Original Article

Nocturnal Arrhythmia during Split-Night Positive Airway Pressure Titration Polysomnography in Obstructive Sleep Apnea Patients at Central Chest Institute of Thailand

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Background: Cardiac arrhythmias are one of the cardiovascular complications from obstructive sleep apnea (OSA). Positive airway pressure (PAP) has been demonstrated as an effective treatment of cardiac arrhythmias in OSA patients.

Objective: To compare nocturnal cardiac arrhythmias and sleep parameters in OSA patients during split-night PAP titration polysomnography (PSG).

Materials and Methods: The present study was a retrospective study, interrupted time series recruited patients that underwent split-night PSG and met diagnostic criteria of OSA by the International Classification of Sleep Disorders-Third Edition with cardiac arrhythmias at Central Chest Institute of Thailand between 2013 and 2019.

Results: Initially, 104 OSA patients with cardiac arrhythmias were enrolled but 33 patients were excluded. Seventy-one patients were analyzed. Most patients were male (57.75%). The average age of patients was 58.08±11.48 years with an average body mass index of 31.79±7.67 kg/m^2. Half of those patients had previous cardiac arrhythmias (57.75%). The most common cardiac arrhythmias were persistent atrial fibrillation at 35.21%. The average left ventricular ejection fraction was 60.04±13.18%. The majority of patients were severe OSA at 92.96%. Sleep parameters were significantly improved in sleep efficiency at 68.07±16.40 and 77.95±15.38 (p<0.001), apnea-hypopnea index at 64.80 with a range of 47.80 to 87.30 and 20.90 with a range of 10.20 to 34.30 (p<0.001), 3% oxygen desaturation index at 17.70 with a range of 7.50 to 44.80 and 2.40 with a range of 0.70 to 8.60 (p<0.001), average oxygen saturation at 88.67±15.53 and 94.39±3.08 (p=0.002), average heart rate at 66.60±11.07 and 63.28±11.84 (p<0.001), lowest heart rate at 41.97±13.30 and 36.61±11.92 (p<0.001), and arousal index at 75.19±30.48 and 38.14±16.09 (p<0.001) after PAP titration, respectively. There was a significant reduction of isolated premature ventricular complexes (PVCs) at 55.29 with a range of 27.06 to 424.80 and 32.56 with a range of 17.05 to 284.68 (p=0.003) after PAP titration.

Conclusion: There was significant reduction of isolated PVCs, and lowest heart rate and sleep parameters were significantly improved in OSA patients with cardiac arrhythmias during split-night PAP titration PSG.

Keywords: Nocturnal cardiac arrhythmias; Sleep parameters; Obstructive sleep apnea (OSA); Positive airway pressure (PAP) titration; Polysomnography

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Obstructive sleep apnea (OSA) has been a common public health problem in clinical practice[1-5]. In Thailand, the prevalence of OSA diagnosed by polysomnography (PSG), defined as having apnea-hypopnea index (AHI) of five events per hour, was 11.4%[5]. Patients with OSA left untreated may suffer from cardiovascular consequences such as hypertension, myocardial infarction, congestive heart failure, or cardiac arrhythmias[6-9].

The pathophysiology of OSA is characterized by repetitive episodes of partial and complete upper airway collapse during sleep, leading to hypoxemia, hypercapnia, and persistent inspiratory efforts against an occluded airway until arousal. As a result, the intrathoracic pressure swings, hence increasing the ventricular wall stress. A subsequent transient

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myocardial ischemia can result in long-term cardiac remodeling. Furthermore, the increase in sympathetic tone also intensifies the risk of cardiac arrhythmias. There are European and Asian studies that have shown that severe OSA is significantly associated with cardiac arrhythmias[10-16]. An Asian study revealed that the incidence of cardiac arrhythmias in OSA patient could be as high as 8%[15].

Positive airway pressure (PAP) is a primary treatment in adult OSA patients across the spectrum of disease severity. It applies a constant pressure throughout the respiratory cycle to splint the airway open.

In Japan, there is a study regarding the effectiveness of PAP in reducing the incidence of cardiac arrhythmias in OSA patients[17]. However, there have not yet been similar studies in Thailand. The present study was conducted to compare nocturnal cardiac arrhythmias and sleep parameters in OSA patients during split-night PAP titration PSG.

Materials and Methods

Subjects and design

The present study enrolled patients aged 18 years or older who underwent split-night PSG with AHI of at least 40 events per hour documented for a minimum of two hours of diagnostic PSG, or AHI of 20 to 40 events per hour, based on clinical judgment by the American Academy of Sleep Medicine (AASM) scoring manual for the scoring of sleep and associated events, version 2.0, 2012[18], and met diagnostic criteria of OSA by the International Classification of Sleep Disorders-Third Edition (ICSD-3)[19], with cardiac arrhythmias at Central Chest Institute of Thailand (CCIT) sleep disorders center between 2013 and 2019.

Patients with uncontrollable cardiac arrhythmias, patients prescribed with new medication within three months prior to PSG, patients with electrolytes imbalance, patients with thyroid diseases, and pregnant patients were excluded.

The present study was a retrospective observational study and interrupted time series design. Each patient's reading was scrutinized by two investigators (AM, AK, or YK) and confirmed by a cardiac electrophysiologist (KM). The polysomnographic data were collected and evaluated according to the criteria of the AASM scoring manual for the scoring of sleep and associated events, version 2.0, 2012[18] by a sleep medicine specialist (KP). The study protocol was approved by the Ethical Review Committee of CCIT (031/2563). The study was conducted in compliance with the Declaration of Helsinki and the International Conference on Harmonization for Good Clinical Practice Guidelines (ICH-GCP).

Statistical analysis

The categorical data were presented as frequency and percentage and the continuous data were presented as mean ± standard deviation (SD), reported to present the center and dispersion of normally distributed data. For non-normally distributed data, median and interquartile range (IQR) would be reported. Categorical and continuous data were compared by using McNemar's test and paired t-test, and Wilcoxon's sign rank test depending on type of data distribution, respectively. A p-value of less than 0.05 was considered as statistical significance. All statistics were performed by using Stata, version 13.1 (StataCorp LP, College Station, TX, USA).

Results

There was 104 patients with OSA and cardiac arrhythmia. Of which, 33 patients were excluded through exclusion criteria, 25 patients did not undergo split-night PAP titration PSG, one patient received new medication three months prior to the study, six patients had incomplete or missing split-night PAP polysomnographic results, and one patient with thyroid disease.

As a result, 71 patients were analyzed including 41 males (57.75%). The mean age was 58.08±11.48 years. The average body mass index (BMI) was 31.79±7.67 kg/m². Average Epworth Sleepiness Scale (ESS) score was 9.58±5.07. Forty-one patients (57.75%) had previous cardiac arrhythmias. The most common cardiac arrhythmia was persistent atrial fibrillation (AF) with 25 patients (35.21%), followed by isolated premature ventricular complexes (PVCs) for 12 patients (16.90%). Five patients (7.04%) underwent radiofrequency ablation and one patient (1.41%) had implantable cardioverter defibrillator (ICD). The three most common underlying diseases were dyslipidemia in 50 patients (70.42%), hypertension in 48 patients (67.61%), and diabetes mellitus in 22 patients, (30.99%). The average AHI was 68.59±31.50 events per hour, dividing into 66 patients with severe disease severity (92.93%) and five patients with moderate disease severity (7.04%). The baseline characteristics of the patients are shown in Table 1.

Sleep parameters were collected during diagnostic and PAP portion of PSG. It was found that sleep efficiency and percentage of rapid eye movement

Table 1. Basic characteristics of patients with obstructive sleep apnea and cardiac arrhythmias who underwent split-night positive airway pressure polysomnography

Demographic data	All patients (n=71)
Basic information	
Sex: male; n (%)	41 (57.75)
Age (years); mean±SD	58.08±11.48
BMI (kg/m^2); mean±SD	31.79±7.67
ESS; mean±SD	9.58±5.07
Neck circumference (cm); mean±SD	39.87±4.39
Hip circumference (cm); mean±SD	111.13±13.92
Waist circumference (cm); mean±SD	106.80±15.90
Underlying diseases	
History of cardiac arrhythmia; n (%)	41 (57.75)
• Persistent AF	25 (35.21)
• Paroxysmal AF	4 (5.63)
• Isolated PVC	12 (16.90)
• Non-sustained VT	1 (1.41)
History of cardiovascular intervention; n (%)	
• Radiofrequency ablation	5 (7.04)
• ICD	1 (1.41)
Other underlying diseases; n (%)	
• Dyslipidemia	50 (70.42)
• Hypertension	48 (67.61)
• Diabetes mellitus	22 (30.99)
• Coronary arterial disease	16 (22.54)
• Asthma	12 (16.90)
• Pulmonary hypertension	9 (12.68)
• Valvular heart disease	7 (9.86)
Other underlying diseases; n (%)	
• Impaired fasting glucose	4 (5.63)
• Ischemic stroke or TIA	3 (4.23)
• COPD	3 (4.23)
• Hyperthyroidism	2 (2.82)
• Hypothyroidism	1 (1.41)
History of heart failure; n (%)	13 (18.31)
LVEF; mean±SD	60.04±13.18
• LVEF <40%; n (%)	3 (5.26)
• LVEF 40 to 49%; n (%)	9 (15.79)
• LVEF >50%; n (%)	45 (78.95)
Current medication; n (%)	
• Beta-blocker	29 (40.85)
• Beta-2 agonist	9 (12.68)
• Non-dihydropyridine calcium channel blocker	7 (9.86)
• ACEI/ARB	28 (39.44)
• Digitalis	9 (12.68)
• Amiodarone	3 (4.23)
• Flecainide	3 (4.23)
• Theophylline	2 (2.82)
• Ivabradine	2 (2.82)
OSA severity; n (%)	
• Severe	66 (92.96)
• Moderate	5 (7.04)
AHI; mean±SD	68.59±31.50

SD=standard deviation; BMI=body mass index; ESS=Epworth Sleepiness Scale; AF=atrial fibrillation; PVC=premature ventricular contraction; VT=ventricular tachycardia; ICD=implantable cardioverter defibrillator; COPD=chronic obstructive pulmonary disease; TIA=transient ischemic attack; LVEF=left ventricular ejection fraction; ACEI=angiotensin-converting enzyme inhibitors; ARB=angiotensin receptor blockers; OSA=obstructive sleep apnea; AHI=apnea-hypopnea index

(REM) sleep increased significantly in PAP portion as compared to diagnostic portion. AHI, 3% oxygen desaturation index (ODI), time with oxygen saturation below 90%, average heart rate, lowest heart rate, and arousal index (ArI) were all found to be significantly lower in PAP portion as compared to diagnostic portion. The sleep parameters of the patients are shown in Table 2.

The present study showed that patients with isolated PVCs had significantly lower number of PVCs during PAP portion. In addition, patients with persistent AF, PACs, and grouped PVCs all exhibited trends of lowering heart rate during PAP portion as shown in Table 3.

Discussion

The present study showed that OSA patients had significantly reduced isolated PVCs and lowest heart rate in diagnostic portion compared with PAP portion during split-night PAP titration PSG. In addition, sleep parameters also improved in various aspects such as better sleep efficiency, higher percentage of REM sleep, lower AHI, lower 3% ODI, oxygen saturation below 90%, and lower arousal index. A previous study in Japan has demonstrated that OSA patients had significantly reduced paroxysmal AF, PVCs, sinus bradycardia, and sinus pause by using continuous positive airway pressure (CPAP)[17]. Moreover, the CPAP therapy significantly improved AHI, arousal index, lowest SpO2, and percentage of SpO2 below 90%.

However, the present study revealed that only isolated PVCs and lowest heart rate significantly decreased, but no statistically significant changes in rate of persistent AF, PACs, and grouped PVCs burden were demonstrated.

Table 2. Sleep parameters of patients with obstructive sleep apnea and cardiac arrhythmias who underwent split-night positive airway pressure polysomnography

Sleep parameters	Split-night polysomnography (n=71)		p-value
	Diagnostic portion	Positive airway pressure portion	
TST (minute); mean±SD	105.91±31.27	259.17±69.83	<0.001#
SE (%); mean±SD	68.07±16.40	77.95±15.39	<0.001#
SL (minute); median (IQR)	13.50 (7.50 to 19.0)	6.50 (2.50 to 15.0)	0.006#
REM latency (minute); median (IQR)	99.25 (69.0 to 121.0)	68.50 (32.0 to 99.0)	0.033#
Stages of sleep (%)			
NREM1; median (IQR)	11.50 (7.20 to 21.90)	11.30 (5.80 to 16.70)	0.039#
NREM2; mean±SD	53.39±21.18	47.95±13.57	0.075
NREM3; median (IQR)	21.50 (0.90 to 38.70)	20.90 (12.80 to 28.30)	0.409
REM; median (IQR)	0.0 (0.0 to 9.65)	19.65 (13.50 to 27.10)	<0.001#
AHI (events/hour); median (IQR)	64.80 (47.80 to 87.30)	20.90 (10.20 to 34.30)	<0.001#
REM-AHI (events/hour); median (IQR)	48.25 (39.75 to 67.85)	16.35 (7.85 to 29.70)	<0.001#
3% ODI (events/hour); median (IQR)	17.70 (7.50 to 44.80)	2.40 (0.70 to 8.60)	<0.001#
ST90 (minute); median (IQR)	1.0 (0.0 to 23.0)	0.0 (0.0 to 6.0)	0.004#
Lowest SpO2 (%); mean±SD	81.21±11.12	83.70±14.60	0.135
Average SpO2 (%); mean±SD	88.67±15.53	94.39±3.08	0.002#
REM-SpO2 (%); mean±SD	83.17±10.67	89.27±8.86	0.004#
Heart rate (beats/minute); mean±SD			
Average heart rate	66.60±11.07	63.28±11.84	<0.001#
Lowest heart rate	41.97±13.30	36.61±11.92	<0.001#
Highest heart rate	96.82±22.39	96.70±23.46	0.969
PLMI (events/hour); median (IQR)	0.0 (0.0 to 0.0)	0.0 (0.0 to 6.70)	0.002#
ArI (events/hour); mean±SD	75.19±30.47	38.14±16.09	<0.001#

SD=standard deviation; IQR=interquartile range; TST=total sleep time; SE=sleep efficiency; SL=sleep latency; REM=rapid eye movement; NREM=non-rapid eye movement; AHI=apnea-hypopnea index; SpO2=oxygen saturation; ODI=oxygen desaturation index; ST90=time with oxygen saturation below 90%; PLMI=periodic limb movements of sleep index; ArI=arousal index

Statistical significance

Table 3. Cardiac arrhythmias in obstructive sleep apnea patients who underwent split-night positive airway pressure polysomnography

Cardiac arrhythmias	Split-night polysomnography (n=71)		p-value
	Diagnostic portion	Positive airway pressure portion	
Rate of persistent AF (bpm); mean±SD	91.96±23.69	85.70±14.49	0.118
PACs (times/hour); median (IQR)	149.33 (33.07 to 230.0)	85.47 (22.52 to 226.0)	0.241
Isolated PVCs (beats/hour); median (IQR)	55.29 (27.06 to 424.80)	32.56 (17.05 to 284.68)	0.003#
Complex PVCs (beats/hour); median (IQR)	107.08 (5.58 to 1088.10)	20.70 (11.77 to 1132.67)	0.844

SD=standard deviation; IQR=interquartile range; AF=atrial fibrillation; bpm=beats per minutes; PACs=premature atrial contractions; PVCs=premature ventricular complexes

Statistical significance

The autonomic nervous system (ANS) is a known key modulator of heart rate fluctuations and rhythm during sleep and nocturnal heart rate reflects a balance between the sympathetic and parasympathetic systems[20]. The autonomic tone may contribute to the occurrence of AF and other arrhythmias. The mechanism of bradycardia is explained by a reflex increase in the vagal tone triggered by a combination of apnea and hypoxemia[21,22].

Sleep is a dynamic state with marked changes in neurophysiologic and biochemical processes[23,24]. In non-rapid eye movement (NREM) sleep, decreases in respiratory rate, blood pressure, and heart rate normally occur[25]. Alternatively, during REM sleep, physiologic variability ensues with mean net increases in respiratory rate, blood pressure, and heart rate[26,27]. Nocturnal heart rate reflects combined inputs from both the parasympathetic, which are primarily

influenced by circadian rhythms, and sympathetic, which are primarily influenced by sleep state cycle, systems.

The present study showed the reduced lowest heart rate in PAP portion compared to diagnostic portion during split-night PAP titration PSG with statistical significance. The present study result was different from the previous Japanese study showing the improved sinus bradycardia and pause after CPAP[17]. The different outcome between both studies might be the difference in racial population. The REM sleep-related bradyarrhythmia syndrome cannot be excluded in this situation. The abnormal ANS including exaggerated vagal tone and acute withdrawal of sympathetic activity during phasic REM events may be the possible mechanism[20].

To date, there are no conclusive epidemiologic or longitudinal intervention studies related specifically to the prevalence, severity, and consequences of cardiac arrhythmias and the effects of OSA treatment[28].

The limitation of the present study is the short duration of using PAP titration of PSG leading to the underestimated prevalence of cardiac arrhythmias occurring paroxysmal, periodic, the association between daytime (or wake) and nocturnal (or sleep) rhythm disturbance, percentage of any sleep stage, and the duration of PAP used. Additionally, the present study enrolled a small sample size. This might lead to lower rate of persistent AF, PACs, and PVCs burden with no statistical significance. Nevertheless, if the study sample size increased and the monitoring period of PAP therapy was longer, the statistically significant results might become more unambiguous.

Conclusion

There was significant reduction of isolated PVCs, lowest heart rate, and sleep parameters were significantly improved in OSA patients with cardiac arrhythmias during split-night PAP titration PSG.

What is already known on this topic?

To date, there are no conclusive epidemiologic or longitudinal intervention studies related specifically to the prevalence, severity, and consequences of cardiac arrhythmias and the effects of OSA treatment.

What this study adds?

There was a significant reduction of isolated PVCs, lowest heart rate, and sleep parameters were significantly improved in OSA patients with cardiac arrhythmias during split-night PAP titration PSG.

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Conflicts of interest

The authors declare no conflict of interest.

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