Continuous Positive Airway Pressure Treatment Decreases the Risk of Atrial Fibrillation Recurrence in Patients with Obstructive Sleep Apnea after Radiofrequency Ablation

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Summary

This study aimed to determine the effect of continuous positive airway pressure (CPAP) therapy on patients with atrial fibrillation (AF) and obstructive sleep apnea (OSA) after radiofrequency ablation (RFCA).

OSA predicts recurrence of AF in patients with AF and OSA after RFCA. However, the effect of CPAP therapy on recurrence of AF in these patients after RFCA is poorly known.

All 122 patients who underwent RFCA from 2017 to 2020 were diagnosed OSA by polysomnography. A total of 62 patients were treated by CPAP, while the remaining 60 were not treated by CPAP. The recurrence of atrial tachyarrhythmia and use of antiarrhythmic drugs were compared between the two groups during a follow-up of 12 months. The outcome of these patients with OSA was compared to a group of 60 AF patients undergoing RFCA without OSA.

Patients undergoing CPAP therapy had a higher AF-free survival rate compared to non-CPAP-treated patients (70.3% versus 31.5%; \( P = 0.02 \)). LAD was associated with the risk of AF recurrence in patients with OSA (HR per mm increase: 1.0; 95% CI: 1.06-1.21; \( P = 0.01 \)). The CPAP nonusers had more than two-fold increased risk of AF recurrence following pulmonary vein isolation (HR: 2.37; 95% CI: 1.21-4.96; \( P = 0.02 \)).

CPAP treatment highly increased arrhythmia-free survival in AF patients accompanied by OSA after RFCA and reduced recurrence of AF in these patients.

Key words: Atrial fibrillation-free survival, Obstructive sleep apnea syndrome, Continuous positive airway pressure therapy

Atrial fibrillation (AF) is the most commonly sustained arrhythmia worldwide. One of the most effective treatments in patients with AF is radiofrequency ablation (pulmonary vein isolation (PVI)), but the relatively high recurrence of AF remains an important limitation to this therapy. It is well known that the efficacy of the procedure is intimately dependent of patient characteristics, including type of AF, its duration, patient age, comorbidities, and echocardiographic parameters, mostly associated with left atrial diameters. Many of these are associated with alteration in intracardiac hemodynamics, causing left atrial overload and its structural and electrical remodeling.

Obstructive sleep apnea (OSA) is an increasingly common disorder of repeated upper airway collapse during sleep, which leads to oxygen desaturation and sleep fragmentation. Consequently, there are recurrent episodes of nocturnal hypoxemia, hypercapnia, endothelial dysfunction, hypercoagulability, and sympathetic overactivity. In the general population, OSA is highly prevalent among patients with AF, and it promotes arrhythmogenesis and impairs treatment efficacy. OSA reduces the efficacy of catheter-based radiofrequency ablation1-13 and pharmacological antiarrhythmic therapy \(^{14,15} \) in AF patients. Continuous positive air pressure (CPAP) represents a standard therapy for patients with severe/moderate OSAS, and its role is to maintain the upper airway open during inspiration. Previous study revealed that CPAP can help to maintain sinus rhythm in AF patients with OSA.\(^ {12,16,17} \)

However, a few other trials found that CPAP did not improve the cardiovascular outcomes and the recurrence of AF was not different in the CPAP-treated patients with OSA compared with non-CPAP-treated patients.\(^ {18} \)

In addition, the therapeutic strategy to the PVI in persistent AF patients remains challenging. The effect of CPAP therapy in persistent AF patients that undergo a PVI using the latest technology is unclear. Hojo, et al. investigated the relationship between OSA and recurrence of atrial fibrillation after pulmonary vein isolation and found that the rate of AF recurrence might not be greater in patients with untreated OSA than in those without OSA and those with treated OSA after repeated PVI for pa...
tients with paroxysmal or short-term persistent AF.20)

This study aimed to explore the effect of CPAP therapy on the AF recurrence rate and arrhythmia-free survival in AF patients (including persistent AF patients) with OSA undergoing RFCA.

Methods

Ethics statement: This study was approved by the ethics committee of China-Japan Friendship Hospital and was registered on the Clinical Experiment Association of China-Japan Friendship Hospital. All the researchers of the study have obtained certificate of clinical experiments of China-Japan Friendship Hospital. All the patients selected in this study signed the informed consent.

Study population: This study is a prospective study. The inclusion criteria in the study were as follows: patients with diagnosis of OSA and AF (persistent AF or documented history of paroxysmal atrial fibrillation). The exclusion criteria were as follows: patients who did not sign the informed consent, patients with craniofacial malformations, patients with neuropsychiatric or thyroid disorders, hemodynamically unstable patients, alcoholics, and drug users. The study group consisted of 122 consecutive patients with OSA and symptomatic AF for AF ablation procedure from the Cardiology Department of China-Japan Friendship Hospital (Beijing, China) from January 2017 to June 2019, with a mean age of 64.1 ± 11 years. The diagnosis of OSA was made by six channels cardiorespiratory polygraphy. OSA was defined as cessation of airflow for > 10 seconds with persistent respiratory effort as seen in the ribcage or abdominal motion and complemented by at least 4% fall in O2 saturation. An apnea-hypopnea index of greater than 15/hour with at least 80% of all events obstructive was required for the definition of OSA.

To examine the effect of CPAP on recurrence of AF, patients were divided into two groups: 62 patients were treated by CPAP (CPAP use at least 5 hours per night and for a minimum of the follow-up duration) after the PVI, while the other 60 were not treated by CPAP.

To evaluate the effect of OSA on arrhythmia recurrence following ablation, patients with OSA (including CPAP users and CPAP nonusers) were compared to the control group of 60 patients of AF without OSA who underwent a PVI [PVI (+) OSA (−)]. The patients in the control group were also consecutive.

Study design: As the patients were involved in the study, the information of anamnesis (including history of smoking), clinical examination (anthropometric indices: height, weight, body mass index (BMI)), cardiorespiratory polygraphy, ECG, Holter ECG, transthoracic echocardiogram, oxyhemoglobin saturation (SaO2), arterial blood gases (ambient air, at rest), and serum lipid profile were collected.

The primary study endpoint was freedom from AF and/or organized atrial tachyarrhythmia at 1 year after the first ablation procedure. Three months later, data of the CPAP device (average residual AHI, effective mean pressure, number of hours of use, nonintentional air leaks) and Holter ECG were recorded.

All the enrolled patients were followed up until the end of the study. Another 3 and 6 months later, the data that were collected at the beginning of the study were recorded again. At the same time, we evaluated the efficacy of CPAP.

Atrial arrhythmia recurrence, defined as any documented atrial tachyarrhythmia episode lasting for > 30 seconds 2 weeks after the ablation, was observed at 1 year after the first ablation procedure.

Transesophageal echocardiogram protocol: All the enrolled patients underwent transesophageal two-dimensional echocardiography (Vivid 7; General Electric Medical Systems, Milwaukee, WI) according to the recommendations of the American Society of Echocardiography. LA internal dimension (LAD) and LV end-diastolic internal dimension (LVDD) were obtained from M-mode measurements in the standard parasternal long-axis view. LV wall motion was evaluated by 2D and M-mode echocardiography images. Standard methods were used to calculate LV systolic fractional shortening and ejection fraction.

Ablation protocol:

The standard AF ablation protocol was as follows:

Two right groin accesses were used for transseptal catheterization. One quadripolar catheter was placed in the coronary sinus and one in the right ventricle. Prior to transseptal access, heparin bolus of 100-150 U/kg and then an infusion of 1,000 U/hour was given to maintain an activated clotting time (ACT) at 300-400 seconds.

Transseptal access was obtained via two separate puncture sites (or patent foramen ovale, if present). A 15-20 mm, decapolar circular mapping catheter was used for mapping (Lasso, Biosense Webster, Baldwin Park, CA, USA), and a 4-mm open irrigated tip ablation catheter (Biosense Webster) was used for delivery of RF energy and radiofrequency ablation.

Fluoroscopy and an electroanatomic system (CARTO or LocaLisa) were used to navigate the catheters. The settings used while delivering radiofrequency energy were as follows: nonirrigated tip ablation-temperature limit of 55°C and a power limit of 35 W; and irrigated tip ablation-temperature limit of 48°C and a power limit of 35 and 30 W on posterior wall. All electrograms were displayed on an electrophysiological recording system. The endpoint of the procedure was the isolation of pulmonary vein potentials in all pulmonary veins. If the patient was on AF, cardioversion was performed to verify the isolation during sinus rhythm. In all patients, isoproterenol up to 30 mg/minute was given to disclose non-PV triggers.

All AADs, except amiodarone, were discontinued five half-lives before the procedure (amiodarone was discontinued 2 weeks before the procedure).

Statistical analysis: Data were analyzed by using SPSS Statistics 20.0 (Chicago, Illinois). The data were expressed as mean ± standard deviation or as an absolute number (percentage). Variables were normally distributed, using Pearson correlation index. T-test was used to analyze the parameters resulting from the estimation of the linear regression model. Baseline clinical variables were compared between groups using Kruskal-Wallis (continuous variables) and chi-square tests (categorical variables). The impact of the variables on event-free survival was assessed.
in a univariate Cox regression analysis. Variables demonstrating significant impact on survival were evaluated in a multivariate model. A \( P \) value < 0.05 was considered statistically significant.

**Results**

**Baseline characteristic of patients:** From January 2017 to June 2019, 122 patients with symptomatic AF and OSA were admitted into our department, of which 62 (50.8%) with OSA were CPAP users (OSA(+) CPAP(+)+ PVI(+)), while 60 (49.2%) were CPAP nonusers (OSA(+) CPAP(−)+ PVI(+)). There were no significant clinical differences (BMI, left atrial size, percentage of persistent AF, use of AADs, etc.) either between the two OSA groups or between the OSA and control groups (OSA(−) CPAP(−) PVI(+) ). Patients with OSA, including CPAP users and CPAP nonusers, had higher rate of the history of hypertension and CAD than those without OSA in the control group (Table I).

**Effect of CPAP therapy on the data on polysomnography, use of AADs, and echocardiogram among the three groups:** CPAP therapy did improve the data on polysomnography, which was AHI, among the CPAP-treated patients (\( P = 0.02 \), and AHI among the non-CPAP-treated patients did not have a statistical significant change before and after the AF ablation. These data were added in Table II.

The degree of the LAD and LVEF changes after the PVI among the three groups were compared to those data before the PVI. LAD in the OSA(+) CPAP(+) PVI(+) group significantly decreased after the CPAP therapy and PVI, whereas LAD in the OSA(+) CPAP(−) PVI(+) group did not change after the PVI protocol without a CPAP therapy (Table II). LVEF did not have a significant change after PVI in the three groups (Table II).

The use of antiarrhythmic drugs after the ablation was significantly different among the three groups (\( P = 0.03 \) (Table III).

**Effect of CPAP therapy on AF recurrence following ablation:** During a follow-up period of 12 months, 46 of the 62 “CPAP users” [OSA (+) CPAP (+)+ PVI (+)], 20 of the 60 “CPAP nonusers” [OSA (+) CPAP(−)+ PVI(+)], and 47 of the 60 non-OSA patients [OSA(−) CPAP(−)+ PVI(+) ] remained in sinus rhythm following the first PVI.

The AF recurrence rate was lower in the “CPAP users” than in the “CPAP nonusers” (25.8% versus 66.7%; \( P = 0.01 \); and the recurrence rate of “CPAP users” was similar to that of patients without OSA (25.8% versus 21.7%; \( P = 0.86 \)). Correspondingly, the AF-free survival
AF-free survival rate among the three groups

Table III. Use of AAD After the PVI Among the Three Groups

<table>
<thead>
<tr>
<th>Use of AAD</th>
<th>OSA (+)</th>
<th>OSA (+)</th>
<th>OSA (−)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Use of AAD</td>
<td>CPAP (+)</td>
<td>CPAP (−)</td>
<td>CPAP (−)</td>
<td></td>
</tr>
<tr>
<td>PVI (+)</td>
<td>(n = 62)</td>
<td>(n = 60)</td>
<td>(n = 60)</td>
<td></td>
</tr>
<tr>
<td>Before PVI</td>
<td>23 (37.1)</td>
<td>23 (38.3)</td>
<td>19 (31.7)</td>
<td>0.52</td>
</tr>
<tr>
<td>After PVI</td>
<td>7 (11.3)</td>
<td>22 (36.6)</td>
<td>18 (30%)</td>
<td>0.03*</td>
</tr>
</tbody>
</table>

Abbreviations as in Table I.

AF recurrence-related AADs/repeat ablation was significantly higher in the “CPAP users” than in the “CPAP nonusers” (70.3% versus 31.5%; P = 0.02) and similar to that of patients without OSA (67.3%; P = 0.85) (Figure).

AF recurrence-related AADs/repeat ablation was significantly higher in the “CPAP users” group than in the “CPAP nonusers” group (67.4% versus 29.5%; P < 0.01).

Clinical variables associated with AF recurrence in patients with OSA: A multivariate analysis was performed in two groups of patients with OSA [OSA(+) CPAP(+), PVI(+) and OSA(+) CPAP(−) PVI(+)], and BMI, LVEF, LAD, history of hypertension, history of CAD, and duration of AF were included. A dummy variable ("CPAP user" = 1 and "CPAP nonuser" = 0) was used in the model.

In all the patients with OSA, LAD was negatively associated with AF-free survival (P < 0.01) in multivariate analysis. LAD then entered a Cox proportional hazard model analysis and was found associated with the risk of AF recurrence in patients with OSA (HR per mm increase: 1.0; 95% CI [confidence interval]: 1.06-1.21; P = 0.01). The “CPAP nonusers” [OSA(+) CPAP(−) PVI(+)] patients had more than two-fold increased risk of AF recurrence following PVI (HR [hazard ratio]: 2.37; 95% CI: 1.21-4.96; P = 0.02) (Table IV).

For the persistent AF patients with OSA, duration of AF and LAD were negatively associated with AF-free survival (P < 0.01, P < 0.01) in multivariate analysis. Duration of AF and LAD were then included into a Cox proportional hazard model analysis and were found associated with the risk of AF recurrence in patients with OSA (1.0 per month increase: 1.0; 95% CI: 0.76-1.48; P = 0.02; HR per mm increase: 1.0; 95% CI: 1.15-1.33; P = 0.03, respectively). The “CPAP nonusers” [OSA(+) CPAP(−) PVI(+)] patients had nearly three-fold increased risk of AF recurrence following PVI (HR [hazard ratio]: 2.93; 95% CI: 1.56-5.33; P = 0.03) (Table V).

Discussion

OSA is a common disorder, in which loss of pharyn-
geal dilator muscle tone during sleep causes recurrent collapse of the upper airway and temporary cessation of breathing. The recurrent apnea-hypopnea episodes cause autonomic alterations, including activation of the sympathetic nervous system and elevation of serum catecholamine levels, increasing both heart rate and blood pressure. Moreover, cortical arousals from sleep and altered sleep quality result in sympathetic nerve activation in OSA patients. Decreased baroreflex sensitivity and increased chemosensitivity contribute to the process by increasing blood pressure and arterial sympathetic nerve activity. Cardiac remodeling, including left ventricle hypertrophy and left atrial enlargement, occurs and can lead to diastolic heart failure and AF.22)

OSA is indeed associated with electrocardiogram modifications23) that can predict future cardiovascular events and predispose to arrhythmia.24,25) AF represents the most common arrhythmia among people with sleep disordered breathing: the prevalence of nocturnal AF in patients with OSA has been estimated to be between 3% and 5%, and the prevalence of AF in patients with OSA has been reported to be between 21% and 49%.26)

OSA is increasingly recognized as a potential risk factor for the development of AF. Many common pathophysiological mechanisms contribute to the high prevalence of cardiac arrhythmias in patients with OSA and the high prevalence of OSA in those with cardiac arrhythmias.26) The leading mechanisms implicated in the development of AF in OSAS patients include (1) an atrial chamber enlargement due to impairment of intrathoracic pressure; (2) tissue stretch and remodeling at the site where the nidus is localized and from which electrical discharges propagate in AF;27) (3) the repetitive oxyhemoglobin desaturation and the reoxygenation that may activate atrial catecholamine-sensitive ion channels, thereby resulting in focal discharges that initiate AF;28) and (4) an instability in autonomic tone.29) Recent work found that OSA resulted in pronounced atrial fibrosis as manifested by intra-atrial conduction delay, reduced atrial voltage, presence of complex atrial electrograms, and electrical silence.29) Other studies revealed that various hemodynamic changes, autonomic dysregulation, and increased oxidative stress during apneic episodes may contribute to AF initiation.30,31)

Prior research has shown that CPAP therapy could be effective in alleviating the burden of AF and improving the effect of AF treatments in OSA patients. Recent study revealed that CPAP reduced the occurrence of paroxysmal AF and other arrhythmias during polysomnography.29) A small prospective observational study showed that patients with CPAP-treated OSA had almost half the rate of AF recurrence compared to untreated patients after cardioversion.30)

OSA has also been associated with a greater risk of AF recurrence after catheter-based AF ablation.31,32) We found in this study that in the non-OSA patient population, AF-free survival after catheter-based AF ablation at 1 year was 67.3%, which was 31.5% in a matched group of OSA patients.

McEvoy, et al. observed whether CPAP prevents major cardiovascular events. They found that the occurrence of AF did not significantly differ between the CPAP- and non-CPAP-treated patients. This conclusion is not contrary to our study, which focuses on the occurrence of AF after the AF ablation in the two different groups of patients (CPAP- and non-CPAP-treated patients).

Our study shows that OSA patients treated with CPAP had significantly lower AF recurrence rate and improved AF-free survival rate following PVI compared with those CPAP-untreated OSA patients. Untreated OSA patients had increased risk of AF recurrence compared to those CPAP-treated OSA patients.

As for the persistent AF patients, the effect of CPAP therapy in persistent AF patients that undergo a PVI is uncertain in the previous study. Hojo, et al.19) discovered that the rate of AF recurrence might not be greater in patients with untreated OSA than in those without OSA and those with treated OSA after repeated PVI for patients with persistent AF, while in our study, we analyzed the effect of CPAP therapy in persistent AF patients that undergo a PVI and found that persistent AF patients with OSA untreated with CPAP had increased risk of AF recurrence following PVI compared with those CPAP-treated patients.

Limitations: As asymptomatic AF recurrences cannot be evaluated only by Holter ECGs, and cannot be found by Holter ECGs one time, patients with asymptomatic AF might be ignored with only one time Holter ECG. These were limitations in finding and evaluating asymptomatic AF recurrence in our study.

Conclusions

OSA-associated electro-anatomical atrial remodeling not only potentiates the risk to develop AF but also limits the success of AF ablation. CPAP therapy could improve the outcomes of PVI in the OSA patient by alleviating these effects.

The higher rates of recurrent AF after PVI in CPAP nonusers reinforce the importance of screening patients with AF for OSA, especially prior to undergoing a PVI, and continuous compliance with CPAP therapy.

Table V. Predictors of AF Recurrence in Persistent AF Patients with OSA (a Cox Proportional Hazard Model Analysis)

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Hazard ratio (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration of AF</td>
<td>1.0 per month increase</td>
<td>0.76–1.48 0.02*</td>
</tr>
<tr>
<td>LAD</td>
<td>1.0 per mm increase</td>
<td>1.15–1.33 0.03*</td>
</tr>
<tr>
<td>CPAP nonuser</td>
<td>2.93</td>
<td>1.56–5.33 0.03*</td>
</tr>
</tbody>
</table>

CI indicates confidence interval and other abbreviations as in Table I.
Conflicts of interest:
None.

References