Pathophysiology and Clinical Presentation of Sleep Apnea

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Outline of Talk

• Pathogenesis of obstructive sleep apnea
• Risk factors for obstructive sleep apnea
• Pathogenesis of consequences of obstructive sleep apnea
• Clinical presentation
Factors in Pathogenesis of Obstructive Sleep Apnea

- Smaller upper airway

Both Craniofacial Size and Obesity Can Alter Upper Airway Size
(Watanabe et al, AJRCCM 165:260, 2002)
Normal Subject Apneic Patient
Subjects with OSA have smaller upper airway in wakefulness

Factors in Pathogenesis of Obstructive Sleep Apnea

- Smaller upper airway
- More collapsible upper airway (more positive critical closing pressure)
Factors in Pathogenesis of Obstructive Sleep Apnea

Why does apnea occur during sleep?

- Increased activation of upper airway dilator muscles during wakefulness to compensate for anatomical compromise of upper airway size (compensation lost during sleep)
OSA Patients Have Elevated Activity of Their Genioglossus Muscle During Wakefulness (as % of Maximum Activity)  
(Mezzanotte et al, JCI 89:1571, 1992)

Evidence from Recording of single Motor Units During Wakefulness in Genioglossus in OSA and Controls  
(Saboisky et al, J Physiol 585:135, 2007)

- No difference in proportion of types of units between OSA and controls (inspiratory, tonic, expiratory, etc.)
- Minimal difference in firing frequency of units between OSA and controls (for some types of units ↓ frequency in OSA)
- In OSA inspiratory units discharged earlier before inspiratory airflow
- Larger action potential in OSA (?renervation)

- Could ↑ in multi-unit EMG activity be consequence of motor unit damage (denervation/renervation) – not compensation
Re-innervation of Genioglossus Motor Units
(Saibosky JD et al, AJRCCM 185:322, 2012)

Concept
Re-innervation of motor units leads to ↑ in area of single motor unit potential

Study

<table>
<thead>
<tr>
<th></th>
<th>14 Controls</th>
<th>17 OSA</th>
</tr>
</thead>
<tbody>
<tr>
<td>AHI (events/hr)</td>
<td>3.7±0.7</td>
<td>4.8±6.1*</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>29.4±1.9</td>
<td>32.2±1.4</td>
</tr>
<tr>
<td>No. of units (total)</td>
<td>700</td>
<td>955</td>
</tr>
</tbody>
</table>

Results

<table>
<thead>
<tr>
<th></th>
<th>Area (uV)</th>
<th>514.6±13.3</th>
<th>589.7±12.2*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>*p&lt;0.001</td>
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SUGGESTS RE-INNERVATION

Factors in Pathogenesis of Obstructive Sleep Apnea

Why does apnea occur during sleep?

- Altered neural control of airway during sleep
Overall Control of Motor Activity of Upper Airway Dilator Muscles (White DP, AJRCCM 172:1363, 2005)

Proposed Schematic of Neural Control of Genioglossus and Sleep/Wake Effects (Horner et al, Can J. Physiol Pharmcol 85:155, 2007)
Factors in Pathogenesis of Obstructive Sleep Apnea

• Why does apnea occur during sleep?
• Altered neural control of airway during sleep
• Loss of upper airway negative pressure reflex during sleep

Loss of Negative Pressure-Upper Airway Reflex in OSA Patients (White DP, AJRCCM 172:1363, 2005)
Factors in Pathogenesis of Obstructive Sleep Apnea

Secondary changes in upper airway
• Reduction in upper airway sensation
• Pharyngeal myopathy
  – Denervation of soft palate muscle fibers
  – Inflammation change in muscle (and epithelium)
  – Change in muscle fiber type

Likely contributes to OSA being a slowly progressive disorder

Altered Upper Airway Dilator Muscle in English Bulldog
(Petrof et al, J Appl Physiol 76:1746, 1994)

A. Control

C. Dog with OSA
Factors in Pathogenesis of Obstructive Sleep Apnea

Fluid shifts at night

The Overnight Reduction in Leg Fluid Volume (LFV) is Correlated with Apnea-Hypopnea Index (AHI)
(Redolfi et al, AJRCCM 179:241, 2009)

The more sedentary, the larger fluid shift

\[ r = -0.802 \]
\[ p < 0.001 \]
\[ n = 23 \]
Changes in Leg Fluid Volume in Non-Obese OSA with Compression Stockings (CS) – a Cross-Over Study
(Redolfi S et al, AJRCCM 184:1062, 2011)

Changes in Neck Circumference in Non-Obese OSA with Compression Stockings (CS) – a Cross-Over Study
(Redolfi S et al, AJRCCM 184:1062, 2011)
Changes in Apnea-Hypopnea Index (AHI) in Non-Obese OSA with Compression Stockings (CS) – a Cross-Over Study
(Redolfi S et al, AJRCCM 184:1062, 2011)

Changes in AHI are quite modest

Risk Factors for Obstructive Sleep Apnea

- Obesity
- Obesity
- Obesity
- Craniofacial disorders
- Retroposed mandible/maxillae
- Adenotonsillar hypertrophy
- Endocrine abnormalities – hypothyroidism/acromegaly
- Post-menopause
- Family aggregation
What Is Link Between Obesity and Obstructive Sleep Apnea?

Fat Is Deposited in Tongue in Obese Subjects
(Nashi et al, Laryngoscope 117:1467, 2007)
A Fat Mouse—New Zealand Obese—Has Been Seen to Sleep Upright to protect his upper airway

The standing sleeping mouse

New Zealand Obese (NZO) Mouse Has Same Craniofacial Size as Wild-Type (NZW) But Larger Tongue, Soft Palate and Lateral Walls (Brennick et al, AJRCCM 179:158, 2009)

<table>
<thead>
<tr>
<th>STRUCTURES</th>
<th>NZO (Fat)</th>
<th>NZW</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Soft palate, mm³</td>
<td>5.86 ± 1.28</td>
<td>4.64 ± 0.88</td>
<td>0.021</td>
</tr>
<tr>
<td>Tongue, mm³</td>
<td>137 ± 26.0</td>
<td>104 ± 18.0</td>
<td>0.003</td>
</tr>
<tr>
<td>Lateral pharyngeal walls, mm³</td>
<td>111 ± 26.9</td>
<td>84.4 ± 16.2</td>
<td>0.014</td>
</tr>
<tr>
<td>Mandible width, mm</td>
<td>7.85 ± 0.37</td>
<td>7.9 ± 0.34</td>
<td>NS (P = 0.76)</td>
</tr>
<tr>
<td>Mandible A–P distance, mm</td>
<td>5.46 ± 0.34</td>
<td>5.2 ± 0.22</td>
<td>NS (P = 0.501)</td>
</tr>
</tbody>
</table>
In New Zealand Obese Mouse, Fat Infiltrates Between Muscle Fibers of Tongue
(Brennick et al, AJRCCM 179:158, 2009)

Relative Role of Obesity and Craniofacial Structure Varies by Ethnic Group
(Lee RWW et al, Sleep 33:1075, 2010)

Comparison of Caucasian and Chinese matched for OSA severity (AHI & min SaO2)

<table>
<thead>
<tr>
<th></th>
<th>Caucasians (Australia) (n=52)</th>
<th>Chinese (Hong Kong) (n=52)</th>
<th>p</th>
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<tbody>
<tr>
<td>Obesity</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>BMI (kg/m2)</td>
<td>30.7±5.7</td>
<td>28.4±4.3</td>
<td>0.03</td>
</tr>
<tr>
<td>Cephalometrics</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cranial base (height, mm)</td>
<td>44.2±2.6</td>
<td>39.2±2.6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Mandible (height, mm)</td>
<td>44.4±3.6</td>
<td>40.3±3.0</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Tongue</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Length of tongue/weight</td>
<td>51.2±4.2</td>
<td>40.2±6.9</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Height of tongue/weight</td>
<td>23.1±2.7</td>
<td>19.1±2.5</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Caucasian = more obese, larger longevity
Chinese = more craniofacial restriction; more sensitive to increases in BMI
Effect of Menopause, Hormone Replacement Therapy on Prevalence of Sleep Apnea
(Bixler et al, AJRCCM 163:608, 2001)

<table>
<thead>
<tr>
<th></th>
<th>Prevalence of AHI &gt;15 episodes/hour</th>
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<tbody>
<tr>
<td></td>
<td>N</td>
<td>95% CI</td>
</tr>
<tr>
<td>Menopause</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre</td>
<td>503</td>
<td>0.6 (0.2-1.8)</td>
</tr>
<tr>
<td>Post</td>
<td>497</td>
<td>3.9 (2.5-6.0)</td>
</tr>
<tr>
<td>Hormone replacement</td>
<td></td>
<td></td>
</tr>
<tr>
<td>With</td>
<td>183</td>
<td>1.1 (0.3-4.3)</td>
</tr>
<tr>
<td>Without</td>
<td>314</td>
<td>5.5 (3.4-8.6)</td>
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See also editorial by Young (AJRCCM 163:597, 2001)

Evidence of Family Aggregation of Sleep Apnea

- United States: Cleveland – family study (Redline et al)
- Scotland – Edinburgh study in “non-obese” apneics (Mathur & Douglas)
- Iceland – study based on genealogy approach (Gislason et al)

No genes yet identified—studies in progress
Mechanisms of Consequences

- Repetitive arousals – sleep fragmentation
- Increased sympathetic activation
- Chronic intermittent hypoxia
- Snoring

Mechanisms for Cardiovascular Consequences of OSA
(Arnardottir E et al, Sleep 32:447, 2009)
Does Snoring Lead to Carotid Artery Atherosclerosis?

Provocative Concept


Heavy Snoring (% of Night >50%) Increases Prevalence of Carotid Atherosclerosis but Not Femoral (Ultrasound)
(Lee SA, et al, Sleep 31:1207, 2008)

Solid bar: carotid atherosclerosis
Striped bar: femoral atherosclerosis
What About Symptoms?

- Snoring – loud, habitual snoring
- Witnessed apnea (uncommon, but more specific)
- With excessive sleepiness (called sleep apnea syndrome)
- Many patients with obstructive apnea during sleep are not excessively sleepy

Epworth Sleepiness Scale
(Johns, Sleep 14:540, 1991)

<table>
<thead>
<tr>
<th>Situation</th>
<th>Score</th>
</tr>
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<tbody>
<tr>
<td>Sitting and reading</td>
<td></td>
</tr>
<tr>
<td>Watching TV</td>
<td></td>
</tr>
<tr>
<td>Sitting inactive in public place</td>
<td></td>
</tr>
<tr>
<td>Passenger in car</td>
<td></td>
</tr>
<tr>
<td>Lying down to rest in afternoon</td>
<td></td>
</tr>
<tr>
<td>Sitting talking to someone</td>
<td></td>
</tr>
<tr>
<td>Sitting after lunch without alcohol</td>
<td></td>
</tr>
<tr>
<td>In a car, stopped for minutes in traffic</td>
<td></td>
</tr>
<tr>
<td><strong>Total (normal ≤10)</strong></td>
<td></td>
</tr>
</tbody>
</table>

_Dozing_

0=Never, 1=Slight chance, 2=Moderate chance, 3=High chance
Questionnaires

Berlin Questionnaire
Questions about snoring
Questions about sleepiness
Questions about hypertension
Questions about age, weight, height, gender, neck circumference, ethnicity
Provides dichotomous outcome – high or low risk for OSA
High and low risk categories decided by consensus

Respiratory Disturbance Index in High and Low Risk Groups from Berlin Questionnaire
Diagnostic Accuracy of Berlin Questionnaire (BQ) in Detecting Sleep-Disordered Breathing (SDB) in Patients with a Recent Myocardial Infarction (MI) (Kuniyoshi FHS et al, Chest 140:1192, 2011)

99 patients with MI (Berlin/sleep study)
64 (65%) – high risk for SDB on BQ

Berlin Questionnaire (BQ)
- Sensitivity: 0.68
- Specificity: 0.34

∴ BQ – modest sensitivity, **POOR SPECIFICITY** – not ideal!!

NEED MORE IN-DEPTH ASSESSMENT OF THESE VARIOUS QUESTIONNAIRE TOOLS

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Multiple Variable Apnea Prediction (Maislin et al, Sleep 18:158, 1995)

Combines
- Symptom score – frequency of snoring, snorting, witnessed apneas
- Age
- Gender
- BMI
to calculate likelihood of apnea, on scale between 0 and 1.
Conclusions

- Upper airway in obstructive sleep apnea is smaller and more collapsible
- Reduction of neuronal activity during sleep in airway dilator muscles involves multiple neurotransmitter systems
- There is secondary damage to upper airway muscles and nerve
- Why does obesity lead to OSA—unknown. Increased tongue fat is a possible mechanism.
Conclusions

• Multiple mechanisms are responsible for consequences of obstructive sleep apnea
  – Repetitive arousals
  – Sympathetic activation
  – Chronic intermittent hypoxia
• Snoring itself may lead to damage to carotid arteries
PATHOPHYSIOLOGY AND CLINICAL PRESENTATION OF SLEEP APNEA

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Large study showing differences in prevalence of sleep apnea in women pre- and post-menopause and on or off hormone replacement therapy.


Interesting article that shows that mice with a genetic abnormality that leads to marked obesity have larger tongues, smaller upper airways and fat infiltration in the tongue compared to wild-type controls. Thus, fat deposition in the tongue could be a major part of mechanism linking obesity to obstructive sleep apnea.


Recent, well conducted study that argues that in normal rats a major normal drive to activate upper airway motoneurons is provided by the neurotransmitter—noradrenaline. This drive declines during sleep and is likely an important part of the normal decline in upper airway motoneuron activity with sleep.


Study that shows family aggregation of sleep apnea in Iceland using the unique genealogy data base. This is an important observation since it means that studies of genetic basis for sleep apnea can be conducted there using this unique population and resources for genetic studies.

*Helpful recent review of control of motoneurons of upper airway dilator muscles and why their activity is altered during sleep.*


*Helpful recent review on neural systems that control a family of hypoglossal motoneurons and how they change with sleep.*


*Study that evaluated upper airway mechanics in individuals under general anesthesia for surgery. They were paralyzed so that the passive mechanical properties of the upper airway could be assessed. Individuals with OSA have much more collapsible upper airways.*


*A brief review that describes how neural circuits controlling sleep interact leading to reduced activation of upper airway dilator muscles during sleep.*


*Provides evidence for sensory impairment as revealed by vibration and 2-point discrimination in upper airway of patients with sleep apnea and snorers as compared to controls.*


*Well done study that uses measures from photographs to assess differences in craniofacial dimensions between patients with OSA and controls. Shows that patients with OSA have reduced mandibular length, mandibular-nasion angle and anterior neck space. Could be useful addition to our clinical evaluation of patients with OSA.*

Interesting study that evaluated role of obesity and craniofacial dimensions in Caucasians with sleep apnea (in Australia) and Chinese with sleep apnea (from Hong Kong). When matched for OSA severity the following are found: Caucasians are more obese than Chinese; Caucasians have larger tongue size than Chinese; Chinese have more craniofacial restriction (smaller cranial base, maxilla, mandible); Chinese are more sensitive to increased weight. The slope of the relationship between BMI and log BMI is greater in Chinese than Caucasians.


Provocative study. Shows that heavy snoring, i.e., snoring for >50% of the sleep period, is associated with an increased risk for atherosclerosis of carotid artery as measured by ultrasound but not femoral. Could heavy snoring and the resulting vibration lead to local vessel wall damage in carotid artery?


Helpful brief review with respect to evidence for and consequences of pharyngeal neuropathy in patients with OSA.


Based on observations over ten year period, shows that sleep apnea is a very slowly progressive disorder.


Shows that patients with OSA have increased activation of their genioglossus muscle during wakefulness. This is presumed to be compensation mechanism for anatomical compromise of the upper airway.


Provocative study. Was done on tongues in n=121 individuals having autopsies at the Medical Examiner’s Office. Demonstrated that there is substantial fat infiltration into tongue. Amount of tongue fat is correlated with BMI. There is a distinct distribution of fat within tongue. Given nature of study, there is no information on whether these subjects had OSA prior to death. Supports the concept that ectopic deposition of fat in
tongue (and possibly other upper airway structures) is mechanism by which obesity leads to OSA.


Study that examined use of compression stockings to reduce leg fluid volume and hence sleep-disordered breathing. Study was done in a small sample of non-obese (BMI<30 kg/m²) patients with OSA (AHI=48.6±26.0). A cross-over design was used. Compression stockings significantly reduced leg fluid volume, neck circumference and apnea-hypopnea index. Effect on AHI was, however, modest. The AHI was reduced from 48.4±26.9 to 31.3±20.2. A modest effect.


Shows correlation between the reduction in leg fluid volume during sleep and the apnea-hypopnea index and the increase in neck circumference with sleep. The change in leg fluid volume correlates with the self-reported amount of sitting during the day. Thus, could being sedentary be a risk factor for obstructive sleep apnea by leading to more fluid shift at night from legs to neck?


Important step forward in understanding motor control of genioglossus in wakefulness in obstructive sleep apnea compared to controls. Did not find expected increase in firing rate of single motor units in genioglossus in OSA compared to controls, as would be predicted by neuromuscular compensation hypothesis. Inspiratory units in OSA patients fired sooner (before onset of inspiration) than controls. The action potentials of motor units in OSA subjects were greater than controls. Thus, the enhanced multi-unit recording of genioglossus EMG in OSA patients might reflect neuropathic changes in the muscle—denervation/renervation.


Study that examined characteristics of action potential of a large number of single motor units in genioglossus in patients with obstructive sleep apnea and controls. A large number of units were recorded from. There was a significant increase in the area of the action potential of motor units in subjects with OSA compared to controls. This is
interpreted as meaning that there must have been neurogenic damage in the genioglossus and that the increased area is compatible with re-innervation.


Brief review summarizing the evidence that there are different physiological phenotypes for obstructive sleep apnea. Particularly focuses on the idea that different individuals respond to the mechanical load of upper airway obstruction in different ways.


Study that showed that in one relevant population—patients with recent myocardial infarction—Berlin Questionnaire performed poorly in identifying patients with OSA. Specificity was only 0.34! Sensitivity was 0.68.


Report from Sleep Heart Health Study that shows that in post-menopausal women hormone replacement therapy is associated with lower prevalence of sleep apnea as defined by AHI >15 episodes/hour.


Found no evidence of differences in genioglossus activity and effect of sleep on this activity in fat Zucker rats compared to lean. Antagonism of serotonin did not reveal evidence of an endogenous serotonin input in either lean or obese Zucker rat.


Insightful editorial that questions whether prevention of sleep-disordered breathing is another indication for hormone replacement therapy.


Report from Wisconsin Sleep Cohort that menopause is associated with increased prevalence of sleep apnea as defined by an AHI >5 episodes/hour.