Obstructive Sleep Apnea 101 / Why Sleep SMART?

First Investigator Meeting
Background and Rationale
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What is OSA?

Obstructive Sleep Apnea

(Click to watch video)
Anatomy of OSA
OSA: The Typical Patient

- Sleepiness
- Male
- Overweight
- Loud snoring
- Middle age or older
OSA: The Typical Patient

• Sleepiness
• Male
• Overweight
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• Note: Stroke Patient ≠ Typical OSA Patient
In-lab polysomnography (PSG): Not for Sleep SMART
Sleep Apnea Test (Nox T3):
Use in Sleep SMART
Obstructive Apnea: Complete blockage of the airway despite effort to breathe. Chest movements gradually increase until airway opens.

Blood oxygen levels reduce to < 3% of baseline value.
CPAP
How does CPAP work?

http://www.mayoclinic.com/health/cpap/MM00716
ResMed AirSense 10 AutoSet
How does automatically-adjusting CPAP (aCPAP) work?

• Traditional approach:
  • CPAP titration in sleep laboratory
  • Rx for home CPAP at fixed pressure

• aCPAP
  • Adjusts pressure automatically, in real time
  • Responds to flow limitation, snoring, or apnea
  • Aims to give lowest effective settings on a continuous basis
Does OSA need to be treated?
Specific outcomes linked to OSA

- Stroke
- Myocardial infarction
- Hypertension
- Hyperlipidemia
- Arrhythmias
- Heart failure
- Increased mortality
- Metabolic Syndrome
- Diabetes
- Erectile Dysfunction
- Depression
- Dementia
- ADHD
- Asthma
Logical Next Steps

• “Should we put a sleep medicine physician in your stroke clinic?”
  • Ron Chervin to Devin Brown, last 10 years
Logical Next Steps

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• “No”
  • Devin Brown to Ron Chervin, last 10 years
Logical Next Steps

•“Should we put a sleep medicine physician in your stroke clinic?”
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•“No”
  •Devin Brown to Ron Chervin, last 10 years
  •But: will gladly reconsider “when we have evidence that OSA treatment works for -- and is tolerated by -- my stroke patients”
What Informs Each Perspective?

• Plausible Biology

• Suggestive Observational Data

• Less Than Definitive Trials
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How could OSA contribute to stroke risk?

• Sleep fragmentation
• Sympathetic activation
• Intermittent hypoxemia / oxidative stress
• Inflammation
Recurrent Apneas
Recurrent Hypoxemia
Recurrent Hypercarbia
Central Venous Pressure
Intracranial Pressure
Arterial Pressure

Figure 1. Respiration (inductive plethysmography), tcPO₂, tcPCO₂, CVP, ICP (epidural), and AP during period with severe OSA (case 1).

How Could Untreated OSA Raise Risk for Stroke or TIA?
How could OSA contribute to stroke risk?

- Atherosclerosis
  - CRP, IL-6, E-selectin, oxidative stress (superoxide)
  - Autonomics, CO₂, endothelial dysfunction
- Cerebral hemodynamics
- Hypercoagulability
  - Platelet activation, increased fibrinogen, EPO
- Sleep Apnea
How could OSA impair stroke recovery?

- Sleep Apnea
  - Free radicals, hypoxia, arrhythmias, decreased cerebral blood flow, decreased cardiac function, hypertension
  - Reduction in: angiogenesis, dendritic/axonal sprouting, angiogenesis, synaptogenesis

- Poor stroke recovery
Plausible Biology is Reversible: CPAP Can Have Dramatic Impact
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OSA after Stroke: Epidemiology

• About 3/4 stroke patients have sleep apnea

• Large majority have obstructive sleep apnea (OSA) rather than central sleep apnea

• Stroke patients seldom screened or treated for OSA

Observational data suggest OSA is a risk factor for:

• Ischemic stroke (incident or recurrent)
• Acute coronary syndrome (ACS)
• Death (and death after stroke)
• Post-stroke adverse functional outcomes
OSA as Risk Factor for first-ever Stroke / ACS

N=967 women over ~7 years: untreated OSA (solid line) vs controls without OSA (dashed), incidence rate of stroke or coronary heart disease was 2.19 vs. 0.54 per 100 person-years; P < 0.0005. (Treated OSA shown in dotted line)

OSA as Risk Factor for Recurrent CV Events

- N=223 post-stroke patients
- Up to 7 years f/u
- Mod-Sev OSA patients who did not tolerate CPAP had more CVEs

OSA as Risk Factor for Mortality (Gen Population)

- N=1651 men
- Followed annually for average of 10 yrs
- Fatal and non-fatal cardiovascular events were more common in severe OSA than less severe, or treated subjects

OSA as Risk Factor for Mortality (After Stroke)

- N=166 post-stroke patients
- Studied 2 months post-stroke; followed for 5 years
- Mod-Sev OSA patients who did not tolerate CPAP had higher mortality

OSA after Stroke → Worse Functional Outcomes

• OSA is associated with:
  • increased dependence after stroke
  • longer acute rehabilitation stays
  • poorer functional outcomes at admission and discharge from rehabilitation
  • poor longer-term functional outcomes

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5 pilot RCTs of CPAP for OSA after acute stroke

• Total N = 307

• Median hrs/night CPAP use:
  • ~ 4 hours on average
  • ~ 5 hours on nights used, or in subjects who accepted PAP

• Results sometimes positive despite inadequate power:
  • Intent to treat analysis of intervention vs controls
  • CPAP adherent vs controls
  • Per protocol analysis

Bravata DM, et al. Sleep 2011; 34:1271-1277
5 pilot RCTs of CPAP for OSA after subacute stroke or in rehab period

• Greater improvement in intervention vs control group in:
  • Stroke-related impairment (Canadian Neurologic Scale); motor function (Functional Independence measure, motor) (one study)
  • Depression (one study)
  • Cognition (two studies)

1 Pilot RCT of CPAP for OSA after TIA

• 2% in intervention group had recurrent vascular events or death vs 12% in control group (p=0.13)
  • Follow-up at 90 days
  • Was underpowered for these outcomes

Safety of CPAP and aCPAP after stroke or TIA

• Across the 5 pilot trials in the acute stroke/TIA period, 307 subjects showed only one SAE related to treatment, and it was expected

• BP reduction is modest (about 2 mm Hg)
So ... should we put a sleep physician in Devin’s stroke clinic?

- AHA/ASA secondary stroke prevention guidelines:

“Given these generally promising albeit mixed results across the randomized trials and the observational cohort studies, what is clearly needed is a randomized trial with adequate sample size to examine whether and the extent to which treatment of sleep apnea with CPAP improves outcomes such as stroke severity, functional status, and recurrent vascular events.”

Equipoise to Perform RCT?

• Treatment of OSA reduces sleepiness, HTN
• Does CPAP help similarly, after stroke?
• Do stroke patients tolerate CPAP?

• Sleep SMART protocol:
  • Participants unlikely to have OSA addressed outside trial
  • Controls forgo OSA treatment for limited period (6 months)
  • Peer-reviewed
  • IRB-approved
  • DSMB-approved

Welcome to Sleep SMART!
(click to play video)