Obstructive Sleep Apnea: A Physiological Approach

Robert L. Owens, MD
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Outline

• Cause(s) of OSA

• Can we measure the causes in an individual?

• Is that useful?
Thoracic pressure swings (↑LV afterload)

What happens when you fall asleep: normal

Ventilation

Ventilatory Demand
What happens when you fall asleep: normal or OSA

Ventilation

Ventilatory Demand

Wake

Sleep

Time

Ventilation ≠ Demand
Because of poor anatomy

Hypoventilation leads to increased ventilatory demand, which will activate upper airway muscles to improve ventilation.

But, muscle recruitment and improvement in ventilation is variable.

Good muscle response achieves acceptable ventilation
Hypoventilation leads to increased ventilatory demand, which will activate upper airway muscles to improve ventilation.

But, muscle recruitment and improvement in ventilation is variable.

Poor muscle response does not achieve acceptable ventilation.
What happens when you fall asleep: OSA

This patient has OSA – when they go to sleep they hypoventilate, and wake themselves up due to: Anatomy, upper airway muscles, arousal threshold, and loop gain.
Better muscles can prevent OSA

For same anatomy, better muscles can lead to stable flow limited breathing, no arousal.

Similarly, with same anatomy and muscle response, a higher arousal threshold may allow respiratory drive to increase enough to recruit muscles sufficiently to sustain ventilation.
Decreased loop gain can help, too

Similarly, a lower loop gain may prevent ventilatory demand from rising above the arousal threshold.

Pathogenesis of sleep apnea

Obstructive Sleep Apnea

- High loop gain
- Poor upper airway muscle response
- Low arousal threshold
- Small, collapsible upper airway
Outline

• Cause(s) of OSA
  • \textit{It might be more than just a fat neck}
• Can we measure the causes in an individual?

• Is that useful?

Can we measure the response to hypoventilation during sleep?
Yes, by letting the airway collapse

With repeated drops, we can measure how much the upper airway is open at different pressures, or at atmospheric pressure (0cmH₂O)

Measuring anatomy
With hypoventilation, ventilatory demand will increase an unknown amount, and some muscle recruitment will occur.

Return to holding pressure opens upper airway and reveals ventilatory demand.
With knowledge of the ventilatory drive, can calculate loop gain of the system, and upper airway gain.
Some CPAP drops, the ventilation will be so low, that the ventilatory drive gets so high that you have an arousal.

Use loop gain to predict ventilatory drive at this point = AT
Automated methods to measure the traits!
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• Cause(s) of OSA
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• Can we measure the causes in an individual?
  • *Yes*
• Is that useful?

Defining Phenotypic Causes of Obstructive Sleep Apnea
Identification of Novel Therapeutic Targets

Danny J. Eckert¹,², David P. White¹, Amy S. Jordan¹,², Atul Malhotra³, and Andrew Wellman⁴

**At a Glance Commentary**

Scientific Knowledge on the Subject

Previous studies have established that there are likely multiple causes of obstructive sleep apnea (OSA). However, most of these studies were limited to investigating one mechanism in isolation, involved relatively small numbers of participants, and were not performed using detailed physiologic measurements. Accordingly, before the current study, the proportion of patients with OSA in whom nonanatomic pathophysiologic features are present was unknown.

What This Study Adds to the Field

This is the largest comprehensive physiologic study to date showing that the causes of OSA are multifactorial and not just anatomically driven. One or more nonanatomic pathophysiologic traits are present in 69% of patients with OSA. We propose a three-point (Passive critical closing pressure of the upper airway, Arousal threshold, Loop gain, and Muscle responsiveness [PALM]) scale to help guide future investigation aimed at developing novel targeted therapies for OSA according to pathophysiologic characterization.

N = 75 subjects

2013
As expected, anatomy worse in those with OSA

But no difference in muscle responsiveness...

A.

Muscle Responsiveness
(%max EMG/Pepti cmH$_2$O)

Controls
OSA
Or Loop Gain between controls and those with OSA

And Arousal Threshold goes the wrong way?!

Harder to wake up (Protective??)
**Pathogenesis of sleep apnea**

- Small, collapsible upper airway
- High loop gain
- Poor pharyngeal muscle response
- Low arousal threshold

**So is this true? Is it just having a fat neck?**

**A new model that includes Effect Modification**

Upper airway passive anatomy

- Open
- Closed

**Exposure**

- No OSA
  - (High LG – CSA?)
  - (Low AT – insomnia?)
- OSA

**Effect modifiers**

**Outcome**
Non anatomical traits are important in some people

Anatomy is important in everyone
Loop gain is important if you have vulnerable anatomy

In this anatomically vulnerable group of patients, whether you have OSA is dependent on LG

Muscle responsiveness is important if you have vulnerable anatomy

No difference in slope, until you get to vulnerable anatomy
Non anatomical traits are important in some people

Upper airway passive anatomy

Exposure

Vulnerable Anatomy

Open

Closed

Loop gain
Arousal threshold
Upper airway gain

Effect modifiers

No OSA

OSA

Outcome

<table>
<thead>
<tr>
<th>PALM Category</th>
<th>Proportion of Patients</th>
<th>Category Cut-Offs</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>23%</td>
<td>Pcrit greater than +2 cm H\textsubscript{2}O</td>
<td>Will always have OSA</td>
</tr>
<tr>
<td>2</td>
<td>58%</td>
<td>Pcrit = 2 to +2 cm H\textsubscript{2}O</td>
<td>Probably should have OSA, but many could be treated without CPAP?</td>
</tr>
<tr>
<td>2a</td>
<td>36%</td>
<td>Pcrit = 2 to +2 cm H\textsubscript{2}O without nonanatomic vulnerability</td>
<td></td>
</tr>
<tr>
<td>2b</td>
<td>64%</td>
<td>Pcrit = 2 to +2 cm H\textsubscript{2}O with nonanatomic vulnerability</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>19%</td>
<td>Pcrit less than −2 cm H\textsubscript{2}O</td>
<td>Probably should not have OSA</td>
</tr>
</tbody>
</table>
Outline

• Cause(s) of OSA
  • *It might be more than just a fat neck*
• Can we measure the causes in an individual?
  • *Yes*
• Is that useful?
  • *Potentially*

Physiology may help:

• Understand the cause of OSA in an individual (or group of people)

• Predict the improvement with non PAP anatomical therapy (e.g. surgery, oral appliance)

• Choose a primary treatment for OSA?

• Predict adherence to therapy?

• Predict symptoms related to OSA?
Why do different people have OSA?

Why do different groups of people have OSA?
Can physiology predict those who respond to oral appliances and surgery?

**SCIENTIFIC INVESTIGATIONS**

**Physiology-Based Modeling May Predict Surgical Treatment Outcome for Obstructive Sleep Apnea**

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Figure 3—The importance of nonanatomical traits is dependent on anatomy.

- Airway generally open
- Vulnerable anatomy
- Airway generally closed

- More impact
- Less impact

- Better
- Anatomy (eg, PCrIt)
- Worse
Can physiology **predict** those who respond to oral appliances and surgery?

Treatments to improve the non-anatomical traits

- **Arousal Threshold**
  - Sedative hypnotics (eszopiclone, trazodone)
  - Behavioral therapy

- **Loop Gain**
  - Oxygen
  - Acetazolamide

+ **non CPAP Anatomy Improvements**
  - Position Therapy
  - Oral Appliance

- **Upper airway muscles**
  - HGNS
  - Drugs?
Targeting the problem

Eckert Clin Sci 2011

Does low ArTH predict adherence?
Does low ArTH predict adherence?

Figure 3 — Objective continuous positive airway pressure (CPAP) compliance separated according to body mass index category.

Data are average nightly values for each participant and mean ± SD.

Figure 1 Probability of having a symptom within each cluster. The conditional probabilities of 12 symptoms (selected from the complete list in Table 2) are shown to highlight the major differences among clusters.

Ye ERJ 2014
• **Endotype** – a subtype of a condition that has a distinct functional or pathobiological mechanism

• **Phenotype** – observable consequences of a disease

<table>
<thead>
<tr>
<th>Genotype</th>
<th>Endotype</th>
<th>Phenotype</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Two copies of Delta 508 mutation</td>
<td>CFTR dysfunction</td>
<td>Cystic Fibrosis</td>
<td>Supportive + ivacaftor</td>
</tr>
<tr>
<td>Many other mutations</td>
<td></td>
<td></td>
<td>Supportive</td>
</tr>
<tr>
<td>Associated with certain HLA genotypes</td>
<td>Decreased insulin production</td>
<td>Diabetes Mellitus</td>
<td>Exogenous insulin</td>
</tr>
<tr>
<td>Various genes implicated</td>
<td>Insulin resistance</td>
<td></td>
<td>Insulin-sensitizing drugs</td>
</tr>
<tr>
<td>(unknown, area of active investigation)</td>
<td>Low arousal threshold</td>
<td>OSA “disturbed sleep”</td>
<td>CPAP, but sedative-hypnotics might be alternative</td>
</tr>
<tr>
<td></td>
<td>High Loop Gain</td>
<td>OSA with cardiovascular disease</td>
<td>CPAP, but Oxygen, acetazolamide might be alternatives</td>
</tr>
<tr>
<td>Moderate AT, moderate LG</td>
<td>OSA “minimally symptomatic”</td>
<td></td>
<td>None needed</td>
</tr>
</tbody>
</table>

Questions?

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