

Sleep-related breathing disorders Pathogenesis

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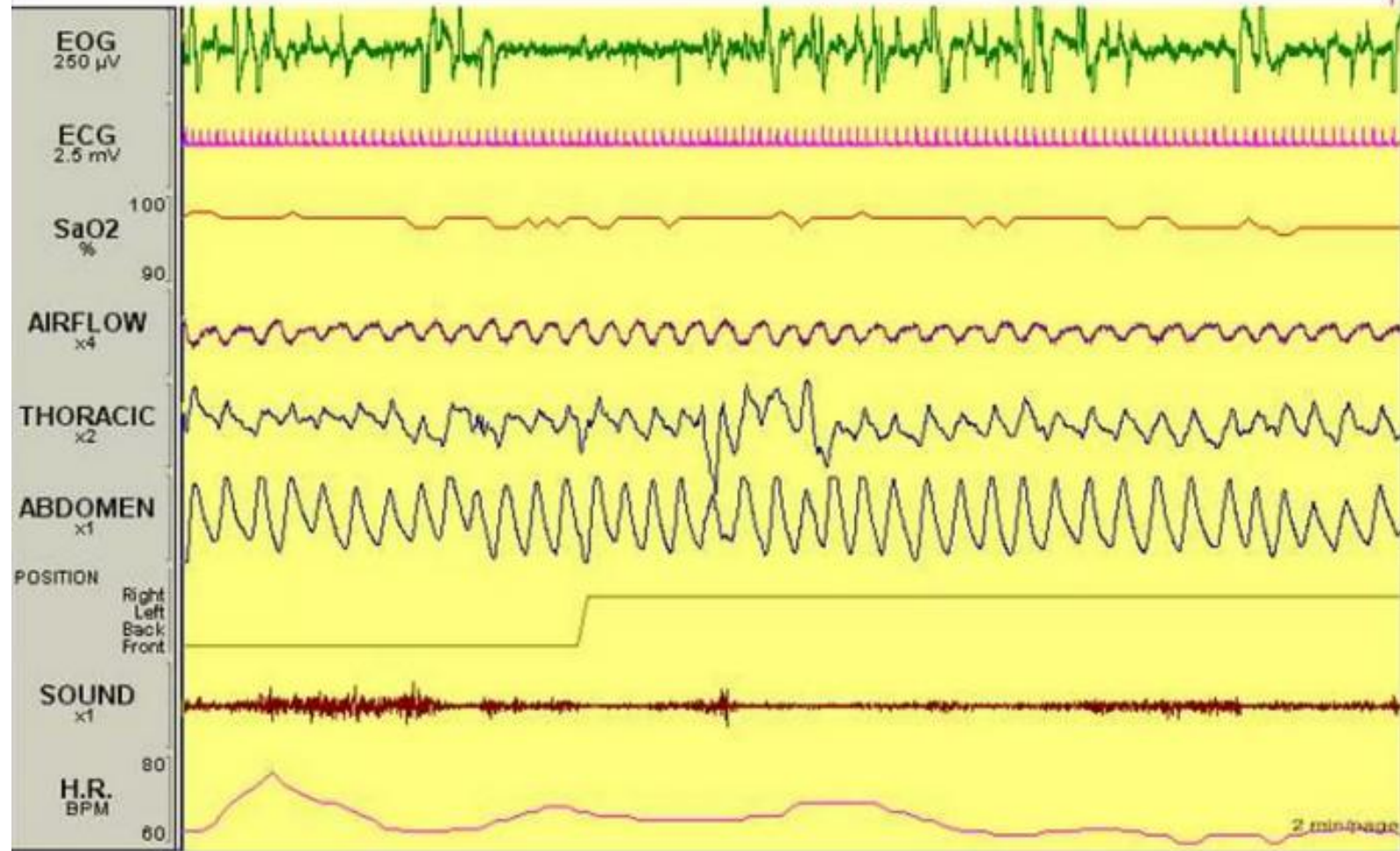
2025

This presentation is an educational material for students of the JLF UK in Martin - elective subject Sleep Related Disorders of Breathing and was created based on resources of teachers working at the JLF UK in the past and present, who have participated in teaching the subject.

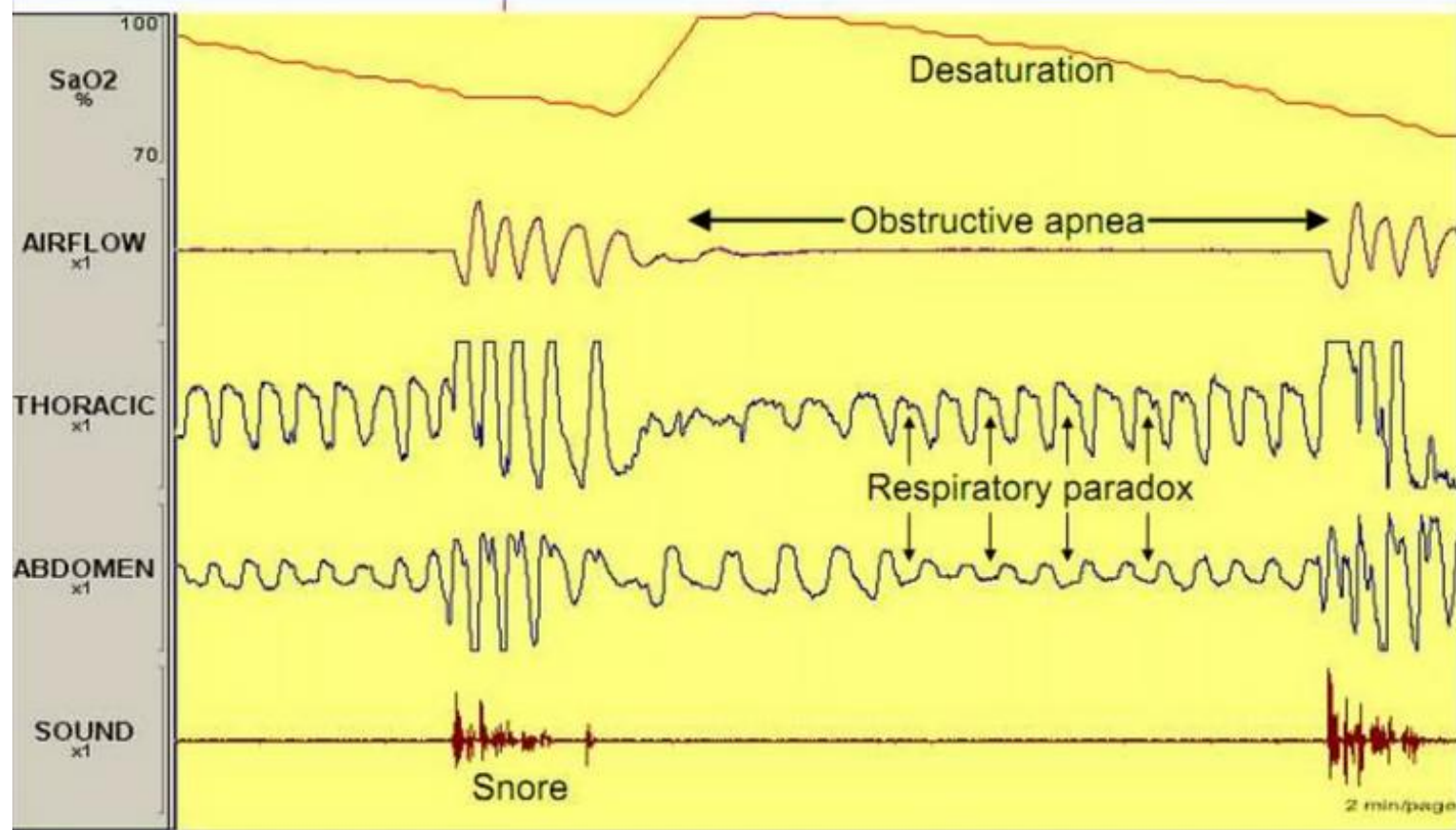
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Where did we stop last time?

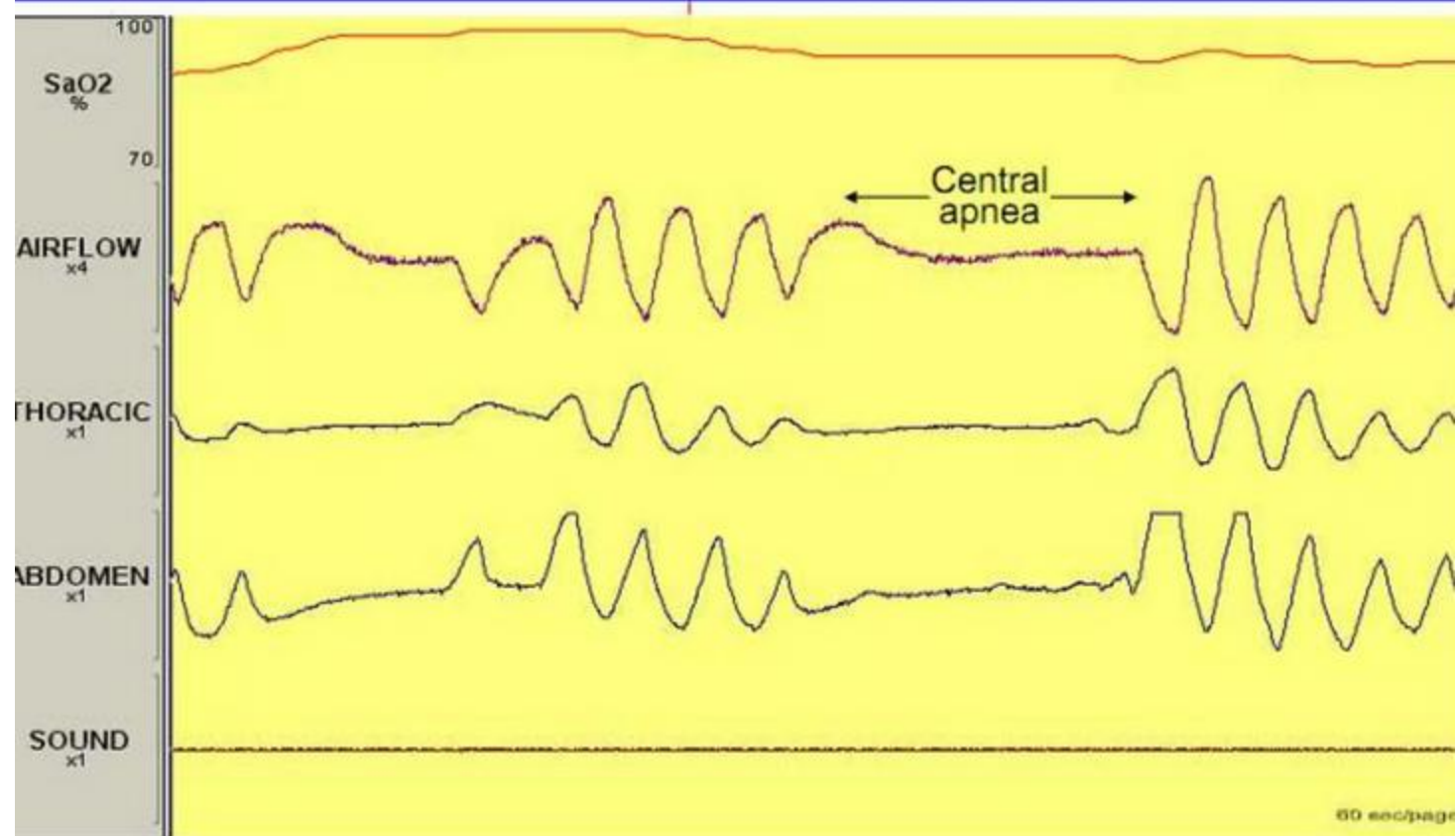
Normal Sleep Study



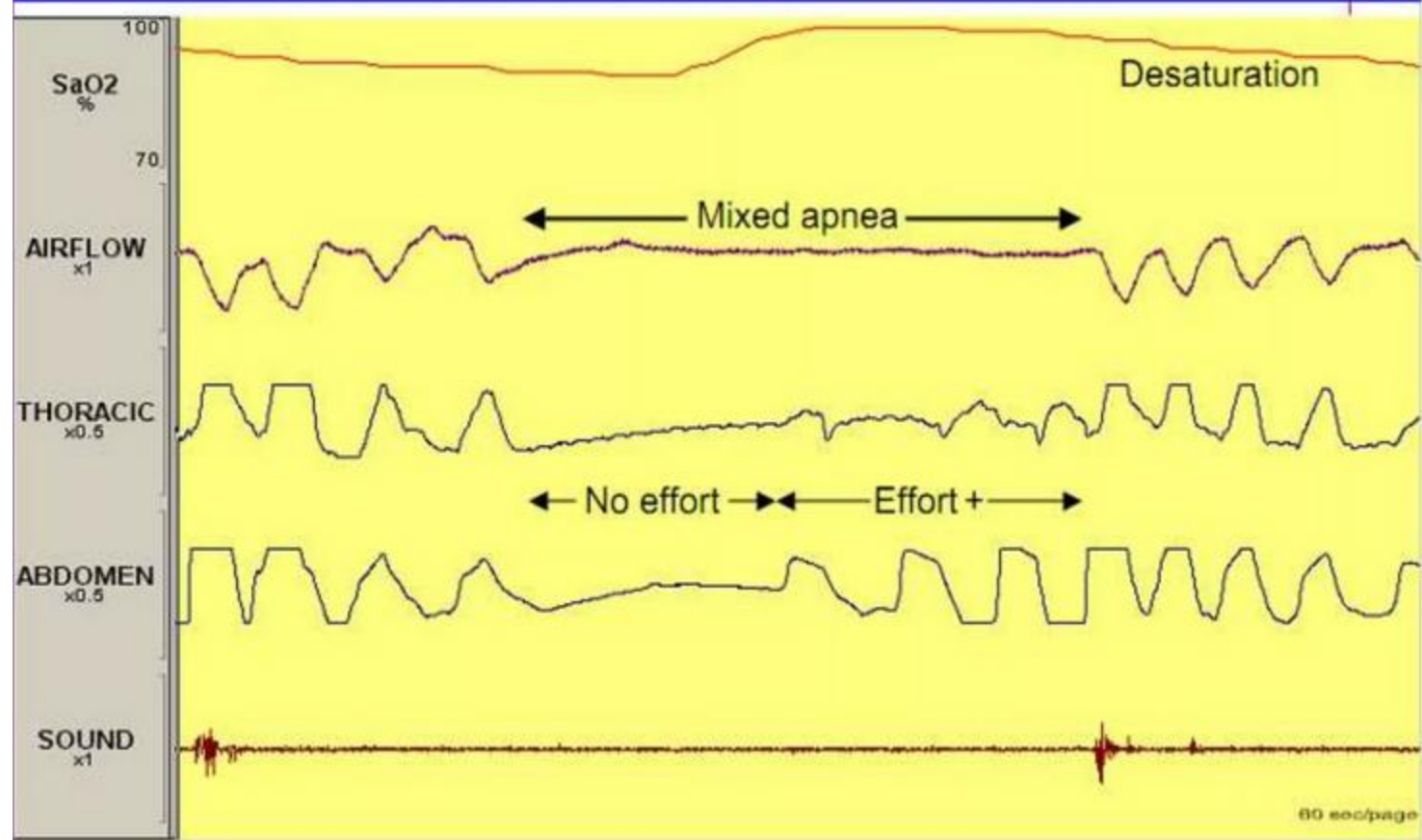
Obstructive apnea: Complete cessation of airflow despite efforts to breathe



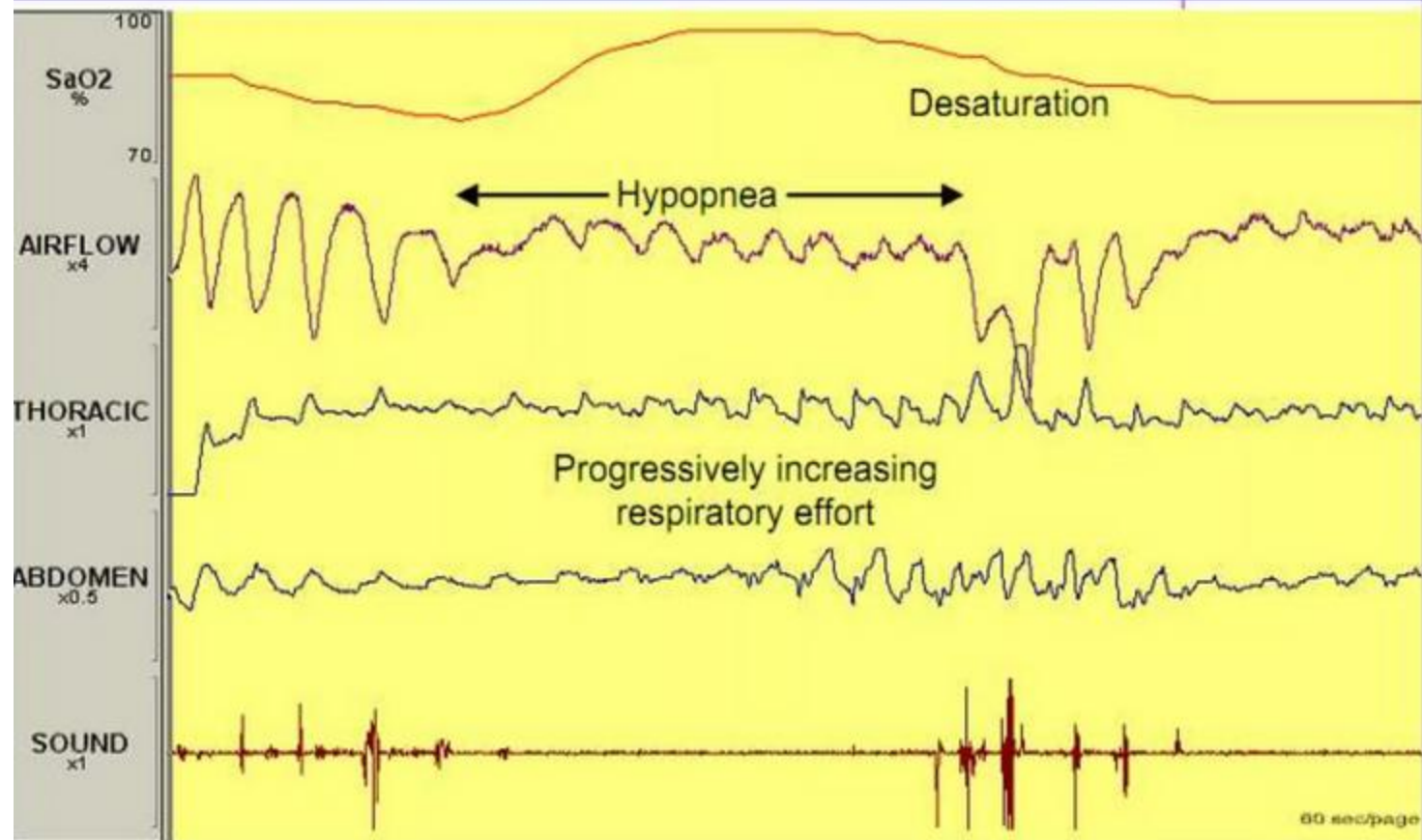
Central apnea: Complete cessation of respiratory effort and airflow



Mixed apnea: Complete cessation of airflow with gradual increase in respiratory effort after an initial absence



Hypopnea: Reduction in airflow compared to baseline, associated with desaturation



Definition

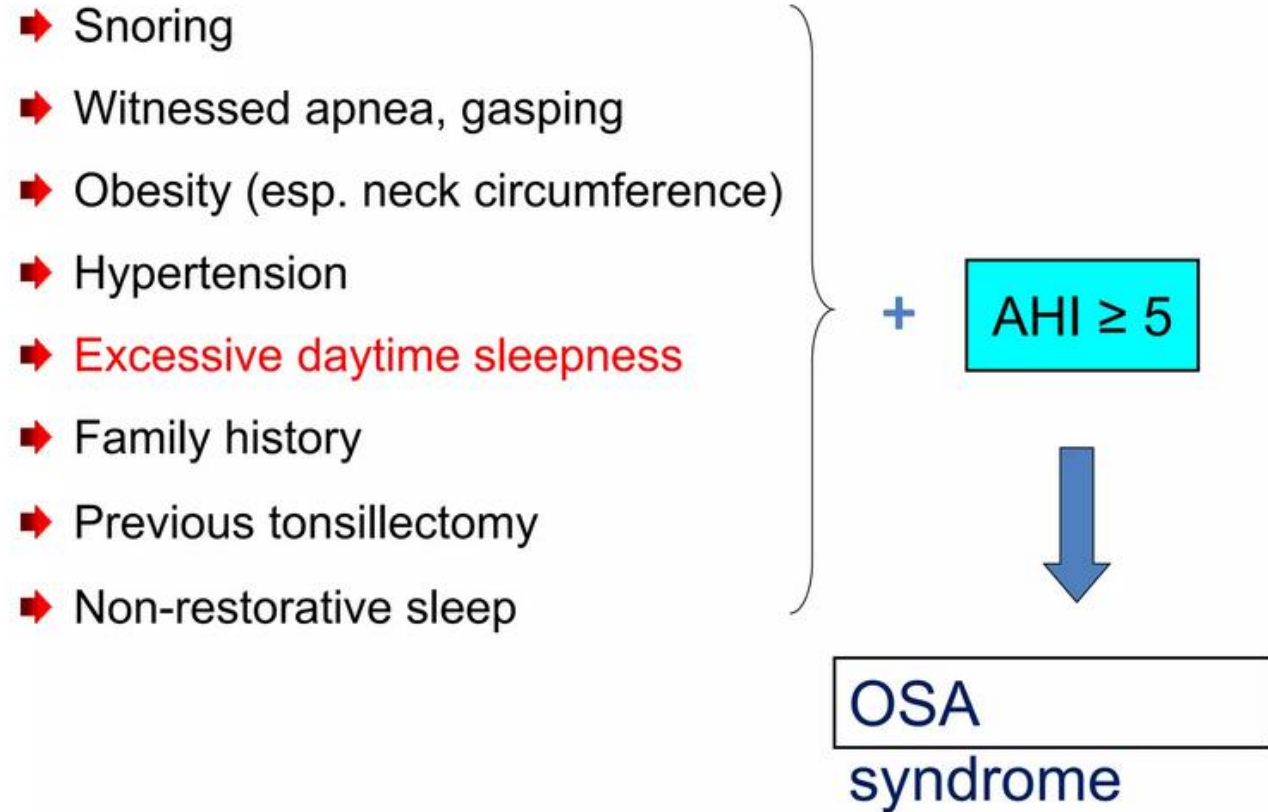
- Sleep-disordered breathing leading to repeated bouts of ventilatory overshoots and undershoots and accompanying swings in arterial blood gases and intrathoracic pressure takes on many forms
- Commonly, sleep-disordered breathing is divided into so-called “central” events, denoting an absence or marked reduction in central respiratory motor output to respiratory pump muscles, or “obstructive” events, which are comprised of respiratory efforts against a closed upper airway
- However, most cyclical sleep-disordered breathing events are driven by anomalies in both anatomical and neurochemical control of upper airway and/or chest wall respiratory musculature.

Are we aware enough?

- OSA associated with excessive daytime sleepiness (EDS) is commonly called obstructive sleep apnea syndrome (OSAS)—also referred to as obstructive sleep apnea-hypopnea syndrome (OSAHS).
- Despite being a common disease, OSAS is under recognized by most primary care physicians in the United States; an estimated 80% of Americans with OSAS are not diagnosed.

- Although recognition of this disorder has increased during the past few decades, data indicate that most individuals affected remain undiagnosed.
- The gap in screening, identification, and effective management of this disorder at the primary care level is vast

Suggestion of sleep apnea

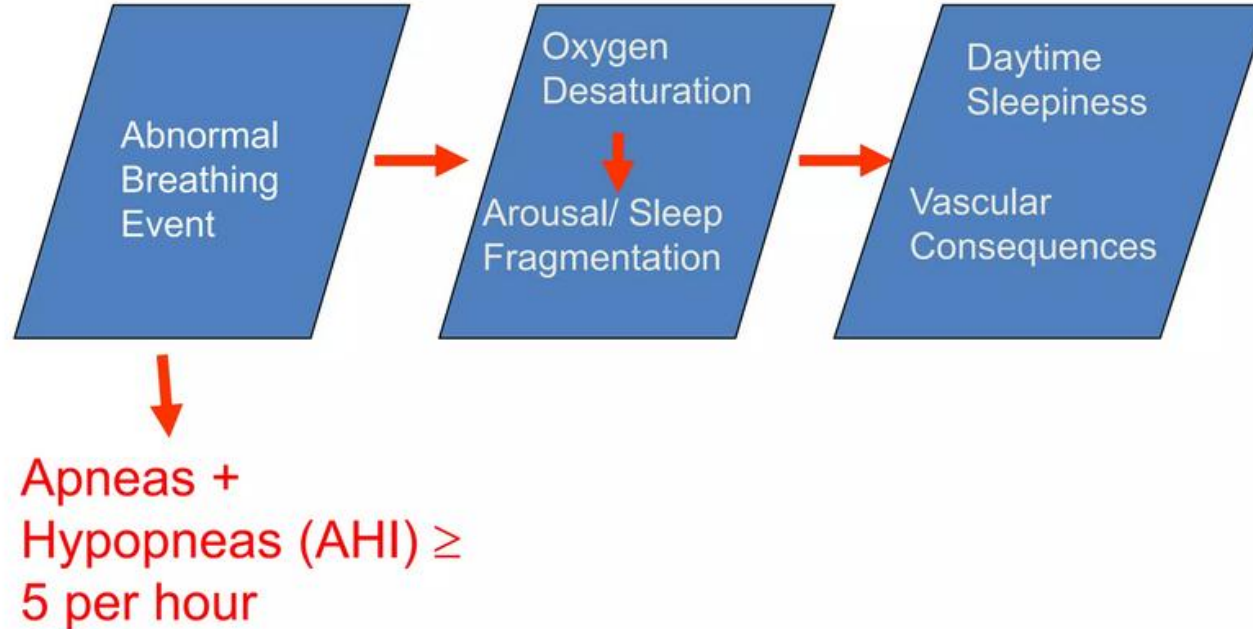


✓ If the sleep study shows apnoeas and hypopnoeas occurring at a rate of more than five times per hour of sleep and is accompanied by excessive daytime sleepiness, a clinical diagnosis of obstructive sleep apnoea-hypopnoea syndrome (OSAHS) can be made

Most common types of sleep-disordered breathing

- Obstructive sleep apnea
- Central sleep apnea
- Mixed / complex sleep apnea
- Hypoventilation syndromes (nocturnal, obesity)

Sleep apnea – hypopnea syndrome



Risk factors and general pathogenesis

- Population-based cross-sectional studies have specified the dominant risk factors for OSA to include excess body weight as the dominant contributor, followed by male gender, and to significant but lesser extents, cranial facial structures and aging

We discuss OSA pathogenesis in three steps

- First we detail structural and functional determinants of an anatomical predisposition for airway closure, an absolutely essential component for OSA.
- The second essential component is sleep. This section emphasizes the effects of the sleeping state on mechanisms underlying both obstructive and central apnea and ventilatory instability.
- Finally, we attempt to integrate anatomical deficits with mechanisms underlying central neurochemical control of breathing stability and compensatory neuromuscular control of upper airway caliber, to explain the cyclical, repetitive nature of OSA.

Obstructive sleep apnea

Obstructive sleep apnoea

- Obstructive sleep apnea (OSA)—also referred to as obstructive sleep apnea-hypopnea (OSAH)—is a sleep disorder that involves cessation or significant decrease in airflow in the presence of breathing effort.
- OSA is characterized by repetitive episodes of complete (apnea) or partial (hypopnea) upper airway obstruction during sleep.

Apnea – a respiratory event where airflow reduced to less than 20% of normal values

Hypopnea – a respiratory event where airflow has reduced to 20-50% of normal values

- Apnea = Cessation of airflow > 10 seconds
- Hypopnea = Decreased airflow $\geq$ 10 seconds associated with:
 - Arousal
 - Oxyhemoglobin desaturation

Measures of Sleep Apnea Frequency

- Apnea Index
 - # apneas per hour of sleep
- Apnea / Hypopnea Index (AHI)
 - # apneas + hypopneas per hour of sleep

Apnea / Hypopnea Index (AHI)

The total combinations of apneas and hypopneas for the entire night divided by the total number of hours one sleeps gives us the apnea/hypopnea index or the AHI.

OSA staging

Absence of OSA = $AHI < 5$.

Mild OSA = $AHI \geq 5$ and < 15 .

Moderate OSA = $AHI \geq 15$ and < 30 .

Severe OSA = $AHI \geq 30$.

UARS – upper airway resistance syndrome, arousal index $> 30/h$ TST plus ESS > 10

Typical patient with OSA

- physiology (obesity, retrognathia, misc.:partial tongue paresis)
- age, sex
- symptoms
- reasons for seeking a sleep laboratory (loud snoring, tired – social factors, BP problems - non-dipper, non-responder, arrhythmias on Holter ECG, microsleep – cannot drive a car safely)

Anatomical determinants of OSA

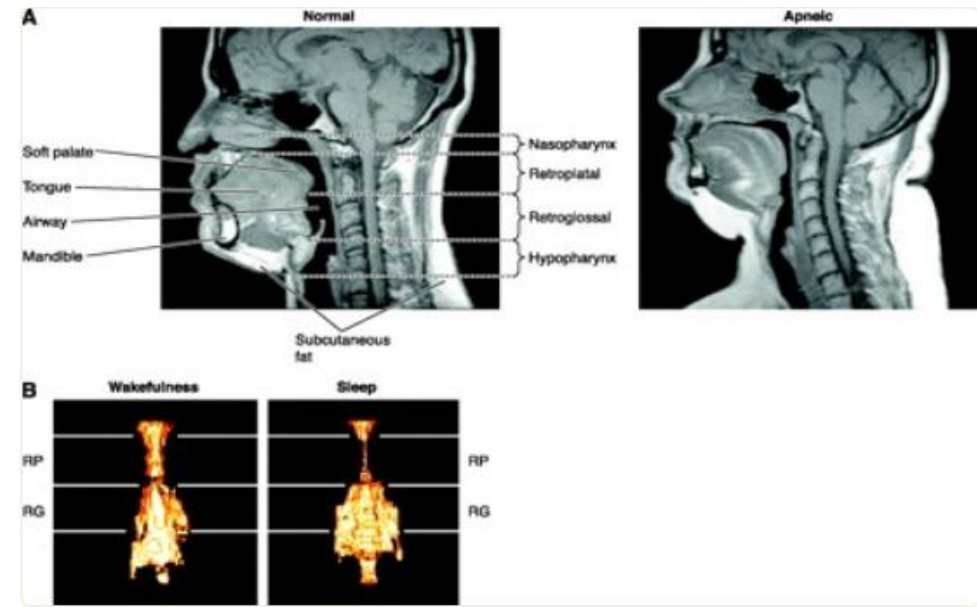
1. Anatomy of the human airway

- The UA is a complex structure required to perform deglutition, vocalization, and respiration – and in humans also speech
- UA obstruction in sleep is most prevalent in humans, because the hyoid bone, a key anchoring site for pharyngeal dilator muscles, is not rigidly attached to the bone
- In other mammals, the hyoid bone is attached to the styloid processes of the skull. Thus the human pharynx has no rigid support except at its extreme upper and lower ends where it is anchored to bone (upper) and cartilage (larynx)
- The pharyngeal cross-sectional area will vary with lumen pressure – there are over 20 skeletal muscles that dilate and stent open the oropharynx

Anatomical determinants of OSA

2. Sites of airway collapse

- Studies using nasal pharyngoscopy, CT and MRI, or pharyngeal pressure monitoring have shown that one or more sites within the oral pharyngeal region are usually where closure occurs in most subjects with OSA, and this region is also smaller in OSA patients versus controls even during wakefulness
- Although the retropalatal region of the oropharynx is the most common site of collapse, airway narrowing is a dynamic process, varying markedly among and within subjects and often includes the retroglottal and hypopharyngeal areas



Anatomical determinants of OSA

3. Soft tissue and bony structure abnormalities

- The reduced size of cranial bony structures in the OSA patient include a reduced mandibular body length, inferior positioned hyoid bone, and retro position of the maxilla - compromising the pharyngeal airspace
- Airway length, from the top of the hard palate to the base of the epiglottis, is also increased in OSA patients, reflecting the increased proportion of collapsible airway exposed to collapsing pressures
- Craniofacial dimensions are primarily inherited, as the relatives of OSA patients demonstrated retroposed and short mandibles and inferiorly placed hyoid bones, longer soft palates, wider uvulas, and higher narrower hard palates than matched controls
- Enlargement of soft tissue structures both within and surrounding the airway contributes significantly to pharyngeal airway narrowing in most cases of OSA. MRI and CT images strongly implicate the thickness of the lateral pharyngeal walls as a major site of airway compromise
- As shown in both humans and rodent models, obesity is a major contributor to airway compression through increased area and volume of pharyngeal fat deposits.

Anatomical determinants of OSA

4. Obesity and lung volume

- Obesity indirectly narrows the upper airway, especially during sleep - increased abdominal fat and recumbent posture reduce lung volumes.

Mechanism of Airway Narrowing:

- Reduced lung volume decreases the “tug” on the trachea and this increases the thickness of the lateral pharyngeal walls, narrowing the airway.
- Lung volume changes affect R_{ua} via pharyngeal dilator muscle activity and this effects persist even after denervation of airway muscles or during muscle paralysis.
- Lung volume effects on airway collapsibility are more pronounced in obese subjects.
- Reduced EELV in obese subjects leads to quicker depletion of lung O₂ stores during apnea, causing severe arterial O₂ desaturation.

Anatomical determinants of OSA

5. Airway edema and surface tension

- Accumulation of even relatively small amounts (~100–200 ml) of edematous fluid enlarges UA soft tissue structures in OSA patients and snorers, especially in the soft palate which may be tugged caudally and constricted during apneas. Local vascular engorgement may also enlarge soft tissues in the UA - both of these processes are supported by cranial displacement of fluid from the lower extremities in supine position
- Surface tension of the liquid lining the mucosa affects the collapsibility of the AU in the same way as it has been well documented in the lungs. A higher surface tension in the UA wall of OSA patients has been reported and surfactant therapy in OSA patients was shown to significantly reduce airway collapsibility and improve AHI by 20–30%.

Anatomical predisposition for airway closure

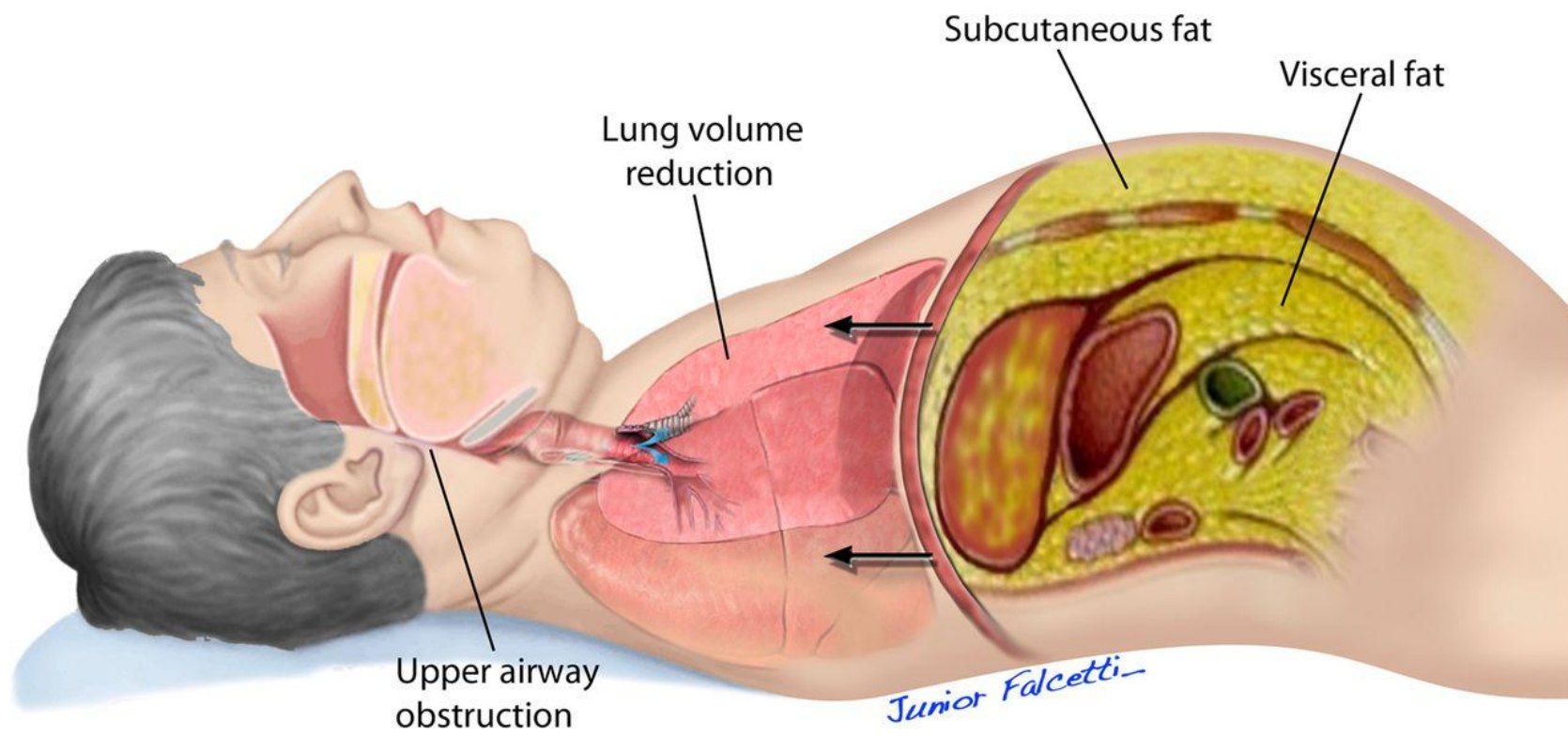
- 1 fat neck habitus, metabolic syndrome
- 2 microgenia, retrogenia
- 3 nasal deformities (eg. after injury)
- 4 acromegaly
- 5 oropharynx anomalies
- 6 hypertrophic tongue
- 7 long uvula
- 8 large tonsils
- 9 myxoedema



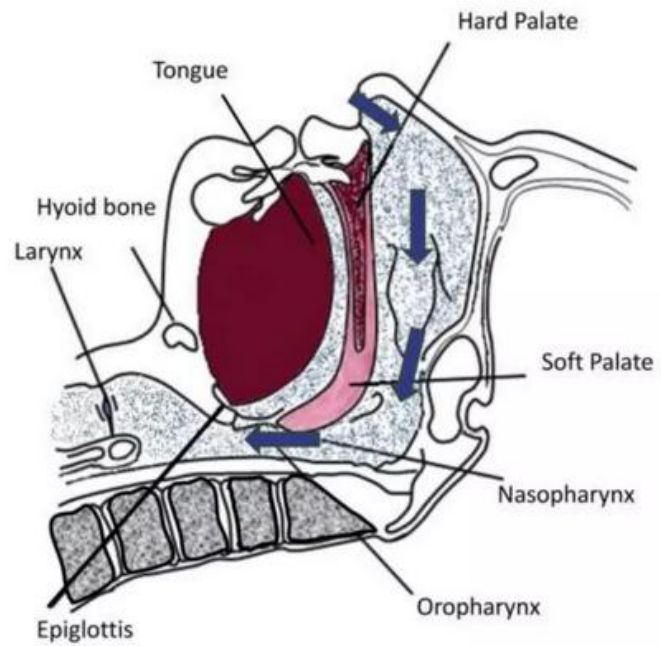
Visceral obesity and OSA

6. Obesity, leptin, and inflammation

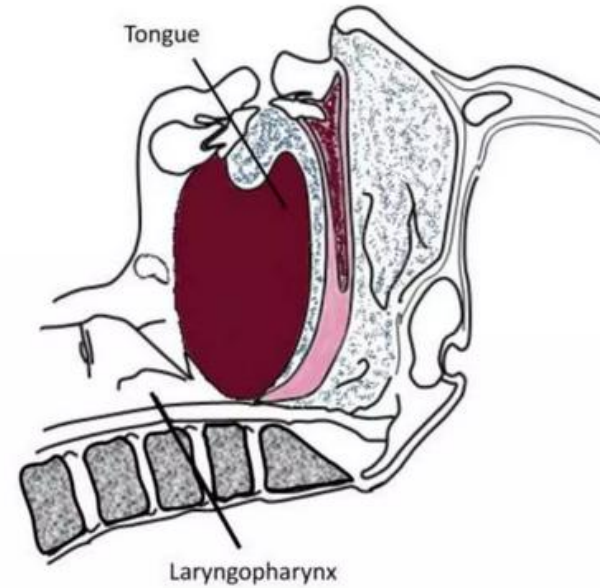
- Visceral fat releases humoral mediators and inflammatory cytokines affecting respiratory control.
- Leptin, an adipocyte-derived factor, impacts respiratory control.
- Impaired leptin signaling in obesity can cause respiratory depression and is linked to obesity hypoventilation syndrome.
- **Inflammatory Cytokines:**
 - Visceral fat releases cytokines like TNF- α and IL-6, elevated in OSA and reduced with CPAP therapy.
 - These cytokines may affect sleep and contribute to local inflammation in OSA patients.
- **Genetic Factors:**
 - Strong heritability of OSA and BMI, with genetic determinants partly related to obesity.
 - Higher OSA prevalence in males, African ancestors, and East Asians.



Sleep Apnea Event

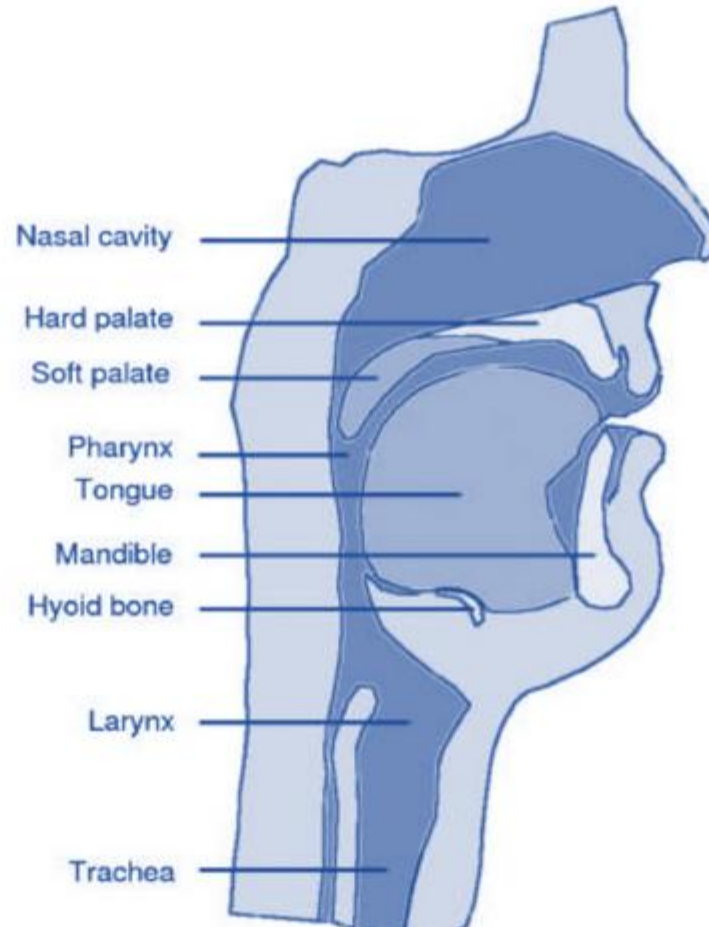


Levitsky – LSU



Adv Physiol Educ 32: 196–202, 2008

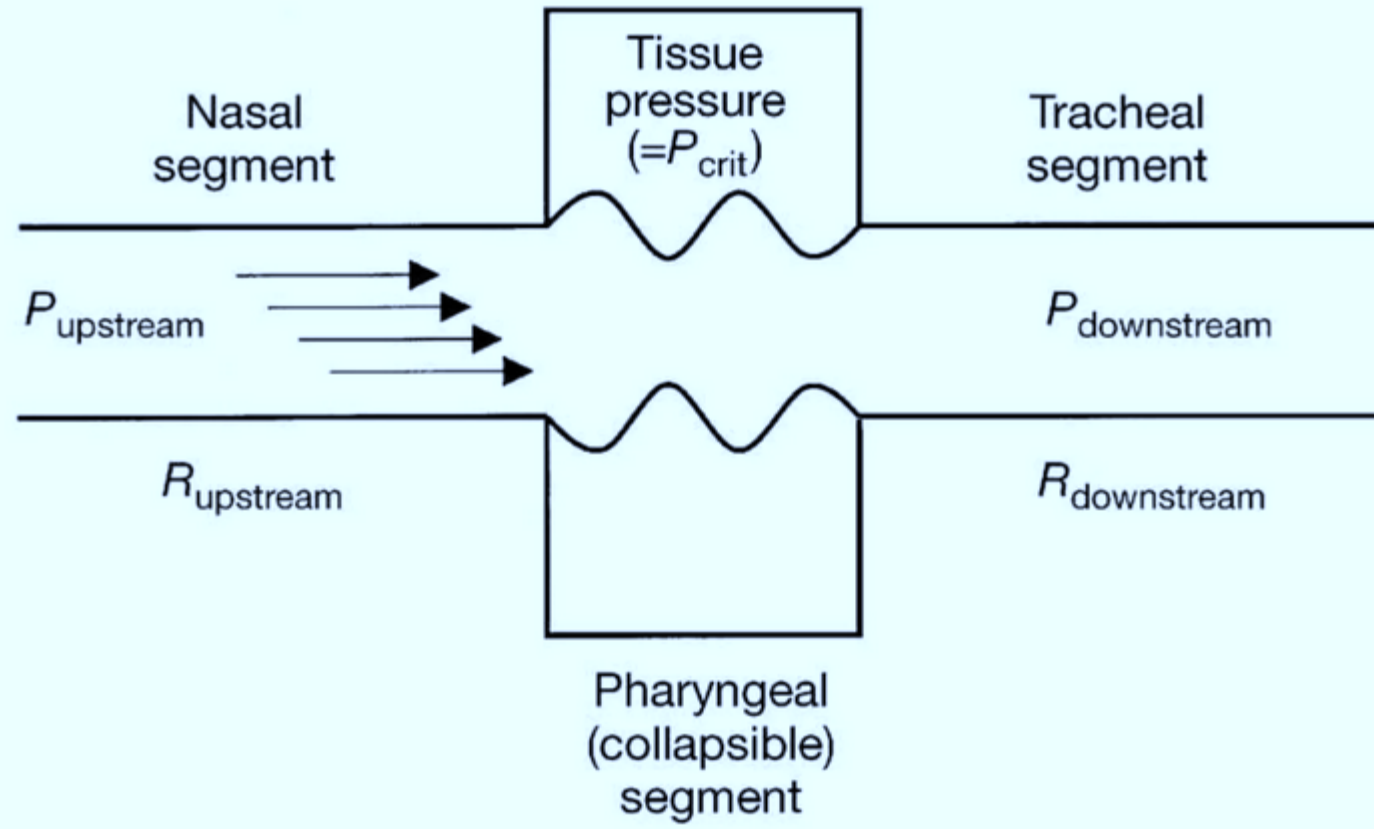
Most of apneic episodes occur within the pharynx, due to the deformation of soft tissue (tongue, soft-palate).

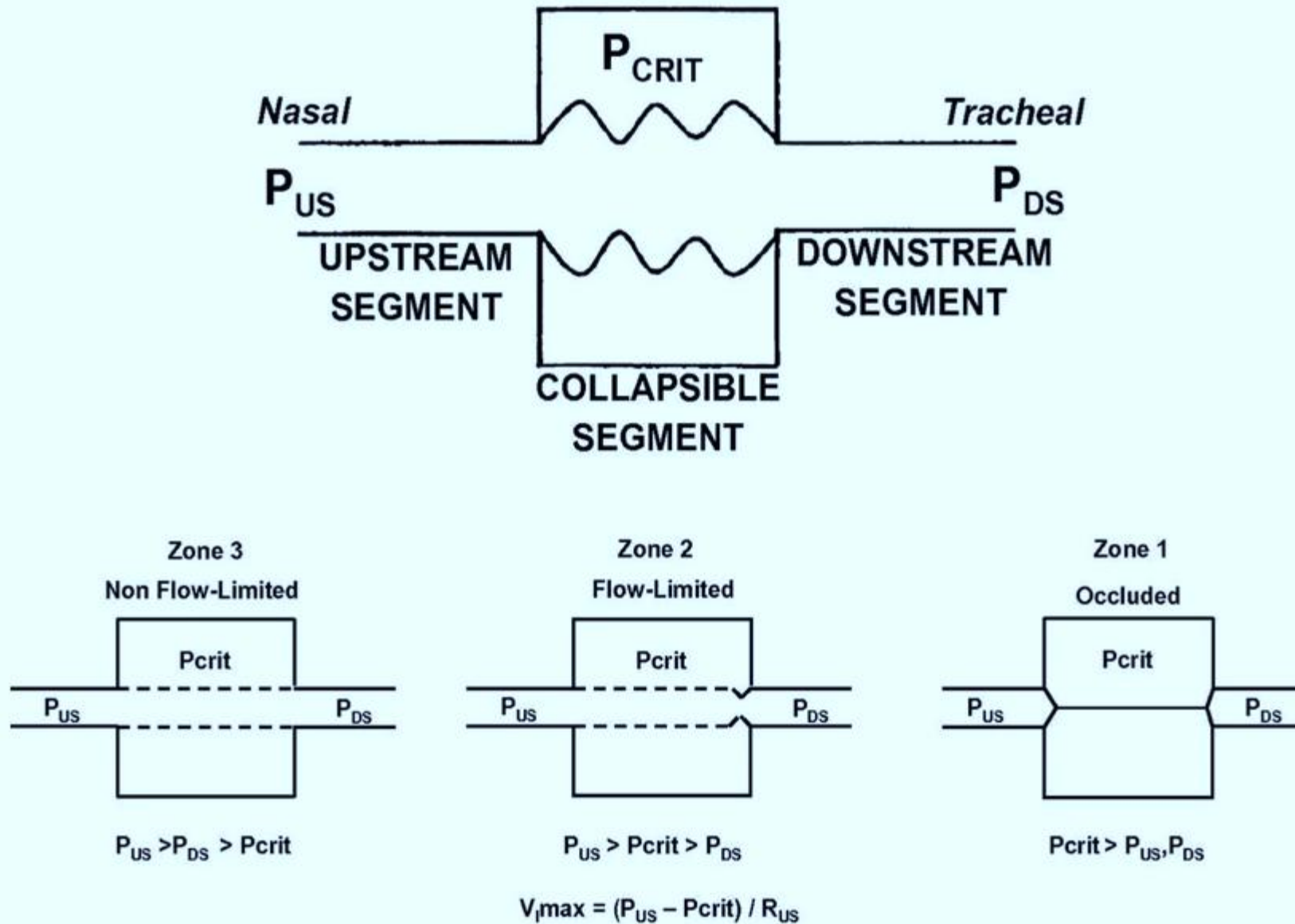


Pharyngeal airway collapse

- Mechanical determinants of airway caliber of the human pharynx in sleep are similar to those regulating caliber of any collapsible tube
- Other well-known biological examples in respiratory physiology include intrathoracic airway collapse upon forced exhalation
- A Starling resistor model developed by Schwartz and colleagues consists of a collapsible tube with a sealed box interposed between two rigid segments
- The critical closing pressure (P_{crit}) of the passive airway is defined as the pressure inside the airway (P_{in}) at which the airway collapses. The pressure gradient during airflow through the system is defined by $P_{upstream} - P_{crit}$ and remains independent of $P_{downstream}$.
- Therefore, with increasing P_{crit} , as the differential between $P_{upstream}$ and P_{crit} decreases, inspiratory airflow limitation will eventually develop, and when the P_{us} falls below P_{crit} , complete airway occlusion occurs.

Starling resistor model of the upper airway with a collapsible (pharyngeal) segment between two rigid tubes (nasal and tracheal).





Different models can be used to explain behavior of the upper airway, including

1. The "balance of forces" Inspiratory negative pressure and extraluminal positive pressure tend to promote pharyngeal collapse.
Upper airway dilator muscles and increased lung volume, airway suction pressure during inspiration tend to maintain pharyngeal patency.
2. The Starling resistor mechanical model.

- The morphologic structure of the upper airway is important in the maintenance of the patent airway during sleep and wakefulness.
- The nasal passage has a bony architecture with the cartilaginous larynx and extra thoracic trachea, which helps produce a conduit for inspiration and expiration of air during sleep and wakeful state.

- The pharynx lacks a strong structural support, and thus potentially collapsible, remains a potential zone for the interruption of airflow.
- The three anatomic segments of the pharynx (nasopharynx, oropharynx, hypopharynx), are liable to collapse resulting in obstruction to airflow during sleep (obstructive sleep apnea).

Pharyngeal airway

- Patency depends on balance of forces that tend to collapse (negative intraluminal pressure and extraluminal pressure) and the contraction of dilator muscles
- Transmural pressure (P_{tm}) = $P_{lumen} - P_{tissue}$
- Closing pressure is P_{tm} at which the pharynx collapses
- $P_{critical}$ – at which airflow ceases completely
- Normal: -8 cm H₂O OSA: > 0 cm H₂O

Factors influencing pharyngeal collapsibility

- Airway patency is promoted by pharyngeal dilator activity and, to a lesser extent, caudal traction on the airway due to lung expansion.
- Airway collapse is due to negative intra-luminal pressure during inspiration and inward pressure from extra-luminal factors, such as adipose tissue within the pharyngeal walls.
- If collapsing pressures exceed dilating pressures, the airway collapses and obstruction ensues

We can distinguish the following situations:

1. “Rigid” tube and free flow:

When the pressure inside the tube is much higher, than the outside pressure and the pressure upstream is greater, than the critical pressure.

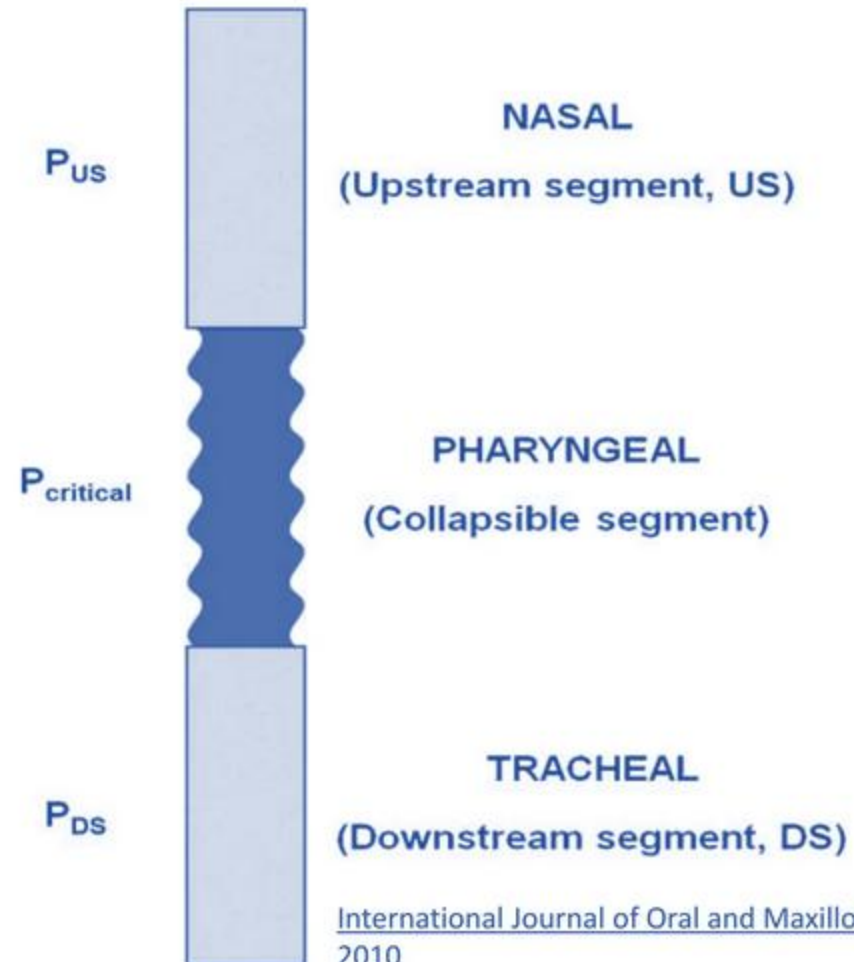
2. Partially collapsible tube and vibration:

When the pressure inside the tube is close to outside pressure and upstream pressure is greater than the critical pressure.

3. Very collapsible tube and choked flow:

When the pressure inside the tube is much lower than outside pressure and upstream pressure is less than the critical pressure.

Starling resistor model of the pharyngeal airway. The pressure required to keep the airway patent (P_{crit}) is a function of the pressure upstream to the collapsing segment (P_{US}).



Upper airway collapse may occur due to:

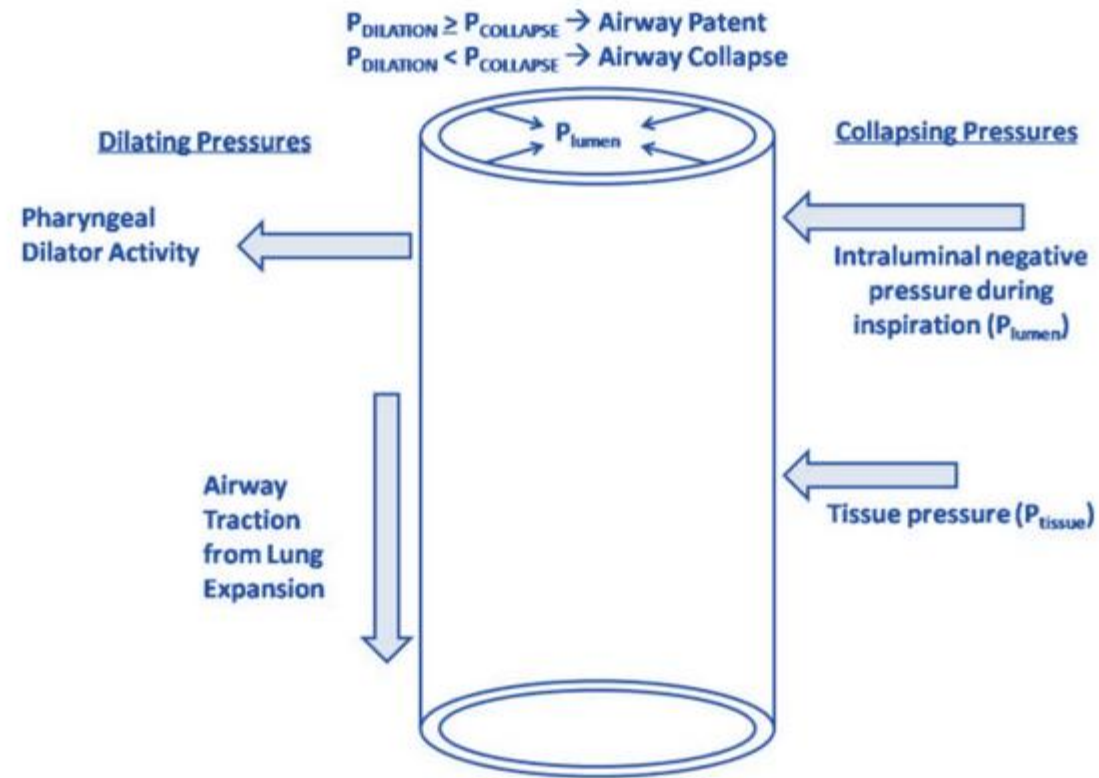
- 1) ↓ UA Size
- 2) Balance of forces
- 3) Increased collapsibility

Anatomic abnormality

Imbalance between activation of diaphragm and UA muscles
Impaired reflex activation of UA dilator muscle activity

Rigid tube / flexible segment

Factors influencing pharyngeal collapsibility.



Pathogenesis

- ➡ The primary problem in the sleep apnea patient is the presence of an anatomically small pharyngeal airway.
- ➡ To prevent airway collapse during wakefulness, the action of the airway dilator muscles is augmented – a neuromuscular compensation for the small airway.
- ➡ With sleep onset, there is a loss of the upper airway reflex which drives this neuromuscular compensation. As a result, dilator muscle activity falls, the pharynx closes and the apnea begins.

- Airflow cessations or reductions produce arousals, fragmented sleep, reductions in blood oxyhemoglobin saturation, and fluctuations in blood pressure and heart rate
- OSA is the most common type of sleep-disordered breathing (SDB) and is characterized by recurrent episodes of upper airway collapse during sleep. These episodes are associated with recurrent oxyhemoglobin desaturations and arousals from sleep.

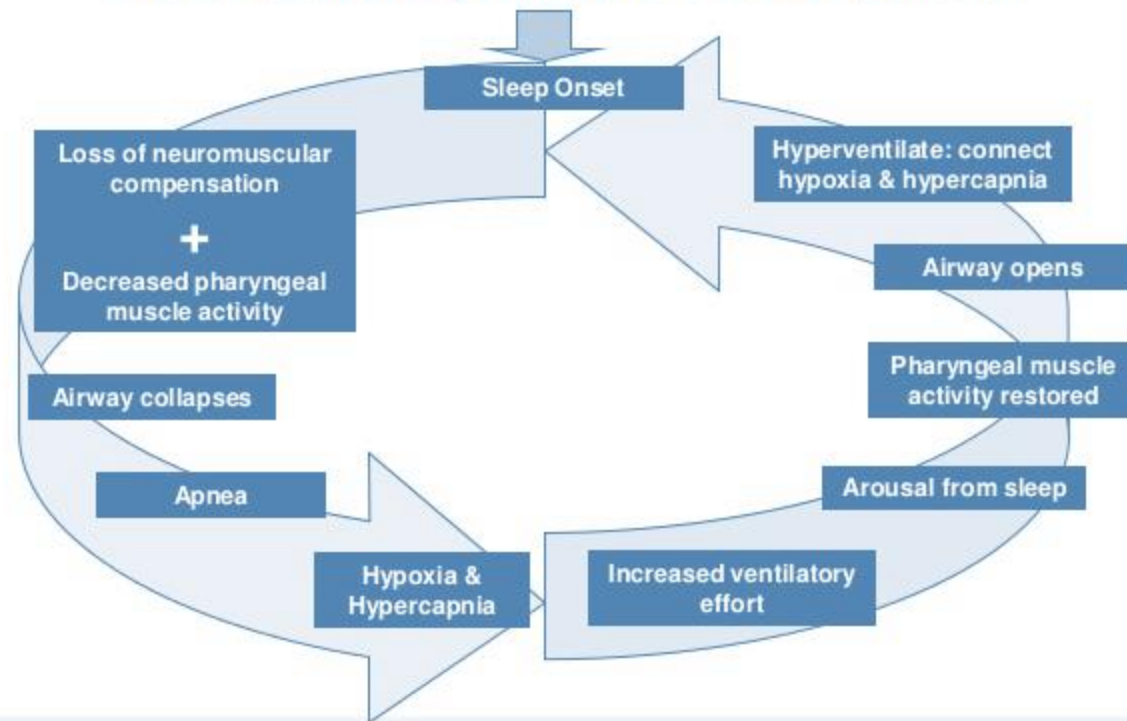
Pathogenesis

- Obstructive sleep apnea is a common disorder characterized by repetitive episodes of pharyngeal (upper) airway collapse or narrowing during sleep
- In people with OSA, pharyngeal muscles relax during sleep and gradually allow the pharynx to collapse.
- The level of pharyngeal collapse varies between patients, but most often occurs at the velopharyngeal level and/or retroglossal level.

- ➡ During wakefulness, airway patency is protected by pharyngeal muscle tone. With sleep there is a loss of muscle tone predisposing to partial or complete upper airway obstruction, particularly in those with already narrow, compliant upper airways.
- ➡ In sleep, the changes are particularly evident in rapid eye movement (REM) sleep, when the loss of muscle tone can be profound.

Pathophysiology of Sleep Apnea

Awake: Small airway + neuromuscular compensation



ESS

Epworth sleepiness
score

0-24 pts

EPWORTH SLEEPINESS SCALE FORM

Instructions: Be as truthful as possible. Print the form. Read the situation in the first column; select your response from the second column; enter that number in the third column. Total all of the entries in the third column and enter the total in the last box.

Situation	Responses	Score
Sitting and Reading	0 = would never doze 1 = slight chance of dozing 2 = moderate chance of dozing 3 = high chance of dozing	
Watching Television	0 = would never doze 1 = slight chance of dozing 2 = moderate chance of dozing 3 = high chance of dozing	
Sitting inactive in a public place, for example, a theater or a meeting	0 = would never doze 1 = slight chance of dozing 2 = moderate chance of dozing 3 = high chance of dozing	
As a passenger in a car for an hour without a break	0 = would never doze 1 = slight chance of dozing 2 = moderate chance of dozing 3 = high chance of dozing	
Lying down to rest in the afternoon	0 = would never doze 1 = slight chance of dozing 2 = moderate chance of dozing 3 = high chance of dozing	
Sitting and talking to someone	0 = would never doze 1 = slight chance of dozing 2 = moderate chance of dozing 3 = high chance of dozing	
Sitting quietly after lunch when you've had no alcohol	0 = would never doze 1 = slight chance of dozing 2 = moderate chance of dozing 3 = high chance of dozing	
In a car while stopped in traffic	0 = would never doze 1 = slight chance of dozing 2 = moderate chance of dozing 3 = high chance of dozing	
TOTAL SCORE		

A score of 10 or greater indicates a possible sleep disorder. Take the completed form to your doctor.

Central sleep apnea (CSA) syndromes

Primary (idiopathic) CSA

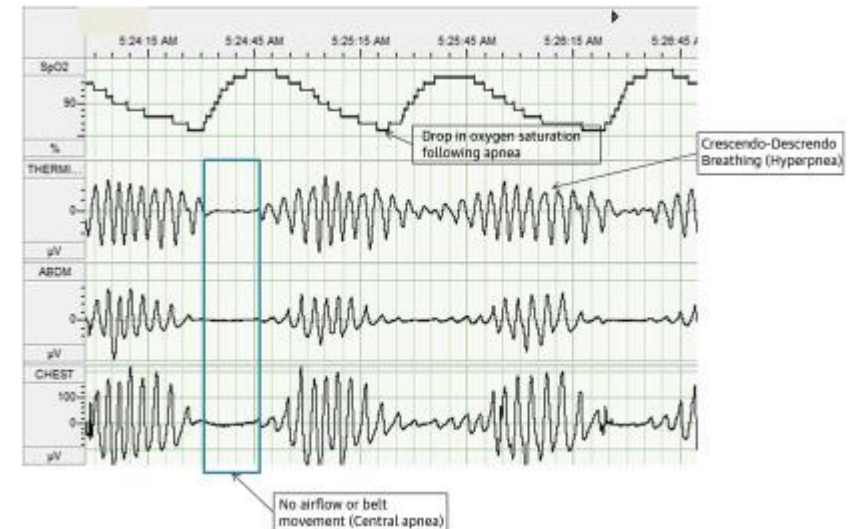
Cheyne-Stokes breathing pattern (chronic heart failure)

CSA due to high-altitude periodic breathing

CSA due to drug or substance (baclofen, opioids, drug abuse)

Primary sleep apnea of infancy

From the American Academy of Sleep Medicine: ICSD-2 2005
(1). ICSD, International Classification of Sleep Disorders.

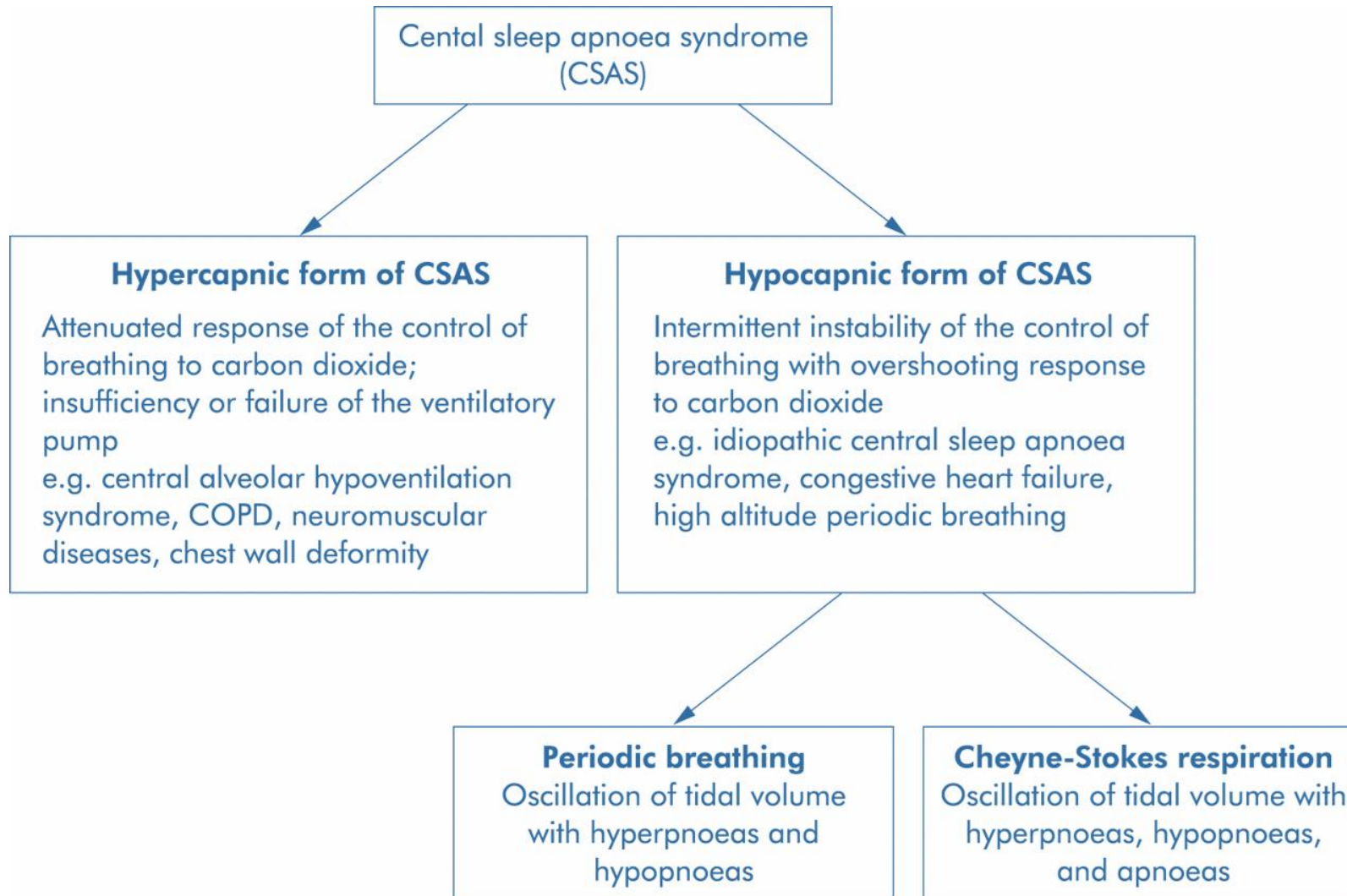


What is congenital central hypoventilation syndrome?

- Congenital central hypoventilation syndrome (CCHS), also known as Ondine's curse, is a rare neurological condition characterized by alveolar hypoventilation and autonomic nervous system dysregulation. CCHS is a life-threatening condition that causes an oxygen shortage and an accumulation of carbon dioxide in the blood. Usually, patients with CCHS require lifelong ventilatory support.
- CCHS affects the autonomic nervous system, which can cause an inability to control breathing, especially during sleep, thereby resulting in an imbalance of oxygen and carbon dioxide in the blood. Usually, when this occurs, the autonomic nervous system will correct by causing the individual to wake up or begin taking deeper breaths; however, in individuals with CCHS, the autonomic nervous system reaction is compromised.
- CCHS is caused by mutations in the **PHOX2B** gene, which is involved in the development of the nervous system in utero. Although most cases of CCHS have been found to be spontaneous in nature (i.e., de novo), it is considered a dominant genetic condition, meaning that only one mutated gene needs to be present for the condition to occur. Therefore, both those assigned female and male at birth can be affected equally.

Love story go wrong?





Pathogenesis

- ➡ Where partial or complete obstruction occurs, the event is terminated by arousal, which is usually brief (<15 s), as a result of the accompanying return of muscle tone.
- ➡ Once patency is restored, sleep resumes, and along with it the tendency to obstruct again.
- ➡ These cyclical obstructions terminated by arousals provide the pathophysiological basis of OSA .

Pathogenesis

- ➡ During the apnea, hypoxia and hypercapnia develop, leading to increasing ventilatory effort.
- ➡ Once this effort reaches a threshold level, the patient arouses. Pharyngeal muscle activity is restored, and the airway opens.
- ➡ The patient then hyperventilates to correct the blood gas derangements, returns to sleep, and the cycle begins again.



Night Sweats



Frequent visits to
the bathroom



Restless sleep & witness
pauses in breathing



Loud snoring



SYMPTOMS OF SLEEP APNEA



Loss of sex drive



Daytime sleepiness



Memory, concentration,
or attention problems



Early morning headache



Waking up to a
dry or sore throat



Choking, gasping for air,
wheezing or chest pain

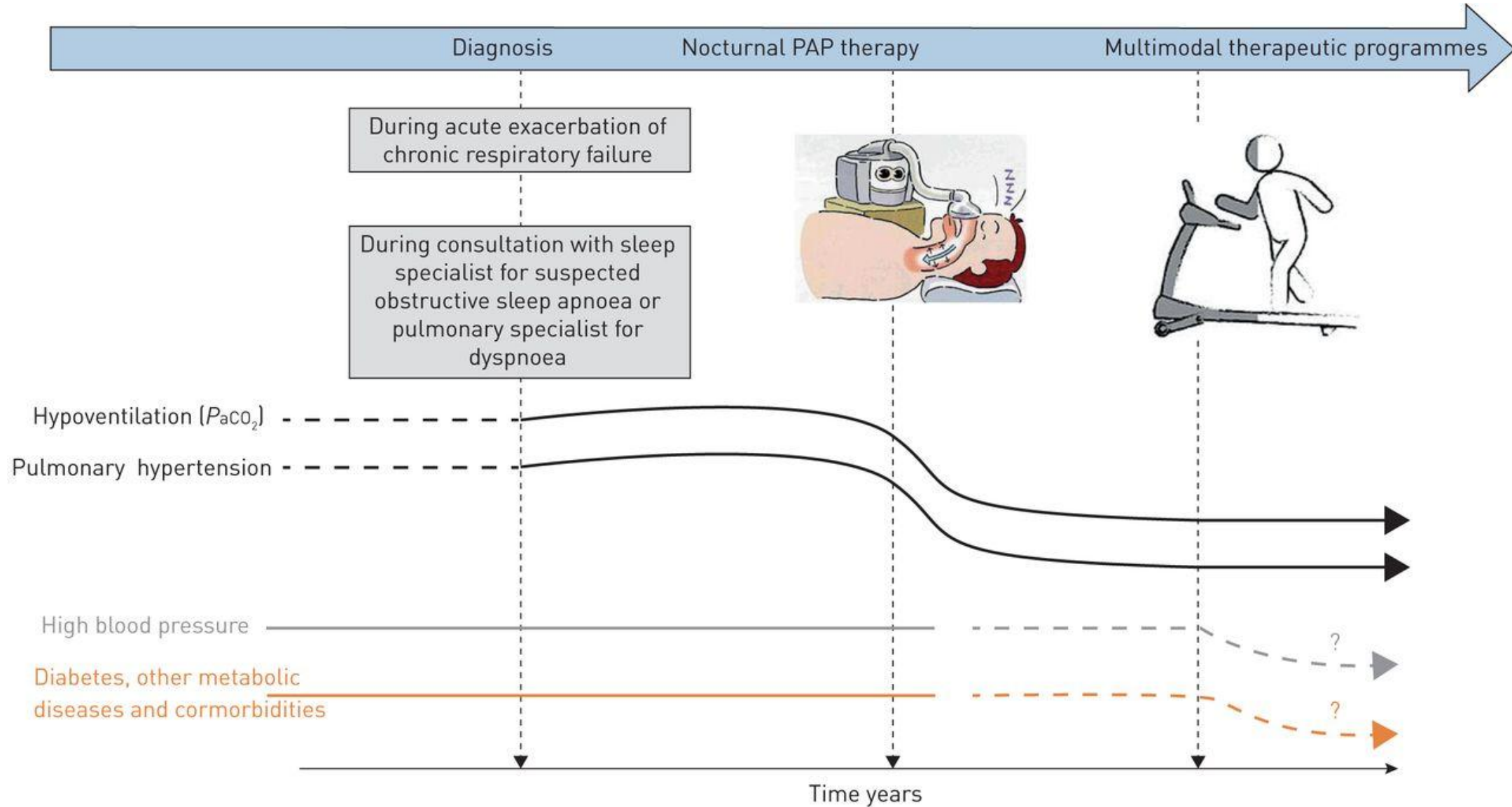
Obesity hypoventilation syndrome

Criteria: SpO₂ Hyposaturation less than 85% for longer than 15% of total sleep time, hypercapnia

Normocapnia 35-45 mmHg or 4,70-6,00 kPa arterial (PaCO₂)

EtCO₂ 30-43 mmHg or 4,00-5,70 kPa end-tidal measurement are less sensitive

Obesity hypoventilation



Obesity hypoventilation syndrome OHS

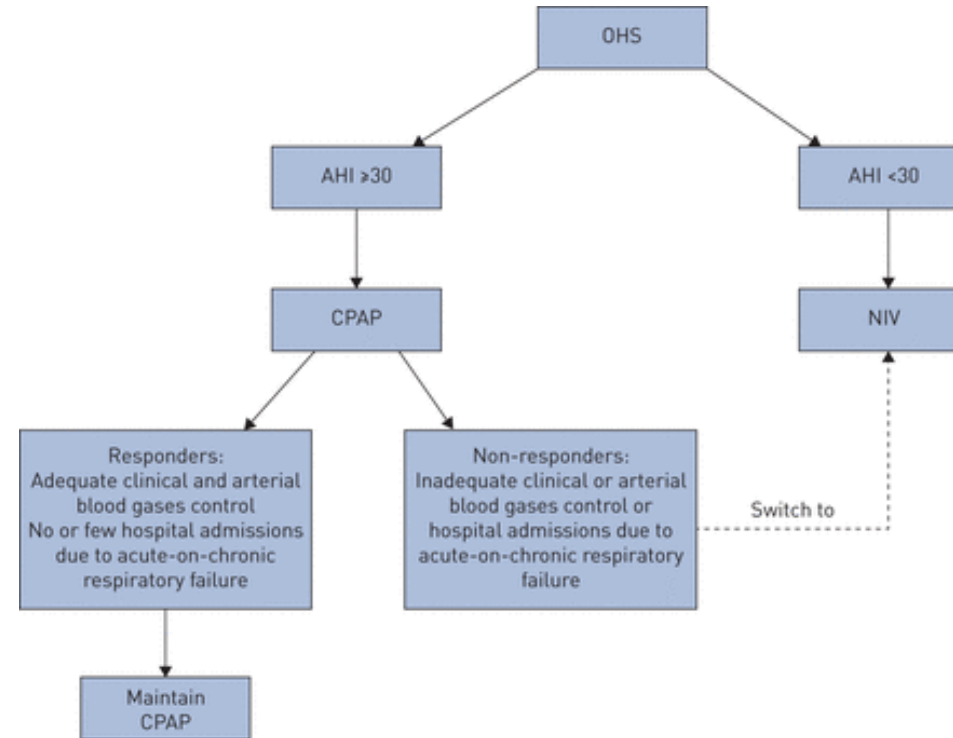
Patients with OHS tend to be severely obese (BMI $\geq 40 \text{ kg} \cdot \text{m}^{-2}$), have severe OSA ($\geq 30 \text{ events} \cdot \text{h}^{-1}$) and are typically hypersomnolent.

Compared with patients with eucapnic OSA and similar BMI, patients with OHS are more likely to report dyspnoea and manifest cor pulmonale

<https://err.ersjournals.com/content/28/151/180097>

	Stage	BMI (kg/m^2)	Intermittent hypercapnia during sleep	HCO_3^- (mmol/L)	PaCO_2 (mmol/L)	Complications
0	At Risk	>30	No	<27	<45	Not necessary
I	Obesity related sleep hypoventilation (ORSH)	>30	Yes	<27	<45	Not necessary
II	Obesity related sleep hypoventilation (ORSH)	>30	Yes	≥ 27	<45	Not necessary
III	Obesity hypoventilation	>30	Not necessary	Not necessary	>45	Absent
IV	Obesity hypoventilation Syndrome	>30	Not necessary	Not necessary	>45	Present

Management of obesity hypoventilation syndrome (OHS)



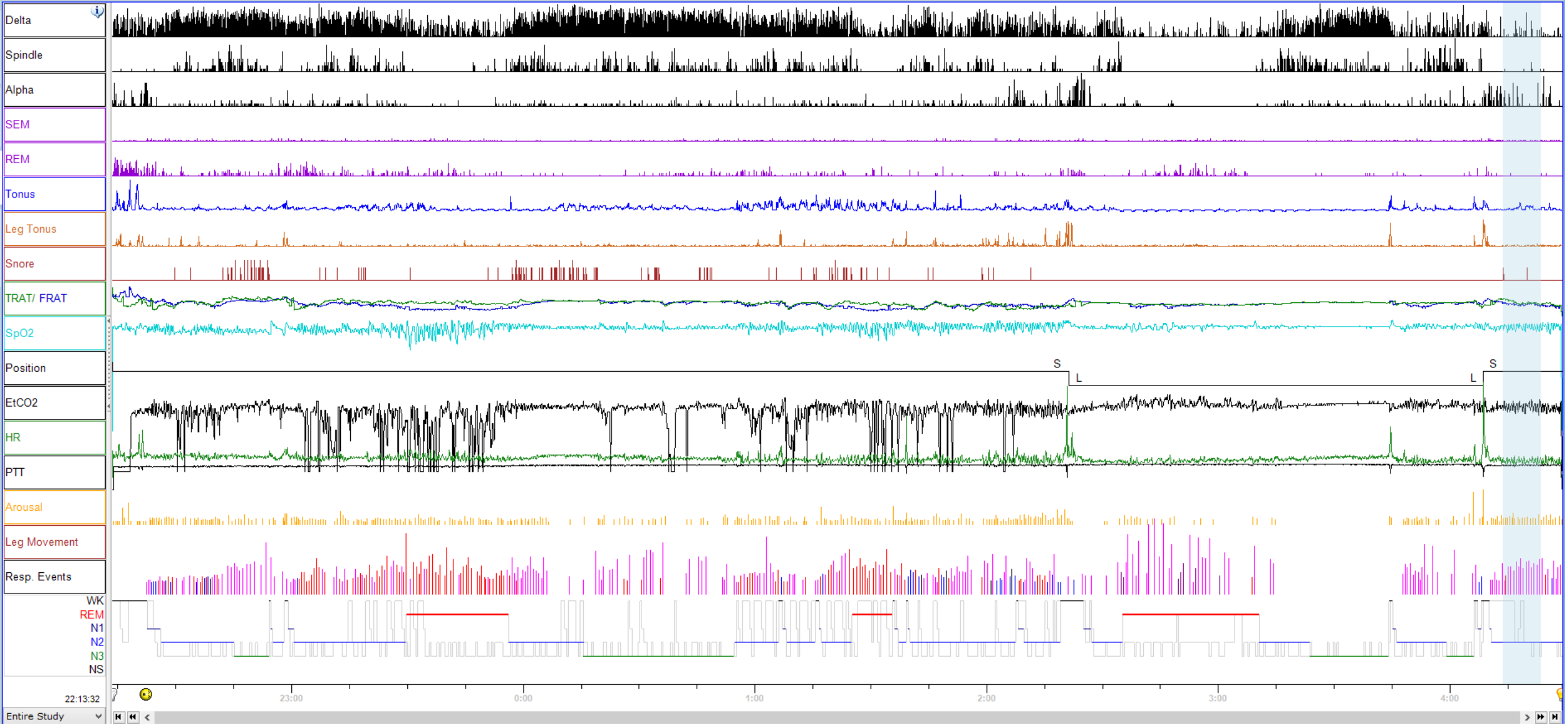
CPAP could be first-line treatment for OHS patients with concomitant severe obstructive sleep apnoea (OSA).

Noninvasive ventilation (NIV, BiPAP) should be considered as first-line therapy for OHS patients with no OSA or milder forms of OSA.

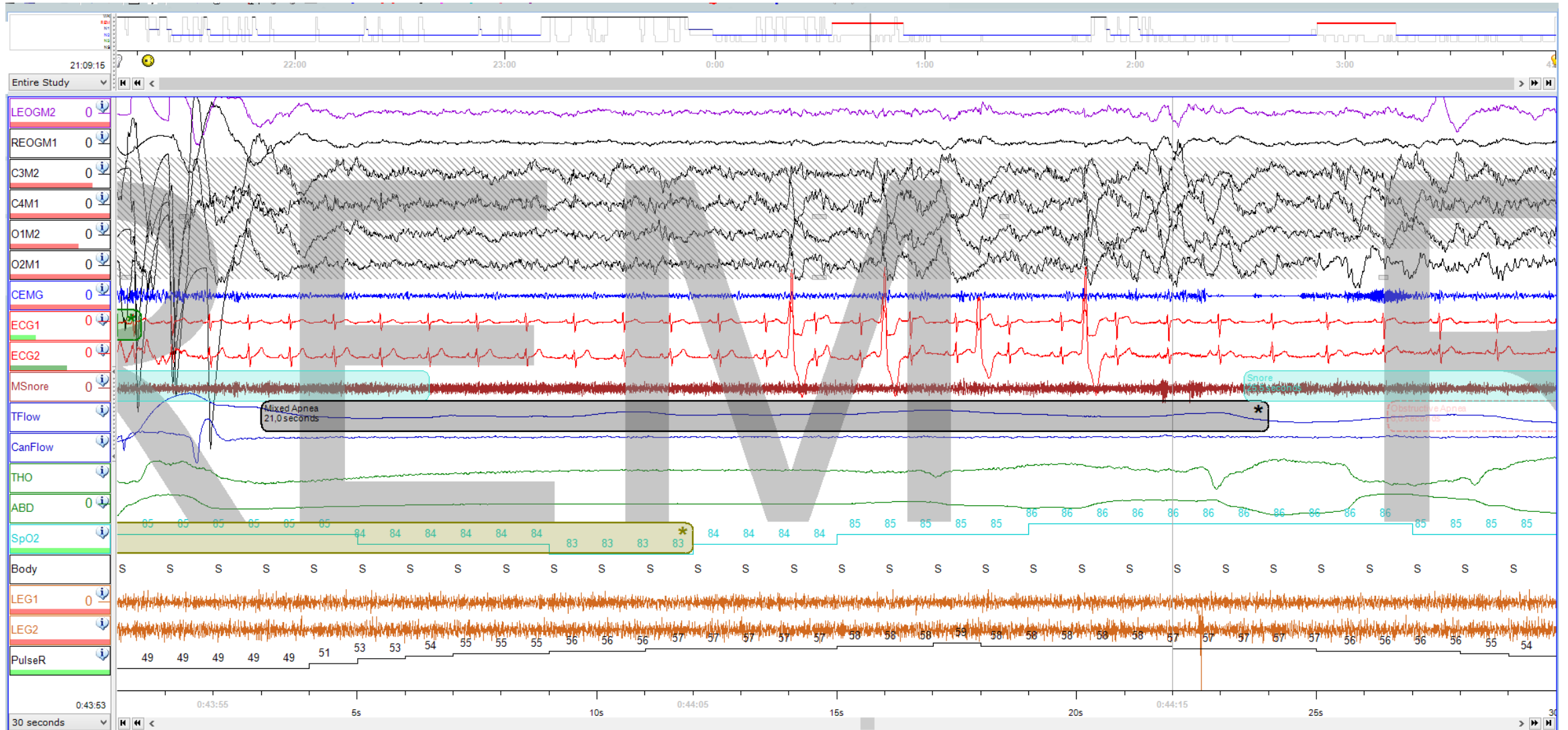
If patients initially treated with CPAP have no favorable response to therapy despite objectively documented high levels of adherence to CPAP, they should be changed to NIV therapy.

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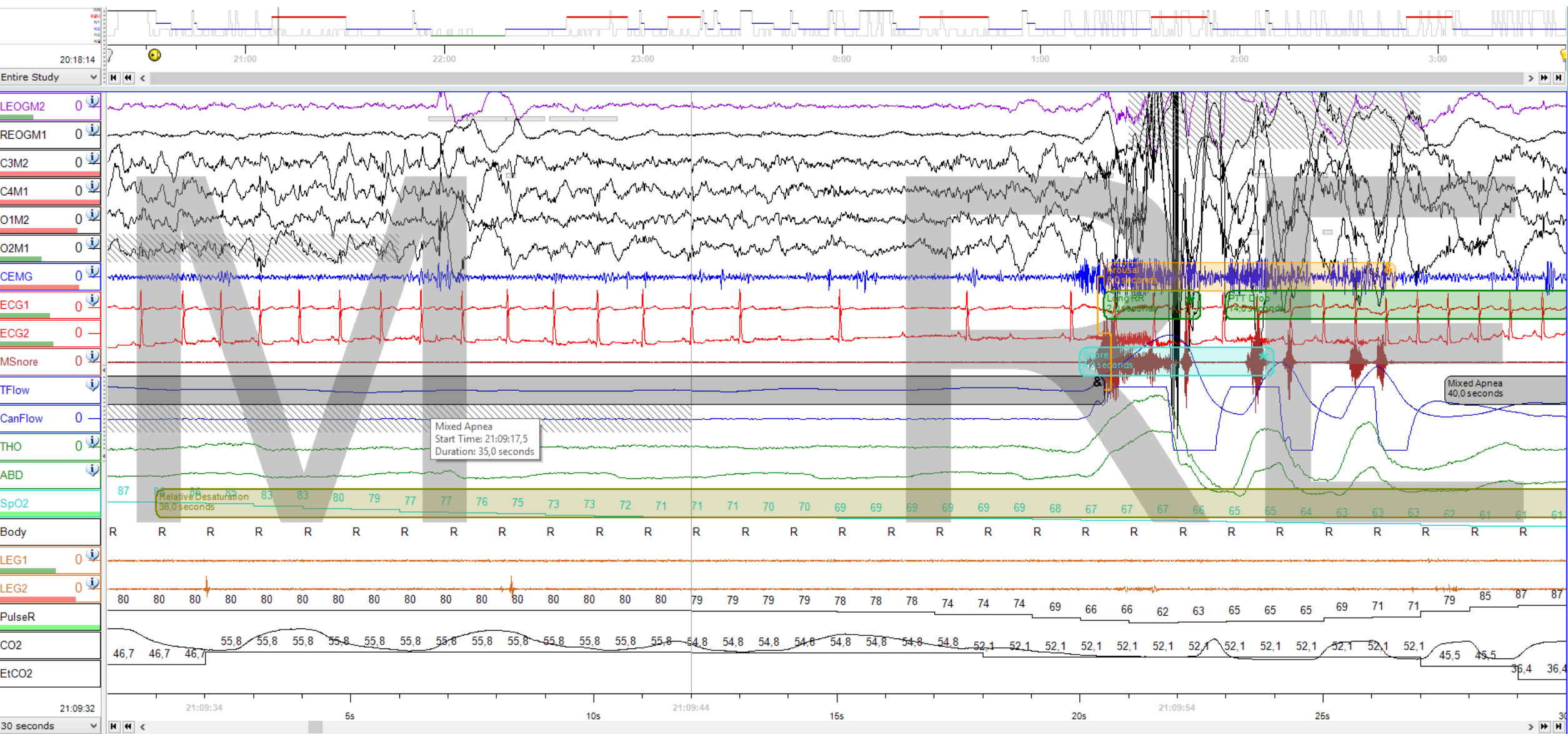
All night PSG trend - Male, 47 yo, AHI=60,7/hTST



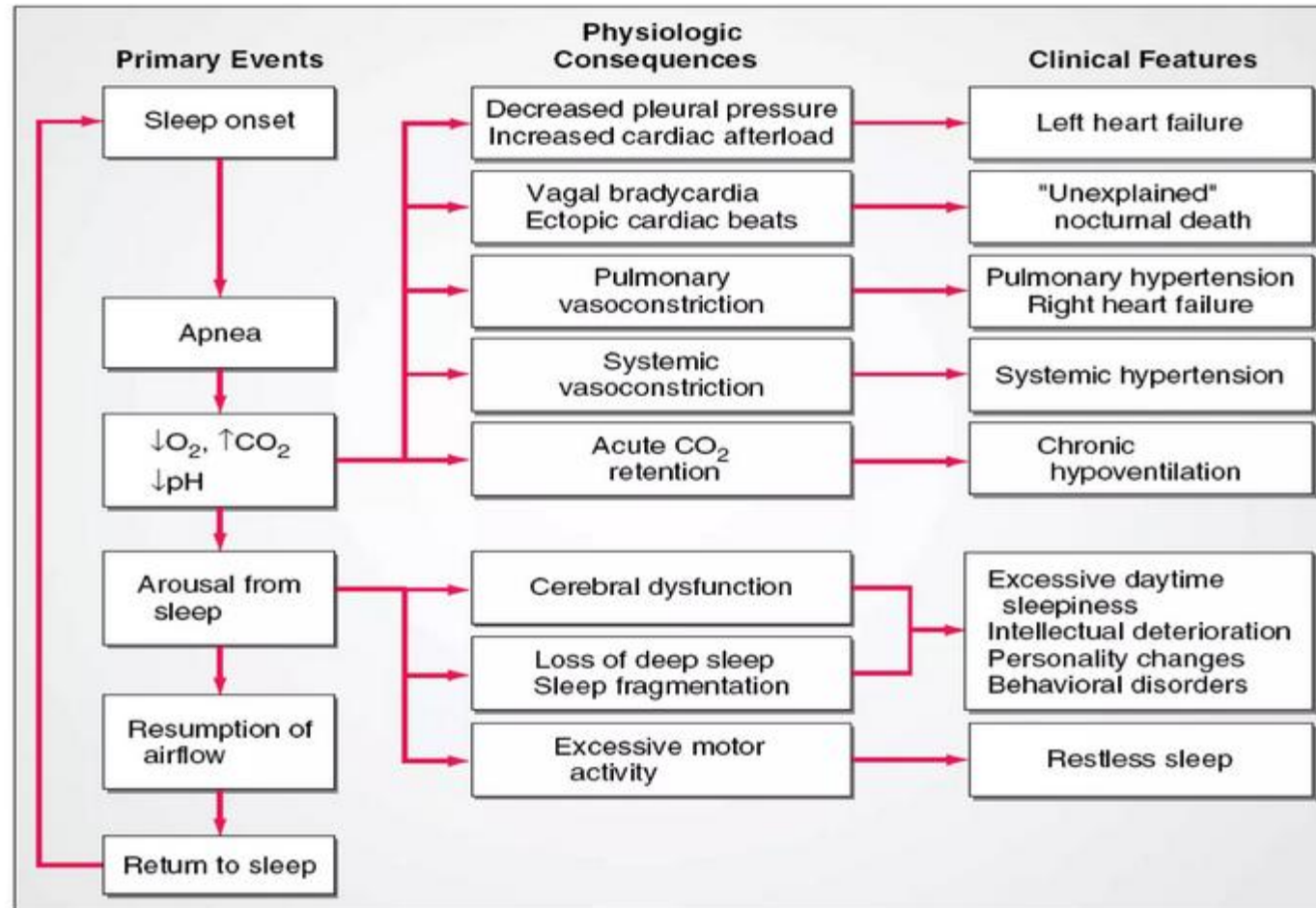
Extrasystoles during mixed apnea&desaturation, REM sleep



Mr.XY:Asystoles during REM&apnoic episodes, desaturation to SpO2 61%, hypercapnia



Consequences





"OK, Mrs. Tully. We want you to relax, get a good night's sleep, and we'll evaluate any sleep issues that you have."