Current Definitions for Sleep Disordered Breathing in Adults

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The Charge

FDA is seeking to promote innovation and expedite the clinical development of devices intended for the diagnosis and treatment of Sleep Disordered Breathing (SDB). How should the following conditions (including their severity, e.g., mild, moderate, severe, if appropriate) be defined for the purpose of creating appropriate inclusion/exclusion criteria for a clinical study for SDB devices?

- Apnea
- Hypopnea
- Sleep Disordered Breathing (SDB)
- Obstructive Sleep Apnea Syndrome (OSAS)
- Central Sleep Apnea Syndrome (CSAS)
- Primary Snoring

http://www.emergingtruths.com/tower_of_babel/tower_of_babel.html

Terminology

- Sleep-Disordered Breathing
  - Umbrella term for a constellation of sleep-related breathing disorders and abnormalities of respiration during sleep that do not meet criteria for a disorder

- Obstructive sleep apnea disorders
- Central sleep apnea syndromes
- Sleep-related hypoventilation disorders
- Sleep-related hypoxemia
- Primary snoring
- Catathrenia

AASM Style Guide for Sleep Medicine Terminology, November 2015.
ICSD-3, 2014.

Obstructive Sleep Apnea (OSA) Syndrome
Center for Medicare/Medicaid Services

- Definition 1:
  - AHI or RDI ≥ 5 events/hour and ≤ 14 events/hour
  - Documents symptoms of excessive daytime sleepiness, impaired cognition, mood disorders or insomnia, or documented hypertension, ischemic heart disease, or history of stroke

- Definition 2:
  - AHI or RDI ≥ 15 events/hour

CMS. NCD for CPAP Therapy for OSA (240.4)
Version Date 3/13/2008.

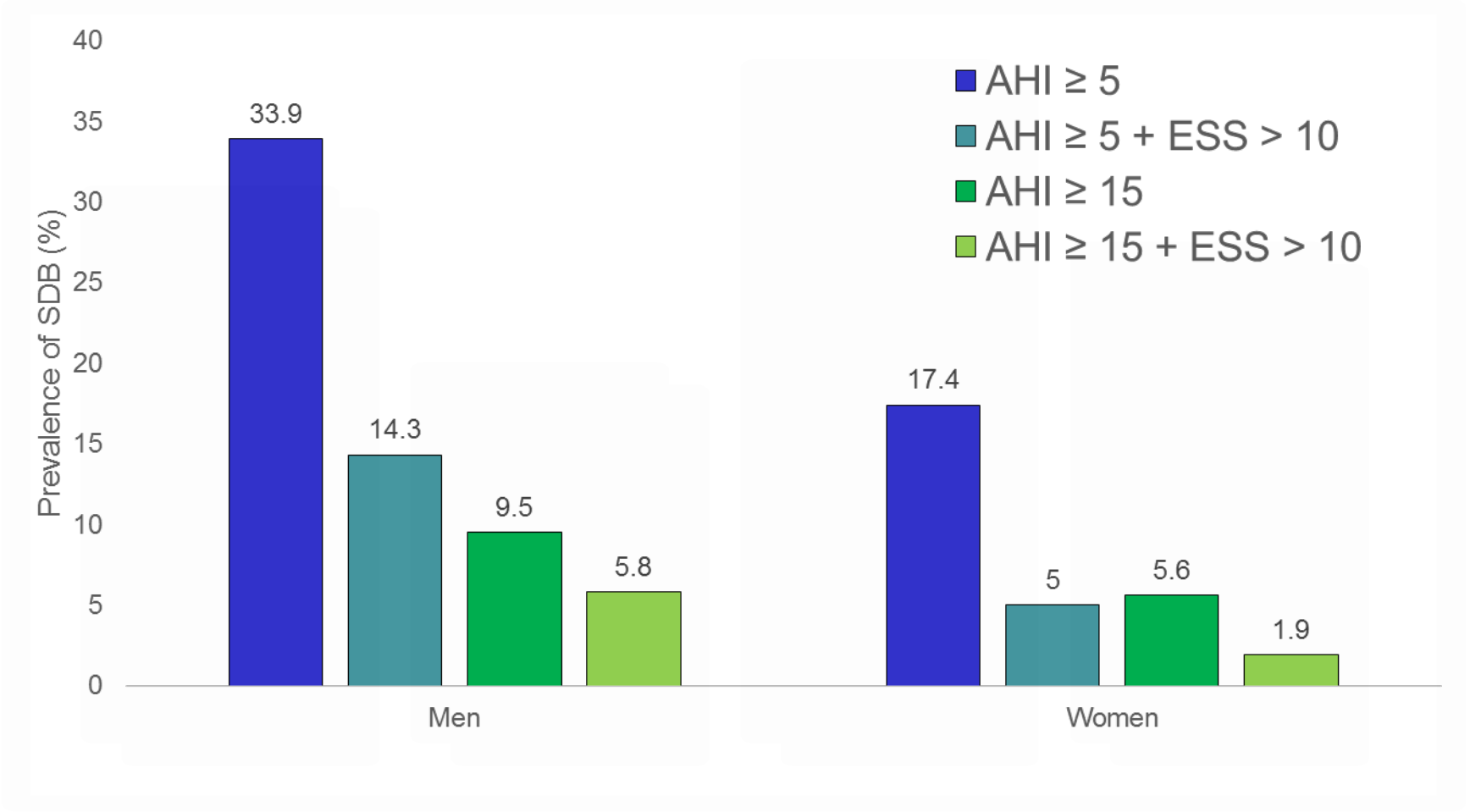
Obstructive Sleep Apnea (OSA) Syndrome
AASM ICSD-3

- Definition 1:
  - PSG or HSAT demonstrates ≥ 5 obstructive respiratory events per hour of sleep
  - The presence of one or more of the following:
    - The patient complains of sleepiness, non-restorative sleep, fatigue, or insomnia symptoms
    - The patient wakes with breath holding, gasping or choking
    - The bed partner or other observer reports habitual snoring, breathing interruptions or both during the patient's sleep.
    - The patient has been diagnosed with hypertension, a mood disorder, cognitive dysfunction, coronary artery disease, stroke, congestive heart failure, atrial fibrillation, or type 2 diabetes mellitus

- Definition 2:
  - PSG or HSAT demonstrates ≥ 15 obstructive respiratory events per hour of sleep

AASM. ICSD-3, 3rd edition, 2014

Prevalence of SDB – Effect of sleepiness symptoms



Peppard P, et al. AJE 2013; 177:1006-1014.

Central Sleep Apnea (CSA) Syndromes

A collection of disorders characterized by central sleep apnea events:

- CSA with Cheyne-Stokes Respiration (CSR)
- CSA due to a medical disorder without CSR
- CSA due to high altitude periodic breathing
- CSA due to a medication or substance
- Primary CSA

AASM. ICSD-3, 3rd edition, 2014

Central Sleep Apnea (CSA) Syndromes
AASM ICSD-3

- PSG demonstrates all of the following:
  - ≥ 5 central apneas/hypopneas per hour of sleep
  - # of central apneas/hypopneas is > 50% of the total number of apneas and hypopneas
  - ONLY for CSB: Pattern of ventilation meets criteria for CSB
- At least one of the following symptoms:
  - Sleepiness
  - Difficulties initiating or maintaining sleep, frequent awakenings, or non-restorative sleep
  - Awakening short of breath
  - Snoring
  - Witnessed apneas

AASM. ICSD-3, 3rd edition, 2014

Primary Snoring

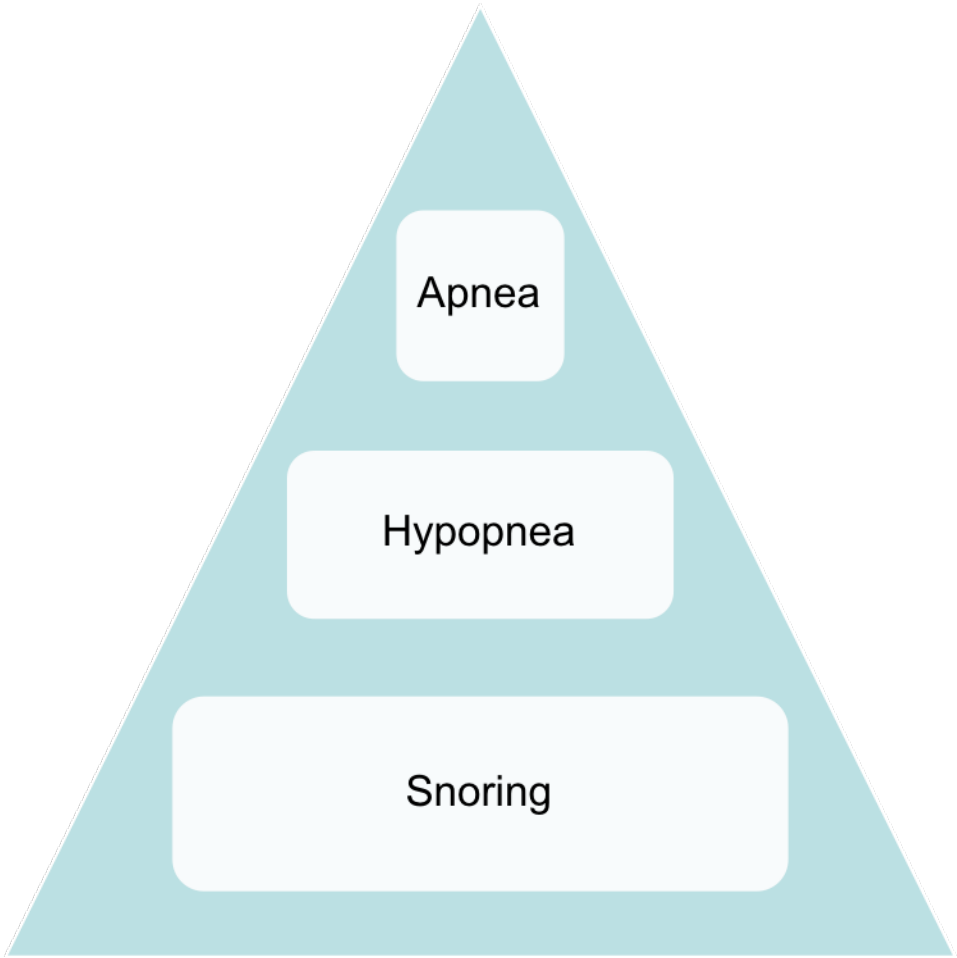
- A respiratory sound generated in the upper airway that typically occurs during inspiration but may also occur in expiration.
- Intensity varies and often will disturb the bed partner's sleep or awaken the patient.
- Snoring without daytime sleepiness/fatigue or evidence of OSA is called primary snoring.

AASM. ICSD-3, 3rd edition, 2014

Terminology

- Apnea
- Hypopnea
- Respiratory effort related arousals
- Snoring
- Central vs. obstructive events
- Periodic breathing

AASM Style Guide for Sleep Medicine Terminology, November 2015.
ICSD-3, 2014.


Apnea
Hypopnea
Snoring

Sensors

Monitoring airflow

- **Pneumotachograph** – direct flow measurement – gold standard
- **Nasal pressure transducer** – used for hypopnea identification or apnea identification when thermal sensor not available
- **Oronasal thermal sensor** – typically used for apnea identification

Alternatives when above not available

- Respiratory Inductive plethysmography (RIP) – sum or flow derived signals
- Polyvinylidene fluoride (PVDF) sum

Sensors

Monitoring effort

- Esophageal manometry – gold standard – invasive
- Dual thoracoabdominal RIP
- Dual thoracoabdominal PDVF belts

Oxygen saturation

- Pulse oximetry with maximum signal averaging time ≤ 3 seconds

Snoring

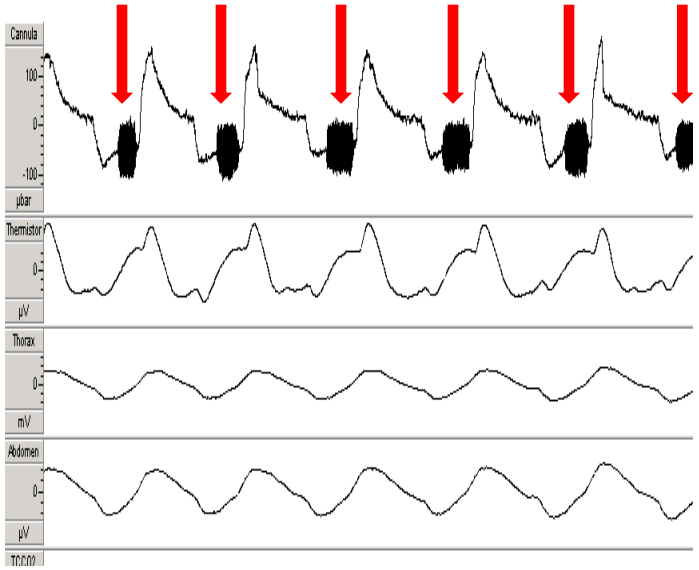
- typically monitored by an acoustic sensor, piezoelectric sensor or nasal pressure transducer.

Signal processing

- Electrode impedances
- Digital resolution
- Sampling rate
- Filtering

Snoring

- A respiratory sound generated in the upper airway that typically occurs during inspiration but may also occur in expiration
- Cardinal symptom of OSA
- Snoring without daytime sleepiness/fatigue or evidence of OSA is called primary snoring.



No clear standardized definitions of snoring

A Definition of Snoring Based on Nasal Pressure Transducer (visualization)

- Lee SA, et al.
  - # of Snores/hour (snore – obvious deflection from background)
  - >3 snores in a 30 second epoch = snoring epoch
  - Snoring sleep time = # of snore epochs/ sleep time
    - Mild: 0-25%
    - Moderate: 25-50%
    - Severe: > 50%

Lee SA, et al. Sleep 2008; 31:1207-1213.

Example Definitions of Snoring Based on Nasal Pressure Transducer (sound)

- Guzman MA, et al.
  - Snore with peak decibel ≥ 40 dB
    - WHO notes increasing adverse health effects wthn average night noise level is ≥ 40 dB/year
  - % of all breaths

- Kim J, et al.
  - Adaptive threshold method
  - ≥ 4x higher than background noise and up to 3s
  - Synchronization with inspiration

Guzman M, et al. JCSM 2017; 13:703-711.
Kim J, et al. J Sleep Res 2017; 26:147-150.
WHO. Night Noise Guidelines for Europe, 2009

How SDB events are defined

- Duration
  - ≥ 10 seconds
- Amplitude
  - How much – 10%, 30%, 50%, 90%?
- Consequence
  - Desaturation
  - Micro-arousal from sleep

Respiratory Events

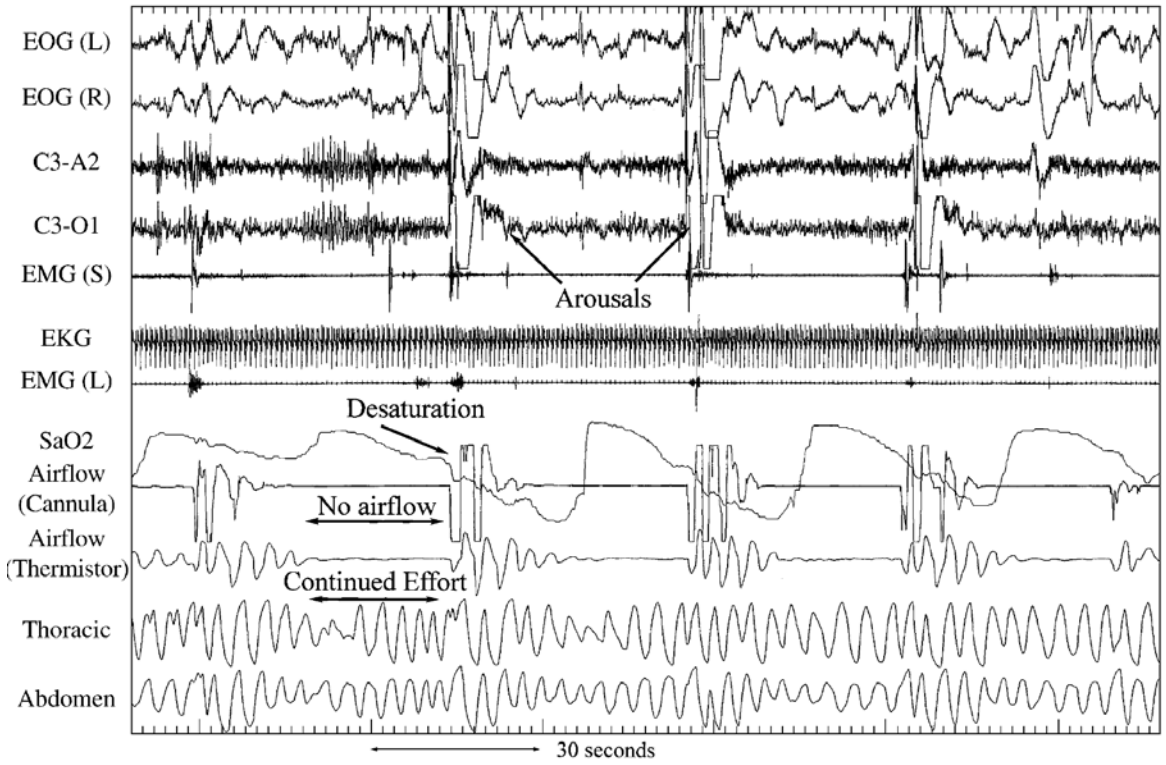
- Apnea
  - A drop in peak signal excursion by ≥ 90% of pre-event baseline for ≥ 10 seconds using an oronasal thermal signal, PAP device flow, or an alternative apnea sensor.
  - No requirement for a desaturation or an arousal

AASM Manual for the Scoring of Sleep and Associated Events, v2.5

Apnea Subtypes

Obstructive Apnea

Continued or increased inspiratory effort throughout the entire period of absent airflow.

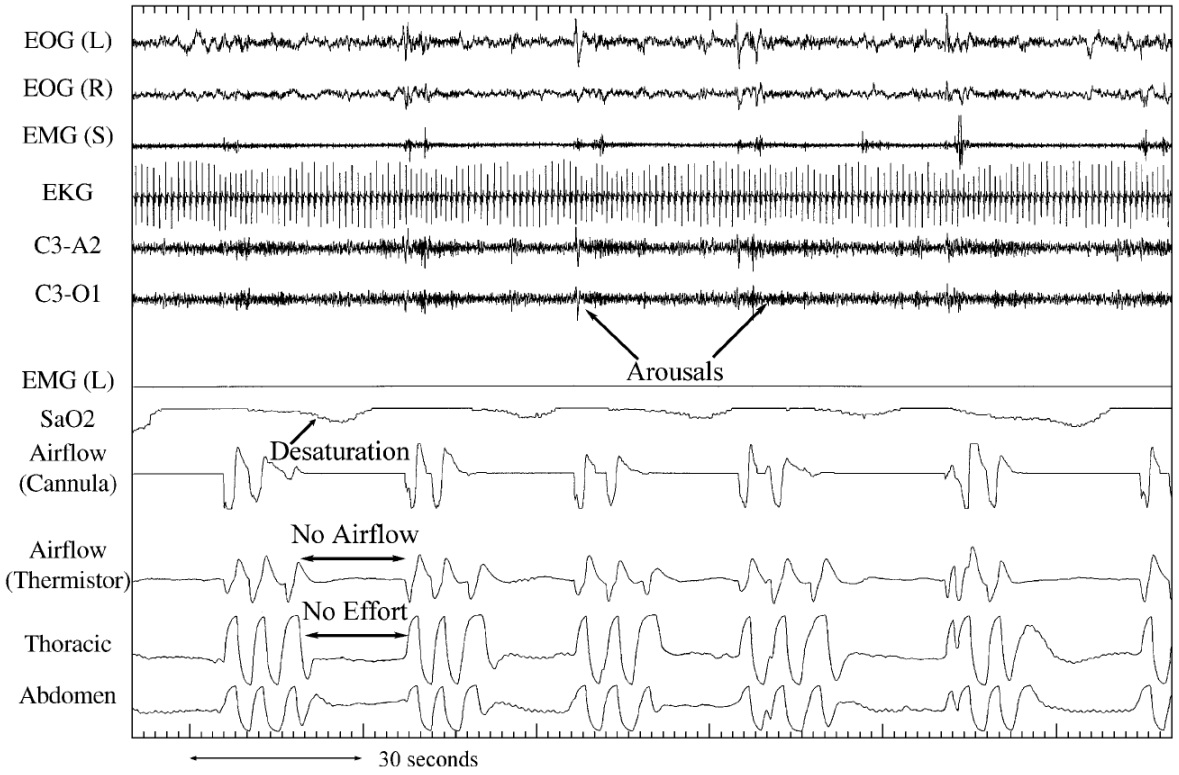


AASM Manual for the Scoring of Sleep and Associated Events, v2.5
Stierer T. Anesth Clin N Am 2005;23:405

Apnea Subtypes

Central Apnea

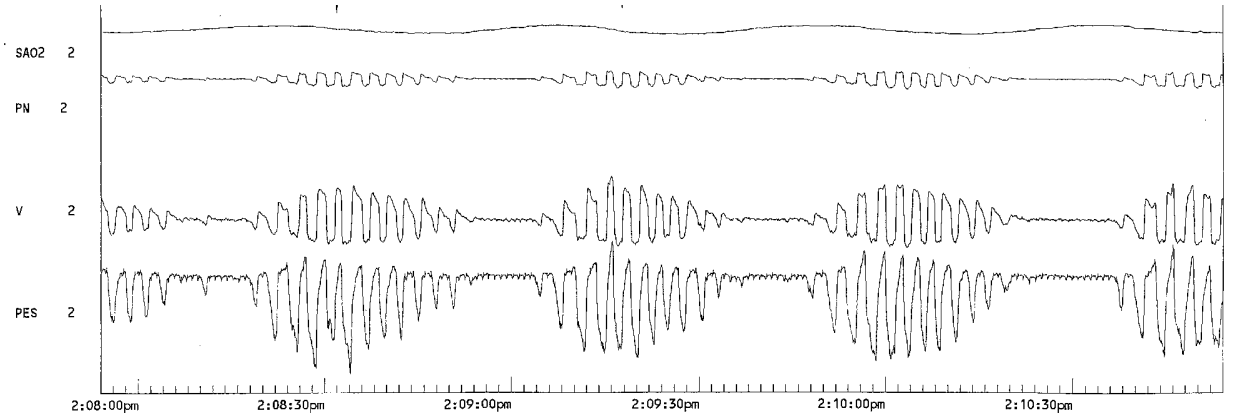
Absent inspiratory effort throughout the entire period of absent airflow.



AASM Manual for the Scoring of Sleep and Associated Events, v2.5
Stierer T. Anesth Clin N Am 2005;23:405

Respiratory Events

- Cheyne-Stokes Breathing
  - Episodes of ≥ 3 consecutive central apneas and/or hypopneas separated by a crescendo/decrescendo change in breathing amplitude with a cycle length of ≥ 40 seconds, AND
  - There are ≥ 5 central apneas and/or central hypopneas per hour of sleep associated with the crescendo/decrescendo breathing pattern recorded over ≥ 2 hours of monitoring.



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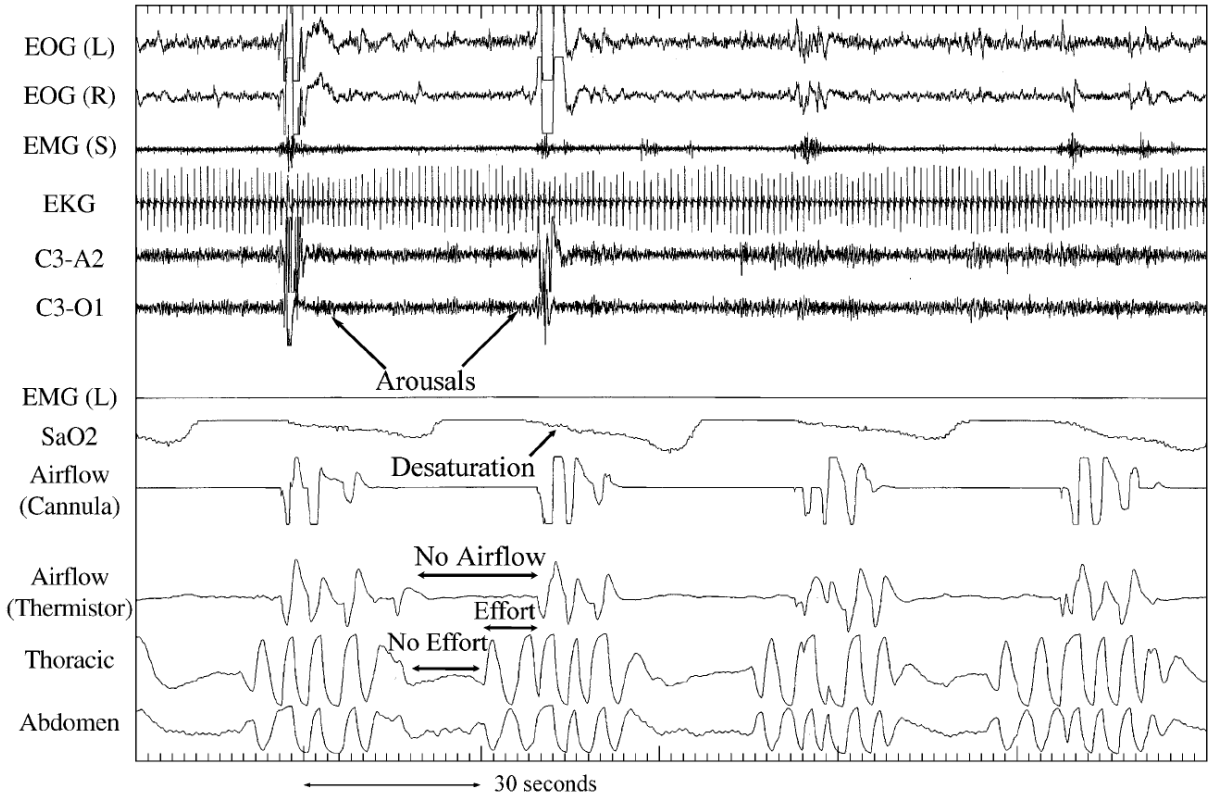
Apnea Subtypes

Mixed Apnea

Absent inspiratory effort in the initial portion of the event, followed by resumption of inspiratory effort in the second portion of the event.



AASM Manual for the Scoring of Sleep and Associated Events, v2.5
Stierer T. Anesth Clin N Am 2005;23:405

Respiratory Events

- Hypopnea (Recommended)
  - A drop in peak signal excursion by ≥ 30% of pre-event baseline for ≥ 10 seconds using nasal pressure, PAP device flow, or an alternative hypopnea sensor, **AND**
  - There is a ≥ 3% oxygen desaturation from the pre-event baseline OR the event is associated with an arousal.

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Respiratory Events

- Hypopnea (Acceptable) – used by CMS
  - A drop in peak signal excursion by ≥ 30% of pre-event baseline for ≥ 10 seconds using nasal pressure, PAP device flow, or an alternative hypopnea sensor.
  - There is a ≥ 4% oxygen desaturation from the pre-event baseline.

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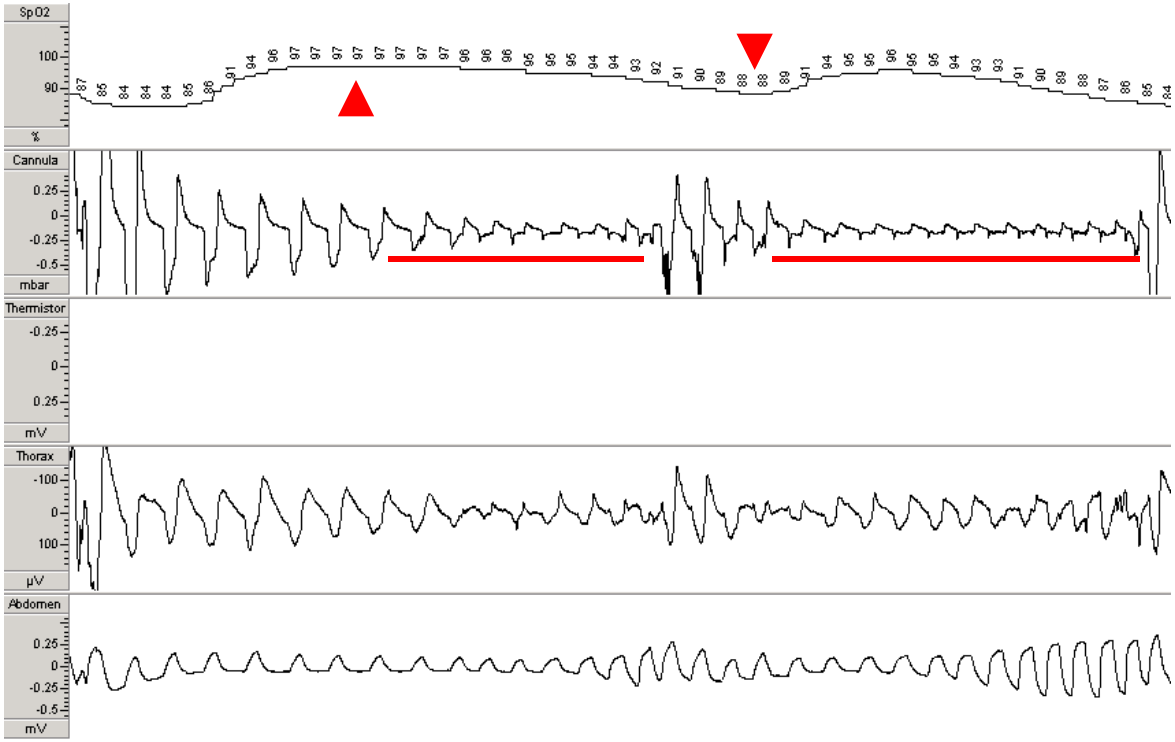
Respiratory Events

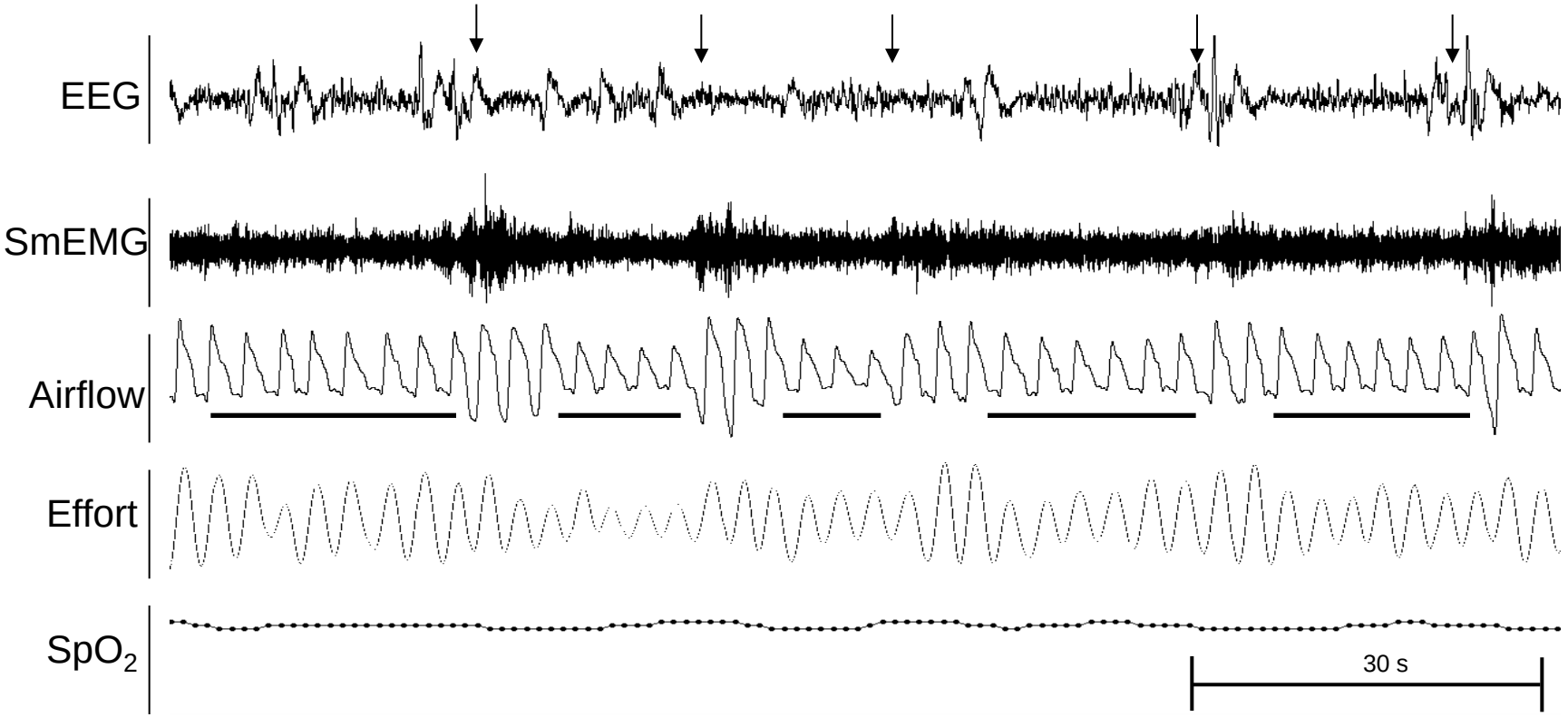
- Hypopnea – Chicago criteria
  - A drop in peak signal excursion of airflow by > 50% of pre-event baseline for ≥ 10 seconds OR
  - A discernible reduction in airflow associated with either a > 3% oxygen desaturation from the pre-event baseline or an arousal.

AASM Task Force. SRBD in Adults: Recommendations for Syndrome Definition and Measurements Techniques in Clinical Research. Sleep 1999;22:667.

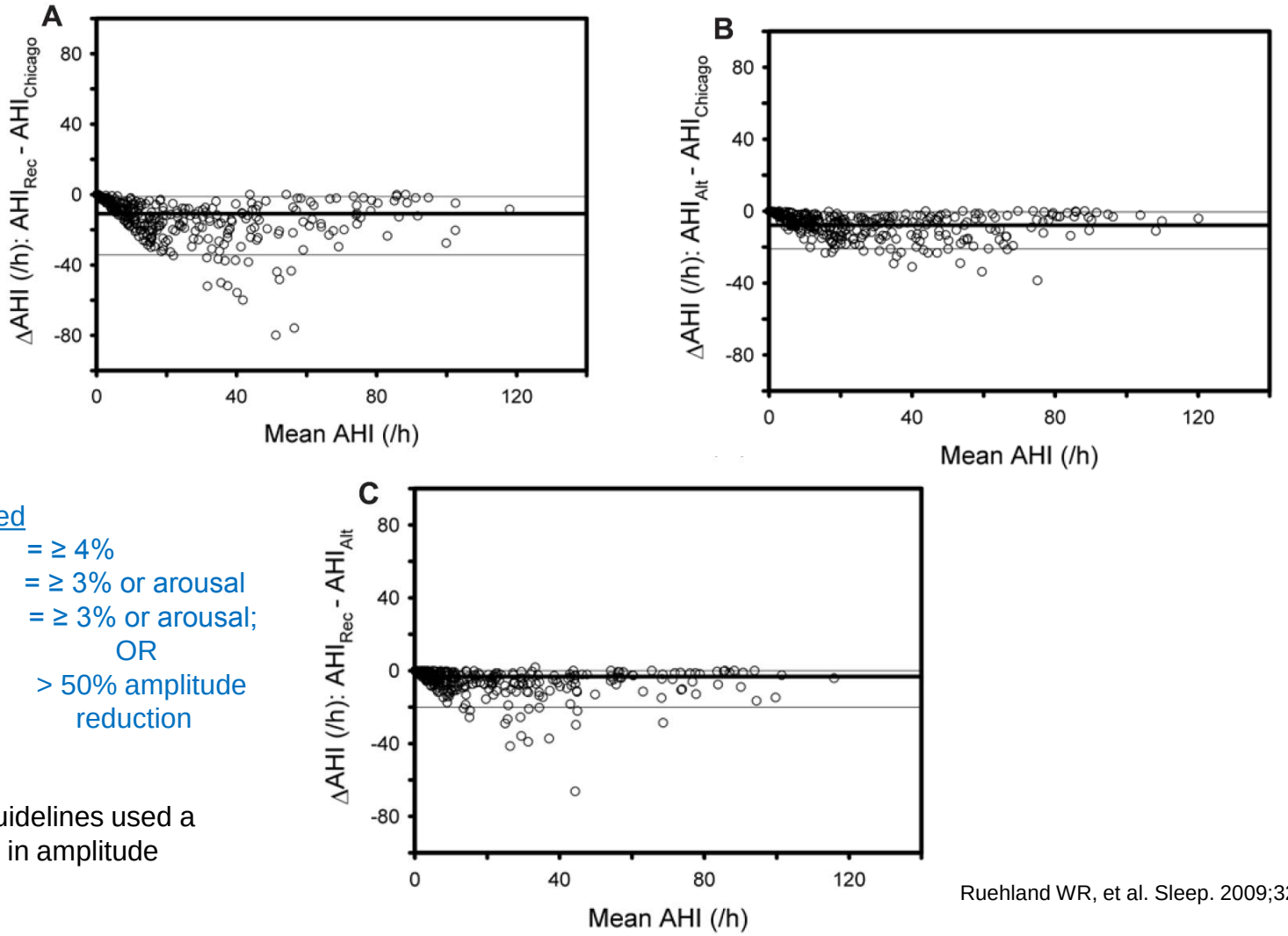
Obstructive Hypopneas with Desaturations



Obstructive Hypopnea with Arousals



Effect of Selection of Different Hypopnea Criteria



Definitions examined

- AASM AHI Rec: = ≥ 4%
- AASM AHI Alt: = ≥ 3% or arousal
- Chicago = ≥ 3% or arousal; OR > 50% amplitude reduction

AASM 2007 guidelines used a 30% reduction in amplitude

Ruehland WR, et al. Sleep. 2009;32:150-7.

Effect of Selection of Different Hypopnea Criteria

Table 3—Percentage of Patients Classified as Positive for OSA by Method and AHI Threshold for OSA Diagnosis (n = 323)

Hypopnea Definition	AHI Cut-off (events/h)		
	≥ 5	≥ 15	≥ 30
Chicago	92%	67%	42%
Recommended	59%	38%	22%
Alternative	76%	50%	31%

$P < 0.001$ for all pair-wise comparisons at all thresholds examined.

Table 4—Equivalent AHI by Method for Various AHI Cut-Points

Parameter	$AHI_{Chicago}$ (events/h)		
	5	15	30
Equivalent AHI_{Rec}	1.4	4.4	10.8
Sensitivity (%)	87.2	82.5	91.0
Specificity (%)	85.2	82.1	89.9
Equivalent AHI_{Alt}	2.8	8.9	18.4
Sensitivity (%)	91.6	90.3	95.5
Specificity (%)	92.6	90.6	95.2

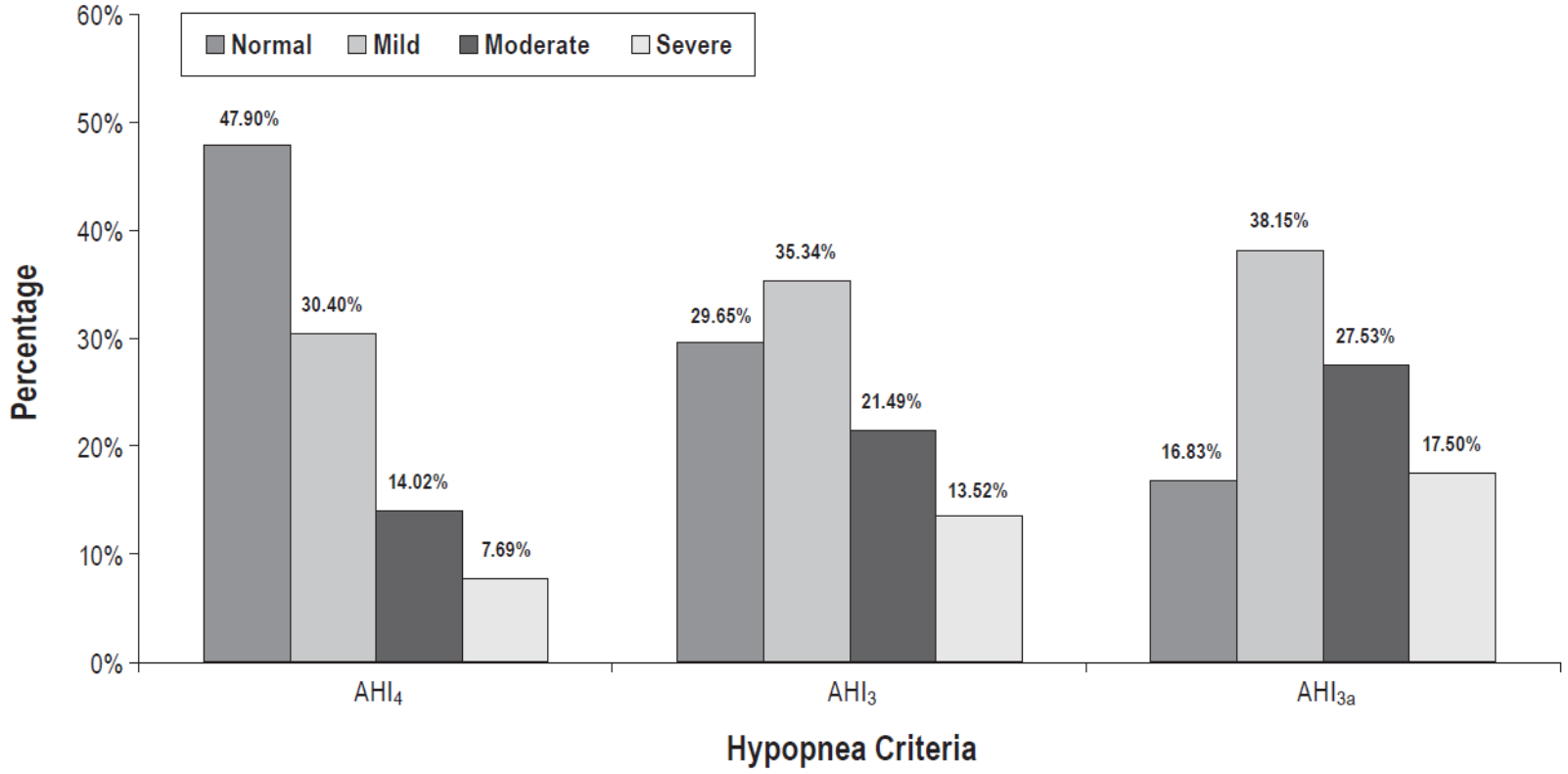
Definitions examined

- AASM AHI Rec: = ≥ 4%
- AASM AHI Alt: = ≥ 3% or arousal
- Chicago = ≥ 3% or arousal; OR > 50% amplitude reduction

AASM 2007 guidelines used a 30% reduction in amplitude

Ruehland WR, et al. Sleep. 2009;32:150-7.

Effects of Hypopnea Classification on SDB Severity



Ho V, et al. Sleep. 2015;38:1887-1892.

Inter-scorer Reliability
Anchoring to Hypoxemia is More Reliable

	Scorers			
	912	**914**	**915**	**ICC**
AHI-flow (using flow only)	25.9	32.9	27.4	0.74
AHI-flow and ≥ 3 % desaturation	11.35	9.97	10.8	0.97
AHI-flow and ≥ 4 % desaturation	6.1	5.4	5.75	0.99
AHI-flow and arousal **only**	5.6	7.2	6.57	0.77
AHI-flow and ≥ 3 % desaturation or arousal	14.1	14.58	14.06	0.95
AHI-flow and ≥ 4% desaturation or arousal	9.75	10.8	17.3	0.94
Arousal index	13.5	20.6	17.3	0.54

Whitney CW Sleep 1998

Hypopnea subtypes

Assess for:

- Snoring during event
- Increased inspiratory flattening of the flow signal compared to baseline
- Thoracoabdominal paradox that occurs during the event

- Obstructive Hypopnea – if <u>any</u> one is present

- Central Hypopnea – if <u>none</u> are present

Many centers do not subclassify hypopneas due to inter-scorer reliability concerns

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Respiratory Events

- Respiratory effort-related arousal (*optional*)
  - Sequence of breaths lasting ≥ 10 seconds characterized by increasing respiratory effort or by flattening of the inspiratory portion of the flow signal leading to an arousal from sleep when the sequence of breaths do not meet criteria for an apnea or hypopnea

Not all centers score RERAs

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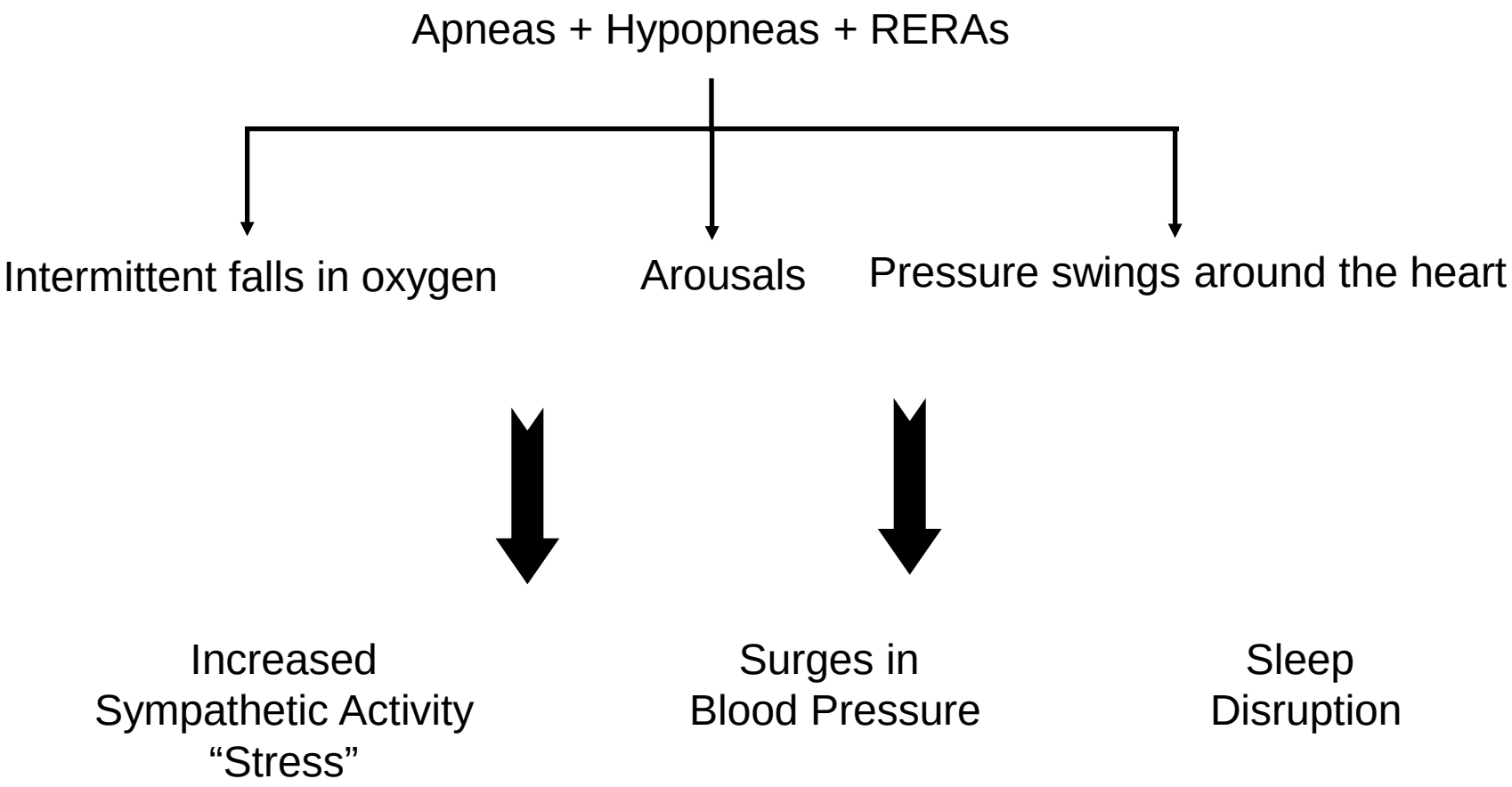
Does it Matter?



Measures of SDB severity

- Apnea-hypopnea index (AHI):
  - # of apneas + hypopneas per hour of sleep
- Respiratory disturbance index (RDI):
  - # of apneas + hypopneas + RERAs per hour of sleep
- Oxygen desaturation index (ODI):
  - ≥ 3% or ≥ 4% oxygen desaturations per hour of sleep
- Respiratory Event Index (REI):
  - # of apneas + hypopneas per hour of monitored time

Clinically Used Severity Scheme

- AHI < 5: Normal
- AHI 5 – 15: Mild
- AHI 15 – 30: Moderate
- AHI ≥ 30 Severe

- Consensus definition
- AHI ≥ 30 was chosen for severe based on an increased risk of HTN from the Wisconsin cohort (4% hypopnea criteria – discernible reduction).

AASM Task Force. SRBD in Adults: Recommendations for Syndrome Definition and Measurements Techniques in Clinical Research. Sleep 1999;22:667.

Is it All About the AHI?

"Most…studies have measured OSA with…the AHI. This degree of data reduction—from a full night of PSG to a single number—conceals a great degree of variation…that can occur between individuals with the same AHI…all commonly used OSA metrics still do not capture many facets of even the blood oxygen saturation…events (eg, depth, rapidity, and duration, clustering, sleep state and within-night variability….) that may be important…."

Peppard P Am J Respir Crit Care Med 2018

Thanks for your attention

Bill Waterson

Questions for Panel 1

- How should respiratory events be defined for clinical trials?
  - How should snoring, hypopneas, and apneas be defined?
  - Should different definitions of hypopneas be allowed?
  - Where is the balance between sensitivity and specificity?

- How should disease severity be defined for clinical trials?
  - Should there be different thresholds of AHI if different definitions are allowed?
  - Should definitions of SDB for clinical trials include symptoms?

- How should non-OSA forms of SDB defined for clinical trials involving digital health technologies?

- Should patient-reported outcomes be included in the definition of SDB?

Questions for Panel 1

For the purpose of creating appropriate inclusion/exclusion criteria for a clinical study for SDB devices, how should the FDA define?:

- Respiratory events
  - Apnea
  - Hypopnea
  - Snoring
- Clinical disorders
  - Sleep Disordered Breathing (SDB)
  - Obstructive Sleep Apnea Syndrome (OSAS)
  - Central Sleep Apnea Syndrome (CSAS)
  - Primary Snoring