Influence of Obstructive Sleep Apnea and its Treatment on Atrial Fibrillation

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Director, Clinical Cardiology
Leon Charney Division of Cardiology
NYU School of Medicine
Introduction

- Anti-arrhythmic drugs and catheter ablation comprise the mainstay of available therapies to maintain sinus rhythm in patients with atrial fibrillation (AF).

- Select group of patients however remain resistant and have recurrent AF despite therapy.

- Patient comorbidities are known to be associated with recurrence of AF in these patients and are often ignored in therapeutic decision making.


Risk Factors for Atrial Fibrillation

- AGE
- Hypertension
- Obesity
- Diabetes Mellitus
- Left Atrial Enlargement

Aggressive treatment of any of these reversible factors with the goal to reduce the future burden of AF has been promoted; however, there remains a paucity of data to support this hypothesis

Sleep Disorders: Next Frontier in Cardiac Management

- Obesity
- Blood pressure
- Diabetes
- Smoking
- Cholesterol
- Sleep disorders

HEART DISEASE
Sleep Apnea is a Significant Comorbidity to Most Cardiac Diseases

<table>
<thead>
<tr>
<th>Condition</th>
<th>OSA comorbidity</th>
<th>US patients M</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug resistant hypertension</td>
<td>83%</td>
<td>7.2</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>76%</td>
<td>5.1</td>
</tr>
<tr>
<td>Diabetes type 2</td>
<td>72%</td>
<td>29.0</td>
</tr>
<tr>
<td>Stroke</td>
<td>63%</td>
<td>6.4</td>
</tr>
<tr>
<td>Pacemakers</td>
<td>59%</td>
<td>3.5</td>
</tr>
<tr>
<td>Arrhythmias</td>
<td>58%</td>
<td>14.4</td>
</tr>
<tr>
<td>Coronary heart disease</td>
<td>57%</td>
<td>16.2</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>49%</td>
<td>3.5</td>
</tr>
</tbody>
</table>

- Source: Seet & Chung, Anesthesia Clin 2010
Introduction

- Obstructive sleep apnea (OSA) is a known risk factor associated with onset and then recurrence of AF after therapy.
- Patients with OSA have evidence of atrial structural and electrical remodeling to account for their predisposition to AF.

## AF Recurrence after Catheter Ablation

### Tang 2009
- **OSA**
  - Events: 26
  - Total: 104
- **Non OSA**
  - Events: 18
  - Total: 74
- **Risk Ratio**
  - M-H, Random, 95% CI: 1.03 [0.61, 1.73]

### Chilukuri 2009
- **OSA**
  - Events: 57
  - Total: 92
- **Non OSA**
  - Events: 62
  - Total: 118
- **Risk Ratio**
  - M-H, Random, 95% CI: 1.18 [0.93, 1.49]

### Chilukuri 2010
- **OSA**
  - Events: 32
  - Total: 48
- **Non OSA**
  - Events: 42
  - Total: 61
- **Risk Ratio**
  - M-H, Random, 95% CI: 0.97 [0.75, 1.26]

### Subtotal (95% CI)
- **OSA**
  - Events: 244
- **Non OSA**
  - Events: 253
- **Risk Ratio**
  - M-H, Random, 95% CI: 1.07 [0.91, 1.27]

### Heterogeneity
- **Tau²**: 0.00
- **Chi²**: 1.24, df = 2 (P = 0.54); I²: 0%
- **Test for overall effect**: Z = 0.85 (P = 0.39)

### Matiello 2010
- **OSA**
  - Events: 33
  - Total: 42
- **Non OSA**
  - Events: 68
  - Total: 132
- **Risk Ratio**
  - M-H, Random, 95% CI: 1.53 [1.21, 1.92]

### Jongnarangsin 2008
- **OSA**
  - Events: 19
  - Total: 32
- **Non OSA**
  - Events: 108
  - Total: 292
- **Risk Ratio**
  - M-H, Random, 95% CI: 1.61 [1.16, 2.22]

### Patel 2010
- **OSA**
  - Events: 173
  - Total: 640
- **Non OSA**
  - Events: 519
  - Total: 2360
- **Risk Ratio**
  - M-H, Random, 95% CI: 1.23 [1.06, 1.43]

### Subtotal (95% CI)
- **OSA**
  - Events: 714
- **Non OSA**
  - Events: 2784
- **Risk Ratio**
  - M-H, Random, 95% CI: 1.40 [1.16, 1.68]

### Heterogeneity
- **Tau²**: 0.01
- **Chi²**: 4.16, df = 2 (P = 0.12); I²: 52%
- **Test for overall effect**: Z = 3.53 (P = 0.0004)

### Total (95% CI)
- **OSA**
  - Events: 958
- **Non OSA**
  - Events: 3037
- **Risk Ratio**
  - M-H, Random, 95% CI: 1.25 [1.08, 1.45]

### Heterogeneity
- **Tau²**: 0.02
- **Chi²**: 9.77, df = 5 (P = 0.08); I²: 49%
- **Test for overall effect**: Z = 3.02 (P = 0.003)

Ng et al; Am J Cardiol 2011
Long-Term Outcome of Catheter Ablation in Atrial Fibrillation Patients with Coexistent Metabolic Syndrome and Obstructive Sleep Apnea: Impact of Repeat Procedures versus Lifestyle Changes

Mohanty, Natale et al. JCE 2014:25; 930-938
Atrial remodeling in obstructive sleep apnea: Implications for atrial fibrillation
Atrial remodeling in obstructive sleep apnea: Complex Electrograms

Hany Dimitri, Michelle Ng, Anthony G. Brooks, Pawel Kuklik, Martin K. Stiles, Dennis H. Lau, Nicholas Antic, Andrew Thornton, David A. Saint, Doug McEvoy, Ral Antic, Jonathan M. Kalman, Prashanthan Sanders

Atrial remodeling in obstructive sleep apnea
Low Voltage

Hany Dimitri, Michelle Ng, Anthony G. Brooks, Pawel Kuklik, Martin K. Stiles, Dennis H. Lau, Nicholas Antic, Andrew Thornton, David A. Saint, Doug McEvoy, Ral Antic, Jonathan M. Kalman, Prashanthan Sanders
Atrial remodeling in obstructive sleep apnea: Conduction Velocity

Hany Dimitri, Michelle Ng, Anthony G. Brooks, Pawel Kuklik, Martin K. Stiles, Dennis H. Lau, Nicholas Antic, Andrew Thornton, David A. Saint, Doug McEvoy, Ral Antic, Jonathan M. Kalman, Prashanthan Sanders

<table>
<thead>
<tr>
<th>Variable</th>
<th>Obese Without OSA</th>
<th>Obese With OSA</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mitral valve early diastole velocity (cm/s)</td>
<td>72 ± 3</td>
<td>66 ± 3</td>
<td>0.16</td>
</tr>
<tr>
<td>Mitral valve late diastole velocity (cm/s)</td>
<td>59 ± 2</td>
<td>61 ± 2</td>
<td>0.57</td>
</tr>
<tr>
<td>Mitral early to late diastole ratio &gt;1</td>
<td>83%</td>
<td>61%</td>
<td>0.06</td>
</tr>
<tr>
<td>Isovolumetric relaxation time (ms)</td>
<td>88 ± 3</td>
<td>90 ± 2</td>
<td>0.69</td>
</tr>
<tr>
<td>Deceleration time (ms)</td>
<td>188 ± 11</td>
<td>192 ± 9</td>
<td>0.81</td>
</tr>
<tr>
<td>Ejection fraction (%)</td>
<td>62.7 ± 1.1</td>
<td>60.1 ± 1.00.11</td>
<td></td>
</tr>
<tr>
<td>Left atrial volume index (ml/m)</td>
<td>16.3 ± 1.2</td>
<td>20.2 ± 1</td>
<td>0.02</td>
</tr>
<tr>
<td>LV mass index (g/m²)</td>
<td>117 ± 8</td>
<td>116 ± 7</td>
<td>0.97</td>
</tr>
<tr>
<td>Mitral annular systolic velocity (cm/s)</td>
<td>5.8 ± 0.3</td>
<td>6.2 ± 0.4</td>
<td>0.34</td>
</tr>
<tr>
<td>Mitral annular early diastolic velocity (cm/s)</td>
<td>−7.9 ± 0.6</td>
<td>−6.4</td>
<td>0.05</td>
</tr>
<tr>
<td>Mitral annular late diastolic velocity (cm/s)</td>
<td>−5.7 ± 0.3</td>
<td>7</td>
<td>−7.3 ± 0.70.00</td>
</tr>
<tr>
<td>Ratio of early to late diastolic annular velocity &gt;1</td>
<td>82%</td>
<td>26%</td>
<td>0.001</td>
</tr>
</tbody>
</table>

Comparison of Cardiac Structural and Functional Changes in Obese Otherwise Healthy Adults With Versus Without Obstructive Sleep Apnea
Physiologic Basis of Atrial Changes in OSA

- LV Diastolic Dysfunction, Increased Afterload
- Swings in intrathoracic pressure causing an increase in left atrial volume and atrial stretch
- Autonomic changes with surges of both sympathetic stimulation and Vagal activation (negative tracheal pressure)
- Intermittent hypoxia
- Oxidative stress
- Inflammation
- Hypercapnia

All of these factors have been variably implicated as causes of fibrosis and thus important mechanisms involved in chronic structural remodeling of the human atrium.
Better Way to Diagnose Sleep Apnea

Polysomnography (PSG)
- Spend a night in a lab
- Requires skilled staff

WatchPAT™
- Sleep in your own bed
- Easy self-administration
Current Therapy

How to sleep comfortably with a CPAP machine
Best Scenario
Effect of Obstructive Sleep Apnea Treatment on Atrial Fibrillation Recurrence

A Meta-Analysis

Ashish Shukla, MD, MPH, Anthony Aizer, MD, MSC, Douglas Holmes, MD, Steven Fowler, MD, David S. Park, MD, PHD, Scott Bernstein, MD, Neil Bernstein, MD, Larry A Chinitz, MD

JACC Clinical Electrophysiology Vol 1 No. 1 2015

- Effect of OSA treatment with continuous positive pressure ventilation (CPAP) on AF recurrence has been evaluated in few studies
- Small study population, variable results.
- Extent of net clinical benefit from use of CPAP in patients with OSA remains inconclusive
- The results of this study present the highest strength of evidence currently available for the association between CPAP use and reduced AF recurrence.
METHODS

• Study done per guidelines of PRISMA statement.

Literature Search
• MEDLINE (from 1950 to December, 2013),
• EMBASE (from 1966 to December, 2013),
• GOOGLE SCHOLAR
• Cochrane Central Register of Controlled Trials
METHODS

Search key terms:
• “atrial fibrillation”
• “obstructive sleep apnea”
• “continuous positive airway pressure”,
• “pulmonary vein isolation”
• “arrhythmia recurrence”
METHODS

Inclusion Criteria:

i) Observational or randomized controlled trial

ii) Effect of CPAP therapy on AF recurrence in patients with OSA

iii) patients with OSA and symptomatic AF referred for index ablation procedure

iv) Outcome reported clinically in terms of arrhythmia recurrence, adherence to CPAP

v) Study duration: more than 6 months
METHODS

Exclusion criteria:

• No evaluation of CPAP and non CPAP users
• No report of arrhythmia recurrence
• No report of CPAP use adherence.
• Non-English language studies
Outcome measures:

**Primary:**
1. Recurrence of AF in CPAP users and non users in patients with OSA

**Secondary:**
1. AF recurrence in patients with PVI and those with no PVI.
2. Evaluation of patient and study characteristics and their effect on study results
Data analysis

• **Summary relative risk (RR)** estimates derived using method of Der Simonian and Laird random effect model
• All analyses performed using standard statistical software (Stata 10.1, Stata corporation, Texas)
• **Heterogeneity**: Chi square and $I^2$ tests
• **Significant heterogeneity**
  a. $p \leq 0.1$ for chi square
  b. $I^2$ statistic more than 56%
• **Publication Bias**
  a. visually by funnel plot
  b. weighted regression test of Egger.
Meta-regression analysis

- To evaluate the relationship of covariates on AF recurrence in patients with CPAP use.

- Study duration
- Body mass index
- Hypertension
- Coronary artery disease
- Anti-arrhythmic drug use
- Percentage of patients with non paroxysmal AF
- Left ventricular ejection fraction

- Patient age
- Male gender
- Diabetes mellitus
- Left atrial dimension
362 potentially relevant studies identified

150 articles retrieved

66 studies retrieved

6 studies included in final analysis

212 articles excluded
   62 duplicates
   82 not sleep apnea patients
   63 irrelevant
   5 expert consensuses

84 articles excluded
   44 Review articles, Editorials, commentaries, Letters
   36 Non human studies
   4 Abstracts only

60 studies excluded
   26 did not meet inclusion criteria
   8 Studies with different study population
   5 Outcome of interests not reported
   9 Insufficient data for inclusion
   12 Non English study
## Characteristics of the included trial

<table>
<thead>
<tr>
<th>Study No.</th>
<th>Authors</th>
<th>Year</th>
<th>Country</th>
<th>Journal published</th>
<th>Baseline patient characteristics in addition to OSA</th>
<th>AF ablation type</th>
<th>Study Duration (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Fein et.al</td>
<td>2013</td>
<td>US</td>
<td>JACC</td>
<td>PVI between 2007 and 2010,</td>
<td>PVI</td>
<td>12</td>
</tr>
<tr>
<td>2</td>
<td>Patel et.al</td>
<td>2010</td>
<td>US</td>
<td>Circulation</td>
<td>patients underwent PVAI</td>
<td>PVI</td>
<td>32</td>
</tr>
<tr>
<td>3</td>
<td>Naruse et.al</td>
<td>2013</td>
<td>Japan</td>
<td>Heart Rhythm</td>
<td>PVI for drug refractory AF.</td>
<td>PVI</td>
<td>18.8</td>
</tr>
<tr>
<td>4</td>
<td>Neilan et.al</td>
<td>2013</td>
<td>US</td>
<td>J Am Heart Assoc.</td>
<td>Patients undergoing PVI</td>
<td>PVI</td>
<td>42</td>
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<tr>
<td>5</td>
<td>Kanagala et. al</td>
<td>2003</td>
<td>US</td>
<td>Circulation</td>
<td>AF/atrial flutter referred for DC cardioversion.</td>
<td>NO PVI</td>
<td>12</td>
</tr>
<tr>
<td>6</td>
<td>Bazan et al.</td>
<td>2013</td>
<td>Spain</td>
<td>Chest</td>
<td>Aflutter/Fib undergoing CTI ablation</td>
<td>NO PVI</td>
<td>12</td>
</tr>
</tbody>
</table>
### Included studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Total patients</th>
<th>CPAP users</th>
<th>AF recurrence (CPAP users)</th>
<th>Recurrence rates (%) CPAP users</th>
<th>CPAP nonusers</th>
<th>AF recurrence (CPAP non users)</th>
<th>Recurrence rates (%) CPAP nonusers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fein et.al</td>
<td>62</td>
<td>32</td>
<td>9</td>
<td>28</td>
<td>30</td>
<td>19</td>
<td>63</td>
</tr>
<tr>
<td>Patel et.al</td>
<td>640</td>
<td>315</td>
<td>105</td>
<td>33</td>
<td>325</td>
<td>178</td>
<td>55</td>
</tr>
<tr>
<td>Naruse et.al</td>
<td>116</td>
<td>82</td>
<td>25</td>
<td>30</td>
<td>34</td>
<td>18</td>
<td>52</td>
</tr>
<tr>
<td>Neilan et.al</td>
<td>142</td>
<td>71</td>
<td>25</td>
<td>35</td>
<td>71</td>
<td>48</td>
<td>68</td>
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<tr>
<td>Kanagala et. al</td>
<td>39</td>
<td>12</td>
<td>5</td>
<td>41</td>
<td>27</td>
<td>22</td>
<td>81</td>
</tr>
<tr>
<td>Bazan et. al</td>
<td>56</td>
<td>27</td>
<td>8</td>
<td>30</td>
<td>29</td>
<td>13</td>
<td>45</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>1025</strong></td>
<td><strong>522</strong></td>
<td><strong>176</strong></td>
<td><strong>33</strong></td>
<td><strong>503</strong></td>
<td><strong>292</strong></td>
<td><strong>58</strong></td>
</tr>
</tbody>
</table>
Effect of use of CPAP on AF recurrence

• CPAP use in patients with OSA was associated with a reduced relative risk of AF recurrence in comparison to non-users

• RR: 0.58; 95% confidence interval (CI): 0.50-0.66; p value < 0.001
Effect of use of CPAP on AF recurrence

<table>
<thead>
<tr>
<th>Study</th>
<th>RR (95% CI)</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fein et.al</td>
<td>0.44 (0.24, 0.82)</td>
<td>6.66</td>
</tr>
<tr>
<td>Patel et.al</td>
<td>0.61 (0.51, 0.73)</td>
<td>59.53</td>
</tr>
<tr>
<td>Naruse et.al</td>
<td>0.58 (0.37, 0.91)</td>
<td>8.65</td>
</tr>
<tr>
<td>Neilan et.al</td>
<td>0.52 (0.37, 0.74)</td>
<td>16.31</td>
</tr>
<tr>
<td>Kanagala et.al</td>
<td>0.51 (0.26, 1.02)</td>
<td>4.60</td>
</tr>
<tr>
<td>Bazan et.al</td>
<td>0.66 (0.33, 1.34)</td>
<td>4.26</td>
</tr>
<tr>
<td>Overall (I-squared = 0.0%, p = 0.902)</td>
<td>0.58 (0.50, 0.67)</td>
<td>100.00</td>
</tr>
</tbody>
</table>

The graph shows the effect of CPAP use on AF recurrence with the overall RR being 0.58 (0.50, 0.67), indicating a significant reduction in AF recurrence when using CPAP.
Publication bias; Heterogeneity (Eggers p = 0.2)
Sensitivity analysis

• 4 studies - CPAP use following PVI - reduced risk of AF recurrence; **RR: 0.58; 95% CI: 0.50-0.67; p value < 0.001**

• 2 studies - CPAP with no PVI - reduced risk for AF recurrence; **RR: 0.58; 95% CI: 0.36-0.96, p value < 0.001**
### Sensitivity analysis based on pulmonary vein isolation

<table>
<thead>
<tr>
<th>Study</th>
<th>RR (95% CI)</th>
<th>Weight %</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Post AF ablation</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fein et.al</td>
<td>0.44 (0.24, 0.82)</td>
<td>6.66</td>
</tr>
<tr>
<td>Patel et.al</td>
<td>0.61 (0.51, 0.73)</td>
<td>59.53</td>
</tr>
<tr>
<td>Naruse et.al</td>
<td>0.58 (0.37, 0.91)</td>
<td>8.65</td>
</tr>
<tr>
<td>Neilan et.al</td>
<td>0.52 (0.37, 0.74)</td>
<td>16.31</td>
</tr>
<tr>
<td>Subtotal (I-squared = 0.0%, p = 0.721)</td>
<td>0.58 (0.50, 0.67)</td>
<td>91.14</td>
</tr>
<tr>
<td><strong>2</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kanagala et.al</td>
<td>0.51 (0.26, 1.02)</td>
<td>4.60</td>
</tr>
<tr>
<td>Bazan et.al</td>
<td>0.66 (0.33, 1.34)</td>
<td>4.26</td>
</tr>
<tr>
<td>Subtotal (I-squared = 0.0%, p = 0.611)</td>
<td>0.58 (0.36, 0.96)</td>
<td>8.86</td>
</tr>
<tr>
<td><strong>Overall (I-squared = 0.0%, p = 0.902)</strong></td>
<td>0.58 (0.50, 0.67)</td>
<td>100.00</td>
</tr>
</tbody>
</table>
Univariate Meta-regression analysis to evaluate effect of patient factors on outcomes

<table>
<thead>
<tr>
<th>Potential Modifier</th>
<th>Studies</th>
<th>Regression Coefficient</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study duration</td>
<td>6</td>
<td>0.001</td>
<td>0.874</td>
</tr>
<tr>
<td>Patient age</td>
<td>6</td>
<td>-0.008</td>
<td>0.558</td>
</tr>
<tr>
<td>Male gender</td>
<td>6</td>
<td>-0.011</td>
<td>0.46</td>
</tr>
<tr>
<td>BMI</td>
<td>5</td>
<td>-0.001</td>
<td>0.96</td>
</tr>
<tr>
<td>Persistent AF</td>
<td>4</td>
<td>-0.01</td>
<td>0.54</td>
</tr>
<tr>
<td>Hypertension</td>
<td>6</td>
<td>-0.006</td>
<td>0.5</td>
</tr>
</tbody>
</table>
Univariate Meta-regression analysis to evaluate effect of patient factors on outcomes

<table>
<thead>
<tr>
<th>Potential Modifier</th>
<th>Studies</th>
<th>Regression Coefficient</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetes mellitus</td>
<td>5</td>
<td>-0.006</td>
<td>0.6</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>4</td>
<td>-0.003</td>
<td>0.85</td>
</tr>
<tr>
<td>LVEF</td>
<td>6</td>
<td>-0.007</td>
<td>0.61</td>
</tr>
<tr>
<td>Left atrial dimension</td>
<td>5</td>
<td>-0.01</td>
<td>0.48</td>
</tr>
<tr>
<td>Antiarrhythmic drug use</td>
<td>5</td>
<td>-0.003</td>
<td>0.34</td>
</tr>
</tbody>
</table>
Conclusion

• 42% relative risk reduction of recurrent atrial fibrillation amongst patients with OSA who use CPAP when compared to non users.

• No significant heterogeneity or publication bias in the results.
Conclusion

• Consistent effect of CPAP use in relative risk reduction of AF recurrence across patient groups irrespective of PVI.

• Univariate meta-regression analyses showed no influence of study duration or patient factors on the outcomes noted.
DISCUSSION

- Patients with AF should be screened for OSA.
- Use of CPAP should be strongly advocated in patients with OSA, irrespective of whether or not they undergo PVI.
- Additional aggressive Lifestyle Modification has a significant impact on recurrence.
- Non- Pulmonary vein triggers might be a contributor for AF in these patients and need further evaluation.
Total Sleep Solution

1. PATIENT SCREENING for OSA & REFERRAL to DIAGNOSIS TEST
   - Cardiologist

2. SLEEP STUDY
   - Dispatch WatchPAT device to patients + upload data

3. STUDY INTERPRETATION
   - OSA Diagnosis
   - Prescription for treatment (CPAP)

4. TREATMENT
   - Equipment provision & setup, patient education, compliance monitoring, processing reimbursement claims

Flow of patients

Stakeholders across the OSA value chain

Referring Physician

IDTF/Hospital-Based Lab

Board certified sleep physician (IDTF/hospital-based lab, independent)

Durable Medical Equipment (DME)

PATIENT MANAGEMENT INTEGRATION
DME/Sleep physician share relevant information with the referring MD: results, compliance data etc.
Patient Experience

Coach guides patient through the initial setup process on the phone.

- Coach contacts patient before the patient receives package and schedules the setup call.

- Patient feels informed about how to prepare for therapy and has an expectation of how to setup with the coach.

- Patient can intuitively understand instructions and get the device running in minutes.