OSA and Atrial Fibrillation - Rationale for Screening

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Outline

- Overview of epidemiology and cardiovascular consequences of sleep apnea
- Mechanistic basis of the relationship between sleep apnea and atrial fibrillation
- Role of sleep apnea in the management of atrial fibrillation
The Occurrence of Sleep-Disordered Breathing among Middle-Aged Adults
The Wisconsin Sleep Cohort, NEJM 1993

<table>
<thead>
<tr>
<th>AGE (YR)</th>
<th>WOMEN</th>
<th>MEN</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>APNEA–HYPOPNEA SCORE</td>
<td>APNEA–HYPOPNEA SCORE</td>
</tr>
<tr>
<td></td>
<td>≥5</td>
<td>≥10</td>
</tr>
<tr>
<td>30–39</td>
<td>6.5 (1.4–11)</td>
<td>4.9 (0.6–9.8)</td>
</tr>
<tr>
<td>40–49</td>
<td>8.7 (4.2–13)</td>
<td>4.9 (1.7–8.1)</td>
</tr>
<tr>
<td>50–60</td>
<td>16 (5.2–26)</td>
<td>5.9 (0.0–12)</td>
</tr>
<tr>
<td>30–60*</td>
<td>9.0 (5.6–12)</td>
<td>5.0 (2.4–7.8)</td>
</tr>
</tbody>
</table>

*Values are adjusted to the age distribution of the survey population.

Risk Factors for OSA

- **Obesity**
  - (Kripke DF, Sleep 1997; Tsai WH, AJRCCM 2003)
- **Middle and advanced age**
  - (Young NEJM 1993)
- **Male sex (until age 50)**
- **Postmenopausal state**
  - (Young T, AJRCCM 2003)
- **Hypertension**
  - (Chobanian AB, JAMA 2003)
- **Heart failure**
  - (Javaheri 1999; Oldenburg 2007)
- **Upper airway anatomic obstruction**
- **African-American, Asian, or Hispanic ethnicity**
  - (Kripke DF, Sleep 1997; Young T, Arch Intern Med 2003)
**, Cardiovascular Consequences of SDB**

- Oxygen Saturation
- Flow
- Respiratory Effort
- Blood Pressure
- Sympathetic Nerve Activity

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**Occurrence of AF in OSA Patients**

*Retrospective analysis of Olmsted County*

Cumulative frequency curves for incident atrial fibrillation (AF) for subjects < 65 years of age with and without obstructive sleep apnea (OSA) during an average 4.7 years of follow-up. \( p = 0.002 \)

Risk of Incident AF

<table>
<thead>
<tr>
<th></th>
<th>HR</th>
<th>95% CI</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>&lt; 65 years old</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (per 10 years)</td>
<td>2.04</td>
<td>1.48 - 2.80</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Male gender</td>
<td>2.66</td>
<td>1.33 - 5.30</td>
<td>0.006</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>2.66</td>
<td>1.46 - 4.83</td>
<td>0.001</td>
</tr>
<tr>
<td><strong>Body mass index</strong></td>
<td>1.07</td>
<td>1.05 - 1.10</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>(per 1 kg/m²)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Decrease in <strong>nocturnal oxygen saturation</strong> (per -1%)*</td>
<td>3.29</td>
<td>1.35 - 8.04</td>
<td>0.009</td>
</tr>
<tr>
<td><strong>≥ 65 yrs old</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heart failure</td>
<td>7.68</td>
<td>4.32 - 13.66</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

*For a 0.5-U change in the logarithm of the difference between awake oxygen saturation and mean nocturnal oxygen saturation.


Intrathoracic Pressure Swings Induced by Simulated Obstructive Apnea promote Arrhythmias in paroxysmal AF

- Patients with an ECG documented history of PAF within the last 12 months; and had sinus rhythm at the time of ECG
- Exclusion criteria: Therapy with amiodarone or dronedarone, severe structural heart disease, history of AF ablation
- 46 patients from 263 eligible

Participants performed:
1) Mueller maneuver (MM);
2) Inspiration against partial inspiratory threshold (ITH);
3) End expiratory breath hold (AP)- central apnea; and
4) Normal breathing (NB)

All Patients underwent sleep studies for OSA

Intrathoracic Pressure Swings Induced by Simulated Obstructive Apnea promote Arrhythmias in paroxysmal AF

![Graph showing the number of subjects with various types of arrhythmias under different conditions (NB, AP, ITH, MM). The graph indicates that Intrathoracic Pressure Swings lead to higher occurrences of arrhythmias, specifically atrial premature beats, ventricular premature beats, non-sustained atrial arrhythmia, and atrial fibrillation.](image)


Intrathoracic Pressure Swings Induced by Simulated Obstructive Apnea promote Arrhythmias in paroxysmal AF

![Graph showing the number of events (e.g., arrhythmias) under different conditions (NB, AP, ITH, MM). The graph indicates that Intrathoracic Pressure Swings lead to a higher number of events, specifically atrial premature beats and ventricular premature beats.](image)

Atrial Fibrillation Promotion With Long-Term Repetitive Obstructive Sleep Apnea in a Rat Model

Effect of Acute OSA on LA Diameter
Comparisons by 2-way repeated measures analysis of variance/Bonferroni-adjusted Student t tests. *p<0.05, **p<0.001 vs. Open. LA = left atrial; OSA = obstructive sleep apnea.
Examples of atrial fibrillation (AF) induction attempts in (A) an open airway rat and (B) an OSA rat, respectively. (C) AF duration. (D) AF inducibility. (E) AF inducibility during acute OSA.

Atrial Fibrillation Promotion With Long-Term Repetitive Obstructive Sleep Apnea in a Rat Model

J Am Coll Cardiol 2014;64:2013–23

Proposed Mechanisms by Which OSA Leads to AF

Decreased Efficacy of AAD for AF in untreated OSA Patients

- 61 patients with OSA & AF treated with Class I / III AAD
- Response to AAD: ≥75% reduction of AF burden on the same AAD for at least 6 months
- Results:
  - 30 patients (49%) were considered “Responders” to AAD
  - Non-response to AAD associated with OSA
    - 52% with severe OSA
    - 23% with mild OSA
    - 25% without OSA
    - Higher AHI (34 episodes /hour)
Low Efficacy of Atrial fibrillation Ablation in severe OSA Patients

Freedom from arrhythmia recurrences after a single ablation procedure.
Matiello et al Europace (2010))

Low Efficacy of Atrial fibrillation Ablation in severe OSA Patients

Freedom from arrhythmia recurrences including the performance of second ablation.
Matiello et al Europace (2010))
Treatment of Obstructive Sleep Apnea Reduces the Risk of Atrial Fibrillation Recurrence After Catheter Ablation

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.

Kaplan-Meier Survival Curves According to Treatment Group

Atrial Fibrillation and OSA

Prevalence of OSA in patients with AF exceeds 50%
- OSA causes AF via one of the following mechanisms:
  - Atrial stretch and remodeling
  - Sympathetic activation
  - Cardiac oxidative stress
- Treatment of AF in AF-OSA patients is only partially effective if OSA is not addressed
- Treatment of OSA is associated with improved control of AF

Home sleep testing
Common CPAP Interfaces: Masks

- Nasal
- Nasal Pillows
- Hybrid
- Full Face
Low Efficacy of Atrial fibrillation Ablation in severe OSA Patients
Matiello et al Europace (2010))

<table>
<thead>
<tr>
<th></th>
<th>HR (95% CI)</th>
<th>P-value</th>
</tr>
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<tbody>
<tr>
<td>Left atrial diameter</td>
<td>1.046 (1.005–1.089)</td>
<td>0.029</td>
</tr>
<tr>
<td>OSA group</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low risk for OSA</td>
<td>1 (—)</td>
<td>—</td>
</tr>
<tr>
<td>Non-severe OSA</td>
<td>1.574 (0.826–3.000)</td>
<td>0.168</td>
</tr>
<tr>
<td>Severe OSA</td>
<td>1.870 (1.106–3.161)</td>
<td>0.019</td>
</tr>
</tbody>
</table>

Physiological effects of SDB

- Respiratory events with OSA and CSA produce similar responses

- Intermittent hypoxia stimulates the carotid baroreceptors resulting in sympathetic nerve activation
  - Peripheral vasoconstriction
  - Enhanced renal sympathetic activity
  - Pattern of “nondipping” blood pressure at night
Atrial Fibrillation in Acute Obstructive Sleep Apnea: Autonomic Nervous Mechanism and Modulation-Dog Model

Clinical manifestations of SDB
Indications for testing

- American college of physicians
  - Sleep study for patients with unexplained daytime sleepiness
  - Sleepiness questionnaires, such as Epworth sleepiness scale, help in assessing severity of OSA
  - Polysomnography for diagnosis, can use portable monitors in patients without serious comorbidities as an alternative

Polysomnography

Courtesy of Drs. Khayat and Pleister
Medical Treatments for OSA

- Weight loss
- Therapy for nasal congestion (allergic rhinitis)
- Lateral decubitus sleeping position (limited use)
- Avoidance of alcohol
- Smoking cessation
- Avoidance of muscle relaxants
- Avoidance of sleep deprivation

Medical Therapies for OSA: Conclusions

- There are no medical therapies that are indicated as primary treatment for OSAS.
- Overweight and obese patients should be counseled on weight loss, in addition to a primary therapy.
- Nasal steroids and non-sedating antihistamines may be useful adjuncts.
Questions about OSA that should be included in routine health maintenance evaluations

- Is the patient obese?
- Is the patient retrognathic
- Does the patient complain of daytime sleepiness?
- Does the patient snore?
- Does the patient have hypertension?
Compliance With CPAP

- Definition of compliance
  - > 4 hours/night on 70% of nights

- Compliance probably about 50 - 60%
  - Patients overestimate nightly use.

- Compliance patterns are determined early.

- Few clear predictors of compliance:
  - Daytime sleepiness
  - More severe disease

Mandibular Repositioning Appliance

Without MAD

With MAD
Association Between Treated and Untreated Obstructive Sleep Apnea and Risk of Hypertension

Log-rank P < .001

Cumulative Incidence, %

Follow-up Time, y

No. at risk
Severe OSA 199 184 141 119 62 37
Moderate OSA 258 222 202 162 114 67
Mild OSA 298 289 260 194 127 59
Without OSA 310 306 269 211 152 72
Provent

Airing
Surgery

- Surgical treatment may be offered as a second line therapy to those with mild to moderate disease.

- May work best when there is a clear anatomic obstruction.

- Patients should be educated that it is not a guaranteed cure.

Atrial Fibrillation in Acute Obstructive Sleep Apnea: Autonomic Nervous Mechanism and Modulation

The expressions levels of c-fos and NGF in the control, OSA, and LL-TS + OSA groups.

Lilei Yu et al. J Am Heart Assoc 2017;6:e006264
Inspire® upper airway stimulation

Association Between Severe OSA (AHI >30) and Arrhythmias in Sleep Heart Health Study  
(Mehra et al, AJRCCM, doi:10.1164/rccm.200509-1442OC)

<table>
<thead>
<tr>
<th>Arrhythmia Type</th>
<th>Unadjusted Odds Ratio</th>
<th>Odds Ratio* (95% CI) Adjusted for Age, Sex, BMI</th>
<th>Odds Ratio* (95% CI) Adjusted for Age, Sex, BMI, CHD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-sustained ventricular tachycardia</td>
<td>4.64 (1.48-14.57)</td>
<td>3.72 (1.13-12.2)</td>
<td>3.40 (1.03-11.2)</td>
</tr>
<tr>
<td>Complex ventricular ectopy</td>
<td>1.96 (1.28-3.00)</td>
<td>1.81 (1.16-2.84)</td>
<td>1.74 (1.11-2.74)</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>5.66 (1.56-20.52)</td>
<td>3.85 (1.00-14.93)</td>
<td>4.02 (1.03-15.74)</td>
</tr>
</tbody>
</table>

BMI=body mass index; CHD=coronary heart disease  
*Results of logistic regression analysis with SDB as the exposure; N=338 without SDB, N=228 with SDB
Intrathoracic Pressure Swings Induced by Simulated Obstructive Apnea promote Arrhythmias in paroxysmal AF

This acute study of OSA-induced AF found that 1 hour of repetitive obstructive respiratory events significantly shortened the ERP and increased the ΣWOV on the atrium and pulmonary veins, which demonstrated that OSA facilitated AF inducibility. Several lines of evidence indicated that the profibrillatory effects of OSA were mediated by hyperactivity of the intrinsic and extrinsic CANS. First, the frequency and amplitude of the neural activity directly recorded from the SLGP (the intrinsic CANS), the LSG (the extrinsic CANS), and the left RSN (the extrinsic CANS) were markedly upregulated after 1 hour of simulated OSA. Second, OSA also increased the SLGP and LSG functions. Third, our data showed that the c-fos and NGF expression levels in the SLGP and the LSG were markedly upregulated in the OSA group. Consequently, we suggested that hyperactivity of the intrinsic and extrinsic CANS plays crucial roles in the process of OSA-induced AF. Another major finding of this study was that noninvasive autonomic nervous modulation, LL-TS, significantly prolonged ERP at all sites and decreased the ΣWOV, the neural activity and function of the SLGP and the LSG, the neural activity of the left RSN, and the c-fos and NGF expression levels in the SLGP and the LSG. This suggested that LL-TS is an alternative noninvasive treatment for OSA-induced AF by effectively inhibiting the hyperactivity of the intrinsic and extrinsic CANS.
Intrathoracic Pressure Swings Induced by Simulated Obstructive Apnea promote Arrhythmias in paroxysmal AF

Correlation (Pearson’s r ¼ 0.54, P ¼ 0.001) between LAESD and severity of OSA (AHI).
Atrial Fibrillation in Acute Obstructive Sleep Apnea: Autonomic Nervous Mechanism and Modulation

Study protocol (A) and changes in blood gases between the control group and the OSA group (n=6) (B). *P<0.05 vs the control group.

Changes in ERP and ΣWOV among the control, OSA, and LL-TS + OSA groups (n=6)
Atrial Fibrillation in Acute Obstructive Sleep Apnea: Autonomic Nervous Mechanism and Modulation

Changes in BP and norepinephrine plasma levels in the OSA (A), control (B), and LL-TS + OSA (C) groups (n=6). *P<0.05 vs the control group; #P<0.05 vs the OSA group.

Lilei Yu et al. J Am Heart Assoc 2017;6:e006264

Atrial Fibrillation in Acute Obstructive Sleep Apnea: Autonomic Nervous Mechanism and Modulation

Autonomic neural activity changes in the control, OSA, and LL-TS + OSA groups.

Lilei Yu et al. J Am Heart Assoc 2017;6:e006264
Treatment of OSA helps to prevent recurrence of AF post cardioversion


Atrial fibrillation (AF)
- Most common cardiac arrhythmia with increasing prevalence
- Hypertension, thyroid disease, coronary disease, cardiomyopathy and structural heart disease commonly associated with risk of developing AF

Relationship of Sympathetic Nerve Activity, BP and OSA

SNA: Microelectrode in sympathetic nerve fascicle of peroneal nerve

Incidence of AF Based on Severity of OSA and Obesity

Body mass index:
- < 25, normal weight
- 25 – 30, overweight
- > 30, obesity

Cumulative frequency of incidence(A) during an average 4.7 years of follow-up, based on interactions between (BMI) and AHI