O

bstructive sleep apnea (OSA) and obesity are reaching epidemic proportions in the United States, both of which are independent predictors for atrial fibrillation (AF). OSA, the most common sleep disorder, is characterized by repetitive upper airway obstruction leading to oxygen desaturation and transient hypercapnia. OSA may contribute to new-onset AF and catheter ablation failure by hypoxemia, sympathetic activation, rises in arterial pressures, and proinflammatory mechanisms. A prior study demonstrated that using continuous positive airway pressure (CPAP) in AF patients with OSA improved cardioversion success rates.

Methods

Patient Population

From January 2004 to May 2008, 3000 consecutive patients underwent PVAI at Sutter Pacific Medical Center, San Francisco, Calif; Texas Cardiac Arrhythmia Institute, Austin, Tex; Metro Health Hospital, Case Western Reserve, Cleveland, Ohio; Akron General Hospital, Akron, Ohio; Stanford University, Palo Alto, Calif; California Pacific Medical Center (S.H., S.B.), San Francisco, Calif; Kansas University (D.L.), Lawrence, Kan; the University of Cincinnati (M.S., E.N.), Cincinnati, Ohio; the Department of Cardiology (L.D.B.), University of Foggia, Foggia, Italy; and the Department of Biomedical Engineering (L.D.B., R.H., A.N.), University of Texas, Austin, Tex.

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All patients with a diagnosis of OSA were selected from a prospectively collected database. Obstructive apnea was defined as cessation of airflow for >10 seconds with persistent respiratory effort as seen in the ribcage or abdominal motion by >50% of baseline signal for >10 seconds with a ≥4% fall in O₂ saturation. The apnea hypopnea index was the total number of sleep apneas and hypopneas per hour of sleep. OSA was defined by the apnea hypopnea index >15/h, and >80% of all apnea/hypopnea events had to be obstructive. Sleep staging was determined using Rechtschaffen and Kales criteria. All patients were queried for a history of sleep apnea confirmed by polysomnography.

Patients with a diagnosis of OSA were divided by CPAP use (Figure 1). All patients in the CPAP group had been treated for a minimum of 3 months before the procedure and continued treatment for the duration of the follow-up period as verified by medical records or patient interview. Patient compliance was self-reported at the initial office visit and at 3 and 6 months. OSA patients were treated nightly at home with a nocturnal nasal CPAP therapy. The mean CPAP pressure was 10.6 ± 1.6 cm H₂O. The non-CPAP group consisted of patients who were not treated or who used CPAP device erratically.

AF was classified according to the 2007 Consensus Statement in HRS/EHRA/ECAS expert Consensus Statement on catheter and surgical ablation of atrial fibrillation: recommendations for personnel, policy, procedures and follow-up: A report of the Heart Rhythm Society (HRS) Task Force on catheter and surgical ablation of AF. The nonparoxysmal AF group consisted of patients with persistent AF or long-standing persistent AF. We defined hypertension as blood pressure >140/80 that was observed at 2 separate office visits.

Baseline C-reactive protein (CRP) blood samples were obtained early in the day after an overnight fast. Plasma and serum levels were collected. Personnel blinded to clinical data performed CRP measurements. An ultrasensitive enzyme-linked immunosorbent assay (ELISA) was used to measure CRP. The interassay coefficient of variation was 5.5%. Preprocedure CRP levels were obtained no earlier than 1 month before the procedure.

Hematoma, pericardial tamponade, PV stenosis, transient ischemic attack, stroke, and all other complications were collected. PV stenosis was determined by CT at the 3-month follow-up. If patients presented with symptoms consistent with stroke, an MRI or CT was performed to assess the severity and territory of the infarct.

Ablation Protocol Before Ablation
Antiarrhythmic drugs were discontinued 4 to 5 half-lives before ablation. Patients on amiodarone discontinued the medication 5 to 6 months before ablation. Patients with persistent or chronic AF had a transesophageal echocardiography or were treated with warfarin for approximately 5 to 6 weeks before the procedure. Warfarin was stopped 2 to 3 days before the procedure and bridged with half dose of low-molecular-weight heparin. Patients who had procedures after June 2006 did not discontinue warfarin before the procedure, and the international normalized ratio (INR) was maintained between 2.0 and 3.5.

Pulmonary Antrum Isolation
All patients underwent the ablation procedure using the same ablation strategy. The details of the ablation procedure have been presented elsewhere. Briefly, our ablation strategy in paroxysmal AF patients include PVAI and posterior wall isolation guided by circular mapping catheter (Lasso-Biosense/Webster, Diamond Bar, Calif) and intracardiac echocardiography (Acuson, Seimens, Mountain View, Calif) and empirical isolation of the superior vena cava. In nonparoxysmal AF patients, all PVs and the entire posterior wall down to the coronary sinus is ablated. In addition, lesions are also delivered on the left side of the septum, and right- and left-sided defragmentation was performed. Radiofrequency energy was delivered with a 3.5-mm open irrigation catheter (Biosense/Webster, 3.5-mm tip). In both groups, a high-dose isoproterenol challenge (20 to 30 μg/min) was performed.
Anticoagulation
A heparin bolus (100 to 150 U/kg) was given before transseptal punctures. The infusion rate was adjusted to keep activated clotting time between 350 to 450 seconds. After PVAI, heparin was discontinued, and intravenous protamine 10 to 15 mg was given. Sheaths were pulled when activated clotting time was <250 seconds. At the end of all procedures, patients were given oral 325 mg of aspirin before leaving the electrophysiology laboratory. Oral anticoagulation with warfarin was resumed on the same night of the procedure. A half dose of subcutaneous low-molecular-weight heparin was administered twice a day until the INR was ≥2. Patients after June of 2005 continued their usual warfarin dose without preprocedural discontinuation while maintaining an INR between 2 to 3.5.11

Follow-Up
All patients were discharged on oral anticoagulation therapy (warfarin). Follow-up was scheduled at 3, 6, 9, and 12 months after the procedure and every 6 months thereafter. If patients were unable to be seen, their status was assessed by a nurse practitioner by telephone and monitoring tests were obtained by the referring physician. During the first 5 months after ablation, cardiac event monitoring was used to assess AF recurrence. Patients were asked to transmit their rhythm status 3 times a day and when they had symptoms consistent with AF. In addition, 48-hour Holter monitoring was performed at 3, 6, 9, and 12 months and every 6 months thereafter. Since June 2007, 48-hour Holter was replaced by 7-day Holter monitoring. At all follow-up visits, patients were asked about compliance of CPAP use.

Statistical Analysis
Continuous data are described as mean±SD and as counts and percent if categorical. The Student t test, 1-way ANOVA, χ² test, and Fisher exact test were used to compare differences across AF types. Multivariable Cox regression was used for identifying significant predictors of AF recurrence while controlling for clinically relevant covariates. All potential confounders were entered into the model based on known or expected clinical relevance, regardless of their statistical significance. Variables included in the model were age, preprocedure left ventricular ejection fraction (LVEF), left atrial (LA) size, hypertension, diabetes, coronary artery disease, non-PV trigger, and type of AF. For the purpose of analysis, LVEF and LA size were categorized into >55 and ≥40 mm, respectively. The number of confounders entered into this model was fairly large and many of those did not show any significant association. To test if excluding nonsignificant covariates from the model improves its predictive ability, a second model was estimated with relatively small number of covariates. This model included the significant predictors from the first model plus 2 additional variables, sex and prior cerebrovascular accident.

The discrimination ability of the models in predicting AF recurrence was assessed by c-statistics and receiver operating characteristic (ROC) curve. The proportional hazard assumption for the covariates was tested by Schoenfeld residual analysis. The test did not have enough evidence to reject the proportionality. It was concluded that the data has satisfied the proportional hazard assumption for this model.

Tests were run to examine the presence of any significant interaction and to identify possible multicollinearity of the covariates. The hazard ratio and 95% confidence interval of AF recurrence were computed. Recurrence-free survival over time was calculated by Kaplan-Meier method. All tests were 2-sided, and a probability value <0.05 was considered statistically significant. Analysis was performed using SAS 9.2 (SAS Institute Inc, Cary, NC).

Results
Patient Characteristics of the Overall Population
Six hundred forty patients (21.3%) patients in this series had OSA. Age, sex, body mass index, pre-CRP level, diabetes type II, hypertension, coronary artery disease, paroxysmal AF, nonparoxysmal AF, pre- and post-LA size, and pre- and post-EF were statistically different in the 2 populations. Patients with OSA had a higher prevalence of non-PV triggers (20% versus 8%, P<0.001). Among the nonparoxysmal patients, those without OSA had a lower prevalence of non-PV triggers compared with patients with OSA (19% versus 31%, P<0.001). Patient demographics are given in Table 1.

Patient Outcomes in the Overall Population
A multivariable Cox proportional hazard model was run to examine association between having OSA and procedure failure. After adjusting for all possible confounders (model 1), it was found that OSA status, non-PV trigger, nonparoxysmal AF, and coronary artery disease were significant predictors of AF recurrence. Whereas including too many covariates into the model helped to explore the potential predictors, it also incurred the risk of model overfitting and reduced the ability of detecting significant association. Therefore, we ran a parsimonious model (model 2) with fewer confounders. The second model had a strong discriminating ability for AF recurrence (ROC, 0.76; 95% confidence interval, 0.72 to 0.79). The hazard ratios from both the models are presented in Table 2.

At the end of the follow-up period (32±14 months), 78% success was achieved in the non-OSA group compared with 73% in the OSA group (P=0.024). Kaplan-Meier curves comparing the event-free survival between the 2 populations are presented in Figure 2. The incidence rate of overall complications in both the groups were identical (P=0.583). Nonetheless, patients in the OSA group had more hematomas...
compared with the non-OSA group (P<0.001) (Table 3). There were not enough complications to perform multivariable regression models for detecting predictors.

**Patient Characteristics and Outcomes of the CPAP and Non-CPAP Populations**

Age, diabetes type II, hypertension, type of AF, antiarrhythmic drugs, and pre-LA size were different in the 2 groups. Patient characteristics are given in Table 4.

Multivariate analysis was performed using similar model building strategy as used for OSA population. The parsimonious model had a strong predicting ability with reasonably high c-statistics (ROC, 0.77; 95% confidence interval, 0.73 to 0.81). Not using CPAP device, coronary artery disease, type of AF, and non-PV triggers were found to be predictors for procedural failure (Table 5). Patients on CPAP had a lower preprocedural CRP level (2.3) than the non-CPAP group (4.0, P=0.01). Patients on CPAP had identical postprocedural CRP level as those without CPAP (3.1 versus 3.9, P=0.93). The non-CPAP patients had higher early recurrence rates than the CPAP group: 178 (55%) versus 105 (33%) respectively (P<0.001). Paroxysmal AF patients who used CPAP had 31 (20%) procedural failures compared with 36 (33%) of the non-CPAP group (P=0.019). Nonparoxysmal AF patients who used CPAP had 128 (79%) success versus 150 (68%) in a non-CPAP population (P=0.032). At the end of the follow-up period (32±14 months), 79% of the non-CPAP group and 68% of the CPAP group were free of AF (P=0.003). Kaplan-Meier curves are given in Figure 3.

**Discussion**

The main findings of our study are (1) the incidence of OSA in patients undergoing PVAI in this series was higher than that found in the general population. (2) OSA was independently associated with PVAI failure. (3) All patients treated with CPAP had higher PVAI success rates than patients not on CPAP. (4) Patients on CPAP had lower baseline CRP levels. (5) Patients with OSA did not have more complications compared with the non-OSA group (P<0.001) (Table 3). There were not enough complications to perform multivariable regression models for detecting predictors.

**Table 2. Multivariable Cox Analysis of Clinical Variables Affecting AF Recurrence (for Overall Population: OSA and Non-OSA)**

<table>
<thead>
<tr>
<th>Variable</th>
<th>HR (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Model 1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-OSA</td>
<td>0.63 (0.48–0.80)</td>
<td>0.003</td>
</tr>
<tr>
<td>Non-PV trigger</td>
<td>7.68 (5.88–10.05)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Age</td>
<td>1.00 (0.99–1.02)</td>
<td>0.996</td>
</tr>
<tr>
<td>LA size &gt;40 mm</td>
<td>0.93 (0.66–1.30)</td>
<td>0.665</td>
</tr>
<tr>
<td>EF &gt;50%</td>
<td>1.03 (0.78–1.37)</td>
<td>0.817</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1.16 (0.91–1.48)</td>
<td>0.246</td>
</tr>
<tr>
<td>Diabetes mellitus type II</td>
<td>1.02 (0.74–1.39)</td>
<td>0.923</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>1.59 (1.15–2.19)</td>
<td>0.005</td>
</tr>
<tr>
<td>AF type (nonparoxysmal)</td>
<td>1.77 (1.34–2.33)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Model 2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-OSA</td>
<td>0.78 (0.64–0.95)</td>
<td>0.015</td>
</tr>
<tr>
<td>Non-PV trigger</td>
<td>8.71 (6.92–10.95)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>1.57 (1.24–1.99)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>AF type, nonparoxysmal</td>
<td>1.53 (1.15–2.03)</td>
<td>0.004</td>
</tr>
</tbody>
</table>

HR indicates hazard ratio; CI, confidence interval.

Model 1: Predictors in the model were age, preprocedure LVEF, LA size, hypertension, diabetes, coronary artery disease, non-PV trigger, and type of AF.

Model 2: This model included the significant predictors from the first model plus 2 additional variables, sex, and history of cerebrovascular accident.

**Table 3. Distribution of Complications in OSA and Non-OSA Populations**

<table>
<thead>
<tr>
<th></th>
<th>PVAI+ OSA (n=2360)</th>
<th>PVAI− OSA (n=640)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No complications</td>
<td>2148 (91)</td>
<td>578 (90)</td>
<td>0.583</td>
</tr>
<tr>
<td>Hematoma</td>
<td>35 (1.5)</td>
<td>32 (5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Mild PV stenosis</td>
<td>47 (2)</td>
<td>14 (2)</td>
<td>0.755</td>
</tr>
<tr>
<td>Severe PV stenosis</td>
<td>15 (0.6)</td>
<td>8 (1)</td>
<td>0.125</td>
</tr>
<tr>
<td>Stroke</td>
<td>21 (0.8)</td>
<td>6 (0.9)</td>
<td>0.818</td>
</tr>
<tr>
<td>Tamponade</td>
<td>11 (0.5)</td>
<td>2 (0.2)</td>
<td>1.000</td>
</tr>
</tbody>
</table>

Values are n (%).

Figure 2. Kaplan-Meier curve comparing freedom from AF recurrence among patients with and without OSA.
Antiarrhythmic drugs 44 (14) 97 (30)

Echo parameters (pre)

Type of AF

Paroxysmal AF 152 (48) 106 (33) <.001
Nonparoxysmal AF 163 (52) 219 (67) <.001

Comorbidities

Diabetes mellitus type II 41 (13) 75 (23) 0.001
Hypertension 168 (53) 224 (69) <.001
Coronary artery disease 48 (15) 48 (15) 0.868
Cerebrovascular accident 5 (2) 11 (3) 0.205

Age, y 49±8 53±12 <.001
Body mass index, kg/m² 30±3 31±2 0.098

values are n (%) or mean±SD.

PVAI+OSA+CPAP indicates OSA patients using CPAP; PVAI+OSA−CPAP, OSA patients not using CPAP.

Prior studies have reported that oxidative stress by cytokines and free radical production may also be involved in onset of new AF and may promote recurrence after PVAI. Hypoxemia, hypercapnia, and atrial stretching caused by higher pressure are stimulants for arrhythmias. CPAP may lower PVAI failure rates in the treated group either by decreasing frequency of hypoxic episodes, by preventing atrial stretch and stimulation of stretch sensitive channels, or /and by raising the nadir value for nocturnal desaturation, which our study did not measure.

Finally, in patients on CPAP, we used the CPAP machine to facilitate shallow breathing during conscious sedation. In patients not treated with CPAP, deeper and more erratic breathing could effect catheter stability and increase the chance of recurrence secondary to ineffective lesions.

The complicaon rates were similar in patients with and without OSA. However, patients in the OSA group had a higher risk of hematomas, which could reflect a more difficult access in patients with significant obesity. However, we were unable to accurately demonstrate this statistically because of the small number of complications.

Limitations

Our study is a retrospective evaluation of a prospectively collected database. The inclusion of noncompliant patients in the control group could have possibly slightly elevated the success rate of the non-CPAP group due to the partial benefit of using CPAP intermittently. Moreover, OSA is underreponed; therefore, the number of patients with OSA in our population maybe underreprersented.
Additionally, in the present study we found non-PV triggers to be a significant predictor for PVAI failure. However, PV reconnection could be a possible factor for procedure failure. Nevertheless, the focus of this study was success after a single procedure and PV reconnection data were not available unless the patient had a redo procedure; thereby PV reconnection was not added to the regression model. All patients reached the procedural end point, which was complete isolation of the PVs. In addition, PV reconnection should occur equally in patients with and without additional triggers; therefore additional triggers should still remain an independent predictor of failure.

**Conclusion**

In our series, OSA was an independent predictor for PVAI failure after a single procedure. Treatment with CPAP improved PVAI success rates in all patients with OSA. Patients who were not treated with CPAP and who had non-PV triggers were 8 times more likely to fail the procedure.

**Disclosures**

Drs Amin Al-Ahmad, David J. Burkhardt, Dhanunjay Lakkireddy, Javier E. Sanchez, Jennifer E. Cummings, Paul Wang, Robert A. Schweikert, Rodney Horton, and Andrea Natale report receiving compensation from St Jude Medical for participation in speaker’s bureaus; Drs David J. Burkhardt, Rodney Horton, Paul Wang, Jennifer E. Cummings, Amin Al-Ahmad, and Andrea Natale report receiving compensation from Biosense Webster for participation in speaker’s bureaus; Drs David J. Burkhardt, Rodney Horton, Paul Wang, Jennifer E. Cummings, Amin Al-Ahmad, and Andrea Natale report receiving compensation from Medtronic for participation in speaker’s bureaus; Drs Amin Al-Ahmad, David J. Burkhardt, Dhanunjay Lakkireddy, Paul Wang, Amin Al-Ahmad, Robert A. Schweikert, Jennifer E. Cummings, and Andrea Natale report receiving compensation from Boston Scientific for participation in speaker’s bureaus; Drs Rodney Horton and Paul Wang report receiving compensation from Hansen Medical for participation in speaker’s bureaus; Drs Robert A. Schweikert, William Lewis, and Jennifer E. Cummings report receiving compensation from Sanofi-Aventis for participation in speaker’s bureaus; Dr Robert A. Schweikert reports receiving compensation from Glaxo-Smith-Kline for participation in speaker’s bureau; Dr Paul Wang reports receiving compensation from Lifewatch for participation in speaker’s bureau; Dr G. Joseph Gallinghouse reports serving as a consultant/advisory board to St Jude Medical and Hansen; Dr Jennifer E. Cummings reports serving as a consultant/advisory board to St Jude Medical and Corazon Consulting; Dr David J. Burkhardt reports serving as a consultant/advisory board to Stereotaxis; Dr Amin Al-Ahmad reports serving as a consultant/advisory board to Lifewatch, EBR Medical, and CyberHeart; Dr William Lewis reports serving as a consultant/advisory board to Boston Scientific and Medtronic; Dr Steven Hao reports serving as a consultant for Medtronic and Biosense Webster; Dr Amin Al-Ahmad reports participation in a research grant from Siemens Medical; and Dr Andrea Natale reports participation in a research grant from St Jude.

**References**

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![Figure 3. Kaplan-Meier curve showing probability of AF-free survival among patients with OSA+CPAP and OSA patients without CPAP.](Image)


**CLINICAL PERSPECTIVE**

Previous studies have shown that in patients with atrial fibrillation and obstructive sleep apnea (OSA), the treatment with continuous positive airway pressure (CPAP) has increased the success rate of the electrical cardioversion. In the present study, we assessed the prevalence of OSA in patients undergoing pulmonary vein antral isolation (PVAI), and examined if effective treatment with CPAP can affect the procedural outcome. Patients with OSA had more extra-PV triggers, more procedural failures, and more hematomas when compared with those without. However, when OSA patients were treated with CPAP during the procedure, the failure rate was significantly decreased possibly because of better catheter stability. After 32±14 months of follow-up, 79% of the CPAP population and 68% of non-CPAP population were free of atrial fibrillation (log-rank *P*=0.003). OSA was found to be an independent predictor for PVAI failure after a single procedure, and treatment with CPAP improved PVAI success rate in all patients with OSA. Whether this effect is temporary rather than long-lasting is unknown.
Safety and Efficacy of Pulmonary Vein Antral Isolation in Patients With Obstructive Sleep Apnea: The Impact of Continuous Positive Airway Pressure
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