Obstructive Sleep Apnea and Co-Morbidities

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Consequences of Sleep Apnea

• Behavioral, Cognitive and Functional impairment

• Increased risk of accidents & injuries

• Increased risk of glucose intolerance/diabetes

• Increased risk of hypertension and cardiovascular disease

• Mortality
Areas Covered Today

- Hypertension
- Coronary artery disease
- Heart Failure
- Arrhythmia (atrial fibrillation)
- Stroke
- Diabetes
Sleep Apnea Risk Factors

• Also CVD Risk Factors
  – Central Obesity
  – Male gender
  – Age
  – Menopause
• Family History
• Small/recessed jaw
Physiological Consequences

- Intrathoracic Pressure Changes
  - Preload, afterload and transmural pressure
  - Trigger baroreceptors

- Hypoxemia, hypercapnia, and arousal
  - SNS overdrive
  - Systemic and Pulmonary Vasoconstriction
  - Abnormal HRV and increased HR
  - Inflammation and oxidative stress
Sleep Apnea and Oxidative Stress

- Recurrent hypoxia and reoxygenation
  - Increase flux of free radicals
  - Induce endothelin expression
  - Suppress NO generation
  - Induce local vasoconstriction changes in vascular permeability

- Results in oxidative stress causing generation of ROS (superoxide)

Prabhakar NR, JAP, 2001
SLEEP-Apnea

PHYSIOLOGIC PERTURBATIONS

- Chronic Intermittent Hypoxia
- Ventilatory Overshoot
- Hyperoxia
- Increased Sympathetic Nervous System Activity
- Intrathoracic Pressure Swings
- Hypercapnia
- Increased Arousals
- Reduced Sleep Duration

INTERMEDIATE MECHANISMS

- Increased Inflammation
- Increased Oxidative Stress
- Metabolic Dysfunction/
  Insulin Resistance
- Hyper-coaguability
- Endothelial Dysfunction
- Autonomic Dysfunction

CLINICAL OUTCOMES

- Systemic Hypertension
- Atherosclerosis
- Diastolic Dysfunction
- Congestive Heart Failure
- Stroke
- Increased Mortality and Sudden Death

CARDIAC ARRHYTHMIAS

Sleep Apnea Highly Prevalent in Cardiovascular Disease

- Drug-Resistant Hypertension: 80% (Logan et al. J. Hypertension 2001)
- Congestive Heart Failure: 50% (Javaheri et al. Circulation 1999)
- Atrial Fibrillation: 45% (Somers et al. Circulation 2004)
- All Hypertension: 35% (Sjostrom et al. Thorax 2002)
- Coronary Artery Disease: 30% (Schafer et al. Cardiology 1999)
- Angina: 30% (Sanner et al. Clin Cardiology 2001)
OSA and Hypertension

• 50% of OSA patients: HTN
  – 30% HTN patients: OSA
  – 70% Drug Resistant patients: OSA
  – Frequent “non-dipping”
  – 2-3 fold increase in incident HTN
  – JNC7: Treatable cause of HTN

• Pathogenesis:
  – Apnea associated arousal and hypoxemia
    • Sympathetic activation
    • Altered fluid balance (hyperaldosteronism)
    • Reduced Slow Wave Sleep
    • Endothelial damage (altered NO balance)
Association Between SDB and Hypertension- SHHS Cohort, \( n=6123 \)

Nieto et al, *JAMA* 2000;283,1829
**Association Between OSA and Incident Hypertension, Wisconsin Sleep Cohort**

<table>
<thead>
<tr>
<th>BASE-LINE APNEA–HYPOPNEA INDEX</th>
<th>Adjusted Odds Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.1–4.9 events/hr</td>
<td>1.0</td>
</tr>
<tr>
<td>5.0–14.9 events/hr</td>
<td>1.42 (1.13–1.78)</td>
</tr>
<tr>
<td>≥15.0 events/hr</td>
<td>2.03 (1.29–3.17)</td>
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<tr>
<td></td>
<td>2.89 (1.46–5.64)</td>
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<td></td>
<td>0.002</td>
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</tbody>
</table>

P for trend††
Cumulative Incidence of HTN in Those without OSA and Untreated OSA

HTN Incidence Rate:
- Treated Severe OSA: 3.21/100 person yrs
- Untreated Severe OSA: 6.83/100 person yrs
Summary: Blood Pressure and OSA

- Linear Increase in BP with increasing AHI, Arousals, Hypoxemia and decreasing SWS
- Relative risk (incidence): 50%
- Stronger effect for essential vs systolic BP and nocturnal BP
- Associations most apparent at an AHI > 15
- Associations reduced with obesity adjustment
- Associations stronger in:
  - <65 yrs.
Change In Blood Pressure with CPAP

SBP Change: -2.48 (-4.31, -.62)  DBP Change: -1.83 (-3.05, -.621)

Bazzano LA Hyper 2007:50
Logan AG J Hyper 2001:19
N= 194 recruited from HTN clinics
  – AHI > 15 (avg 40); Resistant HTN (3.8 drugs)

3 month intervention CPAP vs UC; Outcome: 24h ABPM

3.1 mmHg decrease in 24 hr mBP with CPAP
36% vs 22% dippers at 12 month follow-up
Hours of CPAP α decrease in 24 mean BP (r=.29; p=.006)
HeartBEAT Trial: CPAP More Effective than Oxygen In Lowering Blood Pressure

Change in 24 Hour Mean Arterial Blood Pressure After 3 Months of Treatment

Randomized 318 patients with moderate OSA and CVD to CPAP, Nocturnal Oxygen Supplement (NSO) or Healthy Lifestyle Education (HLSE)

No effect associated with nocturnal oxygen supplementation

Average 2.5 mm Hg improvement despite low CPAP compliance (2.8 hours)

Largest effects for nocturnal diastolic pressure

<table>
<thead>
<tr>
<th></th>
<th>CPAP vs. HLSE</th>
<th>NSO vs. HLSE</th>
</tr>
</thead>
<tbody>
<tr>
<td>24-hr Awake</td>
<td>P=0.04</td>
<td>P=0.09</td>
</tr>
<tr>
<td>Awake</td>
<td>P=0.09</td>
<td>P=0.005</td>
</tr>
</tbody>
</table>
Impact of OSA Treatment on Blood Pressure

- **Average reductions in BP by 2-3 mmHg with CPAP**
  - Meta-analyses of small studies
  - RCTs from Spain and US

- **Greater effects (5 mm Hg) for**
  - More severe OSA
  - Sleepy patients
  - 24 hour BP patterns
  - Poorly controlled BP
  - Greater CPAP adherence  Lozano J Hyper 2010

- **Oral appliances may have comparable BP effect in select pts**
Sleep Apnea and Atherogenesis

• Upregulation of inflammatory mediators
  • IL6, sIL6R, IL-8, TNFα, CRP, (NF-Kappa B)
• Enhanced thrombotic potential
  – PAI-1, P-selectin, fibrinogen,
  – VEGF
• Oxidation of serum proteins and lipids

• Endothelial dysfunction

• Insulin Resistance and Dyslipidemia

Hansson NEJM 352: 2005
OSA Increases Risk of MACE and Restenosis After Percutaneous Coronary Intervention

- 89 consecutive pts with ACS followed for mean 227 days,
  - 57% OSA (AHI>10)
  - Higher CRP but otherwise comparable

- MACE in OSA vs non-OSA:
  - 23.5% vs. 5.3%
  - HR: 11.6 (2.2, 62.2)

- Quantitative Coronary Arteriography
  - Late Loss: 1.28 vs 0.69 mm MLD
  - Binary restenosis: 37% vs 15%
Major Adverse Cardiovascular Events (MACE) In Patients with CAD and OSA

- 407 consecutive patients in CAD
- 38% with ODI >5
- Increased 5-year MACE
  - ♂ AHI ≥10: 28% vs. 16%
  - ♀ AHI ≥10: 20% vs. 14%

<table>
<thead>
<tr>
<th>Composite end point</th>
<th>Hazard Ratio (95% CI)</th>
<th>p Value</th>
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<tbody>
<tr>
<td>ODI ≥ 5</td>
<td>1.59 (1.00–2.51)</td>
<td>0.05</td>
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<tr>
<td>Diabetes</td>
<td>1.85 (1.10–3.12)</td>
<td>0.02</td>
</tr>
<tr>
<td>LV dysfunction</td>
<td>2.17 (1.37–3.44)</td>
<td>0.001</td>
</tr>
<tr>
<td>Coronary intervention</td>
<td>0.50 (0.30–0.84)</td>
<td>0.009</td>
</tr>
</tbody>
</table>

Mooe T AJRCCM 2001:164
### Sleep Apnea and Incident CHD

#### Table 3. Relation of OSA to Incident CHD*

<table>
<thead>
<tr>
<th></th>
<th>AHI (Events per Hour)</th>
<th></th>
<th></th>
<th></th>
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<th>P†</th>
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<tbody>
<tr>
<td></td>
<td>&lt;5.0</td>
<td>5.0 to 14.9</td>
<td>15.0 to 29.9</td>
<td>≥30.0</td>
<td></td>
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<tr>
<td><strong>Men</strong></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>No. of subjects</td>
<td>829</td>
<td>644</td>
<td>282</td>
<td>172</td>
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<tr>
<td>No. of CHD events</td>
<td>114</td>
<td>95</td>
<td>47</td>
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<td><strong>Covariates in model</strong></td>
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</tr>
<tr>
<td>Age, race, BMI, smoking</td>
<td>1.00 (Referent)</td>
<td>0.94 (0.71, 1.24)</td>
<td>1.07 (0.75, 1.52)</td>
<td>1.45 (0.99, 2.13)</td>
<td>0.046</td>
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<tr>
<td>Plus total and HDL cholesterol, lipid-lowering medications, diabetes mellitus</td>
<td>1.00 (Referent)</td>
<td>0.93 (0.70, 1.23)</td>
<td>1.04 (0.73, 1.48)</td>
<td>1.41 (0.96, 2.07)</td>
<td>0.08</td>
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<tr>
<td>Plus SBP, DBP, use of antihypertensive medications</td>
<td>1.00 (Referent)</td>
<td>0.91 (0.69, 1.20)</td>
<td>1.07 (0.75, 1.52)</td>
<td>1.33 (0.91, 1.95)</td>
<td>0.12</td>
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<tr>
<td><strong>Women</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>No. of subjects</td>
<td>1605</td>
<td>610</td>
<td>196</td>
<td>84</td>
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<tr>
<td>No. of CHD events</td>
<td>103</td>
<td>54</td>
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<td><strong>Covariates in model</strong></td>
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<td></td>
</tr>
<tr>
<td>Age, race, BMI, smoking</td>
<td>1.00 (Referent)</td>
<td>1.01 (0.73, 1.45)</td>
<td>0.92 (0.54, 1.55)</td>
<td>0.36 (0.11, 1.16)</td>
<td>0.10</td>
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<tr>
<td>Plus total and HDL cholesterol, lipid-lowering medications, diabetes mellitus</td>
<td>1.00 (Referent)</td>
<td>0.99 (0.71, 1.40)</td>
<td>0.89 (0.52, 1.51)</td>
<td>0.37 (0.12, 1.19)</td>
<td>0.09</td>
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<tr>
<td>Plus SBP, DBP, use of antihypertensive medications</td>
<td>1.00 (Referent)</td>
<td>0.98 (0.69, 1.38)</td>
<td>0.87 (0.51, 1.49)</td>
<td>0.40 (0.12, 1.27)</td>
<td>0.10</td>
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</tr>
</tbody>
</table>

*Results are adjusted hazard ratio (95% confidence interval).
†P for the overall effect of AHI modeled as a continuous variable.
### Pooled Analysis: CAD and OSA

Loke YK Circ Cardiovasc Qual Out 2012

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Weight</th>
<th>Odds Ratio IV, Random, 95% CI</th>
<th>Odds Ratio IV, Random, 95% CI</th>
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<tbody>
<tr>
<td><strong>Predominantly Male</strong></td>
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<tr>
<td>Gottlieb 2010a</td>
<td>25.9%</td>
<td>1.33 [0.91, 1.95]</td>
<td></td>
</tr>
<tr>
<td>Mooe (Unadjusted) 2001</td>
<td>20.5%</td>
<td>1.02 [0.49, 2.13]</td>
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<tr>
<td>Peker 2006</td>
<td>17.6%</td>
<td>4.60 [1.83, 11.58]</td>
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</tr>
<tr>
<td>Shah 2010</td>
<td>21.8%</td>
<td>2.82 [1.46, 5.45]</td>
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<tr>
<td>Subtotal (95% CI)</td>
<td>85.8%</td>
<td>1.92 [1.06, 3.48]</td>
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</tr>
<tr>
<td>Heterogeneity: Tau² = 0.25; Chisq = 10.14, df = 3 (P = 0.02); I² = 70%</td>
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<tr>
<td>Test for overall effect: Z = 2.16 (P = 0.03)</td>
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<tbody>
<tr>
<td><strong>Predominantly Female</strong></td>
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<tr>
<td>Gottlieb 2010b</td>
<td>14.2%</td>
<td>0.40 [0.12, 1.30]</td>
<td></td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>14.2%</td>
<td>0.40 [0.12, 1.30]</td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: Not applicable</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 1.52 (P = 0.13)</td>
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</tbody>
</table>

**Total (95% CI)**

100.0% 1.56 [0.83, 2.91]

Heterogeneity: Tau² = 0.33; Chisq = 13.42, df = 4 (P = 0.004); I² = 74%

Test for overall effect: Z = 1.39 (P = 0.16)

Test for subgroup differences: Chisq = 5.44, df = 1 (P = 0.02), I² = 81.6%
Impact of Treatment on Coronary Artery Disease

- **MOSAIC** (n=391), 6 month intervention, minimally symptomatic
  - No improvement in CV risk score, but improved sleepiness and QoL

- Spanish Network (n=723 non-sleepy; 4 year F/U)
  - Non-significant 17% reduction in CV endpoints

- **SAVE**: Large international study (n>2,000)

- US NIH UO-1 planning studies: BestAIR, SleepTight
Summary: OSA and CAD

• **CAD and OSA co-aggregate**
  - CAD present in 20-25% of OSAHS patients
  - OSA present in 30 to 60% CAD; 70% of patients post-MI

• **Increased CAD in Patients with OSA and active CAD**
  - Increased incidence of MACE (36% vs 7%)
  - MACE incidence correlates with AHI level
  - CPAP treatment reduces MACE Peker AJRCCM 2000; Yumino ACE 2007

• **Sleep Clinic sample**
  - CVD events (fatal and other) 2.7 fold greater with OSA
  - OSA treatment reduced rate to level of snorers Marin Lancet 2005

• **Community sample**
  - CAD events 1.5-fold greater in men with OSA Gottlieb Circ 2010

• **Questions**
  - Relationship in women unclear
  - Reverse causality Charmi Circ 2010
  - Hypoxia-> angiogenesis and reduce infarct size Shah Sleep&Breath 2012
OSA: Risk for Heart Failure

• Surges in BP/Sustained Hypertension
  • Arterial Stiffness, Increased Afterload, Diastolic Dysfunction, Atrial distention

• CAD and CHF: 40-50% increased

  Cyclical Intrathoracic Pressure Swings
  – Changes in Atrial Volume

  Myocyte Injury
  – Catecholamine Excess, Inflammation, Oxidative Stress and Pro-thrombosis
  – Hypoxemia/Ischemia
OSA and Cardiac Morphology

- Increased LVM and LVH
  - Adjusted LVMI: 7% higher in AHI > 5 vs < 5
  - LVH: OR 1.78 (1.14, 2.79)
    

- Impaired LV Diastolic Function

- Increased Left Atrial Size
  - Associated with AHI severity ad E/E’ ratio
    - Oliveira JASE 2008:21:1355
  - Associated with arterial stiffness (PWV)
    - Drager IJC 2009
Prevalence of Sleep Apnea in Stable Heart Failure

Both OSA and CSA are common in heart failure

Epidemiology and Prevention

Prospective Study of Obstructive Sleep Apnea and Incident Coronary Heart Disease and Heart Failure
The Sleep Heart Health Study

Daniel J. Gottlieb, MD, MPH; Gayane Yenokyan, MD, PhD; Anne B. Newman, MD, MPH; George T. O’Connor, MD, MSc; Naresh M. Punjabi, MD, PhD; Stuart F. Quan, MD; Susan Redline, MD, MPH; Helaine E. Resnick, PhD, MPH; Elisa K. Tong, MD, MA; Marie Diener-West, PhD; Eyal Shahar, MD, MPH

Gottlieb et al. Circulation 2010; 122: 325-360
### Sleep Apnea and Incident CHF

#### Table 4. Relation of OSA to Incident Heart Failure*

<table>
<thead>
<tr>
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<th>AHI (Events per Hour)</th>
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<td>No. of subjects</td>
<td>829</td>
<td>644</td>
<td>282</td>
<td>172</td>
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</tr>
<tr>
<td>No. of heart failure events</td>
<td>44</td>
<td>46</td>
<td>25</td>
<td>26</td>
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<tr>
<td>Covariates in model</td>
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<tr>
<td>Age, race, BMI, smoking</td>
<td>1.00 (Referent)</td>
<td>0.96 (0.63, 1.46)</td>
<td>1.17 (0.71, 1.94)</td>
<td>1.61 (0.95, 2.71)</td>
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<td>Plus total and HDL cholesterol, lipid-lowering medications, diabetes mellitus</td>
<td>1.00 (Referent)</td>
<td>0.90 (0.59, 1.38)</td>
<td>1.08 (0.65, 1.80)</td>
<td>1.59 (0.94, 2.69)</td>
<td>0.02</td>
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<tr>
<td>Plus SBP, DBP, use of antihypertensive medications</td>
<td>1.00 (Referent)</td>
<td>0.88 (0.57, 1.35)</td>
<td>1.13 (0.68, 1.89)</td>
<td>1.58 (0.93, 2.66)</td>
<td>0.02</td>
</tr>
<tr>
<td><strong>Women</strong></td>
<td></td>
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<tr>
<td>No. of subjects</td>
<td>1605</td>
<td>610</td>
<td>196</td>
<td>84</td>
<td></td>
</tr>
<tr>
<td>No. of heart failure events</td>
<td>86</td>
<td>54</td>
<td>19</td>
<td>8</td>
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<tr>
<td>Covariates in model</td>
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</tr>
<tr>
<td>Age, race, BMI, smoking</td>
<td>1.00 (Referent)</td>
<td>1.12 (0.79, 1.59)</td>
<td>1.10 (0.66, 1.83)</td>
<td>1.05 (0.50, 2.23)</td>
<td>0.72</td>
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<tr>
<td>Plus total and HDL cholesterol, lipid-lowering medications, diabetes mellitus</td>
<td>1.00 (Referent)</td>
<td>1.15 (0.81, 1.63)</td>
<td>1.06 (0.64, 1.77)</td>
<td>1.19 (0.56, 2.53)</td>
<td>0.90</td>
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<tr>
<td>Plus SBP, DBP, use of antihypertensive medications</td>
<td>1.00 (Referent)</td>
<td>1.13 (0.80, 1.61)</td>
<td>1.01 (0.60, 1.69)</td>
<td>1.19 (0.56, 2.52)</td>
<td>0.83</td>
</tr>
</tbody>
</table>

*Results are adjusted hazard ratio (95% confidence interval).
†P for the overall effect of AHI modeled as a continuous variable.
Reduced Survival in CHF and OSA

- 145 pts with LVEF <45%
- F/U mean 2.9 yrs

Wang H  *J Am Coll Cardiol* 2007; 49:1625-31
Treated Sleep Apnea May be Associated with Improved Survival in HF

Javaheri S et al, AJRCCM epub 23.07.2010

Percent of Cohort Alive

Tested, Diagnosed, Treated, N=258

Not Tested, Not Treated, N=30,065

Hazard ratio = .33 (95% CI = .21-.51), P < .0001

Baseline 1 2 3 4 5 6 7 8

Quarters after HF Onset
OSA: Increases Cardiac Vulnerability for Arrhythmias (Atrial Fibrillation)

- Autonomic Nervous System Imbalance
  - Vagal Tone - shortening of ERP
  - Sympathetic Surges - Triggered early after-depolarizations
  - Animal model - apnea mediated AF attenuated by autonomic blockade (or GP ablation)
    - Ghias JACC 2009

- Myocyte injury
  - Hypoxemia

- Electrical Remodeling
  - Apnea-associated triggers of PAF
Incident Atrial Fibrillation In Sleep Lab Referrals

- N=3542; followed 4.7 yrs
- Incident A Fib: 14%
- In subjects <65 years old, incident A Fib predicted by nocturnal oxygen saturation (per 0.5 U log change, hazard ratio 3.29, 95% CI 1.35 to 8.04).
- In older individuals, Afib predicted by HF

Gami JACC 2007:49
OSA Increases Rate of Recurrent Atrial Fibrillation After Cardioversion

- 12 month recurrent atrial fibrillation
  - 87% of untreated OSA patients, vs
  - 42% in treated OSA, vs
  - 53% cardiac pts with no sleep studies

Kanagala Circulation 2003:107
Nocturnal Arrhythmias In Sleep Heart Health Study

TABLE 3. ADJUSTED AND UNADJUSTED ODDS RATIOS RELATING ARRHYTHMIA OCCURRENCE AND SLEEP-DISORDERED BREATHING

<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>Nonsustained 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>

Mehra et al. AJRCCM 2006
Sleep Apnea Associated with *Incident* and *Recurrent* Atrial Fibrillation

- Sleep Lab Referrals (n=3542) followed 4.7 yrs
  - *Incident* A Fib: **14%**
  - In subjects <65 years old, incident A Fib predicted by nocturnal oxygen saturation (per 0.5 U log change, hazard ratio 3.29, 95% CI 1.35 to 8.04).
    - Gami JACC 2007:49

- 12 month *Recurrent* AF after cardioversion
  - 87% of untreated OSA patients, vs
  - 42% in treated OSA, vs
  - 53% cardiac pts with no sleep studies
    - Kanagala *Circ* 2003:107
Risk of Nocturnal Arrhythmias In Association with Apneas

- Relative Risk: 17.5 (5.3, 58.4)
- 1 excess episode of PAF or NSVT for every 1000 hours of sleep or 40000 respiratory disturbances

- For a person with moderate Sleep Apnea (AHI = 25 events/hour) sleeping 8 hours/night
- 1 excess arrhythmia in 7 months

Monahan JACC 2009
Improved Arrhythmias with CPAP

• In patients referred for OSA:
  – CPAP eliminated or reduced in 9/11 OSA pts Koehler ERJ 1998
  – CPAP reduced heart block during sleep (1,575 to 165) in 17 pts; 12 had complete resolution of HB. Becker AJRCCM 1995:151
  – Heart block, sinus pauses resolved with 2-3 d of CPAP Harbison Chest 2000:118

• In HF and Sleep Apnea:
  – 1 m CPAP 58% reduction in PVCs (170-70/hr) and fall in NE levels (n=18) Ryan Thorax 2005:60:781
OSA and Stroke

• Specific effects on cerebral circulation
  – Snoring vibratory stress → carotid damage
  – Apneas, arousals and intermittent surges in BP in background of IH
    • Cerebral vascular blood flow/vascular auto-regulation
    • Cerebrovascular shearing stress/endothelial dysfunction
Stroke Risk Factors

- Age, Gender, Race
- HTN, A Fib, LVH, Valve disease
- Diabetes, Dyslipidemia, Carotid Atherosclerosis
- Smoking, Alcohol

- *Sleep Disordered Breathing*
  - 35 to 40% of patients with CVD
OSA As A Stroke Factor

• Exacerbate underlying CVD risk factors
  – HTN, diabetes
  – Pro-inflammatory, pro-atherogenic, dyslipidemia

• Trigger Atrial Fibrillation
Acute Stroke and OSA

- High prevalence in peri-stroke period (>60%)
  Bassetti Sleep 1999

- History of SDB associated with timing of stroke
  Iranzo Neurol 2002

- Poorer rehabilitation outcomes and greater functional impairments
  - Kaneko Sleep 2003; Good D Stroke 1996

- Higher mortality
  - OAHI >15 (n=23) associated w a 10 yr aMR 1.76 (1.05,2.95)
    - Sahlin Arch Int Med 2008
## Sleep Apnea and Incident Stroke in Men

<table>
<thead>
<tr>
<th>Covariate</th>
<th>Unadjusted</th>
<th>Age-Adjusted</th>
<th>Fully-Adjusted*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quartile of AHI</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IV: 19.13 – 164.5</td>
<td>3.91</td>
<td>3.05</td>
<td>2.86</td>
</tr>
<tr>
<td></td>
<td>(1.55 – 9.86)</td>
<td>(1.21 – 7.72)</td>
<td>(1.10 – 7.39)</td>
</tr>
<tr>
<td>III: 9.50 – 19.12</td>
<td>2.35</td>
<td>1.97</td>
<td>1.86</td>
</tr>
<tr>
<td></td>
<td>(0.89 – 6.20)</td>
<td>(0.74 – 5.21)</td>
<td>(0.70 – 4.95)</td>
</tr>
<tr>
<td>II: 4.05 – 9.49</td>
<td>1.96</td>
<td>1.86</td>
<td>1.86</td>
</tr>
<tr>
<td></td>
<td>(0.71 – 5.40)</td>
<td>(0.68 – 5.13)</td>
<td>(0.67 – 5.12)</td>
</tr>
<tr>
<td>I: 0.00 – 4.04)</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
</tr>
</tbody>
</table>

*Adjusted for age, BMI, smoking status, SBP, blood pressure medications, diabetes, and race

SHHS: Stroke and OSAHS

• In men,
  – Relative risk 2.86 for an AHI >20
  – Every increment in AHI (between 5 and 25) associated with a 6% increase in stroke

• In women, every increment in AHI (AHI>25) associated with a 2% increase in stroke

Redline AJRCCM 2010
# Pooled Analysis: Stroke and OSA

Loke YK Circ Cardiovasc Qual Out 2012

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Weight</th>
<th>Odds Ratio, IV, Random, 95% CI</th>
<th>Odds Ratio, IV, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Predominantly Male</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arzt 2005</td>
<td>6.0%</td>
<td>3.08 [0.74, 12.81]</td>
<td></td>
</tr>
<tr>
<td>Mooe (Adjusted) 2001</td>
<td>21.3%</td>
<td>2.98 [1.43, 6.20]</td>
<td></td>
</tr>
<tr>
<td>Munoz 2006</td>
<td>15.1%</td>
<td>2.52 [1.04, 6.10]</td>
<td></td>
</tr>
<tr>
<td>Redline 2010a</td>
<td>13.1%</td>
<td>2.86 [1.10, 7.41]</td>
<td></td>
</tr>
<tr>
<td>Yaggi (Unadjusted) 2005</td>
<td>15.6%</td>
<td>3.03 [1.27, 7.21]</td>
<td></td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>71.1%</td>
<td>2.87 [1.91, 4.31]</td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: Tau² = 0.00; Chi² = 0.12, df = 4 (P = 1.00); I² = 0%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 5.09 (P &lt; 0.00001)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

| Predominantly Female            |        |                                |                                |
| Redline 2010b                   | 28.9%  | 1.21 [0.65, 2.25]              |                                |
| Subtotal (95% CI)               | 28.9%  | 1.21 [0.65, 2.25]              |                                |
| Heterogeneity: Not applicable    |        |                               |                                |
| Test for overall effect: Z = 0.60 (P = 0.55) |        |                               |                                |

| Total (95% CI)                  | 100.0% | 2.24 [1.57, 3.19]              |                                |
| Heterogeneity: Tau² = 0.01; Chi² = 5.36, df = 5 (P = 0.37); I² = 7% |        |                               |                                |
| Test for overall effect: Z = 4.45 (P < 0.000001) |        |                               |                                |
| Test for subgroup differences: Chi² = 5.24, df = 1 (P = 0.02), I² = 80.9% |        |                               |                                |
Snoring and Stroke

- Snoring independent of hypoxia- carotid atherosclerosis
- “Response to injury” model
  - Endothelial dysfunction
  - Impaired vasorelaxation after 6 hr vibratory Stress  Cho J-G Sleep 2011
- Heavy Snoring OR 10.2 for carotid plaque

% Plaque in carotids (black) vs Femorals (hashed)

Lee SA Sleep 200
CPAP Use After Stroke

• Potential benefits:
  – Improved blood pressure control
  – Decrease cerebral hypoxemia/limit damage
  – Improve alertness and rehab/Qol
  – Reduce arrhythmia risk

• Potential Challenges
  – Advanced age and functional disability
  – Cognitive deficits-adherence
  – Adequate resolution of central events
  – Facial palsies-mouth leak
IMT Improvement with CPAP

- Increased carotid IMT
- Increased carotid and brachial diameters
- Increased pulse wave velocity (PMV) acutely (late apnea) and chronically

- 4 months CPAP Improves:
  - IMT 9%
  - PMV 10%
OSA and Stroke

• Specific effects on cerebral circulation
  – Snoring vibratory stress → carotid damage
  – Apneas, arousals and intermittent surges in BP in background of IH
    • Cerebral vascular blood flow/vascular auto-regulation
    • Cerebrovascular shearing stress/endothelial dysfunction
Summary: OSA and Stroke

- SDB common post-stroke and also associated with most stroke risk factors
  - Antecedent / response to stroke

- Strong biological & observational data suggesting a causal association between SDB with stroke incidence and stroke-related morbidity & mortality
  - Hypoxemia, a fib, possibly snoring-stress, likely mediators

- Unclear how obstructive vs central SA contribute
  - Treatment implications
Diabetes and Sleep Apnea (SDB)

- Cross-sectional associations between SDB and glucose intolerance
  – Punjabi, 2002&04; Ip, 2002; Meisler 2003; Sulit, 2006

- 2-fold increased incidence of diabetes with habitual snoring
  – Al Delaimy, 2002
# SDB and Metabolic Syndrome

- Insulin Resistance in Adults with SDB associated with hypoxemia and obesity

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Fasting glucose level (n = 2,656)</th>
<th>2-hour glucose level (n = 1,930)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Odds ratio</td>
<td>95% confidence interval</td>
</tr>
<tr>
<td>Respiratory disturbance index (no. of events/hour)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;5.0</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>5.0–14.9</td>
<td>1.27</td>
<td>0.98, 1.64</td>
</tr>
<tr>
<td>≥15.0</td>
<td>1.46</td>
<td>1.09, 1.97</td>
</tr>
<tr>
<td>p for linear trend</td>
<td>0.0090</td>
<td></td>
</tr>
<tr>
<td>Average oxyhemoglobin saturation during sleep (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥95.72</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>94.57–95.71</td>
<td>1.52</td>
<td>1.05, 2.20</td>
</tr>
<tr>
<td>93.32–94.56</td>
<td>1.75</td>
<td>1.21, 2.53</td>
</tr>
<tr>
<td>&lt;93.32</td>
<td>1.95</td>
<td>1.34, 2.84</td>
</tr>
<tr>
<td>p for linear trend</td>
<td>0.0007</td>
<td></td>
</tr>
</tbody>
</table>
IFG and IGT
SHHS (non-diabetic, n=2,588)

<table>
<thead>
<tr>
<th>IGM</th>
<th>Entire analytic sample (n = 2,588)</th>
<th>Nonoverweight (n = 679)*</th>
<th>Overweight/obese (n = 1,909)†</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Unadjusted odds ratio (95% CI)</td>
<td>Adjusted odds ratio (95% CI)†</td>
<td>Unadjusted odds ratio (95% CI)</td>
</tr>
<tr>
<td>IFG</td>
<td>2.0 (1.7–2.4)</td>
<td>1.3 (1.1–1.6)§</td>
<td>1.5 (1–2.3)‖</td>
</tr>
<tr>
<td>IGT</td>
<td>1.3 (1.1–1.6)</td>
<td>1.2 (1–1.4)</td>
<td>1.5 (1–2.1)‖</td>
</tr>
<tr>
<td>IFG plus IGT</td>
<td>2.0 (1.6–2.5)</td>
<td>1.4 (1.1–1.8)§</td>
<td>1.8 (0.9–3.4)‖</td>
</tr>
<tr>
<td>Occult diabetes detected as FPG ≥126 mg/dl</td>
<td>2.4 (1.6–3.6)</td>
<td>1.7 (1.1–2.7)‖</td>
<td>2.3 (0.8–6.6)</td>
</tr>
<tr>
<td>Occult diabetes detected as 2-h OGTT ≥200 mg/dl</td>
<td>1.8 (1.3–2.3)</td>
<td>1.5 (1.2–2.0)§</td>
<td>2.0 (1.1–3.6)‖</td>
</tr>
</tbody>
</table>

Seicean Diab Care 2008: 31
Meta-Analysis of OSA and Incident Diabetes

6 prospective cohort studies
N=5953
Follow up: 3 to 16 yrs
Overall OR: 1.63 (1.09, 2.45)

Wang  Respir 2013
Improvement in HOMA-IR With CPAP Treatment

- 2 month Cross-Over Trial of CPAP vs Sham CPAP in 49 patients with OSA (AHI>15) and IGT

Weinstein Sleep 2012
Cardiovascular Disease and Sleep Apnea

- 50% increased risk of hypertension
  - Non-dipping, Left ventricular hypertrophy

- 50% increased risk coronary heart disease
  - Pro-atherogenic (inflammatory, oxidative stress, metabolic)
  - Endothelial dysfunction

- 70% increased risk of heart failure
  - CHD, hypertension, mechanical stress

- 3-4-fold increased arrhythmias

- 3-fold increased risk of stroke
  - As above, plus snoring related carotid artery trauma?
  - Surges in cerebral blood flow?

- 50%-2-fold increased diabetes
# Cardiovascular Risk Associated with Sleep Apnea May Begin In Childhood

**TABLE 2. UNADJUSTED AND ADJUSTED ODDS OF METABOLIC SYNDROME FOR SLEEP-DISORDERED BREATHING**

<table>
<thead>
<tr>
<th></th>
<th>Unadjusted</th>
<th>p Value</th>
<th>Adjusted</th>
<th>OR (95% CI)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>SDB (AHI ≥ 5)</td>
<td>7.74 (3.10, 19.35)</td>
<td>&lt; 0.001</td>
<td>6.49 (2.52, 16.70)</td>
<td>&lt; 0.001</td>
<td></td>
</tr>
<tr>
<td>Age (per 1-yr increase)</td>
<td>0.99 (0.62, 1.56)</td>
<td>0.95</td>
<td>0</td>
<td>0.95</td>
<td></td>
</tr>
<tr>
<td>Male sex</td>
<td>2.62 (1.30, 5.27)</td>
<td>0.007</td>
<td>1.42 (0.72, 2.82)</td>
<td>0.297</td>
<td></td>
</tr>
<tr>
<td>African-American race/ethnicity</td>
<td>0.86 (0.45, 1.66)</td>
<td>0.66</td>
<td>0.92 (0.50, 1.71)</td>
<td>0.806</td>
<td></td>
</tr>
<tr>
<td>Preterm status</td>
<td>0.90 (0.47, 1.74)</td>
<td>0.76</td>
<td>0.77 (0.39, 1.52)</td>
<td>0.439</td>
<td></td>
</tr>
</tbody>
</table>

*Definition of abbreviations: AHI = apnea-hypopnea index; CI = confidence interval; OR = odds ratio; SDB = sleep-disordered breathing.

* Based on logistic regression analyses with metabolic syndrome as the outcome. Each covariate in the adjusted model was adjusted for all other covariates.
Sleep Apnea: A Novel Modifiable Risk Factor

• Approximately 80% of cardiovascular disease is preventable.
• Standard Risk Factors
  – Overweight and obesity
  – Physical inactivity
  – Diabetes
  – Cigarette smoking
  – High blood pressure
  – Dyslipidemia

• Target Sleep Apnea as a Novel Risk Factor?
  – Stroke, Atrial Fibrillation, Heart Failure
Attributable Risk

- 5 to 20% of Cardiovascular Disease may be preventable by treating/preventing Sleep Apnea
Public Health Implications

• High associated co-morbidities and high prevalence
  – Population attributable risk (public health burden)

• Need improved evidence on role of intervention and who to target

• Opportunities for primary and secondary disease prevention and reduction in health disparities

• Patient centeredness: myapnea.org