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Original article

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Please cite this article as: Kainulainen S, Duce B, Korkalainen H, *et al*. Increased nocturnal arterial pulsation frequencies of OSA patients is associated with an increased number of lapses in a psychomotor vigilance task. *ERJ Open Res* 2020; in press (https://doi.org/10.1183/23120541.00277-2020).

This manuscript has recently been accepted for publication in the *ERJ Open Research*. It is published here in its accepted form prior to copyediting and typesetting by our production team. After these production processes are complete and the authors have approved the resulting proofs, the article will move to the latest issue of the ERJOR online.

Title page

Increased nocturnal arterial pulsation frequencies of OSA patients is associated with an increased number of lapses in a psychomotor vigilance task

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Abstract

Objectives: Besides hypoxemia severity, heart rate variability has been linked to cognitive decline in obstructive sleep apnea (OSA) patients. Thus, our aim was to examine whether the frequency domain features of nocturnal photoplethysmogram (PPG) can be linked to poor performance in psychomotor vigilance task (PVT).

Methods: PPG signals from 567 suspected OSA patients, extracted from Type 1 diagnostic polysomnography, and corresponding results of PVT were retrospectively examined. The frequency content of complete PPGs was determined, and analyses were conducted separately for men (n=327) and women (n=240). Patients were grouped to PVT performance-quartiles based on the number of lapses (reaction times≥500ms) and within-test variation in reaction times. The best (Q1) and worst-performing (Q4) quartiles were compared due the lack of clinical thresholds in PVT.

Results: We found the increase in arterial pulsation frequency (APF) in both men and women was associated with a higher number of lapses. Higher APF was also associated with higher within-test variation in men, but not in women. Median APF (β=0.27, p=0.01), time spent under 90% saturation (β=0.05, p<0.01) female sex (β=1.29, p<0.01), older age (β=0.03, p<0.01), and subjective sleepiness (β=0.07, p<0.01) were significant predictors of belonging to lapses Q4. Only female sex (β=0.75, p<0.01) and depression (β=0.91, p<0.02) were significant predictors of belonging to Q4 based on the within-test variation.

Conclusions: In conclusion, increased APF in PPG provides a possible PSG-indicator for deteriorated vigilance especially in male OSA patients. This finding highlights the connection between cardiorespiratory regulation, vigilance, and OSA. However, our results indicate substantial sex-dependent differences that warrants further prospective studies.

Keywords: oximetry, pulse wave analysis, spectral analysis, vigilance, sleep apnea

Introduction

Obstructive sleep apnea (OSA), characterized by repeated breathing cessations, intermittent hypoxemia, and arousals from sleep, is one of the most prevalent sleep disorders[1]. It has a strong association with various comorbid conditions, such as cerebrovascular, cardiovascular, metabolic, and neurologic diseases [2,3]. It has also been linked to deteriorated outcomes in different domains of cognitive functioning [4], for example in psychomotor vigilance task (PVT) [5]. PVT is a measure of vigilance and the ability to sustain attention. Due to the low learning effect, low-labor test protocol, and minimal subjectivity, PVT is recognized as a reliable test to evaluate neurocognitive performance [6].

Previous studies show that severe intermittent hypoxemia, quantified by the duration, depth, and frequency of oxygen desaturations, is associated with daytime sleepiness and cognitive decline in OSA patients [7-10]. However, desaturation metrics and other parameters quantifying the severity of OSA are not fully capable of explaining the impaired performance in PVT in OSA patients having shallow and short desaturations [10]. This suggests that additional factors could explain the associations between OSA and poor PVT performance. Therefore, novel biomarkers could be extremely useful for patients with relatively stable nocturnal oxygenation despite repetitive breathing cessations.

Nocturnal intermittent hypoxemia can be quantified with a pulse oximeter. Pulse oximetry provides non-invasively information on arterial blood oxygenation (SpO_2) based on the absorption of red and infrared light in the blood volume [11]. In sleep medicine, the photoplethysmogram (PPG) derived from the original absorption signal, is less used than SpO_2 [12]. However, PPG has great potential in the long-term monitoring of cardiorespiratory function, as it is an unobtrusive

measurement technique that contains information on the amplitude and frequency of the arterial pulsations alongside derived SpO_2 [11,12]. Therefore, frequency domain investigations of the PPG could be beneficial as it combines the information of amplitude and frequency changes without peak detection from the PPG which has high uncertainties compared to ECG-based R-peak detection [13].

OSA induces abnormal heart rate variability during sleep due to apneas and hypopneas causing desaturations and arousals from sleep [14]. Moreover, OSA disrupts normal sleep cycles and reduces the time spent in deeper stages of sleep [3]. Deeper stages of sleep are associated with higher parasympathetic drive and lower heart rate; conversely OSA is associated with high nocturnal sympathetic drive and higher heart rates [3,15]. Furthermore, non-dipping nocturnal heart rate and increased resting heart rate in 24-hour Holter ECG have been linked to worsened cognitive performance [16]. As PPG is shown to be a reliable surrogate for ECG [17], we hypothesize that the information content of the PPG signal can be linked to poor performance in PVT.

Thus, the main aim of this study is to examine whether the frequency domain features of nocturnal PPG can be linked to deteriorated vigilance in OSA patients. In addition, we aim to examine whether larger within-test variation in reaction times is associated with spectral features of PPG. As earlier literature shows that PVT performance is highly sex-dependent [10,18], we perform the analyses separately for men and women.

Methods

The initial clinical cohort comprised 912 consecutive suspected OSA patients undergoing polysomnography (PSG) in the Sleep Disorders Center of Princess Alexandra Hospital (Brisbane, Australia). The Institutional Human Research Ethics Committee of the Princess Alexandra Hospital approved the retrospective data collection (HREC/16/QPAH/021 and LNR/2019/QMS/54313). The cohort comprises all patients from the normal clinical inflow of suspected OSA patients between 2015 - 2017. From the initial population, 567 patients were selected into the studied population based on following inclusion criteria: 1) complete demographic and comorbidity information; 2) successful PSG and completed PVT; 3) apnea-hypopnea index (AHI)≥5, and 4) total sleep time in PSG ≥ 4 hours. PSG recordings were conducted and scored with the Compumedics Grael acquisition system and Compumedics ProFusion PSG 4 software (Compumedics, Abbotsford, Australia). PSG recordings were manually scored by experienced sleep technicians; all scorings were conducted in conformity with the American Academy of Sleep Medicine (AASM) 2012 guidelines [19]. None of the included patients had central sleep apnea *i.e.* the proportion of central apneas did not exceed 50% of the total number of apneas.

The PPG signal analysis protocol is illustrated in Figure 1. First, complete PPG signals, measured with transmissive Nonin Xpod 3011 finger pulse oximeter, were exported from each patient. Next, PPG signals were decimated from the original 256 Hz sampling frequency to 64 Hz with anti-aliasing Chebyshev filter to reduce computational load. Signals were further filtered using 8th order Chebyshev type 2 lowpass-filter with 60 dB stop-band ripple threshold and 6 Hz cut-off to eliminate unphysiological noise from decimated PPG. Signals were divided into 512 segments to enable comparison between spectrograms and to retain the temporal changes in frequency content throughout the night (Figure 1). For all patients, the median segment length was 52.2 s,

varying from a minimum of 38.7 s to a maximum of 68.2 s. For all segments, the power spectrum was computed using Welch's periodogram with 8 segments and 50% overlap utilizing the Hamming window to reduce the side-lobe leaking effect. Power spectrums were analyzed in a physiologically relevant arterial pulsation band between 0.5-4 Hz corresponding to heart rates between 30-240 bpm. Power spectrums were further converted into spectrogram images, with the x-axis representing the corresponding segment of the night and y-axis corresponding PPG signal frequency content (Figure 1). The power of each frequency is displayed via a color map in the spectrogram image.

The PVT's were conducted as part of standard clinical protocol utilized in Princess Alexandra hospital. PVT's were timed between 7-9 p.m. in the evening prior to the PSG study. A PEBL PVT program on an ASUS Transformer Pad with an attached keyboard was used [20]. PVT was performed using a 10-minute protocol. The protocol comprises 121 single-trial visual stimuli occurring randomly at 2-10 second intervals. Patients were instructed to use the index finger or thumb of their dominant hand and press the response button as soon as they see the stimulus at the screen. Full trial series were exported from every patient and data on the PVT performance is presented in Table 1. From the series, the number of lapses (reaction times ≥ 500 ms) was computed. In-test variation in repeated reaction times was quantified using Sample Entropy [21]. Before Sample Entropy analyses, the PVT trial series was normalized to achieve zero-mean with a standard deviation of 1 to reduce the baseline effect. The Sample Entropy estimates were computed using the following parameter settings: a template vector with a length of five and a distance-tolerance threshold of 0.4.

Table 1: PVT performance data in all patients (*n* = 567), in men (*n* = 327) and in women (*n* = 240)

	All patients	Male patients	Female patients
Median RT (ms)	378.0 (341.0-440.8)	362 (332.6-410.8)	405 (363.0-477.0)
RRT (1/ms)	2.6 (2.2-2.9)	2.7 (2.4-3.0)	2.4 (2.1-2.7)
Slowest 10% RT (ms)	676.0 (544.3-1025.0)	622.0 (518.3-910.5)	753.5 (578.5-1221.0)
Fastest 10% RT (ms)	297.0 (277.4-334.2)	289.0 (272.5-317.2)	313.0 (285.5-352.0)
Lapses	13 (5-35)	10 (4-21)	19 (9-51)
Sample Entropy	0.31 (0.12-0.71)	0.22 (0.11-0.66)	0.44 (0.16-0.80)

Footnote: All values are presented as median (interquartile range). All PVT performance metrics differed significantly between men and women based on Wilcoxon rank sum test. Abbreviations: PVT = psychomotor vigilance task, RT = reaction time, RRT = mean reciprocal reaction time.

The studied patient population was first divided into men and women. After separation, men and women were grouped to quartiles based on PVT performance as PVT does not have standard clinical thresholds for outcomes. Based on preliminary analyses, differences between quartiles 1,2, and 3 were relatively small in men. In women, the difference between quartiles 1 and 2 and between quartiles 3 and 4 was small. For clarity and to achieve more coherent and informative results, we decided only to present the differences in PPG frequency content in patients with

normal and notably impaired vigilance. Thus, only the best (Q1) and the worst (Q4) quartiles based on the number of lapses and Sample Entropy are compared in detail. All reported comorbidities are based on medical records and interviews in a sleep clinic. Group-median spectrograms were defined for Q1 and Q4. Stationary group-median power spectrums were extracted from the spectrogram. In addition, peak-power frequencies indicating the dominant arterial pulsation frequency (APF) were computed from individual spectrograms and from the median spectrograms of Q1 and Q4. For plotting purposes, the APF curves were smoothed via moving average filter having a 25-point window. The cumulative distribution function (CDF) of APF in the peak frequency curve was computed from median spectrograms together with 95% confidence intervals via Kaplan-Meier estimates. Statistical difference of cumulative distribution functions between Q1 and Q4 was computed using a two-sided Kolmogorov-Smirnov test. To evaluate the possible confounding effect of reported comorbidities and to analyze multivariate models' sensitivity and specificity, stepwise logistic regression with Bayesian Information Criterion (BIC) was used within the whole population to assess the probability of belonging to Q4. The model was adjusted for sex, age, BMI, chronic obstructive pulmonary disease (COPD), hypertension, depression, smoking status, and subjective sleepiness assessed with the Epworth Sleepiness Scale (ESS). Sleep stage distributions and parameters describing OSA severity (Table 2) were investigated by inputting them to regression models separately. After estimating the most significant predictor variables, their performance was evaluated by computing receiver operating characteristic (ROC) curves and corresponding areas under the curves (AUC). All data analyses and statistical testing were performed using MatLab (ver. 2018b, MathWorks Inc, USA) with custom-made functions and functions in Statistics and Machine Learning Toolbox and Signal Processing Toolbox.

Table 2: Demographic, polysomnographic (PSG) and comorbidity data and statistical analyses between the best (Q1) and worst-performing (Q4) quartiles based on lapses and sample entropy of reaction times in a psycho-motor vigilance task.

	Males (*n* = 327)				Females (*n* = 240)			
	Lapses		Sample Entropy		Lapses		Sample Entropy	
	Q1 (<4)	Q4 (>21)	Q1 (<0.105)	Q4 (>0.656)	Q1 (<9)	Q4 (>51)	Q1 (<0.163)	Q4 (>0.800)
Demographic parameters								
Patients (n)	88	80	82	82	66	59	60	60
Age (y)	**51.1 (40.7-61.7)**	**56.9 (48.4-67.1)**	52.8 (40.5-65.3)	55.4 (44.9-62.2)	54.3 (44.7-60.3)	58.8 (50.3-64.8)	54.1 (45.1-62.3)	55.9 (45.5-62.2)
BMI (kg/m^2)	32.9 (28.7-37.8)	34.7 (29.8-39.5)	34.5 (30.9-40.4)	33.7 (29.5-37.8)	37.0 (32.3-44.4)	36.0 (31.8-47.1)	38.7 (32.5-45.8)	36.0 (29-42.7)
Comorbidities								
COPD	6 (6.8)	8 (10.0)	5 (6.1)	5 (6.1)	5 (7.6)	8 (13.6)	5 (8.3)	6 (10.0)
Hypertension	26 (29.6)	35 (43.8)	32 (39.0)	30 (36.6)	22 (33.3)	29 (49.2)	22 (36.7)	22 (36.7)
Depression	8 (9.1)	13 (16.3)	6 (7.3)	13 (15.9)	14 (21.2)	15 (25.4)	10 (16.7)	14 (23.3)
Smokers	13 (14.8)	13 (16.3)	14 (17.1)	12 (14.6)	6 (9.1)	10 (17.0)	8 (13.3)	9 (15.0)
ESS (score)	9 (6-15)	10 (6-14)	8 (5-12)	10 (5-13)	**9 (6-12)**	**13 (6-18)**	11 (6-15)	9 (5-13)
PSG parameters								
Total sleep time (h)	**5.4 (4.8-6.1)**	**4.9 (4.5-5.8)**	5.3 (4.7-6.1)	5.2 (4.6-5.9)	5.4 (6.0-4.7)	5.6 (4.9-6.4)	5.6 (5.0-6.2)	5.7 (4.9-6.3)
N1 (%)	15.5 (10.6-23.8)	14.1 (8.7-21.5)	15.4 (9.3-22.1)	14.7 (9.6-25.7)	7.9 (5.7-10.8)	8.1 (5.8-12.8)	8.0 (5.6-13.3)	8.9 (6.0-14.4)
N2 (%)	47.3 (42.3-52.9)	49.5 (42.6-57.9)	48.2 (42.2-56.1)	45.8 (39.6-54.1)	47.1 (41.4-53.4)	49.0 (40.3-61.2)	47.3 (41.5-53.4)	49.2 (40.4-53.0)
N3 (%)	16.2 (7.4-23.1)	14.9 (5.0-24.2)	14.6 (7.7-23.8)	15.1 (9.4-23.4)	24.2 (17.3-29.9)	21.6 (12.0-29.3)	23.0 (17.4-29.3)	20.6 (15.2-29.4)
REM (%)	18.0 (13.7-22.4)	17.0 (12.9-20.6)	18.8 (14.7-22.4)	15.8 (11.6-22.8)	18.5 (12.9-23.3)	19.1 (12.9-22.5)	19.0 (13.0-21.8)	19.2 (12.1-24.8)
AI (events/h)	33.5 (22.4-46.8)	31.6 (22.1-45.6)	31.5 (19.5-42.9)	35.1 (23.1-47.2)	21.3 (30.4-16.1)	24.3 (15.5-33.8)	23.1 (16.0-32.0)	22.7 (18.3-32.4)
AHI (events/h)	29.8 (13.4-49.2)	28.6 (19.9-44.3)	25.0 (15.3-42.3)	28.8 (18.9-53.8)	16.0 (9.3-29.7)	15.8 (10.1-37.7)	17.6 (10.1-27.2)	15.0 (8.9-31.0)
ODI (events/h)	20.4 (6.7-32.9)	21.0 (9.9-37.4)	16.8 (7.5-30.1)	20.0 (8.3-36.6)	11.5 (5.2-26.8)	13.3 (5.6-25.6)	12.5 (5.1-24.6)	9.3 (4.0-21.6)
$t_{90\%}$ (min)	6.8 (1.3-46.8)	15.6 (1.7-98.2)	12.4 (1.4-44.7)	8.9 (0.8-50.4)	4.6 (0.8-32.8)	11.5 (1.0-63.5)	4.3 (0.5-42.8)	3.4 (0.3-45.6)
mDD (%)	4.9 (4.1-7.4)	5.3 (4.4-7.5)	5.6 (4.1-8.0)	5.1 (4.1-6.6)	5.0 (4.1-6.4)	5.1 (4.3-6.0)	4.7 (4.0-6.2)	4.9 (4.1-6.0)

Footnote: Data is presented as number (% of population or quartile) or median (interquartile range) where appropriate. Bolded values indicate statistical difference ($p<0.05$) between Q1 and Q4 in the corresponding sex. Wilcoxon rank sum and χ^2 tests were used where appropriate. Abbreviations: BMI = body mass index, COPD = chronic obstructive pulmonary disease, ESS = Epworth sleepiness scale, N1-N3 = non-rapid eye movement sleep stages 1-3, REM = rapid eye movement sleep, AI = arousal index, AHI = apnea-hypopnea index, ODI = oxygen desaturation index, $t_{90\%}$ = time spent under 90% oxygenation, mDD = median desaturation depth.

Results

Differences in demographics, comorbidities, and PSG parameters

The PVT performance data is presented in Table 1. Demography, comorbidity, and PSG data of Q1 and Q4 with respect to both PVT outcome variables are presented in Table 2. The comparison between men and women shows that women have a significantly higher number of lapses and consistently longer reaction times than men (Table 1). Conversely, women suffer from substantially less severe OSA based on AHI, ODI, and $t_{90\%}$ (Table 2). In addition, a substantially lower degree of sleep disruption is seen women, having a higher amount of N3 sleep, a lower amount of N1 sleep, and a lower arousal index (Table 2).

Sub-group analysis between men in Q1 and Q4 based on lapses revealed, that patients belonging to Q4 were significantly older (p = 0.02) and had shorter total sleep time in PSG (p = 0.02) (Table 1). Q4 tended to comprise higher number of hypertensive (43.8% vs. 29.6%, p = 0.05) and depressed (16.3% vs. 9.1%, p = 0.16) patients compared to Q1. In addition, patients in lapses Q4 had a trend towards more severe nocturnal hypoxemia seen as increased $t_{90\%}$ (15.6 vs 6.8 min, p = 0.12). In Sample Entropy comparison, Q1 and Q4 were highly similar based on demographics, PSG parameters, and comorbidities (Table 1).

Female patients in lapses Q4 were subjectively sleepier (ESS: 9 vs. 13, p = 0.01) compared to Q1 (Table 1). Q4 tended to comprise higher number of hypertensive (p = 0.07) and older patients (p = 0.06) with longer TST (p = 0.06) compared to Q1. No difference between Sample Entropy Q1 and Q4 were observed.

Frequency domain analysis of the PPG signal

A comparison of male OSA patients in Q1 and Q4 based on lapse count showed significantly higher APF in Q4 (Figure 2 A-B). The median power spectrum exhibited a clear pulse peak shift towards higher APF and reduced power in Q4 (Figure 2 C). Furthermore, the CDF of temporal APFs contained significantly (p<0.001) higher values in male patients belonging to Q4 (Figure 2 D). Median spectrograms for Sample Entropy Q1 and Q4 indicated higher APF and larger frequency variation in males belonging to Q4 with significantly higher temporal APF values (p<0.001) (Figure 3, A-B, and D). The median power spectrum exhibited only a moderate pulse peak shift towards higher APF but higher power in Q4 (Figure 3 C).

Comparison of female OSA patients in Q1 and Q4 based on lapse count showed that median spectrograms of females in Q4 exhibit only slightly higher APF compared to female patients in Q1 (Figure 4 A-B). The median power spectrum showed a moderate pulse peak shift towards higher APF and reduced power in Q4 (Figure 4 C). The cumulative distribution of temporal APFs contained significantly higher values in Q4 than in Q1 (Figure 4 D). In the comparison between Sample Entropy Q1 and Q4, median spectrograms and median power spectrums were highly similar (Figure 5 A-C). However, females in Q1 had a trend towards slightly higher (p = 0.09) temporal APF values in cumulative distribution (Figure 5 D).

Regression analysis

Based on stepwise regression analyses, median APF was found to be a significant predictor of belonging to lapses Q4 (β = 0.270, standard error = 0.109, p = 0.013) alongside female sex (β = 1.286, standard error = 0.267, p < 0.001), $t_{90\%}$ (β = 0.050 standard error = 0.02, p < 0.001), age (β = 0.031, standard error = 0.010, p = 0.002) and subjective sleepiness (β = 0.073, standard error =

0.024, p = 0.002) (Table 3). In contrast, only female sex (β = 0.748, standard error = 0.249, p = 0.002) and depression (β = 0.906, standard error = 0.362, p = 0.012) were significant predictors in belonging to Q4 based on Sample Entropy (Table 3). Sleep stage distribution, AHI or Arousal Index were not associated with increased probability of belonging to Q4 of lapses or Sample Entropy (Table 3).

Based on models constructed by logistic stepwise regression, ROC curves and AUC values were determined to evaluate models' sensitivity and specificity in classifying patients to Q1 and Q4 based on lapses (Figure 6). Univariate models show that mAPF and ESS have the best differentiation capability with AUC of only 0.5960 and 0.6067, respectively. By utilizing a multivariate approach including sex, age, ESS score together with mAPF or t90%, AUC reaches 0.7314 and 0.7349, respectively (Figure 6). For comparison, AHI was able to differentiate Q1 and Q4 patients with a sensitivity of 65.5% and specificity of 32.9% with 15 events/h cut-off and was not a significant predictor of belonging to lapses Q4. In addition, ESS was able to differentiate Q1 and Q4 patients with a sensitivity of 25.6% and specificity of 81.7% when using a 16-point cut-off.

Table 3: Stepwise regression models for estimated β-coefficients and corresponding odds for belonging to Q4 instead of Q1.

	Lapses				Sample Entropy			
	OR	*β*	*S. error*	*p*	*OR*	*β*	*S. error*	*p*
Female sex	3.62	1.29	0.27	< 0.01	2.11	0.75	0.25	<0.01
Age (y)	1.03	0.03	0.01	< 0.01	-	-	-	-
BMI (kg/m^2)	-	-	-	-	-	-	-	-
Hypertension	-	-	-	-	-	-	-	-
Smoking	-	-	-	-	-	-	-	-
COPD	-	-	-	-	-	-	-	-
Depression	-	-	-	-	2.47	0.91	0.36	< 0.02
ESS (score)	1.08	0.07	0.02	< 0.02	-	-	-	-
AHI (1/h)	-	-	-	-	-	-	-	-
$t_{90\%}$ (per 10 min)	1.05	0.05	0.02	<0.01	-	-	-	-
AI (1/h)	-	-	-	-	-	-	-	-
N1 (%)	-	-	-	-	-	-	-	-
N2 (%)	-	-	-	-	-	-	-	-
N3 (%)	-	-	-	-	-	-	-	-
REM (%)	-	-	-	-	-	-	-	-
Median APF (1/min)	1.31	0.27	0.11	< 0.02	-	-	-	-

Footnote: This analysis comprises the whole population (n = 567), where quartiles are defined for lapses (Q1: 0-4 lapses; Q4: over 35 lapses) and Sample Entropy (Q1: 0-0.12; Q4: over 0.71) separately. Both models are computed using the logit-link function. Models were constructed using constant starting model, Bayesian Information Criterion (BIC) as a model entering criterion and treating the response variable as a categorical variable. All models were constructed by separately inputting investigated polysomnography-based parameters. Parameters that were excluded from the final regression model based on BIC are marked with a hyphen. Abbreviations: OR = odds ratio, S. error = standard error in *β*, BMI = Body mass index, COPD = chronic obstructive pulmonary disease, ESS = Epworth Sleepiness Scale, AHI = apnea-hypopnea index, $t_{90\%}$ = time spent under 90% saturation, AI = arousal index, APF = Arterial pulsation frequency, REM = rapid eye-movement sleep.

Discussion

In this study, we compared photoplethysmogram (PPG)-derived arterial pulsation frequencies (APF) and frequency-domain features between OSA patients within the best and worst PVT performance quartiles. We found increased APF and higher nocturnal variance of the frequencies in the worst-performing male OSA patients compared to the best-performing patients. However, differences in PPG features diminished in female patients and were not as clearly distinguishable. Stepwise regression analysis revealed that higher APF and $t_{90\%}$ are associated with a higher number of lapses in PVT. These results imply that increased APF together with more severe nocturnal hypoxemia may provide a PSG-marker for impaired vigilance in male OSA patients. In addition, findings are in line with previous studies, indicating that female sex, and older age are independent risk factors for poor PVT performance.

The frequency content of nocturnal PPG exhibits a clear difference between males in the worst-performing (Q4) and the best-performing (Q1) quartiles based on both lapses and Sample Entropy. APF was found to vary more in both Q4s and have significantly higher values compared to Q1s. Furthermore, in lapses Q4s the increased APF was also observed in the group-median power spectrum together with reduced power of the peak frequencies (Figure 2 C and 4 C). Higher APF is due to increased heart rate; OSA and intermittent hypoxemia (Table 2 and 3) elevate the nocturnal sympathetic activity, heart rate and blood pressure [22-24]. As seen in Table 2, males in lapses Q4 had a minor trend for more severe hypoxemia together with shorter TST. However, increase in $t_{90\%}$ significantly elevated the odds of belonging to Q4 based on lapses (Table 3). Conversely, this was not found in Sample Entropy Q4 despite the higher APF. Moreover, the association between APF and Sample Entropy diminished in stepwise regression (Table 3) and power reduction of peak frequencies in Q4 was not observed (Figures 3 C and 5 C). This implies, that the spectrograms,

which retain the temporal changes in the PPG signal, associate better to the deteriorated vigilance than median APF. It could also be speculated that there is a substantial inter-individual variation in cardiac response to hypoxemia and breathing cessations. Especially older male patients seem to be vulnerable to nocturnal sympathetic overdrive (Table 1), making APF a useful tool for assessment of the risk for deteriorated vigilance in male OSA patients.

Analysis comprising only female patients showed smaller differences between best and worst performers in the frequency content of PPG. Based on previous studies, women tend to perform worse than males in PVT [10,18,25], which was observed in this cohort also (Table 1). Women also exhibit a higher resting heart rate and different cardiac regulation sensitivity [26]. Furthermore, in both Q1 and Q4 women had substantially milder OSA, longer total sleep time, a larger amount of N3 sleep and less N1 sleep than men (Table 2), which can partly explain the obtained results. Moreover, females had a higher Q4 threshold than men both in lapses and SE as well as significantly higher ESS scores in lapses Q4 (Table 1 and 2). These results indicate a clear difference between men and women in vigilance deterioration and baseline sleepiness in best and worst-performing quartiles. This was however expected as we have previously shown that also OSA and OSA-related sleepiness are sex-dependent [9,27]. Based on the current body of evidence regarding the association between OSA and impaired vigilance [7,8,10], it could be speculated that more severe intermittent hypoxemia, self-reported sleepiness and fatigue, comorbid depression and older age are better indicators of poor vigilance for female OSA patients than changes in PPG frequency domain features. The present stepwise regression analyses strongly support this conclusion (Table 3), as female sex, and comorbid depression were significant predictors of large within-test variation.

Elevated intermittent sympathetic activity leads to higher blood pressure[22] and further, to higher nocturnal heart rate [24] which associates to deteriorated vigilance especially in men via increased APF (Figures 2-3). One of the reasons behind this association could be sympathetic overdrive and its effect on hemodynamics and cerebrospinal fluid oscillations in slow-wave (SW) sleep. Recent literature shows that SW oscillations in N2 and N3 sleep drives the oscillations in cerebral blood volume (CBV) and cerebrospinal fluid (CSF), enabling protein clearance from the brain via glymphatic system [28,29]. Under high blood pressure, the protein clearance process via oscillation of CBV and CSF can be disrupted and even reversed [28]. In addition, glymphatic propulsion associates with cardiac pulsations and breathing pulsations [30]. Therefore, untreated OSA as a chronic condition can contribute to the accumulation of proteins in the brain over time [31-33], and thus, together with hypoxemia-induced neuronal brain damage lead to cognitive decline [10]. In this study, only a minor difference between Q1 and Q4 in the amount of N3 sleep was found (Table 2). This implies, that higher APF, which is linked to elevated sympathetic tone and blood pressure, could be a marker for the declined ability of SWS to perform protein clearance regardless of the amount of SWS. Moreover, higher heart rate [16], elevated blood pressure [34], elevated sympathetic tone [22], and moderate-to-severe OSA [2,35] are associated with comorbid cerebral small vessel disease, which could also explain the poor vigilance in male patients having higher APF (Figures 2-3). To test this hypothesis, a large prospective study combining current protocol with PPG analysis within different sleep stages, MR imaging, and CSF protein analysis is warranted.

It is noteworthy, that the presented method does not include the exact detection of pulse peaks in PPG for pulse detection. This is, however, advantageous as PPG waveforms are in part modulated by the functioning of the aortic valve and mechanical properties of the arteries that carry the pulse

wave. In addition, the computation of spectrograms and spectrums is fast and convenient; the presented scheme can be easily implemented in existing diagnostic methods such as PSG or home sleep apnea testing. These findings together with previous studies imply, that the assessment of OSA severity and evaluation of related daytime dysfunctions could be conducted using pulse oximeter measurements and deep learning [9,10,36]. This would further facilitate referrals to in-depth examinations for those with the highest risk of severe consequences of OSA. To assess specifically the risk of deteriorated vigilance, we compiled univariate models for the three most important predictors (ESS score, $t_{90\%}$, and median APF) of belonging to the lapses Q4 and also different combinations of the multivariate models (Figure 6). The ROC analyses revealed that none of the three parameters are capable of producing meaningful predictions alone, and suffer from from a high number of false positives with high sensitivity. However, when either mAPF, ESS or $t_{90\%}$ are combined with sex and age, models' sensitivity and specificity outperform the univariate models and the differentiation capability of the AHI (Figure 6). However, to produce a more reliable model, similar analyses has to be conducted in various patient cohorts to optimize the used predictor variables and related β-coefficients.

This study has certain limitations. First, the median total sleep times were short, which is most likely due to a common first-night effect in PSG. It is acknowledged, that for a more comprehensive analysis, nocturnal PPG recordings from multiple nights would be needed. However, the current protocol consisting of PVT prior to PSG mitigates the first-night effect to PVT results. Second, our data does not include sleep diary or long-term actigraphy. Chronic sleep deprivation is shown to affect the PVT performance to a large extent [37]; therefore the lack of this data is a limitation. Third, we could not consider motivational aspects affecting PVT performance such as having a driver's license or being a professional driver. These factors affect

also the ESS scores, and we acknowledge that this is a limitation. Fourth, a complete record of the patients' medication at the time of measurement was not available. It is acknowledged, that for example, psychoactive medication can affect the PVT results and medications such as beta-blockers can affect the arterial pulsation waveforms. We minimized this effect in stepwise regression by adjusting for comorbidities, but we acknowledge that this is a limitation. Fifth, the existence of hypertension is based on medical records and earlier diagnosis. Thus, the cohort may comprise patients with undiagnosed arterial hypertension. In addition, hypertension was treated as a dichotomous variable due to the lack of blood pressure follow-ups of the patients in this cohort. Sixth, besides PVT, other concentration and sleepiness tests such as Osler test and Maintenance of wakefulness test exist. Combining these tests with the PVT, a more comprehensive overview of the patient's daytime performance and symptoms would be achieved.

In conclusion, APF shifted to higher frequencies and increased median frequency of the PPG provides a PSG-marker for poor psychomotor vigilance task performance in male OSA patients. These findings highlight the connection of sleep disorders to cardiorespiratory regulation. In addition, the presented method could help in detecting those OSA patients at the highest risk of deteriorated vigilance.

Disclosure statement

Financial Disclosure: During conduction of the present study, funding was received from the Research Committee of the Kuopio University Hospital Catchment Area for the State Research Funding (projects 5041767, 5041768, 5041776, 5041779, 5041782 and 5041780), the Academy of Finland (Decision numbers 313697 and 323536), Seinäjoki Central Hospital, the Competitive State Research Financing of Expert Responsibility Area of Tampere University Hospital (grants VTR3221 and VTR3228), Business Finland (decision number 5133/31/2018), Paulo Foundation, Päivikki & Sakari Sohlberg Foundation, The Research Foundation of the Pulmonary Diseases, Finnish Cultural Foundation, Tampere Tuberculosis Foundation, and the Respiratory Foundation of Kuopio Region.

Non-financial Disclosure: The authors declare that they have no conflict of interests.

Author contributions: J.T., A.K., S.M., and T.L. devised the project and the main conceptual ideas for the experiments. S.K., H.K., and B.D carried out the data collection and preparation. S.K, H.K, A.L., B.D., L.K., R.H., and E.A. carried out the analysis and interpretation. S.K. drafted the manuscript, and prepared the figures together with H.K and L.K. All the authors have revised the manuscript critically, approved the version submitted for publication and have agreed to be accountable for all aspects of the work.

Acknowledgements: We want to thank Dr. Arie Oksenberg for his contribution and sleep medicine expertise in our common research effort.

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Figure captions:

Figure 1: Illustrative description of the decomposition of photoplethysmogram (PPG) signal. The complete preprocessed PPG signal is first divided into 512 segments. All segments are equal in length except the last segment, which length is the number of remaining sampling points if the signal is not divisible with 512. The frequency content within the nth segment is determined using Welch's method: the segment is divided to eight parts with a 50% overlap. For every part, a power spectral density estimate is computed and then averaged. After this procedure is completed for every 512 segments, they are ordered into a spectrogram image for temporal interpretation of the frequency content within the signal.

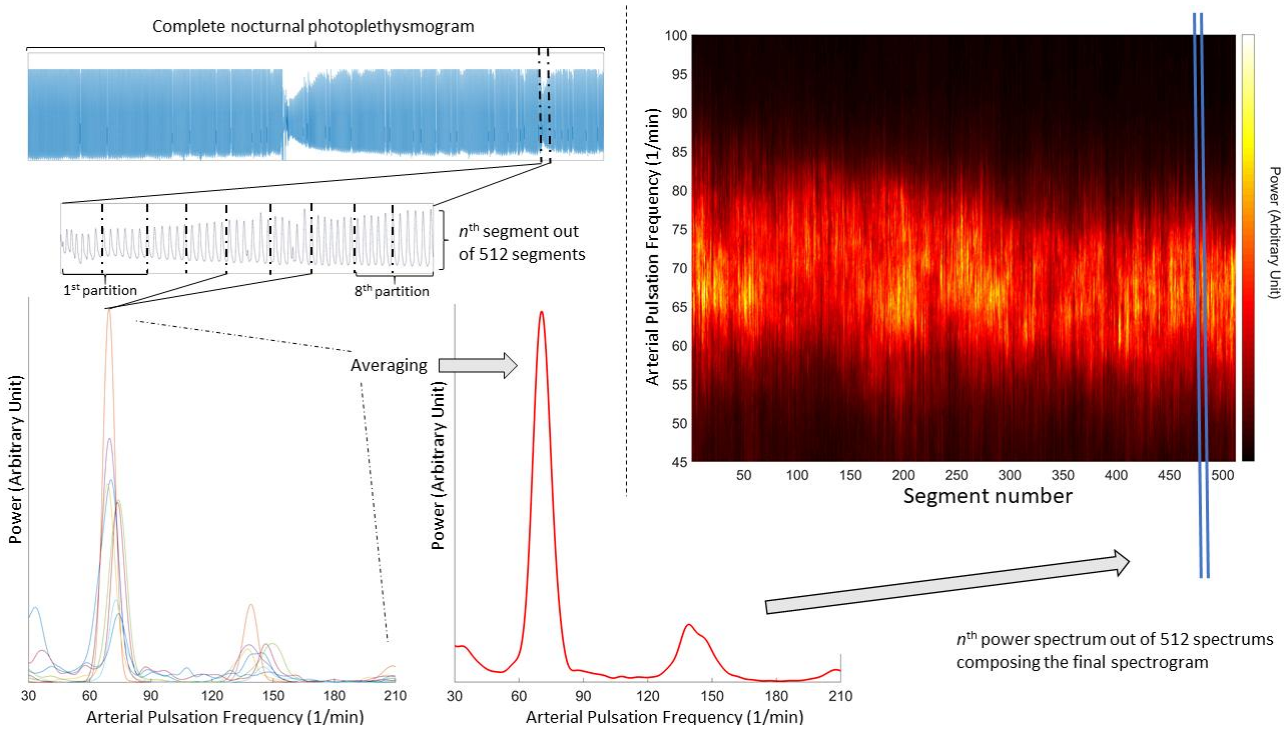
Figure 2: Comparison of male OSA patients in the best (Q1, n = 88) and the worst-performing quartiles (Q4, n = 80) based on lapse count in PVT. Median spectrograms (color map represents power of each pulsation frequency) of males in Q4 exhibit higher arterial pulsation frequency (APF) and variance compared to males in Q1 (A and B). The median power spectrum reveals a clear pulse peak shift towards higher APF and reduced power in Q4 (C). The cumulative distribution function (CDF) of APF with 95% confidence intervals contains significantly ($p < 0.001$) higher values in males belonging to the worst-performing quartile (D). The peak-frequency curve indicates the specific frequency in each segment having the highest power.

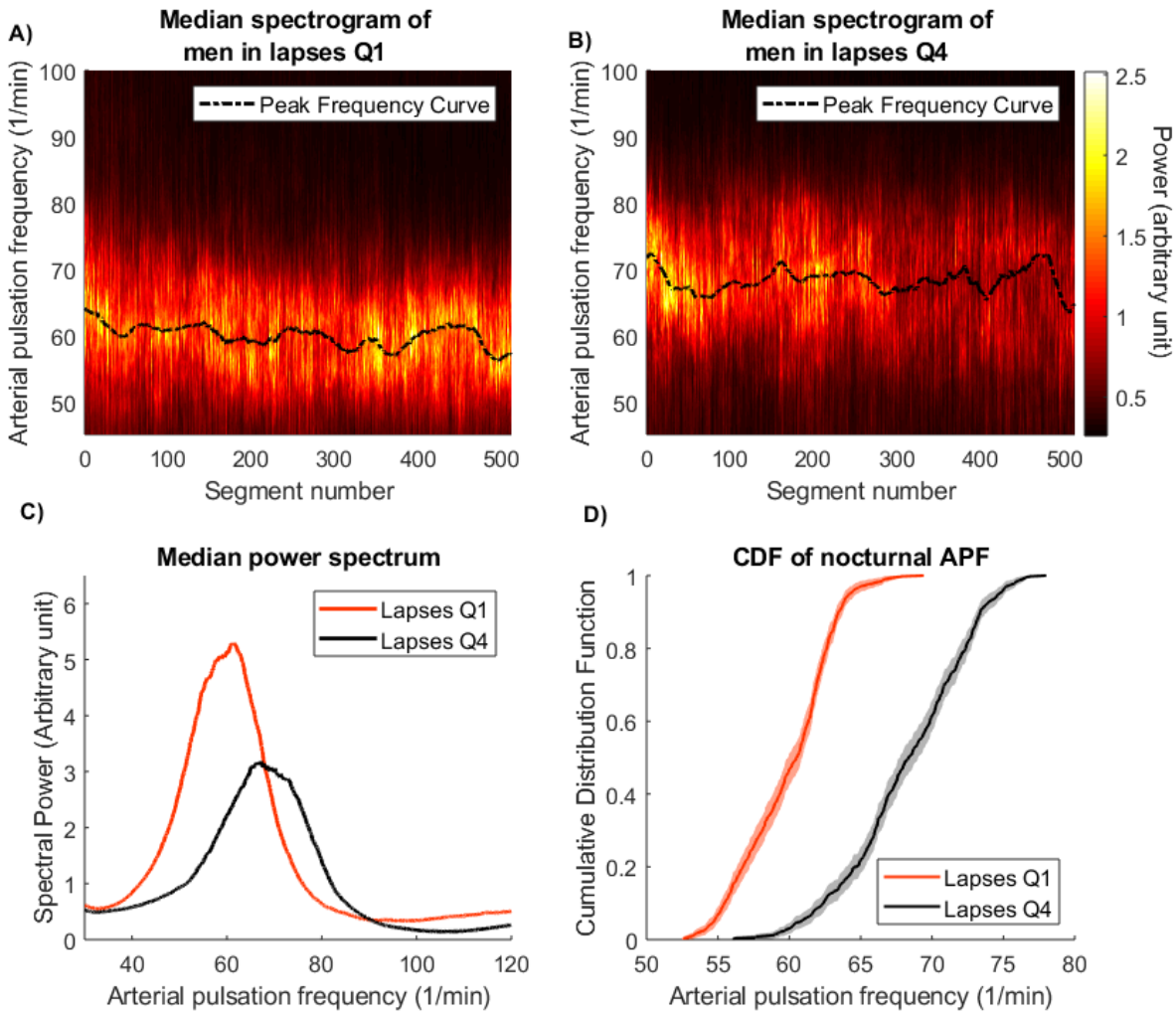
Figure 3: Comparison of male OSA patients in the best (Q1, n = 82) and the worst performing quartiles (Q4, n = 82) based on Sample Entropy (SE) in PVT. Median spectrograms (color map represents power of each pulsation frequency) indicate higher APF and larger variation in males belonging to Q4 (A and B), together with significantly higher APFs ($p < 0.001$) in cumulative distribution function (CDF) (D). However, the median power spectrum exhibits only a moderate pulse peak shift towards higher APR and higher power in Q4 (C). The peak-frequency curve indicates the specific frequency in each segment having the highest power.

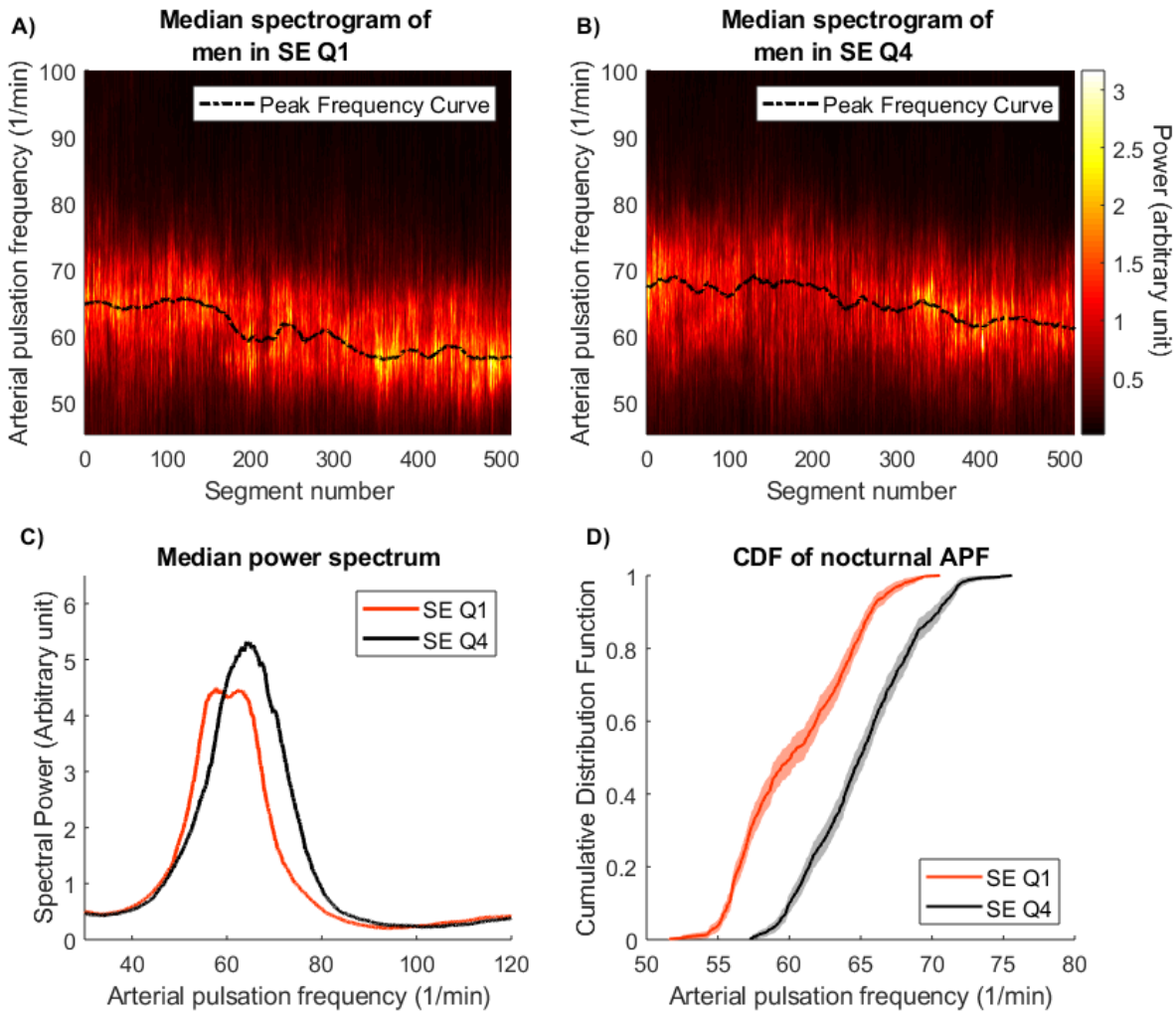
Figure 4: Comparison of female OSA patients in the best (Q1, n = 66) and the worst-performing quartiles (Q4, n = 59) based on lapse count in the PVT. Median spectrograms (color map represents power of each pulsation frequency) of females in Q4 exhibit slightly higher arterial pulsation frequency (APF) compared to females in Q1 (A and B). The median power spectrum shows a small shift towards higher APF in pulse peak location between Q1 and Q4, and reduced power in Q4 (C). The cumulative distribution function of temporal APF with 95% confidence intervals contain slightly ($p < 0.05$) higher values in the worst-performing quartile (D). The peak-frequency curve indicates the specific frequency in each segment having the highest power.

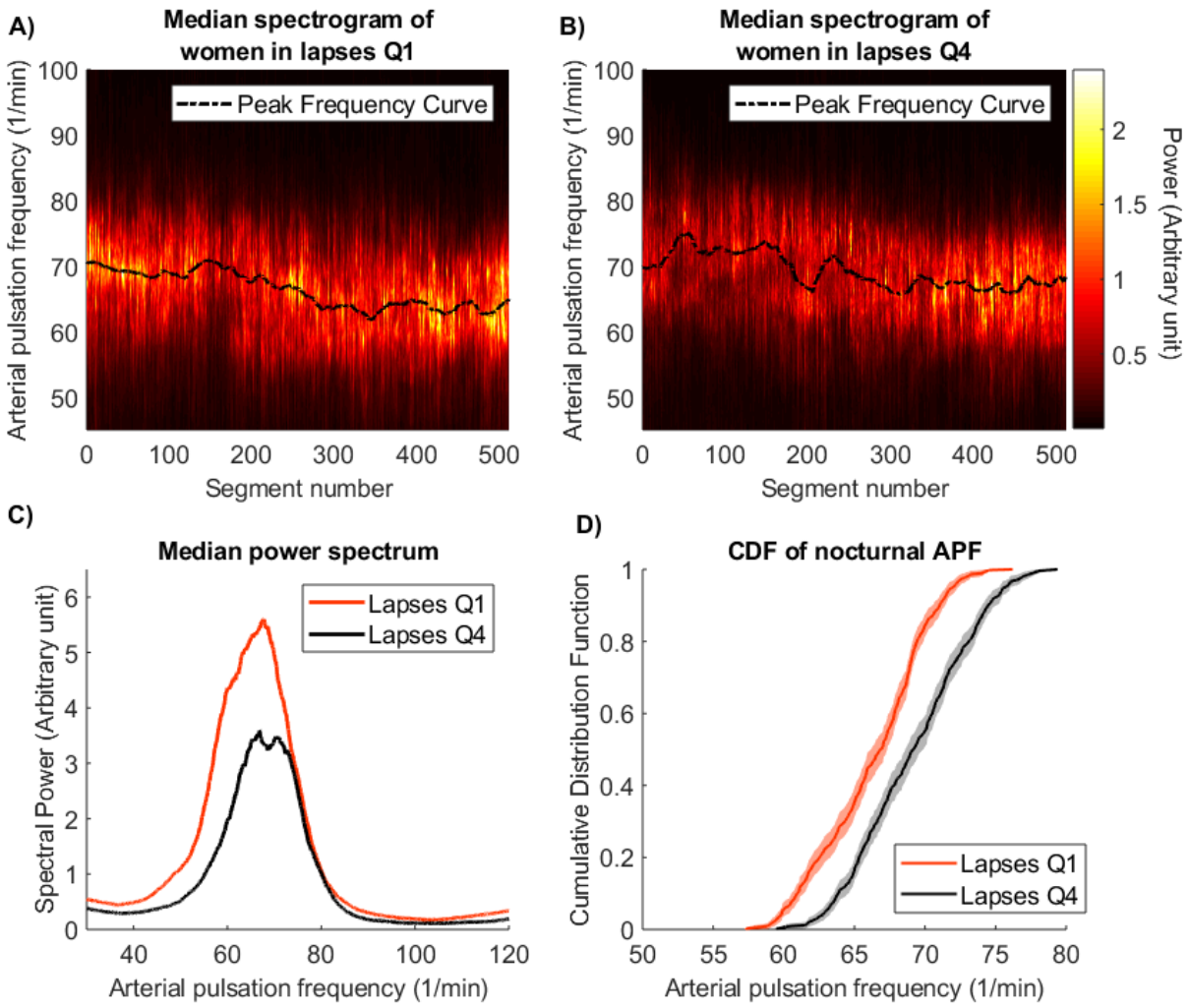
Figure 5: Comparison of female OSA patients in the best (Q1, n = 60) and the worst performing quartiles (Q4, n = 60) based on Sample Entropy (SE) in PVT. Median spectrograms (color map represents power of each pulsation frequency) indicate similar APF and overall frequency content in both quartiles. Furthermore, median power spectrums exhibit similar pulse peak locations and power. In the cumulative distribution function (CDF) of APFs, the difference was not statistically significant ($p = 0.09$). The peak-frequency curve indicates the specific frequency in each segment having the highest power.

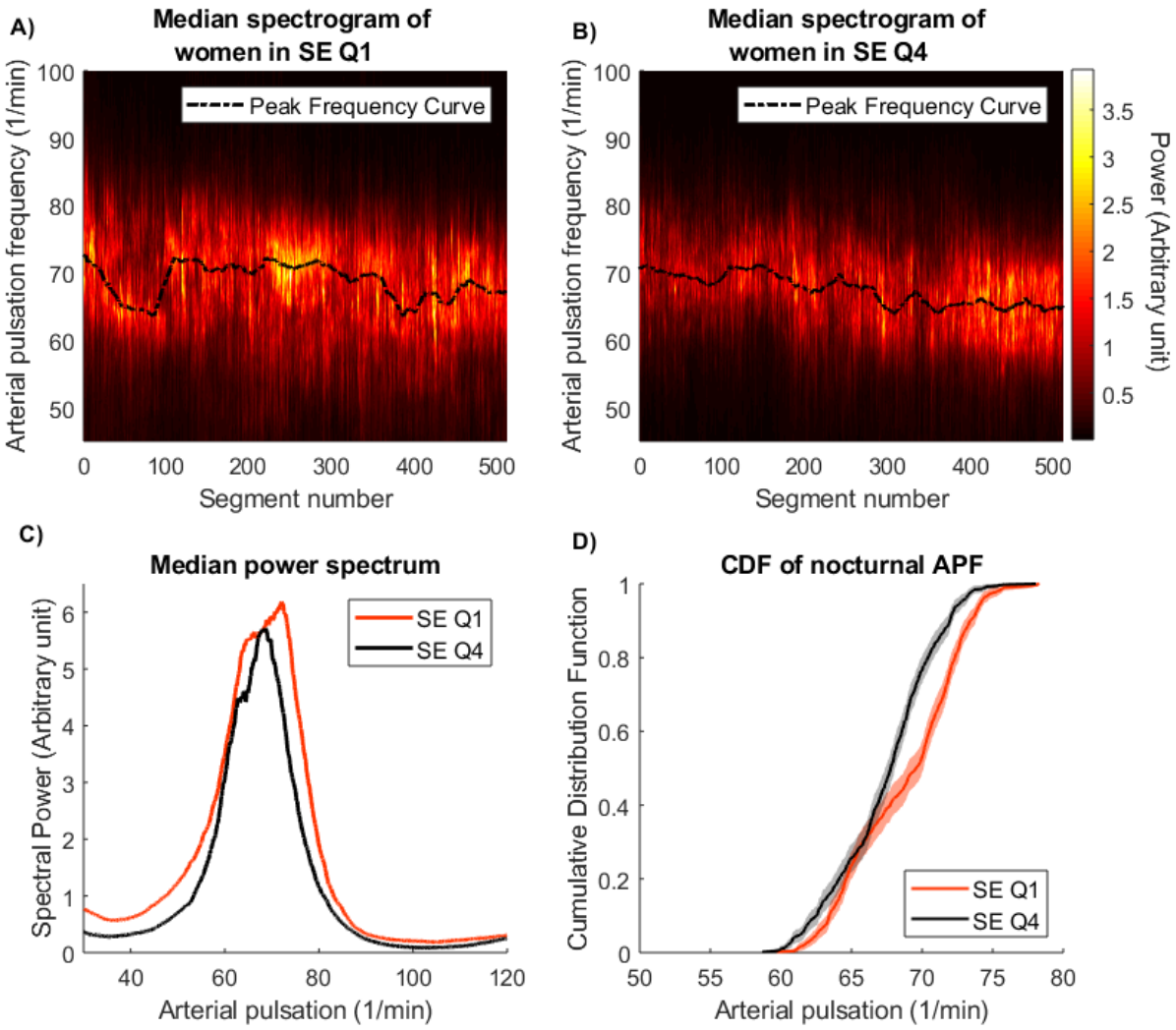
Figure 6: Receiver operating characteristic (ROC) curves and corresponding areas under the curves (AUC) for the assessment of belonging to the worst performing quartile based on lapses. Only the significant ($p<0.05$) predictor variables, determined in stepwise logistic regression, are used in multivariate and univariate estimations of models' sensitivity and specificity.

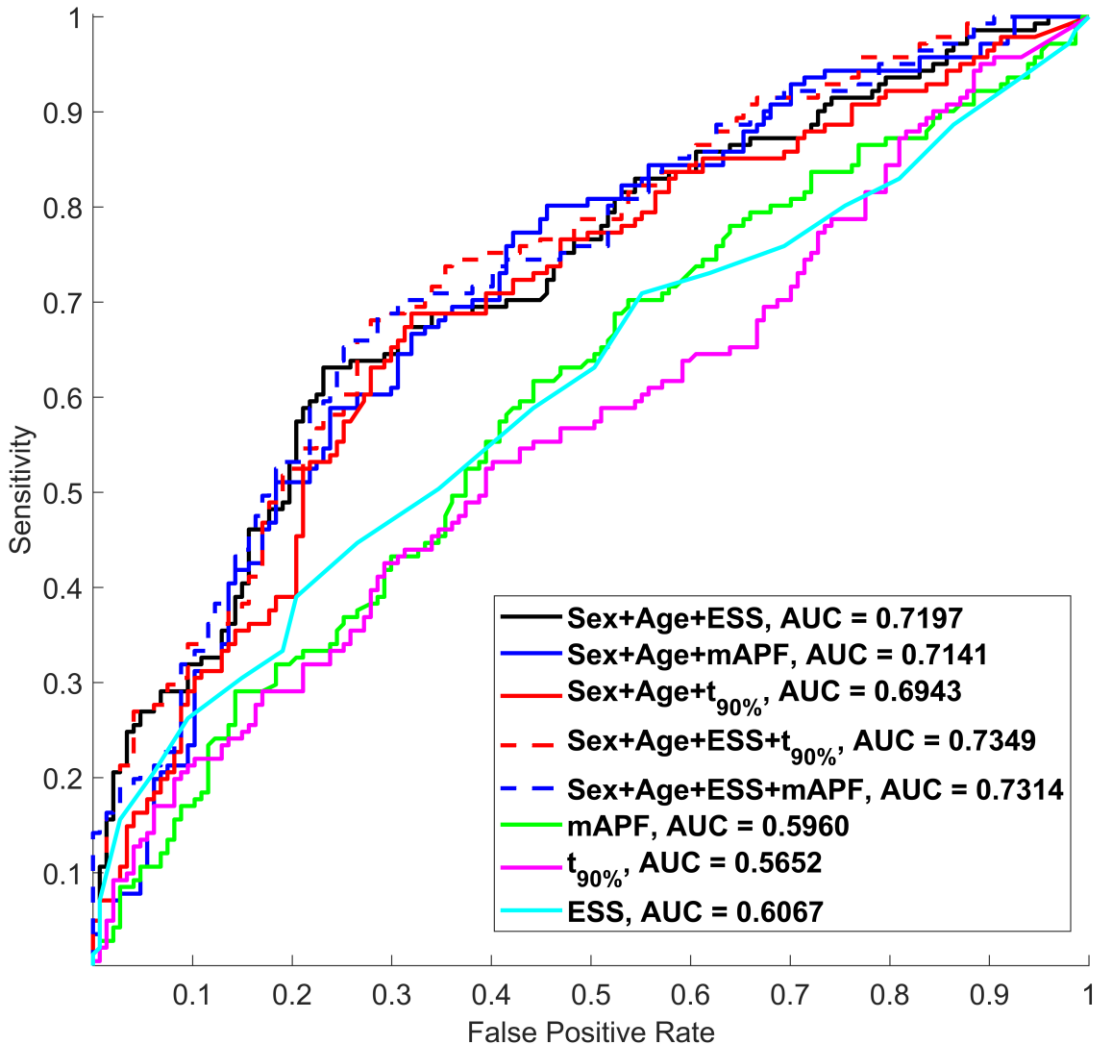

Complete nocturnal photoplethysmogram
n^{th} segment out of 512 segments
1st partition
8th partition
Averaging
Power (Arbitrary Unit)
Arterial Pulsation Frequency (1/min)
30
60
90
120
150
180
210
Arterial Pulsation Frequency (1/min)
Segment number
Power (Arbitrary Unit)
n^{th} power spectrum out of 512 spectrums composing the final spectrogram


A)
Median spectrogram of men in lapses Q1
Peak Frequency Curve
Arterial pulsation frequency (1/min)
Segment number
B)
Median spectrogram of men in lapses Q4
Peak Frequency Curve
Arterial pulsation frequency (1/min)
Segment number
Power (arbitrary unit)
C)
Median power spectrum
Lapses Q1
Lapses Q4
Spectral Power (Arbitrary unit)
Arterial pulsation frequency (1/min)
D)
CDF of nocturnal APF
Lapses Q1
Lapses Q4
Cumulative Distribution Function
Arterial pulsation frequency (1/min)


A)
Median spectrogram of men in SE Q1
Peak Frequency Curve
Arterial pulsation frequency (1/min)
Segment number
B)
Median spectrogram of men in SE Q4
Peak Frequency Curve
Arterial pulsation frequency (1/min)
Segment number
Power (arbitrary unit)
C)
Median power spectrum
SE Q1
SE Q4
Spectral Power (Arbitrary unit)
Arterial pulsation frequency (1/min)
D)
CDF of nocturnal APF
SE Q1
SE Q4
Cumulative Distribution Function
Arterial pulsation frequency (1/min)


A)
Median spectrogram of women in lapses Q1
Peak Frequency Curve
Arterial pulsation frequency (1/min)
Segment number
B)
Median spectrogram of women in lapses Q4
Peak Frequency Curve
Arterial pulsation frequency (1/min)
Segment number
Power (Arbitrary unit)
C)
Median power spectrum
Lapses Q1
Lapses Q4
Spectral Power (Arbitrary unit)
Arterial pulsation frequency (1/min)
D)
CDF of nocturnal APF
Lapses Q1
Lapses Q4
Cumulative Distribution Function
Arterial pulsation frequency (1/min)


A)
Median spectrogram of women in SE Q1
Peak Frequency Curve
Arterial pulsation frequency (1/min)
Segment number
B)
Median spectrogram of women in SE Q4
Peak Frequency Curve
Arterial pulsation frequency (1/min)
Segment number
Power (Arbitrary unit)
C)
Median power spectrum
SE Q1
SE Q4
Spectral Power (Arbitrary unit)
Arterial pulsation (1/min)
D)
CDF of nocturnal APF
SE Q1
SE Q4
Cumulative Distribution Function
Arterial pulsation (1/min)


Sensitivity
False Positive Rate
0.1
0.2
0.3
0.4
0.5
0.6
0.7
0.8
0.9
1
Sex+Age+ESS, AUC = 0.7197
Sex+Age+mAPF, AUC = 0.7141
Sex+Age+t90%, AUC = 0.6943
Sex+Age+ESS+t90%, AUC = 0.7349
Sex+Age+ESS+mAPF, AUC = 0.7314
mAPF, AUC = 0.5960
t90%, AUC = 0.5652
ESS, AUC = 0.6067