OSA IN CHILDREN (PART 1)

SNORING IS MORE THAN JUST A LOUD NUISANCE!

David Gozal, MD, MBA, PhD

Professor and Dean
Vice President Health Affairs

MARSHALL UNIVERSITY
Joan C. Edwards School of Medicine

OBJECTIVES

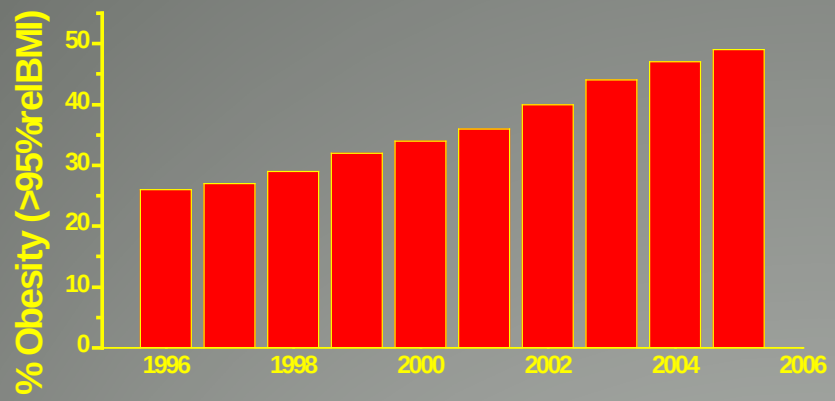
1) Overview of obstructive sleep apnea (OSA) in Children – A “growing” problem
2) Diagnostic challenges of OSA – Osler has failed us
3) Phenotypic variance – steps to personalized medicine
4) Treatment of OSA in children – more complicated than we think – other speakers

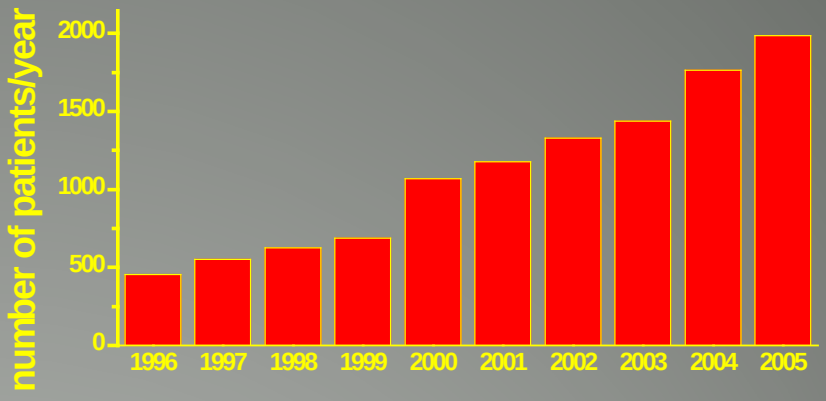
OBSTRUCTIVE SLEEP APNEA

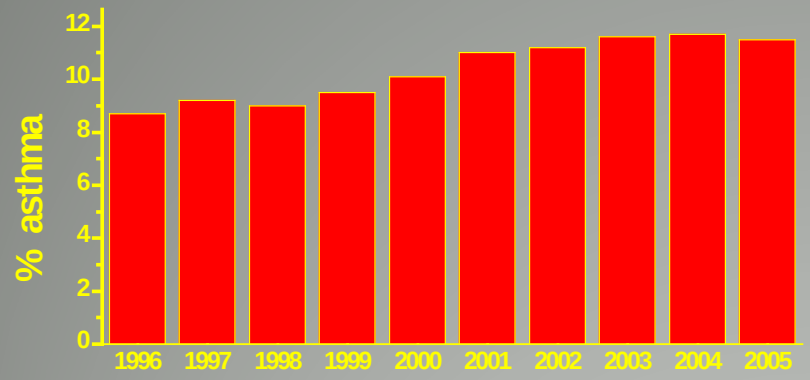
- Intermittent partial or complete occlusion of the upper airway during sleep
- Profound disturbances in homeostatic gas exchange, frequent arousals and disturbed sleep architecture
- Initial description of OSA in 1880 by McKenzie
- First described in children in 1976 by Guilleminault and colleagues

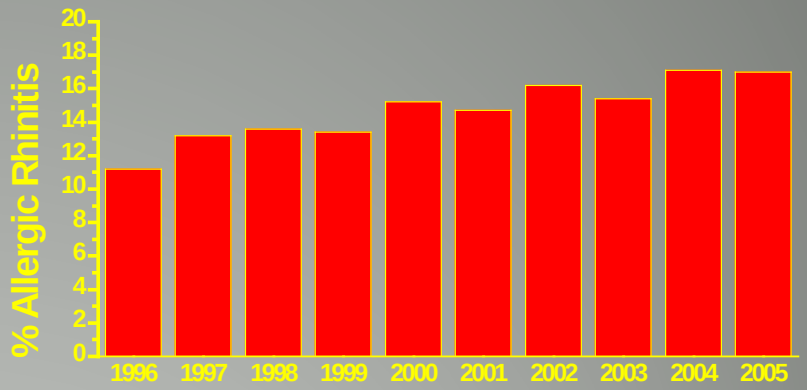
GUILLEMINAULT ET. AL. *PEDIATRICS* 58, 1976

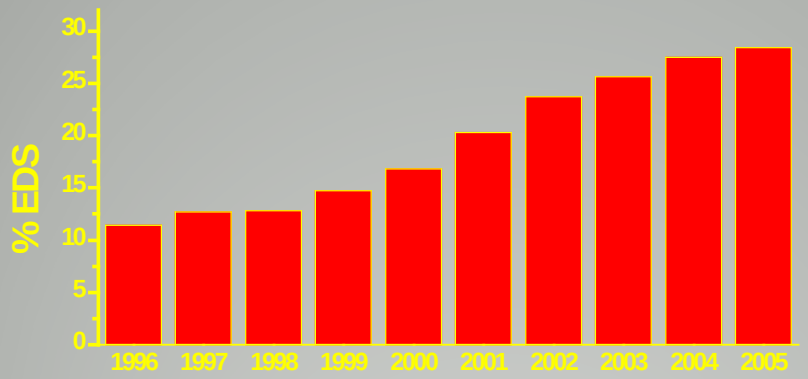
Temporal Trends in a Busy US Pediatric Sleep Clinic



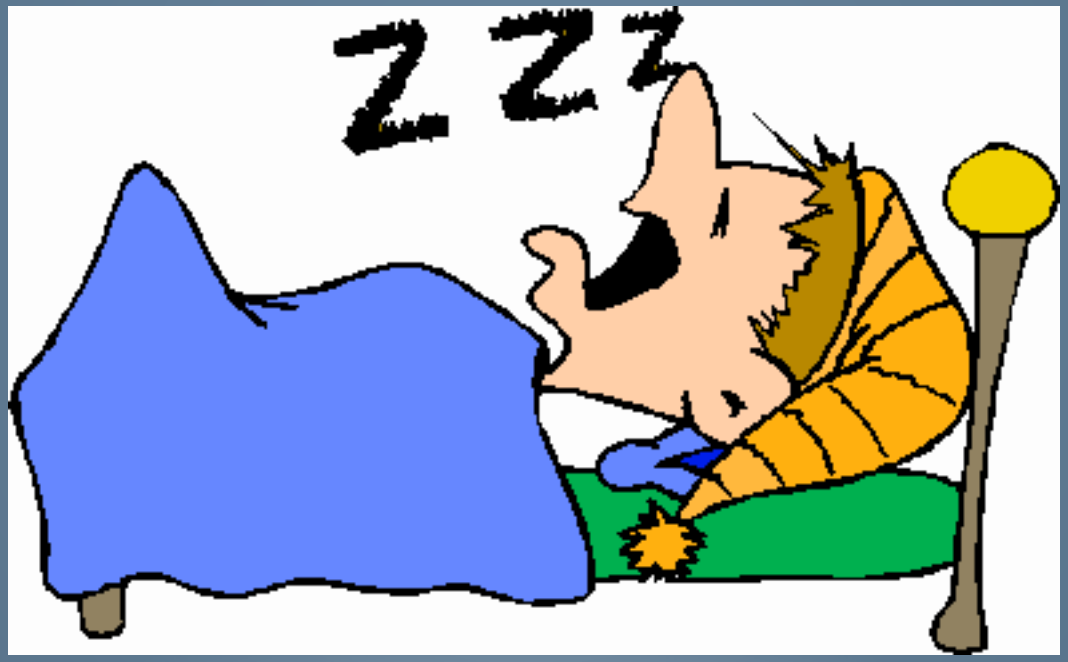






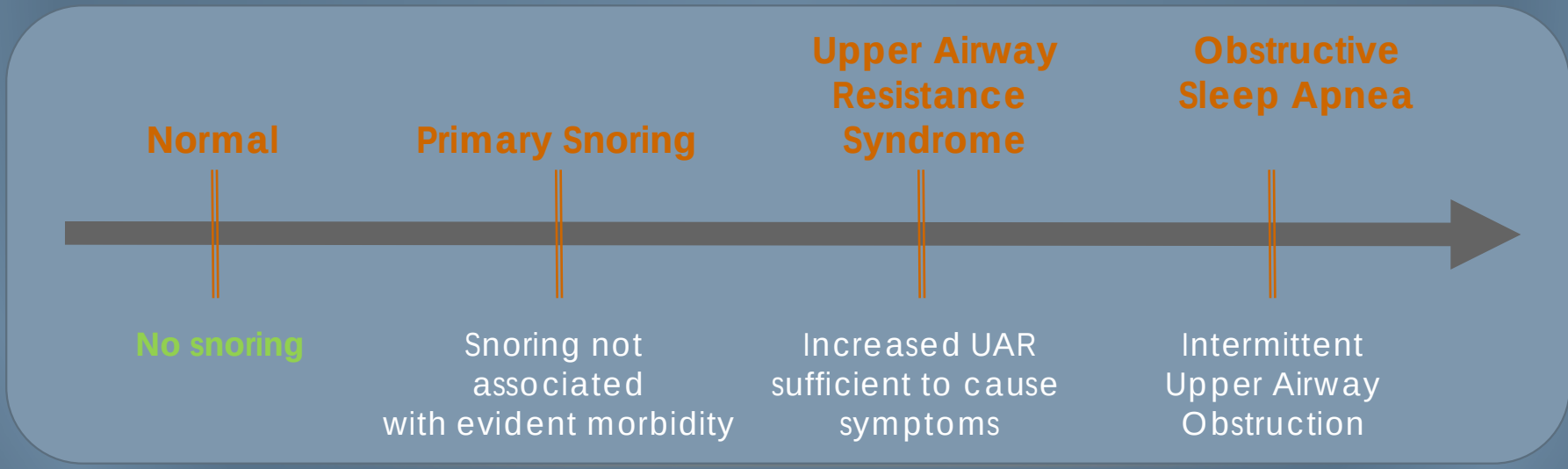


PREVALENCE OF OSA IN CHILDREN

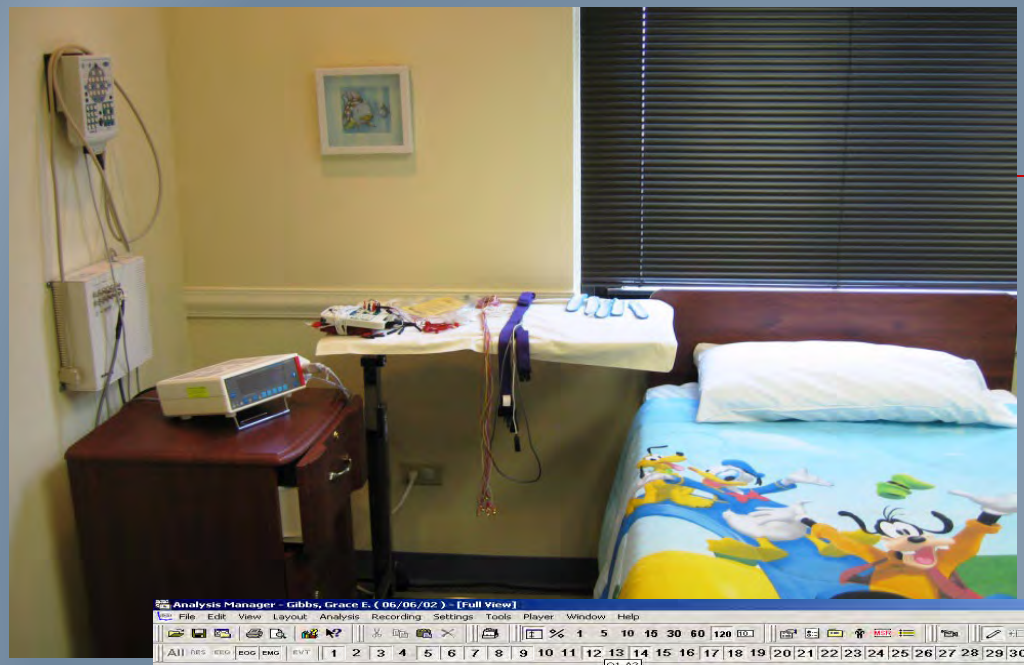


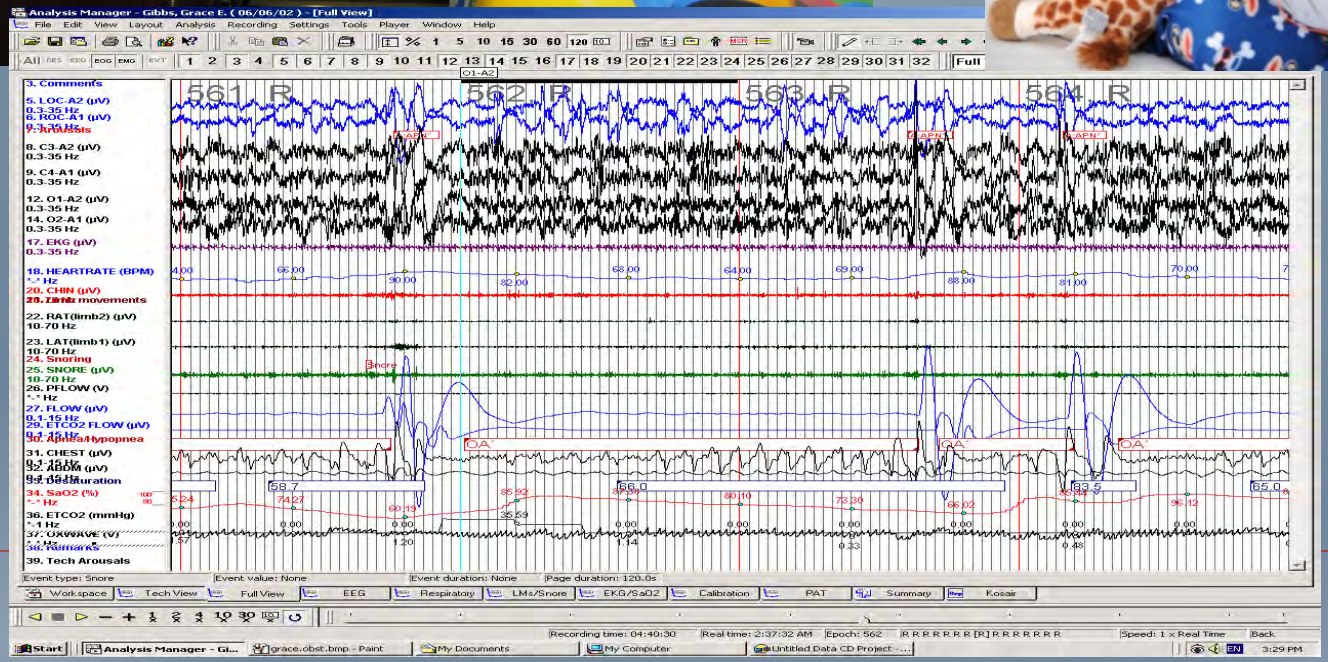
PREVALENCE IN CHILDREN

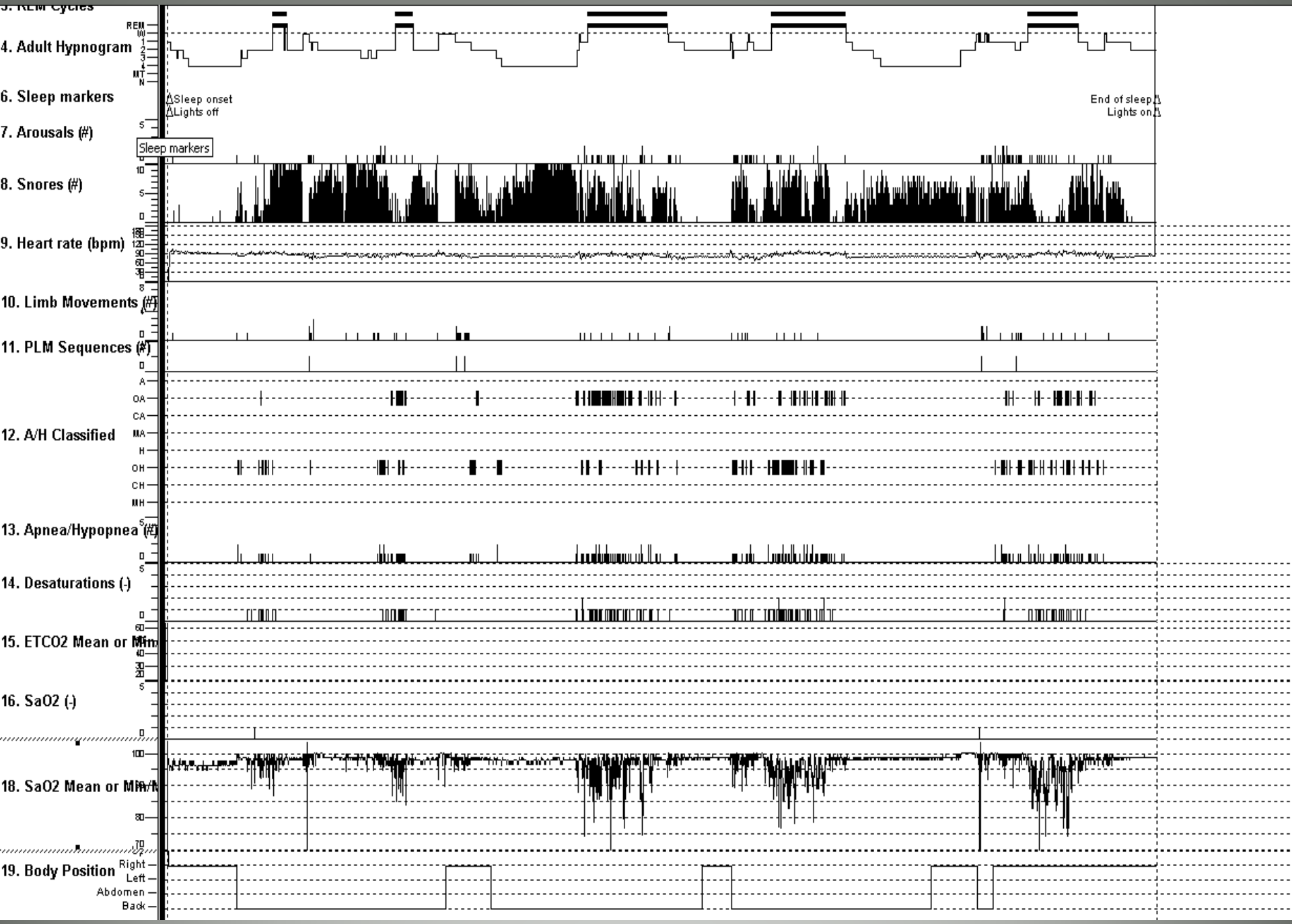
- Snoring during sleep is highly prevalent
  - Affecting up to 27% of children
- 7-12% with habitual snoring (>3 times or more/week)
- Using stringent criteria, OSA is estimated to affect 2-3% of all children

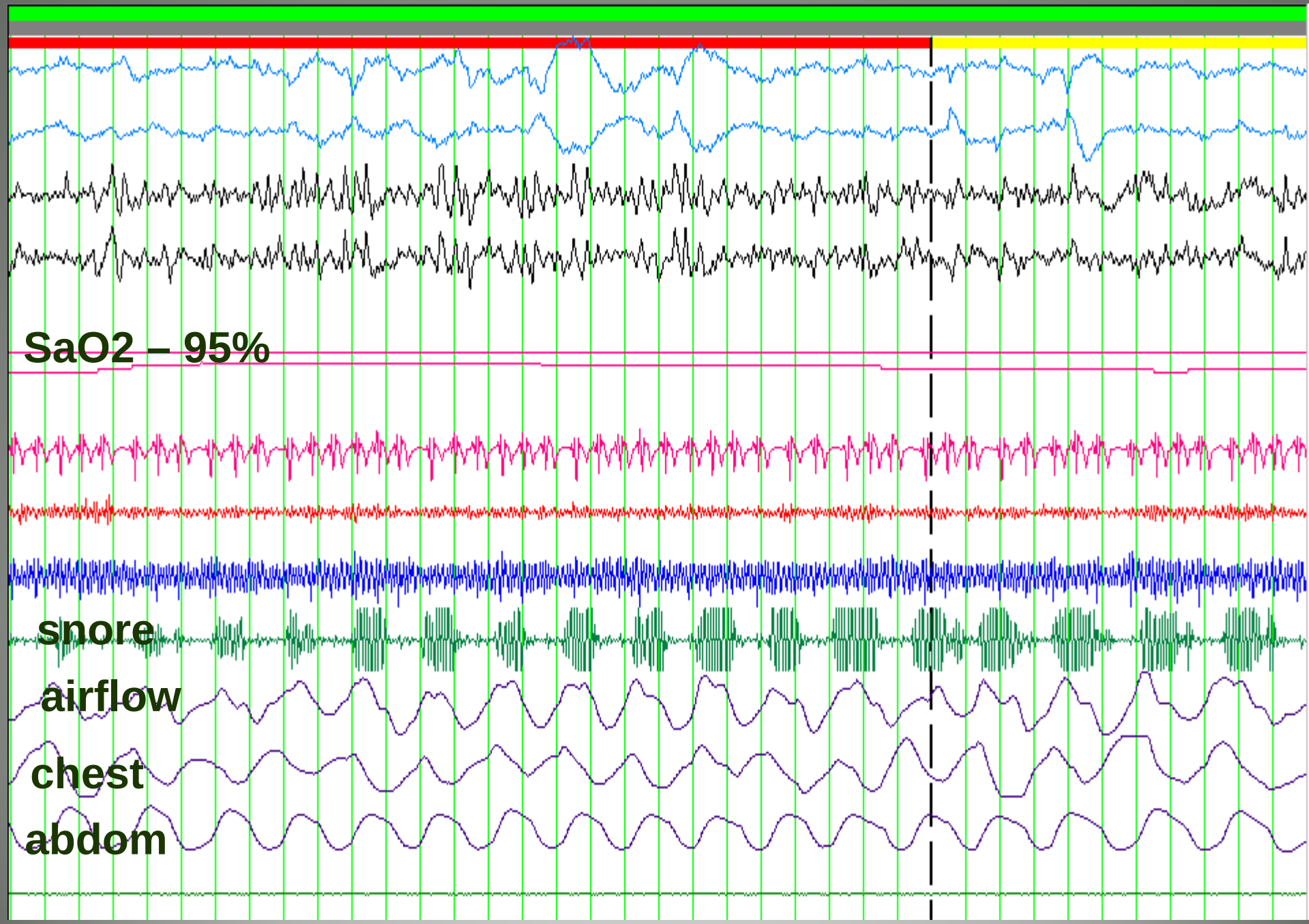


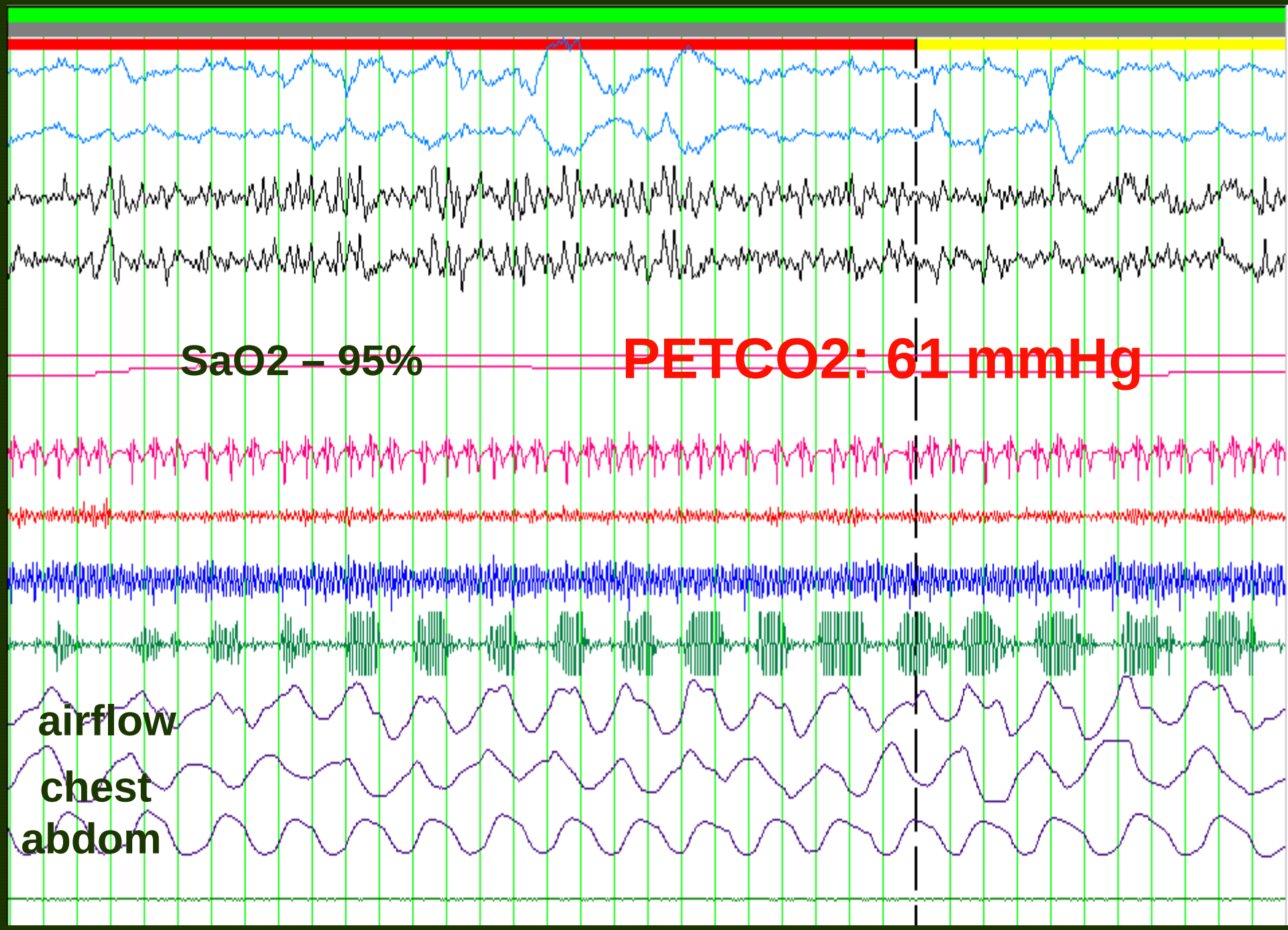
Polysomnography

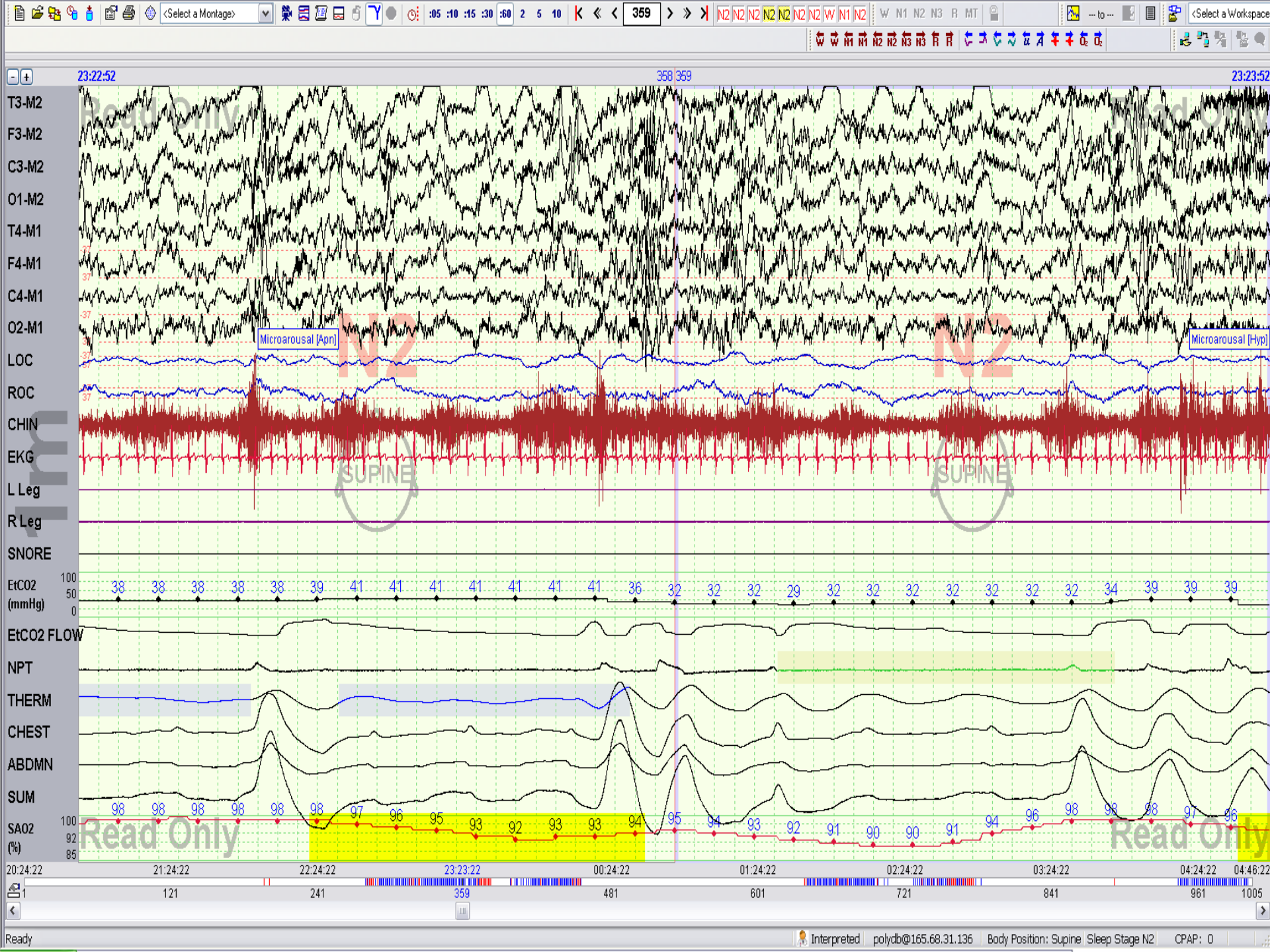


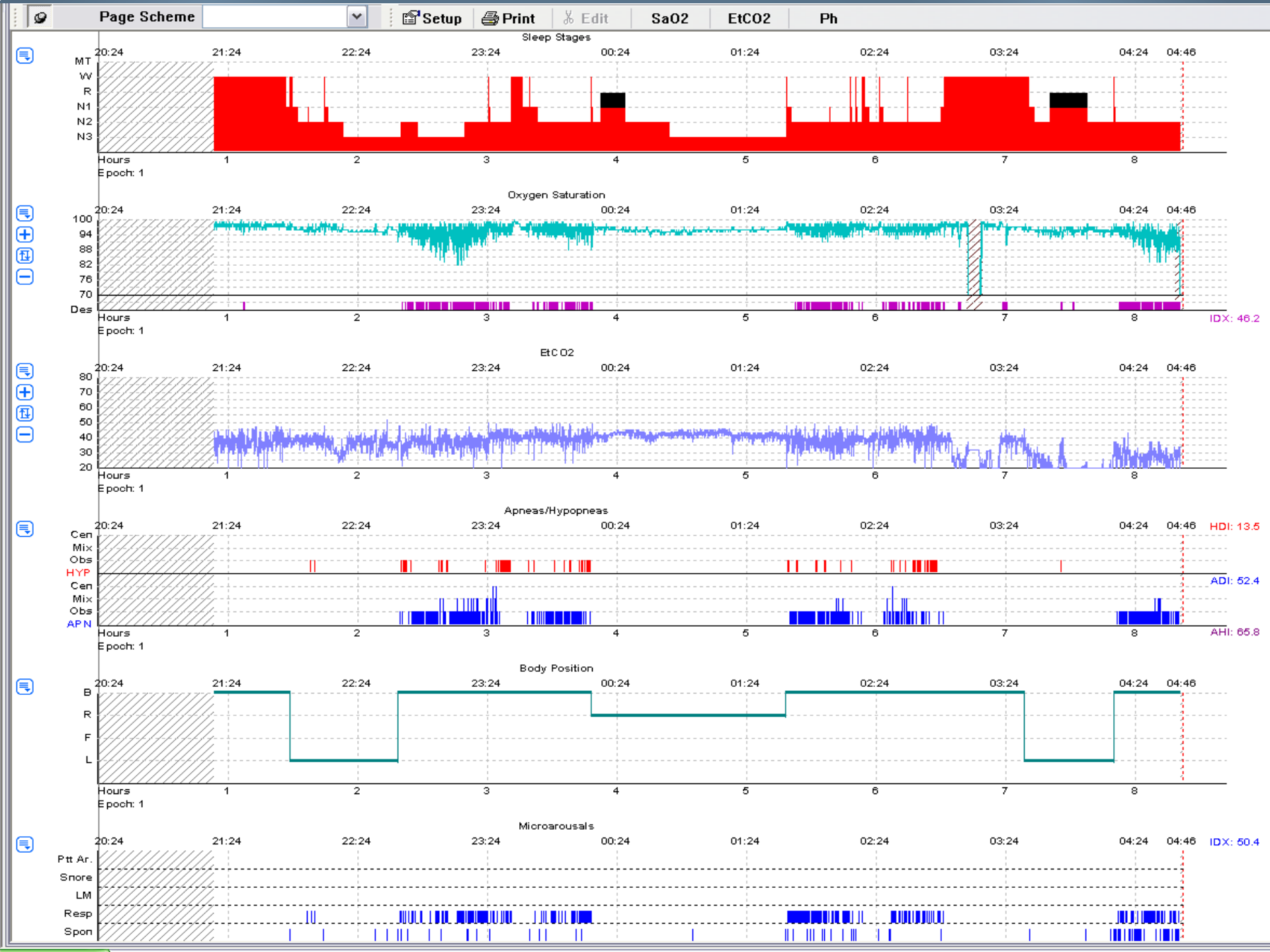



5. REM Cycles
4. Adult Hypnogram
REM
W
1
2
3
4
MT
N
6. Sleep markers
Sleep onset
Lights off
End of sleep
Lights on
7. Arousals (#)
Sleep markers
8. Snores (#)
9. Heart rate (bpm)
10. Limb Movements (#)
11. PLM Sequences (#)
12. A/H Classified
A
OA
CA
MA
H
OH
CH
MH
13. Apnea/Hypopnea (#)
14. Desaturations (-)
15. ETCO2 Mean or Min
16. SaO2 (-)
18. SaO2 Mean or Min
19. Body Position
Right
Left
Abdomen
Back


SaO2 – 95%
snore
airflow
chest
abdom

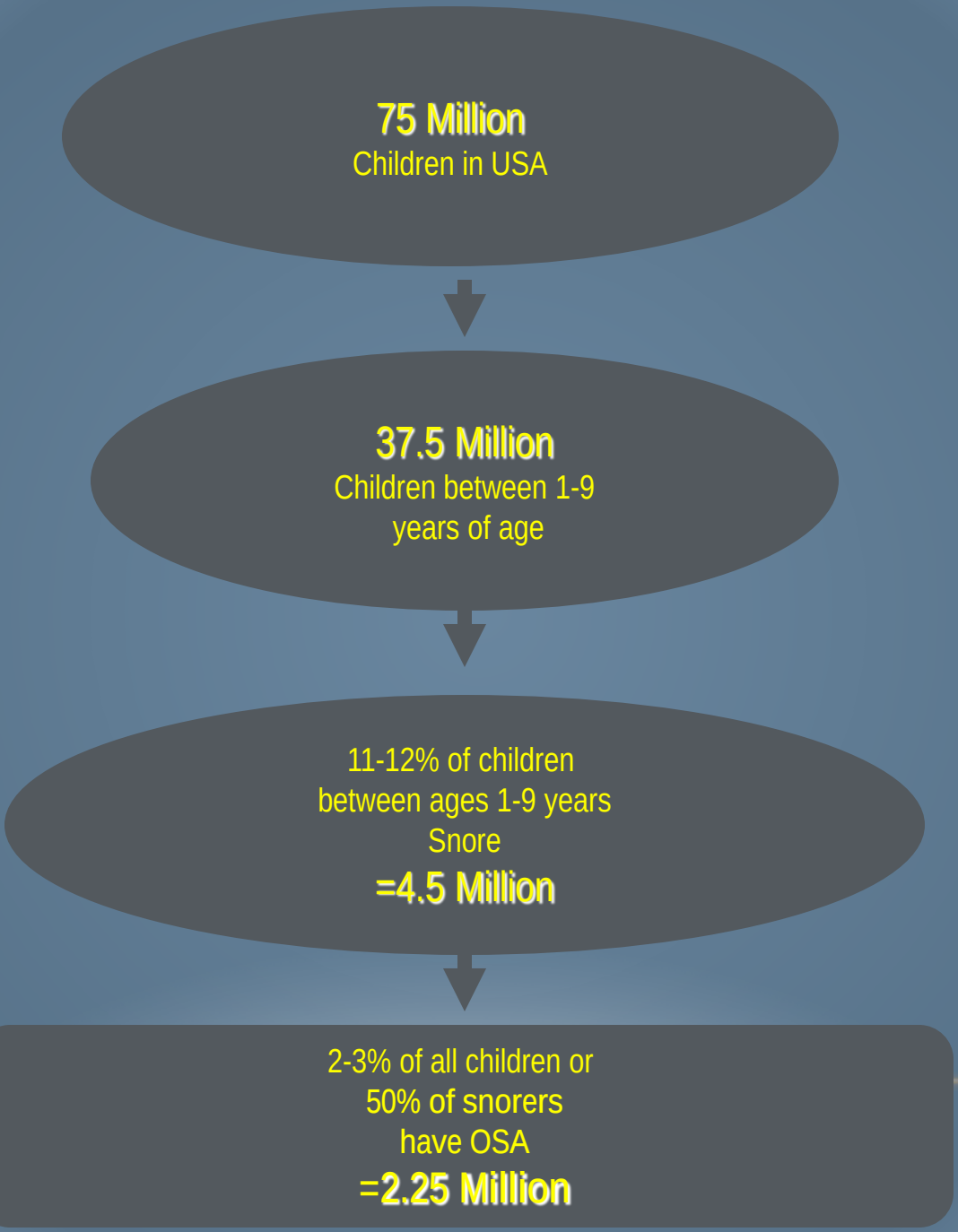

SaO2 – 95%
PETCO2: 61 mmHg
airflow
chest
abdom


23:22:52
358 359
23:23:52
T3-M2
F3-M2
C3-M2
O1-M2
T4-M1
F4-M1
C4-M1
O2-M1
LOC
ROC
CHIN
EKG
L Leg
R Leg
SNORE
EtCO2 (mmHg)
EtCO2 FLOW
NPT
THERM
CHEST
ABDMN
SUM
SA02 (%)
Microarousal [Apn]
Microarousal [Hyp]
N2
N2
SUPINE
SUPINE
Read Only
Read Only
Read Only
20:24:22
21:24:22
22:24:22
23:23:22
00:24:22
01:24:22
02:24:22
03:24:22
04:24:22
04:46:22
Ready
Interpreted
polydb@165.68.31.136
Body Position: Supine
Sleep Stage N2
CPAP: 0


Page Scheme
Setup
Print
Edit
SaO2
EtCO2
Ph
Sleep Stages
MT
W
R
N1
N2
N3
Hours
Epoch: 1
Oxygen Saturation
Des
IDX: 46.2
EtCO2
Apneas/Hypopneas
Cen
Mix
Obs
HYP
APN
HDI: 13.5
ADI: 52.4
AHI: 65.8
Body Position
B
R
F
L
Microarousals
Ptt Ar.
Snore
LM
Resp
Spon
IDX: 50.4
20:24
21:24
22:24
23:24
00:24
01:24
02:24
03:24
04:24
04:46

OSA SEVERITY

OSA SEVERITY	CHILDREN	ADULTS
MILD	(1-2)<AHI<5	5<AHI<15
MODERATE	5<AHI<10	15<AHI<30
SEVERE	AHI>10	AHI>30


75 Million
Children in USA
37.5 Million
Children between 1-9
years of age
11-12% of children
between ages 1-9 years
Snore
=4.5 Million
2-3% of all children or
50% of snorers
have OSA
=2.25 Million

Conditions Associated With Obstructive Sleep Apnea In Children:

- **Adenotonsillar hypertrophy**
- **Obesity**
- African American, Asian
- Allergic Rhinitis
- Asthma
- Micrognathia
- Down Syndrome
- Craniofacial syndromes (Treacher-Collins, mid-facial hypoplasia, Crouzon syndrome, Apert syndrome, Pierre Robin sequence, etc..)
- Achondroplasia
- Mucopolysaccharidoses
- Macroglossia
- Sickle cell disease
- Myelomeningocele
- Cerebral palsy
- Neuromuscular disorders (Duchenne muscular dystrophy, spinal muscular atrophy, etc.)
- Cleft palate repair and velopharyngeal flap
- Foreign body

Gozal, 2005

Pertinent Clinical Findings In Pediatric Obstructive Sleep Apnea:

- **During Sleep**
  - Habitual snoring
  - Difficulty breathing during sleep with snorting episodes
  - Restless sleep and frequent awakenings
  - Excessive sweating
  - Night terrors
  - Enuresis
  - Breathing pauses reported by parents
- **During Daytime:**
  - Mouth breathing and limited nasal airflow
  - Chronic rhinorrhea
  - Adenoid facies
  - Recurrent ear infections
  - Difficulty swallowing
  - Pectus excavatum
  - Retrognathia
  - Enlarged neck circumference
  - Truncal obesity
  - Frequent visits to primary care physician for respiratory-related symptoms

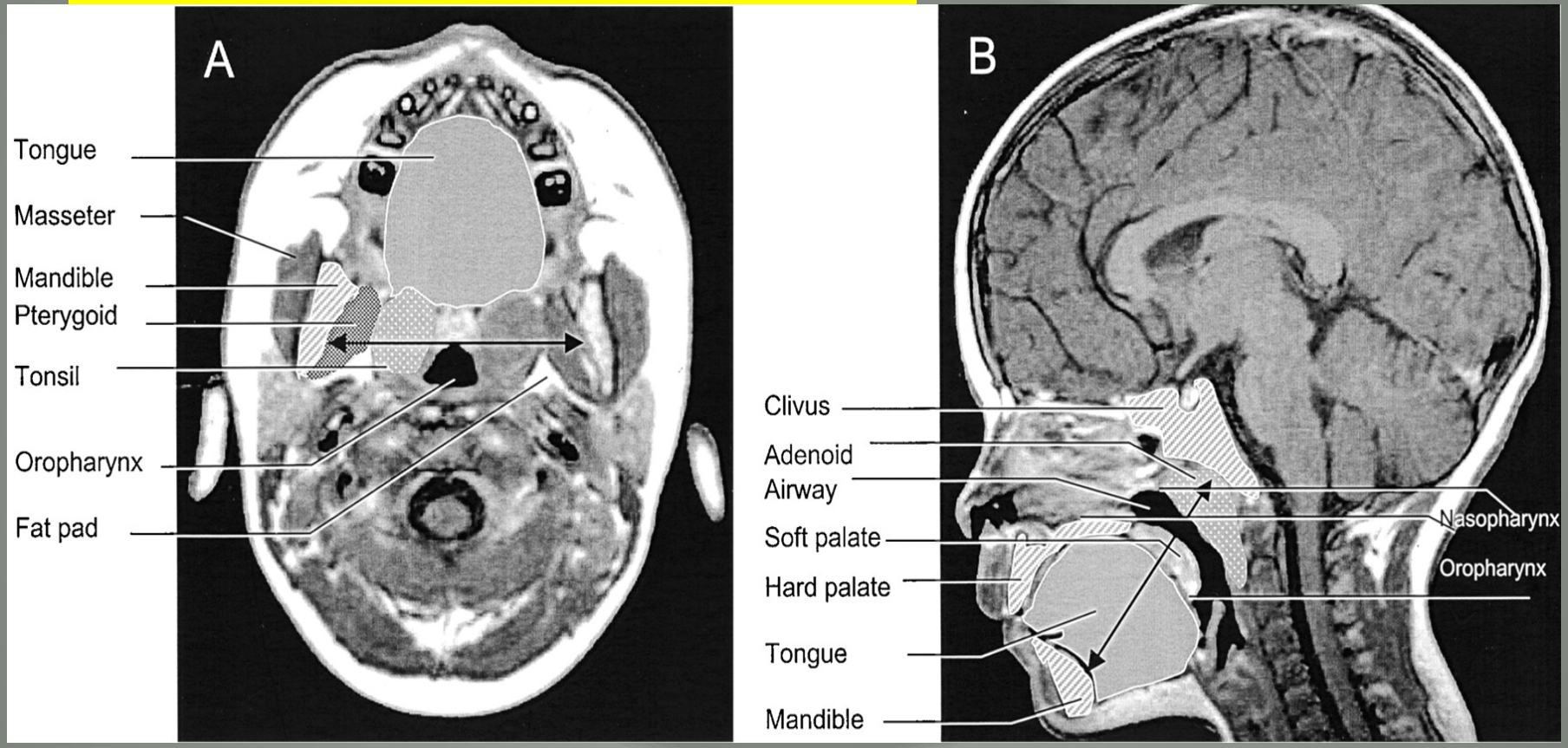
Gozal, 2005

Pertinent Clinical Consequences In Pediatric Obstructive Sleep Apnea:

- Neurobehavioral deficits (poor school performance, learning deficits, aggressive behavior, moodiness, shyness and social withdrawal)
- Attention Deficit / Hyperactivity Disorder-Like Behaviors
- Depression and low self-esteem
- Excessive daytime sleepiness
- Systemic hypertension
- Left ventricular hypertrophy
- Pulmonary hypertension and cor pulmonale
- Failure to thrive
- Reduced quality of life
- Enuresis nocturna

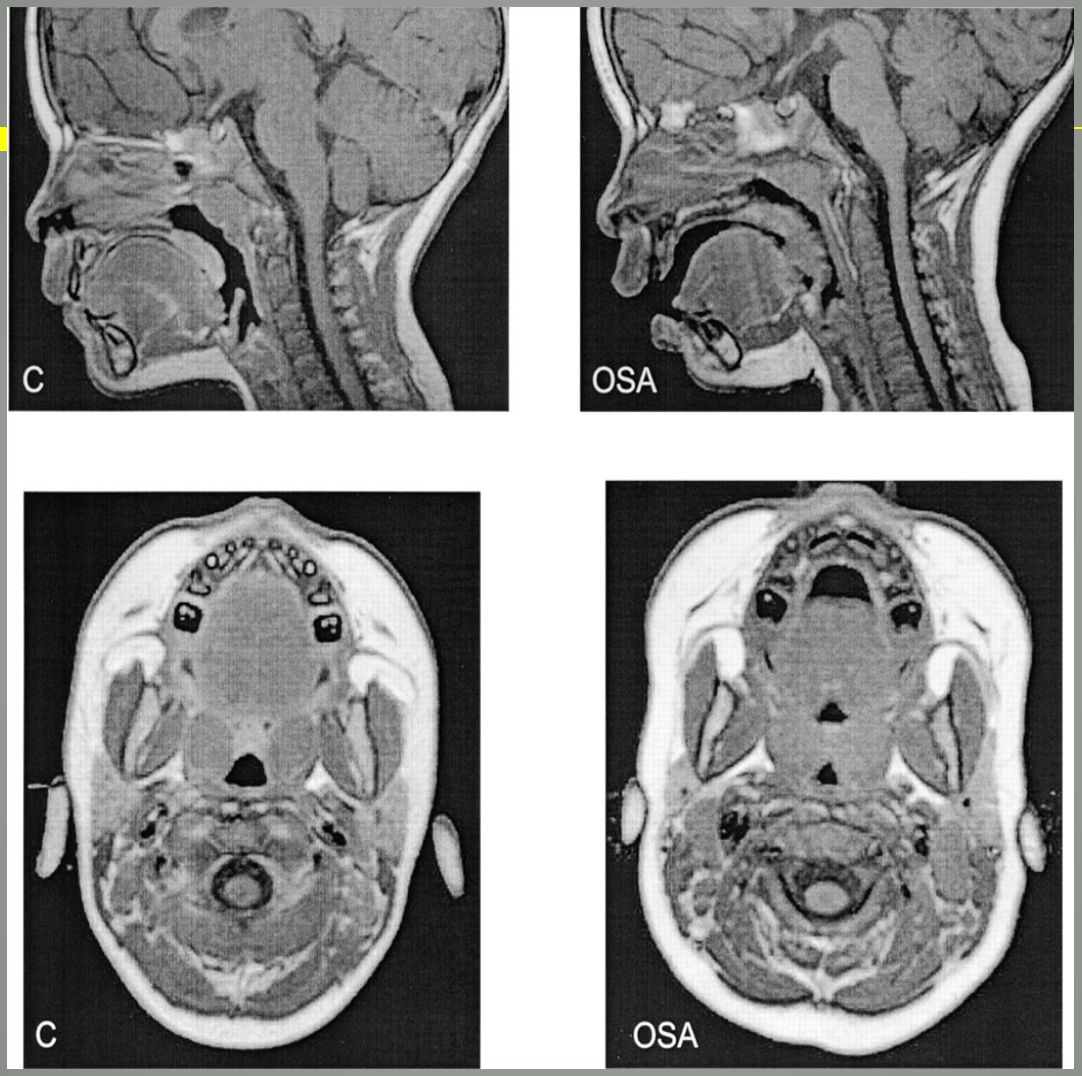
Gozal, 2005

Upper Airway MRI



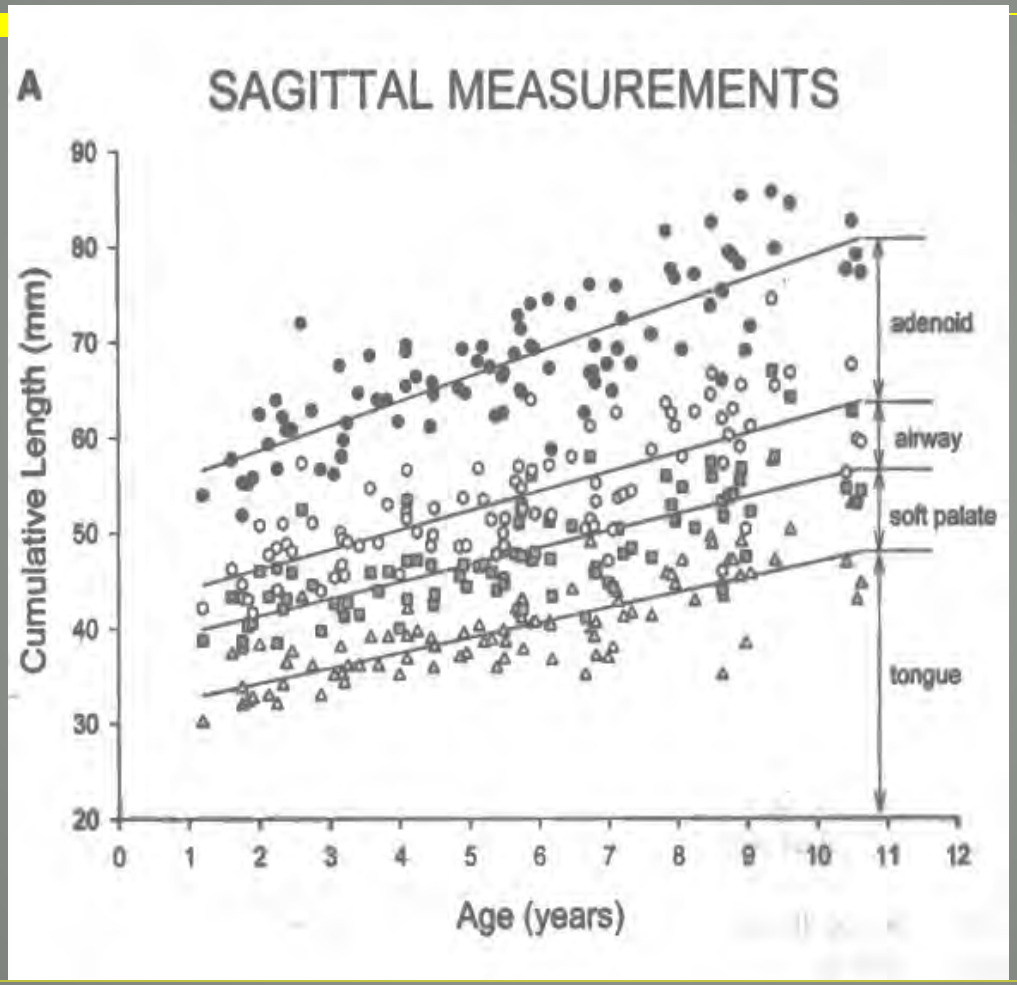
Arens, *AJRCCM* 2002; 165:117

Upper Airway MRI



Arens, *AJRCCM* 2002; 165:117

Upper Airway MRI



Arens, *AJRCCM* 2002; 165:117

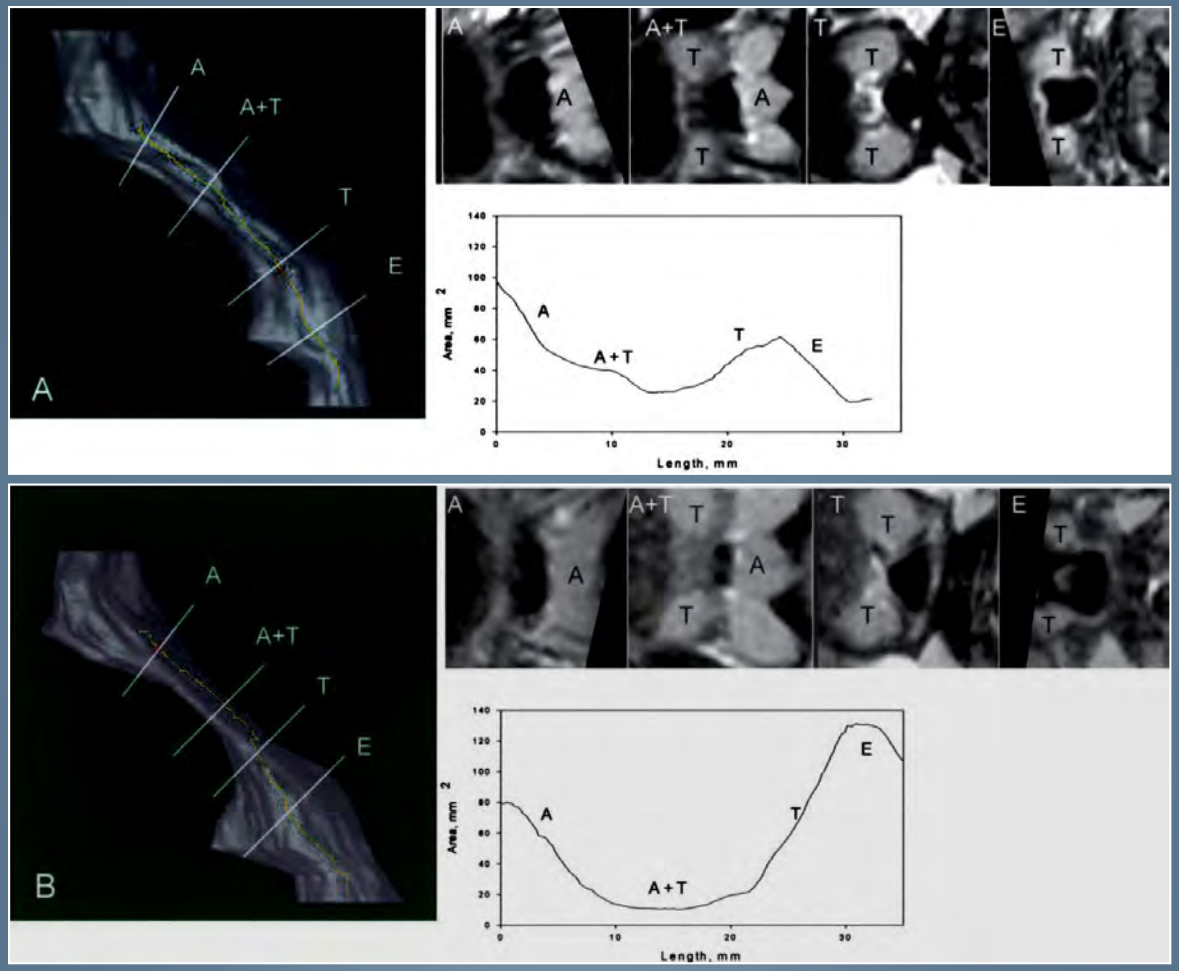
PATHOPHYSIOLOGY

- Transition to sleep results in elevations of upper airway resistance – reductions in airway diameter and reduced tone of the pharyngeal dilator muscles.
- In children the most common abnormality is adenotonsillar hypertrophy which increases pharyngeal resistance and episodic airway collapse
- Adenoidal growth occurs primarily from infancy through childhood, and reduces in size during adolescence. Tonsillar tissue similarly grows in early childhood.

HUDGEL ET. AL. *J APPL PHYSIOLOGY* 56, 1976. TANGEL ET. AL. *J APPL PHYSIOL* 70, 1991.
MARCUS ET. AL. *J APPL PHYSIOL* 77, 1994

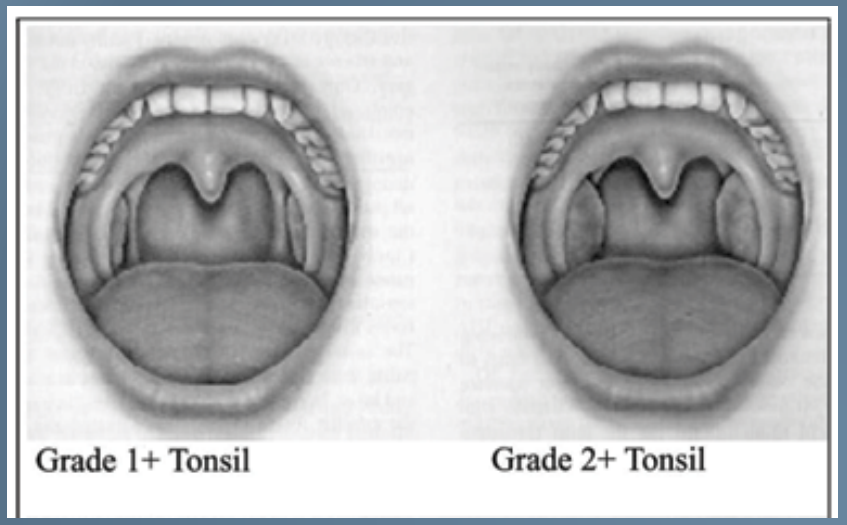
Control

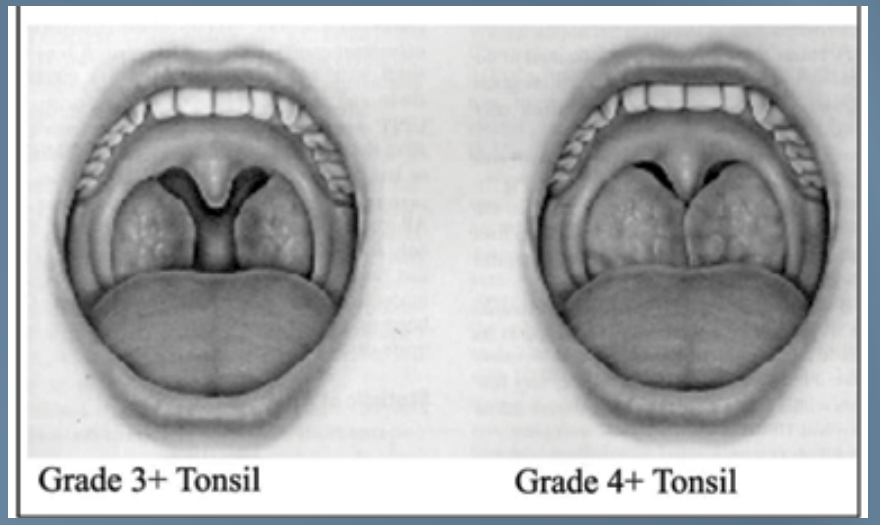
OSA



Arens et al. Am J Respir Crit Care Med 2002

DIAGNOSIS - BRODSKY





Grade 0: Tonsil in Palantine Fossa
Grade 1: Tonsil occupying less than 25% of oropharynx Grade 2: Tonsil occupying 25-50% of oropharynx Grade 3: Tonsil occupying 25-50% of oropharynx
Grade 4: Tonsil occupying more than 75% of oropharynx

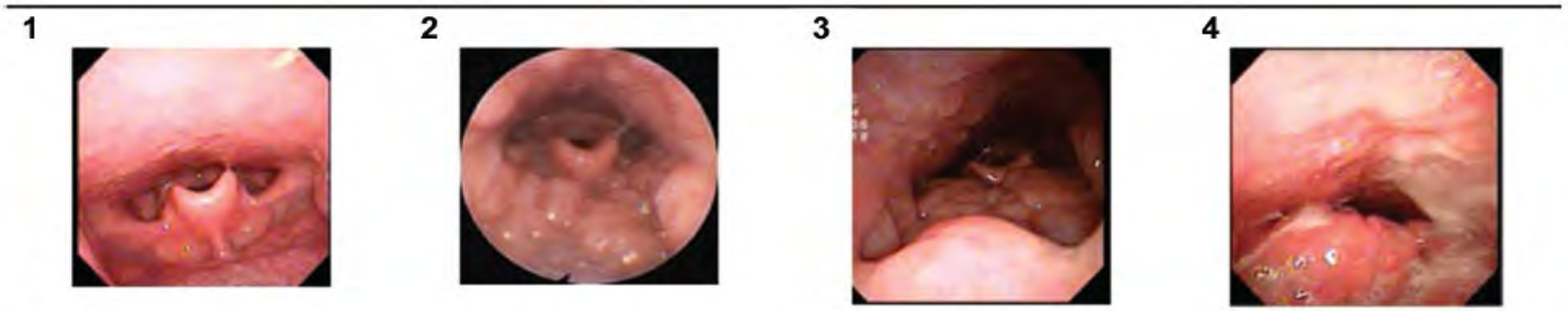
AMERICAN ACADEMY OF OTOLARYNGOLOGY—HEAD AND NECK SURGERY FOUNDATION

Otolaryngology–Head and Neck Surgery
2016, Vol. 154(1) 171–174

Short Scientific Communication—Pediatric Otolaryngology

A Pediatric Grading Scale for Lingual Tonsil Hypertrophy

Norman R. Friedman, MD[1,2], Jeremy D. Prager, MD[1,2], Amanda G. Ruiz[1,2], and Eric J. Kezirian, MD, MPH[3]

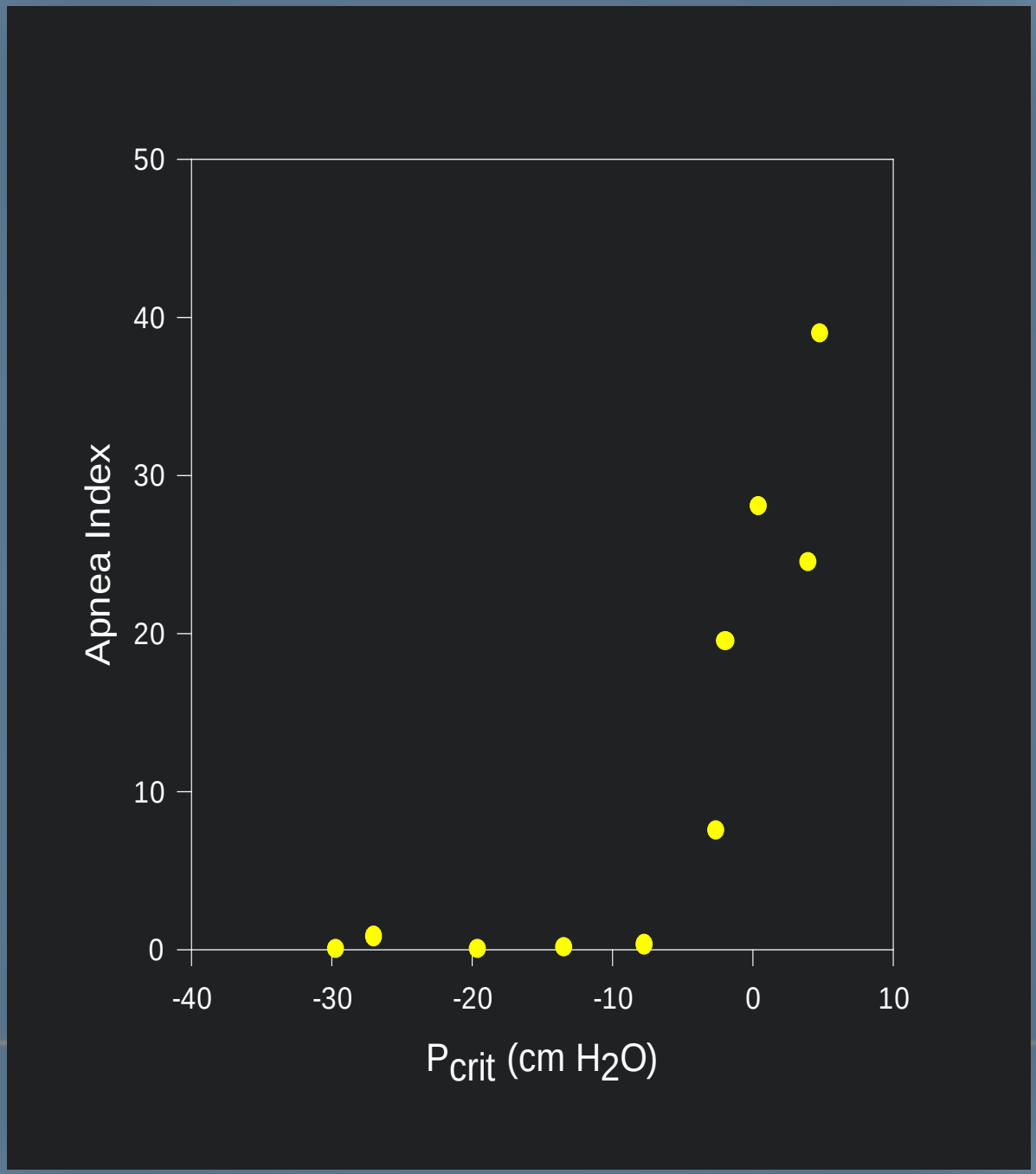


Grade 1. None to minimal
Grade 2. Mild: < 50% filling vallecula
Grade 3. Moderate: > 50% effacement of vallecula
Grade 4. Severe: Unable to visualize epiglottis

PATHOPHYSIOLOGY

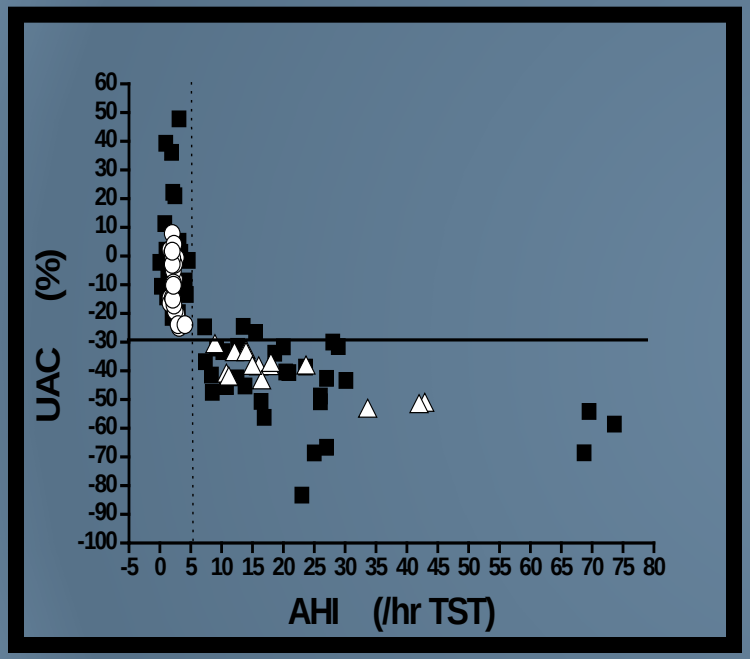
- MRI has shown that children with OSA have significantly larger adenoids and tonsils than controls, despite proportionate somatic growth of the airway
- The presence of markedly enlarged adenotonsillar tissues may not always lead to OSA
- Complex interactions between the anatomical components of the upper airway, and other factors such as upper airway tone, respiratory drive, etc.

ARENS ET. AL. *AM J RESPIR CRIT CARE MED* 164, 2001 .
ARENS ET. AL. *AM J RESPIR CRIT CARE MED*165, 2002

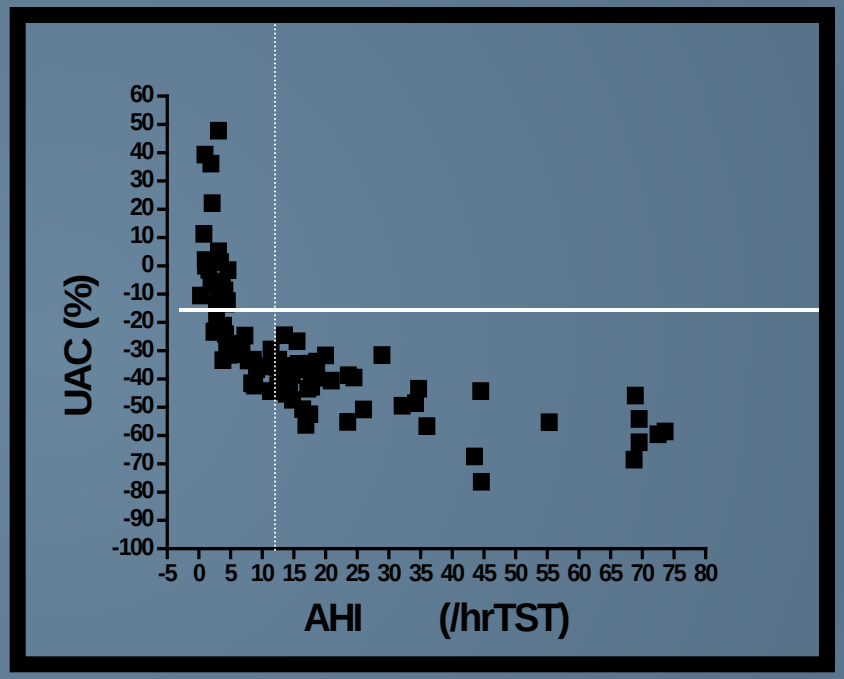


Marcus et al, 1998

Group I



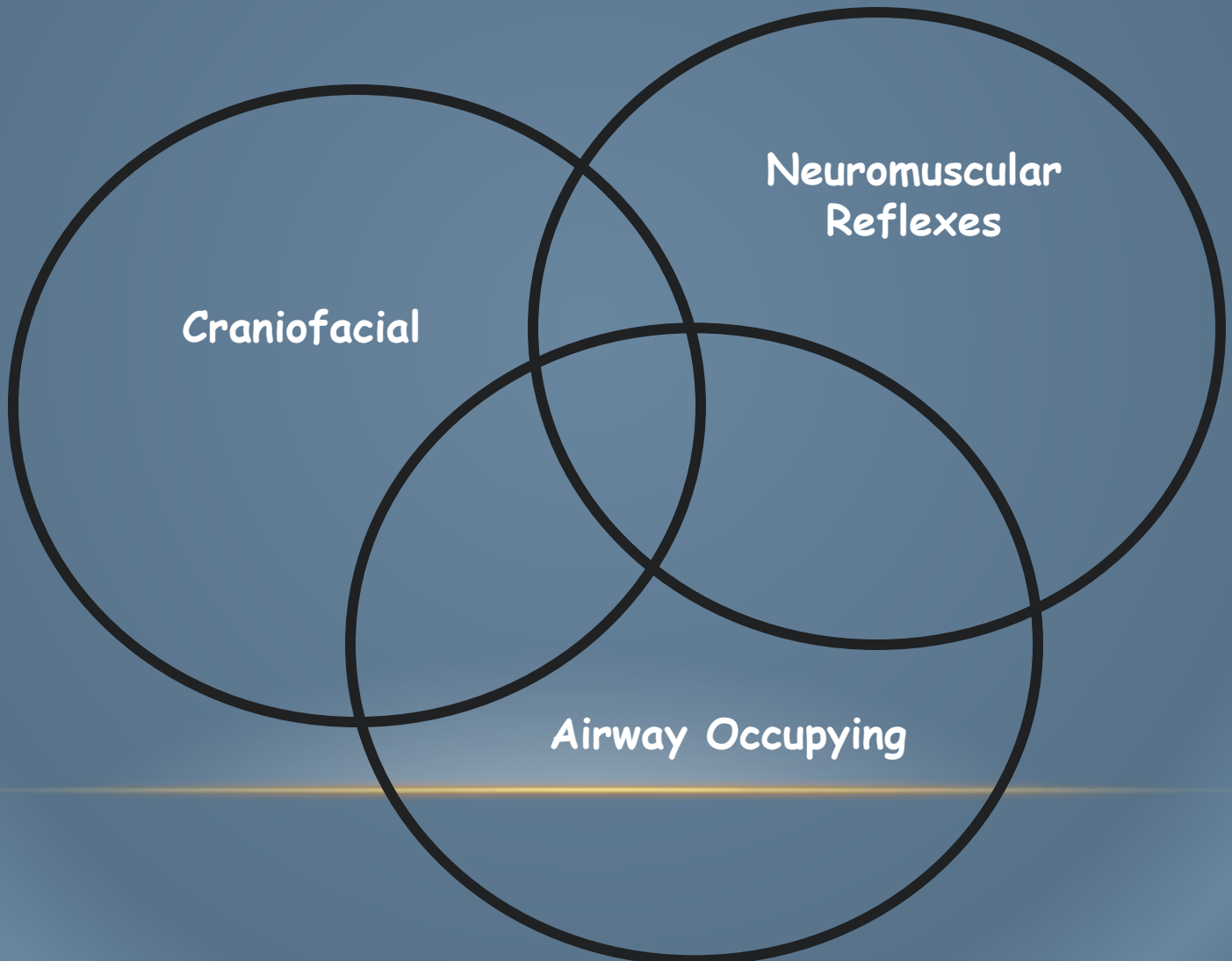
Group II



Upper airway collapsibility is increased in OSA

Gozal & Burnside, AJCCM, 2004

The multiple pathophysiological interactome of pediatric OSA



GENETIC AND ETHNIC FACTORS

- African Americans are at a higher risk for age, sex and body mass index
- OSA is clustered in families
- OSA is likely polygenic with genes impacting oral mucosa thickness and facial structure playing deterministic roles in the pathogenesis of OSA

PALMER LJ ET. AL. *AM J RESPIR CRIT CARE MED* 169, 2004.
REDLINE S ET. AL. *AM J RESPIR CRIT CARE MED* 151, 1995.
REDLINE S ET. AL. *AM J RESPIR CRIT CARE MED* 155, 1997

TABLE 1— Risk Factors Associated With Childhood Obstructive Sleep Apnea Syndrome

Adenotonsillar hypertrophy
Obesity
Hypotonia/muscular weakness
Prematurity
Nasoseptal obstruction
Enlarged soft palate or uvula
Macroglossia
Hypotonic pharynx
Lingual tonsils
Lymphatic malformations
Metabolic storage disorder
Micrognathia
Maxillary hypoplasia
Vascular neoplasms—hemangioma

OBESITY AND OSA

- The prevalence of OSA increases to 20% to 40% in the obese population
- Similarly the presence of obesity clearly adds significantly to the risk of developing OSA in children
  - Kaditis AG et. al. *Sleep Breath* 31, 2006.Tauman et. Al. *Paediatr Respir Rev* 7, 2006.
- For every increase in BMI by 1 kg/m^2, the OSA risk increases by 12% in children
  - Redline S, Tishler PV, Schluchter M, Aylor J, Clark K, Graham G. Am J Respir CritCare Med 1999;159:1527 – 1532.

OBESITY AND OSA - PATHOPHYSIOLOGY

- Tomography has shown obese subjects have fatty deposition in the pharyngeal area
- Fatty deposits encroach on the airway, and furthermore alter the shape of the airway contributing to airway narrowing
- Obesity affects ventilation through mass loading of the respiratory system.
  - Adipose tissue in the abdominal wall and thorax increases the global respiratory load, reducing intrathoracic volume and diaphragm excursion, particularly when supine,
  - Decreases lung volumes and oxygen reserve, while increasing the work of breathing during sleep

HORNER ET. AL. *EUR RESP J* 2, 1989..
NAIMARK A ET. AL. J APPL PHYSIOL 15, 1960.

The NANOS study

- Cross-sectional
- Prospective
- Multicenter study in Spain
- N=248
- (54.4% males)
- BMI of >28 kg/m2 (>95 percentile adjusted for age and sex)
- Ages 3–14 y
- BMI ≥ 95th percentile for age and sex
- Random selection
- Pediatric Sleep Questionnaire (PSQ)
- Physical examination
- Medical history
- Nasopharyngoscopy
- PSG recordings

Table 1—Clinical and anthropometric characteristics of the study cohort (n = 248)

Anthropometric measures	
Sex	Male: 135 (54.4%) Female: 113 (45.6%)
Age (y)	10.8 ± 2.6 (range 3–14)
Weight (kg)	64.2 ± 21.2 (20.5–130.0)
Height (m)	1.49 ± 0.17 (1.03–1.90)
BMI (kg/m^2)	28.0 ± 4.7 (19.3–57.7)
BMI z-score	1.28 ± 0.53 (1–3)
BMI percentile	96.8 ± 0.6 (95–98)
Neck circumference (cm)	34.1 ± 3.8 (15–47)
Waist circumference/hip circumference	0.90 ± 0.07 (0.74–1.22)
Systolic BP (mmHg)	110.7 ± 17.5 (80–180)
Diastolic BP (mmHg)	65.7 ± 11.5 (40–100)
Medical history	
Obesity-Related	
SGA	2.2%
Increased weight for gestational age	4%
Early onset of accelerated weight gain	47.3%
Onset of obesity (y)	4.2 ± 3.2
Surgical	
Tonsillectomy	3.5%
Adenoidectomy	9.5%
T&A	10.2%
Respiratory	
Rhinitis	10.7%
Asthma	20.5%
Bronchitis	9.0%
Endocrinologic	
Diabetes mellitus	3.6%
Insulin resistance	1.2%
Arterial hypertension	1.6%
Dyslipidemia	3.2%
Hypothyroidism	1.6%
Frequent symptoms	
Dry mouth	53.2%
Restless sleep	35.8%
Attention problems	30%

BMI, body mass index; BP, blood pressure; SGA, small for gestational age; T&A, adenotonsillectomy.

Alonzo-Alvarez et al. Sleep 2014

Table 3—Polysomnographic measures in 248 obese children

Respiratory measures	
No. of respiratory events	34.8 ± 63.0
No. of central apneas	2.35 ± 6.10
No. of obstructive apneas	6.29 ± 25.23
No. of mixed apneas	0.50 ± 3.26
No. of hypopneas	14.51 ± 36.33
No. of flow-limited events	12.10 ± 19.65
RDI	5.58 ± 9.90
REMS RDI	6.41 ± 14.67
NREMS RDI	4.75 ± 9.70
Supine RDI	6.26 ± 14.80
ORDI	5.06 ± 9.57
Central AHI	0.37 ± 1.04
OAHI	3.39 ± 8.79
Apnea index	1.43 ± 4.95
Hypopnea index	2.32 ± 5.78
Flow-limited index	1.92 ± 2.93
Baseline SaO_2	98.13 ± 1.53
Mean SaO_2	96.38 ± 1.57
Nadir SaO_2	90.31 ± 5.13
T 90%	1.10 ± 6.64
ODI	2.84 ± 9.37
Peak $P_{ET}CO_2$ (mmHg)	46.27 ± 6.72
$P_{ET}CO_2$ > 50 mmHg (%TST)	3.99 ± 12.95
Mean heart rate	77.77 ± 12.08
Sleep measures	
Total time in bed (TTB; min)	480.28 ± 46.01
Total sleep time (TST; min)	380.24 ± 69.16
Sleep efficiency (%)	78.95 ± 12.77
NREMS latency (min)	33.79 ± 26.90
REMS latency (min)	144.45 ± 79.53
Awake (%TST)	21.53 ± 16.72
N1 (%)	9.67 ± 8.13
N2 (%)	45.72 ± 12.48
N3 (%)	31.83 ± 24.31
REMS (%)	15.72 ± 6.57
No. of arousals	65.55 ± 60.70
Arousal index	11.07 ± 10.71
No. of PLMS	8.07 ± 17.81
PLM Index	1.33 ± 3.07

Table 4—Prevalence and severity of OSAS based on different cutoff criteria in 248 obese children

Diagnostic criterion	Prevalence (95% CI)	Severity-based prevalence: Mild OSAS (≥ 3 & < 5/h TST)	Moderate OSAS (≥ 5 & < 10/h TST)	Severe OSAS (≥ 10/h TST)
OSAS (RDI ≥ 3/h TST)	39.5% (33.4-45.6%)	26 (10.5%) (6.5-14.5%)	32 (12.9%) (8.5-17.3%)	40 (16.1%) (11.4-20.9%)
OSAS (ORDI ≥ 3/h TST)	35.9% (29.9 41.9%)	24 (9.7%) (5.8-13.6%)	26 (10.5%) (6.5-14.5%)	39 (15.7%) (11-20.5%)
OSAS (OAHI ≥ 3/h TST)	21.5% (16.3-26.6%)	20 (8.1%) (4.5-11.7%)	13 (5.3%) (2.7-8.2%)	20 (8.1%) (4.5-11.7%)
OSAS (OAHI > 1/h TST	46.6% (40.6-53%)	–	–	–

OAHI, obstructive apnea hypopnea index; ORDI, obstructive respiratory disturbance index; OSAS, obstructive sleep apnea syndrome; RDI, respiratory disturbance index; TST, total sleep time.

Table 5—Categorical distribution of sleep disordered breathing in 235 obese children

NPSG Indices	Normal (No Snoring & < 3/h TST)	Primary Snorer (Snoring & < 3/h TST)	Mild OSAS (≥ 3 & < 5/h TST)	Moderate OSAS (≥ 5 & < 10/h TST)	Severe OSAS (≥ 10/h TST)
RDI	66 (28.1%) (22.1-34%)	75 (31.9%) (25.7-38.1%)	23 (9.8%) (5.8-13.8%)	31 (13.2%) (8.7-17.7%)	40 (17%) (12-22%)
ORDI	69 (29.4%) (23.3-35.4%)	79 (33.6%) (27.4-39.9%)	22 (9.4%) (5.4-13.3%)	26 (11.1%) (6.8-15.3%)	39 (16.6%) (11.6-21.6%)
OAHI	76 (32.3%) (26.1-38.5%)	107(45.5%) (38.9-52.1%)	19 (8.1%) (4.4-11.8%)	13 (5.5%) (2.4-8.7%)	20 (8.5%) (4.7-12.3%)

Categorical assignments were based on respiratory disturbance indices and objective assessment of snoring during NPSG. Because no assessment of snoring was possible in 13 subjects, the number of subjects and the percentage of the total are reported for 235 children. OAHI, obstructive apnea-hypopnea index; ORDI, obstructive respiratory disturbance index; OSAS, obstructive sleep apnea syndrome; RDI, respiratory disturbance index; TST, total sleep time.

Alonzo-Alvarez et al. Sleep 2014

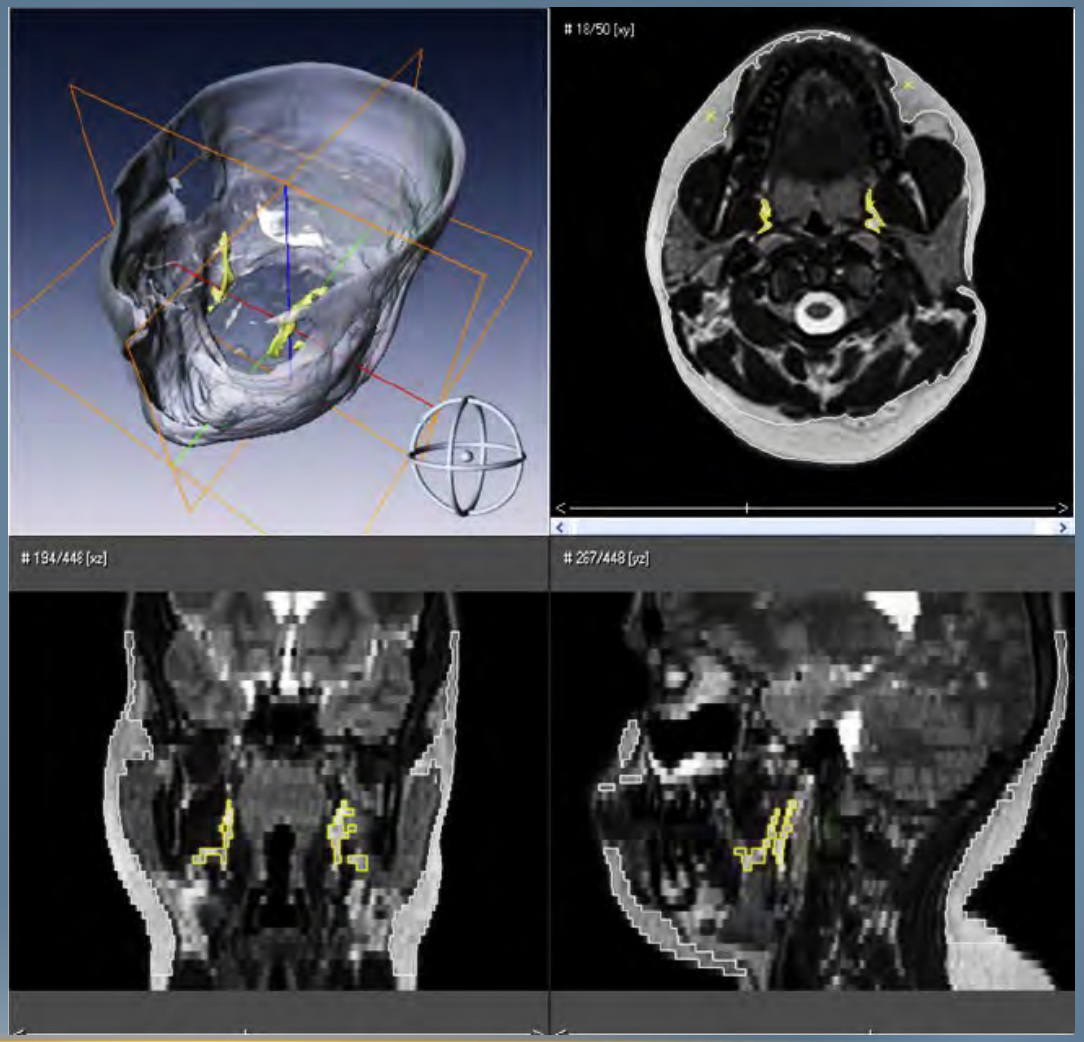
- Presence of obesity is a major risk factor for OSA.

- In obese children at any level of OSA severity, the size of adenoids and tonsils required to achieve that level of breathing disturbance during sleep is smaller compared to lean children.

Dayyat et al, CHEST 2007

Head and neck fat composition

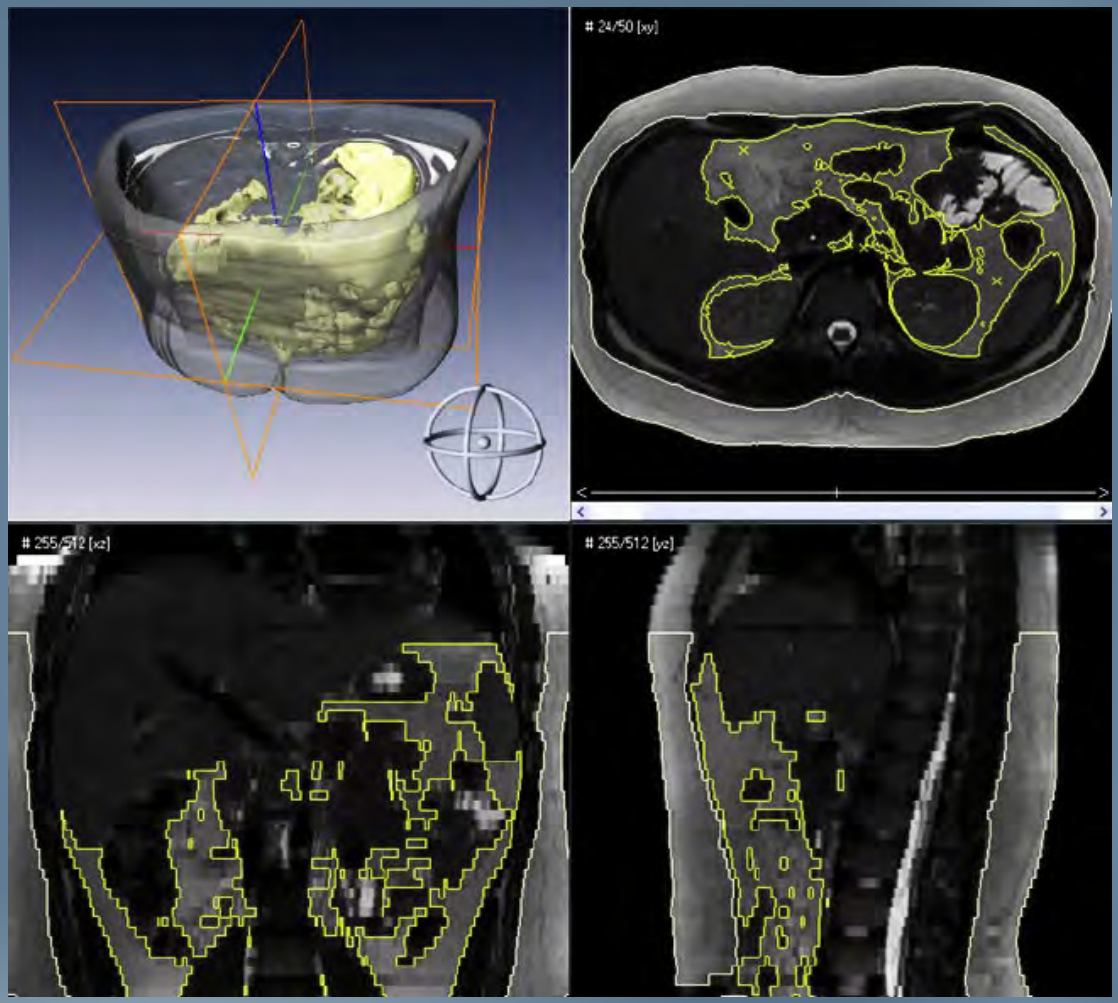
Surface rendering of the head and neck with three-dimensional reconstructions of the subcutaneous fat (*gray*) and parapharyngeal fat pads (*yellow*) of a subject with obstructive sleep apnea syndrome (*top left*), mid-tonsillar axial view (*top right*), coronal view (*bottom left*), and sagittal view (*bottom right*).



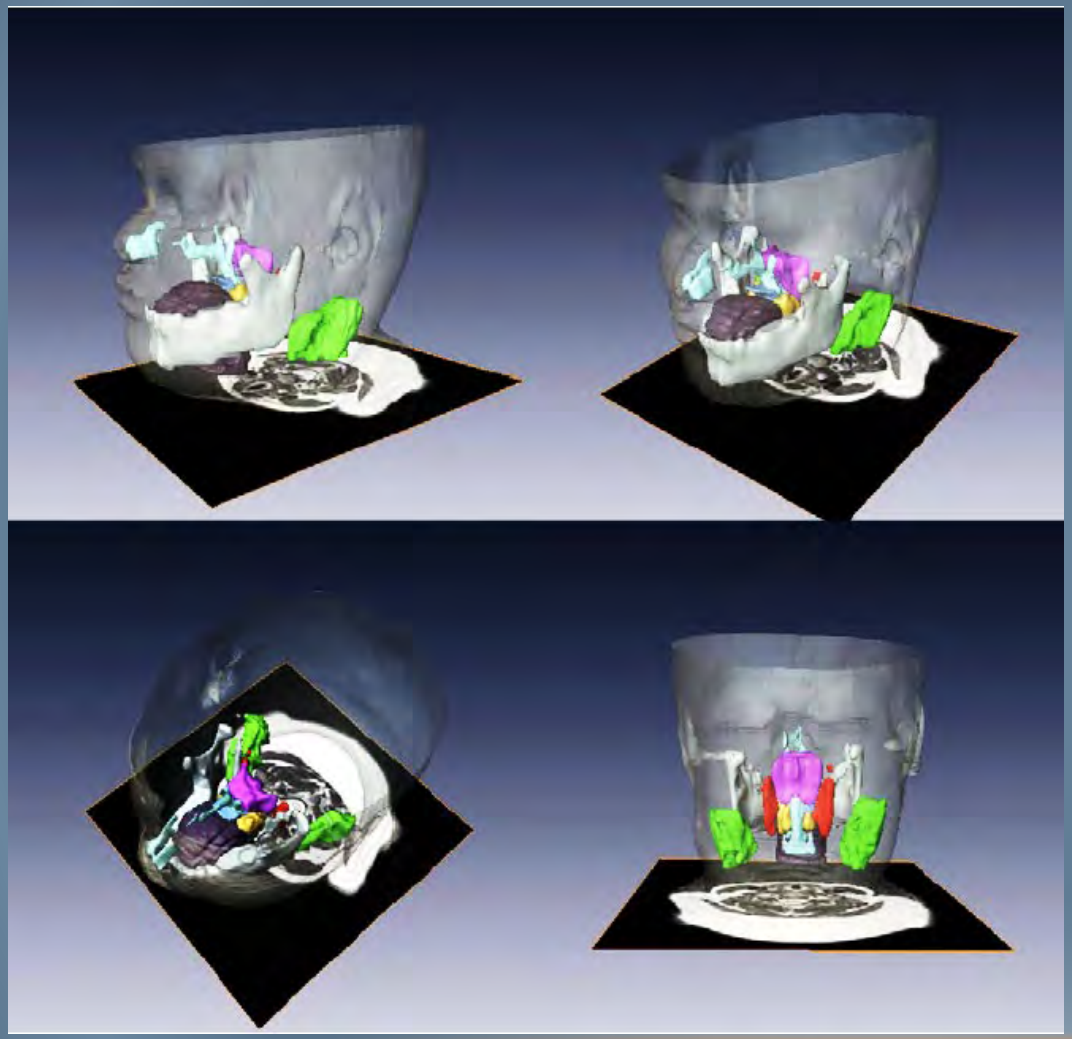
ARENS ET AL. AM J RESPIR CRIT CARE MED 2010

Abdominal fat composition

Surface rendering of the abdomen with three-dimensional reconstructions of the subcutaneous fat (gray) and visceral fat (yellow) of a subject with obstructive sleep apnea syndrome (top left), axial view (top right), coronal view (bottom left), and sagittal view (bottom right).



Arens et al. Am J Respir Crit Care Med 2010



- Increased size of upper airway lymphoid tissues in obese children.
- Increased size of the para pharyngeal fat pads in obese children.
- Increased abdominal visceral fat but not subcutaneous fat in obese children.

ARENS ET AL. AM J RESPIR CRIT CARE MED 2010

ELSEVIER

Sleep Medicine 10 (2009) 75–86

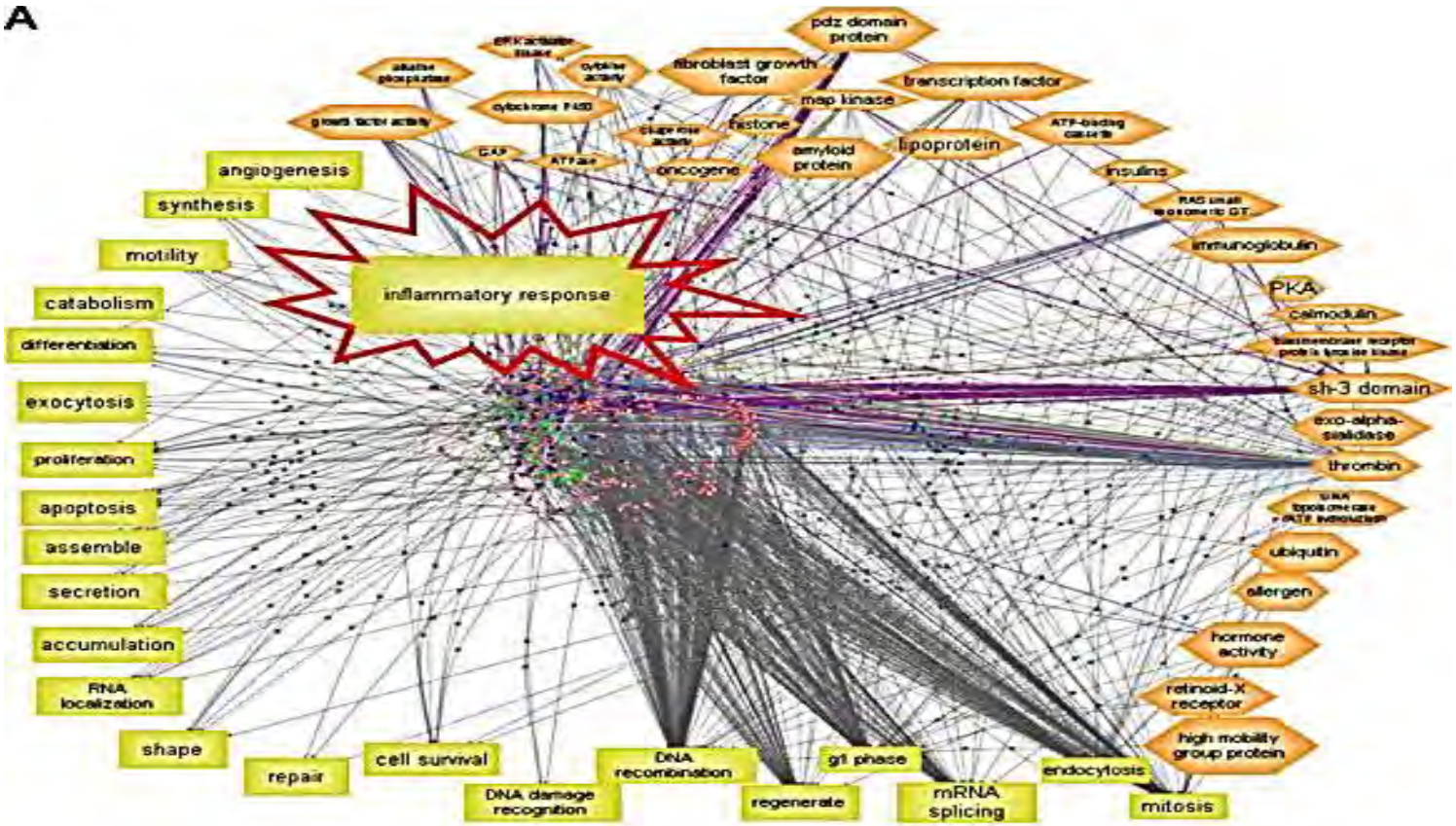
SLEEP MEDICINE

www.elsevier.com/locate/sleep

Original Article

Genome-wide gene expression profiling in children with non-obese obstructive sleep apnea ☆

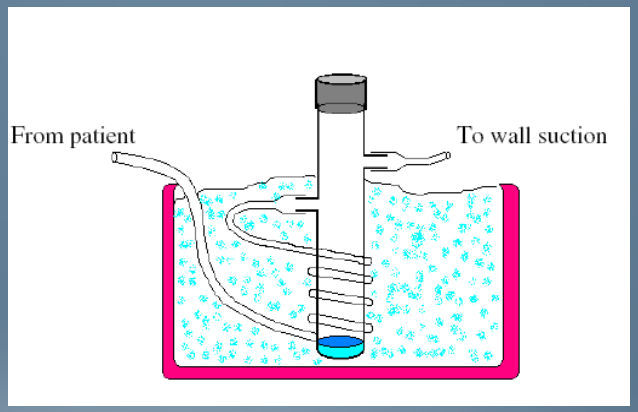
Abdelnaby Khalyfa [a], Oscar Sans Capdevila [b], Mohamed O. Buazza [a], Laura D. Serpero [a], Leila Kheirandish-Gozal [a,b], David Gozal [a,b,*]

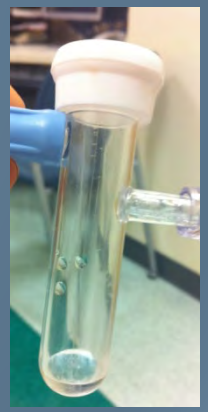


Upper Airway Inflammatory Markers in Exhaled Condensate

- Exhaled condensate from the upper airway was collected in children with polysomnographically demonstrated OSA and in control children
- Measured Prostaglandin E2 (a cyclo-oxygenase 2 product) and Leukotrienes B4 and Cysteinyl leukotriene (LTC4, LTD4, LTE4).

Method used to collect upper airway condensate





Goldbart et al., CHEST 2006

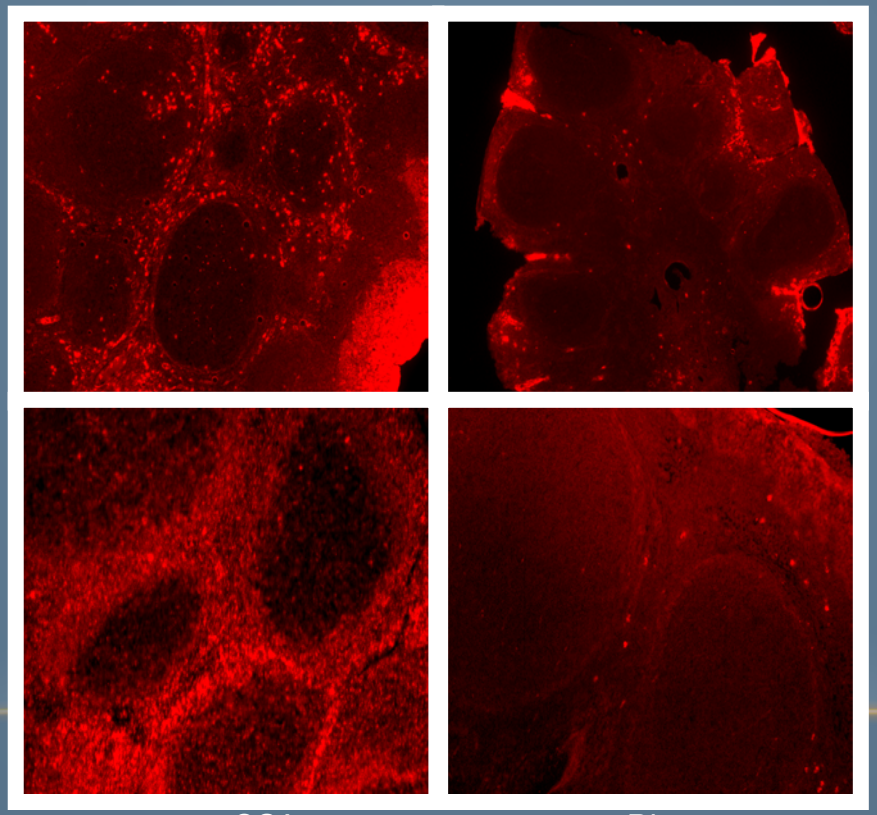
Increased inflammation in the upper airway tissue

- Increased T cell lymphocytes in upper airway tissues of adults with OSA.

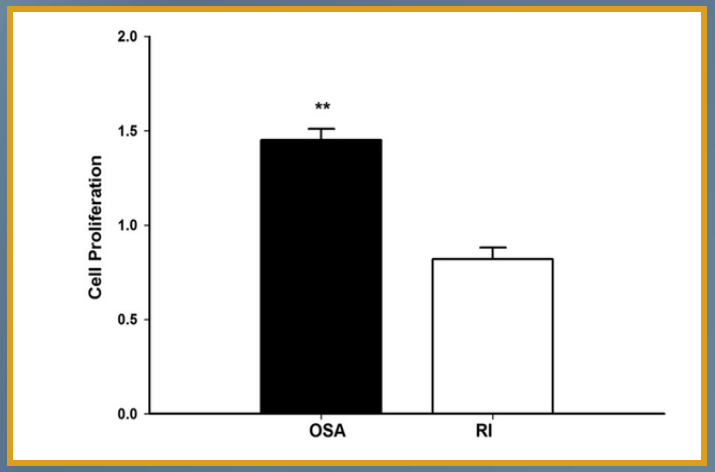
Boyd et al, AJRCCM 2004

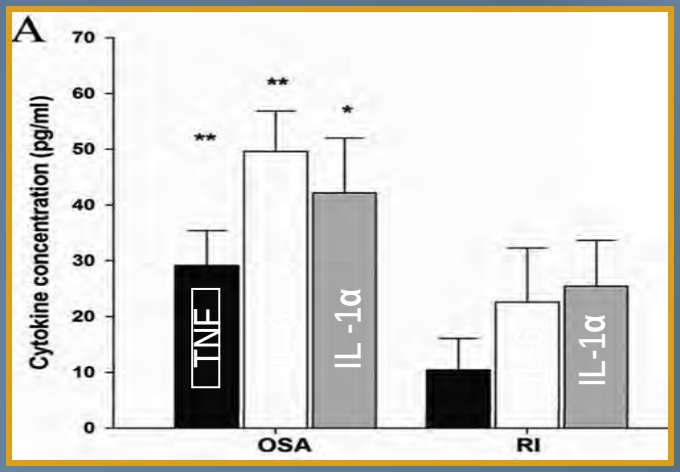
- Leukotrienes are increased in tonsillar and adenoidal tissues from children with OSA compared to those with recurrent infections (tonsillitis).

Goldbart et al., AJRCCM 2005



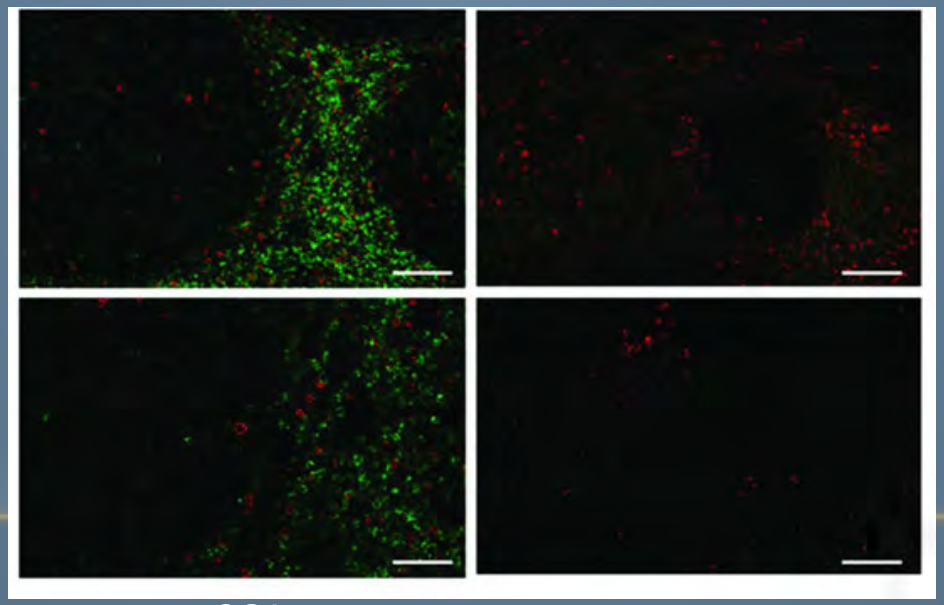
T cell Lymphocytes





Green cells: CD4+ T cell lymphocytes

Red cells: CD8+ T cell lymphocytes



OSA RI

Kim et al, Pediatr Res. 2009

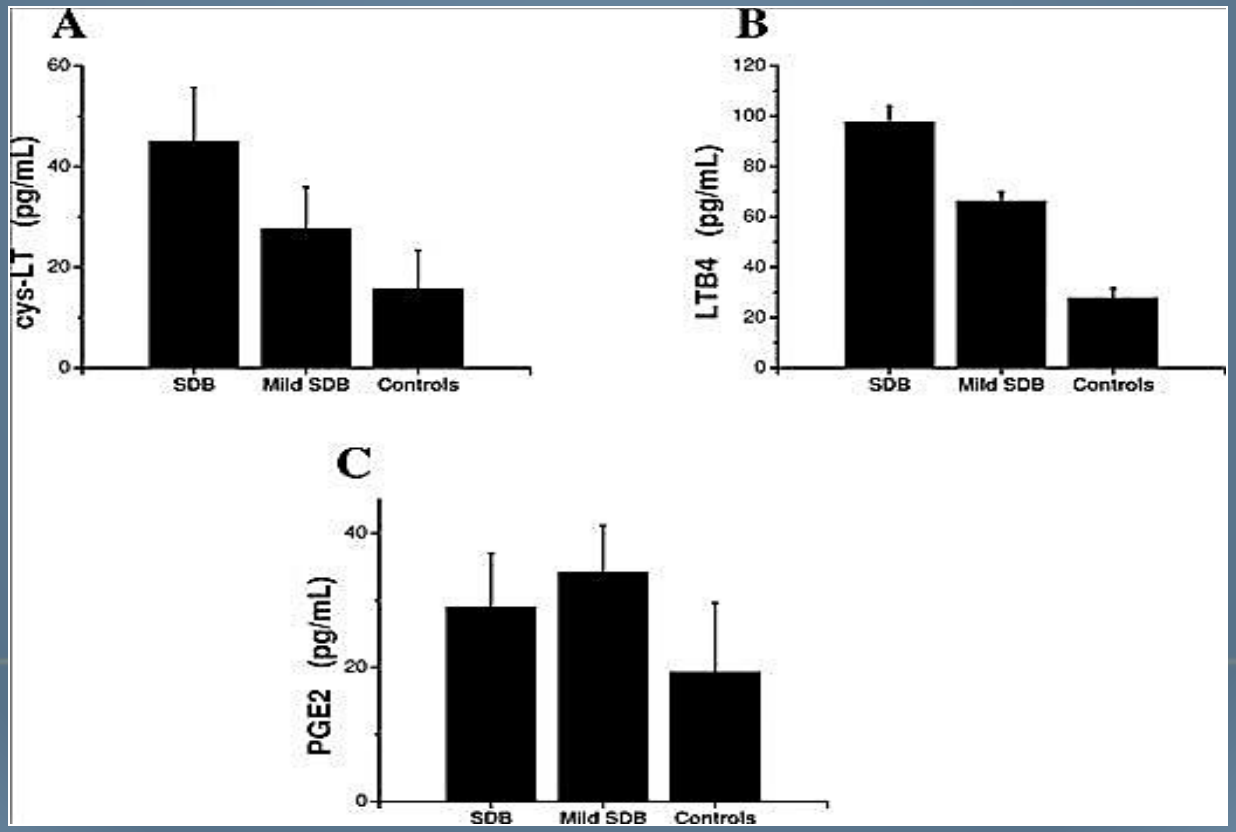
EVIDENCE OF INCREASED INFLAMMATION IN THE UPPER AIRWAY OF CHILDREN WITH OSA

- Prostanglandin E2 (regulates inflammatory mediation) and cysteinyl leukotrienes (involved in proliferation of smooth muscle) are increased in exhaled upper airway condensates from children with OSA.

Goldbart et al., CHEST 2006

- Significant reduction in vitro adenotonsillar proliferation with corticosteroids.

Kheirandish-Gozal, ERJ 2009



Clinical Presentation of Pediatric OSA types I and II.

	Type I	Type II
Excessive daytime sleepiness	+	++++
Weight gain	–	++
Hyperactive behavior	++++	– or +
Truncal obesity	– or +	+++
Enlarged neck circumference	– or +	+++
Enlarged Tonsils/Adenoids	++++	++
Depression and low self-esteem	+	+++
Shyness and social withdrawal	+	+++
Left ventricular hypertrophy	++	++++
Systemic hypertension	+	++++
Recurrent ear infections	+++	– or +
Insulin Resistance	–	++++
Dyslipidemia	+	++++
Elevated C-Reactive Protein	++	++++
Elevated Liver Enzymes	–	++

Dayyat E et al. Sleep Med Clinics 2007

QUESTIONS?