Sleep Apnea Pathophysiology
-Rankin Lab of Pulmonary Med-


Skatrud


Badr


Xie


Smith


Morgan


Cheneul


Palta


Young


Marcus


Berssenbrugge


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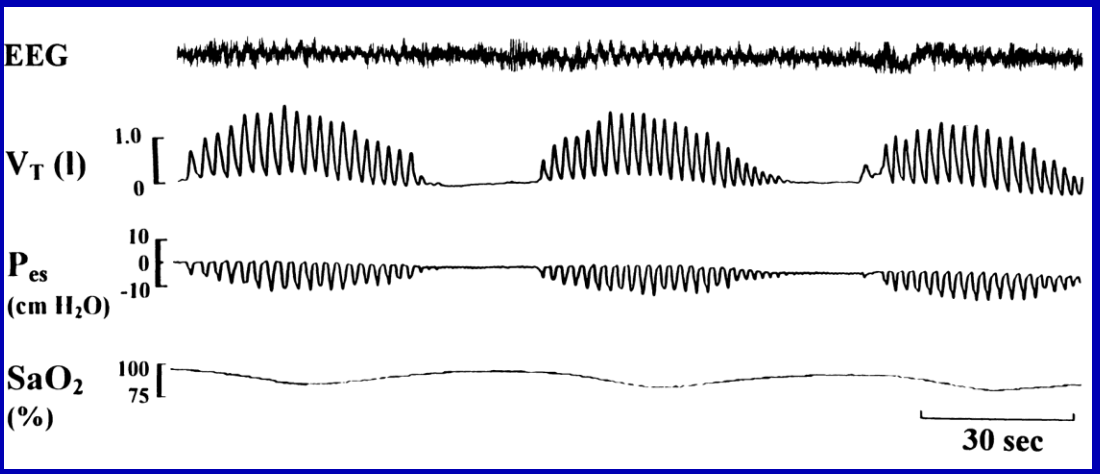
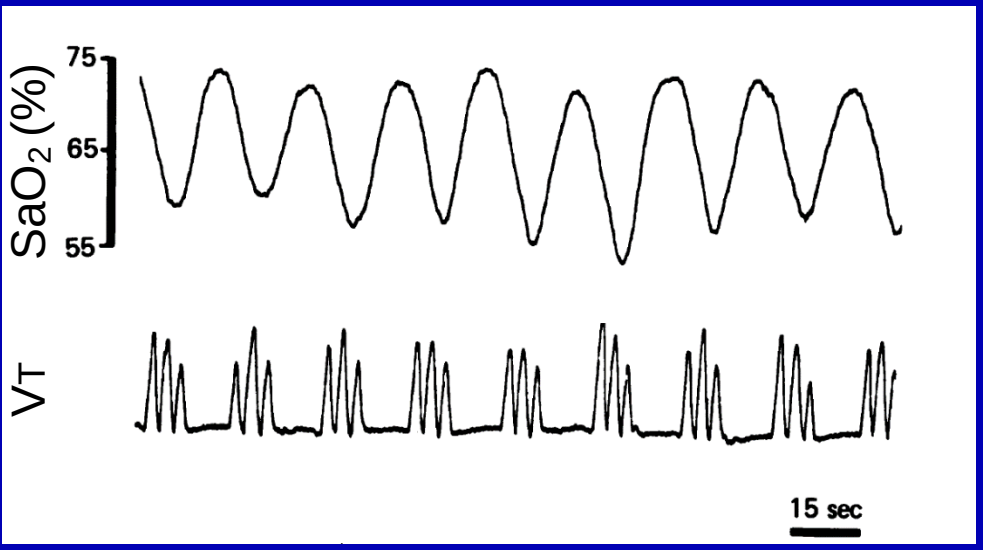
Sleep-Induced Disordered Breathing

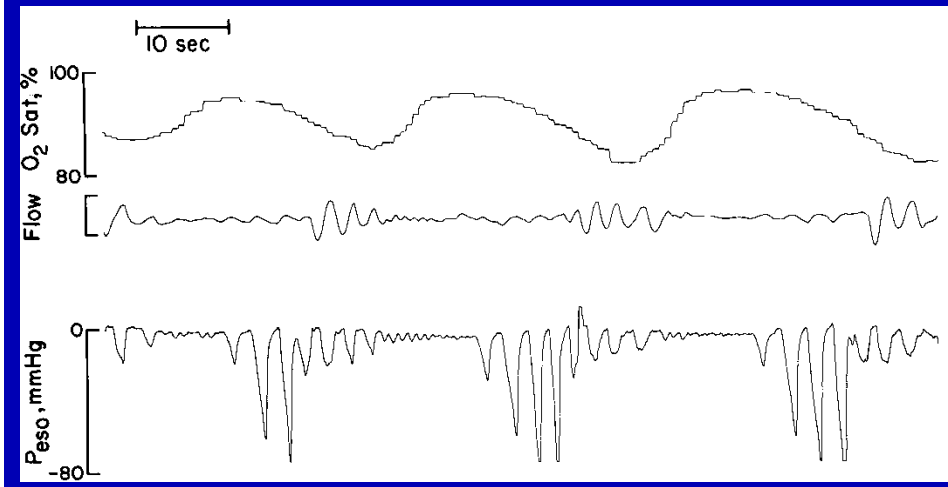


CHF

Prevalence: 34% men, 17% women
Risk:Obesity,sex, age, craniofacial
CV sequellae?Pathogenesis?

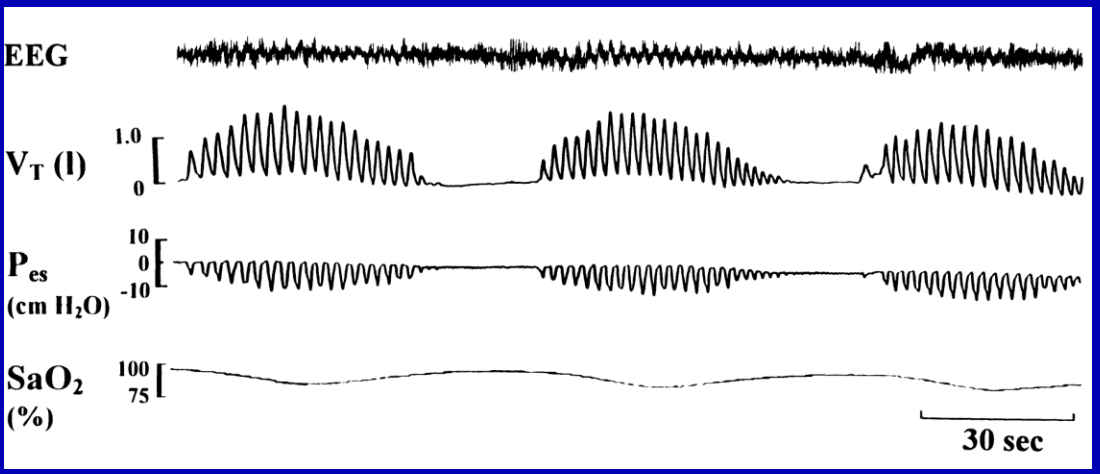


Hypoxia / Opiates

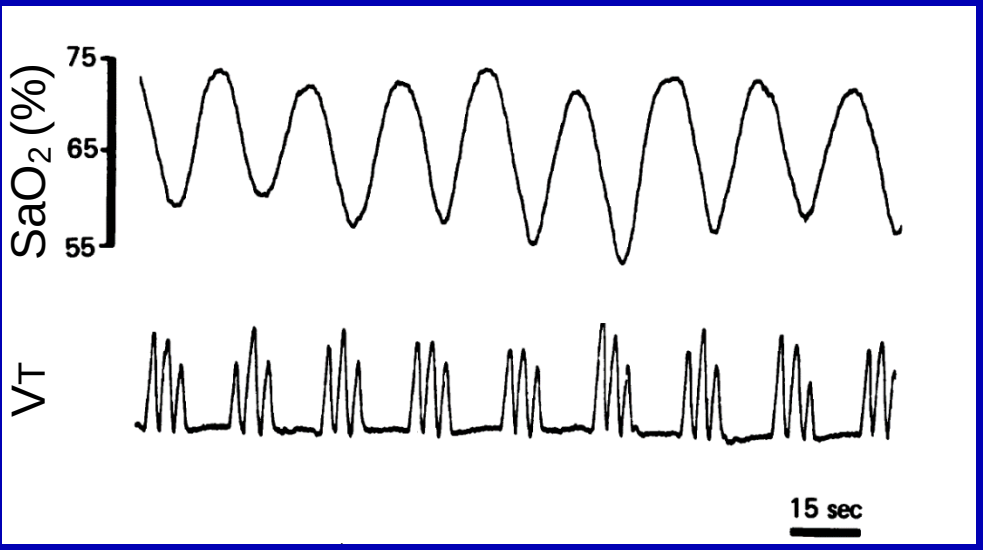


OSA

Pathogenesis of Sleep-Induced Disordered Breathing



CHF



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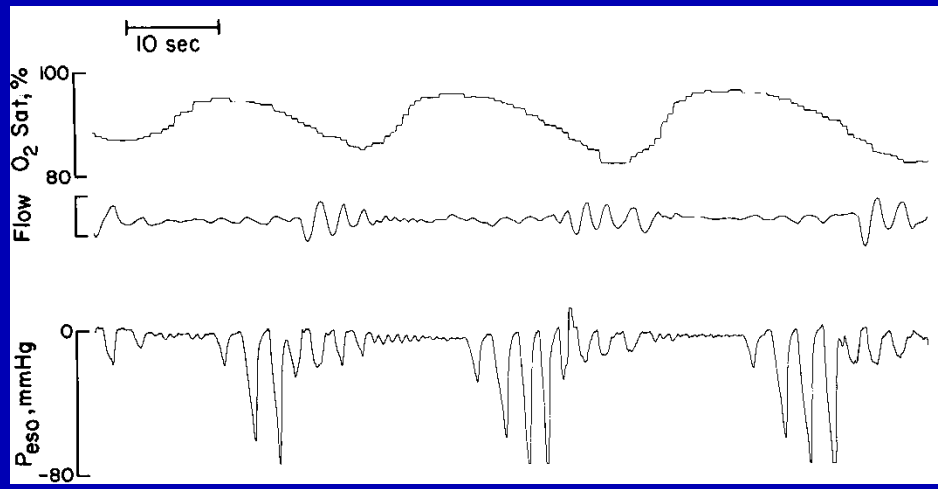
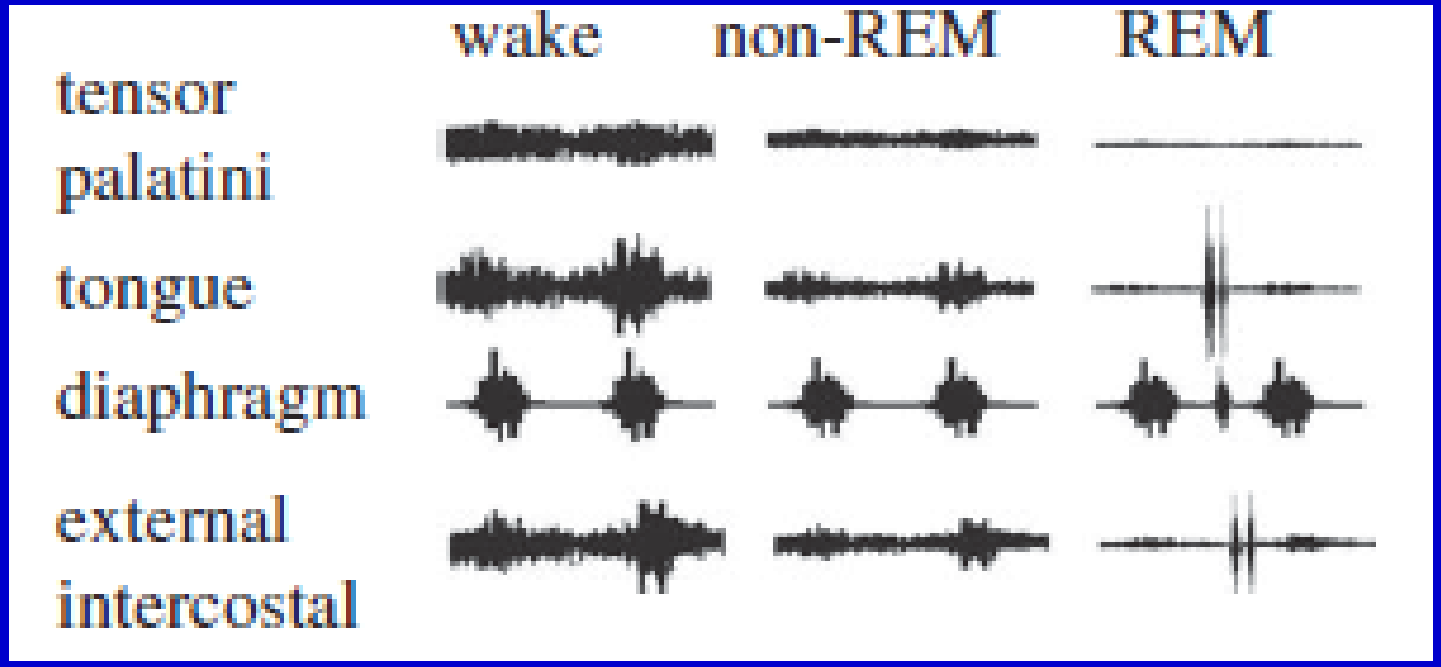


OSA

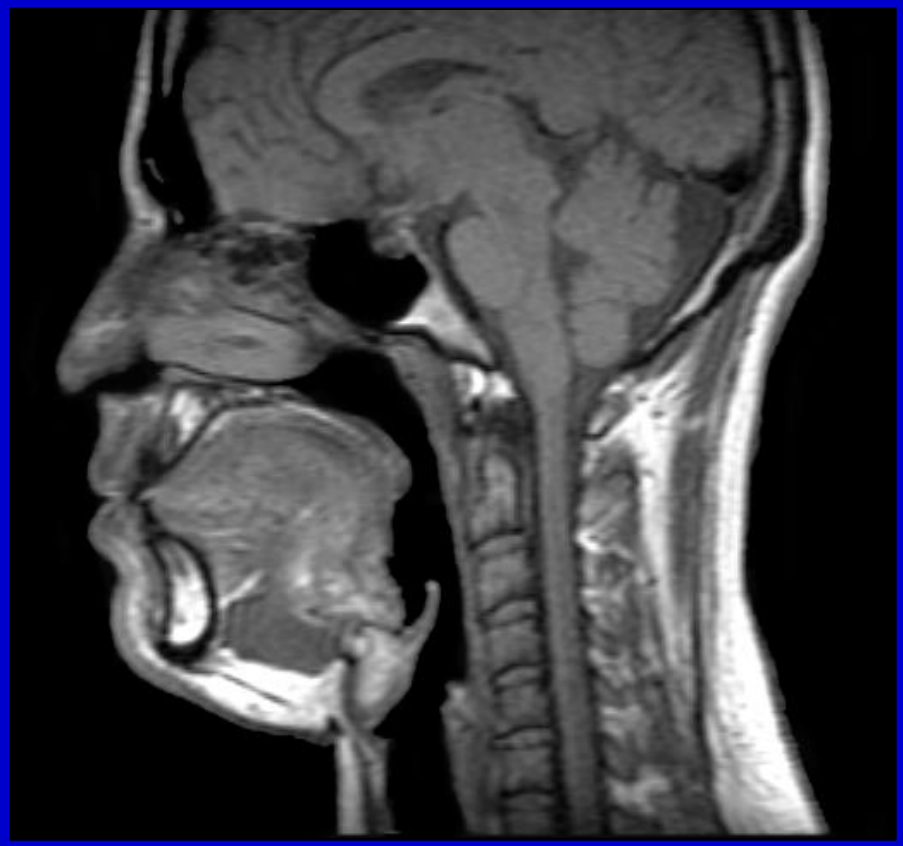
Removing the Wakefulness Resp Stimulus (Horner,2009)



-SLEEP : Suppresses orexinergic,noradrenergic,seretonergic neurons
-Unmasks sensitive chemoreception /apneic threshold
-Removes immediate load compensation

Anatomically Compromised Airway Required for OSA!

Normal [Awake] Apneic



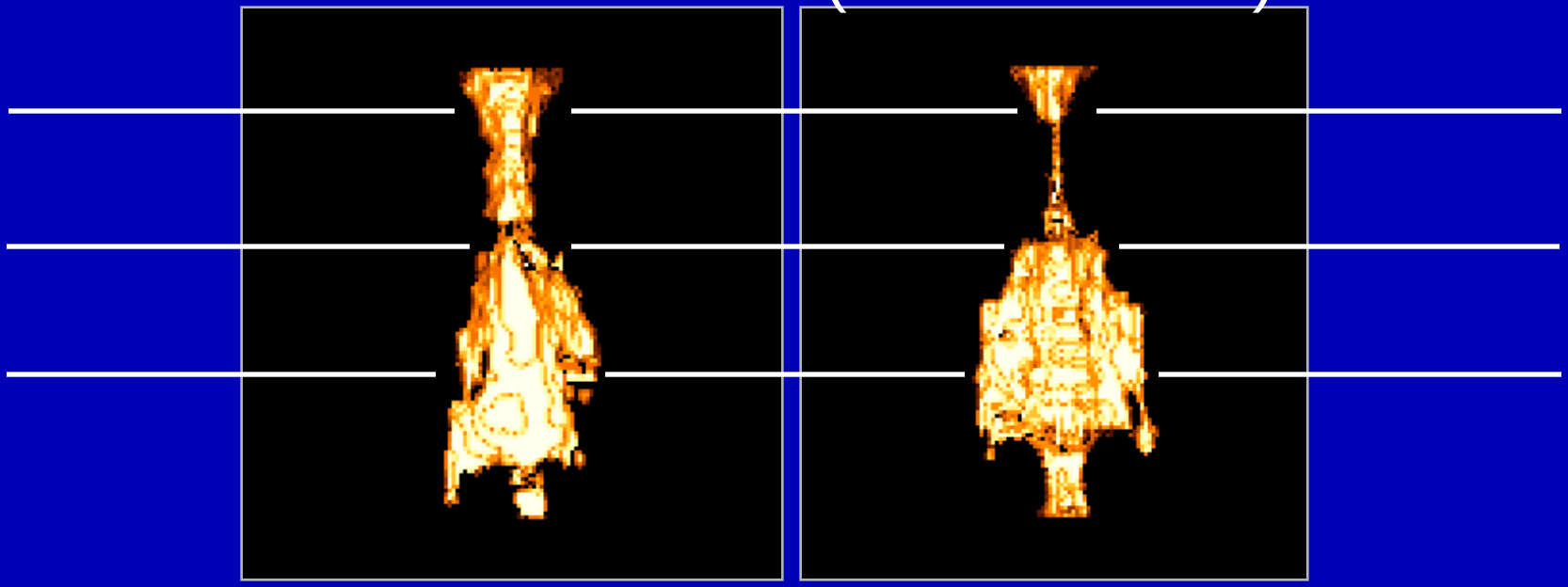
Sleep = Decreased airway dilator muscle tone, decreased lung volume /traction on upper airway, airway edema.

(Schwab, 1995)

Sleep Effect on Upper Airway Calibre in OSA

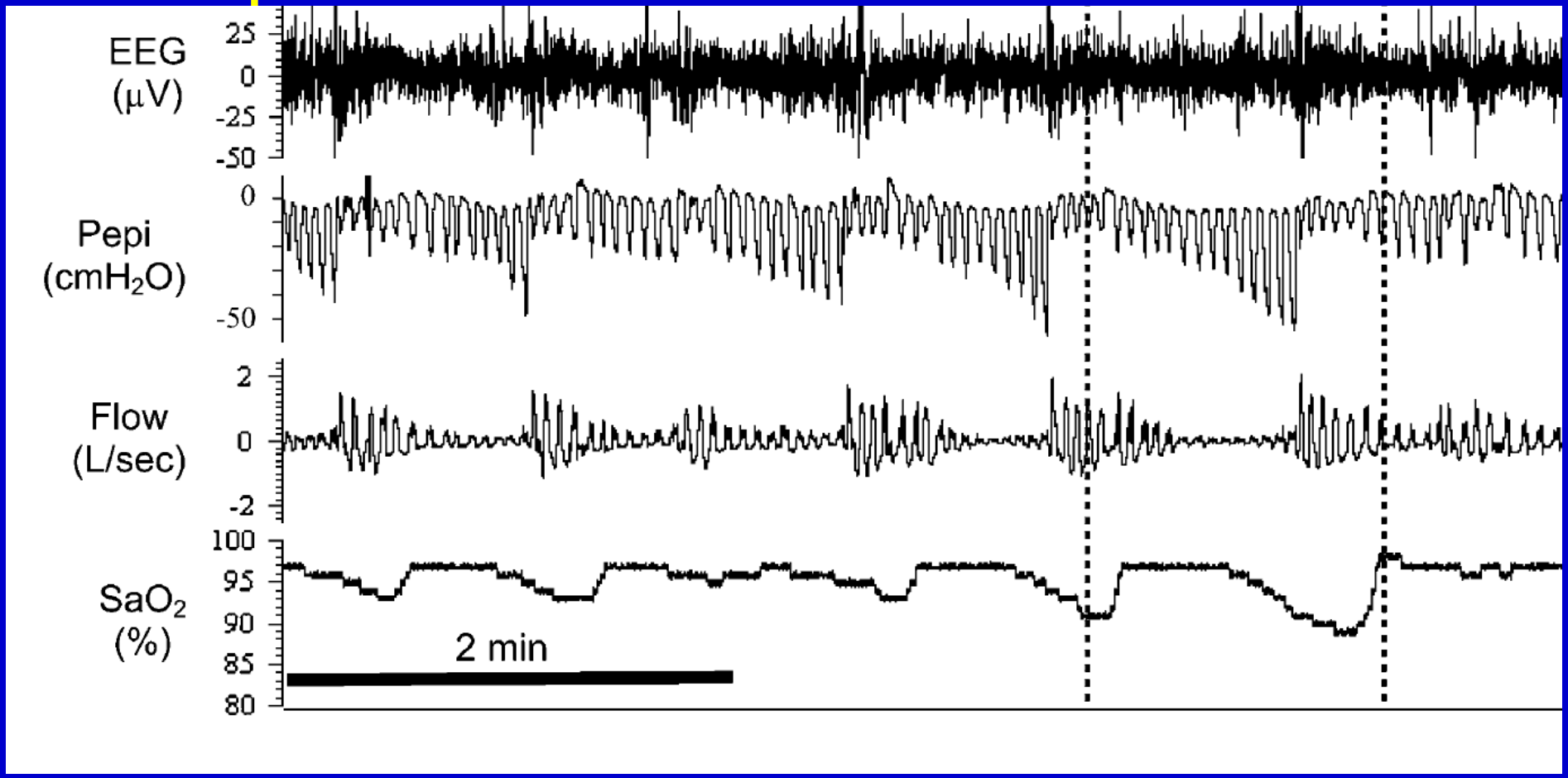
Wakefulness

Sleep Onset
(↓ Tonic EMG)



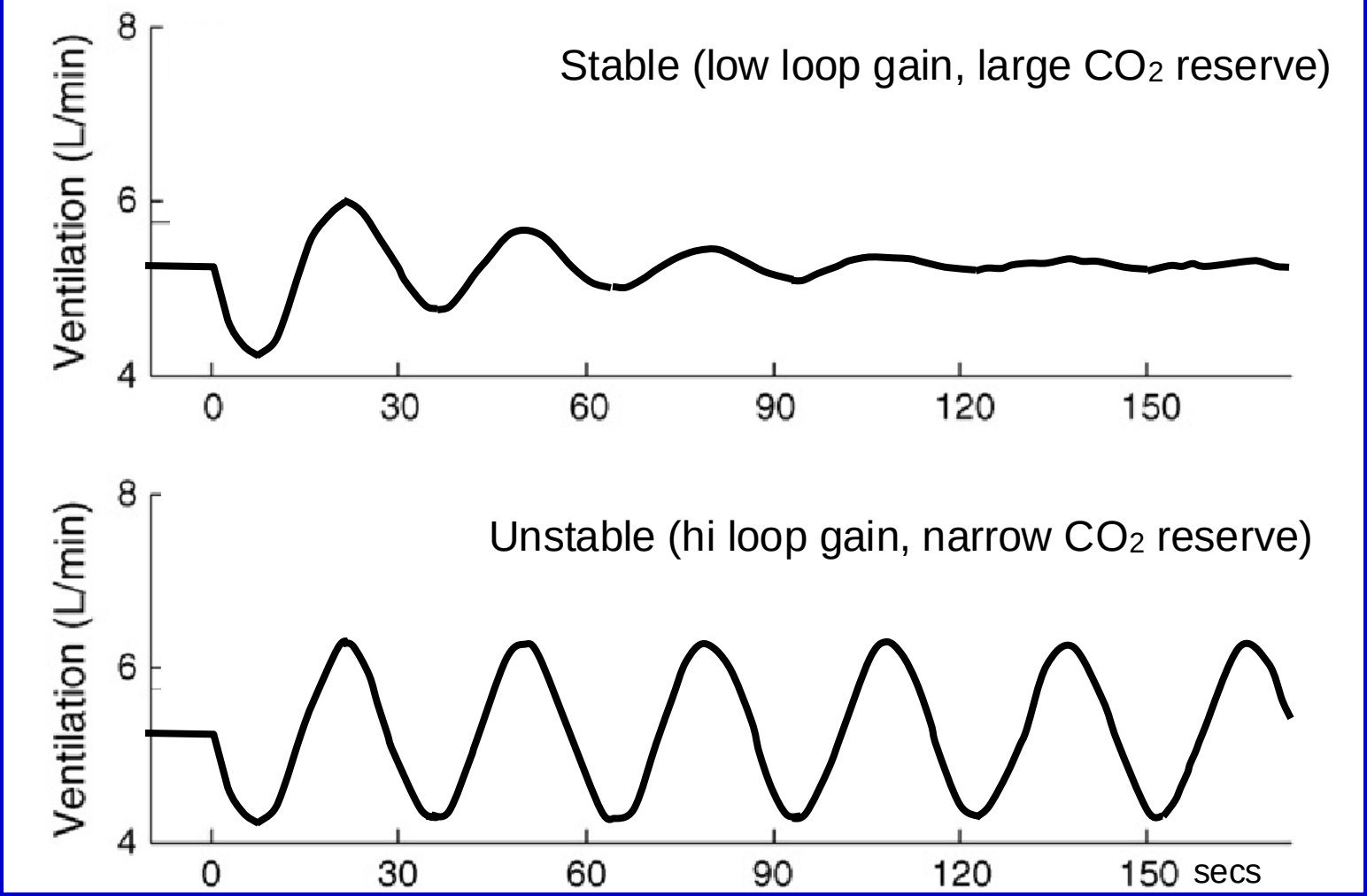
2-4x ↑ R_{UA} in most healthy humans in NREM contributing to hypoventilation (+2-6 mmHg PaCO2 >awake)

Repeated Obstructive Apneas/Arrousals/VE Overshoots

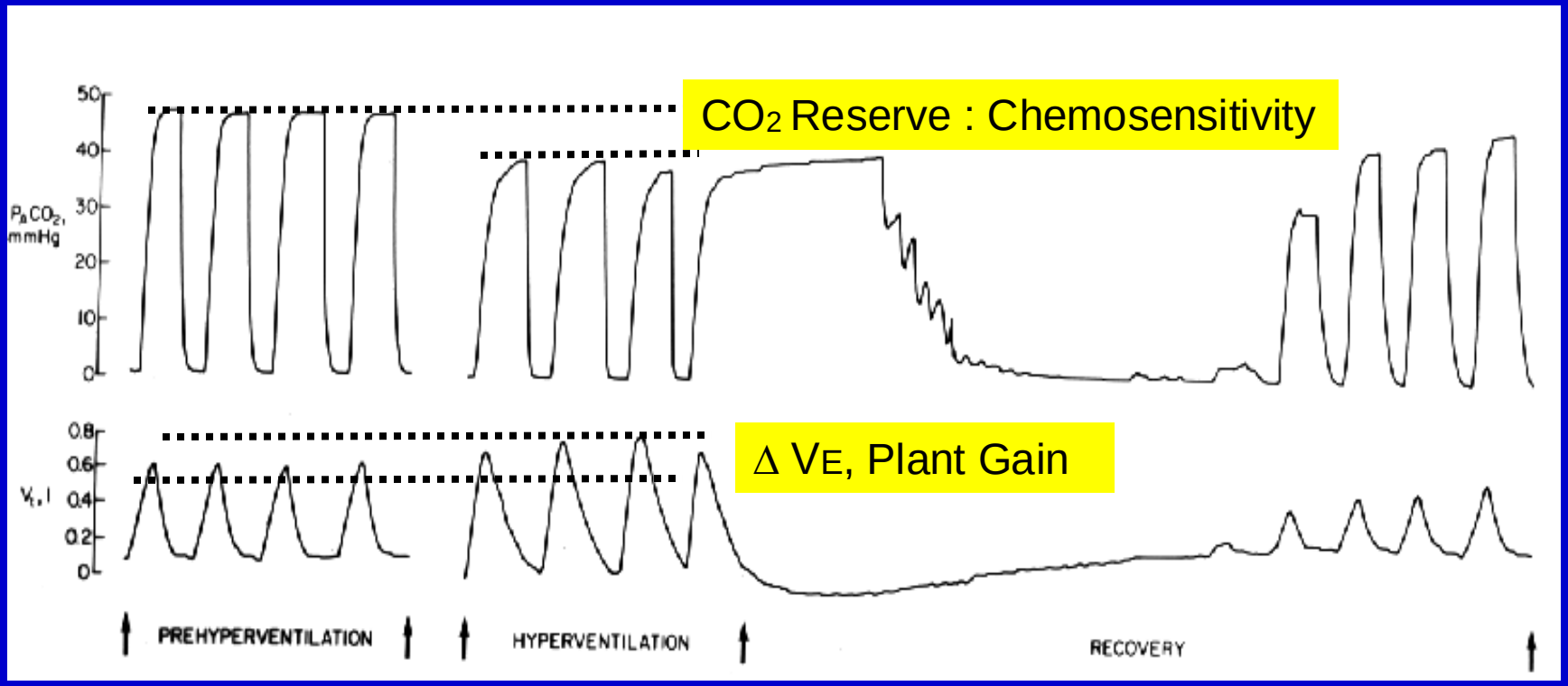


Role of resp control system chemosensitivity/ loop gain on ventilatory stability

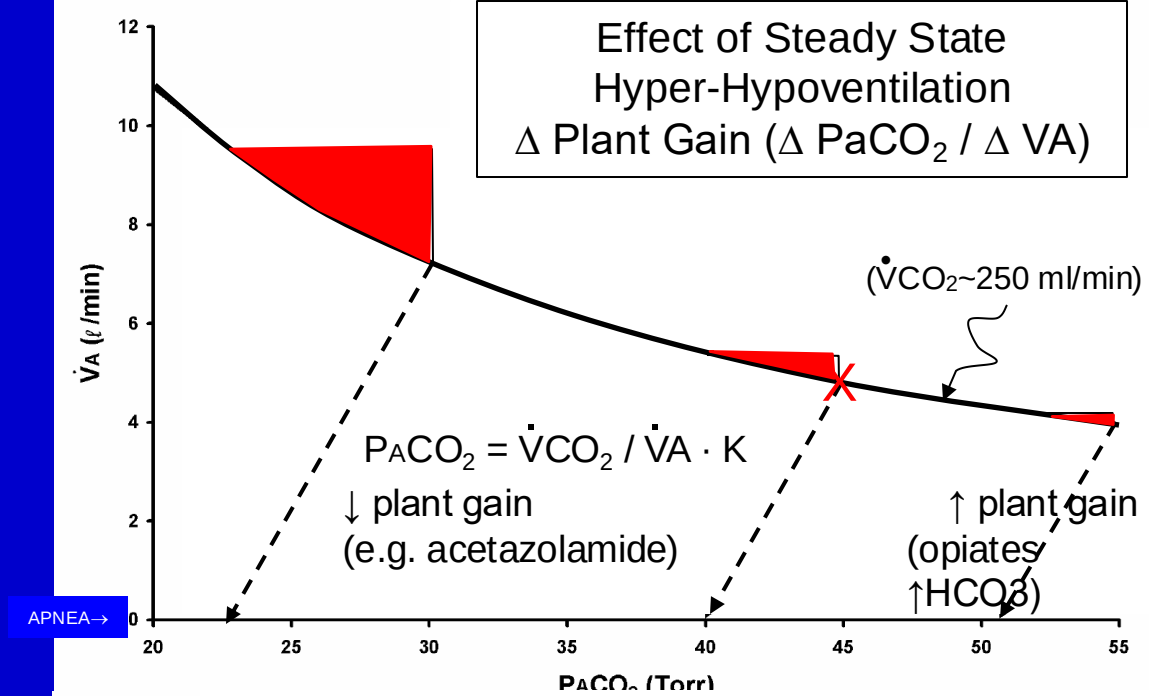
Susceptibility to Central Instability Depends On Controller, Plant Gains - CO_2 Reserve

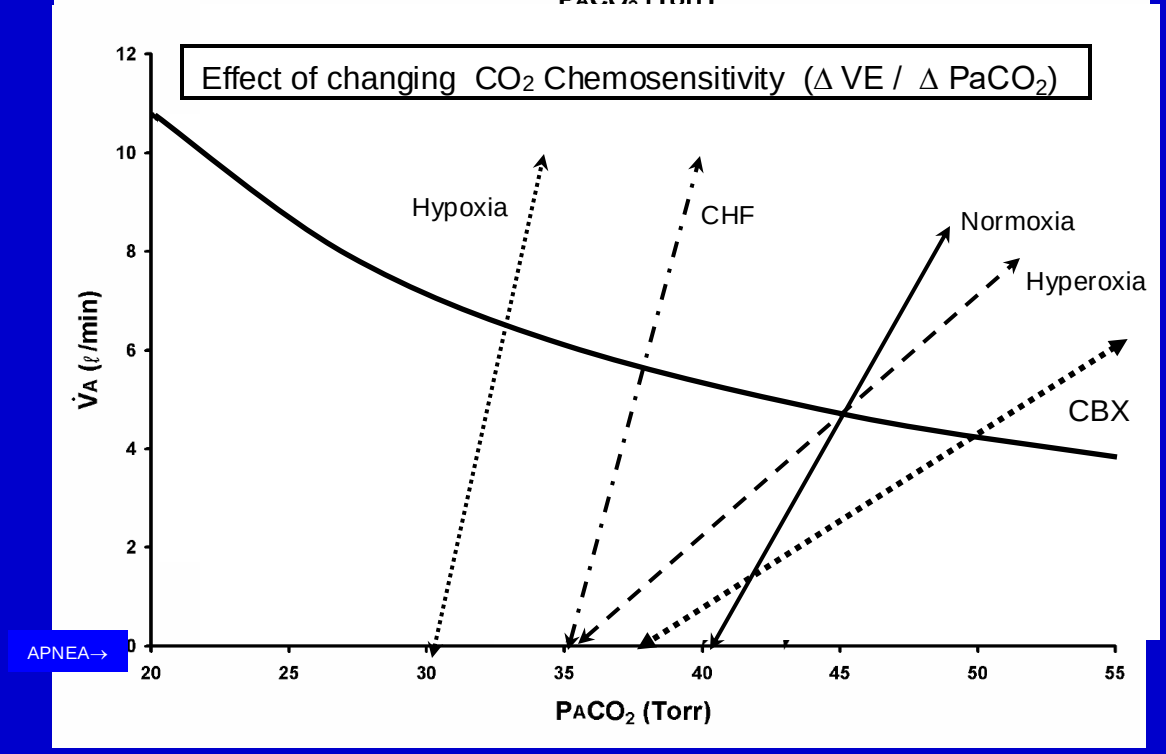


NREM Sleep Unmasks a Sensitive Hypocapnic-Induced Apneic Threshold



Susceptibility to Central Apnea / Instability determined by: chemosensitivity (ΔV_E / $\Delta PaCO_2$) and plant gain ($\Delta PaCO_2/\Delta V_E$)



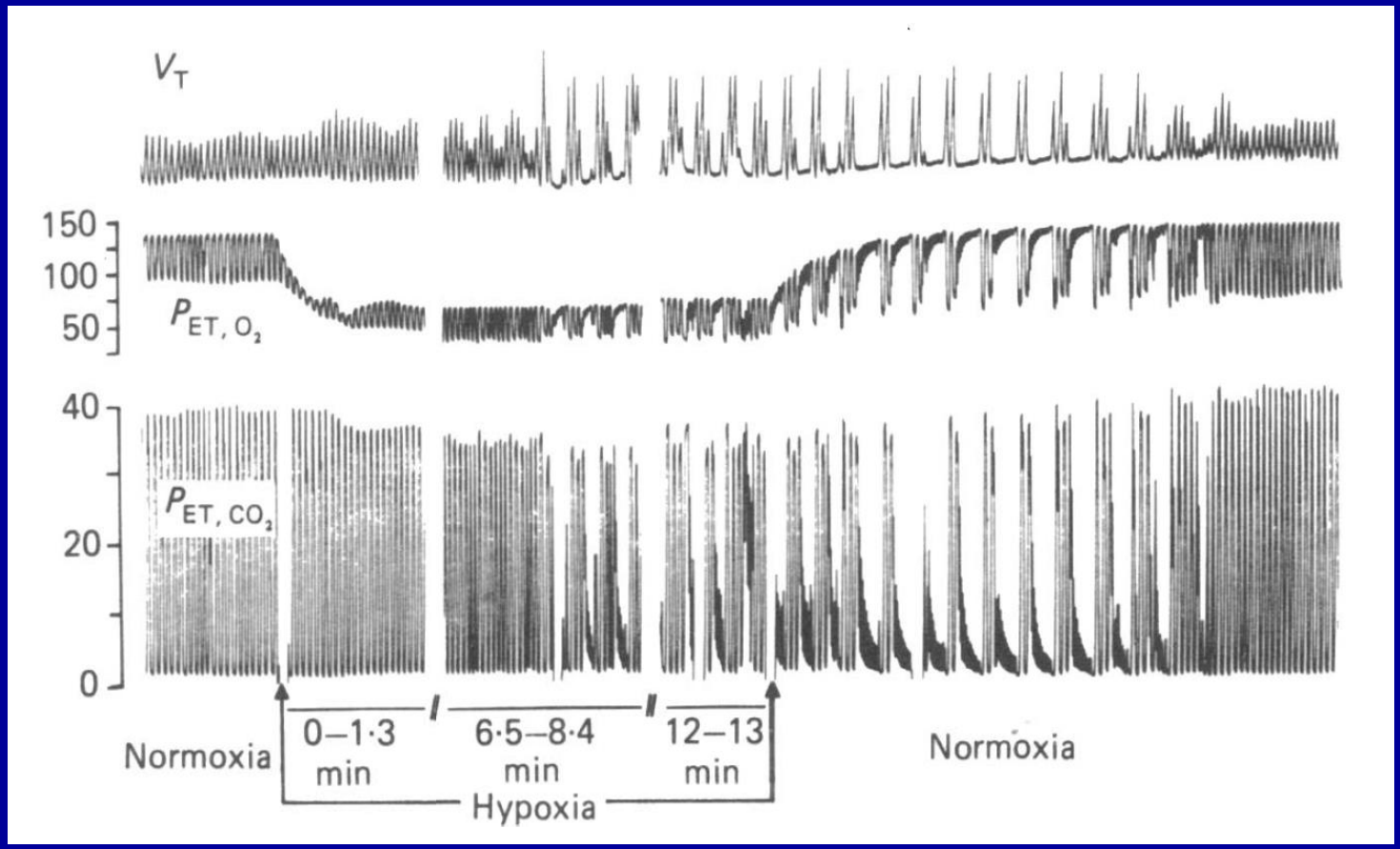


Chemoreceptor/ plant gains determine vent stability (Khoo et al, 1982, 2000)

Experimental/ clinical evidence supports engineers' models (Skatrud,Xie,et al1983-2020)

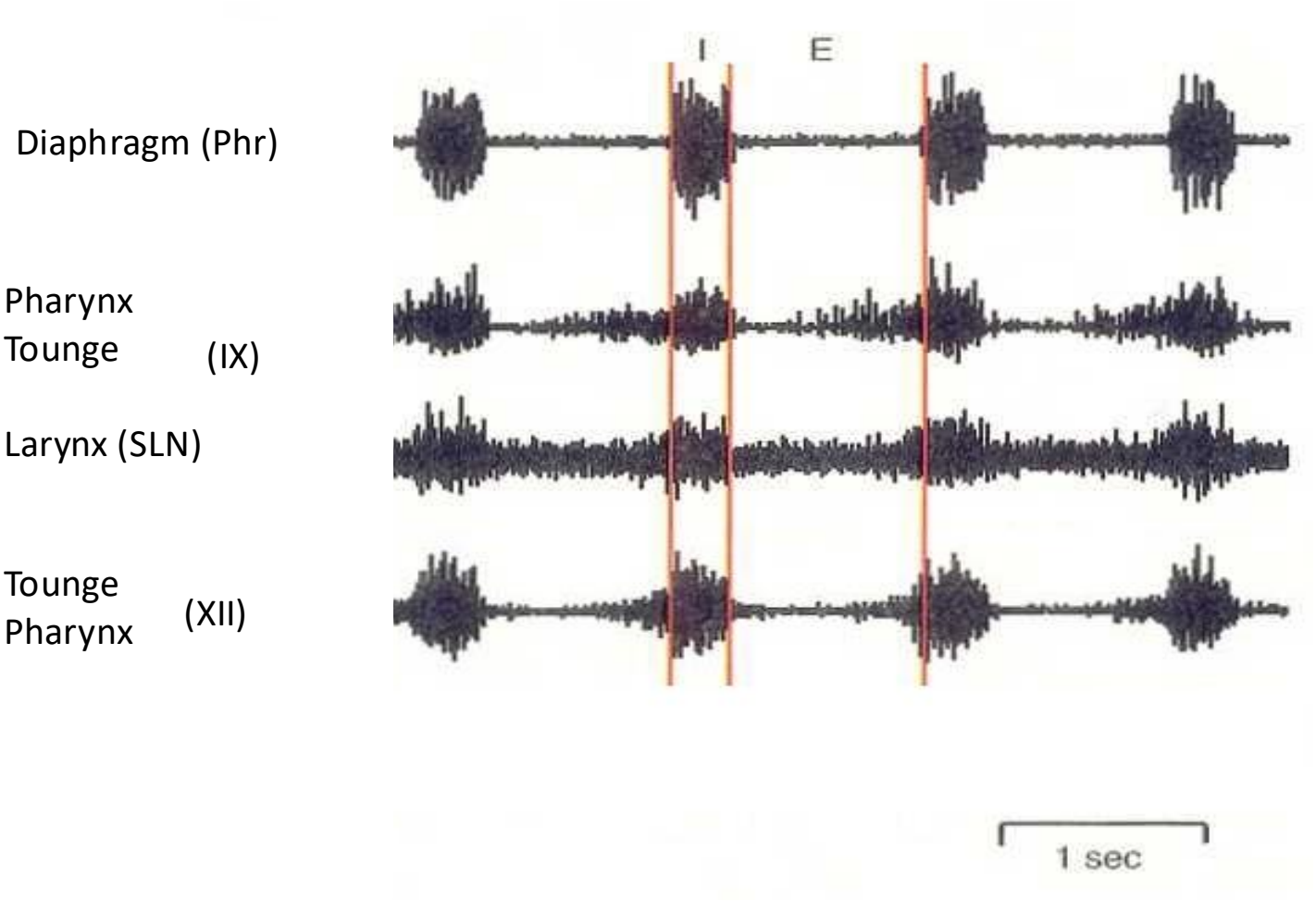
Periodic Breathing in Hypoxic Sleep
Example of a CO2 Sensitized ApneicThreshold

(Berssenbrugge, 1983)

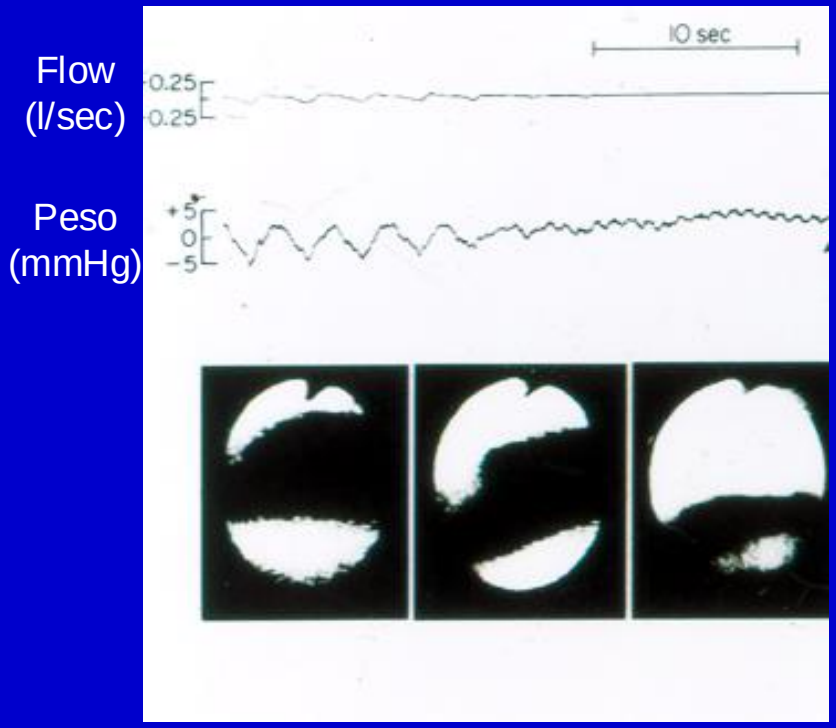


Apneas prevented via maintained eucapnia

Coordination of Central Respiratory Efferent Outputs to Chest Wall and Upper Airway. –Effects on airway of reduced central drive ?



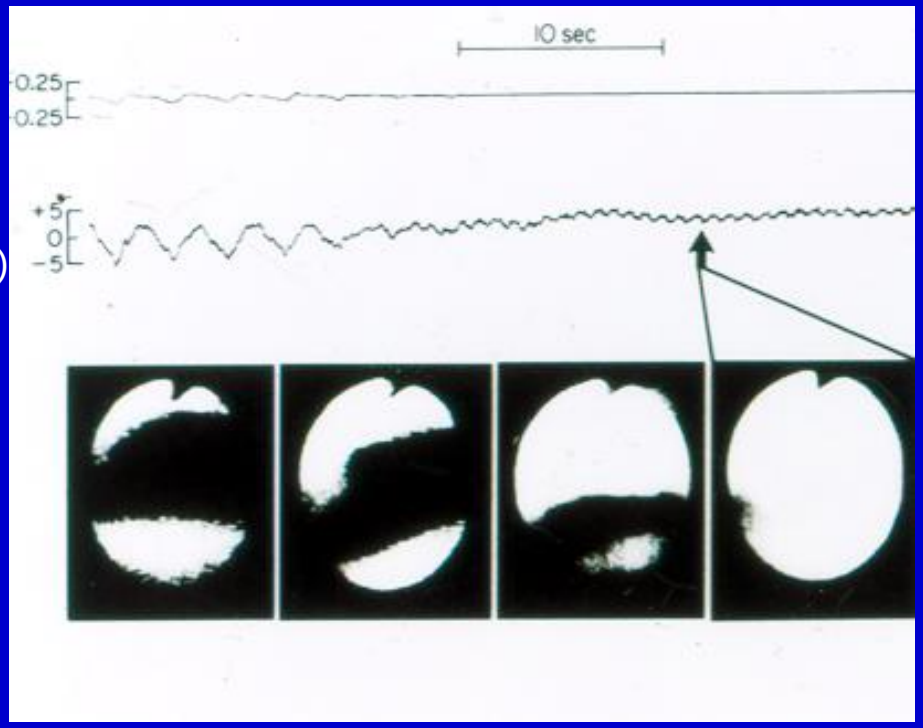
Consequences of Central Apnea / Instability to Patency of a Collapsible Airway



Spontaneous Central Apnea

(Badr, et al., 1995)

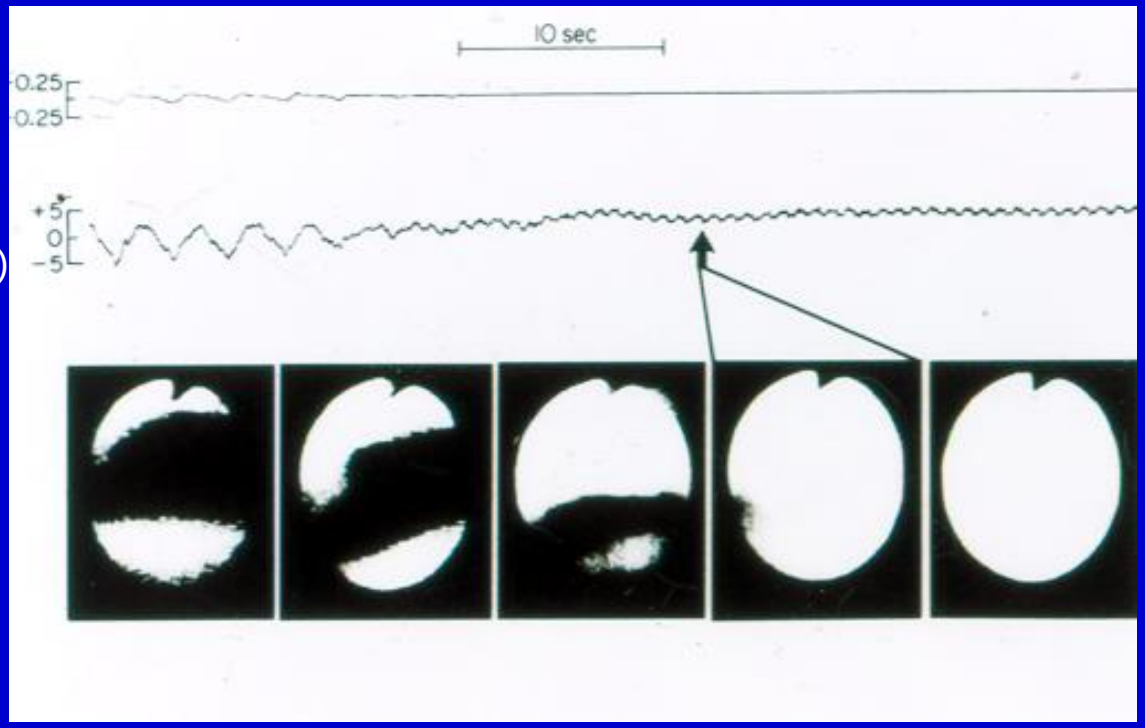
Consequences of Central Apnea / Instability to Patency of a Collapsible Airway



Spontaneous Central Apnea ⇒ Airway Narrow / Closure

(Badr, et al., 1995)

Consequences of Central Apnea / Instability to Patency of a Collapsible Airway



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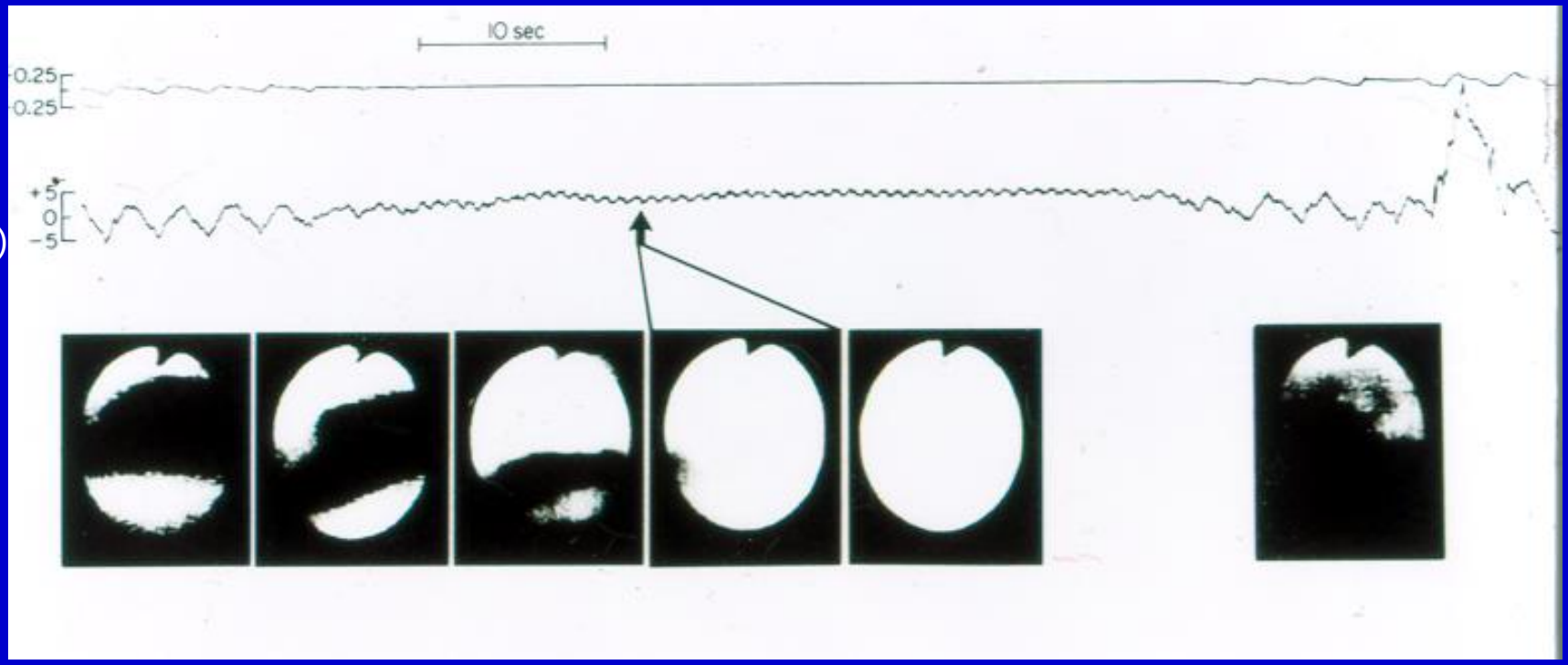
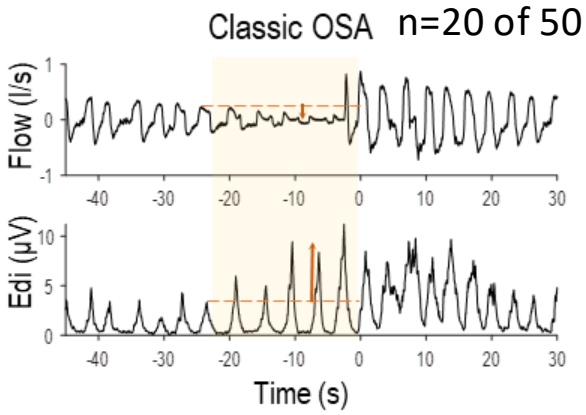
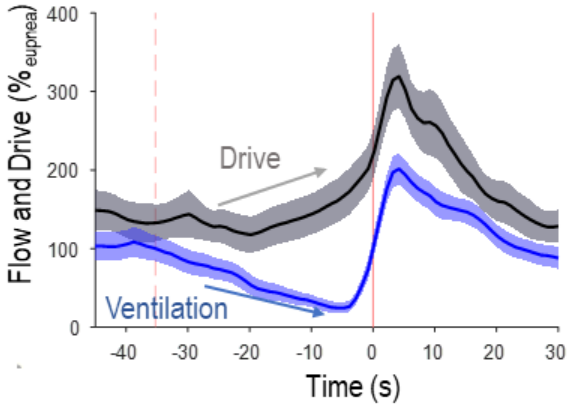


Spontaneous Central Apnea + Collapsible Airway = OSA

Does decreased/oscillating central drive to breathe play a significant role in OSA? Use of EMGdi!

Role of Oscillating/Declining Central Respiratory Motor Output (EMG_{di}) to OSA in 50 moderate to severe OSA patients





(Gell et al 2022)

Role of Central Instability in OSA

Collapsible Airway + High Loop Gain + Sleep

↓

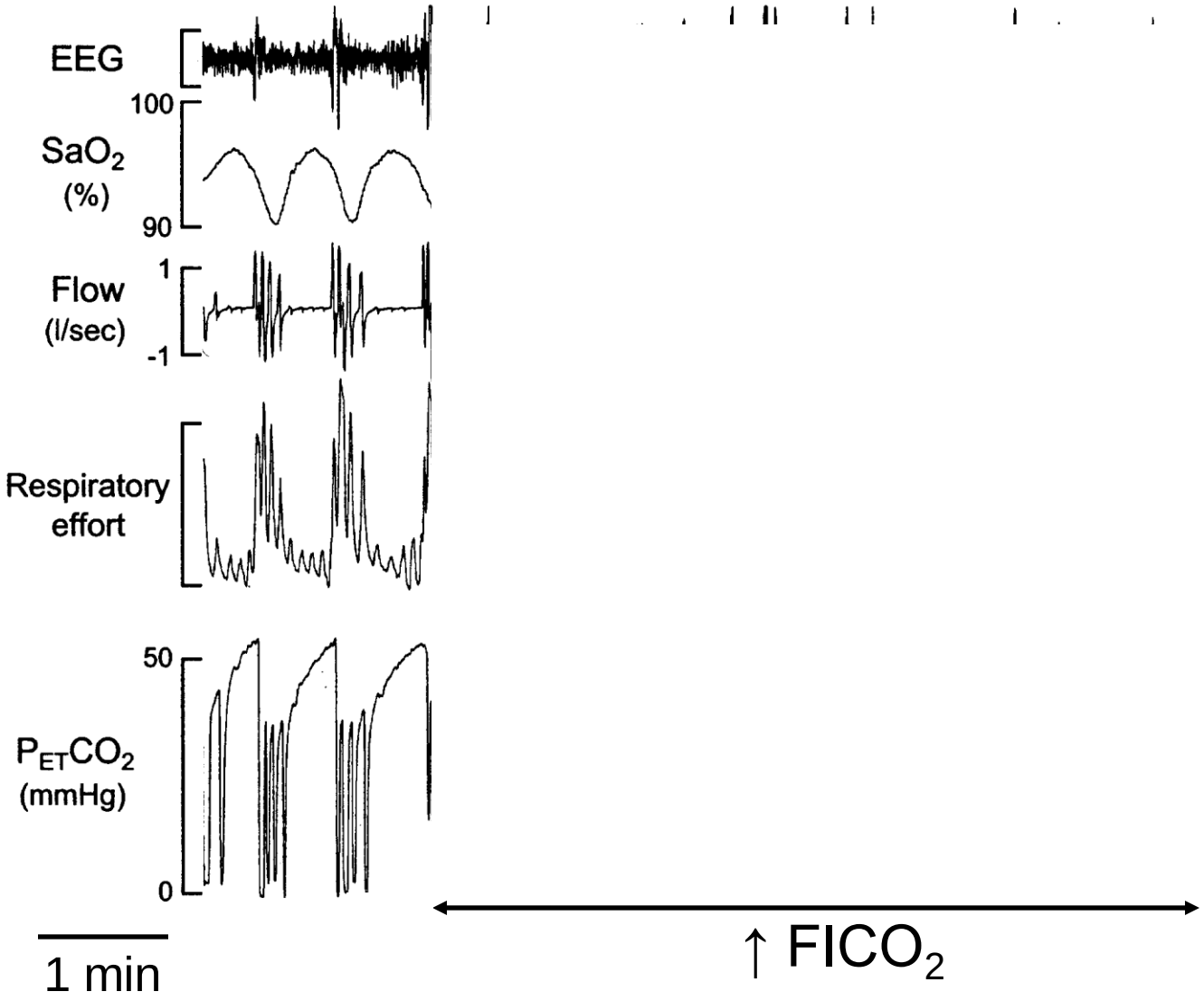
Central Instability of Resp. Motor Output
(…to both upper airway + chest wall pump muscles)

↓

Cyclical Obstructions
(at nadir of oscillating resp. drive)

Supplemental O2/ CO2/Acetazolamide = sig ↓OSA
(Xie;Wellman;Edwards)

Obstructive Sleep Apnea (OAI 35- 65 /hr; Pcrit +2-5cmH2O)



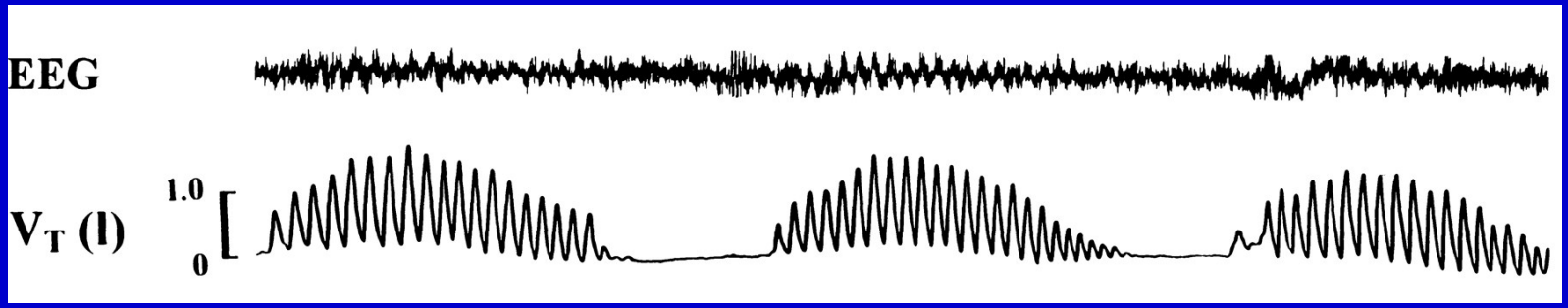
In 19 of 23 OSA patients ↑ $PaCO_2$ 1-4 mmHg prevents central instability, recruits airway dilators = ↓ OSA > 75% (Xie, 2013)

Summary: Sleep Apnea Pathogenesis

- Increasing prevalence of OSA (1993-2020)
- Sleep: ↑ airway collapsibility + critical dependence on ↕ $PaCO_2$
- Stability of central respiratory motor output dependent on chemosensitivity/plant gains
- Most OSA driven by airway collapsibility plus oscillating/declining central drive
- Beyond CPAP? Rx tailored to individual patient airway collapsibility, dilator muscle recruitability, arousability, loop gain

Recent advances/problems

Dilemma of CHF-induced periodicity



- > 50% prevalence in CHF
- sleep disordered breathing exacerbates CHF
- ↑ carotid chemoreflex sensitivity,airway edema;
- ↓ cerebral vascular response to ↕ PaCO2
- RCT of CPAP, ASV, phrenic nerve stimulation
- +ive effects of exercise training, nocturnal O2, acetazolamide,diuretics

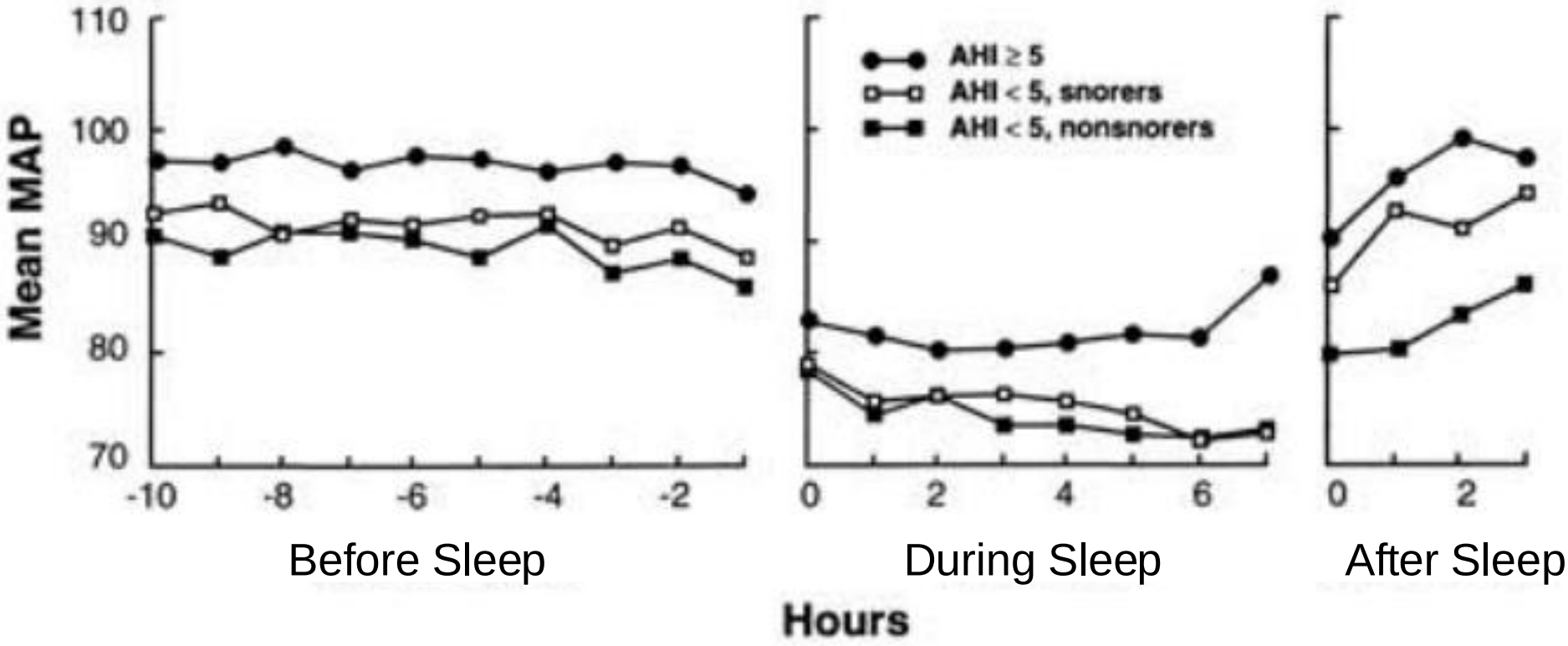
Promising Pharmacotherapy for OSA

- Rodents: sleep-induced ↓ tonic pharyngeal dilator muscle activity via withdrawal of noradrenergic input (NREM) + inhibitory muscarinic processes (REM)
- OSA patients: noradrenergic + anti-muscarinic pharmacotherapy over 1-30 nights = ↑ pharyngeal EMG activity in sleep + ↓ AHI and hypoxic burden (50-60%) with minimal side effects

(Aishah, 2023; Taranto-Montemumo, 2019; Perger, 2022)

Day and Nighttime ↑ MAP with Mild SDB

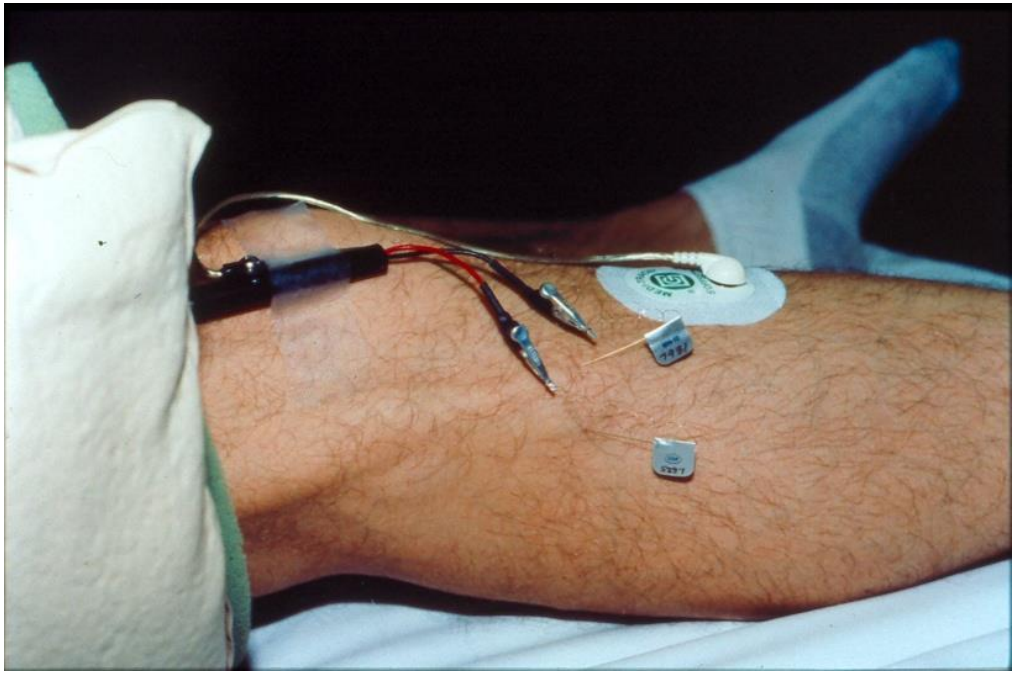
(Wisconsin Sleep Cohort-Hla et al1994)



Cause : Effect??

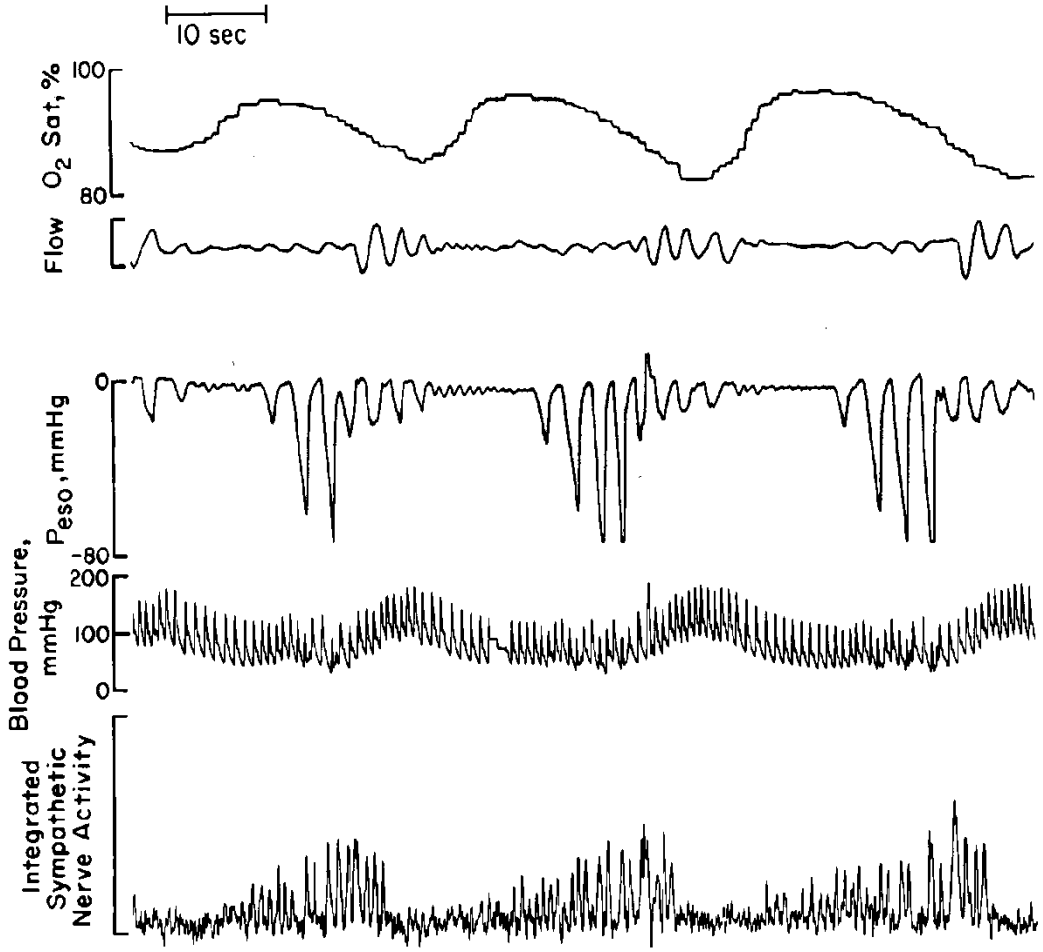
(Morgan et al -Rodents, /Humans1996-2019}

Recording postganglionic muscle sympathetic nerve activity (MSNA) in humans

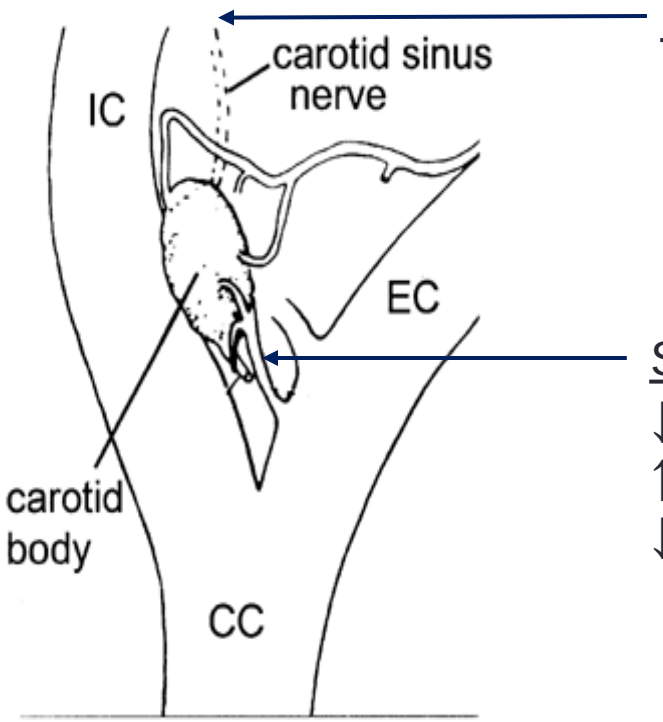


OSA causes nightly exposure to intermittent hypoxia/transient arousals/acute repetitive sympathetic ,BP responses

Dempsey, *et al*. Physiol Rev 90:47-112, 2010



Key Player: Apnea-Induced ,Chemoreflex-mediated sympathoexcitation /central effects/hypersensitization



Response

↑ V_E

↑ Sympathetic outflow

↑ Central CO2 chemosensitivity

Stimulus

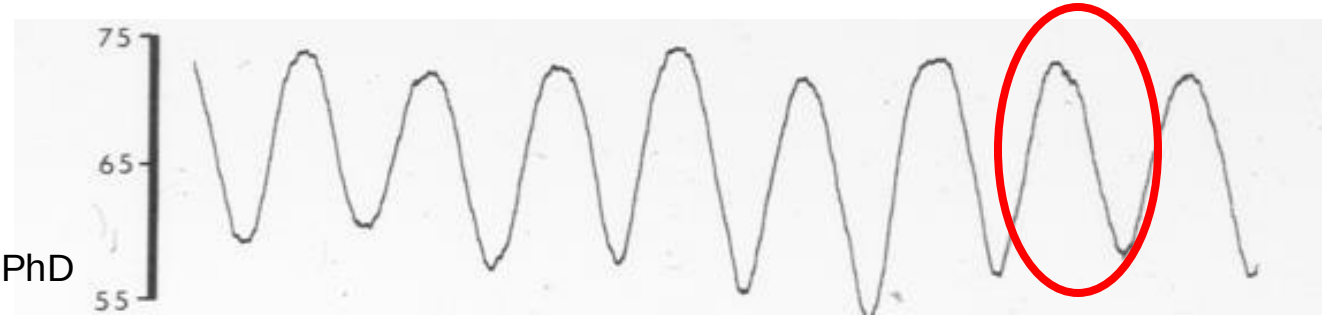
↓ PaO_2

↑ $PaCO_2$

↓ pH

Daytime CV Effects of Sleep Apnea-Induced Chronic Intermittent Hypoxemia (CIH)

Gregg Semenza, MD, PhD
Nobel Laureate 2019



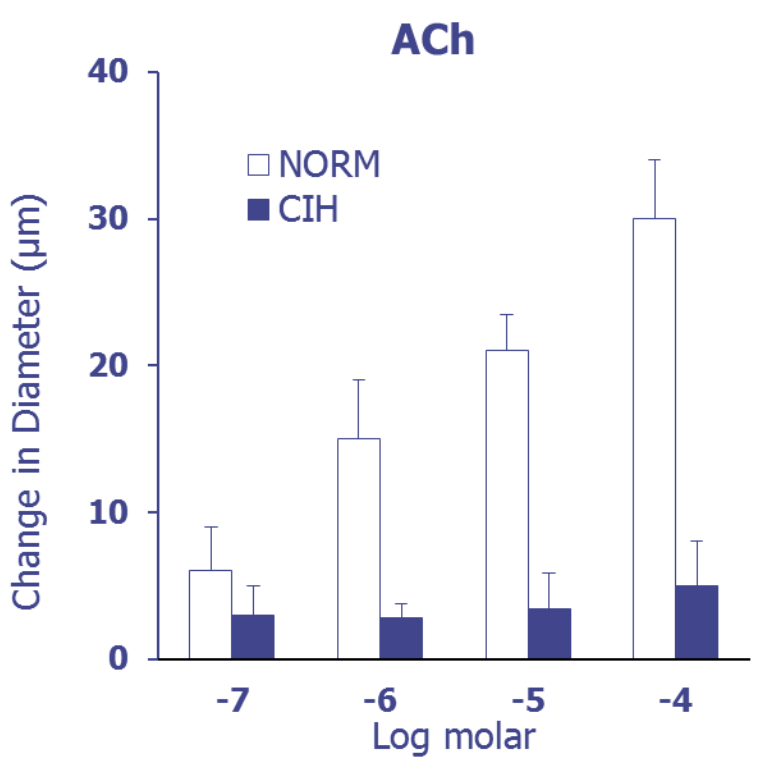
↑ pro-oxidant HIF-1α + ↓ anti-oxidant HIF-2α
↑↑ oxidative stress, ↑↑ pro-inflammatory molecules

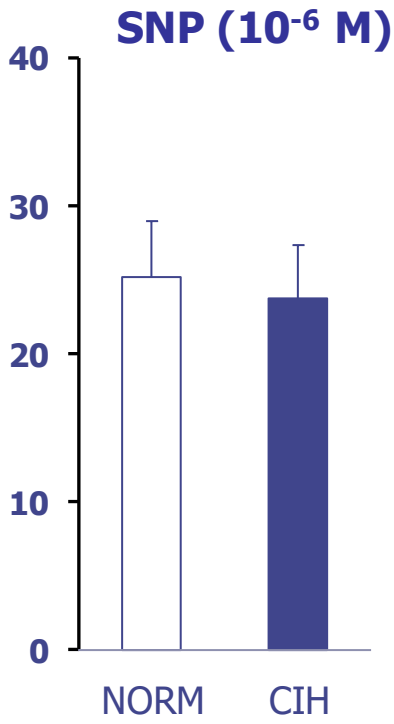
Neural Structures Throughout Chemo Pathway

Systemic resistance vessels

↑ chemosensitivity, ↑ sympathetic vasoconstriction, endothelial dysfunction

2 Wks CIH = +13 mmHg MAP, ↓Acetylcholine (ACh)-induced vasodilation in isolated gracilis artery/middle cerebral artery;(enhanced vasoconstriction via norepinephrine.)

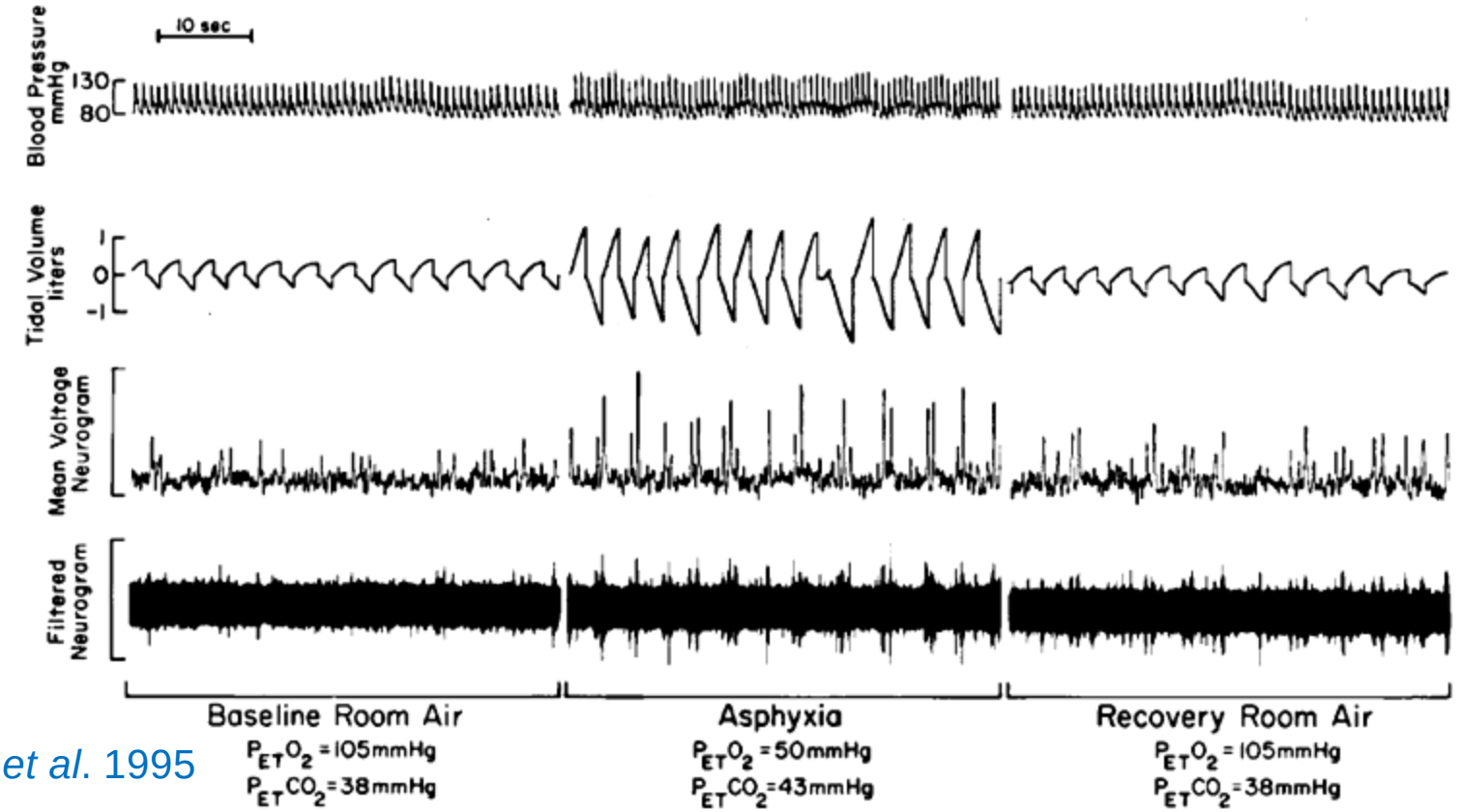




… CIH impaired endothelial function via ↓ bioavailability of nitric oxide

Phillips, *et al.* Am J Physiol 286:H388-H393, 2004

Brief (20 mins) asphyxia or IH (NOT hypercania alone) in healthy humans causes sympathetic activation that outlasts the chemical stimuli



Morgan *et al*. 1995

Persistent after-effects of 2 wks IH ↑ MSNA/MAP in healthy humans (Tamisier, *et al*. 2012)

Mechanisms of CIH-Induced Hypertension

Rapid deoxygenation/reoxygenation cycles → oxidative stress at multiple locations in chemoreflex pathway

↓

↑ AT_1R in CB and RVLM

↓

Persistent tonic and hypoxia-induced SNS activity

Endothelial dysfunction, ↑ stiffness, ↑ AT_1R in systemic arteries

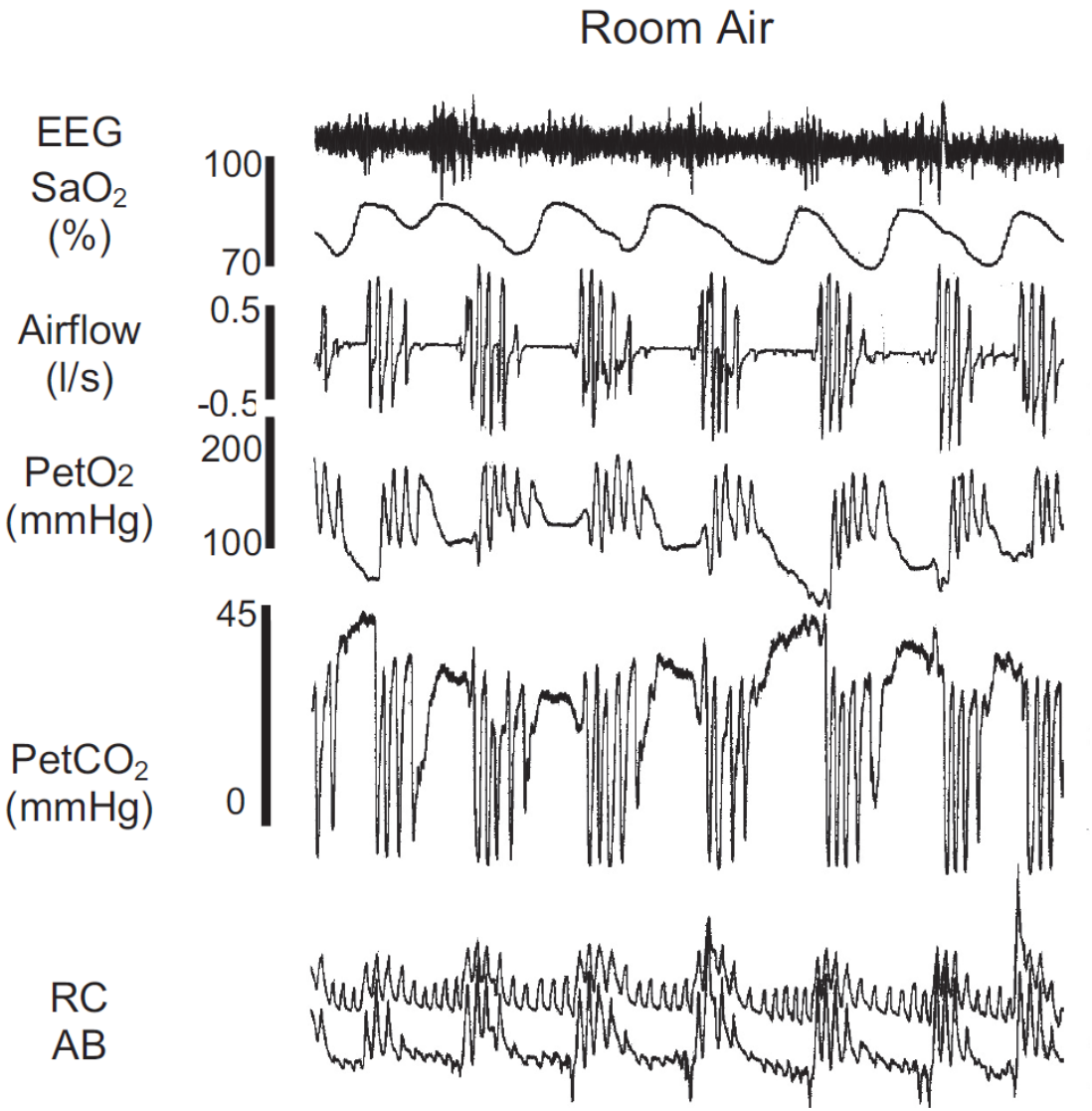
↑AT_1R signaling important for both neural (CB and brainstem) and vascular consequences of IH!
(Morgan et al, Clin.Exp Hypertension,2019)

-N=12,000 middle-aged, overweight participants studied during sleep over several months (2023)

-Findings support that regularity of sleep timing /duration- night to night regularity of OSA as sig risk factors for hypertension

Human OSA with High Chemosensitivity: Effects of ↑ FIO_2

Human OSA with High Chemosensitivity, sensitive apneic threshold, collapsible airway

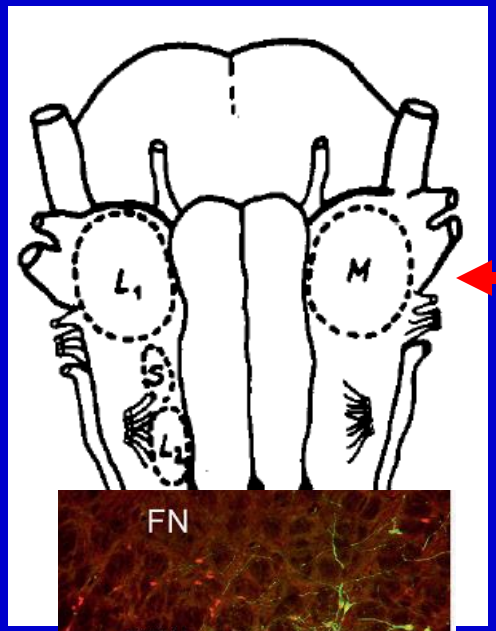


In 7 of 19 OSA patients ↑ SaO_2 = ↓ OSA 65-80%
(Xie 2013, Wellman 2008)

CV Effects of Chronic Intermittent Hypoxia (CIH) in Rodents/Humans (Morgan,Skatrud,Xie et al., 1995-2020)

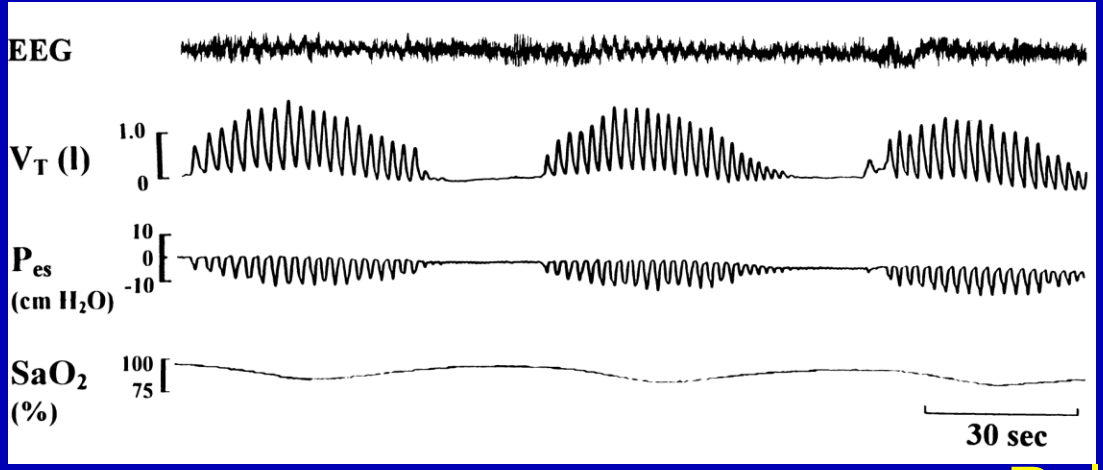
- Rodents:↑ MAP and SNA over 2 weeks of IH
- ↑ Carotid chemo sensitivity
- isolated gracilis and cerebral arteries responses measured to vasodilator and constrictor agents
- MSNA in OSA patients
- After-effects of IH on MSNA in healthy humans
- Role of oxidative stress/angiotension receptors in hypertensive response

Carotid/Medullary Chemo Interdependence Required for Central Apnea/Periodicity



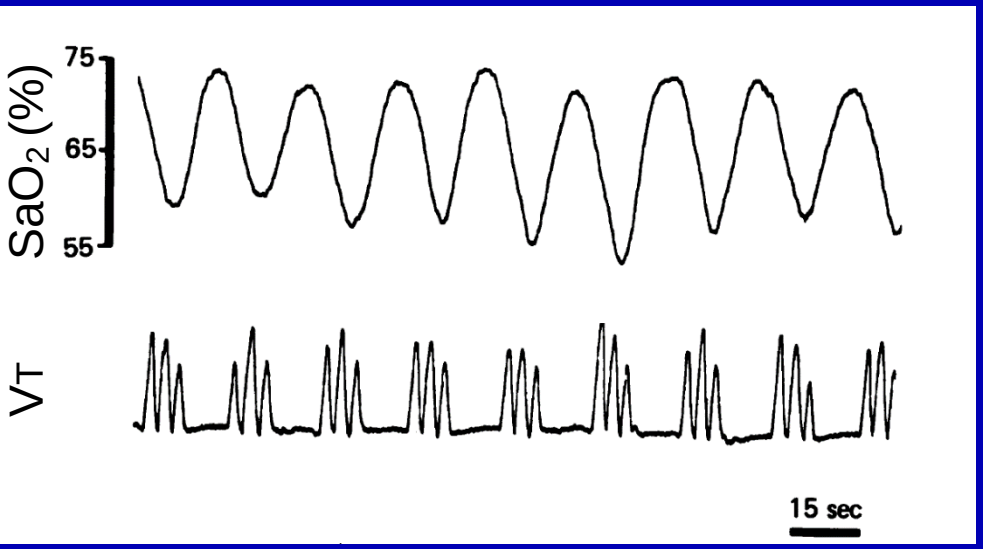
(Smith et al, 2007:Nakayama et al, 2002;Dempsey,Gibbons, 2023)

Why Cyclical Apnea in Sleep?

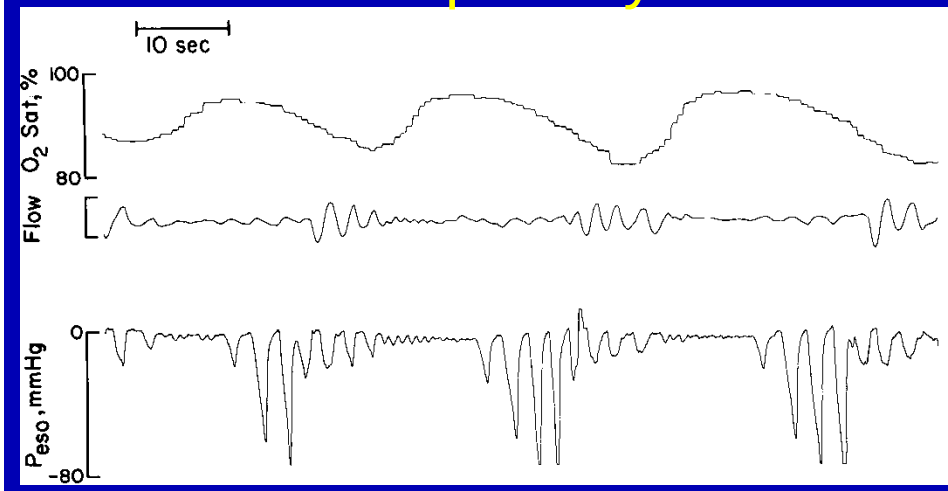


CHF

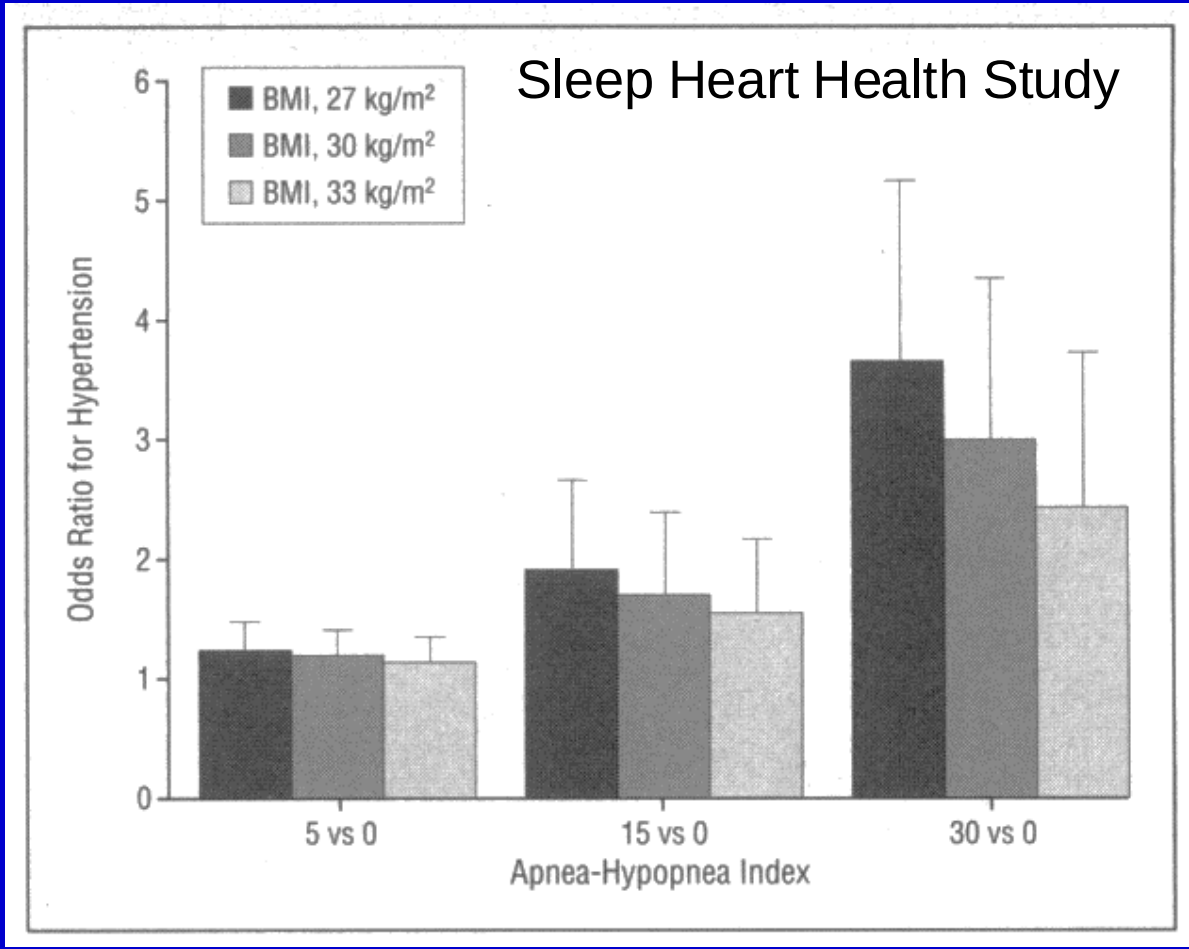
Role of airway dilator muscle recruitability,arousability,loop gain, central instability + airway collapsibility.



Hypoxia / Opiates

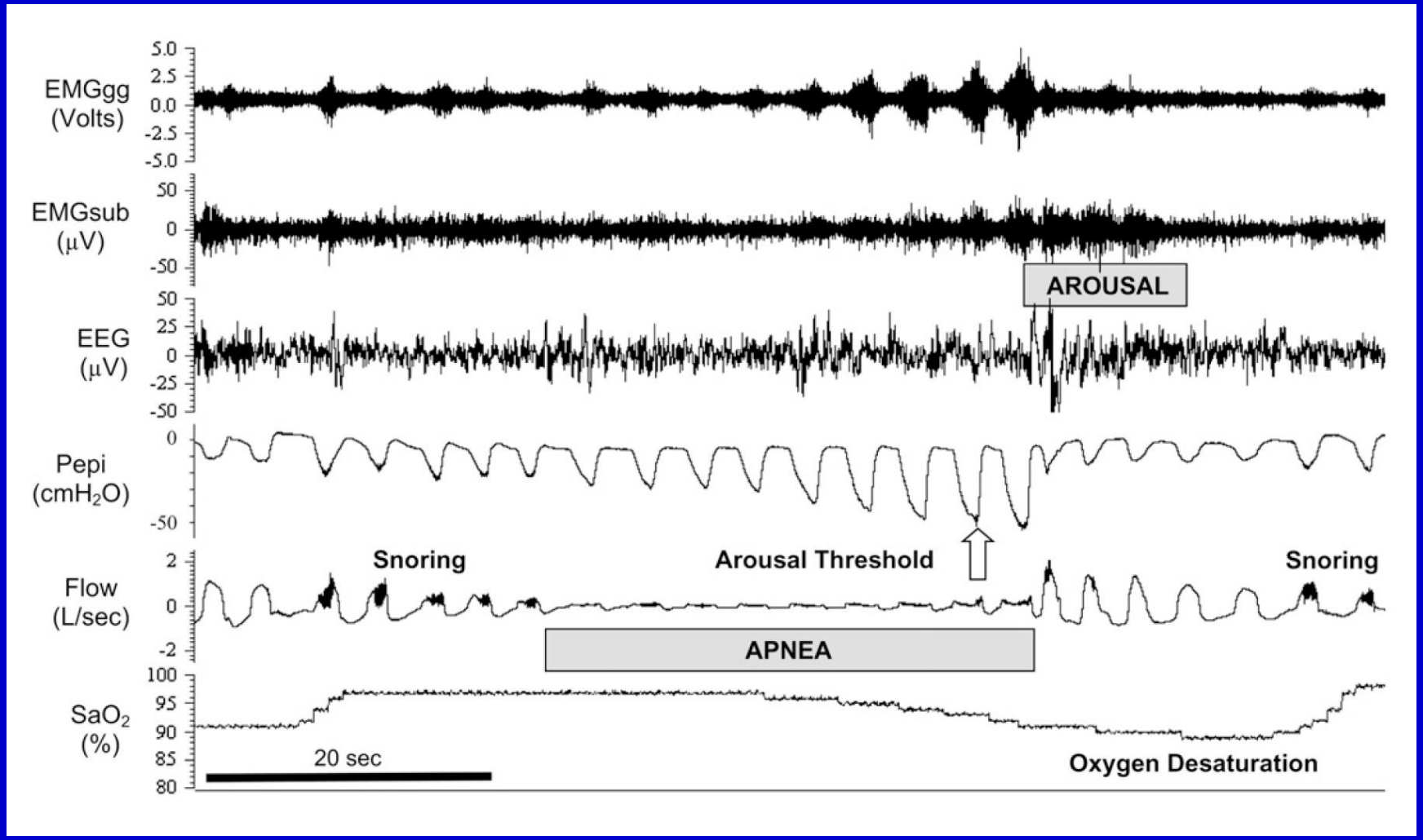


OSA



80-90% prevalence of OSA in refractory hypertension!
-comorbidities confound OSA :BP association;
-inconsistent effects of CPAP treatment on BP

Obstructive Sleep Apnea: Multiple Causes of Cyclical Obstructions/Overshoots?



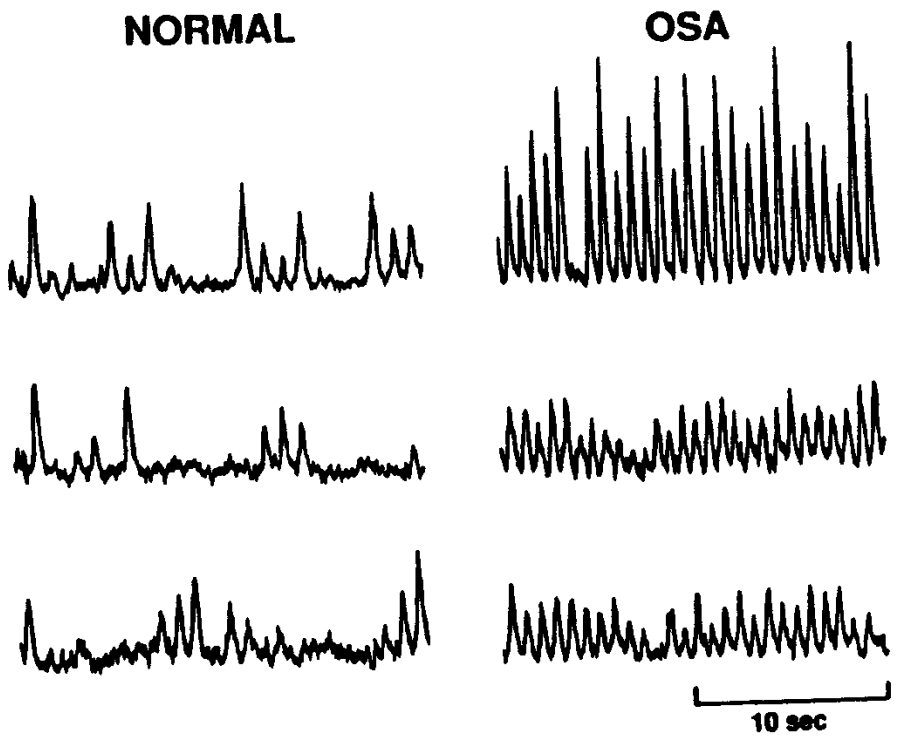
Dilator muscle recruitability, cortical arousability, plant gain/ chemosensitivity

Central instability → obstructions

Sleep Disordered Breathing and Hypertension

- Acute CV effects of sleep apnea
- Associations of hypertension/ SNA with AHI/hypoxic burden in OSA
- Confounding comorbidities /Inconsistent CPAP treatment effects on daytime BP

Basal sympathetic nerve activity/MAP in daytime normoxia are enhanced in OSA
Cause:Effect?... Or comorbidities??



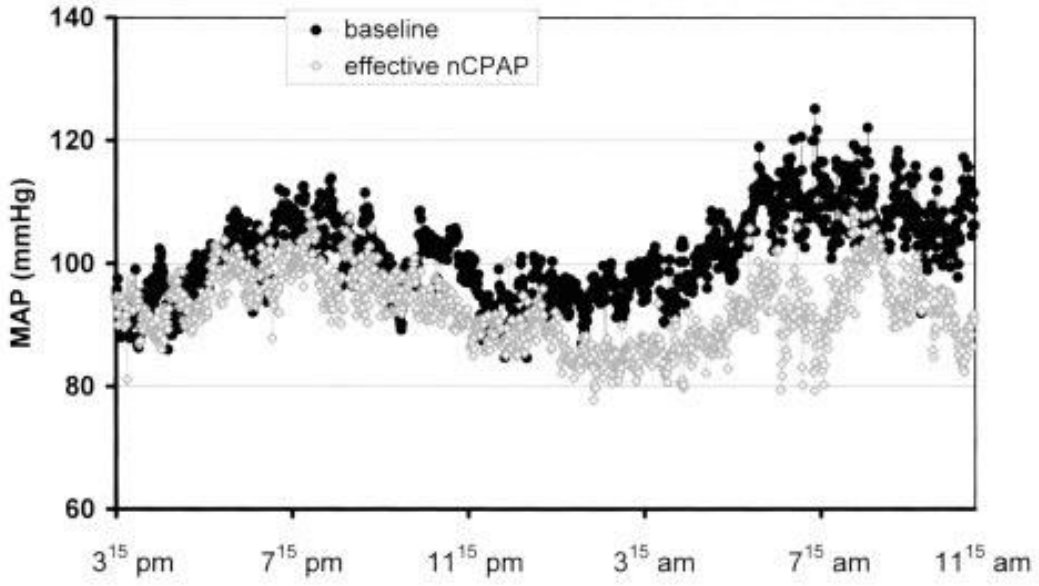
Somers *et al*. 1995

Therapeutic vs Non-Therapeutic CPAP on BP

n=32 OSA, 9 weeks CPAP

– Therapeutic CPAP ↓ AHI 65-5; ↓ MAP 10±11 day/night

– Non-therapeutic CPAP ↓ AHI 65-33; MAP no change



Becker, *et al*. Circulation 107:68-73, 2003

Sleep Disordered Breathing and Hypertension

- Experimental OSA effects on daytime BP--canine model
- Intermittent hypoxia after-effects: rodents, healthy humans
- Population studies relating sleep duration, timing, disruption to hypertension

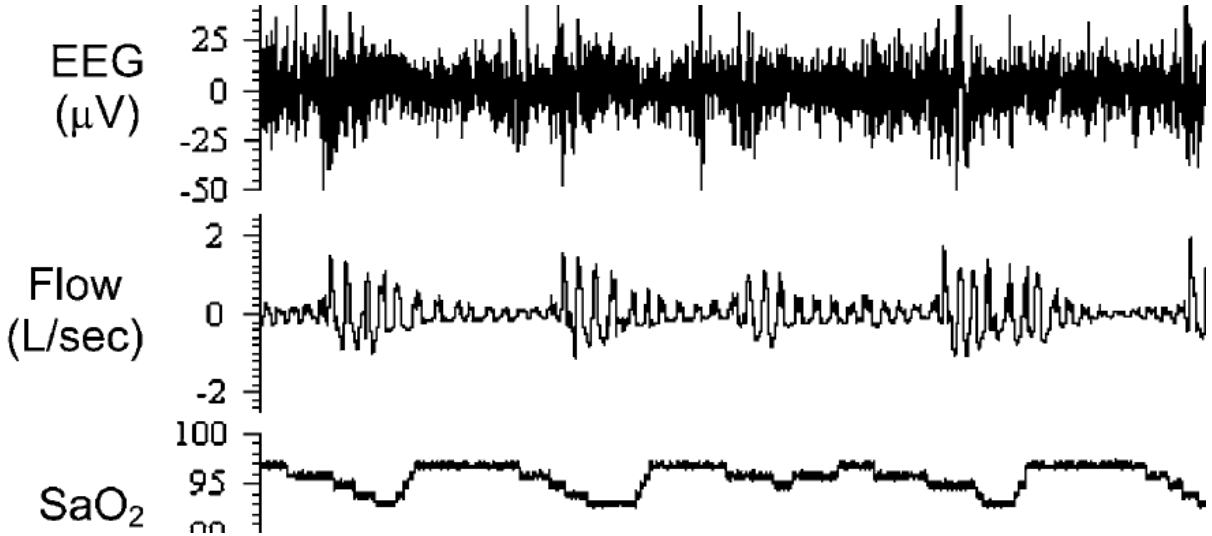
Study Questions: Sleep

1. Why does NREM sleep predispose to sleep disordered breathing?
2. How might each of the following contribute to sleep disordred breathing?
   a) ↑ chemosensitivity
   b) Transient arousals from sleep
   c) ↑ $PaCO_2$ during eupnea (i.e. increased plant gain)
   d) Recessed mandible
   e) Excess body fat
   f) Chronic heart failure

Questions (cont'd)

3. For a given duration of an apneic episode, what additional factors determine the severity of the accompanying arterial HbO2 desaturation?
4. What evidence supports the idea that OSA frequently involves a "central" as well as "airway obstruction"?

Sleep Apnea-Induced Chronic Intermittent Hypoxemia (CIH), Sleep State Disruption



Evidence for Daytime CV/Metabolic/Cognitive Effects of CIH

<u>OSA Patients</u>

- Correlative/ prospective
- CPAP treatment effects

<u>Healthy Rodents/Canines</u>

- Mimic CIH of OSA for 8-10 hrs/day; days-weeks
- Separate sleep state disruption from CIH effects

<u>Healthy Humans</u>

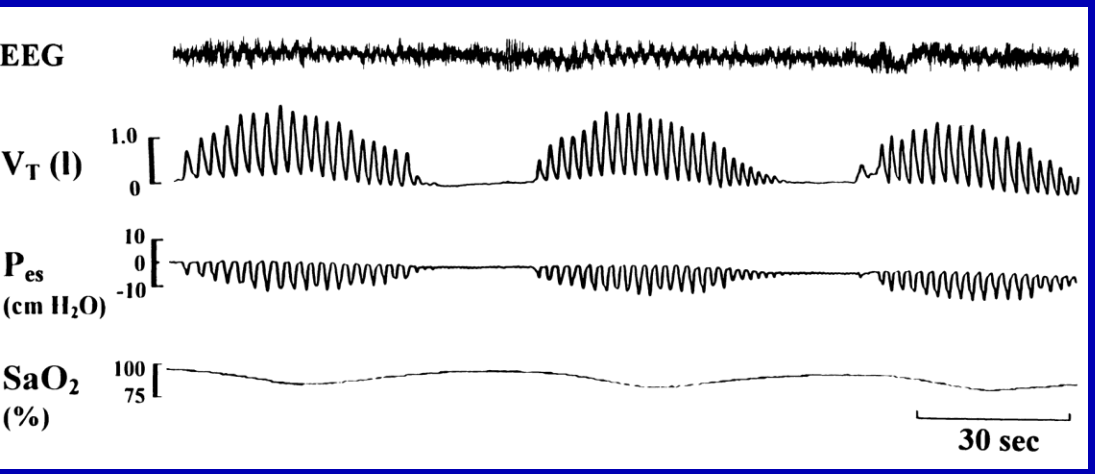
- Mimic CIH of OSA for days

Summary: Control of Breathing / Sleep Apnea

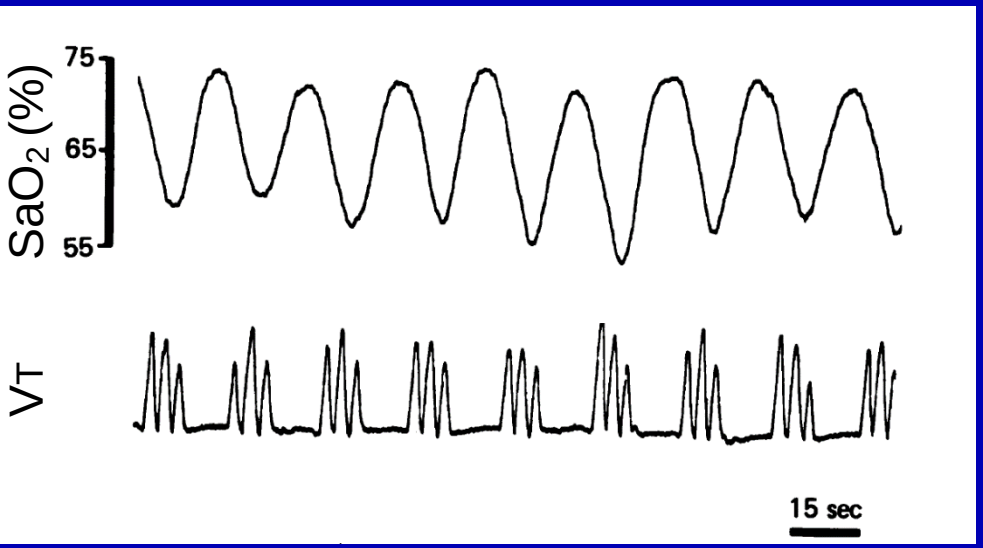
- Aim - O_2 / CO_2 regulation / mechanical efficiency
- 3 Component control system
  - Central integration / rhythm
  - Chemical / mechanical feedback
  - Distribution of efferent output
- Plasticity

- Loss of tonic/phasic wakefulness inputs—role of CNS neurotransmitters
- Cyclical sleep apnea pathogenesis via ↑ airway collapsibility/central instabilities/transient arousals
- Implications for treatment: OSA, central SA, mixed SA

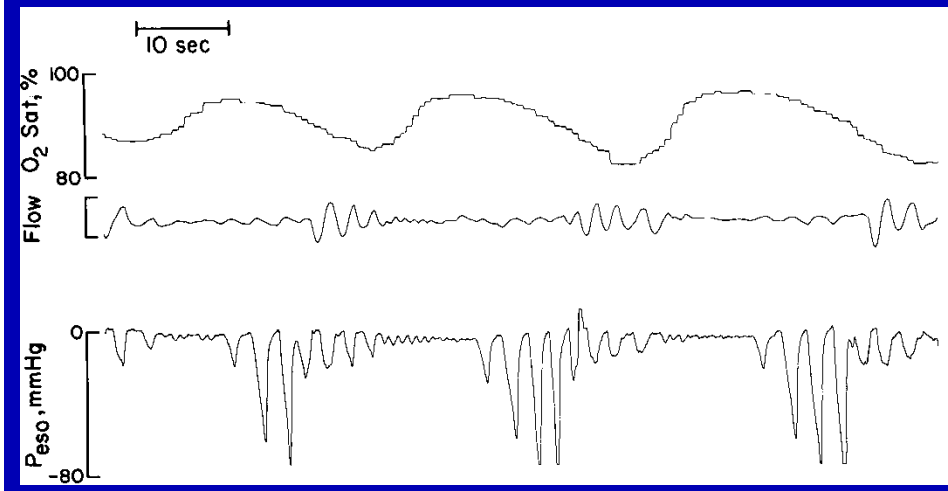
Sleep-Induced Breathing Instabilities / Airway Obstructions



CHF



Hypoxia / Opiates



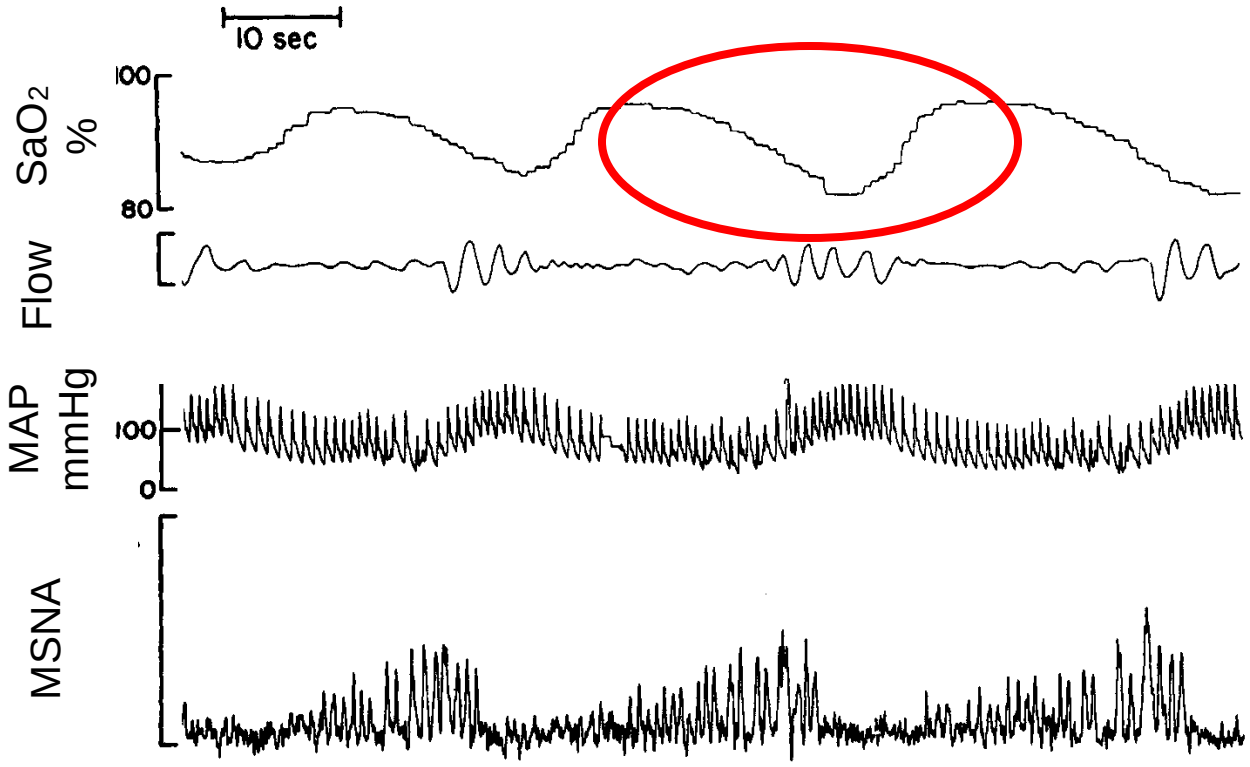
OSA

Daytime consequences??

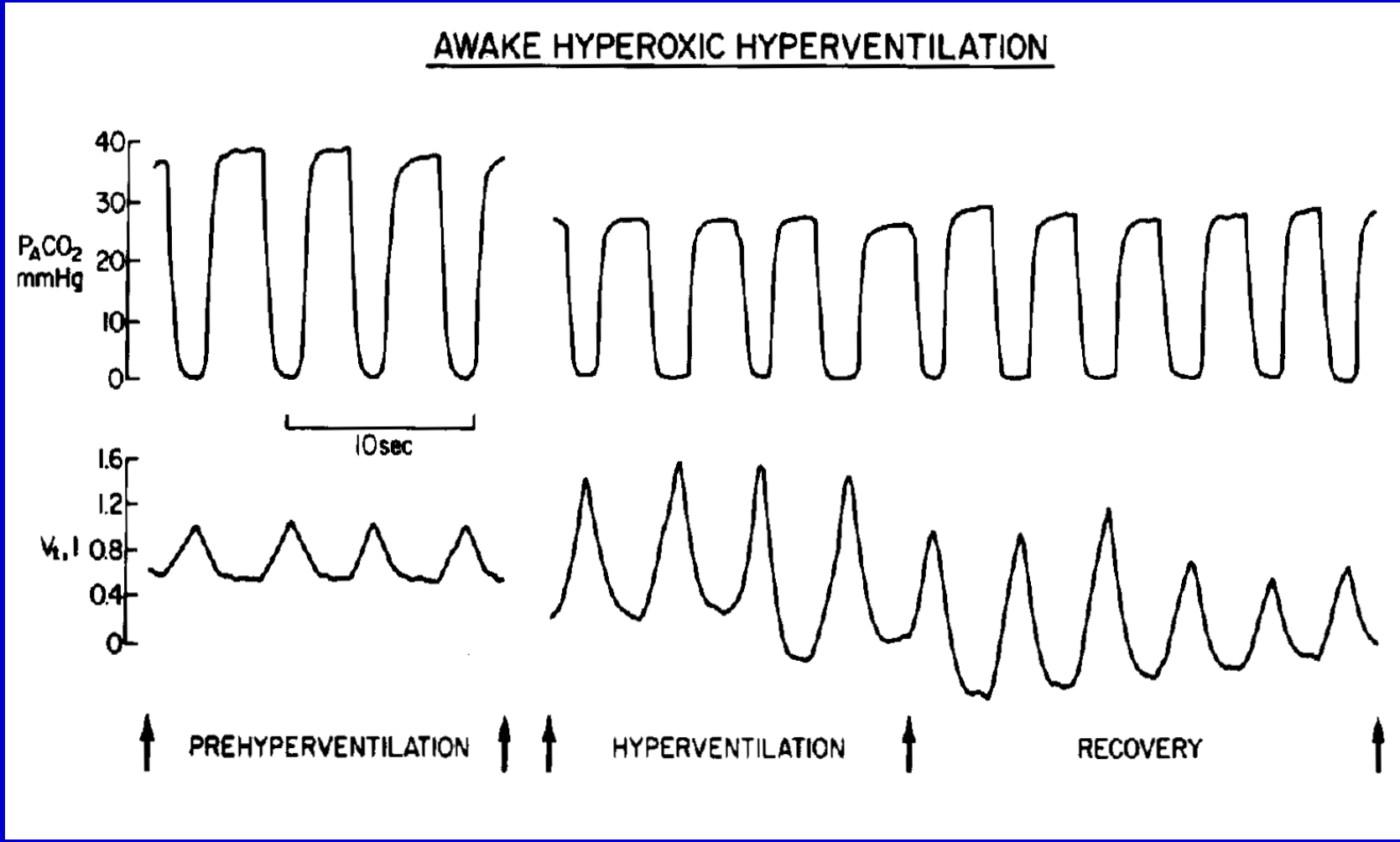
Summary: Sleep Apnea

- Prevalence/risk factors
- Daytime consequences
- Pathogenesis via removing wakefulness "drive" to upper airway and chest wall
- High loop gain drives instability
- OSA = collapsible airway + oscillating, ↓ central drive
- Personalized treatment??..beyond CPAP?
- Application to neonate/ children?

ACUTE CV Effects of OSA/IH During Sleep



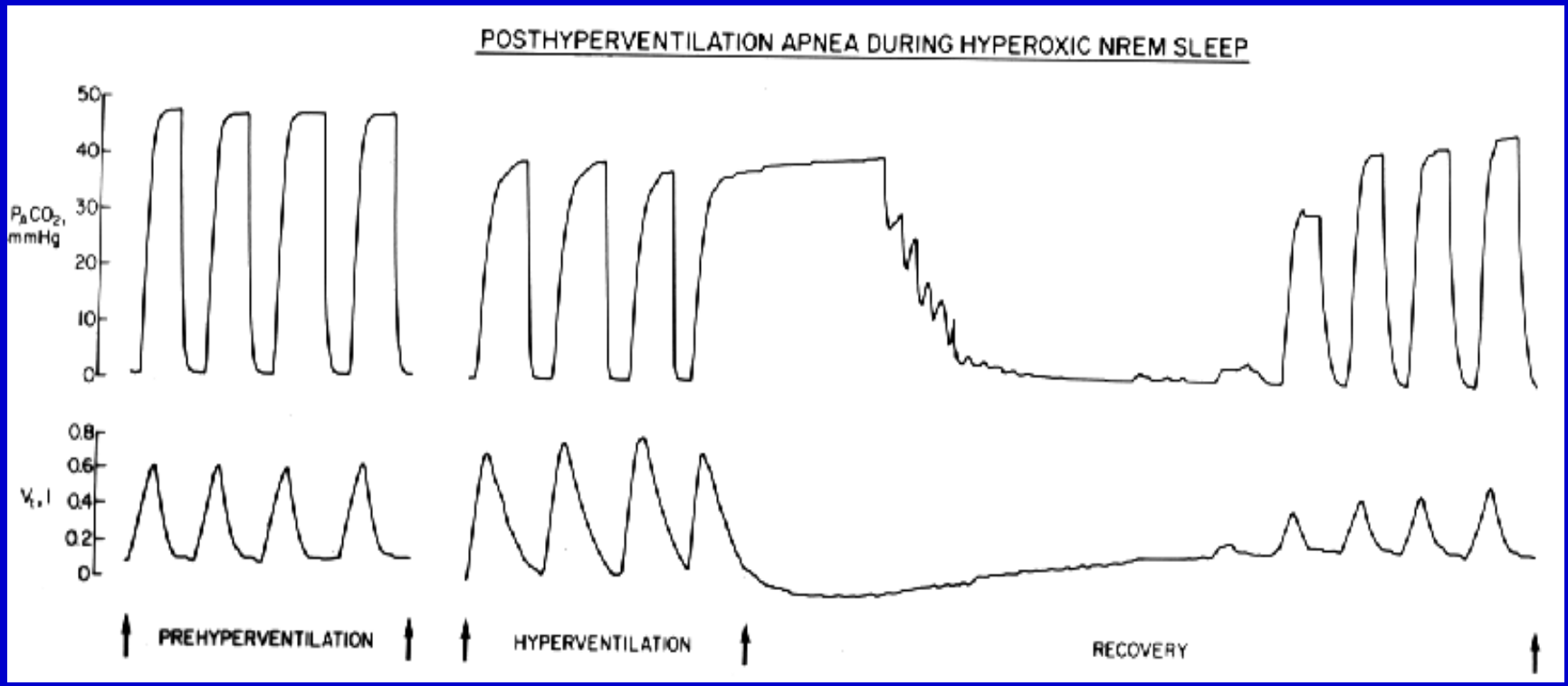
Carry-over effects: Hi SNA continues post IH; causes daytime hypertension via ↑ SNA plus endothelial dysfunction; reduced vasodilation of isolated vessels.



(Skatrud + Dempsey, 1983)

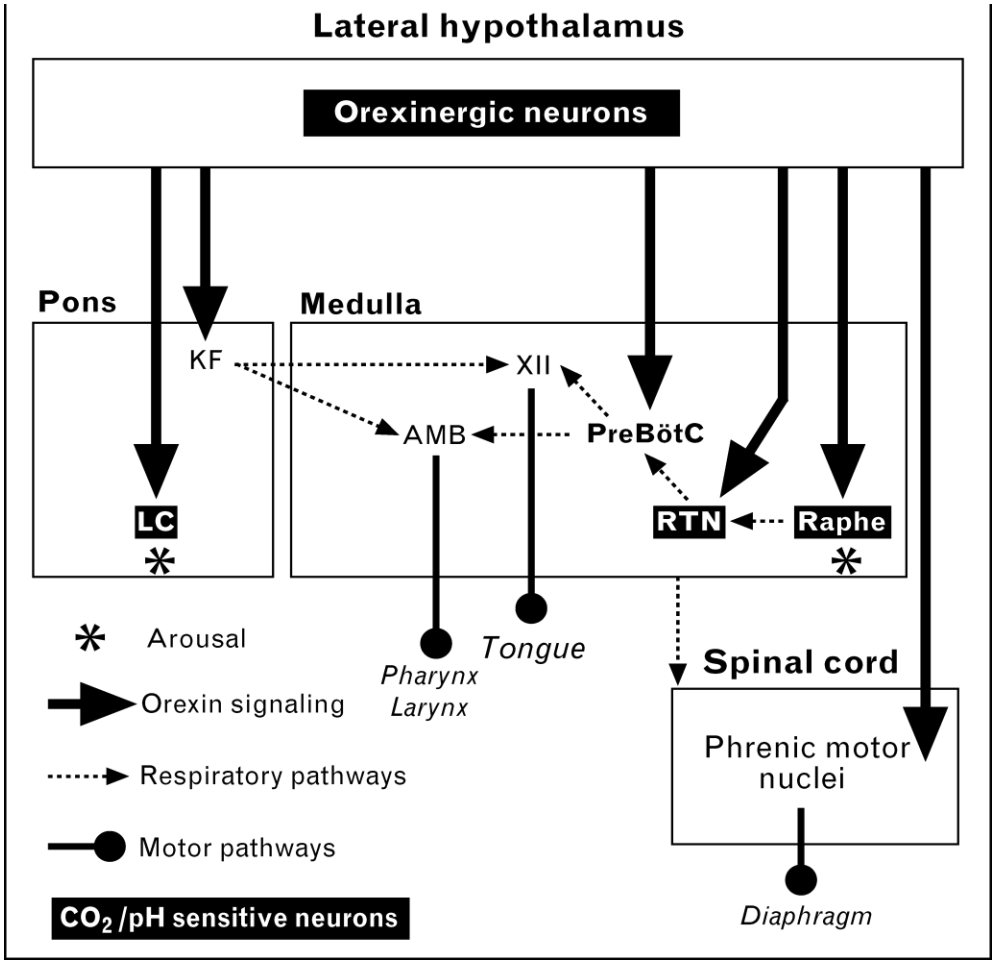
Continued breathing despite hypocapnia coincides with pre-inspiratory cortical potentials

NREM Sleep Unmasks a Sensitive Hypocapnic-Induced Apneic Threshold



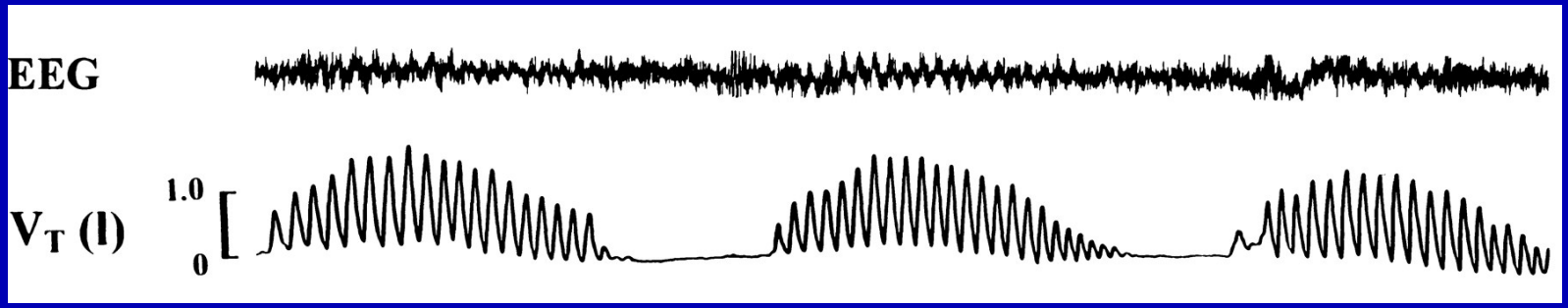
Hypocapnic-induced apnea DOES NOT include pre-inspiratory cortical potentials

Orexinergic Hypothalamic Neurons: Origins of the Wakefulness Drive to Breathe?



Gestreau, 2008

Loop Gain Determines V_E Undershoot/Overshoot/Stability



Loop gain = controller gain x plant gain

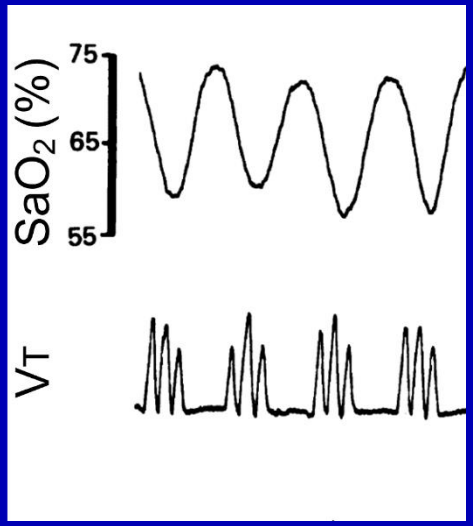
(chemosensitivity +transient arousal)

(how effectively Δ VE = Δ PaCO2)

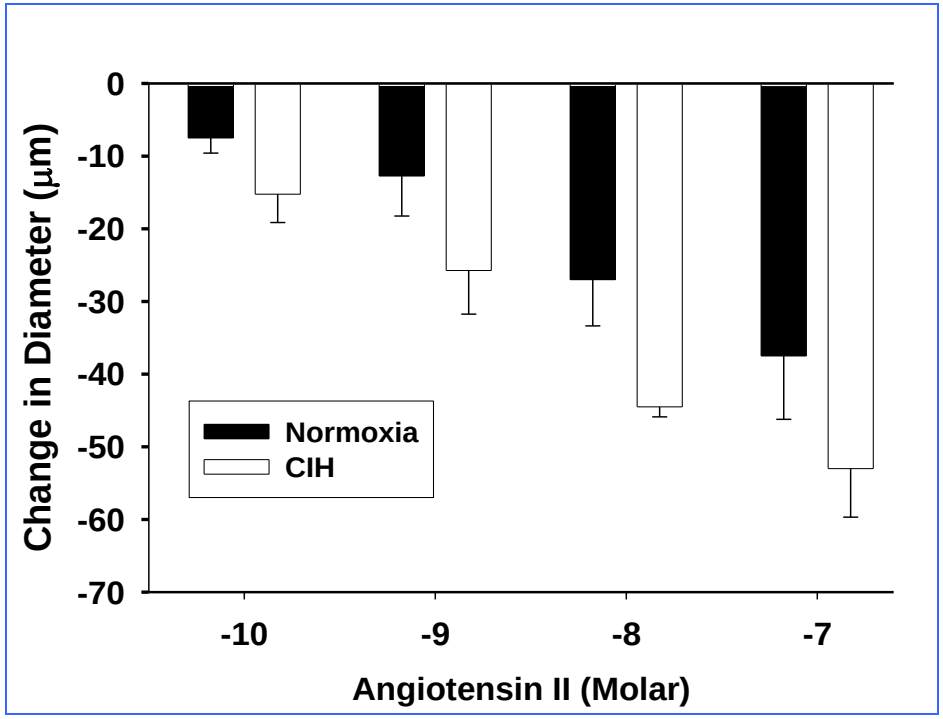
Severity of Sleep – Disordered Breathing

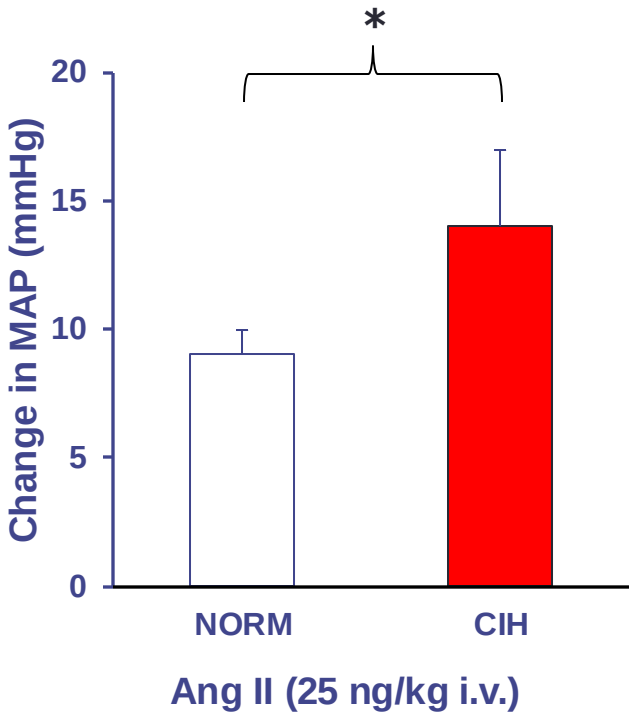
- Number of apneas/hypopneas per hr (AHI)
- Hypoxic “Burden” of SDB
- HbO2 desaturation per event:
  - -event duration
  - -initial level of HbO2 sat
  - -lung volume
  - -VO2
  - -cardiac output

  Arousals/sleep state quality



↑ Ang II-induced vasoconstriction and pressor response





… role of Ang II receptors in CIH-induced vascular dysfunction?

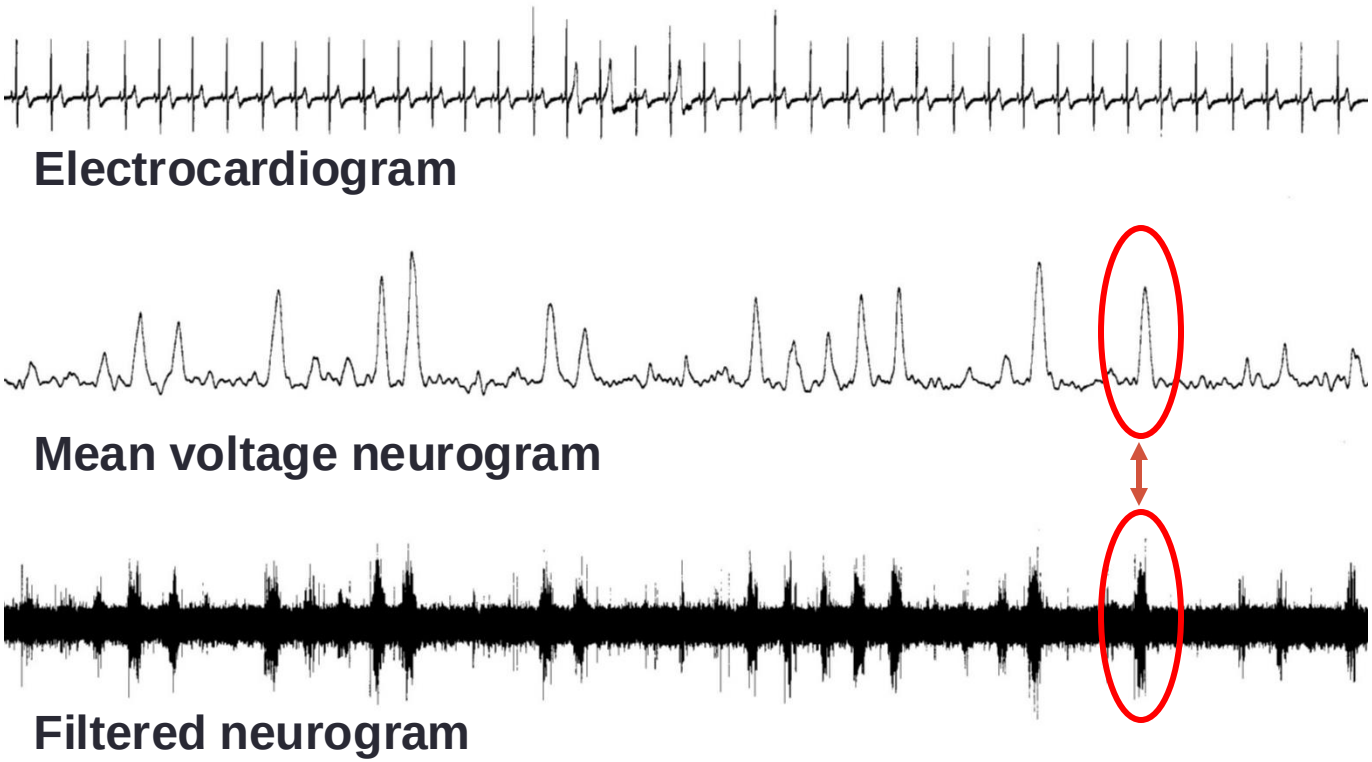
Phillips, *et al*. J Appl Physiol 100:1117-1123, 2006

Interim summary: neural effects of CIH in rats

Chronic, daily exposure to IH (10-12 hr/day):

- ↑ basal sympathetic outflow, an effect that persists when animals are normoxic (*i.e.* "carryover")
- ↑ chemoreflex control of LSNA and ventilation (dependent on signaling through AT_1R)
- activates AT_1R-superoxide-NADPH oxidase pathway in carotid body
  - ✓↑ AT_1R expression
  - ✓↑ superoxide production
  - ✓↑ $gp91^{phox}$ subunit of NADPH oxidase
- ↑ expression of AT_1R in RVLM (↑ AT_1R:AT_2R ratio)

Sympathetic outflow to skeletal muscle



Question

How do apneas during sleep cause increases in sympathetic nerve activity and blood pressure that carry over to the daytime, when blood gases are normal?

Chemoreflex control of sympathetic activity in humans with OSA

Effects of intermittent hypoxia in rat model:

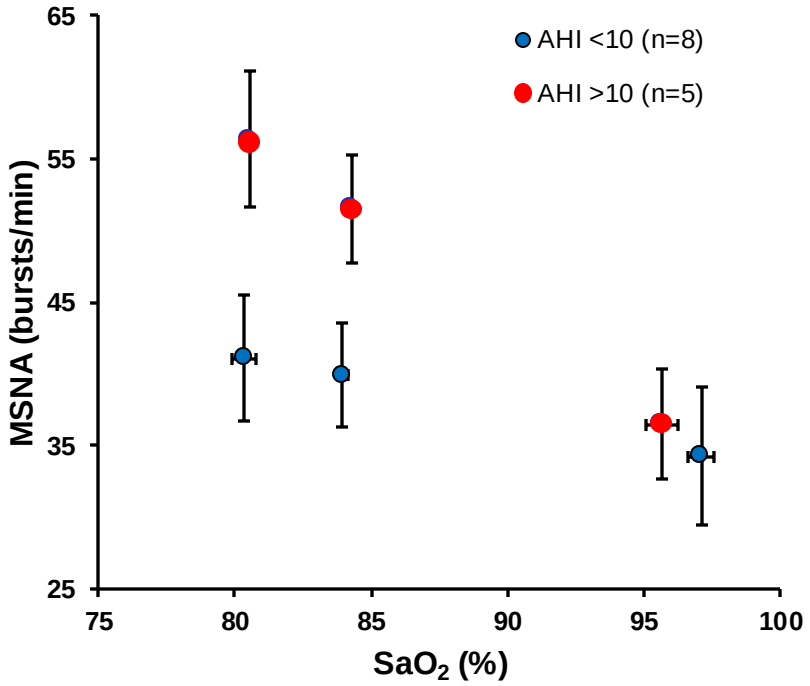
- blood pressure
- sympathetic nervous system activity
- chemoreflex sensitivity
- vascular structure and function

Treatment of Sleep Apnea?

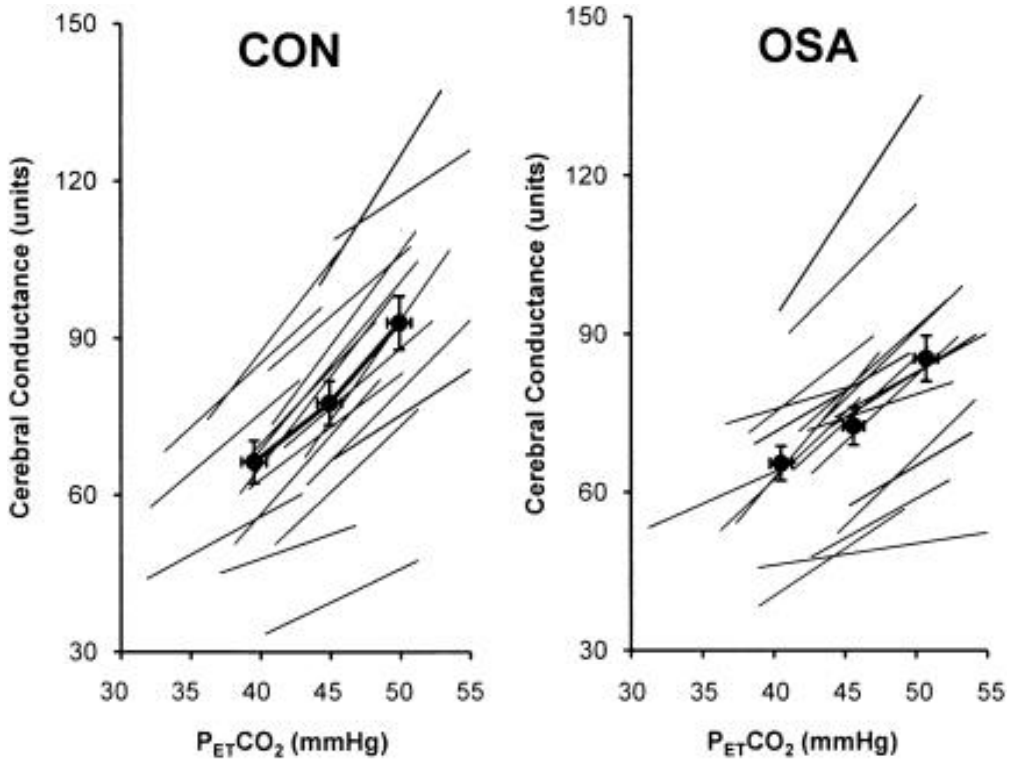
- Prevent obstruction via positive airway pressure - compliance problem
- Recruit upper airway muscle dilators and / or prevent sleep-induced tonic inhibition via electrical/pharmacologic stimulation
- Stabilize oscillations in central respiratory motor output for central and obstructive apneas via ↓ loop gain, servoventilation … the dilemma of CHF!
- Treatments tailored to individual patient airway collapsibility, airway dilator muscle recruitability, loop gain, arousability

MSNA / VE response to acute hypoxia is augmented in mild sleep disordered breathing

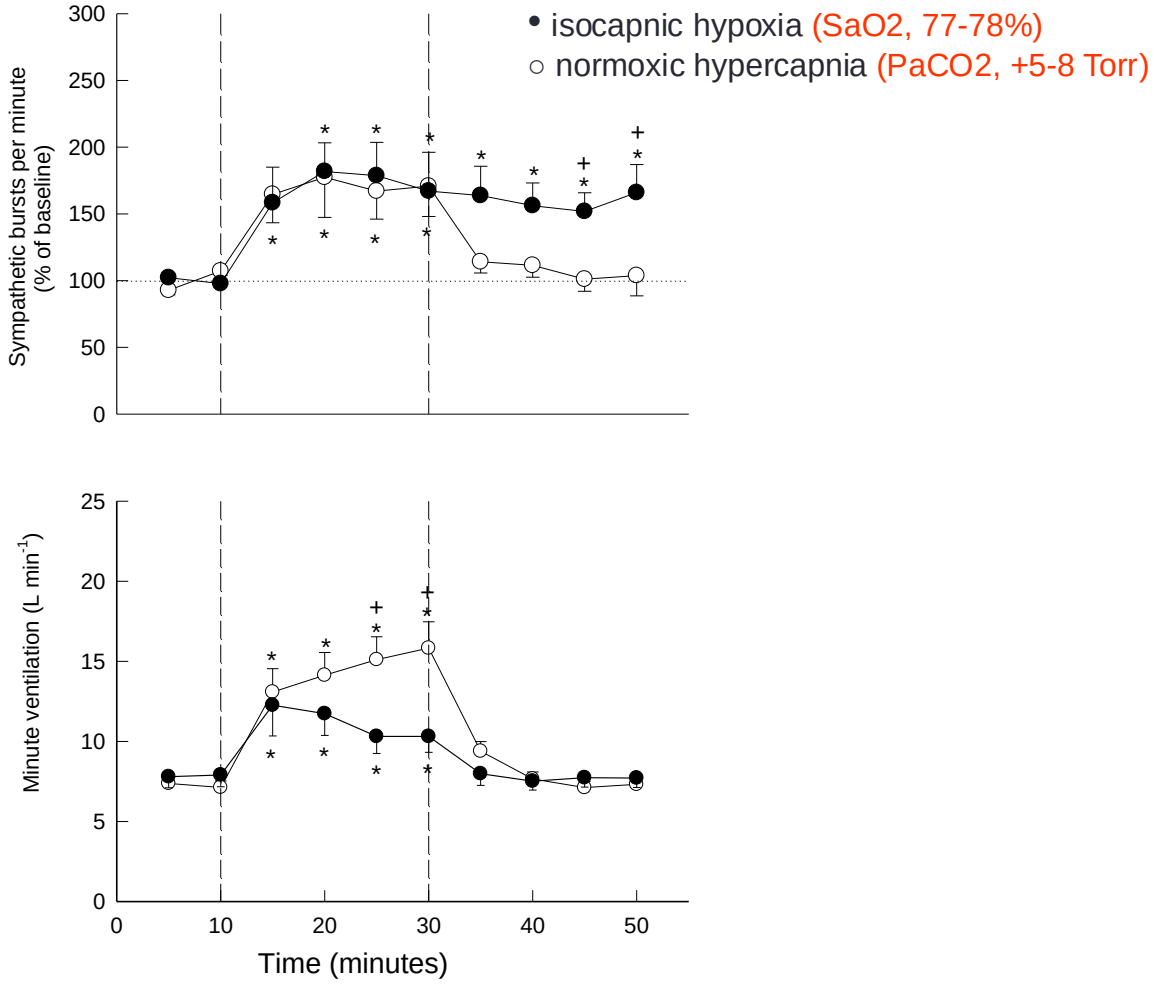
- patients with newly diagnosed, untreated hypertension
- MSNA measured during exposure to graded isocapnic hypoxia



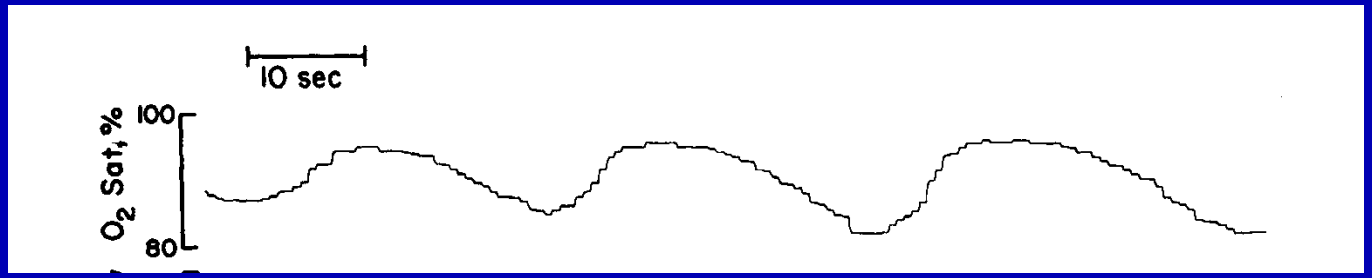
OSA impairs hypercapnic vasodilation in cerebral circulation



Hypoxia (but not hypercapnia) causes persistent sympathetic activation in healthy humans



Xie et al., 2001

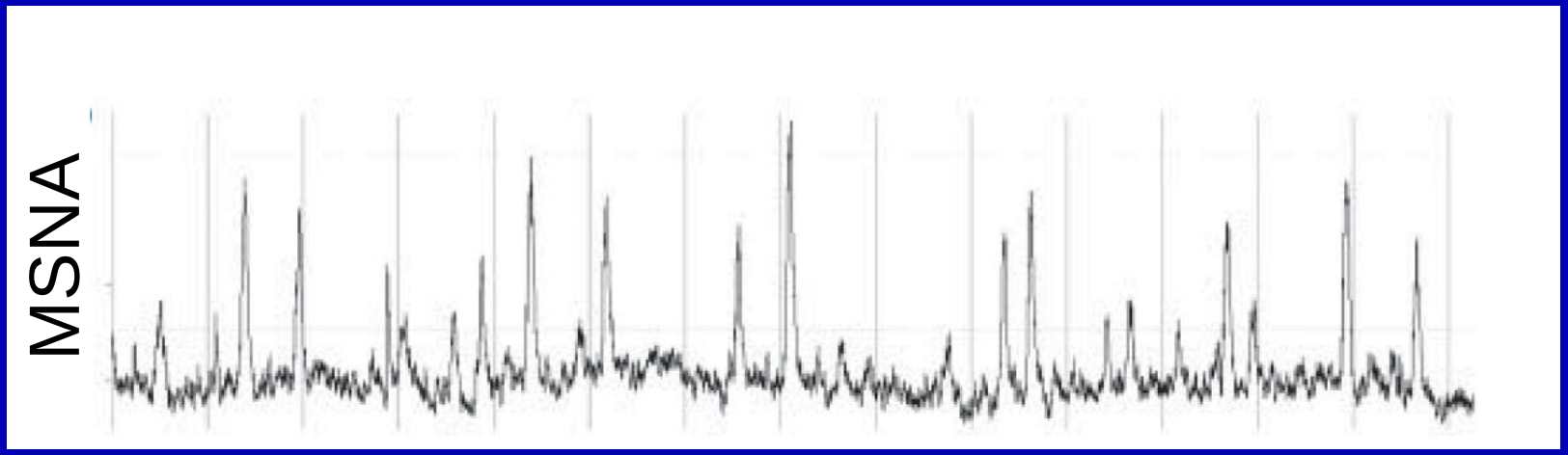


"14 Nights of Intermittent Hypoxia Elevate Daytime Blood Pressure in HEALTHY Humans" (Tamisier et al., 2011)

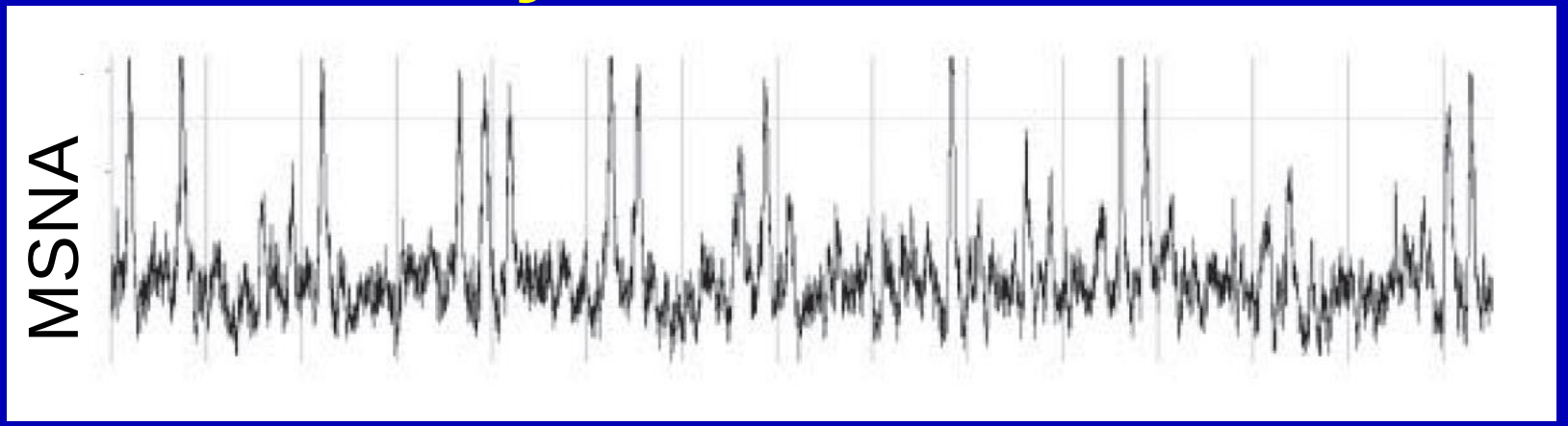
[8h/night, SaO_2 85-95%, 30 cycles/hr]

- ↑ chemoreflex,↓ baroreflex sensitivities
- Endothelial dysfunction
- ↑ insulin resistance
- Increased daytime MSNA/BP

Pre-Exposure to IH



One Day Post 2 Weeks IH



[…↓ baroreflex control of MSNA]

Conclusions/Clinical Implications

In patients with OSA, CIH-induced impairments in neurovascular regulation and local control of resistance vessels:

- contribute to hypertension and other cardiovascular disease
- may compromise tissue perfusion and oxygen delivery at rest and during acute stresses such as exercise and episodes of OSA

-Potential therapeutic targets for preventing or reversing the adverse cardiorespiratory effects of OSA via reducing carotid chemoreceptor tonic activity/sensitivity (eg via CBX, block of CB purinergic receptors).
-Hypertensive effects of irregular timing/durations /quality of sleep!?...also night to night irregularity of OSA?

Multiple Sleep-Induced Alterations in Breathing Stability/Airway Patency

- ↓ metabolic requirement: ↓VA:VCO2
- ↑ airway collapsibility via inhibition of tonic drive to upper airway dilator musculature
- ↓ lung volume
- ↑ chest wall compliance
- critical dependence of ventilatory control on variations in PaCO2 (in NREM)
- Transient arousals/sleep state disruptions
- Loss of immediate VE compensation for resistive or elastic respiratory loads