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ORIGINAL PAPER

Can dynamic and static pupillary responses be used as an indicator of autonomic dysfunction in patients with obstructive sleep apnea syndrome?

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Abstract
Purpose We aimed to reveal whether static and dynamic pupillary responses can be used for the detection of autonomic nervous system (ANS) dysfunction in patients with obstructive sleep apnea syndrome (OSAS).
Methods We included in this study patients with OSAS, who were divided into three groups according to the apnea–hypopnea index (AHI) (group 1, mild [$n = 20$]; group 2, moderate [$n = 20$]; and group 3, severe [$n = 20$]), and healthy controls (group 4, $n = 20$). Pupillary responses were measured using a pupillometry system.
Results Static (mesopic PD, $P = 0.0019$; low photopic PD, $P = 0.001$) and dynamic pupil responses (resting diameter, $P = 0.004$; amplitude of pupil contraction, $P < 0.001$; duration of pupil contraction, $P = 0.022$; velocity of pupil contraction, $P = 0.001$; and velocity of pupil dilation, $P = 0.012$) were affected in patients with different OSAS severities. Also, AHI was negatively correlated with mesopic PD ($P = 0.008$), low photopic PD ($P = 0.003$), resting diameter ($P = 0.001$), amplitude of pupil contraction ($P < 0.001$), duration of pupil contraction ($P = 0.011$), velocity of pupil contraction ($P < 0.001$), and velocity of pupil dilation ($P = 0.001$).
Conclusion We detected pupil responses innervated by the ANS were affected in the OSAS patients. This effect was more significant in the severe OSAS patients. Therefore, the pupillometry system can be an easily applicable, noninvasive method to detect ANS dysfunction in the OSA patients.

Keywords Pupillometry · Obstructive sleep apnea syndrome · Autonomic dysfunction · Diabetic autonomic neuropathy

Introduction

Obstructive sleep apnea syndrome (OSAS) can be defined as a syndrome that is characterized by recurrent full or partial obstructed attacks of the upper airway during sleep, causing nighttime snoring and daytime sleepiness [1, 2]. It has been reported that OSAS, which is characterized by decreased blood oxygen saturation, is associated with cardiovascular diseases and diabetes mellitus and can cause serious

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morbidity and mortality [3–6]. The diagnosis of OSAS is made with the apnea–hypopnea index (AHI) > 5/h in the polysomnography record, which is a test based on the simultaneous and continuous recording of neurophysiological, cardiac, respiratory, physiological, and other physical parameters overnight [7]. The apnea–hypopnea index (AHI) measures the number of times that an abnormally low breathing rate or complete cessation of breathing occurs every hour [8]. According to AHI, patients can be classified as simple snoring (AHI < 5/h), mild OSAS (5/h ≤ AHI ≤ 15/h), moderate OSAS (15 < AHI < 30/h), and severe OSAS (AHI ≥ 30/h) [9]. The sympathetic nervous system (SNS) activity increases with the stimulation of peripheral and central chemoreceptors caused by chronic hypoxia, hypercarbia, and respiratory acidosis in patients with OSAS [10, 11]. Similarly, because of the autonomic nervous system (ANS), dysfunction developing in these patients, the sympathetic tone increased during daytime [12].

The pupillary light reflex innervated by the ANS is defined as the pupil's response to light. While the circular muscles of the iris cause the pupil to constriction, the radial muscles (dilator pupillae) cause dilatation. The circular muscles of the iris, whose functions are regulated by the parasympathetic nervous system (PNS), cause the pupil to constriction, while the radial muscles (dilator pupillae), whose functions are regulated by the sympathetic nervous system (SNS), cause dilatation [13]. In PNS dysfunction, pupil constriction is delayed in light exposure, while in SNS dysfunction, the dilation of the pupil in the dark is delayed. In addition, the pupil response may vary depending on many diseases affecting the neuronal pathways of the visual system [14–17]. Measurement of pupillary responses can be done noninvasively and objectively in different light conditions with automatic pupillometry, which enables obtaining pupillary response with infrared pupillography [18, 19].

ANS dysfunction is considered to play an important role in OSAS-related morbidity. ANS evaluation can be done using invasive and labor-intensive methods such as heart rate variability (HRV), blood pressure (BP), and BP variability (BPV) [20, 21]. Therefore, in this study, it was aimed to reveal whether pupillary responses can be used in the detection of autonomic dysfunction in the OSAS patients.

Methods

Study design

Patients who were diagnosed with OSAS (group 1, mild [n = 20]; group 2, moderate [n = 20]; and group 3, severe [n = 20]), after polysomnography (PSG) taken in the sleep disorder department of the chest diseases clinic of Dicle University Hospital and referred to the Department of Ophthalmology for eye examination and healthy controls (group 4, n = 20), were included in this study. We obtained approval from the Dicle University School of Medicine ethics committee for the study. Our study was conducted according to the Declaration of Helsinki, and written informed consent was obtained from all patients before the measurement.

Subjects and measurements

We performed a complete ophthalmologic examination for all subjects included in this study. Patients who did not have any systemic disease, who did not have iris pupil pathology, who did not have pseudo exfoliation, who did not have glaucoma, who did not have previous intraocular surgery or inflammatory disease, who did not use eye drops with the potential to affect pupillary responses, and who did not use systemic anticholinergic drugs were included in the study.

A single experienced clinician made all pupillometry measurements (MonPack One; Metrovision, Pérenchies, France). Pupillary responses (both static [scotopic, mesopic, low photopic, and high photopic] and dynamic [resting PD, contraction amplitude, latency, duration, velocity of contraction, dilation latency, duration, and velocity at rest]) were detected using a pupillometry system in each subject included in the study. The average of three consecutive measurements was taken. Measurements were made at a similar time to reduce the effect of circadian changes.

According to the international 10–20 electrode system, with 44-channel digital video polysomnography; electroencephalography (EEG), electrooculography (EOG), chin and both pretibial electromyography (EMG), electrocardiography (ECG), oximeter, pulse transit time (PTT), thoraco-abdominal breathing effort, oro-nasal airflow, snoring sound, pulse and

body position were recorded. A sleep technician was present during the entire recording.

Statistical analysis

SPSS 26.0 version (Chicago, IL, USA) was used for all statistical analyzes. Descriptive statistics were used for demographic analysis of the groups. One-way ANOVA analysis was used for comparison between different groups. Tukey's test was used in post hoc analysis to determine whether there was a significant difference in paired comparisons of the groups. We used Pearson correlation analysis to analyze the correlation between AHI and static and dynamic pupillary responses in patients with OSAS.

Results

The mean ages of the study participants were 47.25 ± 6.86, 51.25 ± 11.11, 48.10 ± 8.40, and 48.35 ± 11.05 years in groups 1, 2, 3, and 4,

Table 1 Demographic and clinical characteristics of the study participants

Characteristic	Group 1 (mild OSAS; AHI, 5–14.9)	Group 2 (moderate OSAS; AHI, 15–30)	Group 3 (severe OSAS; AHI, > 30)	Group 4 (control)	*P* value
Age (years) (mean ± SD)	47.25 ± 6.86	51.25 ± 11.11	48.10 ± 8.40	48.35 ± 11.05	0.57
Sex (n, %)					
Female	9 (45)	12 (60)	11 (50.0)	10 (50.0)	
Male	11 (55)	8 (40)	9 (50.0)	10 (50.0)	0.81
OSAS duration (years) (mean ± SD)	3.60 ± 1.90	7.35 ± 1.81	8.55 ± 1.79	–	< 0.001*
AHI	7.25 ± 1.98	21.20 ± 4.89	58.94 ± 14.31	–	< 0.001*

AHI apnea–hypopnea index, *OSAS* obstructive sleep apnea syndrome, *SD* standard deviation

Table 2 Static pupillometry measurements of the study participants

Pupil diameter (PD) (mm)	Group 1 (mild OSAS; AHI, 5–14.9)	Group 2 (moderate OSAS; AHI, 15–30)	Group 3 (severe OSAS; AHI, > 30)	Group 4 (control)	Analysis of variance among groups**		Pairwise comparisons (post hoc analysis***)
					F	*P* value	*P* value
Scotopic PD	3.97 ± 0.77	3.53 ± 0.61	3.57 ± 0.70	3.75 ± 0.86	1.468	0.230	
Mesopic PD	3.08 ± 0.65	2.94 ± 0.34	2.58 ± 0.43	3.11 ± 0.79	3.500	0.019*	GR 1 to GR 2: 0.873
							GR 1 to GR 3: 0.041*
							GR 1 to GR 4: 0.998
							GR 2 to GR 3: 0.217
							GR 2 to GR 4: 0.780
							GR 3 to GR 4: 0.025*
Low photopic PD	2.57 ± 0.44	2.45 ± 0.40	2.36 ± 0.39	3.02 ± 0.72	6.531	0.001*	GR 1 to GR 2:0.867
							GR 1 to GR 3: 0.549
							GR 1 to GR 4: 0.037*
							GR 2 to GR 3: 0.945
							GR 2 to GR 4: 0.004*
							GR 3 to GR 4: 0.001*
High photopic PD	2.33 ± 0.39	2.62 ± 1.06	2.33 ± 0.52	2.45 ± 0.42	0.866	0.462	

AHI apnea–hypopnea index, *GR* group

*$P < 0.05$, **analysis of variance, ***Tukey's test

Table 3 Dynamic pupillometry measurements of the study participants

Characteristics	Group 1 (mild OSAS; AHI, 5–14.9)	Group 2 (moderate OSAS; AHI, 15–30)	Group 3 (severe OSAS; AHI, > 30)	Group 4 (control)	Analysis of variance among groups**		Pairwise comparisons (post hoc analysis***)
					F	*P* value	*P* value
Resting diameter (mm)	3.94 ± 0.61	4.00 ± 0.47	3.52 ± 0.61	4.20 ± 0.63	4.794	0.004*	GR 1 to GR 2 = 0.985
							GR 1 to GR 3 = 0.117
							GR 1 to GR 4: 0.488
							GR 2 to GR 3: 0.052*
							GR 2 to GR 4:0.706
							GR 3 to GR 4: 0.002*
Amplitude of pupil contraction (mm)	1.68 ± 0.32	1.79 ± 0.23	1.37 ± 0.49	1.79 ± 0.25	6.891	< 0.001*	GR 1 to GR 2: 0.713
							GR 1 to GR 3: 0.027*
							GR 1 to GR 4: 0.713
							GR 2 to GR 3: 0.001*
							GR 2 to GR 4: 1.00
							GR 3 to GR 4: 0.001*
Latency of pupil contraction (ms)	185.00 ± 34.88	181.75 ± 22.87	180.10 ± 31.18	167.200 ± 23.91	1.486	0.225	
Duration of pupil contraction (ms)	375.05 ± 79.38	380.10 ± 74.39	336.80 ± 73.96	411.25 ± 67.36	3.414	0.022*	GR 1 to GR 2: 0.996
							GR 1 to GR 3: 0.364
							GR 1 to GR 4: 0.414
							GR 2 to GR 3: 0.257
							GR 2 to GR 4: 0.545
							GR 3 to GR 4: 0.011*
Velocity of pupil contraction (mm/s)	7.16 ± 1.69	5.94 ± 1.83	5.24 ± 1.63	6.93 ± 0.95	6.512	0.001*	GR 1 to GR 2: 0.076*
							GR 1 to GR 3: 0.001*
							GR 1 to GR 4: 0.969
							GR 2 to GR 3: 0.488
							GR 2 to GR 4: 0.195
							GR 3 to GR 4: 0.005*
Latency of pupil dilation (ms)	559.90 ± 101.79	561.60 ± 82.72	516.60 ± 70.47	571.65 ± 77.16	1.700	0.174	

Table 3 continued

Characteristics	Group 1 (mild OSAS; AHI, 5–14.9)	Group 2 (moderate OSAS; AHI, 15–30)	Group 3 (severe OSAS; AHI, > 30)	Group 4 (control)	Analysis of variance among groups**		Pairwise comparisons (post hoc analysis***)
					F	*P* value	*P* value
Duration of pupil dilation (ms)	1645.75 ± 370.99	1791.60 ± 96.74	1633.30 ± 329.06	1700.40 ± 133.85	1.520	0.216	
Velocity of pupil dilation (mm/s)	2.73 ± 0.93	2.94 ± 0.48	2.41 ± 0.58	3.04 ± 0.37	4.86	0.012*	GR 1 to GR 2: 0.719 GR 1 to GR 3: 0.388 GR 1 to GR 4: 0.407 GR 2 to GR 3: 0.048* GR 2 to GR 4: 0.957 GR 3 to GR 4: 0.012*

AHI apnea–hypopnea index, *GR* group

* $P < 0.05$; **analysis of variance; ***Tukey's test

respectively. Mean disease durations of OSAS in groups 1, 2, and 3 were 3.60 ± 1.90, 7.35 ± 1.81, and 8.55 ± 1.79 years, respectively. There were 42 (52.5%) female subjects and 38 (47.5%) male subjects in this study. (Table 1).

According to the one-way variance analysis, we found that mesopic PD and low photopic PD were significantly different in the groups (F[3,76] = 3.500; P = 0.0019 and (F[3,76] = 6.531; P = 0.001, respectively). When we made the paired comparison of static pupillometry measurements, mesopic PD was significantly detected lower in the group 3 than the group 1 and 4 (P = 0.041, and P = 0.025, respectively). In addition, low photopic PD in the groups 1, 2, and 3 was significantly lower than that in the group 4 (P = 0.037, P = 0.004, and P = 0.001) (Table 2).

According to the one-way ANOVA analysis, among the groups included in the study, we determined the resting diameter (F[3,76] = 4.794; P = 0.004), the amplitude of pupil contraction (F[3,76] = 6.891; $P < 0.001$), the duration of pupil contraction (F[3,76] = 3.414; P = 0.022), the velocity of pupil contraction (F[3,76] = 6.512; P = 0.001), and velocity of pupil dilation (F[3,76] = 4.86; P = 0.012) to be significantly different. When we made the paired comparison of the static pupillometry measurements, the resting diameter was significantly detected lower in the group 3 than that in the groups 2 and 4 (P = 0.052 and P = 0.002). Similarly, the amplitude of pupil contraction was significantly lower in the group 3 than that in the groups 1, 2, and 3 (P = 0.027, P = 0.001, and P = 0.001, respectively). In addition, the duration of pupil contraction was significantly detected lower in the group 3 than that in the group 4 (P = 0.011). Although the velocity of pupil contraction was significantly lower in the group 3 than that in the groups 1 and 4 (P = 0.001 and P = 0.005, respectively), this value was significantly lower in the group 2 than that in the group 1 (P = 0.076). In addition, the velocity of pupil dilation was significantly lower in group 3 than that in groups 2 and 4 (P = 0.048 and P = 0.012) (Table 3).

We detected a negative correlation between AHI and mesopic PD (r = − 0.293, P = 0.008), low photopic PD (r = − 0.323, P = 0.003) (Fig. 1), resting diameter (r = − 0.352, P = 0.001), amplitude of pupil contraction (r = − 0.384, $P < 0.001$), duration of pupil contraction (r = − 0.283, P = 0.011), velocity of pupil contraction (r = − 0.408, $P < 0.001$),

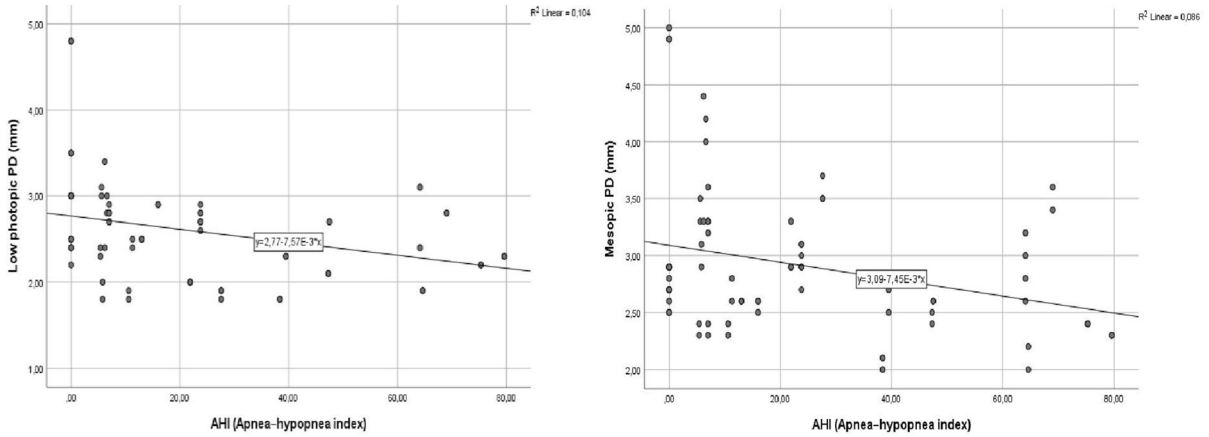

Fig. 1 Correlation between apnea–hypopnea index (AHI) and static pupil responses (mesopic and low photopic pupil diameter)

and velocity of pupil dilation ($r = -0.353$, $P = 0.001$) (Fig. 2).

Discussion

We detected that both the static pupillary responses (mesopic and low photopic) and dynamic pupillary responses (the resting diameter, the amplitude of pupil contraction, the duration of pupil contraction, the velocity of pupil contraction, and the velocity of pupil dilation) were affected in patients with OSAS. In these patients, AHI was also negatively correlated with the mesopic PD, the low photopic PD, the resting diameter, the amplitude of pupil contraction, the duration of pupil contraction, the velocity of pupil contraction, and the velocity of pupil dilation.

Information about neural pathways that control pupil responses can be obtained by evaluating pupillary reactions. PNS works basically in pupil contraction, whereas the effect of SNS is minimal. Therefore, the SNS controls PD at rest, whereas PD in light and pupillary function parameters developing in response to light reflect PNS function. However, both PNS and SNS are involved in redilation. In PNS dysfunction, pupil constriction is delayed in light exposure, while, in SNS dysfunction, it can be seen that pupil dilation is delayed in the dark environment. It has been determined that disturbances in the pupil function will be detected before the findings related to ANS dysfunction in the cardiovascular system appear [22–27].

It is believed that many systemic diseases affecting patients with OSAS are caused by SNS hyperactivity [28]. In contrast, it has been reported that PNS dysfunction may play a role in ANS dysregulation in patients with OSAS [29]. Therefore, it may be important to evaluate pupil responses for screening ANS, which may be an important pathological reason for morbidity and mortality in patients with OSAS where autonomic neuropathy can be observed [30–32].

Changes in the SNS–PNS balance in OSAS have been found using HRV analysis. In addition, increased sympathetic vascular reactivity during wakefulness has been reported in these patients owing to ANS dysfunction [33].

Similar to the results of this study, a study comparing mild OSAS with a control group reported that pupil responses were affected as an indicator of ANS dysfunction [34]. In a study, it was reported that pupil responses were affected as an indicator of ANS dysfunction, similar to the results of current study. But, only 10 patients with mild OSAS were included in this study, and the generalization of this study is limited. However, in our study, patients were diagnosed with OSAS disease in the presence of polysomnography, and patients were grouped according to their OSAS severity. In addition, in our study, the pupillometric results of patients with OSAS of different severity were evaluated. Therefore, our data are stronger and uniquely in the literature.

Unlike the results of this study, it has been reported that there is no difference between primary snorers and children with OSAS in terms of pupillometric measurements. The reason for the different results obtained in this study can be considered as the

prominence of ANS dysfunction in children with OSAS over time. However, in this study, levels of plasma norepinephrine were reported to be significantly higher in the severe OSAS patients [35]. Similarly, increased systolic and diastolic BP, ANS dysfunction, and increased catecholamine levels in urine have been reported in patients with OSAS [36].

While the limitations of this study are the relatively small number of participants and the fact that it is a cross-sectional study conducted in a single center, the potentially valuable aspect of this study is that it is the

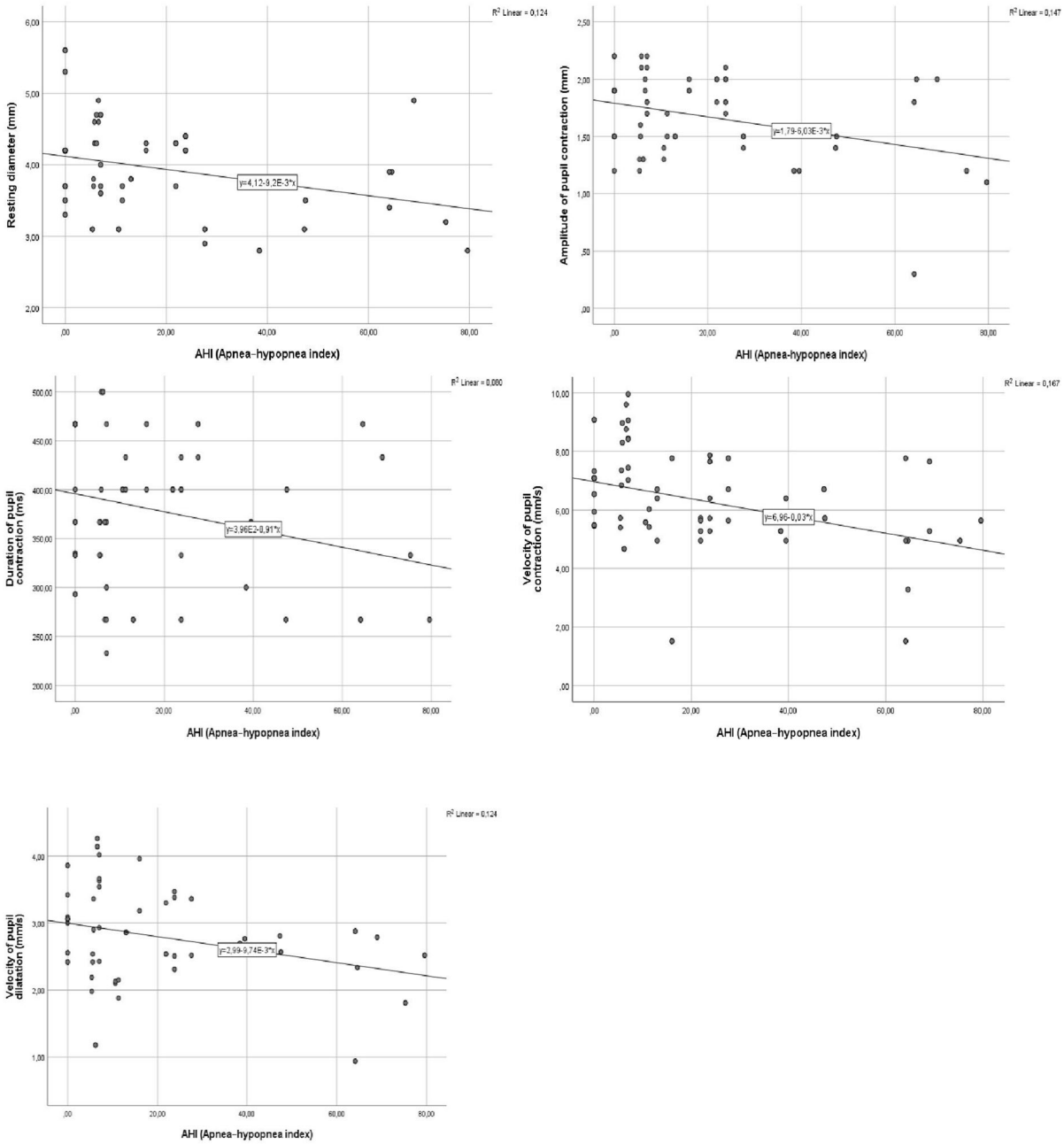

Fig. 2 Correlation between apnea–hypopnea index (AHI) and dynamic pupil responses (resting diameter, amplitude of pupil contraction, duration of pupil contraction, velocity of pupil contraction, and velocity of pupil dilation)

first study to report that impaired pupillary responses, which may be an indicator of ANS dysfunction in patients with OSAS, can be detected with an easily applicable automated pupilometer.

In conclusion, according to the results of this study, it was determined that static and dynamic pupillary responses controlled by the autonomic nervous system were affected in the OSAS patients. This effect was more significant in the severe OSAS patients. Also, a negative correlation was found between AHI and pupillary responses. Therefore, the pupillometry system can be an easily applicable, non-invasive method to detect ANS dysfunction in patients with OSAS. However, studies with larger series and multicenter are needed.

Declaration

Conflict of interest All authors certify that they have no affiliations with or involvement in any organization or entity with any financial interest (such as honoraria; educational grants; participation in speakers' bureaus; membership, employment, consultancies, stock ownership, or other equity interest; and expert testimony or patent–licensing arrangements) or non-financial interest (such as personal or professional relationships, affiliations, knowledge, or beliefs) in the subject matter or materials discussed in this manuscript.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.
Informed consent Written informed consent was obtained from the participants.

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