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Assessment of microcirculation among patients with obstructive sleep apnea after CPAP treatment

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Abstract

Introduction and Objective. Obstructive sleep apnea (OSA) is distinguished by recurrent partial or complete obstruction of the upper airways during sleep. The prevalence of OSA worldwide is estimated at 3–24% of the general population. Patients with OSA are predisposed to having endothelial dysfunction due to different mechanisms. The aim of a study was to assess the impact of 3 -month CPAP treatment on microcirculation among patients with OSA, and to determine changes in blood pressure after implemented therapy.

Materials and Method. The study included 30 patients with newly-diagnosed OSA. Microcirculation assessment was performed by Laser Doppler Flowmetry before and 3 months after implementation of CPAP therapy. Patients were also asked to perform measurements of blood pressure twice, 7 days prior to the appointment.

Results. Improvement was observed in selected PORH parameters, such as AH, which was significantly increased after 3 months of treatment of CPAP ($p<0.05$). There was also a significant decrease in the RL/BZ parameter. Other PORH parameters did not differ significantly. Blood pressure, both diastolic and systolic, significantly decreased after therapy.

Conclusions. Current study does not exactly explain the accurate mechanism underlying the changes of PORH after CPAP treatment among patients with OSA. However, it was demonstrated that 3 months adequate treatment improved endothelial function among the studied group. Assessment of microcirculation by LDF PORH protocol is a promising method, due to simplicity for the examinator, and non-invasive procedure. Due to the small study group, further investigation of microcirculation among patients with OSA should be performed, including the influence of co-morbidities and medications intake.

Key words

obstructive sleep apnea, microcirculation, CPAP

INTRODUCTION

Obstructive sleep apnea (OSA) is distinguished by recurrent partial or complete obstruction of the upper airways during sleep [1]. The prevalence of OSA worldwide is estimated at 3–24% of the general population. However, in many well-developed countries, especially with a high percentage of obese individuals, OSA affects more than 50% of the population [2]. The most common manifestation of OSA is snoring during sleep, whereas daytime symptoms include chronic fatigue and somnolence during daily activities [3]. The assessment of daytime sleepiness could be performed by using the Epworth Sleeping Scale (ESS) or STOP-Bang Questionnaire, which are known as useful and easy screening tools to separate patients with high risk of OSA and continue further diagnosis [4].

Overnight polysomnography is considered to be the method of choice in diagnosing obstructive sleep apnea, central sleep apnea, and other sleep disorders [3]. However, full polysomnography is a time-consuming and complex method, thus more simplified procedures such as polygraphy are used in clinical practice as a sufficient diagnosis of OSA [5].

Continuous positive airway pressure (CPAP) is considered to be the method of choice in non-invasive OSA therapy. The device continuously delivers air during both respiratory phases [6]. In the case of intolerance of CPAP, there are other modes of ventilation, such as bilevel positive airway pressure (BPAP), with different pressures during inspiration and expiration, which could be more acceptable [6]. Moreover, there are some alternative, non-invasive methods, such as the implementation of mandibular advancement device (MAD), which maintains the tongue and mandible in an appropriate position, resulting in a decrease in the risk of collapsing upper airways during sleep [7]. An indispensable element of treatment in every OSA stage is lifestyle modification, such as the withdrawal of alcohol and sleeping pills, weight loss, and avoidance of the supine position during sleep [8]. In the case of unsuccessful treatment with non-invasive methods, there are some alternative methods such as upper airway surgery, for example, soft palate operation and positional therapy [8].

Intermittent disturbed airflow via upper airways due to obstruction during sleep among patients with OSA leads to apnea/hypopnea episodes and consequent intermittent

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hypoxaemia and hypercapnia [9]. Patients with OSA are predisposed to have endothelial dysfunction due to the mechanism mentioned below. Hypoxaemia promotes the production of pro-inflammatory factors, such as interleukin 6 (IL-6) and tumour necrosis factor alfa (TNF-alfa), which lead to the migration of leukocytes and accumulation of macrophages and fat cells in the vessel wall, which promote endothelial damage and increase the risk of atherosclerosis [10]. On the other hand, reoxygenation, which occurs after episodes of hypopnea/apnea, promotes reactive oxygen species (ROS) production, leading to systemic oxidative stress [11]. ROS via different complex mechanisms contribute to endothelial dysfunction, among others by reacting with proteins and nucleic acids, causing DNA failure and cellular destruction, and secondly by enhancing the expression of leukocyte-specific (L-selectin and integrins) and endothelial-specific adhesion molecules (E-selectin, P-selectin, ICAM-1, and VECAM-1) [10]. In addition, the expression of endothelial nitric oxide synthetase (eNOS) is impaired among patients with OSA, which results in decreased concentration and secretion of nitric oxide (NO), which is essential in the proper regulation of endothelium. Moreover, interrupted sleep induces enhanced nocturnal cortisol release and consequent dysregulation in the hypothalamus–pituitary–adrenal axis, which contributes to an increased risk of hypertension [12]. Taking into account the mechanisms detailed above, endothelial dysfunction among patients with OSA contributes to microcirculation impairment, which increases the risk of cardiovascular events such as myocardial infarction and stroke in this group of patients [13].

Microcirculation is defined as the system of vessels with diameters less than 100 um and consists of arterioles, venules, metarterioles, and capillaries. Laser-Doppler flowmetry (LDF) is a non-invasive and innovative method used to assess endothelial function. The post- occlusive reactive hyperaemia (PORH) protocol, which obtains results automatically, allows for sensitive detection of endothelial disorders [14].

OBJECTIVE

The aim of a study was to assess the impact of 3 -month CPAP treatment on microcirculation among patients with OSA, and to determine changes in blood pressure after the implemented therapy.

MATERIALS AND METHOD

The study was carried out in 2021–2024 among 39 volunteer patients newly-diagnosed OSA. Overnight polysomnography was performed without adaptation night Polysomnographic data were recorded by the devices Alice 6 LDe and NOXA 1. During the procedure, the apnea-hypopnea index (AHI) was calculated by adding all apneas and hypopneas, and then dividing the result by total sleep time. OSA was diagnosed by the presence of AHI >5/h. The severity of OSA was divided into mild, moderate, and severe depending on AHI: mild – 5–14/h, moderate – 15–29/h, and severe – over 30/h. Inclusion criteria were patients with *de novo* diagnosed OSA, without any previous treatment, and qualification to CPAP treatment as first choice therapy. Exclusion criteria included central sleep apnea, intolerance of CPAP, prior CPAP therapy, diabetes mellitus, any change of drugs that may have an influence on endothelial function, and estimated glomerular filtration rate (eGFR) <30 ml/min/1.73m^2. Patients were also asked to perform measurements of blood pressure twice, 7 days prior to the appointment. Because of intolerance to CPAP (time of use <4 h/day) or absence at follow-up appointments, 9 patients were excluded from the study and were not included in the statistical evaluation. The characteristics of patients is presented in Table 1.

Table 1. General characteristics of patients

	Research group (N=30)		
	Mean	Median	SD
Age (y)	63.5	65.0	7.81
Weight (kg)	94.45	94.75	15.13
BMI (kg/m^2)	31.74	31.33	4.1
ESS score	10.9	11.0	2.28
AHI (/h)	46.11	46.75	13.55
Smoker – current – ex	 3 (10%) 11 (36.67%)	 -	 -

BMI - body mass index; ESS – Epworth Sleeping Scale; AHI – apnea-hypopnea index

Laboratory analysis. Blood samples were collected in the morning from fasting subjects. The concentration of LDL cholesterol was calculated by using the Friedwald equation, under the condition that triglycerides were below 400 mg/ dl, with the formula: LDL (mg/dl) = TC (mg/dl) – HDL (mg/dl) – TG (mg/dl)/5 (Tab. 2).

Table 2. Morphological and biochemical parameters among research group

Parameters	Research group (N=30)		
	Mean	Median	SD
CRP (mg/l)	3.9	3.62	2.77
Total cholesterol (mg/dl)	195.36	192.4	23.7
LDL-C(mg/dl)	117.04	114.5	25.01
non-HDL-C (mg/dl)	145.88	141.0	27.41
HDL-C (mg/dl)	48.93	45.5	11.29
Triglycerides (mg/dl)	148.83	130.5	63.22
Fasting glucose (mg/dl)	99.47	97.5	14.56
HbA1c%	5.63	5.7	0.58
Uric acid (mg/dl)	6.14	6.05	0.81
Hgb (g/dl)	14.54	14.35	1.33
MCV (fl)	88.38	88.65	4.2
MCH (pg)	30.58	30.5	0.71

CRP – C-reactive protein; LDL – C-low-density lipoprotein cholesterol; HDL-C – high-density lipoprotein cholesterol; Hgb – haemoglobin; MCV – mean cell volume; MCH – mean cell haemoglobin

Assessment of microcirculation. Microcirculation assessment was performed by Laser Doppler Flowmetry (LDF) (moorVMSLDF-MOOR Instruments, Axminster, Devon, UK) before, and 3 months after implementation of CPAP therapy. Participants were advised to refrain from caffeine and alcohol consumption, avoid intensive exercise and all tobacco products and e-cigarettes for at least 24 hours before the examination. The study was performed in a quiet

room, where the temperature was constant around 22–24 °C, between 15:00 – 19:00. Examination was performed after 15 min of participant acclimatization to the examination room conditions, and after 15 min in the supine position, during which study was performed. The pressure cuff was adjusted according to the arm circumference and placed 3 cm above the elbow flexion. The probe was attached to the medial surface of a non-dominant arm, 10 cm below the elbow flexion. Measurements and the PORH test protocol were performed according to the manufacturer`s recommendations (sequence in Tab 3).

Table 3. PORH test protocol

Test parameter [units]	Value
Resting flow time [s]	20
Occlusion time [s]	180
Cuff pressure [mmHg]	30 mmHg above systolic blood pressure, measured directly before the examination
Flow after occlusion [s]	360

The resting level (RL), biological zero (BZ), and maximum level (MZ) measurements were calculated as perfusion units (PU). The (PF-RF)/RF and (PF-BZ)/BZ values were calculated as % change. Time to zero increase (T0), time to recovery (TR), time to maximum level (TM), and time to half-decay (TH) values were recorded as second (s). The area occlusion (AO) and area of hyperaemia (AH) were also recorded as thearea under the curve.

Statistical analysis. The first step in statistical data analysis was to check the data distributions. The analysis carried out using histograms and the Shapiro-Wilk test showed that the vast majority of data distributions deviated from the normal distribution curve. In this situation, non-parametric data analysis methods were used for further analysis. Descriptive statistics and count distributions were calculated for the survey data. In order to detect differences between data groups, the Mann-Whitney U test (in the case of independent groups) and the sign test (in the case of dependent groups) were used; the differences were graphically presented on frame-and-whisker charts. In order to detect relationships between variables, the Spearmann r correlation coefficient was used. In all analyses, the critical significance level was $p<0.05$. All calculations were performed using the Statistica v.13.3 programme.

RESULTS

The study was completed by 30 patients aged 50–76 years, in which men were the majority (76.67 %). The vast majority of patients were treated for hypertension (80%) or dyslipidaemia (63.33%), and more than half were obese (63.33%) with a mean BMI of 31.74 kg/m^2. Among other co-morbidities, prediabetes was distinguished (33.33%). Patients with hypertension were treated mainly by ACE/ARBs inhibitors (75%), beta-blockers (62.5%), calcium blockers (37.5%), and non-thiazide diuretics (20.83%). Other types of anti-hypertensive drugs were less commonly used.

Assessment of the average ambulatory measurements of blood pressure, measured 7 days prior to the first appointment, compared to measurements performed 7 days before the second appointment after 3 months of CPAP therapy, showed a statistically significant reduction in systolic and diastolic blood pressure independently from the prior diagnosis of hypertension.

Table 4. Comparison between blood pressure values before and 3 months after CPAP therapy

Parameters (mmHg)	Baseline			3 months			p
	Mean	Median	SD	Mean	Median	SD	
Systolic blood pressure	130.93	132	13.62	126.3	129	15.57	0.000013*
Diastolic blood pressure	82.37	80	12.70	78.7	80	8.77	0.001384*

* ($p<0.05$)

Results of the assessment of microcirculation performed by LDF in the PORH protocol Rare presented in Table 5.

Table 5. Comparison between Laser Doppler flowmetry parameters – resting level (RL) and other PORH parameters before and 3 months after using CPAP therapy

Parameters	Baseline			3 months			p
	Mean	Median	SD	Mean	Median	SD	
RL (PU)	24.8	19.1	14.85	20.52	18.93	8.38	0.85
BZ (PU)	5.72	4.9	2.3	6.33	5.65	2.54	0.58
ML (PU)	87.63	67.25	58.43	86.1	77.4	35.7	0.58
RL/BZ	4.36	3.62	2.51	3.52	3.5	1.49	0.045*
ML/BZ	15.92	13.75	10.46	14.95	13.1	8.9	0.85
ML/RL	4.55	3.2	4.72	4.86	3.96	2.76	0.36
AO (units/s)	2512.91	1896.7	2051.4	2103.94	1936.3	736.79	0.85
AH (units/s)	891.23	771.05	413.56	1070.67	982.05	473.16	0.000523*
AH/AO	0.49	0.44	0.3	0.57	0.54	0.3	0.1
T0 (s)	0.23	0.23	0.21	0.28	0.21	0.33	1
TR (s)	1.16	0.86	0.89	1.28	1.25	0.66	0.46
TM (s)	23.87	7.84	66.34	21.49	7.82	51.84	0.2
TH (s)	34.24	19.55	64.16	32.47	18.66	49.4	0.2

* $p<0.05$

Table 6. R- Spearmann`s correlation between selected parameters and PORH values obtained from baseline microcirculation examination

Variable	ML	ML/BZ	ML/RL
Age	0.071	0.41*	0.20
Systolic BP baseline	-0.14	-0.09	-0.45 *
ESS score	-0.35	-0.60*	-0.36
Non-HDL C	0.12	0.23	0.45*
HbA1c%	0.37*	0.06	-0.13

BP- blood pressure; ESS - Epworth Sleeping Scale; non-HDL-C - non high-density lipoprotein cholesterol; *- $p<0.05$

It was demonstrated that RL/BZ ratio differed significantly and was reduced, compared before and after therapeutic intervention ($p<0.05$) (Fig. 1a). Moreover, there was a significant increase in the value of AH after 3 months of treatment of CPAP ($p<0.05$) (Fig. 1b).

Moreover, the RL/BZ ratio also differed significantly and was reduced, compared with before and after therapeutic intervention ($p<0.05$). In the rest of the PORH parameters,

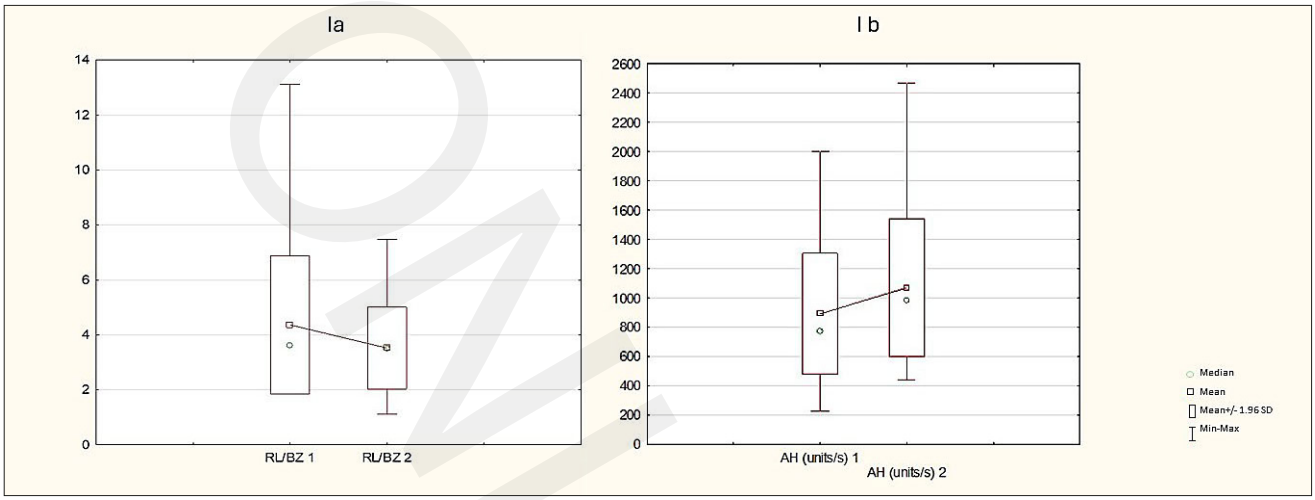

Figure 1a. RL/BZ values in patients before (RL/BZ 1) and after 3 months (RL/BZ 2) of CPAP therapy; p= 0.044610*. **1b**. AH values in patients before (AH 1) and after 3 months (AH 2) of CPAP therapy; p= 0.000523*.
SD- standard deviation, *- statistically significant

including flow parameters (RL, BZ, ML, ML / RL) and time parameters (T0, TR, TM TH), there were no significant differences.

The U Mann-Whitney`s test was performed to detect any correlation between co-morbidities and values measured during the PORH protocol, where $p<0.05$ was statistically significant. The study demonstrated that obesity was correlated with superior values of AHI ($p=0.006678$) and ESS score ($p=0.013342$). A similar positive interconnection was found among patients with dyslipidaemia and AHI ($p=0.011077$) and ESS score ($p=0.013342$). Patients with prediabetes had lower values of baseline RL ($p=0.036602$) and baseline BZ ($p=0.000816$), compared to patients without carbohydrate metabolism disorder.

The r-Spearmann`s correlation test was performed which showed some significant correlation between different biochemical parameters or general characteristic parameters, and PORH values performed at baseline. A positive, statistically significant correlation was found between HbA1c% and ML. ML/BZ values were positively correlated with age, and negatively with ESS score ($p<0.05$ for both). ML/RL values were positively correlated with non-HDL cholesterol concentration, and negatively with baseline systolic blood pressure ($p<0.05$ for both).

DISCUSSION

The endothelial dysfunction among patients with OSA is caused by various mechanisms, such as inflammation, oxidative stress, and impaired NO synthesis and release. Moreover, OSA is rarely a separate disease, since it commonly co-exists with other co-morbidities such as hypertension and obesity. The main risk factor of OSA is obesity, which is confirmed by the results of the current study. In addition, obesity increases the risk of other metabolic disorders such as dyslipidemia and pre-/diabetes. All these disorders have an unquestionable impact on endothelial function via different phenomena and biochemical pathways, and should therefore be considered during interpretation of results. In the current literature, there is also evidence that there is a difference in endothelial function between men and women with OSA [15], which could be a result of endocrine impact; however, further research is required.

LDF is known as the preferred technique for assessing skin microcirculation; however, in its traditional form it is dependent on external measurement conditions and should therefore be performed using provocation tests, such as PORH, iontophoresis of vasoactive factors (noradrenaline, acetylcholine, sodium nitroprusside) and local heating [16]. Due to the non-invasive protocol, in the current study a PORH test was performed to assess the microcirculation. It should be emphasized, that the PORH mechanism has not been accurately clarified. Previous studies, however, have underlined that many factors are involved in the PORH reaction, such as nitric oxide, prostaglandins, myogenic, and metabolic factors, as well as large-conductance calcium-activated potassium (BKCa). This suggests that PORH is an essential non-invasive method for assessing cardiovascular risk [17]. According to Shirazi et al., the most reproducibility parameters of PORH are ML and RL, while ML/RL and TM are less reliable and reproducible [18].

The current study demonstrated a significant increase in AH and decrease in RL/BZ values after treatment. Changes in AH values indicate improvement in endothelial function, which are results similar to those obtained in other studies [19, 20]. On the contrary, RL/BZ have not yet been reported in recent studies. Cabalero-Eraso et al. performed a study among a smaller group of non-hypertensive, obese patients with OSA, which should be considered in the interpretation [19]. In the study performed by Muñoz-Hernandez et al., the number of patients was comparable; however, in the current study, the population was older and patients with co-existing diabetes were excluded from the study. AH is also known as a good predictor of microvascular function as it shows the intensity and duration of the response, which is slower among patients with OSA compared to healthy controls [19]. AH was also investigated in another study based on the flow-mediated dilation (FMD) of the brachial artery in response to post-ischemic reactive hyperaemia, where AH was impaired among patients with cardiovascular risk factors (CRF), such as diabetes, hypertension and dyslipidaemia. Mitchell et al. performed a study on a large group (n=2,640) using the above-mentioned method; however, the conclusion of the study

suggests that the impairment of hyperaemic flow among patients with CRF is a consequence of decreasing the stimulus for dilation, such as reduction of synthesis and release of NO, rather than impairing endothelial function [21].

Trzepizur et al. performed a prevocational test with acetylcholine iontophoresis, which is known as an endothelium-dependent vasodilation factor, with LDF assessment of microcirculation among patients with OSA [22]. The results showed a significantly lower response of microcirculation for acetylcholine injection in patients with OSA, compared to the control group. Furthermore, the authors divided the patients with OSA into 2 groups with different kind of treatment for 2 months – CPAP treatment and MAD. The results demonstrated significant improvement in both group in response of microcirculation for acetylcholine infusion; however, MAD was less efficacious than CPAP in reducing AHI and nocturnal oxygen desaturations.

In the current study, patients with co-existing diabetes were excluded, thus it is reported that diabetes significantly disturbs endothelial function. Bakker et al. performed a cross-sectional study on 141 patients divided into 4 subgroups; control, patients with OSA, patients with diabetes mellitus type 2 (DM 2), and patients with OSA and co-existing DM2 [23]. A placebo-controlled trial was performed to compare sham and active CPAP among the latter group, with assessment of endothelial function by measuring brachial artery diameter after FMD and nitroglycerin-induced dilation. The authors concluded that a combination of OSA and DM2 had a greater influence on endothelial dysfunction than the effect with each diseases alone; additionally, 3 months of CPAP treatment did not significantly improve endothelial function in this group of patients. There is no recent evidence on the influence of prediabetes on microcirculation disorders assessed by non-invasive methods, such as FMD and LDF.

A significant reduction in blood pressure was also demonstrated in the current study. CPAP therapy reduces episodes of nocturnal hypoxia, which results in reduction in the number of awakenings during sleep. A possible explanation for this phenomena is that stimulation of the sympathetic nervous system is reduced and the level of nocturnal cortisol is lowered, resulting in lower blood pressure during the day.

A limitation of the study is the small study group; thus, further studies should be performed on a larger group. Despite the small size of the group, the obtained results showed a significant improvement in microcirculation. Moreover, patients included in the study were taking statins and hypotensive drugs, such as ACE-I/ARB, which could also have an impact on endothelial function. However during 3 month period between each appointment there were no changes in treatment.

CONCLUSIONS

The study does not exactly explain the accurate mechanism underlying the changes of PORH after CPAP treatment among patients with OSA. However, it was demonstrated that 3 months adequate treatment improved endothelial function among the studied group. The assessment of microcirculation by LDF PORH protocol is a promising method, due to its simplicity for the examinator and non-invasive procedure. Due to small study group, further investigation of microcirculation among patients with OSA should be performed, including the influence of comorbidities and intake of medications. In future, it would be helpful to estimate the response to the treatment for patients with OSA according to other CRF and severity of OSA.

Institutional Review Board Statement. The study was conducted in accordance with the Declaration of Helsinki and approved by the Ethics Committee of the Medical University of Lublin, Poland (Protocol Code: KE-0254/17/2020).

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