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Cardiac effects of CPAP treatment in patients with obstructive sleep apnea and atrial fibrillation

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Abstract

Purpose Obstructive sleep apnea (OSA) has been recognized as an independent risk factor for the development and progression of atrial fibrillation (AF). We aimed to investigate the changes in heart rate and atrial and ventricular ectopy after continuous positive airway pressure (CPAP) treatment in patients with OSA and AF.

Methods Consecutive patients with AF underwent ambulatory sleep monitoring, and OSA was defined as an Apnea-Hypopnea-Index (AHI) ≥ 5/h. Treated patients completed in-laboratory CPAP titration study. A 24-h ECG Holter was performed at baseline and at 3 and 6 months after CPAP treatment.

Results One hundred patients (70% males) with AF were included in the final analysis. OSA was diagnosed in 85% of patients. There were no significant changes in mean 24-h heart rate in patients with paroxysmal or permanent AF at 3 and 6 months of treatment compared to baseline. In patients with paroxysmal AF ($n = 29$), atrial and ventricular ectopy counts/24 h significantly decreased at 3 months compared to baseline (median (IQR) 351 (2049) to 57 (182), $P = 0.002$; 68 (105) to 16 (133), $P = 0.01$ respectively). At 6 months follow-up, the atrial ectopy count/24 h significantly decreased in patients with paroxysmal AF compared to baseline (median (IQR) 351 (2049) to 31 (113), $P = 0.016$, $n = 14$). In patients with permanent AF ($n = 15$), there was a significant reduction in ventricular ectopy count/24 h at 3 months compared to baseline (median (IQR) 100 (1116) to 33 (418), $P = 0.02$).

Conclusions There is a significant decrease in atrial and ventricular ectopy count/24 h in patients with AF and OSA at 3 and 6 months of CPAP treatment compared to baseline.

Keywords Obstructive sleep apnea · Atrial fibrillation · Continuous positive airway pressure · Atrial ectopy · Ventricular ectopy · CPAP compliance · Arrhythmia · Ambulatory sleep monitoring

Abbreviations

AF	Atrial fibrillation
AHI	Apnea-Hypopnea-Index
CPAP	Continuous positive airway pressure
ECG	Electrocardiogram
OSA	Obstructive sleep apnea
PSG	Polysomnography
TST	Total sleep time

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1 Introduction

Obstructive sleep apnea (OSA) is characterized by repeated upper airway obstructions during sleep. OSA has been recognized as an independent risk factor for the development and progression of atrial fibrillation (AF) [1]. OSA increases the recurrence of AF after surgical ablation [1]. In addition, OSA is associated with increased frequency of AF in patients with coronary artery disease [2]. Patients with OSA have a higher incidence of AF after coronary artery bypass graft surgery compared to patients without OSA [2].

The mechanism underlying the association between OSA and AF involves the effects of hypoxia and oxidative stress, intrathoracic pressure swings, systemic inflammation, and sympathetic hyperactivity [3]. The results of these effects include electrical and structural remodeling of the atria and ventricles [4]. Nocturnal hypoxemia is an independent risk factor for the development of new-onset AF [5]. Hypoxia prolongs atrial refractory periods and decreases velocity and increases heterogeneity of conduction [6]. Increased negative intrathoracic pressure causes acute stretch of myocardial wall and intrathoracic vessels evident by proximal aortic dilation and increased left ventricular volumes [7]. These structural changes along with an increase in transmural gradients may create an arrhythmogenic milieu. In healthy individuals, an induction of apnea by the Mueller maneuver, which involves an inspiration against closed mouth and nose, caused prolonged myocardial repolarization and induced ventricular premature beats [8]. Induced apneas cause a significant increase in negative intrathoracic pressure [8] and aortic wall transmural pressure [9]. In addition, induced apneas decrease left ventricular ejection fraction, increase afterload, and result in left ventricular systolic dysfunction [10]. Termination of apneas resulted in substantial increase in left ventricular ejection fraction [10]. Thus, repeated intrathoracic pressure swings during cycles of apneas and hyperventilation in OSA may trigger and/or increase the occurrence of atrial and ventricular arrhythmia [10].

In addition, intrathoracic pressure swings, sympathetic hyperactivity, and inflammatory mediators induce atrial remodeling which plays a role in the recurrence of AF [11]. Further, obesity and hypertension, frequent comorbidities with OSA, are associated with left atrial and ventricular enlargement which may contribute to the recurrence of AF in patients with OSA [3].

The standard treatment of moderate and severe OSA is continuous positive airway pressure (CPAP) treatment. CPAP treatment prevents the collapse of the upper airways and the physiological consequences of the obstruction. Therefore, CPAP treatment may prevent hypoxia, oxidative stress, and sympathetic hyper-stimulation induced by OSA. Evidence showed that CPAP decreases sympathetic activity both during day and night in patients with OSA [12]. In addition, CPAP treatment reduces markers of sympathetic stimulation such as 24-h urinary catecholamine excretion and plasma norepinephrine levels [13]. Moreover, CPAP was found to increase baroreceptor sensitivity and decrease inflammation and oxidative stress [14]. Previous studies show an improvement in cardiac electrical and structural remodeling associated with OSA, and improved inter- and intra-atrial electromechanical conductions in these patients after CPAP treatment [15]. Non-randomized studies suggest that CPAP treatment of OSA may help to maintain sinus rhythm after electrical cardioversion and improve the success rates of catheter ablation in patients with AF [16].

Thus, CPAP treatment may decrease the occurrence and/or recurrence of AF and other tachyarrhythmias associated with OSA. However, a limited number of studies were conducted on this topic and the evidence regarding therapeutic effects of CPAP treatment in patients with AF is insufficient [3]. In this study, we aimed to investigate the changes in heart rate and other electrocardiogram (ECG) Holter measures after CPAP treatment of OSA in patients with AF.

2 Methods

2.1 Study design

This is a prospective non-randomized interventional study involved adult patients with AF. Ethical approval was obtained from University Health Network and St. Michael's Hospital Research Ethics Boards. Participants were evaluated for OSA by unattended ambulatory sleep testing. Patients who had been identified with OSA were treated with CPAP therapy. Treated patients completed in-laboratory CPAP titration study. Treated patients were evaluated with an (ECG Holter monitoring at baseline and at 3 and 6 months post-treatment. The changes in heart rate and atrial and ventricular ectopy counts were assessed at 3 and 6 months after CPAP treatment compared to baseline.

2.2 Study sample

Consecutive non-selected patients were recruited from two major arrhythmia clinics in Toronto, ON, Canada. Recruitment was completed between June 2016 and March 2017. Inclusion criteria were (1) adult patients over 18 years old; (2) male and female patients; (3) previously documented AF (ECG or ECG Holter); (4) patients are clinically stable on antiarrhythmic medications, if required, during the duration of the study and follow-up period; and (4) patients are able to provide an informed consent. The following exclusion criteria were applied: (1) a previous diagnosis and/or treatment of OSA, (2) a sleep study within 6 months prior to recruitment, and (3) an inability to provide an informed consent. We did not exclude any patients with cardiovascular or chronic diseases. Informed consent was obtained from all individual participants included in the study

2.3 Diagnosis of OSA by ambulatory sleep testing

All consecutive non-selected patients with AF underwent two nights of unattended ambulatory sleep testing in-home (level II) [17]. A portable sleep monitor that is suitable for self-application in a home-based environment (Somté PSG (v2) sleep monitor (P/N: 8023-0001-02, Compumedics Limited) along with an electroencephalogram (EEG) monitoring was

used. The ambulatory sleep testing involved a concurrent recording of EEG, electrooculogram, electromyogram, electrocardiogram (ECG), airflow, snore, respiratory effort, body position, limb movement, oxygen saturation, pulse rate, and pulse waveform. Studies were recorded and scored according to the American Academy of Sleep Medicine (AASM) criteria. The ESPRIT NOVA client access (The Neurozone MSH Inc. Canada) software was utilized for automatic analysis of polysomnogram data. Following the initial analysis, studies were manually scored and edited by a qualified sleep technologist. Scorers were blinded to identification data. Scoring of the second night was independent of the first-night results. Further, sleep studies were reviewed and interpreted by a sleep specialist. The following standard AASM criteria were used for the diagnosis and classification of OSA: (1) OSA is defined as an AHI $\geq$ 5/h total sleep time (TST); (2) mild OSA: AHI $\geq$ 5 and < 15/h TST; (3) moderate OSA: AHI $\geq$ 15 and < 30/h TST; and (4) severe OSA: AHI $\geq$ 30/h TST. For assessment of OSA symptoms and features, we administered the STOP-BANG questionnaire (STOP: Snoring; Tired; Observed stop breathing; and high Blood; Pressure; BANG: BMI > 35 kg/m^2, age > 50, neck circumference > 40 cm, and gender male) [18], Epworth sleepiness scale, and Fatigue severity scale.

2.4 Study intervention

2.4.1 Continuous positive airway pressure treatment

Patients who were identified to have OSA by the ambulatory sleep testing were referred for CPAP treatment as appropriate. The decision for treatment was made by a sleep specialist considering the AHI level and/or symptoms including snoring, excessive daytime sleepiness, and/or fatigue. Patients were set up on Resmed Airsense 10 Elite CPAP device: a premium fixed-pressure device with integrated humidifier, cellular connectivity, and advanced event detection. The set up and mask fitting procedure were performed by experienced CPAP clinicians from CPAP Direct Ltd. at the Sleep and Alertness Clinic in Toronto, ON. The initial recommended pressure was recommended by a sleep specialist.

2.5 Follow-up procedures

2.5.1 Split-night CPAP titration study

Participants underwent an overnight in-laboratory split-night polysomnography (PSG) for CPAP titration at the Sleep and Alertness Clinic within 1 week of CPAP initiation. The first half of the study was a diagnostic part and the second half was a titration for CPAP. The split-night study requires recording and analysis of same parameters as the standard diagnostic PSG. The split-night titration study was conducted and scored according to the standard AASM guidelines and was reviewed by a sleep specialist. CPAP devices were adjusted to the optimum pressure obtained from the split-night titration study.

2.6 24-h ECG Holter monitor

Evaluation of the heart rate and rhythm was performed at baseline and after 3 and 6 months of CPAP treatment using a 24-h ECG Holter monitor. Outcome measures included mean 24-h heart rate, total beats, percentage of ventricular beats, percentage of supraventricular beats, maximum heart rate, tachycardia beats (over 100 bpm) and its percentage, minimum heart rate, bradycardia beats (less than 50 bpm) and its percentage, pauses over 2.5 s, and longest RR interval duration in seconds. In addition, ventricular ectopic beats were analyzed and included the following measures: total ventricular ectopic beat count; number of single beats, pairs, total runs, and number of beats in runs, longest run, fastest run, and R on T phenomenon. Moreover, supraventricular ectopic beats were analyzed including total supraventricular ectopic beat count, the number of single beats, pairs, total runs, and number of beats in runs, longest run, fastest run, and aberrant conduction.

2.7 Assessment of CPAP compliance

Participants' compliance with CPAP treatment was remotely monitored at 2 weeks, and 1, 3, and 6 months post-treatment. Compliance assessment at 2 weeks and 1 month was used for an initial assessment of patients' adherence to CPAP treatment in order to address difficulties or intolerance to treatment. The compliance assessment at 3 and 6 months after CPAP treatment was used in the analysis and comparisons of changes in outcome measures. Compliance assessment included the average usage reported as hours per night and percentage of compliance (days of use). Compliance was further divided into usage for 5 h or more per night or usage of fewer than 5 h per night during usage days.

2.8 Statistical analysis

Statistics were performed using the SPSS statistical software (version 23). Independent sample *t* test was used to compare means of continuous variables, and chi-square test was used to compare proportions of categorical variables. Non-parametric Wilcoxon signed ranks test for matched pairs was used to evaluate changes in heart rate, and atrial and ventricular ectopy counts from baseline to 3 and 6 months after treatment.

3 Results

3.1 Population characteristics

A total of 123 patients consented to participate in the study. Nineteen patients dropped out before completing ambulatory sleep testing. Another four patients had an unsuccessful sleep recording, and reliable sleep data was not available for them. Therefore, the final analysis included 100 patients with AF. Of those patients, 70% had paroxysmal AF, and 30% had permanent AF. Demographic and clinical characteristics of the study sample are shown in Table 1. Patients were on stable medical regimen during the study duration and follow-up period.

3.2 Diagnosis of OSA by the ambulatory sleep monitoring

OSA was detected in 85% of patients ($n = 100$) including 91% of males and 70% of females. The AHI of the two nights of sleep testing was averaged to give a mean AHI for each participant. The mean AHI of patients was 19.7 ± 17/h (range 0.35–90/h). In patients with OSA ($n = 85$), the mean AHI was 23 ± 16/h (range 5–90/h). According to the AASM criteria of the severity classification, 45% of patients had mild OSA (AHI > 5 and below 15), 27% had moderate OSA (AHI ≥ 15 and below 30), and 28% had severe OSA (AHI ≥ 30).

3.3 Assessment of CPAP compliance

The average compliance of CPAP usage was 80% during the follow-up period. Compliance of using CPAP for more than 5 h per night was 81%. The average usage of CPAP was 5.6 ± 2 h/night. From 44 patients, eight patients were non-compliant with usage of CPAP for 5 h or more per night.

3.4 Changes in outcome measures after treatment

3.4.1 Effects on heart rate

There was no significant change in average 24-h heart rate at 3 months compared to baseline in both patients with paroxysmal ($n = 44$) and permanent ($n = 15$) AF.

At 6 months follow-up, there was no significant change in average 24-h heart rate in patients with paroxysmal ($n = 14$) and permanent ($n = 9$) AF compared to baseline (see Tables 2 and 3, Figs. 1 and 2).

Table 1 Clinical characteristics of the study sample, with a comparison between patients with and without OSA

	Total ($n = 100$)	OSA ($n = 85$)	Non-OSA ($n = 15$)	P value
Age (years)	63 ± 13	65 ± 13	55 ± 14	$P = 0.009$*
Gender	70% M, 30% F	75% M, 25% F	40% M, 60% F	$P = 0.000$*
BMI (kg/m^2)	29 ± 6	29 ± 6	25 ± 4	$P = 0.008$*
BMI ≥ 30 kg/m^2	33%	40%	8%	$P = 0.02$*
BMI > 35 kg/m^2	11%	12.5%	8%	$P = 0.6$
STOP-BANG ≥ 3	84%	89%	64%	$P = 0.01$*
ESS ≥ 10	22%	22%	21%	$P = 0.9$
FSS ≥ 3	54%	60%	21%	$P = 0.008$*
Hypertension	49%	53%	27%	$P = 0.06$
Diabetes	11%	12%	7%	$P = 0.5$
Coronary artery disease	7%	7%	7%	$P = 0.9$
History of stroke	8%	9%	0	$P = 0.2$
Heart failure	3%	3%	0	$P = 0.4$
Hyperlipidemia	42%	42%	40%	$P = 0.8$
Cardiomyopathy	2%	2%	0	$P = 0.6$
Pacemaker insertion	3%	4%	0	$P = 0.4$
Previous AF/flutter ablation	20%	19%	27%	$P = 0.4$
Cardiac valve replacement	2%	2%	0	$P = 0.5$
Beta-blocker	50%	87%	13%	$P = 0.007$*
Antiarrhythmic (class Ic, III)	31%	29%	20%	$P = 0.4$
Ca-blocker	30%	29%	20%	$P = 0.5$

Independent sample t test was used to compare means of continuous variables, and chi-square test was used to compare proportions of categorical variables. Values are expressed as mean ± standard deviation or percentage of total *indicates statistical significance ($P<0.05$)

AF atrial fibrillation, *BMI* body-mass-index, *cm* centimeters, *ESS* Epworth sleepiness scale, *FSS* fatigue severity scale, *F* females, *M* males, *N* number, *OSA* obstructive sleep apnea

Table 2 The outcome in patients with paroxysmal AF after 3 and 6 months of CPAP treatment compared to baseline

	Baseline ($n = 29$)		3 months ($n = 29$)			6 months ($n = 14$)		
	Mean (SD)	Median (IQR)	Mean (SD)	Median (IQR)	*P* value	Mean (SD)	Median (IQR)	*P* value
Average daily heart rate (beats/min)	68 (10)	65 (15)	67 (12)	66 (15)	$P = 0.4$	67 (13)	67 (9)	$P = 0.7$
Ventricular ectopy/24 h	1746 (7924)	68 (105)	151 (305)	16 (133)	$P = 0.01$*	2380 (8022)	25 (758)	$P = 0.08$
Supraventricular ectopy/24 h	1214 (1774)	351 (2049)	310 (705)	57 (182)	$P = 0.002$*	128 (222)	31 (113)	$P = 0.016$*

Wilcoxon signed rank test for matched pairs was used to detect changes from baseline to 3 and 6 months after treatment

SD standard deviation, *IQR* interquartile ratio, * indicates statistically significant *P* value < 0.05

3.4.2 Effects on atrial and ventricular ectopy

In patients with paroxysmal AF ($n = 29$), there was a significant reduction in atrial premature beat count/24 h ($P = 0.002$) at 3 months of CPAP treatment compared to baseline (median (IQR) 351 (2049) to 57 (182), $P = 0.002$). In addition, there was a significant decrease in ventricular premature beat count/24 h compared to baseline (median (IQR) 68 (105) to 16 (133), $P = 0.01$) (refer to Table 2 and Fig. 1).

In patients with permanent AF ($n = 15$), there was a significant reduction of ventricular premature beat count/24 h at 3 months of CPAP treatment compared to baseline (median (IQR) 100 (1116) to 33 (418), $P = 0.02$) (see Table 3 and Fig. 2).

At 6 months after CPAP treatment in patients with paroxysmal AF, there was a significant reduction in atrial premature beat count/24 compared to baseline (median (IQR) 351 (2049) to 31 (113), $P = 0.016$, $n = 14$). However, there was no significant decrease in ventricular premature beat count/24 h ($P = 0.08$) in these patients (Table 2 and Fig 1).

In patients with permanent AF ($n = 9$), there was no significant reduction of ventricular premature beat count/24 h ($P = 0.06$) at 6 months of treatment compared to baseline (refer to Table 3 and Fig. 2).

4 Discussion

Previous studies showed that CPAP treatment is associated with a significant reduction in AF recurrence [19, 20]. In addition, CPAP treatment was associated with a reduction in heart rate in patients with OSA and paroxysmal and permanent AF; however, it did not reach statistical significance [21]. Further, CPAP treatment was associated with a significant reduction in nocturnal atrial and ventricular ectopy in patients with OSA [22]. A study in patients with OSA and congestive heart failure showed a significant reduction in nocturnal ventricular ectopy after CPAP treatment [23]. However, the effects of CPAP treatment on atrial and ventricular ectopy in patients with OSA and AF have not been previously investigated. In this study, we aimed to determine the changes in average daily heart rate and atrial and ventricular ectopy in patients with OSA and paroxysmal and permanent AF.

In our study, there was no significant effect on average heart rate at 3 and 6 months after treatment compared to baseline in patients with paroxysmal and permanent AF. Mean 24-h heart rate of the study sample at baseline was 71.36 ± 13.62 bpm, which indicates that heart rate was well controlled with medications at baseline. In addition, total sample size may not be adequate to detect significant differences. This may explain the absence of changes in heart rate after CPAP treatment in the total study group. Patients with paroxysmal AF were in sinus rhythm during the 24-h monitoring at baseline. There was one patient who had 8% AF at baseline, which decreased to 1% AF at the T3 follow-up holter. Another three patients had brief runs of AF at baseline holter but were in sinus rhythm during follow-up holter.

Moreover, this study detected a potentially beneficial effect after CPAP treatment in patients with paroxysmal AF represented by a significant reduction in average count of atrial ectopy at 3 and 6 months of treatment compared to

Table 3 The outcome in patients with permanent AF after 3 and 6 months of CPAP treatment compared to baseline

	Baseline ($n = 15$)		3 months ($n = 15$)			6 months ($n = 9$)		
	Mean (SD)	Median (IQR)	Mean (SD)	Median (IQR)	*P* value	Mean (SD)	Median (IQR)	*P* value
Average daily heart rate (beats/min)	76 (10)	76 (11)	72 (11)	72 (16)	$P = 0.1$	76 (10)	70 (19)	$P = 0.7$
Ventricular ectopy/24 h	932 (1571)	100 (1116)	430 (918)	33 (418)	$P = 0.02$*	75 (93)	31 (152)	$P = 0.06$

Wilcoxon signed rank test for matched pairs was used to detect changes from baseline to 3 and 6 months after treatment

SD standard deviation, *IQR* interquartile ratio, * indicates statistically significant *P* value < 0.05

baseline (Fig. 1). Frequent atrial premature beats are associated with an increased risk of AF [24]. Sympathetic and vagal imbalance caused by the obstructive events during OSA may increase the risk of premature atrial contractions, which is associated with increased recurrence of AF early after cardioversion [25]. In addition, simulation of OSA in patients with paroxysmal AF induced atrial premature contractions, which trigger occurrence and/or recurrence of AF episodes [26]. Therefore, reduction of average atrial ectopy count in patients with paroxysmal AF may decrease occurrence and/or recurrence of AF. However, this effect needs longitudinal well-designed randomized controlled studies to validate.

Further, our study shows a significant reduction of average count of ventricular ectopy in both patients with paroxysmal and permanent AF at 3 months after CPAP treatment compared to baseline (Figs. 1 and 2). OSA is associated with a high prevalence of premature ventricular contractions and ventricular tachycardia [27]. In addition, OSA has been considered a strong predictor of life-threatening ventricular arrhythmia in patients with heart failure and implantable cardioverter-defibrillator [28]. In a metanalysis, sleep disordered breathing was associated with an increased risk of appropriate ICD therapy in patients with heart failure [29]. Ventricular arrhythmia has been mainly reported during the apneic phase of OSA and with a nocturnal oxygen saturation below 60%, and during obstructive events longer than 40 s [23]. Although the severity of OSA correlates with the occurrence of ventricular arrhythmia, such arrhythmias have been detected even in mild and moderate OSA. [27] Previous studies showed a reduction in average ventricular premature beats after CPAP treatment in patients with OSA [21]. This study confirms a significant reduction of average ventricular ectopy count in patients with paroxysmal and permanent AF at 3 months after CPAP treatment compared to baseline. However, the clinical effects of reduced premature ventricular beats in patients with AF have not been previously investigated. The reduction of ventricular ectopy may decrease the risk of potentially dangerous ventricular tachycardia. Possible therapeutic benefits of our findings need further investigation.

There are a number of critical factors which influence the response to CPAP treatment including adherence and compliance, duration of treatment, baseline state of cardiac function, and other cardiovascular and medical comorbidities. Our population consisted of patients with no significant cardiovascular comorbidities and was medically stable on antiarrhythmic medications. In addition, 20% of patients had a history of ablation procedure of AF. These results may not apply to a wider population with different characteristics. In the general population, compliance with CPAP treatment is variable; 29 to 83% of patients use the CPAP for less than 4 h per night [30]. We achieved 80% compliance rate in our study population. Compliance with CPAP treatment is crucial to demonstrate the efficacy of treatment.

We applied different strategies to improve CPAP compliance which are reliant on patients' education and long-term care. Patients underwent mask fitting procedure and a careful selection of appropriate mask to ensure a proper seal and maintain patient's comfort and tolerance of the pressure. In

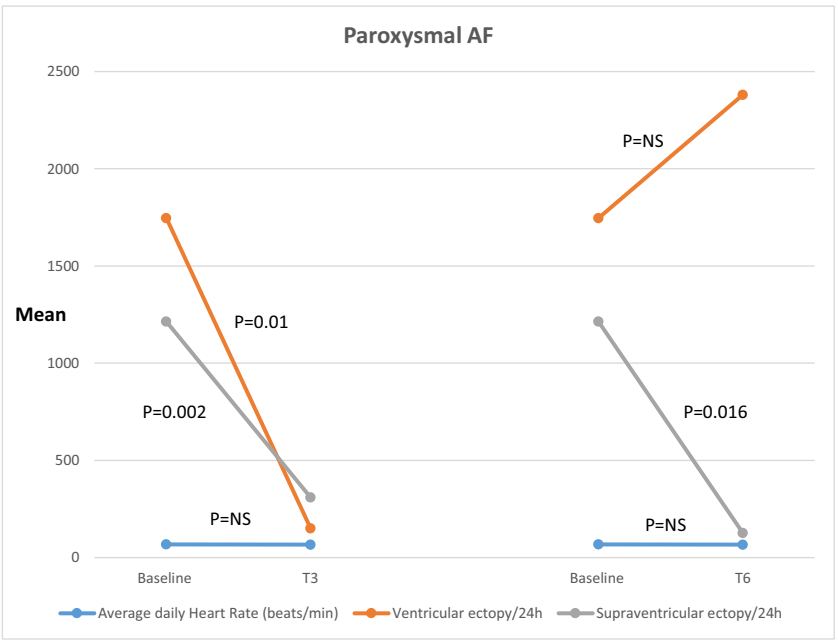

Fig. 1 The outcome in patients with paroxysmal AF after 3 and 6 months of CPAP treatment compared to baseline

Mean outcome variable at baseline and three (T3) and six months (T6) after CPAP treatment in patients with paroxysmal atrial fibrillation (AF). NS: non-significant

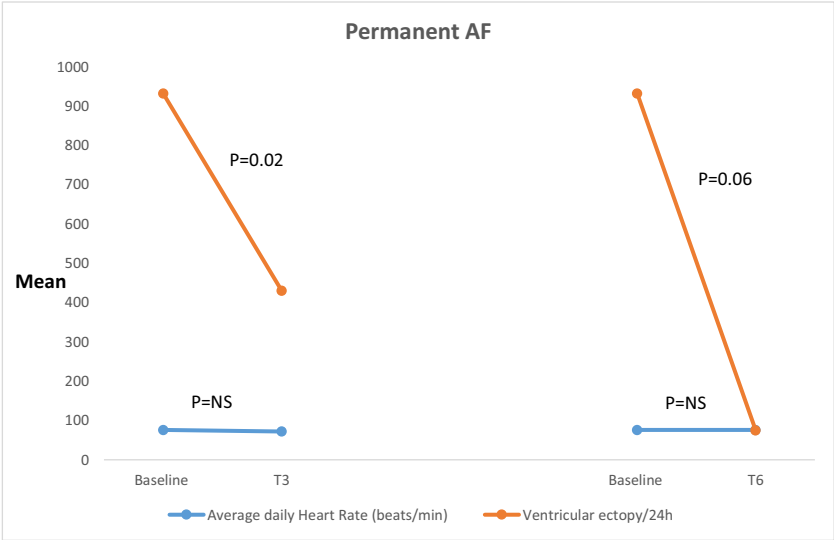

Fig. 2 The outcome in patients with permanent AF after 3 and 6 months of CPAP treatment compared to baseline

Mean outcome variable at baseline and three (T3) and six months (T6) after CPAP treatment in patients with permanent atrial fibrillation (AF). NS: non-significant

addition, participants were educated on proper mask fitting, cleaning procedure, operating the machine, humidity adjustment, and possible technical problems or side effects of CPAP. Minor side effects of CPAP were experienced by some patients in this study including nasal dryness and eyes irritation. Moreover, CPAP machines provided to participants were supplied with heated humidifiers, which prevent or minimize nasal symptoms. Furthermore, we performed a frequent remote download of the compliance reports. Any issues with patients' compliance were addressed early during the course of treatment. We observed that engaging patients with an online self-monitoring application was helpful for improving adherence to treatment. Moreover, some patients reported improved symptoms of arrhythmia including palpitations and shortness of breath, and improved level of energy after treatment. However, we did not objectively assess these outcomes; yet, these positive changes could be an important factor for improving CPAP compliance. It should be noted that this was a population who are not presenting to a sleep clinic compared to most sleep apnea referrals one would expect a lower rate of compliance. Therefore, long-term care and continuous support for patients treated with CPAP therapy are recommended. Further methods to increase and maintain adherence to CPAP treatment should be investigated.

The findings of this study may indicate the potential of CPAP treatment to reverse electrical and/or structural remodeling associated with OSA, and therefore, may decrease occurrence and/or recurrence of AF. This may direct future research to investigate effects of CPAP treatment on atrial and ventricular remodeling in patients with AF, and the clinical relevance of these findings. CPAP treatment may provide a homogenous conduction within the atria and ventricles, which may decrease the risk of atrial and ventricular arrhythmias on the long-term. Further investigation of the effects of CPAP treatment in randomized controlled studies is needed. Future studies should address the level of compliance and other possible confounding factors; when evaluating the impact of CPAP treatment on AF.

5 Limitations

This study may be limited by observational and selection bias, which we tried to minimize by recruiting non-selected consecutive patients. In addition, in-laboratory PSG was not offered to patients who had negative, inconclusive, or technically inadequate home sleep studies ($n = 4$). Also, a number of patients declined CPAP treatment and others discontinued the treatment at some point during follow-up ($n = 23$). These patients were not included in the final analysis of treatment effects. The study did not achieve a complete level of CPAP compliance despite full monitoring and support, which may indicate challenges of CPAP adherence which should be addressed to enhance efficacy of CPAP treatment. Another limitation is the non-randomized study design and lack of a control group. Moreover, the inability to detect significant changes in heart rate and in ventricular ectopy counts at 6 months could be related to inadequate sample size. This study was part of a larger clinical study in which the sample size was calculated to estimate the prevalence of OSA in

patients with AF [31]. Therefore, this study may not be powered to detect statistically significant changes in heart rate after CPAP treatment. In addition, patients were evaluated with a 24-h ECG Holter monitor, which may not cover sufficient period to accurately assess the changes in arrhythmia frequency. Also, patients were not evaluated for recurrence of AF and changes in symptoms, hospitalization, and need of cardioversion during the follow-up period. These effects may be useful to interpret the clinical effects related to CPAP treatment on arrhythmia burden and frequency. Further, detailed sleep diary at time of holter was not obtained. Therefore, we were only able to interpret heart rate and atrial and ventricular ectopy during the total 24-h period. Assessing the effects of CPAP on nocturnal heart rate or nocturnal ectopy was not possible.

Despite these limitations, this study points to significant positive effects of CPAP treatment on the frequency of atrial and ventricular ectopy in patients with AF, which may reduce the recurrence of AF on the long-term. The clinical relevance of these findings on AF burden is difficult to conclude. This study may be the first step in recognition of positive effects of CPAP treatment, with adequate compliance, in patients with AF, but requires support in future appropriately designed randomized clinical trials.

6 Conclusion

There was a significant reduction in atrial ectopy count/24 h in patients with paroxysmal AF at 3 months after CPAP treatment compared to baseline. This effect was sustained at 6 months evaluation. In addition, there was a significant reduction in ventricular ectopy counts/24 h in both patients with paroxysmal and permanent AF at 3 months of CPAP treatment compared to baseline. However, there was no significant change in ventricular ectopy count/24 h in these patients at 6 months. The clinical relevance of these findings needs further investigations in randomized controlled studies powered to detect significant changes.

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Funding The Neurozone MSH Inc. Canada provided the equipment of home sleep testing for participants in the study. CPAP devices and supplies were provided by the CPAP Direct Ltd.

Compliance with ethical standards

Ethical approval was obtained from University Health Network and St. Michael's Hospital Research Ethics Boards.

Conflict of interest

CS has shares in the Neurozone MSH Inc. Canada which provided the equipment for the ambulatory sleep testing and the analysis of the sleep reports testing system. AA, DN, and PD have no conflicts of interest to disclose.

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.

References

1. Voight J, Akkaya M, Somasundaram P, Karim R, Valliani S, Kwon Y, et al. Risk of new-onset atrial fibrillation and stroke after radiofrequency ablation of isolated, typical atrial flutter. Heart Rhythm. 2014;11(11):1884–9. https://doi.org/10.1016/j.hrthm.2014.06.038.
2. Mooe T, Gullsby S, Rabben T, Eriksson P. Sleep-disordered breathing: a novel predictor of atrial fibrillation after coronary artery bypass surgery. Coron Artery Dis. 1996;7(6):475–8.
3. Abumuamar AM, Mollayeva T, Sandor P, Newman D, Nanthakumar K, Shapiro CM. Efficacy of continuous positive airway pressure treatment in patients with cardiac arrhythmia and obstructive sleep apnea: what is the evidence? Clinical Medicine Insights: Therapeutics. 2017;9(Supplementary Material_734227): 1179559X17734227. https://doi.org/10.1177/1179559X17734227.
4. Dimitri H, Ng M, Brooks AG, Kuklik P, Stiles MK, Lau DH, et al. Atrial remodeling in obstructive sleep apnea: implications for atrial fibrillation. Heart Rhythm. 2012;9(3):321–7. https://doi.org/10.1016/j.hrthm.2011.10.017.
5. Chen C-Y, Ho C-H, Chen C-L, Yu C-C. Nocturnal desaturation is associated with atrial fibrillation in patients with ischemic stroke and obstructive sleep apnea. JCSM. 2017;13(5):729–35. https://doi.org/10.5664/jcsm.6594.
6. Jeong E-M, Liu M, Sturdy M, Gao G, Varghese ST, Sovari AA, et al. Metabolic stress, reactive oxygen species, and arrhythmia. J Mol Cell Cardiol. 2012;52(2):454–63. https://doi.org/10.1016/j.yjmcc.2011.09.018.
7. Chan KH, Wilcox I. Obstructive sleep apnea: novel trigger and potential therapeutic target for cardiac arrhythmias. Expert Rev Cardiovasc Ther. 2010;8(7):981–94. https://doi.org/10.1586/erc.10.80.
8. Camen G, Clarenbach CF, Stöwhas A-C, Rossi VA, Sievi NA, Stradling JR, et al. The effects of simulated obstructive apnea and hypopnea on arrhythmic potential in healthy subjects. Eur J Appl Physiol. 2013;113(2):489–96. https://doi.org/10.1007/s00421-012-2457-y.
9. Clarenbach CF, Camen G, Sievi NA, Wyss C, Stradling JR, Kohler M. Effect of simulated obstructive hypopnea and apnea on thoracic aortic wall transmural pressures. J Appl Physiol. 2013;115(5):613–7. https://doi.org/10.1152/japplphysiol.00439.2013.
10. Orban M, Bruce CJ, Pressman GS, Leinveber P, Romero-Corral A, Korinek J, et al. Dynamic changes of left ventricular performance and left atrial volume induced by the mueller maneuver in healthy young adults and implications for obstructive sleep apnea, atrial fibrillation, and heart failure. Am J Cardiol. 2008;102(11):1557–61. https://doi.org/10.1016/j.amjcard.2008.07.050.
11. Mazza A, Bendini MG, Cristofori M, Nardi S, Leggio M, De Cristofaro R, et al. Baseline apnoea/hypopnoea index and high-sensitivity C-reactive protein for the risk of recurrence of atrial fibrillation after successful electrical cardioversion: a predictive

model based upon the multiple effects of significant variables. Europace. 2009;11(7):902–9. https://doi.org/10.1093/europace/eup107.
12. Narkiewicz K, Kato M, Phillips BG, Pesek CA, Davison DE, Somers VK. Nocturnal continuous positive airway pressure decreases daytime sympathetic traffic in obstructive sleep apnea. Circulation. 1999;100(23):2332–5.
13. Mills PJ, Kennedy BP, Loredo JS, Dimsdale JE, Ziegler MG. Effects of nasal continuous positive airway pressure and oxygen supplementation on norepinephrine kinetics and cardiovascular responses in obstructive sleep apnea. Europace. 2006;100(1):343–8. https://doi.org/10.1152/japplphysiol.00494.2005.
14. Karamanlı H, Özol D, Ugur KS, Yıldırım Z, Armutçu F, Bozkurt B, et al. Influence of CPAP treatment on airway and systemic inflammation in OSAS patients. Sleep & Breathing. 2014;18(2):251–6. https://doi.org/10.1007/s11325-012-0761-8.
15. Bayir PT, Demirkan B, Bayir O, Duyuler S, Firat H, Güray U, et al. Impact of continuous positive airway pressure therapy on atrial electromechanical delay and P-wave dispersion in patients with obstructive sleep apnea. Ann Noninvasive Electrocardiol. 2014;19(3):226–33. https://doi.org/10.1111/anec.12106.
16. Linz D, McEvoy RD, Cowie MR, Somers VK, Nattel S, Lévy P, et al. Associations of obstructive sleep apnea with atrial fibrillation and continuous positive airway pressure treatment: a review. JAMA Cardiol. 2018;3(6):532–40. https://doi.org/10.1001/jamacardio.2018.0095.
17. A comparison of two nights of ambulatory sleep testing in arrhythmia patients. - PubMed - NCBI. (n.d.). Retrieved August 1, 2018, from https://www.ncbi.nlm.nih.gov/pubmed/29973998
18. Abumuamar AM, Dorian P, Newman D, Shapiro CM. The STOP-BANG questionnaire shows an insufficient specificity for detecting obstructive sleep apnea in patients with atrial fibrillation. J Sleep Res. 2018;0(0):e12702. https://doi.org/10.1111/jsr.12702.
19. Holmqvist F, Guan N, Zhu Z, Kowey PR, Allen LA, Fonarow GC, et al. Impact of obstructive sleep apnea and continuous positive airway pressure therapy on outcomes in patients with atrial fibrillation—results from the Outcomes Registry for Better Informed Treatment of Atrial Fibrillation (ORBIT-AF). Am Heart J. 2015;169(5):647–654.e2. https://doi.org/10.1016/j.ahj.2014.12.024.
20. Kanagala R, Murali NS, Friedman PA, Ammash NM, Gersh BJ, Ballman KV, et al. Obstructive sleep apnea and the recurrence of atrial fibrillation. Circulation. 2003;107(20):2589–94. https://doi.org/10.1161/01.CIR.0000068337.25994.21.
21. Dediu GN, Dumitrache-Rujinski S, Lungu R, Frunză S, Diaconu C, Bartoş D, et al. Positive pressure therapy in patients with cardiac arrhythmias and obstructive sleep apnea. Pneumologia. 2015;64(1):18–22.
22. Harbison J, O'Reilly P, McNicholas WT. Cardiac rhythm disturbances in the obstructive sleep apnea syndrome: effects of nasal continuous positive airway pressure therapy. Chest. 2000;118(3):591–5.
23. Ryan CM, Usui K, Floras JS, Bradley TD. Effect of continuous positive airway pressure on ventricular ectopy in heart failure patients with obstructive sleep apnoea. Thorax. 2005;60(9):781–5. https://doi.org/10.1136/thx.2005.040972.
24. Acharya T, Tringali S, Bhullar M, Nalbandyan M, Ilineni VK, Carbajal E, et al. Frequent atrial premature complexes and their association with risk of atrial fibrillation. Am J Cardiol. 2015;116(12):1852–7. https://doi.org/10.1016/j.amjcard.2015.09.025.
25. Linz D, Hohl M, Ukena C, Mahfoud F, Wirth K, Neuberger H-R, et al. Obstructive respiratory events and premature atrial contractions after cardioversion. Eur Respir J. 2015;45(5):1332–40. https://doi.org/10.1183/09031936.00175714.
26. Schlatzer C, Schwarz EI, Sievi NA, Clarenbach CF, Gaisl T, Haegeli LM, et al. Intrathoracic pressure swings induced by simulated obstructive sleep apnoea promote arrhythmias in paroxysmal atrial fibrillation. Europace. 2016;18(1):64–70. https://doi.org/10.1093/europace/euv122.
27. Namtvedt SK, Randby A, Einvik G, Hrubos-Strøm H, Somers VK, Røsjø H, et al. Cardiac arrhythmias in obstructive sleep apnea (from the Akershus Sleep Apnea Project). Am J Cardiol. 2011;108(8):1141–6. https://doi.org/10.1016/j.amjcard.2011.06.016.
28. Serizawa N, Yumino D, Kajimoto K, Tagawa Y, Takagi A, Shoda M, et al. Impact of sleep-disordered breathing on life-threatening ventricular arrhythmia in heart failure patients with implantable cardioverter-defibrillator. Am J Cardiol. 2008;102(8):1064–8. https://doi.org/10.1016/j.amjcard.2008.05.057.
29. Kwon Y, Koene RJ, Kwon O, Kealhofer JV, Adabag S, Duval S. Effect of sleep-disordered breathing on appropriate implantable cardioverter-defibrillator therapy in patients with heart failure: a systematic review and meta-analysis. Circ Arrhythm Electrophysiol. 2017;10(2):–e004609. https://doi.org/10.1161/CIRCEP.116.004609.
30. Weaver TE, Grunstein RR. Adherence to continuous positive airway pressure therapy: the challenge to effective treatment. Proc Am Thorac Soc. 2008;5(2):173–8. https://doi.org/10.1513/pats.200708-119MG.
31. Abumuamar AM, Dorian P, Newman D, Shapiro CM. The prevalence of obstructive sleep apnea in patients with atrial fibrillation. Clin Cardiol. 2018;41(5):601–7. https://doi.org/10.1002/clc.22933.