

Pulse transit time in patients with sleep-disordered breathing

Marwa El-Sayed El-Naggar

Background Pulse transit time (PTT) represents a noninvasive marker of sleep fragmentation in patients with obstructive sleep apnea–hypopnea syndrome (OSAHS). Little is known regarding changes in PTT in patients with excessive daytime sleepiness associated with nocturnal inspiratory flow limitation (IFL) without apneas or desaturation.

Patients and methods A total of 20 patients with nocturnal IFL were age and sex matched with a group of patients with OSAHS and another without significant breathing disorders during sleep [nonflow limited (NFL)]. PTT arousal index (PTT Ar) is the number of PTT arousals per hour.

Results Overall, 20 patients with IFL were age and sex matched with two groups: one with OSAHS and another without significant sleep-disordered breathing (SDB) (NFL). There was a significant increase in the median BMI of the IFL group compared with the NFL group (40 vs. 30; $P < 0.05$) but not with the OSAHS group (40 vs. 44; $P > 0.05$). The PTT Ar in the IFL group (36.5/h) was significantly higher than that in the NFL group (16.3/h) and lower than that observed in the OSAHS group (60/h; $P < 0.001$). PTT Ar correlated positively with BMI, apnea–hypopnea index, oxygen desaturation

index, respiratory disturbance index, snoring index, and Epworth sleepiness scale.

Conclusion The PTT Ar increased with SDB with significantly higher values in patients with excessive daytime sleepiness associated with nocturnal IFL compared with controls. Patients with IFL were mainly females with an elevated BMI. Thus, PTT could be used as a marker of sleep fragmentation apart from electroencephalogram in the diagnosis of SDB.

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Department of Chest Disease, Faculty of Medicine, Banha University, Banha, Egypt

Correspondence to Marwa El-Sayed El-Naggar, MD, Lecturer of Chest Diseases, Department of Chest Disease, Faculty of Medicine, Banha University, Banha, 13512, Egypt; Tel: +20 100 062 9891; e-mail: marwa_141282@hotmail.com

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Introduction

Occurrence of apneas and hypopneas is associated with cyclic fluctuations of the autonomic nervous system which means increase in the parasympathetic activity during apneas followed by increase in the sympathetic activity at the end of apnea resulting in arousal [1]. Among autonomic markers, pulse transit time (PTT) has been used for sleep-disordered breathing (SDB) screening and follow-up [2]. The PTT is the time taken for the pulse pressure waveform to travel from the aortic valve to the periphery to be detected by the finger probe. So, sympathetic activation increases blood pressure and vascular tone and stiffens the arterial wall resulting in shortening of the PTT [3].

In obstructive sleep apnea (OSA), obstruction of the upper airway results in a decrease in blood pressure. The consequent reduction in vascular tone is associated with a longer time for the pulse wave to reach the periphery and results in an ‘increment’ in the PTT [4]. The effect of such airway obstruction is arousal from sleep and resumption of a patent upper airway with increased blood pressure, stiffening of the arterial wall, and increased vascular tone leading to a ‘decrement’ in the PTT [5]. It is well known that not all obstructive respiratory events end with arousal. Indeed, in normal patients ‘nonvisible’ sleep fragmentation induced by repeated auditory stimulation has been found to cause

significant daytime sleepiness [6]. Inspiratory flow limitation (IFL) during sleep occurs when airflow remains constant despite an increase in respiratory effort. This respiratory event has been recognized as an important parameter for identifying SDBs [7]. IFL can be observed as flattening of the sinusoidal shape on PSG. Absence of increased inspiratory flow despite elevated negative intrathoracic pressure can be indicated physiologically by IFL which indicates effort increase [8]. Few published data are available comparing PTT indices in persons with obstructive sleep apnea–hypopnea syndrome (OSAHS) with those presenting with excessive daytime sleepiness (EDS) in whom sleep studies exhibit IFL without apneas or desaturation.

Aim

The aim of this study was to detect the PTT in patients with EDS and IFL without apneas, hypopneas, and/or desaturations during sleep and if it differs from patients with OSAHS, and from other patients with no evidence of IFL or any other SDB.

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Patients and methods

A total of 50 patients were included in this study. Patients were referred to sleep laboratory at Banha University Hospital between August 2016 and May 2017. Informed consent was obtained from all individuals before participation. Sleep studies were performed using a polysomnographic device (SOMNO Screen Plus; SOMNO Medics GmbH, Randersacker, Germany). The polysomnography consists of pulse oximetry, electroencephalogram, electrooculogram, ECG, electromyogram, thoracic and abdominal belts, body position sensor, assessment of respiratory flow and pressure by nasal thermistor and nasal cannula, and bipolar channel limb movements (tibialis anterior). Electrodes and sensors were directly attached to patients by sleep physiologist. Data acquisition was obtained immediately after signal detection by preprocessed computer (DOMINO Software, ver. 2.6.0; SOMNO Medics GmbH).

The polysomnographic data were then subjected to automatic interpretation and revised by manual assessment according to American Academy of Sleep Medicine criteria [9]. IFL has been demonstrated (always by visual inspection) as flattening of the peak of the nasal cannula pressure transducer waveform (at least four successive breath). It is often associated with snoring and not associated with a 3 or 4% SaO₂ drop. The duration of flow limitation is considered from the time of the start of flattening of the waveform till it returns to baseline shape [10]. Apneas and hypopneas were scored manually according to American Academy of Sleep Medicine criteria [9]. The respiratory disturbance index (RDI) represented the sum of the apnea–hypopnea index (AHI) and the flow limitation index. The PTT was calculated automatically using the manufacturer’s analysis software and was defined as the interval between the ECG R wave and the point corresponding to 50% of the height of the ascending pulse waveform (detected by finger probe). PTT values are available with every heartbeat and are over sampled at 5 Hz to ensure no values are neglected. The PTT was continuously monitored, and PTT arousals were automatically obtained from the raw PTT signal; a PTT arousal or ‘deceleration’ was defined as a decline in the PTT signal of 15 ms, lasting 5 s [5]. The PTT deceleration or ‘arousal’ index was defined as the number of PTT arousals, that is, decelerations per hour of total sleep time [PTT arousal index (PTT Ar)]. An IFL group was selected based on a history of EDS and nocturnal snoring associated with an elevation of RDI without significant increase in AHI (<5/h). The IFL group was compared with another two groups (i) patients with

OSAHS with AHI more than 15 [obstructive sleep apnea syndrome (OSAS)] and (ii) nonflow limited (NFL) group: those referred to the sleep service in whom sleep study had demonstrated the absence of significant SDB, that is, both AHI and RDI less than 5/h. All patients in the IFL and OSAS groups presented with snoring, difficulty in waking up, morning headache, EDS, and with a level of tiredness experienced by the patients with Epworth sleepiness score (EPSS) more than 10. Patients in the NFL group had simple snoring, insomnia, nightmares, and generalized fatigue. Exclusion criteria included the following: patients with hypoventilation from the baseline diagnostic investigation (>20 min spent <90%) [11], patients with technically compromised polysomnograms (including those where percentage failure of flow signal was 20% or greater), and patients who spent less than 4 h in bed.

Statistical analysis

The collected data were tabulated and analyzed using SPSS, version 20 software (SPSS Inc., Chicago, Illinois, USA). Categorical data presented with number and percent. Fisher’s exact test is used to detect significant association between the studied groups and hypertension and cardiac diseases in data with expected cell value less than 5. Data were tested for normality, and non-normal quantitative data were expressed as median, range, and IQR. Kruskal–Wallis test and Spearman’s correlation coefficient (ρ) were used as tests of significance for nonparametric data. Significant Kruskal–Wallis test result was followed by Tamahan test to detect significant pairs. The accepted level of significance in this work was stated at 0.05 ($P \leq 0.05$ was considered significant).

Results

A total of 50 patients who underwent complete sleep studies were divided into three groups:

Group I: 20 patients with IFL during sleep.

Group II: 20 patients with OSAHS.

Group III: 10 patients with no significant SDB as a control group.

All groups were age and sex matched. The mean BMI of the IFL group was significantly higher than NFL group, with no significant difference between IFL and OSAHS group. The PTT Ar in the IFL groups was significantly higher than that found in the NFL group, denoting the higher degree of cardiovascular arousal in the IFL group. The highest level of PTT Ar was found in the OSAHS group, denoting the highest degree of

Table 1 Comparison between the studied groups regarding demographic and clinical findings

	IFL (n=20; female=12)			OSAS (n=20; female=12)			NFL (n=10; female=6)			P value
	Median	Range	IQR	Median	Range	IQR	Median	Range	IQR	
Age (years)	52	29–57	13	49.5	34–58	15	44.5	35–55	11	>0.05
BMI (kg/m ²)	40	26.7–52.7	13.3	44	27.6–49.2	10.1	30	25–35	4.8	<0.05
AHI	3.6	1.6–21.5	1.7	38.1	1.1–84.4	40.6	1.4	0.7–3	1.4	<0.001
RDI	10.3	3.6–25.5	12.5	44.1	1.2–94.4	38.8	1.4	0.74.2	1.95	<0.001
ODI	7.9	3.5–37.6	2.8	69.5	1–97.6	33.3	1.2	0.8–3.1	1.1	<0.001
Mean oxygen saturation	94	92–96	2.5	92	90–96	4	95	94–97	2.5	<0.001
Snoring index	184.2	108.7–800.8	129.4	382	84.8–790.9	446.4	70	50–143.3	50.3	<.001
PTT arousal/deceleration index	36.5	15.9–48.5	19.6	60	15.2–82.9	17.7	16.3	14.2–30.1	11.2	<0.001
EPSS	14	10–20	4	19	11–22	4	10	5–12	4.5	<0.001
Hypertension		5/20			5/20			0/20		0.25
Cardiac disease		1/20			1/20			0/20		0.79

AHI, apnea–hypopnea index; EPSS, Epworth sleepiness scale; IFL, inspiratory flow limited; IQR, interquartile range; NFL, nonflow limited; ODI, oxygen desaturation index; OSAS, obstructive sleep apnea syndrome; PTT, pulse transit time; RDI, respiratory disturbance index.

Table 2 Correlation between pulse transit time arousal and important factors

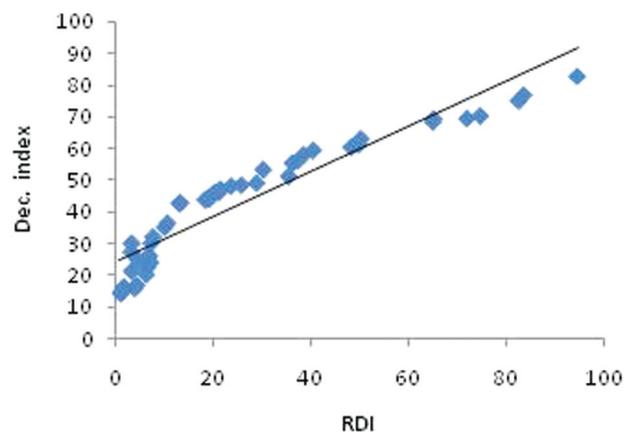
	PTT arousal	P value
Age	0.16	>0.05
BMI	0.355	<0.05
AHI	0.997	<0.05
RDI	0.988	<0.05
ODI	0.988	<0.05
Mean oxygen saturation	–0.630	<0.05
Snoring index	0.681	<0.05
EPSS	0.745	<0.05

AHI, apnea–hypopnea index; EPSS, Epworth sleepiness scale; ODI, oxygen desaturation index; PTT, pulse transit time; RDI, respiratory disturbance index.

cardiovascular arousal compared with the other groups (Table 1). The PTT Ar was found to significantly positively correlate with the BMI, AHI, oxygen desaturation index (ODI), snoring index, and EPSS of the studied groups. It was also significantly negatively correlated with mean oxygen saturation. There was no significant correlation between PTT Ar and age of the studied groups (Table 2 and Fig. 1).

Discussion

OSAHS is defined by quantifying apneas and hypopneas associated with symptoms suggesting sleep interruption [8]. Patients with flow limitation demonstrate electroencephalogram changes and clinical symptoms indicating sleep fragmentation [8]. In this study, it was reported that the BMI of the IFL group (median BMI of 40 kg/m²) did not differ significantly from the OSAHS group (median: 44 kg/m²); however, both groups were significantly higher than the NFL group (median: 30 kg/m²). This suggests that a subset of obese predominantly female individuals may present with EDS related to IFL rather than exhibiting apneas or hypopneas associated with desaturation. Palombini *et al.* [7] found a positive association between BMI and IFL

Figure 1

Correlation between deceleration index (PTT Ar) and RDI. Dec., deceleration; PTT Ar, PTT arousal index; RDI, respiratory disturbance index.

on studying nocturnal polysomnography of 1042 individuals. This result matched with Chakrabarti *et al.* [12], who reported that the BMI of the IFL cohort (mean BMI of 34.25 kg/m²) did not differ significantly from the OSAHS cohort (mean BMI 36.31 kg/m²) but was significantly higher than NFL group. In this study, it was found that the PTT Ar was greater in adult patients presenting with EDS and exhibiting nocturnal IFL in comparison with another group without significant SDB. This supports that the presence of nocturnal IFL represents a potentially significant pathogenic mechanism in the development of EDS. On the contrary, PTT Ar was significantly higher in patients with OSAHS compared with patients with IFL. Smith *et al.* [4] reported the ability of PTT to detect the changes in inspiratory effort and the presence of microarousals. In a study done by Chakrabarti *et al.* [12], 20 patients meeting criteria for the IFL cohort (mean AHI=3.84/h; RDI=17.71/h) were age and sex matched with 20 OSAHS patients (mean AHI=48.93 h) and 20 control 'NFL' patients. The

PTT deceleration index in the IFL cohort ($33.67 \pm 23.34/h$) was significantly higher than that measured in the control NFL cohort ($23.89 \pm 18.88/h$) but significantly lower than that measured in the OSAHS cohort ($55.21 \pm 29.30/h$; three-way analysis of variance; $F=8.76$; $P<0.001$) [12]. Moreover, in a study done on a group of 16 children by Pépin *et al.* [13], they found that the evaluation of respiratory effort using PTT improves the detection of respiratory events and microarousal especially in rapid eye movement and slow wave sleep. Nisbet *et al.* [14] analyzed 422 respiratory events in 81 children with a diagnosis ranging from simple snoring to severe OSA. They observed that significant postevent increase in heart rate and fall in PTT occurred in all groups ($P<0.05$), with greater response found in relation to OSAHS, nonrapid eye movement sleep (NREM), cortical arousal, hypopneas, and oxygen desaturation. On the contrary, a study of pediatric patients with OSAHS, those with upper airway resistance syndrome, primary snorers, and healthy patients reported that the PTT Ar did not significantly differ between the OSAHS and upper airway resistance syndrome groups, but was significantly lower in primary snorers and 'healthy normals' [15]. However, that study included only patients with a mild degree of OSAHS with a mean AHI of 10.6 compared with 38.1 events/h in the OSAHS group in the present study, potentially accounting for the greater difference in PTT Ar reported in the current study.

In the present work, there were significant positive correlations between PTT Ar and AHI, RDI, ODI, snoring index, and EPSS. In a study of 144 patients with OSA, PTT Ar correlated significantly with the RDI and with the arousal index [16]. Moreover, Chakrabarti *et al.* [12] found significant correlations between PTT Ar and AHI, RDI, and ODI, whereas no significant correlations were found between PTT Ar and snoring index and EPSS. In another study, CPAP titration was evaluated in two groups with OSAS. The pressure in the first group was set to eliminate IFL and in the other was set to eliminate apnea and hypopnea only. The pressure was higher in the first group and associated with more improvement in daytime wakefulness [17]. Moreover, Chakrabarti *et al.* [18] observed statistically significant associations between CPAP compliance and lower PTT in 27 patients with IFL. A limitation of the present study is that PTT indices may be affected by sleep fragmentation owing to external stimuli or nonrespiratory events, the presence of artifact caused by interference with the photoplethysmographic signal at the finger probe, or separation of ECG leads by chest wall movement. In addition, PTT can be affected by

the presence of marked respiratory variation especially during REM sleep [4]. This may be a factor contributing to the elevated PTT Ar in the NFL patients with no evidence of SDB.

Conclusion

This study demonstrates that the PTT arousal index, a marker of sleep fragmentation, was found to be significantly higher in a group of patients presenting with EDS with IFL in comparison with patients without significant SDB supporting the concept that the occurrence of nocturnal flow limited breathing may represent another mechanism in the pathogenesis of EDS. Other studies on PTT Ar and the effect of CPAP on it are recommended.

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Conflicts of interest

There are no conflicts of interest.

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