

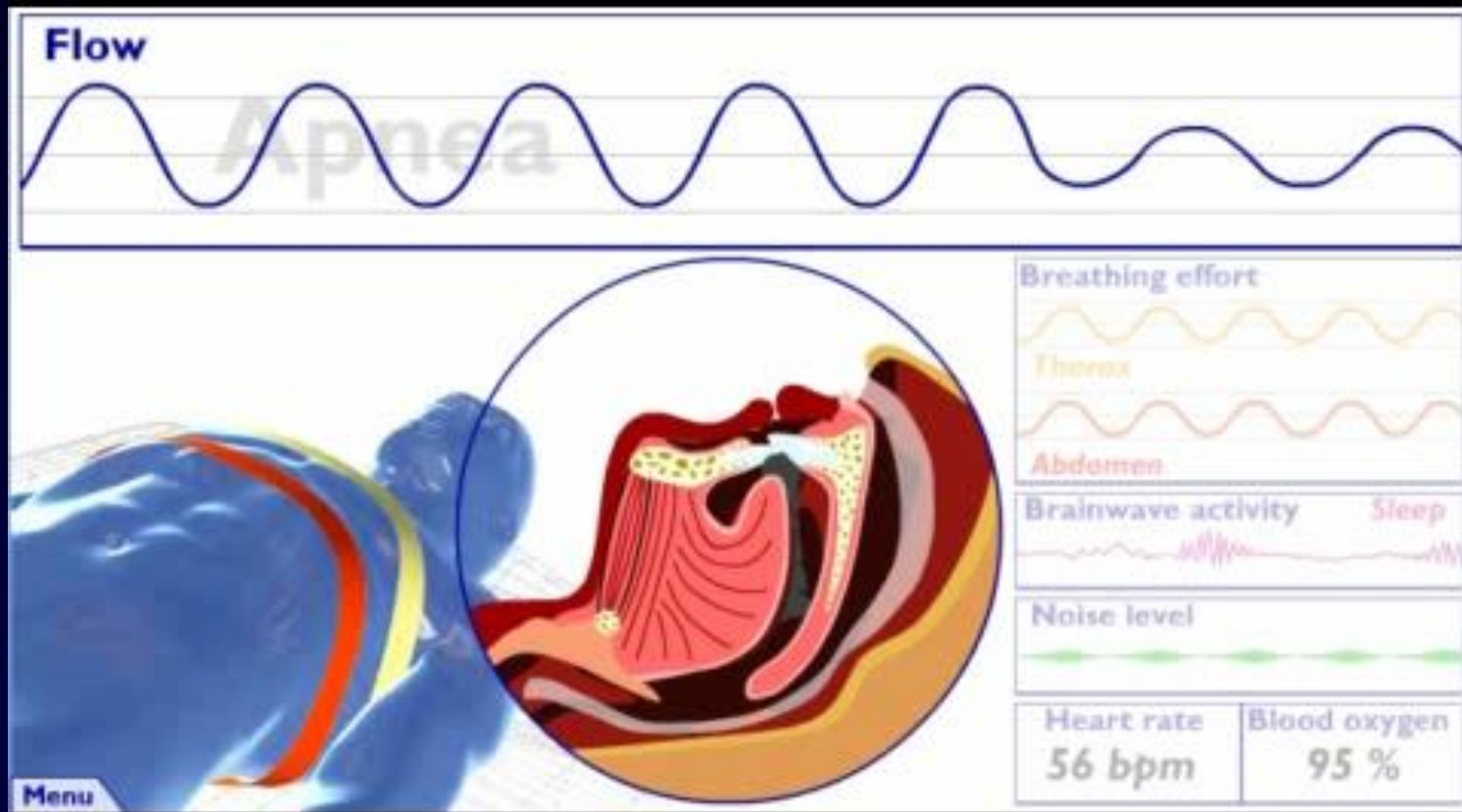
Sleep apnea as a risk factor of AF and cardiovascular disease

Sungha Park MD PhD
Yonsei University College of Medicine
Division of Cardiology

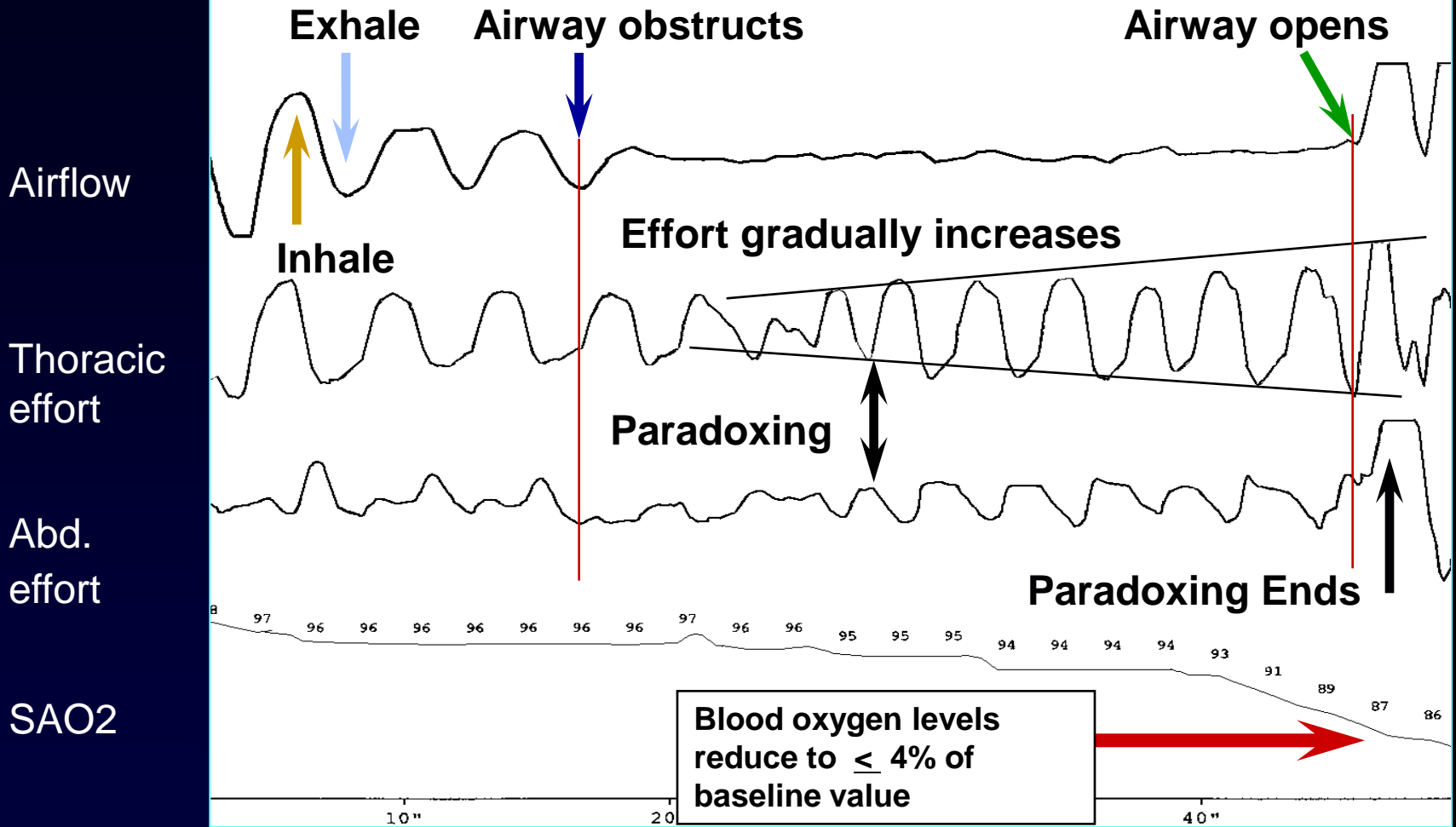
Contents

- **OSA and CVD: pathophysiologic mechanism**
- OSA and CVD
- OSA and Arrhythmia(Atrial fibrillation)

What is sleep apnea



EKG



Obstructive Apnea A blockage of the airway despite efforts to breath. Notice the effort gradually increasing ending in airway opening.

Definition of apnea/hypopnea

- Apnea: More than **90% decrease** in airflow **with effort for more than 10 seconds**
- Hypopnea
 1. More than **50% decrease in airflow** with either **desaturation of more than 3% or arousal** for more than 10 seconds
 2. More than 30% decrease in airflow with **desaturation of more than 4%** for more than 10 seconds

Introduction

- AHI > 5 with symptoms (such as daytime somnolence: Epworth score > 9)
- Prevalent in 5-10% of the general population → 20% including subjects without sx (AHI ≥ 5)
- AHI 5-14(mild), 15-29(moderate), ≥ 30(Severe)
- 85% of significant OSA: undiagnosed

Expert consensus document. J Am Coll Cardiol 2008;52(8):686-717

Signs, symptoms and risk factors

- Disruptive snoring
- Witnessed apnea, gasping
- Obesity and/or enlarged neck
- Retrognathia, crowded appearing oropharynx
- Hypersomnolence
- Male gender, increasing age
- Increased BP, morning headache

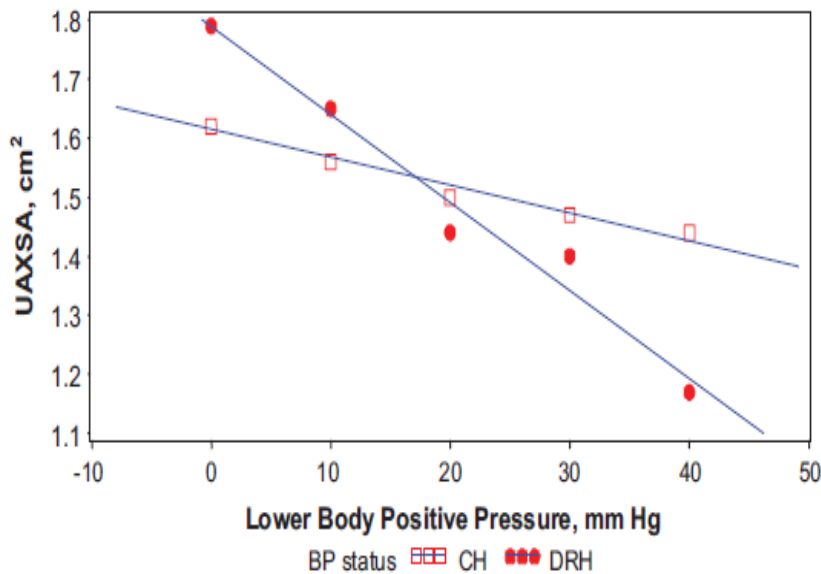
Expert consensus document. J Am Coll Cardiol 2008;52(8):686-717

Influence of Lower Body Positive Pressure on Upper Airway Cross-Sectional Area in Drug-Resistant Hypertension

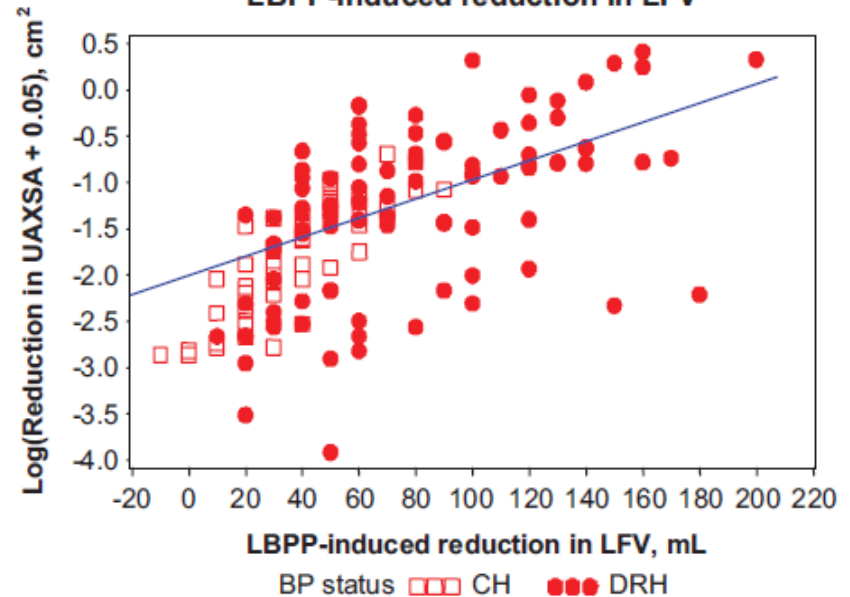
Oded Friedman, T. Douglas Bradley, Alexander G. Logan

Friedman O et al. Hypertension 2013;61:240-245

UAXSA versus LBPP



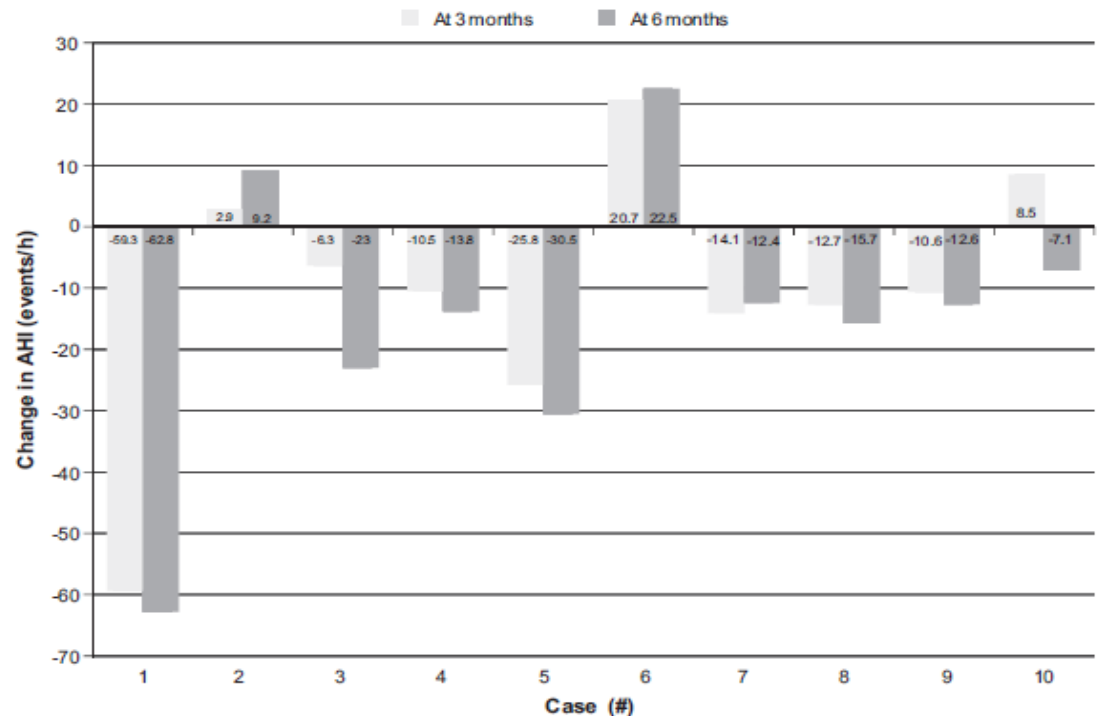
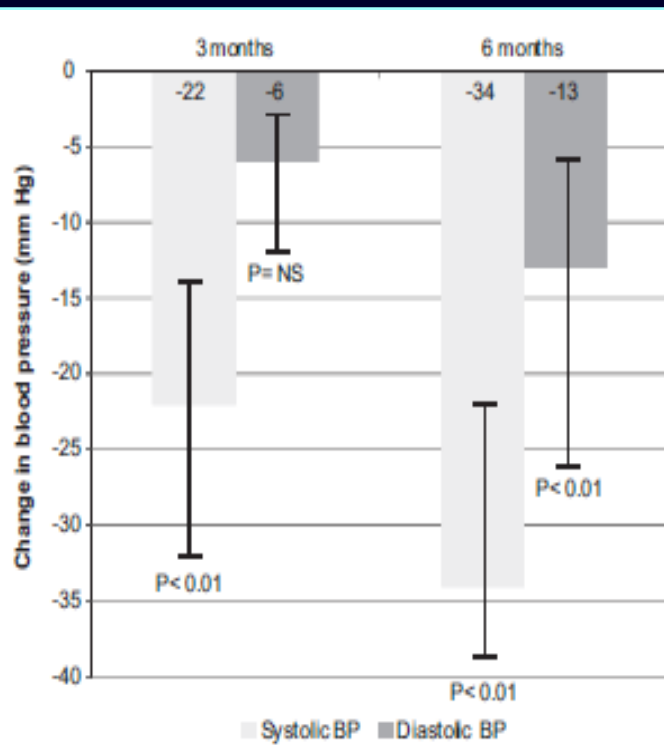
Reduction in UAXSA versus LBPP-induced reduction in LFV



Effects of Renal Sympathetic Denervation on Blood Pressure, Sleep Apnea Course, and Glycemic Control in Patients With Resistant Hypertension and Sleep Apnea

Adam Witkowski, Aleksander Prejbisz, Elżbieta Florczak, Jacek Kądziera, Paweł Śliwiński, Przemysław Bieleń, Iona Michałowska, Marek Kabat, Ewa Warchoń, Magdalena Januszewicz, Krzysztof Narkiewicz, Virend K. Somers, Paul A. Sobotka, Andrzej Januszewicz

Hypertension 2011;58:559-565



Screening and diagnostic tests

- Questionnaires: Berlin Questionnaire, Epworth Sleepiness scale
- Overnight oximetry → Not recommended
- Home based/ambulatory polysomnography
- In hospital attended polysomnography

Berlin Questionnaire

CATEGORY 1(총 2점 positive)

1. 코골이가 있나요 ? (a:1점) a. 예 b. 아니오 c. 모름
만약 코를 곤다면 ...
2. 코골이 소리가 어떤가요 ? (c or d: 1점)
a. 숨소리보다 약간 크다 b. 말소리만큼 크다 c. 말소리보다 크다 d. 매우 크다 (옆방에서 들릴 정도로)
3. 얼마나 자주 코골이가 있나요 ?(a or b:1점)
a. 거의 매일 b. 일주일에 3~4회 c. 일주일에 1~2회 d. 한달에 1~2회 e. 거의 없거나 없다
4. 코골이로 사람들을 성가시게 한 적이 있나요?(a: 1점) a. 예 b. 아니오 c. 모름
5. 수면 중에 무호흡이 있는 것을 다른 사람이 알고 있나요?(a or b: 2점)
a. 거의 매일 b. 일주일에 3~4회 c. 일주일에 1~2회 d. 한달에 1~2회 e. 거의 없거나 없다

CATEGORY 2(총 2점 positive)

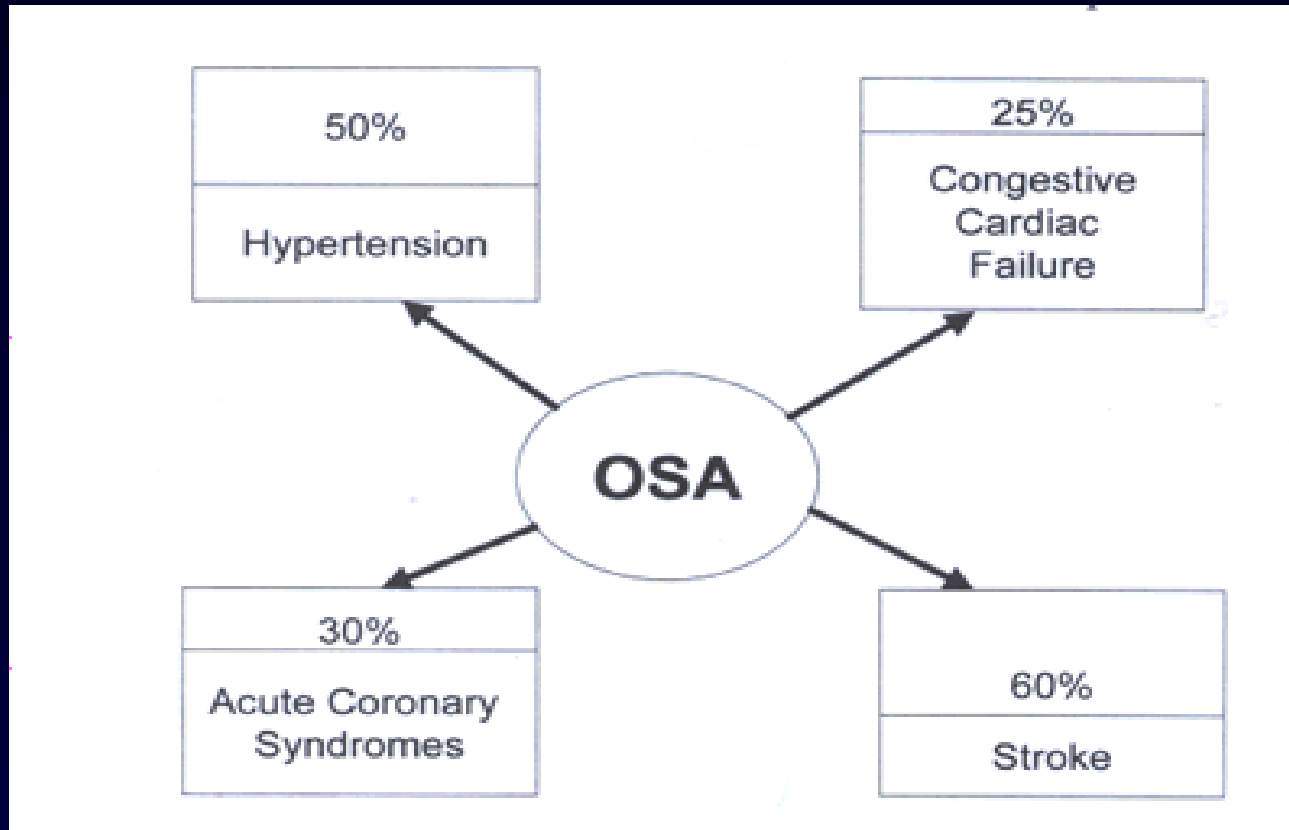
6. 수면 후에 얼마나 자주 피곤함을 느끼나요?(a or b: 1점)
a. 거의 매일 b. 일주일에 3~4회 c. 일주일에 1~2회 d. 한달에 1~2회 e. 거의 없거나 없다
7. 깨어있을 때에 피곤함을 느끼나요?(a or b:1점)
a. 거의 매일 b. 일주일에 3~4회 c. 일주일에 1~2회 d. 한달에 1~2회 e. 거의 없거나 없다
8. 자동차 운전 중에 잠이 든 적이 있나요?(a: 1점)
a. 거의 매일 b. 일주일에 3~4회 c. 일주일에 1~2회 d. 한달에 1~2회 e. 거의 없거나 없다

CATEGORY 3(a or BMI more than 30kg/m²: positive)

9. 고혈압을 앓고 있나요? a. 예 b. 아니오

High risk: $\geq 2/3$ categories positive

Obstructive Sleep Apnea and other Cardiovascular Diseases



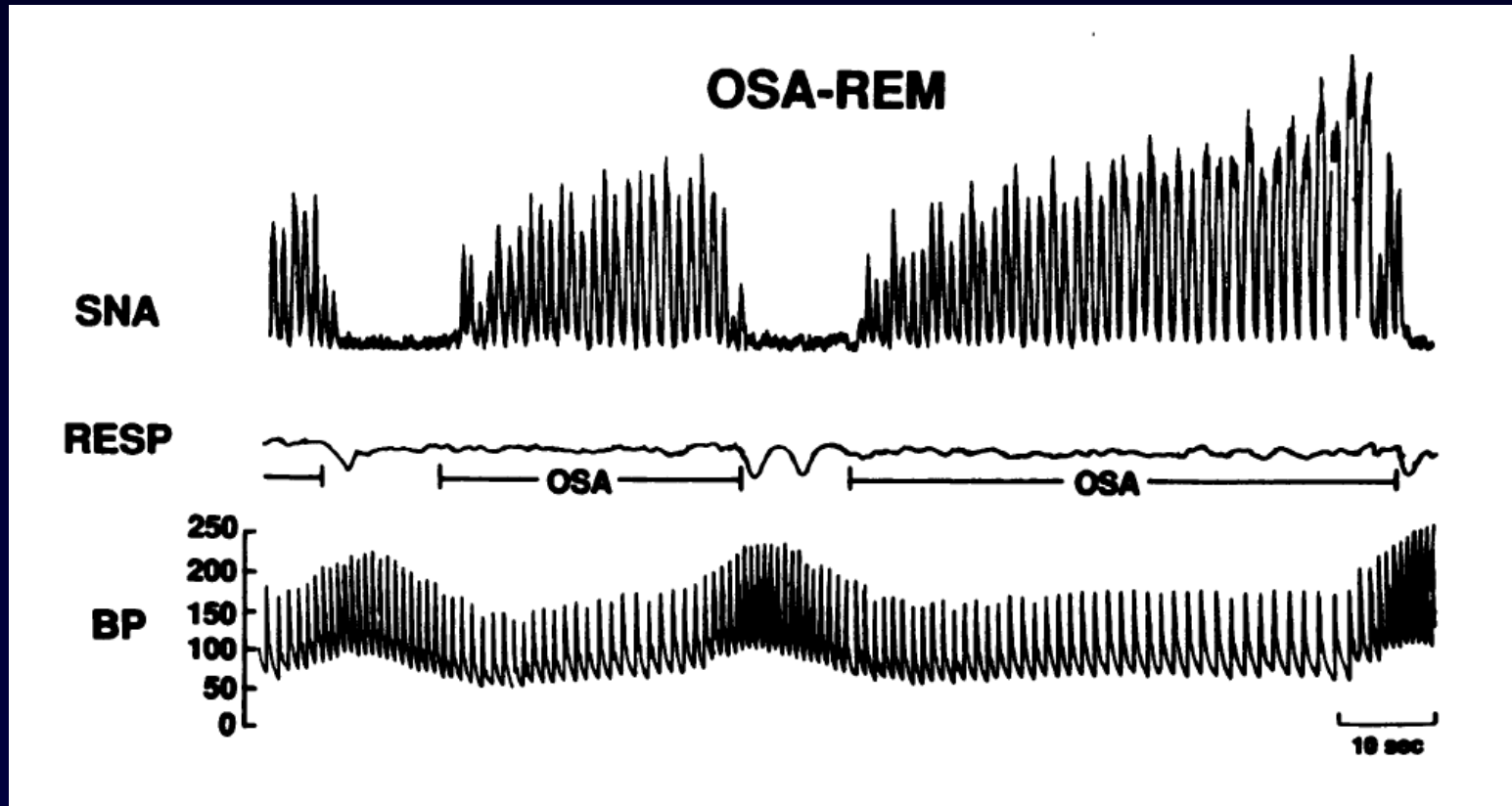
www.rjmatthewsmd.com/Definitions/img/osa-fig3.gif

Sympathetic Neural Mechanisms in Obstructive Sleep Apnea

Virend K. Somers, Mark E. Dyken, Mary P. Clary, and Francois M. Abboud

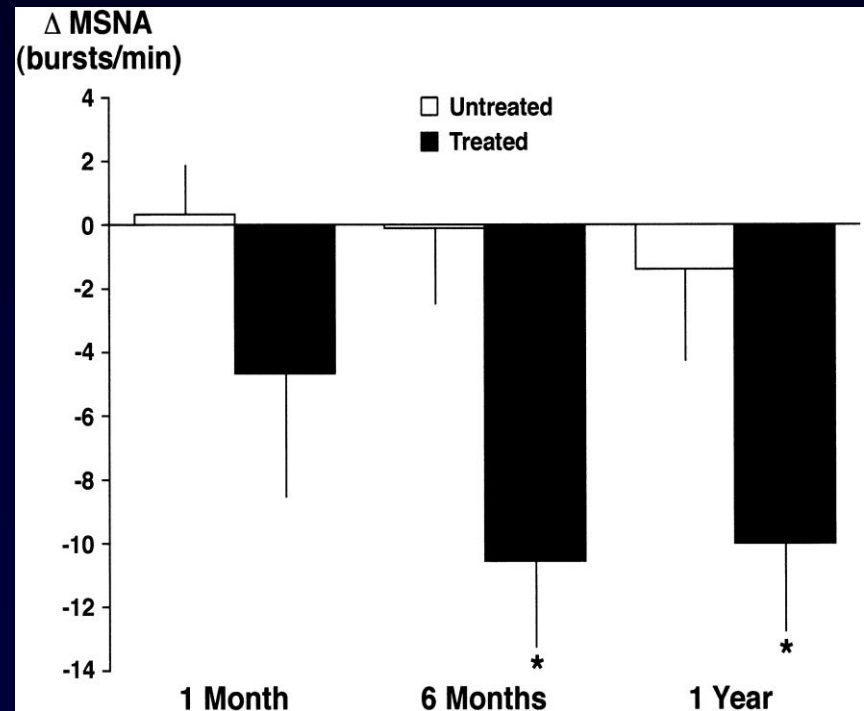
Departments of Internal Medicine and Neurology and the Cardiovascular Center, University of Iowa College of Medicine, Iowa City, Iowa 52242

J Clin Invest 1995;96: 1897-1904



Sympathetic System: Muscle Nerve Activity

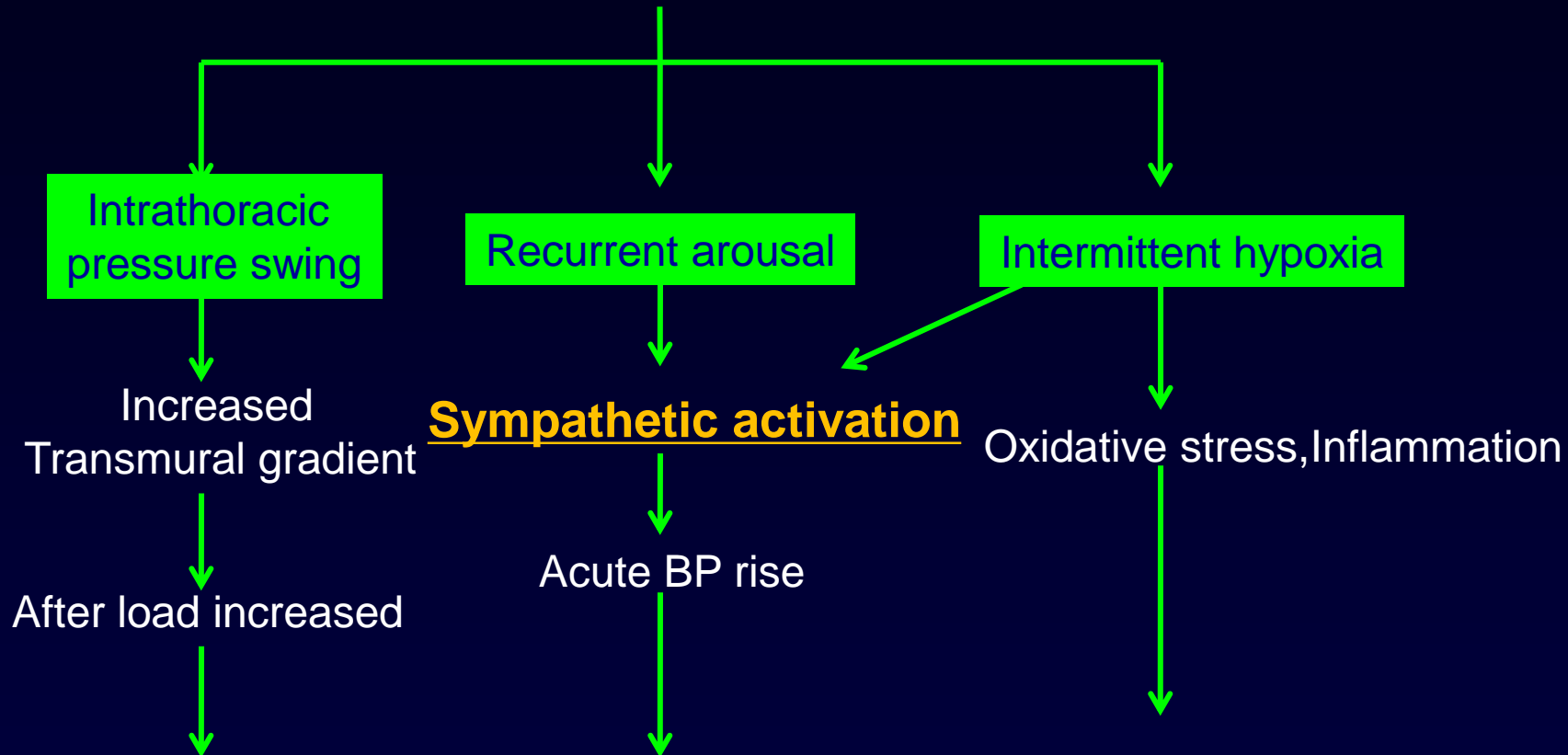
- Compared muscle sympathetic nervous activity (MSNA) of blood vessels in **untreated** and **treated OSA** at **baseline** and after **1, 6, 12 months of CPAP**
- MSNA was similar during repeated measurements in the untreated group
- In contrast, MSNA decreased significantly over time in patients treated with CPAP



Narkiewicz et al. Circulation 1999;100:2332-2335

OSA and cardiovascular disease

Obstructive sleep apnea



1. LA volume increase, LV remodeling, LV dysfunction
2. Sustained hypertension, vascular inflammation
3. Increased arrhythmogenicity, increased risk of MI, sudden cardiac death

Kohler M and Stradling JR. Nat Rev Cardiol 2010;7:677-685

Contents

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Prevalence of OSA in Hypertension

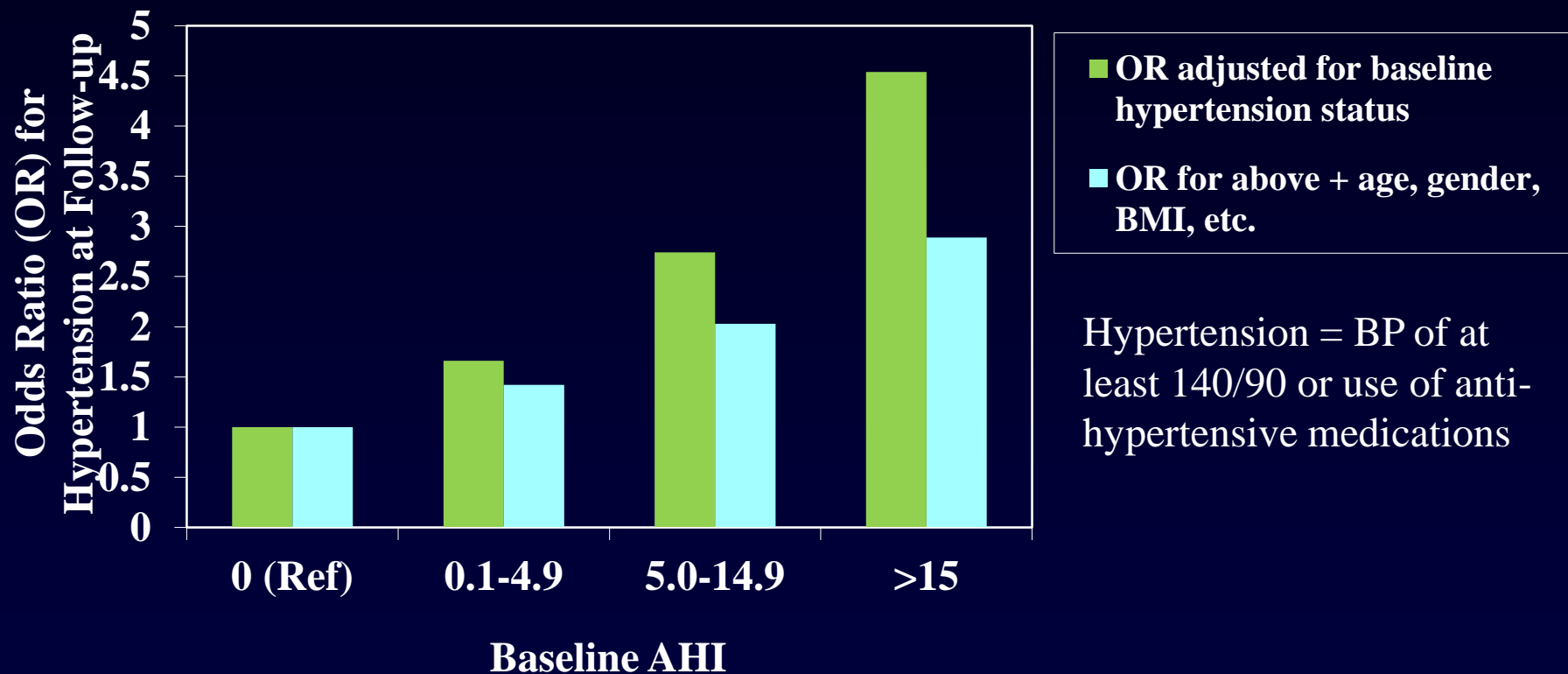
- About 50% of OSA patients are hypertensive
- 30-50% of hypertensive patients also have OSA, often undiagnosed
- OSA patients are more likely to be nocturnal “non-dippers”
- Up to 80% of resistant hypertension patients

Wisconsin Sleep Cohort Study

- A prospective, population-based study of the association between objectively measured sleep-disordered breathing and hypertension
- 709 subjects with follow up of 4 years
- Age 30 – 65 years

Peppard et al: NEJM, 2000

Association Between Sleep Apnea and Incident Hypertension During 4 Year Follow Up Period



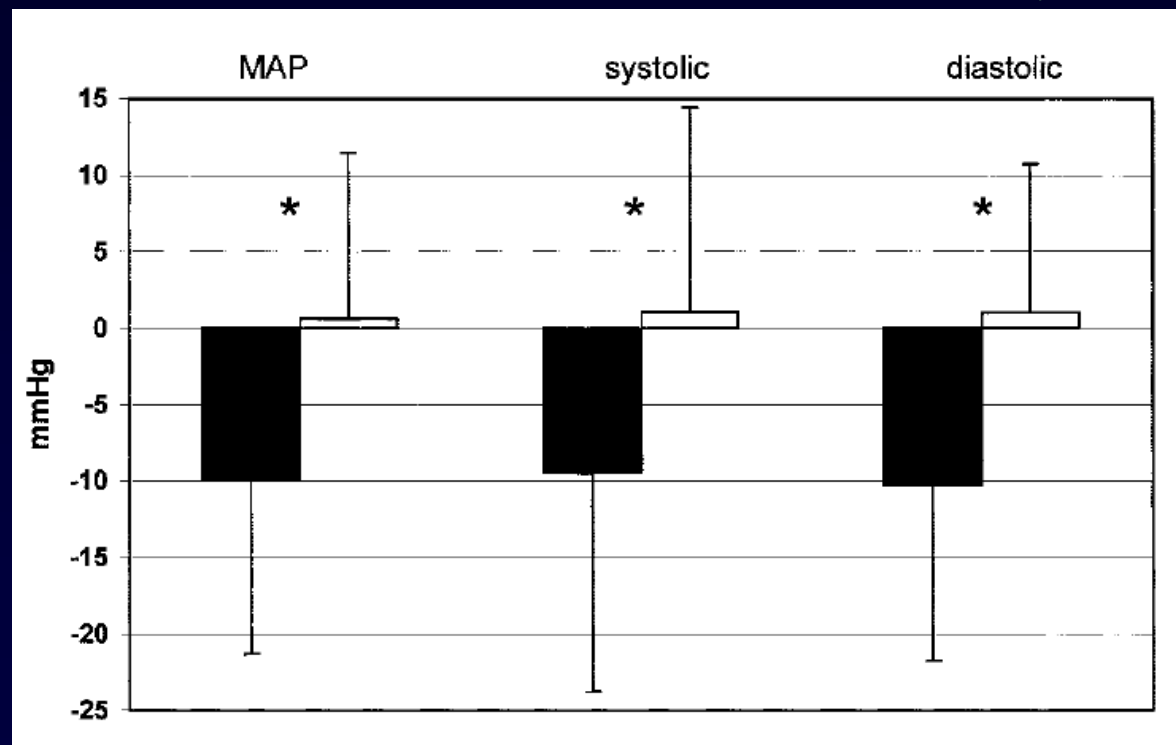
Showed a linear relationship between severity of sleep apnea and incidence of new hypertension (42%, 2 fold, 3 fold)

Peppard et al, NEJM 342:1378-1384, 2000

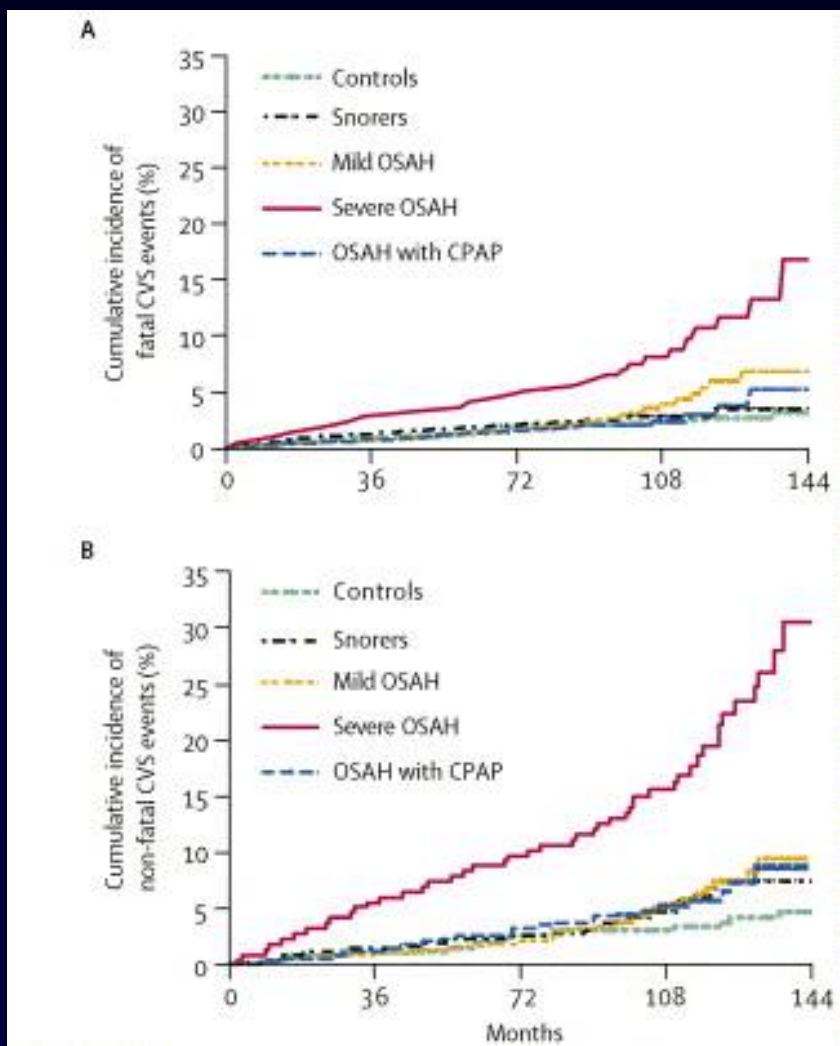
Effect of Nasal Continuous Positive Airway Pressure Treatment on Blood Pressure in Patients With Obstructive Sleep Apnea

Heinrich F. Becker, MD; Andreas Jerrentrup, MD; Thomas Ploch, Dipl Psych; Ludger Grote, MD; Thomas Penzel, PhD; Colin E. Sullivan, MD; J. Hermann Peter, MD

Becker HF et al, Circulation 2003;107:68-73



CAD and Treatment of OSA



- Prospective observational study (10.1 ± 1.1 years)
- 264 healthy men, 377 snorer, 403 mild OSAH, 235 severe OSAH, 372 OSAH with CPAP
- Untreated with severe OSA vs. Healthy controls (CPAP-treated OSA)
 - Adjusted OR compared with control
2.87 (1.17 – 7.51): fatal
3.17 (1.12 – 7.51): non-fatal

Marin et al., Lancet 2005

Yonsei University Cardiology OSA registry



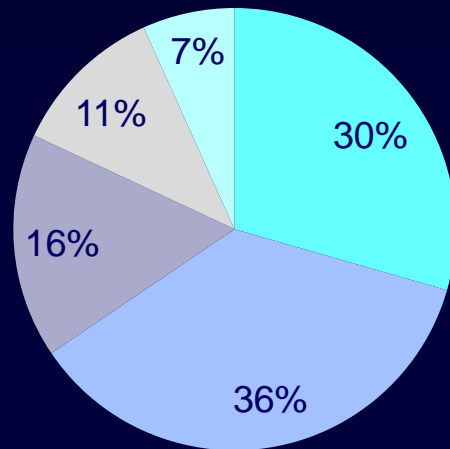
Validation of Embletta portable diagnostic system for
identifying patients with suspected obstructive sleep apnoea
syndrome (OSAS)

SUSANNA S.S. NG, TAT-ON CHAN, KIN-WANG TO, JENNY NGAI, ALVIN TUNG, FANNY W.S. KO AND
DAVID S.C. HUI

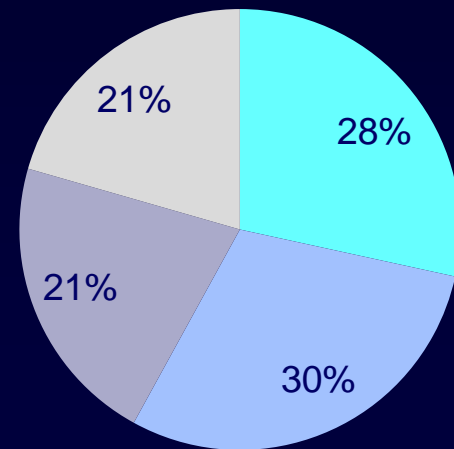
PSG registry

- 2011/1 – 2013/3
- Average age : 53.8
- Female : 213 , Male :663

Diagnosis

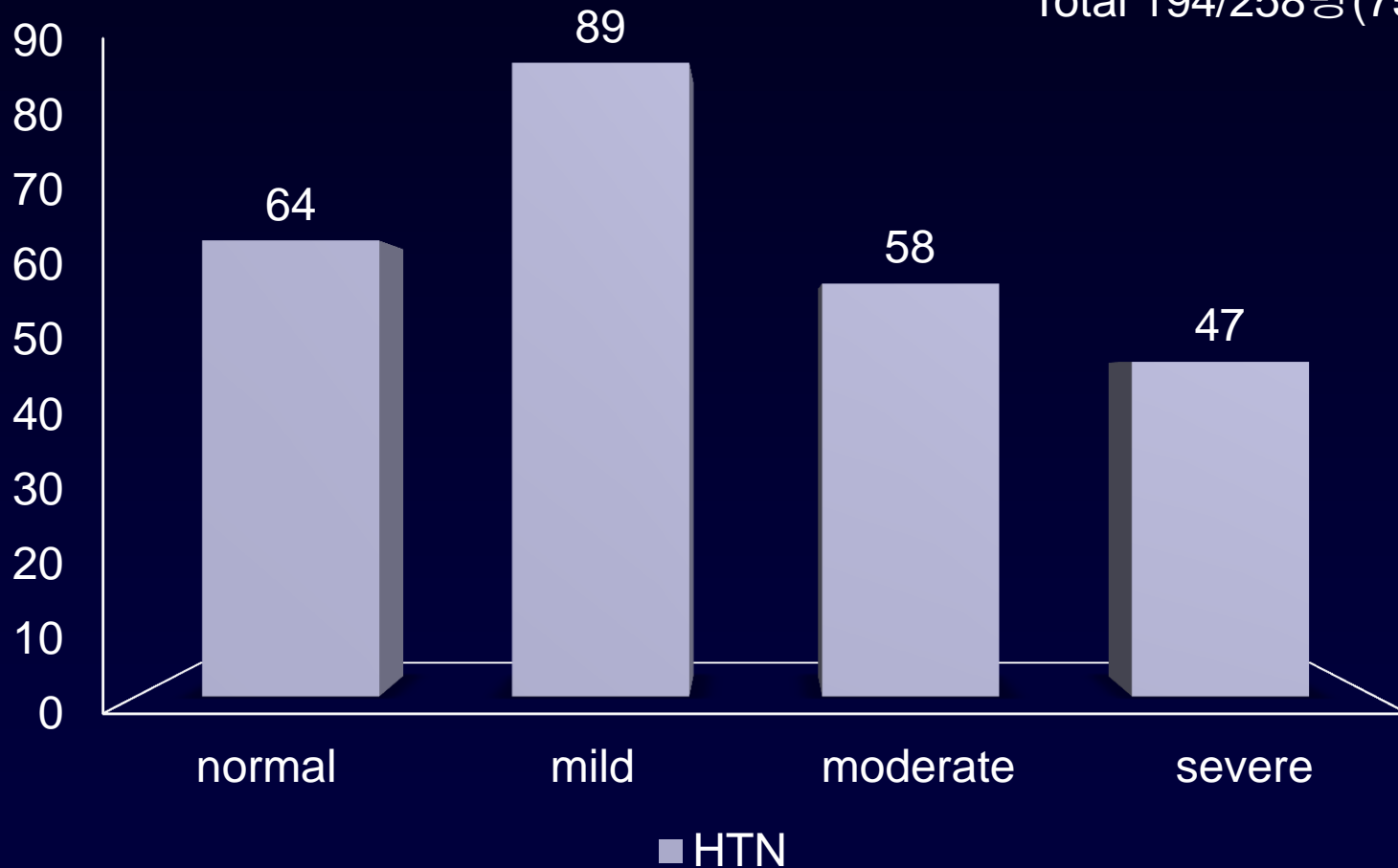


Result



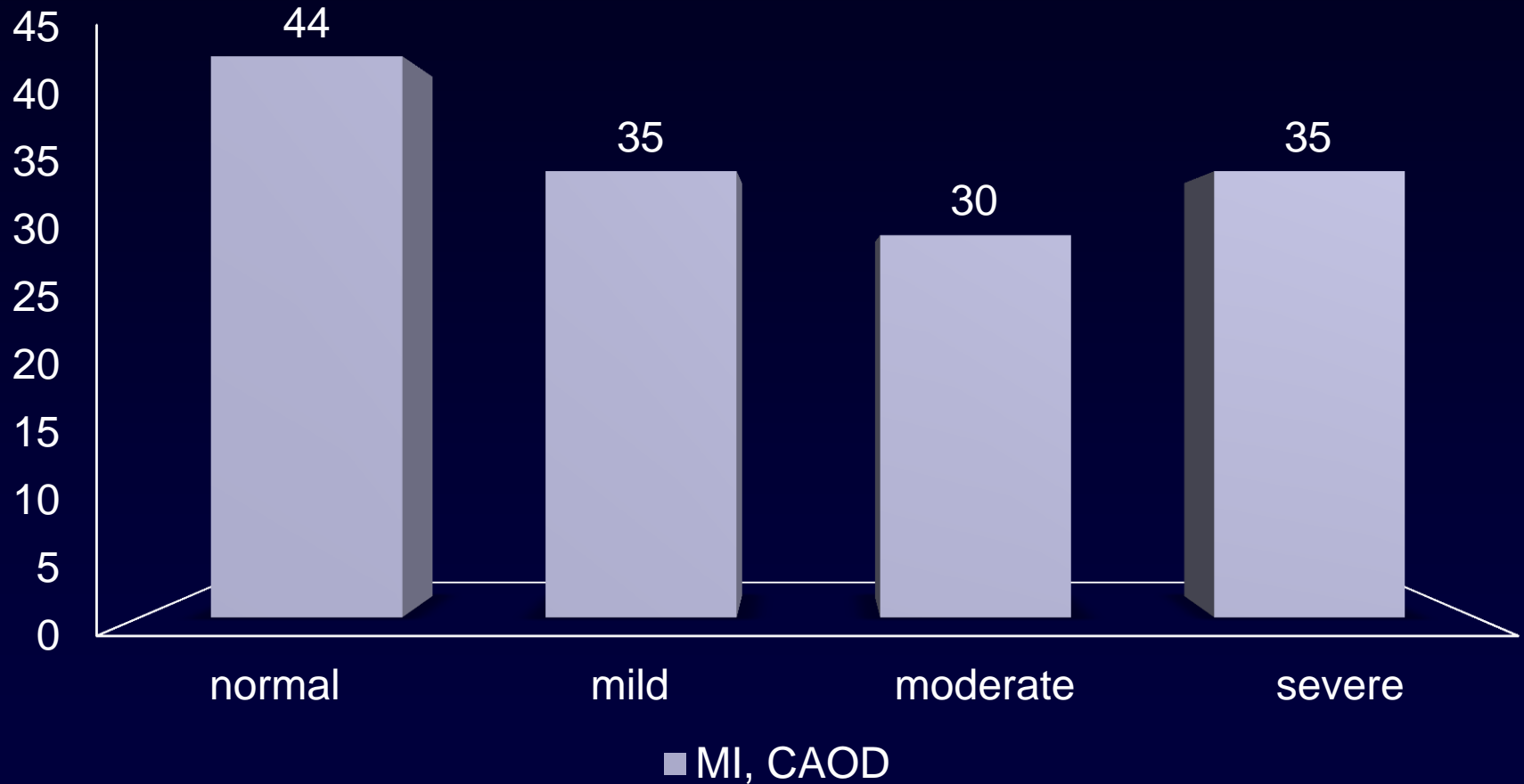
Portable PSG 결과

Total 194/258명(75.0%)



Portable PSG 결과

Total 100/144명(69.4%)



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- OSA and CVD: pathophysiologic mechanism
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- **OSA and Arrhythmia(Atrial fibrillation)**

Modulation of autonomic activity by OSA

- Recurrent sleep fragmentation, Hypoxemia, hypercapnia → Increased sympathetic activity
- Prolonged apnea and hypoxemia(diving reflex) → increased **parasympathetic activity of the heart** through the ganglionated plexus with increased **sympathetic activity of peripheral vessels**

Leung RST. Prog Cardiovasc Dis 2009;51(4):324-338

Cardiovascular Consequences of Sleep Apnea Cardiac Arrhythmias

- 48% and 52% of OSA patients with **arrhythmia** during a single night of study-Apnea Tx with CPAP improved it. Guilleminault C. Am J Card 1983;52:490-4. Hoffstein. Chest 1994;106:466-71
- 46 % of SDB patients with rhythm disturbance, **mostly at night**. Apnea Tx with CPAP significantly reduces the rhythm disturbance. Simantirakis Eur Heart J 2004; 25: 1070-6
- **59% prevalence of OSA** in patients with **permanent pacemakers** Garrigue S et al. Circulation 2007;115:1703-1709
- **BMI, AHI, and severity of hypoxemia** directly correlated with frequency and severity of arrhythmia in these studies

Cardiovascular Consequences of Sleep Apnea

Cardiac Arrhythmias

TABLE 3. ADJUSTED AND UNADJUSTED ODDS RATIOS RELATING ARRHYTHMIA OCCURRENCE AND SLEEP-DISORDERED BREATHING

Arrhythmia Type	Unadjusted Odds Ratio	Odds Ratio* (95% CI) Adjusted for Age, Sex, BMI	Odds Ratio* (95% CI) Adjusted for Age, Sex, BMI, CHD
Nonsustained ventricular tachycardia	4.64 (1.48–14.57)	3.72 (1.13–12.2)	3.40 (1.03–11.2)
Complex ventricular ectopy	1.96 (1.28–3.00)	1.81 (1.16–2.84)	1.74 (1.11–2.74)
Atrial fibrillation	5.66 (1.56–20.52)	3.85 (1.00–14.93)	4.02 (1.03–15.74)

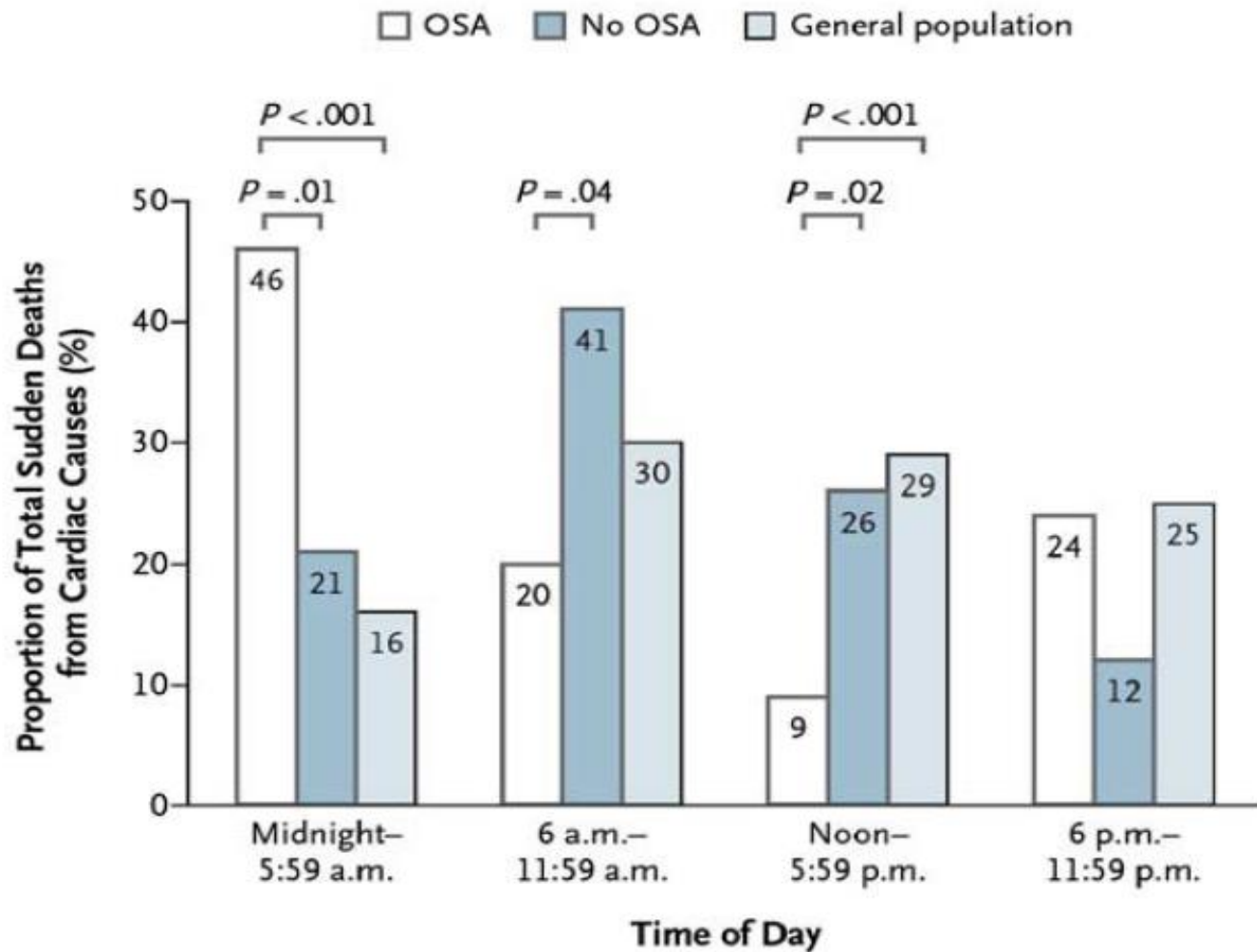
Definition of abbreviations: BMI = body mass index; CHD = coronary heart disease; CI = confidence interval.

* Results of logistic regression analysis with SDB as the exposure, n = 228 with SDB and n = 338 without SDB.

Those untreated with RDI>30 over 4 years

Mehra, R et al. Nocturnal Arrhythmias with SDB. The SHHS. Am J Respir Crit Care Med Vol 173. pp 910-916, 2006

OSA and timing of SCD

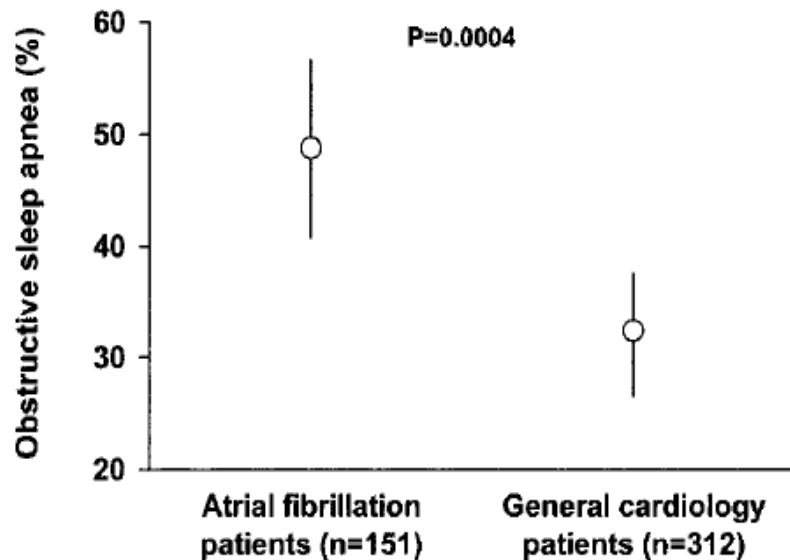


Leung RST. Prog Cardiovasc Dis 2009;51(4):324-338

Association of Atrial Fibrillation and Obstructive Sleep Apnea

Apoor S. Gami, MD; Gregg Pressman, MD; Sean M. Caples, MD; Ravi Kanagala, MD;
Joseph J. Gard, BS; Diane E. Davison, RN, MA; Joseph F. Malouf, MD; Naser M. Ammash, MD;
Paul A. Friedman, MD; Virend K. Somers, MD, PhD

Gami AS et al. *Circulation* 2004;110:364-367

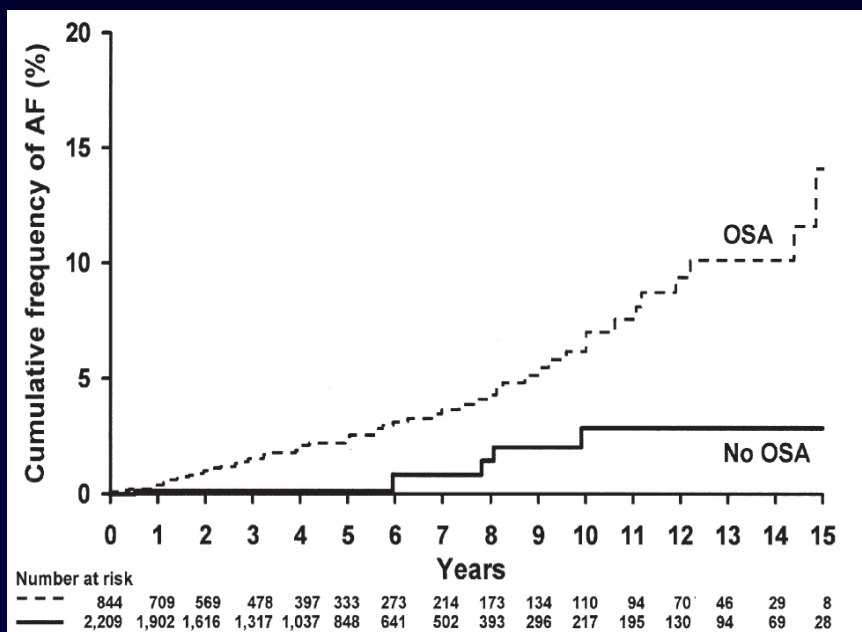


	OR	95% CI	OR and 95% CI	P
Body mass index	1.11	1.06-1.16		<0.0001
Neck circ	1.02	0.97-1.07		0.439
Hypertension	1.27	1.01-1.61		0.039
Diabetes mellitus	1.23	0.96-1.57		0.104
Atrial fibrillation	2.19	1.40-3.42		0.0006

Obstructive Sleep Apnea, Obesity, and the Risk of Incident Atrial Fibrillation

Apoor S. Gami, MD,*† Dave O. Hodge, MS,‡ Regina M. Herges, BS,‡ Eric J. Olson, MD,†§ Jiri Nykodym, BS,*† Tomas Kara, MD,*† Virend K. Somers, MD, PhD, FACC*†||

J Am Coll Cardiol 2007;49(5):565-571



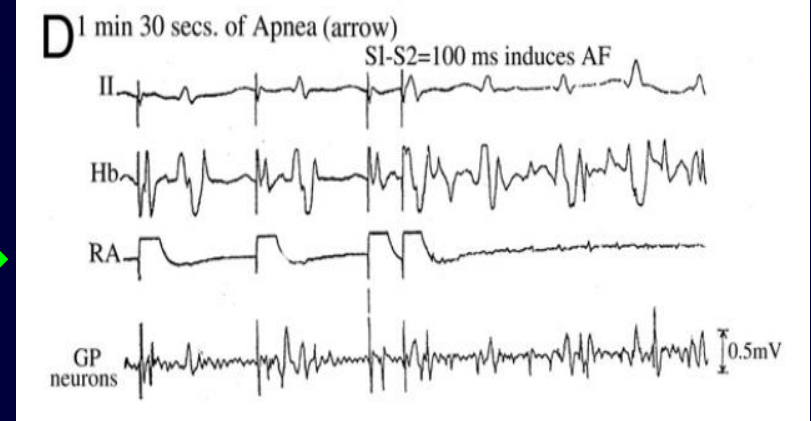
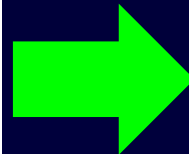
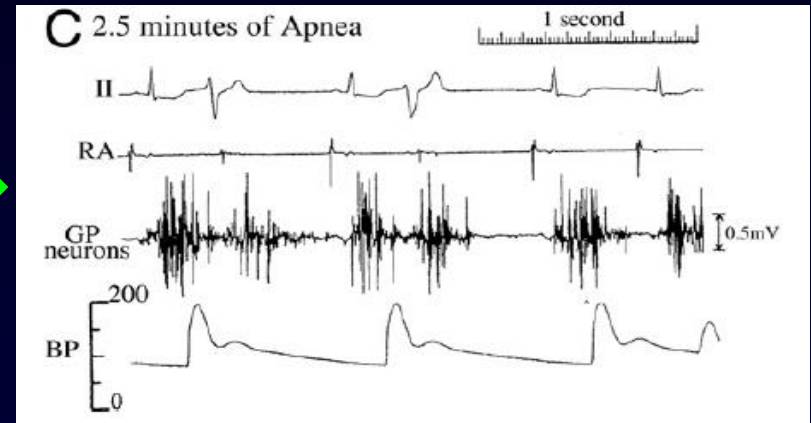
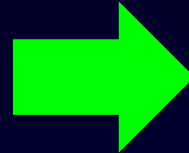
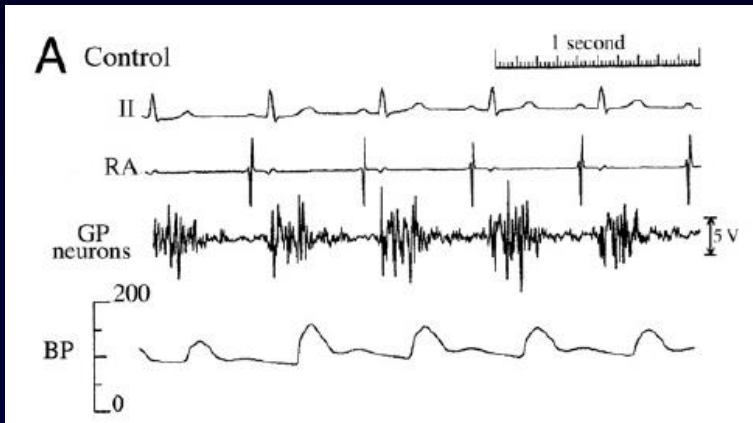
	HR	95% CI	p Value
<65 yrs old			
Age (per 10 yrs)	2.04	1.48-2.80	<0.001
Male gender	2.66	1.33-5.30	0.006
Coronary artery disease	2.66	1.46-4.83	0.001
Body mass index (per 1 kg/m ²)	1.07	1.05-1.10	<0.001
Decrease in nocturnal oxygen saturation (per -1%)*	3.29	1.35-8.04	0.009
≥65 yrs old			
Heart failure	7.68	4.32-13.66	<0.001

Mechanism for association of OSA and atrial fibrillation

- Autonomic disturbance
- Hypoxemia and hypoxemia induced oxidative stress
- Pulmonary hypertension and systemic hypertension
- Excessive negative intrathoracic pressure: stretch mediated channel activation
- Increased systemic inflammation
- Increased LA, LV transmural pressure during airway obstruction: LA remodeling, diastolic dysfunction
- Swim reflex during prolonged apnea

The Role of Ganglionated Plexi in Apnea-Related Atrial Fibrillation

Ghias M et al. *J Am Coll Cardiol* 2009;54(22):2075-2083



B After RPA GP ablation-Apnea 2 min, no capture, no AF



	AF	No AF	p Value
Before ablation (n = 11)	8	3	0.009
After ablation (n = 6)	0	6	

	Capture	No Capture	p Value
Before ablation (n = 11)	10	1	0.005
After ablation (n = 6)	1	5	

Ghias M et al. J Am Coll Cardiol 2009;54(22):2075-2083

Cardiovascular Consequences of Sleep Apnea

Atrial Fibrillation 12 months after cardioversion

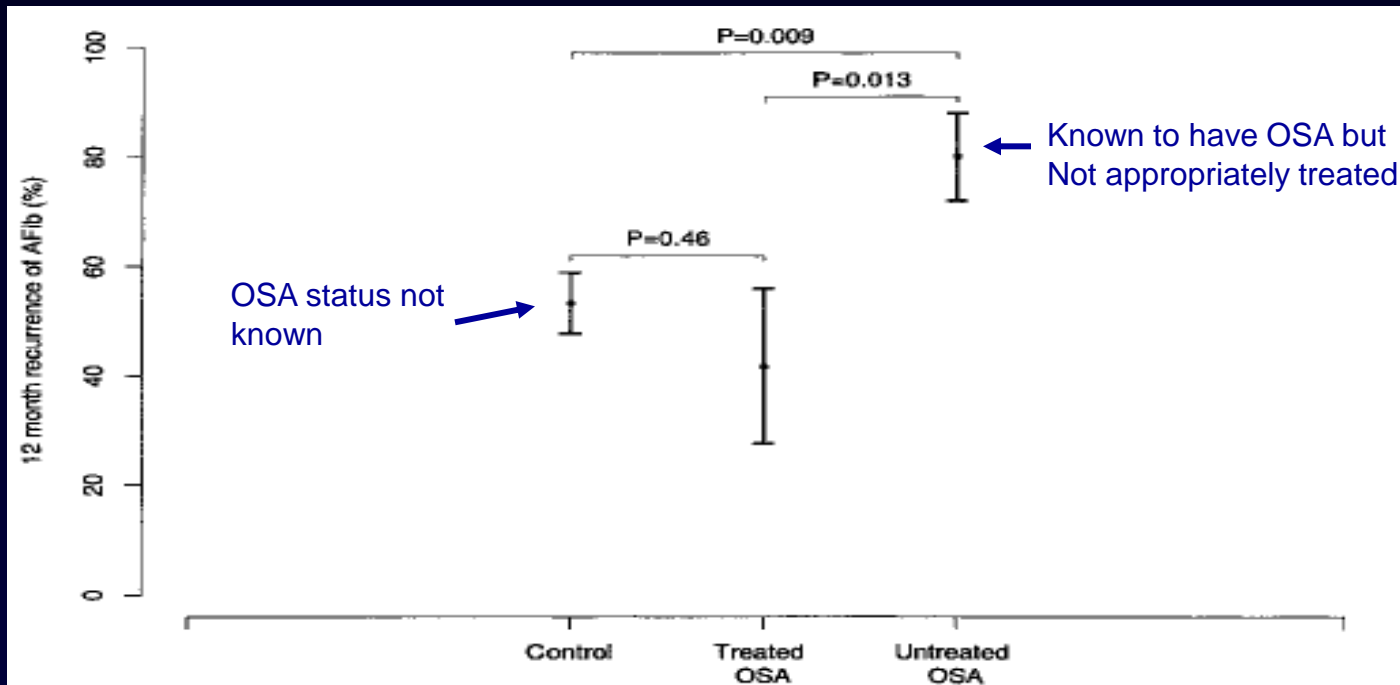


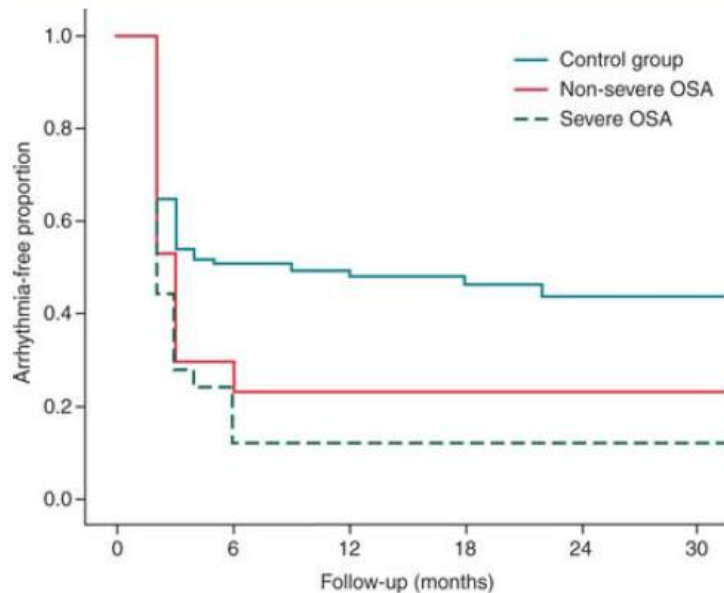
Figure 1. Recurrence of AF at 12 months comparing patients who did not have sleep studies (controls) with treated OSA patients and with untreated (including noncompliant) OSA patients (mean \pm SD).

Kanagala et al. OSA and the Recurrence of Afib. Circulation 2003

Low efficacy of atrial fibrillation ablation in severe obstructive sleep apnoea patients

Maria Matiello^{1†}, Mercé Nadal^{1†}, David Tamborero¹, Antonio Berruezo¹, Josep Montserrat^{1,2}, Cristina Embid^{1,2}, Jose Rios³, Julián Villacastín⁴, Josep Brugada¹, and Lluís Mont^{1*}

Europace 2010;12:1084-1089



Patients at risk	0	6	12	18	24
Low risk OSA	132	56	32	23	15
Non-severe OSA	17	11	8	5	3
Severe OSA	25	5	1	1	1

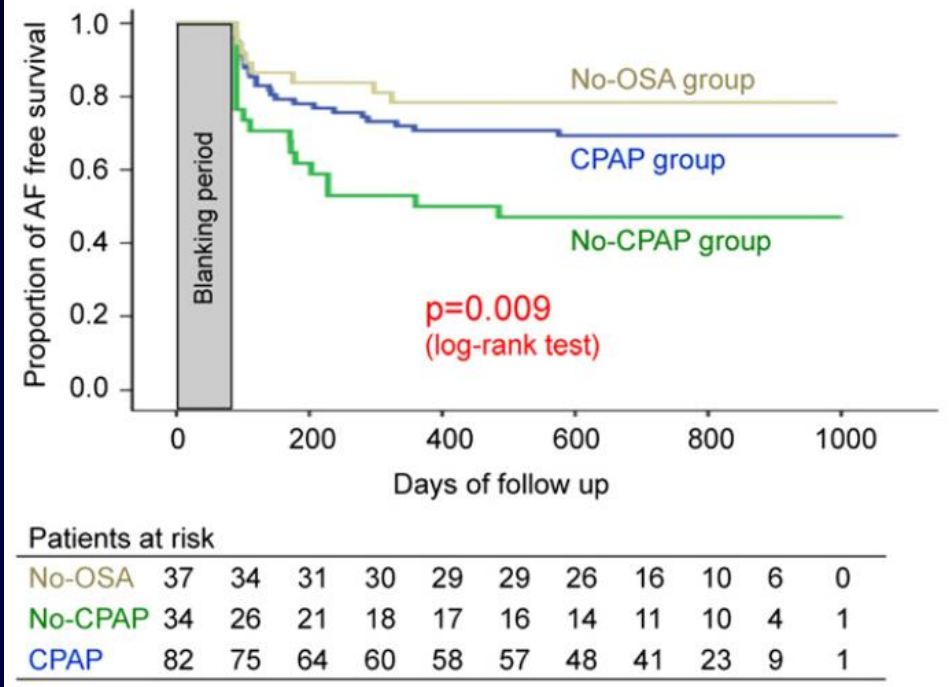
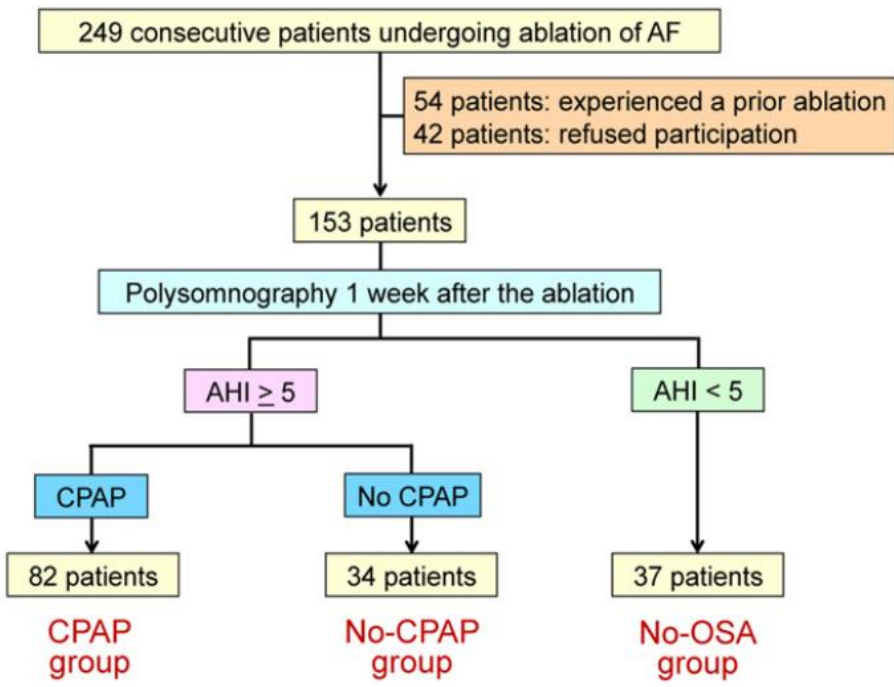
Table 3 Final model of Cox's regression model for arrhythmia recurrence

	HR (95% CI)	P-value
Left atrial diameter	1.046 (1.005–1.089)	0.029
OSA group		
Low risk for OSA	1 (—)	—
Non-severe OSA	1.574 (0.826–3.000)	0.168
Severe OSA	1.870 (1.106–3.161)	0.019

OSA, obstructive sleep apnoea.

Concomitant obstructive sleep apnea increases the recurrence of atrial fibrillation following radiofrequency catheter ablation of atrial fibrillation: Clinical impact of continuous positive airway pressure therapy

Naruse Y et al Heart Rhythm 2013;0:1-7



**Sleep apnea &
Atrial fibrillation ablation
prognosis
in Yonsei Cardiovascular
center**

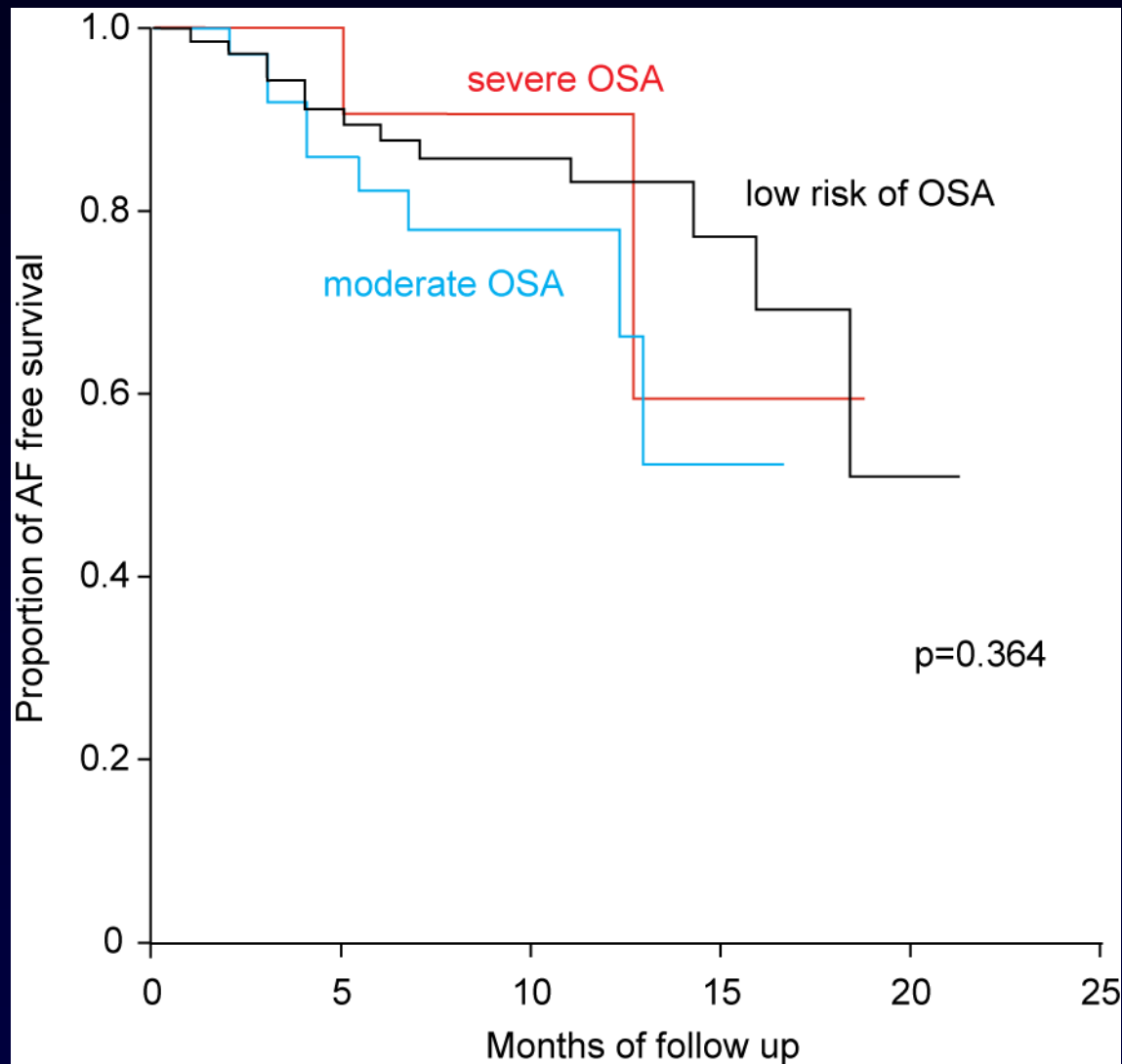
Baseline characteristics

	Low risk for OSA (AHI<10)	Moderate OSA (10<AHI<30)	Severe OSA (AHI≥30)	P value
Patients	80	47	16	
Type of AF				0.198
Paroxysmal AF (%)	44 (55%)	24 (51.1%)	13 (81.2%)	
Persistent AF (%)	36 (45%)	23 (48.9%)	3 (18.8%)	
Age (years)	57.7±10.2	60±9.1	61.4±8.4	0.25
Male sex (%)	51 (63.7%)	43 (91.5%)	13 (81.3%)	0.006
LA diameter (mm)	41.7±6	43.5±5.6	40.5±5.8	0.121
LVEDD (mm)	49.1±4.4	49.9±4.2	48.7±4.5	0.536
LVESD (mm)	32.5±4.4	33±6.1	32.3±3.8	0.829
LV mass (g)	162.6±43.4	169.8±37.1	164.2±42.3	0.644
LV ejection fraction (%)	64.4±7.2	63.1±6.5	65.6±6.9	0.382
Body mass index (kg/m ²)	25±3	25.1±2.5	25.5±2.9	0.783
Neck Circumference (cm)	37.2±3	38.1±2.2	39±2.3	0.03
Hypertension (%)	35 (43.8%)	27 (57.4%)	10 (62.5%)	0.079
DM (%)	11 (13.8%)	6 (12.8%)	4 (25%)	0.411
Recurrence after 3 months (%)	13 (16.3%)	11 (23.4%)	2 (12.5%)	0.841

Procedural details

	Low risk for OSA (AHI<10)	Moderate OSA (10<AHI<30)	Severe OSA (AHI≥30)	P value
Patients	80	47	16	
Ablation time (min)	91.4±25.1	101.8±29.5	84.8±31.9	0.046
Fluoroscopy time (min)	42.2±13.9	45.9±14.8	38.4±11.8	0.137
Procedural time (min)	193.1±38.8	205±50.9	177.2±43.7	0.076

Kaplan-Meier curves for AF recurrence according to severity of OSA



Predictor of Atrial fibrillation recurrence (>3 months after RFA)

	OR (95% CI)	P value
Early recurrence of AF	3.72 (1.39-9.97)	0.009
Persistent AF	3.32 (1.02-10.82)	0.047
Male	0.6 (0.161-2.26)	0.453
Age	1.05 (0.99-1.11)	0.097
Hypertension	0.92 (0.32-2.65)	0.875
DM	0.57 (0.13-2.58)	0.467
BMI	0.96 (0.8-1.15)	0.624
LA diameter	0.99 (0.9-1.1)	0.837
LV mass	1 (0.99-1.02)	0.729
Low risk of OSA	-	
Moderate risk of OSA	1.07 (0.35-3.33)	0.904
High risk of OSA	0.7 (0.1-5.18)	0.729

Conclusion

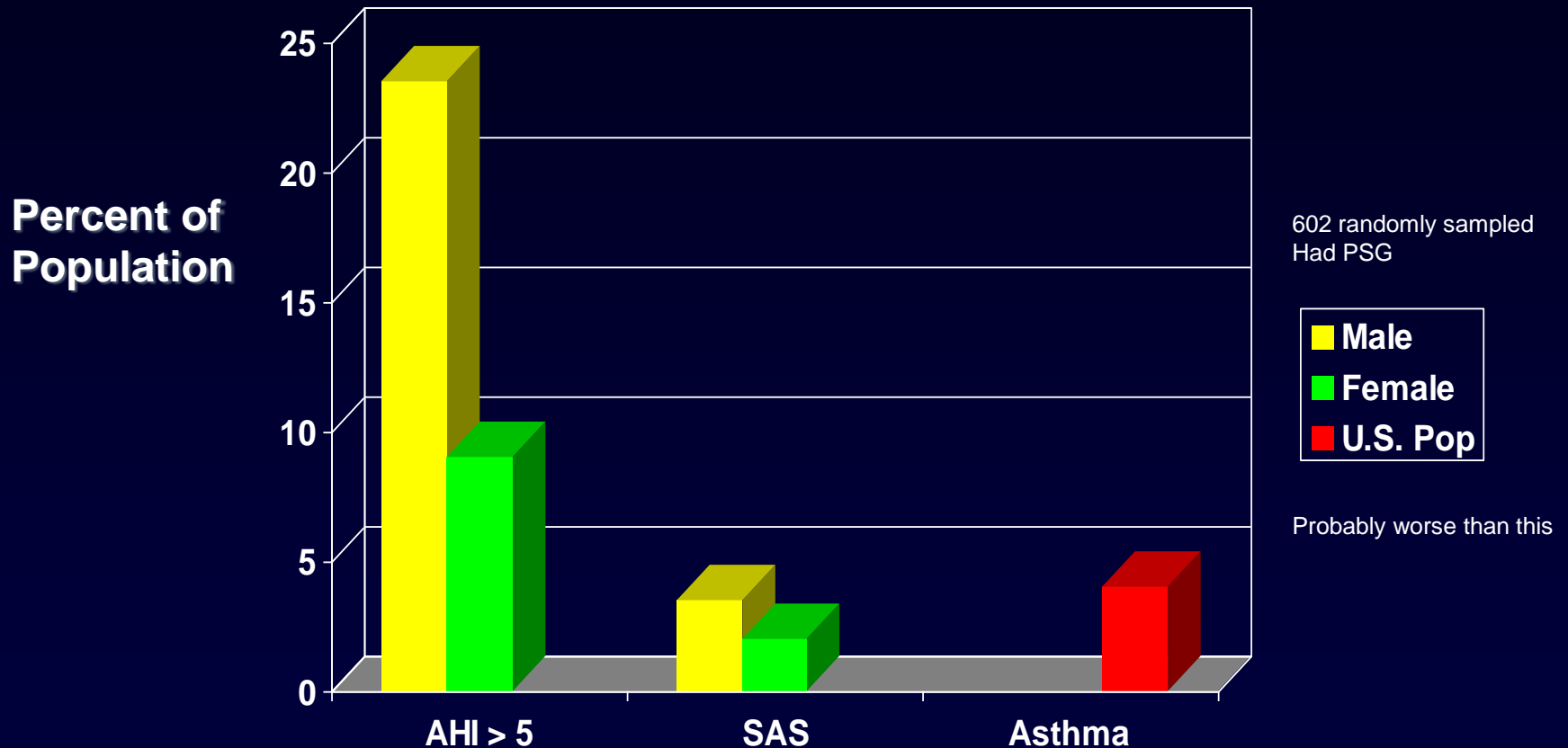
- OSA is highly prevalent in the general population as is an independent risk factor for cardiovascular disease
- OSA is associated with high incidence of nocturnal arrhythmia, including AF
- OSA as an independent risk factor for AF recurrence after catheter ablation → Not so sure at this time!

Thank you



Prevalence of Sleep Apnea

30-60 year olds



Adapted from Young T et al. N Engl J Med 1993;328.

Clinical Guidelines for the Use of Unattended Portable Monitors in the Diagnosis of Obstructive Sleep Apnea in Adult Patients

Portable Monitoring Task Force of the American Academy of Sleep Medicine

Task Force Members: Nancy A. Collop, M.D.¹ (Chair); W. McDowell Anderson, M.D.²; Brian Boehlecke, M.D., M.S.P.H.³; David Claman, M.D.⁴; Rochelle Goldberg, M.D.⁵; Daniel J. Gottlieb, M.D., M.P.H.⁶; David Hudgel, M.D.⁷; Michael Sateia, M.D.⁸; Richard Schwab, M.D.⁹

- At a minimum, PM must record airflow, respiratory effort and blood oxygenation
- Eligible personnel should review all the raw data
- **PM studies may be used for unattended studies in the patient's home**

J Clin Sleep Med 2007;3(7):737-747

Subgroup analysis :

Polysomnography results between OSA patients (AHI>15) with and without CPAP treatment

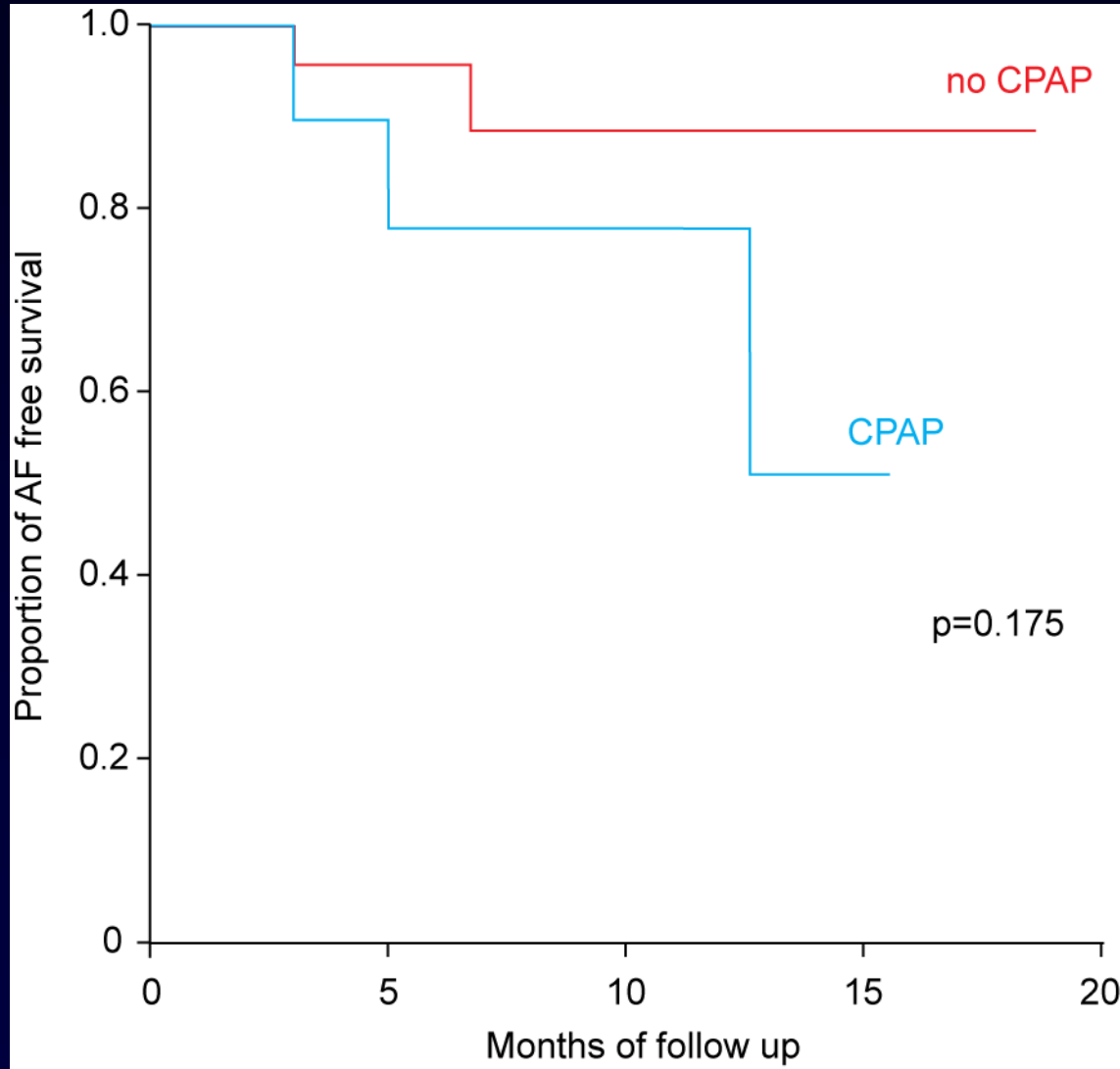
	No CPAP	CPAP	P value
Patients	31	11	
Epworth sleepiness scale	6.7±3.7	4.5±3.1	0.121
Sleep quality index	10.4±6.6	10.8±4.9	0.584
AHI (apneas + hypopneas/hours)	28.9±11.8	29.3±12	0.932
Duration of obstructive apnea (s)	22.6±5.5	25.2±5.4	0.119
Duration of hypopnea (s)	24.8±4.3	27.5±6.6	0.165
Oxygen saturation (%)	94.5±1.2	95±1.7	0.24
Desaturation (number/hours)	26.9±12	24.6±8.1	0.797

Subgroup analysis : Procedural details between OSA patients (AHI>15) with and without CPAP treatment

	No CPAP	CPAP	P value
Patients	31	11	
Ablation time (min)	101.9±26.5	75.1±33.6	0.033
Fluoroscopy time (min)	44±15.5	43.3±12.4	0.966
Procedural time (min)	199±47	180.4±47.2	0.345

Subgroup analysis :

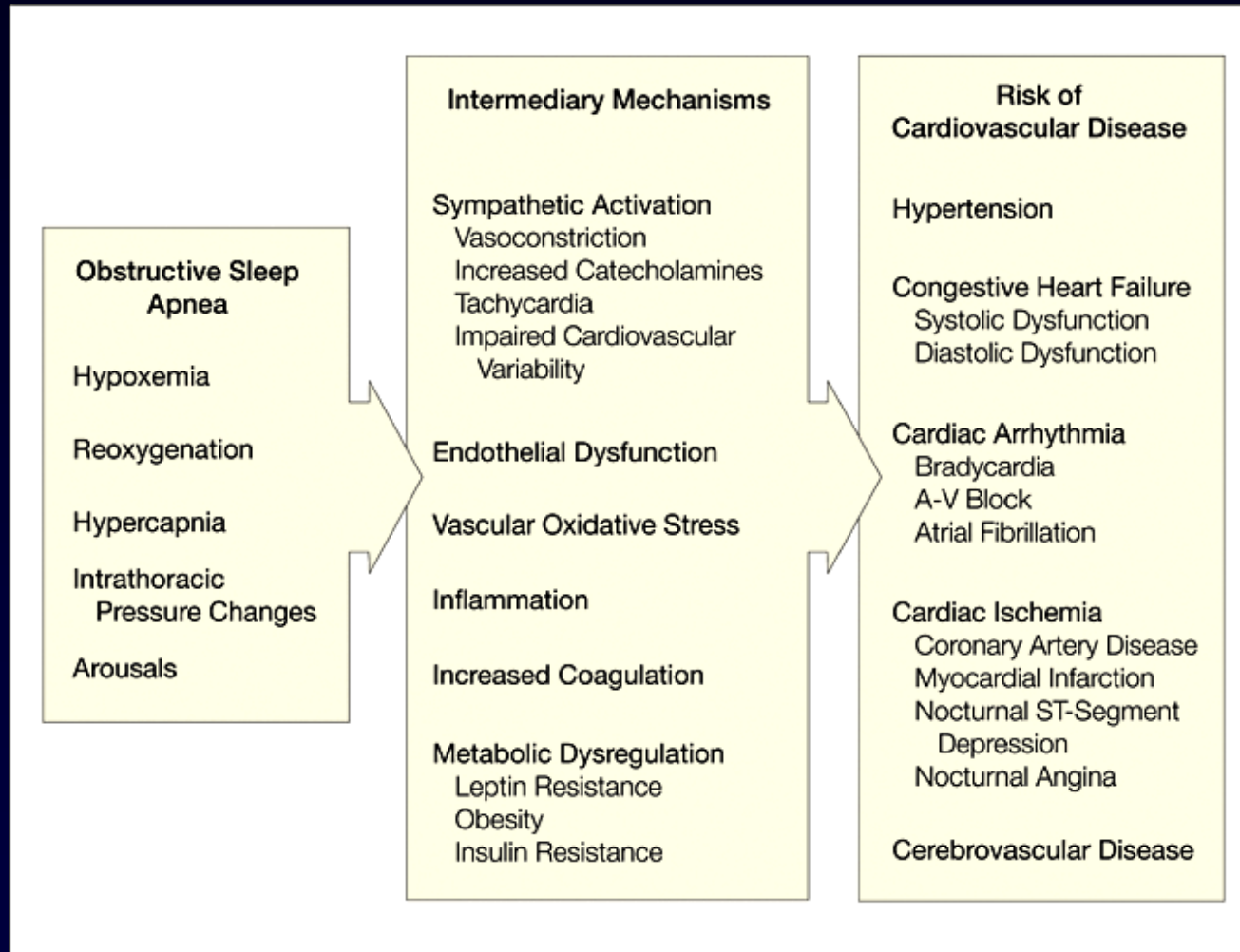
Karplan Meier curves of AF recurrence between OSA patients (AHI>15) with and without CPAP treatment



Pathophysiologic mechanisms during wakefulness

- **Sympathetic Activity and Impaired Cardiovascular Variability**
 - Heightened daytime levels of sympathetic drive
 - Faster heart rates, blunted heart rate variability, and increased blood pressure variability
- **Vascular Dysfunction**
 - **Impaired endothelial function**: elaboration of endogenous vasoactive substances (endothelin, a potent, long-lasting vasoconstrictor), decreased levels of nitric oxide (a powerful vasodilator)
- **Systemic Inflammation**
 - Increased serum levels of C-reactive protein and amyloid A
 - Promoting the release of inflammatory cytokines, such as interleukin (IL)-6 and tumor necrosis factor (TNF)- α

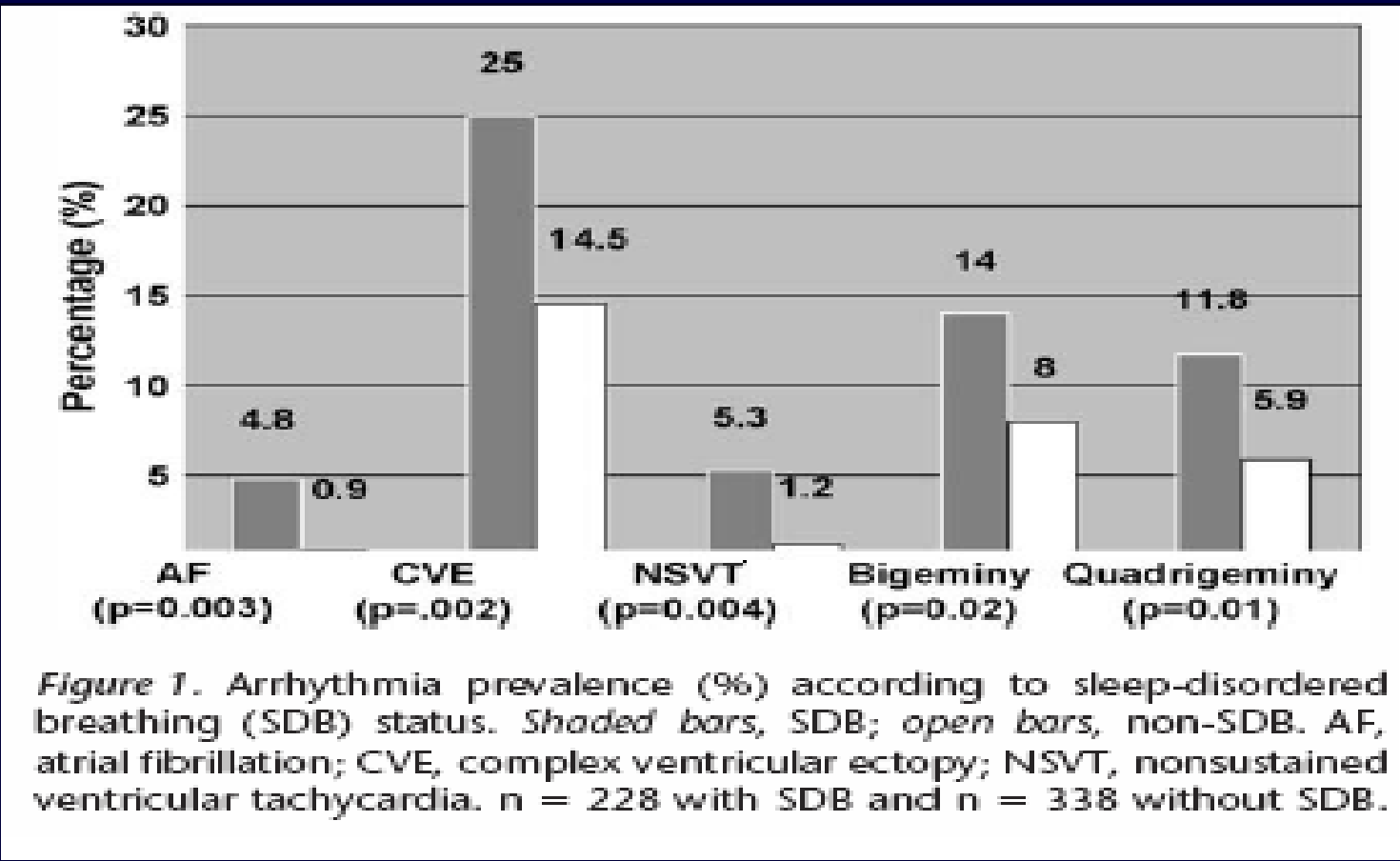
Mechanisms Contributing to Risk of Cardiovascular Disease



Shamsuzzaman, A. S. M. et al. JAMA 2003;290:1906-1914.

JAMA

Cardiovascular Consequences of Sleep Apnea **Cardiac Arrhythmias**



PSG '95-'98 then repeated '01-'02. Followed severe (only) untreated-could not be on CPAP- OSA\CSA ≥ 40yo (>30RDI) for 4 years and controlled for (matched the groups for) race, sex, age, ethnicity, BMI. Not for CAD, CABG, Chol, PTCA, HTN

Mehra, R et al. Nocturnal Arrhythmias with SDB. The SHHS. Am J Respir Crit Care Med Vol 173. pp 910-916, 2006

Polysomnography results

	Low risk for OSA (AHI<10)	Moderate OSA (10<AHI<30)	Severe OSA (AHI≥30)	P value
Patients	80	47	16	
Epworth sleepiness scale	6.4±4	6.9±4.1	6±3.4	0.723
Sleep quality index	9.8±5.3	10.1±6	11.5±6.4	0.561
<u>AHI (apneas + hypopneas/hours)</u>	<u>3.6±3.1</u>	<u>17.2±5.6</u>	<u>41.2±9.7</u>	<u><0.001</u>
Duration of obstructive apnea (s)	11.2±9.7	20.2±6.6	24.9±6.4	<0.001
Duration of hypopnea (s)	19.9±7	24.4±5.4	24.6±3.8	<0.001
Oxygen saturation (%)	95.5±1.3	94.9±1.4	94.4±1.1	0.001
Desaturation (number/hours)	3.5±3.2	15.6±6.6	36.9±9.9	<0.001