Outcome Measures in OSA
Defining Our Treatment Goal

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Overview

• What are the effects of SDB?
• What changes do our treatments make?
• What metrics are available?
• What metrics should we follow?
• Conclusions

Effects of Sleep Disordered Breathing (SDB)

• Physiologic
  – Increased incidence of MI, CVA, H/T
    • Epidemiology studies, SHHS
    • Animal studies, Biomarker studies
• Behavioral / Cognitive
  – Daytime sleepiness, increased MVA incidence up to 7x
  – MVA risk in men evident w/ snoring alone w/o OSA Young 1997
• Social
  – Snoring, disruption of marital harmony

What metrics are available?

• Cardiovascular morbidity
• Cognitive function / motor vehicle accidents
• Other physiologic / metabolic parameters
• Snoring (after all, that’s what brings them in, and that’s what patients judge treatment by)
• PSG?
Cardiovascular Disease (SHHS)

- Heart failure, stroke Shahar 2001
- Ischemic changes in the brain Ding 2004
  - Arousals, not AHI
- Association with Hypertension Redline 2005
  - Could not correlate a specific parameter of PSG
- Right Heart Function Dursunoglu 2006

- Multiple other demographic and physiologic parameters that are followed are yielding important data

http://www.jhuccct.com/shhs/

Cardiovascular disease (SHHS) cont.

- NO association of carotid plaques with RDI (AHI)
  - Also looked at degree of hypoxemia and freq of arousals
- All differences in carotid plaques were explained by confounding factors (for CVD)
- Is there NO association of carotid plaques with OSA, or just not with these parameters? Wattanakit 2007

Neurophysiologic Effects - testing

- Attention is impaired Balkin 2004
  - PVT (reliable, no learning, sensitive)
- Meta analysis of neurophysiologic effects of SDB Beebe 2003
  - Vigilance and cognitive functioning impaired
  - Intellectual and verbal functioning relatively spared
  - These improve with treatment (CPAP)
- Cognitive function testing does not correlate w/ AHI Boland 2002 (from SHHS)

Cognitive Function - patient report measures

- Epworth Sleepiness Scale Johns 1991
  - 0-24 scale for “chance of dozing”
  - Average if 7 for medical students, 14 for OSA patient
- Functional Outcomes of Sleep Questionnaire (FOSQ) Weaver 1997
  - Measures impact of sleepiness on functioning
- Calgary Sleep Apnea Quality of Life Index Flemons 1997
  - Captures QOL, performance, mood
- Stanford Sleepiness Scale Hoddes 1973
  - Measure of sleepiness on a 1-7 scale meant to be used at different times during the day for comparison
Metabolic measures?

- Elevated IL-6, TNF-alpha, CRP
  
- Hormonal changes—fT4, testosterone, LH, SHBG
  
- Relationship to diabetes, ILGF-1, sympathetic tone
  
- Free oxygen radicals increased in OSA, decrease w/ CPAP

Will these measures ultimately be what we follow to determine treatment effectiveness? For diagnosis?

HbA1c for OSA?

Snoring

- Subjective spouse measures are “gold standard”
  
- Surrogate measure with VAS, “bother scale”, etc
  
- Objective sound measurements difficult, but possible, to quantify
  
- SNAP frequency analysis analyzes snoring frequency and amplitude
  
- Algorithm proprietary

Polysomnography Measures

- Multiple measures possible, a few are popular
  
  - Apnea Hypopnea Index (AHI)
  
  - Respiratory Disturbance Index (RDI)
  
  - Minimum O2 Saturation
  
  - Arousals
  
  - Time in REM sleep
  
  - Total apnea time
  
  - Total sleep time below 90% saturation

Does a polysomnogram alone define this disease?

Definitions of Disease

- Sleep Disordered Breathing - Recurrent episodes of cessation of respiration (apnea) or decrements in air flow (hypopnea) which may disrupt sleep
**Definition of Apneic Events on PSG**

- **Apnea** - Cessation of breathing during sleep for >10 sec
- **Hypopnea** - Decrease in air flow of >50% associated with a fall in SaO2 >4% +/- EEG arousal
- **Apnea Hypopnea Index (AHI)** - The number of apneas + hypopneas per hour of sleep; add RERAs/hour to get the Respiratory Disturbance Index (RDI)

**Definitions of Disease by PSG**

- **Obstructive Sleep Apnea** (25% males, 9% females, Young 1993)
  - AHI >5 events/hour
- **Obstructive Sleep Apnea Syndrome** (4% m, 2% f, Young 1993)
  - AHI >5 events/hour with symptoms (eg. daytime sleepiness)
- **Upper Airway Resistance Syndrome**
  - Repeated arousals 2' to upper airway resistance or snoring

**Concept of Disease Continuum**

- **No Obstruction**
- **Snoring**
- **Airway Resistance**
- **Sleep Hypopnea**
- **Sleep Apnea**

**What level of disease on PSG justifies treatment?**

- Is there an AHI cut off?
  - Elevated AHI with no sleepiness, hypertension or co-morbidity?
  - Tiredness with a ‘normal’ AHI?
  - Desaturation only?

- How about length of apneas and hypopneas?

- What do we follow on the PSG over time?
  - A1? Desaturation?
Polysomnography measures

- How well do PSG measures correlate with other measures?
- Weaver 2005
  - Analyze PSG/non-PSG measures in mild-moderate OSAS
  - FOSQ, SNORE, SF-36, ESS, PVT
  - No significant association between AHI and any baseline or outcomes non-PSG measure
  - Conclusion: PSG measures do not capture all elements of OSAS and should not be used exclusively to evaluate treatment response

PSG and Tiredness from Sleep Heart Health Study

- Analysis of 1115 patients in the SHHS Kapur 2005
- AHI > 15 45.7% of patients with were sleepy
- AHI > 30 51.4% of patients with were sleepy
- AHI did correlate with sleepiness (p< .01)

<table>
<thead>
<tr>
<th>AHI</th>
<th>Sleepy Patients</th>
<th>Non-sleepy Patients</th>
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<td>31.6</td>
<td>45.7%</td>
<td>51.4%</td>
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Statistically significant, but clinically significant?
Not very discriminating for the clinician

Treatment “Effectiveness”

- Haraldsson tested patients with SDB and normals on a driving simulator (at the Saab factory)
- Performed UP3 on patients with SDB
- Found that patients with SDB uniformly improved after UP3 REGARDLESS OF CHANGES IN AHI
- Did these patients with improved alertness and no change in AHI FAIL treatment? Haraldsson 1995

Treatment Guidelines (cont)

What metric describes the PHYSIOLOGY of the disease?
- PSG???
- Cardiovascular effects (H/T, MI, CAD)
- Sleepiness testing (MSLT, MWT, PVT)
- Endocrine/metabolic effects (CRP, sympathetic tone, IL-6)

- Are the physiologic changes that cause cardiovascular effects the same as the physiologic changes that cause sleepiness or metabolic effects?
Is there one metric for everyone?

There is differential susceptibility in OSA patients and in their physiologic measures, just as there are for patients with sleep deprivation and many other diseases.

One physiologic measurement is not sufficient to describe the disease and disease effects in an individual patient—like measuring blood lipids (Total Chol, HDL, LDL).

Treatment Guidelines

“In the majority of patients without coexisting conditions…the primary reason to test for and treat sleep apnea is the potential to improve the quality of life”

Flemons NEJM 2002

Treatment Guidelines (cont)

“Clinicians do not make decisions about treatment on the basis of AHI alone because it correlates poorly with QOL and the severity of symptoms and does not help to determine the risk of MVA.”

Flemons NEJM 2002

Consensus Statement on Treatment Criteria in OSA

Daniel I. Loube, MD, FCCP; Peter C. Gay, MD, FCCP
Kingman P. Strohl, MD, FCCP; Allan I. Pack, MD, PhD
David P. White, MD, FCCP; Nancy A. Collop, MD, FCCP

CHEST 1999; 115:863–866

CPAP treatment is indicated for all OSA patients with an RDI>30 events per hour, regardless of symptoms.

Treatment with CPAP is indicated for patients with an RDI of 5 to 30 events per hour accompanied by symptoms of excessive daytime sleepiness, impaired cognition, mood disorders, insomnia, or documented cardiovascular diseases to include hypertension, ischemic heart disease, or stroke.
Conclusions

- The proper metric or groups of metrics to measure this disease and guide our treatment is unclear
  - PSG alone does not appear to fully describe the disease
- It is likely that measures of physiology (tiredness, CV morbidities, serology) are what we should ultimately treat, not a number on the PSG
- Metrics should include what is important to the doctor (CV morbidity, MVA) AND the patient (how do I feel)?
- We should strive to define the physiology more completely and develop more robust metrics to define sleep disordered breathing