Cardiovascular Disease and Sleep Disordered Breathing: Where are We Now?

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Tristate Symposium
May 4, 2018
### Conflict of Interest Disclosures for Speakers

1. I do not have any relationships with any entities **producing, marketing, re-selling, or distributing** health care goods or services consumed by, or used on, patients, OR

2. I have the following relationships with entities **producing, marketing, re-selling, or distributing** health care goods or services consumed by, or used on, patients.

<table>
<thead>
<tr>
<th>Type of Potential Conflict</th>
<th>Details of Potential Conflict</th>
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<tbody>
<tr>
<td>Grant/Research Support</td>
<td>NIH NHLBI R01 HL 109493, 1U01HL125177</td>
</tr>
<tr>
<td>Consultant</td>
<td>None</td>
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<tr>
<td>Speakers' Bureaus</td>
<td>None</td>
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<tr>
<td>Financial support</td>
<td>Royalties from Up to Date, Fees from AASM, Fees from NIH for NIH study section service</td>
</tr>
<tr>
<td>Other</td>
<td>Institution has received positive airway pressure machines and equipment from Philips Respironics and Resmed for research purposes.</td>
</tr>
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</table>

3. The material presented in this lecture has no relationship with any of these potential conflicts, OR

4. This talk presents material that is related to one or more of these potential conflicts, and the following objective references are provided as support for this lecture:
Objectives

- Describe normal cardiovascular physiology during sleep
- Discuss prevalence and mechanisms linking sleep apnea and cardiovascular disease
- Review the association of sleep apnea and hypertension and resistant hypertension including treatment benefit
- Discuss inter-relationships of sleep apnea with heart failure, cardiac arrhythmia and stroke including treatment implications
- Understand the contribution of sleep apnea to coronary heart disease, mortality and sudden cardiac death with a focus on recent clinical trial data
## REM versus NREM Sleep

<table>
<thead>
<tr>
<th>Physiologic Variable</th>
<th>NREM</th>
<th>REM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate</td>
<td>Regular</td>
<td>Irregular</td>
</tr>
<tr>
<td>Respiratory rate</td>
<td>Regular</td>
<td>Irregular</td>
</tr>
<tr>
<td>Blood pressure</td>
<td>Regular</td>
<td>Variable</td>
</tr>
<tr>
<td>Skeletal muscle tone</td>
<td>Preserved</td>
<td>Reduced</td>
</tr>
<tr>
<td>Brain O₂ consumption</td>
<td>Reduced</td>
<td>Increased</td>
</tr>
<tr>
<td>Ventilatory response</td>
<td>Slight ↓</td>
<td>Reduced</td>
</tr>
<tr>
<td>Temperature</td>
<td>Normal</td>
<td>Poikilothermic</td>
</tr>
</tbody>
</table>
“Don’t ever go to sleep. Too many people die there.”

Mark Twain
....but Sleep is Cardioprotective
Sympathetic-Nerve Activity and Mean Blood Pressure while Awake and in Sleep

Heart Rate, Mean Blood Pressure, Sympathetic-Burst Frequency and Amplitude during Wakefulness and Sleep

- HR and BP significantly lower in NREM compared to wakefulness
- Sympathetic activity lower in slow wave sleep compared to other sleep states
- During REM sleep, sympathetic activation increased compared to other sleep stages and exceeded that of wakefulness

Diurnal Variability of Blood Pressure Surges

- Going to bed
  - Awake
  - Sleep
  - Arising
  - Awake

- mmHg
  - 200
  - 150
  - 100
  - 50

- 6PM
  - Midnight
  - 6AM
  - Noon

1. Sleep-trough surge = Morning SBP - Lowest nighttime SBP
2. Prewaking surge = Morning SBP - Prewake SBP
3. Rising BP surge = Morning SBP on rising - SBP on supine <30 min before rising
4. ME difference = Morning SBP - Evening SBP (by home BP self-measured)

SBP, systolic BP
Morning Predisposition of Myocardial Infarction

Circadian rhythm is present with peak incidence at 9AM. 3-fold increase in MI within the first 3 hours of awakening.

Circadian Variation of Cardiovascular Events

Why?

• Autonomic fluctuations related to REM sleep
• BP surges
• Peak cortisol levels
• Peak levels of systemic markers of inflammation and thrombotic markers

Marler et al. Stroke 1989
Sleep is Cardio-Protective, but....

Lown et al. Circulation 1973
...not in Sleep Apnea
Nocturnal Predilection for Sudden Cardiac Death in OSA

Gami AS NEJM 2005:352
“Don’t ever go to sleep. Too many people die there.”

Mark Twain
Each night when I go to sleep, I die.
And then the next morning,
when I wake up, I am reborn.
Obstructive Sleep Apnea  
A Highly Prevalent, Under-recognized Physiologic Stressor

- **17% of the general adult population, increasing with obesity epidemic**
  - Nearly 1 in 15 affected by at least moderate sleep apnea
  - 85% of cases estimated to be undiagnosed!
    - Kapur VK et al Sleep and Breath 2002
  - 84% and 93% of individuals with AHI moderately or severely elevated (ie candidates for sleep apnea treatment), were undiagnosed in the MESA study
    - Minority predilection, health disparities issue
      - Chen X et al SLEEP 2015

- **30-40% of patients with coronary disease**

- **> 50% of patients with diabetes or hypertension or heart failure**
Pathophysiologocial Effects

EEG

ECG

BP

Abd

Chest

Vt (air flow)

100

75 Pulse Oxygen Saturation

20 sec Time (minutes)
Sleep Apnea

POTENTIALLY MODIFIABLE RISK FACTORS:
- Obesity
- Craniofacial Abnormalities
- Adenotonsillar Hypertrophy
- Endocrine Disorders
- Neurologic Disorders

NON-MODIFIABLE RISK FACTORS:
- Male Sex
- Race/Ethnicity
- Genetics
- Age
- Congenital Syndromes (i.e. Down’s syndrome)

PHYSIOLOGIC PERTURBATIONS:
- Chronic Intermittent Hypoxia
- Ventilatory Overshoot Hyperoxia
- Increased Sympathetic Nervous System Activity
- Intrathoracic Pressure Swings
- Hypercapnia
- Sleep Fragmentation/Increased Arousals
- Reduced Sleep Duration
- REM Sleep Fragmentation

INTERMEDIATE MARKERS:
- Increased Inflammation
- Increased Oxidative Stress
- Metabolic Dysfunction
- Insulin Resistance
- Hypercoaguability
- Endothelial Dysfunction
- Autonomic Dysfunction

CLINICAL OUTCOMES:
- Systemic Hypertension
- Ischemic Heart Disease/Atherosclerosis
- Diastolic Dysfunction
- Congestive Heart Failure
- Cardiac Arrhythmias
- Stroke
- Increased Mortality and Sudden Death

OSA Prevalence in Cardiovascular Diseases

Candidate Mechanisms

**Digging Deeper**

- Autonomic Nervous System Disturbances
- Intrathoracic Pressure Alterations
- Hypercapnia
- Intermittent Hypoxia
- Systemic Inflammation and Oxidative Stress
Sympathetic Nervous System Activation in Obstructive Sleep Apnea

Decrease CPAP pressure from 8 to 6

BP = blood pressure; CPAP = continuous positive airway pressure; REM = rapid eye movement; RESP = respiration; SNA = sympathetic nerve activity

Sympathetic Nervous System Activation in OSA *During Wakefulness*

Normal controls: $34 \pm 3$ bursts/min  
$p = 0.003$

Sleep Apnea: $59 \pm 14$ bursts/min,
Female-Predominant Associations of and Endothelial Function in OSA

- Female vascular endothelium may be more sensitive to hypoxemia leading to reduced NO bioavailability
- Different vascular reactivity in men and women in OSA
  - Perhaps only men with severe OSA have vascular dysfunction
- Estrogens are known to improve endothelial function likely via induction of increased NO bioavailability
- Alterations of sex-specific hormones in OSA may represent a key factor in increasing vulnerability to vascular dysfunction

Female-Predominant Associations of Endothelial Dysfunction in OSA

- Vascular endothelium is influenced by sex hormones and differences in endothelial function may exist.
- 2 studies used different techniques, i.e. FMD via BAUS versus PAT (the latter operator independent).
- Identified association of OSA severity (AHI and hypoxia) with measures of vascular dysfunction.

Faulx MD; et al. Sex influences endothelial function in sleep-disordered breathing. SLEEP 2004;27(6):1113-20.
Upper Airway Occlusion Leads to Negative Intrathoracic Pressure Swings

- Increased preload
- Increased LV afterload (increased transmural pressure)
- Impaired diastolic function
- Atrial and aortic enlargement

Change in atrial volume $\rightarrow$ AF
Cardiopulmonary Ramifications of Upper Airway Occlusion


Sajkov D et al Prog Cardiovasc Dis 2009;51
Pro-Inflammatory and Atherogenic Effects

- Upregulation of inflammatory mediators
  - IL6*, sIL6R*, IL-8, TNFα, CRP, (NF-Kappa B)
- Enhanced thrombotic potential
  - PAI-1*, fibrinogen*, P-selectin
  - VEGF
- Oxidation of serum proteins and lipids*
- Endothelial dysfunction*
- Insulin Resistance and Dyslipidemia

Hansson NEJM 352: 2005

Sleep Apnea and Cytokines
Cleveland Family Study

Interleukin-6

Soluble IL-6 Receptor

**UNADJUSTED**

- **p=0.0007**

**ADJUSTED**

- **p=0.81**

**UNADJUSTED**

- **p<0.0001**

**ADJUSTED**

- **p=0.0007**

Mehra R et al, Arch of Int Med 2006
**Sleep Apnea and PAI-1**

**Cleveland Family Study**

<table>
<thead>
<tr>
<th>n=567</th>
<th>Change in PAI-1 given 5 unit AHI increase</th>
<th>Difference in slopes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>AHI &lt; 15</strong></td>
<td>1.10 (1.02, 1.16)</td>
<td>0.01</td>
</tr>
<tr>
<td><strong>AHI ≥ 15</strong></td>
<td>0.99 (0.97, 1.01)</td>
<td>0.32</td>
</tr>
</tbody>
</table>

Mehra R et al  AJRCCM 2010
Sleep Apnea and Fibrinogen
Cleveland Family Study

<table>
<thead>
<tr>
<th>AHI</th>
<th>Change in Fibrinogen given 5 unit AHI increase</th>
<th>Difference in slopes</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 15</td>
<td>9.56 (4.26, 14.87)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>≥ 15</td>
<td>-1.14 (-3.29, 1.02)</td>
<td>0.30</td>
</tr>
</tbody>
</table>

Mehra R et al  AJRCCM 2010
Oxidative Stress and Inflammation Differentially Elevated in Objective versus Subjective Reduced Sleep Duration in Obstructive Sleep Apnea

- n=147 participants of the SASS study
- **Inverse association of PSG-TST and MPO**
  - -20.28, -37.48 -3.08,
  - p = 0.021
- **Inverse association of oxidized LDL and SR-SD**
  - 0.98, 0.96-0.99,
  - p = 0.027
  - 2% ox-LDL reduction per hour increase SR-SD

Chronic intermittent hypoxia model in ovariectomized adult female rats

Systemic estradiol administration was protective in terms of blood pressure, ventilation measures and oxidative stress in brain and adrenal glands

Estradiol Protection of Cardiorespiratory Dysfunction and Oxidative Stress in Intermittent Hypoxia

Laoufa et al SLEEP 2017
**Randomized Controlled Trial**

**Effect of CPAP on Measures of Vascular Function and Inflammation**

<table>
<thead>
<tr>
<th>% Change</th>
<th>Sham (n=71)</th>
<th>CPAP (n=72)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Blood Pressure (morning)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SBP</td>
<td>0.338 ± 0.986</td>
<td>-2.516 ± 0.979</td>
<td>0.042</td>
</tr>
<tr>
<td>DBP</td>
<td>1.884 ± 1.347</td>
<td>-2.156 ± 1.338</td>
<td>0.035</td>
</tr>
<tr>
<td><strong>Systemic Inflammation</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IL-6</td>
<td>19.941 ± 8.571</td>
<td>8.837 ± 8.245</td>
<td>0.35</td>
</tr>
<tr>
<td>Soluble IL-6R</td>
<td>2.789 ± 1.833</td>
<td>-2.872 ± 1.764</td>
<td>0.028</td>
</tr>
<tr>
<td><strong>Vascular Measures (morning)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>difference</em></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Augmentation Index</td>
<td>-0.2 ± 1.3</td>
<td>6.5 ± 1.4</td>
<td>0.009</td>
</tr>
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</table>


Respiratory Institute Research Day award, Neurologic Institute Research Day award, SLEEP meeting award
Sex-Specific Alterations in Oxidative Stress in a Randomized Controlled Trial of CPAP versus Sham CPAP for OSA Treatment

- Overall significant difference in SBP, DBP, soluble IL-6 receptor, AI in CPAP vs sham

- PON and MPO with significant gender*group interaction

- Soluble IL-6 receptor with 0% change in female sham, 3.5% ↑ male sham CPAP; 6.4% ↓ in female CPAP, 0.9% ↑ male CPAP

Sleep Disordered Breathing and Hypertension
### Obstructive Sleep Apnea and Incident Hypertension

**The New England Journal of Medicine**

**Prospective Study of the Association Between Sleep-Disordered Breathing and Hypertension**

Paul E. Peppard, Ph.D., Terry Young, Ph.D., Mari Palta, Ph.D., and James Skatrud, M.D.

<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>
</tr>
<tr>
<td>P for trend†</td>
<td>2.89 (1.46–5.64)</td>
</tr>
<tr>
<td></td>
<td>0.002</td>
</tr>
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</table>
Prospective Association of Treated and Untreated Obstructive Sleep Apnea and Risk of Hypertension

n=1889, Spanish study

Declined CPAP: ~2-fold increased risk of incident hypertension

CPAP Non-adherent: ~80% increased risk of incident hypertension

Treated: ~30% reduction in risk of incident hypertension

Marin JAMA. 2012; 307 (20): 2169
Impact of Sleepiness on Treatment Effect of Sleep Apnea

In patients with OSA without daytime sleepiness (n=725), CPAP compared with usual care did not result in a statistically significant reduction in incidence of hypertension or CV events over 4-year median follow-up.

Subgroup analysis of those using CPAP>=4 hours demonstrated CV benefit.

Barbe et al. JAMA, 2012
Sleep Apnea, Endothelial Dysfunction and Non-Dipping Blood Pressure

Increasing AHI and ODI associated with reduction in PAT ratio, p=0.04 and 0.05 respectively.

4% increased odds of non-dipping blood pressure per unit increase of AHI or ODI, p=0.012 and 0.009 respectively.

Seif F, J Sleep Res 2013 and Seif F, J Hypertension 2013
Higher Resistant Blood Pressure in Severe OSA on Intensive Anti-hypertensive Regimen

Intensive anti-hypertensive medication regimen

Walia et al. Journal of Clinical Sleep Medicine 2014
Change in Blood Pressure with CPAP in OSA

SBP Change: -2.46 (-4.31, -.62)

DBP Change: -1.83 (-3.05, -.62)

- 16 RCTs with n=1166 participants
- Modest but significant reductions in:
  - Office SBP (-3.2mmHg), DBP (-2.9mmHg)
  - 24-hour DBP (-3.5mmHg)
  - 24-hour mean arterial BP (-3.6mmHg)
  - Night-time SBP (-4.9mmHg)
  - Mean night-time BP (-2.7mmHg)

Bazzano LA *Hyper* 2007:50
Haentjens et al. *Archives of Internal Medicine* 2007
Schein J of Hypertension; 2014
Spanish Clinical Trials in an All-Female Sample: Improvement in Blood Pressure and Quality of Life with CPAP vs Control in Moderate to Severe OSA

Continuous Positive Airway Pressure Improves Quality of Life in Women with Obstructive Sleep Apnea
A Randomized Controlled Trial

Francisco Campos-Rodriguez¹, Carlos Queipo-Corona², Carmen Carmona-Bernal³, Bernabe Jurado-Gamez⁴, Jose Cordero-Guevara⁵, Nuria Reyes-Nuñez⁶, Fernanda Troncoso-Acevedo⁷, Araceli Abad-Fernandez⁷, Joaquin Teran-Santos⁸, Julián Caballero-Rodriguez⁹, Mercedes Martín-Romero¹¹, Ana Encabo-Motino¹², Lírios Sacristán-Bou¹³, Javier Navarro-Esteva¹⁴, María Somoza-González¹⁵, Juan F. Masa¹⁶, María A. Sánchez-Quiroga¹⁷, Beatriz Jara-Chinarro¹⁸, Belen Orosa-Bertol¹⁹, and Miguel A. Martínez-García²⁰; on behalf of the Spanish Sleep Network.

Effect of continuous positive airway pressure on blood pressure and metabolic profile in women with sleep apnoea

Francisco Campos-Rodriguez¹, Monica Gonzalez-Martinez², Angeles Sanchez-Armengol³, Bernabe Jurado-Gamez⁴, Jose Cordero-Guevara⁵, Nuria Reyes-Nuñez⁶, Maria F. Troncoso⁶,⁷, Araceli Abad-Fernandez⁷, Joaquin Teran-Santos⁸, Julián Caballero-Rodriguez⁹, Mercedes Martin-Romero¹¹, Ana Encabo-Motino¹², Lírios Sacristán-Bou¹³, Javier Navarro-Esteva¹⁴, María Somoza-González¹⁵, Juan F. Masa¹⁶, María A. Sánchez-Quiroga¹⁷, Beatriz Jara-Chinarro¹⁸, Belen Orosa-Bertol¹⁹, and Miguel A. Martinez-Garcia²⁰; on behalf of the Spanish Sleep Network.

Multicenter, open-label randomized controlled trial in 307 consecutive women diagnosed with moderate to severe OSA (apnea–hypopnea index, >15) in 19 Spanish sleep units.

Campos-Rodriguez, et al.. Eur Respi J. 2017 Aug 10;50(2)
CPAP versus Oxygen in Obstructive Sleep Apnea

Gottlieb DJ, Punjabi NM, Mehra R, et al.
Effect of CPAP in Obstructive Sleep Apnea and Resistant Hypertension: HIPARCO trial

- Improvement in 24-hour BP measures driven by reduction in nocturnal BP
- ~2-4 mmHg reduction in nocturnal BP measures

Martinez-Garcia et al. JAMA 2013; 310(22): 2407-2415
Sleep Apnea and Hypertension

- Sustained effect of OSA on BP increases even during the daytime
- OSA is risk factor for HTN independent of confounders, e.g. obesity
- Treatment of OSA in patients with HTN reduces BP consistently in RCTs
- Extent of reduction clinically relevant
  - 1-2 mmHg mean differences in blood pressure are associated with reduced odds of stroke, major cardiovascular events and heart failure
- Clinical trials suggest that sleepy vs non-sleepy patients may derive more BP lowering benefit from CPAP and greater benefit in preventing HTN occurrence
- Patients with OSA and resistant HTN represent a particularly responsive group to BP lowering from CPAP
- Women appear to derive the same extent of benefit in terms of BP reduction with greater benefit in those with more severe OSA
- OSA recognized as an identifiable cause of HTN cited in the 8th report of the JNC hypertension guidelines

Sleep Disordered Breathing and Heart Failure
Mechanisms of OSA leading to Worsening HF

Brisco AND Goldberg, Curr Heart Fail Rep 2010
Schematic representation of the potential bidirectional relationship between obstructive and central sleep apnea sleep (OSA and CSA, respectively) and heart failure (HF)

Takatoshi Kasai et al. Circulation. 2012;126:1495-1510
Sleep Disordered Breathing and Post-Discharge Mortality in Acute Heart Failure

n=1117 consecutive hospitalized patients

Figure 2 Kaplan–Meier post-discharge survival plot of acute heart failure patients by sleep disordered breathing status. OSA, obstructive sleep apnoea. CSA, central sleep apnoea. nmSDB, no or minimal sleep disordered breathing.

Figure 3 Kaplan–Meier post-discharge survival plot of acute heart failure patients by treatment status. The plot includes acute heart failure patients who survived 6 months post-discharge and had their treatment status verified.

Central Sleep Apnea is a Predictor of Cardiac Readmission in Hospitalized Patients With Systolic Heart Failure

RAMI KHAYAT, MD.1 WILLIAM ABRAHAM, MD.1,2 BRIAN PATT, BS.1 VINCENT BRINKMAN, MD.2 JACOB WANNEMACHER, BA.1 KYLE PORTER, MAS.3 AND DAVID JARJOURA, PhD3

Khayat R et al. J Card Fail 2012

Important practical implications

• Mean cost per CHF readmission is $13,000, with a 25.1 percent readmission rate.
• Reduction in readmission rates likely simultaneously reduce costs and improve quality of care.
• Public and private payers have increasingly targeted readmissions as a focus of pay-for-performance initiatives.


Desai et al. Rehospitalization for Heart Failure: Predict or Prevent?. Circulation.2012; 126: 501-506

CSA

Predictor of 6-month cardiac readmission

Adjusted rate ratio

1.53, p=0.03
CANPAP
Canadian Continuous Positive Airway Pressure for Patients with Central Sleep Apnea and Heart Failure

- CPAP adherence 3.6 hours
- 57% patients with AHI suppressed to ≤15 with CPAP compared to control (post-hoc)

Sustained improvement in intermediate measures (left ventricular ejection fraction, plasma norepinephrine levels and 6-minute walk distance)

SERVE-HF multicenter RCT
n=1325, mean f/u 3.5 years
ASV vs Medical management
Symptomatic HF, LVEF <45%
Predominant CSA
Primary end point: All-cause mortality or unplanned HF hospitalization
No difference in primary end point, trend favoring control (non-ASV)
  • HR, 1.14; 95% CI: 0.97-1.33, p=0.10

Increased cardiovascular mortality in ASV arm compared to control
  • 10%/y in ASV vs 7.5%/y in control
  • HR, 1.34; 95% CI: 1.07-1.67

Preliminary results were made public by the sponsor, ResMed Inc, in May 2015 with an urgent Field Safety Notice.

No offsetting improvement in HF symptoms or functional status.

Clinicians were advised that ASV would now be contraindicated for treatment of CSA in symptomatic HF and reduced LVEF.

Key methodological considerations

- Type 1 statistical error
  - CV mortality was not one of the three pre-specified primary end points but was among 20 pre-specified secondary end points.
  - However, given large magnitude of the effect on cardiovascular mortality, it would be imprudent to dismiss this finding.

- High percentage of crossover
  - 17% received PAP in control arm and 29% did not receive or discontinued ASV in ASV arm.

- Device-patient dyssynchrony, high default inspiratory and expiratory pressures.
• 2016 update based upon SERVE-HF results
• ASV: increased cardiac mortality in LVEF<45% and moderate or severe CSA
  • Standard level recommendation against use of ASV in CHF-associated CSA in patients with LVEF<45%
• Option level recommendation for use of ASV in treatment of CHF-associated CSA in patients with LVEF>45% or mild CHF-related CSA
• Findings not generalizable to OSA in HF or CSA without HF

Remaining Questions

• PAP deleterious in reduced systolic function and intravascular volume depletion?
  – Subgroup analysis did not support this explanation
• Increased ventilation due to PS from ASV may worsen respiratory alkalosis, with a increase in potassium excretion, thus predisposing to fatal arrhythmia
• Is CSA a bystander or epiphenomenon?
• CSA is a marker of poor prognosis, however, is it a compensatory mechanism?
• Increase in deaths without preceding hospitalization, SCD?
• ADVENT-HF trial
  – Effect of Adaptive Servo Ventilation on Survival and Hospital Admissions in Heart Failure
  – HFREF patients with either predominantly central or predominantly obstructive SDB, may be able to shed more light in due course (NCT01128816)
Mechanisms underlying increased mortality risk in patients with heart failure and reduced ejection fraction randomly assigned to adaptive servoventilation in the SERVE-HF study: results of a secondary multistate modelling analysis

Christine Eulenburg, Karl Wegscheider, Holger Woehrle, Christiane Angermann, Marie-Pia d’Ortho, Erland Erdmann, Patrick Levy, Anita K Simonds, Virend K Somers, Faiez Zannad, Helmut Teschler, Martin R Cowie

- Increased CV death without previous hospital admission (SCD?) and CV death after a life-saving event in ASV versus control
- In LVEF <30%, ASV increased CV death without previous hospital admission
- Lower CSR proportion (<20%) may have better outcomes on ASV compared to control

On-treatment analysis performed according to actual treatment received
OT analysis affected by physician or patient preference and reduces the power of randomization
29% of those in the ASV arm did not start or discontinued prematurely
17% of those randomized to control crossed over to ASV
Could withdrawal of ASV in the intervention arm have increased mortality?
OT as-treated analysis suggested superficially that exposure to $ASV_{MV}$ was not associated with increased CV mortality, but this analysis is open to bias due to patient and/or physician preferences in treatment decisions
As-treated-as-randomized OT analysis results were similar to the original ITT analysis consistent with a harmful effect of $ASV_{MV}$ on cardiovascular mortality

CAT-HF Trial

- Terminated early due to SERVE-HF
- 126 with HF and moderate to severe SDB randomized to ASV + optimized medical therapy vs OMT alone
- Decompensated HF (systolic and preserved) and a range of SDB
- Average CPAP usage 2.7 hrs/day at 6 months
- Composited endpoint did not differ between the groups (death, CV hospitalizations, % change 6 minute walk) at 6 months
- Pre-specified subgroup analysis: positive impact of ASV effect in HF-pEF

Physiologic Effects of Transvenous PNS

• Multicenter RCT, n=151
• Unilateral transvenous PNS
• ITT analysis
• More patients randomized to intervention had >50% reduction in AHI compared to control

Sleep Apnea and Heart Failure

- SDB is prevalent in HF, may lead to HF and associated with disease progression
- Sleep apnea associated with increased post-discharge mortality and hospital readmission in acute HF
- ASV not indicated in central predominant sleep apnea and systolic HF (EF<45%); SCD likely contributor
- Possible PAP benefit in HF in:
  - Preserved EF
  - OSA
  - Lower CSR burden
- On treatment analysis was not associated with increased CV mortality, however, on-treatment, as-randomized was associated with increased CV mortality in SERVE-HF
- Unilateral transvenous phrenic nerve stimulation holds promise as novel therapy for central predominant sleep apnea in terms of reduction of SDB severity and improvement in functional outcomes
Sleep Disordered Breathing and Cardiac Arrhythmia and Stroke
Putative Obstructive Sleep Apnea and Cardiac Arrhythmia Pathophysiologic Pathways

May A, Van Wagoner D, Mehra R. CHEST 2016
Prevalence of Nocturnal Cardiac Arrhythmias According to Sleep Disordered Breathing Status

Group-Matched by Age, Sex, Race, BMI

Adjusted OR  95% CI

Atrial Fibrillation  4.5  1.2, 17
CVE or NSVT  1.8  1.2, 2.8
AF or NSVT  3.7  1.7, 8.0
CVE Odds > 7.0, 50-60 years old

Mehra R AJRCCM 2006
Obstructive 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

Nocturnal Hypoxia as a Predictor of Stroke
Outcomes of Sleep Disorders in Older Men Study, n=3028

<table>
<thead>
<tr>
<th>Percent of sleep time with SaO2&lt;90%</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;1% (reference)</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>1 to &lt;3.5%</td>
<td>1.29 (0.87, 1.92)</td>
<td>1.31 (0.87, 1.98)</td>
</tr>
<tr>
<td>3.5 to &lt;10%</td>
<td>1.24 (0.74, 2.07)</td>
<td>1.15 (0.67, 1.98)</td>
</tr>
<tr>
<td>10%+</td>
<td>1.83 (1.12, 2.98)</td>
<td>1.71 (1.02, 2.86)</td>
</tr>
<tr>
<td>p-trend</td>
<td>0.02</td>
<td>0.07</td>
</tr>
</tbody>
</table>

**Model 1 Adjusted for age, clinic, race, body mass index, and smoking, diabetes, total cholesterol, HDL cholesterol, and statin use.**

***Model 2 Model 1 plus hypertension and resting SaO2

Sleep Apnea and Atrial Fibrillation/Stroke

- SDB-AF epidemiologic data: High strength of association OR~4 after consideration of confounders
- Retrospective data suggest that sleep apnea treatment reduces recurrence of AF
- Epidemiologic data from the Sleep Heart Health Study suggests vulnerability of men to incident development of stroke and perhaps a protective influence of arousal frequency
- Nocturnal hypoxia predicts stroke in older men
Sleep Disordered Breathing and Coronary Artery Disease and Cardiovascular Mortality
# Obstructive 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>
<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>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>
</tbody>
</table>

Covariates in model:

- Age, race, BMI, smoking
- Plus total and HDL cholesterol, lipid-lowering medications, diabetes mellitus
- Plus SBP, DBP, use of antihypertensive medications

### Hazard Ratios for Incident CHD in “Younger” Men

**Men: Age < 70 years**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Predictor Variable</th>
<th>Hazard Ratio</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Incident CHD</td>
<td>AHI &lt; 5 vs. AHI ≥ 30</td>
<td>1.68</td>
<td>1.02 – 2.76</td>
</tr>
<tr>
<td></td>
<td>AHI continuous (per 10 unit increase)</td>
<td>1.10</td>
<td>1.00 – 1.21</td>
</tr>
</tbody>
</table>

*Gottlieb et al. Circulation 2010; 122: 325-360*
Sex-Specific Association of Sleep Apnea Severity With Subclinical Myocardial Injury, Ventricular Hypertrophy, and Heart Failure Risk in a Community-Dwelling Cohort: The Atherosclerosis Risk in Communities–Sleep Heart Health Study

Gabriela Querejeta Roca, MD; Susan Redline, MD, MPH; Brian Claggett, PhD; Natalie Bello, MD, MPH; Christie M. Ballantyne, MD; Scott D. Solomon, MD; Amil M. Shah, MD, MPH

Box-and-whisker plot of hs-TnT levels among OSA categories stratified by sex.

Kaplan–Meier survival curves for the risk of HF or death of moderate/severe OSA vs none/mild OSA stratified by sex.

Left ventricular mass index (LVMI) among OSA categories stratified by sex.

Gabriela Querejeta Roca et al. Circulation. 2015;132:1329-1337
CPAP and Cardiac Event risk in Severe OSA


n~1500, 10-year follow-up period

Untreated OSA

OR 2.9 for incident non-fatal CVD after multiple risk factor adjustment
Sleep Apnea, Snoring, Incident Cardiovascular Events and All-Cause Mortality in Multi-Ethnic Adult Populations: MESA


HR 1.90 composite CV
HR=2.06 MI
HR=2.39 Angina
HR=2.62 All-cause mortality

Obstructive Sleep Apnea and All-Cause Mortality

Survival Probability

Apnea-hypopnea index (events/hr)
- < 5.0
- 5.0 – 14.9
- 15.0 – 29.9
- ≥ 30.0

Numbers at risk:
- 6294
- 6205
- 6110
- 6001
- 5868
- 5732
- 5566
- 5411
- 4756
- 2357
- 300

Total Deaths:
- 0
- 59
- 143
- 241
- 359
- 478
- 616
- 757
- 875
- 989
- 1046

### Obstructive Sleep Apnea and All-Cause Mortality

<table>
<thead>
<tr>
<th>AHI (events/hr)</th>
<th>N</th>
<th>Person years</th>
<th>Deaths</th>
<th>Mortality Rate</th>
<th>Adjusted Odds Ratios (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Men &lt; 70 years</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 5.0</td>
<td>985</td>
<td>8,220</td>
<td>91</td>
<td>11.1</td>
<td>1.00</td>
</tr>
<tr>
<td>5.0 – 14.9</td>
<td>694</td>
<td>5,697</td>
<td>82</td>
<td>14.4</td>
<td>1.24 (0.90 – 1.71)</td>
</tr>
<tr>
<td>15.0 – 29.9</td>
<td>322</td>
<td>2,623</td>
<td>47</td>
<td>17.9</td>
<td>1.45 (0.98 – 2.14)</td>
</tr>
<tr>
<td>&gt; 30.0</td>
<td>168</td>
<td>1,355</td>
<td>28</td>
<td>20.7</td>
<td>2.09 (1.31 – 3.33)</td>
</tr>
<tr>
<td><strong>Men &gt; 70 years</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 5.0</td>
<td>277</td>
<td>2,055</td>
<td>125</td>
<td>60.8</td>
<td>1.00</td>
</tr>
<tr>
<td>5.0 – 14.9</td>
<td>282</td>
<td>2,176</td>
<td>111</td>
<td>51.0</td>
<td>0.92 (0.70 – 1.20)</td>
</tr>
<tr>
<td>15.0 – 29.9</td>
<td>140</td>
<td>1,029</td>
<td>67</td>
<td>65.1</td>
<td>1.23 (0.90 – 1.68)</td>
</tr>
<tr>
<td>&gt; 30.0</td>
<td>74</td>
<td>517</td>
<td>36</td>
<td>69.6</td>
<td>1.27 (0.86 – 1.86)</td>
</tr>
</tbody>
</table>

Punjabi NM et al, PLOS One 2010
n=2717, mean follow-up of 3.7 yrs
- Primary end-point occurred in 229 CPAP group (17.0%) vs 207 usual care group (15.4%)
- HR= 1.10; 95% CI, 0.91 to 1.32; P=0.34
- Secondary analyses: those adherent to CPAP therapy had a lower risk of stroke (hazard ratio, 0.56; 95% CI, 0.32 to 1.00; P=0.05)

Mean CPAP adherence – 3.3 hours

Was study powered to show a change?

Duration of f/u inadequate?

Those with severe sleep apnea and hypoxia were excluded

Generalizability
  - Male predominant
  - 60% Asian
  - Mean BMI 28.8 kg/m²
  - Baseline ESS score 7.3
Sleep Apnea and Cardiovascular Disease/Mortality

- OSA is highly prevalent in patients with CAD
- Untreated severe OSA increases the risk for major adverse coronary events and mortality
- **Effective** OSA treatment with CPAP may reduce coronary event rates
- Large RCT data suggest lack of improvement of CV mortality with treatment of OSA with CPAP, however, power of study, generalizability and suboptimal CPAP adherence limits interpretability
  - Post-hoc analysis suggests improvement in stroke outcomes
- RCT data suggest improvements in sleepiness and quality of life measures in OSA in those with CV risk with CPAP treatment
- Poor CPAP adherence remains a problem in effective interpretation of OSA clinical trials
Sleep Apnea: A Novel Modifiable Cardiac Risk Factor
Jury In or Out?

• A substantial proportion 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

*Estimated that 5 to 20% of Cardiovascular Disease may be preventable by treating/preventing Sleep Apnea*
Sleep and Cardiopulmonary Disease

NHLBI-funded Sleep Related Respiratory and Electrophysiological Atrial Fibrillation Predictors
Predictors of AF in a longitudinal study of ~3000 participants of the MrOS Sleep Study

NHLBI-funded RCT to examine effect of sleep apnea treatment on CV biomarkers

SASS
Sleep Apnea Stress Study

NHLBI-funded Sleep apnea and Atrial Fibrillation Electrophysiology: Biomarkers and Evaluating Atrial Triggers

SAFEBEAT

NHLBI-funded multicenter cohort study to phenotype PHTN including sleep testing

Transvenous Phrenic Nerve Stimulation Device for CSA Treatment

NHLBI ARRA funded trial Multi-center trial to examine utility of nocturnal supplemental oxygen in treating patients at high CV risk with sleep apnea

NHLBI-funded RCT to examine effect of sleep apnea treatment on CV biomarkers