Parameters of Overnight Pulse Wave under Treatment in Obstructive Sleep Apnea

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Key Words

Pulse wave attenuation · Cardiovascular risk assessment · Obstructive sleep apnea · Continuous positive airway pressure · Pulse propagation time · Pulse rate acceleration · Autonomic state

Abstract

Background: Sleep-related breathing disorders may promote cardiovascular (CV) diseases. A novel and differentiated approach to overnight photoplethysmographic pulse wave analysis, which includes risk assessment and measurement of various pulse wave characteristics, has been evaluated in obstructive sleep apnea (OSA). **Objectives:** The purpose of this study was to assess if and which of the differentiated pulse wave characteristics might be influenced by OSA treatment with positive airway pressure (PAP). **Meth-**

ods: The study included two protocols. In the case-control study (group A), pulse wave-derived CV risk indices recorded during PAP therapy were compared with those obtained in age, body mass index, and CV risk class-matched patients with untreated OSA ($n = 67/67$). In the prospective PAP treatment study (group B), 17 unselected patients undergoing a full-night sleep test at baseline and after 23 ± 19 weeks of treatment were analyzed. **Results:** In untreated OSA patients (group A), the overnight hypoxic load was increased (SpO_2 index 38.7 ± 17.5 vs. 24.0 ± 11.1 , $p < 0.001$) and the pulse wave attenuation index (PWA-I) was lower (29.4 ± 9.2 vs. 33.5 ± 11.8 , $p = 0.022$) than in treated patients. In group B, PAP therapy reduced the hypoxic load and increased the PWA-I significantly. The composite CV risk index was slightly but not significantly reduced. **Conclusions:** PAP therapy modified the hypoxic load and pulse wave-derived markers. The PWA-I – associated with sympathetic vascular tone – was most prominently modified by PAP. This novel approach to markers of CV function should be further evaluated in prospective studies.

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Introduction

Obstructive sleep apnea (OSA) is characterized by repetitive reductions (hypopneas) or cessations (apneas) of airflow due to a collapse of the upper airway during sleep. These events are associated with intermittent hypoxemia, arousal from sleep, sleep fragmentation, and blood pressure elevation [1, 2]. The breathing disorder has been associated with sympathetic activation, inflammatory responses, oxidative stress, and arterial stiffness [3, 4]. OSA has been associated with cardiovascular (CV) and metabolic disorders, including coronary artery disease, heart failure, stroke, and atrial fibrillation, and constitutes an independent risk factor for arterial hypertension [5–14]. The hypoxic component of OSA was associated with all-cause mortality in the Sleep Heart Health Study [15].

Several studies have addressed the question whether positive airway pressure (PAP) therapy has an impact on CV disease in OSA. Hui et al. [16] described a reduction of the intima media thickness in OSA patients receiving PAP. PAP has been shown to reduce blood pressure in treatment-resistant hypertension [17]. Javaheri et al. [18] retrospectively analyzed the data of 30,719 newly diagnosed heart failure patients and reported a reduction of mortality in those diagnosed with and treated for OSA. In addition, a significant improvement in pulse wave parameters (reflective index and pulse wave velocity) suggesting vasoconstriction was achieved during PAP [19, 20]. Despite these direct potentially positive vascular effects, several studies failed to demonstrate a beneficial effect of PAP treatment on general measures of CV function [21].

A novel approach to the assessment of CV risk based on overnight finger pulse oximetry and pulse wave analysis was recently described [22]. As compared to other methods of pulse wave analysis, this method provides a differentiated analysis of pulse wave attenuation, pulse rate acceleration, pulse propagation time (PPT), respiration-related pulse rate oscillation (RRPO), and various measures of hypoxia during the night [22, 23]. A combined analysis algorithm was found to predict individual CV risk according to an established risk factor matrix in a multicenter setting of 520 subjects referred for evaluation of sleep apnea [23].

Previous data have shown that continuous PAP (CPAP) may improve recurrent hypoxia, arousal from sleep, and sympathetic hyperactivity leading to profound changes in acute hemodynamics, long-term CV functional mechanisms, and CV structure. However, CV response to PAP treatment is not uniform and may vary substan-

tially between OSA patients. In the current study, we asked if and which of the pulse wave-derived variables, particularly those influenced by hypoxia and sympathetic activation, may be modified by PAP treatment in patients with established OSA.

Study Design and Methods

Study Population

The study population consisted of two groups: a cross-sectional group of patients with PAP therapy that was compared to matched untreated OSA patients (group A), and a longitudinal study of OSA patients before and during PAP treatment (group B).

Group A included 67 consecutive patients who were admitted to the sleep laboratory for a PAP follow-up evaluation at Bethanien Hospital, Solingen, Germany. Additionally, 67 control patients were identified in the population of the Composite Biosignal Risk Score multicenter study. They were admitted for diagnosis of sleep-disordered breathing (2009–2011) and studied before treatment initiation ($n = 495$; post hoc analysis) [23]. All subjects were carefully characterized regarding their CV status and risk profile and matched for age, gender, body mass index (BMI), and ESH/ESC (European Societies of Hypertension and Cardiology) risk class (table 1; low risk = classes 1 and 2; moderate risk = class 3; high risk = classes 4 and 5) according to the current guideline [24].

Group B consisted of 10 consecutive patients at Bethanien Hospital, Solingen, Germany, and 7 patients from the Sahlgrenska University Hospital, Gothenburg, Sweden, who underwent a baseline diagnostic sleep study and a subsequent sleep study with PAP treatment (12 patients with CPAP, 1 with automatic PAP, 2 with bilevel PAP, 1 with adaptive servo-ventilation, and 1 with open PAP; table 2). The CV risk score was identified according to the standards described above.

Sleep Study and Finger Pulse Wave Recording

Patients underwent polysomnography or polygraphic recordings according to the local routines for ambulatory or attended sleep investigations as previously described [23]. In addition, a pulse oximeter device (SOMNOcheck II/R and K, SOMNOcheck II, or SOMNOcheck micro; Weinmann, Hamburg, Germany) containing a modified pulse oximeter module (ChipOx; Corscience, Erlangen, Germany) was attached to the finger. Recordings were performed within the expected nocturnal sleeping period. The polysomnography recordings were performed in the laboratory under personal supervision with lights-out periods between 22.30 and 6.00. Also, the polygraphic recordings were in part performed as laboratory assessments with comparable time windows. Sleep studies were evaluated in accordance with the American Academy of Sleep Medicine criteria [25]. All evaluated recordings had a minimum of 4 h of valid pulse wave recording.

Pulse Wave Analysis

The pulse wave was continuously sampled with 100 Hz, and PPT data were summarized as means of the overall sleeping period. A detailed description of the technical aspects, the algorithm, and the parameter extraction has been published elsewhere [22, 23, 26]. In short, the pulse wave signal was obtained by digital

Table 1. Anthropometric data, sleep study results, and pulse wave parameters in treated and untreated patients with OSA

Variable	Untreated OSA (n = 67)	PAP-treated group (n = 67)	p value
<i>Anthropometric and CV data</i>			
Age, years	62±13 (67)	63±12 (67)	0.986 ^a
BMI	32.3±7.6 (67)	31.6±6.5 (67)	0.820 ^b
Systolic blood pressure, mm Hg	133±19 (66)	134±16 (67)	0.862 ^b
Diastolic blood pressure, mm Hg	80±11 (66)	77±11 (67)	0.072 ^b
Resting heart rate, bpm	72±14 (66)	66±10 (67)	0.020 ^b
PAP treatment duration, weeks	–	115±152 (66)	–
PAP treatment compliance, h/night	–	5.3±2.2 (52)	–
ESH/ESC classification: low, moderate, high risk ^d	11, 12, 44	10, 11, 46	0.934 ^c
<i>Sleep study results</i>			
AHI, /h	23.8±18.2 (64)	4.5±6.8 (67)	0.000 ^b
Oxygen desaturation index (4% desaturations), /h	19.2±16.6 (67)	5.3±7.4 (67)	0.000 ^b
Mean saturation, %	94.2±2.5 (67)	95.8±1.8 (67)	0.000 ^b
<i>Data from the pulse wave analysis</i>			
PWA-I, /h	29.4±9.2 (67)	33.5±11.8 (67)	0.026 ^b
PR-I, /h	24.6±18.7 (67)	24.6±26.0 (67)	0.222 ^b
PPT, ms	160±31 (67)	158±32 (67)	0.639 ^a
SpO ₂ -I (2% desaturations), /h	38.7±17.5 (67)	24.0±11.1 (67)	0.000 ^b
Time below 90%, min	40.1±73.1 (67)	6.4±19.1 (67)	0.000 ^b
Time in symmetric desaturations, min	19.2±36.2 (67)	4.1±12.3 (67)	0.000 ^b
Chronotropic response to hypoxia (PR-I – SpO ₂ -I), /h	–14.2±26.1 (67)	0.6±26.9 (67)	0.006 ^b
RRPO	32.9±12.0 (67)	29.4±14.1 (67)	0.014 ^b
Composite Biosignal Risk Score	0.60±0.33 (67)	0.45±0.31 (67)	0.003 ^b

Values are means ± SD with numbers of patients in parentheses. ^a t test. ^b Mann-Whitney U test. ^c χ^2 test. ^d Low = ESH/ESC classes 1 + 2; moderate = ESH/ESC class 3; high = ESH/ESC classes 4 + 5.

photoplethysmography from pulse oximetry equipment during the night. The recording generates a single, unfiltered pulse wave signal (fig. 1). Several parameters were computed from this raw signal:

- 1 The pulse wave attenuation describes the relative change of the pulse wave amplitude compared to the mean amplitude of the preceding period. Pulse wave attenuations are caused by peripheral vasoconstriction which is associated with electroencephalogram arousal from sleep, autonomic arousals following resumption of ventilation after obstructive respiratory disturbances, and/or increased sympathetic activation of vascular alpha receptors [27–29]. The degree of nocturnal finger pulse wave attenuation is positively associated with elevated daytime systolic blood pressure [30]. On the other hand, mild pulse wave attenuations are common in healthy individuals. In the current study, the pulse wave attenuation index (PWA-I) is defined as the number of pulse wave attenuations (10–30% from baseline) per hour in the overnight recording.
- 2 PPT describes the time interval between the systolic peak and the peak of the reflecting pulse wave in milliseconds. A reduction of the PPT indicates increased arterial stiffness, and the signal correlates with the augmentation index obtained at the radial artery [23].

- 3 The mean RRPO is defined as the pulse rate variability in relation to the frequency band of breathing (0.15–0.4 Hz). It provides an indicator of the respiratory sinus arrhythmia.
 - 4 The pulse rate acceleration index (PR-I) represents the number of accelerations of the pulse rate of ≥10% from baseline per hour.
 - 5 The hypoxia index (SpO₂-I) is defined as the number of 2% oxygen desaturation events per hour.
 - 6 The difference between the PR-I and the SpO₂-I (PR-I – SpO₂-I) reflects the ‘chronotropic response to hypoxia’ which may be dampened in respiratory and cardiac disease as well as diabetes and autonomic neuropathy.
 - 7 ‘Time below SpO₂ 90%’ indicates the time in significant hypoxia during the night.
 - 8 ‘Time in symmetric desaturations’ reflects the time spent with periodic symmetric desaturation. It is used as an indicator of central breathing disorders such as Cheyne-Stokes respiration and/or central apneas.
 - 9 ‘Irregular pulse’ is based on the pulse-to-pulse time interval during the recording and is used to detect episodes with suspected arrhythmia.
- The Composite Biosignal Risk Score is derived from the information embedded in the parameters described above using a neu-

Table 2. Anthropometric data, sleep study results, and pulse wave parameters before and during PAP treatment in 17 patients

Variable	Baseline	During PAP	p value
<i>Anthropometric and CV data</i>			
Age, years	56±16 (17)	–	–
BMI	29.4±4.6 (16)	29.6±4.5 (17)	0.032 ^a
Systolic blood pressure, mm Hg	129±17 (16)	126±12 (17)	0.519 ^a
Diastolic blood pressure, mm Hg	79±8 (16)	77±10 (17)	0.460 ^a
Resting heart rate, bpm	62±8 (16)	62±8 (15)	0.168 ^b
ESH/ESC classification: low, moderate, high risk ^d	10, 0, 7	9, 2, 6	0.562 ^c
<i>Sleep study results</i>			
AHI, /h	33.0±23.4 (17)	3.8±5.1 (17)	0.001 ^b
Oxygen desaturation index (4% desaturations), /h	29.5±20.5 (17)	2.9±3.0 (16)	0.001 ^b
Mean saturation, %	93.8±2.3 (17)	95.8±2.3 (17)	0.000 ^b
<i>Data from the pulse wave analysis</i>			
PWA-I, /h	26.4±6.9 (17)	38.0±13.4 (17)	0.001 ^a
PR-I, /h	29.3±18.6 (17)	31.1±28.4 (17)	0.332 ^b
PPT, ms	168±42 (17)	166±39 (17)	0.492 ^b
SpO ₂ -I (2% desaturations), /h	41.1±16.8 (17)	18.8±9.4 (17)	0.000 ^a
Time below 90%, min	35.9±71.2 (17)	16.2±58.2 (17)	0.001 ^b
Time in symmetric desaturations, min	26.4±34.7 (17)	2.7±7.1 (17)	0.012 ^b
Chronotropic response to hypoxia (PR-I – SPO ₂ -I), /h	–11.8±24.4 (17)	12.3±30.8 (17)	0.022 ^b
RRPO	35.5±11.6 (17)	33.1±13.4 (17)	0.567 ^a
Composite Biosignal Risk Score	0.53±0.33 (17)	0.41±0.35 (17)	0.105 ^a

Values are means ± SD with numbers of patients in parentheses. ^a Paired t test. ^b Wilcoxon signed-rank test. ^c Fisher's exact test with Freeman-Halton extension. ^d Low = ESH/ESC classes 1 + 2; moderate = ESH/ESC class 3; high = ESH/ESC classes 4 + 5.

ro-fuzzy procedure. The output is a number between 0 (low risk) and 1 (high risk). This score has been validated against the ESH/ESC risk matrix [23].

Statistical Analysis

Statistical analyses were performed using IBM SPSS Statistics for Windows (version 22.0.; IBM Corp., Armonk, N.Y., USA). Statistical matching was done using the method of propensity scores by applying the SPSS syntax [31]. The method summarizes several factors like age, gender, BMI, and ESH/ESC risk score in order to identify the best-fit pairs. As a consequence, not all factors are always matched. Actually, the gender factor received a lower priority in a number of cases in order to get otherwise better matched pairs.

In short, a logistic regression was calculated with PAP treatment (yes/no) as the dependent variable and age, gender, BMI, and ESH/ESC risk score as the independent variables. The resulting regression coefficients were then used to calculate propensity scores for each data set. In the following step, statistical twins were identified from the data sets of patients by selecting those resulting in minimal propensity score differences. Descriptive statistics are presented as means ± standard deviations (SD). Data distribution was analyzed using the Shapiro-Wilk test. The effect of PAP therapy on pulse wave parameters in the case-control study (group A) was analyzed using Student's t test. Within-group treatment effects

(group B) were assessed with the paired t test or Fisher's exact test. In case of nonnormally distributed data, the Mann-Whitney U test (group A) or the Wilcoxon signed-rank test (group B) was used. A value of $p < 0.05$ was considered as statistically significant.

Statement of Ethics

The study was approved by the local ethical committees of the respective participating centers. All patients provided their written informed consent.

Results

Sixty-seven OSA patients (50 male, 17 female) who were treated with PAP (treatment duration 26.0 ± 34.8 weeks, daily use 5.3 ± 2.2 h/day, 13 CPAP, 2 bilevel PAP, 1 adaptive servo-ventilation, and 1 open CPAP) and 67 matched pairs with newly diagnosed OSA (55 male, 12 female) participated in the subprotocol A of the study. The two groups did not differ significantly in terms of age, BMI, number of hypertensive patients, and ESH/ESC risk class. The apnea-hypopnea index (AHI) in the untreated

Fig. 1. Representative examples of selected polysomnography channels from a male patient in the 2-min view. **a** Diagnostic recording. **b** Recording with PAP therapy. Flow = Respiratory flow derived from nasal cannula; SpO₂ = oxygen saturation; PF = pulse frequency; Pleth = plethysmogram (pulse wave).

patients was $23.8 \pm 18.2/\text{h}$; there were a mean of <5 respiratory disturbances per hour in the PAP-treated group ($p < 0.001$; table 1).

The analysis of the overnight pulse wave recording showed a highly significant difference in the total Composite Biosignal Risk Score between untreated and treated patients ($p = 0.003$). The pulse wave parameters showed significant differences in the hypoxia-related variables (all $p < 0.001$), the chronotropic response to hypoxia (PR-I – SpO₂-I; $p = 0.006$), the PWA-I ($p = 0.026$), and the RRPO ($p = 0.14$). The PR-I and the PPT did not show any significant changes (table 1).

In the subprotocol B (longitudinal), sleep apnea was sufficiently treated in patients with moderate to severe sleep apnea at baseline (AHI at baseline vs. AHI at follow-up, $p = 0.001$; table 2). Mean PAP compliance was 5.3 ± 2.8 h/night, but there was no significant change in blood pressure and heart rate. The Composite Biosignal Risk Score was reduced substantially; however, the difference failed to reach statistical significance ($p = 0.11$). As ex-

pected, all the hypoxia-related parameters were significantly reduced after PAP treatment. The difference between PR-I and SpO₂-I (PR-I – SpO₂-I) and the PWA-I increased significantly ($p = 0.022$ and 0.001 , respectively). There was no significant change of PR-I, RRPO, or PPT before and after PAP therapy (table 2).

Discussion

This is the first study to address the effect of PAP treatment on several finger pulse wave parameters in OSA patients. PAP treatment significantly modified pulse wave parameters which are proposed to reflect CV function and disease. As expected, hypoxia-related parameters were all significantly reduced during PAP. In addition, the PWA-I, a marker of sympathetic vascular tone, was significantly modified after PAP treatment, suggesting an offloading of sympathetic activity. The overnight CV risk index, a marker of overall CV risk, was changed by PAP treatment.

PAP therapy is associated with a reduction of periodic hypoxia, sympathetic activity, and blood pressure along with an improvement in sleep quality. All these factors have been related to an improvement in CV health [32, 33]. Finger vascular capillary hemodynamics and shunting are strongly influenced by changes in oxygen saturation. Hypoxia is known not only to influence circulation in the local vascular bed but also sympathetic activity resulting from chemosensory reflexogenic activation [34]. As expected, there was a reduction of the $\text{SpO}_2\text{-I}$ following PAP therapy, and the derived parameter $\text{PR-I} - \text{SpO}_2\text{-I}$ (reflecting the chronotropic response to hypoxemia) increased significantly in both subprotocols. It is also noteworthy that the 4% oxygen desaturation index improved more markedly than the 2% desaturation index ($\text{SpO}_2\text{-I}$) used in the pulse wave algorithm. This indicates that small variations in oxygenation still persist under PAP treatment. These small variations may influence the net pulse wave signal under study, but their exact qualitative and quantitative significance remains to be determined.

The algorithm for further analysis of the pulse wave signal has previously been described in detail [23]. A consistent increase in the PWA-I was found in both subprotocols of the current study. This increase in the PWA-I is interesting in many respects. In a previous study, a higher number of small pulse wave attenuations, as reflected by a higher PWA-I, was associated with a lower CV risk in patients with suspected sleep apnea [22]. Our current results also showed a higher PWA-I under treatment than at baseline. The PWA-I of the current algorithm describes the number of reductions in the pulse wave amplitude in a mild range from 10 to 30%. Although the physiological origin of these smaller attenuations remains to be determined, their relative increase following treatment of OSA with PAP might suggest that they reflect an off-loading of high sympathetic tone. Consequently, it is tempting to propose that a higher PWA-I may reflect less fragmented sleep with fewer arousals allowing for more spontaneous small attenuations. Indeed, a previous study using peripheral arterial tone reported a positive correlation between daytime blood pressure and the amount of more pronounced pulse wave attenuations during sleep [30]. These profound pulse wave attenuations have been associated with electroencephalogram-verified arousal intensity [35]. These hypotheses need to be further explored in future studies.

There were no relevant changes in PPT or PR-I following PAP treatment. The PPT has been shown to reflect arterial stiffness. Surprisingly, despite the improvements

in hypoxia and the reduction of arousals compatible with sympathetic off-loading, there were no significant differences in these variables between the treated and untreated condition. PPT is known to correlate strongly with blood pressure in cross-sectional studies [36]. Considering that there was no blood pressure change in the current study, the lack of PPT change with PAP treatment was not unexpected. The PR-I, which reflects overnight pulse rate variability, is more complex and may be influenced by both hemodynamic changes and chronotropic influences. Reduction of sleep-related breathing disturbances may, on the one hand, reduce the apnea-induced variations in heart rate. On the other hand, sympathetic off-loading is known to increase heart rate variability. We were not able to discriminate between these two possible mechanisms with the PR-I.

The current study included a careful classification of CV risk factors, and pulse wave parameters were analyzed centrally by a single scorer. On the other hand, this was an explorative study which lacked an appropriate power calculation and correction for multiple comparisons. Therefore, it does not allow for final conclusions, generalizations (gender disparity), or further stratifications.

We did not aim to redo the general linear modeling analysis [23, 26] in a smaller cohort of individuals due to a lack of statistical power. In particular, the previously identified confounding factors like age, BMI, or sleep apnea were kept constant (longitudinal analysis) or were adjusted for in the case-control design.

Patients were treated with different PAP appliances. However, the aim of this study was to show the changes in pulse wave parameters under sufficient treatment and not to compare different therapeutic options. The matching process including age, BMI, gender, and ESH/ESC risk class yielded well-balanced groups, but part of the observed between-group differences may not be attributed to treatment conditions alone. It should be mentioned that investigations concerning the retest variability of overnight pulse wave recordings suggested that changes across the spectrum of pulse wave parameters were mostly related to the night-to-night variability of mild sleep apnea (data on file). Our novel method has shown a strong association with established CV risk estimates in cross-sectional studies [23, 26], which were superior to traditional measures of sleep and sleep apnea derived from traditional sleep recordings. However, the capacity of the method for the prediction of prospective CV outcomes still needs to be determined.

We systematically studied the influences of underlying CV diseases or medications, but the effects of both factors on the pulse wave overlapped strongly (data not shown). It is, therefore, impossible to decide if a certain pulse wave pattern is caused by the medication or the underlying disease.

Finally, the data describe means of the recording period. Thus, the current analysis does neither allow a description of the course of the pulse wave parameters throughout the sleeping period nor an analysis during smaller time periods.

In conclusion, from this longitudinal and cross-sectional analysis, it is suggested that PAP therapy modifies nocturnal hypoxia and the PWA-I and improves the Composite Biosignal Risk Score which includes several aspects of the pulse wave characteristics. Our results support the hypothesis that advanced pulse wave analysis during sleep may be helpful to noninvasively determine the CV effects of PAP treatment in OSA. Future studies are needed to further characterize the predictive value of pulse wave parameters in this context.

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