Obstructive Sleep Apnea and Co-Morbidities

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Brigham and Women’s Hospital and Beth Israel Deaconess Medical Center
Areas Covered Today

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

- Family History
- Small/recessed jaw

- Also CVD Risk Factors
  - Central Obesity
  - Male gender
  - Age
  - Menopause
Physiological Mechanisms

- **Airway Occlusion ➔ Intra-thoracic Pressure Changes**
  - Preload, afterload and transmural pressure
  - Trigger baroreceptors

- **Hypoxemia, hypercapnia, and arousal**
  - Sympathetic Nervous System overdrive
  - Systemic and pulmonary vasoconstriction
  - Inflammation and oxidative stress
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
- Myocardial Dysfunction
- Heart Failure
- Stroke
- Cardiac Arrhythmias
- Increased Mortality and Sudden Death

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: Hypertension (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 OSA and Hypertension- SHHS Cohort, n=6123

Nieto et al, *JAMA* 2000;283,1829
Adjusted Odds Ratio (95% CI)

- 0.1–4.9 events/hr: 1.0
- 5.0–14.9 events/hr: 1.42 (1.13–1.78)
- ≥15.0 events/hr: 2.03 (1.29–3.17)

P for trend‡: 2.89 (1.46–5.64), 0.002
Association Between Treated and Untreated Obstructive Sleep Apnea and Risk of Hypertension


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)
Effect of CPAP on Blood Pressure in Patients With Obstructive Sleep Apnea and Resistant Hypertension: The HIPARCO Randomized Clinical Trial

Miguel Angel Martinez Garcia, MD, PhD; Francisco Capote, MD, PhD; Francisco Campos-Rodriguez, MD, PhD; Patricia Lloberes, MD, PhD;

- 194 patients recruited from HTN clinics
  - AHI > 15 (avg 40); Resistant HTN (3.8 drugs)
- 3 month intervention CPAP vs Usual Care
- Outcome: 24 hour Blood Pressure pattern

KEY FINDINGS

- CPAP resulted in an average of
  - 3.1 mmHg decrease in 24 hr mean BP with CPAP
  - Increased nocturnal dippers to 36% from 22%
  - 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 3 months:
- CPAP
- Nocturnal Oxygen Supplement (NSO)
- Healthy Life Style Education (HLSE)

FINDINGS:

No effect associated with nocturnal oxygen supplementation

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

Largest effects for nocturnal diastolic pressure
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
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%

### Hazard Ratio and 95% CI

<table>
<thead>
<tr>
<th>Composite end point</th>
<th>Hazard Ratio and 95% CI</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ODI ≥ 5</td>
<td>1.59 (1.00–2.51)</td>
<td>0.05</td>
</tr>
<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
OSA Associated with more Coronary Events & Restenosis After Percutaneous Coronary Intervention

- 89 consecutive pts with Acute Coronary Syndrome followed for mean 227 days,
  - 57% OSA (AHI>10)
  - Higher CRP but otherwise comparable
- Coronary Events in OSA vs non-OSA:
  - 23.5% vs. 5.3%
  - HR: 11.6 (2.2, 62.2)
- Quantitative Coronary Arteriography
  - Restenosis: 37% vs 15%
## Sleep Apnea and Incident Coronary Heart Disease

### 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>
<th></th>
</tr>
</thead>
<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>
</tr>
<tr>
<td><strong>Men</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of subjects</td>
<td>829</td>
<td>644</td>
<td>282</td>
<td>172</td>
<td></td>
</tr>
<tr>
<td>No. of CHD events</td>
<td>114</td>
<td>95</td>
<td>47</td>
<td>40</td>
<td></td>
</tr>
<tr>
<td><strong>Covariates in model</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</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>
</tr>
<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>
</tr>
<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>
</tr>
<tr>
<td><strong>Women</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<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 CHD events</td>
<td>103</td>
<td>54</td>
<td>17</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td><strong>Covariates in model</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<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>
</tr>
<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>
</tr>
<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>
</tr>
</tbody>
</table>

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

Gottlieb et al. Circulation 2010; 122: 325-360
Pooled Analysis: Coronary Artery Disease 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>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>
<td></td>
</tr>
<tr>
<td>Peker 2006</td>
<td>17.6%</td>
<td>4.60 [1.83, 11.58]</td>
<td></td>
</tr>
<tr>
<td>Shah 2010</td>
<td>21.8%</td>
<td>2.82 [1.46, 5.45]</td>
<td></td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>85.8%</td>
<td>1.92 [1.06, 3.48]</td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: Tau² = 0.25; Chi² = 10.14, df = 3 (P = 0.02); I² = 70%</td>
<td></td>
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</tr>
<tr>
<td>Test for overall effect: Z = 2.16 (P = 0.03)</td>
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</tr>
<tr>
<td>Predominantly Female</td>
<td></td>
<td></td>
<td></td>
</tr>
<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>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td>100.0%</td>
<td>1.56 [0.83, 2.91]</td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: Tau² = 0.35; Chi² = 13.42, df = 4 (P = 0.004); I² = 74%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 1.39 (P = 0.16)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for subgroup differences: Chi² = 5.44, df = 1 (P = 0.02), I² = 81.6%</td>
<td></td>
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</tr>
</tbody>
</table>
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

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

- **Community sample**
  - CAD events 1.5-fold greater in men with OSA

- **Questions**
  - Relationship in women unclear
  - Reverse causality
  - Hypoxia-> angiogensis and reduce infarct size
OSA: Risk for Heart Failure

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

- Via Increase in Coronary Artery Disease Risk

- Cyclical Intrathoracic Pressure Swings
  - Changes in Afterload; Atrial Volume

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

- **Increased Left Ventricular Mass**
  - Ventricular Mass: 7% higher in AHI > 5 vs < 5
  - Left Ventricular Hypertrophy
    - Odds Ratio: 1.78 (1.14, 2.79)

- **Impaired LV Diastolic Function**

- **Increased Left Atrial Size**
  - Associated with AHI severity and 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
## Table 4. Relation of OSA to Incident Heart Failure*

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<tr>
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<th>AHI (Events per Hour)</th>
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<tbody>
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<td></td>
<td>&lt;5.0</td>
</tr>
<tr>
<td><strong>Men</strong></td>
<td></td>
</tr>
<tr>
<td>No. of subjects</td>
<td>829</td>
</tr>
<tr>
<td>No. of heart failure events</td>
<td>44</td>
</tr>
<tr>
<td><strong>Covariates in model</strong></td>
<td></td>
</tr>
<tr>
<td>Age, race, BMI, smoking</td>
<td>1.00 (Referent)</td>
</tr>
<tr>
<td>Plus total and HDL cholesterol, lipid-lowering medications, diabetes mellitus</td>
<td>1.00 (Referent)</td>
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<td>Plus SBP, DBP, use of antihypertensive medications</td>
<td>1.00 (Referent)</td>
</tr>
<tr>
<td><strong>Women</strong></td>
<td></td>
</tr>
<tr>
<td>No. of subjects</td>
<td>1605</td>
</tr>
<tr>
<td>No. of heart failure events</td>
<td>86</td>
</tr>
<tr>
<td><strong>Covariates in model</strong></td>
<td></td>
</tr>
<tr>
<td>Age, race, BMI, smoking</td>
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*Results are adjusted hazard ratio (95% confidence interval).
†P for the overall effect of AHI modeled as a continuous variable.

Gottlieb et al. Circulation 2010; 122: 325-360
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 refractory period
  - Sympathetic Surges- Triggered early after-depolarizations
  - Animal model- apnea mediated AF attenuated by autonomic blockade (or GP ablation)

- **Myocyte injury**
  - Hypoxemia

- **Electrical Remodeling**
  - Apnea-associated triggers of PAF
Sleep Apnea Associated with Incident and Recurrent Atrial Fibrillation

- Sleep Lab Referrals (n=3542) followed 4.7 yrs
  - *Incident* Atrial Fibrillation: 14%
  - In subjects <65 years old, incident A Fib predicted by nocturnal oxygen saturation
    - per 0.5 U log change, hazard ratio 3.29 (1.35,8.04).
  - 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
### 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>Adjusted for Age, Sex, BMI</th>
<th>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
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
Stroke Risk Factors

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

- Sleep Apnea
  - 35 to 40% of patients with CVD
OSA and Stroke

- Exacerbate underlying CVD risk factors
  - Hypertension, diabetes, pro-inflammatory, pro-atherogenic, dyslipidemia

- Trigger Atrial Fibrillation

- Specific effects on cerebral circulation
  - Snoring vibratory stress → carotid damage
  - Apneas, arousals and BP surges
    - Cerebral vascular blood flow/vascular auto-regulation
    - Cerebrovascular shearing stress/endothelial dysfunction
Acute Stroke and OSA

• High OSA prevalence in peri-stroke period (>60%)

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

• Higher mortality
  – OAHI >15 (n=23) associated with a 10 yr adjusted mortality rate of 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>IV: 19.13 – 164.5</td>
<td>3.91 (1.55 – 9.86)</td>
<td>3.05 (1.21 – 7.72)</td>
<td>2.86 (1.10 – 7.39)</td>
</tr>
<tr>
<td>III: 9.50 – 19.12</td>
<td>2.35 (0.89 – 6.20)</td>
<td>1.97 (0.74 – 5.21)</td>
<td>1.86 (0.70 – 4.95)</td>
</tr>
<tr>
<td>II: 4.05 – 9.49</td>
<td>1.96 (0.71 – 5.40)</td>
<td>1.86 (0.68 – 5.13)</td>
<td>1.86 (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 OSA

• 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><strong>Predominantly Male</strong></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><strong>Heterogeneity</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tau²</td>
<td>0.00</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chi²</td>
<td>0.12</td>
<td></td>
<td></td>
</tr>
<tr>
<td>df</td>
<td>4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>P value</td>
<td>1.00</td>
<td></td>
<td></td>
</tr>
<tr>
<td>I²</td>
<td>0%</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Test for overall effect</strong></td>
<td>Z</td>
<td>5.09 (P &lt; 0.000001)</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 value                       | 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

Lee SA Sleep 2008

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

Drager LF AJRCCM 2005:172:613
Drager LF AJRCCM 2007:176:706
Jelic S Sleep 2002:25:8
Summary: OSA and Stroke

• Sleep apnea common post-stroke and also associated with most stroke risk factors
  – Antecedent / response to stroke

• Strong biological & observational data suggest a causal association between sleep apnea with stroke incidence and stroke-related morbidity & mortality
  – Hypoxemia, a fib, possibly snoring-stress, likely mediators

• Unclear how obstructive vs central sleep apnea contribute
  – Treatment implications
Diabetes and Sleep Apnea

• 2-fold increased incidence of diabetes with habitual snoring
  – Al Delaimy, 2002

• Cross-sectional associations between OSA and glucose intolerance
  – Punjabi, 2002&04; Ip, 2002; Meisler 2003; Sulit, 2006
## OSA and Glucose Metabolism

- Insulin Resistance in Adults with OSA 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 95% confidence interval</td>
<td>Odds ratio 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>1.00</td>
</tr>
<tr>
<td>5.0–14.9</td>
<td>1.27 0.98, 1.64</td>
<td>1.09 0.88, 1.35</td>
</tr>
<tr>
<td>≥15.0</td>
<td>1.46 1.09, 1.97</td>
<td>1.44 1.11, 1.87</td>
</tr>
<tr>
<td>p for linear trend</td>
<td>0.0090</td>
<td>0.0096</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>1.00</td>
</tr>
<tr>
<td>94.57–95.71</td>
<td>1.52 1.05, 2.20</td>
<td>1.16 0.88, 1.53</td>
</tr>
<tr>
<td>93.32–94.56</td>
<td>1.75 1.21, 2.53</td>
<td>1.14 0.86, 1.52</td>
</tr>
<tr>
<td>&lt;93.32</td>
<td>1.95 1.34, 2.84</td>
<td>1.40 1.05, 1.88</td>
</tr>
<tr>
<td>p for linear trend</td>
<td>0.0007</td>
<td>0.0321</td>
</tr>
</tbody>
</table>
# Impaired Glucose Metabolism in Overweight and Normal Weight OSA

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>1.8 (1.5–2.2)¶</td>
</tr>
<tr>
<td>IGT</td>
<td>1.3 (1.1–1.6)</td>
<td>1.2 (1–1.4)</td>
<td>1.2 (1–1.5)</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>1.7 (1.3–2.3)¶</td>
</tr>
<tr>
<td>Occult diabetes detected as</td>
<td>2.4 (1.6–3.6)</td>
<td>1.7 (1.1–2.7)¶</td>
<td>2.1 (1.4–3.3)§</td>
</tr>
<tr>
<td>FPG ≥126 mg/dl</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Occult diabetes detected as</td>
<td>1.8 (1.3–2.3)</td>
<td>1.5 (1.2–2.0)§</td>
<td>1.6 (1.2–2.1)§</td>
</tr>
<tr>
<td>2-h OGTT ≥200 mg/dl</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Seicean Diab Care 2008: 31
Pooled 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)
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

2 months of CPAP Improved insulin levels by 28% in those with Severe OSA
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>
<thead>
<tr>
<th></th>
<th>Unadjusted</th>
<th></th>
<th>Adjusted</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR (95% CI)</td>
<td>p Value</td>
<td>OR (95% CI)</td>
<td>p Value</td>
</tr>
<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>
</tr>
<tr>
<td>Age (per 1-yr increase)</td>
<td>0.99 (0.62, 1.56)</td>
<td>0.95</td>
<td>0.90 (0.47, 1.74)</td>
<td>0.76</td>
</tr>
<tr>
<td>Male sex</td>
<td>2.62 (1.30, 5.27)</td>
<td>0.007</td>
<td></td>
<td></td>
</tr>
<tr>
<td>African-American race/</td>
<td>0.86 (0.45, 1.66)</td>
<td>0.66</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ethnicity</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Preterm status</td>
<td>0.90 (0.47, 1.74)</td>
<td>0.76</td>
<td></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.

Redline S. et al. AJRCCM 2007
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
A groundbreaking network for research and patient support

MyApnea.Org: Recruiting 50,000 adults with OSA and parents of children with sleep apnea to participate in a network that will:

- Enable them to guide what researchers study, describe outcomes they view as most important, and provide data for efforts to improve OSA diagnosis and treatment
- Provide a dashboard of sleep, health and risk measures based on personal data they submit by survey, their CPAP or other devices
- Support them with “how to” information
- Connect them with others to share problems and learn what works
You can help by joining this movement:

- Sign up on: www.myapnea.org
- Tell patients about this network and encourage them to sign up