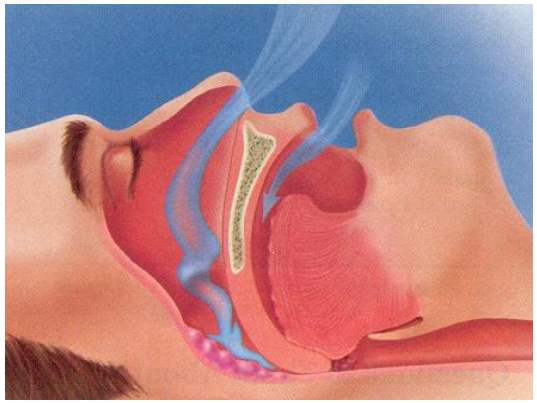

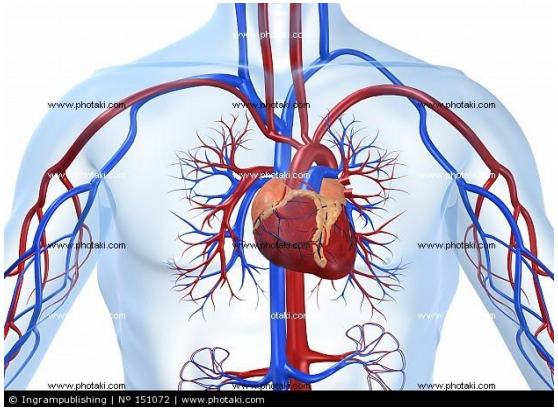

Cardiovascular Disease and Sleep Disordered Breathing: *Where are We Now?*

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Professor of Medicine

Sleep Disorders Center, Neurologic Institute

Respiratory Institute

Heart and Vascular Institute

Department of Molecular Cardiology, Lerner Research Institute

Cleveland Clinic

Tristate Symposium

May 4, 2018

Conflict of Interest Disclosures for Speakers

☐ 1. I do not have any relationships with any entities **producing**, **marketing, re-selling, or distributing** health care goods or services consumed by, or used on, patients, **OR**

■ 2. I have the following relationships with entities **producing**, **marketing, re-selling, or distributing** health care goods or services consumed by, or used on, patients.

Type of Potential Conflict	Details of Potential Conflict
Grant/Research Support	NIH NHLBI R01 HL 109493, 1U01HL125177
Consultant	None
Speakers' Bureaus	None
Financial support	Royalties from Up to Date, Fees from AASM, Fees from NIH for NIH study section service
Other	Institution has received positive airway pressure machines and equipment from Philips Respironics and Resmed for research purposes.

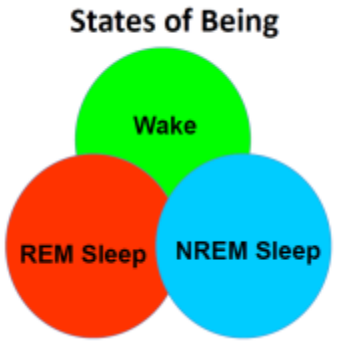
■ 3. The material presented in this lecture has no relationship with any of these potential conflicts, **OR**

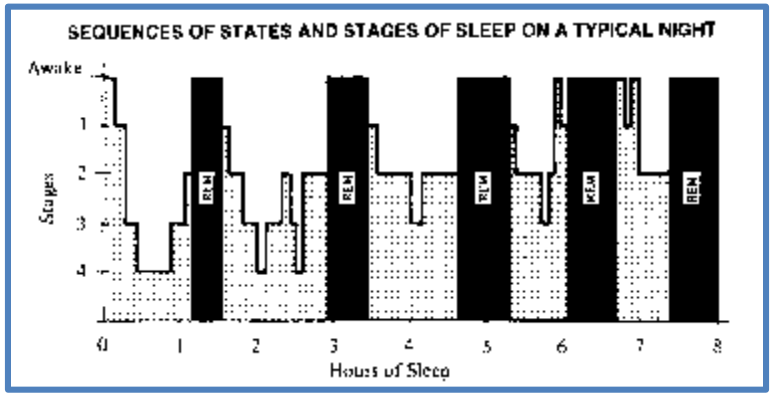
☐ 4. This talk presents material that is related to one or more of these potential conflicts, and the following objective references are provided as support for this lecture:

Objectives

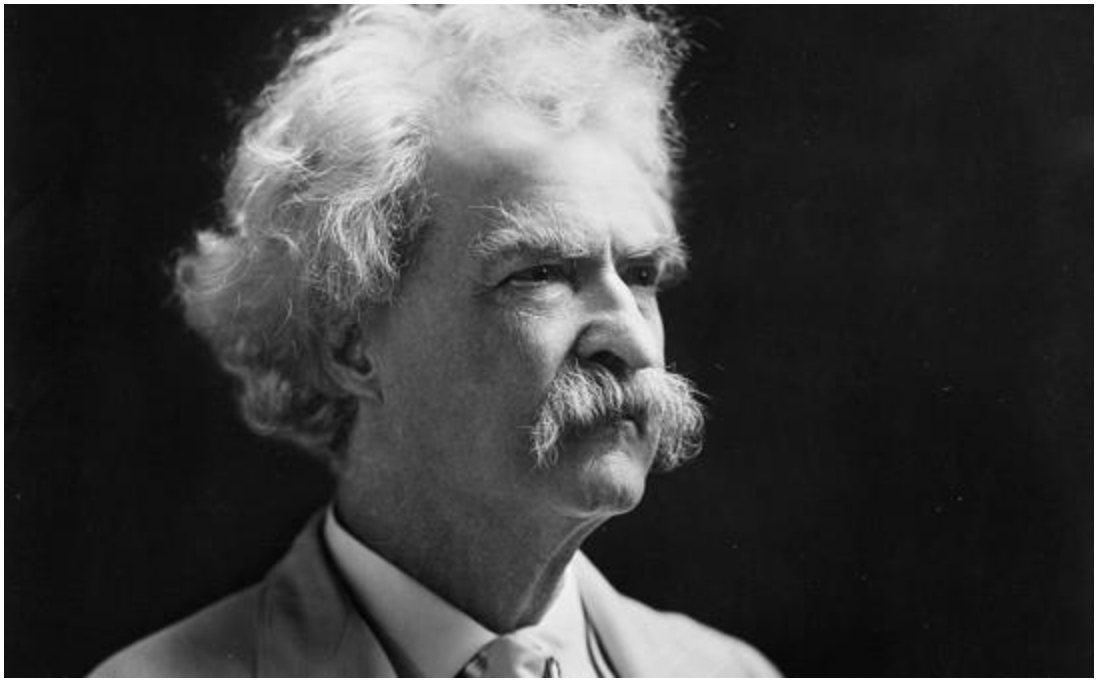
- Describe normal cardiovascular physiology during sleep
- Discuss prevalence and mechanisms linking sleep apnea and cardiovascular disease
- Review the association of sleep apnea and hypertension and resistant hypertension including treatment benefit
- Discuss inter-relationships of sleep apnea with heart failure, cardiac arrhythmia and stroke including treatment implications
- Understand the contribution of sleep apnea to coronary heart disease, mortality and sudden cardiac death with a focus on recent clinical trial data

REM versus NREM Sleep





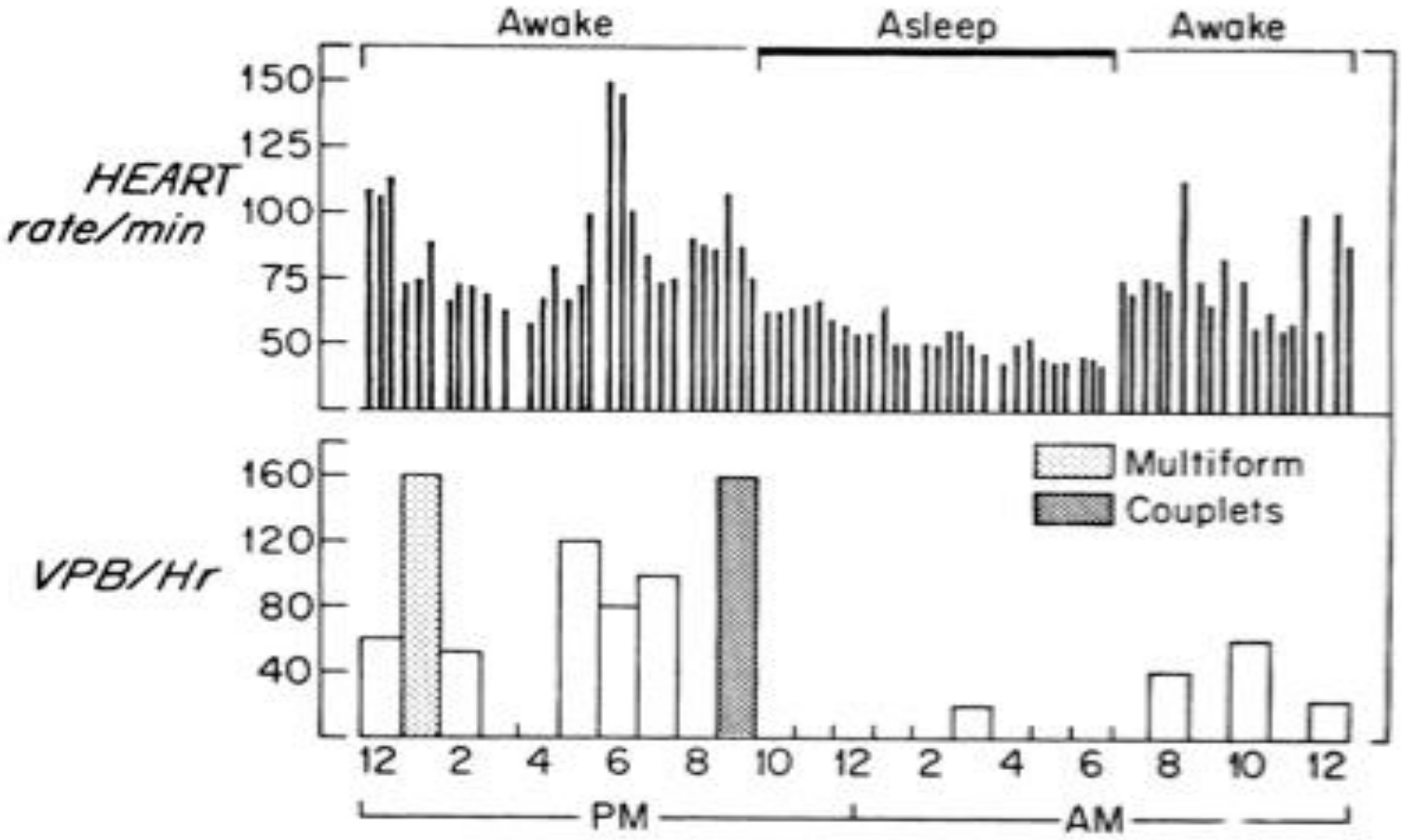
Physiologic Variable	*NREM*	*REM*
Heart rate	Regular	Irregular
Respiratory rate	Regular	Irregular
Blood pressure	Regular	Variable
Skeletal muscle tone	Preserved	Reduced
Brain O2 consumption	Reduced	Increased
Ventilatory response	Slight ↓	Reduced
Temperature	Normal	Poikilothermic



“Don’t ever go to sleep. Too many people die there.”

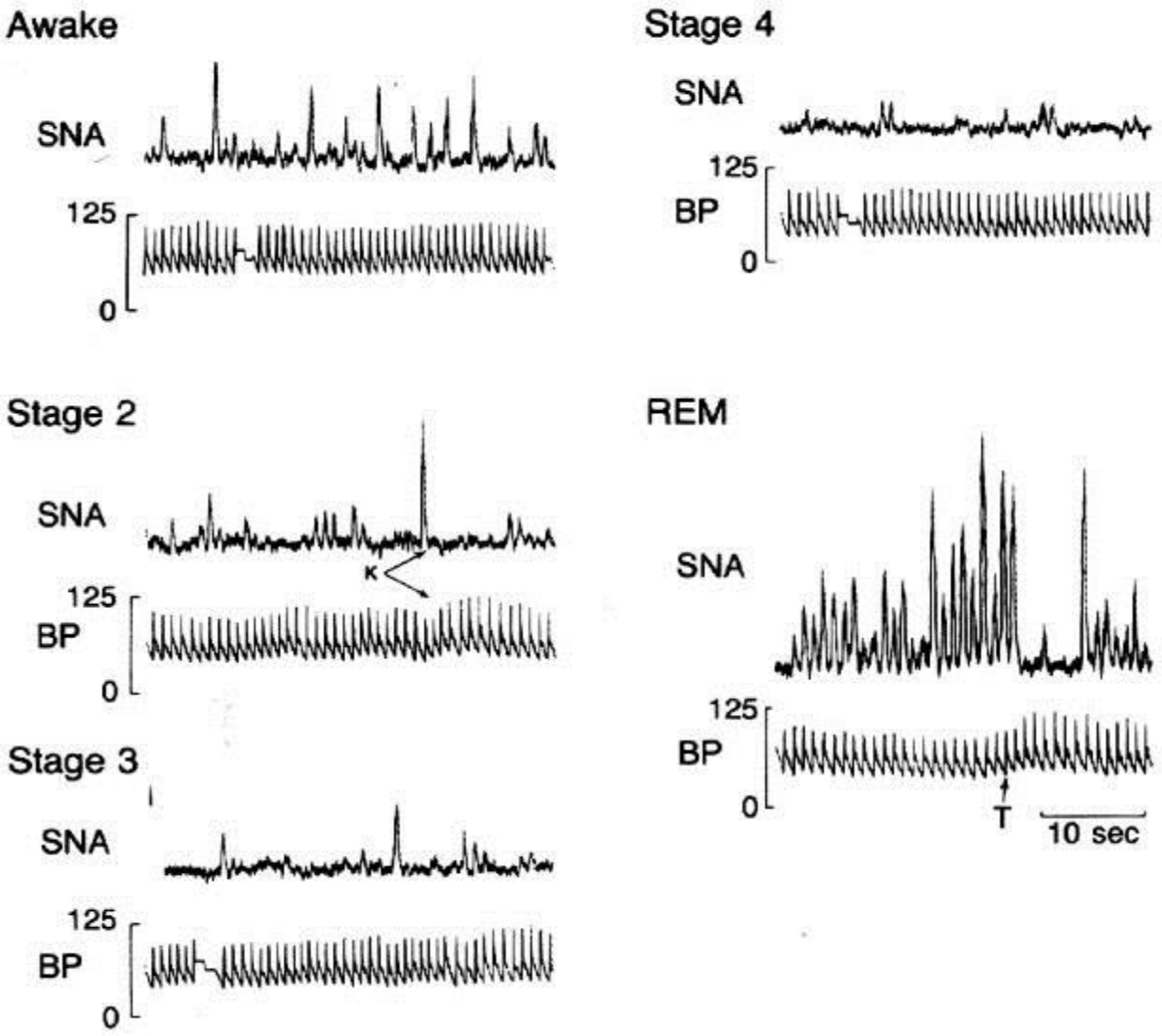
Mark Twain

….but Sleep is Cardioprotective



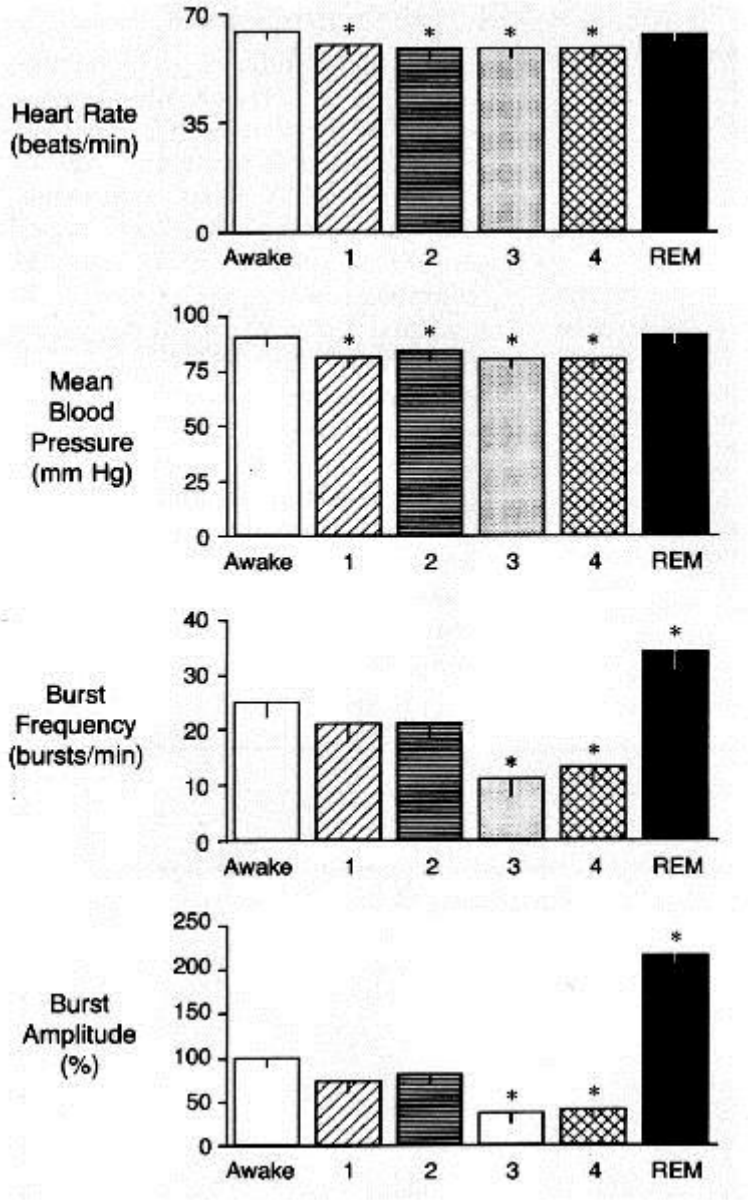
Lown et al. Circulation 1973

Sympathetic-Nerve Activity and Mean Blood Pressure while Awake and in Sleep



Somers VK et al. N Engl J Med 1993;328:303-307.

Heart Rate, Mean Blood Pressure, Sympathetic-Burst Frequency and Amplitude during Wakefulness and Sleep

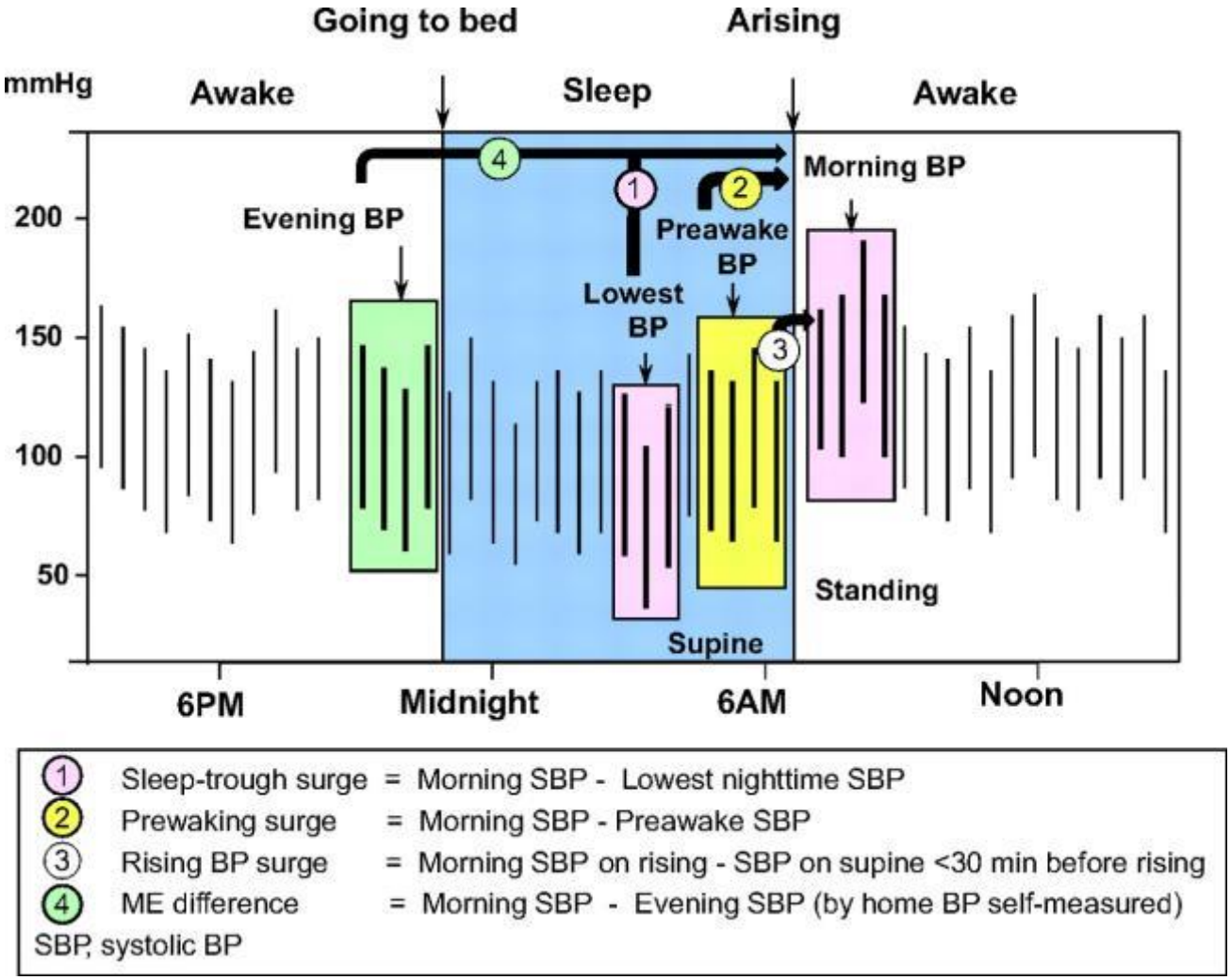


- HR and BP significantly lower in NREM compared to wakefulness
- Sympathetic activity lower in slow wave sleep compared to other sleep states
- During REM sleep, sympathetic activation increased compared to other sleep stages and exceeded that of wakefulness

The NEW ENGLAND JOURNAL of MEDICINE

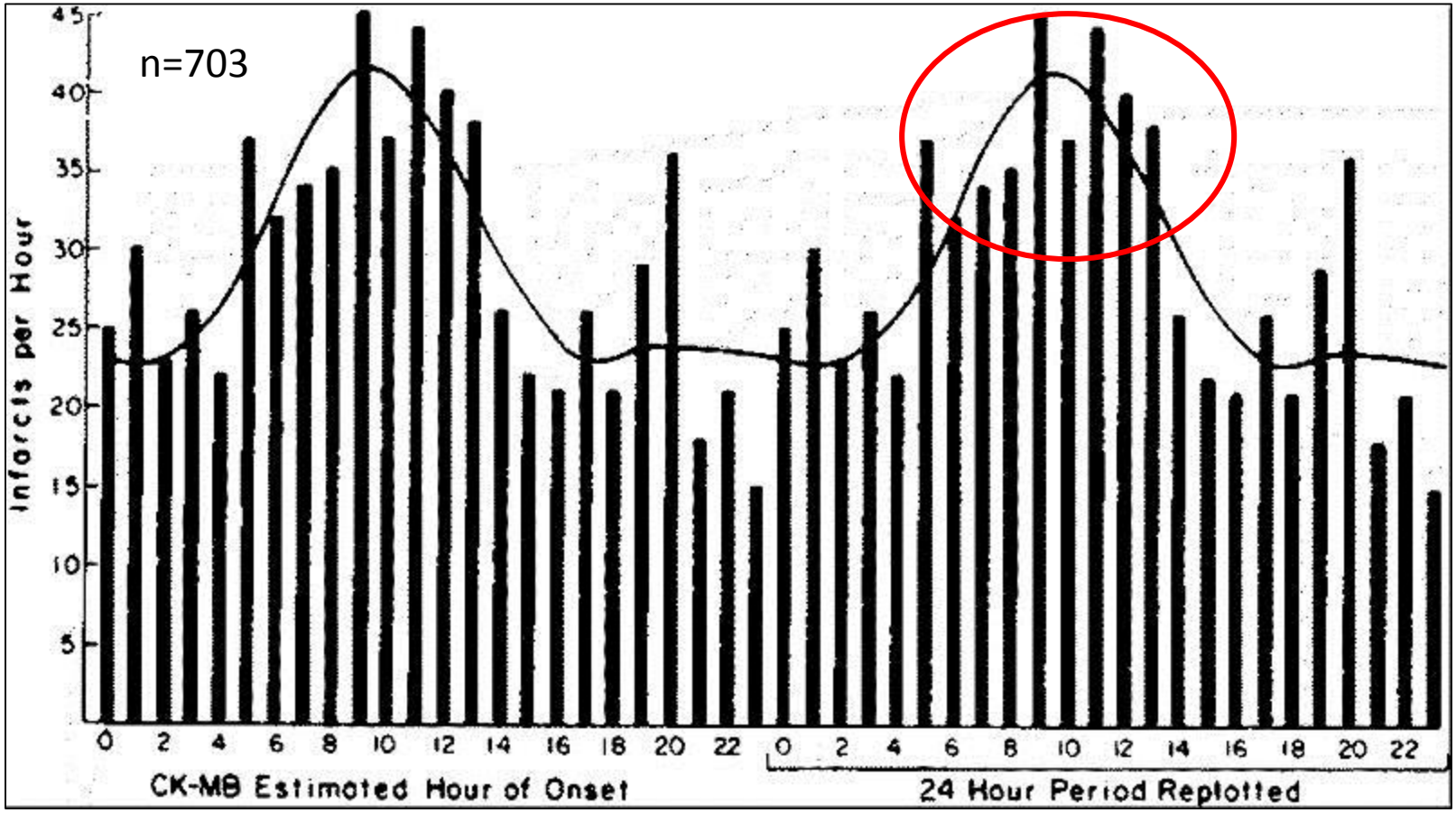
Somers VK et al. N Engl J Med 1993;328:303-307.

Diurnal Variability of Blood Pressure Surges



Kario K Hypertension. 2010;56:765-773

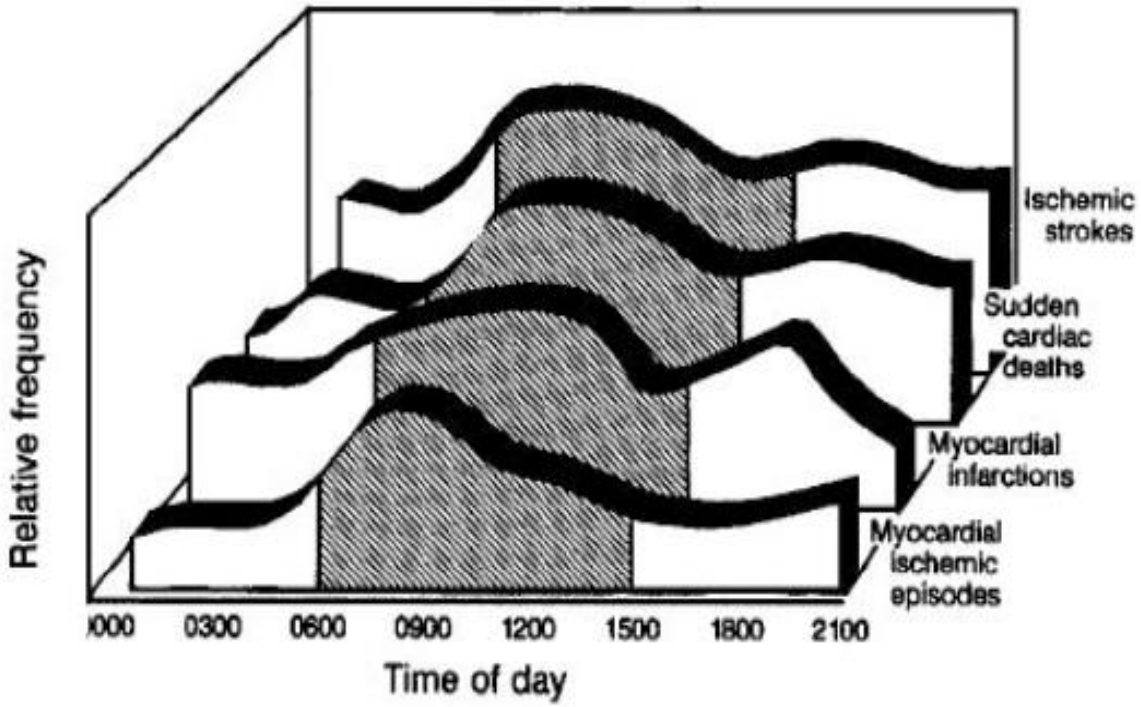
Morning Predisposition of Myocardial Infarction



Circadian rhythm is present with peak incidence at 9AM
3-fold increase in MI within the first 3 hours of awakening

Muller JE et al. N Engl J Med 1985;313:1315-1322.

Circadian Variation of Cardiovascular Events

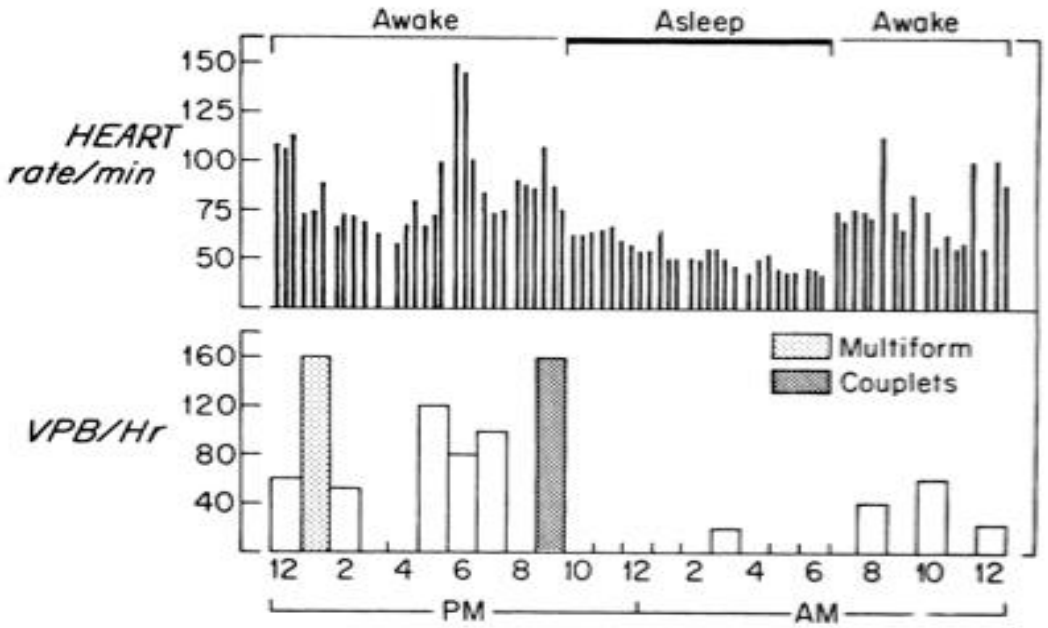


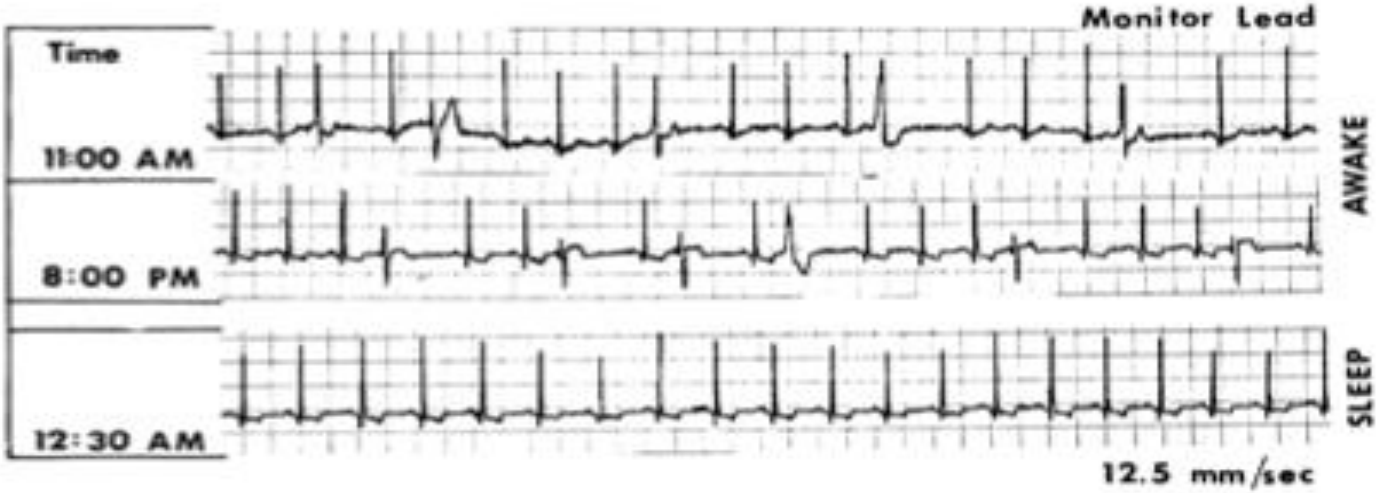
Why?

- *Autonomic fluctuations related to REM sleep*
- *BP surges*
- *Peak cortisol levels*
- *Peak levels of systemic markers of inflammation and thrombotic markers*

Marler et al. Stroke 1989

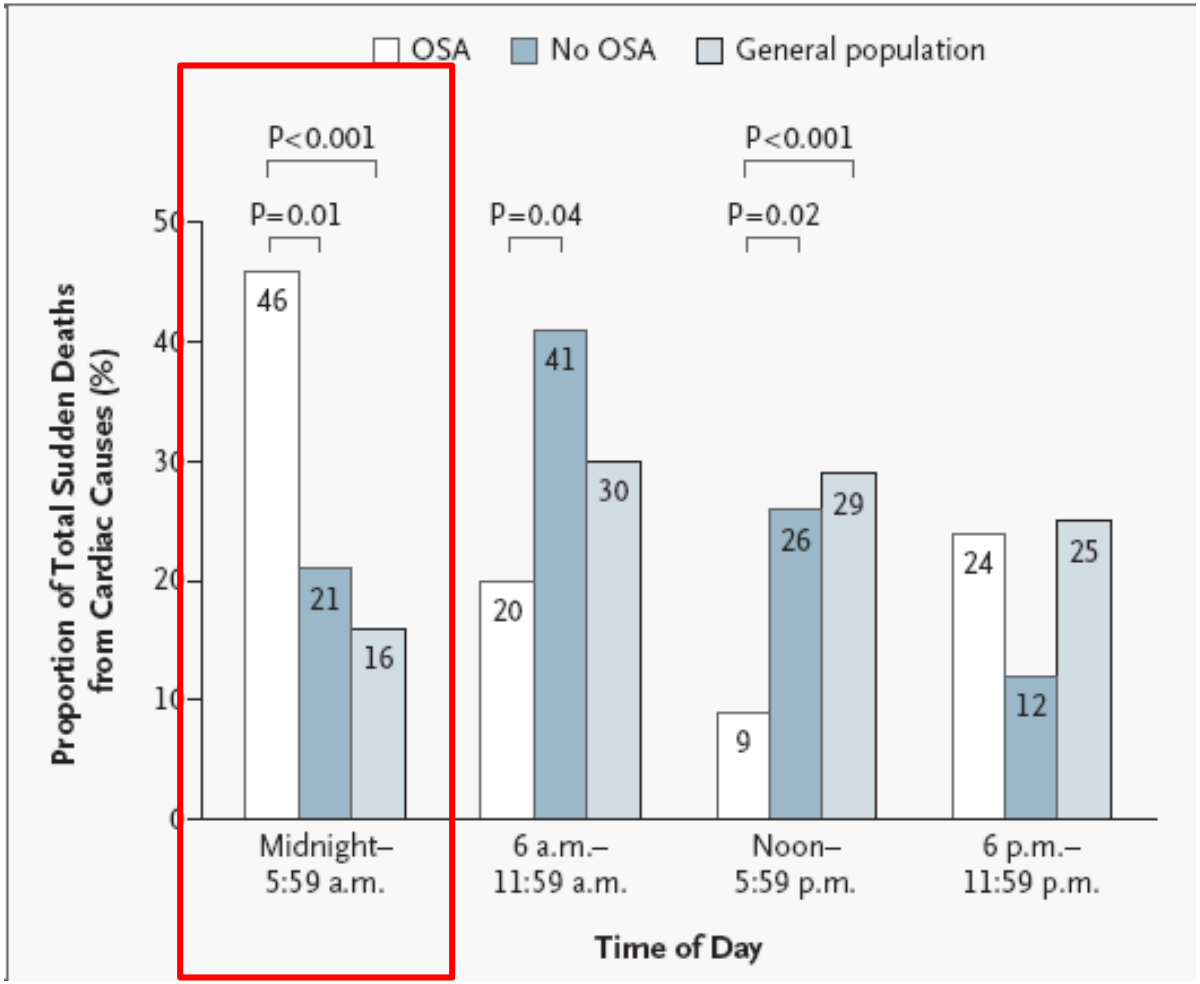
Sleep is Cardio-Protective, but….



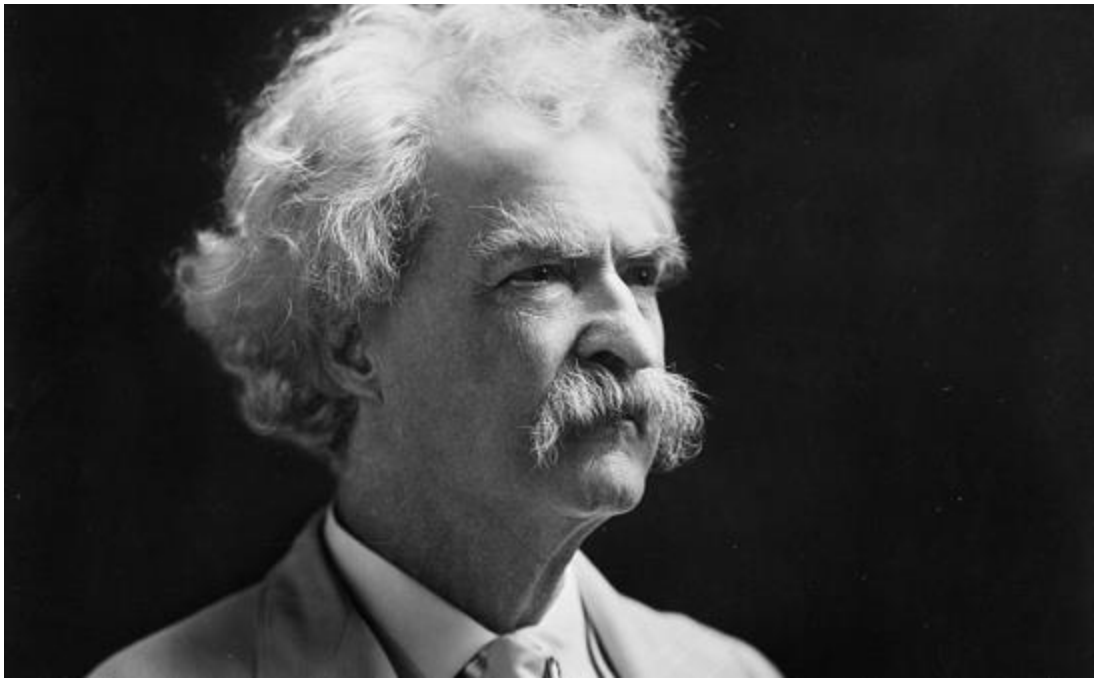


Lown et al. Circulation 1973

…not in Sleep Apnea Nocturnal Predilection for Sudden Cardiac Death in OSA



Gami AS *NEJM* 2005:352

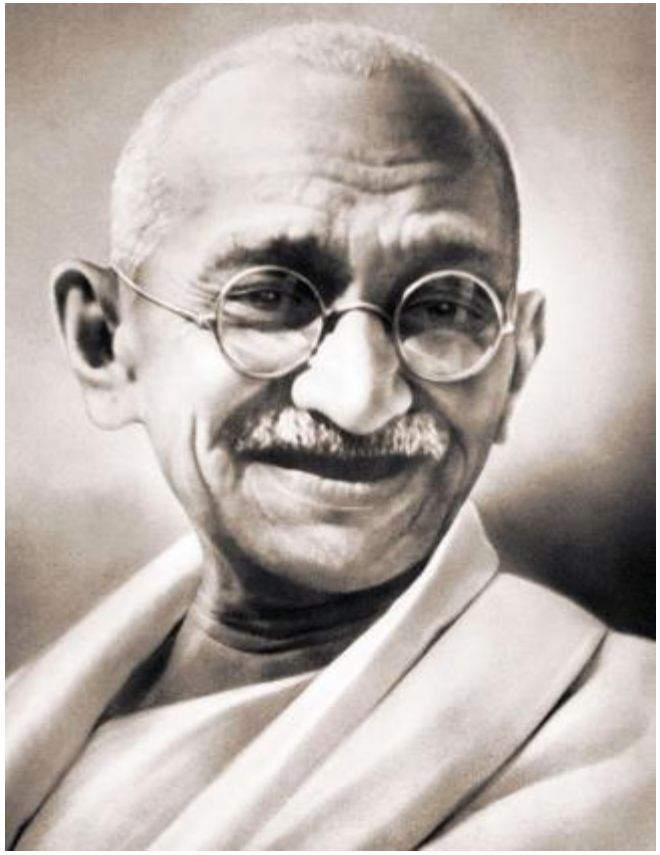


“Don’t ever go to sleep. Too many people die there.”

?

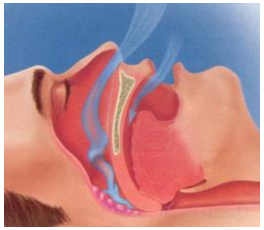
Mark Twain

Each night when I go to sleep, I die.
And then the next morning,
when I wake up, I am reborn.

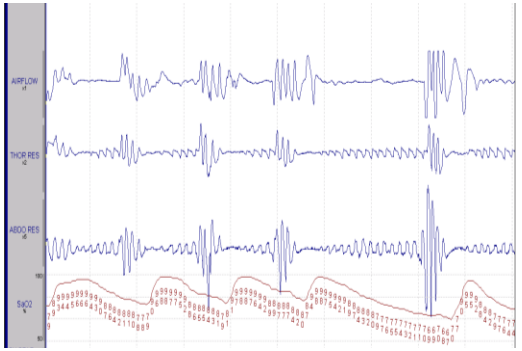


Obstructive Sleep Apnea

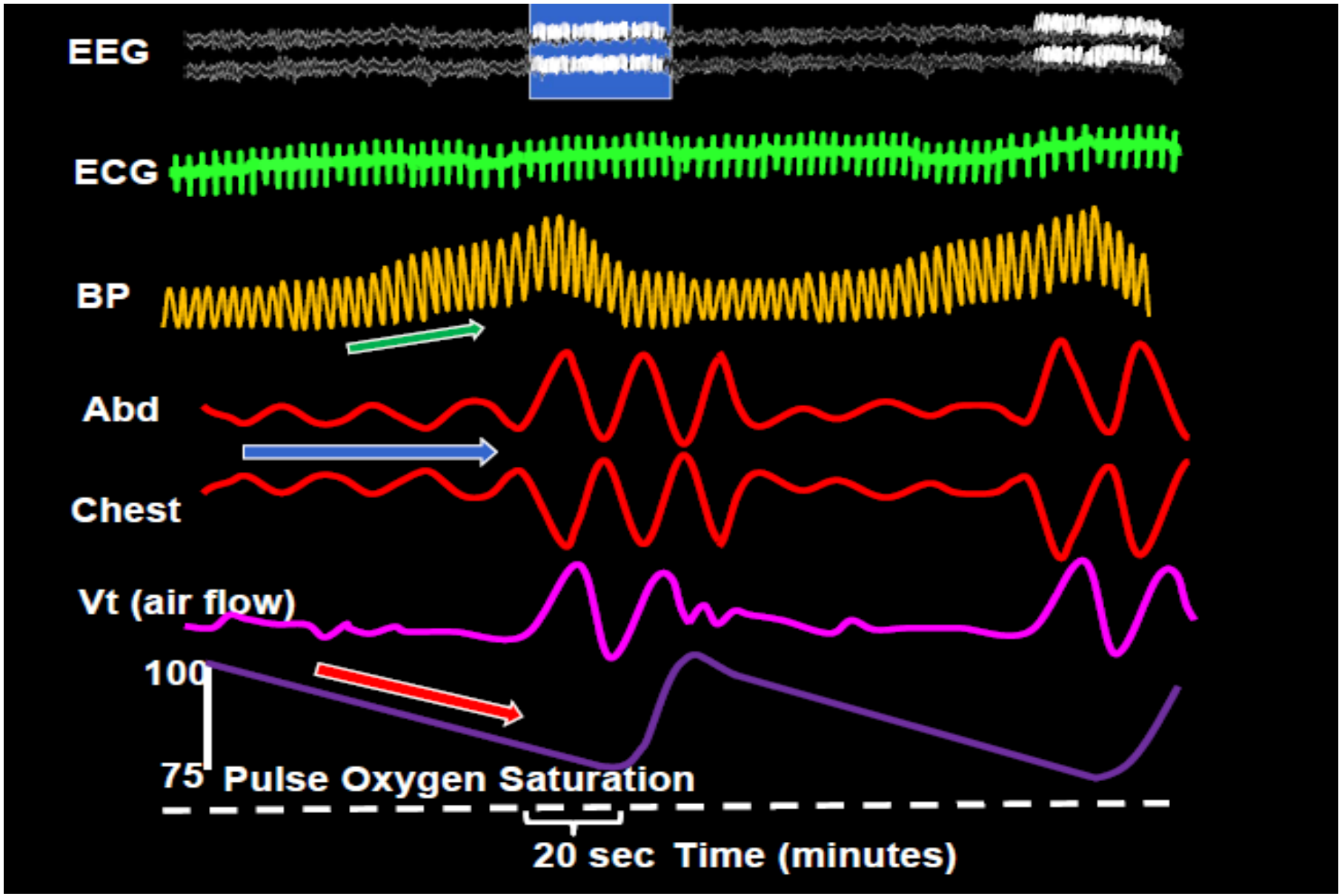
A Highly Prevalent, Under-recognized Physiologic Stressor

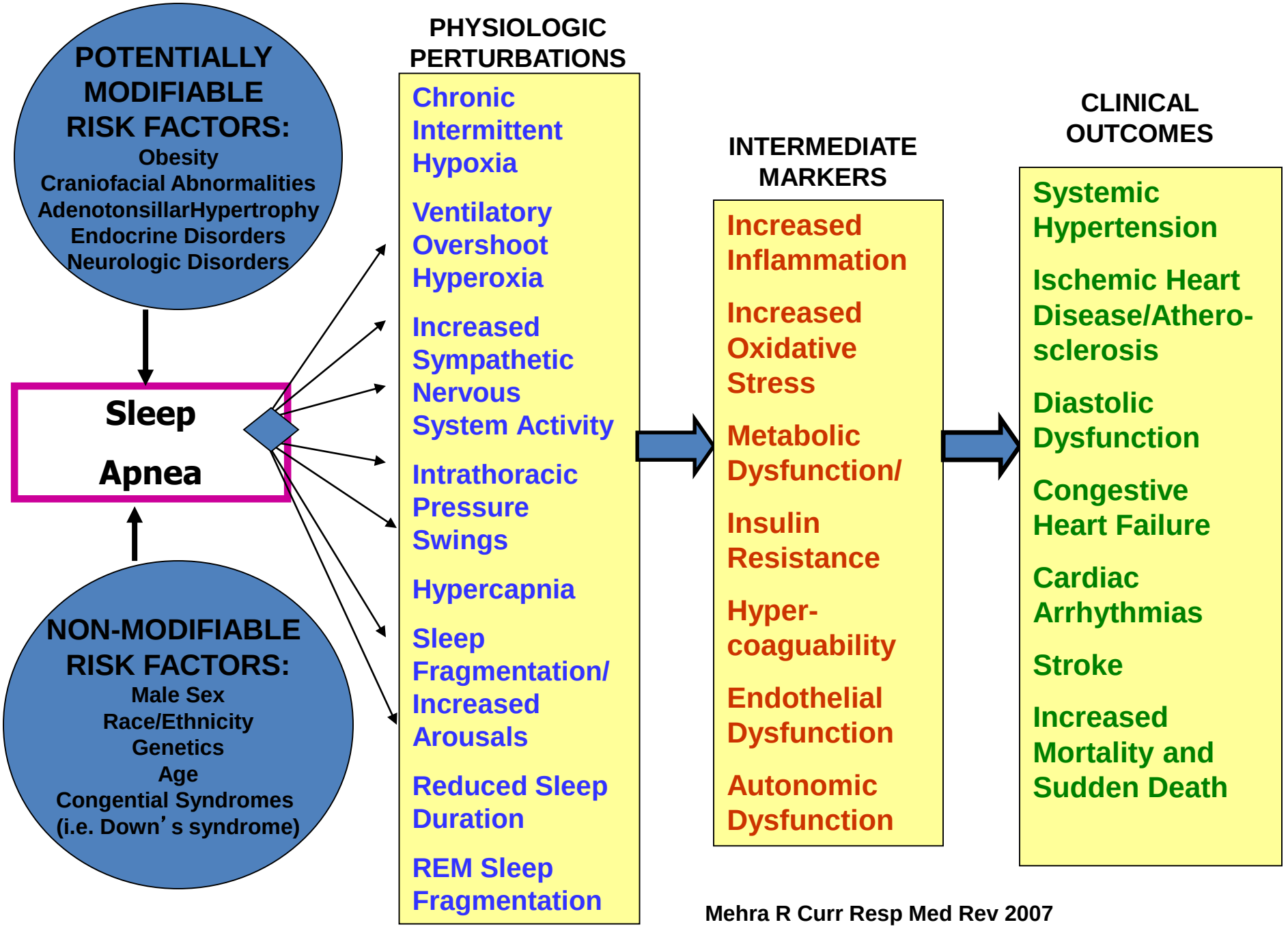


- **17% of the general adult population, increasing with obesity epidemic**
  - **Nearly 1 in 15 affected by at least moderate sleep apnea**
  - Young et al NEJM 1993, Peppard et al. Am J Epi 2013
  - **85% of cases estimated to be undiagnosed!**
  - Kapur VK et al Sleep and Breath 2002
  - **84% and 93% of individuals with AHI moderately or severely elevated (ie candidates for sleep apnea treatment), were undiagnosed in the MESA study**
  - **Minority predilection, health disparities issue**
  - Chen X et al SLEEP 2015
- **30-40% of patients with coronary disease**
  - Mooe T et al Chest 1996; Schaker et al H Cardiol 1999; Leung RS et al AJRCCM 2001
- **> 50% of patients with diabetes or hypertension or heart failure**



Pathophysiological Effects

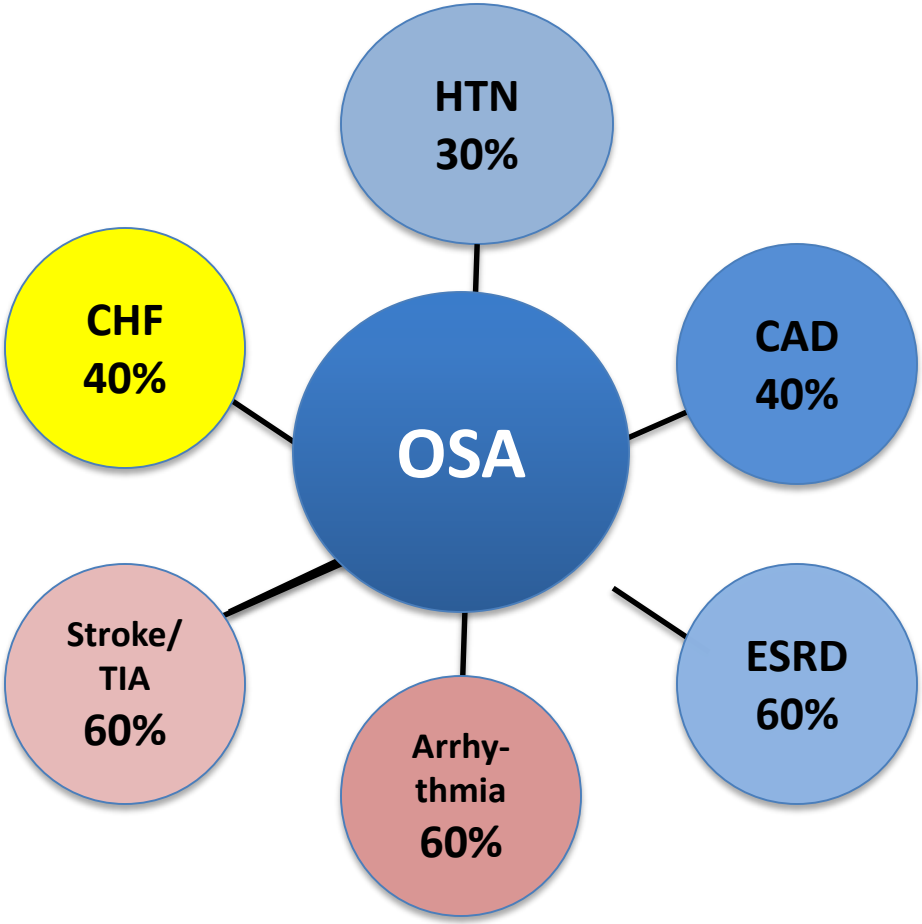




Mehra R Curr Resp Med Rev 2007

OSA Prevalence in Cardiovascular Diseases

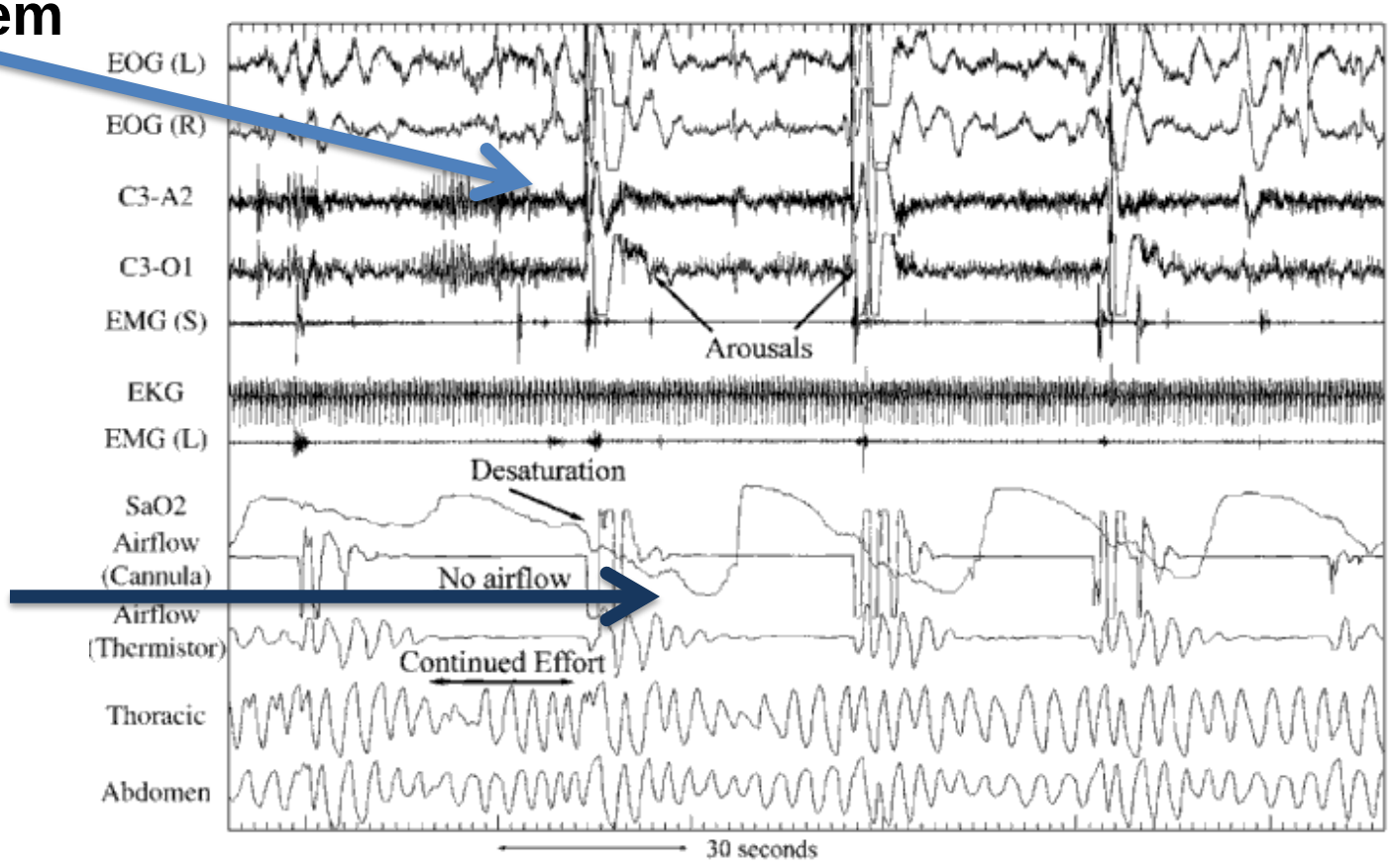
Cepeda-Valery B, Acherjee S, Romero-Corral, et al. Curr Cardiol Rep 2014; 16: 535.



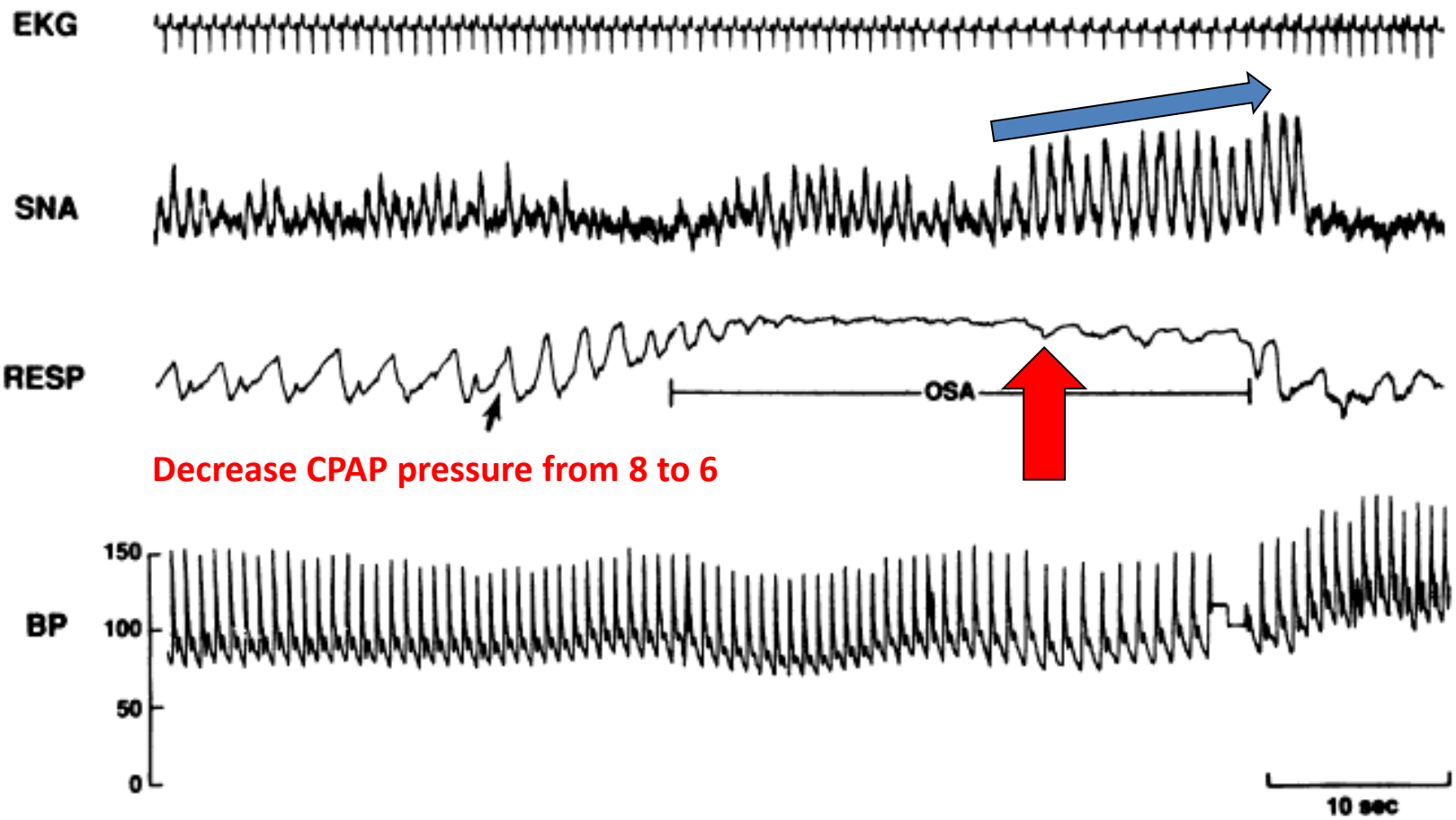
Candidate Mechanisms

Digging Deeper

- **Autonomic Nervous System Disturbances**
- **Intrathoracic Pressure Alterations**
- **Hypercapnia**
- **Intermittent Hypoxia**
- **Systemic Inflammation and Oxidative Stress**



Sympathetic Nervous System Activation in Obstructive Sleep Apnea

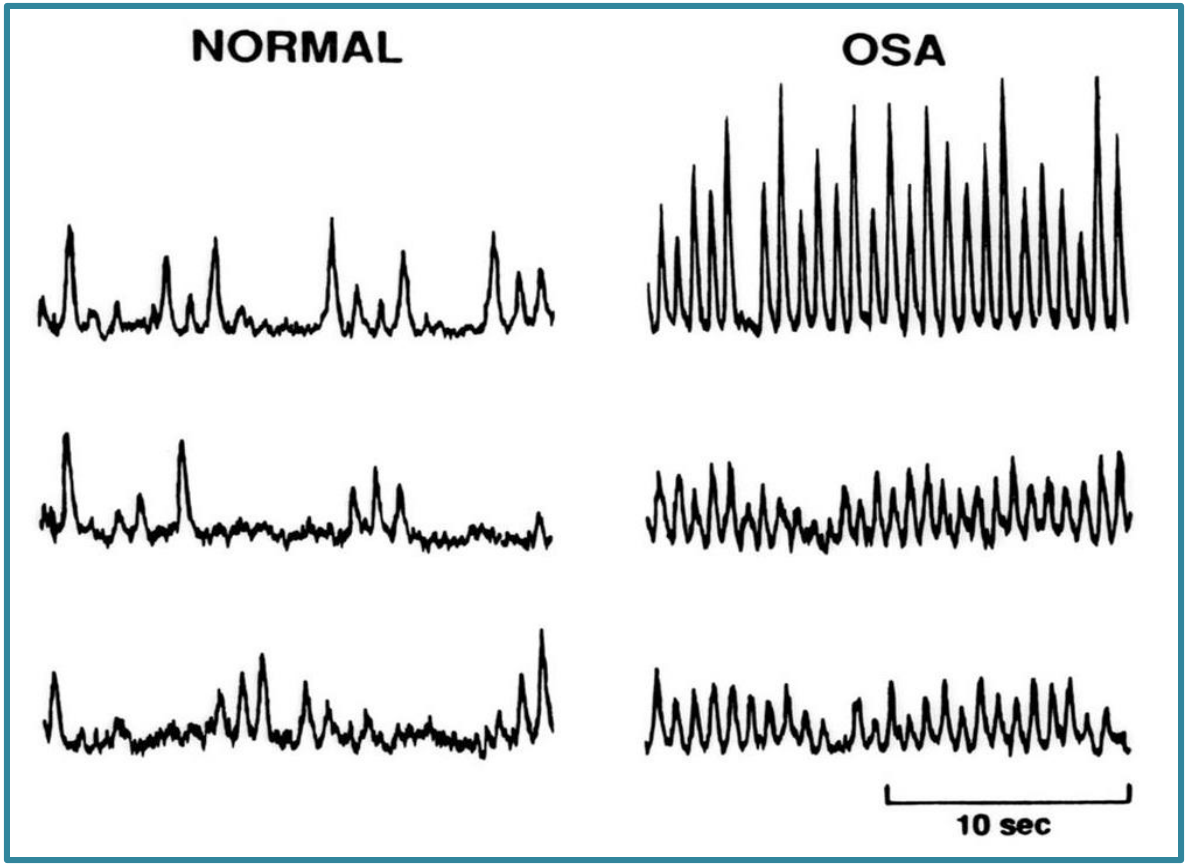


Somers et al. *J Clin Invest*. 1995;96:1897.

BP = blood pressure; CPAP = continuous positive airway pressure; REM = rapid eye movement; RESP = respiration; SNA = sympathetic nerve activity

Sympathetic Nervous System Activation in OSA *During Wakefulness*

Normal controls: 34±3bursts/min **Sleep Apnea: 59±14 bursts/min, p=0.003**



Female-Predominant Associations of and Endothelial Function in OSA

- Female vascular endothelium may be more sensitive to hypoxemia leading to reduced NO bioavailability
- Different vascular reactivity in men and women in OSA
  - Perhaps only men with severe OSA have vascular dysfunction
- Estrogens are known to improve endothelial function likely via induction of increased NO bioavailability
- Alterations of sex-specific hormones in OSA may represent a key factor in increasing vulnerability to vascular dysfunction

Levenson J, et al.Gender differences in wall shear-mediated brachial artery vasoconstriction and vasodilation . *J Am Coll Cardiol* . 2001 ; 38 (6): 1668 – 1674
Moro PJ , , et al . Gender differences in response to cold pressor test assessed with velocity-encoded cardiovascular magnetic resonance of the coronary sinus . *J Cardiovasc Magn Reson* . 2011 ; 13 : 54
Rossi P , et al. Gender differences in artery wall biomechanical properties throughout life . *J Hypertens* . 2011 ; 29 (6): 1023 – 1033

Female-Predominant Associations of Endothelial Dysfunction in OSA

Table 3—Multivariate Regression Analysis: Modeling Flow-Mediated Dilation

Flow-Mediated Dilation

Variable	β coefficient (SE)	*P* value
Sex, 1 = man	-6.13 (1.09)	< .001
Age, y	-0.08 (0.03)	.013
log(BMI), kg/m^2	-2.33(2.16)	.283
SDB, AHI ≥ 15	-4.35 (1.86)	.022
Sex × AHI interaction	5.19 (2.31)	.027
Hypertension, 1 = yes	-1.73 (1.20)	.151
Current smoking, 1 = yes	-2.48 (1.07)	.022
Current alcohol, 1 = yes	2.27 (0.98)	.022

BMI refers to body mass index; AHI, apnea-hypopnea index.

Table 4—Multivariate Regression Analysis: Modeling Peak Blood Flow

Peak Blood Flow

Variable	β coefficient (SE)	*P* value
Sex, 1 = man	-39.3 (17.2)	.024
Age, y	-0.91 (0.40)	.025
log(BMI), kg/m^2	-16.0 (30.9)	.607
log(AHI), events/h	-15.1 (6.8)	.033
Sex × AHI interaction	19.8 (7.8)	.012
Hypertension, 1 = yes	63.1 (26.8)	.021
Hypertension × AHI interaction	-23.1 (10.3)	.030
Current smoking, 1 = yes	-22.4 (12.3)	.071

BMI refers to body mass index; AHI, apnea-hypopnea index.

- **Vascular endothelium is influenced by sex hormones and differences in endothelial function may exist**
- **2 studies used different techniques, i.e. FMD via BAUS versus PAT (the latter operator independent)**
- **Identified association of OSA severity (AHI and hypoxia) with measures of vascular dysfunction**

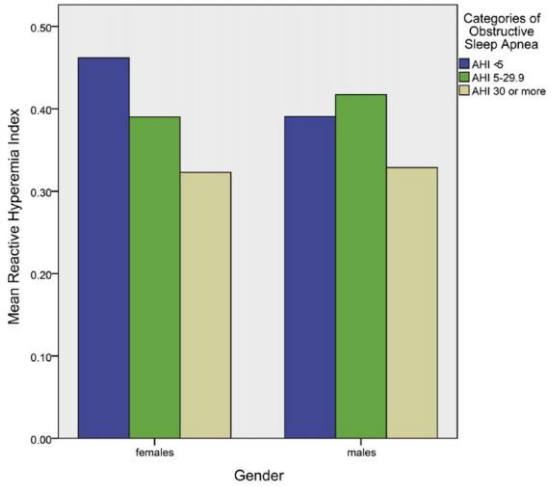


FIGURE 1. Mean values of reactive hyperemia index according to AHI categories, showing a dose-response pattern of mean reactive hyperemia index among women but not among men. AHI = apnea-hypopnea index.

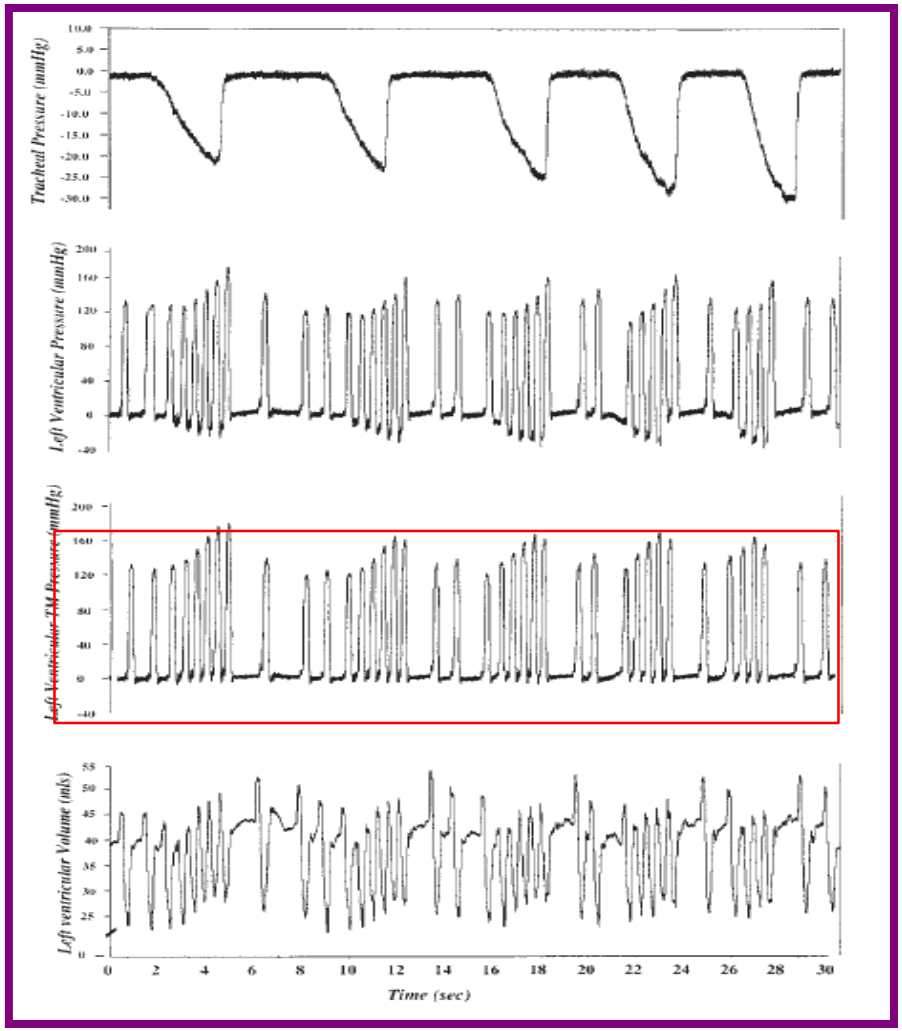
Bandby, et al.CHEST 2013; 144(3):915–922

Faulx MD; et al. Sex influences endothelial function in sleep-disordered breathing. SLEEP 2004;27(6):1113-20.

Upper Airway Occlusion Leads to Negative Intrathoracic Pressure Swings

- Increased preload
- Increased LV afterload (increased transmural pressure)
- Impaired diastolic function
- Atrial and aortic enlargement

Change in atrial volume → AF



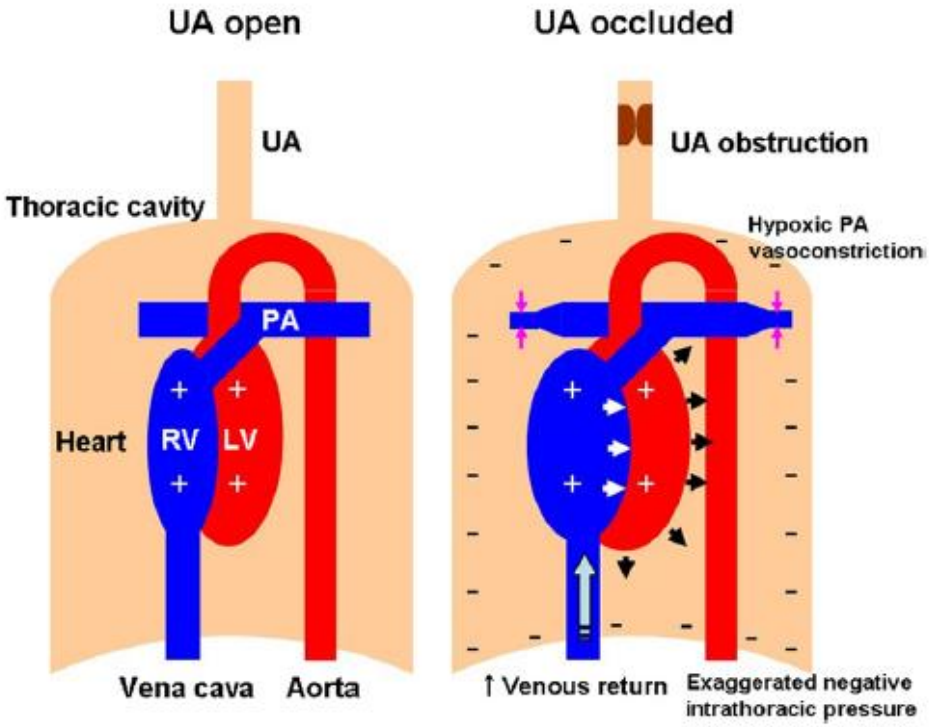
Tracheal Pressure (mmHg)

LV Pressure (mmHg)

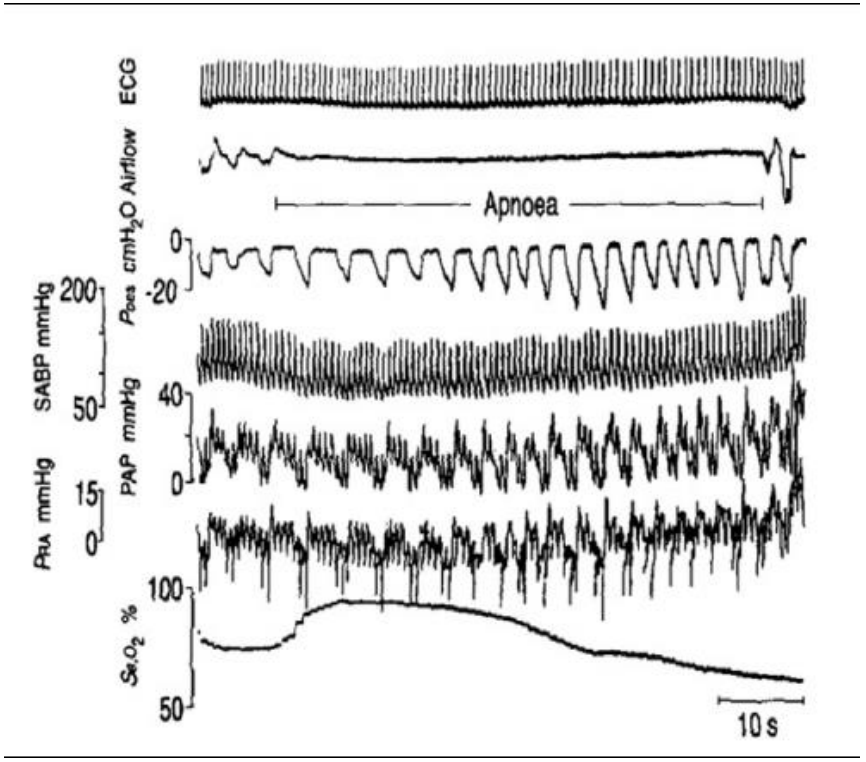
LV Transmural Pressure (mmHg)

LV End Systolic Volume (mL)

Cardiopulmonary Ramifications of Upper Airway Occlusion



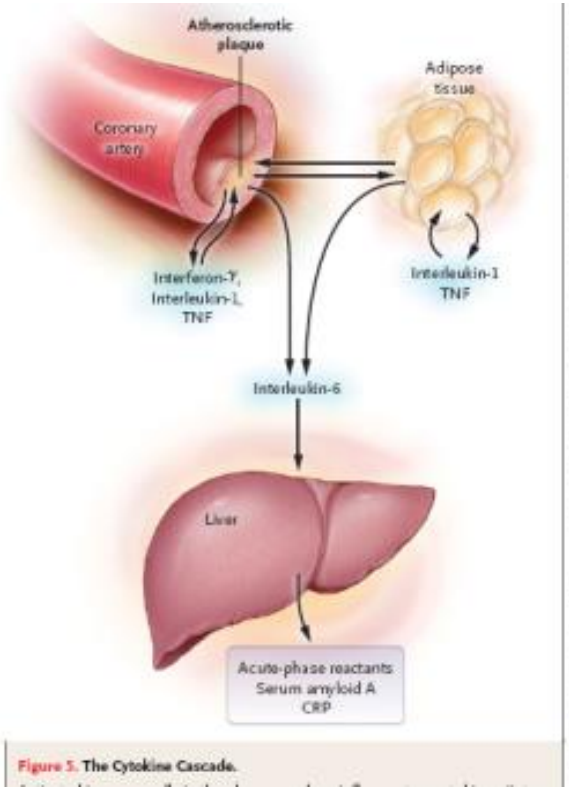
Kasai T, J Am Coll Cardiol. 2011 Jan 11;57(2):119-27



Sajkov D et al Prog Cardiovasc Dis 2009;51

Pro-Inflammatory and Atherogenic Effects

- Upregulation of inflammatory mediators
    - IL6*, sIL6R*, IL-8, TNFα, CRP, (NF-Kappa B)
- Enhanced thrombotic potential
  - PAI-1*, fibrinogen*, P-selectin
  - VEGF
- Oxidation of serum proteins and lipids*
- Endothelial dysfunction*
- Insulin Resistance and Dyslipidemia

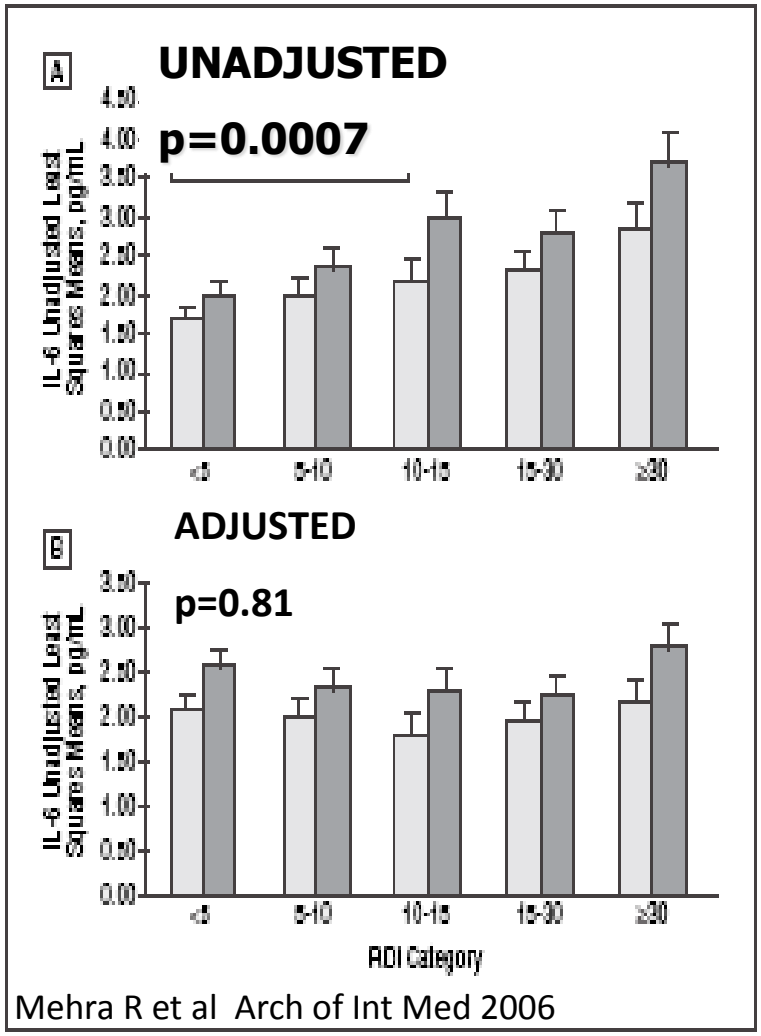


Hansson *NEJM* 352: 2005

Nadeem R. J Clin Sleep Med. 2013 Oct 15;9(10):1003-12, Mehra R et al AJRCCM 2010, Mehra R et al Arch of Int Med 2006, Paz Y Mar H et al, CHEST 2016, Xie X Sleep Med. 2013 Nov;14(11):1139-50.

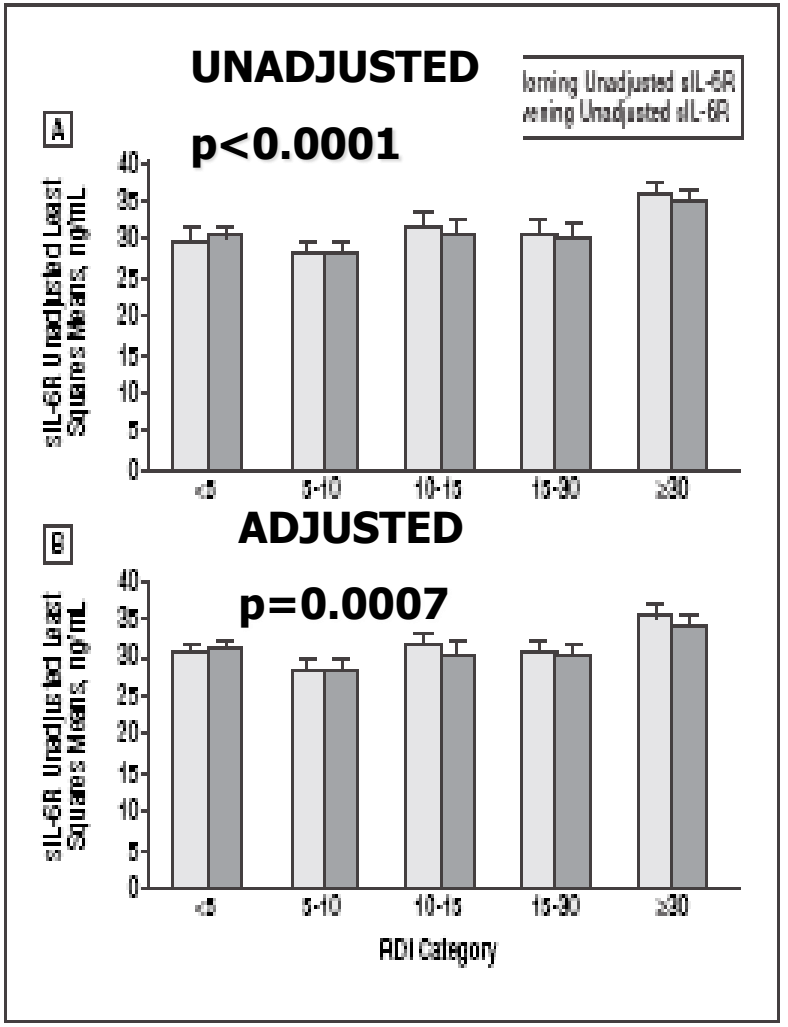
Sleep Apnea and Cytokines
Cleveland Family Study

Interleukin-6



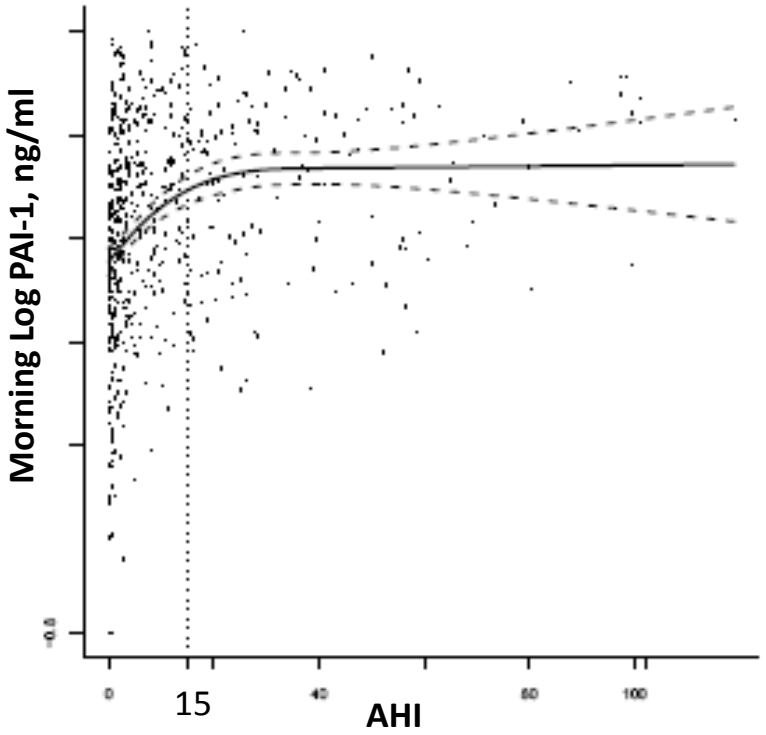
Mehra R et al Arch of Int Med 2006

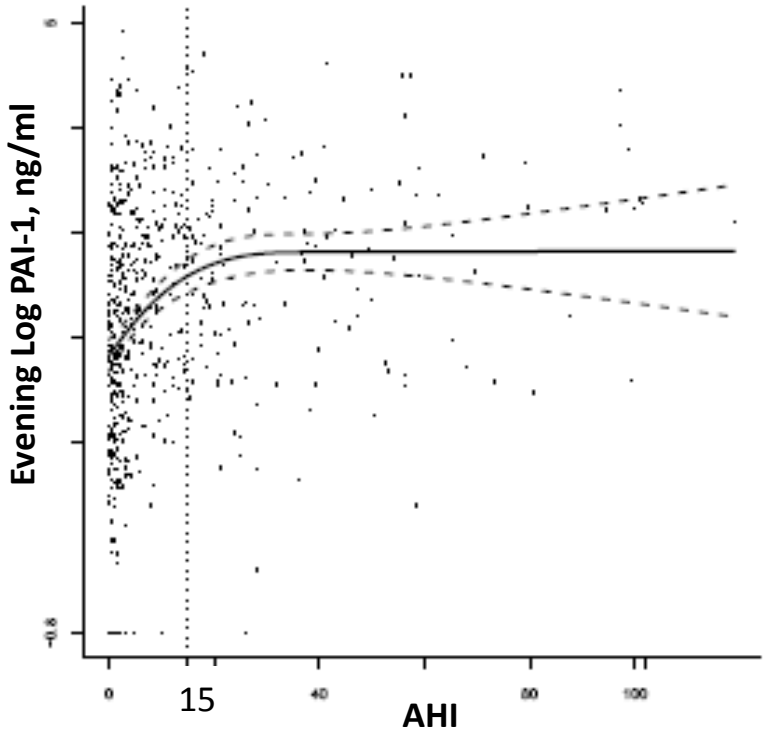
Soluble IL-6 Receptor



Sleep Apnea and PAI-1

Cleveland Family Study

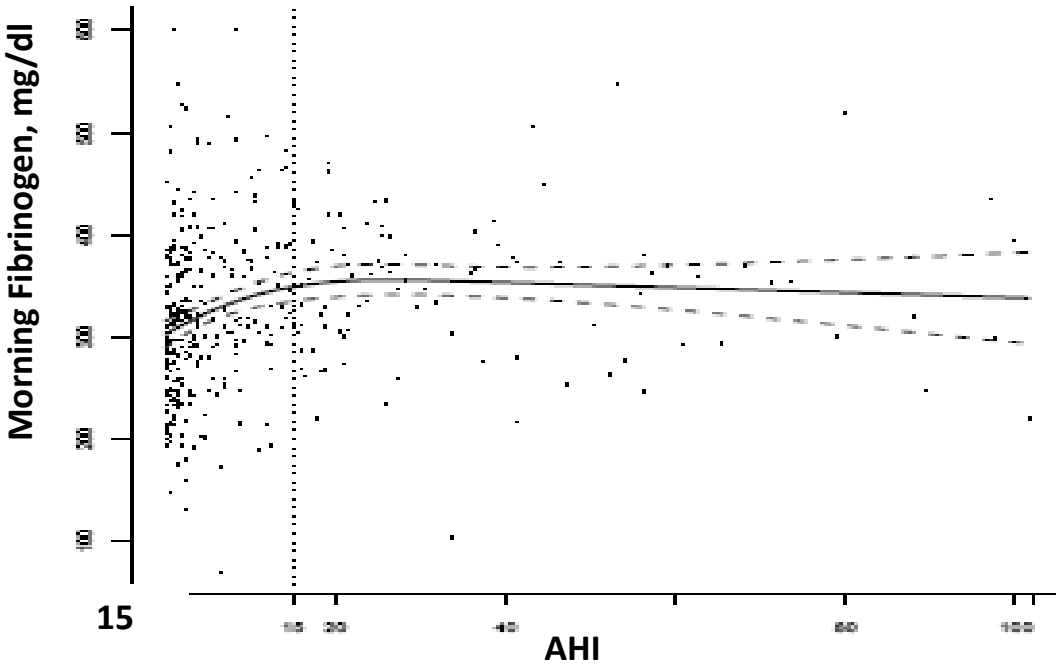




n=567	Change in PAI-1 given 5 unit AHI increase		Difference in slopes
AHI < 15	**1.10 (1.02, 1.16)**	**0.01**	**0.01**
AHI ≥ 15	0.99 (0.97, 1.01)	0.32	

Mehra R et al AJRCCM 2010

Sleep Apnea and Fibrinogen
Cleveland Family Study

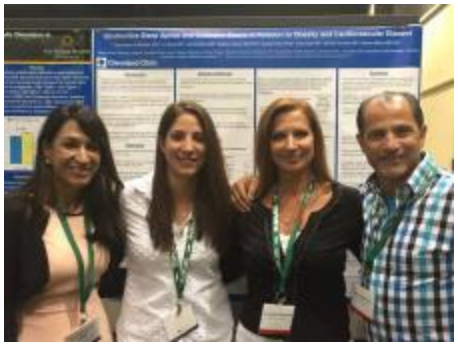


n=518	Change in Fibrinogen given 5 unit AHI increase		Difference in slopes
AHI < 15	**9.56 (4.26, 14.87)**	**< 0.001**	**0.001**
AHI ≥ 15	-1.14 (-3.29, 1.02)	0.30	

Mehra R et al AJRCCM 2010

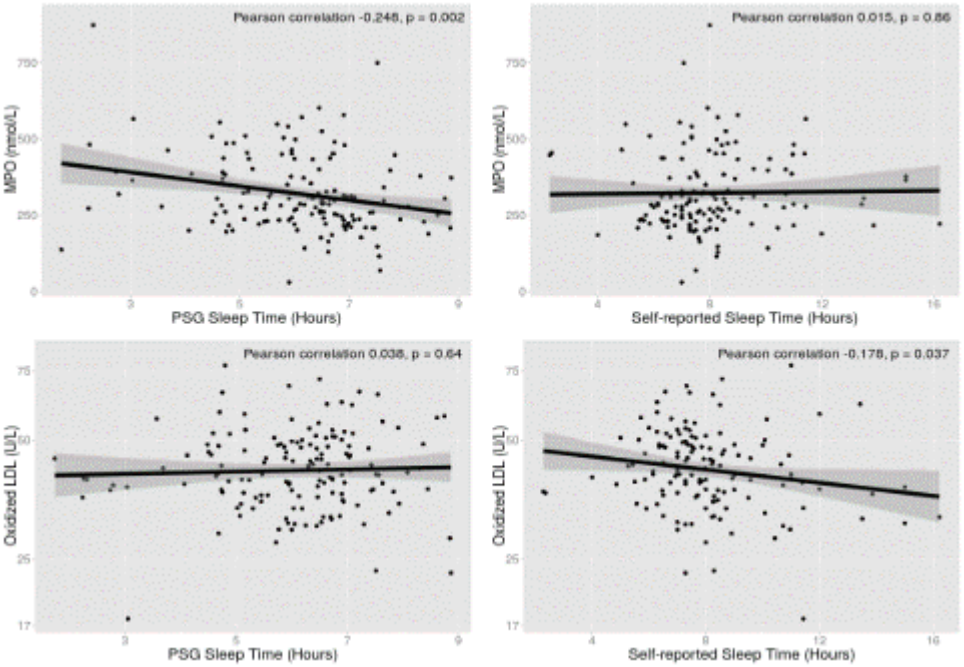
Oxidative Stress and Inflammation Differentially Elevated in *Objective versus Subjective Reduced Sleep Duration* in Obstructive Sleep Apnea

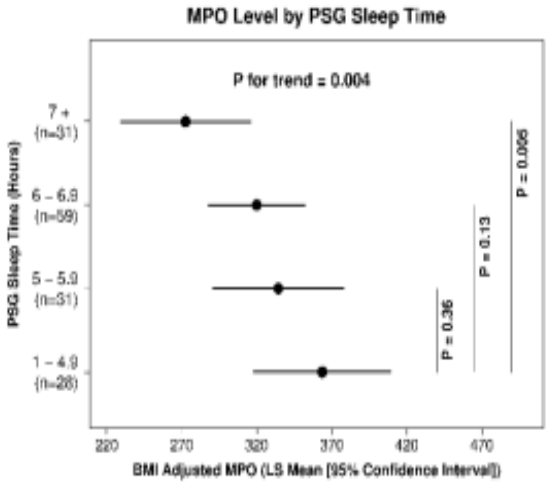
SASS
Sleep Apnea Stress Study

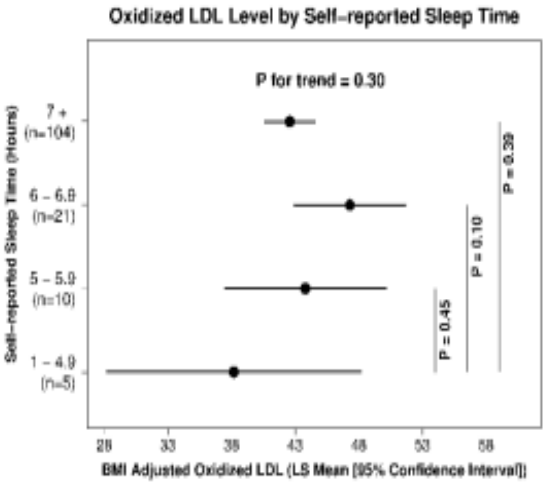


Theresanne Demartino MSII

- n=147 participants of the SASS study
- *Inverse association of PSG-TST and MPO*
  - -20.28, -37.48- -3.08,
  - p = 0.021
- *Inverse association of oxidized LDL and SR-SD*
  - 0.98, 0.96-0.99,
    p = 0.027
  - 2% ox-LDL reduction per hour increase SR-SD



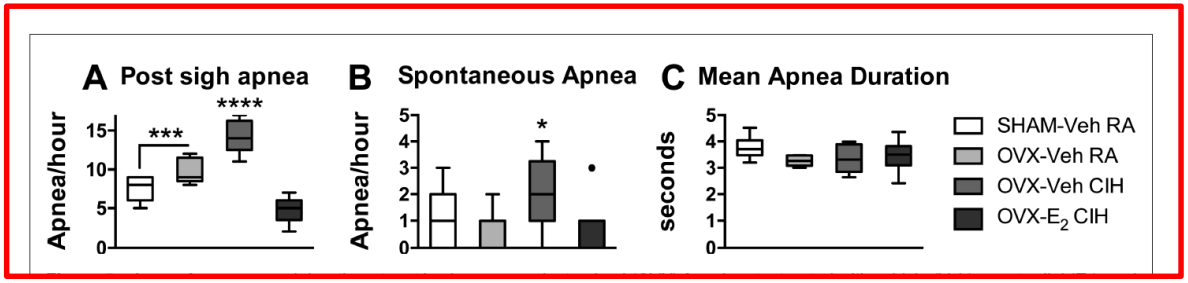


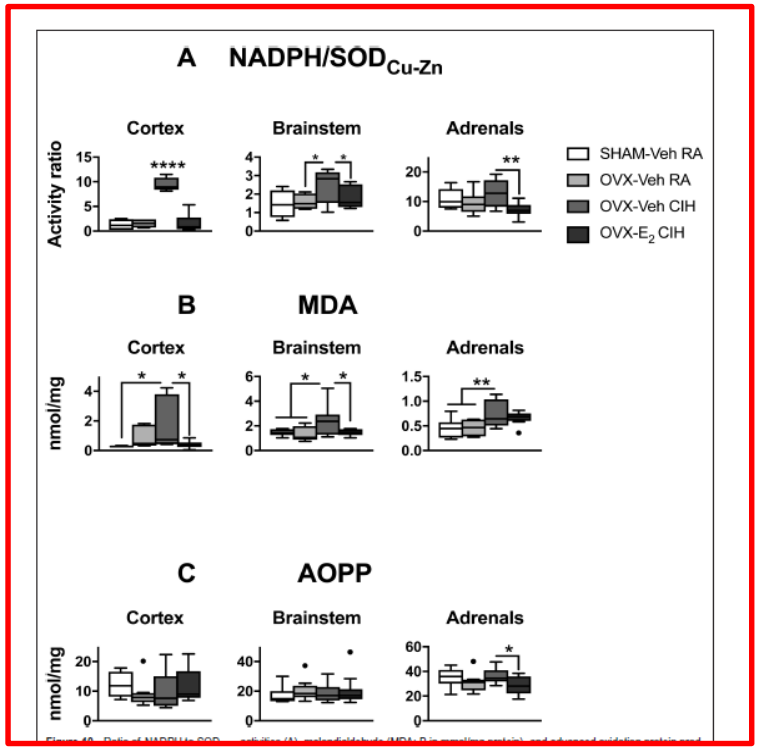


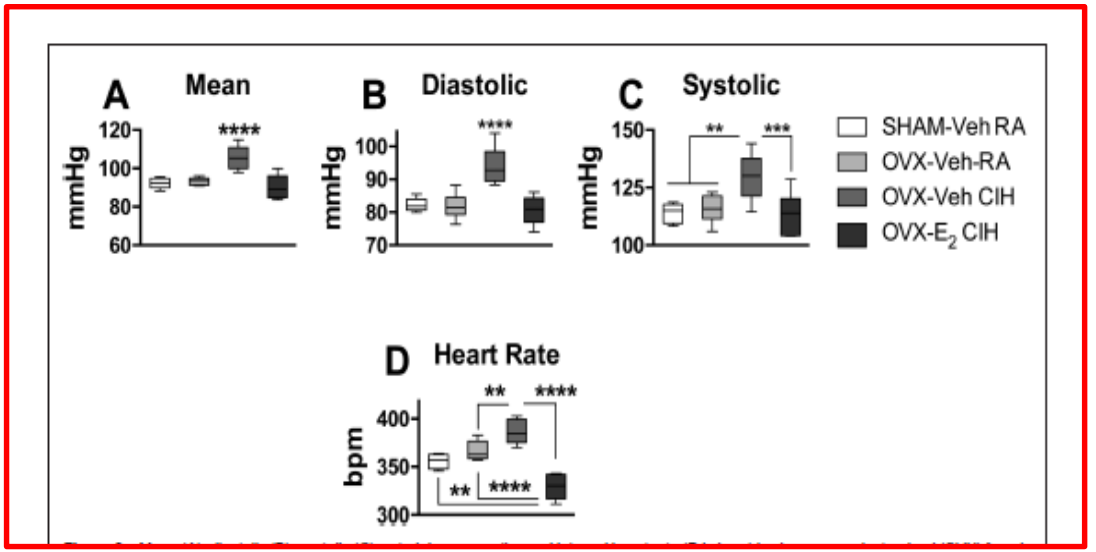
DeMartino T*, El Ghoul R*, et al, Sleep 2016, July 39; 1361-9. 2016

Estradiol Protection of Cardiorespiratory Dysfunction and Oxidative Stress in Intermittent Hypoxia

- Chronic intermittent hypoxia model in ovariectomized adult female rats
- Systemic estradiol administration was protective in terms of blood pressure, ventilation measures and oxidative stress in brain and adrenal glands



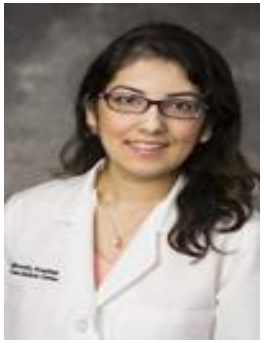




Laoufa et al SLEEP 2017

Randomized Controlled Trial
Effect of CPAP on Measures of Vascular Function and Inflammation

SASS
Sleep Apnea Stress Study



Fareeha Ashraf MD

Hugo Paz y Mar MD

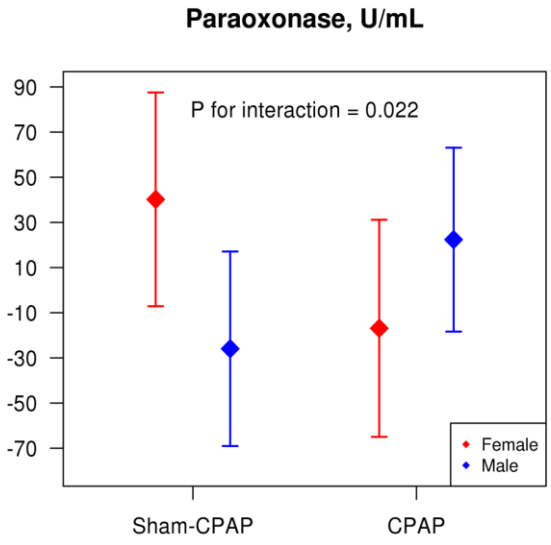
% Change	Sham (n=71)	CPAP (n=72)	p-value
Blood Pressure (morning)			
SBP	0.338 ± 0.986	-2.516 ± 0.979	**0.042**
DBP	1.884 ± 1.347	-2.156 ± 1.338	**0.035**
Systemic Inflammation			
IL-6	19.941 ± 8.571	8.837 ± 8.245	0.35
Soluble IL-6R	2.789 ± 1.833	-2.872 ± 1.764	**0.028**
Vascular Measures (morning) *difference			
Augmentation Index	-0.2 ± 1.3	6.5 ± 1.4	**0.009**

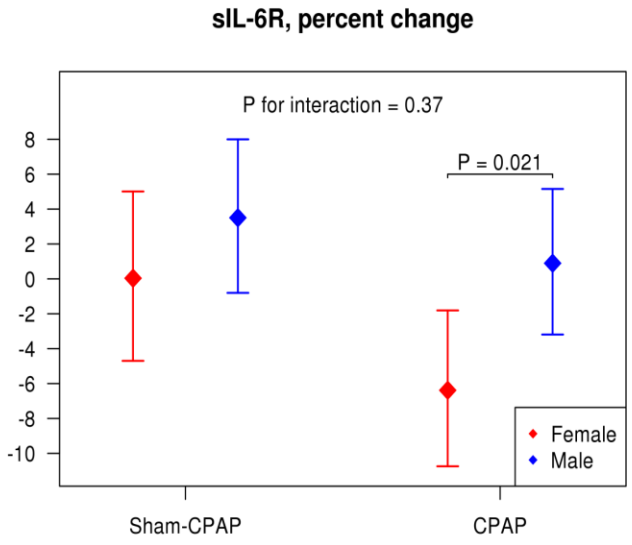
Paz Y Mar HL*, Hazen SL, Tracy RP, Strohl KP, Auckley D, Bena J, Wang L, Walia HK, Patel SR, Mehra R. Effect of Continuous Positive Airway Pressure on Cardiovascular Biomarkers: The Sleep Apnea Stress Randomized Controlled Trial. Chest. 2016 Jul;150(1):80-90.

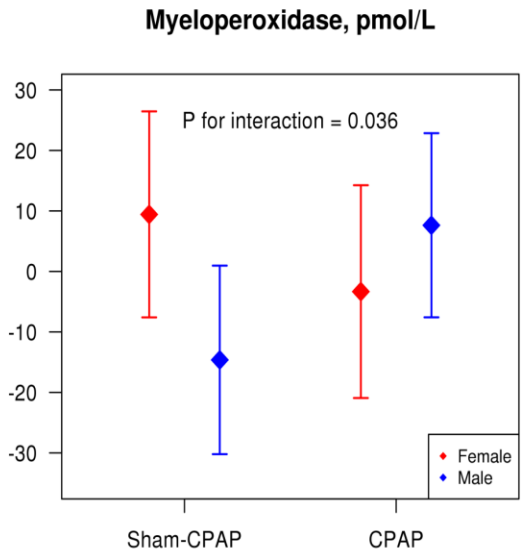
Respiratory Institute Research Day award, Neurologic Institute Research Day award, SLEEP meeting award

Sex-Specific Alterations in Oxidative Stress in a Randomized Controlled Trial of CPAP versus Sham CPAP for OSA Treatment

SASS Sleep Apnea Stress Study







- Overall significant difference in SBP, DBP, soluble IL-6 receptor, AI in CPAP vs sham
- PON and MPO with significant gender*group interaction
- Soluble IL-6 receptor with 0% change in female sham, 3.5% ↑ male sham CPAP; 6.4% ↓ in female CPAP, 0.9% ↑male CPAP

Paz Y Mar HL*, Hazen SL, Tracy RP, Strohl KP, Auckley D, Bena J, Wang L, Walia HK, Patel SR, Mehra R. Effect of Continuous Positive Airway Pressure on Cardiovascular Biomarkers: The Sleep Apnea Stress Randomized Controlled Trial. Chest. 2016 Jul;150(1):80

Sleep Disordered Breathing and Hypertension

Obstructive Sleep Apnea and *Incident* Hypertension

The New England Journal of Medicine

VOLUME 342 MAY 11, 2000 NUMBER 19

PROSPECTIVE STUDY OF THE ASSOCIATION BETWEEN SLEEP-DISORDERED BREATHING AND HYPERTENSION

PAUL E. PEPPARD, PH.D., TERRY YOUNG, PH.D., MARI PALTA, PH.D., AND JAMES SKATRUD, M.D.

BASE-LINE APNEA–HYPOPNEA INDEX	ADJUSTED ODDS RATIO (95% CI)
0.1–4.9 events/hr	1.0
5.0–14.9 events/hr	1.42 (1.13–1.78)
≥15.0 events/hr	2.89 (1.46–5.64)
P for trend‡	0.002

Prospective Association of Treated and Untreated Obstructive Sleep Apnea and Risk of Hypertension

n=1889, Spanish study

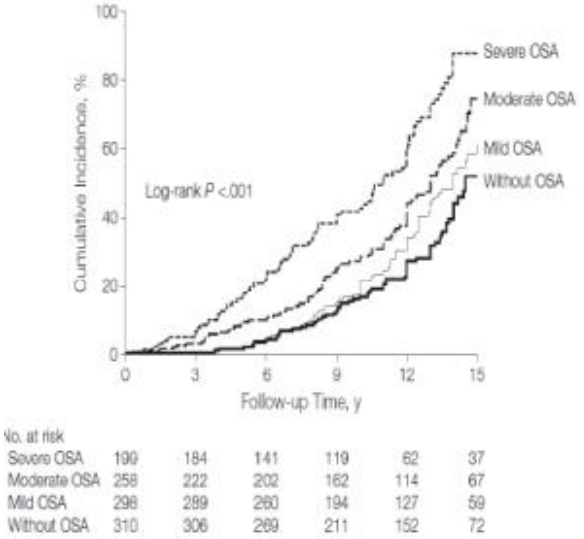


Table 4. Cox Proportional Hazards Regression Models of Incident Hypertension in Patients With OSA With Multiple Imputations[a]

		Patients With OSA			
	Controls (n = 310)	Ineligible for CPAP Therapy (n = 462)	Declined CPAP Therapy (n = 195)	Nonadherent to CPAP Therapy (n = 98)	Treated With CPAP Therapy (n = 824)
Baseline AHI, mean (SD)	2.6 (1.3)	14.2 (6.6)	37.1 (16.3)	31.3 (13.4)	41.2 (19.9)
	Hazard Ratio (95% CI)				
Model 1, adjusted for AHI, age, and sex	1 [Reference]	1.63 (1.25-2.12)	2.89 (2.18-3.84)	2.70 (1.90-3.83)	1.47 (1.24-1.88)
Model 2, adjusted for model 1 + SBP and DBP	1 [Reference]	1.57 (1.20-2.05)	2.78 (2.08-3.70)	2.50 (1.75-3.56)	1.17 (0.90-1.51)
Model 3, adjusted for model 2 + BMI	1 [Reference]	1.46 (1.12-1.91)	2.54 (1.90-3.39)	2.20 (1.90-3.39)	1.01 (0.78-1.31)
Model 4, adjusted for model 3 + baseline covariates[b]	1 [Reference]	1.39 (1.06-1.82)	2.23 (1.36-3.01)	1.96 (1.36-2.83)	0.83 (0.63-1.11)
Model 5, adjusted for model 4 + change in BMI	1 [Reference]	1.33 (1.01-1.75)	1.96 (1.44-2.66)	1.78 (1.23-2.58)	0.71 (0.53-0.94)

Declined CPAP: ~2-fold increased risk of incident hypertension

CPAP Non-adherent: ~80% increased risk of incident hypertension

Treated: ~30% reduction in risk of incident hypertension

Marin JAMA. 2012; 307 (20): 2169

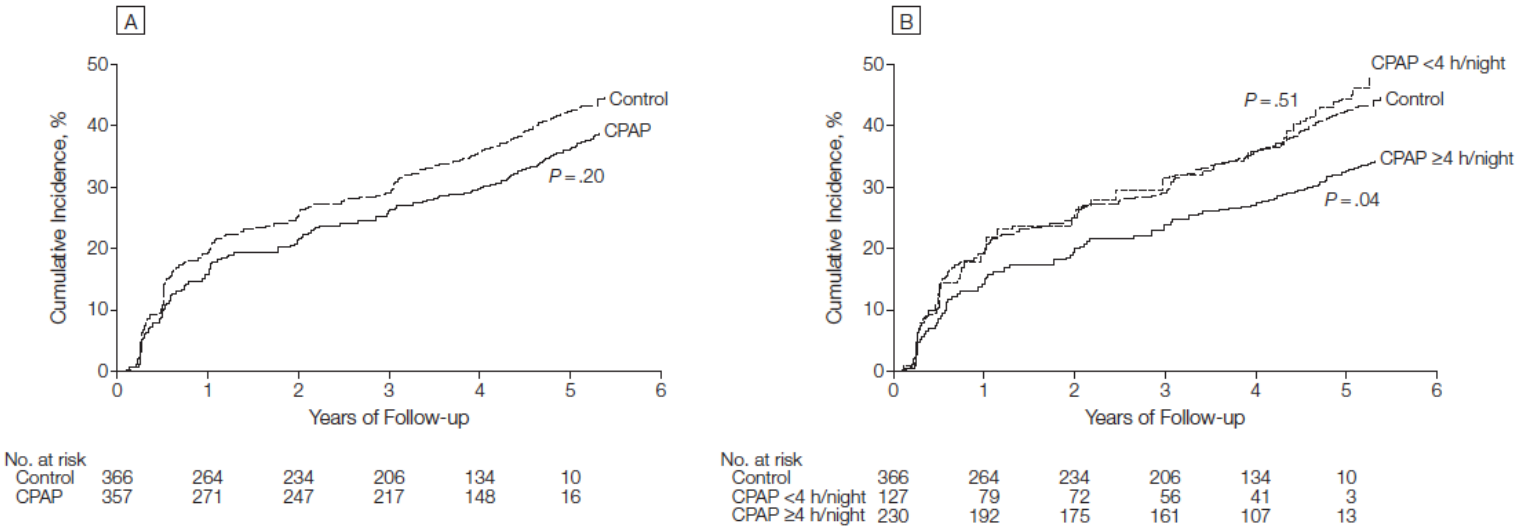
Impact of Sleepiness on Treatment Effect of Sleep Apnea

ORIGINAL CONTRIBUTION

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

Figure 2. Cumulative Incidence of Hypertension or Cardiovascular Events During Follow-up



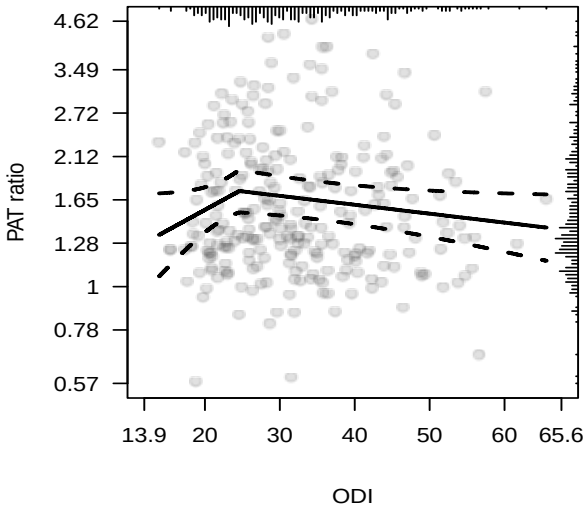
A, Cumulative incidence of hypertension or cardiovascular events for the intervention groups during follow-up and the *P* value for the incidence density ratio of continuous positive airway pressure (CPAP) vs control (Wald test). B, Panel A with CPAP group stratified according to adherence (<4 vs ≥4 h/night) and the *P* values for their incidence density ratios in reference to the control group.

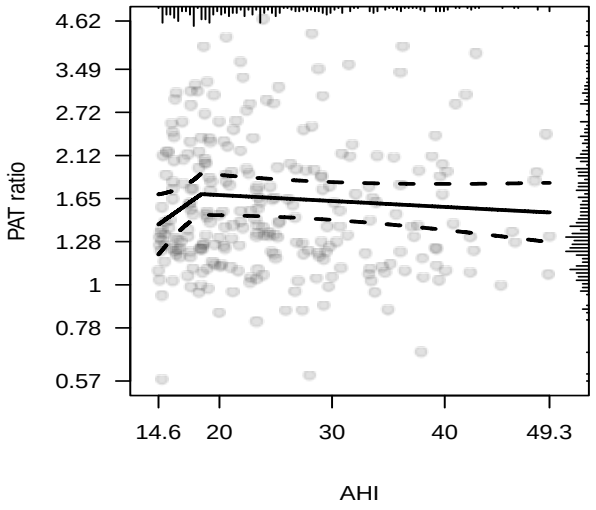
- In patients with OSA ***without daytime sleepiness (n=725)***, CPAP compared with usual care did not result in a statistically significant reduction in incidence of hypertension or CV events over 4- year median follow up
- Subgroup analysis of those using CPAP>=4 hours demonstrated CV benefit

Barbe et al. JAMA, 2012

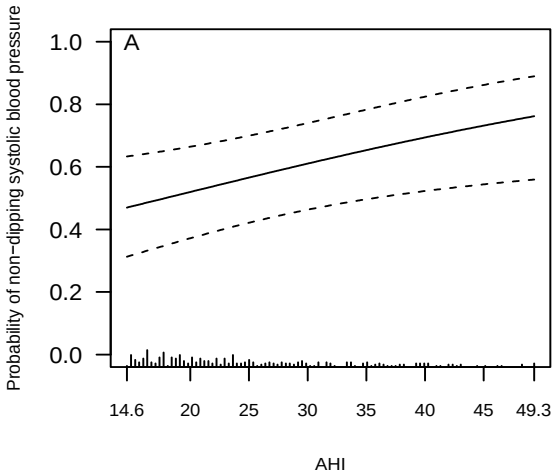
Sleep Apnea, Endothelial Dysfunction and Non-Dipping Blood Pressure

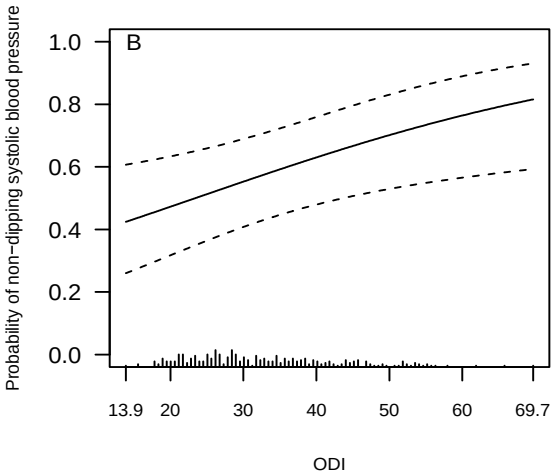
Fadi Seif MD





Increasing AHI and ODI associated with reduction in PAT ratio, p=0.04 and 0.05 respectively

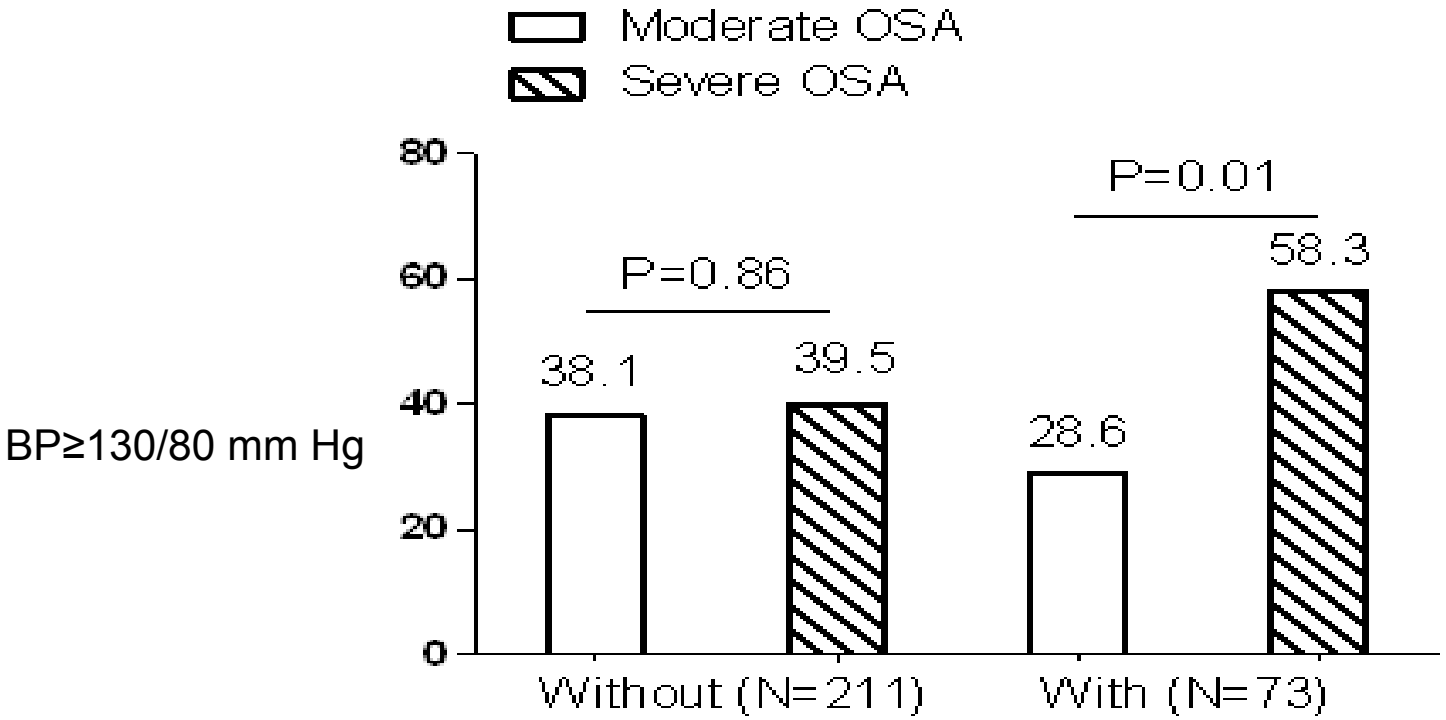




4% increased odds of non-dipping blood pressure per unit increase of AHI or ODI, p=0.012 and 0.009 respectively

Seif F, J Sleep Res 2013 and Seif F, J Hypertension 2013

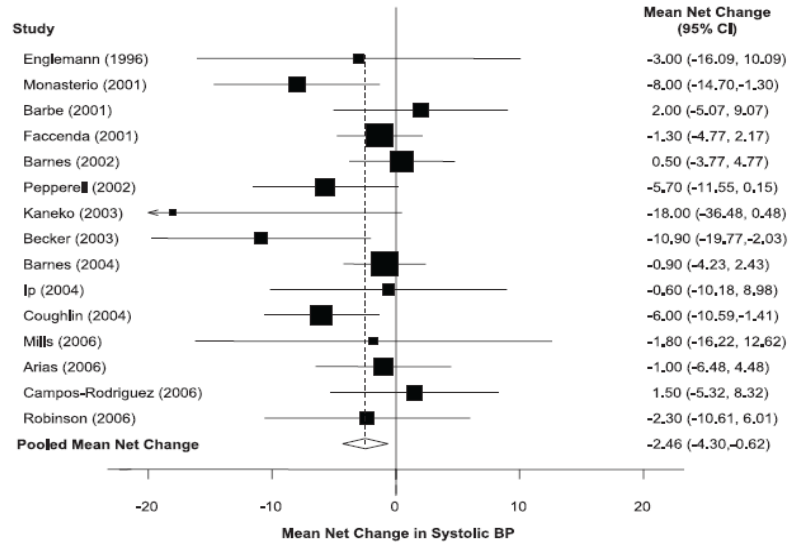
Higher Resistant Blood Pressure in Severe OSA on Intensive Anti-hypertensive Regimen



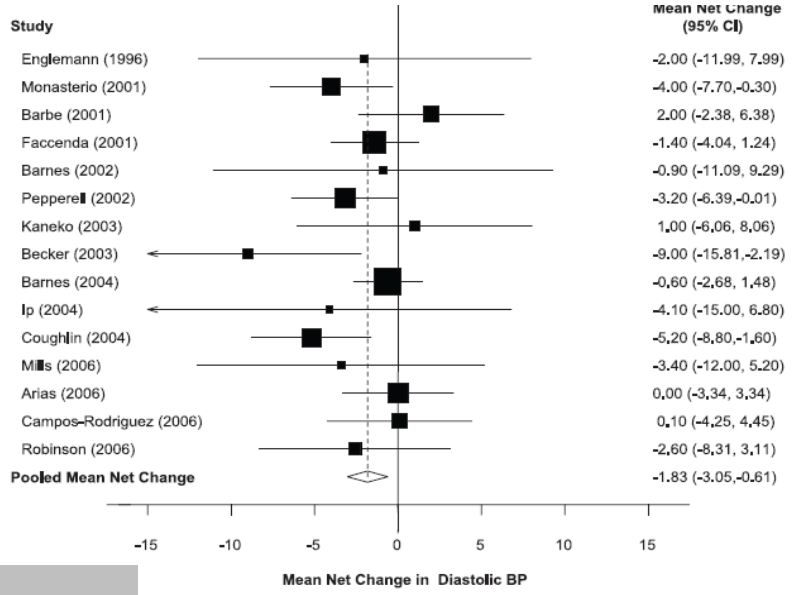
Walia et al. Journal of Clinical Sleep Medicine 2014

Change in Blood Pressure with CPAP in OSA

SBP Change: -2.46 (-4.31,-.62)



DBP Change: -1.83 (-3.05,-.62)



- **16 RCTs with n=1166 participants**
- **Modest but significant reductions in:**
  - **Office SBP (-3.2mmHg), DBP (-2.9mmHg)**
  - **24-hour DBP (-3.5mmHg)**
  - **24-hour mean arterial BP (-3.6mmHg)**
  - **Night-time SBP (-4.9mmHg)**
  - **Mean night-time BP (-2.7mmHg)**

Bazzano LA *Hyper* 2007:50
Haentjens et al. Archives of Internal Medicine 2007
Schein J of Hypertension; 2014

Spanish Clinical Trials in an All-Female Sample: Improvement in Blood Pressure and Quality of Life with CPAP vs Control in Moderate to Severe OSA

ORIGINAL ARTICLE

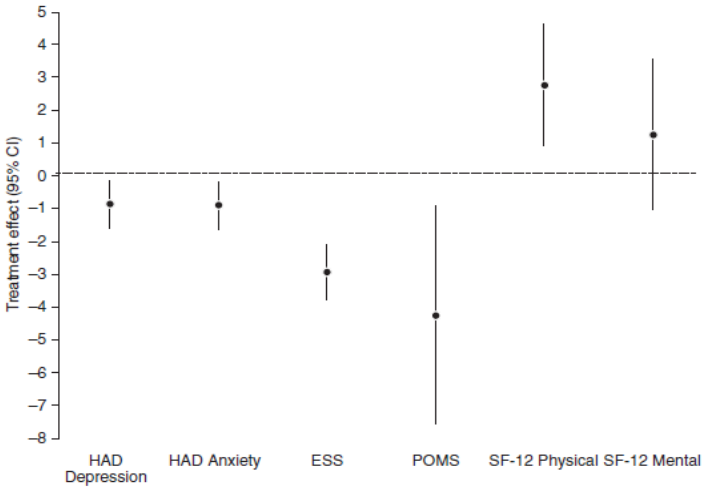
Continuous Positive Airway Pressure Improves Quality of Life in Women with Obstructive Sleep Apnea
A Randomized Controlled Trial

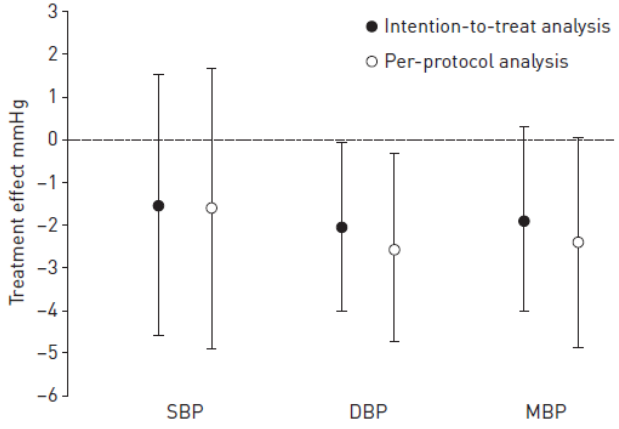
Francisco Campos-Rodriguez[1], Carlos Queipo-Corona[2], Carmen Carmona-Bernal[3], Bernabe Jurado-Gamez[4], Jose Cordero-Guevara[5], Nuria Reyes-Nuñez[1], Fernanda Troncoso-Acevedo[6], Araceli Abad-Fernandez[7], Joaquin Teran-Santos[8,9], Julian Caballero-Rodriguez[10], Mercedes Martin-Romero[11], Ana Encabo-Motiño[12], Lirios Sacristan-Bou[13], Javier Navarro-Esteva[14], Maria Somoza-Gonzalez[15], Juan F. Masa[9,16], Maria A. Sanchez-Quiroga[17], Beatriz Jara-Chinarro[18], Belen Orosa-Bertol[19], and Miguel A. Martinez-Garcia[9,20]; on behalf of the Spanish Sleep Network*

CrossMark

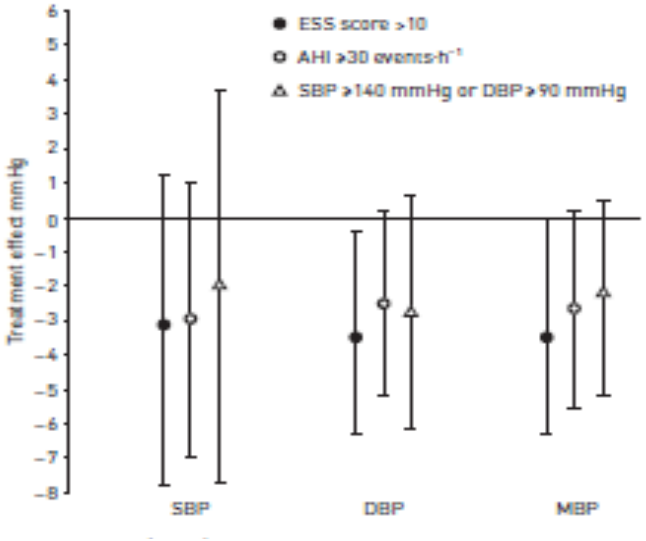
Effect of continuous positive airway pressure on blood pressure and metabolic profile in women with sleep apnoea

Francisco Campos-Rodriguez[1], Monica Gonzalez-Martinez[2], Angeles Sanchez-Armengol[3], Bernabe Jurado-Gamez[4], Jose Cordero-Guevara[5], Nuria Reyes-Nuñez[1], Maria F. Troncoso[6,7], Araceli Abad-Fernandez[8], Joaquin Teran-Santos[7,9], Julian Caballero-Rodriguez[10], Mercedes Martin-Romero[11], Ana Encabo-Motiño[12], Lirios Sacristan-Bou[13], Javier Navarro-Esteva[14], Maria Somoza-Gonzalez[15], Juan F. Masa[7,16], Maria A. Sanchez-Quiroga[17], Beatriz Jara-Chinarro[18], Belen Orosa-Bertol[19] and Miguel A. Martinez-Garcia[20] on behalf of the Spanish Sleep Network[21]





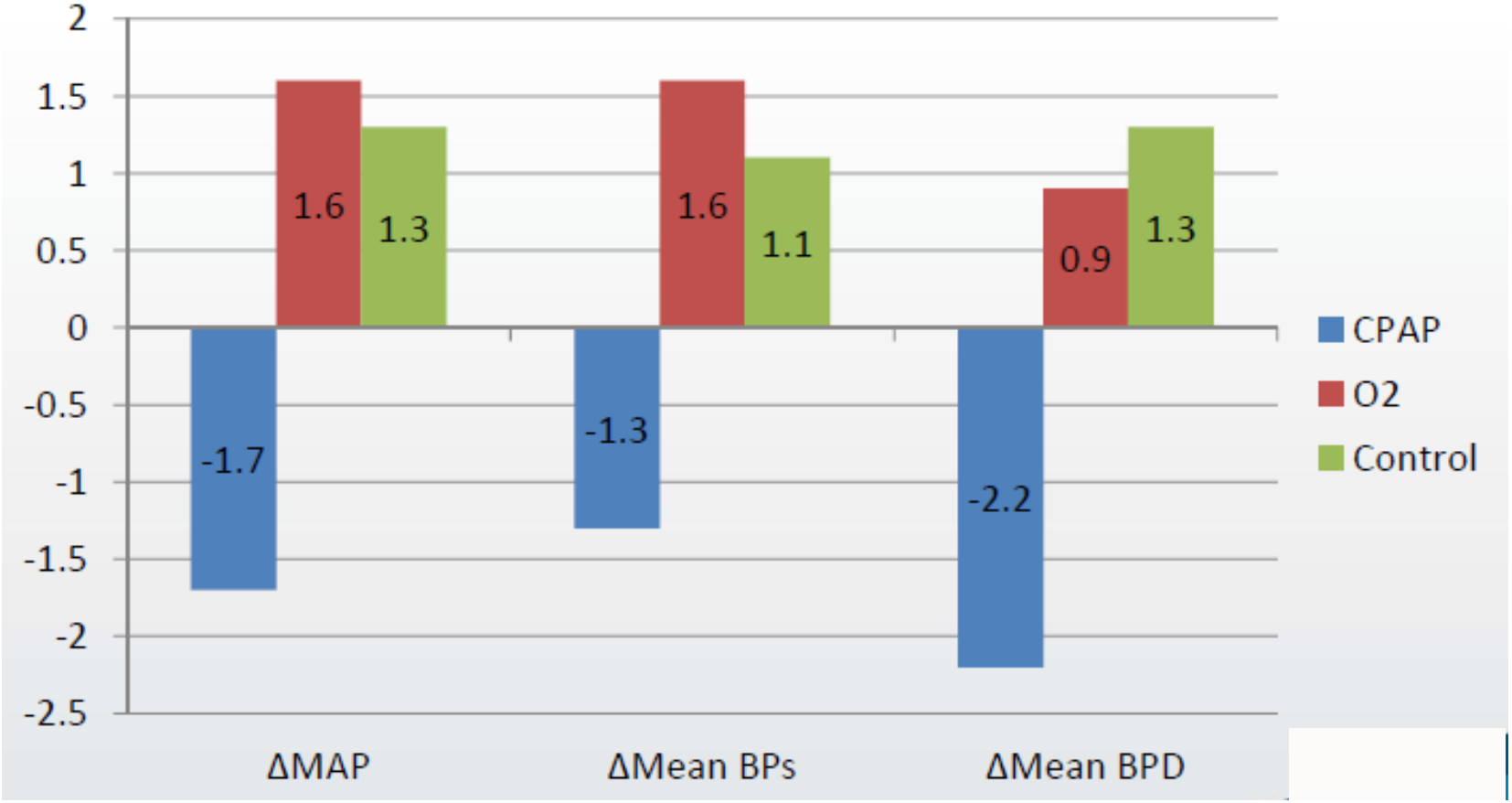
Multicenter, open-label randomized controlled trial in 307 consecutive women diagnosed with moderate to severe OSA (apnea–hypopnea index, >15) in 19 Spanish sleep units.



Campos-Rodriguez, et al.. Eur Respi J. 2017 Aug 10;50(2)
Campos-Rodriguez F, Queipo-Corona C, Carmona-Bernal C, et al. Am J Respir Crit Care Med 2016; 194: 1286–1294.

CPAP versus Oxygen in Obstructive Sleep Apnea

N Eng J Med. 2014 Jun 12: 370(24): 2276-85
Gottlieb DJ, Punjabi NM, Mehra R, et al.



Effect of CPAP in Obstructive Sleep Apnea and Resistant Hypertension: HIPARCO trial

Table 3. Effect of Continuous Positive Airway Pressure Treatment on Blood Pressure Levels in the Intention-to-Treat Population

	Mean (SD)							
	CPAP Group (n = 98)		Control Group (n = 96)		Intergroup Crude[a] Differences (95% CI)	*P* Value	Intergroup Adjusted[b] Differences (95% CI)	*P* Value
	Baseline	Follow-up	Baseline	Follow-up				
BP variables, mm Hg[c]								
24-h mean BP	103.9 (9.6)	99.8 (14.6)	102.9 (9.6)	102.1 (18.2)	3.1 (0.6 to 5.6)	.02	3.9 (1.3 to 6.6)	.004
24-h SBP	144.9 (11.7)	140.2 (13.1)	143.5 (13.2)	142.3 (17.1)	3.1 (−0.6 to 6.7)	.10	4.2 (0.4 to 8.0)	.03
Diurnal	147.2 (12.1)	144.0 (13.7)	145.1 (13.3)	142.5 (16.2)	−0.3 (−4.0 to 3.5)	.89	1.1 (−2.9 to 5.2)	.59
Nocturnal	141.2 (15.8)	134.6 (16.4)	140.4 (16.8)	137.8 (19.4)	3.7 (−0.8 to 8.2)	.11	5.8 (1.1 to 10.5)	.02
24-h DBP	83.4 (11.1)	79.5 (11.5)	82.6 (10.0)	82.1 (12.7)	3.2 (1.0 to 5.4)	.005	3.8 (1.4 to 6.1)	.002
Diurnal	85.7 (11.6)	82.7 (12.5)	84.6 (10.4)	83.2 (13.2)	1.5 (−0.8 to 3.9)	.20	2.3 (−0.1 to 4.8)	.07
Nocturnal	78.5 (12.4)	75.4 (11.7)	78.6 (11.1)	77.5 (13.5)	2.1 (−0.6 to 4.7)	.13	3.3 (0.5 to 6.1)	.02
Valley BP								
24-h SBP	111.9 (15.4)	106.2 (17.8)	111.0 (14.3)	103.3 (20.2)	−2.6 (−7.9 to 2.6)	.32	−0.4 (−6.0 to 5.3)	.90
24-h DBP	59.6 (11.6)	57.4 (11.1)	60.3 (11.0)	58.4 (13.1)	0.5 (−2.3 to 3.3)	.71	2.2 (−0.7 to 5.1)	.14
Peak BP								
24-h SBP	161.8 (18.0)	150.5 (25.1)	160.2 (17.3)	149.6 (28.9)	−0.3 (−8.0 to 7.4)	.93	0.5 (−7.5 to 8.6)	.89
24-h DBP	93.9 (13.7)	88.4 (14.2)	92.8 (12.4)	92.8 (14.0)	5.0 (1.8 to 8.3)	.003	5.7 (2.3 to 9.2)	.001
BMI	34.3 (5.7)	34.5 (5.2)	33.6 (6.9)	33.6 (6.0)	−0.4 (−1.8 to 1.0)	.54	0.1 (−0.4 to 0.7)	.64
ESS	8.9 (4.0)	5.5 (4.1)	9.3 (4.0)	9.0 (4.5)	3.3 (2.3 to 4.2)	<.001	3.4 (2.4 to 4.3)	<.001
Heart rate, beats/min	70.3 (11.7)	70.1 (14.8)	73.3 (11.1)	73.0 (11.7)	0.9 (−2.3 to 4.0)	.59	0.6 (−2.8 to 3.9)	.74
Variability	11.7 (3.6)	11.9 (4.4)	11.6 (3.5)	12.6 (4.3)	0.8 (−0.5 to 2.0)	.24	0.4 (−0.8 to 1.6)	.52

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); BP, blood pressure; CPAP, continuous positive airway pressure; DBP, diastolic blood pressure; ESS, Epworth Sleepiness Scale; SBP, systolic blood pressure.

[a] Adjusted by baseline BP values.

[b] Adjusted by baseline BP, AHI, ESS, dipper or riser status, and previous cardiovascular events.

[c] Crude differences calculated as (change in CPAP group) − (change in control group).

- **Improvement in 24-hour BP measures driven by reduction in nocturnal BP**
- **~2-4 mmHg reduction in nocturnal BP measures**

Martinez-Garcia et al. JAMA 2013; 310(22): 2407-2415

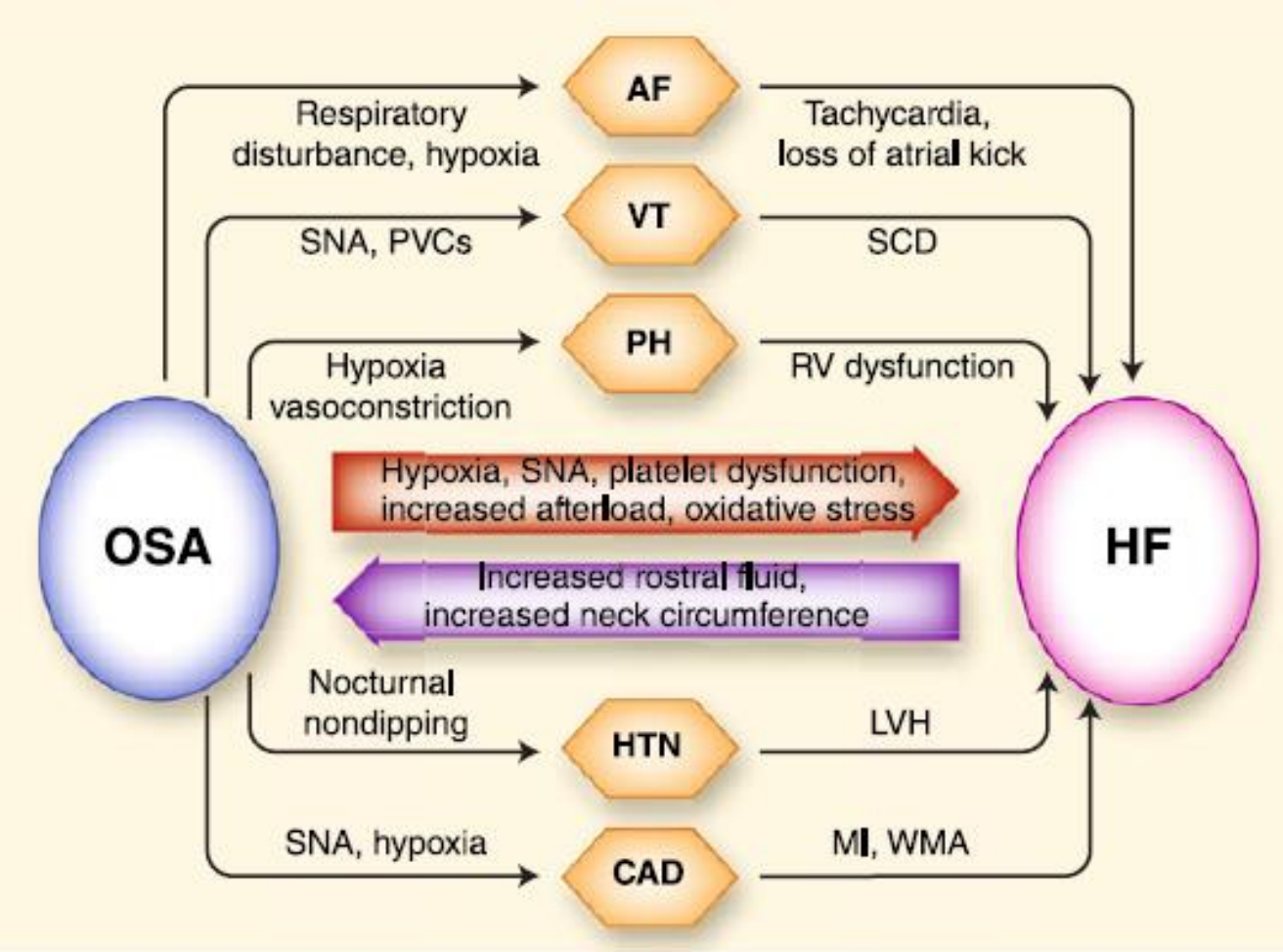
Sleep Apnea and Hypertension

- Sustained effect of OSA on BP increases even during the daytime
- OSA is risk factor for HTN independent of confounders, e.g. obesity
- Treatment of OSA in patients with HTN reduces BP consistently in RCTs
- Extent of reduction clinically relevant
  - 1-2 mmHg mean differences in blood pressure are associated with reduced odds of stroke, major cardiovascular events and heart failure
- Clinical trials suggest that sleepy vs non-sleepy patients may derive more BP lowering benefit from CPAP and greater benefit in preventing HTN occurrence
- Patients with OSA and resistant HTN represent a particularly responsive group to BP lowering from CPAP
- Women appear to derive the same extent of benefit in terms of BP reduction with greater benefit in those with more severe OSA
- OSA recognized as an identifiable cause of HTN cited in the 8th report of the JNC hypertension guidelines

Turnbull et al. Lancet. 2003; 362:1527-1535.

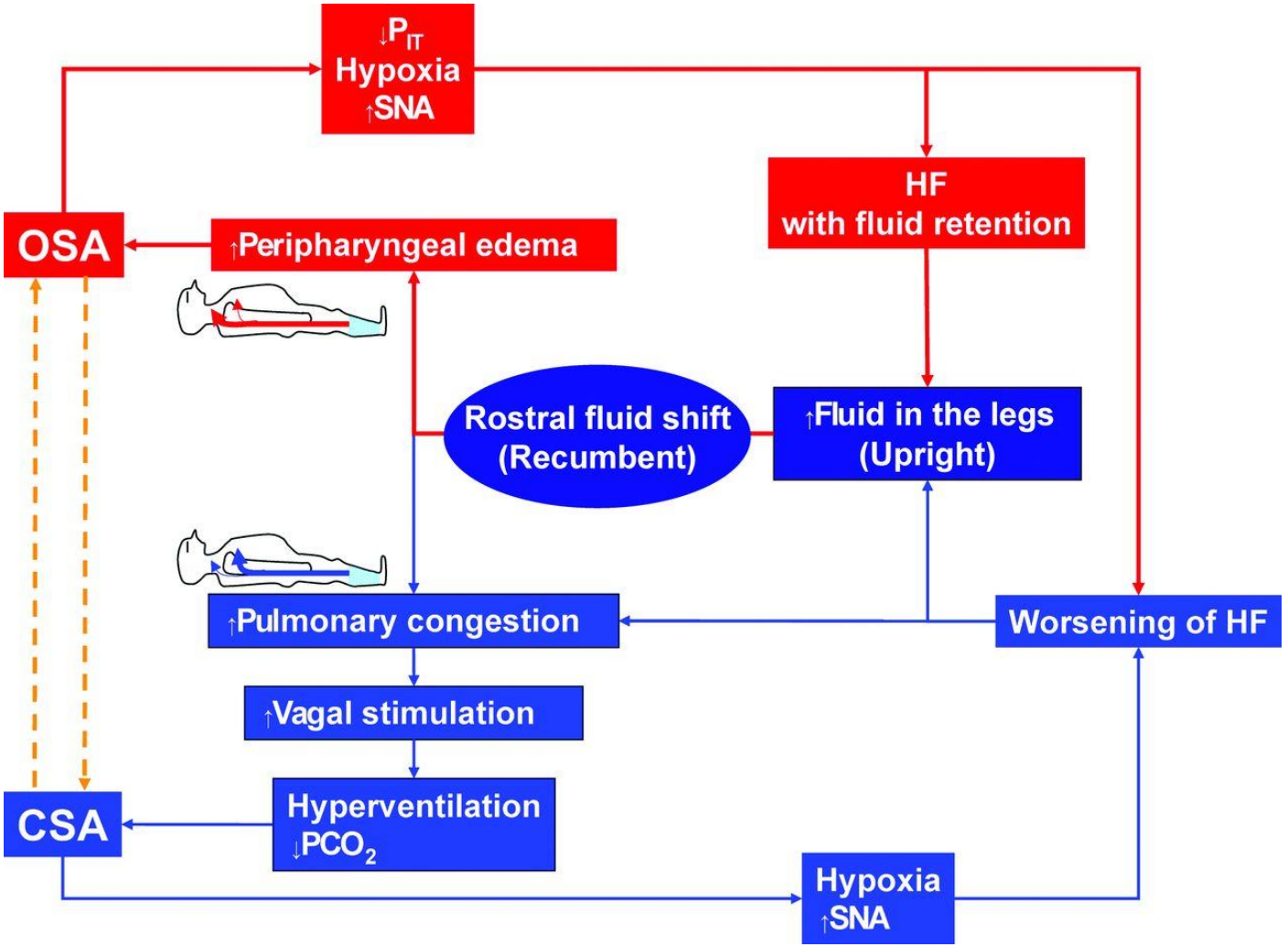
Sleep Disordered Breathing and Heart Failure

Mechanisms of OSA leading to Worsening HF



Brisco AND Goldberg, *Curr Heart Fail Rep* 2010

Schematic representation of the potential bidirectional relationship between obstructive and central sleep apnea sleep (OSA and CSA, respectively) and heart failure (HF)



American Heart Association

Takatoshi Kasai et al. Circulation. 2012;126:1495-1510

Sleep Disordered Breathing and Post-Discharge Mortality in Acute Heart Failure

n=1117 consecutive hospitalized patients

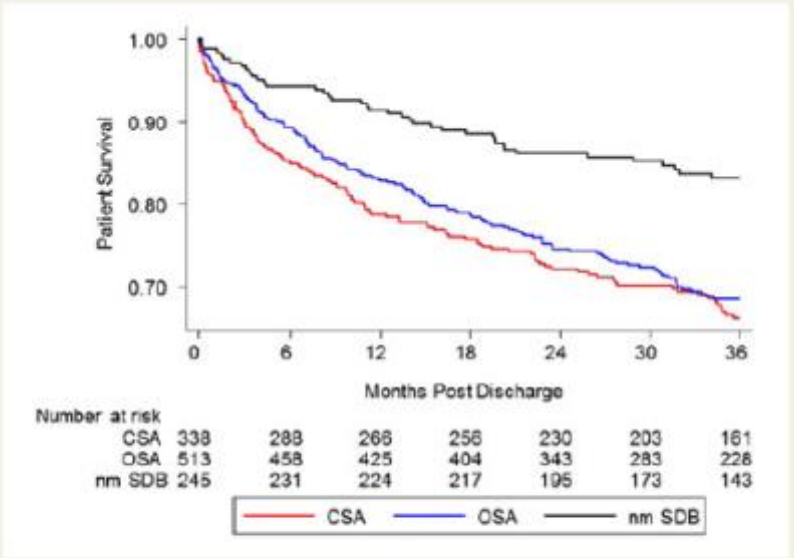


Figure 2 Kaplan–Meier post-discharge survival plot of acute heart failure patients by sleep disordered breathing status. OSA, obstructive sleep apnoea. CSA, central sleep apnoea. nmSDB, no or minimal sleep disordered breathing.

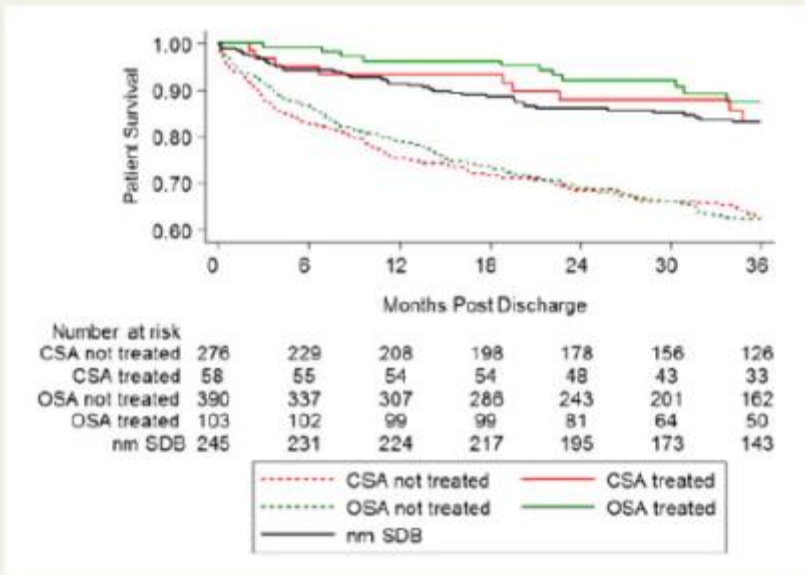
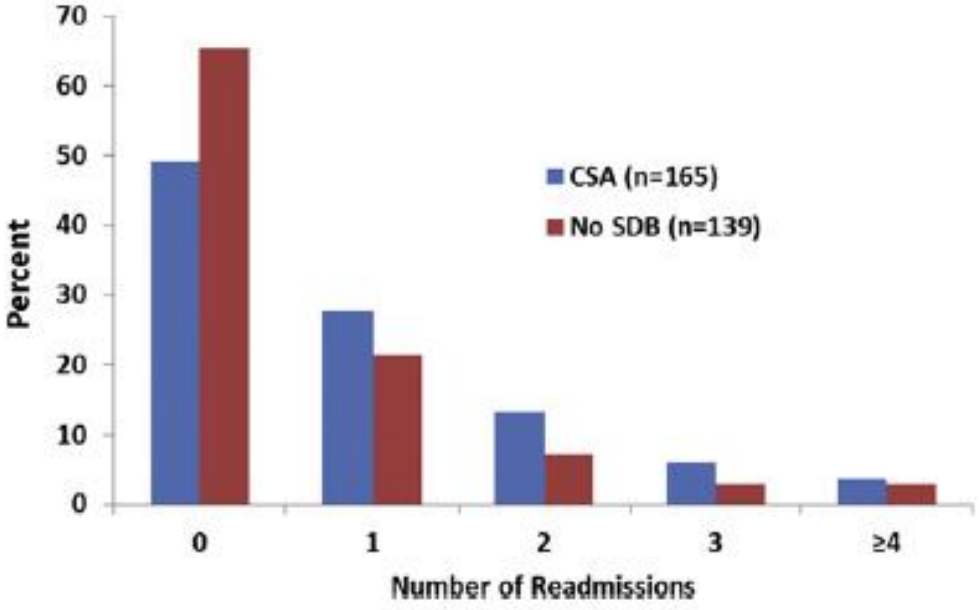


Figure 3 Kaplan–Meier post-discharge survival plot of acute heart failure patients by treatment status. The plot includes acute heart failure patients who survived 6 months post-discharge and had their treatment status verified.

Khayat R, et al. Eur Heart J. 2015

Central Sleep Apnea is a Predictor of Cardiac Readmission in Hospitalized Patients With Systolic Heart Failure

RAMI KHAYAT, MD,[1] WILLIAM ABRAHAM, MD,[1,2] BRIAN PATT, BS,[1] VINCENT BRINKMAN, MD,[2]
JACOB WANNEMACHER, BA,[1] KYLE PORTER, MAS,[3] AND DAVID JARJOURA, PhD[3]



CSA

Predictor of 6-month cardiac readmission

Adjusted rate ratio 1.53, p=0.03

Khayat R et al. J Card Fail 2012

Important practical implications

- Mean cost per CHF readmission is $13,000, with a 25.1 percent readmission rate.
- Reduction in readmission rates likely simultaneously reduce costs and improve quality of care
- Public and private payers have increasingly targeted readmissions as a focus of pay-for-performance initiatives

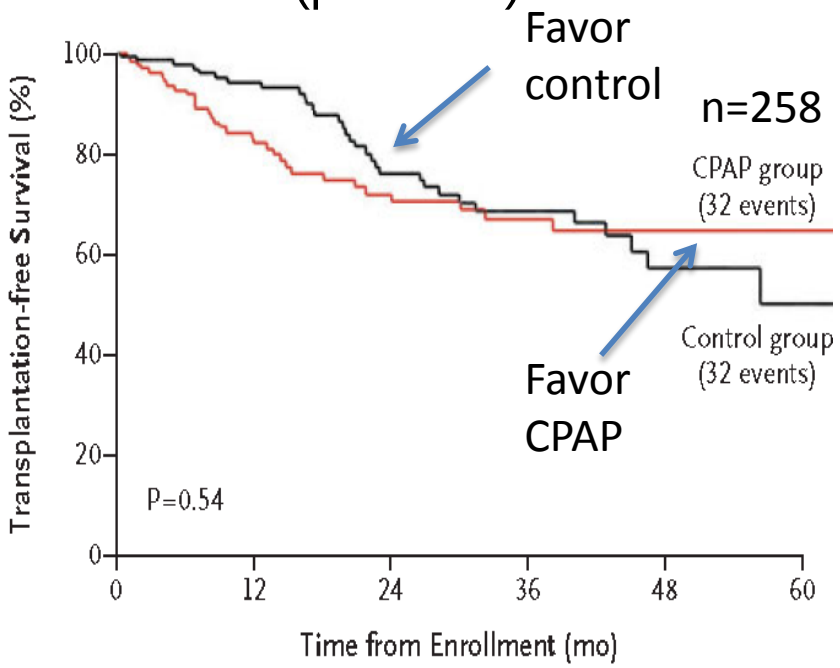
http://www.beckershospitalreview.com/quality/6-stats-on-the-cost-of-readmission-for-cms-tracked-conditions.html

Desai et al. Rehospitalization for Heart Failure: Predict or Prevent?. Circulation.2012; 126: 501-506

CANPAP

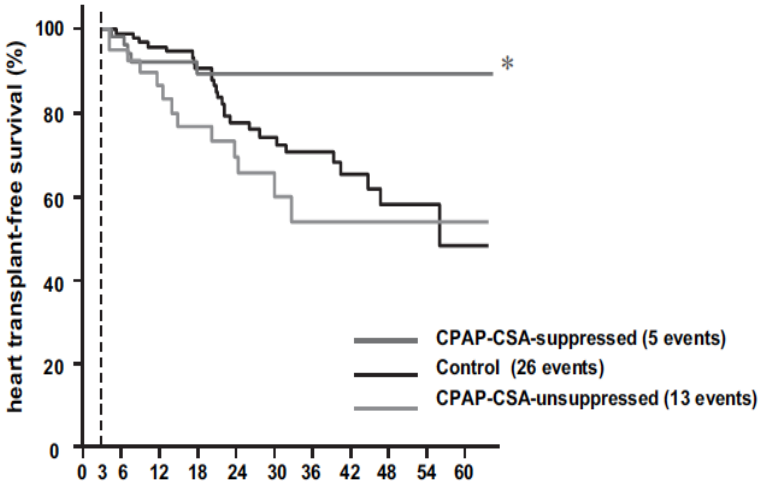
Canadian Continuous Positive Airway Pressure for Patients with Central Sleep Apnea and Heart Failure

- CPAP adherence 3.6 hours
- 57% patients with AHI suppressed to ≤15 with CPAP compared to control (post-hoc)



No. at Risk

CPAP group	128	104	79	59	49	42	33	24	20	12	6
Control group	130	117	96	79	59	46	37	27	19	12	4



number at risk

CPAP-CSA-suppressed (n=57)	51	38	31	27	23	21	15	11	7	3	
Control (n=110)	99	83	71	50	41	33	22	15	9	3	
CPAP-CSA-unsuppressed (n=43)	36	27	22	18	12	9	6	6	4	2	

Sustained improvement in intermediate measures (left ventricular ejection fraction, plasma norepinephrine levels and 6-minute walk distance

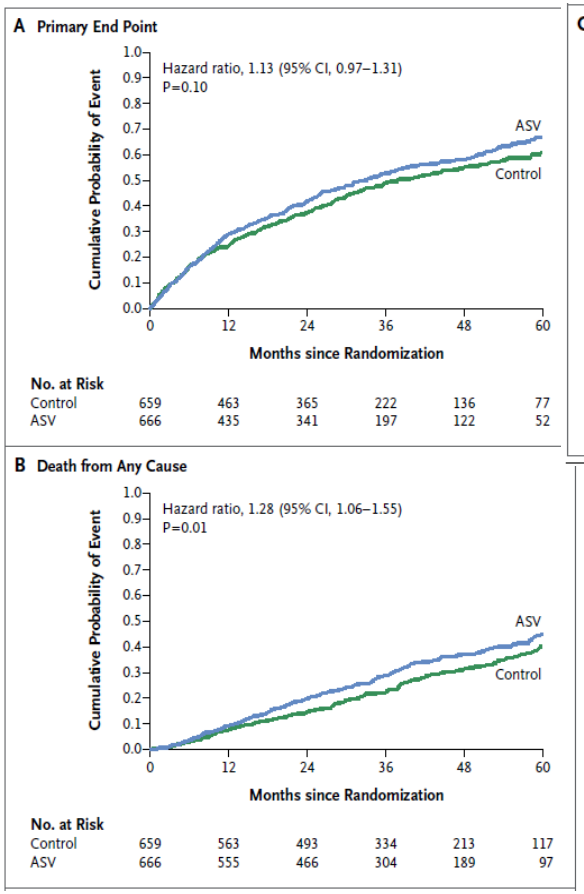
Bradley et al., *N Engl J Med* 2005; Arzt et al *Circulation* 2007

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 SEPTEMBER 17, 2015 VOL. 373 NO. 12

Adaptive Servo-Ventilation for Central Sleep Apnea in Systolic Heart Failure

- **SERVE-HF multicenter RCT**
- **n=1325, mean f/u 3.5 years**
- **ASV vs Medical management**
- **Symptomatic HF, LVEF ≤45%**
- **Predominant CSA**
- **Primary end point: All-cause mortality or unplanned HF hospitalization**
- **No difference in primary end point, trend favoring control (non-ASV)**
  - **HR, 1.14; 95% CI: 0.97-1.33, p=0.10**



Cowie MR, et al. N Engl J Med 2015;373: 1095–105.

- **Increased cardiovascular mortality in ASV arm compared to control**
- **10%/y in ASV vs 7.5%/y in control**
- **HR, 1.34; 95% CI: 1.07-1.67**

A Paradigm Shift in the Treatment of Central Sleep Apnea in Heart Failure

Reena Mehra, MD, FCCP
Cleveland, OH
Daniel J. Gottlieb, MD, MPH, FCCP
Boston, MA

- Preliminary results were made public by the sponsor, ResMed Inc, in May 2015 with an urgent Field Safety Notice
- No offsetting improvement in HF symptoms or functional status
- Clinicians were advised that ASV would now be contraindicated for treatment of CSA in symptomatic HF and reduced LVEF
- Key methodological considerations
  - Type 1 statistical error
    - CV mortality was not one of the three pre-specified primary end points but was among 20 pre-specified secondary end points
    - However, given large magnitude of the effect on cardiovascular mortality, it would be imprudent to dismiss this finding
  - High percentage of crossover
    - 17% received PAP in control arm and 29% did not receive or discontinued ASV in ASV arm
  - Device-patient dyssynchrony, high default inspiratory and expiratory pressures

SPECIAL ARTICLES

Updated Adaptive Servo-Ventilation Recommendations for the 2012 AASM Guideline: "The Treatment of Central Sleep Apnea Syndromes in Adults: Practice Parameters with an Evidence-Based Literature Review and Meta-Analyses"

R. Nisha Aurora, MD, MHS[1]; Sabin R. Bista, MD[2]; Kenneth R. Casey, MD, MPH[3]; Susmita Chowdhuri, MD[4]; David A. Kristo, MD[5]; Jorge M. Mallea, MD[6]; Kannan Ramar, MD[7]; James A. Rowley, MD[8]; Rochelle S. Zak, MD[9]; Jonathan L. Heald, MA[10]

[1]Johns Hopkins University, School of Medicine, Baltimore, MD; [2]University of Nebraska Medical Center, Omaha, NE; [3]William S. Middleton Memorial Veterans Hospital, Madison, WI; [4]John D. Dingell VA Medical Center and Wayne State University, Detroit, MI; [5]University of Pittsburgh, Pittsburgh, PA; [6]Mayo Clinic Florida, Transplant Center, Jacksonville, FL; [7]Mayo Clinic, Rochester, MN; [8]Department of Medicine, Wayne State University School of Medicine, Detroit, MI; [9]Sleep Disorders Center, University of California, San Francisco, San Francisco CA; [10]American Academy of Sleep Medicine, Darien, IL

- 2016 update based upon SERVE-HF results
- ASV: increased cardiac mortality in LVEF<45% and moderate or severe CSA
  - Standard level recommendation against use of ASV in CHF-associated CSA in patients with LVEF<45%
- Option level recommendation for use of ASV in treatment of CHF-associated CSA in patients with LVEF>45% or mild CHF-related CSA
- Findings not generalizable to OSA in HF or CSA without HF

Aurora RN, et al. J Clin Sleep Med. 2016 May 15;12(5):757-61.

Remaining Questions

- PAP deleterious in reduced systolic function and intravascular volume depletion?
  - Subgroup analysis did not support this explanation
- Increased ventilation due to PS from ASV may worsen respiratory alkalosis, with a increase in potassium excretion, thus predisposing to fatal arrhythmia
- Is CSA a bystander or epiphenomenon?
- CSA is a marker of poor prognosis, however, is it a compensatory mechanism?
- Increase in deaths without preceding hospitalization, SCD?
- ADVENT-HF trial
  - Effect of Adaptive Servo Ventilation on Survival and Hospital Admissions in Heart Failure
  - HFREF patients with either predominantly central or predominantly obstructive SDB, may be able to shed more light in due course (NCT01128816)

Mechanisms underlying increased mortality risk in patients with heart failure and reduced ejection fraction randomly assigned to adaptive servoventilation in the SERVE-HF study: results of a secondary multistate modelling analysis

Christine Eulenburg, Karl Wegscheider, Holger Woehrle, Christiane Angermann, Marie-Pia d'Ortho, Erland Erdmann, Patrick Levy, Anita K Simonds, Virend K Somers, Faiez Zannad, Helmut Teschler, Martin R Cowie

- Increased CV death *without* previous hospital admission (SCD?) and CV death after a life-saving event in ASV versus control
- In LVEF<30%, ASV increased CV death *without* previous hospital admission
- Lower CSR proportion (<20%) may have better outcomes on ASV compared to control

n=1325

	n (%)	Hazard ratio	95% CI	$p_{interaction}$
CSR <20%	237 (18%)	0·64	0·40–1·02	0·021
CSR 20–50%	439 (33%)	1·31	0·92–1·86	0·021
CSR >50%	490 (37%)	1·36	1·01–1·83	0·021
LVEF >36%	340 (37%)	0·85	0·56–1·30	0·039
LVEF 31–36%	243 (18%)	0·84	0·54–1·32	0·039
LVEF ≤30%	486 (26%)	1·38	1·02–1·86	0·039

159 (12%) patients had missing data for Cheyne-Stokes respiration (CSR) and 256 patients (19%) had missing data for left ventricular ejection fraction (LVEF). In these categories of patients with missing data for CSR and LVEF, the HR values for hospital admission for worsening heart failure were 0·85 (95% CI 0·51–1·42) for missing CSR and 1·21 (0·80–1·83) for missing LVEF. Adjusted for implantable cardioverter defibrillator, CSR proportion at baseline, and baseline LVEF; significant interactions are reported.

Table 4: Associations between adaptive servoventilation treatment and hospital admission for worsening heart failure

Eulenburg C, et al. Lancet Respir Med. 2016 Nov;4(11):873-881

SLEEP

CrossMark

SERVE-HF on-treatment analysis: does the on-treatment analysis SERVE its purpose?

T. Douglas Bradley[1,2]

Affiliations: [1]Dept of Medicine, University of Toronto, Toronto, ON, Canada. [2]Sleep Research Laboratories, University Health Network Toronto Rehabilitation Institute and Toronto General Hospital, Toronto, ON, Canada.

Correspondence: T. Douglas Bradley, University Health Network Toronto General Hospital, 9N-943, 200 Elizabeth Street, Toronto, ON, M5G 2C4, Canada. E-mail: douglas.bradley@utoronto.ca

- On-treatment analysis performed according to actual treatment received
- OT analysis affected by physician or patient preference and reduces the power of randomization
- 29% of those in the ASV arm did not start or discontinued prematurely
- 17% of those randomized to control crossed over to ASV
- Could withdrawal of ASV in the intervention arm have increased mortality?
- OT as-treated analysis suggested superficially that exposure to ASV_{MV} was not associated with increased CV mortality, but this analysis is open to bias due to patient and/or physician preferences in treatment decisions
- As-treated-as-randomized OT analysis results were similar to the original ITT analysis consistent with a harmful effect of ASV_{MV} on cardiovascular mortality

Woehrle H, et al. Adaptive servo ventilation for central sleep apnoea in heart failure: SERVE-HF on-treatment analysis. Eur Respir J 2017; 50: 1601692.

CAT-HF Trial

- Terminated early due to SERVE-HF
- 126 with HF and moderate to severe SDB randomized to ASV + optimized medical therapy vs OMT alone
- Decompensated HF (systolic and preserved) and a range of SDB
- Average CPAP usage 2.7 hrs/day at 6 months
- Composited endpoint did not differ between the groups (death, CV hospitalizations, % change 6 minute walk) at 6 months
- Pre-specified subgroup analysis: positive impact of ASV effect in HF-pEF

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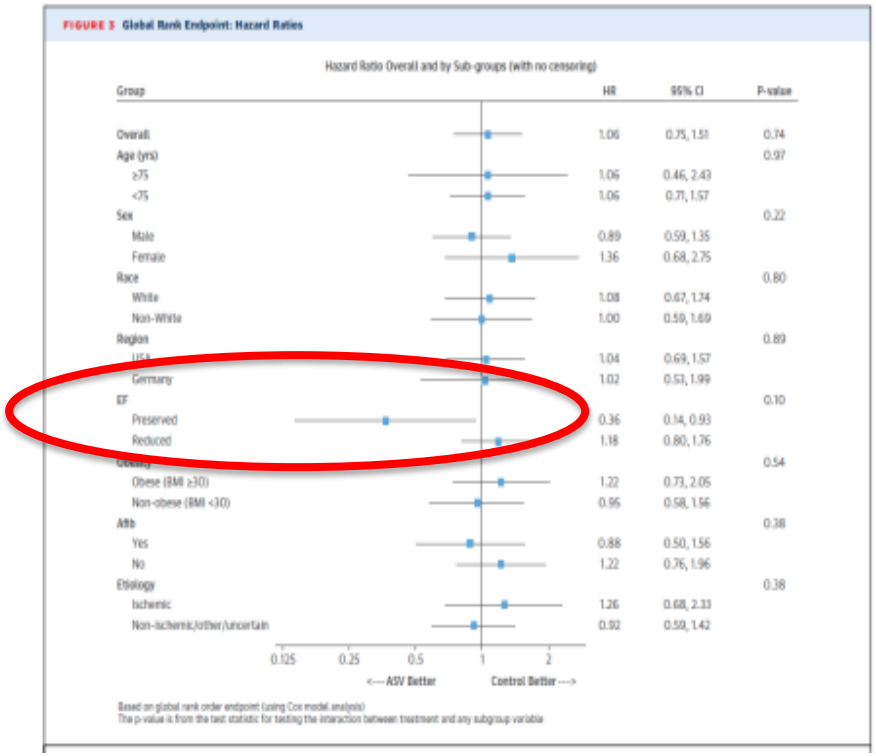
Cardiovascular Outcomes With Minute Ventilation–Targeted Adaptive Servo-Ventilation Therapy in Heart Failure

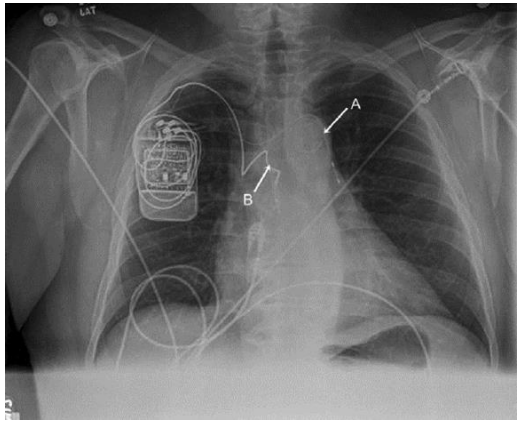
The CAT-HF Trial

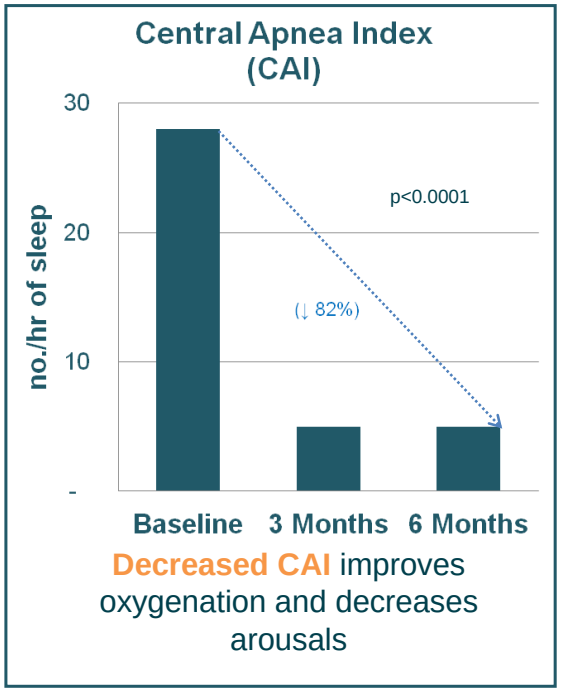
Christopher M. O'Connor, MD,[a,b] David J. Whellan, MD,[c] Mona Fiuzat, PharmD,[a] Naresh M. Punjabi, MD, PhD,[d] Gudaye Tasissa, PhD,[a] Kevin J. Anstrom, PhD,[a] Adam V. Benjafield, PhD,[e] Holger Woehrle, MD,[f,g] Amy B. Blase, BS,[a] JoAnn Lindenfeld, MD,[h] Olaf Oldenberg, MD[i]



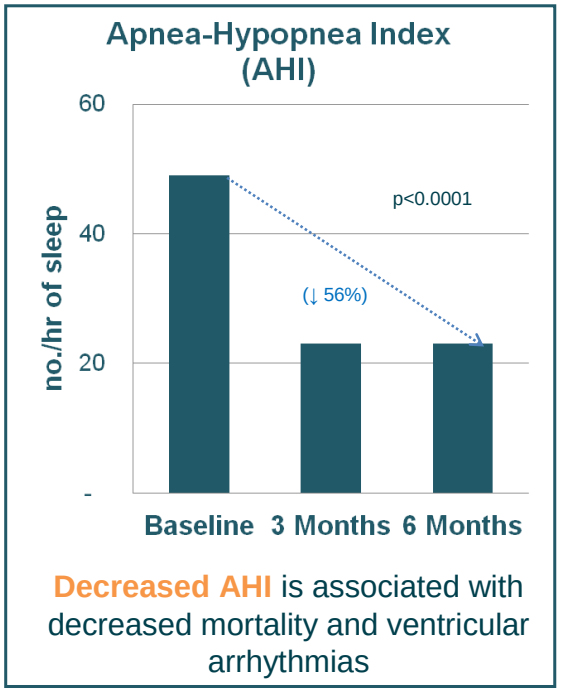
O'Connor CM, et al. J Am Coll Cardiol. 2017 Mar 28;69(12):1577-1587

Physiologic Effects of Transvenous PNS

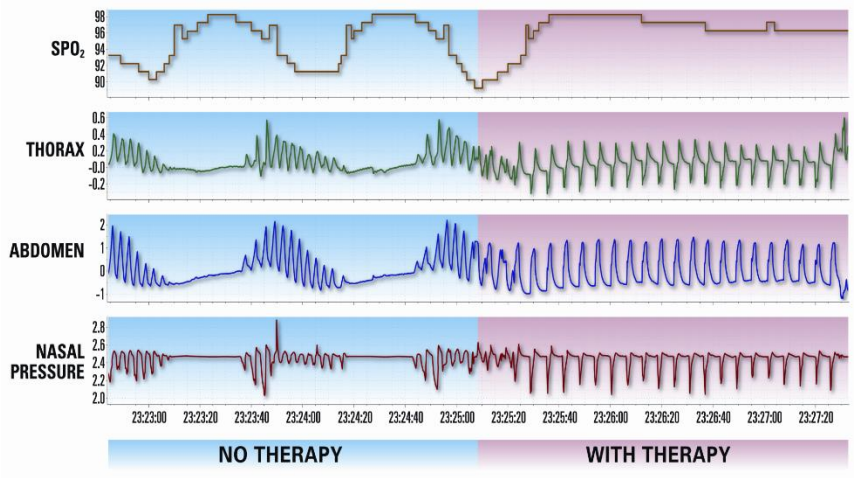




Decreased CAI improves oxygenation and decreases arousals



Decreased AHI is associated with decreased mortality and ventricular arrhythmias



Abraham WT, et al. JACC Heart Fail. 2015 May;3(5):360-9.
Ponikowski P, et al. Eur Heart J. 2012 Apr;33(7):889-94.

- Multicenter RCT, n=151
- Unilateral transvenous PNS
- ITT analysis
- More patients randomized to intervention had >50% reduction in AHI compared to control

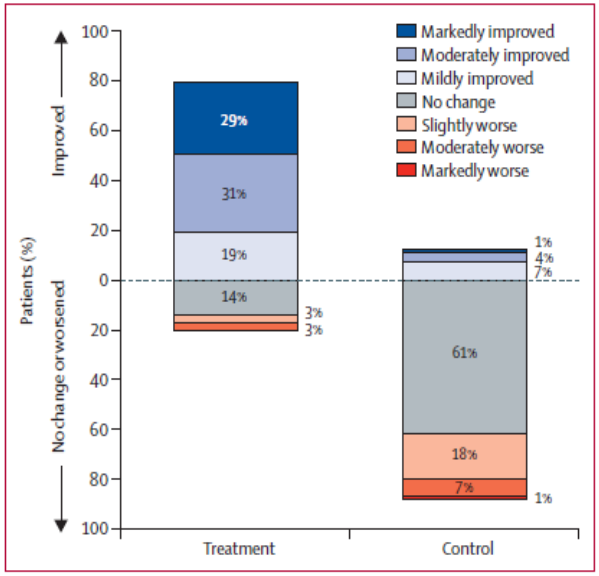


Figure 3: **Percentage of patient responses to the patient global assessment**
Patients were asked, "Specifically in reference to your overall health, how do you feel today as compared to how you felt before having your device implanted: markedly improved, moderately improved, mildly improved, no change, slightly worse, moderately worse, or markedly worse?". 58 (100%) of 58 patients in the treatment group and 72 (99%) of 73 in the control group answered the assessment.

Transvenous neurostimulation for central sleep apnoea: a randomised controlled trial

Maria Rosa Costanzo, Piotr Ponikowski, Shahrokh Javaheri, Ralph Augostini, Lee Goldberg, Richard Holcomb, Andrew Kao, Rami N Khayat,

	Baseline		6 months' follow-up		Change from baseline		Between-group difference	One-sided p value
	Treatment (N=58)	Control (N=73)	Treatment (N=58)	Control (N=73)	Treatment (N=58)	Control (N=73)		
Primary endpoint								
Patients with ≥50% reduction in apnoea–hypopnoea index from baseline*			35 (51%, 39–64)†	8 (11%, 5–20)			41% (25–54)	<0·0001‡
Secondary endpoints§								
Central apnoea index (events per h)								
Mean	31·7 (18·6)	26·2 (16·2)	6·0 (9·2)	23·3 (17·4)	−25·7 (18·0)	−2·9 (17·7)	−22·8 (17·8)	<0·0001¶
Median	30·1 (15·6 to 42·6)	21·0 (13·9 to 35·2)	1·4 (0·3 to 7·0)	21·8 (9·7 to 34·6)	−26·2 (−40·0 to −12·5)	−2·5 (−11·4 to 7·8)		
Apnoea–hypopnoea index (events per h)								
Mean	49·7(18·9)	43·9 (17·3)	25·9 (20·5)	45·0 (20·3)	−23·9 (18·6)	1·1 (17·6)	−25·0 (18·1)	<0·0001‖
Median	48·9 (34·8 to 60·4)	39·0 (31·2 to 54·3)	21·2 (10·7 to 35·4)	41·8 (23·0 to 59·7)	−22·8 (−38·2 to −9·6)	0·0 (−6·0 to 15·2)		
Arousal index (events per h)								
Mean	45·6 (18·9)	44·0 (19·5)	25·4 (14·3)	38·9 (19·5)	−20·2 (18·9)	−5 (18·1)	−15·2 (18·5)	<0·0001‖
Median	40·6 (34·1 to 63·6)	43·6 (29·0 to 55·3)	21·9 (15·8 to 32·5)	36·6 (24·5 to 55·8)	−18·5 (−32·1 to −6·4)	−3·5 (−15·6 to 5·2)		
Percent of sleep in rapid eye movement								
Mean	10·8% (6·6)	11·8% (7·2)	12·6% (8·7)	11·2% (7·4)	1·8% (8·2)	−0·6% (7·8)	2·4% (7·9)	0·0244¶
Median	9·8% (6·3 to 14·5)	12·5% (7·8 to 16·1)	13·7% (5·2 to 17·6)	10·5% (6·2 to 16·0)	1·2% (−3·9 to 7·3)	−0·1% (−4·9 to 3·0)		
Patients with marked or moderate improvement in patient global assessment**			35/58 (60%, 47–73)	4/72†† (6%, 2–14)			55% (40–68)	<0·0001‡
Oxygen desaturation ≥4% index (events per h)								
Mean	43·8 (21·5)	37·3 (18·0)	24·7 (21·0)	40·9 (21·3)	−19·1 (18·4)	3·6 (17·3)	−22·7 (17·8)	<0·0001‖
Median	41·0 (29·5 to 56·1)	33·1 (24·8 to 49·6)	19·5 (8·0 to 37·3)	39·1 (26·1 to 56·9)	−19·0 (−33·4 to −3·0)	2·8 (−6·1 to 14·1)		
Epworth Sleepiness Scale score								
Mean	10·7 (5·3)	9·3 (5·7)	7·1 (4·1)	9·4 (6·1)	−3·6 (5·6)	0·1 (4·5)	−3·7 (5·0)	<0·0001¶
Median	11·0 (7·0 to 14·0)	9·0 (5·0 to 13·0)	6·0 (4·0 to 9·0)	8·0 (4·0 to 14·0)	−3·5 (−7·0 to −1·0)	−1·0 (−2·0 to 2·0)		

Data are n (%, 95% CI), n/N (%, 95% CI), mean (SD), or median (IQR). *Assessed in intention-to-treat population. †N=68. ‡p value from Fisher's exact test. §Assessed in the per-protocol population. ¶p value from Mann-Whitney U test for difference in change from baseline between groups. ‖p value from two-group Student's t test for difference in change from baseline between groups. **In questionnaire patients were asked "Specifically in reference to your overall health, how do you feel today as compared to how you felt before having your device implanted? Markedly improved, moderately improved, mildly improved, no change, slightly worse, moderately worse, or markedly worse". ††One patient in the control group did not complete the patient global assessment.

Table 2: **Primary effectiveness and secondary hierarchically-tested endpoints**

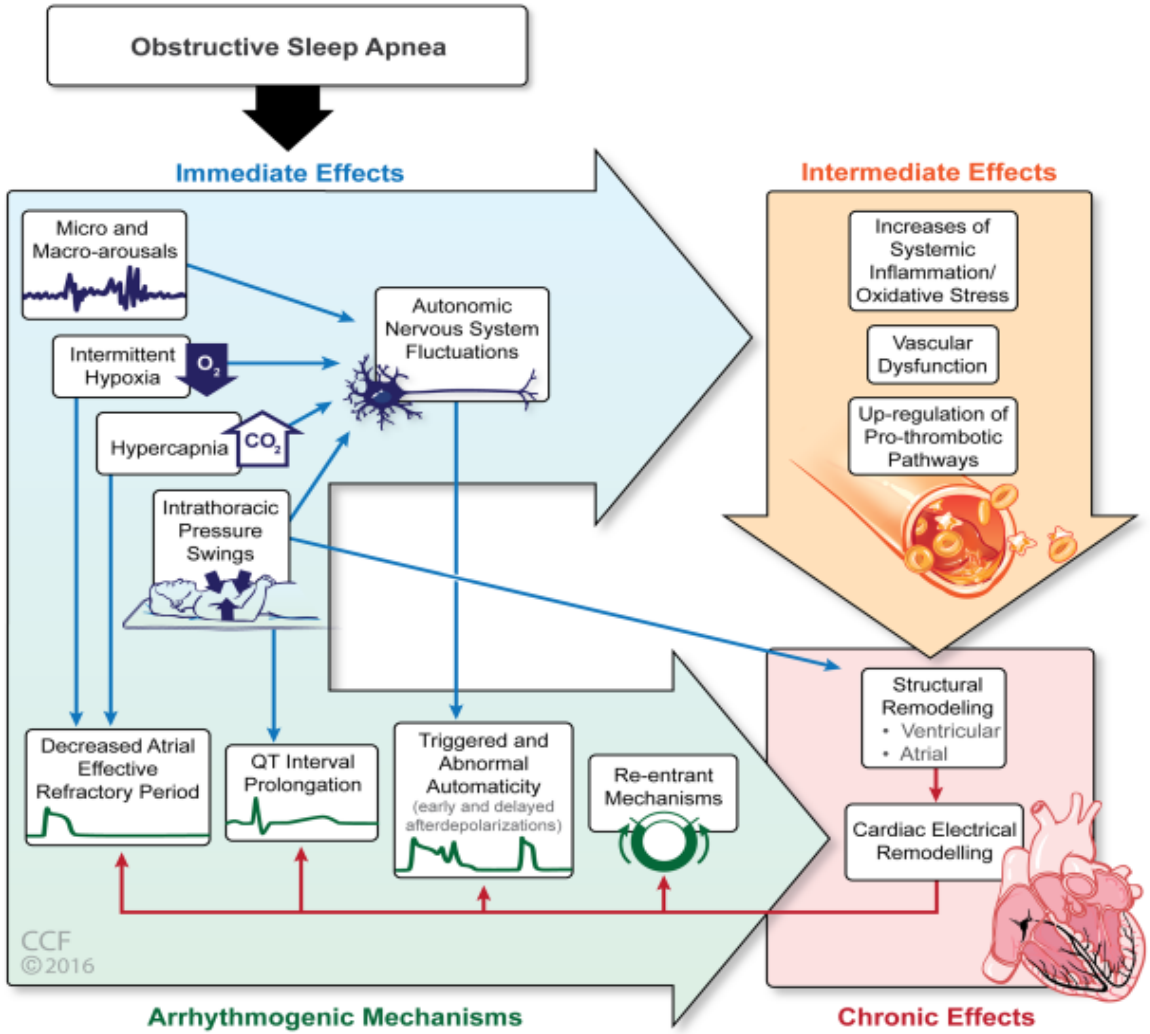
Costanzo MR, et al., Lancet 2016;388:974–82

Sleep Apnea and Heart Failure

- SDB is prevalent in HF, may lead to HF and associated with disease progression
- Sleep apnea associated with increased post-discharge mortality and hospital readmission in acute HF
- ASV not indicated in central predominant sleep apnea and systolic HF (EF<45%); SCD likely contributor
- Possible PAP benefit in HF in:
  - Preserved EF
  - OSA
  - Lower CSR burden
- On treatment analysis was not associated with increased CV mortality, however, on-treatment, as-randomized was associated with increased CV mortality in SERVE-HF
- Unilateral transvenous phrenic nerve stimulation holds promise as novel therapy for central predominant sleep apnea in terms of reduction of SDB severity and improvement in functional outcomes

Sleep Disordered Breathing and Cardiac Arrhythmia and Stroke

Putative Obstructive Sleep Apnea and Cardiac Arrhythmia Pathophysiologic Pathways

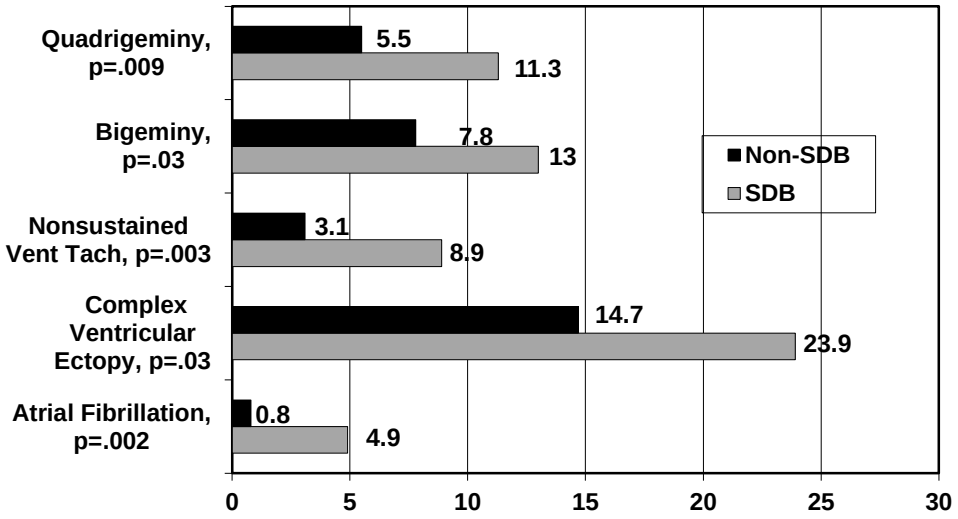


May A, Van Wagoner D, Mehra R. CHEST 2016

Prevalence of Nocturnal Cardiac Arrhythmias According to Sleep Disordered Breathing Status

Group-Matched by Age, Sex, Race, BMI

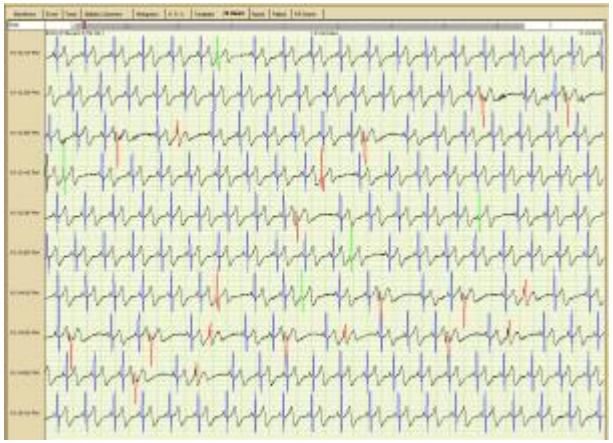
Sleep Heart Health Study

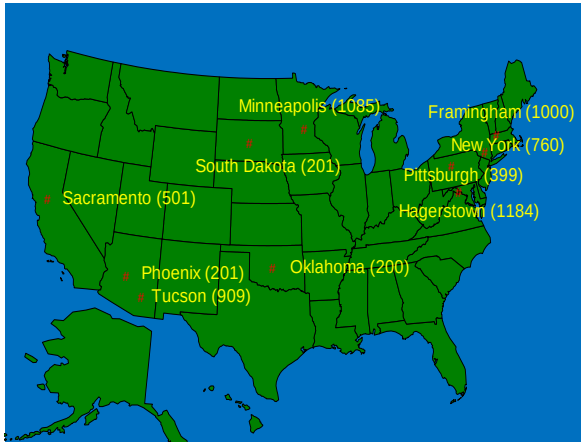


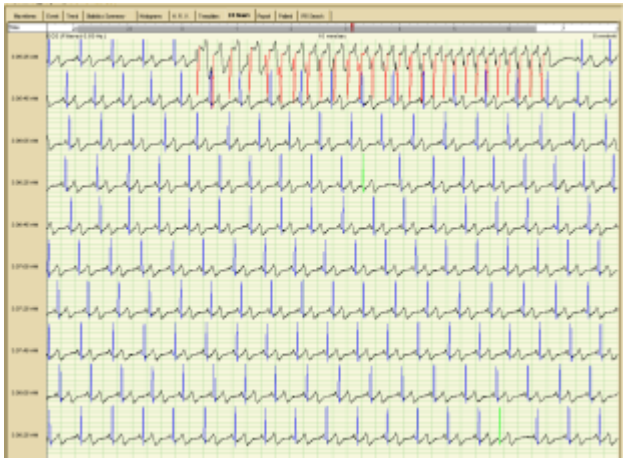
Mehra R *AJRCCM* 2006

	Adjusted OR	95% CI
Atrial Fibrillation	4.5	1.2, 17
CVE or NSVT	1.8	1.2, 2.8
AF or NSVT	3.7	1.7, 8.0

CVE Odds > 7.0, 50-60 years old







Obstructive Sleep Apnea and Incident Stroke in Men

Covariate	Unadjusted	Age-Adjusted	Fully-Adjusted*
Quartile of AHI			
IV: 19.13 – 164.5	3.91 (1.55 – 9.86)	3.05 (1.21 – 7.72)	2.86 (1.10 – 7.39)
III: 9.50 – 19.12	2.35 (0.89 – 6.20)	1.97 (0.74 – 5.21)	1.86 (0.70 – 4.95)
II: 4.05 – 9.49	1.96 (0.71 – 5.40)	1.86 (0.68 – 5.13)	1.86 (0.67 – 5.12)
I: 0.00 – 4.04)	1.00	1.00	1.00

*Adjusted for age, BMI, smoking status, SBP, blood pressure medications, diabetes, and race

Redline et al. Am J Respir Crit Care Med Vol 182. pp 269–277, 2010

Nocturnal Hypoxia as a Predictor of Stroke

Outcomes of Sleep Disorders in Older Men Study, n=3028

Percent of sleep time with SaO2<90%		
<1% (reference)	1.00	1.00
1 to <3.5%	1.29 (0.87, 1.92)	1.31 (0.87, 1.98)
3.5 to <10%	1.24 (0.74, 2.07)	1.15 (0.67, 1.98)
10%+	**1.83 (1.12, 2.98)**	**1.71 (1.02, 2.86)**
p-trend	**0.02**	0.07

**Model 1 Adjusted for age, clinic, race, body mass index, and smoking, diabetes, total cholesterol, HDL cholesterol, and statin use.

***Model 2 Model 1 plus hypertension and resting SaO2

Stone KL, et al Sleep. 2016 Mar 1;39(3):531-40.

Sleep Apnea and Atrial Fibrillation/Stroke

- SDB-AF epidemiologic data: High strength of association OR~4 after consideration of confounders
- Retrospective data suggest that sleep apnea treatment reduces recurrence of AF
- Epidemiologic data from the Sleep Heart Health Study suggests vulnerability of men to incident development of stroke and perhaps a protective influence of arousal frequency
- Nocturnal hypoxia predicts stroke in older men

Sleep Disordered Breathing and Coronary Artery Disease and Cardiovascular Mortality

Obstructive Sleep Apnea and Incident CHD

Table 3. Relation of OSA to Incident CHD*

	AHI (Events per Hour)				
	<5.0	5.0 to 14.9	15.0 to 29.9	≥30.0	P†
Men					
No. of subjects	829	644	282	172	
No. of CHD events	114	95	47	40	
Covariates in model					
Age, race, BMI, smoking	1.00 (Referent)	0.94 (0.71, 1.24)	1.07 (0.75, 1.52)	1.45 (0.99, 2.13)	0.046
Plus total and HDL cholesterol, lipid-lowering medications, diabetes mellitus	1.00 (Referent)	0.93 (0.70, 1.23)	1.04 (0.73, 1.48)	1.41 (0.96, 2.07)	0.08
Plus SBP, DBP, use of antihypertensive medications	1.00 (Referent)	0.91 (0.69, 1.20)	1.07 (0.75, 1.52)	1.33 (0.91, 1.95)	0.12

Incident CHD In "Younger" Men

Men: Age < 70 years

Outcome	Predictor Variable	Hazard Ratio	95 % CI
Incident CHD	**AHI < 5 vs. AHI ≥ 30**	**1.68**	**1.02 – 2.76**
	AHI continuous (per 10 unit increase)	**1.10**	**1.00 – 1.21**

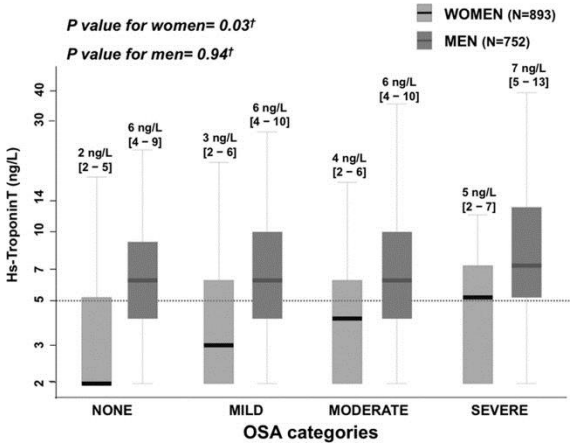
Gottlieb et al. Circulation 2010; 122: 325-360

Sex-Specific Association of Sleep Apnea Severity With Subclinical Myocardial Injury, Ventricular Hypertrophy, and Heart Failure Risk in a Community-Dwelling Cohort

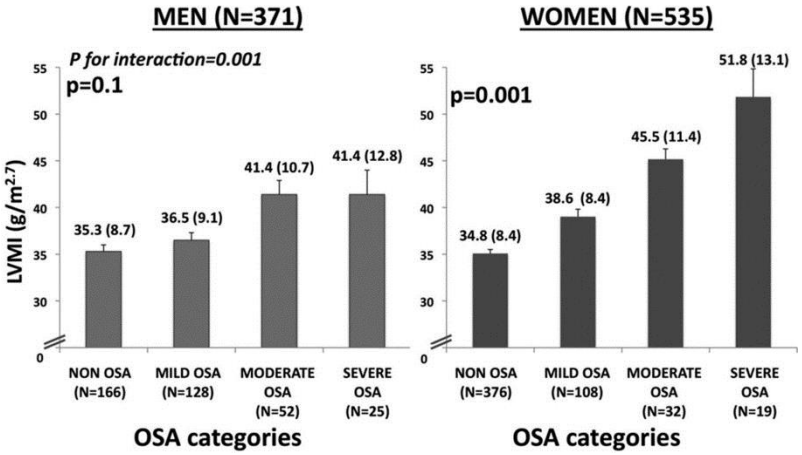
The Atherosclerosis Risk in Communities–Sleep Heart Health Study

Gabriela Querejeta Roca, MD; Susan Redline, MD, MPH; Brian Claggett, PhD; Natalie Bello, MD, MPH; Christie M. Ballantyne, MD; Scott D. Solomon, MD; Amil M. Shah, MD, MPH

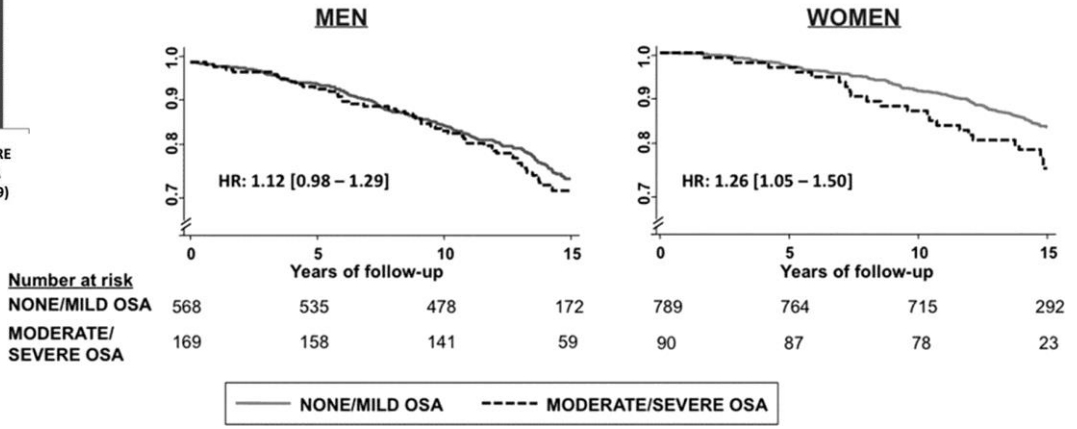
Box-and-whisker plot of hs-TnT levels among OSA categories stratified by sex.



Left ventricular mass index (LVMI) among OSA categories stratified by sex.



Kaplan–Meier survival curves for the risk of HF or death of moderate/severe OSA vs none/mild OSA stratified by sex.

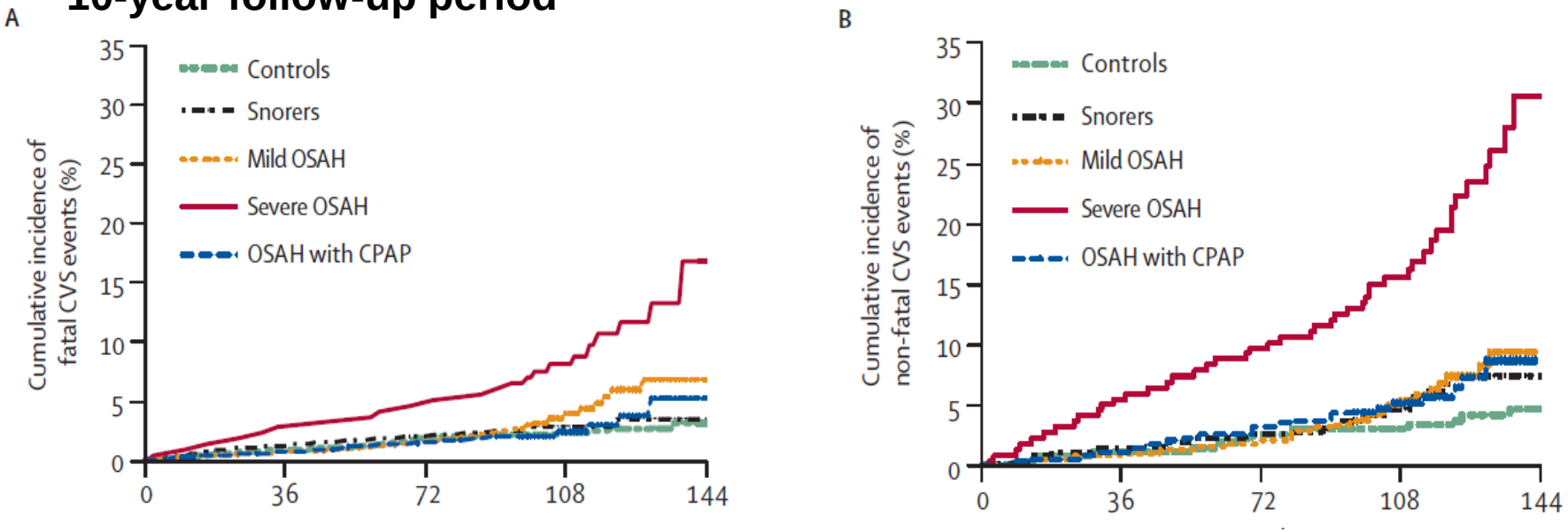


Gabriela Querejeta Roca et al. Circulation. 2015;132:1329-1337

CPAP and Cardiac Event risk in Severe OSA

Marin JM et al. Lancet 2005; 365: 1046-54.

n~1500,
10-year follow-up period



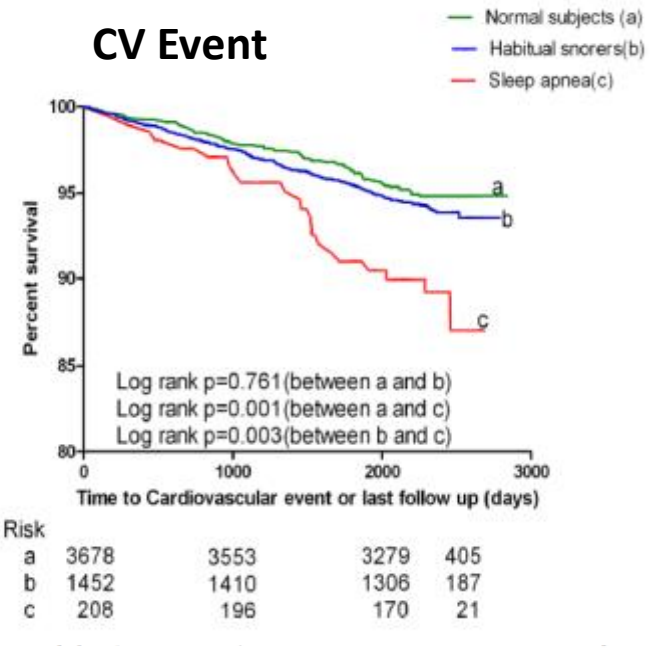
Fatal MI or stroke

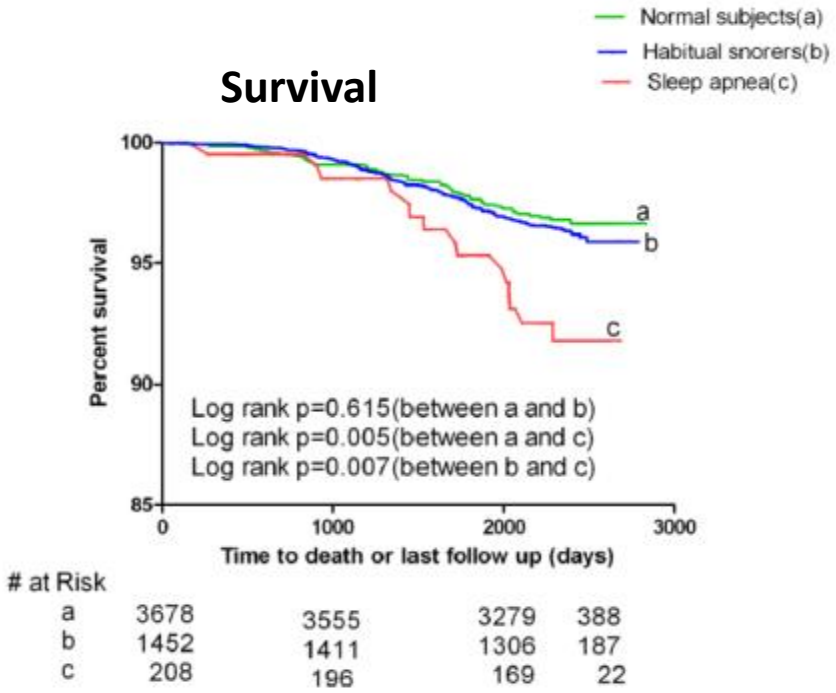
Untreated OSA

OR 2.9 for incident non-fatal CVD after multiple risk factor adjustment

Non-fatal MI or stroke or need for revascularization

Sleep Apnea, Snoring, Incident Cardiovascular Events and All-Cause Mortality in Multi-Ethnic Adult Populations: MESA





Outcome	# of events	Univariate hazard ratio (95% CI)	*p* value	Multivariate hazard ratio (95% CI)	*p* value
Composite	310	2.02 (1.31–3.12)	0.002	1.90 (1.21–2.98)	0.005
Hard CHD	128	1.94 (0.98–3.81)	0.056	2.06 (1.02–4.16)	0.045
MI	107	1.79 (0.83–3.85)	0.140	2.02 (0.91–4.48)	0.061
Angina	180	3.08 (1.92–4.96)	<0.001	2.39 (1.44–3.97)	0.001
Stroke	76	1.05 (0.33–3.32)	0.940	1.15 (0.36–3.74)	0.811
All-cause mortality	189	2.21 (1.30–3.74)	0.003	2.62 (1.51–4.55)	0.001

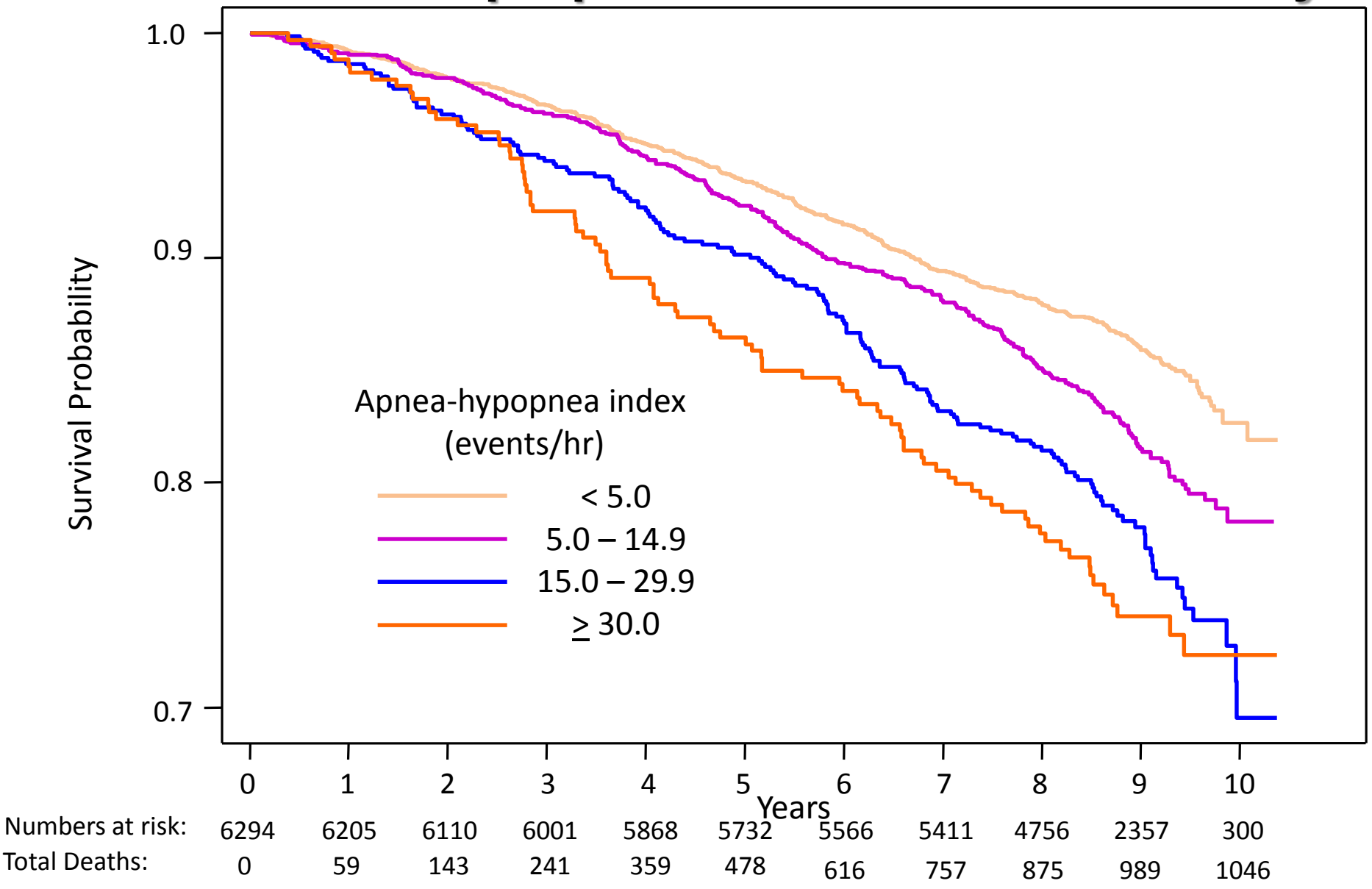
Multivariable model were adjusted for age, gender, race/ethnicity, BMI, cigarette smoking, diabetes mellitus, total cholesterol, HDL, triglycerides, systolic blood pressure, BP medication use, statin use, benzodiazepine use and current alcohol use.

[a] Participants reporting physician-diagnosed sleep apnea compared to those not reporting sleep apnea.

Yeboah J, et al. Atherosclerosis. 2011 Dec;219(2):963-8.

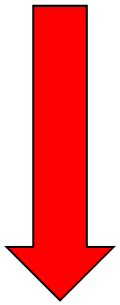
HR 1.90 composite CV
HR=2.06 MI
HR=2.39 Angina
HR=2.62 All-cause mortality

Obstructive Sleep Apnea and All-Cause Mortality



Obstructive Sleep Apnea and All-Cause Mortality

AHI (events/hr)	N	Person years	Deaths	Mortality Rate	Adjusted Odds Ratios (95% CI)
Men ≤ 70 years					
< 5.0	985	8,220	91	11.1	1.00
5.0 – 14.9	694	5,697	82	14.4	1.24 (0.90 – 1.71)
15.0 – 29.9	322	2,623	47	17.9	1.45 (0.98 – 2.14)
> 30.0	168	1,355	28	20.7	2.09 (1.31 – 3.33)
Men > 70 years					
< 5.0	277	2,055	125	60.8	1.00
5.0 – 14.9	282	2,176	111	51.0	0.92 (0.70 – 1.20)
15.0 – 29.9	140	1,029	67	65.1	1.23 (0.90 – 1.68)
> 30.0	74	517	36	69.6	1.27 (0.86 – 1.86)



Punjabi NM et al, PLOS One 2010

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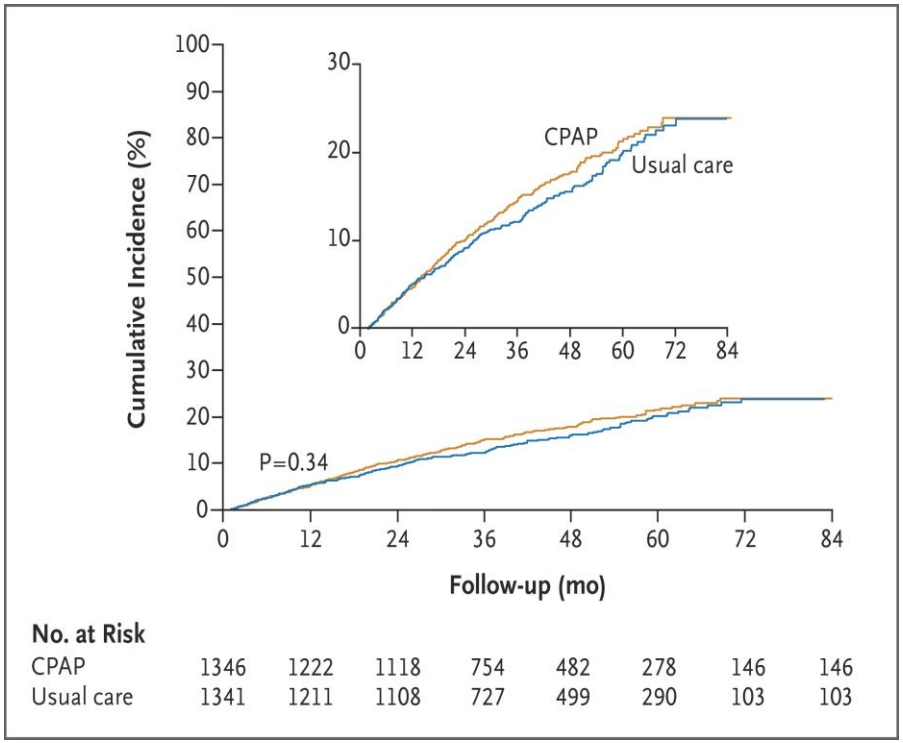
ESTABLISHED IN 1812 SEPTEMBER 8, 2016 VOL. 375 NO. 10

CPAP for Prevention of Cardiovascular Events in Obstructive Sleep Apnea



n=2717, mean follow-up of 3.7 yrs

- Primary end-point occurred in 229 CPAP group (17.0%) vs 207 usual care group (15.4%)

-HR= 1.10; 95% CI, 0.91 to 1.32; P=0.34

-Secondary analyses: those adherent to CPAP therapy had a lower risk of stroke (hazard ratio, 0.56; 95% CI, 0.32 to 1.00; P=0.05)

McEvoy RD et al. N Engl J Med 2016;375:919-931

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CPAP for Prevention of Cardiovascular Events in Obstructive Sleep Apnea

Table 3. Other Outcomes.*

Outcome	CPAP Group (N=1346)					Usual-Care Group (N=1341)					Adjusted Difference in Change from Baseline (95% CI)†	P Value
	Baseline		End of Study		Change from Baseline	Baseline		End of Study		Change from Baseline		
	no. of patients with data	value	no. of patients with data	value		no. of patients with data	value	no. of patients with data	value			
Blood pressure — mm Hg												
Systolic	1351	132±16	1166	132±16	0.7±17‡	1333	131±16	1158	132±16	1.[illegible]±17	−0.4 (−1.5 to 0.8)	0.55
Diastolic	1351	80±11	1166	79±16	−0.9±11	1333	79±11	1158	79±10	−0.[illegible]±11	−0.7 (−1.4 to 0.0)	0.05
Epworth Sleepiness Scale score	1346	7.3±3.6	1221	4.2±3.5	−3.1±4.1	1341	7.5±3.6	1188	6.8±4.4	−0.[illegible]±4.3	−2.5 (−2.8 to −2.2)	<0.001
Hospital Anxiety and Depression Scale												
Anxiety score	1351	4.6±3.7	1220	3.8±3.6	−0.8±3.6	1336	4.6±3.6	1190	4.2±3.6	−0.[illegible]±3.5	−0.4 (−0.6 to −0.2)	0.002
Depression score	1351	5.1±3.9	1220	4.3±3.6	−0.8±4.0	1336	5.2±3.9	1190	5.1±3.8	−0.[illegible]±3.8	−0.8 (−1.0 to −0.5)	<0.001
SF-36§												
Physical-component summary score	1345	45.4±7.7	1218	46.9±8.0	1.3±7.5	1332	45.1±7.8	1189	45.9±8.1	0.6[illegible]7.6	0.9 (0.3 to 1.4)	0.002
Mental-component summary score	1342	52.6±8.6	1218	53.6±8.0	1.0±8.9	1332	52.3±8.7	1189	52.4±8.8	0.0[illegible]8.9	1.2 (0.6 to 1.8)	<0.001
EQ-5D utility score¶	—	—	1252	0.8±0.3	—	—	—	1229	0.8±0.3	—	0.02 (0.00 to 0.05)	0.03

* Plus–minus values are means ±SD.
† Analysis of covariance was used to compare the change from baseline in the CPAP group with that of the usual-care group; the analysis was adjusted for the baseline value.
‡ The change in systolic blood pressure from baseline to the end of the study is not apparent because mean blood pressure values were rounded to the nearest integer value.
§ Scores on the Medical Outcomes Study 36-Item Short-Form Health Survey (SF-36) range from 0 to 100, with higher scores indicating better quality of life with respect to either the physical or mental component.
¶ Utility scores on the European Quality of Life–5 Dimensions questionnaire (EQ-5D) are described in the Supplementary Appendix. The EQ-5D was administered only at the end of the study.

- Mean CPAP adherence – 3.3 hours
- Was study powered to show a change?
- Duration of f/u inadequate?
- Those with severe sleep apnea and hypoxia were excluded
- Generalizability
  - Male predominant
  - 60% Asian
  - Mean BMI 28.8 kg/m^2
  - Baseline ESS score 7.3

McEvoy RD et al. N Engl J Med 2016;375:919-931

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Sleep Apnea and Cardiovascular Disease/Mortality

- OSA is highly prevalent in patients with CAD
- Untreated severe OSA increases the risk for major adverse coronary events and mortality
- Effective OSA treatment with CPAP may reduce coronary event rates
- Large RCT data suggest lack of improvement of CV mortality with treatment of OSA with CPAP, however, power of study, generalizability and suboptimal CPAP adherence limits interpretability
  - Post-hoc analysis suggests improvement in stroke outcomes
- RCT data suggest improvements in sleepiness and quality of life measures in OSA in those with CV risk with CPAP treatment
- Poor CPAP adherence remains a problem in effective interpretation of OSA clinical trials

Sleep Apnea:
A Novel Modifiable Cardiac Risk Factor
Jury In or Out?

- A substantial proportion of cardiovascular disease is preventable
- Standard Risk Factors
  - Overweight and obesity
  - Physical inactivity
  - Diabetes
  - Cigarette smoking
  - High blood pressure
  - Dyslipidemia
- **Target Sleep Apnea as a Novel Risk Factor**

Estimated that 5 to 20% of Cardiovascular Disease may be preventable by treating/preventing Sleep Apnea

Sleep and Cardiopulmonary Disease

NHLBI-funded Sleep Related Respiratory and Electrophysiological Atrial Fibrillation Predictors

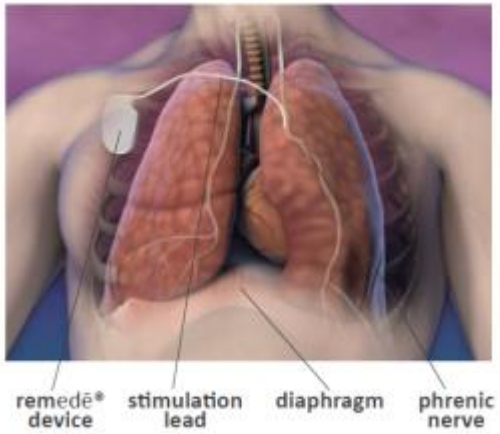
Predictors of AF in a longitudinal study of ~3000 participants of the MrOS Sleep Study

NHLBI-funded RCT to examine effect of sleep apnea treatment on CV biomarkers

SASS

Sleep Apnea Stress Study

Transvenous Phrenic Nerve Stimulation Device for CSA Treatment



NHLBI-funded Sleep apnea and Atrial Fibrillation Electrophysiology: Biomarkers and Evaluating Atrial Triggers

PVDOMICS

NHLBI-funded multicenter cohort study to phenotype PHTN including sleep testing

NHLBI ARRA funded trial Multi-center trial to examine utility of nocturnal supplemental oxygen in treating patients at high CV risk with sleep apnea