

Sleep, Sleep Apnea, and Systemic Hypertension

Virend K. Somers, MD, PhD



Identification of pressure and pulsatility in blood flow - 1727

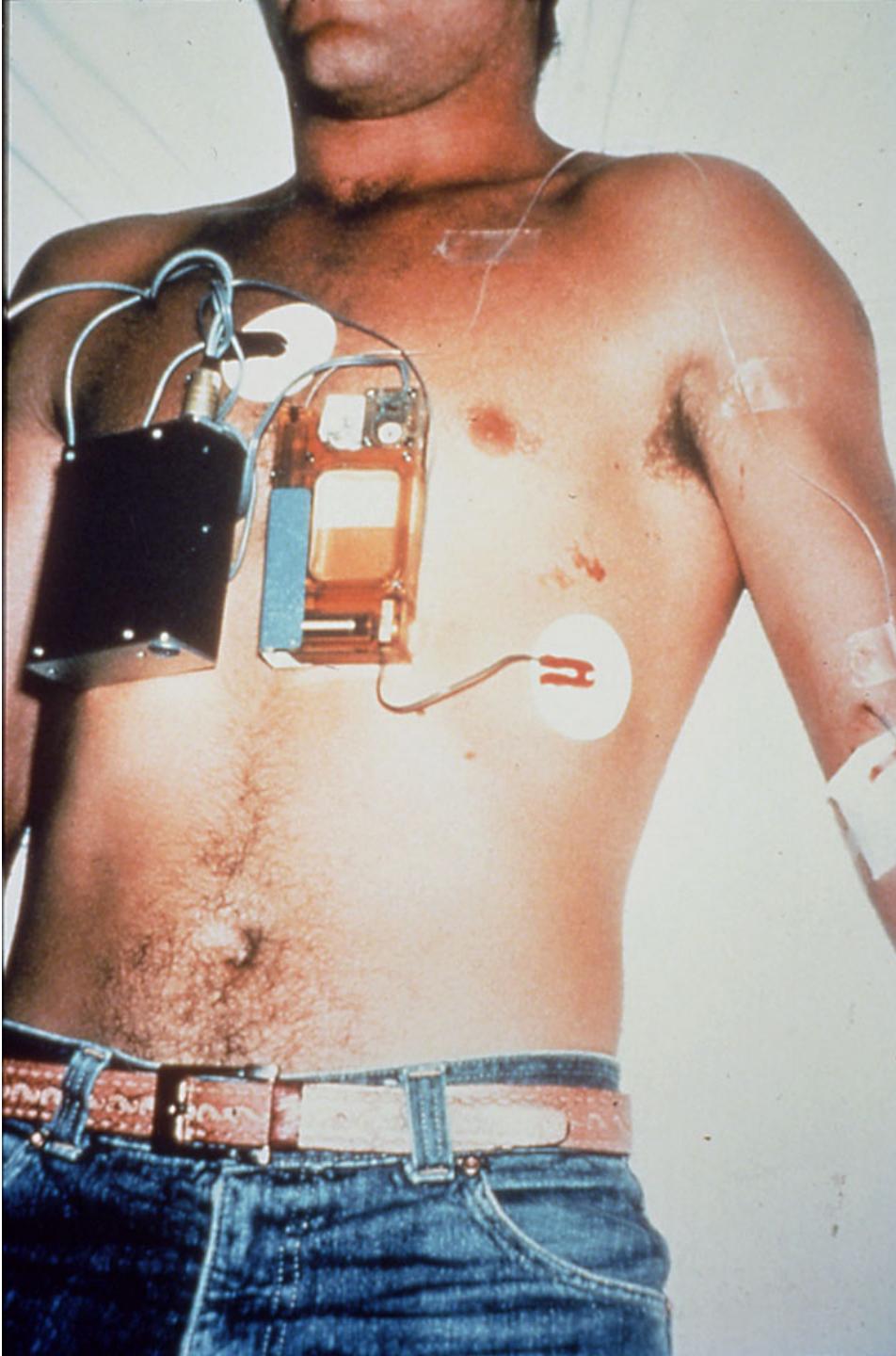
- A - William Osler
- B - William Harvey
- C- William Penn
- D - William Tell
- E – Reverend Stephen Hales

De Motu Cordis –
William Harvey, 1628



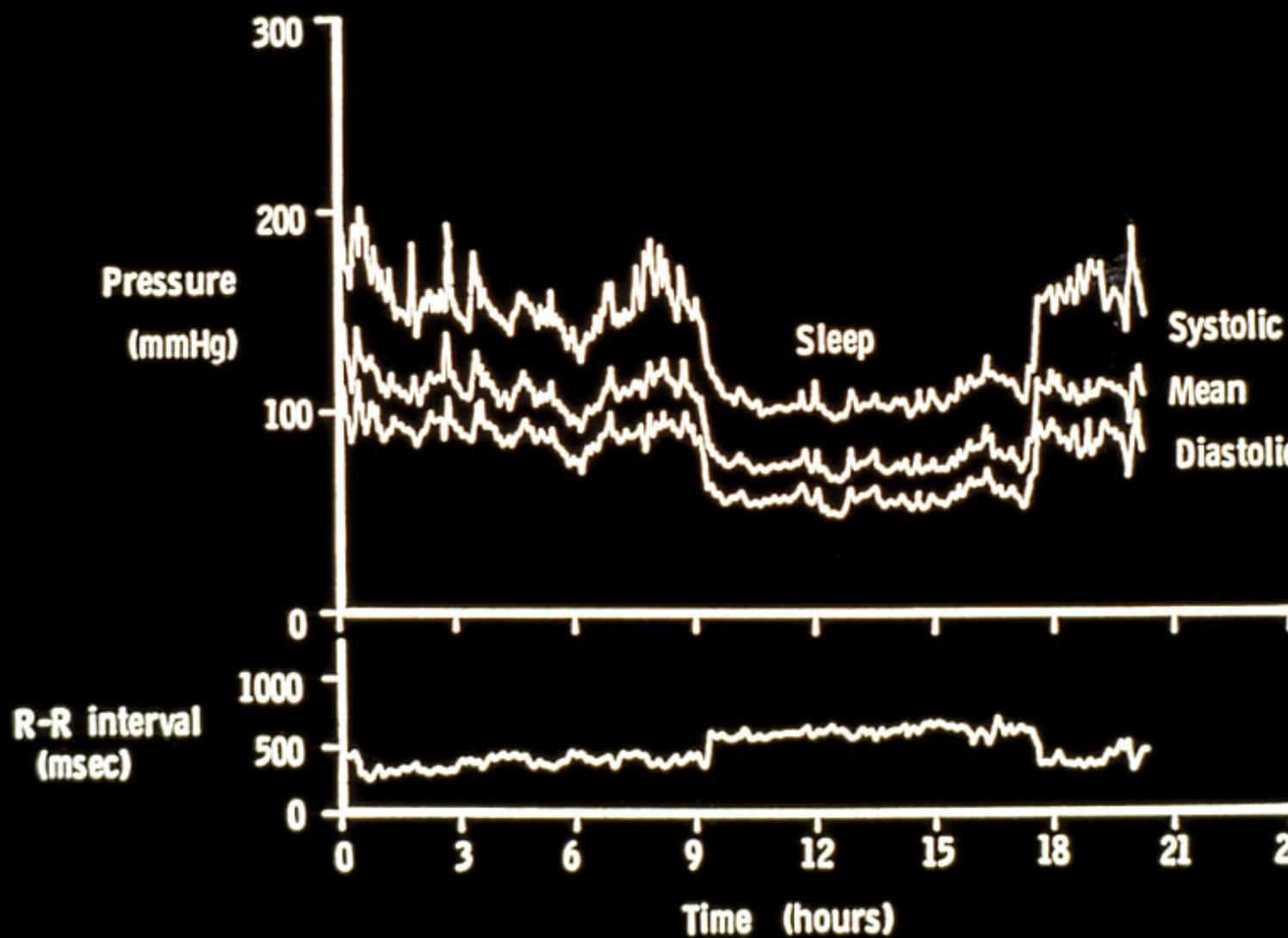
Sleep and Blood Pressure Control

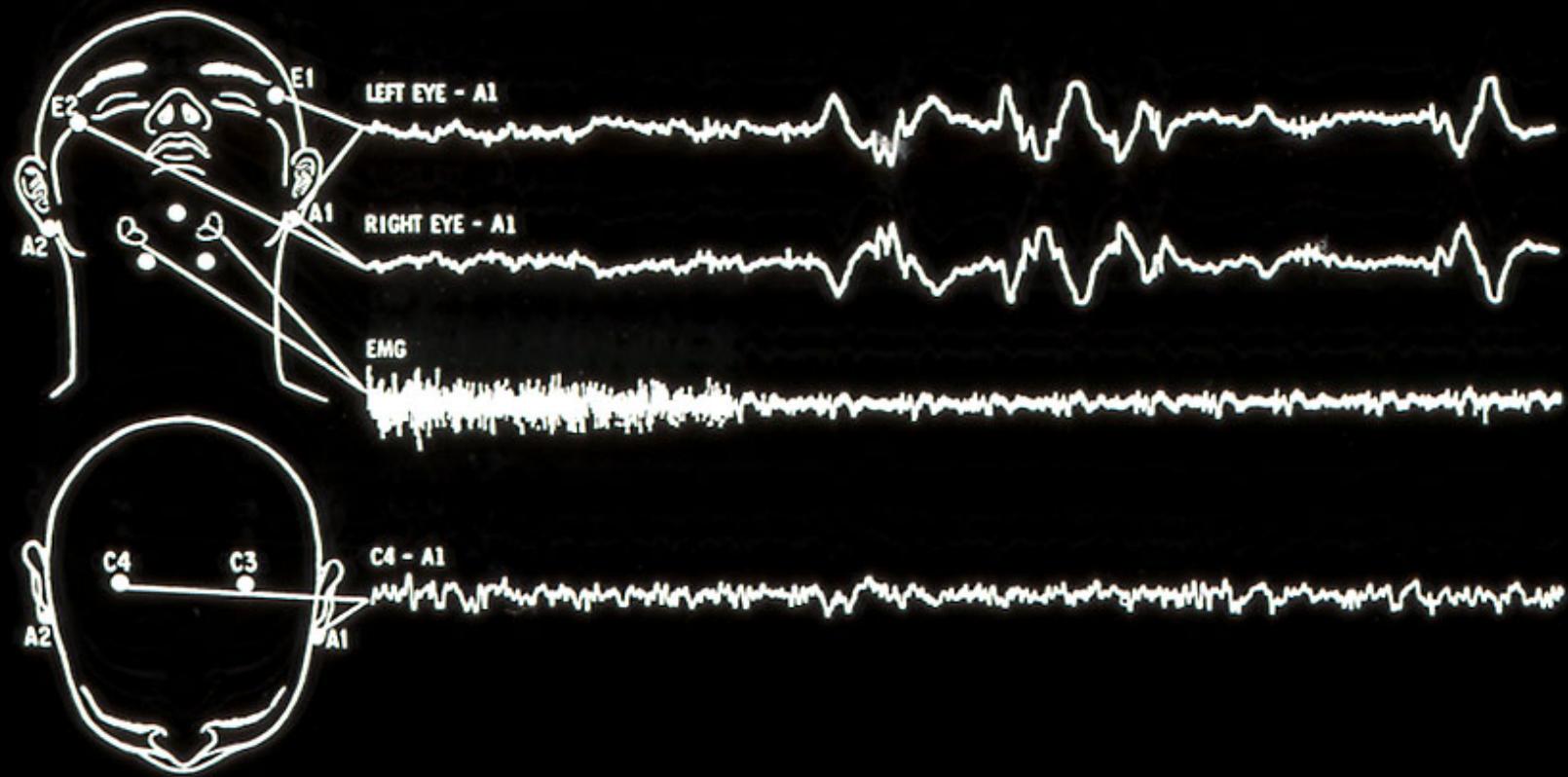
- **Physiology of sleep**
- **Obstructive sleep apnea**
- **Sleep deprivation**

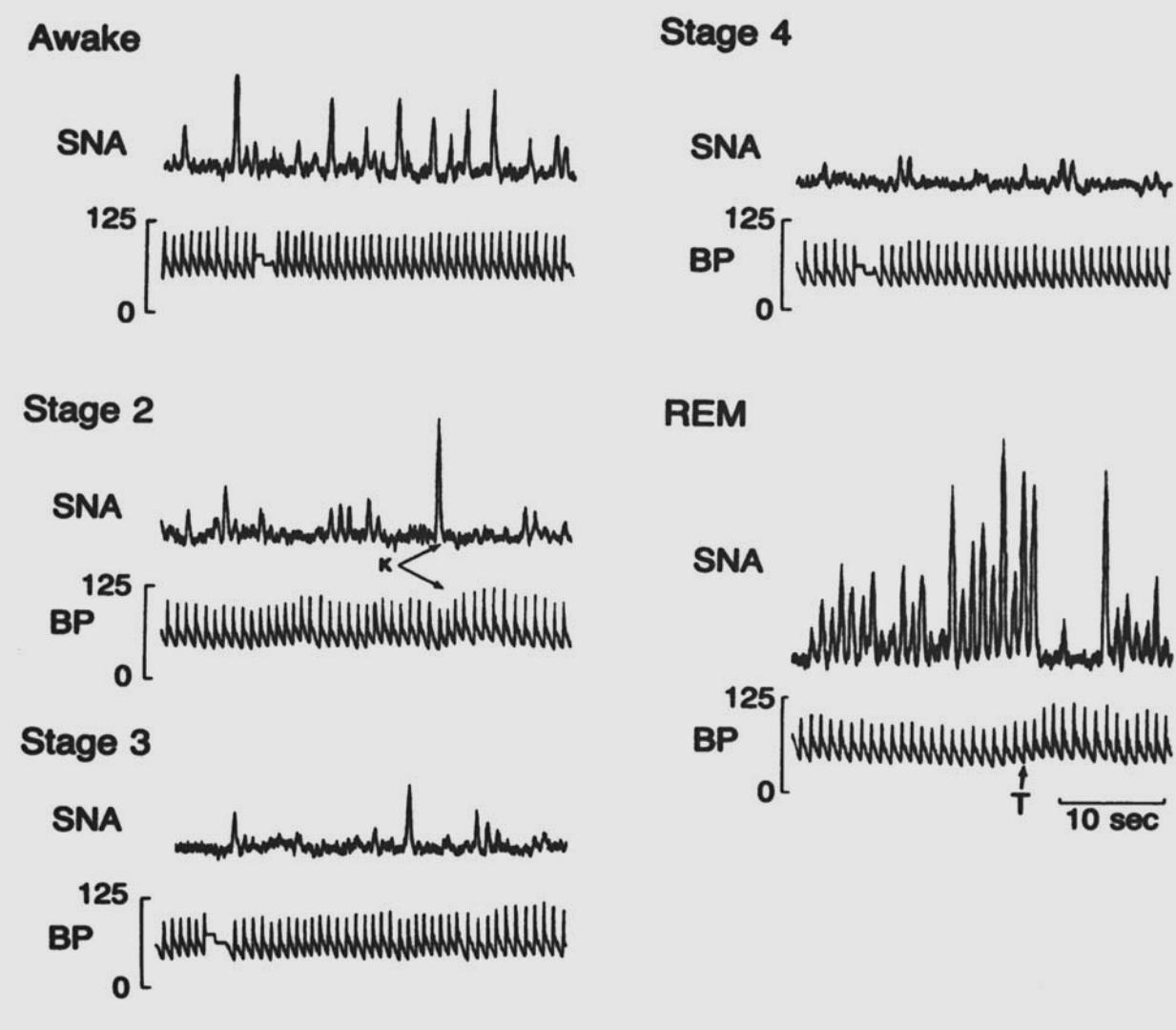


INTRA-ARTERIAL AMBULATORY BLOOD PRESSURE

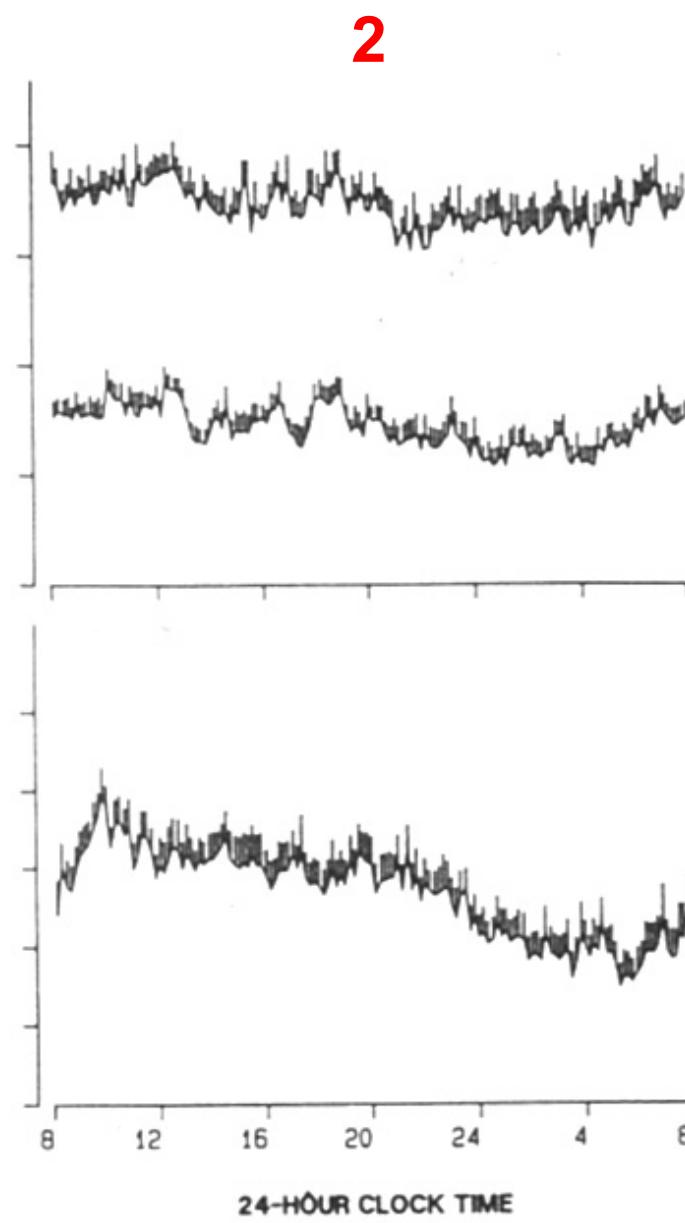
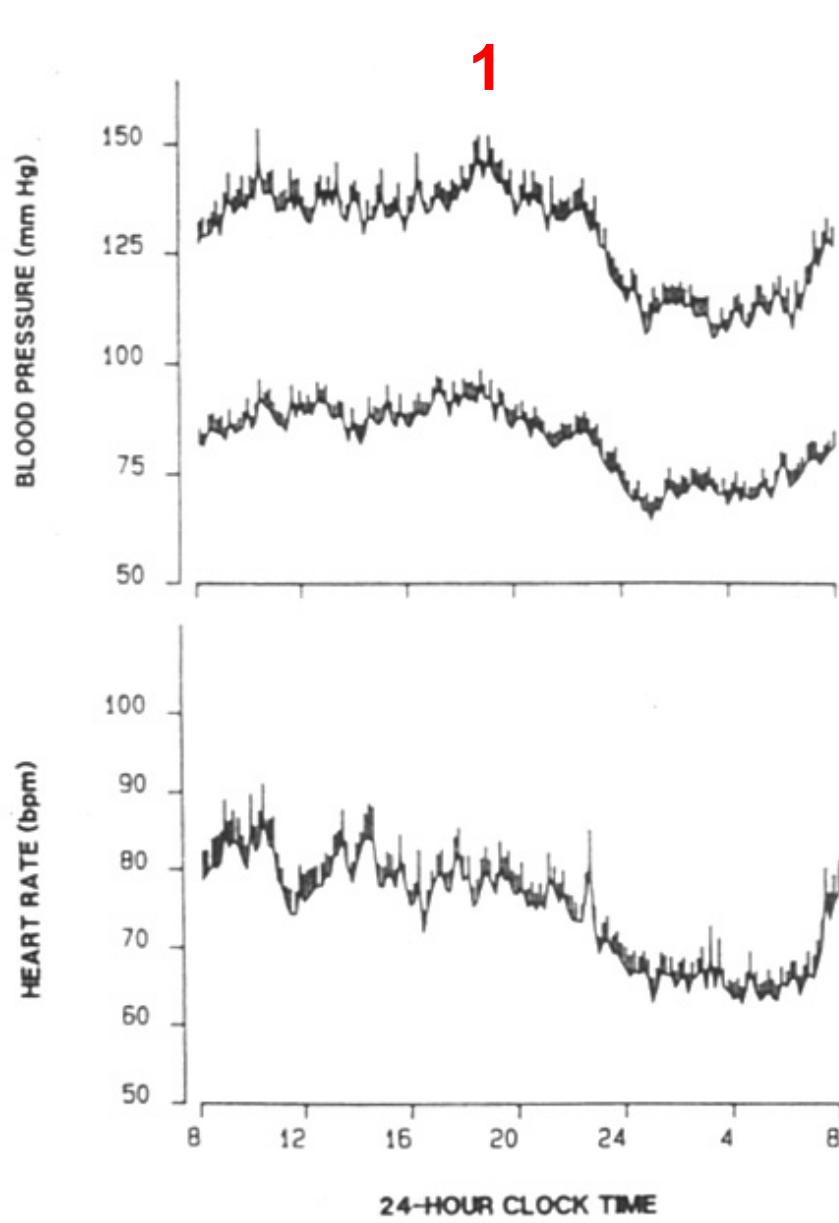
Patient RF



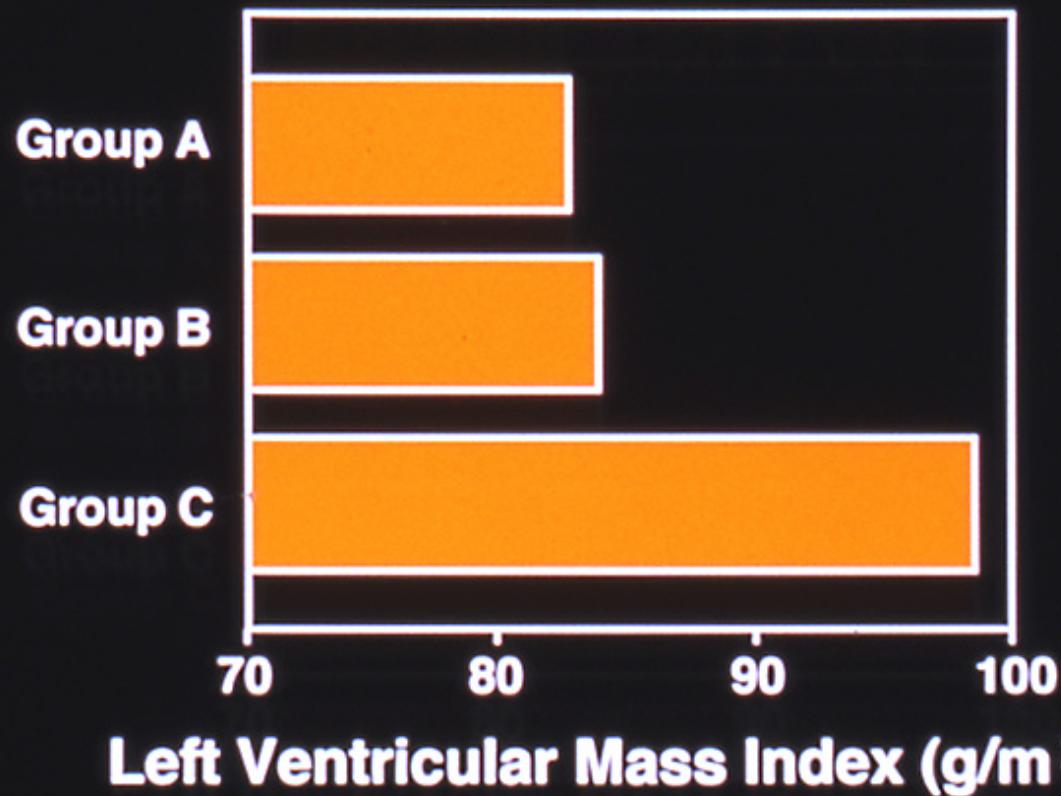




Somers et al: NEJM, 1993



Relationship Between Nocturnal BP Fall and LVH



Verdecchia et al
Circulation, 1990

Reprinted from
American Journal of Ophthalmology
Vol. 117, No. 5, May 15, 1994

Nocturnal Arterial Hypotension and Its Role in Optic Nerve Head and Ocular Ischemic Disorders

Sohan Singh Hayreh, M.D., M. Bridget Zimmerman, Ph.D., Patricia Podhajsky, B.S.N.,
and Wallace L. M. Alward, M.D.

Nocturnal Fall of Blood Pressure and Silent Cerebrovascular Damage in Elderly Hypertensive Patients

Advanced Silent Cerebrovascular Damage in Extreme Dippers

Kazuomi Kario, Takefumi Matsuo, Hiroko Kobayashi, Masahiro Imiya,
Miyako Matsuo, Kazuyuki Shimada

Abstract To study the relation between diurnal blood pressure variations and silent cerebrovascular damage, we performed both 24-hour ambulatory blood pressure monitoring and brain magnetic resonance imaging in 131 elderly asymptomatic hypertensive patients. Silent cerebrovascular damage was identified by the magnetic resonance imaging findings of lacunae (low intensity in T₁-weighted images and high intensity in T₂-weighted images) and advanced periventricular hyperintense lesions (on T₂-weighted images). The frequency of silent cerebrovascular damage in the 100 patients with sustained hypertension was greater than that in the 31 patients with white coat hypertension. We further classified the former group into nondippers (nocturnal reduction of systolic pressure by <10% of awake systolic pressure; n=46), dippers (reduction by ≥10% to <20%; n=38), and extreme dippers (reduction by ≥20%; n=16). The extent of silent cerebrovascular damage was least severe in the dipper group ($P<.05$). This J-shaped relation was

not found either with the cardiac hypertrophy detected by electrocardiography or with the renal damage assessed by urinary albumin excretion. More than half of the extreme dippers were patients with isolated systolic hypertension, and this prevalence was significantly greater than that in dippers or in nondippers (21% and 30%, respectively). Extreme dippers also had greater variability of pressure (standard deviation of awake systolic pressure) than dippers. Our results indicate that in addition to nondipping, extreme dipping (marked nocturnal fall of blood pressure) should be considered a type of abnormal diurnal blood pressure variation in elderly patients with hypertension who are likely to have advanced silent cerebrovascular damage. (*Hypertension*. 1996;27:130-135.)

Key Words • blood pressure monitoring • circadian rhythm • elderly • hypertension • cerebrovascular disorders

Low blood pressure and early death of elderly people with dementia

*Zhenchao Guo, Matti Viitanen, Laura Fratiglioni,
Bengt Winblad*

Patients with dementia generally have lower blood pressure than people without dementia.^{1,2} Low blood pressure has been linked to excess mortality among elderly people.^{3,4} We investigated a relation between low blood pressure and increased mortality among people with dementia.

The Kungsholmen Project is a longitudinal study of ageing and dementia in all people in Kungsholmen district, Stockholm, Sweden, aged 75 years and older on Oct 1, 1987.¹ We included 1810 (74·6%) in the initial survey. In two phases (screening and clinical examination) we diagnosed 225 as demented according to the criteria of the Diagnostic and Statistical Manual of Mental Disorders, third edition. Of these 225 patients, we analysed blood pressure measurements from 202. Dementias were: Alzheimer's disease (112), vascular dementia (48), secondary dementia (19), and unspecified or questionable dementia (23). We determined severity with the

Sleep and Blood Pressure Control

- Physiology of sleep
- Obstructive sleep apnea
- Sleep deprivation

Case Review

- 18 yr old Caucasian male
- BP 150-180/90-110 despite combined therapy with amlodipine, enalapril, hydrochlorothiazide and clonidine patch
- Evaluated for pheo, primary aldo, renovascular and renal causes
- Mild cognitive impairment
- Mother denied daytime somnolence or snoring

Prior Evaluation

- Dexamethasone suppression test
- Renal angiogram and renal vein renin measurements
- Urine metanephhrines
- Plasma renin and aldosterone
- CT adrenals
- Calcium and PTH levels

Sleep Study

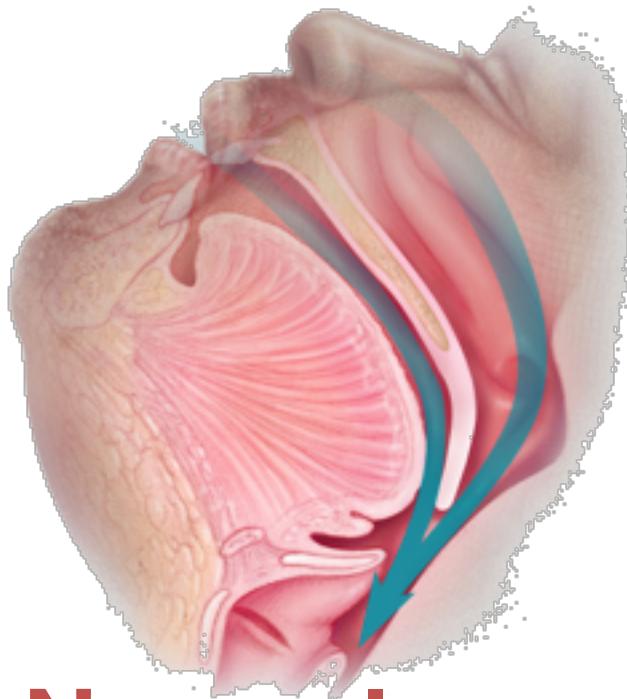
- Mother accompanied patient to sleep lab
- Apnea/hypopnea index: 33 events per hour, predominantly obstructive
- Significant positional component
- Nocturnal de-saturation from 98% when awake to nadir of 79% during REM on back

Treatment

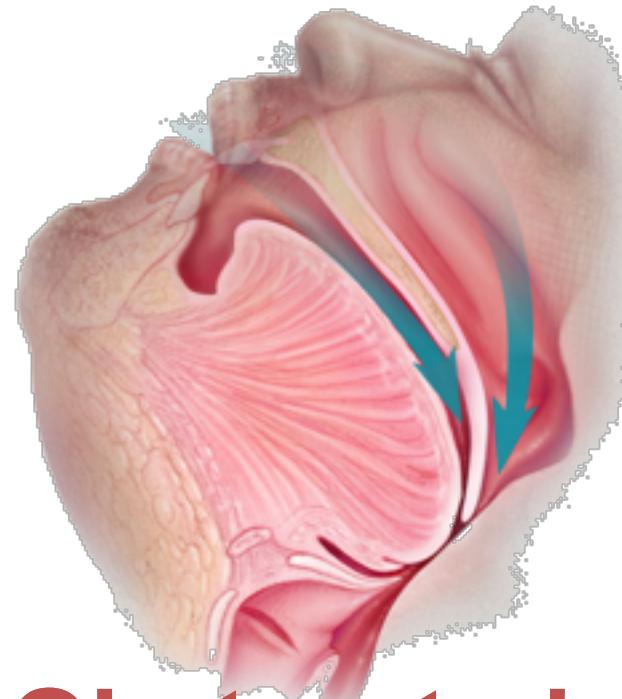
- CPAP treatment at 10 cm H₂O reduced AHI to 4 events per hour
- 3 months later- BP averaging 125/85 on enalapril 5mg daily
- Mother notes he is finally able to watch a movie from beginning to end
- Working as a greeter at Walmart

What is OSA?

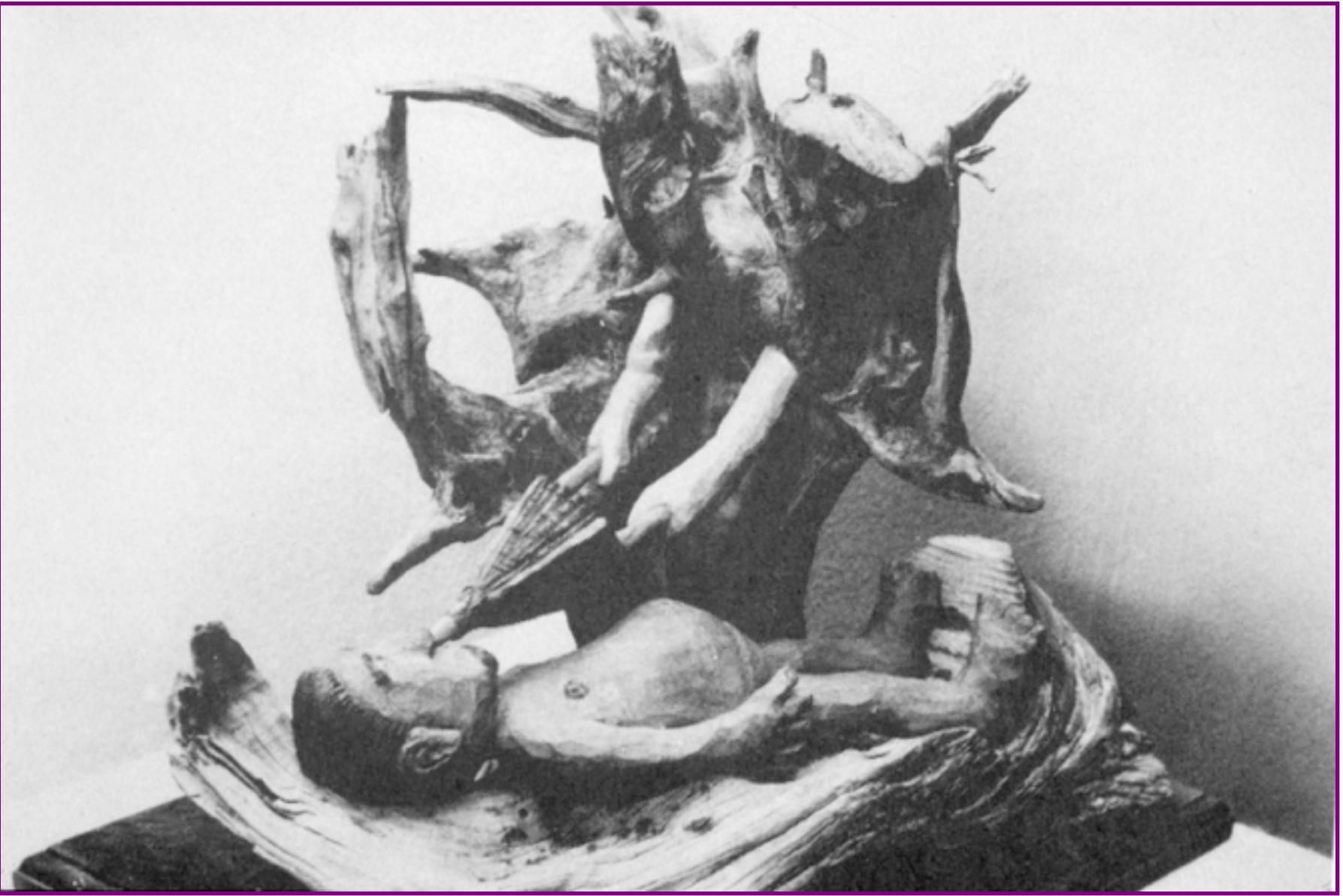
Cessation or reduction of airflow due to complete (**APNEA**) or partial (**HYPOPNEA**) closure of the upper airway.



Normal

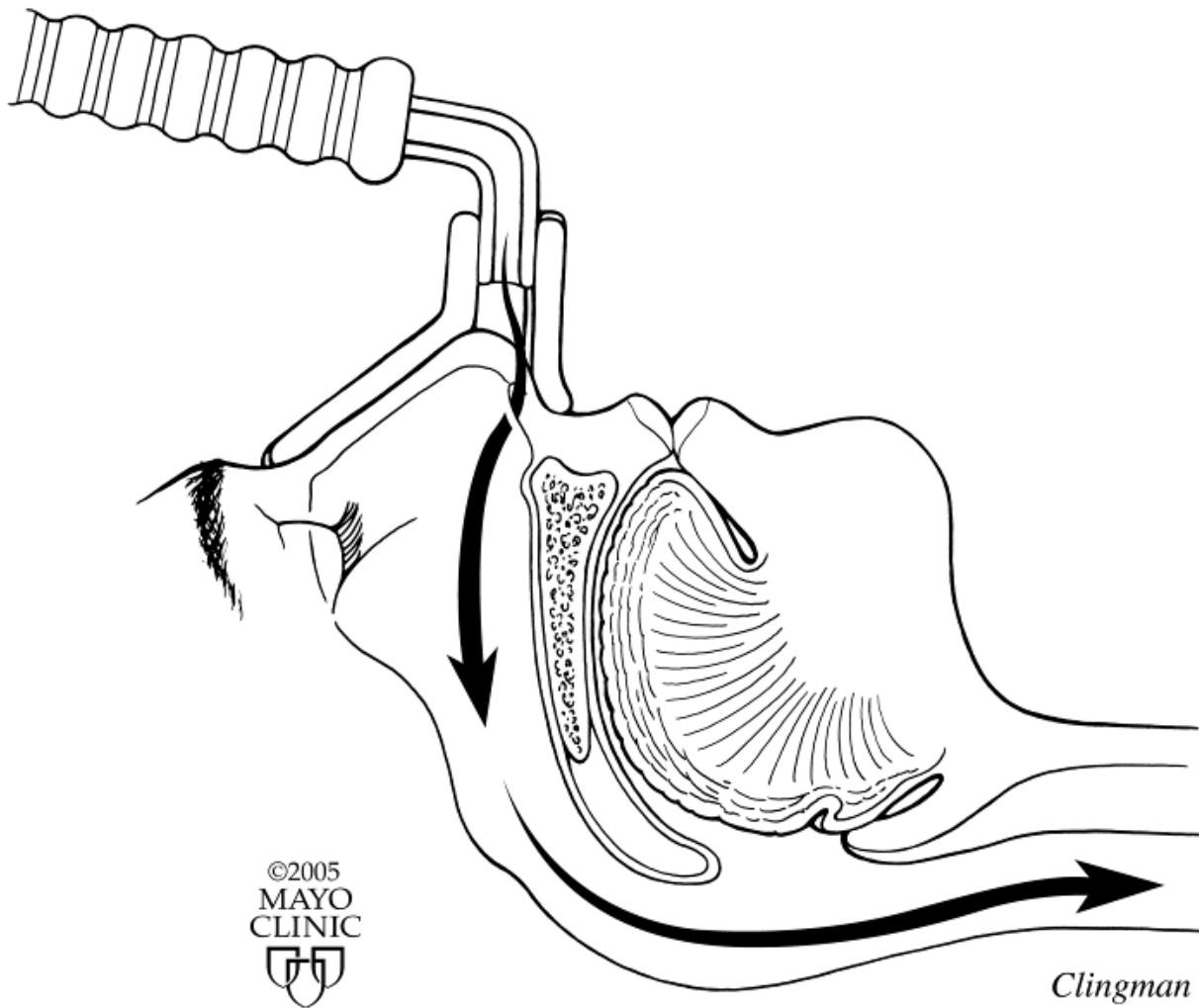


Obstructed



CP1020561-52

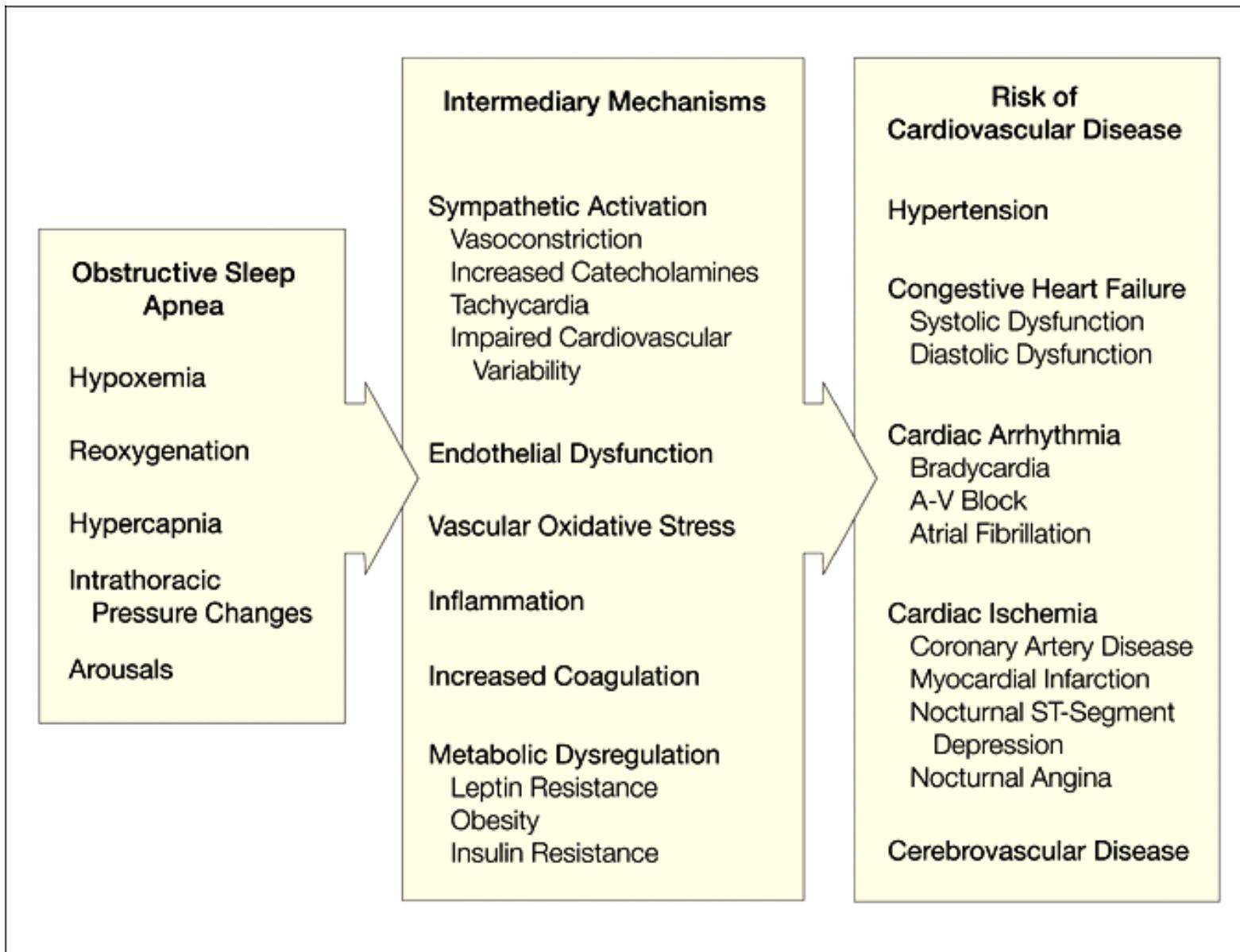
CPAP



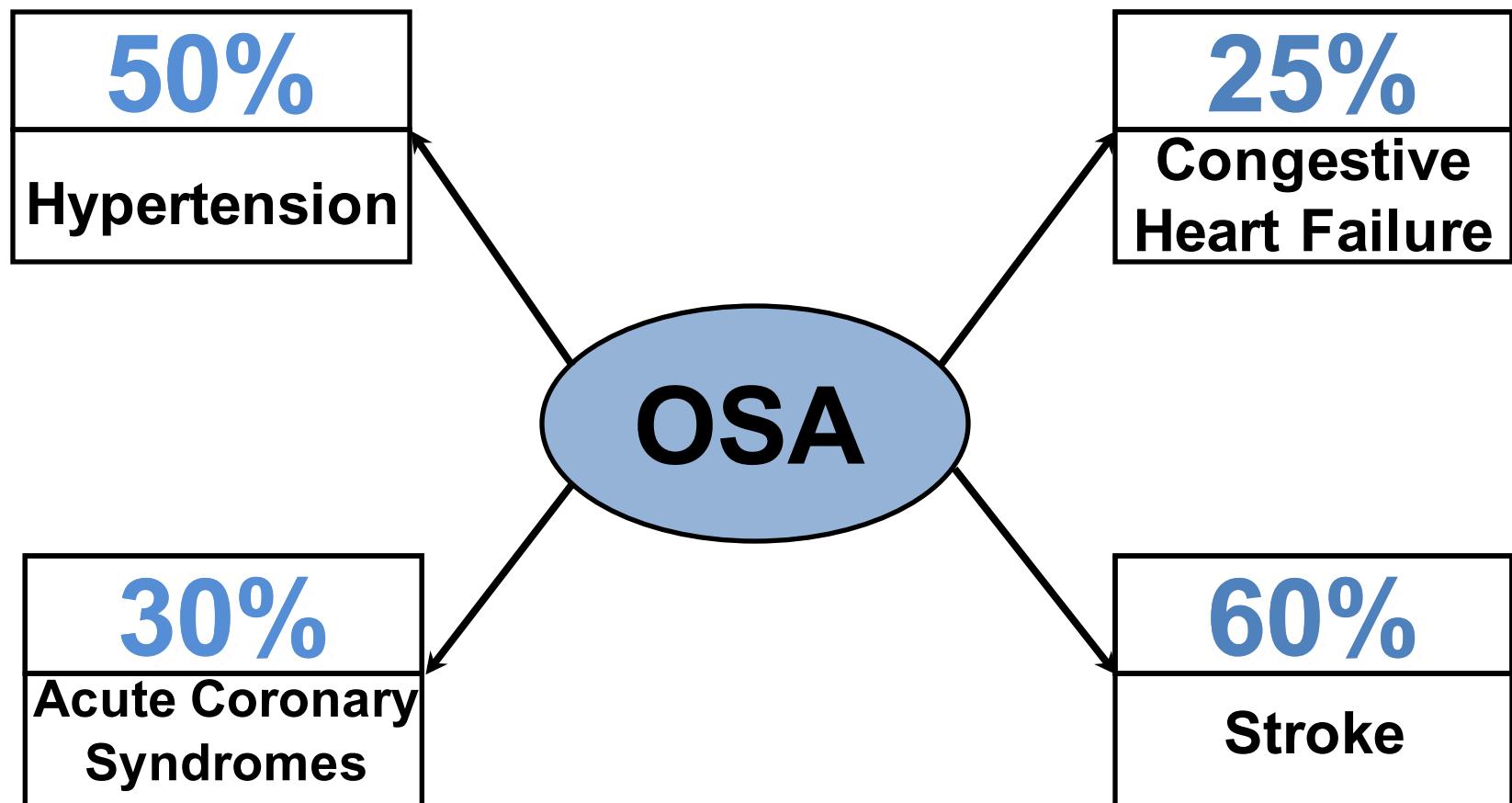
Does OSA “Cause” Cardiovascular Disease?

If so, does treatment of OSA modify cardiovascular outcomes?

Does CPAP Treatment of OSA reduce BP in Patients with Hypertension?



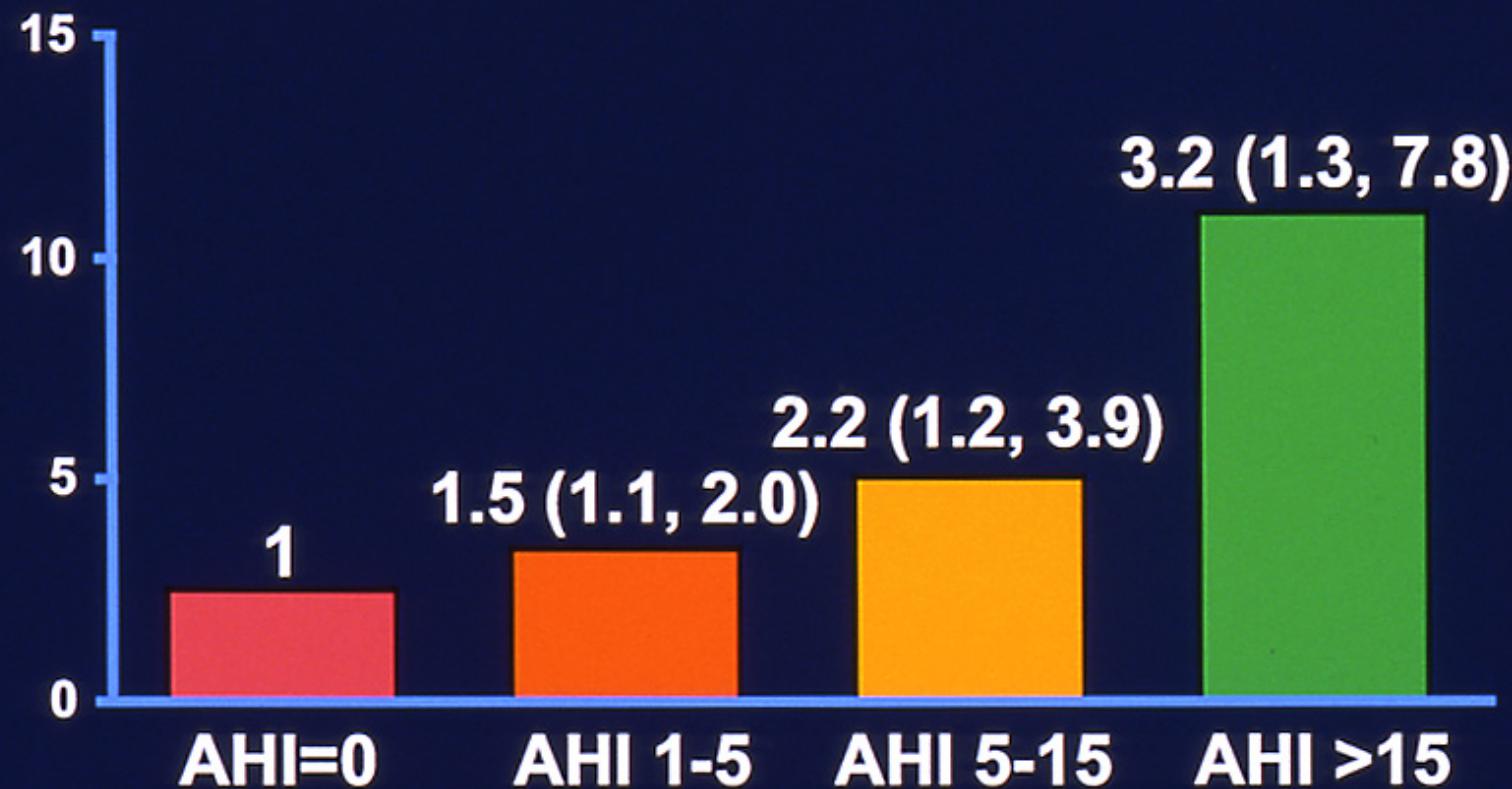
Prevalence of OSA in CVD Patients



Association ≠ Causality

- **Common risk factors**
 - Obesity
 - Male > female gender
 - Advancing age
- **Lack of prospective longitudinal studies**
 - Case-control methods predominate
 - Precludes establishment of a temporal relationship
- **The AHI is imperfect**
- **Lack of randomized, interventional, controlled trials**
 - Reliability of observational studies?
 - Is risk modifiable?—vascular remodeling
 - Substantial placebo effect of CPAP device

Odds Ratios* for Incident Hypertension at 4-Year F-U with Baseline AHI >0 Wisconsin Sleep Cohort Study



*Adjusted for age, sex, smoking, ALC, BMI, neck girth

Peppard et al: NEJM 2000

Joint National Committee on Hypertension

- JNC VI – 1997 - consider OSA as a cause of resistant hypertension, especially in obese patients.
- JNC VII – 2003 - OSA first on the list of identifiable causes of hypertension (JAMA)

Initial Treatment of Hypertension NEJM, 348, 2003.

Case study – 50 yo African American male, 20 lbs overweight, BP 160/110.

Work up includes primary aldo, pheochromocytoma and renovascular hypertension.

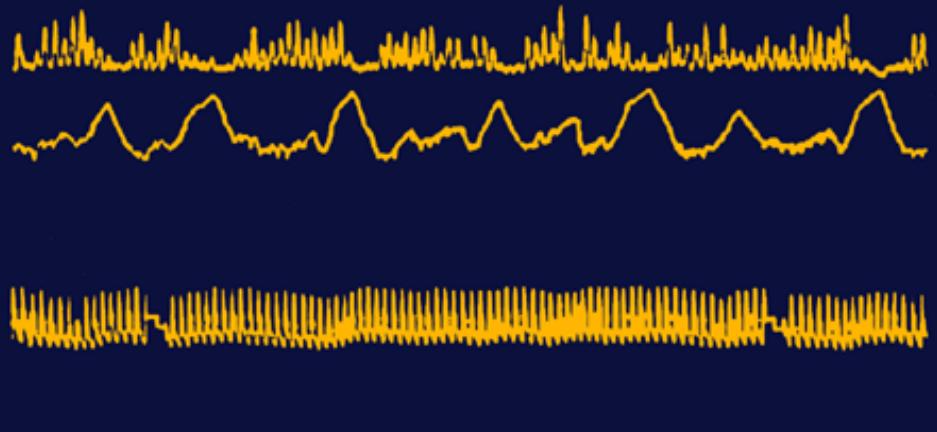
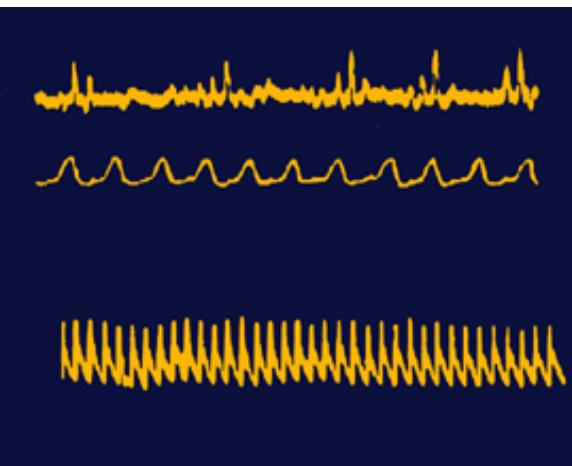
No mention of sleep apnea

Normal

Sleep Apnea

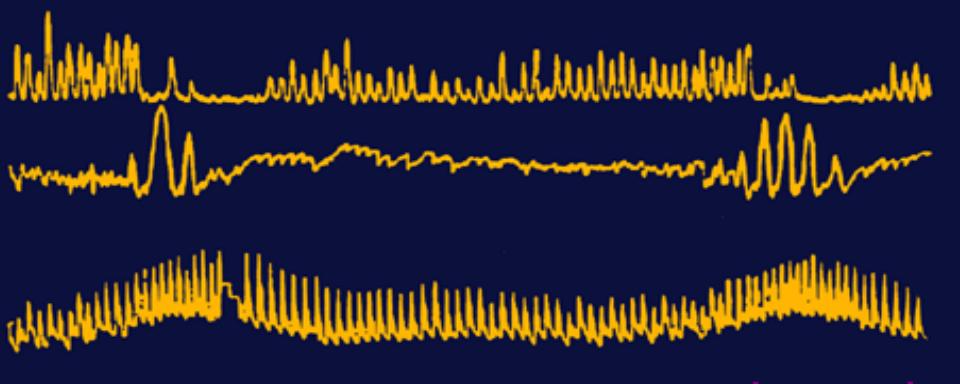
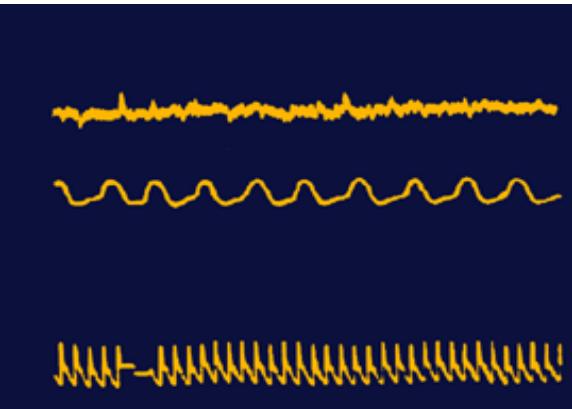
Awake

SNA
RESP
200
BP 100
0



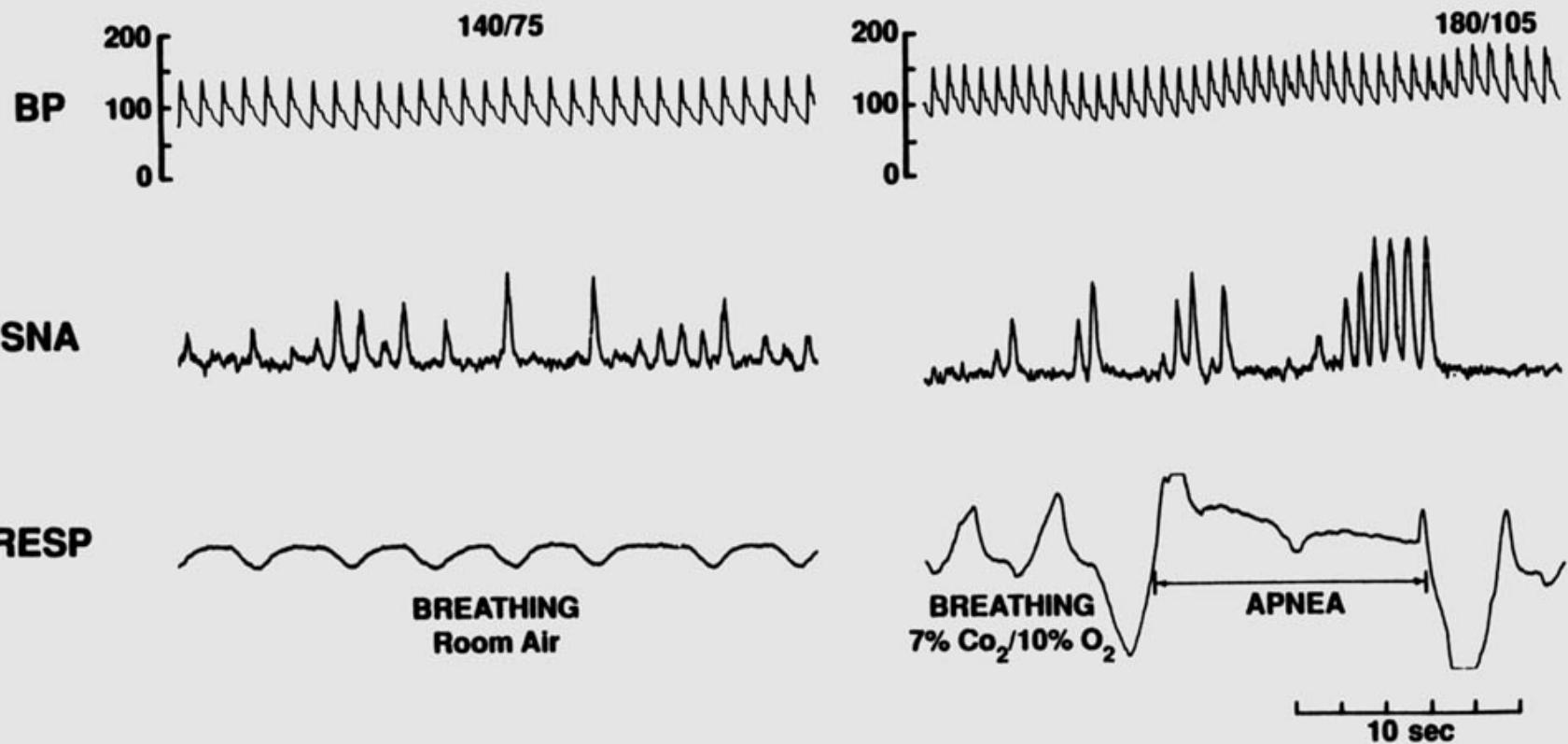
Stage IV

SNA
RESP
200
BP 100
0

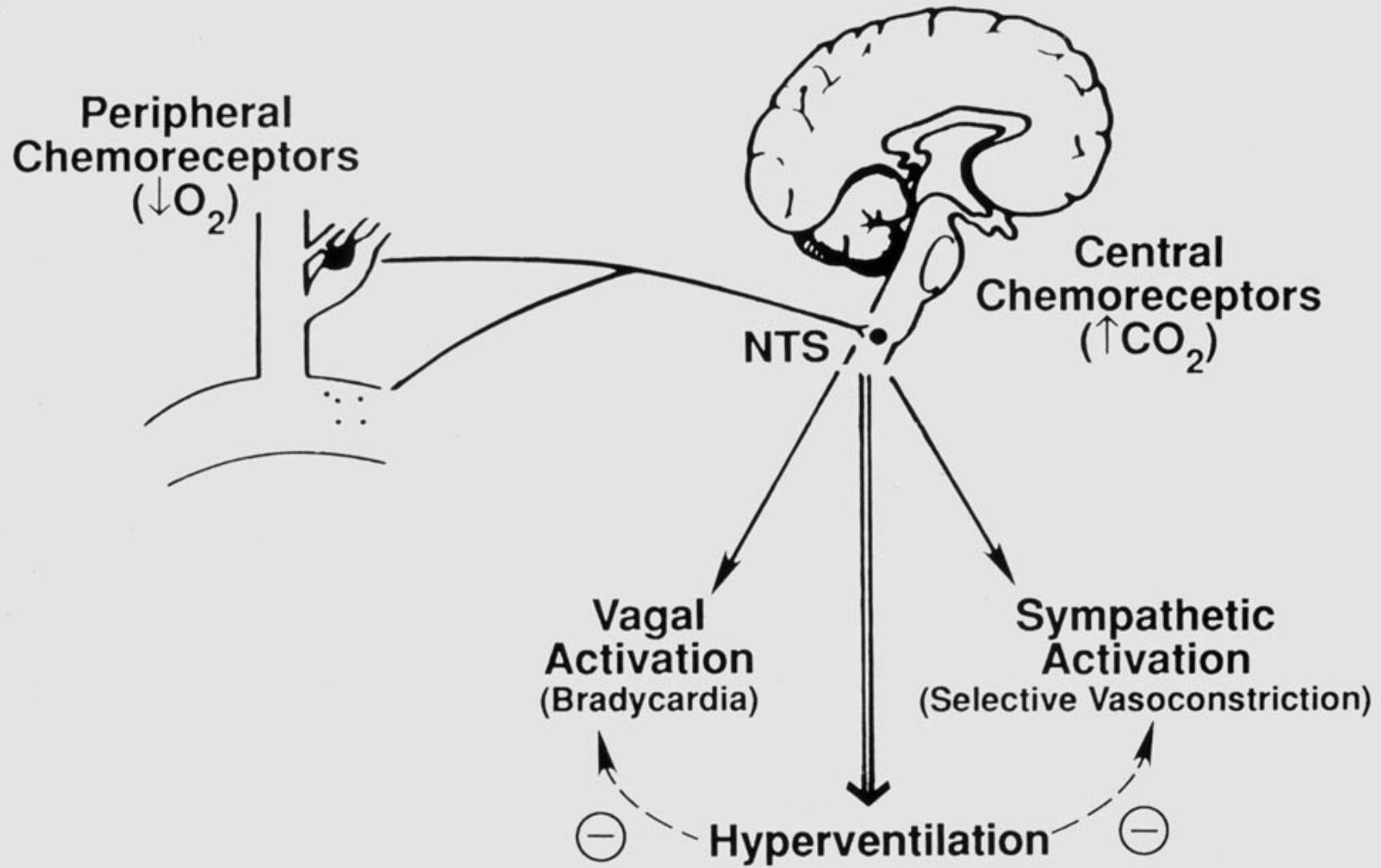


10 sec

Hypoxia, Hypercapnia and Voluntary Apnea Increase SNA and BP



Somers et al: Clin Exp Hypertension, 1989



Cardiovascular Research, 1982, **16**, 163–172

Increased sensitivity of the arterial chemoreceptor drive in young men with mild hypertension

ANDRZEJ TRZEBSKI,* MALGORZATA TAFIL, MAREK ZOLTOWSKI, AND
JACEK PRZYBYLSKI

*From the Department of Physiology, Institute of Physiological Sciences, Medical Academy, Warsaw and the
Department of Pathophysiology Institute of Tuberculosis, 00-927 Warsaw, Poland*

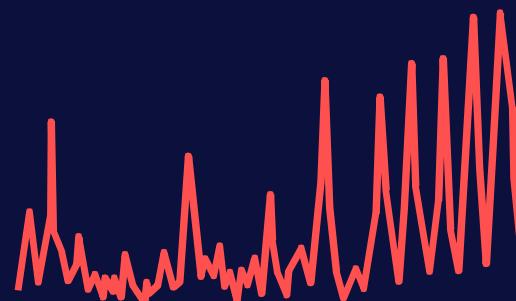
Potentiated SNA Response to Apnea in Borderline Hypertension

Apnea on 10% O₂

Normotensive

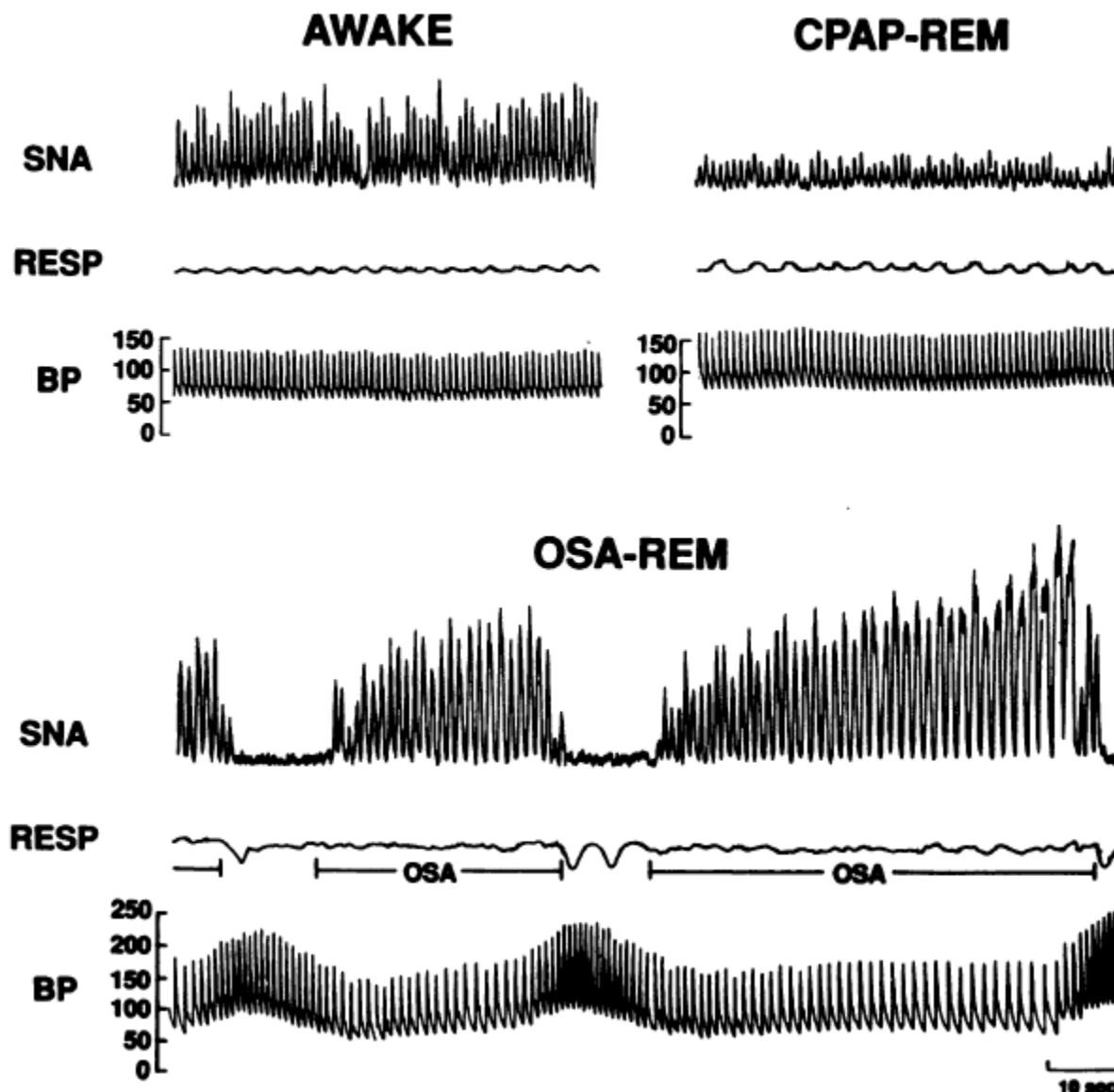


Hypertensive



10 secs

Somers et al: Hypertension, 1988



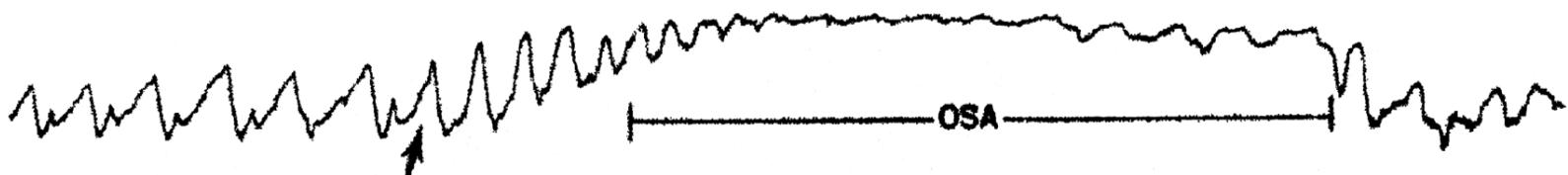
EKG



SNA



RESP



CPAP
Withdrawal

BP

150
100
50
0

Increase in sympathetic activity
immediately after CPAP withdrawal

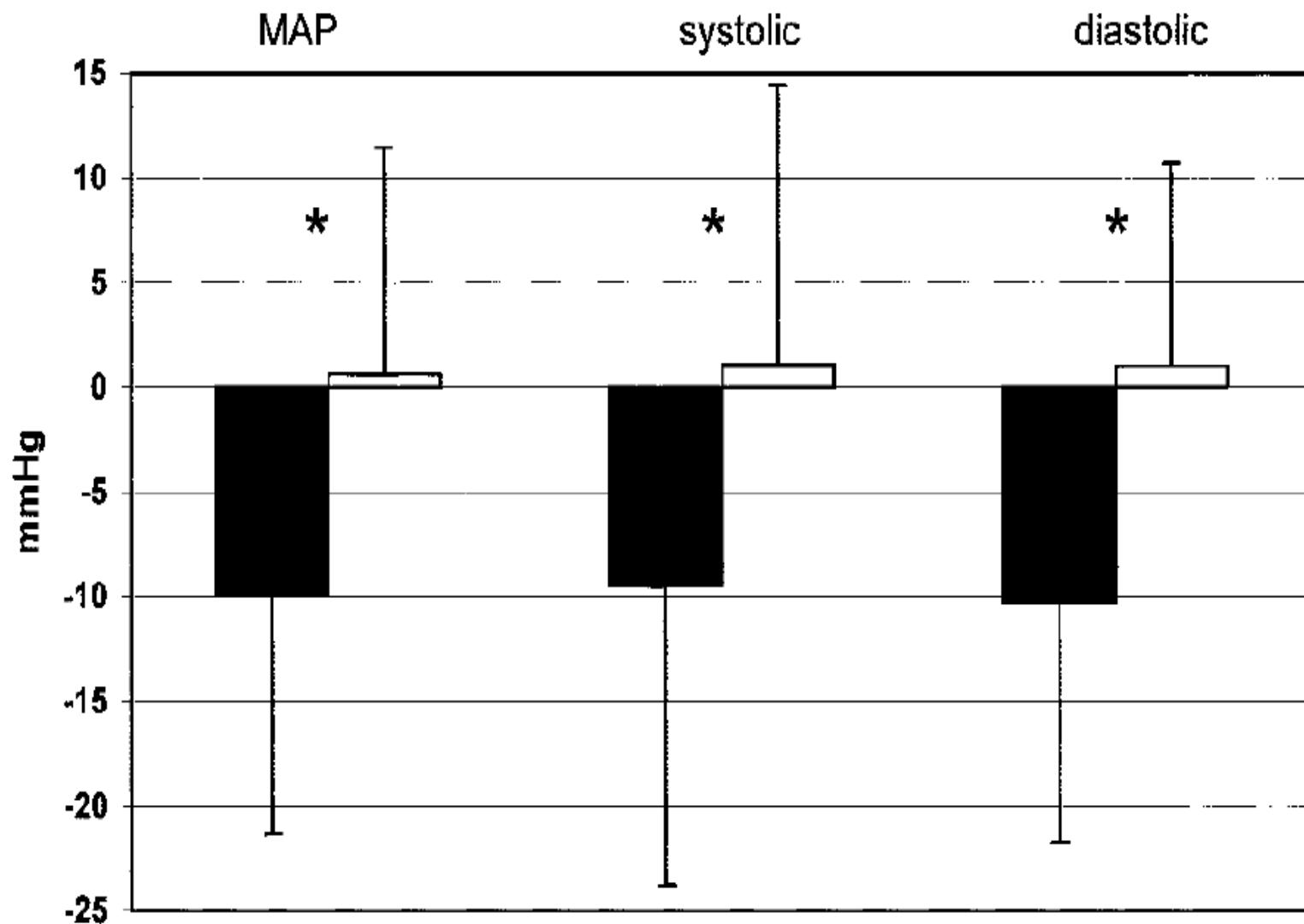
10 sec

CPAP Treatment of Systemic Hypertension

Systemic Hypertension

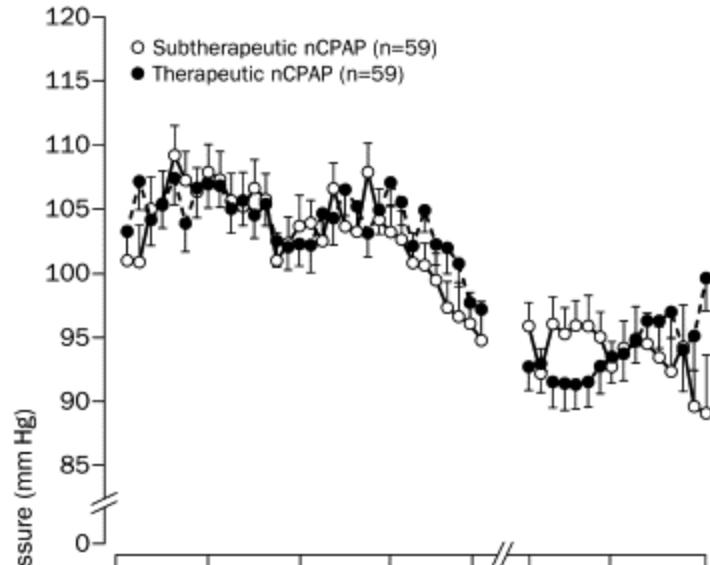
- **Dozens of observational studies suggest a link between OSA and HTN**
- **CPAP can acutely reduce BP during sleep**
- **The bigger question: Does the effect of CPAP translate to diurnal reductions in BP?**
- **CPAP Interventional Trials**

Changes in blood pressure with effective (closed bars) and subtherapeutic CPAP

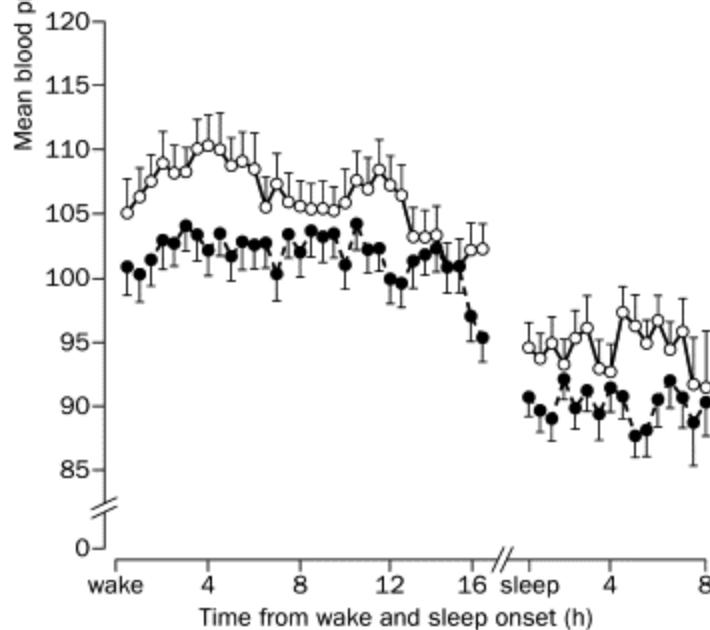


RCT 1 Month CPAP vs Subtherapeutic CPAP

Baseline



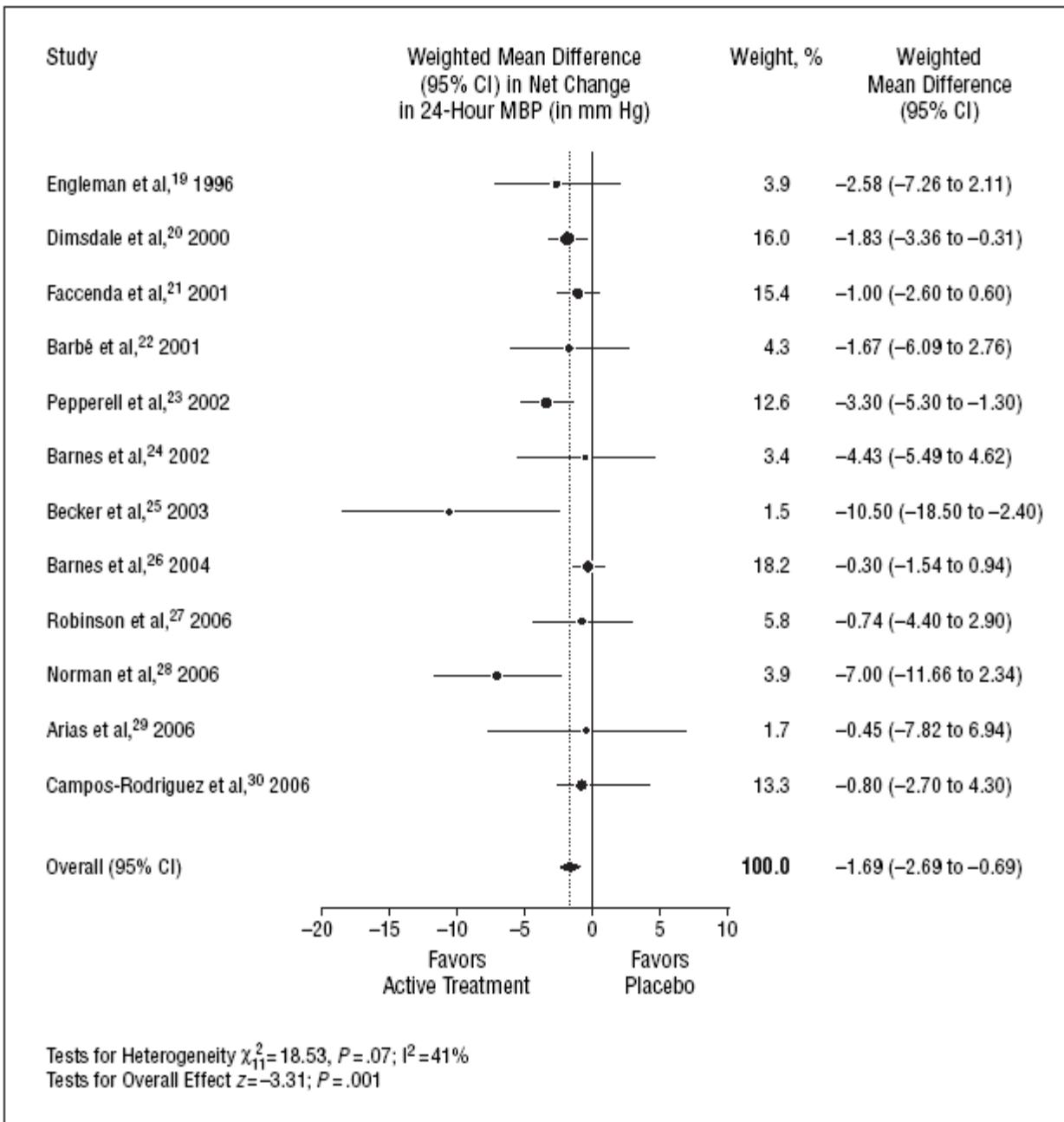
At 1 month



Reduced BP
Day and Night
Mean 3.3 mmHg

Pepperell, *Lancet*, 2002

Meta-Analysis



Haentjens
Arch Intern Med
 2007

The influence of excessive daytime sleepiness (EDS) on the antihypertensive response to CPAP: ? A common pathway

**Treatment with Continuous Positive Airway Pressure Is Not Effective in
Patients with Sleep Apnea but No Daytime Sleepiness**

A Randomized, Controlled Trial

Barbe

Annals of Internal Medicine

2001



Scan for Author
Video Interview

Effect of Continuous Positive Airway Pressure on the Incidence of Hypertension and Cardiovascular Events in Nonsleepy Patients With Obstructive Sleep Apnea

A Randomized Controlled Trial

Ferran Barbé, MD

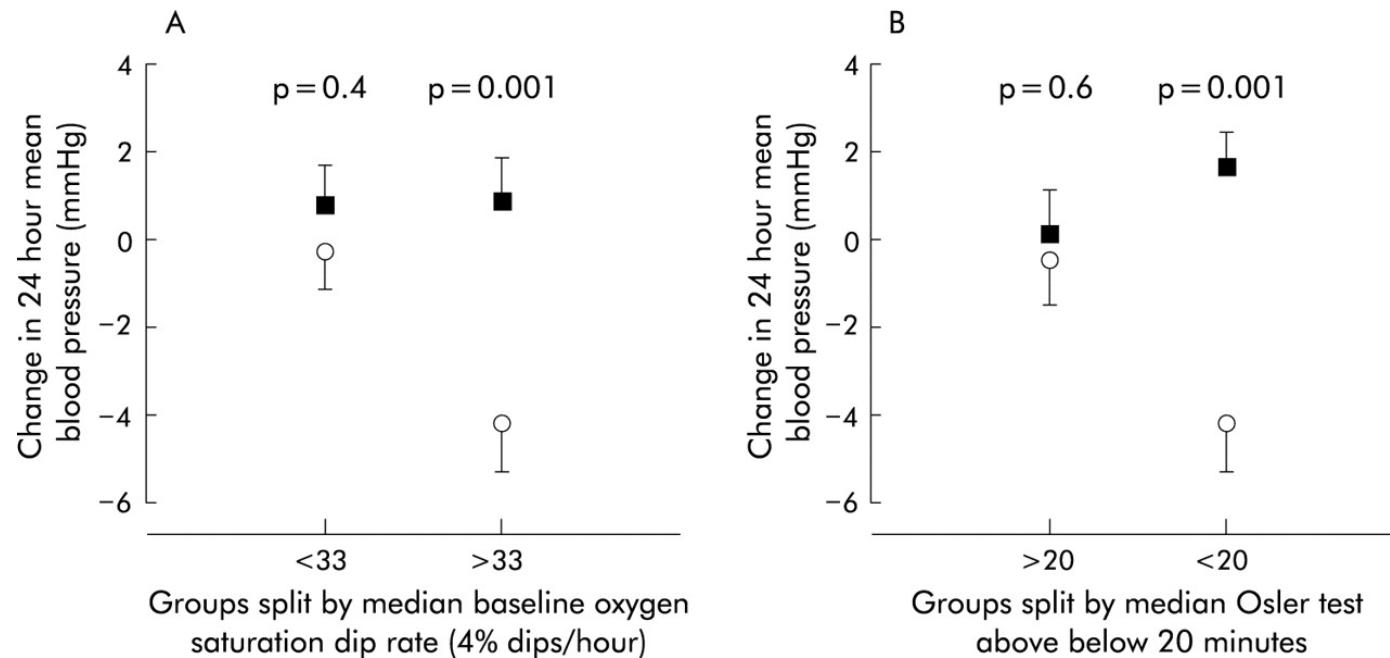
Ignacio Durán-Cantolla, MD

Context Continuous positive airway pressure (CPAP) is the first-line treatment for patients with obstructive sleep apnea (OSA). However, the evidence for all

JAMA 2012

Incident HTN or CV event
ESS of 10 or less
CPAP vs. no intervention
723 pts followed for 4 yrs
CPAP: No significant reduction in outcomes
? underpowered

The BP Lowering Effect Interacts with Hypoxemia and Sleepiness (and Adherence)



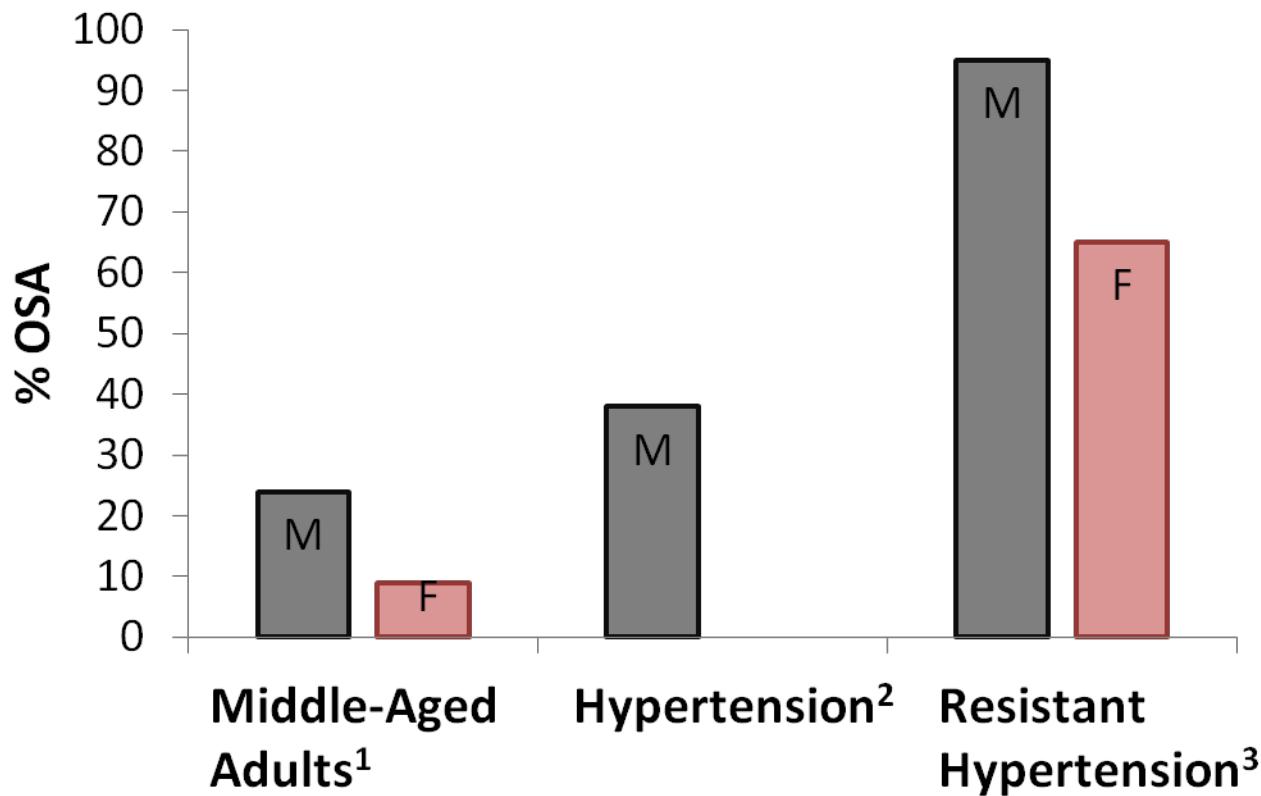
Black squares – Control
Open circles - CPAP

Robinson, 2004

Thorax
ONLINE

OSA and its Treatment in Resistant Hypertension

Prevalence of OSA



¹Young et al., NEJM 1993. AHI \geq 5 events/hr

²Worsnop et al., AJRCCM 1998. AHI \geq 5 events/hr

³Logan et al., J Hyperten 2001. AHI \geq 10 events/hr

Table 1. Secondary Forms of Hypertension Associated With Resistant Hypertension

Conditions	Prevalence in Resistant Hypertension, %	Diagnostic Tests	Treatment	Level of Evidence ^a
Obstructive sleep apnea ³⁴	60-70	Polysomnography	Continuous positive airway pressure ^{41,42}	High
Primary aldosteronism ³⁵⁻³⁸	7-20	Serum aldosterone, plasma renin activity	Spironolactone, eplerenone, or surgical resection of tumor in unilateral aldosterone-producing adenoma ³⁷⁻⁴⁰	High
Renal artery stenosis ^{34,43}	2-24	Duplex Doppler ultrasonography, computed tomographic angiography, or magnetic resonance angiography	Renal revascularization in selected patients ^{44,45}	High
Renal parenchymal disease ³⁴	1-2	Serum creatinine	Correction of underlying causes if possible ²	High
Drug-induced or heavy alcohol use ^{9,34}	2-4	History taking	Discontinuation of offending agents ²	Moderate
Thyroid disorders ³⁴	<1	Thyrotropin, free thyroxine	According to underlying disorders ²	Moderate

Vongpatanasin, JAMA 2014;311(21):2216-24

Effect of CPAP on Blood Pressure in Patients With Obstructive Sleep Apnea and Resistant Hypertension

The HIPARCO Randomized Clinical Trial

Miguel-Angel Martínez-García, MD, PhD; Francisco Capote, MD, PhD; Francisco Campos-Rodríguez, MD, PhD; Patricia Lloberes, MD, PhD; María Josefa Díaz de Atauri, MD, PhD; María Somoza, MD, PhD; Juan F. Masa, MD, PhD; Mónica González, MD, PhD; Lirios Sacristán, MD; Ferrán Barbé, MD, PhD; Joaquín Durán-Cantolla, MD, PhD; Felipe Alzpuru, PhD; Eva Mañas, MD, PhD; Bienvenido Barreiro, MD, PhD; Mar Mosteiro, MD, PhD; Juan J. Cebrián, MD, PhD; Mónica de la Peña, MD, PhD; Francisco García-Río, MD, PhD; Andrés Maimó, MD, PhD; Jordi Zapater, MD; Concepción Hernández, MD, PhD; Nuria Grau SanMartí, MD, PhD; Josep María Montserrat, MD, PhD; for the Spanish Sleep Network

METHOD

- CPAP vs usual care for 3 months
- N=194; Patients with both resistant HTN and OSA ($AHI \geq 15$)
- ITT analysis

RESULTS

- CPAP decreased
 - 24-h MAP by 3.1 mmHg ($p=0.02$)
 - 24-h DBP by 3.2 mmHg ($p=0.005$)
- CPAP did not significantly reduce 24-h SBP (- 3.1 mmHg; $p=0.1$)

Table 4. Effect of Continuous Positive Airway Pressure Treatment on Prevalence of Blood Pressure Patterns

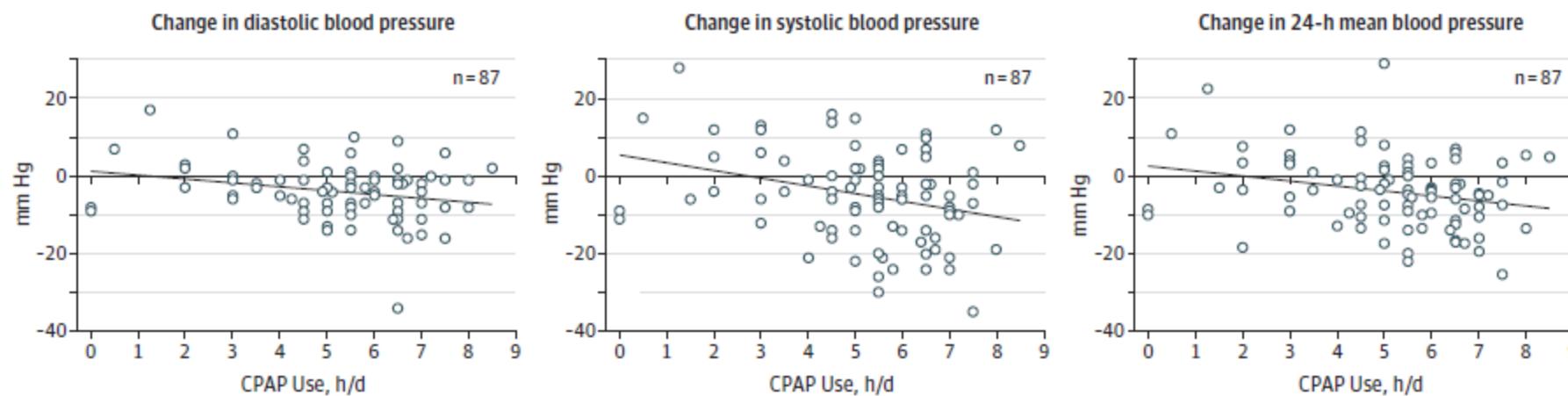
	No. (%)					
	CPAP Group (n = 98)		Control Group (n = 96)		OR (95% CI) ^a	P Value
	Baseline	Follow-up	Baseline	Follow-up		
Prevalence dipper pattern	25 (25.5)	35 (35.9)	25 (26.0)	21 (21.6)	2.4 (1.2-5.1)	.02
Prevalence riser pattern	27 (27.6)	20 (20.5)	34 (35.4)	35 (36.8)	0.45 (0.23-0.91)	.03

Abbreviations: CPAP, continuous positive airway pressure; OR, odds ratio.

ratio (95% CI) of dipper or riser pattern 12 weeks after CPAP treatment relative

^a Adjusted for baseline status. Control group data were reference values. Odds

Figure 2. Correlation Between Changes in 24-Hour Mean, Systolic, and Diastolic Blood Pressure and Number of Hours of Continuous Positive Airway Pressure Use

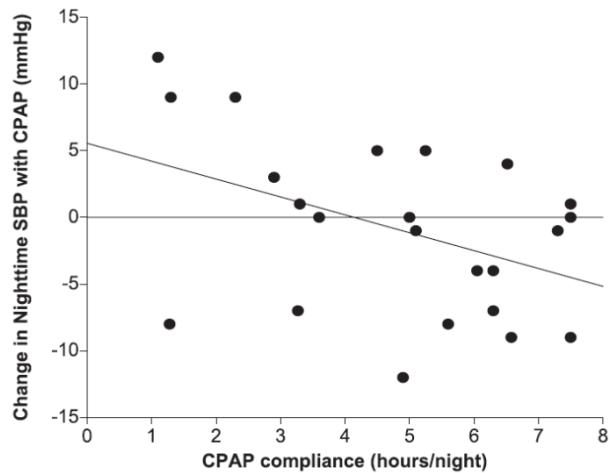
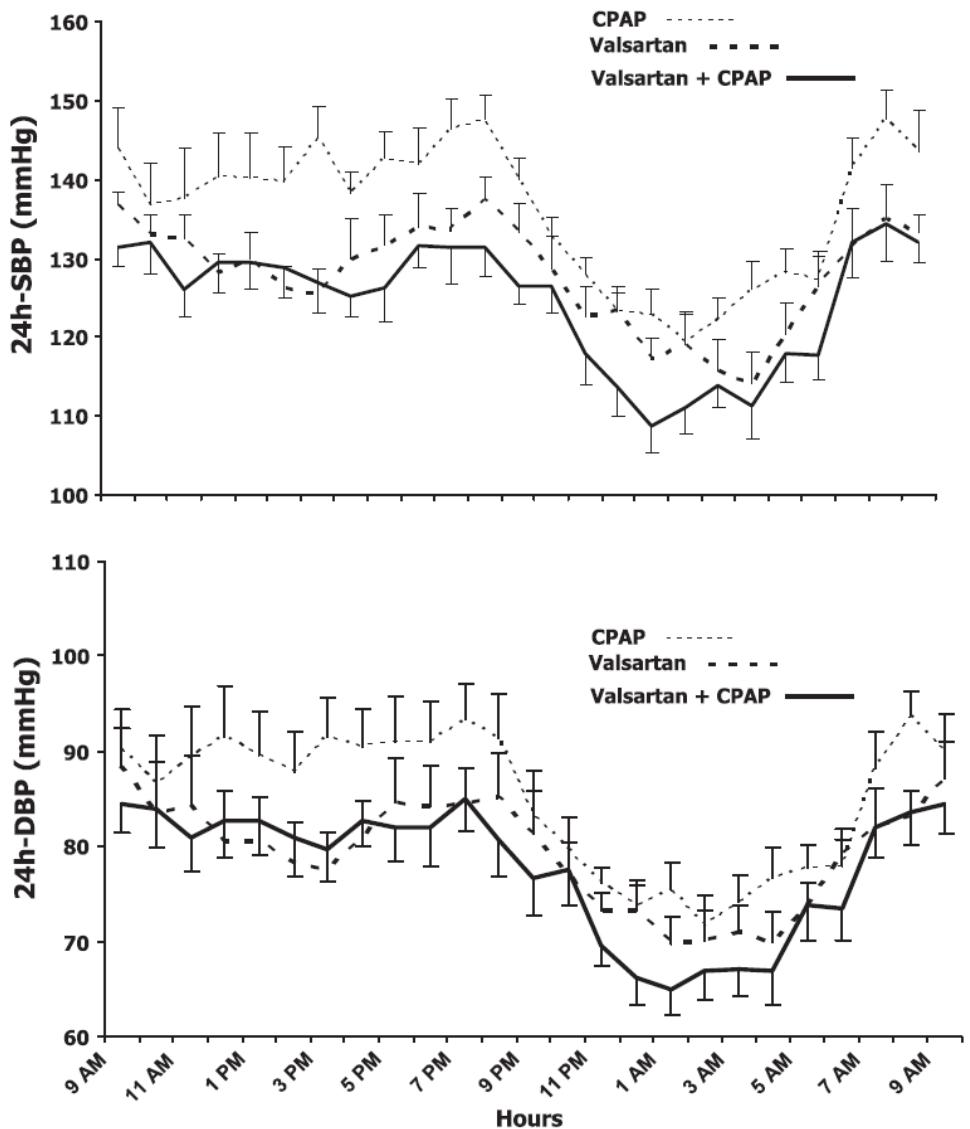


Correlation between continuous positive airway pressure (CPAP) use and change in blood pressure in the patients of the CPAP group who finished the follow-up.

Comparative Effectiveness

- Should all hypertensives with OSA be treated?
- Differential effects of OSA treatment (CPAP vs. non-CPAP)
- Drug therapy

Open Label Continuation



Sleep and Blood Pressure Control

- Physiology of sleep
- Obstructive sleep apnea
- Sleep deprivation

Original Articles

Short Sleep Duration as a Risk Factor for Hypertension Analyses of the First National Health and Nutrition Examination Survey

James E. Gangwisch, Steven B. Heymsfield, Bernadette Boden-Albala, Ruud M. Buijs, Felix Kreier,
Thomas G. Pickering, Andrew G. Rundle, Gary K. Zammit, Dolores Malaspina

(Hypertension. 2006;47:833-839.)

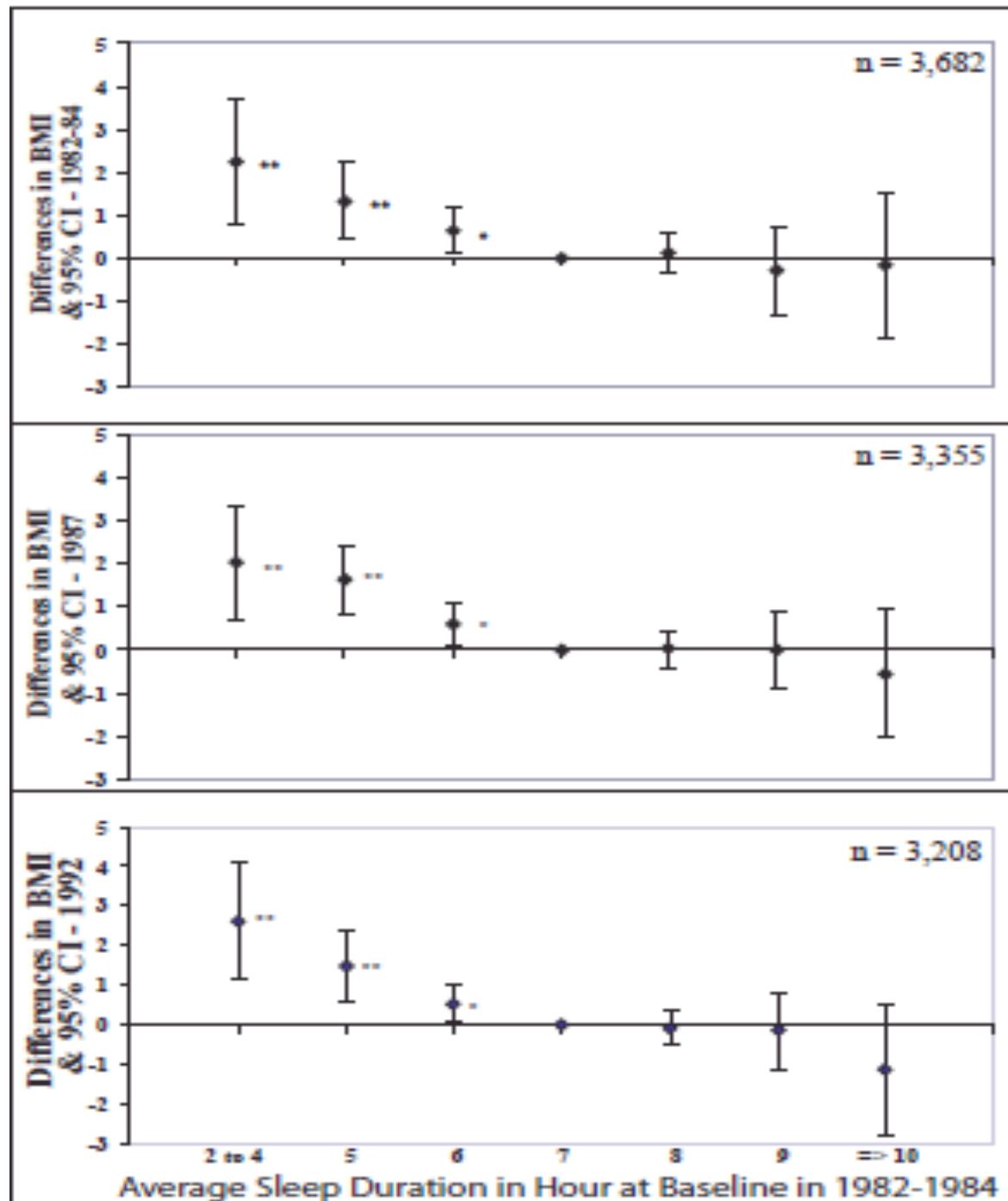
**Sleep duration of five hours
or less was associated
with a two-fold increase in
risk of hypertension**

Short sleep duration and obesity

Epidemiologic evidence

NHANES I

Gangwisch, Sleep 2005;
Patel, Am J Epidemiology
2006



Sleep Deprivation and Energy Balance

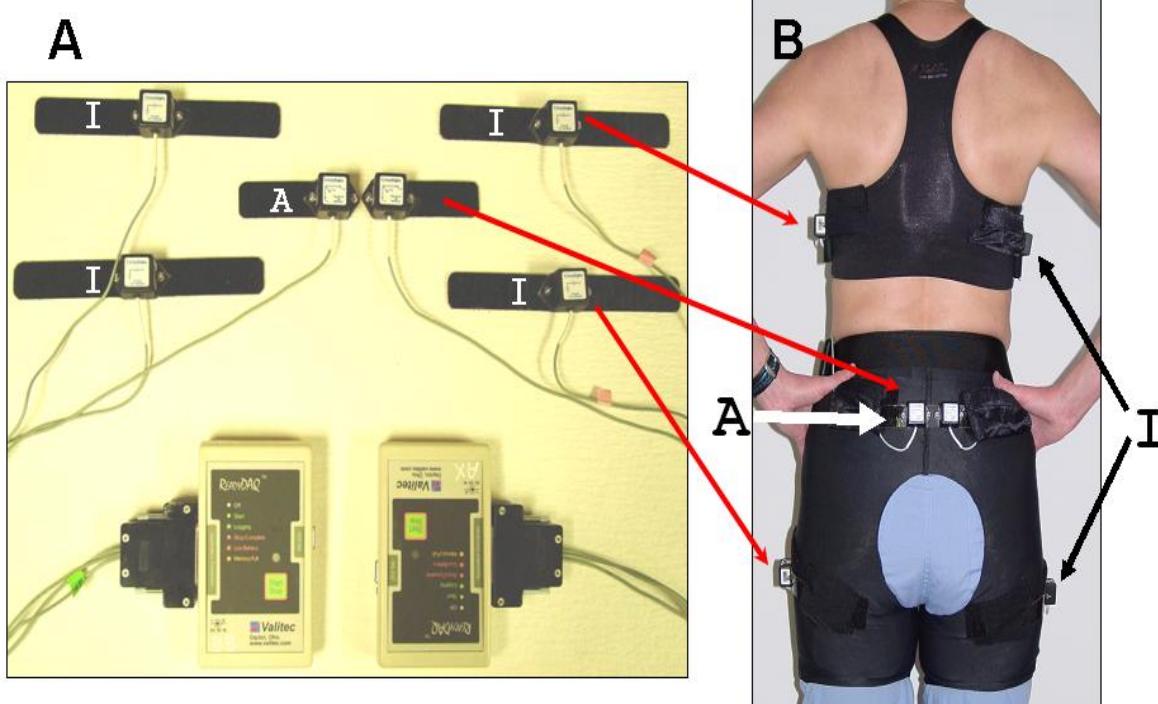
Mayo Sleep Monitoring System (MSMS)

- Custom-modified sleep/wake monitoring system based on Compumedics Siesta 802
- 64 channels, 512 Hz, 16 bit resolution
 - Electroencephalogram (EEG)
 - Electro-oculogram (EOG)
 - Electromyogram (EMG)
 - Electrocardiogram (ECG)
 - Extensible, allows addition of more channels
- Specialized electrode placement to allow safe, 23 hour/day monitoring
- telemetry allowing real-time monitoring
- <1 kg, wearable, unobtrusive



Sleep Deprivation and Energy Balance

Outcomes – energy expenditure

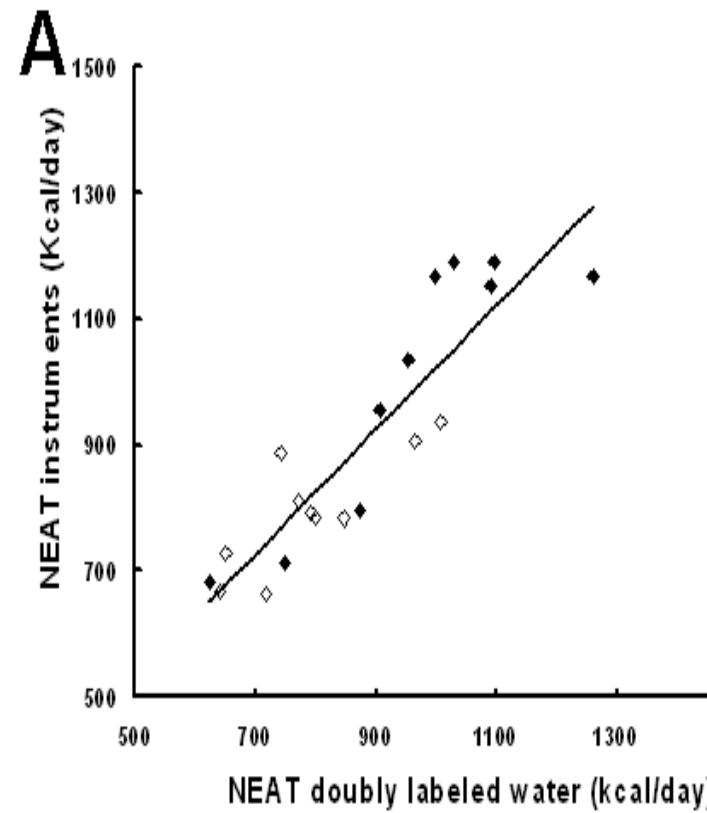


six sensors (left panel):

- **four inclinometers (I)**
- **two triaxial accelerometers (A)**
- **14 axes of data are binned and stored every half-second on two data loggers.**

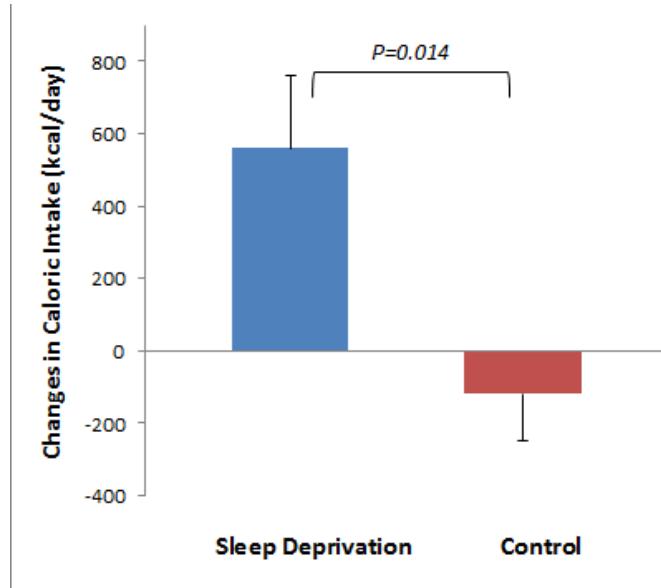
Specially designed undergarments (right panel)

Levine, Science 1999; Levine, Science 2005; Levine, *Acta Physiol Scand* 2005



Sleep Restriction Increases Caloric Intake

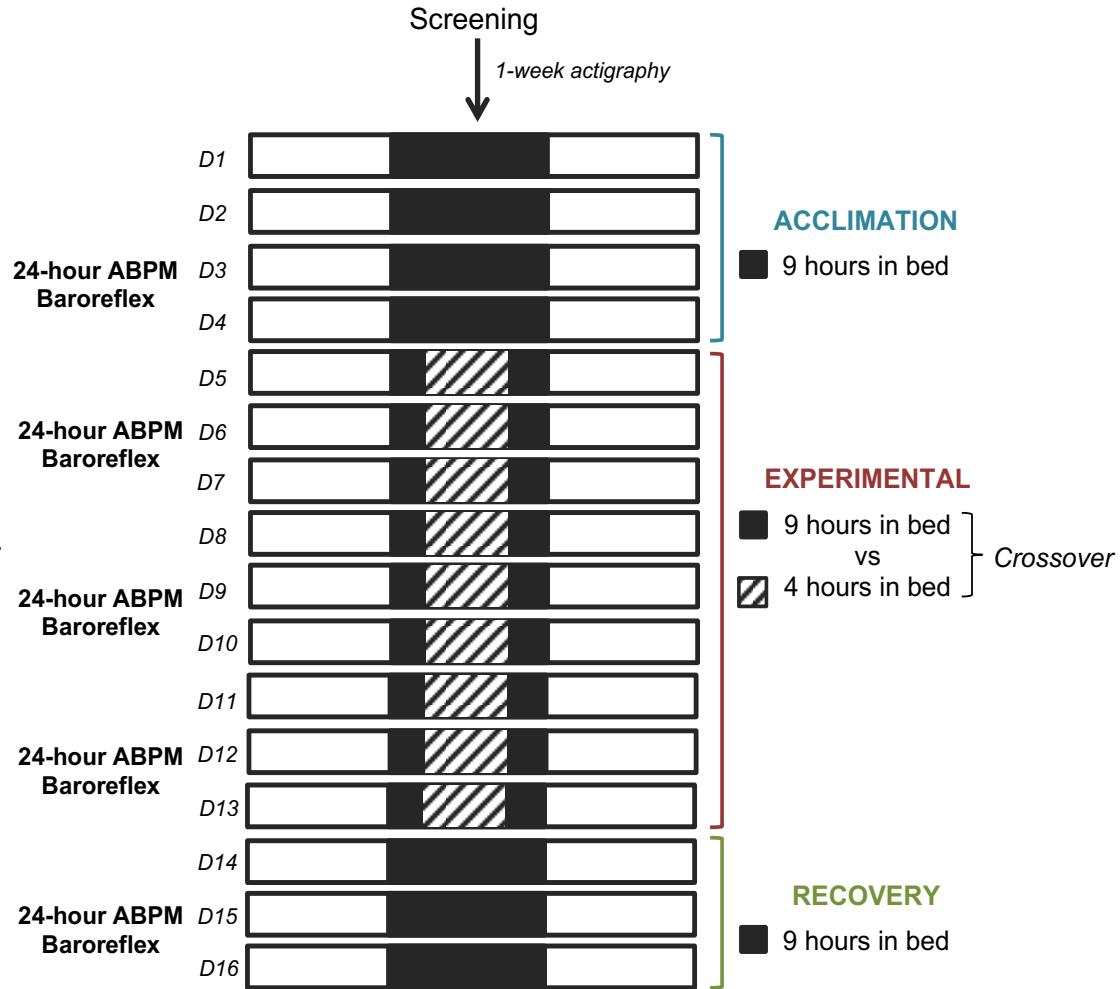
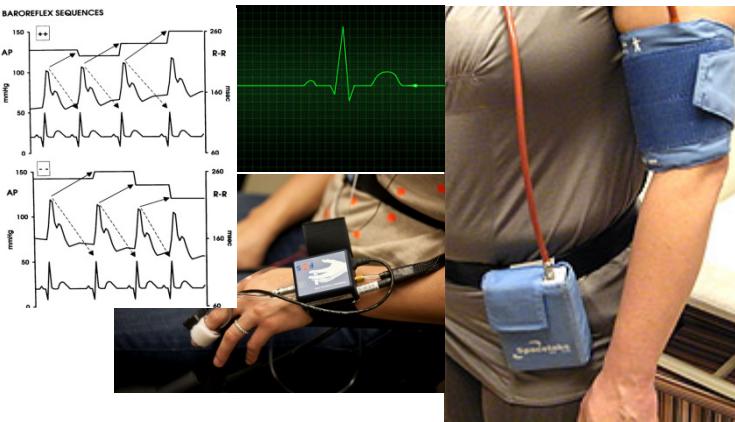
- Randomized trial, N=17
- Habitual sleep vs. 8 days of sleep restriction of 2/3 of normal sleep time; ad libitum access to food



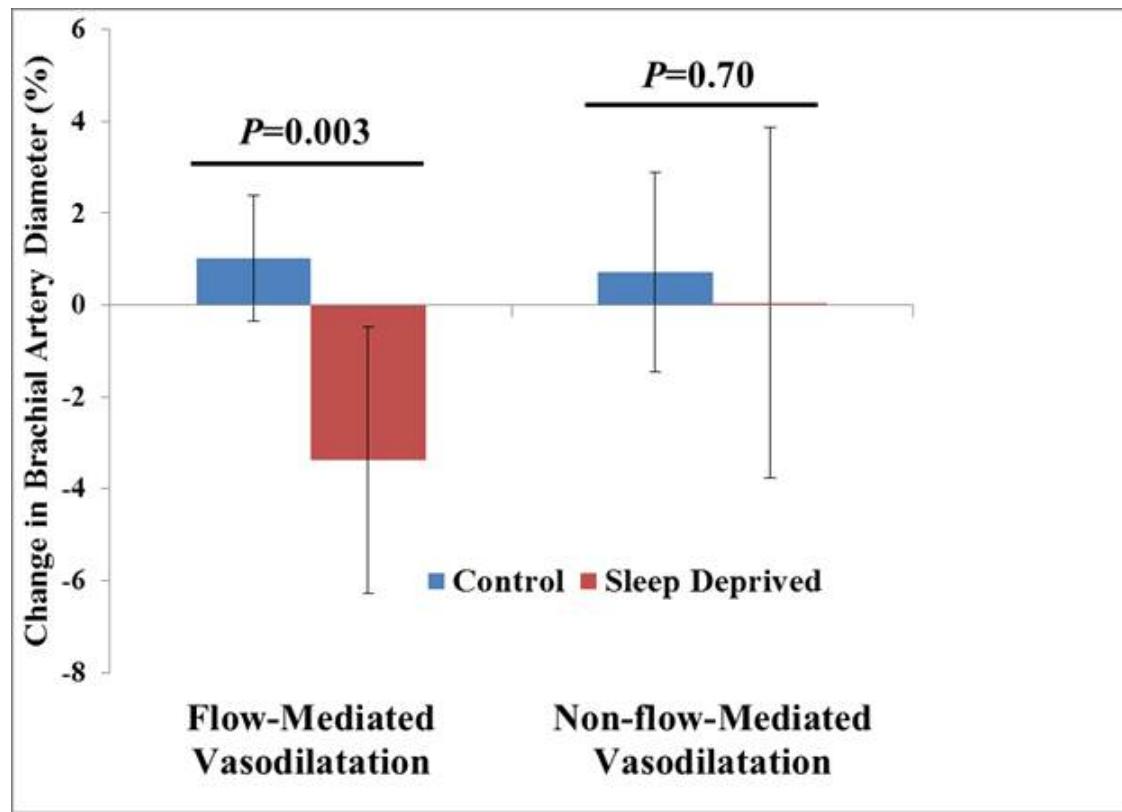
- No changes in activity energy expenditure
→ weight gain after sleep deprivation
 $(+1.1 \pm 1.1 \text{ kg}, P=0.039)$

Methods

- 14 healthy subjects
 - 6 males
 - age 24 ± 1 years
 - BMI $24 \pm 1 \text{ kg/m}^2$



Sleep Restriction Impairs Endothelial Function



Calvin et al., 2014

Nurses Health Study

71617 women 45-65 years

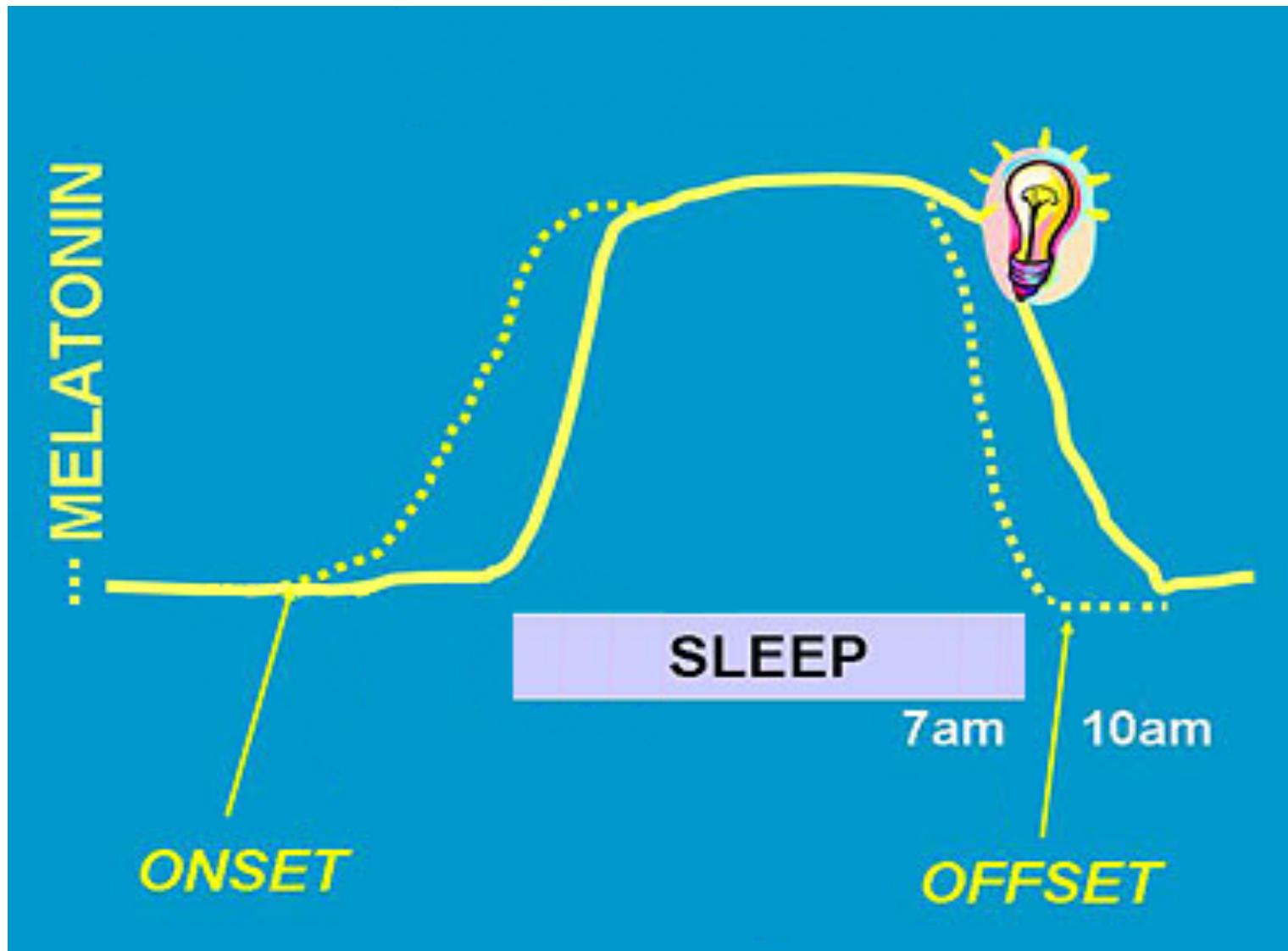
10 year follow-up of Incident CHD

(Ayas et al 2003)

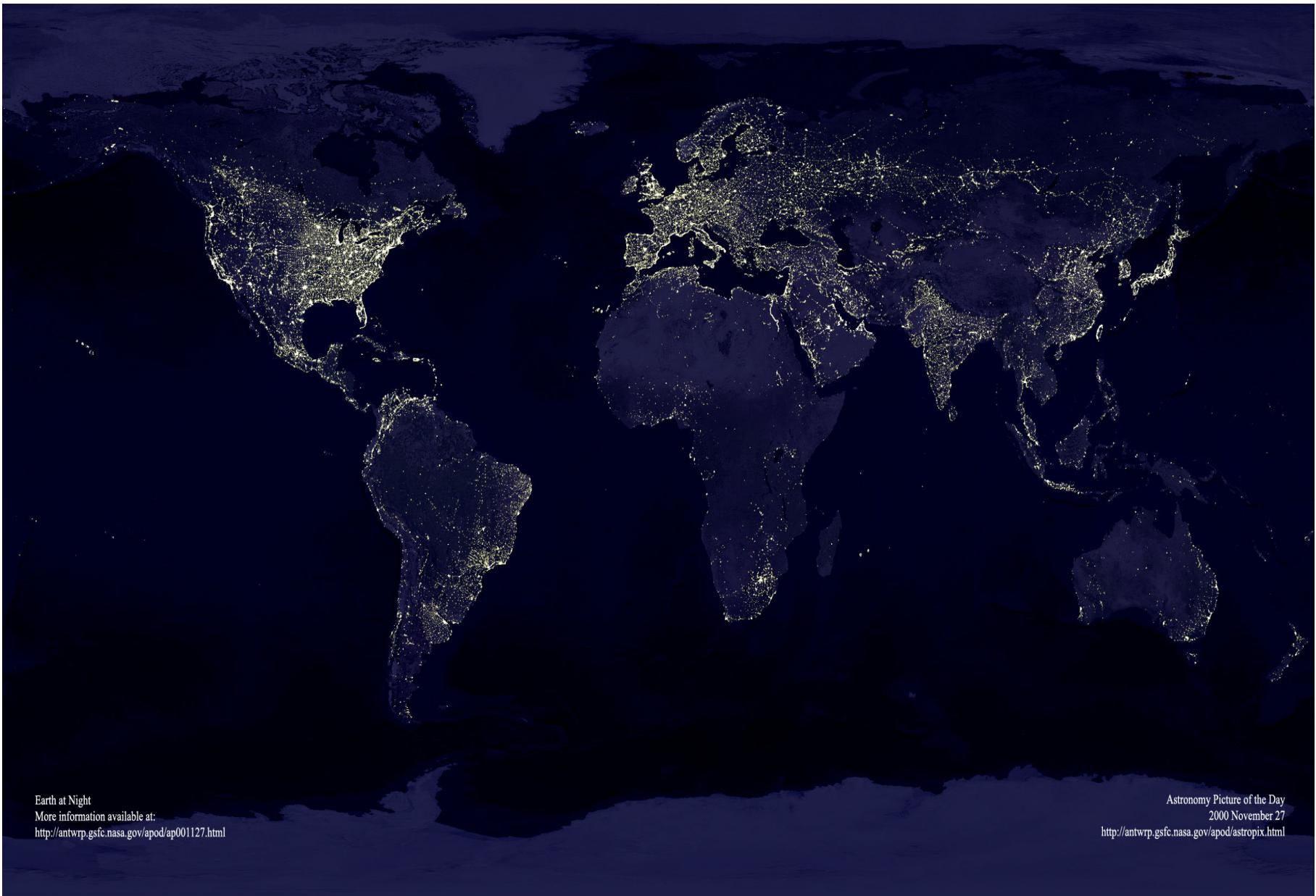
Sleep Duration	Relative Risk	Confidence Interval
5 hours	1.82	1.34 – 2.41
6 hours	1.30	1.08 – 1.57
7 hours	1.06	0.89-1.26
8 hours	1	1



Increase of Melatonin and Induction of Sleep by Darkness



Kripke DF, 2012



Earth at Night

More information available at:

<http://antwrp.gsfc.nasa.gov/apod/ap001127.html>

Astronomy Picture of the Day

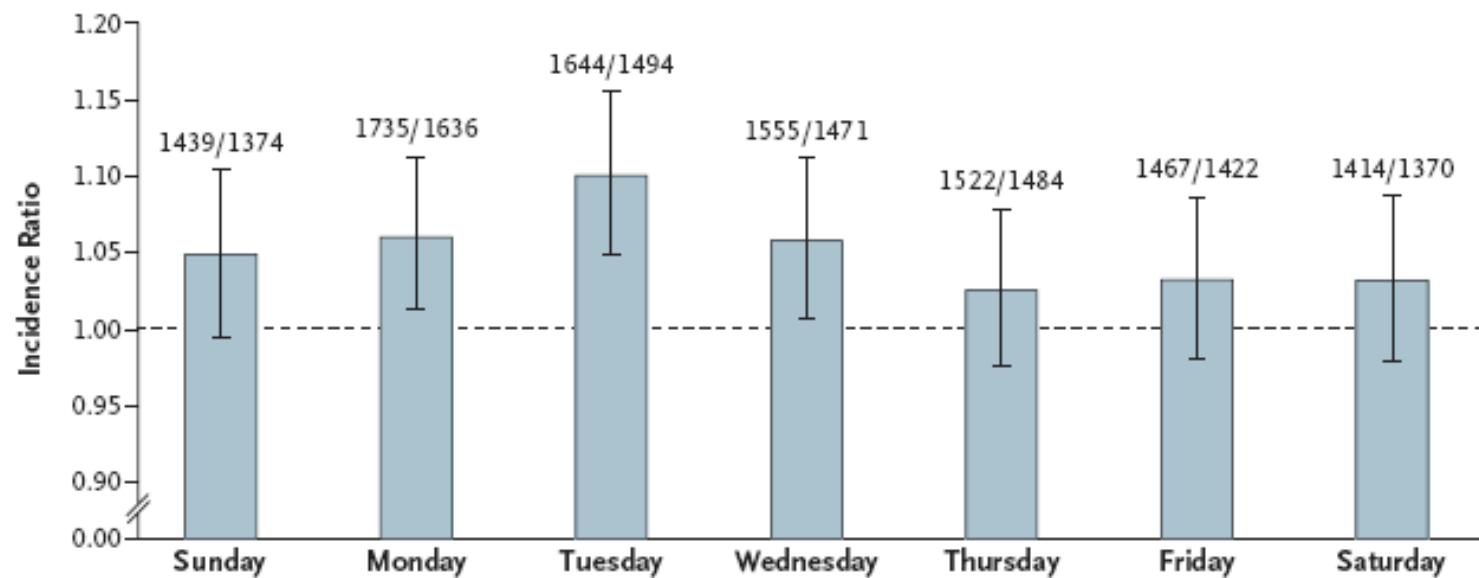
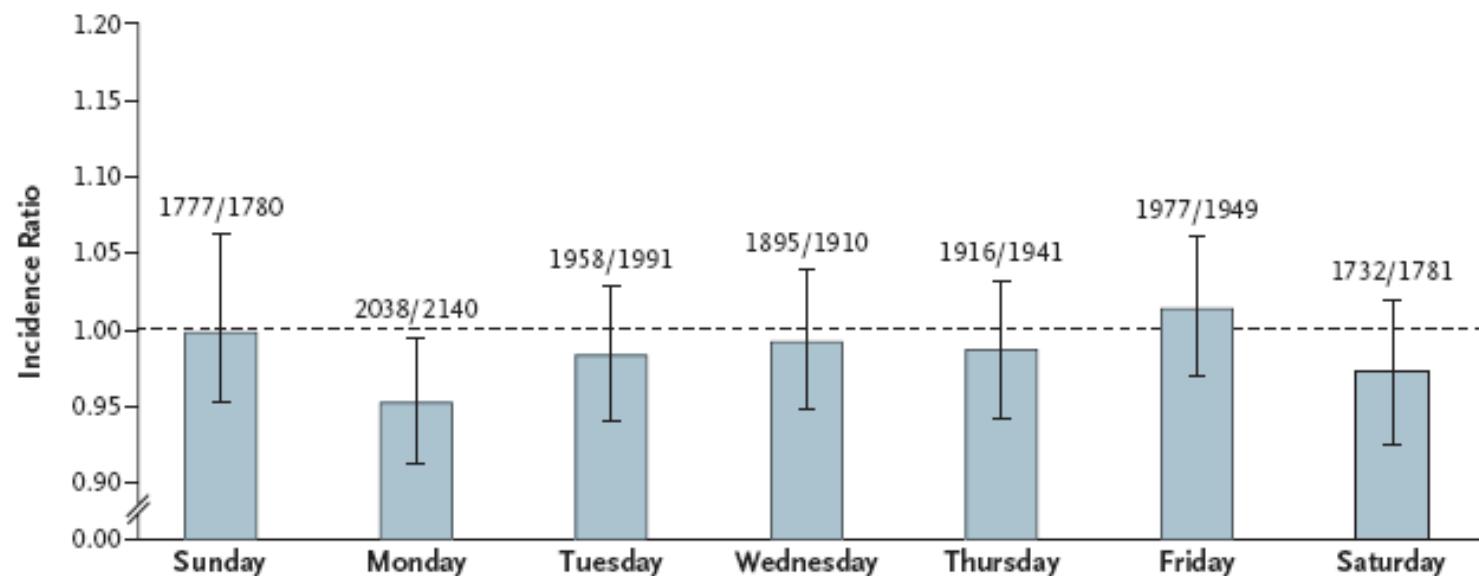
2000 November 27

<http://antwrp.gsfc.nasa.gov/apod/astropix.html>



Shifts to and from Daylight Saving Time and Incidence of MI

(Janszky and Ljung, *New Engl J Med*, 2008)

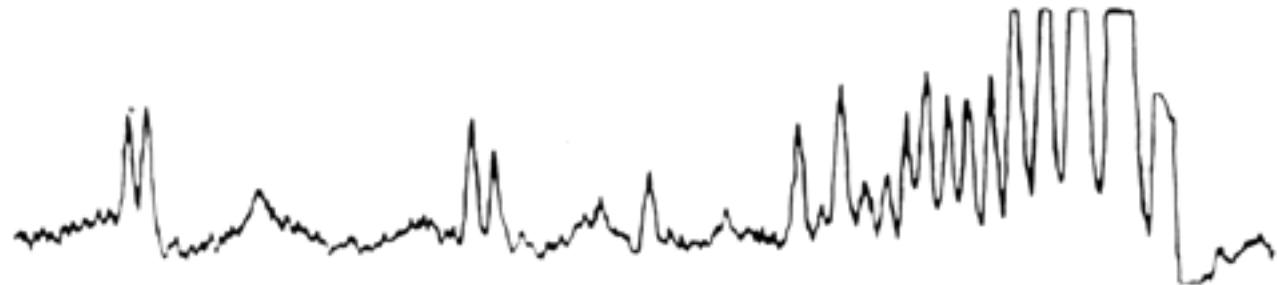
A Spring**B Autumn**

Sleep and Blood Pressure Control

- Physiology of sleep
- Obstructive sleep apnea
- Sleep deprivation

Effect of Apnea, Hypoxia, and Hypercapnia (Sleep Apnea) on Sympathetic Nerve Activity

Sympathetic Neurogram



Respiration



Breathing

10% O₂/7% CO₂/83% N₂

Apnea
5 sec

Subject A.A.

Table 1—Potential Confounders of Placebo-Controlled Trials of Effects of CPAP on Blood Pressure

Baseline variation in

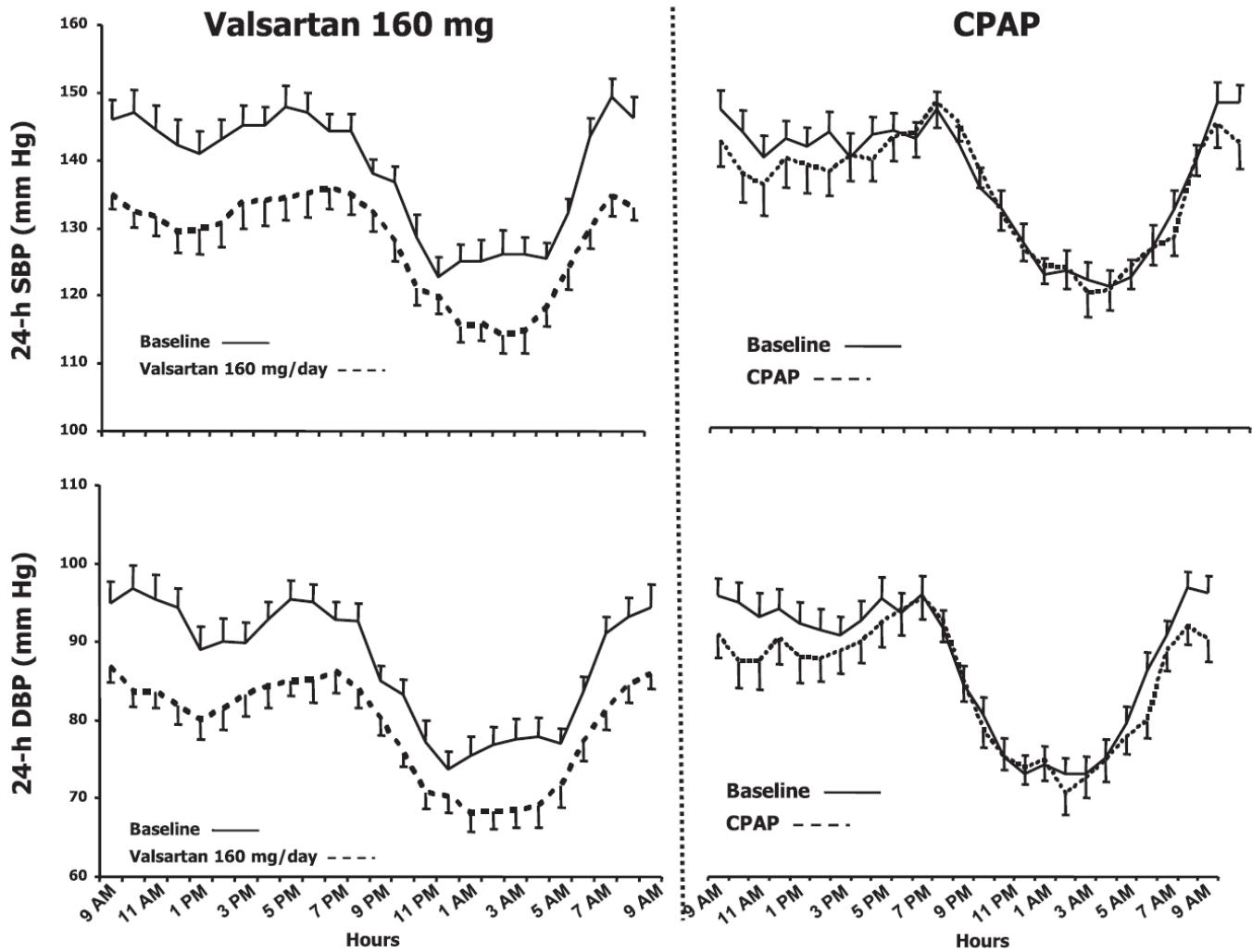
- Age
- Body mass index
- Measurement and severity of OSA (AHI, degree of oxyhemoglobin desaturation)
- Blood pressure—some normotensive and others hypertensive; differing methods for blood pressure measurement (ambulatory vs individual cuff)
- Drug therapy for hypertension
- Daytime sleepiness and method of measurement (subjective vs objective)
- Duration of treatment (2 to 12 weeks)
- Different control strategies (subtherapeutic CPAP, oral placebo)
- Variation in compliance with treatment among subjects
- Studies conducted predominantly in men
- Differential effects on daytime vs nighttime vs mean 24-h blood pressure

Shift Work Type Disorder



- **15.5 million American adults are affected by shiftwork**
 - ✓ **5% work in the evening**
 - ✓ **4% on permanent night shift**
 - ✓ **4% on rotating shifts**
- **Shiftwork is hazardous!**
 - ✓ **Increased health risk**
 - ✓ **Increased accident risk**
 - ✓ **Increased social/family problems**

Comparison of Continuous Positive Airway Pressure and Valsartan in Hypertensive Patients with Sleep Apnea



Patient History

- 44 yo WM, truck driver
- Resistant hypertension, on thiazide, ACE-I, amlodipine, BP 168/98
- 5 ft 9 in, 280 lbs (not muscle)
- Admits to daytime somnolence
- Ambulatory BP awake 156/96, asleep 150/94