Journal of the American College of Cardiology
© 2013 by the American College of Cardiology Foundation
Published by Elsevier Inc.

Vol. 62, No. 4, 2013
ISSN 0735-1097/$36.00
http://dx.doi.org/10.1016/j.jacc.2013.03.052

Treatment of Obstructive Sleep Apnea Reduces the Risk of Atrial Fibrillation Recurrence After Catheter Ablation

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Objectives The aim of this study was to examine the effect of continuous positive airway pressure (CPAP) therapy on atrial fibrillation (AF) recurrence in patients with obstructive sleep apnea (OSA) undergoing pulmonary vein isolation (PVI).

Background OSA is a predictor of AF recurrence following PVI. However, the impact of CPAP therapy on PVI outcome in patients with OSA is poorly known.

Methods Among 426 patients who underwent PVI between 2007 and 2010, 62 patients had a polysomnography-confirmed diagnosis of OSA. While 32 patients were "CPAP users" the remaining 30 patients were "CPAP nonusers." The recurrence of any atrial tachyarrhythmia, use of antiarrhythmic drugs, and need for repeat ablations were compared between the groups during a follow-up period of 12 months. Additionally, the outcome of patients with OSA was compared to a group of patients from the same PVI cohort without OSA.

Results CPAP therapy resulted in higher AF-free survival rate (71.9% vs. 36.7%; $p = 0.01$) and AF-free survival off antiarrhythmic drugs or repeat ablation following PVI (65.6% vs. 33.3%; $p = 0.02$). AF recurrence rate of CPAP-treated patients was similar to a group of patients without OSA (HR: 0.7, $p = 0.46$). AF recurrence following PVI in CPAP nonuser patients was significantly higher (HR: 2.4, $p < 0.02$) and similar to that of OSA patients managed medically without ablation (HR: 2.1, $p = 0.68$).

Conclusions CPAP is an important therapy in OSA patients undergoing PVI that improves arrhythmia free survival. PVI offers limited value to OSA patients not treated with CPAP. (J Am Coll Cardiol 2013;62:300–5) © 2013 by the American College of Cardiology Foundation

Atrial fibrillation (AF) is the most commonly encountered arrhythmia in clinical practice and a major cause of morbidity and mortality (1). Its rising prevalence and associated economic cost underscore the importance of effective therapies (2,3). Pulmonary vein isolation (PVI) is an effective treatment in selected patients with AF; however, the relatively high recurrence rate remains an important limitation (4–7). It is well established that the success rate of PVI is highly dependent of patient characteristics, including age, obesity, atrial size, the presence of hypertension, mitral valve disease, and arrhythmia type and duration (8).

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Manuscript received December 18, 2012; revised manuscript received February 11, 2013, accepted March 7, 2013.

AF is exceedingly prevalent in patients with obstructive sleep apnea (OSA) (9,10). Mechanisms by which OSA increases the risk of AF include: 1) intermittent nocturnal hypoxemia and hypercapnia; 2) enhanced sympathetic tone with surges in blood pressure during apneic episodes leading to left atrial stretch through pressure and volume overload; 3) increased oxidative stress and inflammatory processes

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contributing to left atrial remodeling and fibrosis (11–13). These mechanisms may act as both triggers and perpetuators of AF, potentially explaining the limited efficacy of arrhythmia-controlling interventions, including pulmonary vein isolation (14–18). Continuous positive airway pressure (CPAP) ventilation prevents episodes of hypoxia and hypercapnia and attenuates the sympathetic tone in patients with OSA (19,20). While CPAP has been shown to

decrease AF recurrence following cardioversion, its effect on arrhythmia control in patients undergoing AF ablation procedures is limited (18,21). The purpose of this study was to examine the effect of CPAP therapy on AF recurrence in patients with OSA undergoing PVI.

Methods

Study population. The study group consisted of consecutive patients with OSA and symptomatic AF identified from the prospectively collected database of patients referred for an index AF ablation procedure at Beth Israel Deaconess Medical Center (Boston, Massachusetts) from July 2007 to January 2010. The diagnosis of OSA was established by a single polysomnography study and confirmed by previously described criteria (22). In brief, OSA was defined as cessation of airflow for >10 s with persistent respiratory effort as seen in the ribcage or abdominal motion and complemented by at least ≥4% fall in O2 saturation. In addition, an apnea hypopnea index of greater than 15/h with at least 80% of all events obstructive was required for the definition of OSA.

To examine the effect of CPAP on arrhythmia recurrence, the group of patients with OSA was divided into "CPAP users" [PVI (+) OSA (+) CPAP (+)] and "CPAP nonusers" [PVI (+) OSA (+) CPAP (-)]. The diagnosis of OSA and assignment to therapy groups [CPAP (+) and CPAP (-)] was established at least 3 months before the planned PVI. As such, "CPAP users" had used CPAP daily for a minimum of 3 months prior to the index PVI and continued to use CPAP throughout the follow-up duration. There were no crossovers between the groups.

Study endpoints. The primary study endpoint was freedom from AF and/or organized atrial tachyarrhythmias at 1 year after the first ablation procedure. The secondary study endpoint was freedom from AF and/or organized atrial tachyarrhythmias at 1 year off antiarrhythmic drugs (AADs) or redo ablation procedures. Arrhythmia recurrence was defined as any documented atrial tachyarrhythmia episode lasting for >30 s that occurs after a 2-week blanking period following the ablation procedure.

In order to assess the effect of OSA itself on arrhythmia recurrence following PVI, the primary endpoint of arrhythmia-free survival in patients with OSA (both CPAP users and CPAP nonusers) was compared to the control group of 30 patients without the diagnosis of OSA who underwent a PVI. This group of patient was randomly selected from the same database [PVI (+) OSA (-)]. In addition, we examined the effect of PVI on arrhythmia-free survival in a cohort of 22 OSA patients using CPAP whose AF was treated medically [PVI (-) OSA (+) CPAP (+)] with a rhythm control strategy. This cohort of patients was identified through International Classification of Diseases 9 coding of the institutional billing records for the same period of time (July 2007 to January 2010) and was not part of the AF ablation database. Similar to the ablation groups, this group of patients was followed by a cardiologist and a rhythm control strategy was attempted by either electrical cardioversion and/or antiarrhythmic drug therapy. The study protocol and consent forms were approved by the Institutional Review Board.

Abbreviations and Acronyms

AAD = antiarrhythmic drug
AF = atrial fibrillation
BMI = body mass index
CPAP = continuous positive airway pressure
LAD = left atrial dimension
OSA = obstructive sleep apnea
PVI = pulmonary vein isolation

Ablation protocol. All AADs, except amiodarone, were discontinued 5 half-lives before the procedure (amiodarone was discontinued 2 weeks before the procedure). Our standard approach to AF ablation has been previously described (23). Briefly, diagnostic decapolar catheters were placed in the coronary sinus and the anterolateral right atrium. An intracardiac ultrasound catheter (AcuNav, Biosense Webster, Inc, Diamond Bar, California) was placed in the right atrium. Two transseptal punctures were made, through which the mapping/ablation catheter and the multielectrode circular mapping catheters (Lasso, Biosense Webster) were advanced into the left atrium. Unfractionated heparin was administered to maintain an activated clotting time of 250 to 350 s for the duration of the procedure. PVI was performed by isolating all pulmonary veins with demonstration of entrance and exit block from each vein. After PVI, isoproterenol infusion to effect was administrated to examine acute reconnection and to identify nonpulmonary vein triggers. Left atrial ablation lines (roof line, mitral isthmus line, and/or posterior left atrial line) or ablation of extra-PV atrial triggers were performed in patients with inducible sustained AF or atrial tachyarrhythmia at the operator's discretion on the basis of electroanatomic mapping information obtained during the arrhythmia. At the initiation of the study, our center was performing AF ablation using the 8-mm-tip catheter (NaviStar, Biosense Webster); however, during the study, we switched to a 3.5-mm open irrigation tip catheter (Navistar Thermocool, Biosense Webster).

Follow-up. After the procedure, patients were administered AADs (usually class IC agents or sotalol) and warfarin. Long-term follow-up consisted of both clinic visits (1, 3, 6, and 12 months) and 2-week transtelephonic monitoring (with auto- and patient-trigger capabilities) at 3, 6, and 12 months. Additional transtelephonic monitoring was performed based on symptoms between visits. At each outpatient visit, patients were queried for symptoms and a 12-lead electrocardiogram was obtained. In the absence of any documented arrhythmia recurrence, AADs were discontinued between 3 and 6 months after the initial procedure. Patients with documented recurrence of atrial tachyarrhythmias were treated with AADs or offered repeat ablation procedures at their provider's discretion. In patients undergoing a repeat ablation, the same follow-up approach was used. The follow-up duration of the study was 1 year.

Data collection. All data including clinical patient characteristics, comorbidities, medication history, and follow up was retrospectively collected from the review of the

electronic medical records. Compliance with CPAP therapy was part of standard pre-procedural evaluation as well as follow-up clinic visits. Most patients had a cardiac magnetic resonance imaging prior to PVI, allowing for determination of the left ventricular ejection fraction and left atrial size measurements. For the small number of patients without a magnetic resonance imaging, anatomic data was recorded from transthoracic echocardiogram or cardiac computed tomography. Left atrial diameter was recorded from the 4-chamber view, irrespective of modality. The size of the left atrium was not assessed in non-PVI control group, as they did not undergo corresponding pre-procedure imaging.

Statistical analysis. Baseline clinical variables were compared between groups using Kruskal-Wallis (continuous variables) and chi-square tests (categorical variables). Event-free survival was estimated by the Kaplan-Meier survival function. Pairwise comparisons of survival rates were made using log-rank test. The impact of the following variables on event-free survival was assessed in a univariate Cox regression analysis: age, gender, left atrial size, body mass index (BMI), ejection fraction, the presence of hypertension, diabetes, coronary artery disease, and AF form (paroxysmal or persistent). Variables demonstrating significant impact on survival were evaluated in a multivariate model. Confidence intervals for parameter estimates were calculated using bootstrapping technique. A p value <0.05 was considered statistically significant. Analyses were conducted using IBM SPSS Statistics 20.0 (Chicago, Illinois).

Results

Baseline patient characteristics. From July 2007 to January 2010, 426 patients with symptomatic AF were referred to our institution for an index PVI. Forty patients with insufficient data (most lived at a distance and lost to follow-up) were excluded. From the remainder, 62 patients (16%) had a polysomnography-confirmed diagnosis of OSA. Thirty-two patients with OSA (51.6%) were CPAP-users while 30 patients (48.4%) were CPAP nonusers (Fig. 1). There were no significant clinical differences between the 2 OSA groups and between the OSA groups and the 2 control groups (Table 1). Importantly, all 4 groups were balanced in regard to BMI, left atrial size, percentage of persistent AF, and number of failed AADs. The majority of patients were hypertensive and male, had a BMI that was near obese, equally split between persistent and paroxysmal AF, and were treated with an average of 1.4 antiarrhythmic medications.

CPAP therapy and arrhythmia recurrence following ablation. During a follow-up period of 1 year, 23 of the 32 "CPAP-users" [PVI (+) OSA (+) CPAP (+)], 11 of the 30 "CPAP nonusers" [PVI (+) OSA (+) CPAP (-)], and 20 of the 30 non-OSA patients [PVI (+) OSA (-)] remained in SR following the first PVI. The atrial tachyarrhythmia–free survival rate was significantly higher in the "CPAP users" compared with the "CPAP nonusers" (71.9% vs. 36.7%; $p = 0.01$); and similar to that of patients without OSA (66.7%; $p = 0.94$) (Fig. 2).

Arrhythmia-free survival off AADs/repeat ablation was significantly higher in the "CPAP users" group compared with the "CPAP nonuser" group (65.6% vs. 33.3%; $p = 0.02$).

There was no significant difference in the frequency of repeat ablation procedures between the CPAP-users, CPAP nonusers, and non-OSA control group (15.6%, 26.7%, and 20%, respectively; $p = 0.56$).

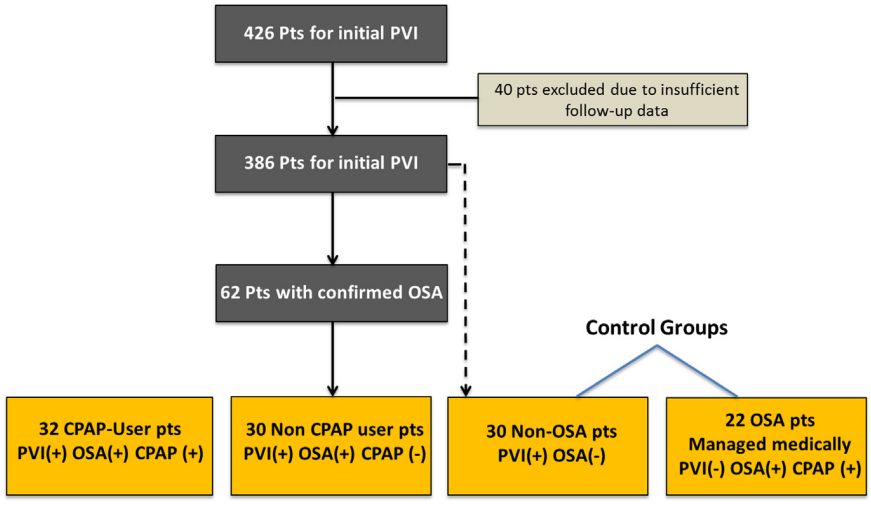

Figure 1 Study Cohort: Flowchart

Flow diagram showing the establishment of the study cohort and division into treatment groups (shown in **dark gray** and control groups in **light gray**). CPAP = continuous positive airway pressure; OSA = obstructive sleep apnea; pts = patients; PVI = pulmonary vein isolation.

Table 1 Baseline Characteristics of Study Groups

Variable	PVI (+) / OSA (+) / CPAP (+) (n = 32)	PVI (+) / OSA (-) / CPAP (-) (n = 30)	PVI (+) / OSA (-) / CPAP (-) (n = 30)	PVI (-) / OSA (+) / CPAP (+) (n = 22)	p Value
Age, yrs	56.8 ± 1.2	58.5 ± 1.4	58.5 ± 1.4	55.0 ± 1.6	0.27
Male	23 (76.7)	23 (71.9)	23 (71.9)	16 (72.7)	0.96
BMI, kg/m^2	28.77 ± 0.45	29.58 ± 0.40	29.58 ± 0.40	30.69 ± 0.99	0.11
Persistent AF	17 (56.7)	16 (50.0)	16 (50.0)	12 (54.5)	0.95
Hypertension	21 (70.0)	21 (65.6)	21 (65.6)	15 (68.2)	0.81
Diabetes	6 (20.0)	6 (18.6)	6 (18.6)	4 (18.2)	1.00
CAD	8 (26.7)	6 (18.6)	6 (18.6)	5 (22.7)	0.88
LVEF, %	60.2 ± 1.5	59.5 ± 0.94	59.5 ± 0.94	59.3 ± 2.0	0.96
LAD, mm	54.5 ± 0.91	55.9 ± 1.1	55.9 ± 1.1	—	0.51*
No. AAD	1.47 ± 0.12	1.34 ± 0.10	1.34 ± 0.10	1.00 ± 0.15	0.07

Values are mean ± SE or n (%). * = LAD was not available in PVI (-) group.

AAD = antiarrhythmic drugs; AF = atrial fibrillation; BMI = body mass index; CAD = coronary artery disease; CPAP = continuous positive airway pressure; LAD = left atrial dimension; LVEF = left ventricular ejection fraction; OSA = obstructive sleep apnea; PVI = pulmonary vein isolation.

The effect of PVI on arrhythmia recurrence in patients with OSA. The effect of PVI on arrhythmia-free survival in patients with OSA was examined by comparing the group of CPAP-users patients who underwent PVI with a group of CPAP-treated OSA patients [PVI (-) OSA (+) CPAP (+)] with AF who were treated medically (Fig. 2). Arrhythmia-free survival was significantly higher in the group of patients who underwent PVI (71.9% vs. 45.5%; p = 0.02).

Clinical variables associated with AF recurrence. Because left atrial dimension (LAD) data were not available for the PVI (-) group, 2 separate sets of analyses were performed, 1 for the 3 PVI (+) groups, and 1 for all 4 groups. In univariate analysis in PVI (+) groups only LAD was negatively associated with AF-free survival (p < 0.01). LAD then was entered into a multivariate model that included group designation as the second variable. The PVI (+) OSA (-) group served as control for pairwise comparisons. The PVI (+) OSA (+) CPAP (-) patients had more than 2-fold increased risk of AF recurrence (hazard ratio [HR]: 2.15; 95% confidence interval: 1.10 to 5.44; p = 0.02) following PVI (Table 2). In contrast, CPAP-treated patients had event-free survival similar to that of patients without OSA (HR: 0.7; 95% confidence interval: 0.3 to 1.59; p = 0.39). LAD was associated with the risk of AF recurrence (HR per mm increase: 1.1; p < 0.01).

In a 4-group univariate analysis the presence of hypertension (p = 0.04) and persistent AF (p < 0.01) were negatively associated with AF-free survival.

These variables were included in the second multivariate model. The PVI (-) group was used as the control for pairwise comparisons. Both PVI (+) OSA (-) and PVI (+) OSA (+) CPAP (+) groups demonstrated approximately 2-fold AF risk reduction (HR: 0.48 to 0.52; p < 0.05). In contrary, the PVI (+) OSA (+) CPAP (-) group showed an AF recurrence rate similar to the PVI (-) group (HR: 1.12; p = 0.65). The presence of HTN and persistent AF were associated with approximately 2-fold increase in AF recurrence risk (Table 3).

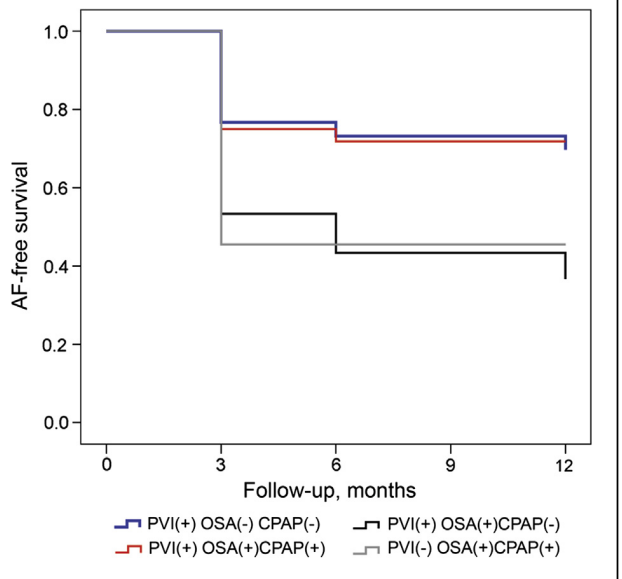

Figure 2 Kaplan-Meier Survival Curves According to Treatment Group

Log-rank p = 0.02. AF = atrial fibrillation; other abbreviations as in Figure 1.

Discussion

Major findings. The main findings of the study are: 1) OSA patients treated with CPAP had significantly

Table 2 Multivariate Predictors of AF Recurrence in PVI (+) Patients (Comparison to PVI (+) OSA (-) Group)

	Multivariate		
	Hazard Ratio	95% Confidence Interval	p Value
LAD	1.1 per mm increase	1.04–1.18	0.003
PVI (+) OSA (+) CPAP (+)	0.7	0.3–1.59	0.39
PVI (+) OSA (+) CPAP (-)	2.15	1.10–5.44	0.02

Abbreviations as in Table 1.

Table 3 Multivariate Predictors of AF Recurrence (Comparison to PVI (-) Group)

	Hazard Ratio	95% Confidence Interval	p Value
Persistent AF	1.91	1.27–3.22	0.007
HTN	2.16	1.15–5.23	0.015
PVI (+) OSA (-)	0.53	0.25–0.96	0.048
PVI (+) OSA (+) CPAP (+)	0.48	0.22–0.91	0.03
PVI (+) OSA (+) CPAP (-)	1.12	0.71–1.92	0.65

HTN = hypertension; other abbreviations as in Table 1.

improved outcome following PVI with overall lower arrhythmia recurrence rate; and 2) Arrhythmia-free survival off AADs was significantly higher in patients treated with CPAP. In fact, CPAP therapy resulted in improved arrhythmia-free survival that was not different than those of patients without OSA. Conversely, we found that untreated OSA patients had increased risk of arrhythmia recurrence that was similar to OSA patients treated medically without PVI. We found no difference in the rates of repeat PVI procedures performed between the groups.

Relationship between OSA and AF. OSA is increasingly recognized as a potential risk factor for the development of AF. While the mechanisms by which OSA predisposes to the development and recurrence of AF is uncertain, recent work by Dimitri et al. demonstrated OSA patients to have both structural and electrical atrial changes (24). They 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. These substrate changes may potentially contribute to the development and maintenance of AF (24). The interdependence of AF duration, increased atrial pressure, and left atrial structural changes were reflected in our multivariate modeling. Additionally, various hemodynamic changes, autonomic dysregulation, and increased oxidative stress during apneic episodes may contribute to AF initiation. The effects of CPAP therapy on reversing these changes have not been yet determined.

Effects of CPAP therapy. Prior research has shown the use of CPAP therapy in the treatment of OSA to be effective in mitigating the burden of AF and improving the effectiveness of AF treatments. In a Japanese study, the use of CPAP reduced the occurrence of paroxysmal AF and other arrhythmias during polysomnography (25). In a small prospective observational study, Kanagala et al. showed that patients with CPAP-treated OSA had almost half the rate of AF recurrence compared to untreated patients after cardioversion (21).

OSA has also been associated with a greater risk of AF recurrence after catheter-based AF ablation (15,18). We found that in the non-OSA patient population, arrhythmia-free survival at 1 year approximated 70% compared with 53% in an otherwise matched group of OSA patients. This is consistent with the divergent success rates reported by Jongarangsin et al. (63% and 41%) and more dramatic than described by Patel et al. (78% and 71%) (15,18).

Our analysis shows that CPAP therapy is associated with better procedural outcome in the OSA patient population undergoing PVI. We demonstrated CPAP to be so efficacious that OSA treated patients had an arrhythmia recurrence rate that matched that of patients without the diagnosis of OSA. In contrast, CPAP nonusers were over 2 times more likely to have arrhythmia recurrence compared to CPAP users. Importantly, we found that PVI offered minimal benefit to OSA patients that were not compliant with CPAP, with rates of AF recurrence no different than OSA patients managed medically. These findings suggest that unless a patient is "optimized" from the standpoint of OSA, there may be little value in pursuing invasive treatment procedures.

Study limitations. The principle limitation of the present study was that it is a retrospective evaluation of a prospectively collected database and therefore can be a subject to selection bias. Importantly, polysomnography was not performed systematically in all patients but per clinical suspicious again subjected to selection bias and underdiagnoses of OSA. Limited data regarding the severity of a patient's OSA and details of its management were available. While we saw no significant differences in clinical demographics between the study groups, inherent unaccounted confounders in these nonrandomized groups may be present. Similarly, the patients not using CPAP might generally be less compliant with medical regimen, in turn exaggerating the effects of CPAP. Decisions to use AAD and repeat ablation procedures were left to the discretion of the treating physicians and were not controlled for.

The medical management control group represents a different patient population, and the clinical details that prompted medical management versus those patients referred for ablation could not be captured. Some caution should be made in extrapolating too much from its comparison to the ablation group. Last, OSA is often underdiagnosed; therefore, the incidence of OSA in our patient population may be underrepresented.

Last, the fairly small number of patients and endpoints may have resulted in overfitting of the multivariate model. In attempt to minimize this possibility, we included only variables that demonstrated significance in univariate testing and performed bootstrapping to support the validity of our multivariate model. However, these results have to be interpreted with caution until confirmed in larger studies.

Conclusions

The presence of OSA with its associated electroanatomical atrial remodeling not only potentiates the risk to develop AF, but also limits the success of AF ablation. CPAP therapy may very well help mitigate these effects, improving the outcomes of PVI in the OSA patient population. The higher rates of recurrent AF following PVI seen in CPAP

nonusers reinforces the importance of appropriate patient selection, continuous compliance with CPAP therapy, and highlights an avenue to further improve long-term success of ablation. Careful attention should be paid to screening patients with AF for OSA, especially prior to undergoing a PVI, and ensuring compliance with CPAP therapy. This study's findings call for a randomized controlled trial evaluating the use of CPAP for AF patients with OSA.

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Key Words: ablation ■ atrial fibrillation ■ continuous positive airway pressure ■ obstructive sleep apnea.