Low efficacy of atrial fibrillation ablation in severe obstructive sleep apnoea patients

Maria Matiello††, Mercé Nadal††, David Tamborero†, Antonio Berruezo†, Josep Montserrat†,2, Cristina Embid†,2, Jose Rios3, Julián Villacastín4, Josep Brugada†, and Lluís Mont†*

1Arrhythmia Section, Cardiology Department, Thorax Institute, Hospital Clínic Universitari, Institut de Investigació Biomèdica August Pi i Sunyer (IDIBAPS), University of Barcelona, Villarroel, 170, 08036 Barcelona, Catalonia, Spain; 2CIBER de enfermedades respiratorias (ISCii), Madrid, Spain; 3Laboratory of Biostatistics & Epidemiology, Universitat Autonoma de Barcelona; Statistics and Methodology Support Unit, Hospital Clínic Universitari, IDIBAPS, Barcelona, Catalonia, Spain; and 4Unidad de Arritmias, Hospital Clínico Universitario San Carlos, Madrid, Spain

Received 25 October 2010; accepted after revision 12 April 2010; online publish-ahead-of-print 20 May 2010

Aims

Atrial fibrillation (AF) ablation efficacy varies according to patients’ clinical characteristics. Although the association of obstructive sleep apnoea (OSA) and AF is well established, data on AF ablation efficacy in OSA are scarce. The aim of this study was to clarify the effect of OSA on the outcome of AF ablation.

Methods and results

A series of 174 consecutive patients without polysomnography submitted to circumferential pulmonary vein ablation were included in the study. All patients were assessed by Berlin Questionnaire (BQ) and underwent an echocardiogram and a clinical evaluation. Patients with a high BQ score, indicating high risk for OSA, participated in a sleep study. Diagnoses were classified according to the apnoea–hypopnoea index (AHI) as mild (AHI < 10/h), non-severe (AHI 10–30/h), or severe (AHI ≥ 30/h) OSA. Follow-up consisted of outpatient visits and 24 or 48 h Holter monitoring at 1, 4, and 7 months, and every 6 months thereafter. Any episode of AF or left atrial (LA) flutter was considered recurrence. Fifty-one (29.3%) patients had high BQ scores. The sleep study showed that 17 (9.8%) and 25 (14.4%) of these patients had non-severe and severe OSA, respectively. One-year arrhythmia-free probability after a single ablation procedure was 48.5% in patients with low risk for OSA (low BQ score or AHI < 10/h), 30.4% in the non-severe OSA group (10 ≤ AHI < 30/h) and 14.3% in the severe OSA group (AHI ≥ 30). Anteroposterior LA diameter [hazard ratio (HR) = 1.046, 95% confidence interval (CI): 1.005–1.089; P = 0.029] and severe OSA (HR = 1.870, 95% CI: 1.106–3.161; P = 0.019) were the independent predictors of arrhythmia recurrence.

Conclusion

In patients with AF ablation, the presence of severe OSA is an independent predictor for AF ablation failure.

Keywords

Obstructive sleep apnoea • Atrial fibrillation • Catheter ablation

Introduction

Patients with obstructive sleep apnoea (OSA) show a high prevalence of atrial fibrillation (AF), ranging from 32 to 49%,1–3 although a causal relationship has not been definitively established. Studies that analyse the role of OSA in AF recurrence after cardioversion are scarce, but suggest higher AF recurrence in untreated OSA patients and AF improvement after OSA treatment with continuous positive airway pressure (CPAP).4

Arrhythmia recurrence remains an important limitation of AF ablation. It is well known that AF ablation success is highly dependent on patient characteristics. Age, atrial size, history of hypertension, mitral valve disease, and type and duration of AF are the factors that affect the efficacy of the procedure.5,6 Uncovering new conditions that may influence ablation success could result in better patient selection and outcomes. Three recent studies have analysed the influence of OSA in AF ablation success, presenting opposite results: Jongnarangsin et al.7 showed that OSA was the strongest predictor of ablation failure in a retrospective study. The recent paper by Chilukuri et al.8 shows similar results when comparing low and high risk of OSA suspected by Berlin Questionnaire (BQ); however, in a prospective analysis,

---

† These authors have equally contributed to the study.
* Corresponding author. Tel: +34 93 227 5551; fax: +34 93 451 3045, Email: lmont@clinic.ub.es

Published on behalf of the European Society of Cardiology. All rights reserved. © The Author 2010. For permissions please email: journals.permissions@oxfordjournals.org.
Tang et al. found no relationship between OSA suspected by BQ results and ablation success. We hypothesized that OSA may be an independent factor associated with arrhythmia recurrence after a single AF ablation procedure. Therefore, the aim of the study was to analyse the effect of OSA on the outcome of AF ablation in a prospective study, by combining the results of BQ and sleep studies to further stratify the risk.

**Methods**

**Study population**

A series of 174 consecutive patients with documented symptomatic AF that underwent a first AF ablation procedure at our institution from January 2005 to December 2007 were included in the study. Exclusion criteria were age <18 or >75 years, anteroposterior left atrial (LA) diameter at transthoracic echocardiography >55 mm, LA thrombus detected by transoesophageal echocardiography, and the presence of a mechanical prosthetic heart valve. Patients were included after written informed consent was obtained. No patient refused consent and no patient was lost to follow-up. The study protocol was approved by the institutional Ethics Committee.

**Ablation procedure**

Antiarrhythmic drug therapy was stopped at least five half-lives before the ablation, except in patients receiving amiodarone. Oral anticoagulation was stopped 3 days prior to the procedure and low molecular-weight heparin was administered up to 12 h before the ablation. Patients underwent cardiac resonance imaging and transoesophageal echocardiography prior to ablation.

Catheters were introduced percutaneously through the femoral vein and a transseptal puncture was performed to access the LA. A bolus of 5000–6000 IU of heparin was administered according to patient weight, followed by additional boluses to maintain an activated clotting time of >250 s. Ablation was performed under intravenous sedation with midazolam and analgesia with meperidine and phentanyln. Oxygen saturation and invasive arterial blood pressure were monitored throughout the procedure. A three-dimensional map was constructed using an electroanatomical mapping system (CARTO, Biosense-Webster or NAVX, St Jude Corporation) to support the creation and validation of radiofrequency (RF) lesions.

Continuous RF lesions were delivered surrounding each ipsilateral pulmonary vein (PV) until dissociation or disappearance of the local electrogram inside the encircled areas was achieved. Ablation lines were also deployed along LA roof in all patients and along LA posterior wall in 157 patients (85.8%), joining contralateral encircling lesions as described previously. Radiofrequency lesions were performed using either a thermocouple-equipped 8 mm-tip catheter (Celsius, Biosense-Webster) at a target temperature of 55°C and maximum output of 50 W or an irrigated-tip catheter (Celsius Thermocool, Cordis, Biosense-Webster) at 45°C target temperature and 40 W maximum power output.

**Sleep apnoea assessment**

The BQ, administered to all study participants prior to ablation, is a simple, validated method of identifying patients with OSA, with a sensitivity of 0.86, specificity of 0.77, and positive predictive value of 0.89 in AF patients. The 10 questions are divided in three sections: 5 questions about snoring and apnoea behaviour, 4 about daytime sleepiness, and 1 concerning hypertension or obesity. High risk for OSA is assigned if positive BQ responses are obtained in two or more of the following criteria: (i) persistent symptoms (>3 times per week) for at least two snoring questions, (ii) persistent (>3 times per week) somnolence during daytime and/or while driving, and (iii) history of hypertension or a body mass index >30 kg/m².

A domiciliary respiratory sleep study was performed in patients considered at high risk for OSA by BQ. Data were acquired with ApneaLink. The absence of airway flow for >10 s was considered apnoea and a discernible flow reduction for >10 s followed by a 3% fall of SaO₂ was considered hypopnoea. Obstructive sleep apnoea diagnosis was established when the apnoea—hypopnoea index (AHI), or number of apnoeas and hypopnoeas per hour, exceeded 10; AHI ≥ 30 was considered severe OSA. The respiratory sleep apnoea was not performed in patients with low BQ scores; they were included in the low OSA risk group, along with patients having an AHI < 10.

**Follow-up**

Follow-up consisted of outpatient visits and 24 or 48 h Holter monitoring at 1, 4, and 7 months after ablation, and every 6 months thereafter if the patient remained asymptomatic. Patients were asked to report any symptoms of arrhythmia between scheduled visits and encouraged to document recurrences by an electrocardiogram performed at their emergency ward. A transthoracic echocardiogram and magnetic resonance angiography were routinely performed between 4 and 6 months after ablation.

All patients continued on oral anticoagulation to maintain an international normalized ratio of between 2.0 and 3.0 for at least 2 months after ablation. Previous antiarrhythmic therapy was maintained for at least 1 month to manage early recurrences and then discontinued 1–3 months after ablation if there were no recurrences.

The primary endpoint of the study was freedom from any documented episode of AF or atrial flutter lasting >30 s, after a single ablation procedure and without antiarrhythmic therapy. Arrhythmic episodes within the first 3 months after the procedure, often described as transient recurrences related to atrial inflammatory processes following RF lesions, were not considered in the evaluation of final success rates.

**Statistical analysis**

Continuous variables were expressed as mean ± SD and compared by one-way analysis of variance. Post hoc analyses were performed by the Bonferroni test. Categorical variables were expressed as percentages and compared using the χ² analysis. Arrhythmia-free survival curves for each group were presented as the Kaplan–Meier plots and compared by log-rank test. Cox regression analysis was used to determine the predictors of arrhythmia recurrence using backward stepwise selection with criteria of P ≤ 0.05 for inclusion and P ≥ 0.10 for removal from the model, including as covariates the following variables: OSA group, body mass index, age, sex, structural heart disease, type of AF, hypertension, LA diameter, left ventricular end-diastolic diameter, and left ventricular ejection fraction. A full Cox analysis including the interaction term between the covariates of the final multivariate model was also performed. A two-sided P-value of ≤0.05 was considered statistically significant. Statistical analyses were performed using SPSS for Windows Version 12.0 (SPSS Inc., Chicago, IL, USA).

**Results**

**Obstructive sleep apnoea evaluation**

On the basis of BQ evaluation, 51 (29.3%) patients were considered at high risk for OSA and underwent a sleep study. Diagnoses were non-severe OSA in 17 patients (9.8%, mean AHI of...
18.1 ± 6.7/h) and severe OSA in 25 (14.4%, mean AHI of 53.5 ± 16.1/h). Nine patients (eight from the severe OSA group) were under CPAP treatment before and after the ablation procedure. Baseline characteristics of patients according to BQ score and OSA severity are depicted in Table 1. Obstructive sleep apnoea patients had slightly larger left ventricular dimensions and larger body mass index when compared with the control group, as well as a higher incidence of hypertension and structural heart disease.

### Ablation procedure

There were no significant differences between OSA groups in procedural data or complications related to ablation procedure (Table 2).

#### Table 1 Differences in baseline patient characteristics between the OSA groups

<table>
<thead>
<tr>
<th></th>
<th>Low risk for OSA (low BQ score or AHI &lt; 10)</th>
<th>Non-severe OSA (high BQ score and 10 &lt; AHI &lt; 30)</th>
<th>Severe OSA (high BQ score and AHI ≥ 30)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients</td>
<td>132</td>
<td>17</td>
<td>25</td>
<td></td>
</tr>
<tr>
<td>Type of AF</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Paroxysmal AF</td>
<td>79 (59.8%)</td>
<td>10 (58.8%)</td>
<td>9 (36.0%)</td>
<td>0.086</td>
</tr>
<tr>
<td>Persistent AF</td>
<td>38 (28.8%)</td>
<td>3 (17.6%)</td>
<td>9 (36.0%)</td>
<td></td>
</tr>
<tr>
<td>Longstanding AF</td>
<td>15 (11.4%)</td>
<td>4 (23.5%)</td>
<td>7 (28.0%)</td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>51.2 ± 11.8</td>
<td>57.9 ± 9.0</td>
<td>55.6 ± 9.4</td>
<td>0.057</td>
</tr>
<tr>
<td>Male sex</td>
<td>97 (73.5%)</td>
<td>14 (82.4%)</td>
<td>24 (96.0%)a</td>
<td>0.047</td>
</tr>
<tr>
<td>LA diameter (mm)</td>
<td>41.8 ± 5.0</td>
<td>41.4 ± 5.8</td>
<td>44.5 ± 5.9</td>
<td>0.078</td>
</tr>
<tr>
<td>LV end-diastolic diameter (mm)</td>
<td>51.2 ± 4.8</td>
<td>54.1 ± 4.0a</td>
<td>53.4 ± 4.3a</td>
<td>0.006</td>
</tr>
<tr>
<td>LV end-systolic diameter (mm)</td>
<td>32.8 ± 5.1</td>
<td>35.2 ± 5.2a</td>
<td>35.6 ± 4.8a</td>
<td>0.036</td>
</tr>
<tr>
<td>LV ejection fraction (%)</td>
<td>59.5 ± 8.6</td>
<td>56.3 ± 7.8</td>
<td>54.4 ± 12.1</td>
<td>0.056</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>26.7 ± 3.2</td>
<td>29.0 ± 3.4a</td>
<td>29.3 ± 3.0a</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hypertension</td>
<td>45 (34.0%)</td>
<td>12 (70.6%)a</td>
<td>16 (64.0%)a</td>
<td>0.001</td>
</tr>
<tr>
<td>Sinus rhythm at baseline</td>
<td>50 (38.3%)</td>
<td>5 (30.8%)</td>
<td>9 (37.5%)</td>
<td>0.768</td>
</tr>
<tr>
<td>Structural heart disease</td>
<td>15 (11.3%)</td>
<td>2 (11.7%)</td>
<td>7 (28.0%)a</td>
<td>0.001</td>
</tr>
</tbody>
</table>

OSA, obstructive sleep apnoea; BQ, Berlin Questionnaire; AHI, apnoea–hypopnoea index; AF, atrial fibrillation; LA, left atrial; LV, left ventricular.

*aSignificant differences when compared with low risk for OSA group.

#### Table 2 Procedural details

<table>
<thead>
<tr>
<th></th>
<th>Low risk for OSA (low BQ score or AHI &lt; 10)</th>
<th>Non-severe OSA (high BQ score and 10 &lt; AHI &lt; 30)</th>
<th>Severe OSA (high BQ score and AHI ≥ 30)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients</td>
<td>132</td>
<td>17</td>
<td>25</td>
<td></td>
</tr>
<tr>
<td>Procedural time (min)</td>
<td>137.1 ± 50.6</td>
<td>139.1 ± 29.4</td>
<td>158.9 ± 56.2</td>
<td>0.091</td>
</tr>
<tr>
<td>Fluoroscopy time (min)</td>
<td>30.0 ± 16.6</td>
<td>28.5 ± 7.1</td>
<td>35.5 ± 12.2</td>
<td>0.702</td>
</tr>
<tr>
<td>RF delivery time (min)</td>
<td>33.5 ± 16.3</td>
<td>37.7 ± 15.5</td>
<td>37.3 ± 16.2</td>
<td>0.514</td>
</tr>
<tr>
<td>Complications</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cerebrovascular accident</td>
<td>1 (0.7%)</td>
<td>1 (5.9%)</td>
<td>0 (0%)</td>
<td>0.164</td>
</tr>
<tr>
<td>Transient cerebrovascular ischaemia</td>
<td>3 (2.2%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td></td>
</tr>
<tr>
<td>Transient inferior myocardial ischaemia</td>
<td>1 (0.7%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td></td>
</tr>
</tbody>
</table>

OSA, obstructive sleep apnoea; BQ, Berlin Questionnaire; AHI, apnoea–hypopnoea index; RF, radiofrequency.

Ablation outcome

Mean follow-up was 17.0 ± 11.5 months. On the basis of the Kaplan–Meier estimates, the proportion of arrhythmia-free patients at 1-year follow-up, after a single procedure and without antiarrhythmic treatment, was 48.5% in the low risk for OSA group, 30.4% in the non-severe OSA group, and 14.3% in the severe OSA group. Overall arrhythmia recurrences were significantly higher in the severe OSA patients (Figure 1).

A second ablation procedure was performed in 39 (29.5%) patients of the low risk for OSA group, in 8 (47.1%) of the non-severe OSA group, and in 11 (44.0%) of the severe OSA group. Overall, the arrhythmia-free proportion at 1-year follow-up in the present series was 68.8, 43.8, and 14.3%, respectively, including a second procedure as warranted (Figure 2).
Predictors of arrhythmia recurrence

In the present series, LA diameter and severe OSA were predictors of arrhythmia recurrence after a single ablation procedure (Table 3). Interaction term between both covariates obtained a \( P = 0.974 \), indicating that they were independent.

Continuous positive airway pressure treatment

Overall, nine patients were under CPAP before ablation and two additional patients initiated the therapy after the procedure. All 11 patients were from the severe OSA group and had arrhythmia recurrences during follow-up.

Discussion

Main findings

The results of the study suggest that the presence of severe OSA is a powerful predictor of ablation failure, independently of atrial enlargement, obesity, or hypertension that may co-exist in OSA patients. This finding could influence decisions regarding ablation. One of the limitations of AF ablation is the relatively high recurrence rate, ranging from 20 to 50%. Atrial enlargement and persistent vs. paroxysmal AF have been previously identified as independent risk factors for recurrences. Our results open a new area for research to uncover which mechanisms may be implicated. Our data are in agreement with two recently published retrospective studies, by Jongnarangsin et al.\(^7\) and Chilukuri et al.\(^8\). The Jongnarangsin study found similar risk for ablation failure and also showed that obesity was not an independent risk factor when OSA was included in the multivariate model. Although complex fractionated atrial electrograms defragmentation was used as the ablation technique, the observed efficacy was quite similar to our observations. The retrospective research design was the main limitation of this study; some undiagnosed OSA patients may have been included in the non-OSA group for analysis. Our analysis included a prospective BQ screening of all patients, looking for symptomatic patients and minimizing the probability of missing OSA diagnoses. Furthermore, all patients with high risk of OSA underwent a sleep study to confirm OSA diagnosis and were divided into two groups according to OSA severity. Tang et al.\(^9\) did not find any relationship between OSA and ablation success. However, they divided the population into two categories
Obstructive sleep apnoea and atrial fibrillation

Obstructive sleep apnoea is a sleep-related disorder characterized by repeated airflow interruptions during sleep. The pathogenesis of AF in OSA is not clearly understood, although it seems to be independent of other concomitant risk factors such as hypertension and obesity.

A diverse range of mechanisms secondary to intermittent nocturnal desaturation observed in OSA, such as intermittent hypoxaemia and hypercapnia, autonomic imbalance with an increased sympathetic tone, cardiac diastolic dysfunction, inflammatory response, or endothelial dysfunction, could play a role in the LA enlargement, electrical remodelling, or fibrosis that can initiate or predispose to AF. The reason for low AF ablation efficacy in this subgroup of patients is also unclear. Sauer et al. described OSA as a clinical predictor of acute PV reconnection during PV isolation. One possibility could be the presence of AF triggers outside the PVs and LA. It is also reasonable to assume that AF in OSA is not related to PV firing as in other forms of AF, and perhaps, a more extensive arrhythmic substrate is present.

We also observed that most arrhythmia recurrences occurred in the first 6 months of follow-up. After this period, the Kaplan–Meier recurrence curves run in parallel. Stabilization of the recurrence rate might have been due to appropriate post-ablation treatment of most of the recognized risk factors associated with AF disease.

In our population, only nine of the patients in the high-risk OSA were treated with CPAP before ablation. Ablation success apparently did not differ from the untreated in this group. Although this retrospective observation in such a small population does not permit a definitive conclusion, it suggests that once the damage to the atrium is established, CPAP cannot restore stable rhythm. This fact, together with previous observations suggesting a positive effect of CPAP in early stages, would favour earlier detection and treatment of OSA in AF patients. However, randomized studies should be performed to further clarify this possibility.

Study limitations

Since this was an observational study, the proportion of OSA patients were unbalanced, and although the high arrhythmia recurrence rate among severe OSA caused that it appeared as an independent predictor of AF ablation failure, our results should be taken with caution. Further studies are required to confirm our data.

Another limitation is that the only patients who complete a sleep study were those identified by the BQ as at high risk for OSA. Therefore, some patients with OSA could have been misclassified and included in the low risk for OSA group. Nevertheless, underdiagnosed patients would probably present a non-severe OSA since they do not present important somnolence or snoring symptoms. Furthermore, the inclusion of patients with OSA in the low risk for OSA group would not contradict our hypothesis, since it would have minimized the differences. Therefore, our observations should be reliable. Another important limitation is that the follow-up is mainly based on documented arrhythmia recurrences, so subclinical or infrequent episodes would have been undetected. However, all of the groups were controlled with the same recording methods, so this should not have affected the results.

Conclusions

Severe OSA is an independent predictor for low probability of AF ablation success in terms of arrhythmia recurrence.

Conflict of interest: none declared.

Funding

D.T. was supported by a grant from Institut de Investigació Biomèdica August Pi i Sunyer (IDIBAPS). The project was partially funded by grants from the Fund for Health Research (FIS PI050081) and Thematic Networks for Health Cooperative Research Grant (REDSINCOR RD06/0003/008), both from the Spanish Ministry of Health, Madrid, Spain.

References