Evaluating changes in pulse transit time drop index in patients with obstructive sleep apnea before and during CPAP therapy

Elham Kalantari1 | Forough Kalantari2 | Maryam Edalatifard3 | Besharat Rahimi3

1Department of Pulmonology, Isfahan University of Medical Sciences, Isfahan, Iran
2Department of Nuclear Medicine, Rasoul Akram Hospital, Iran University of Medical Sciences, Tehran, Iran
3Advanced Thoracic Research Center, Tehran University of Medical Sciences, Tehran, Iran

Correspondence
Besharat Rahimi, Advanced Thoracic Research Center, Tehran University of Medical Sciences, Tehran, Iran.
Email: besharatrahimi@yahoo.com

Funding information
None.

Abstract
Airflow limitation in patients with obstructive sleep apnea (OSA) leads to arousal, increased sympathetic nervous system activity, and elevated blood pressure, which causes a decrease in pulse transit time (PTT). The present study aims to evaluate the effect of CPAP therapy on PTT in patients with moderate to severe OSA. This was a cross-sectional study. Split-night polysomnography (PSG) study was performed for each participant with apnea-hypopnea index (AHI) ≥ 15 before and during CPAP therapy. The PTT was calculated as the time interval between the R wave of the electrocardiogram and the following arrival point in fingertip photoplethysmography. PTT drop was defined as a fall in the PTT curve of ≥ 15 ms lasting at least for 3 s and at most for 30 s. PTT drop index was defined as the number of drops in PTT that occur per hour of sleep. A total of 30 patients were included. PTT significantly increased, and PTT drop index significantly decreased during CPAP therapy (P < 0.001). PTT was significantly correlated to sleep efficiency (rₛ = −0.376, P = 0.049) and oxygen desaturation index (ODI) (rₛ = −0.428, P = 0.018). PTT drop index was strongly correlated to AHI (rₛ = 0.802, P < 0.001), respiratory disturbance index (RDI) (rₛ = 0.807, P < 0.001), ODI (rₛ = 0.693, P < 0.001), arousal index (rₛ = 0.807, P < 0.001), and periodic leg movement (PLM) index (rₛ = 0.400, P = 0.035). Overall, the findings from this study indicated that the PTT drop index is a non-invasive and useful marker for evaluating the severity of OSA and the effectiveness of treatment in patients with moderate to severe OSA.

KEYWORDS
continuous positive airway pressure, CPAP, obstructive sleep apnea, pulse transit time
1 | INTRODUCTION

Obstructive sleep apnea (OSA) is a common sleep-related breathing disorder characterized by apneas, hypopneas, and respiratory effort-related arousals (RERAs) caused by the repetitive partial or total collapse of the upper airway during sleep. Polysomnography (PSG) is the gold standard diagnostic test for OSA. Apnea and hypopneas lead to hypoxemia, which results in chemoreflex activation and overactivity of the sympathetic nervous system.

Pulse transit time (PTT) reflects autonomic imbalances and is a non-invasive marker of respiratory effort and arousal in patients with OSA. It represents the time taken for the pulse pressure waveform to travel from the aortic valve to the periphery (usually the finger). PTT is measured by calculating the time between the R wave of the electrocardiogram (ECG) and the arrival of the pulse wave to distal arterial sites detected by a finger photoplethysmogram. PTT reflects changes in peripheral arterial resistance and intrathoracic pressure and is inversely correlated with blood pressure; with sympathetic activation and increasing blood pressure, the PTT decreases. Moreover, a decrease in intrathoracic pressure during obstructed breathing is associated with a drop in blood pressure, which may be followed by a rise in PTT. Therefore, PTT is an indirect marker of sleep fragmentation and can be used to monitor arousal from sleep due to respiratory events.

Continuous positive airway pressure (CPAP) is the mainstay of therapy for adults with OSA, which reduces the frequency of respiratory events and improves blood pressure. The present study aimed to evaluate changes in PTT and PTT drop index before and during CPAP.

2 | METHODS

2.1 | Patients

Adult patients (age ≥ 18 years) with moderate to severe OSA referred to our sleep clinic from November 2016 to October 2019 were eligible. The diagnosis of OSA was established according to AASM guidelines. Patients with an apnea-hypopnea index (AHI) ≥ 15 and < 30 were considered to have moderate OSA, and those with AHI ≥ 30 were considered to have severe OSA. Patients with a history of chronic obstructive pulmonary disease (COPD) or any other chronic respiratory, liver, and kidney diseases were excluded. We also excluded patients with drug-resistant hypertension, heart failure, and those who receive sedative-hypnotic drugs.

2.2 | Polysomnography

A split-night PSG study was performed for each participant before and during CPAP therapy. PSG data were recorded using the SOMNOScreen PSG system. The standard PSG incorporated electrocardiography, electroencephalography, electrooculography, pulse oximetry, snoring voice recording, electromyography (submental and bilateral anterior tibialis), thoracic and abdominal movements, thermal sensors, and oronasal airflow. Fingertip pulse oximetry and plethysmography were used to monitor oxygen saturation and the termination of the pulse wave. The PSG data were then interpreted automatically and revised manually according to the American Academy of Sleep Medicine criteria.

2.3 | PTT measurement

The PTT was calculated as the time interval between the R wave of the electrocardiogram (ECG) and the arrival of the pulse wave to distal arterial sites detected by a finger photoplethysmogram. PTT reflects changes in peripheral arterial resistance and intrathoracic pressure and is inversely correlated with blood pressure; with sympathetic activation and increasing blood pressure, the PTT decreases. Moreover, a decrease in intrathoracic pressure during obstructed breathing is associated with a drop in blood pressure, which may be followed by a rise in PTT. Therefore, PTT is an indirect marker of sleep fragmentation and can be used to monitor arousal from sleep due to respiratory events.

Continuous positive airway pressure (CPAP) is the mainstay of therapy for adults with OSA, which reduces the frequency of respiratory events and improves blood pressure. The present study aimed to evaluate changes in PTT and PTT drop index before and during CPAP.

1. Respiratory PTT: PTT falls following respiratory events (apnea and hypopnea).
2. Flow limitation PTT: PTT drops following a decrease in upper airflow (which does not meet the criteria for apnea or hypopnea) along with increased respiratory effort.
3. Periodic leg movement PTT: PTT falls following periodic leg movement.
4. Snoring PTT: PTT falls following snoring.
5. Heart rate PTT: PTT falls following an increase in heart rate.
6. Body position PTT: PTT falls following a change in body position.
7. Spontaneous PTT: PTT falls without any recognized physiologic event.

2.4 | Statistical analysis

Statistical analyses were performed using the SPSS software version 25. Shapiro–Wilk test was used to assess normal distribution. Normally distributed variables were expressed as mean ± standard deviation (SD). Median and interquartile range (IQR) were calculated for non-
normally distributed variables. Spearman’s correlation analysis was applied to assess the correlation between PTT and PSG variables. Changes in PTT and PSG variables before and during CPAP therapy were assessed via paired samples t-tests.

3 | RESULTS

3.1 | Patients characteristics

A total of 30 patients with moderate to severe OSA were studied. The mean age was 53.4 ± 11.4 years. Nineteen patients (63.3%) were male. The mean body mass index (BMI) was 33.9 ± 5.3. Obesity (BMI ≥ 30) was detected in 25 patients (83.3%). The AHI ranged from 10.6 to 157.4 before CPAP therapy. Severe OSA was found in 28 patients (93.3%). The mean PTT and PTT drop index before treatment were 309.7 ± 19.6 ms and 34.7 ± 24.4, respectively.

3.2 | Association between PTT and demographic and polysomnographic findings

As is shown in Table 1, PTT was significantly correlated to sleep efficiency and oxygen desaturation index (ODI). No significant association was found between AHI, RDI, and arousal index (P > 0.05). PTT drop index was strongly correlated to AHI, respiratory disturbance index (RDI), ODI, arousal index, and periodic leg movement (PLM) index (Figure 1).

3.3 | Changes in PTT and polysomnographic parameters after CPAP therapy

Changes in PTT and other polysomnographic parameters before and after initiation of CPAP therapy are summarized in Table 2. PTT significantly increased, and the PTT drop index significantly decreased after CPAP therapy (P < 0.001) (Figure 2). Among PTT drop index parameters, a significant decrease in respiratory, PLM, and snore indexes was found (Table 2). AHI, RDI, sleep efficiency, sleep latency, REM, ODI, average SPO2, arousal, and PLM index improved significantly after CPAP therapy (Table 2).

4 | DISCUSSION

Obstruction of the upper respiratory tract during sleep in patients with OSA leads to arousal, increased sympathetic nervous system activity, and increased blood pressure, followed by a PTT drop. Therefore, measurements of the PTT drop index can, directly and indirectly, reflect the severity of OSA. In the present study, we observed a strong direct correlation between the PTT drop index and AHI, RDI, ODI, and arousal index, which may confirm this claim. We also monitored changes in PTT and PSG parameters before and after initiation of CPAP therapy. PTT [ms] increased significantly, and the PTT drop index decreased significantly following CPAP therapy. Among PSG parameters, AHI, RDI, sleep efficiency, sleep latency, REM, ODI, average SPO2, and arousal index improved significantly after CPAP therapy.

Although associations between PTT and PSG parameters were evaluated in some previous studies, only a few had investigated the changes in PTT after positive airway pressure therapy. In a similar study by Schwartz et al., PTT drop index changes before and after CPAP therapy were evaluated. The authors observed a significant decrease in RDI, ODI, arousal index, as well as PTT drop index just after CPAP therapy. Investigating identifiable causes of PTT drop before and after CPAP is a unique feature of the present study. Not surprisingly, the majority of PTT drops occurred due to respiratory events, which resolved significantly after CPAP therapy. These findings may indicate that by preventing airflow obstruction, CPAP subsides respiratory events and autonomic overactivity, leading to a lower rate of PTT drops during sleep.

| Table 1 | Correlation between pulse transit time and demographic and polysomnographic findings |
|---------|---------------------------------|
|         | PTT                                     | PTT drop index                             |
|         | rs   | P value      | rs   | P value      |
| Age     | 0.320 | 0.085       | -0.175 | 0.354 |
| BMI     | -0.089 | 0.642       | 0.092 | 0.628 |
| AHI     | -0.208 | 0.271       | 0.802 | <0.001 |
| RDI     | -0.213 | 0.259       | 0.807 | <0.001 |
| TST     | -0.146 | 0.458       | -0.195 | 0.321 |
| Sleep efficiency | -0.376 | 0.049   | -0.110 | 0.577 |
| Sleep latency | 0.181 | 0.357     | -0.042 | 0.831 |
| REM     | 0.151 | 0.444       | -0.364 | 0.057 |
| ODI     | -0.428 | 0.018       | 0.693 | <0.001 |
| Average SPO2 | 0.354 | 0.055       | -0.342 | 0.065 |
| Arousal index | -0.186 | 0.325 | 0.807 | <0.001 |
| PLM index | 0.355 | 0.064       | 0.400 | 0.035 |

Abbreviations: AHI: apnea-hypopnea index; BMI: body mass index; ODI: oxygen desaturation index; PLM: periodic limb movement; RDI: respiratory disturbance index; TST: total sleep time.
PLM PTT and snore PTT indexes also improved significantly after CPAP therapy. PLM is characterized by repetitive stereotypical movements of the lower extremities during sleep. It was shown that PLM is associated with increased heart rate and blood pressure as well as EEG arousals and was remarked as a risk factor for nocturnal arrhythmia and hypertension in patients with sleep-related breathing disorders. We showed that the PTT drop index is significantly correlated to the PLM index, and we observed that the PLM index decreased significantly after CPAP therapy. In contrast to our findings, a significant increase in the PLM index

**FIGURE 1** Correlation between PTT drop index and AHI ($r_s = 0.802, P < 0.001$) (A), ODI ($r_s = 0.693, P < 0.001$) (B), and arousal index ($r_s = 0.807, P < 0.001$) (C). AHI, apnea-hypopnea index; ODI, oxygen desaturation index; PTT, pulse transit time.
was reported after CPAP therapy in some previous studies, especially in patients with severe OSA. To our knowledge, no previous study has evaluated changes in the PTT drop index related to PLM before and after CPAP therapy.

Snoring is a sound produced by the vibration of the upper airway’s soft tissues during sleep and indicates increased upper airway resistance and pharyngeal collapsibility. Snoring is a common symptom among OSA patients and usually is associated with excessive daytime sleepiness and an increased risk of cardiovascular diseases.

A limited number of previous studies have shown changes in the autonomic system following snoring in patients with OSA and those with primary snoring. A recently published study has demonstrated that snoring in pregnant women is associated with a significant PTT drop. Spontaneous PTT was another important determinant of the PTT drop index, which did not change significantly following CPAP therapy. This finding may indicate that spontaneous arousals and autonomic activations during sleep increase with age, and AHI has no major impact on that. This might justify no change in spontaneous PTT before and after CPAP therapy.

The findings from the current study should be interpreted cautiously due to some major limitations. Small sample size, single-night study, and lack of follow-up are the most important limitations of this study. Since the PTT drop index reflects changes in blood pressure and autonomic nervous system, which are among the main risk factors of cardiovascular disease and mortality in OSA patients, the long-term monitor of PTT drop index changes in OSA patients receiving CPAP therapy might be of great importance. Furthermore, due to the lack of a healthy control group, the importance of each subindex of the PTT drop index is undetermined.

Here, we showed that the PTT drop index is strongly correlated to AHI, RDI, ODI, and arousal index, which may confirm the utility of the PTT drop index as a non-invasive marker of OSA severity. We also demonstrated that CPAP therapy significantly improved PTT drop index and some PSG parameters, including AHI, RDI, sleep efficiency, sleep latency, REM, ODI, average SPO2, PLM index, and arousal index. Among subindexes of PTT drop index, respiratory, PLM, and snore PTT reduced

| TABLE 2 PTT and other polysomnographic parameters before and after CPAP therapy |
|---------------------------------|-----------------|---------------|-----------------|
|                                 | Before CPAP     | After CPAP     | P-value         |
| PTT, ms [mean ± SD]            | 309.7 ± 19.6    | 315.0 ± 16.3   | <0.001          |
| PTT drop index [median (IQR)]  | 29.6 (13.4–55.0)| 11.7 (4.2–20.6)| <0.001          |
| Respiratory PTT [median (IQR)] | 8.7 (1.4–34.3)  | 1.4 (0.0–4.8)  | <0.001          |
| Flow limitation PTT [median (IQR)] | 0.0 (0.0–0.0) | 0.0 (0.0–0.0) | 0.593          |
| PLM PTT [median (IQR)]         | 0.3 (0.0–3.5)   | 0.0 (0.0–0.6)  | 0.009          |
| Snore PTT [median (IQR)]       | 3.7 (1.5–5.5)   | 1.1 (0.3–4.4)  | 0.014          |
| Heart rate PTT [median (IQR)]  | 0.0 (0.0–0.0)   | 0.0 (0.0–0.0)  | 1.000          |
| Body position PTT [median (IQR)] | 0.0 (0.0–0.0) | 0.0 (0.0–0.0) | 0.317          |
| Spontaneous PTT [median (IQR)] | 4.9 (1.9–11.6)  | 4.8 (1.7–10.9) | 0.888          |
| AHI [mean ± SD]                | 75.3 ± 37.0     | 28.1 ± 13.4    | 0.008          |
| RDI [mean ± SD]                | 76.1 ± 36.4     | 29.4 ± 13.4    | <0.001         |
| TST, min [mean ± SD]           | 143.6 ± 49.8    | 175.3 ± 55.4   | 0.094          |
| Sleep efficiency [median (IQR)] | 78.6 (66.2–87.3)| 82.2 (78.8–92.3)| 0.006         |
| Sleep latency, [median (IQR)]  | 8.9 (6.1–22.9)  | 6.6 (3.8–10.1) | 0.030          |
| REM, % of TST [median (IQR)]   | 0.1 (0.0–8.7)   | 22.6 (12.5–31.9)| <0.001       |
| ODI [mean ± SD]                | 66.6 ± 38.6     | 18.1 ± 3.3     | <0.001         |
| Average SPO2 [median (IQR)]    | 90.5 (88.8–92.3)| 92.5 (91.5–94.3)| <0.001       |
| Arousal index [median (IQR)]   | 46.7 (27.7–72.6)| 19.5 (15.7–25.1)| <0.001       |
| PLM index [median (IQR)]       | 12.5 (1.9–32.5) | 4.0 (1.2–8.6)  | 0.005          |

Abbreviations: AHI, apnea-hypopnea index; IQR, interquartile range; ODI, oxygen desaturation index; PLM, periodic limb movement; RDI, respiratory disturbance index; TST, total sleep time.
significantly following CPAP therapy, but no change in spontaneous PTT was detected.

ACKNOWLEDGEMENT
The authors would like to thank all the study participants for their participation.

CONFLICT OF INTEREST
None of the authors has any conflict of interest to disclose.

ETHICS STATEMENT
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. The protocol of this study was reviewed and approved by the Ethics Committee of Tehran University of Medical Sciences. Written informed consent was obtained from all patients included in the study.

AUTHOR CONTRIBUTIONS
EK contributed to conducting the research, interpreting data, and revising the manuscript, FK contributed to conducting the research and revising the manuscript, ME contributed to the ideas of this study and revising the manuscript, and BR contributed to the ideas of this study, conducting the research, interpreting data and revising the manuscript.

DATA AVAILABILITY STATEMENT
Data from this trial are available upon reasonable request and approval by the corresponding author.

ORCID
Maryam Edalatifard https://orcid.org/0000-0003-3669-5409

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