Sleep Apnea Phenotyping

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Dr. Malhotra has declared no conflicts of interest related to the content of his presentation.
Increased prevalence of sleep apnea in US adults over the last 20 years.

- "Sleep apnea" = apnea-hypopnea index ≥15 events per hour.
- Data from the National Health and Nutrition Examination Surveys and the Wisconsin Sleep Cohort Study.
- American Journal of Epidemiology 2013; DOI: 10.1093/aje/kws342
• 13% were normal
• 33% had mild OSA
• 30% had moderate OSA
• 23% had severe OSA
Inadequate Anatomy

Compensatory Reflex

↑Activity of Pharyngeal Dilators (GG)

Sleep Fragmentation

Maintains Upper Airway Patency

Sleep Onset

Loss of Reflex

↓Activity of Pharyngeal Dilators

Arousal

Neurocognitive Sequelae

Cardiovascular Sequelae

↑Endothelin
↓Vagus

Sympathetic Activation

↑Respiratory Effort

Hypoxia + Hypercapnia

Airway Collapse

Jordan et al. Lancet 2013
OSA Phenotypes

- Mechanisms underlying OSA are highly variable.
- There are likely to be multiple mechanistic pathways which when targeted in individuals are likely to improve OSA.

SLEEP 2009; Thorax 2010; AJRCCM 2014
Obstructive Sleep Apnea  
Underlying Mechanisms

- Anatomy
- Pharyngeal dilator muscle control asleep
- Arousal Threshold
- Loop gain
- Lung volume
- Vascular
Pharyngeal anatomy explains only a minimal portion of the variability in AHI
Obstructive Sleep Apnea Underlying Mechanisms

- Anatomy
- Pharyngeal dilator muscle control asleep
- Arousal Threshold
- Loop gain
- Lung volume
- Vascular
BASAL GG EMG ACTIVITY IS HIGHER IN OSA PTS. THAN CONTROLS

% of Maximal GG EMG Activity

CONTROLS (N=14)

OSA PTS. (N=11)

* = p < .05 vs. controls

JCI 1991
Most OSA patients have some periods of stable breathing

- Studied GGEMG, TPEMG, EELV etc

- Genioglossus activity was invariably high during stable breathing

- Genioglossus is necessary and sufficient to stabilize breathing spontaneously in OSA
Pharyngeal Motor Control Studies

1. Genioglossal But Not Palatal Muscle Activity Relates Closely to Pharyngeal Pressure
   Malhotra et al. AJRCCM 2000a, 2000b AJRCCM 2002

2. Within-breath control of genioglossal muscle activation in humans: effect of sleep-wake state
   J. Physiol. 2003

3. Control of upper airway muscle activity in younger vs older men during sleep onset
   J. Physiol. 2004

4. The impact of wakefulness stimulus on pharyngeal motor control
   Lo et al. Thorax 2007

5. Mechanisms of Compensation
Correlation Between Negative Epiglottic Pressure and GG Peak Phasic Activation (one man awake and asleep)

Epiglottic Pressure (cm H$_2$O)

<table>
<thead>
<tr>
<th>Epiglottic Pressure</th>
<th>GG Peak (% of max)</th>
</tr>
</thead>
<tbody>
<tr>
<td>-16</td>
<td>10</td>
</tr>
<tr>
<td>-14</td>
<td>20</td>
</tr>
<tr>
<td>-12</td>
<td>30</td>
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<tr>
<td>-10</td>
<td>40</td>
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<tr>
<td>-8</td>
<td>50</td>
</tr>
<tr>
<td>-6</td>
<td>60</td>
</tr>
<tr>
<td>-4</td>
<td>70</td>
</tr>
<tr>
<td>-2</td>
<td>80</td>
</tr>
</tbody>
</table>

R = -0.976
p = <0.0001

awake
R = -0.611
p = 0.0265

Malhotra et al.
AJRCCM 2000
Combined Mechanoreceptive and Chemoreceptive Stimuli

<table>
<thead>
<tr>
<th>Condition</th>
<th>Baseline</th>
<th>IRL</th>
<th>Hypoxia</th>
<th>Hypoxia-IRL</th>
<th>CO2</th>
<th>CO2-IRL</th>
</tr>
</thead>
<tbody>
<tr>
<td>GGEMG (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Max</td>
<td></td>
<td></td>
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</tbody>
</table>

AJRCCM 2002
Pharyngeal dilator muscles can respond during stable sleep if stimuli are given in sufficient magnitude and for adequate duration.
Healthy subject, 
Pcrit = -0.11 cmH$_2$O

OSA patient, 
AHI = 52 events/hr, 
Pcrit = -0.27 cmH$_2$O
Aging Influences on Pharyngeal Anatomy and Physiology: The Predisposition to Pharyngeal Collapse

Atul Malhotra, MD, Yaqi Huang, PhD, Robert Fogel, MD, Stan Lazic, Giora Pillar, MD, PhD, Marianna Jakab, MSc, Ron Kikinis, MD, David P. White, MD

R = -0.55, p < 0.001
Genioglossus premotoneurons and the negative pressure reflex in rats

Nancy L. Chamberlin¹, Matthias Eikermann², Philipp Fassbender¹, David P. White² and Atul Malhotra²

¹Department of Neurology, Beth Israel Deaconess Medical Center and Harvard Medical School, Boston, MA 02115, USA
²Divisions of Sleep Medicine and Pulmonary/Critical Care Medicine, Brigham and Women’s Hospital and Harvard Medical School, Boston, MA 02115 USA
A  baseline

Raw
GG
EMG

MTA
GG
EMG

Airway
Negative
Pressure

B  bilateral muscimol in peribex region

Raw
GG
EMG

MTA
GG
EMG

Airway
Negative
Pressure

50 cm water
1 sec
Single Motor Units and SFEMG

- Wilkinson SLEEP 2008
- Saboisky J Physiol. 2007, JAP 2012
- Wilkinson SLEEP 2010a, 2010b
- McSharry SLEEP 2012, in review

- High frequency sampling of EMGs
- Can “see” activity of single cells in humans
- Has opened possibility of pharmacological targets
Pharyngeal Muscle Control

There are likely to be subgroups of patients who respond to efforts to augment muscle activation. Perhaps targeting this subgroup would make sense in pharmacological studies (JAP 2008). Increasing UA muscle response may be deleterious in patients with unstable ventilatory control.
Obstructive Sleep Apnea
Underlying Mechanisms

- Anatomy
- Pharyngeal dilator muscle control asleep
- Arousal Threshold
- Loop gain
- Lung volume
Gleeson et al. – 1990 Am Rev Respir Dis

PEAK NEGATIVE ESOPHAGEAL PRESSURE FOR THE BREATH PRECEDING AROUSAL FROM SLEEP (-CM H₂O)

HYPOXIA
HYPERCAPNIA
ADDED RESISTIVE LOAD
Arousal Threshold – Double-edged Sword

- A low arousal threshold could lead to premature arousal with inadequate time to accumulate respiratory stimuli
- A high arousal threshold could lead to substantial hypoxemia and hypercapnia with end-organ impact
- Therapies to manipulate arousal threshold are likely to benefit some patients and theoretically hurt others
- PPG funded (PI: Saper)

Saboisky et al. Thorax 2010
Trazodone Increases Arousal Threshold in Obstructive Sleep Apnea

Raphael C Heinzer, David P White, Amy S Jordan, Yu L Lo, Louise Dover, Karen Stevenson, Atul Malhotra
Eszopiclone increases the respiratory arousal threshold and lowers the apnoea/hypopnoea index in obstructive sleep apnoea patients with a low arousal threshold

Danny J. ECKERT, Robert L. OWENS, Geoffrey B. KEHLMANN, Andrew WELLMAN, Shilpa RAHANGDALE, Susie YIM-YEH, David P. WHITE and Atul MALHOTRA
Sleep Disorders Program, Division of Sleep Medicine, Brigham and Women’s Hospital and Harvard Medical School, Boston, MA 02115, U.S.A.
Pharmacology Studies of Sedation/Anesthesia

- Differential effects of isoflurane and propofol on genioglossus muscle function and breathing. *Anesthesiology* 2008
- Sugammadex *Brit J. Anesth.* 2008
- Pentobarbital *Anesthesiology* 2009
- *Rocuronium vs. Cisatracurium* *AJCC* 2009
- Pentobarbital in humans *ERJ* 2010

- Agents have differential effects on the upper airway

  Chamberlin et al.
Arousal Threshold Summary

• Arousal threshold is highly variable in OSA
• Agents can raise the arousal threshold without suppressing UAM activity
• Can buy time to activate respiratory muscles using endogenous respiratory stimuli
Obstructive Sleep Apnea
Underlying Mechanisms

- Anatomy
- Pharyngeal dilator muscle control asleep
- Arousal Threshold
- Loop gain
- Lung Volume
- Vascular function
Thermostat Analogy
Cheyne Stokes Respirations
Loop gain vs. AHI

$r = 0.36$

$p = 0.076$
Atmospheric $P_{crit}$ Group

$AHI$ (episodes/hour)

Loop gain

$r = 0.88$
$p = 0.0016$

AJRCCM 2004
Obstructive Sleep Apnea
Underlying Mechanisms
High Loop Gain

Administer agents to reduce loop gain:

- Oxygen (Resp Phys 2008)
- Acetazolamide (Sleep 2013, J. Physiol. 2012)
Cardiovascular and Respiratory Reflexes

Genioglossus
Local upper airway receptors
Ventrolateral Medulla
Nucleus of the solitary tract
+Cortex
+
+
Tensor palatini
+
+
Orexin
PPT/LDT
LC Raphe
VXII

Malhotra et al.
Lancet 2013
Obstructive Sleep Apnea Underlying Mechanisms

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Lung Volume Story

- EELV can alter pharyngeal mechanics
- Van De Graaf JAP ; Begle ARRD
- Mechanisms debated
- Prior studies during wakefulness are confounded

- Stanchina et al. SLEEP 2003
- Owens et al. JAP 2010, JCSM 2011, JAP 2013
- Jordan et al. JAP 2010
Sleep Apnea in the Elderly

• OSA in the elderly may have fewer consequences than in younger at least for cardiovascular consequences
• Mechanisms underlying OSA may be more anatomical than ventilatory control driven
• Different mechanisms may influence consequences e.g. less negative intrathoracic pressures in older vs. younger OSA at arousal

Sleep in press, PLOS One in press
**Disclosures /Funding**

Grants PI: Malhotra
- NIH and AHA

Industry (none since May 2012)
- Pfizer
- Apnexit
- SGS
- Philips
- SHC
- Apnicure
Change in Ventilatory Effort Across an Obstructive Apnea

Effort Index = \frac{(E2 - E1)}{E2}
Effort Index may be a Reasonable Surrogate for Loop Gain

Effort Index

Loop Gain

R = 0.96
P < 0.05
Which of the following leads to increased loop gain?

1. A reduction in controller gain
2. A reduction in plant gain
3. A reduction in circulatory delay
4. Benzodiazepines
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39%  26%  13%  23%
Which of the following best describes the role of arousal threshold in sleep apnea?

1. The arousal threshold is similar in OSA vs. controls
2. Carbon dioxide is thought to be the main factor contributing to arousal from sleep
3. Lowering arousal threshold consistently leads to worsening hypoxemia
4. Raising arousal threshold can contribute to upper airway dilator muscle activation in select patients
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Which of the following is true regarding the Pcrit of the pharyngeal airway?

1. A very positive Pcrit is protected from sleep apnea
2. A very negative Pcrit is typical of morbid obesity
3. Pcrit explains less than half of the variance in the occurrence of obstructive sleep apnea
4. A reduction in Pcrit is typical following major weight loss
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![Bar chart]

1. 12%
2. 6%
3. 55%
4. 27%
Which of the following is true regarding sleep apnea therapy?

1. CPAP is rarely tolerated by patients with symptomatic OSA
2. Treatment of the underlying cause of OSA is a viable approach to targeting OSA therapy
3. Treatment of sleep apnea is unproven apart from improvement in symptoms
4. The majority of OSA patients are currently receiving some form of therapy
Which of the following is true regarding sleep apnea therapy?

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