Sleep Apnea and Non-PV Triggers:

KHRS 2017

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1. **[Atrial fibrillation and obstructive sleep apnea: a fortuitous association?].**
   Leszek A, Perrier A, Carballo S.
   PMID: 25438374
   Similar articles

2. **Obstructive sleep apnea and atrial fibrillation: understanding the connection.**
   Oza N, Baveja S, Khayat R, Houmsse M.
   PMID: 24731146
   Similar articles

3. **Obesity, Exercise, Obstructive Sleep Apnea, and Modifiable Atherosclerotic Cardiovascular Disease Risk Factors in Atrial Fibrillation.**
   Miller JD, Aronis KN, Chrispin J, Patil KD, Marine JE, Martin SS, Blaha MJ, Blumenthal RS, Calkins H.
   PMID: 26718677   Free Article
Sleep Apnea and AF:

Is the link real?

- Cause and effect relationship
- Co-travelers (shared risk factors)
Atrial Fibrillation and Sleep Apnea

1. Association between AF and OSA

2. Mechanistic relationship between AF and OSA

3. Substrate and triggers of AF in patients with OSA
   - Implication for therapy (screening, ablation)
Prevalence of AF in patients with OSA

Sleep Heart Health Study

• Prospective longitudinal cohort in 6,400 participants
• Aimed to assess arrhythmia prevalence in patients with SA
• All patients underwent sleep testing
• 228 individuals with severe SA were compared to 338 individuals without OSA

➢ Patients with SA had ~5 fold increased risk of AF
➢ Adjusted risk (Age, BMI, CAD) of 4.02 [1.03–15.74]; 95%CI)

EJ Benjamin, Am J Respir Crit Care Med 2006
Incidência de AF em pacientes com OSA

Registro de estudo de sono de Olmsted County

3500 indivíduos sem AF na base linearmente seguidos.

- OSA é um preditor independente para novos episódios de AF
- HR de 2,18

Gami AS, JACC 2007
The prevalence of OSA in patients with AF

Unknown (10-70%) based on retrospective studies

Prospective evaluation (unpublished data)

- Prospective Multicenter study (Boston, Texas)
  - Sleep study in all patients refereed for AF ablation
  - 125 consecutive patients with paroxysmal and persistent AF without previous diagnosis of OSA
  - Home sleep testing
The prevalence of OSA in patients with AF

Prospective evaluation (unpublished data)

- Prospective Multicenter study (Boston, Texas)
  - Sleep study in all patients referred for AF ablation
  - 125 consecutive patients with paroxysmal and persistent AF without previous diagnosis of OSA

- 45% have sleep apnea
- 25% have ≥moderate OSA
Mechanistic Relationship

1. Negative intra-thoracic pressure
2. Autonomic imbalance
3. Structural remodeling

- Acute effects
- Chronic effects
Acute effects of OSA are mediated by changes in intrathoracic Pressures

Linz D, Heart Rhythm 2011

Mechanistic Relationship
Mechanistic Relationship

Effect of vagal blockade on AERP and AF inducibility

Linz D, Heart Rhythm 2011
Mechanistic Relationship

Chronic effects mediated by remodeling of the atria

Iwasaki Yu-Ki, JACC 2014
Mechanistic Relationship

OBSTRUCTIVE SLEEP APNEA (OSA)
- Negative intrathoracic pressure changes
- Autonomic nervous-system activation

ACUTE OSA
- Acute left atrial dilation/stretch
- Atrial fibrillation promotion

CHRONIC REPETITIVE OSA (months to years)
- CHRONIC CARDIAC REMODELING:
  - LV dilation
  - LV hypertrophy
  - Diastolic dysfunction

  - LA dilatation
  - LA stretch
  - p-38 phosphorylation
  - LA fibrosis
  - LA connexin-43 remodeling

  - Connexin-43 lateralization
  - Reduced connexin-43 expression

Atrial fibrillation (AF) substrate

Atrial fibrillation threshold

Increased peaks in AF risk caused by individual OSA-episodes

Substrate due to repeated OSA-episodes

Increasing AF risk

Increasing time (months to years)
The Effect of OSA on AF Recurrence
Patients with untreated OSA have a greater risk of AF recurrence after DCCV.
Patients with OSA have a greater risk of AF recurrence after PVI

Ng CY, Am J Card 2011
OSA and AF Recurrence

- OSA is common in patients with AF
- AF recurrence is higher in patients with OSA

Can treatment of OSA improve PVI outcome?
Effect of CPAP on PVI outcome

- Retrospective study design
- Paroxysmal and persistent
- PVI ± CTI (no other lines)

426 Pts for initial PVI

386 Pts for initial PVI

62 Pts with confirmed OSA

40 pts excluded due to insufficient follow-up data

32 CPAP users pts PVI(+) OSA(+) CPAP(+)

30 Non CPAP user pts PVI(+) OSA(+) CPAP (-)

30 Non-OSA pts PVI(+) OSA(-)

22 OSA pts Managed medically PVI(-) OSA(+) CPAP (+)

Anter E, JACC 2013
# Effect of CPAP on PVI outcome

<table>
<thead>
<tr>
<th>Variable</th>
<th>PVI (+) / OSA (+) / CPAP (+) (n=32)</th>
<th>PVI (+) / OSA (-) / CPAP (-) (n=30)</th>
<th>PVI (+) / OSA (-) / CPAP (-) (n=30)</th>
<th>PVI (-) / OSA (+) / CPAP (+) (n=22)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years), M ±SE</td>
<td>56.8 ± 1.2</td>
<td>58.5 ± 1.4</td>
<td>58.5 ± 1.4</td>
<td>55.0 ± 1.6</td>
<td>0.27</td>
</tr>
<tr>
<td>Gender n, (% Male)</td>
<td>23 (76.7)</td>
<td>23 (71.9)</td>
<td>23 (71.9)</td>
<td>16 (72.7)</td>
<td>0.96</td>
</tr>
<tr>
<td>BMI (kg/m2), M±SE</td>
<td>28.77 ± 0.45</td>
<td>29.58 ± 0.40</td>
<td>29.58 ± 0.40</td>
<td>30.69 ± 0.99</td>
<td>0.11</td>
</tr>
<tr>
<td>Persistent AF n, (%)</td>
<td>17 (56.7)</td>
<td>16 (50.0)</td>
<td>16 (50.0)</td>
<td>12 (54.5)</td>
<td>0.95</td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>21 (70.0)</td>
<td>21 (65.6)</td>
<td>21 (65.6)</td>
<td>15 (68.2)</td>
<td>0.81</td>
</tr>
<tr>
<td>Diabetes, n (%)</td>
<td>6 (20.0)</td>
<td>6 (18.6)</td>
<td>6 (18.6)</td>
<td>4 (18.2)</td>
<td>1.00</td>
</tr>
<tr>
<td>CAD, n (%)</td>
<td>8 (26.7)</td>
<td>6 (18.6)</td>
<td>6 (18.6)</td>
<td>5 (22.7)</td>
<td>0.88</td>
</tr>
<tr>
<td>LVEF (%), M±SE</td>
<td>60.2 ± 1.5</td>
<td>59.5 ± 0.94</td>
<td>59.5 ± 0.94</td>
<td>59.3 ± 2.0</td>
<td>0.96</td>
</tr>
<tr>
<td>LAD(mm), M±SE</td>
<td>54.5 ± 0.91</td>
<td>55.9 ± 1.1</td>
<td>55.9 ± 1.1</td>
<td>-----</td>
<td>0.51*</td>
</tr>
<tr>
<td># AAD, M±SE</td>
<td>1.47 ± 0.12</td>
<td>1.34 ± 0.10</td>
<td>1.34 ± 0.10</td>
<td>1.00 ± 0.15</td>
<td>0.07</td>
</tr>
</tbody>
</table>
Effect of CPAP on PVI outcome

Results:

- Freedom from AF after PVI was higher in CPAP users compared with the CPAP non-users: 71.9% vs. 36.7%; p=0.01

- Patients with treated OSA had similar outcome to that of patients without OSA (p=0.94)

- Patients with untreated OSA who underwent PVI had outcome that was similar to that of patients who did not undergo PVI at all (~40%; p=0.56).
Effect of CPAP on PVI outcome
Effect of CPAP on PVI outcome

**FIGURE 3** AF Recurrence in Users Versus Nonusers of CPAP in 2 Groups of Patients With OSA: PVI and Non-PVI Groups

<table>
<thead>
<tr>
<th>Study ID</th>
<th>RR (95% CI)</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>No PVI</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kanagala et al</td>
<td>0.51 (0.26, 1.02)</td>
<td>4.43</td>
</tr>
<tr>
<td>Bazan et al</td>
<td>0.66 (0.33, 1.34)</td>
<td>4.10</td>
</tr>
<tr>
<td>Subtotal (I-squared = 0.0%, p = 0.611)</td>
<td>0.58 (0.36, 0.96)</td>
<td>8.53</td>
</tr>
<tr>
<td>Post PVI</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Jongnarangsin et al</td>
<td>0.70 (0.40, 1.24)</td>
<td>3.68</td>
</tr>
<tr>
<td>Patel et al</td>
<td>0.61 (0.51, 0.73)</td>
<td>57.34</td>
</tr>
<tr>
<td>Fein et al</td>
<td>0.44 (0.24, 0.82)</td>
<td>6.42</td>
</tr>
<tr>
<td>Naruse et al</td>
<td>0.58 (0.37, 0.91)</td>
<td>8.33</td>
</tr>
<tr>
<td>Neilan et al</td>
<td>0.52 (0.37, 0.74)</td>
<td>15.71</td>
</tr>
<tr>
<td>Subtotal (I-squared = 0.0%, p = 0.782)</td>
<td>0.58 (0.50, 0.67)</td>
<td>91.47</td>
</tr>
<tr>
<td>Overall (I-squared = 0.0%, p = 0.919)</td>
<td>0.58 (0.51, 0.67)</td>
<td>100.00</td>
</tr>
</tbody>
</table>
Atrial Substrate in patients with PAF and OSA
Atrial Substrate and Triggers of Paroxysmal Atrial Fibrillation in Patients with Obstructive Sleep Apnea

Elad Anter, MD, Luigi Di Biase, MD, PhD, Eran Leshem, MD, Fernando M. Contreras-Valdes, MD, Juan Viles-Gonzales, MD, Alfred E. Buxton, MD, Guy Kulbak, MD, Rim N. Halaby MD, Robert J. Thomas, MD, MMSc, Andrea Natale, MD, Mark E. Josephson, MD

- Prospective, multi-center study design
- N= 172 patients
- Aimed to characterize the atrial substrate in patients with PAF and OSA:
  - Voltage distribution, electrograms, and conduction properties
  - Frequency and distribution of AF triggers
  - Role of extra-PV triggers on long-term arrhythmia control

Accepted for publication Circulation A&E 2017
Atrial Substrate and Triggers of Paroxysmal Atrial Fibrillation in Patients with Obstructive Sleep Apnea

Patient population:

- Patients with symptomatic PAF without known sleep apnea presenting for first PVI
- All patients underwent sleep study before (≤ 30d) or after (≤ 90d) the ablation procedure
- In attempt to evaluate the atrial substrate specific for sleep apnea, patients with CAD, CHF, significant valvular abnormality, untreated hypertension or diabetes were excluded
- To evaluate the baseline atrial substrate and avoid measurements related to acute electrical remodeling, only patients presented in sinus rhythm were included
Atrial Substrate and Triggers of Paroxysmal Atrial Fibrillation in Patients with Obstructive Sleep Apnea

172 patients were enrolled to the study

- Insufficient accessibility for sleep testing
  - Non-Compliance

133 completed sleep study

- AF/AT precluding mapping

118 completed mapping study

110 adhered to F/U period of ≥12 months

- 43 without OSA apnea-hypopnea index <5
- 43 with OSA apnea-hypopnea index ≥15
Atrial Substrate in patients with PAF and OSA

Methods:

- RA mapping was performed during pCS pacing (600-800ms)
- LA mapping was performed during dCS pacing
- Triggers of AF were determined before and after PVI
  
  AF triggers defined as: APC’s initiating sustained AF

- Isoproterenol infusion with or w/o adenosine, CV during isoproterenol
- Trigger localization was estimated based on the earliest activation site, and pattern of activation from multiple left and right atrial catheters
- Triggers were ablated, followed by repeated provocation until elimination
- Follow-up duration of 12 months
Atrial Substrate and Triggers of Paroxysmal Atrial Fibrillation in Patients with Obstructive Sleep Apnea

172 patients were enrolled to the study

133 completed sleep study

118 completed mapping study

110 adhered to 1 F/U period of 12 months

43 [PVI] [OSA] [Triggers]

43 with OSA [PVI] [-OSA] [Triggers]

50 with OSA [PVI] [OSA] [-Triggers]

48 without OSA [-PVI] [OSA] [-Triggers]
Atrial Substrate in patients with PAF without OSA

Right Atrium

Left Atrium
Atrial Substrate in patients with PAF and OSA
Atrial Substrate in patients with PAF and OSA

Biatrial Voltage Map

Right Atrial Septum EGM

Left Atrial Septum EGM
Triggers of AF in patients with OSA

Baseline

<table>
<thead>
<tr>
<th></th>
<th>Non-OSA</th>
<th>OSA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-inducible</td>
<td>10/43</td>
<td>8/43</td>
</tr>
<tr>
<td>PV trigger</td>
<td>28/43</td>
<td>27/43</td>
</tr>
<tr>
<td>Non-PV trigger</td>
<td>5/43</td>
<td>8/43</td>
</tr>
</tbody>
</table>

Post PVI

<table>
<thead>
<tr>
<th></th>
<th>Non-OSA</th>
<th>OSA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-inducible</td>
<td>5/43</td>
<td>18/43</td>
</tr>
<tr>
<td>PV trigger</td>
<td>5/43</td>
<td>11.6%</td>
</tr>
<tr>
<td>Non-PV trigger</td>
<td>5/43</td>
<td>41.8%</td>
</tr>
</tbody>
</table>

P=0.003
Scar as anchor for rotational activity in OSA
Clinical outcome of Extra-PV trigger ablation

Arrhythmia-Free Survival vs. Follow-up, months

(+) OSA (+) PVI (+) Trigger vs. (+) OSA (+) PVI (-) Trigger: log-rank p=0.03
(-) OSA (+) PVI (+) Trigger vs. (-) OSA (+) PVI (-) Trigger: log-rank p=0.64
Summary and Future directions

- Growing body of evidence implicating sleep apnea in atrial remodeling and promotion of the AF substrate

- Changes are both substrate and trigger-based

- PAF in patients with OSA is often associated with areas of low voltage and slow conduction, predominantly affecting the left anterior septum

- These zones are a common source of extra-PV triggers and localized circuits (rotors) of AF

- Ablation of these low voltage zones is associated with improved clinical outcome in patients with PAF and OSA.

- PVI alone (even in patients with PAF) may not be sufficient, and at the least requires evaluation of extra PV triggers
Summary and Future directions

However...

- Similar phenotype can be observed in patients without sleep apnea (often in persistent AF), such that sleep apnea may act as a facilitator rather than a cause.

- In the meantime, patients with AF should at least be screened for OSA as part of a wider approach for cardiovascular and AF risk reduction (i.e., ARREST-AF)

- Data on AF and OSA are largely observational. There is an urgent need for randomized trails to evaluate the impact of sleep apnea and its therapy on cardiovascular risk reduction

- Prevention and early diagnosis may be better than treatment of advanced disease (it may explain discrepancies in respond to Rx)
SLA-AF

SLeep Apnea Management after AF ablation

- Prospective randomized controlled multicenter study in 600 pts
- Patients with AF referred for ablation with a positive Watchpat sleep study (AHI ≥15)
- 1:1 randomization to either to catheter ablation (control arm) or catheter ablation + OSA therapy (treatment arm).
- 1st end-point: single procedure freedom from AF off AADs at 1y
- 2nd end-point: changes in endothelial function, and atrial size 1yr

Elad Anter, Vivek Reddy
The BIDMC Approach

CardioVascular Institute at Beth Israel Deaconess Medical Center

Cardiology – Sleep Medicine Program

Welcome
Our multidisciplinary Cardiology – Sleep Medicine Program offers people with atrial fibrillation screening for sleep apnea as part of their cardiology care. Follow-up care is provided by our sleep medicine team.

What is sleep apnea?
A common disorder in which pauses in breathing or shallow breathing disrupts sleep.

What is atrial fibrillation?
An irregular heartbeat caused by disorganized beating of the upper heart chambers. Though rarely life-threatening, it can cause stroke and increase the risk of heart failure.

What is an ablation?
A procedure in which an electrophysiologist uses energy (usually radiofrequency) to make small scars in the heart tissue to prevent abnormal electrical signals from moving through the heart.

How do we know there is an association between sleep apnea and atrial fibrillation?
Multiple scientific studies in recent years have documented this connection.

Sleep Apnea and the Heart

- Sleep apnea is common in the general population, affecting approximately 42 million Americans.
- Sleep apnea is common in patients with heart disease, especially those with cardiac arrhythmias.
- About 50% of people with sleep apnea have not been diagnosed.
- Diagnosis and treatment can improve heart health and overall well-being.

Do You Have Sleep Apnea?
As part of your treatment, you will receive a small, wrist-mounted diagnostic device that is easy to operate. Its fast, accurate results make this home sleep test equivalent to sleep-lab testing.