysis was used to investigate associations between the coefficient of variation of ODI and possible predictors of night-to-night variability. The probability of underdiagnosing moderate or severe OSA (mean ODI <15/h) based on a single-night oximetry was calculated. For detailed statistical methods see online supplementary.

Statistical analysis was performed with STATA 14 (StataCorp, College Station, TX, USA).

Results

Participants

Within the original RCTs, 109 previously optimally CPAP-adherent OSA patients were randomised to CPAP-withdrawal. Four patients dropped out of the study and 28 patients did not perform nocturnal pulse oximetry on a nightly basis during the two-week study period. Thus complete pulse oximetry data over the study period were available from 77 patients. These 77 patients entered the final analysis. The patient flow is shown in **figure 1**. Baseline characteristics of the participants are shown in **table 1**.

Table 1. Patient characteristics.

	n = 77
Age, years	62.6 (9.4)
Gender (M/F)	65/12
BMI at baseline, kg/m^2	33.8 (6.1)
Neck circumference, cm	44.4 (3.9)
Never smoker, n (%)	33 (42.9)
Current smoker, n (%)	9 (11.7)
Former smoker, n (%)	35 (45.4)
Hypertension, n (%)	58 (75.3)
Diabetes, n (%)	16 (20.8)
Dyslipidaemia, n (%)	31 (40.3)
Coronary artery disease, n (%)	10 (13.0)
AHI at diagnosis, events/h	41.5 (20.1)
ODI at diagnosis, events/h	37.0 (18.4)
ODI off CPAP in pre-trial screening, events/h	29.7 (15.8)
ESS at diagnosis	14.0 (3.1)
Mean number of nights of pulse oximetry during study period	12 (1.8)

Data are presented as mean (standard deviation) unless otherwise mentioned. CPAP = continuous positive airway pressure. BMI = body mass-index. AHI = apnoea-hypopnoea-index. ODI = oxygen-desaturation-index. ESS = Epworth Sleepiness Scale (max. 24 points).

Course of ODI during two weeks

Patients underwent nocturnal pulse oximetry for 13 nights of CPAP-withdrawal. Mean ODI at baseline on CPAP was 3.5 (4.4). In response to CPAP-withdrawal, the ODI (group mean) increased to 22.1/h (17.4) on day 1 and plateaued thereafter as shown in **e-figure 1**. A full return of OSA was therefore assumed on the second night of therapy-withdrawal and night-to-night variability was analysed from day 2-13 of CPAP-withdrawal. **E-figure 2** exemplarily shows the ODI over the study period in four different patients.

Night-to-night-variability in ODI

A considerable night-to-night variability in OSA severity throughout the study period was found. The coefficient of variation (CV) of ODI was 31.1% (16.5) as shown in **table 2** and visualised in **e-figure 3**.

Table 2. Spread of the coefficient of variation of ODI.

	CV	**log CV**
Mean (Standard deviation)	31.1 (16.5)	3.3 (0.5)
Minimum / Maximum	8.7 / 89.4	2.2 / 4.5
Median (interquartile range)	28.0 (21.9 – 37.8)	3.3 (3.1 – 3.6)

When categorizing OSA severity depending on the patients' highest and lowest ODI throughout the study period, 78% of patients switched between clinical categories of OSA severity. Only 22% of participants remained in the same category throughout the study period, while 52% changed by one category, 25% changed to the extent of two categories and one participant even switched between three categories (no vs. severe OSA). When using the highest ODI during the study period, 62% of patients were diagnosed with severe OSA, whereas only 16% of patients had severe OSA, if the night with the lowest ODI was considered (**figure 2**). Maximal individual differences in ODI between nights are illustrated in **figure 3**. 62.3% of participants had maximal differences in ODI between different nights of 10-30/h. A difference of less than 10/h between nights was observed in only 15.6% of patients.

Clinical predictors of night-to-night variability

In univariate regression analysis, ODI off CPAP in the pre-trial screening, ODI at diagnosis and body mass index (BMI) on the day of the baseline sleep study showed a statistically significant negative association with the log coefficient of variation (**e-table 1**). Multivariable regression analysis including BMI and ODI off CPAP from the pre-trial screening showed an independent negative association between OSA severity and night-to-night variability (**table 3**). However the model explained the variability only to a small amount.

Table 3. Predictors of the log coefficient of variation of ODI (multivariate regression).

	β	95% confidence interval	*p* - value
BMI	-0.09	-0.03/0.01	0.180
ODI off CPAP pre-trial screening	-0.25	-0.02/-0.00	***0.024***

BMI: body-mass-index; ODI: oxygen desaturation index. $R^2 = 0.1210$.

The ODI at diagnosis was removed from the model due to a high interrelationship with ODI off CPAP from the pre-trial screening ($r=0.56$, $p<0.001$). Residual analysis of the final model did not display any violation of the regression assumptions. OSA severity remained a statistically significant negative predictor of night-to-night-variability after correcting for age and gender.

Probability of underestimating the severity of OSA

The probability of measuring an ODI <15/h in at least one night in patients with moderate or severe OSA (ODI >15/h) based on mean ODI over two weeks was estimated to be up to 60% in patients with moderate OSA and up to 10% in patients with a severe OSA (**figure 4**). Only patients with a mean ODI >40/h were consistently diagnosed each night with at least moderate OSA (ODI >15/h).

Pulse rise-index

Data on nocturnal pulse rise-indices (>6/min) as surrogate marker for arousals were available in 44 participants (57%). The CV of the pulse rise-index was 23.1% (SD 8.4) compared to the CV of ODI of 28.6% (SD 14.3) over the study period in the same subgroup of patients.

Discussion

Two weeks of repeated nocturnal pulse oximetry in patients with OSA during CPAP therapy withdrawal have demonstrated considerable and sustained night-to-night variability of OSA to a considerable and possibly clinically relevant amount as evidenced by a coefficient of variation of ODI of >30%. OSA of moderate severity was missed with a probability of up to 60% in at least one night of repeated nocturnal oximetry and a difference in ODI >10/h between nights was found in 84% of patients with OSA. Only 22% of participants – primarily patients with severe OSA – did not change severity group, whereas more than three quarters of patients switched between conventional severity-categories. This is the first study on night-to-night variability of OSA over a period of two weeks thus providing new insight into the night-to-night variability of OSA. The findings of our study implicate the necessity to reconsider current diagnostic algorithms and treatment decisions in patients with OSA as well as of conventional severity thresholds of OSA.

The findings of a high night-to-night variability in OSA in this study may be generalized to other patients with OSA since we included a wide range of OSA severity (ODI at diagnosis 11-103/h), age (33-77 years) and BMI (23-55 kg/m2), and may be expected to be even higher in patients with comorbidities not present in the current study population, e.g. patients with heart failure or obesity hypoventilation syndrome. Regression analysis of clinical characteristics revealed that the night-to-night variability seems to be rather unpredictable. However, patients with mild OSA seem to have a higher night-to-night variability than patients with severe OSA. This leads to the conclusion that single-night diagnostic sleep studies are prone to miss OSA in patients with milder disease and that repeated measurements, e.g. using a level III sleep study over one week, will help to improve diagnostic accuracy and thus treatment decision making.

Two to three nights of repeated sleep studies in different patient populations have previously demonstrated differences in measures of sleep apnoea severity such as apnoea-hypopnoea-index (AHI) or ODI, but to a lesser extent [14, 15, 18]. The percentage of patients with a change in AHI of >10/h in a repeated sleep study was reported to be 12-65% [13, 14, 18, 19, 24]. However, these studies were limited by the relatively low number of repetitive sleep studies as none of those was based on more than four sleep studies. Other authors also reported categorical changes in 40-50% of patients during two to four nights of sleep monitoring [19, 25, 26]. Severity category changes between

no/mild and moderate OSA (AHI or ODI ≥15/h) seem clinically relevant as in some centres patients with mild disease are less likely to be treated. However, treatment decisions are mainly based on symptoms, thus making disease severity based on sleep studies in cases of proven OSA less relevant. However, the high possibility of a false negative sleep study in cases of suspected OSA has to be kept in mind. In our study population, the possibility of an ODI <15/h in a random night was up to 60% in patients with moderate OSA (ODI 15-30/h) and up to 10% in patients with severe OSA (ODI >30/h) based on the mean ODI over 12 nights, respectively. Only patients with a mean ODI >40/h over two weeks were categorised as having at least moderate OSA (ODI <15/h) in each individual night. In comparison to previous studies, our findings show a higher probability of underestimating OSA. Other authors stated that 16-20% of patients would not have received CPAP treatment based on a single-night sleep study but were recommended treatment as a consequence of one to three repeated sleep studies [24, 25, 27]. Comparing the distribution of OSA severity categories between the night with the lowest and the highest ODI in this study, the percentage of patients diagnosed with moderate to severe OSA doubled from 44% to 87%, or in other words, the percentage of patients diagnosed with no/only mild OSA decreased from 56% to 13%. A lower variability in AHI was reported in the largest study on variability of sleep-disordered breathing based on three consecutive nights of portable home sleep monitoring with only 10% of patients changing between no/mild and moderate OSA [28]. When using the same approach and analysing only the first three nights in the current study, 18.2% of patients changed category based on a threshold of ODI of 15/h, compared to 42.9% when including 12 nights. In accordance with our finding, Le Bon et al.[16] and Ward et al.[29] reported a higher variability in AHI in mild to moderate compared to severe OSA.

OSA seems to be highly variable from night to night. This may be pathophysiologically explained by the nature of OSA. Most patients show alternating episodes of stable breathing and episodes of obstructive apnoeas and hypopnoeas during the course of a night. Baseline upper airway dilator tone and the effectiveness of mechanisms counteracting upper airway collapse vary during sleep [30]. The most important influencing factors are sleep stage and sleep position, whereby supine position and REM sleep facilitate upper airway collapse [30-32]. Other factors that influence OSA severity are the intake of alcohol and sedatives [24]. It may be assumed that the ratio of our participants' sleep positions and sleep stages differed between nights, therefore, affecting the severity of OSA each night

differently. However, to our knowledge, there is no reliable data on the variability of sleep positions and stages over several nights.

The current study has some limitations. Since we did not use polysomnography, the impact of sleep stage and position on OSA remains speculative. However, nocturnal finger pulse oximetry is suitable to study the natural course of disease severity in patients with known OSA due to minimal interference with sleep quality in patients' home environment compared to a level I or in-laboratory sleep study. To directly assess arousals, a polysomnogram is needed. However, analysis of the pulse rise index as surrogate marker of arousals in a subset of patients found a similar variability as in oxygen-desaturation index indicating that not only intermittent hypoxia but probably also sleep fragmentation varies highly from night to night in OSA. A potential limitation is that there was no restriction of alcohol or sedative drugs for participants during the study period. Furthermore, the use of a sham-CPAP or an ineffective nasal device in patients on CPAP withdrawal might have influenced sleep quality. But there was no difference in night-to-night variability of OSA between groups using different subtherapeutic devices. Whether CPAP withdrawal leads to variability in OSA that will be washed-out over time is unknown. However, we found no difference in OSA variability between the first and the second week of CPAP-withdrawal (mean difference=1.6%, p=0.4 from paired t-test).

This study's findings have important clinical implications. A single-night level I sleep study is currently the gold standard for evaluating patients with suspicion of sleep-disordered breathing. Generally, OSA is confirmed in case of an AHI >15/h or an AHI >5/h plus typical symptoms [12]. The high possibility of measuring an ODI <15/h in a random night in patients with a mean ODI >15/h over the study period makes the current practice questionable. Patients potentially benefiting from OSA treatment might be missed, or a less effective alternative treatment to CPAP such as a mandibular advancement device might be offered to patients with supposed mild OSA actually suffering from severe OSA. The results of this study imply the usage of repeated sleep studies in diagnostic algorithms in case of a negative sleep study in patients with high suspicion of OSA. Repeated measurements increase diagnostic accuracy and thus allow more accurate treatment recommendations in patients with OSA.

Awareness of a high night-to-night variability of OSA is not only important for daily clinical practice but also for research, especially when comparing treatments or testing novel therapy devices. In interventional clinical trials, a high level of outcome measurement repeatability is required. OSA

variability or instability must be considered for participant inclusion (OSA severity), study design (single vs. repeated sleep studies) and sample size estimation (standard deviation of AHI or ODI). Despite a more or less stable mean OSA severity in a study population, a high individual night-to-night variability has to be taken into account.

Conclusions

OSA severity seems to be considerably variable from night to night. Single-night diagnostic sleep studies are prone to misestimate the true severity of OSA. Thus, treatment decisions should possibly be based on prolonged sleep studies, especially in milder OSA and in minimally symptomatic patients as these patients might also benefit from treatment of OSA.

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Figure Captions

Figure 1. Patient flow.

Figure 2. Distributions of obstructive sleep apnoea (OSA) severity based on the individual highest and lowest OSA severity category during the two-week study period (n = 77). ODI <5/h: no OSA; ODI 5-15/h: mild OSA; ODI 15-30/h: moderate OSA; ODI >30/h: severe OSA.

Figure 3. Variation of difference in ODI (events/hour) between the night with the lowest ODI and the night with the highest ODI in the patients.

Figure 4. Probability of misdiagnosing OSA based on a random night in different categories of OSA severity. Vertical dashed lines indicate ODI-thresholds of 5/h, 15/h and 30/h.

Figure 1

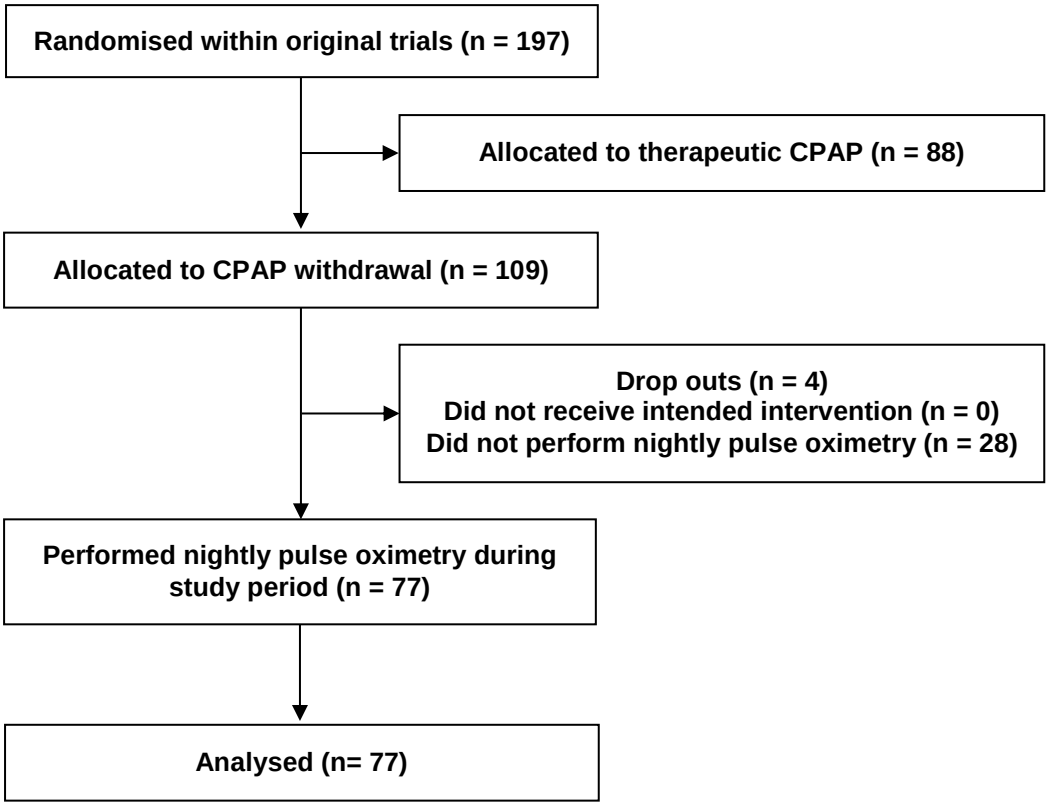

Randomised within original trials (n = 197)
Allocated to therapeutic CPAP (n = 88)
Allocated to CPAP withdrawal (n = 109)
Drop outs (n = 4)
Did not receive intended intervention (n = 0)
Did not perform nightly pulse oximetry (n = 28)
Performed nightly pulse oximetry during study period (n = 77)
Analysed (n= 77)

Figure 2

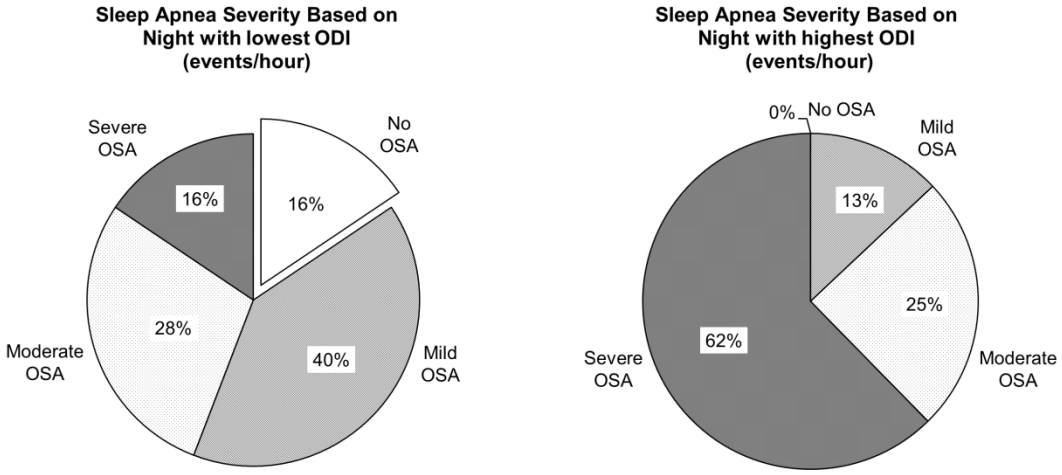

Sleep Apnea Severity Based on Night with lowest ODI (events/hour)
Severe OSA
No OSA
16%
16%
28%
40%
Moderate OSA
Mild OSA
Sleep Apnea Severity Based on Night with highest ODI (events/hour)
0%
No OSA
Mild OSA
13%
25%
62%
Severe OSA
Moderate OSA

Figure 3

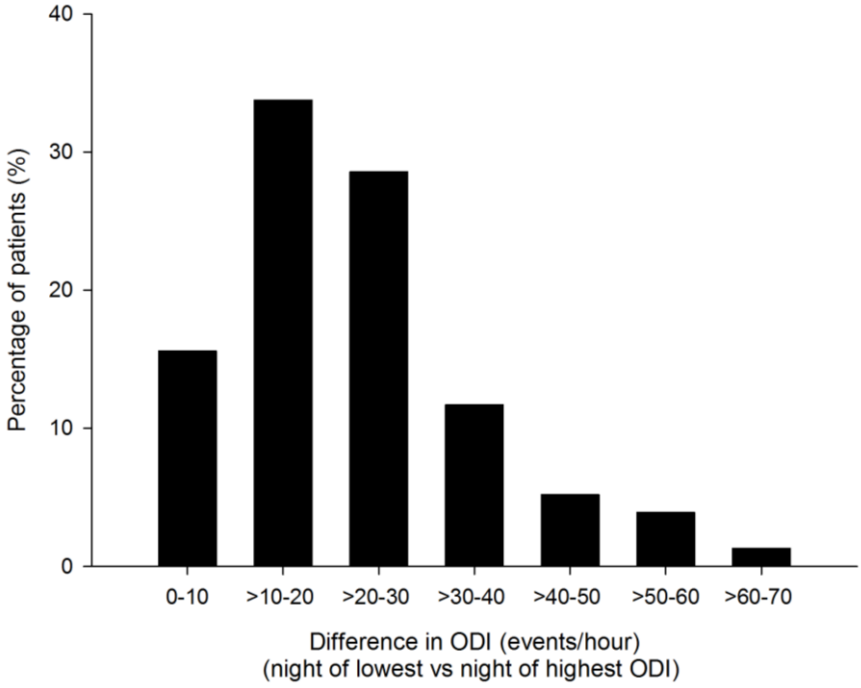
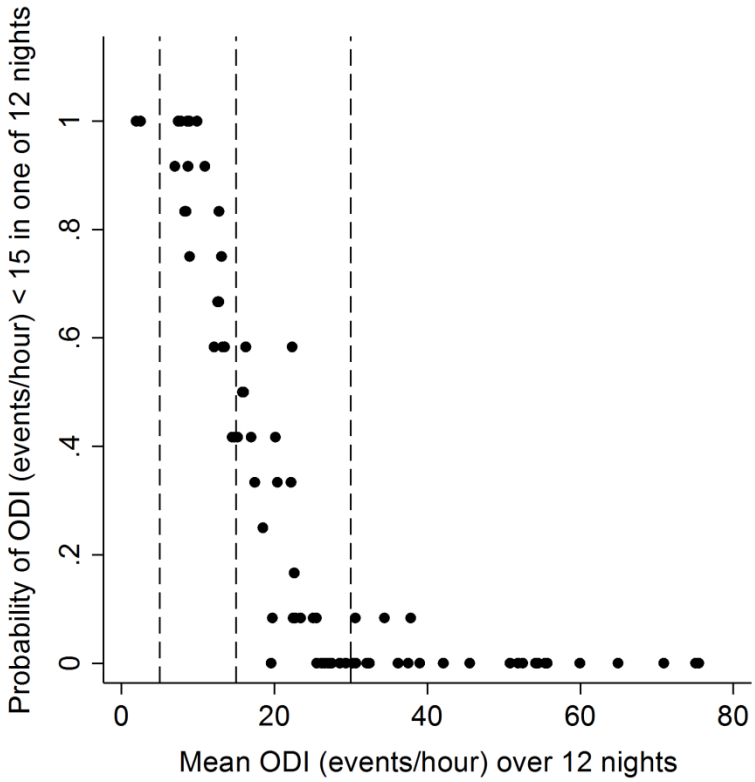

40
30
20
10
0
Percentage of patients (%)
0-10
>10-20
>20-30
>30-40
>40-50
>50-60
>60-70
Difference in ODI (events/hour)
(night of lowest vs night of highest ODI)

Figure 4


Probability of ODI (events/hour) < 15 in one of 12 nights
0
.2
.4
.6
.8
1
0
20
40
60
80
Mean ODI (events/hour) over 12 nights