17th Annual Sleep Medicine Virtual Course

Saturday, March 22, 2025

Innovation in the Management of Obstructive Sleep Apnea

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Conflict of Interest Disclosures for Speakers

David T. Kent, MD disclosed relationships with Inspire (investigator in ADHERE and PREDICTOR trials), Invicta Medical (consultant and site PI) and Nyxoah SA (Scientific Advisory Board Member)

The relevant financial relationships have been mitigated.

Learning Objectives

Upon completion of this course, attendees should be able to:

1. Understand the rationale and mechanism of multilevel surgical management of obstructive sleep apnea (OSA).
2. Discuss the anatomic impacts of positive pressure therapy and existing surgical therapies for treating OSA.
3. Describe innovations such as upper airway stimulation and glucagon-like peptide-1 receptor agonists in managing OSA.

Disclosures

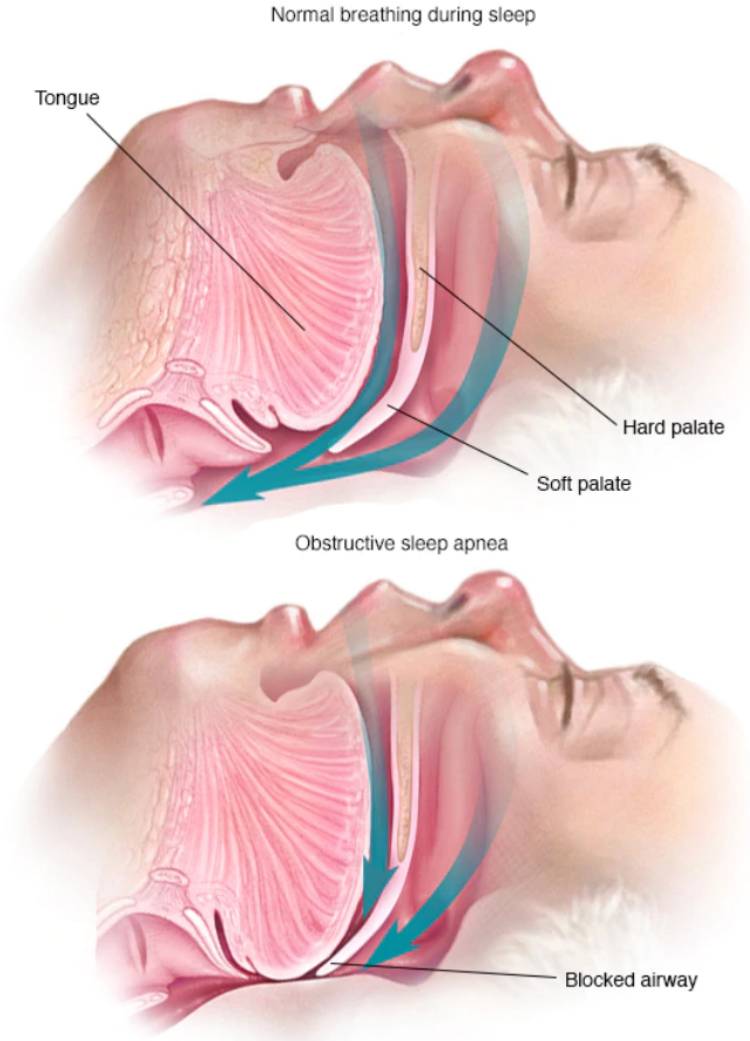
- Consultant
  - Restera
- Scientific Advisory Boards
  - Nyxoah SA
- Intellectual Property Interests
  - Listed as an inventor on US and international patents and applications owned by Vanderbilt University and licensed to Nyxoah SA
- Research Support
  - Inspire Medical Systems, Inc
  - Restera
  - Nyxoah SA

Funding Support

- NHLBI 1R01HL161635: The Effect of Ansa Cervicalis Neurostimulation on Airway Patency in Obstructive Sleep Apnea

Obstructive Sleep Apnea

- Increased collapsibility of upper airway structures during sleep
  - **Hypotonia of pharyngeal musculature**
  - Decline in end-expiratory lung volume
  - Altered control of ventilation
  - Other non-anatomic mechanisms
- Susceptibility varies between individuals
- Obesity potentiates airway collapse



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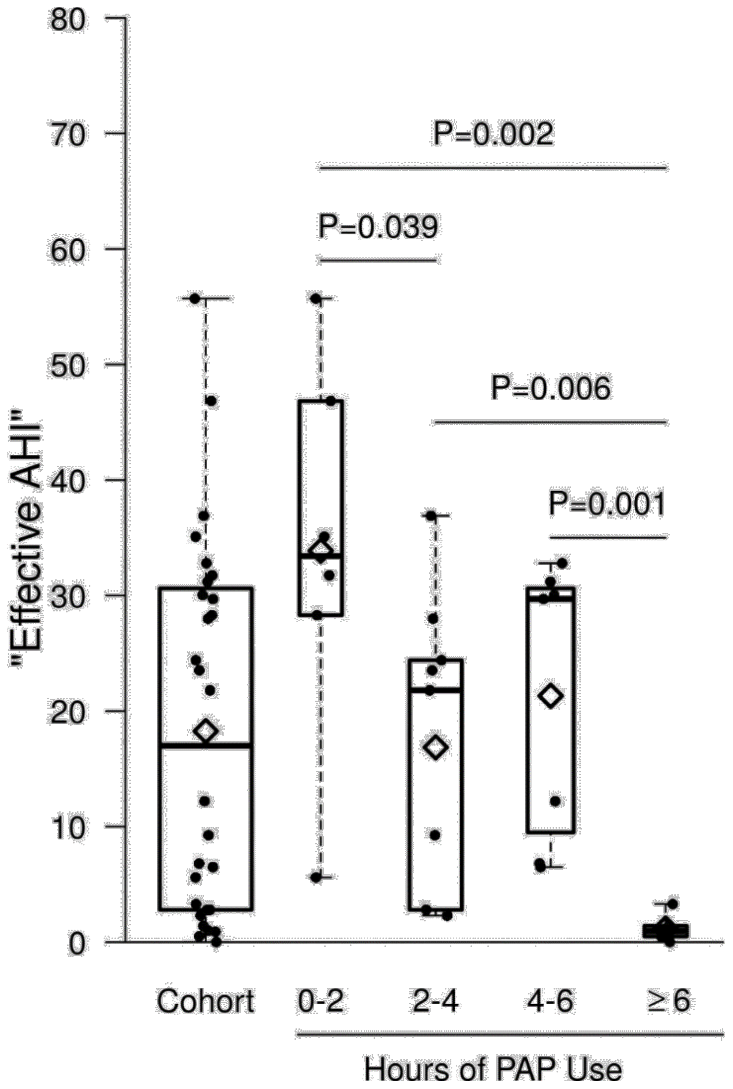
PAP and Effective AHI

- 28 severe OSA patients and partial CPAP compliance
  - Mean AHI: 67.9
- Tested for residual OSA using WatchPAT device
- ≥ 6h use: Effective AHI < 5
- < 6h use: residual mod-sev OSA in 63.6%



Boyd et al. Sleep, 2016.

Some back-of-the-envelope calculations

- 29.4 million Americans with OSA
  - X ~50% non-adherent / not accepting of CPAP
  - = ~14.7 million Americans with OSA (potentially) intolerant of PAP

Sleep Surgery: The Past

Palatal Surgery for Snoring (1955)

A SURGICAL PROCEDURE FOR THE RELIEF OF SNORING

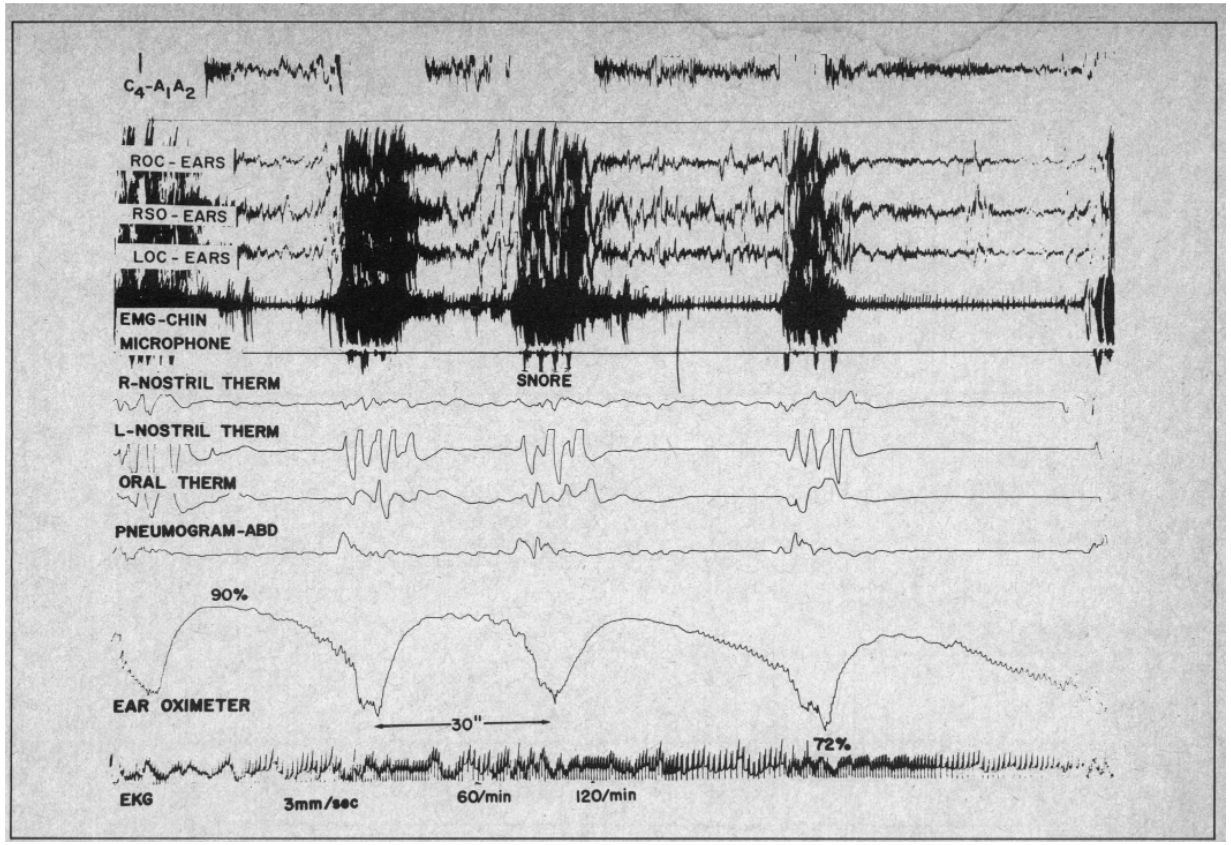
C. J. Heinberg, M.D., F.A.C.S.
Pensacola, Florida

A very interesting and astute observation was made by Doctor Leo Schwartz, of New York City, that, in some instances, in which adults addicted to snoring had tonsillectomies performed and the operator inadvertently removed the posterior pillar of the fauces. that the snoring was relieved.

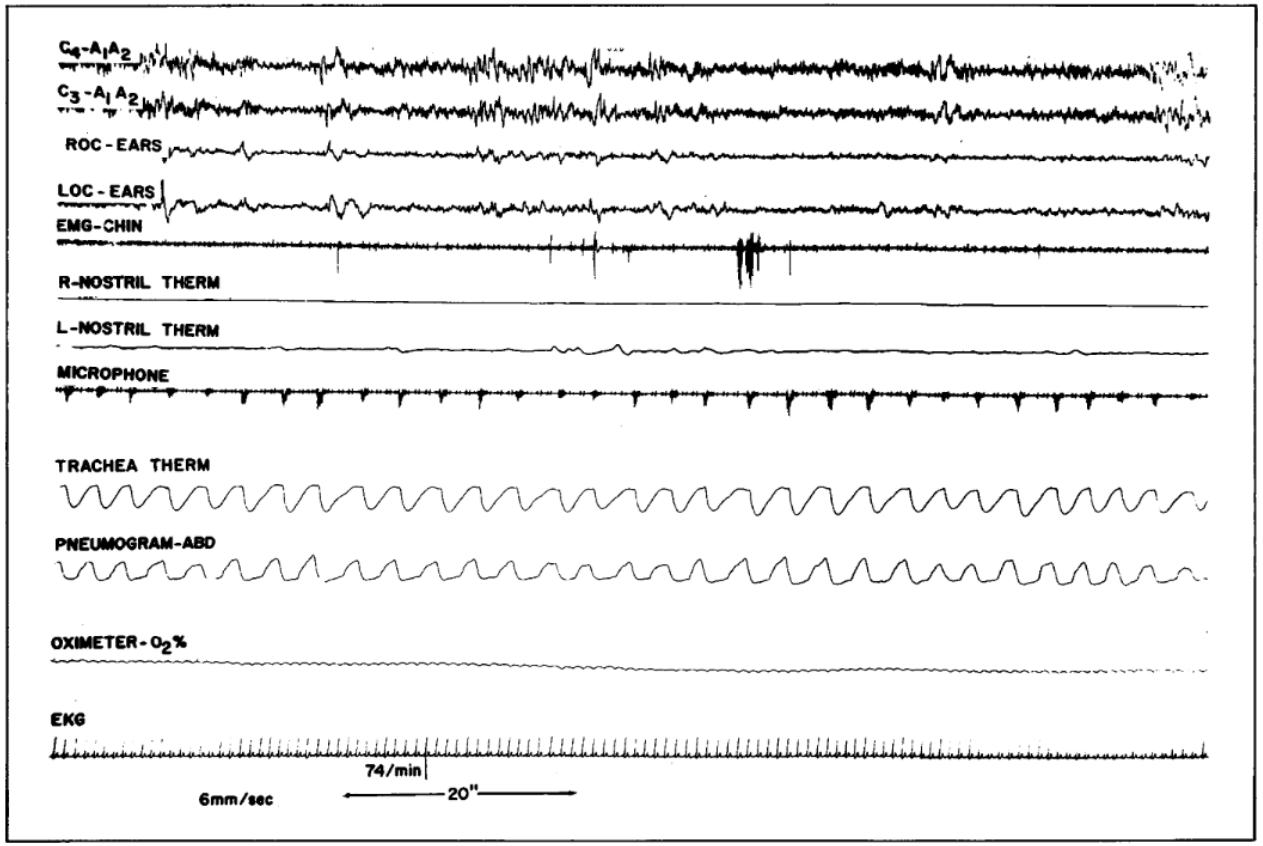
The operation, devised by me, consists of a triangular incision made on each side of the uvula with the apex toward the hard palate and the base of the triangle at the rim of the isthmus of sufficient size to cause tension. The underlying muscles are divided and removed from the entire area, leaving the posterior submucous and mucous membrane intact. The margins are then approximated by suturing. The uvula, if elongated, is shortened by partial staphlyectomy to render it of normal length.

Heinberg CJ. Eye Ear Nose Throat Monthly, 1955.

Tracheostomy: 1978



Before Tracheostomy



After Tracheostomy

Weitzman et al. Arch Nuer, 1978.

Uvulopalatopharyngoplasty: 1981

- 12 patients
- 9 with symptomatic improveme
- 8 with PSG improvement
  - AI: 54 ± 28 → 27.9 ± 27.7 /h
- CPAP (for OSA… in humans…) invented the same year in AUS

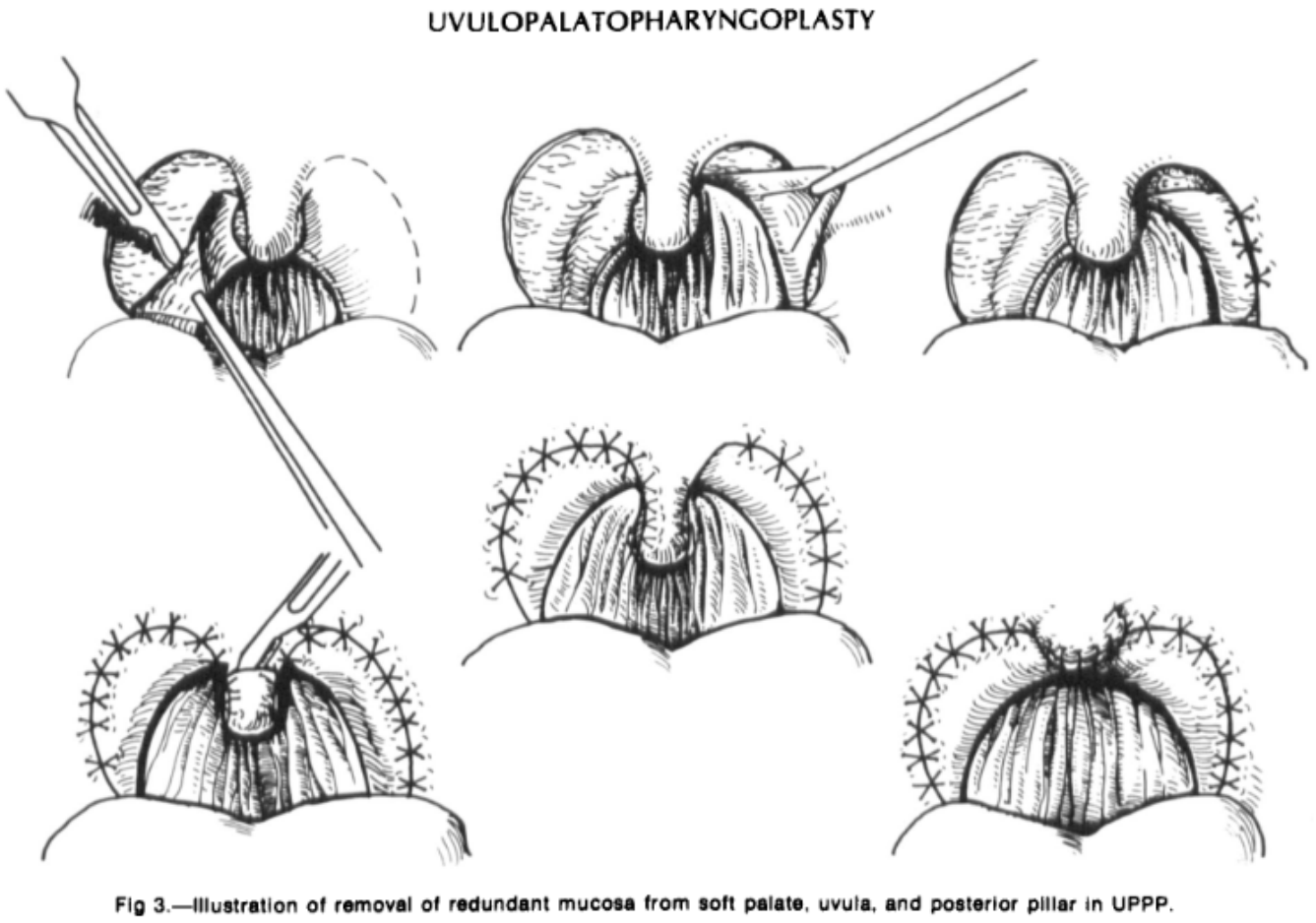
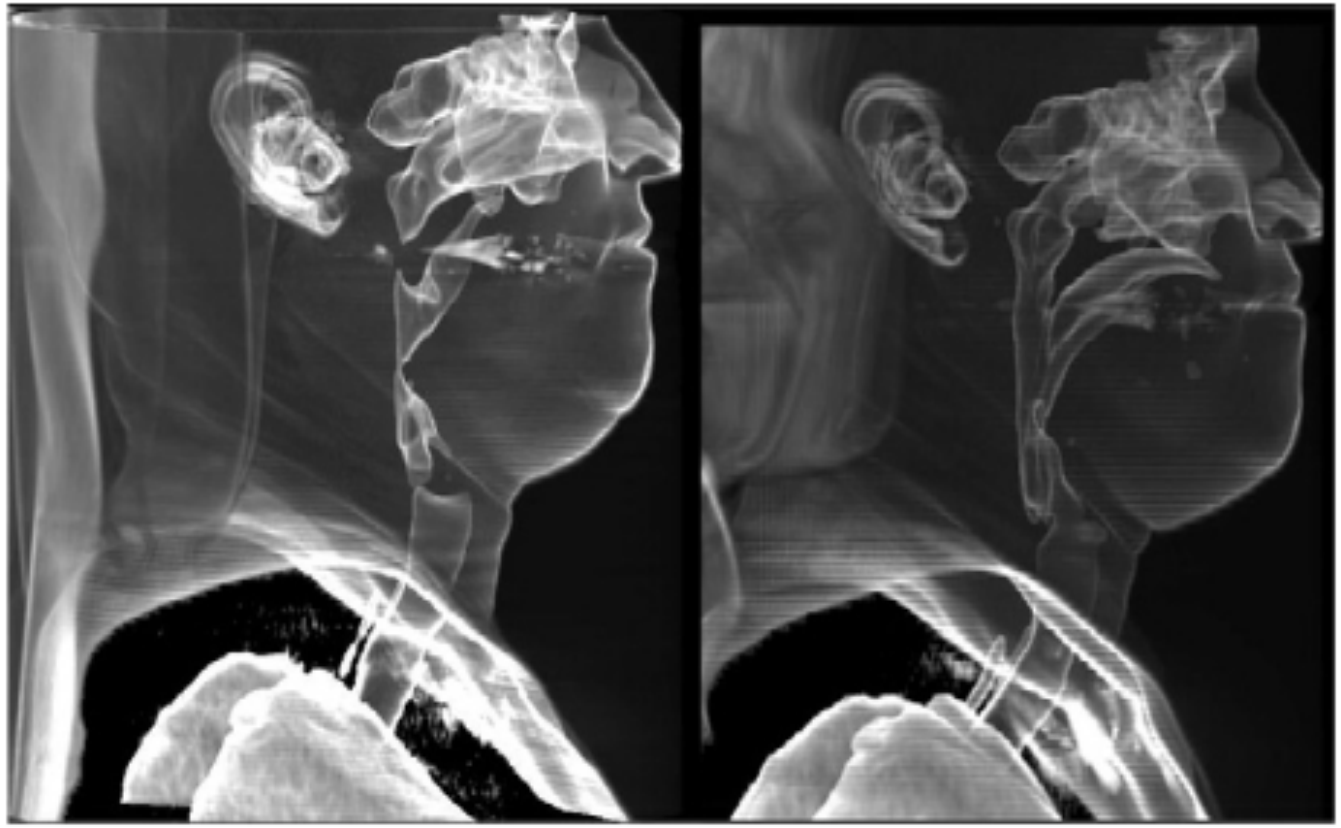


Fig 3.—Illustration of removal of redundant mucosa from soft palate, uvula, and posterior pillar in UPPP.

Fujita et al. OTOHNS, 1981.

Maxillomandibular Advancement: 1983

- MMA: First case report, 1983
  - First case series later that decade



Powell et al. Bull Eur Physiopathol Respir, 1983.

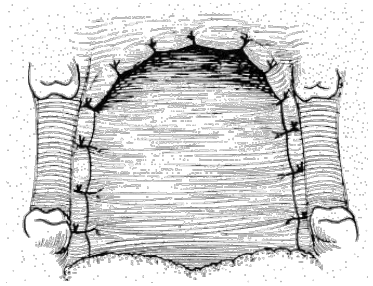
Innovations in Sleep Surgery: The Present

- Comprehensive training and sleep disorder management
- Refining procedural selection
- Expansion of treatment options

The Modern Sleep Surgeon

- Comprehensive sleep management
  - Insomnia
  - Restless leg syndrome
  - Parasomnias
  - **Sleep-Disordered Breathing**
    - CPAP
    - Oral Appliances
    - Positional Therapy
    - **Surgery**
      - Reduce CPAP barriers
      - Cure OSA
      - Salvage: Reduce OSA burden

Where Have We Gotten Since 1981?

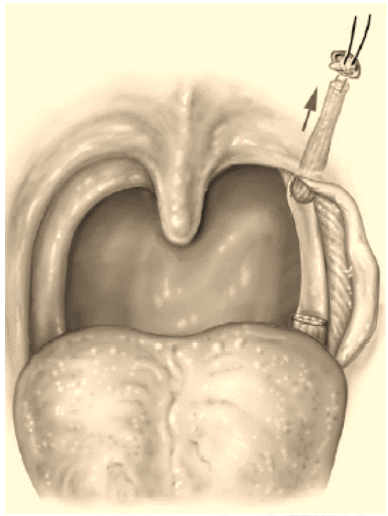


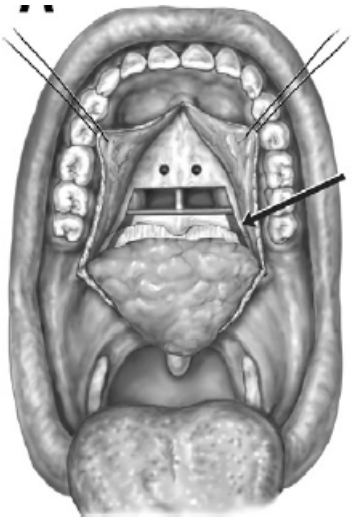
Uvulopalatopharyngoplasty

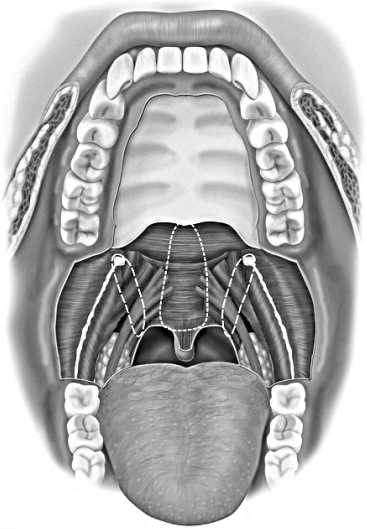
Better surgery?

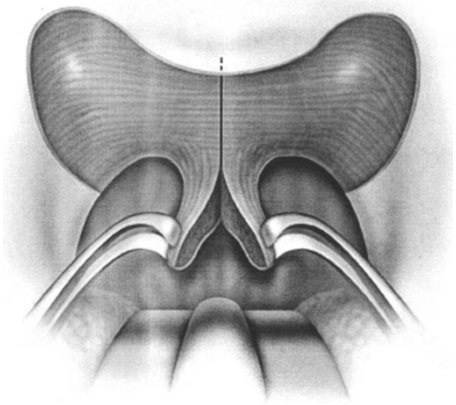
And/Or…

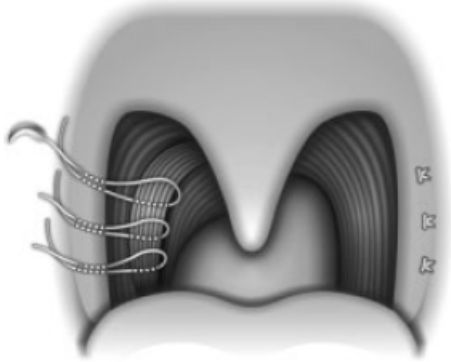
<u>Better patient selection?</u>



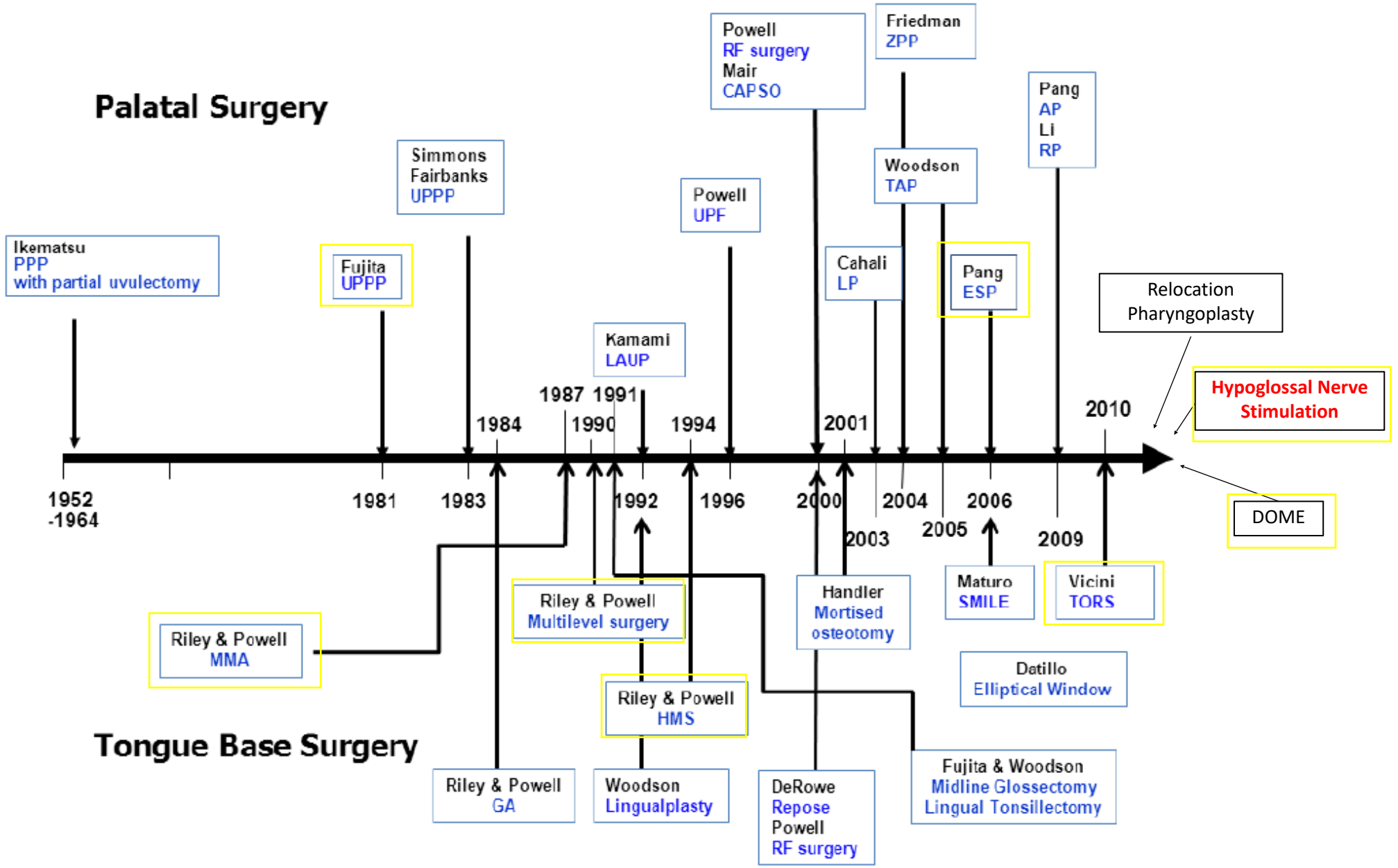






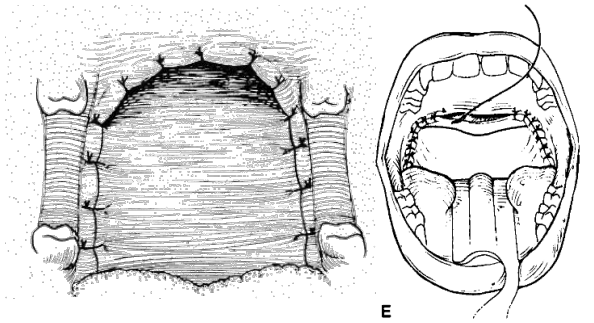


Expansion Sphincter Pharyngoplasty, Z-palatoplasty, Lateral Pharyngoplasty, Relocation Pharyngoplasty, Anterior Palatoplasty, Barbed Suture Pharyngoplasty…


Palatal Surgery
Ikematsu
PPP
with partial uvulectomy
Fujita
UPPP
Simmons
Fairbanks
UPPP
Powell
UPF
Powell
RF surgery
Mair
CAPSO
Friedman
ZPP
Woodson
TAP
Cahali
LP
Pang
ESP
Pang
AP
Li
RP
Relocation
Pharyngoplasty
Hypoglossal Nerve
Stimulation
DOME
Kamami
LAUP
1952
-1964
1981
1983
1984
1987
1990
1991
1992
1994
1996
2000
2001
2003
2004
2005
2006
2009
2010
Riley & Powell
MMA
Riley & Powell
Multilevel surgery
Riley & Powell
HMS
Riley & Powell
GA
Woodson
Lingualplasty
Handler
Mortised
osteotomy
DeRowe
Repose
Powell
RF surgery
Maturo
SMILE
Vicini
TORS
Datillo
Elliptical Window
Fujita & Woodson
Midline Glossectomy
Lingual Tonsillectomy
Tongue Base Surgery

Better Surgery: Problems with UP3

1. Midline resection → cicatricial scarring
   - Simmons/Fairbanks UP3
     - Most widely used UP3 variation



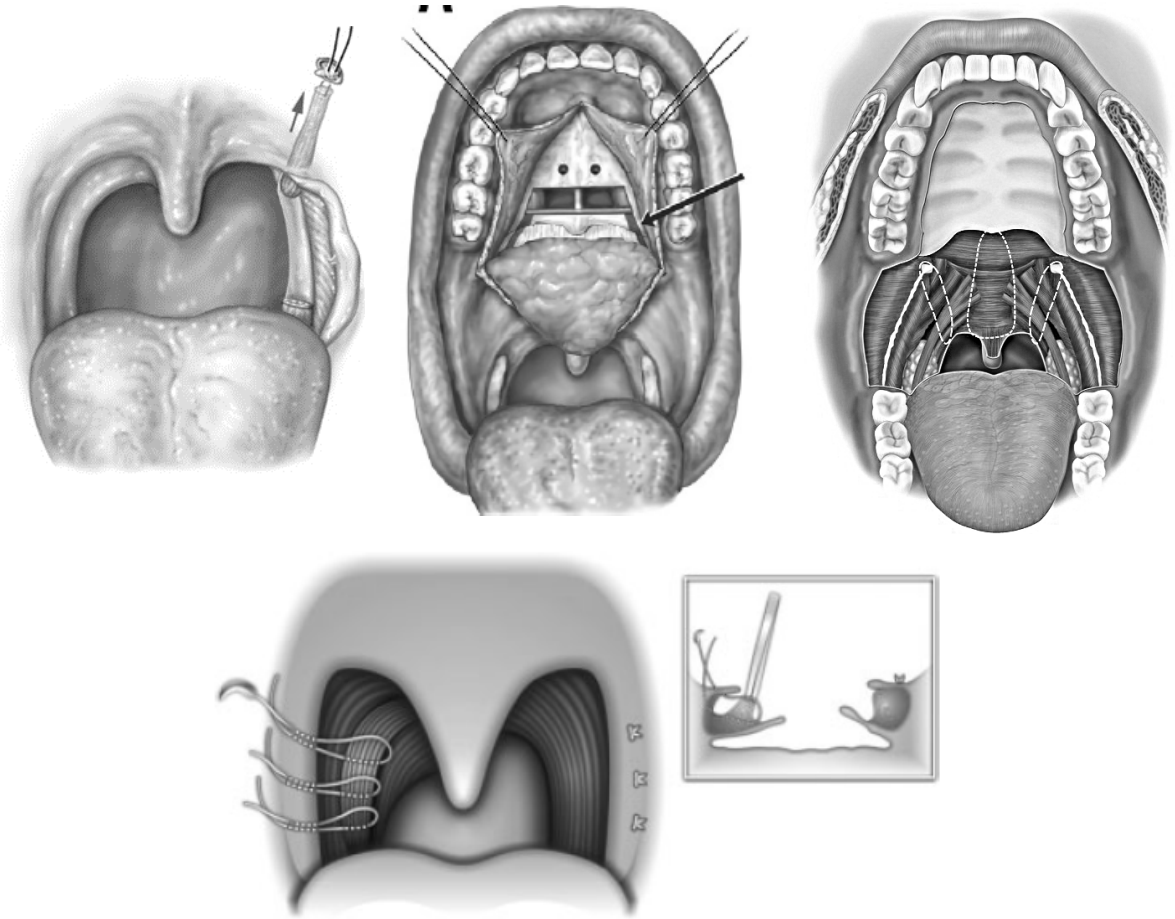
What we've learned about palate surgery over the last ~40 years

1. Nasopharyngeal stenosis and VPI are the enemy
2. Lateral port dilation is safer and more desirable
3. The uvula should probably be spared
4. **Predictors of response**:
    1. Lower BMI
    2. Larger tonsils
    3. "Smaller" tongue

Better Surgery: UP3 Modifications

1. Midline resection → cicatricial scarring
   - Simmons/Fairbanks UP3
     - Most widely used UP3 variation

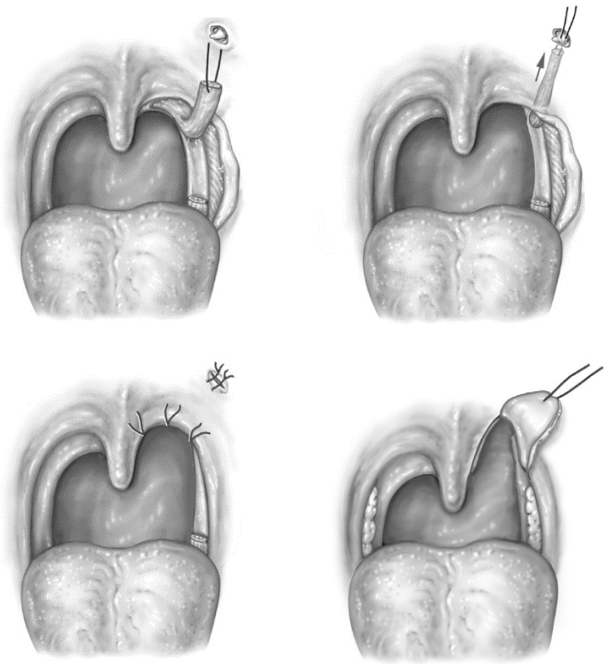
2. Lateral port dilation is safer and more desirable
   - Still shortens vertical palate length
   - Focus of most modern palatal techniques



Expansion Sphincter Pharyngoplasty

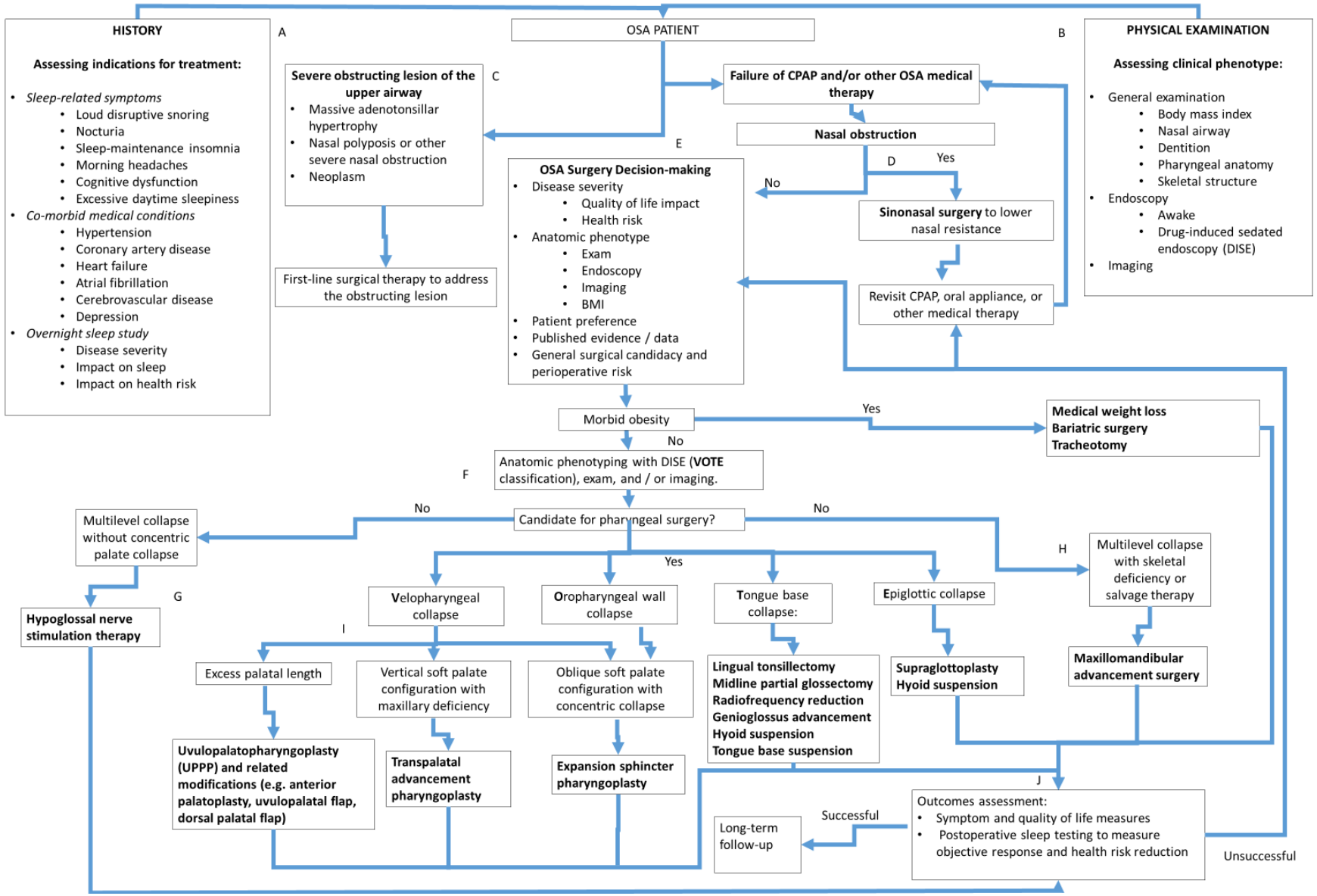
- 2009, N=45 (23 ESP, 22 UP3)
  - Tonsils 1-2+, FTP 3-4, **BMI < 30**
  - **BMI: 28.7**
  - Sher: ESP 82.6% vs UP3 68.1%
  - AHI
    - UP3: 38.1 ± 6.46 → **19.6** ± 7.9
    - ESP: 44.2 ± 10.2 → **12.0** ± 6.6
- 2016 meta-analysis (N = 143)
  - **Pooled Sher success: 86.3 %**

BMI	Sher
27.5	90
-	89.2
28.7	82.6
32	80



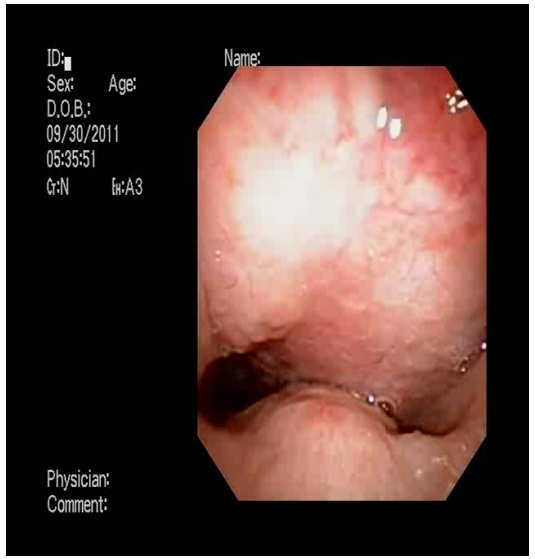
Pang and Woodson. OTOHNS, 2007. Pang et al. Eur Arch Oto, 2016.

Procedural Selection and Anatomic Phenotyping

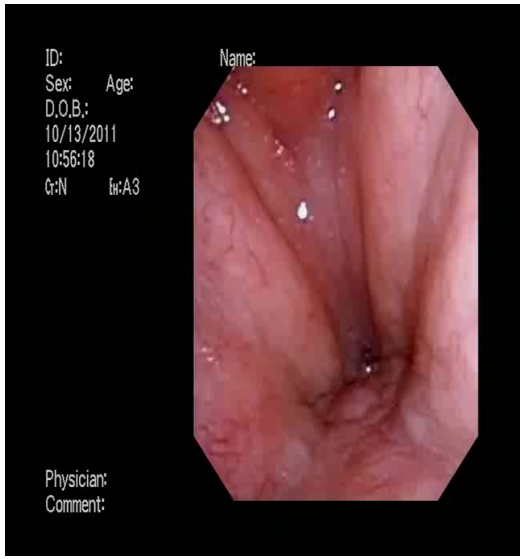


Anatomic Phenotyping: DISE

- 1991: Pringle and Croft
- Multiple forms of sedation
  - Midazolam
  - Dexmedetomidine (pediatrics)
  - Propofol
    - **Most common**
- Titrated controlled infusion vs manual titration
- Allows simulation of sleep to assess anatomic sites of collapse



Anterior-posterior palatal collapse



Circumferential palatal collapse

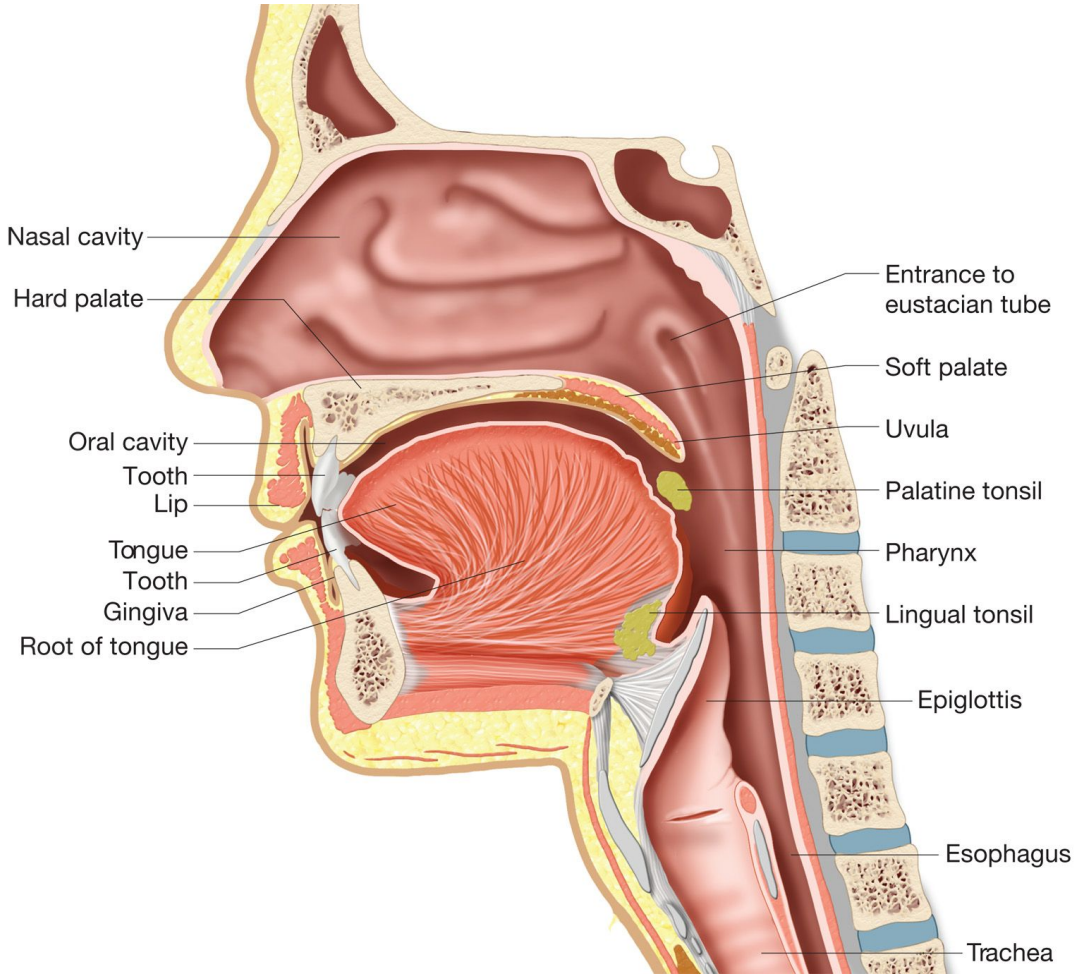
Drug-Induced Sleep Endoscopy (DISE)

- Advantages
  - Dynamic assessment of sleep
  - Directly visualize anatomic structures and patterns of collapse
  - Valid
  - Moderate-to-good test-retest and interrater reliability

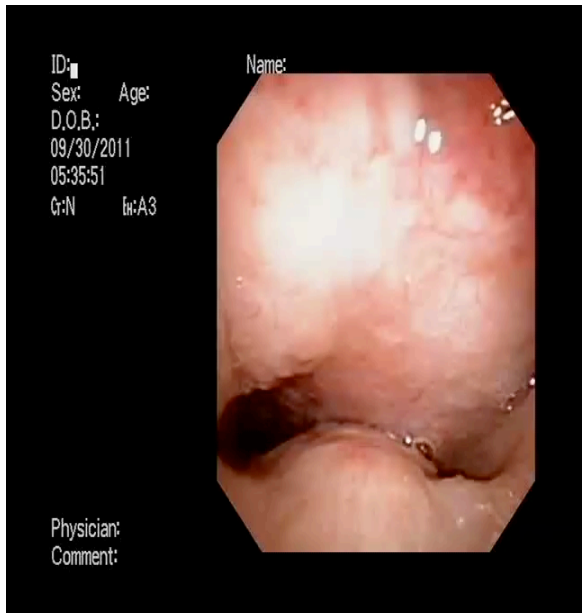
- Disadvantages
  - Costly
  - Time consuming
  - Risks of general anesthesia

Relevant Anatomy

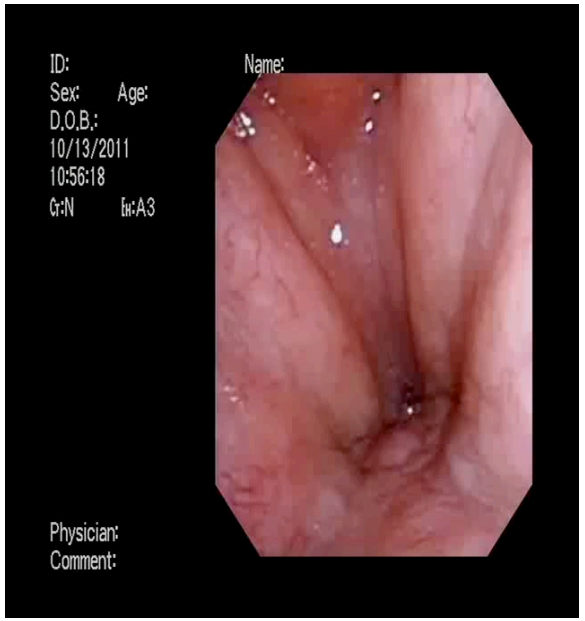
- Soft Palate
- Lateral pharyngeal walls
- Tongue
- Epiglottis



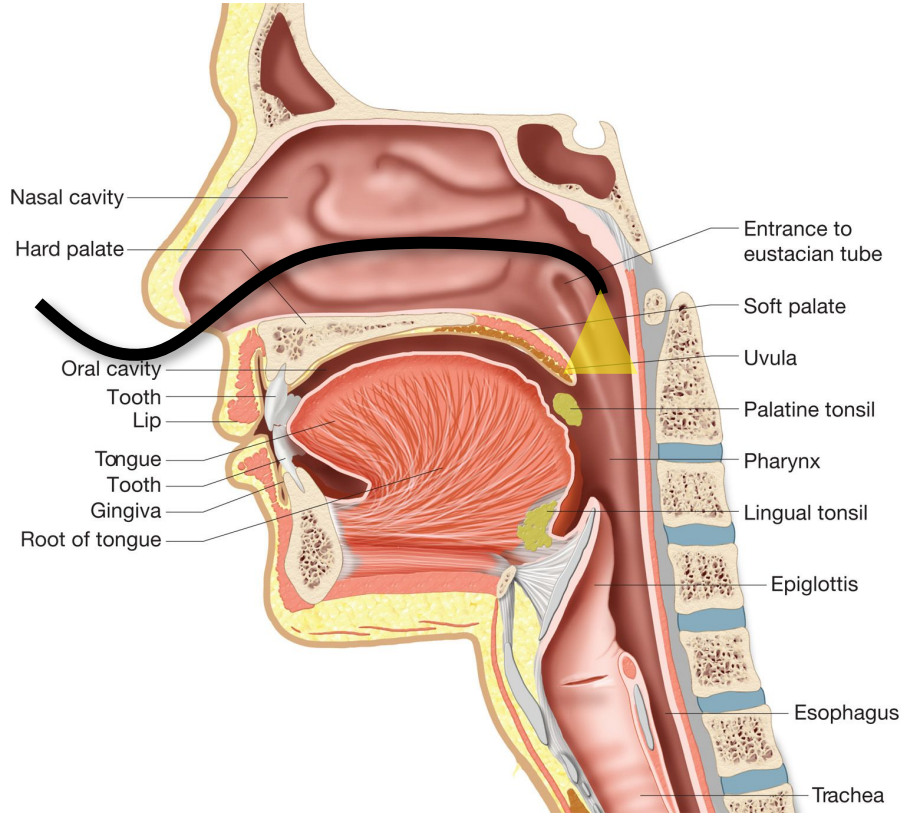
Palatal Collapse: Endoscopic View



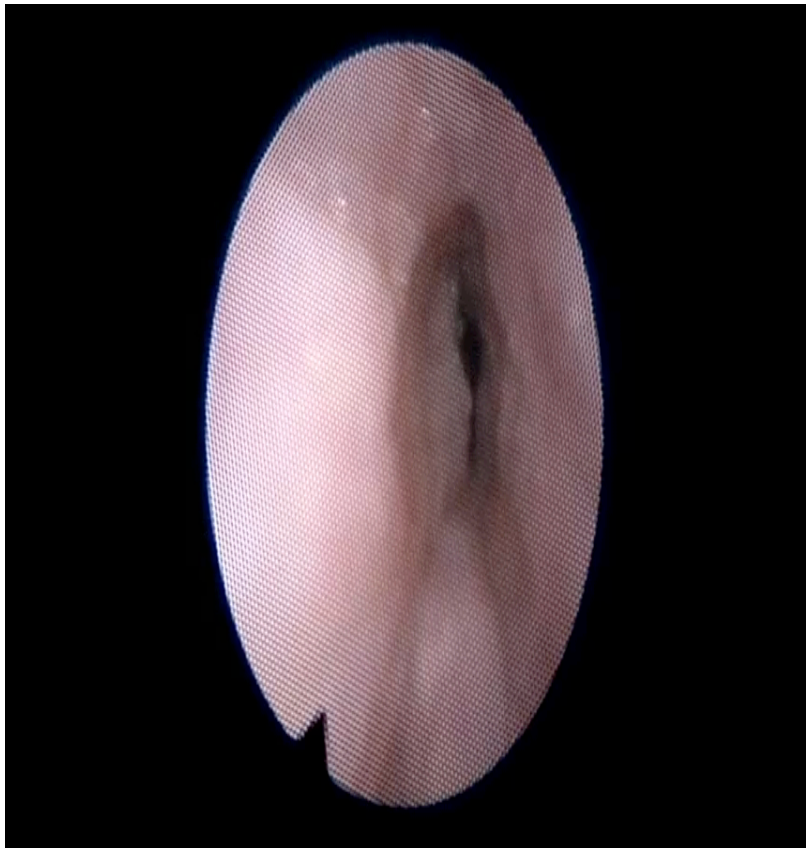
Anterior-posterior palatal collapse

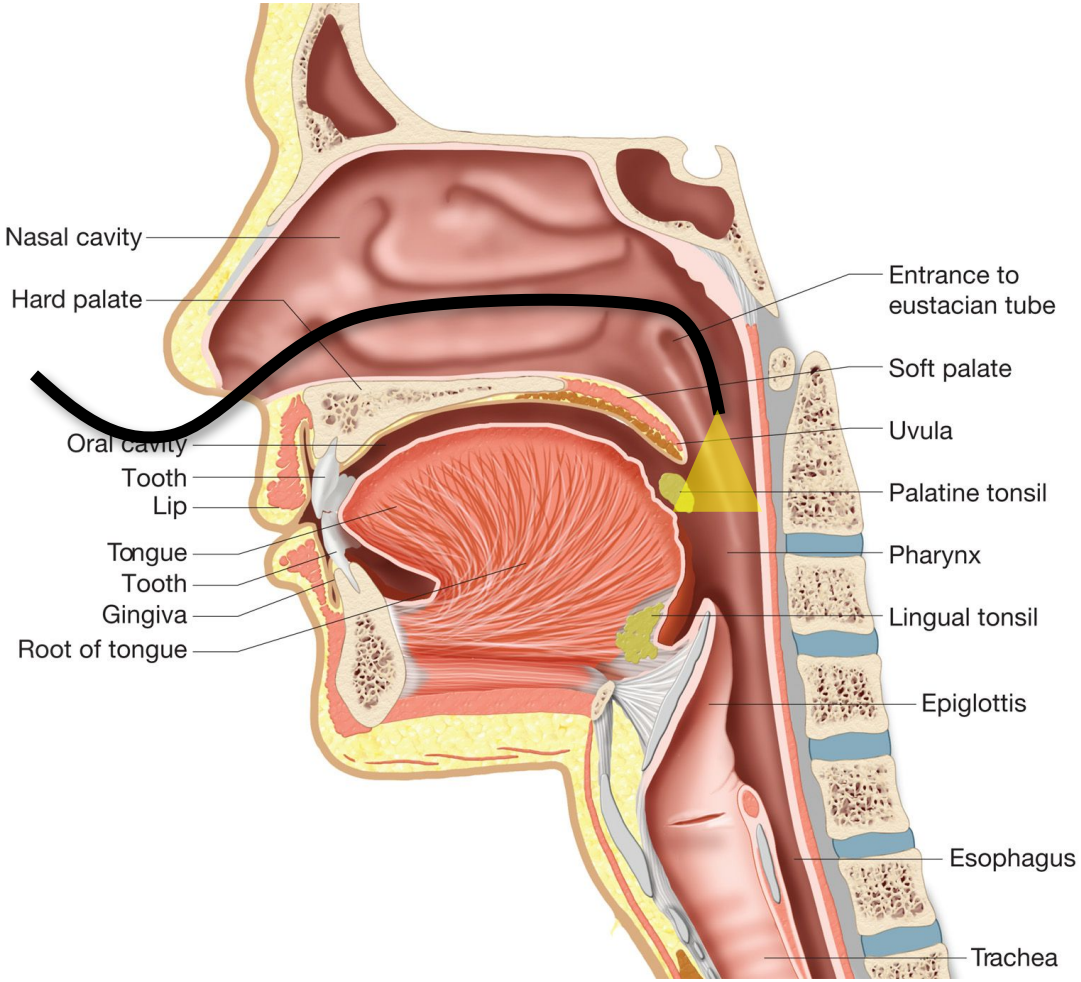


Circumferential palatal collapse

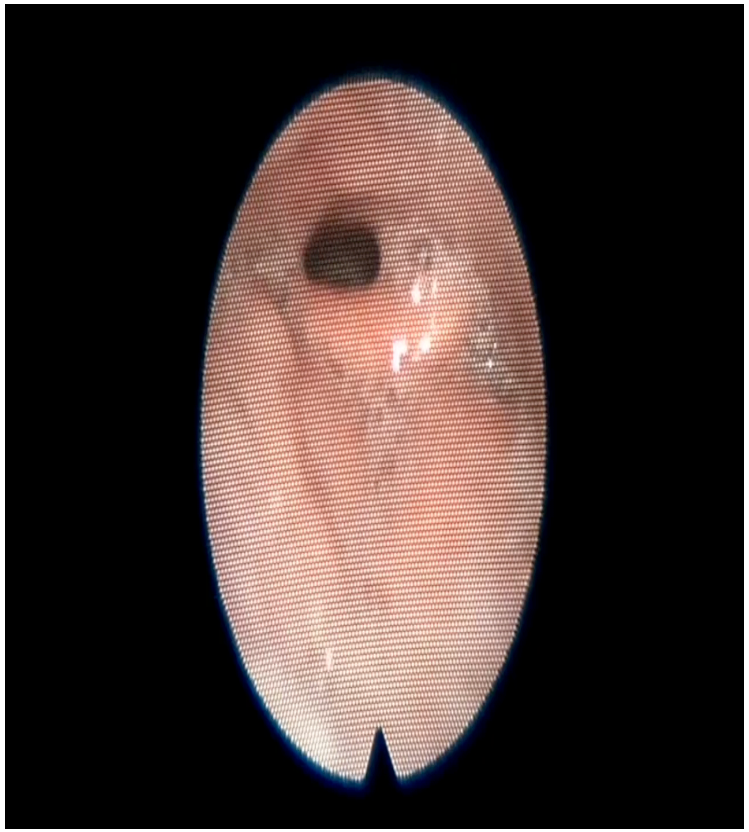


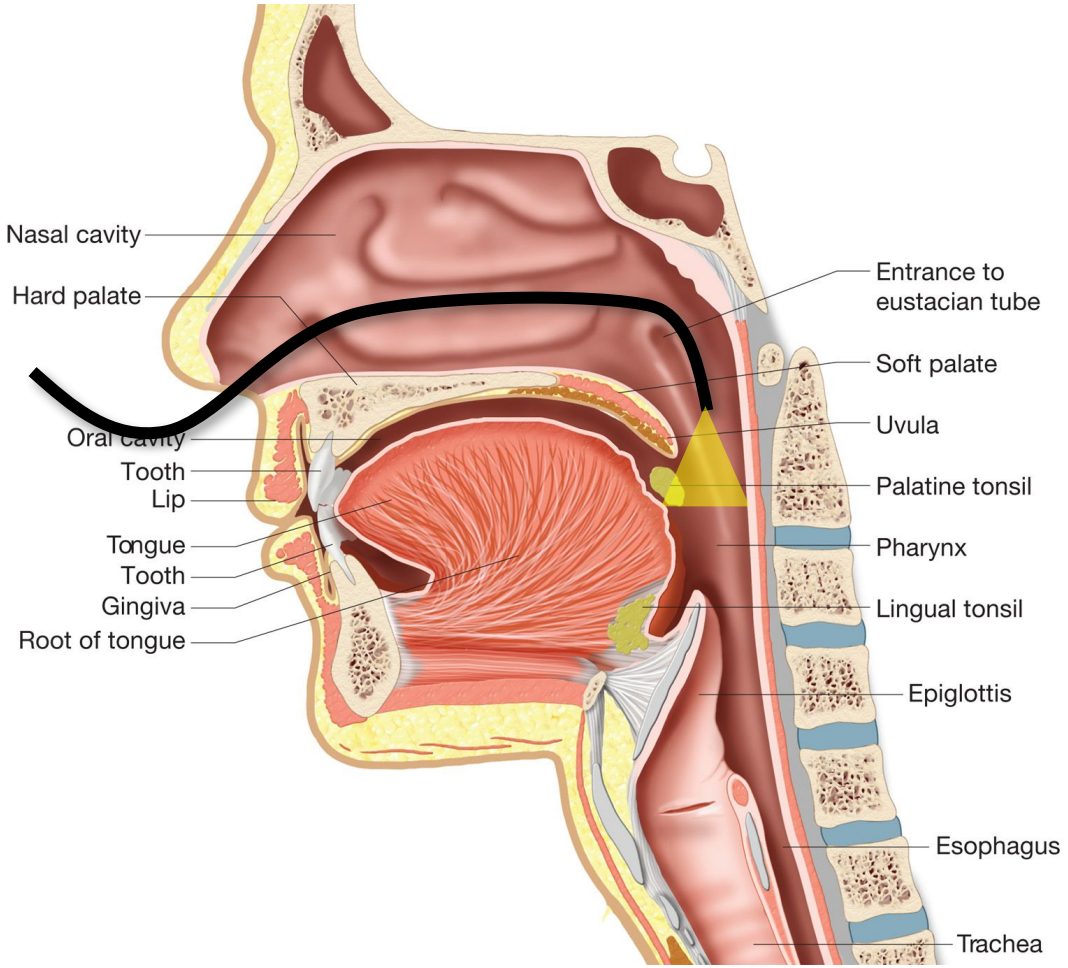
Lateral Wall Collapse: Endoscopic View



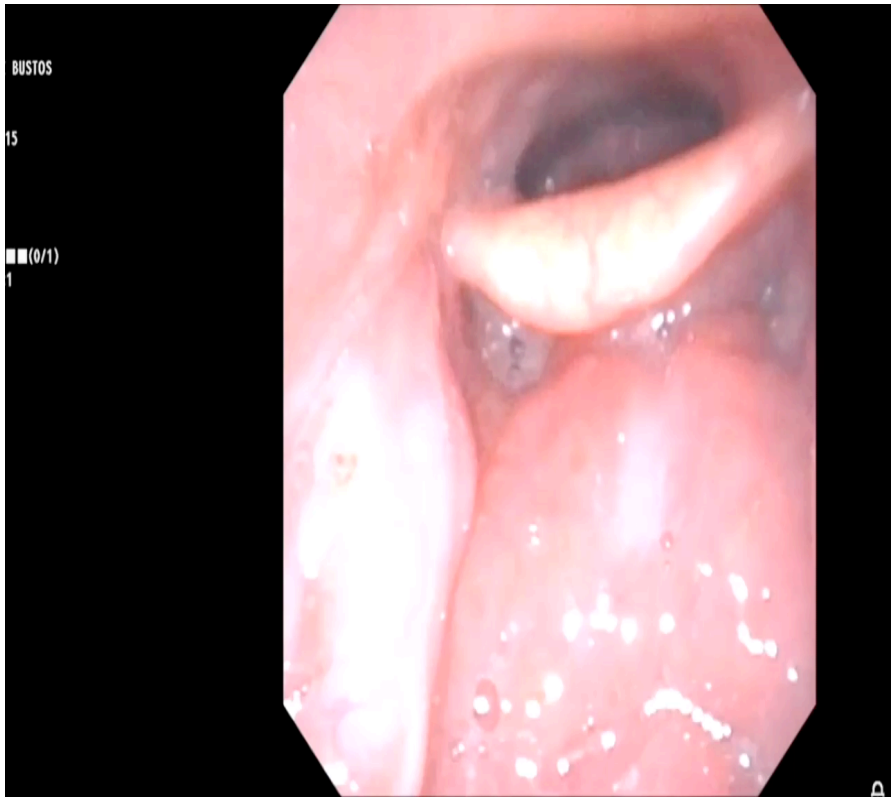


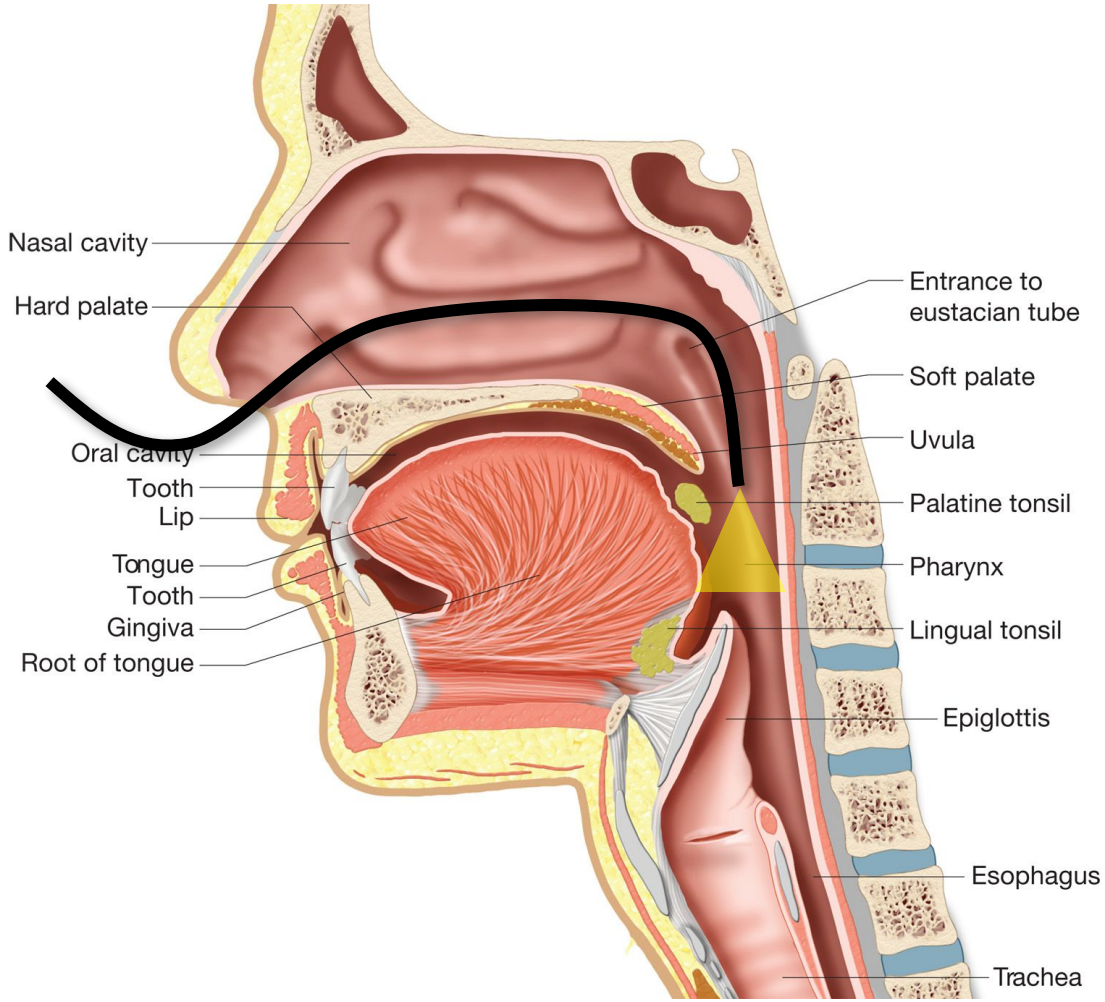
Tongue Base Collapse: Endoscopic View





Epiglottic Collapse: Endoscopic View





VOTE Classification

- Most widely studied system
- Structure-based assessment
- Each structure is assigned a degree and pattern of collapse
- Descriptive but avoids undue complexity

STRUCTURE	DEGREE OF OBSTRUCTION[a]	CONFIGURATION[c]		
		A-P	LATERAL	CONCENTRIC
Velum				
Oropharynx lateral walls[b]				
Tongue Base				
Epiglottis				

Kezirian EJ et al. Eur Arch Otorhinolaryngol, 2011.

Drug-Induced Sleep Endoscopy and Surgical Outcomes: A Multicenter Cohort Study

Katherine K. Green, MD, MS; David T. Kent, MD; Mark A. D'Agostino, MD; Paul T. Hoff, MS, MD; Ho-Sheng Lin, MD; Ryan J. Soose, MD; M. Boyd Gillespie, MD, MSc; Kathleen L. Yaremchuk, MD; Marina Carrasco-Llatas, Md PhD; B. Tucker Woodson, MD; Ofer Jacobowitz, MD, PhD; Erica R. Thaler, MD; José E. Barrera, MD; Robson Capasso, MD; Stanley Yung Liu, MD, DDS; Jennifer Hsia, MD; Daljit Mann, MD; Taha S. Meraj, MD; Jonathan A. Waxman, MD, PhD; Eric J. Kezirian, MD, MPH

- N = 275, multi-center
- 4 blinded reviewers

- Moderate interrater reliability (K = 0.40 – 0.60)
- +O: poorer surgical outcomes (0.51; 95% CI: 0.27 – 0.93)
- T2: lower odds in mod-sev OSA (0.52; 95% CI: 0.28 – 0.98)

Green KK et al. Laryngoscope, 2018.

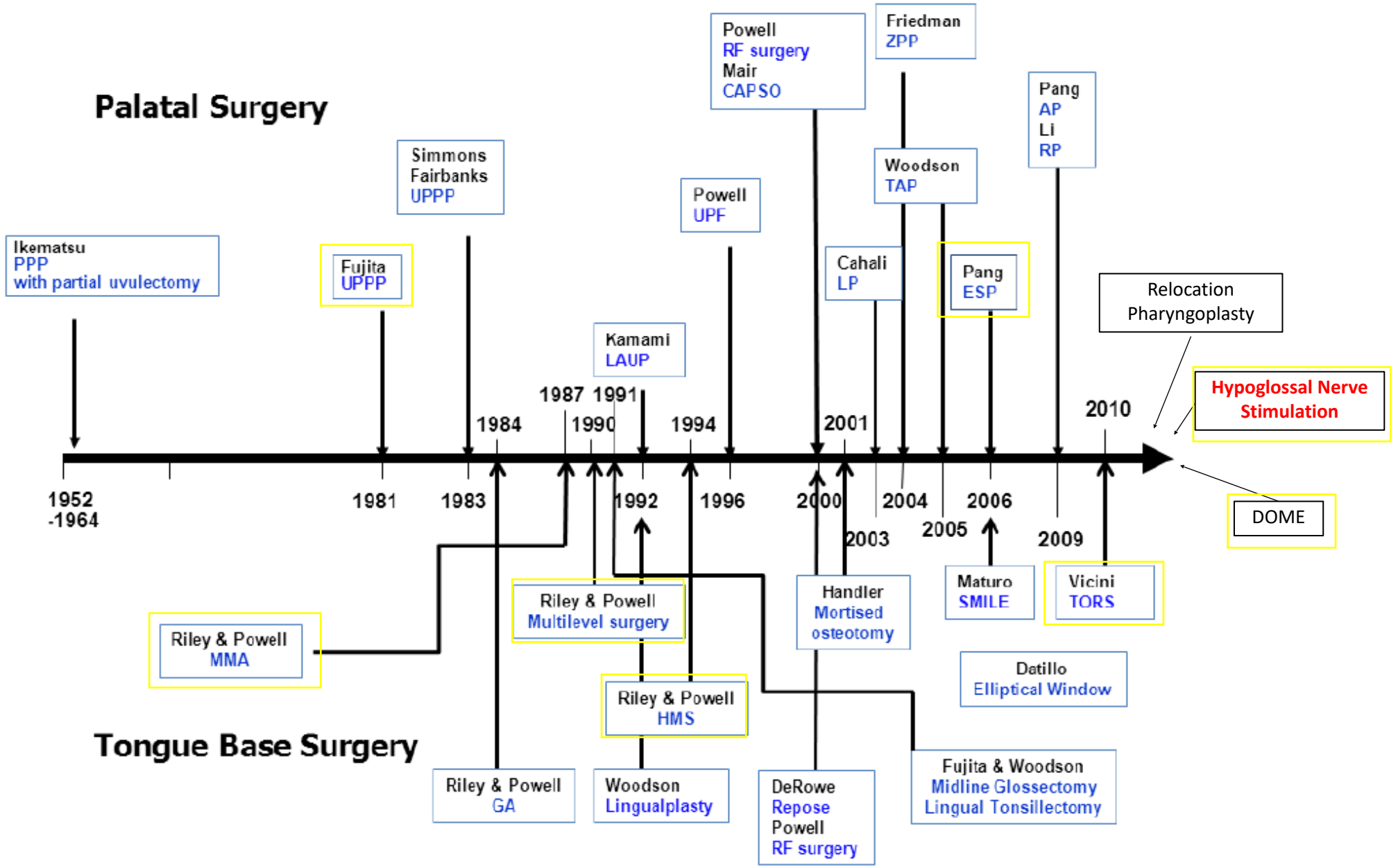
Drug-Induced Sleep Endoscopy and Hypoglossal Nerve Stimulation Outcomes: A Multicenter Cohort Study

Phillip Huyett, MD; David T. Kent, MD; Mark A. D'Agostino, MD; Katherine K. Green, MD, MS; Ryan J. Soose, MD; Thomas M. Kaffenberger, MD; B Tucker Woodson, MD; Colin Huntley, MD; Maurits S. Boon, MD; Clemens Heiser, MD; Amelie Birk, MD; Maria V. Suurna, MD; Ho-Sheng Lin, MD; Jonathan A. Waxman, MD, PhD; Eric J. Kezirian, MD, MPH

- N = 343 patients undergoing HNS implantation, 10 centers
- 4 blinded reviewers

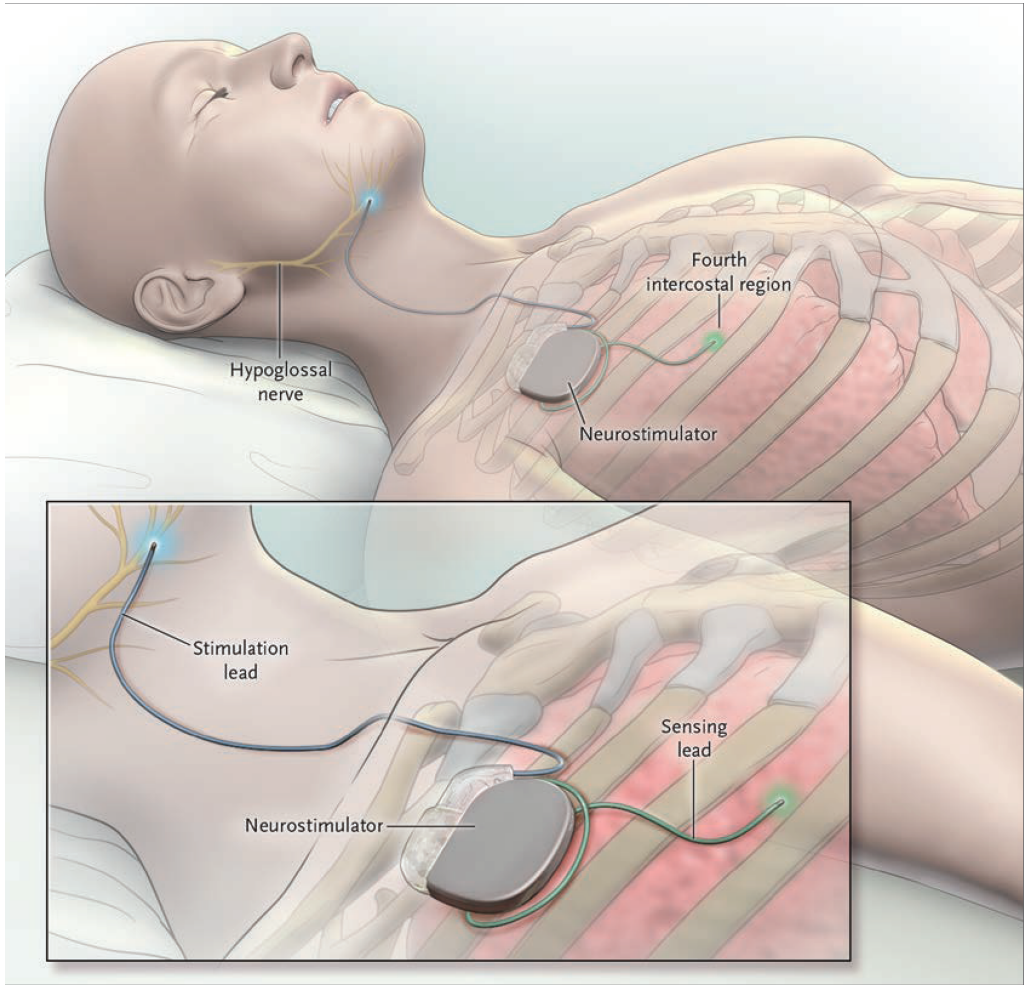
- 72.6% response rate ($Sher_{15}$) overall
- V2 vs V0 ΔAHI: −26.8 ± 14.9 vs. −19.2 ± 12.8 /h; p = 0.02
- T2 vs non-T2 surgical response: 78% vs. 68%, p = 0.043
- O2 vs non-O2 surgical response 58% vs. 74%, P = 0.042

Huyett P et al. Laryngoscope, 2021.

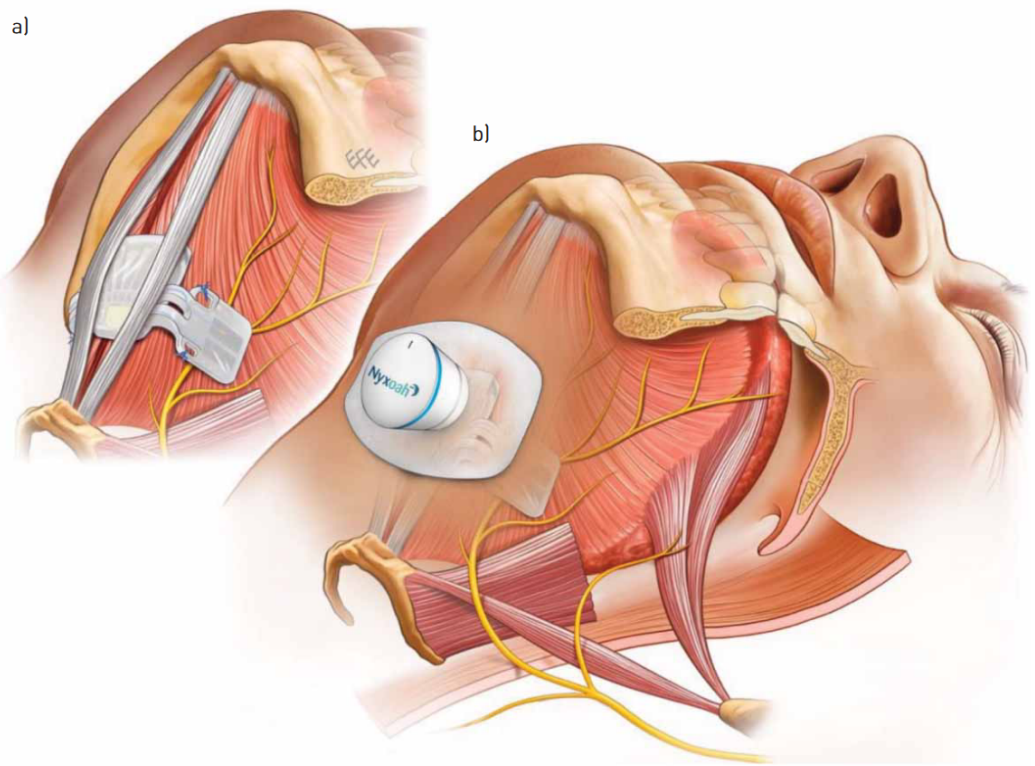

Palatal Surgery
Ikematsu
PPP
with partial uvulectomy
Fujita
UPPP
Simmons
Fairbanks
UPPP
Powell
UPF
Powell
RF surgery
Mair
CAPSO
Friedman
ZPP
Woodson
TAP
Cahali
LP
Pang
ESP
Pang
AP
Li
RP
Relocation
Pharyngoplasty
Hypoglossal Nerve
Stimulation
DOME
Kamami
LAUP
1952
-1964
1981
1983
1984
1987
1990
1991
1992
1994
1996
2000
2001
2003
2004
2005
2006
2009
2010
Riley & Powell
MMA
Riley & Powell
Multilevel surgery
Riley & Powell
HMS
Riley & Powell
GA
Woodson
Lingualplasty
Handler
Mortised
osteotomy
DeRowe
Repose
Powell
RF surgery
Maturo
SMILE
Vicini
TORS
Datillo
Elliptical Window
Fujita & Woodson
Midline Glossectomy
Lingual Tonsillectomy
Tongue Base Surgery

Hypoglossal Nerve Stimulation

- Multiple systems in development
- Only one currently FDA approved (April 2014)
- Consists of:
  - Respiratory sensing lead
  - CN XII stimulation lead
  - Implantable pulse generator

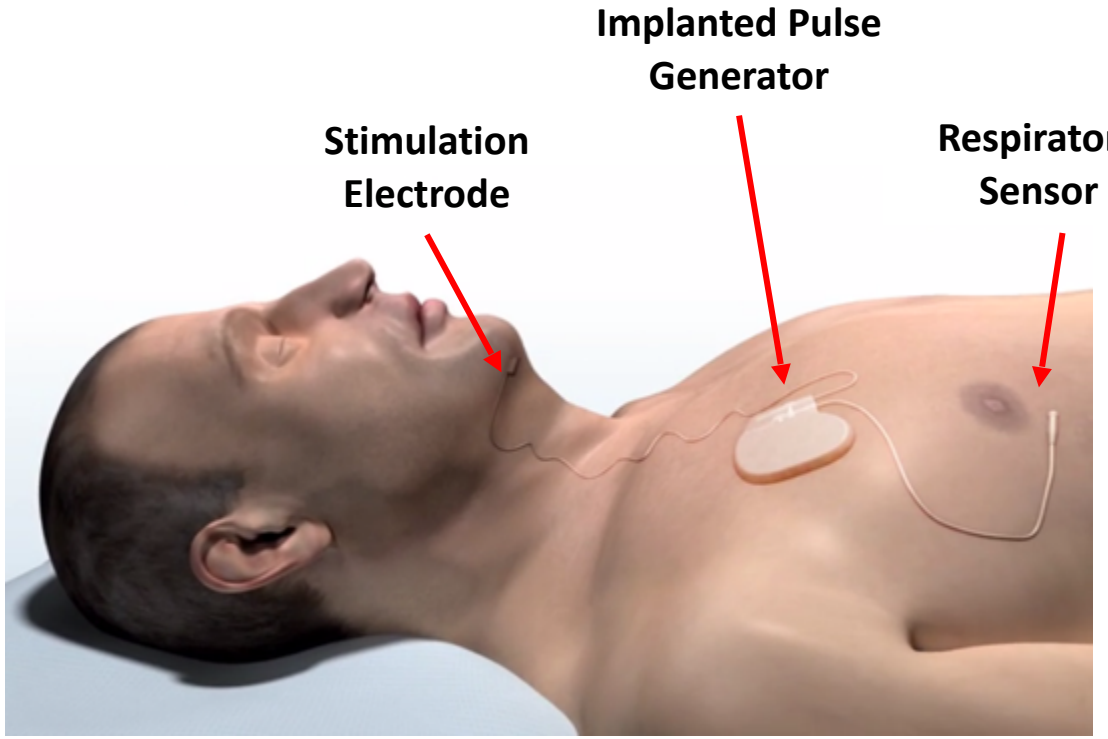


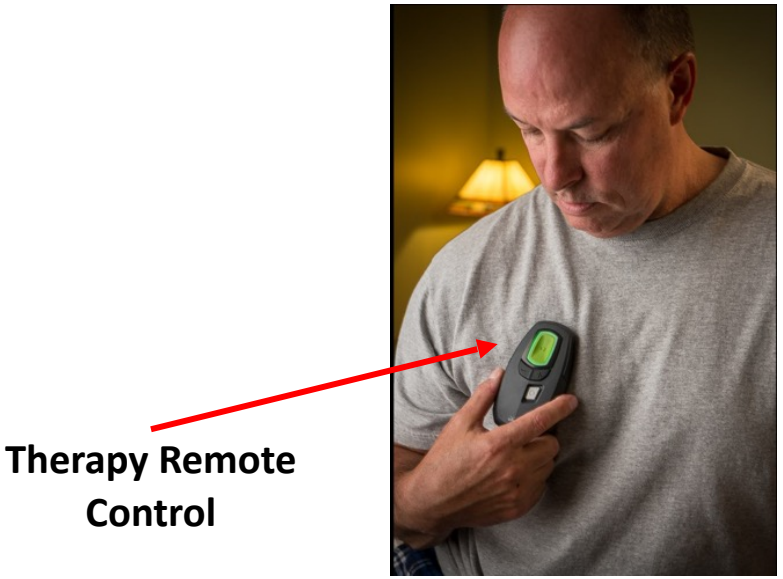
Others in development



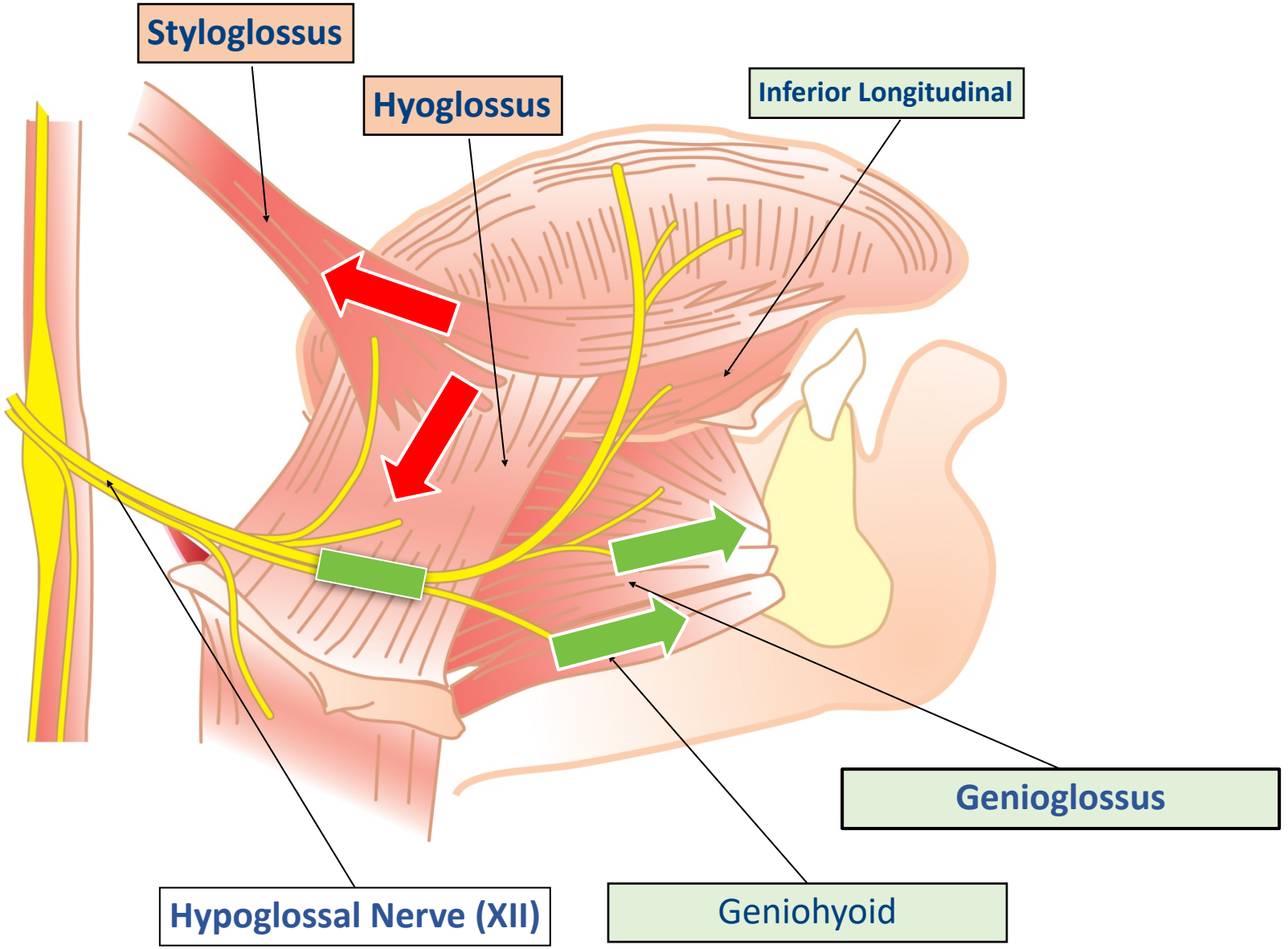
The Inspire System

- 2-incision implant
- Unilateral, closed loop, intermittent stimulation paced to respiratory effort
  - Tripolar cuff electrode on distal hypoglossal nerve (medial division)
- Stimulates tongue protrusor muscles ONLY
- IPG: ~8-11 years, not rechargeable

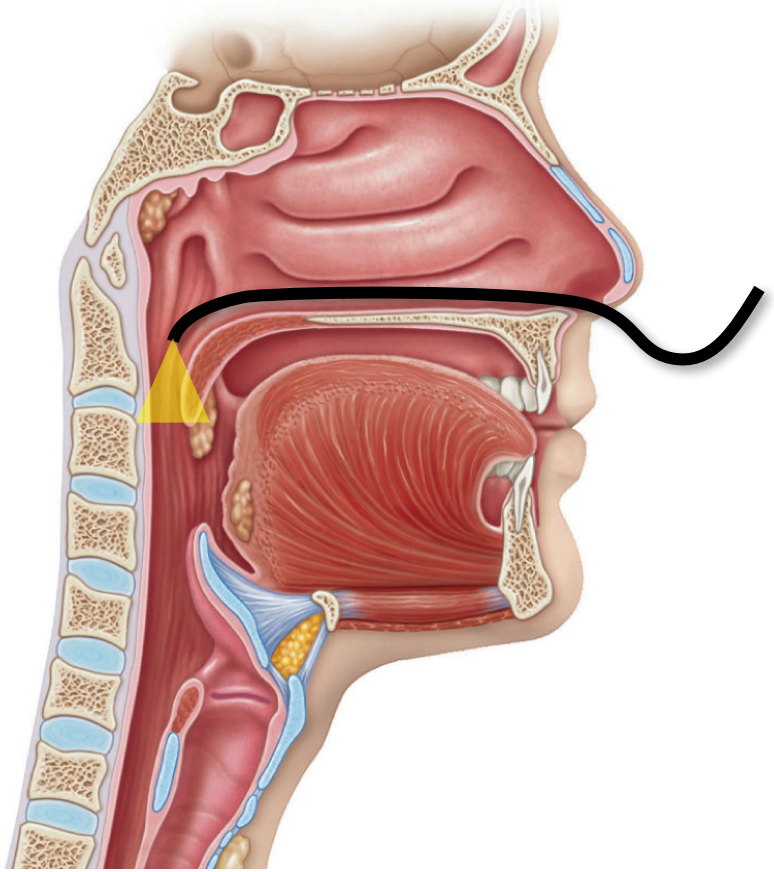




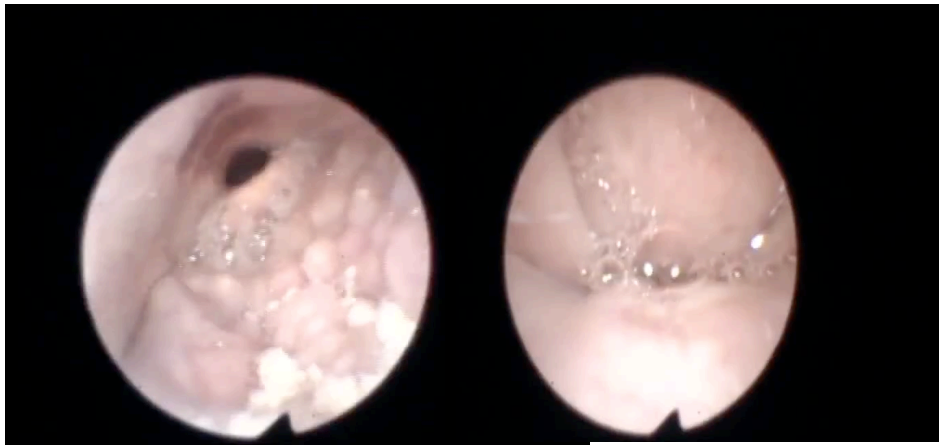
HNS: Mechanism of Action



HNS: Mechanism of Action

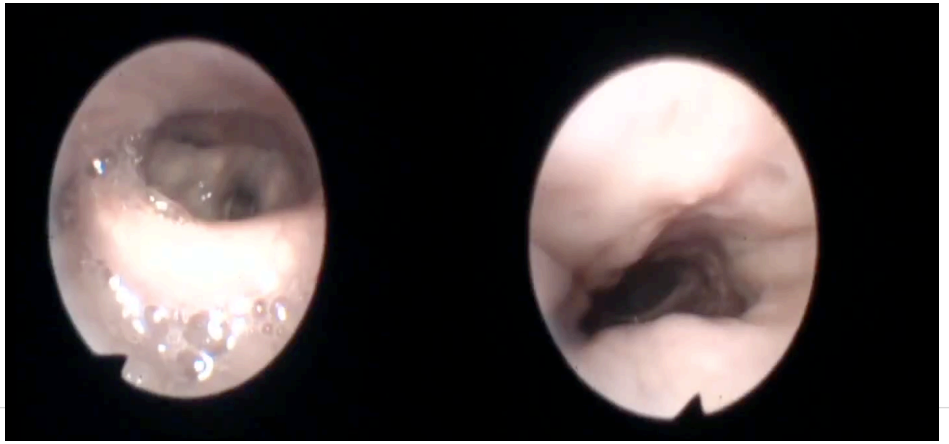


No Stimulation



Base of Tongue Palate

Stimulation



Base of Tongue Palate

STAR Trial

- 126 patients at 22 centers with moderate-to-severe OSA (20 ≥ AHI ≤ 50)

- Exclusion Criteria:
  - **BMI > 32**
  - **Concentric palatal collapse on DISE**
  - Other factors: Neuromuscular dz, severe CV dz, psychiatric dz, comorbid sleep disorders

- Titration study at 2m, 6m
- Efficacy PSG at 12m

Strollo PJ Jr et al. N Engl J Med. 2014

Feasibility Study

- Part 1:
  - Broad selection criteria: AHI ≥ 25, BMI < 35, no anatomic restriction
    - 20 completed analysis
      - 6/20 responders
    - **7 underwent DISE**

  - Responder analysis:
    - BMI ≤ 32, AHI ≤ 50: 55% success rate, p<0.01
    - DISE:
      - 3 **without** CCC: Responders
      - 4 **with** CCC: Non-responders

Van de Heyning et al. Laryngoscope, 2012.

Feasibility Study

- Part 2:
  - BMI ≤ 32, 20 ≥ AHI ≤ 50, no CCC
  - 8 completed analysis
  - 7/8 responders

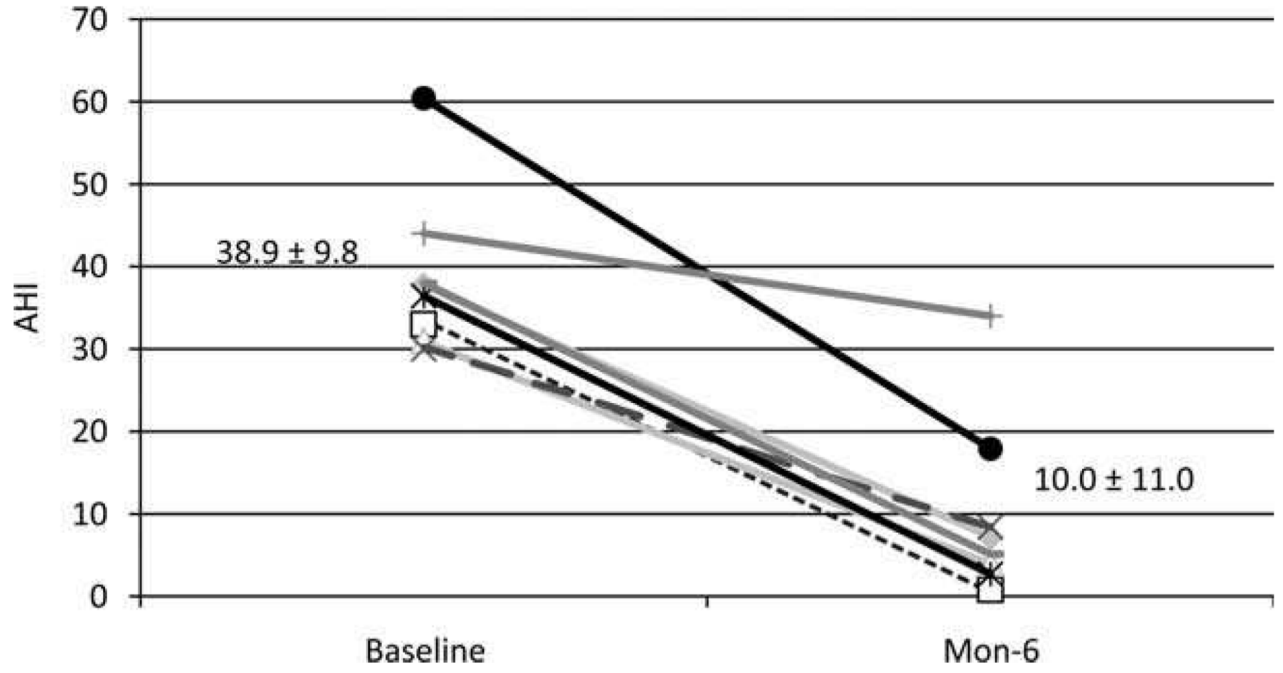


Fig. 4. Summary of part 2 subjects' apnea hypopnea index (AHI) at baseline and 6 months postimplant is shown.

Van de Heyning et al. Laryngoscope, 2012.

Back to STAR

- 126 patients at 22 centers with moderate-to-severe OSA (20 ≥ AHI ≤ 50)
- No BMI > 32 or CCC
- Titration study at 2m, 6m
- Efficacy PSG at 12m

Strollo PJ Jr et al. N Engl J Med. 2014

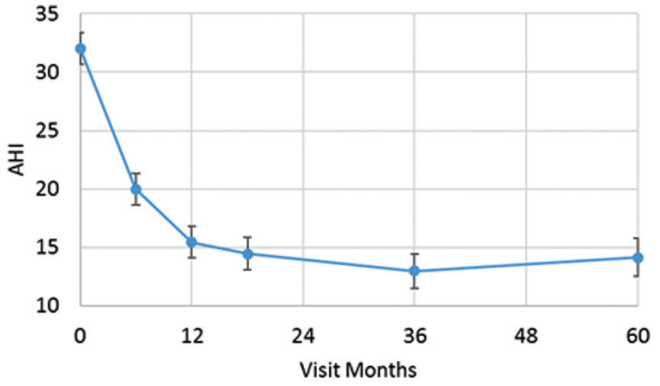
STAR Trial Results: 1-Year Outcomes

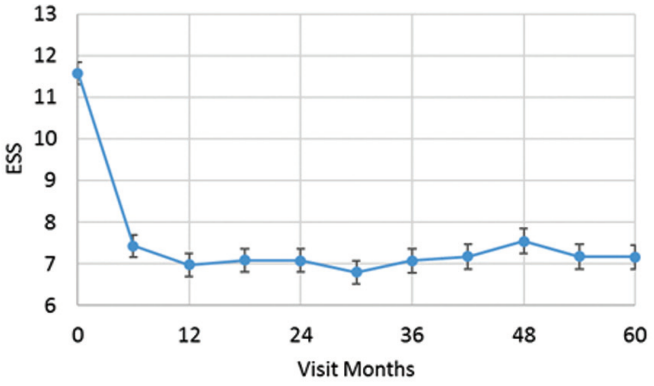
- Breathing and oxygenation improved
  - Mean AHI: 32 → 15
    - Median: 29.3 → 9.0
  - Oxygen Desaturation Index: 28.9 → 13.9
    - Median: 25.4 → 7.4
- Quality of Life and Daytime Sleepiness improved
  - FOSQ: 14.3 → 17.3
  - ESS 11.6 → 7.0
- Daily use: 86%
- **"Surgical Success:" AHI decrease >50% and <20: 66%**

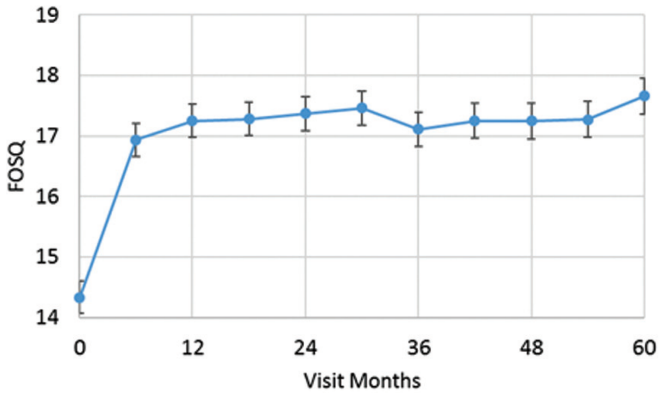
Strollo PJ Jr et al. N Engl J Med. 2014

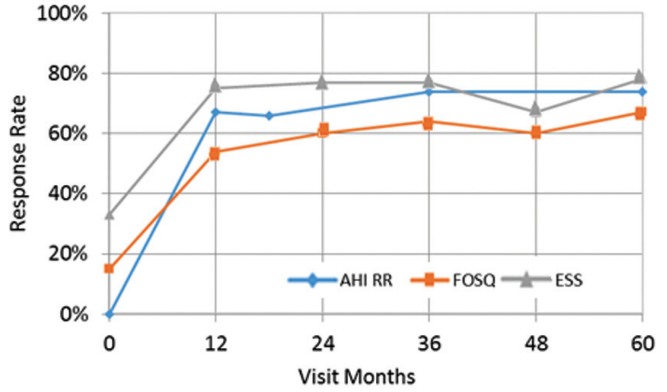
STAR: 5-year Outcomes

- At 60 months, N: 126 → 71
- AHI: 32 → 12.4, p<0.001
- ODI: 28.9 → 9.9, p<0.001
- FOSQ: 14.3 → 18, p<0.001
- ESS 11.6 → 6.9, p<0.001









VANDERBILT UNIVERSITY MEDICAL CENTER

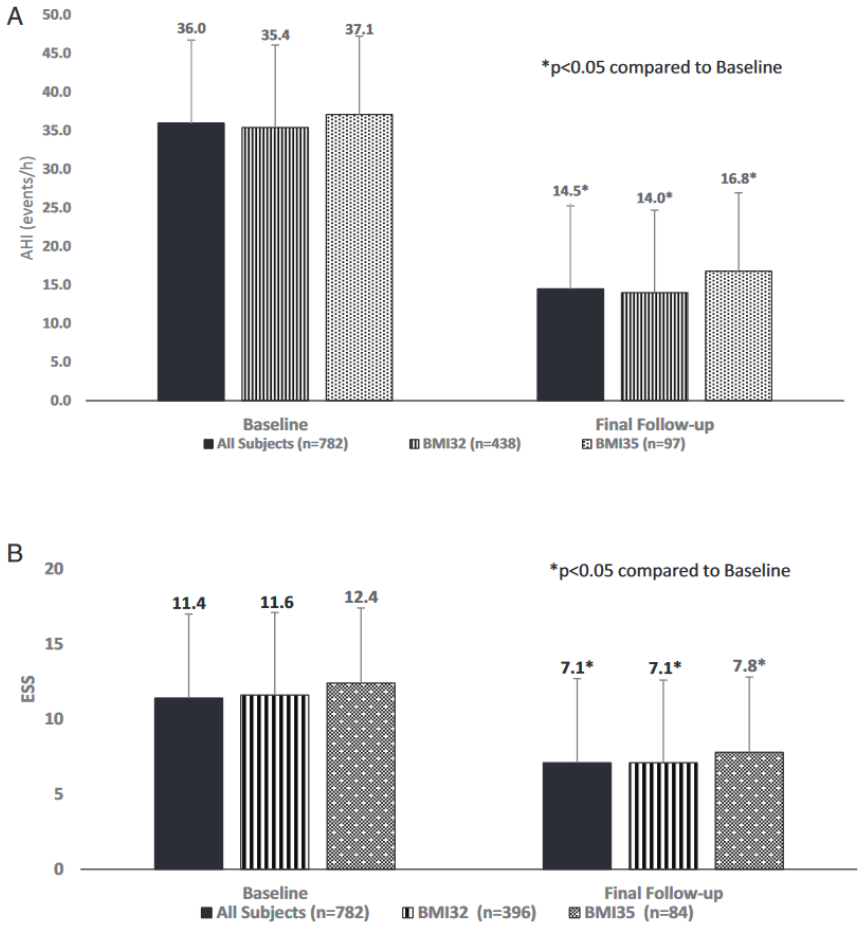
Woodson BT et al. Otolaryngol Head Neck Surg. 2018.

ADHERE: US Post-Market Study

- 15 ≥ AHI ≤ 65, no CCC
  - BMI 29.3 ± 3.9
- 1,849 enrolled; 843 with 12m data

- Mean AHI: 36.0 ± 15.7 → 14.5 ± 14.9, p<0.05
- Mean ESS: 11.2 ± 5.6→ 7.1 ± 4.6, p<0.05

- Surgical success
  - BMI_{35} vs BMI_{32}: 59.8% vs. 72.2%, P = .02

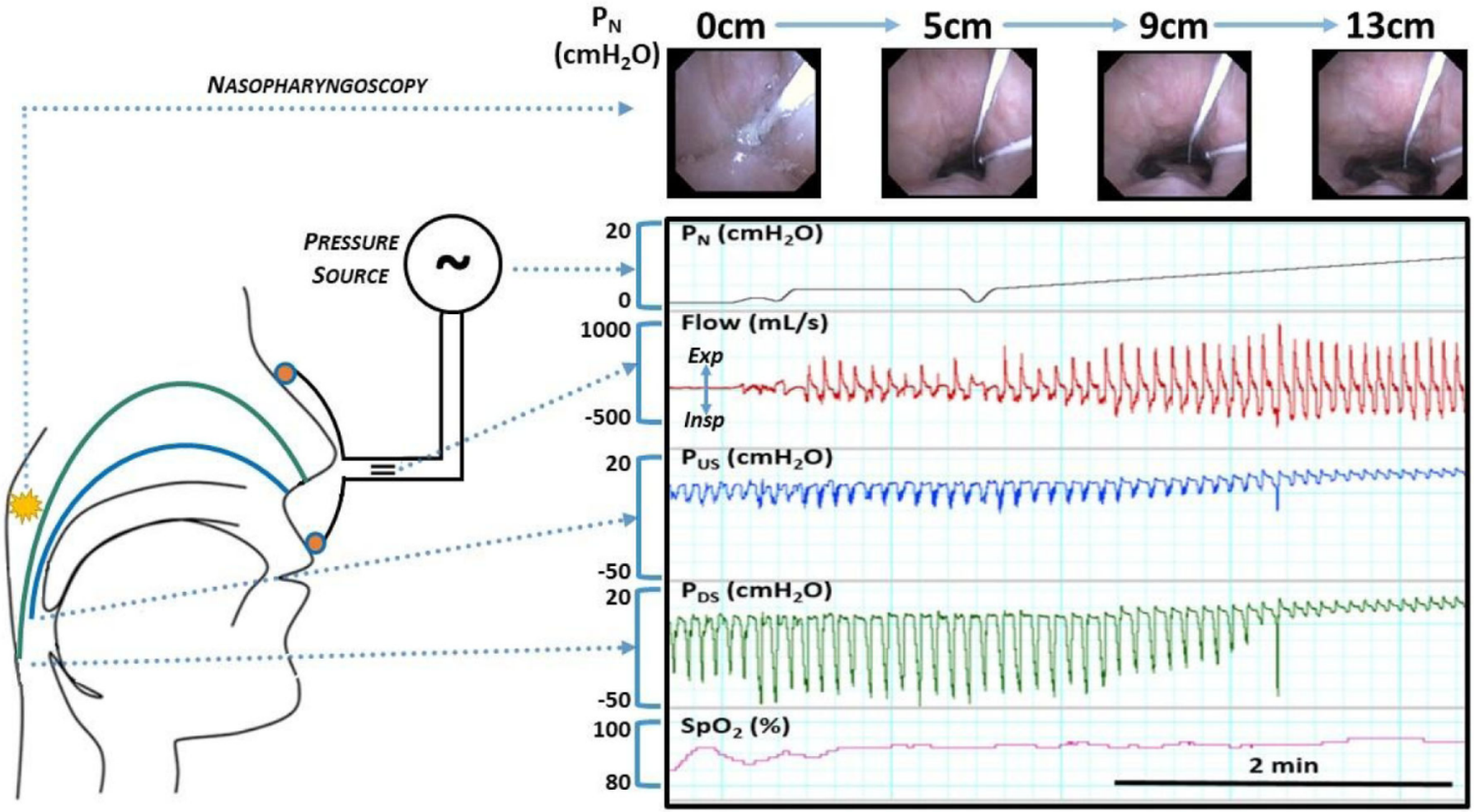


Suurna et al. Laryngoscope, 2021.

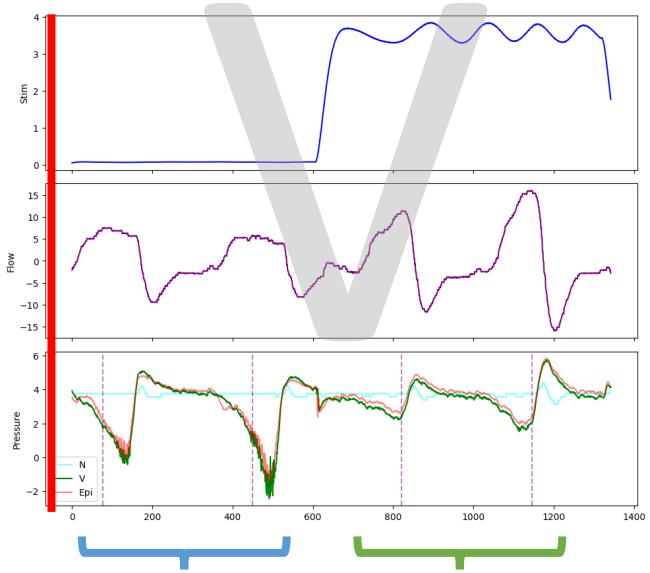
Innovation in Sleep Surgery: The Future

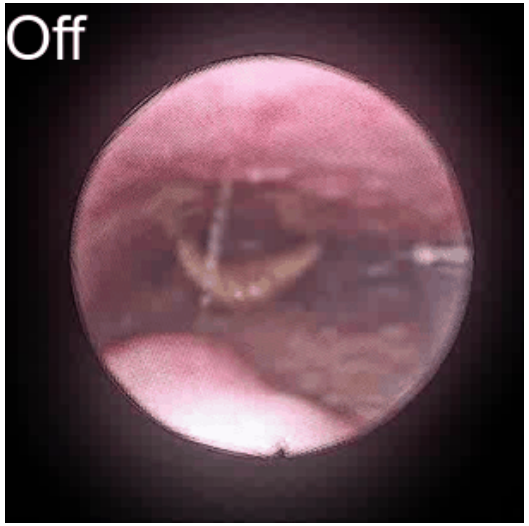
- Improved anatomic phenotyping
- Non-anatomic phenotyping
- Therapeutic innovations

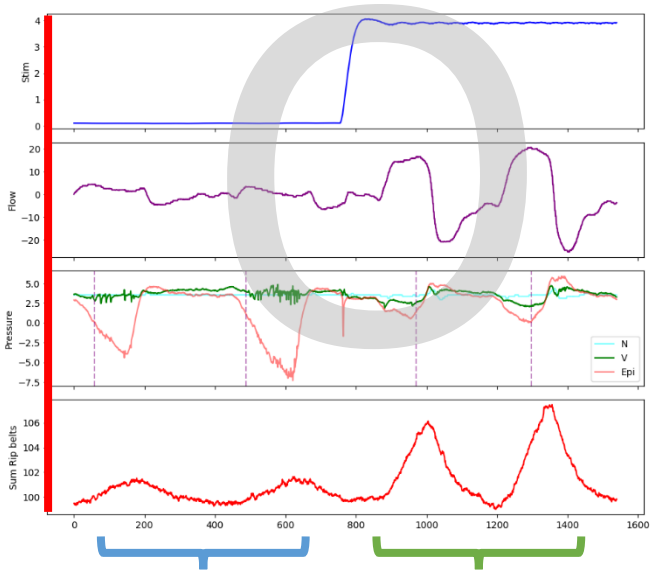
Improving Anatomic Phenotyping: Beyond DISE

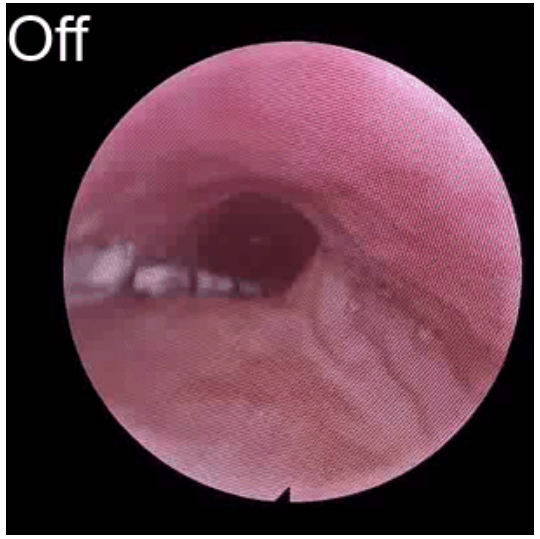


Dedhia RC et al. ORL J Oto Relat Spec, 2022.



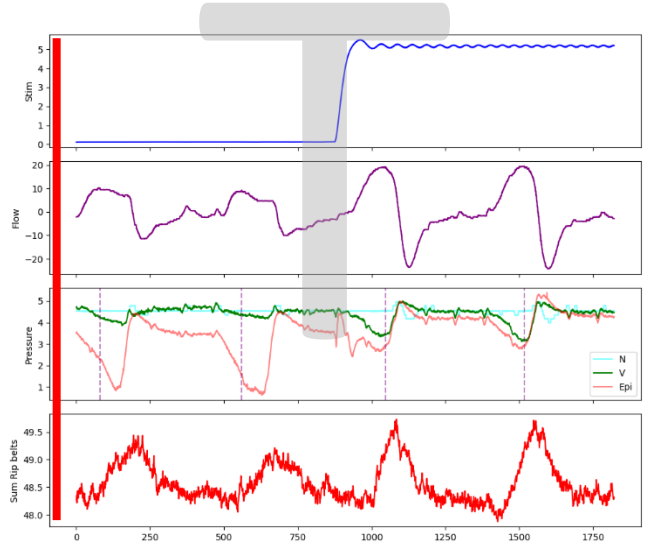


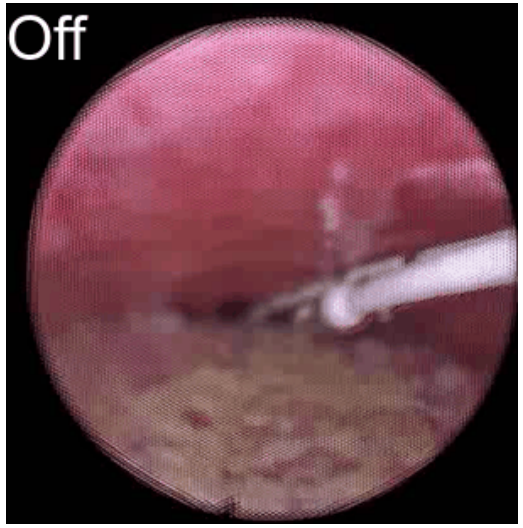




FLS @V Non-FL

FLS @V Non-FL





FLS @T Non-FL

FLS @E Non-FL

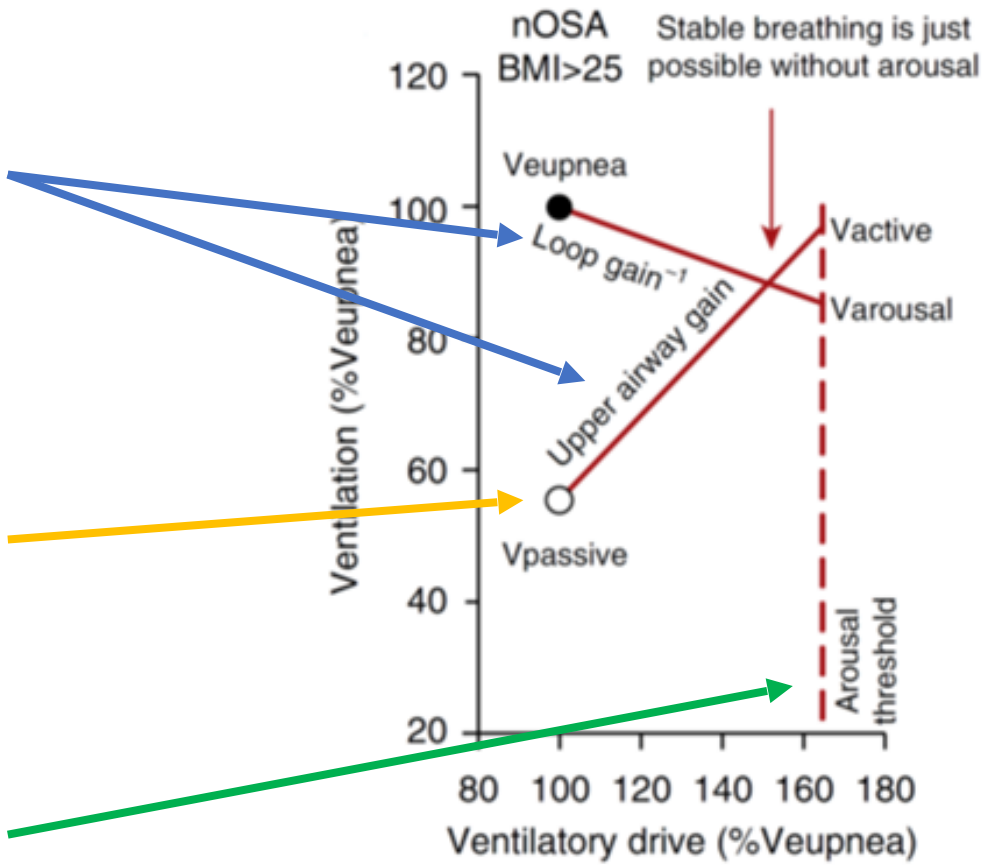
Non-Anatomic Phenotyping: PALM Scale

- Pcrit
  - Non-anatomic measure of airway collapsibility
- Arousal Threshold
  - Ventilation or airway pressure threshold leading to awakening
- Loop Gain
  - Central ventilatory control system sensitivity
- Muscle Responsiveness
  - Airway dilator muscle response to negative pressure

Eckert et al, AJRCCM 2013

Putting Phenotyping Together

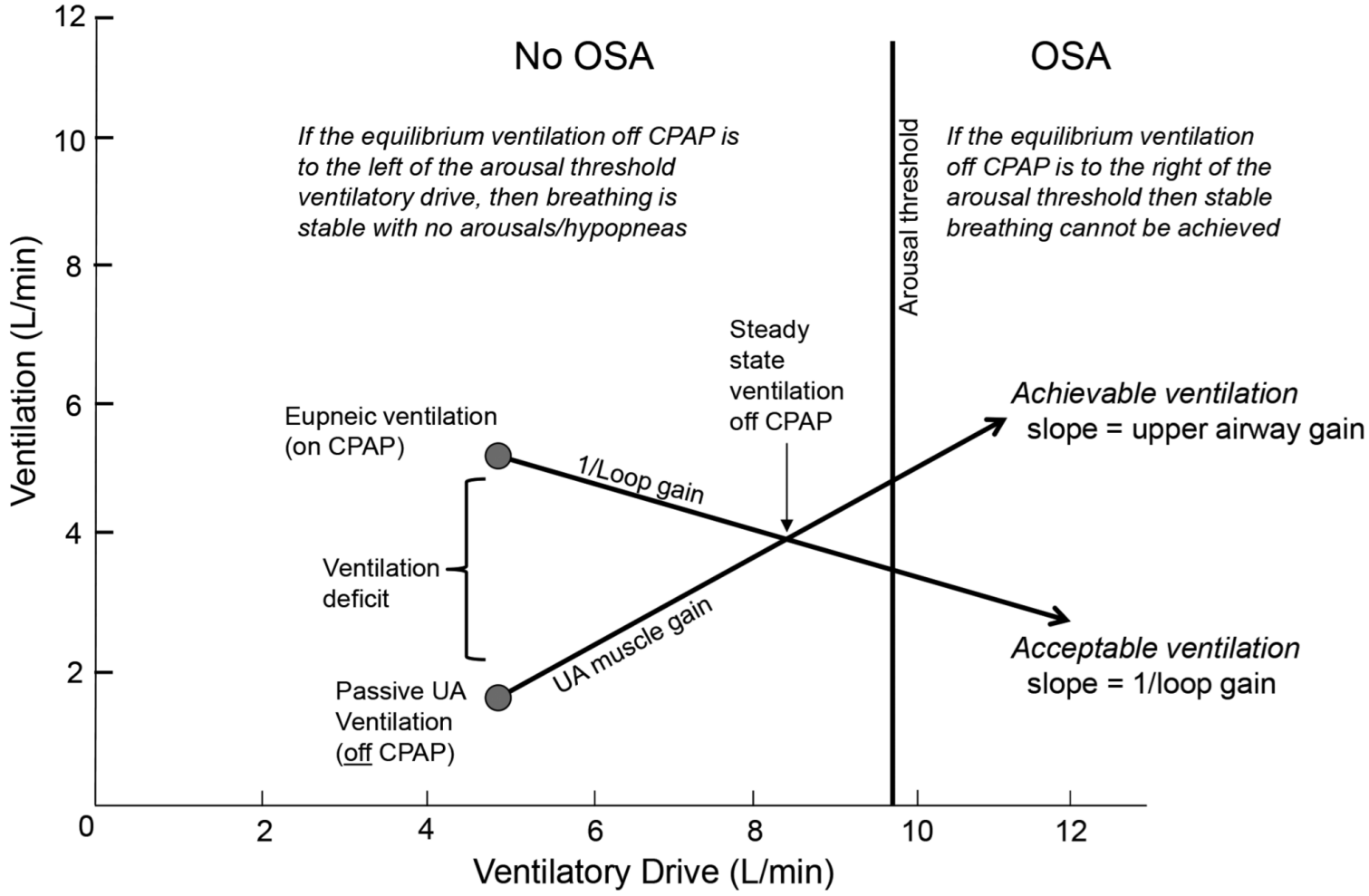
- Loop gain and upper airway gain (muscle responsiveness) control how much ventilation can be achieved with increasing effort
- P_{crit}: determines inspiratory negative pressure airway can tolerate
- Arousal threshold: Ventilatory drive tolerated before arousal



Sands et al, AJRCCM 2014

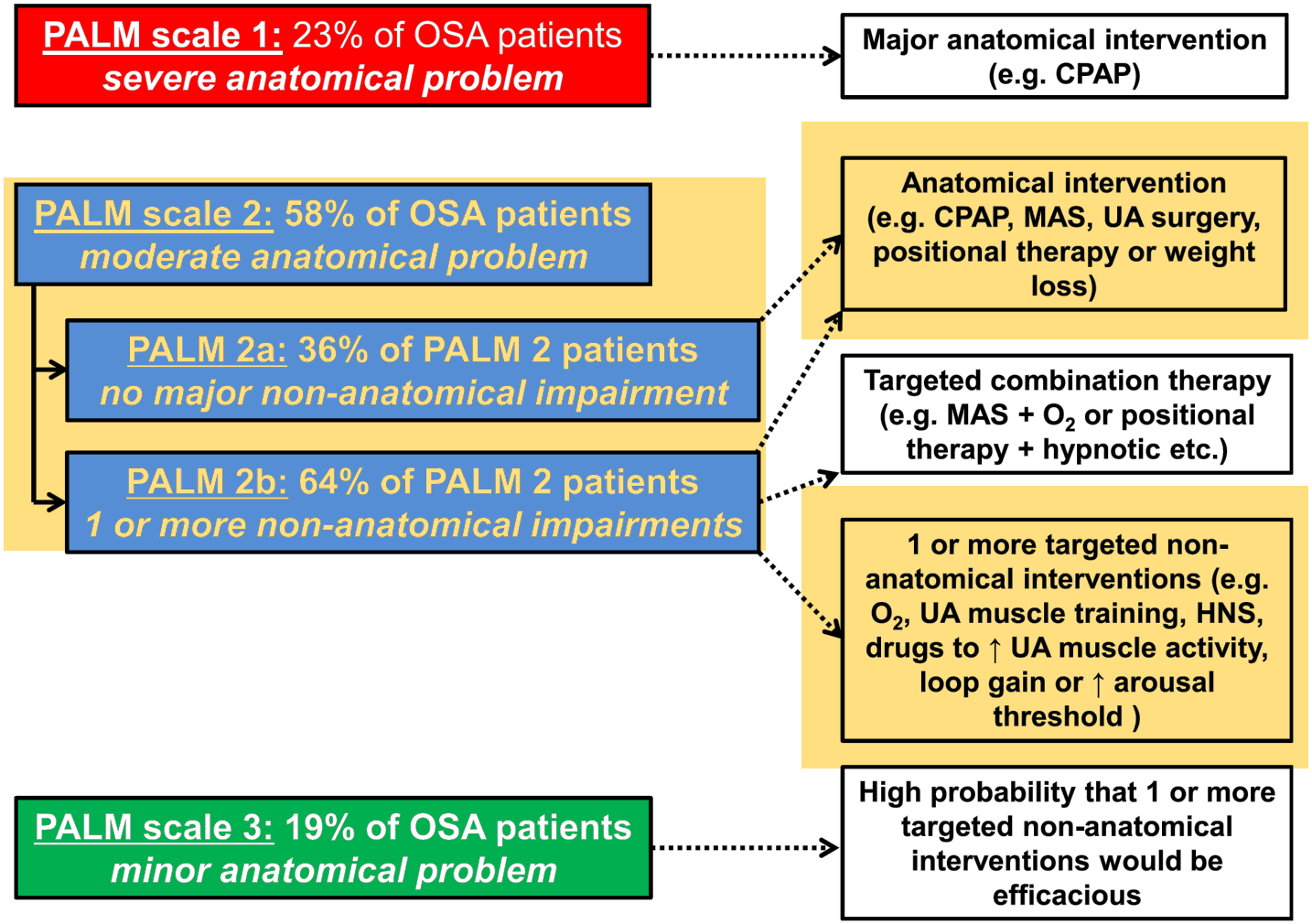
Putting Phenotyping Together

- No OSA
  - Stable breathing possible without arousal
- OSA
  - Ventilatory drive cannot achieve adequate ventilation before arousal



Owens et al, Sleep 2015

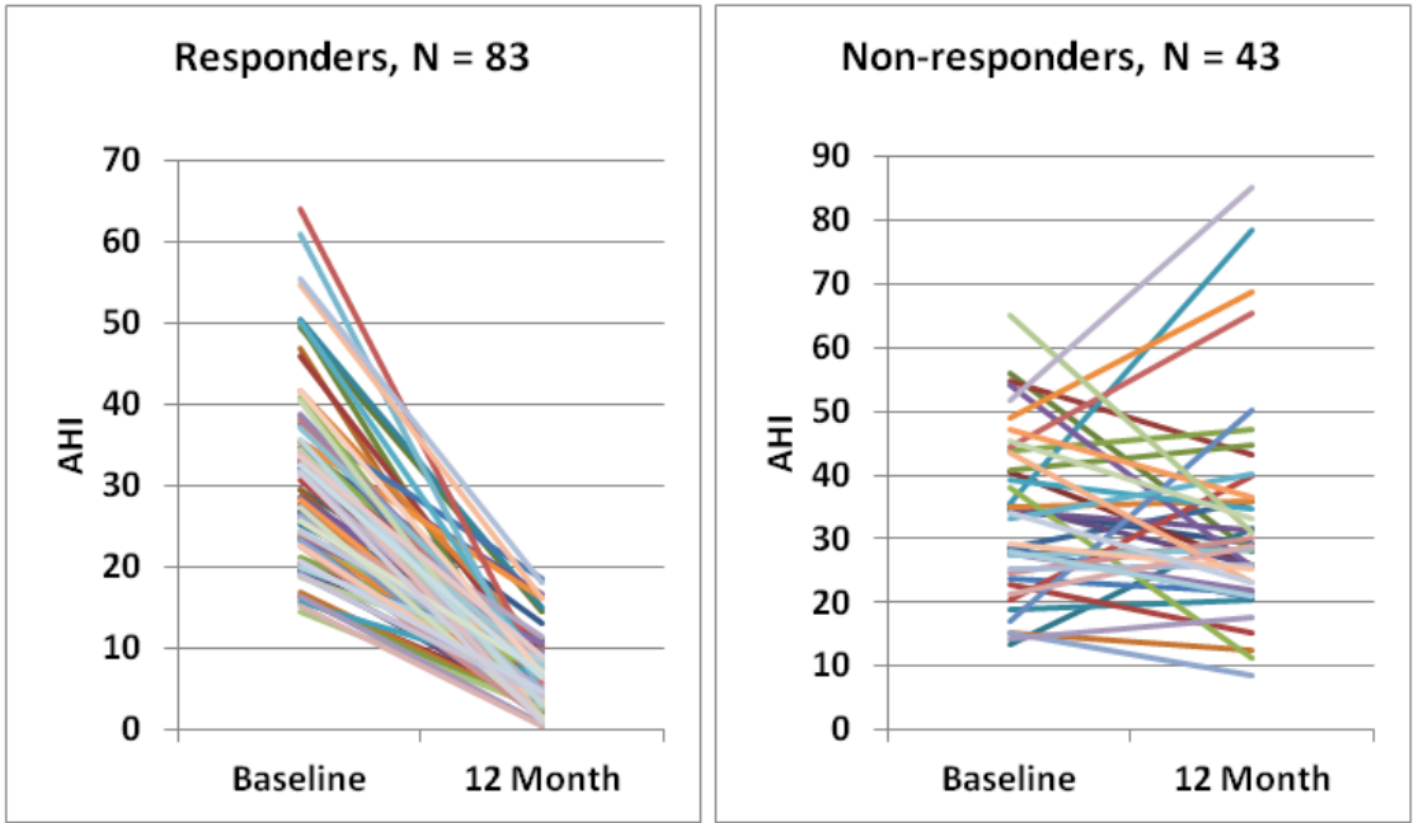
Phenotyping and Therapy Selection



Eckert, Sleep Med Reviews 2016.

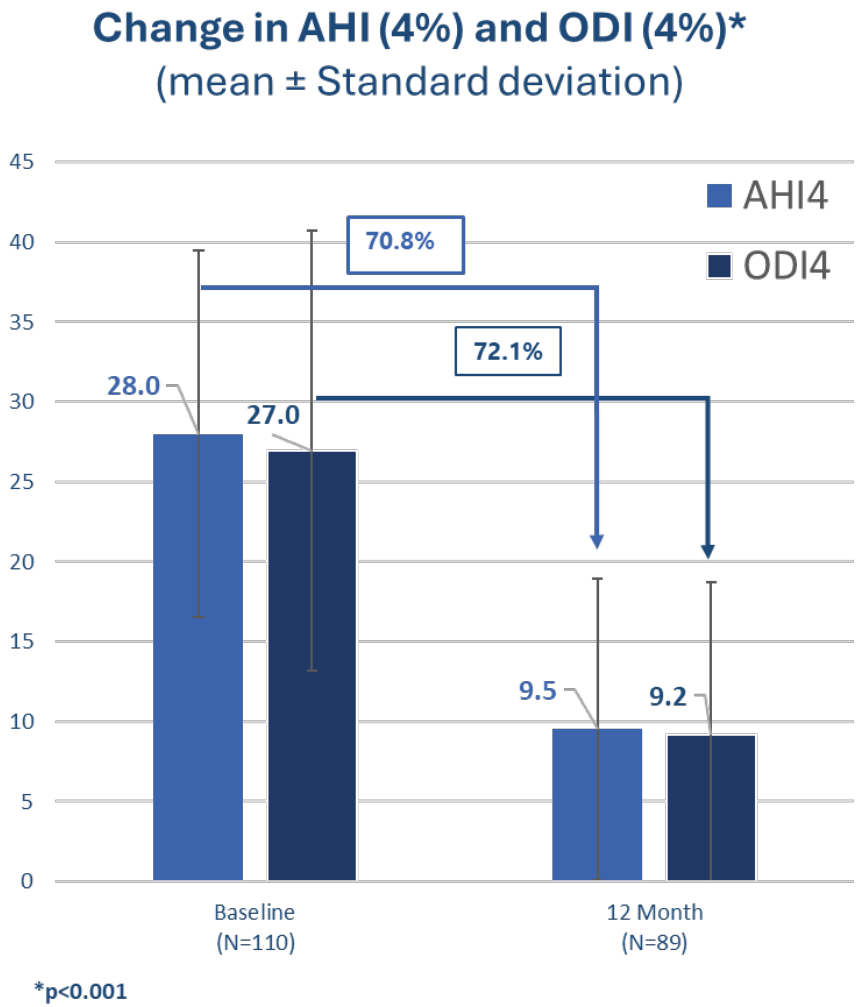
Therapeutic Innovations: HNS Responders and Non-Responders

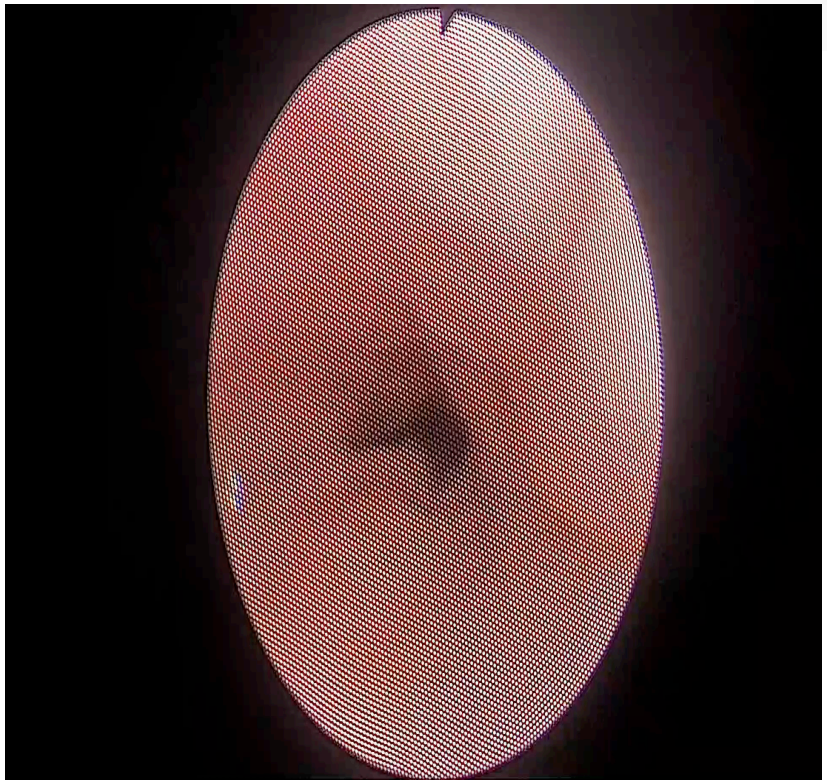
- 1y Responder Rate: 66%
  - AHI <5: 29%
- 5y
  - Follow up: 56.3%
  - Responder rate: 63%
  - AHI <5: 44%



Strollo P et al. NEJM, 2014. Woodson BT et al. Otolaryngol Head Neck Surg. 2018.

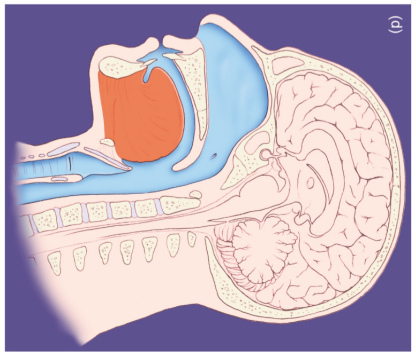
Is Bilateral HNS A Paradigm Shift?



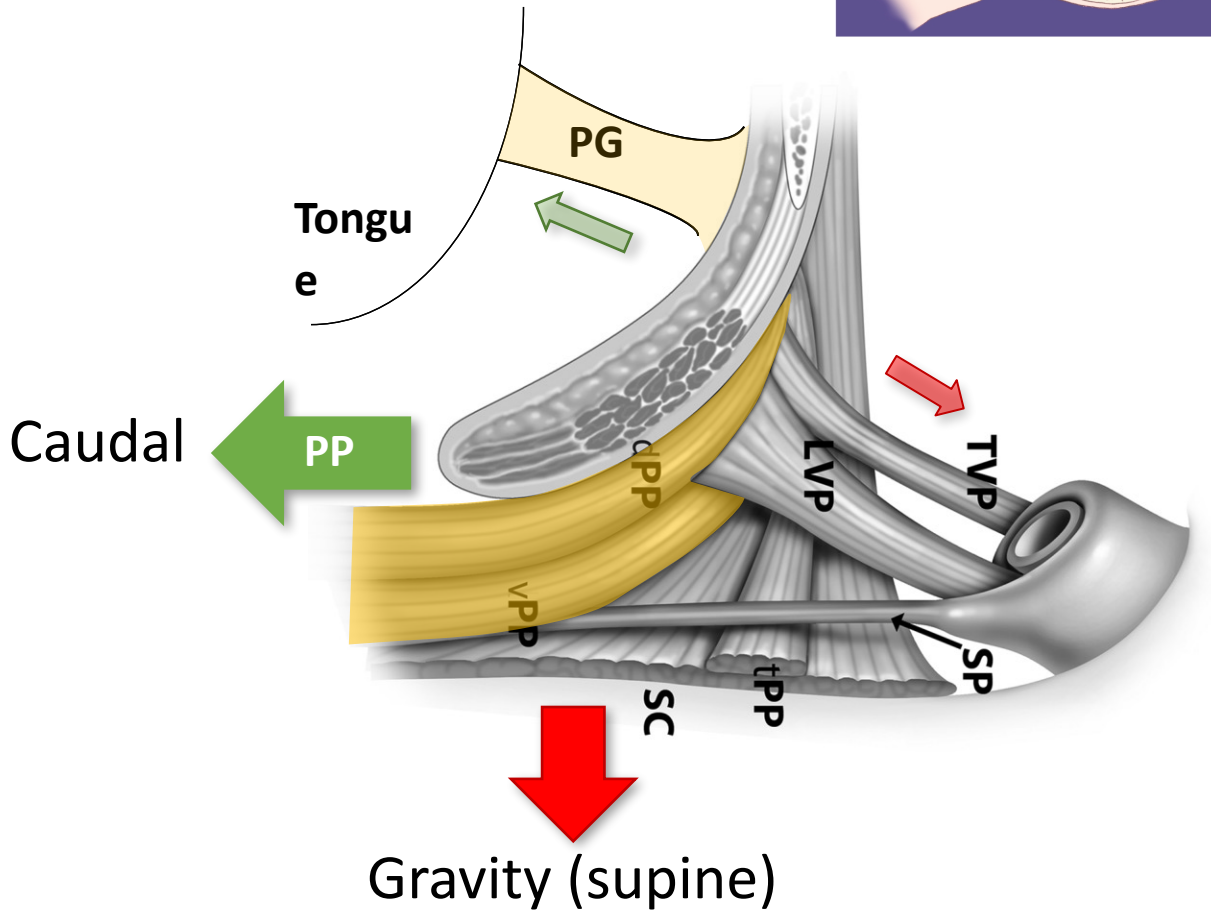


*Not peer reviewed

Why Might HNS Fail?



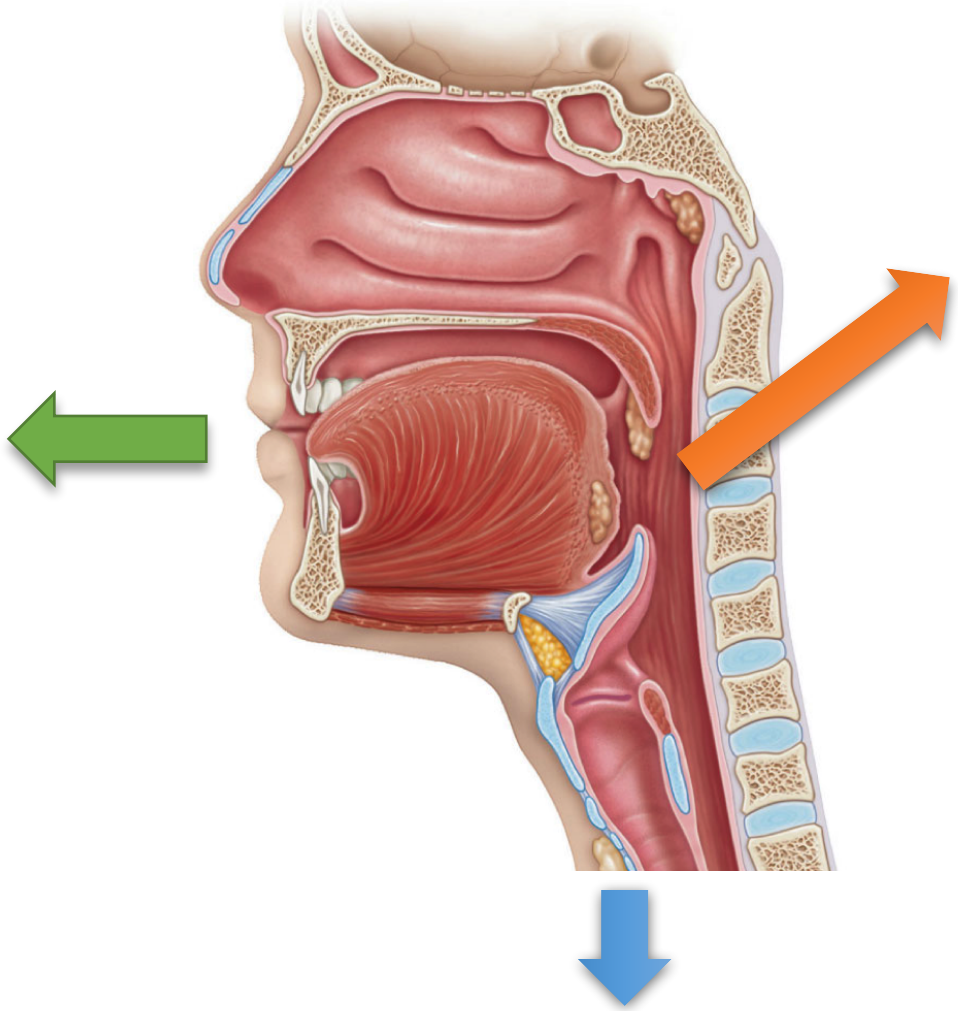
- Palatal “advancement” is not physiologic
- Palate hinges to open
  - Palatoglossus and palatopharyngeus are levers
- No extrinsic palatal musculature for **anterior** displacement
  - Displaces **caudally** (downwards) to open



Olszewska E. Laryngoscope Investig Otolaryngol, 2019; Davidson TM. Sleep Med, 2003.

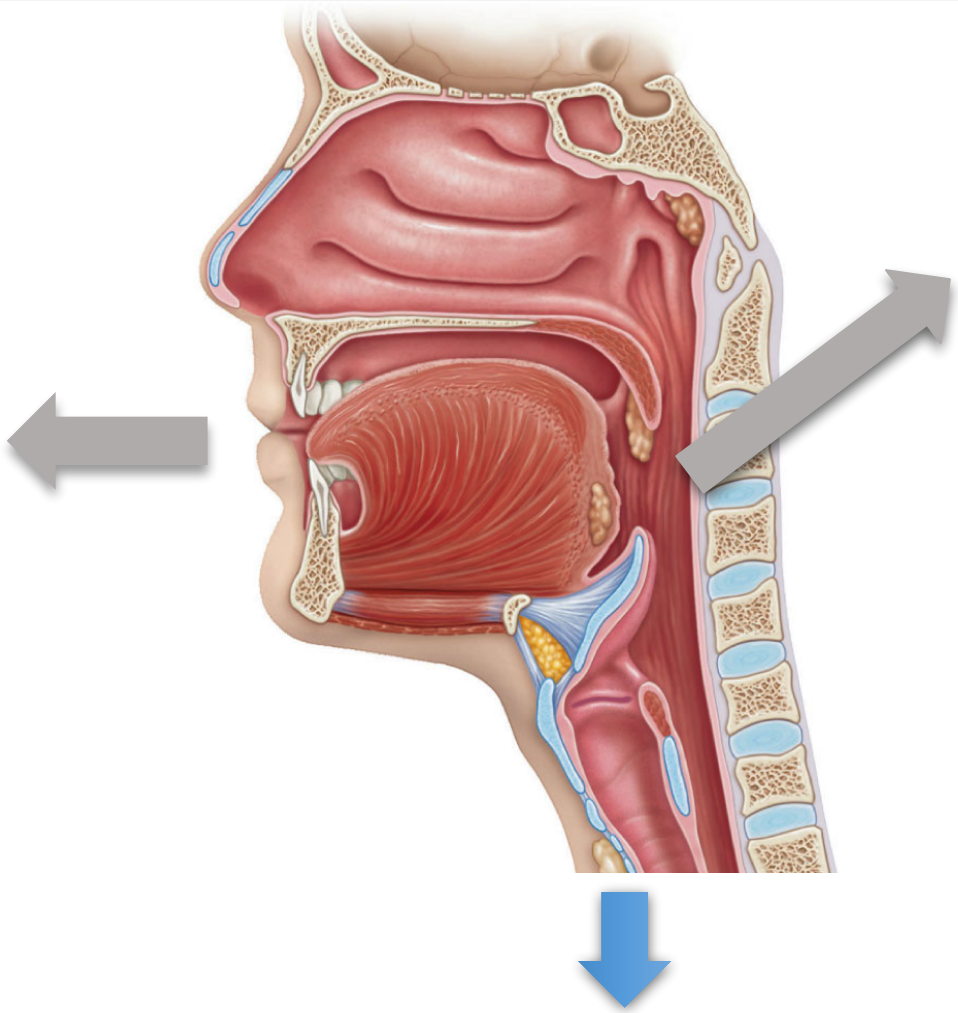
Mechanisms Supporting Pharyngeal Airway

- Three physiologic supporting mechanisms
  1. Genioglossus Tone
  2. Intrinsic Pharyngeal Muscle Tone
  3. Tracheal Traction

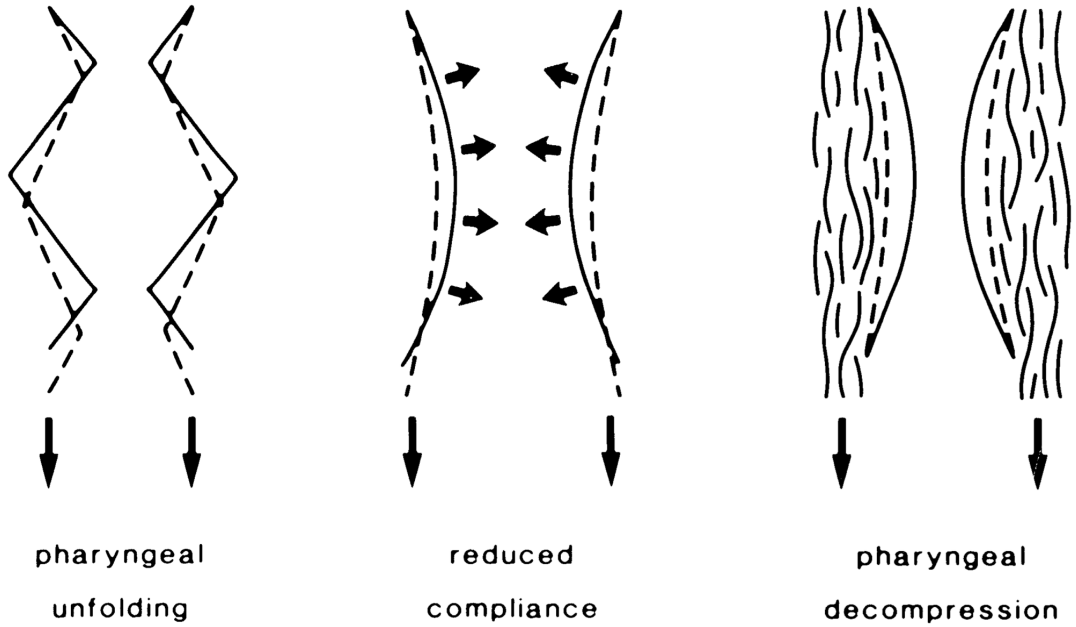


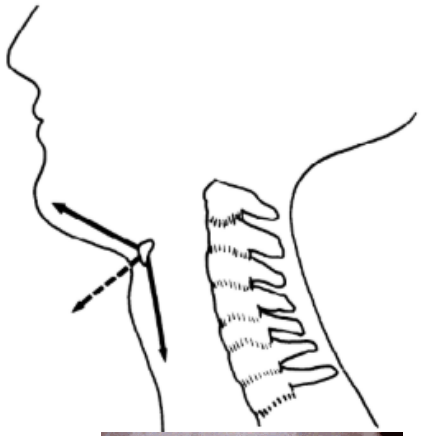
Mechanisms Supporting Pharyngeal Airway

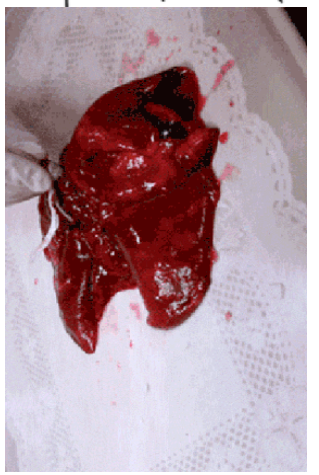
- The pharynx is extrinsically modifiable in anterior-posterior **and caudal** directions
- Pharyngeal surgery, including craniofacial surgery and HNS, primarily modify A-P dimension
- Three physiologic supporting mechanisms
  1. Genioglossus Tone
  2. Intrinsic Pharyngeal Muscle Tone
  3. **Tracheal Traction (lung volume)**
- Opposing forces may have synergistic effects



Tracheal Traction Is Determined by Lung Volume







1. Relieves airflow obstruction during sleep and anesthesia ($V_{I}max$)
2. Decreases pharyngeal collapsibility (P_{CRIT})
3. Improves sleep apnea (AHI) and lowers CPAP requirement

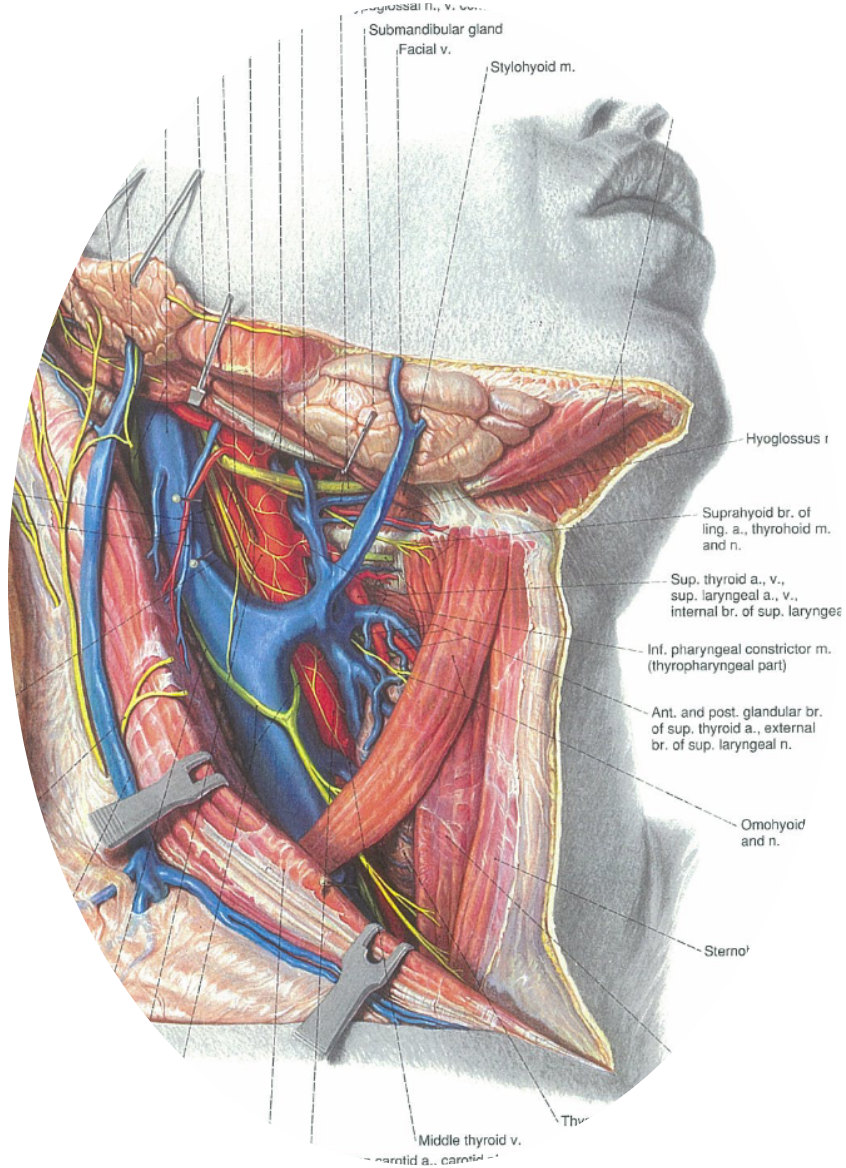
Thut DC et al. J Appl Physiol 75(5): 2084-90, 1993
Rowley JA et al. J Appl Physiol. 1996; 80(6):2171-2178

Squier SB et al. J Appl Physiol 109(4): 977–985, 2010
Hillman DR et al. . J Appl Physiol 2013;115(3):337-45

Heinzer R et al. Am J Respir Crit Care Med. 2005 Jul 1; 172(1): 114–117
Heinzer et al. Thorax. 2006 May; 61(5): 435–439

Van de Graff WB. J Appl Physio, 1988.

Ansa Cervicalis Stimulation = Tracheal Traction?



- The human hyolaryngeal complex is highly mobile
  - Speech, swallowing adaptations
- Strap musculature enables a wide degree of control
  - Innervated by the **ansa cervicalis**

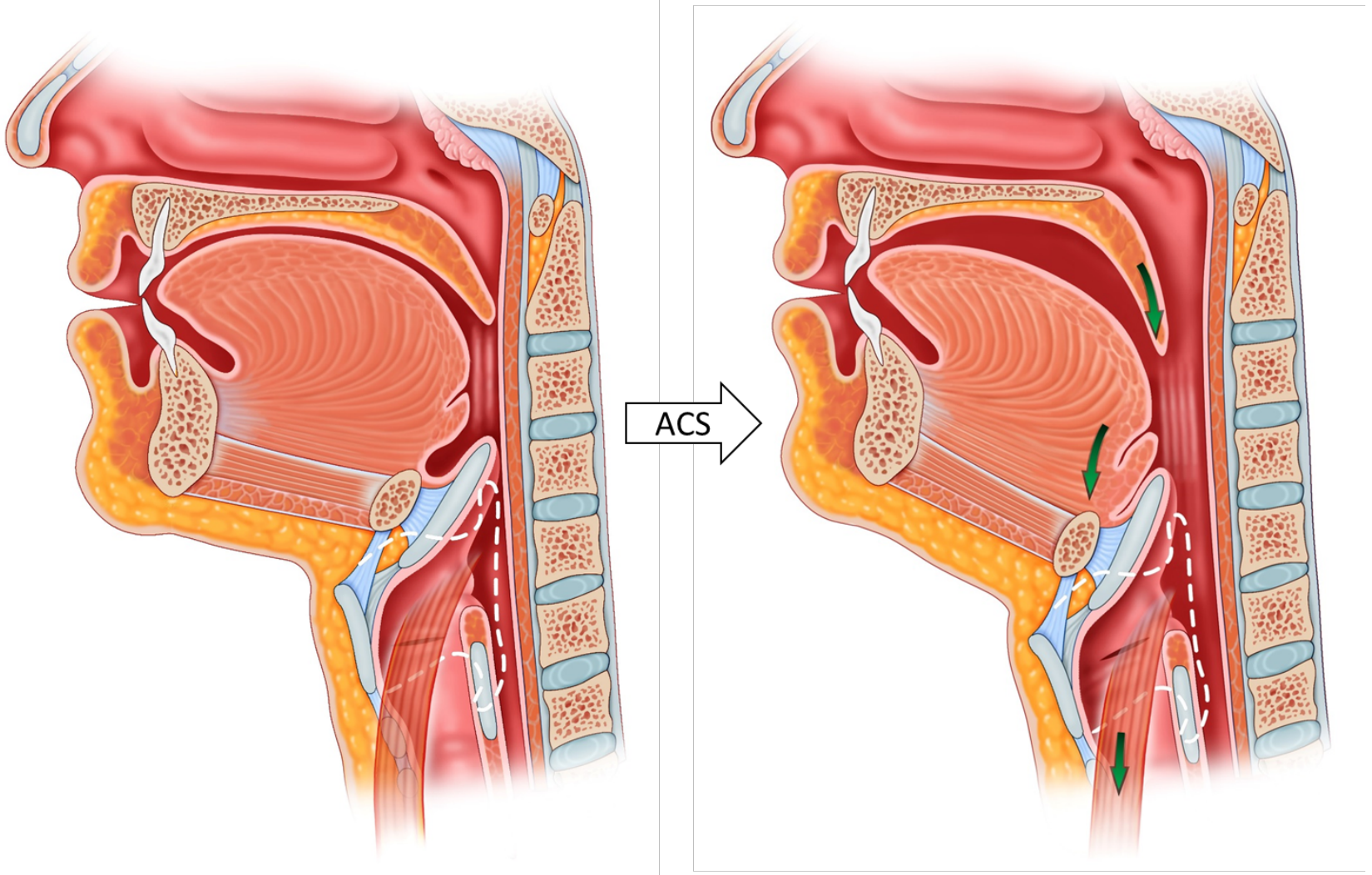
A Little Self-Experimentation

HNS

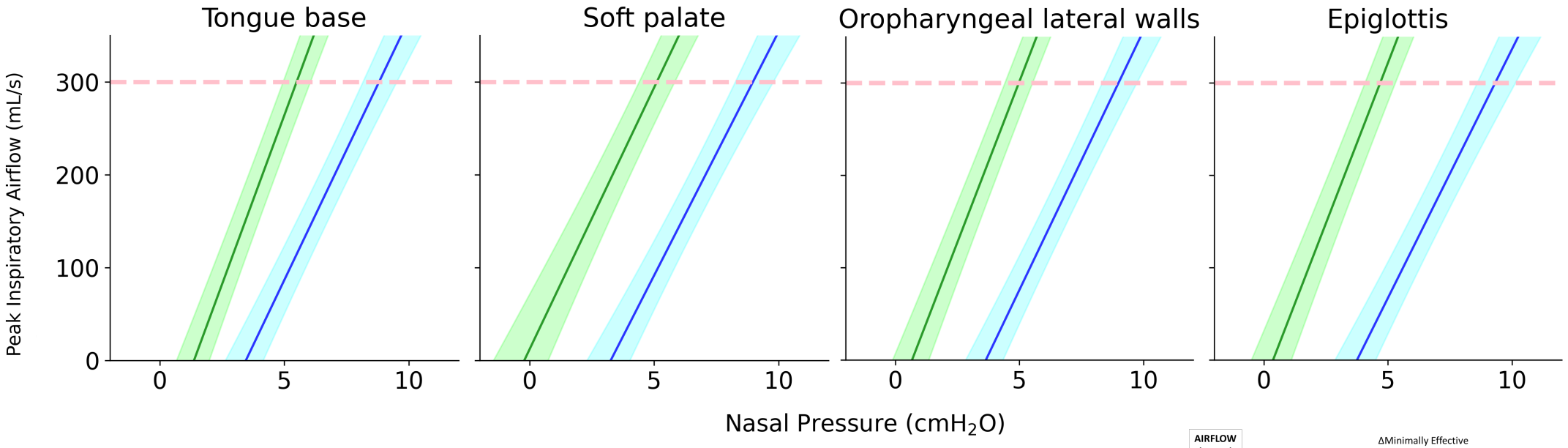
ACS

ACS: Proposed Mechanisms of Action

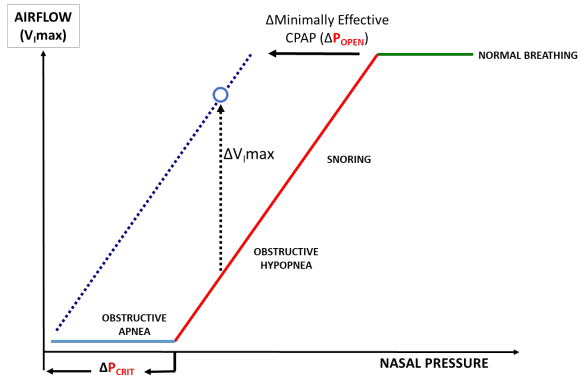
1. Palate tensioning/ opening
2. Palate unloading
3. Lateral wall stabilization
4. Anterior epiglottic tilt



ACS: Pressure-Flow Plots by FLS (Model)

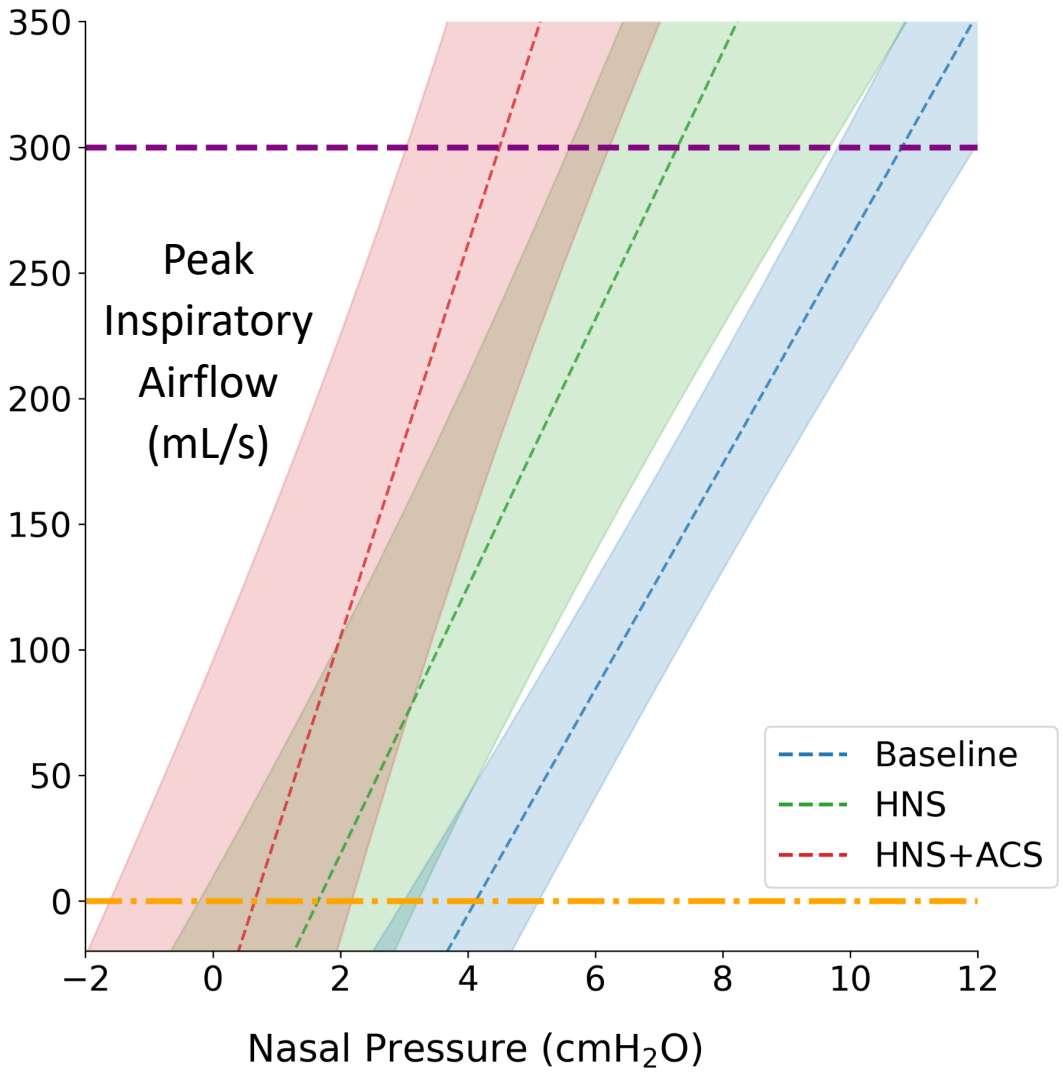


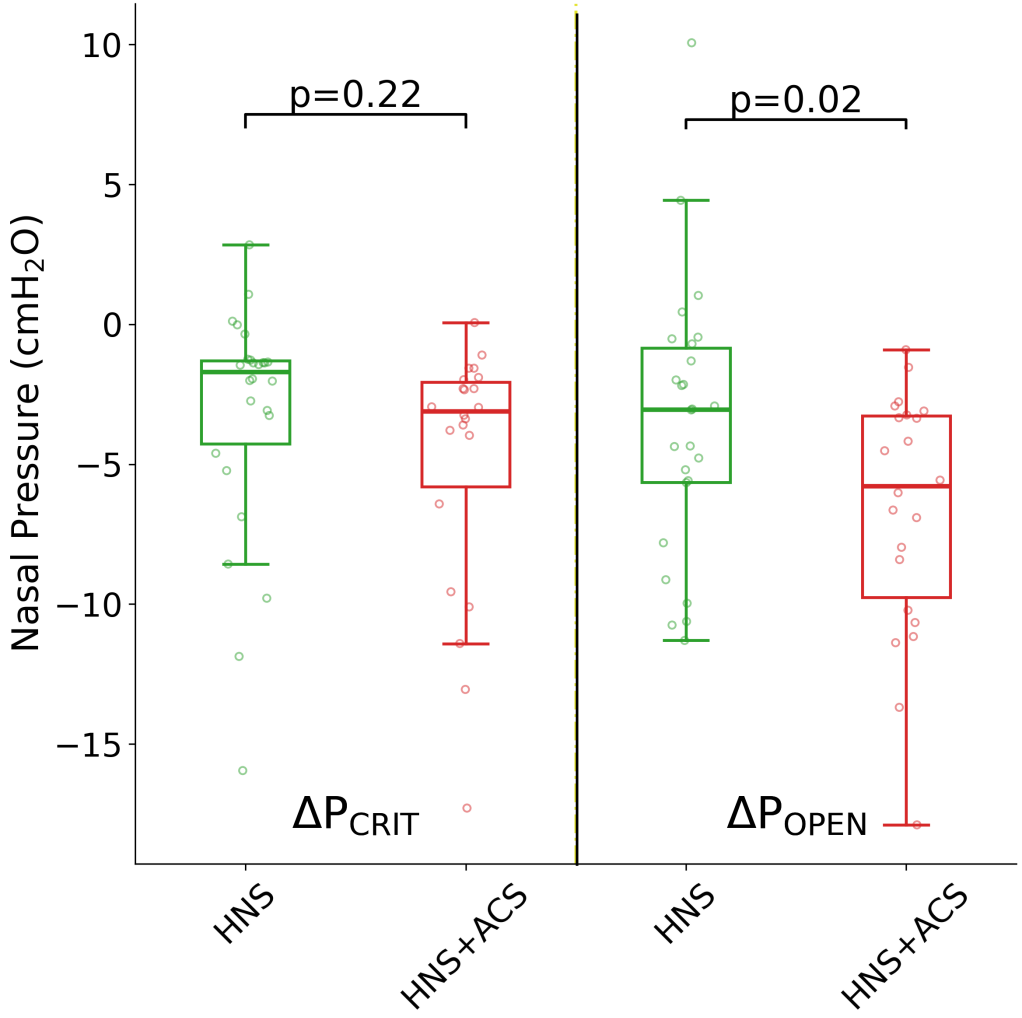
FLS	Δ P_{CRIT} (cmH_2O)	Δ P_{OPEN} (cmH_2O)
V	-3.46 [-4.36, -2.57]	-3.86 [-4.67, -3.06]
O	-2.97 [-3.58, -2.37]	-4.01 [-4.70, -3.30]
T	-2.08 [-2.67, -1.49]	-3.31 [-3.97, -2.65]
E	-3.38 [-4.09, -2.67]	-4.63 [-5.42, -3.84]



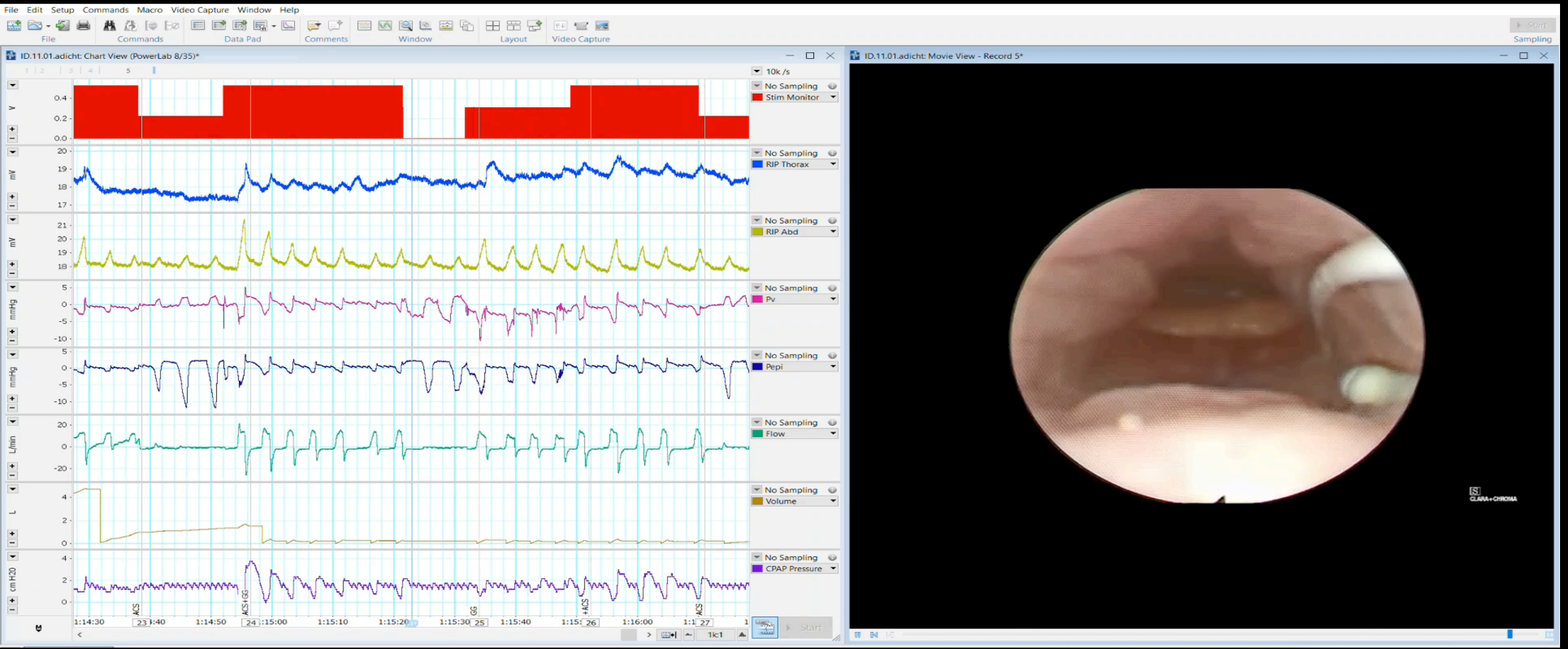
Li et al. Eur Resp J, 2024.

HNS+ACS (N=29)





		ΔP_{CRIT}	p	ΔP_{OPEN}	p
Baseline	**→ HNS**	-2.5 [-3.7, -1.2]	**<0.05**	-3.5 [-5.2, -1.8]	**<0.05**
Baseline	**→ HNS+ACS**	-3.5 [-4.7, -2.3]	**<0.05**	-6.3 [-7.7, -4.9]	**<0.05**
HNS	**→ HNS+ACS**	-1 [-2.2, 0.3]	0.119	-2.8 [-4, -1.6]	**<0.05**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No Sampling
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RIP Abd
Pv
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CPAP Pressure
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Conclusions

- Sleep surgery has evolved from a handful of surgical options to a wide variety of anatomically targeted interventions
- Hypoglossal nerve stimulation represents a paradigm shift as an augmentation of muscle responsiveness – not anatomy altering
- Diagnostic and phenotyping processes continue to evolve
- New therapeutic interventions (ACS) hold promise