Systemic manifestations of Sleep Apnea

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Introduction

- Growing epidemic of obesity in an aging population.
- Obstructive sleep apnea (OSA) is increasingly encountered in clinical practice.
- Various systemic manifestations of sleep apnoea have increasingly been recognised.
- Cardiovascular
- Metabolic
- Neurocognitive

Sleep apnea & Cardiovascular disease

- Acute cardiopulmonary stressors consequent to repetitive upper airway collapse.

- Ample biologic plausibility that OSA imparts increased cardiovascular risk, independent of comorbid disease.

- Observational studies have suggested strong associations with multiple disorders, such as systemic hypertension, heart failure, cardiac arrhythmias, and pulmonary hypertension.

- ***Effects are cumulative over time***.

Sleep Apnea & Cardiovascular pathophysiology

- ***Mechanisms***

- **Acute cardiovascular (CV) stressors result from repetitive upper airway closure**

- Hypoxemia

- Reoxygenation

- Swings in intrathoracic pressure

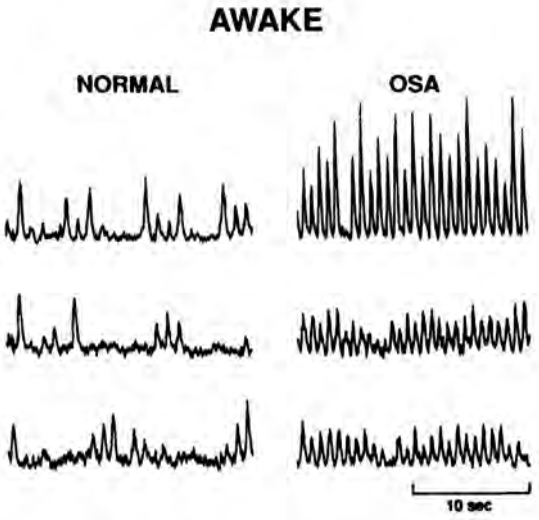
- Central nervous system (CNS) arousals

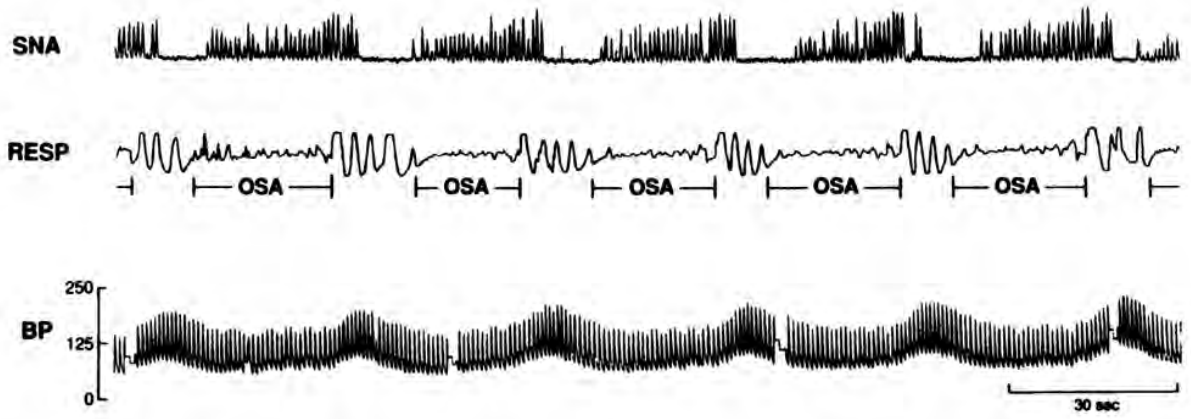
- **Daytime abnormalities in sympathetic nervous system function and heart rate variability**

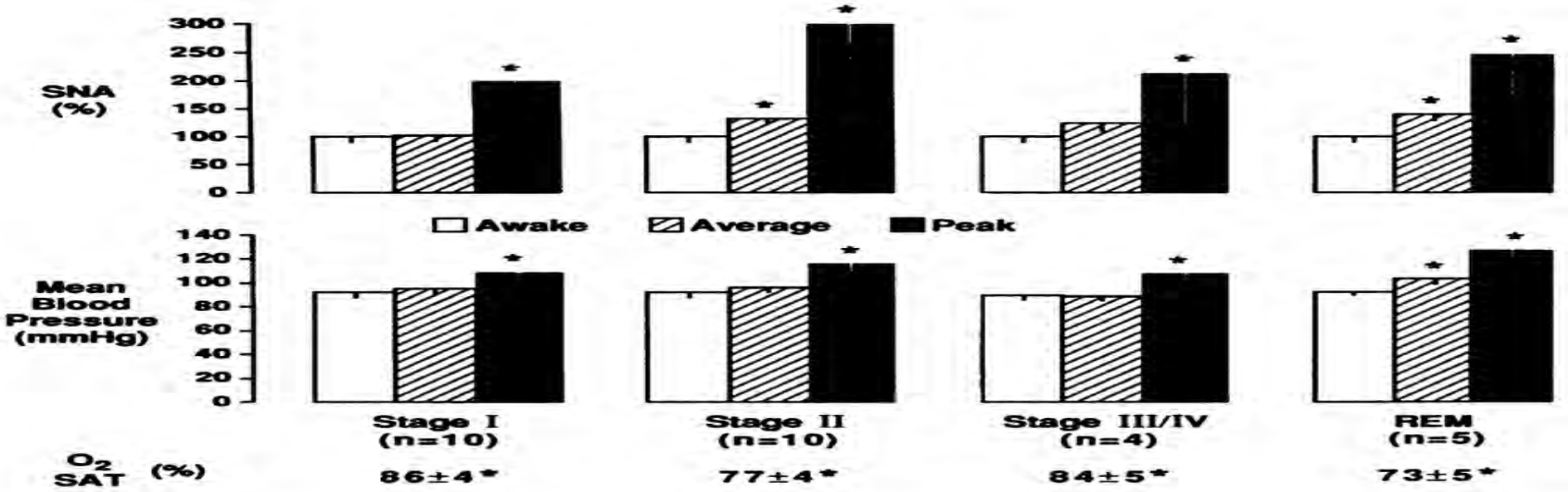
Sympathetic Neural Mechanisms in Obstructive Sleep Apnea

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

- BP, HR, sympathetic nerve activity (SNA), and PSG recorded during wakefulness and sleep in 10 patients with OSA.
- Also obtained after treatment with CPAP in 4 patients.
- Awake SNA also measured in 10 age- and sex matched control subjects and in 5 obese subjects without a history of OSA.







- Peak sympathetic activity (measured over the last 10 s of each apneic event) increased during stage II sleep and during REM sleep (both $P < 0.001$).

- CPAP decreased SNA and BP during sleep ($P < 0.03$).

J. Clin. Invest. 1995. 96:1897-1904

Hypoxemia

- Stimulation of peripheral arterial chemoreceptors.
- Increased sympathetic efferent traffic during hypoxemic stimulation.
- Demonstrated by direct peripheral intraneural electrode recordings.
- OSA - Exaggerated chemoreflex response to hypoxemic stimulation
- Resulting in acute peripheral vasoconstriction and consequent acute increases in arterial blood pressure (BP).

Somers V et al. J Clin Invest 1991;87:1953–1957.
Valbo AB et al.Physiol Rev 1979;59:919–957.

Reoxygenation

- Promote oxidative stress through formation of reactive oxygen species.

- A cascade that may be associated with heightened inflammation and mitochondrial dysfunction.

Am J Respir Crit Care Med Vol 162. pp 566–570, 2000

Enhanced Release of Superoxide from Polymorphonuclear Neutrophils in Obstructive Sleep Apnea

Impact of Continuous Positive Airway Pressure Therapy

RICHARD SCHULZ, SIAMAK MAHMOUDI, KATJA HATTAR, ULF SIBELIUS, HORST OLSCHEWSKI, KONSTANTIN MAYER, WERNER SEEGER, and FRIEDRICH GRIMMINGER

Division of Pulmonary and Critical Care Medicine, Department of Internal Medicine, Justus-Liebig-University, Gießen, Germany

OSA - “priming” of neutrophils for enhanced respiratory burst.

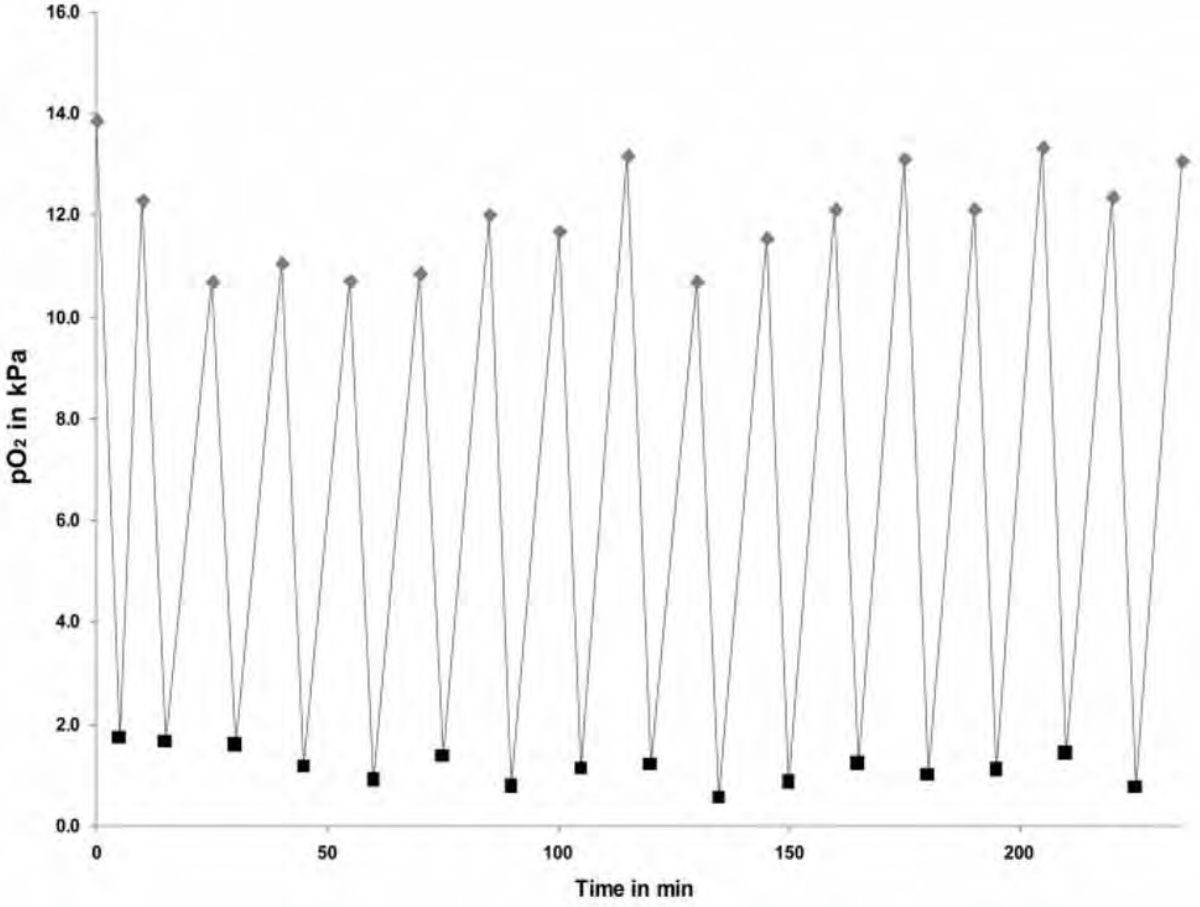
Might have major impact on the development of cardiovascular disorders

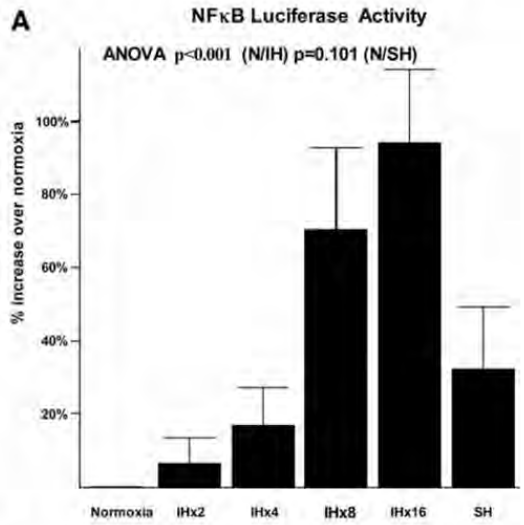
Virtually fully reversed by effective CPAP therapy.

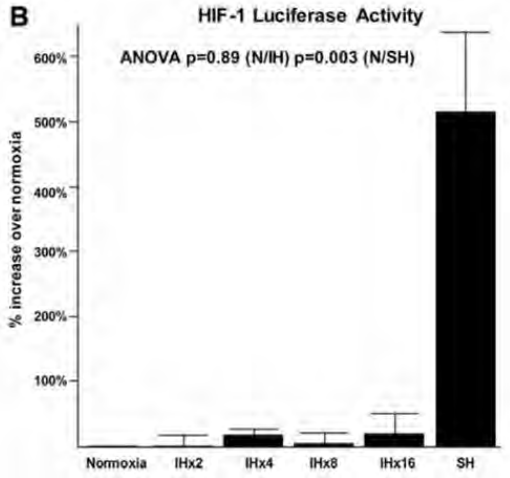
Selective Activation of Inflammatory Pathways by Intermittent Hypoxia in Obstructive Sleep Apnea Syndrome

Silke Ryan, Cormac T. Taylor and Walter T. McNicholas

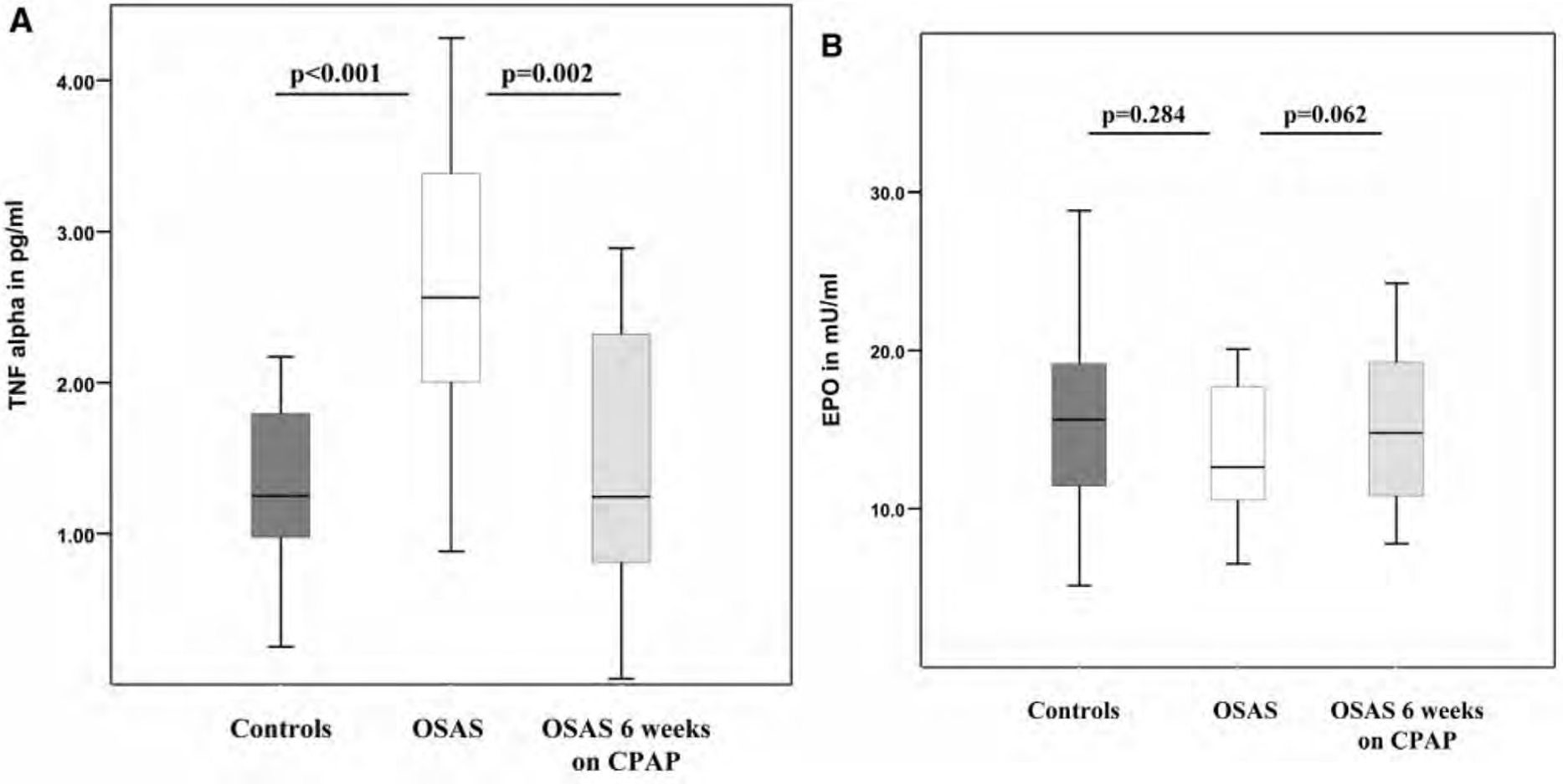
Circulation 2005;112;2660-2667



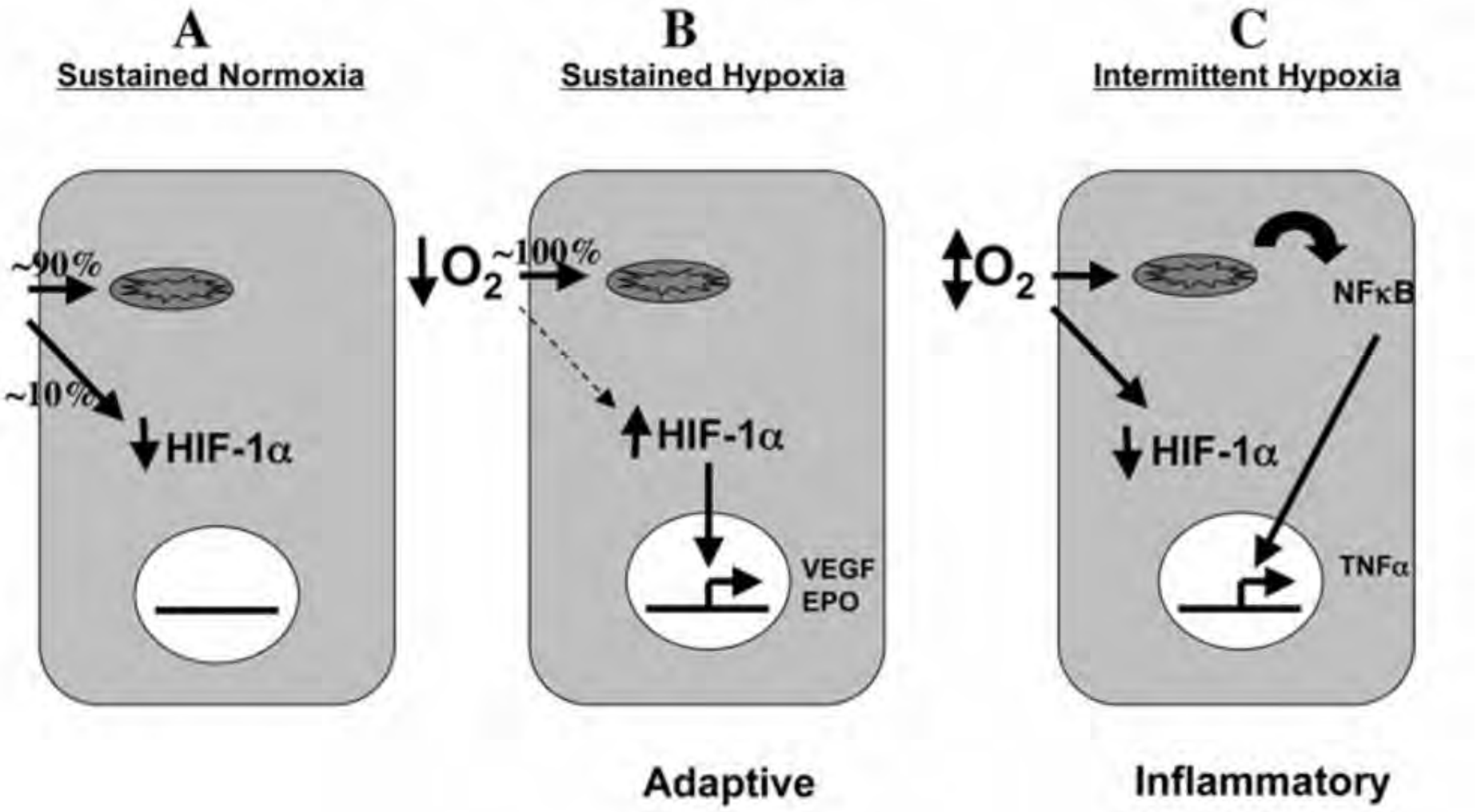




IHR (Intermittent hypoxia reoxygenation)



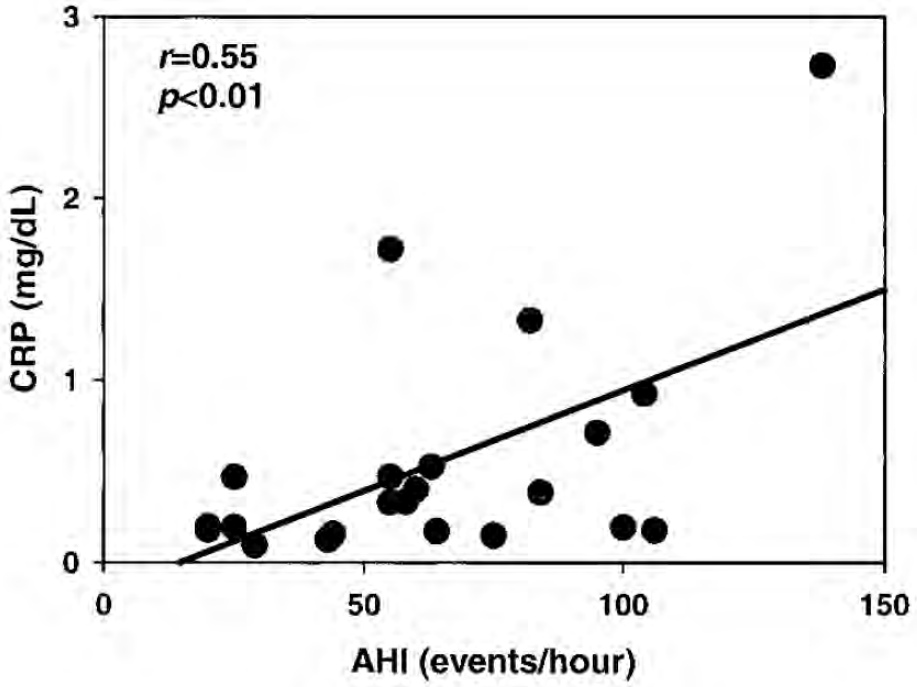
Selective activation of inflammatory over adaptive pathways

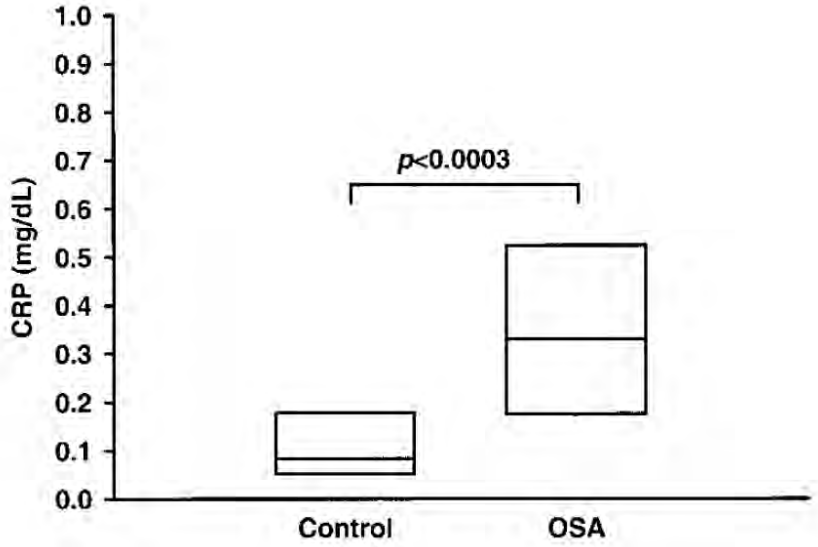

A
Sustained Normoxia
B
Sustained Hypoxia
C
Intermittent Hypoxia
~90%
~10%
HIF-1α
O2
~100%
HIF-1α
VEGF
EPO
O2
NFκB
HIF-1α
TNFα
Adaptive
Inflammatory

Elevated C-Reactive Protein in Patients With Obstructive Sleep Apnea

Abu S.M. Shamsuzzaman, Mikolaj Winnicki, Paola Lanfranchi, Robert Wolk, Tomas Kara, Valentina Accurso and Virend K. Somers

Circulation 2002;105;2462-2464; originally published online May 6, 2002;





In multivariate **analysis, CRP levels were independently associated with OSA severity (F = 6.8, *P = 0.032).***

- **Role of lung inflation**
- Under conditions of uninterrupted ventilation, lung inflation plays a role in homeostasis.

- This sympatholysis is incomplete during the apneas and hypopneas characteristic of OSA.
- **Intrathoracic pressure swings**
- Apneas - Marked reductions in intrathoracic pressure.

- Acute changes in PAP and blood flow and increased afterload.

- Enhanced venous return - Acute leftward septal shift and alterations in transmural cardiac pressures, with impedance of LV filling and increase in myocardial oxygen demand.

Bonsignore MR et al. Eur Respir J 1994;7:786–805.
Shiomi T et al. Chest 1991;100:894–902.

CNS Arousals

- Apneas and hypopneas terminate with CNS arousals - Sleep fragmentation and neurocognitive sequelae in OSA.

- Associated with important effects on CV function - Abrupt increases in sympathetic tone, heart rate, and BP.
- **Intermediary mechanisms**
- Endothelial dysfunction in OSA - Some studies.

- Role of reduced levels of nitric oxide, in the mediation of vascular disease and BP regulation in OSA.

- Serum endothelin – Levels may be higher in patients with OSA compared with control subjects.
- Glucose intolerance, Coagulation abnormalities.

- *Carlson J, Rangemark C, Hedner J. Attenuated endothelium-dependent vascular relaxation in patients with sleep apnoea. J Hypertens 1996; 14:577–584.*

- *Kato M, Roberts-Thomson P, Phillips B. Impairment of endothelium dependent vasodilation of resistance vessels in patients with obstructive sleep apnea. Circulation 2000;102:2607–2610.*

- *Ip MS, Lam B, Chan LY, Zheng L, Tsang KW, Fung PC, Lam WK. Circulating nitric oxide is suppressed in obstructive sleep apnea and is reversed by nasal continuous positive airway pressure. Am J Respir Crit Care Med 2000;162:2166–2171.*

- *Phillips BG, Narkiewicz K, Pesek CA, Haynes WG, Dyken ME, Somers VK. Effects of obstructive sleep apnea on endothelin-1 and blood pressure. J Hypertens 1999;17:61–66.*

Cause and effect – Not so easy although

- Shared risk factors—Obesity and advancing age - Primary determinants of SDB, HTN, HF, and PH.

- Renders the disentanglement of the independent effects of OSA on clinical disease challenging.

- Relative paucity of high-level, evidence-based data, such as interventional treatment trials of OSA in the setting of CV disease.

- Much of the above findings - Case–control studies.

- Some have rendered negative associations between OSA and other biomarkers associated with CV risk, including serum levels of BNP and troponin T.

Plasma Brain Natriuretic Peptide in Obstructive Sleep Apnea

Anna Svatikova, BA, Abu S. Shamsuzzaman, MBBS, PhD, Robert Wolk, MD, PhD, Bradley G. Phillips, PharmD, Lyle J. Olson, MD, and Virend K. Somers, MD, PhD

Am J Cardiol 2004;94:529–532.

Cardiac Troponin T in Obstructive Sleep Apnea

Apoor S. Gami, Anna Svatikova, Robert Wolk, Eric J. Olson, Carolyn J. Duenwald, Allan S. Jaffe and Virend K. Somers

Chest 2004;125;2097-2100
DOI 10.1378/chest.125.6.2097

Conclusions: Despite the fact that some patients with OSA may experience nocturnal ischemia, this study shows that patients with severe OSA and coexisting CAD do not have nightly episodes of myocardial injury detectable by the current-generation cardiac troponin T assay.

(CHEST 2004; 125:2097–2100)

Sleep apnea & Systemic Hypertension

- Normal individuals – Sleep - Reduced BP compared with wakefulness – ‘‘dipping’’ phenomenon.
- Systolic and diastolic BP may ↓ 10–15%.
- Sleep apnea - Blunts the dipping - Heightened cardiovascular risk.

- Observational studies - Hypertension and OSA often coexist and that subjects with OSA tend to have higher BPs than matched controls.

- Apnea - Acute peripheral vasoconstriction - ↑ in BP during sleep.

- Evidence mounting to support a probable causative role for OSA in diurnal hypertension as well

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.

TABLE 3. ADJUSTED ODDS RATIOS FOR HYPERTENSION AT A FOLLOW-UP SLEEP STUDY, ACCORDING TO THE APNEA–HYPOPNEA INDEX AT BASE LINE.*

BASE-LINE APNEA–HYPOPNEA INDEX	ODDS RATIO, ADJUSTED FOR BASE-LINE HYPERTENSION STATUS	ODDS RATIO, ADJUSTED FOR BASE-LINE HYPERTENSION STATUS AND NONMODIFIABLE RISK FACTORS (AGE AND SEX)	ODDS RATIO, ADJUSTED FOR BASE-LINE HYPERTENSION STATUS, NONMODIFIABLE RISK FACTORS, AND HABITUS (BMI AND WAIST AND NECK CIRCUMFERENCE)	ODDS RATIO, ADJUSTED FOR BASE-LINE HYPERTENSION STATUS, NONMODIFIABLE RISK FACTORS, HABITUS, AND WEEKLY ALCOHOL AND CIGARETTE USE
	odds ratio (95% confidence interval)			
0 events/hr†	1.0	1.0	1.0	1.0
0.1–4.9 events/hr	1.66 (1.35–2.03)	1.65 (1.33–2.04)	1.42 (1.14–1.78)	1.42 (1.13–1.78)
5.0–14.9 events/hr	2.74 (1.82–4.12)	2.71 (1.78–4.14)	2.03 (1.29–3.19)	2.03 (1.29–3.17)
≥15.0 events/hr	4.54 (2.46–8.36)	4.47 (2.37–8.43)	2.89 (1.47–5.69)	2.89 (1.46–5.64)
P for trend‡	<0.001	<0.001	0.002	0.002

N Engl J Med 2000;342:1378–1384.

Effects of CPAP

- CPAP - Acutely attenuates sympathetic drive and nocturnal BP in patients with OSA.

- Data regarding effects on daytime BP - Difficult to interpret.

- Observational studies – Uncontrolled/highly select populations - Improvements in daytime BP control with the use of CPAP.

- Randomized, placebo-controlled studies - Variable results - May be the best indicator of the antihypertensive effects of CPAP

Ali N et al. Chest 1992;101:1526–1532.
Dimsdale JE et al.Hypertension 2000;35:144–147.

Ambulatory blood pressure after therapeutic and subtherapeutic nasal continuous positive airway pressure for obstructive sleep apnoea: a randomised parallel trial

Justin C T Pepperell, Sharon Ramdassingh-Dow, Nicky Crosthwaite, Rebecca Mullins, Crispin Jenkinson, John R Stradling, Robert J O Davies

- 118 normotensive men with OSA.
- Randomised parallel trial .
- Therapeutic or subtherapeutic nasal CPAP for 1 month.
- Primary outcome was the change in 24-h mean blood pressure.

Lancet 2002; 359:204–210.

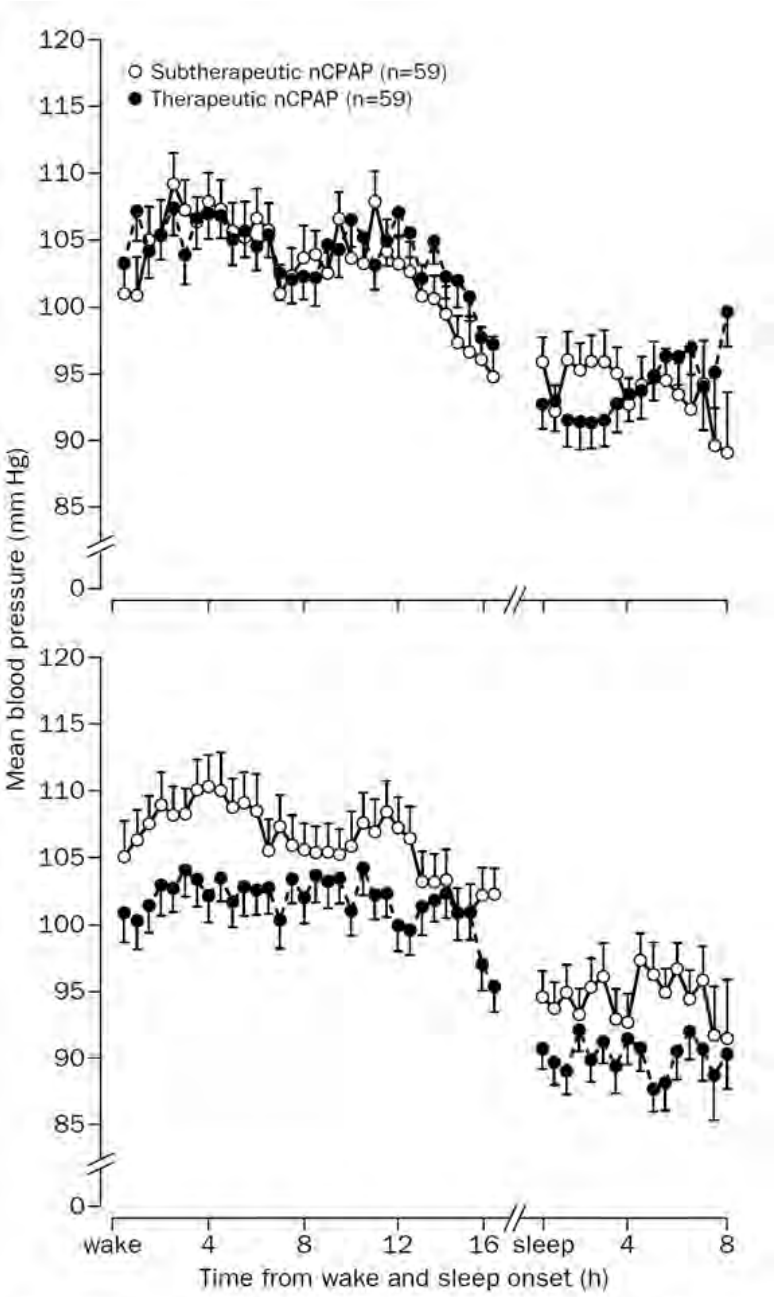


Figure 2: **Mean ambulatory blood pressure profile before (top) and after (bottom) treatment.**

Therapeutic CPAP ↓ MAP by 2·5 mm Hg (SE 0·8)
Subtherapeutic nCPAP ↑ by 0·8 mm Hg (0·7)
(difference –3·3 [95% CI –5·3 to –1·3];p=0·0013, unpaired t test).

Benefit seen in both systolic and diastolic blood pressure

During both sleep and wake.

Benefit was larger in patients with more severe sleep apnoea

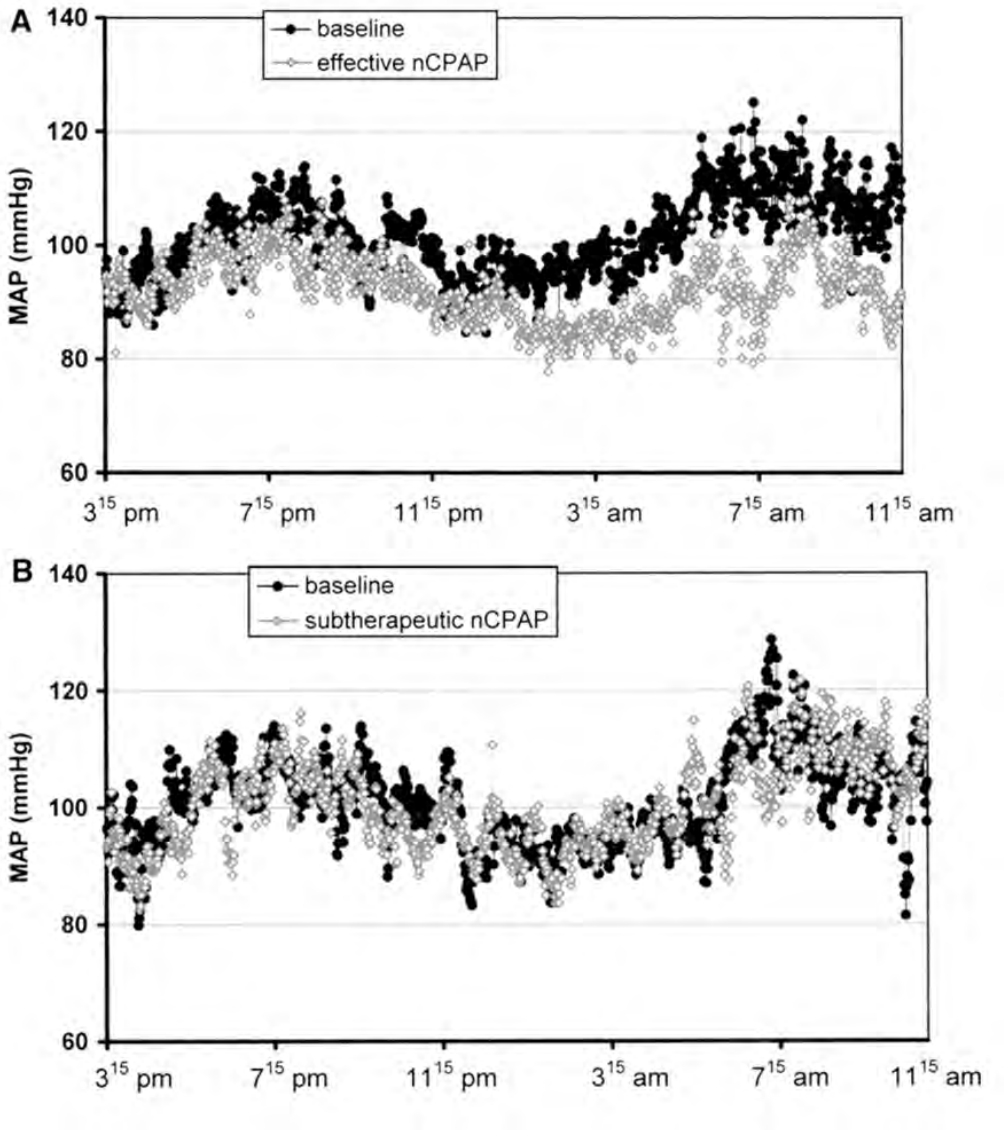
Independent of the baseline blood pressure.

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

Heinrich F. Becker, Andreas Jerrentrup, Thomas Ploch, Ludger Grote, Thomas Penzel, Colin E. Sullivan and J. Hermann Peter

Circulation 2003;107;68-73; originally published online Dec 9, 2002;

- 60 consecutive patients with moderate to severe OSA.
- Randomly assigned to either effective or subtherapeutic nCPAP for 9 weeks on average.
- Nocturnal PSG and continuous NIBP recording for 19 hours was performed before and with treatment.
- Apneas and hypopneas reduced by 95% and 50% in the therapeutic and subtherapeutic groups, respectively.



MAP ↓ by 9.9 ± 11.4 mm Hg with effective nCPAP

No relevant change occurred with subtherapeutic nCPAP (*P-0.01).*

Mean, diastolic, and systolic blood pressures all decreased significantly both at night and during the day.

Predicted to reduce coronary heart disease event risk by 37% and stroke risk by 56%.

The Impact of Continuous Positive Airway Pressure on Blood Pressure in Patients With Obstructive Sleep Apnea Syndrome

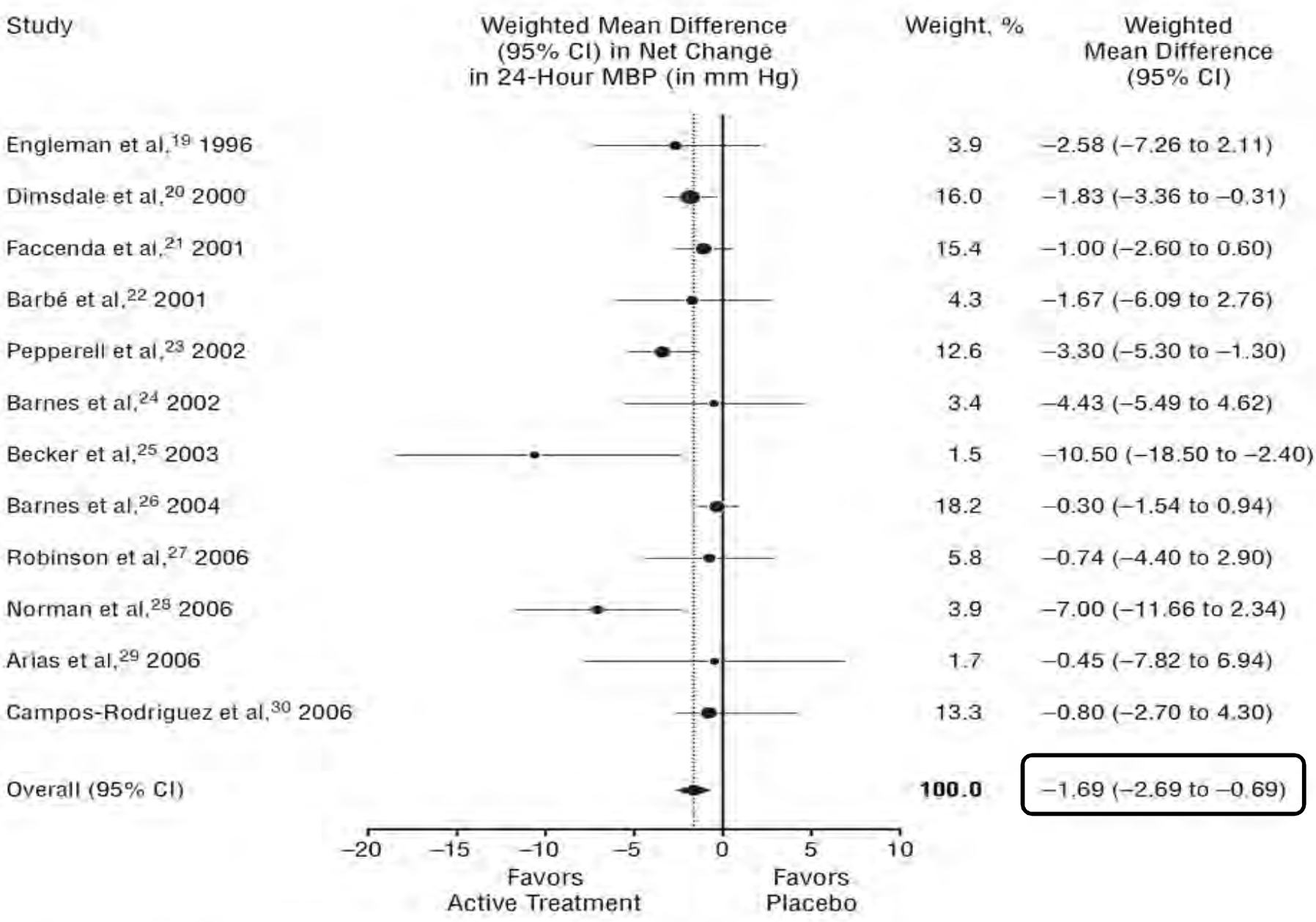
Evidence From a Meta-analysis of Placebo-Controlled Randomized Trials

Patrick Haentjens, MD, PhD; Alain Van Meerhaeghe, MD; Antonio Moscariello, MD; Sonia De Weerdt, MD; Kris Poppe, MD, PhD; Alain Dupont, MD, PhD; Brigitte Velkeniers, MD, PhD

Table 1. Design Characteristics of the Trials Included in the Meta-analyses

Source*	Site	Study Design	Study Duration, wk	Actively Treated Group	Placebo-Treated Group	Effective CPAP Use, h/Night†	Sample Size‡	Dropout Rate, %
Engleman et al,[19] 1996	Edinburgh, Scotland	Crossover	3	CPAP	Sham	4.3	13	29
Dimsdale et al,[20] 2000	San Diego, Calif	Parallel	1	CPAP	Sham	. . .	21/18	0
Faccenda et al,[21] 2001	Edinburgh	Crossover	4	CPAP	Sham	3.3	68	13
Barbé et al,[22] 2001	Multicenter study, Spain	Parallel	6	CPAP	Sham	. . .	29/25	2
Pepperell et al,[23] 2002	Oxford, England	Parallel	4	CPAP	Sham	4.5	48/47	19
Barnes et al,[24] 2002	Heidelberg and Daw Park, Australia	Crossover	8	CPAP	Oral tablet	3.5	28	33
Becker et al,[25] 2003	Marburg, Germany	Parallel	9	CPAP	Sham	5.5	16/16	53
Barnes et al,[26] 2004	Melbourne and Adelaide, Australia	Crossover	12	CPAP	Oral tablet	3.3	89	14
Robinson et al,[27] 2006	Oxford	Crossover	4	CPAP	Sham	4.8	32	9
Norman et al,[28] 2006	San Diego	Parallel	2	CPAP	Sham	6.7	18/15	0
Arias et al,[29] 2006	Madrid, Spain	Crossover	12	CPAP	Sham	6.0	11/10	1
Campos-Rodriguez et al,[30] 2006	Sevilla, Spain	Parallel	4	CPAP	Sham	4.7	68	8

Arch Intern Med. 2007;167:757-765



Tests for Heterogeneity $\chi^2_{11} = 18.53$, $P = .07$; $I^2 = 41\%$
Tests for Overall Effect $z = -3.31$; $P = .001$

- **IS THE EVIDENCE ENOUGH ??**

- High rate of subject dropout in trials.

- Data from these subjects not included in an ITT analysis.

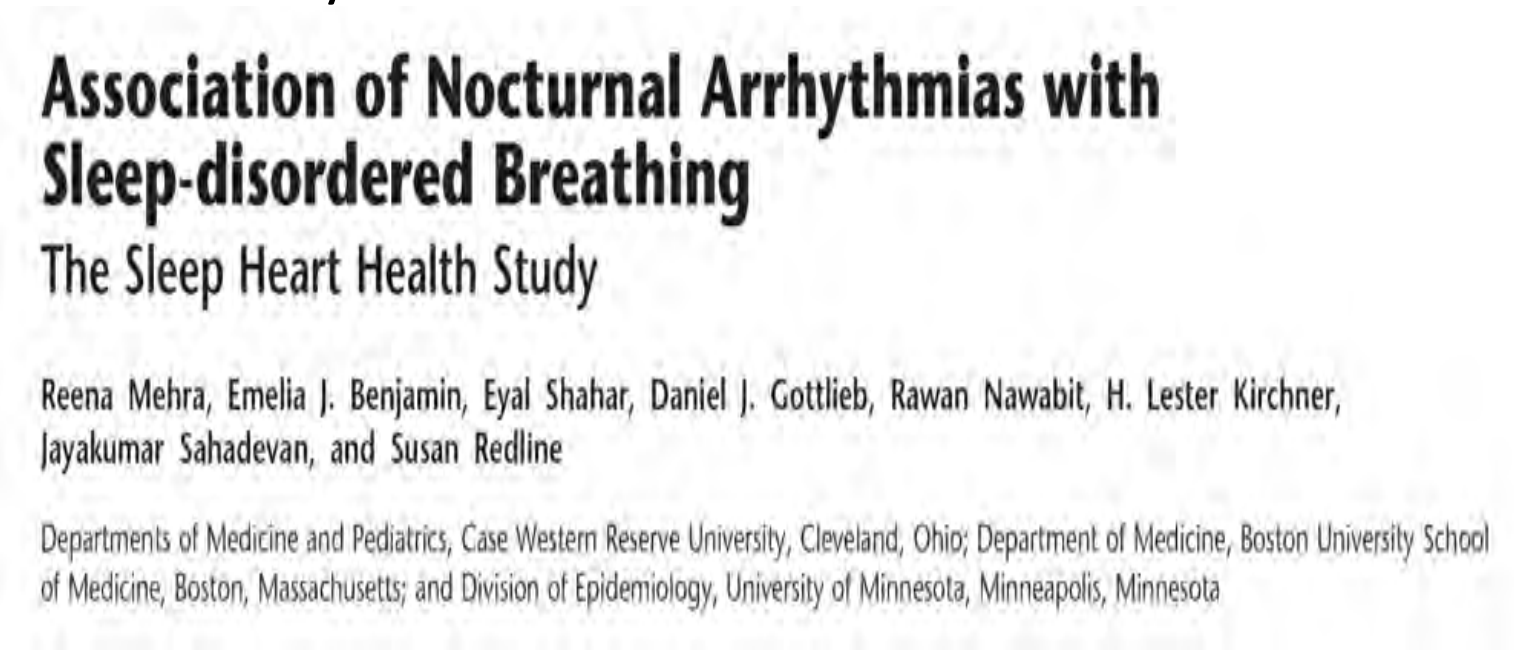
- Majority of subjects were treated with various antihypertensive medications.

- Most of the trials were limited to normotensive individuals.

- Further research needed on the BP-lowering properties of OSA treatment in hypertensive populations.

Cardiac Arrhythmias and Cardiovascular Mortality

- Observational studies - Association between OSA and various nocturnal arrhythmias.



Association of Nocturnal Arrhythmias with Sleep-disordered Breathing

The Sleep Heart Health Study

Reena Mehra, Emelia J. Benjamin, Eyal Shahar, Daniel J. Gottlieb, Rawan Nawabit, H. Lester Kirchner, Jayakumar Sahadevan, and Susan Redline

Departments of Medicine and Pediatrics, Case Western Reserve University, Cleveland, Ohio; Department of Medicine, Boston University School of Medicine, Boston, Massachusetts; and Division of Epidemiology, University of Minnesota, Minneapolis, Minnesota

- Prevalence of arrhythmias compared in two samples of participants .
- Frequency matched on age, sex, race/ethnicity, and BMI.
- 228 subjects with SDB and 338 subjects without SDB.

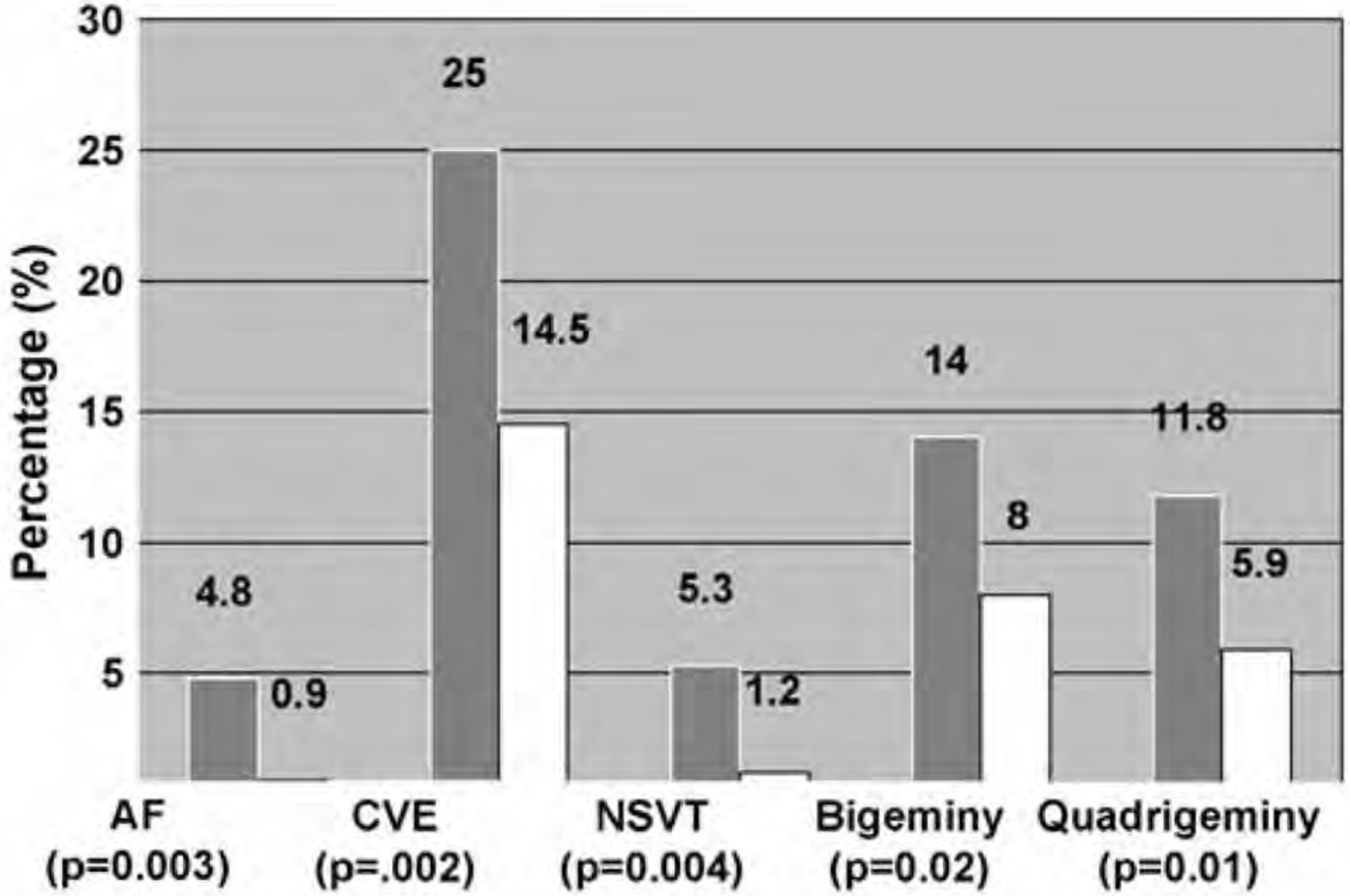

30
25
20
15
10
5
Percentage (%)
4.8
0.9
25
14.5
5.3
1.2
14
8
11.8
5.9
AF
(p=0.003)
CVE
(p=.002)
NSVT
(p=0.004)
Bigeminy
(p=0.02)
Quadrigeminy
(p=0.01)

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.

Individuals with severe SDB have a 2 to 4 fold higher odds of complex arrhythmias than those without even after adjustment for potential confounders.

Similar rates of bradycardias and conduction delays between those with severe OSA and those without significant OSA.

However , Bradyarrhythmias are commonly encountered in OSA

Am J Respir Crit Care Med Vol 173. pp 910–916, 2006

- *Guilleminault C et al. Cardiac arrhythmia and conduction disturbances during sleep in 400 patients with sleep apnea syndrome. Am J Cardiol 1983;52:490–494.*

- *Grimm W et al**. Outcome of** patients with **sleep apnea-associated severe bradyarrhythmias after continuous positive airway pressure therapy**. Am J Cardiol 2000;86:688–692.*

- *Becker H et **al.Reversal of sinus arrest and atrioventricular conduction block** in patients with sleep apnea during **nasal continuous positive airway pressure**. Am J Respir Crit Care Med 1995;151:215–218.*

- Bradyarrythmias may correlate with the severity of disordered breathing.

- Can occur with a structurally normal heart.

- May be attenuated by effective CPAP therapy.

OSA & Atrial fibrillation

- Continuous cardiac monitoring with an atrial defibrillator .
- Nearly 75% of episodes of persistent AF in patients with OSA occurred in the overnight hours (8 P.M.–8 A.M.)

Mitchell ARJ et al. Am Heart J 2003;146:902–907.

- Nocturnal hypoxemia associated with OSA influences the incidence of atrial fibrillation.

Gami AS et al. J Am Coll Cardiol 2007;49:565–571.

Obstructive Sleep Apnea and the Recurrence of Atrial Fibrillation

Ravi Kanagala, MD; Narayana S. Murali, MD; Paul A. Friedman, MD; Naser M. Ammash, MD;
Bernard J. Gersh, MB ChB, DPhil; Karla V. Ballman, PhD;
Abu S.M. Shamsuzzaman, MD, PhD; Virend K. Somers, MD, PhD

Circulation. 2003;107:2589-2594.

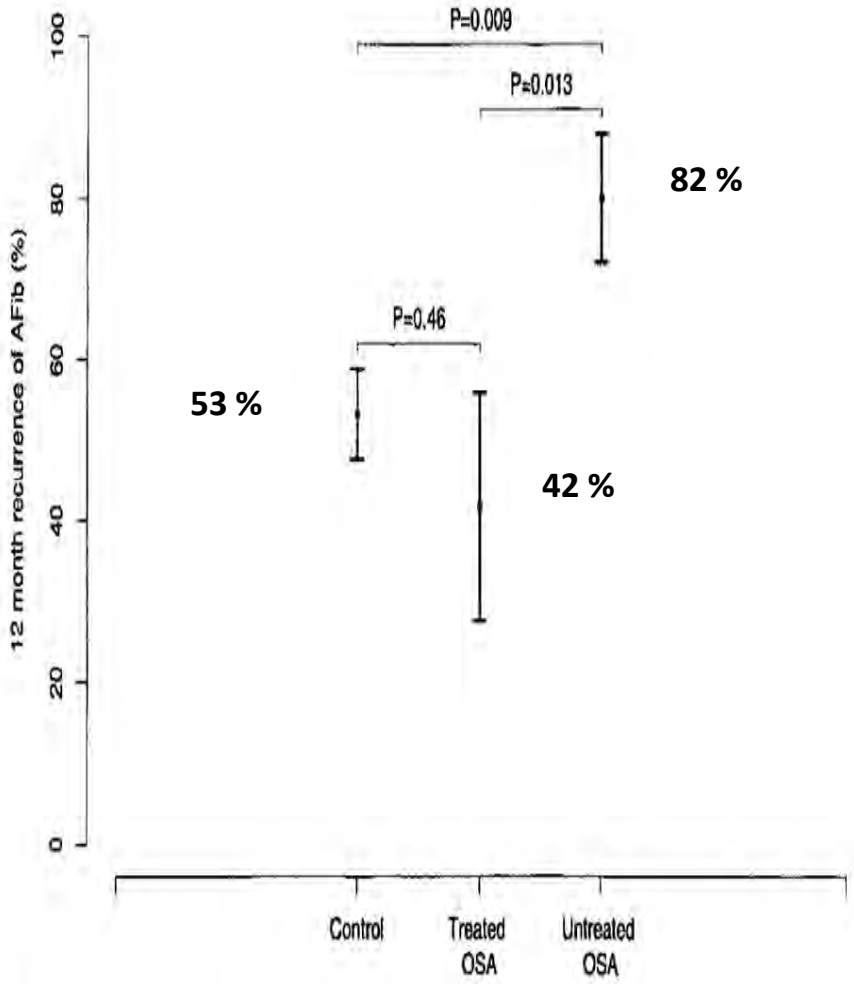


Figure 1. Recurrence of AF at 12 months comparing patients who did not have sleep studies (controls) with treated OSA patients and with untreated (including noncompliant) OSA patients (mean±SD).

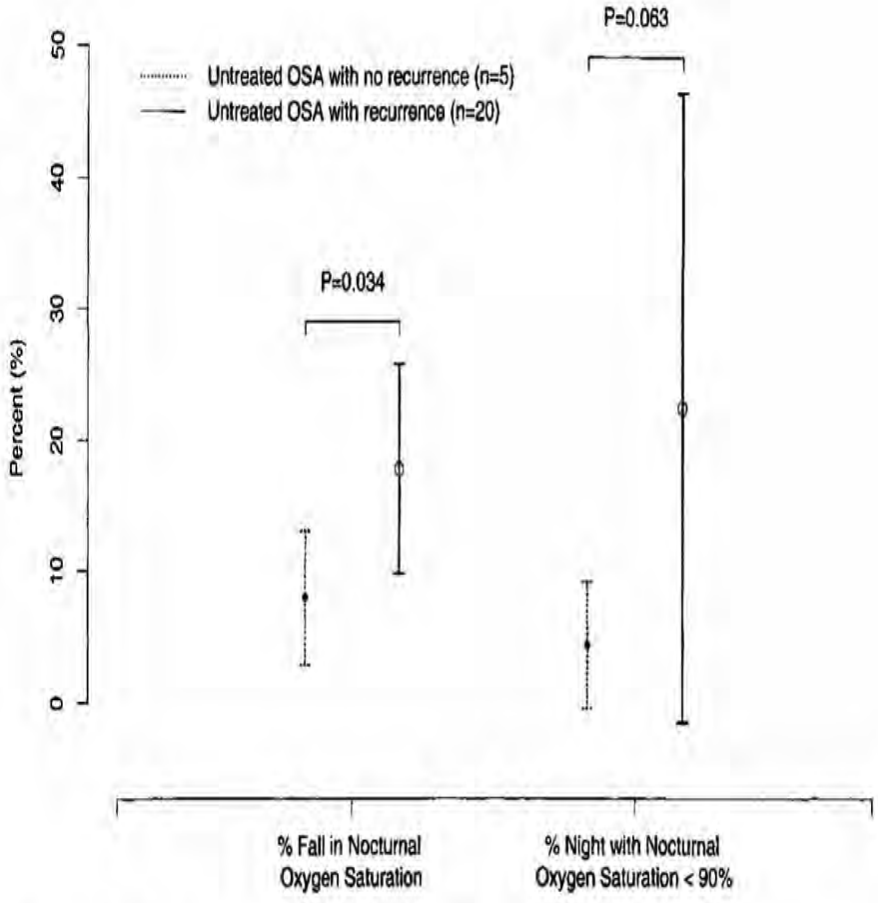


Figure 2. Relationship between oxygen saturation and recurrence of AF in OSA patients. A box-plot comparison of percent fall in nocturnal O_2 saturation (left) and percent of night with O_2 saturations <90% (right) between the untreated OSA patients with recurrence of AF and those without (mean±SD).

- Patients with untreated OSA have a higher recurrence of AF after cardioversion than patients without a polysomnographic diagnosis of sleep apnea.

- Appropriate treatment with CPAP in OSA patients is associated with lower recurrence of AF.

- ***Are the results conclusive enough ??***

- None of these observational data can convincingly implicate OSA as an independent cause of new onset atrial fibrillation.

- Additional longitudinal cohort studies and outcome based interventional trials are needed to characterize the relationship between OSA and atrial arrhythmias.

Ventricular arrythmias & OSA

Ventricular arrhythmias have been reported in patients with OSA

Causative role for OSA in serious arrhythmias or sudden death not been definitively proven.

Risk of sudden death from cardiac causes in the general population
Peaks - 6 a.m. to noon , Nadir - Midnight to 6 a.m.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Day–Night Pattern of Sudden Death in Obstructive Sleep Apnea

Apoor S. Gami, M.D., Daniel E. Howard, B.S., Eric J. Olson, M.D., and Virend K. Somers, M.D., Ph.D.

N Engl J Med 2005;352: 1206–1214.

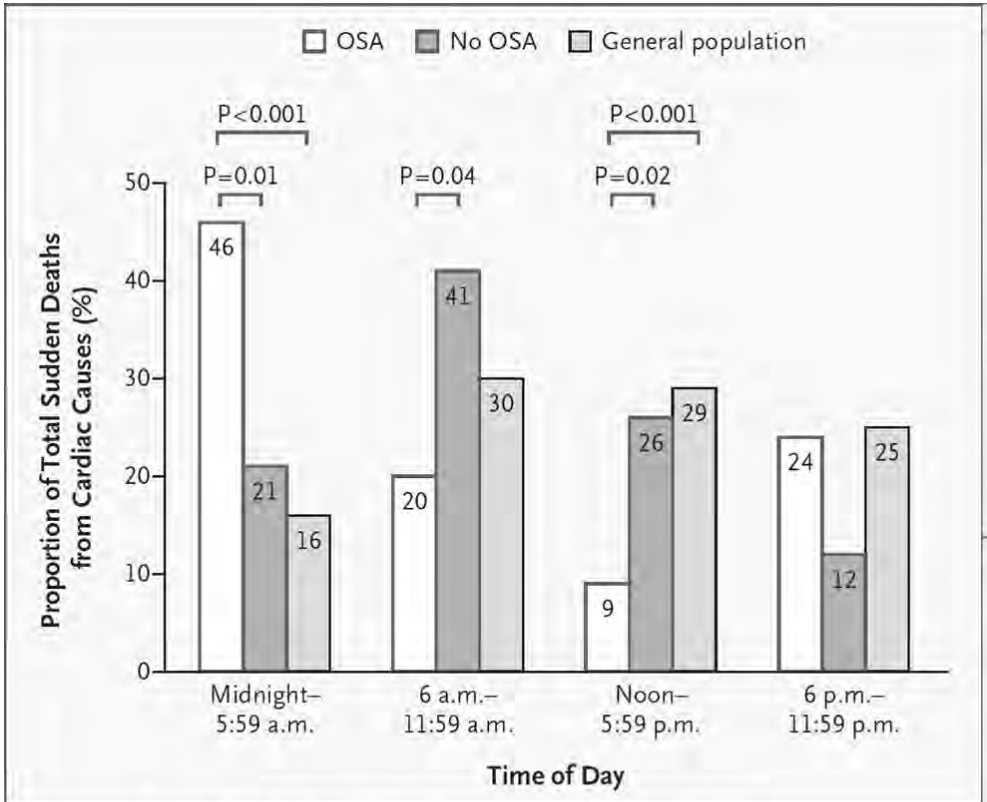


Figure 1. **Day–Night Pattern of Sudden Death from Cardiac Causes in 78 Persons with and 34 Persons without Obstructive Sleep Apnea (OSA) and in the General Population.**

Data for the general population were derived from Cohen et al.[1]

Study suggests that OSA may influence time of sudden cardiac death

Does not clearly demonstrate that OSA heightens the risk of sudden death from cardiac causes.

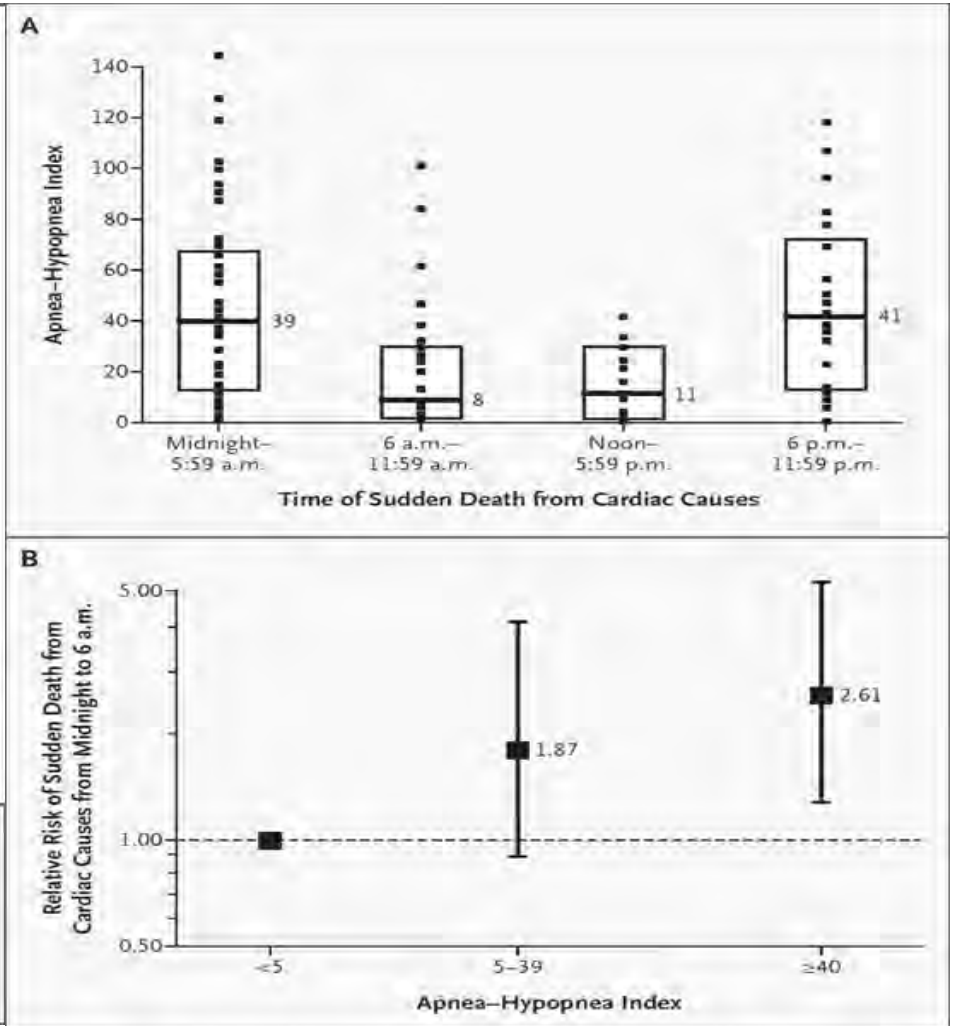


Figure 2. **The Apnea–Hypopnea Index for Persons with Sudden Death from Cardiac Causes during Six-Hour Intervals (Panel A) and the Relative Risk of Sudden Death from Cardiac Causes from Midnight to 6 a.m. for Persons with Mild-to-Moderate Obstructive Sleep Apnea and for Persons with Severe Obstructive Sleep Apnea (Panel B).**

In Panel A, the line within each box represents the median apnea–hypopnea index, and the box represents the interquartile range (25th percentile to 75th percentile). Each black square represents one person. The figure includes data from persons with and from persons without obstructive sleep apnea (P<0.001). In Panel B, the reference group consists of 34 persons without obstructive sleep apnea. There are 39 persons in the group with the apnea–hypopnea index of 5 to 39, and 39 persons in the group with the apnea–hypopnea index of 40 or more. The squares represent the relative risk point estimates, and the I bars the 95 percent confidence intervals.

Long-term cardiovascular outcomes in men with obstructive sleep apnoea-hypopnoea with or without treatment with continuous positive airway pressure: an observational study

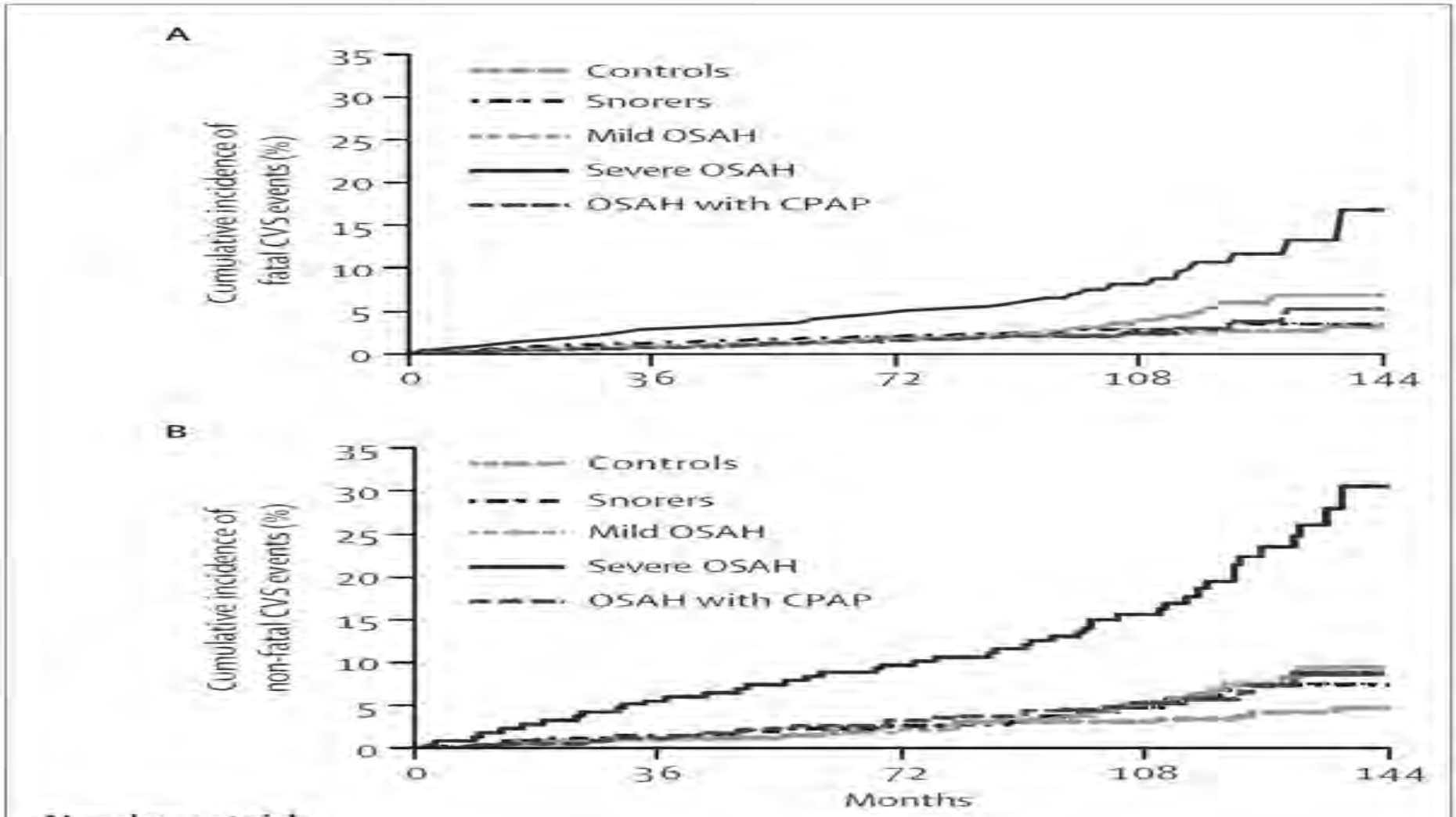
Jose M Marin, Santiago J Carrizo, Eugenio Vicente, Alvar G N Agusti

	Healthy men (n=264)	Simple snorers (n=377)	Untreated mild-moderate OSAH (n=403)	Untreated severe OSAH (n=235)	OSAH treated with CPAP (n=372)
Non-fatal cardiovascular events					
Number of events	12	22	36	50	24
Events per 100 person years	0·45	0·58	0·89	2·13*	0·64
Cardiovascular death					
Number of events	8	13	22	25	13
Events per 100 person years	0·3	0·34	0·55	1·06†	0·35

OSAH=obstructive sleep apnoea-hypopnoea syndrome; CPAP=continuous positive airway pressure. *$p<0.0001$ versus healthy men; †$p=0.0012$.

Table 2: **Incidence of cardiovascular events during the 10-year follow-up in healthy men, snorers, and patients untreated and treated for OSAH**

Lancet 2005; 365: 1046–53



Numbers at risk

Controls	264	262	259	258
Snorers	377	372	361	232
Mild OSAH	403	401	392	264
Severe OSAH	235	229	221	167
OSAH with CPAP	372	364	361	229

Figure 2: **Cumulative percentage of individuals with new fatal (A) and non-fatal (B) cardiovascular events in each of the five groups studied**

	Unadjusted odds ratio (95% CI)	p	Part adjusted odds ratio (95% CI)	p	Fully adjusted odds ratio (95% CI)	p
Age, years	1·09 (1·06–1·11)	<0·0001	1·09 (1·05–1·11)	0·0005	1·09 (1·04–1·12)	0·001
Diagnostic group						
Snoring	1·04 (0·51–1·34)	0·61	1·03 (0·41–1·46)	0·74	1·03 (0·31–1·84)	0·88
Untreated mild-moderate OSAH	1·19 (0·74–1·89)	0·09	1·16 (0·55–2·11)	0·59	1·15 (0·34–2·69)	0·71
Untreated severe OSAH	3·98 (1·74–6·13)	0·003	3·02 (1·44–7·33)	0·015	2·87 (1·17–7·51)	0·025
CPAP	1·06 (0·55–1·91)	0·45	1·05 (0·45–2·09)	0·65	1·05 (0·39–2·21)	0·74
Cardiovascular disease	3·66 (1·98–4·07)	<0·0001			2·54 (1·31–4·99)	0·005

OSAH=obstructive sleep apnoea-hypopnoea, CPAP=continuous positive airway pressure. Variables included in the fully adjusted model were age, diagnostic group, presence of cardiovascular disease, hypertension, diabetes, lipid disorders, smoking status, alcohol use, systolic and diastolic blood pressure, blood glucose, total cholesterol, triglycerides, and current use of antihypertensive, lipid-lowering, and antidiabetic drugs. Variables included in the part adjusted model were those included in the fully adjusted model except hypertension and presence of cardiovascular disease.

Table 3: **Unadjusted, part adjusted, and fully adjusted odds ratio for cardiovascular death associated with clinical variables and diagnosis status, according to the logistic-regression analysis**

Study - Among the most persuasive to argue that OSA has detrimental effects on long-term CV outcomes.

IMPLICATIONS

Biased by potential and difficult-to-measure influences related to treatment noncompliance

Imbalances in some confounding variables at baseline (such as prevalence of hypertension and glucose intolerance).

OSA & Cerebrovascular disease

- Associations reported primarily in cross-sectional and case-control studies.

- Unclear if OSA is a direct contributor to stroke incidence.

- Comorbidities and risk factors are commonly seen in both diseases.

- **INVESTIGATING THE RELATIONSHIP**
- *Mohsenin V et al.Arch Phys Med Rehabil 1995;76:71–76.*
- *Dyken ME et al. Stroke 1996;27:401–407.*
- *Bassetti C et al.Sleep 1999;22:217–223.*

- *Snoring and risk of cardiovascular disease in women.*
  Hu FB et al. J Am Coll Cardiol 2000;35:308–313.
- Prospective study - Self-reported snoring is an independent risk factor for stroke in women.

Association of Sleep-disordered Breathing and the Occurrence of Stroke

Michael Arzt, Terry Young, Laurel Finn, James B. Skatrud, and T. Douglas Bradley

Sleep Research Laboratory of the Toronto Rehabilitation Institute, Center for Sleep Medicine and Circadian Biology, University of Toronto, Toronto, Ontario, Canada; and Departments of Population Health Sciences and Medicine, University of Wisconsin School of Medicine, Madison, Wisconsin

- Hypotheses - SDB is associated with an increased prevalence of stroke and also with an increased incidence of stroke.

- For first hypothesis - Cross-sectional analysis of the Wisconsin Sleep Cohort Study (1475 pts).

- For second hypothesis - Longitudinal analysis of the same cohort (1189 pts).

Am J Respir Crit Care Med Vol 172. pp 1447–1451, 2005

TABLE 2. ADJUSTED ODDS RATIOS FOR THE PREVALENCE OF STROKE FOR SUBJECTS GROUPED BY THE APNEA–HYPOPNEA INDEX

	Model 1A		Model 2A		Model 3A	
AHI (*events/h*)	OR (*95% CI*), adjusted for age, sex, BMI, alcohol, and smoking	p Value	OR (*95% CI*), adjusted for age, sex, BMI, alcohol, smoking, and hypertension	p Value	OR (*95% CI*), adjusted for age, sex, BMI, alcohol, smoking, diabetes, and hypertension	p Value
< 5*	1.0		1.0		1.0	
⩾ 5 to < 20	0.50 (0.11–2.33)	0.38	0.48 (0.10–2.27)	0.36	0.49 (0.10–2.81)	0.36
⩾ 20	4.33 (1.32–14.24)	0.02	3.87 (1.19–12.63)	0.02	3.83 (1.17–12.56)	0.03

Definition of abbreviations: AHI = apnea–hypopnea index; BMI = body mass index; CI = confidence interval; OR = odds ratio.

* This category served as the reference group.

TABLE 3. ADJUSTED ODDS RATIOS FOR THE INCIDENCE OF STROKE FOR SUBJECTS GROUPED BY THE APNEA–HYPOPNEA INDEX

	Model 1B		Model 2B		Model 3B	
AHI (*events/h*)	OR (*95% CI*), unadjusted	p Value	OR (*95% CI*), adjusted for age, sex	p Value	OR (*95% CI*), adjusted for age, sex, and BMI	p Value
< 5*	1.0		1.0		1.0	
⩾ 5 to < 20	0.40 (0.05–3.18)	0.39	0.35 (0.05–2.69)	0.31	0.29 (0.04–2.36)	0.25
⩾ 20	4.31 (1.31–14.15)	0.02	4.48 (1.31–15.33)	0.02	3.08 (0.74–12.81)	0.12

For definition of abbreviations, *see* Table 2.

* This category served as the reference group.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Obstructive Sleep Apnea as a Risk Factor for Stroke and Death

H. Klar Yaggi, M.D., M.P.H., John Concato, M.D., M.P.H., Walter N. Kernan, M.D., Judith H. Lichtman, Ph.D., M.P.H., Lawrence M. Brass, M.D., and Vahid Mohsenin, M.D.

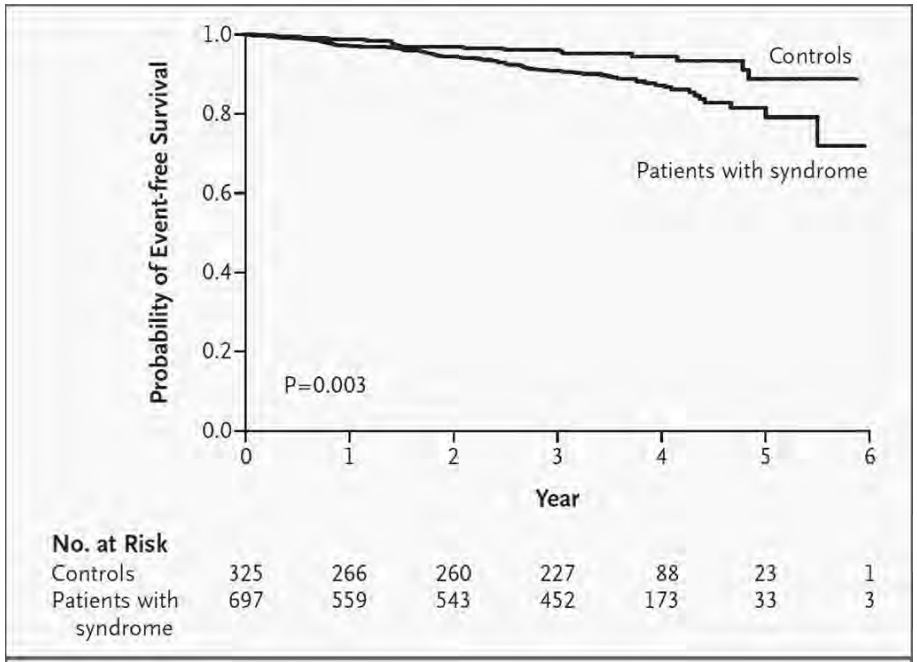


Figure 1. Kaplan–Meier Estimates of the Probability of Event-free Survival among Patients with the Obstructive Sleep Apnea Syndrome and Controls.

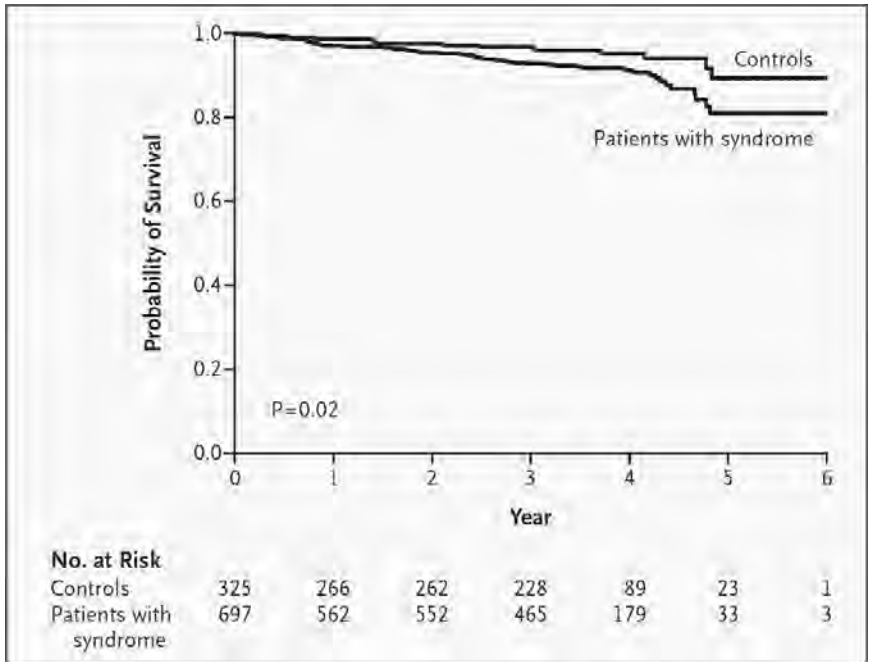


Figure 2. Kaplan–Meier Estimates of the Probability of Overall Survival among Patients with the Obstructive Sleep Apnea Syndrome and Controls.

Longitudinal data (mean follow-up, 3.4 yr)

N Engl J Med 2005;353:2034-41.

More than 1,000 patients with preexisting OSA.

Table 2. **Unadjusted and Adjusted Hazard Ratios for the Risk of Stroke or Death from Any Cause.***

Covariate	Unadjusted Hazard Ratio (95% CI)	Adjusted Hazard Ratio (95% CI)
Age (yr)	1.09 (1.06–1.11)	1.08 (1.06–1.11)
Male sex	0.99 (0.62–1.60)	0.78 (0.48–1.28)
Race		
White (reference group)	1.00	1.00
Black	0.96 (0.39–2.38)	0.98 (0.39–2.46)
Other	0.91 (0.42–1.98)	0.94 (0.43–2.05)
Body-mass index	0.99 (0.97–1.02)	0.99 (0.96–1.02)
Current smoker	1.21 (0.90–1.64)	1.46 (0.78–2.98)
Current consumption of alcohol	1.03 (0.86–1.22)	0.94 (0.75–1.18)
Diabetes mellitus	1.56 (1.02–2.59)	1.31 (0.76–2.26)
Atrial fibrillation	1.56 (0.79–3.12)	0.91 (0.45–1.86)
Hyperlipidemia	1.04 (0.64–1.68)	1.01 (0.61–1.66)
Hypertension	1.48 (0.95–2.28)	1.19 (0.75–1.90)
Obstructive sleep apnea syndrome	2.24 (1.30–3.86)	1.97 (1.12–3.48)

Table 3. **Trend Analysis for the Relationship between Increased Severity of the Obstructive Sleep Apnea Syndrome and the Composite Outcome of Stroke or Death from Any Cause (N=1022).***

Severity of Syndrome	Stroke or Death		Mean Follow-up Period	Hazard Ratio (95% CI)
	No. of Events	No. of Patients		
			yr	
AHI ≤3 (reference score)	13	271	3.08	1.00
AHI 4–12	21	258	3.06	1.75 (0.88–3.49)
AHI 13–36	20	243	3.09	1.74 (0.87–3.51)
AHI >36	34	250	2.78	3.30 (1.74–6.26)

- Not powered to detect potential differences related to treatment of OSA.

- In contrast to findings in the Marin cohort, there did not appear to be treatment effects in more than half of patients who were either treated with CPAP, lost weight, or underwent upper airway surgery.

- OTHER WAY ROUND – Stroke may itself predispose to sleep-disordered breathing. (Case – control studies).

- ***Possible mechanisms ??***

- Disruption of central respiratory control mechanisms.

- Central sleep apnea or brainstem-mediated upper airway reflexes that may cause obstructive apneas or hypopneas.

Time Course of Sleep-related Breathing Disorders in First-Ever Stroke or Transient Ischemic Attack

OLGA PARRA, ADRIÁ ARBOIX, SIRAJ BECHICH, LUIS GARCÍA-EROLES, JOSEP M. MONTSERRAT, JOSEP ANTONI LÓPEZ, EUGENI BALLESTER, JOSEP M. GUERRA, and JUAN JOSÉ SOPEÑA

Servei de Pneumologia and Neurology, Hospital del Sagrat Cor, Barcelona, Spain; and Institut Clinic de Pneumologia i Cirurgia Toràcica (ICPCT), Hospital Clínic, Universitat de Barcelona, Barcelona, Spain

Prospective study - 161 consecutive patients admitted to the stroke unit.

Portable respiratory recording (PRR) study performed within 48–72 h after admission (acute phase), and subsequently after 3 mo (stable phase).

Am J Respir Crit Care Med Vol 161. pp 375–380, 2000

SLEEP-RELATED BREATHING DISORDERS AND STROKE SUBTYPE*

	Transient Ischemic Attack	Ischemic Stroke	Hemorrhagic Stroke	Total
Demographics				
Patients, n	39	112	10	161
Age, yr	69.7 ± 10.1	72.5 ± 8.9	73 ± 10.5	72 ± 9
BMI, kg/m^2	27.3 ± 4.6	26.2 ± 3.7	26.7 ± 2.6	26.6 ± 3.9
Epworth Sleepiness Scale	4.7 ± 3.3	4.9 ± 3.3	4.3 ± 2.1	4.8 ± 3.3
Sleep parameters				
AHI	19.4 ± 16.7	21.5 ± 15.7	25 ± 11.9	21.2 ± 15.7
OAI	5.9 ± 10.2	3.9 ± 7.8	5.4 ± 6.7	4.5 ± 8.4
CAI	3.32 ± 7.9†	5.9 ± 10.1	11.1 ± 15.1†	5.6 ± 10.1
CSB, n (%)	8 (20.5%)	31 (27.7%)	3 (30%)	42 (26.1%)
AHI				
> 10	24 (61.5%)	83 (74.1%)	9 (90%)	116 (72%)
> 30	10 (25.6%)	31 (27.7%)	4 (40%)	45 (28%)
CT_{90}, %	8.2 ± 13.1	8.1 ± 17.8	5.7 ± 7.1	7.8 ± 15.7

TIME COURSE OF SLEEP RESPIRATORY DISTURBANCES: DIFFERENCES BETWEEN THE ACUTE AND STABLE PHASE IN A SUBGROUP OF 86 PATIENTS

Clinical Parameter	Acute Phase	Stable Phase
Age, yr	71.8 ± 9.3	71.8 ± 9.3
BMI, kg/m^2	27.0 ± 4.3	26.8 ± 3.9
ESS	4.8 ± 3.2	4.5 ± 2.8
AHI	22.4 ± 17.3	16.9 ± 13.8†
OAI	4.7 ± 8.6	4.6 ± 7.3
CAI	6.2 ± 10.2	3.3 ± 7.6*
AHI		
> 10	60 (69.6%)	53 (61.6%)
> 30	28 (32.6%)	17 (19.8%)
CSB, n	17	6
CT_{90}, %	8.9 ± 16.4	6.5 ± 16.7

Prevalence of SRBD in patients with first-ever stroke or TIA is higher than expected from the available epidemiological data

No correlation was found between neurological location and the presence or type of SRBD.

Obstructive events seem to be a condition prior to the neurological disease whereas central events and CSB could be its consequence.

Other mechanisms of increased Stroke risk in OSA

- Effects on atherogenesis and blood vessel function.

- Strong association with atrial fibrillation.

- OSA promotes thrombosis.
- Enhanced platelet aggregation and activation.
- Elevated fibrinogen levels .
- Diminished fibrinolytic activity.

- Doppler measurements – Suggest that apneic events are associated with reduced cerebral blood flow
- Can result in cerebral hypoxia.

- CPAP treatment has been shown to reverse some of these findings.
- Impact of treatment - Yaggi and colleagues - May be limited and needs further evaluation.

- Bokinsky G et al. ***Spontaneous platelet activation and aggregation*** during obstructive sleep apnea and its response to therapy with nasal CPAP: a preliminary investigation. Chest 1995;108:625–630. 61.

- Eisensehr I et ***al.Platelet activation***, epinephrine, and blood pressure in obstructive sleep apnea syndrome. Neurology 1998;51:188–195.

- Wessendorf TE et al.***Fibrinogen levels*** and obstructive sleep apnea in ischemic stroke. Am J Respir Crit Care Med 2000;162:2039–2042.

- Rangemark C et al. ***Platelet function and fibrinolytic activity*** in hypertensive and normotensive sleep apnea patients. Sleep 1995;18:188–194.

OSA & Heart Failure

- HF and OSA - closely linked.
- Strong associations with aging and obesity
- Prevalence of OSA – Approx. 40% in patients with HF referred to a clinical sleep laboratory.

Sin DD et al. Am J Respir Crit Care Med 1999;160:1101–1106.

- Framingham study - ↑ BMI - Directly correlated with incident HF.
- Effect may be mediated, at least in part, by OSA.
- Incident AF (associated with OSA) -An important risk factor for HF.
- Cascade of physiological responses to repetitive upper airway closure in OSA may exert deleterious effects on cardiac function, particularly in the already compromised heart.

- **OSA, HF & CPAP – Why so much noise??**

- Despite advances in treatment with drugs, lifestyle modifications, and therapeutic devices - Mortality from HF continues to ↑.

Controlled Trial of Continuous Positive Airway Pressure in Obstructive Sleep Apnea and Heart Failure

Darren R. Mansfield, N. Claire Gollogly, David M. Kaye, Meroula Richardson, Peter Bergin, and Matthew T. Naughton

Departments of Respiratory Medicine and Cardiology, Alfred Hospital, Monash University; and Baker Heart Research Institute, Melbourne, Australia

55 patients with CHF and OSA - Randomized to 3 months of CPAP or control (Optimal med. No placebo) groups.

End points were changes in LVEF , overnight urinary NE excretion, blood pressure, and quality of life.

Am J Respir Crit Care Med Vol 169. pp 361–366, 2004

TABLE 2. ENDPOINT OUTCOME MEASURES

Control Group	(*n* = 21)	CPAP Group (*n* = 19)	p Value*
LVEF, %			
Baseline	33.6 ± 2.6	37.6 ± 2.5	
3 mo	35.1 ± 3.1	42.6 ± 0.3	
Δ	1.5 ± 1.4	5.0 ± 1.0†	0.04
UNE, nmol/mmol creatinine			
Baseline	21.3 ± 1.9	23.5 ± 4.8	
3 mo	22.9 ± 3.9	13.7 ± 2.5	
Δ	1.6 ± 3.7	−9.9 ± 3.6‡	0.036
Mean BP, mm Hg			
Baseline	105 ± 3	99 ± 3	
3 mo	99 ± 3	100 ± 2	
Δ	−6 ± 3	1 ± 3	NS
$\dot{V}O_2$ peak, ml/kg/min			
Baseline	16.4 ± 0.7	20.3 ± 1.2	
3 mo	16.3 ± 0.7	20.3 ± 1.3	
Δ	−0.2 ± 0.5	0 ± 0.8	NS
NYHA class			
Baseline	2.4 ± 0.2	2.2 ± 0.2	
3 mo	2.4 ± 0.2	2.3 ± 0.2	
Δ	0 ± 0	0.1 ± 0.1	NS
Epworth Sleepiness Scale			
Baseline	8.8 ± 0.9	9.5 ± 0.9	
3 mo	9.9 ± 1.0	6.9 ± 1.0	
Δ	1.1 ± 0.8	−3.1 ± 1.4Δ	0.01
BMI, kg/m²			
Baseline	33.3 ± 1.2	33.6 ± 1.0	
3 mo	33.5 ± 1.2	33.9 ± 1.1	
Δ	0.2 ± 0.3	0.3	0.2
AHI, events per hour			
Baseline	26.6 ± 4.5	25.0 ± 4.1	
3 mo	18.2 ± 2.8	2.9 ± 0.8	
Δ	−8.4 ± 3.6	−21.1 ± 3.8†	< 0.001
Minimum Sp_{O_2}, %			
Baseline	77.2 ± 3.9	79.6 ± 2.6	
3 mo	77.2 ± 3.5	91.1 ± 0.9	
Δ	0.0 ± 1.6	11.5 ± 2.7†	0.001

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Cardiovascular Effects of Continuous Positive Airway Pressure in Patients with Heart Failure and Obstructive Sleep Apnea

Yasuyuki Kaneko, M.D., John S. Floras, M.D., D.Phil., Kengo Usui, M.D., Ph.D., Julie Plante, M.D., Ruzena Tkacova, M.D., Ph.D., Toshihiko Kubo, M.D., Ph.D., Shin-ichi Ando, M.D., Ph.D., and T. Douglas Bradley, M.D.

- 24 patients with LVEF $\leq$ 45 % and OSA who were receiving optimal medical treatment for HF underwent PSG.
- On the following morning, their BP, HR and LV dimensions and LVEF were assessed by echocardiography.
- Randomly assigned to receive medical therapy either alone (12 patients) or with the addition of CPAP (12 patients) for 1 month.

N Engl J Med 2005;353:2025-33.

Table 3. **Heart Rate and Blood Pressure.***

Variable	Control Group			Group Receiving Continuous Positive Airway Pressure		
	Base Line	1 Mo	P Value	Base Line	1 Mo	P Value
Heart rate (beats/min)	67±4	67±4	NS	68±3	64±3	0.007†
Systolic blood pressure (mm Hg)	128±7	134±8	NS	126±6	116±5	0.02‡
Diastolic blood pressure (mm Hg)	60±4	58±3	NS	62±4	59±2	NS

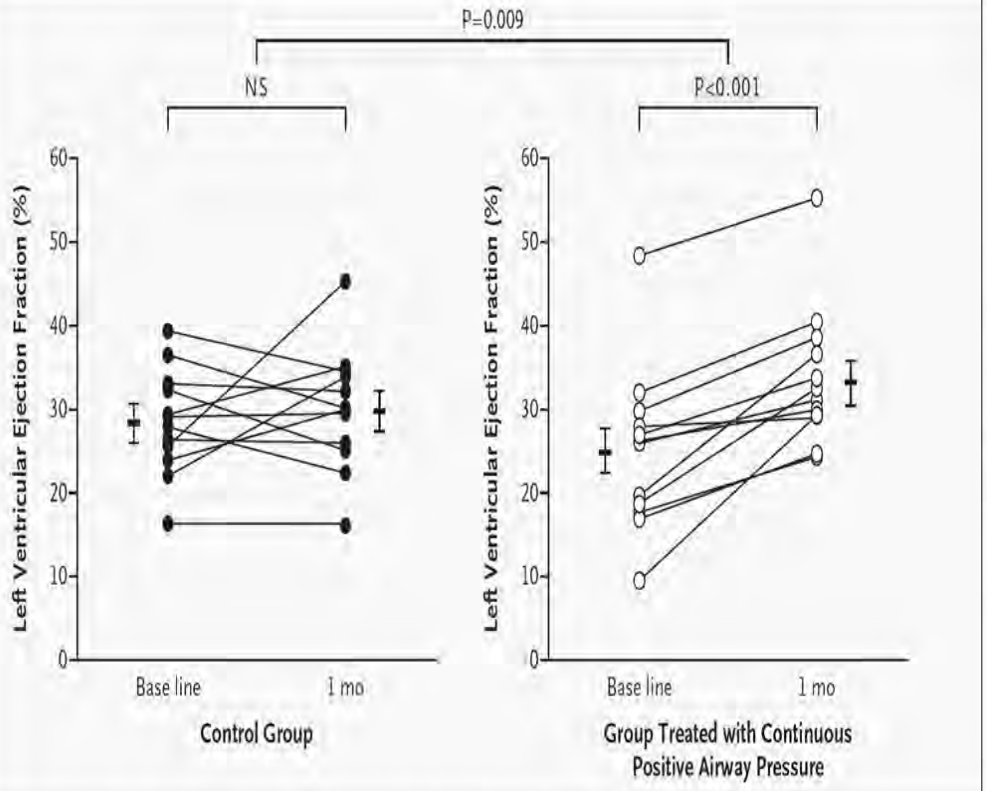


Figure 1. Individual Values for the Left Ventricular Ejection Fraction in All Patients.

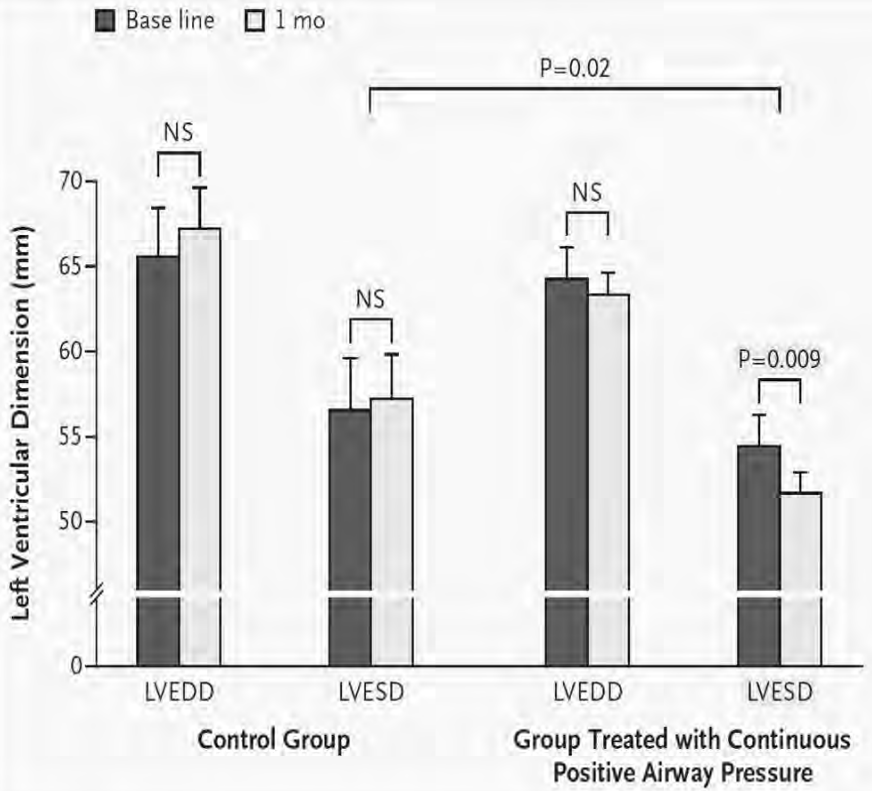


Figure 2. **Mean (±SE) Changes in Left Ventricular Dimensions.**

ORIGINAL ARTICLE

Continuous Positive Airway Pressure for Central Sleep Apnea and Heart Failure

- Hypothesis – CPAP would improve the survival rate without heart transplantation of patients who have central sleep apnea and heart failure.

- 258 patients (after medical optimization) with HF (24.5 $\pm$ 7.7) and CSA (AHI-40±16).

- Randomly assigned to receive CPAP (128 patients) or no CPAP (130 patients).

- Followed for a mean of two years.

CANPAP Trial. N Engl J Med 2005;353:2025-33.

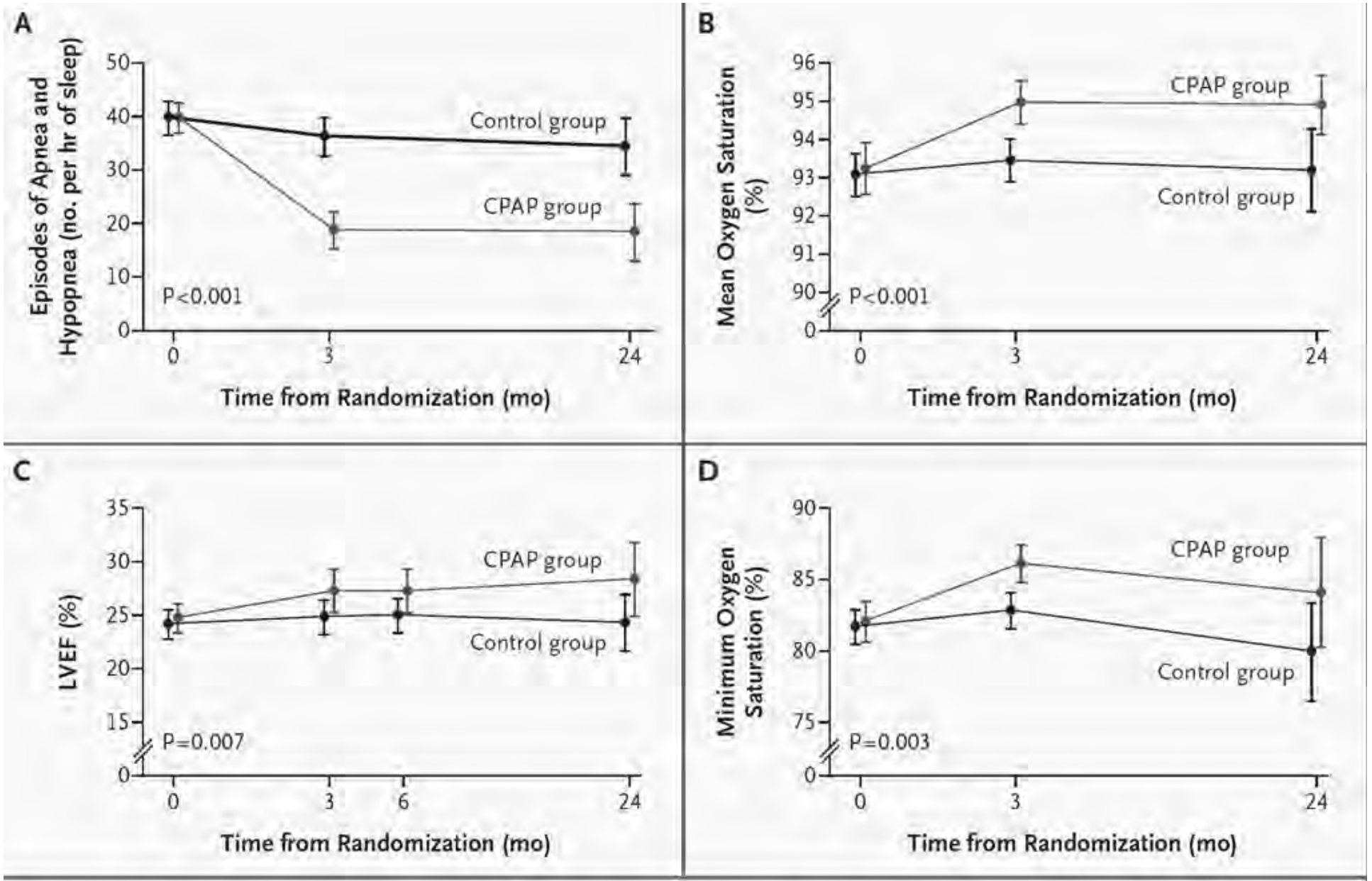
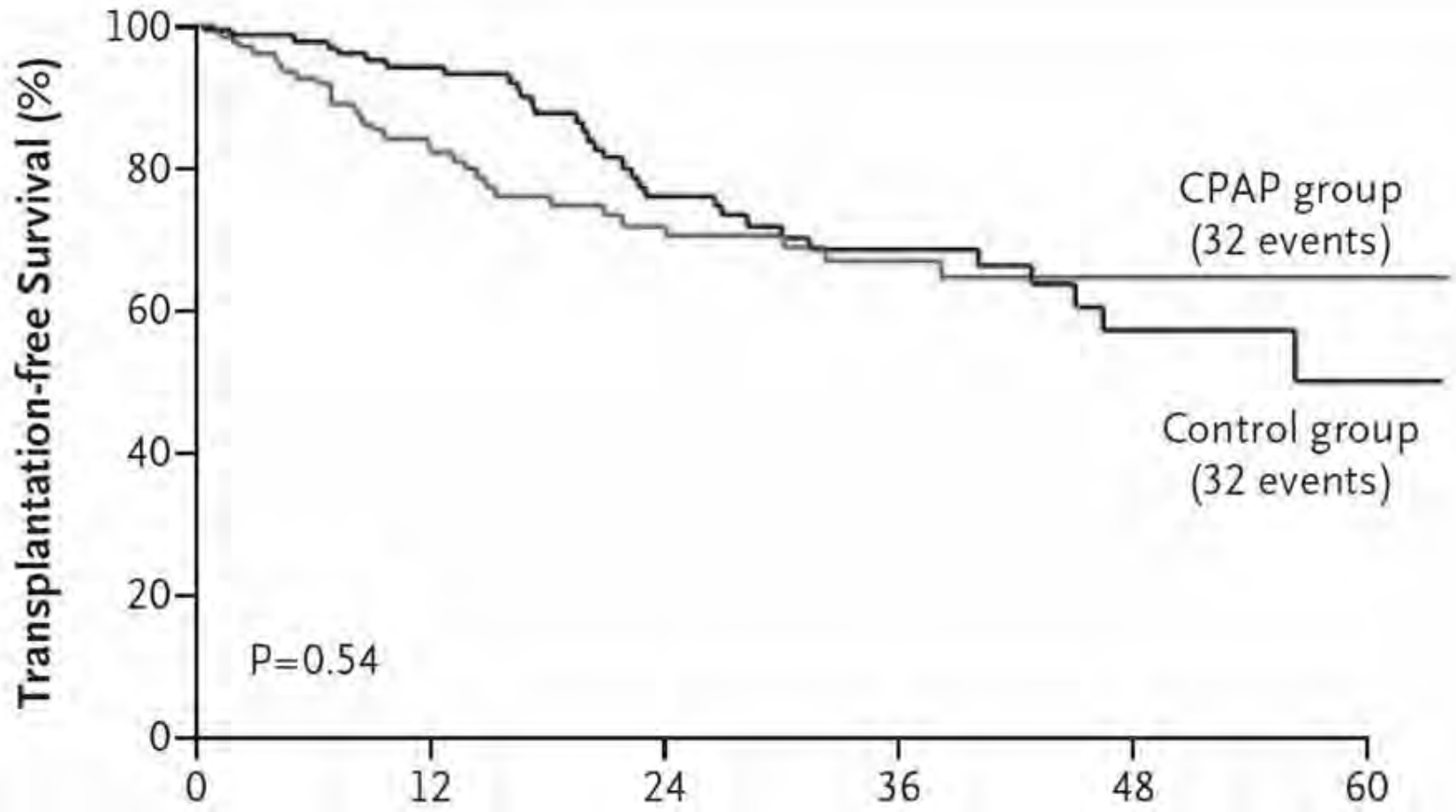


Figure 1. **Effect of CPAP on the Frequency of Episodes of Apnea and Hypopnea, Mean and Minimal Nocturnal Oxygen Saturation, and Left Ventricular Ejection Fraction.**



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

Figure 3. Heart-Transplantation–free Survival.

Auto-titrating continuous positive airway pressure therapy in patients with chronic heart failure and obstructive sleep apnoea: a randomized placebo-controlled trial

Lindsay A. Smith[1]*, Marjorie Vennelle[2], Roy S. Gardner[3], Theresa A. McDonagh[4], Martin A. Denvir[1], Neil J. Douglas[2], and David E. Newby[1]

[1]*Cardiovascular Research, Centre for Cardiovascular Science, University of Edinburgh, Chancellor's Building, 49 Little France Crescent, Edinburgh EH16 4SB, UK;* [2]*Department of Sleep Medicine, University of Edinburgh, UK;* [3]*Western Infirmary, Glasgow, UK; and* [4]*Royal Brompton Hospital, London, UK*

- 26 patients with stable symptomatic CHF and OSA.
- Randomized to nocturnal auto-titrating CPAP or sham CPAP for 6 weeks each in crossover design.
- Co-primary endpoints - Changes in peak VO2 and 6 MWD.
- Secondary endpoints - Changes in LVEF, plasma neurohormonal markers, and QOL measures.
- Mean CPAP and sham CPAP usage – No significant difference.

Table 3 Effect of continuous positive airway pressure and sham continuous positive airway pressure on quality of life and cardiac function

	Baseline	Sham	CPAP	Treatment effect	*P*-value
Echocardiography					
LVESD (mm)	50 ± 11	51 ± 13	51 ± 14	−0.1 (−0.4 to 0.3)	0.79
LVEDD (mm)	61 ± 10	63 ± 12	63 ± 12	0.0 (−0.4 to 0.3)	0.83
FS (%)	18 ± 7	20 ± 8	19 ± 6	0.1 (−3.3 to 3.6)	0.95
LVEF (%)	29 ± 10	30 ± 10	30 ± 10	0.7 (−1.8 to 3.2)	0.56
Exercise capacity					
6 MW (m)	550 ± 121	552 ± 121	546 ± 124	0 (−14 to 14)	0.98
Exercise time (min)	10.0 ± 2.3	9.7 ± 3.0	9.8 ± 3.1	0.2 (−0.3 to 0.7)	0.44
Peak VO_2 (mL/kg/min)	14.8 ± 4.2	14.7 ± 4.6	14.5 ± 4.2	−0.2 (−0.9 to 0.4)	0.48
VE/VCO_2 slope	32 ± 5	33 ± 7	33 ± 8	−0.3 (−1.9 to 1.4)	0.73
Quality of life					
Minnesota	38 ± 27	34 ± 28	36 ± 29	1.0 (−4.3 to 6.4)	0.70
SF-36—physical	34 ± 16	35 ± 14	34 ± 14	−1.0 (−3.6 to 1.6)	0.43
SF-36—mental	51 ± 10	50 ± 11	49 ± 12	−0.5 (−4.2 to 3.2)	0.79
Daytime sleepiness					
ESS	10 ± 5	8 ± 5	7 ± 4	−1 (−1.9 to 0.0)	0.04
OSLER (min)	27 ± 15	29 ± 13	30 ± 14	0.7 (−2.2 to 3.6)	0.63

Findings may relate in part to methodologic limitations, such as the lack of a follow-up PSG to confirm treatment efficacy with autotitrating CPAP .

Currently limited data regarding the impact of OSA treatment on important HF endpoints calls for further interventional trials.

European Heart Journal (2007) 28, 1221–1227

OSA & Pulmonary hypertension

THE INFLUENCE OF SHORT PERIODS OF INDUCED ACUTE ANOXIA UPON PULMONARY ARTERY PRESSURES IN MAN[1]

HURLEY L. MOTLEY, ANDRE COURNAND, LARS WERKO, AARON HIMMELSTEIN AND DAVID DRESDALE

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Received for publication May 19, 1947

METHODS. The influence of breathing 10 per cent oxygen in nitrogen has been studied on 5 unanesthetized, conscious white males in a resting basal

6. *Pulmonary artery blood pressure*, mm. Hg		
Systolic	21.9	35.1
Diastolic	6.0	13.0
Mean	13.1	23.0

Am J Physiol 1947;150:315–320.

Hypoxic pulmonary vasoconstriction

- Critical autoregulatory mechanism important in maintaining an appropriate V/ Q relationship.
- Over time - Pulmonary vascular remodeling - May not be reversible.
- Demonstrated in populations with advanced lung disorders.
- OSA pathophysiology - Could also provide a basis for chronic elevations in PAP.
- Precisely defining the role of OSA in the genesis of PH has been difficult for a number of reasons.

Difficulties in establishing association

- Various methods for diagnosis of PH - in OSA studies.
- Doppler echocardiography - Varying right heart/PAP thresholds.
- Previous definitions - Systolic PAP > 40 mm Hg and echocardiographic Doppler measurements.
- May be particularly challenging to obtain in obese patients with OSA.
- PH and OSA - Common risk factors—Obesity and aging – Confounding.
- A PASP >40 mm Hg - Found in 6%of otherwise normal individuals > 50 yrs and in 5% of individuals with a BMI > 30 kg/m^2
- Finding appropriate control groups - Matched subjects with PH but no OSA – Quite Challenging.

OSA & Pulmonary hypertension

- SDB - Part of the category of respiratory disorders associated with PH. (2009 PAH guidelines).

- Limited epidemiologic data - Numerous case series, comprised primarily of male patients.

- Suggest a prevalence of PH in OSA ranging from 17 to 52% .

- The largest published sample - 220 subjects with OSA - 17% met diagnostic criteria for PH.

Chaouat A et al. Chest 1996;109:380–386.

- Population-based data are currently lacking.

Early studies

- Sleep stage–dependent increases in PAP, with more marked changes occurring during REM sleep.

Coccagna G et al. Bull Physiopathol Respir (Nancy) 1972;8:1159–1172.

- Most early clinical studies - Abnormalities in underlying lung function sufficient to induce daytime hypoxemia were required for the development of PH and right heart failure.

- Support - Severity of sleep-disordered breathing, as measured by the AHI, and PAP elevations often failed to correlate.

- Not all studies adequately excluded increases in left atrial pressure as a contributor to the development of daytime increases in PAP.

Am. J. Respir. Crit. Care Med., Vol 149, No. 2, 02 1994, 416-422.

Pulmonary hypertension and hypoxemia in obstructive sleep apnea syndrome

D Sajkov, RJ Cowie, AT Thornton, HA Espinoza and RD McEvoy
Department of Thoracic Medicine, Royal Adelaide Hospital, South Australia, Australia.

27 patients with OSAS in whom clinically significant lung or cardiac diseases were excluded.

- 11 OSAS patients (41%) – PAH -(Mean PAP $\leq$ 26 mm Hg).
- Pts. With PH - More hypoxemic during daytime wakefulness than patients without PH - Could either contribute to or result from PH.
- Hypoxemia in PH patients could not be explained by impairment of lung function, greater body mass, or a higher prevalence of smoking.
- Lung disease is not a prerequisite for PH in OSAS.

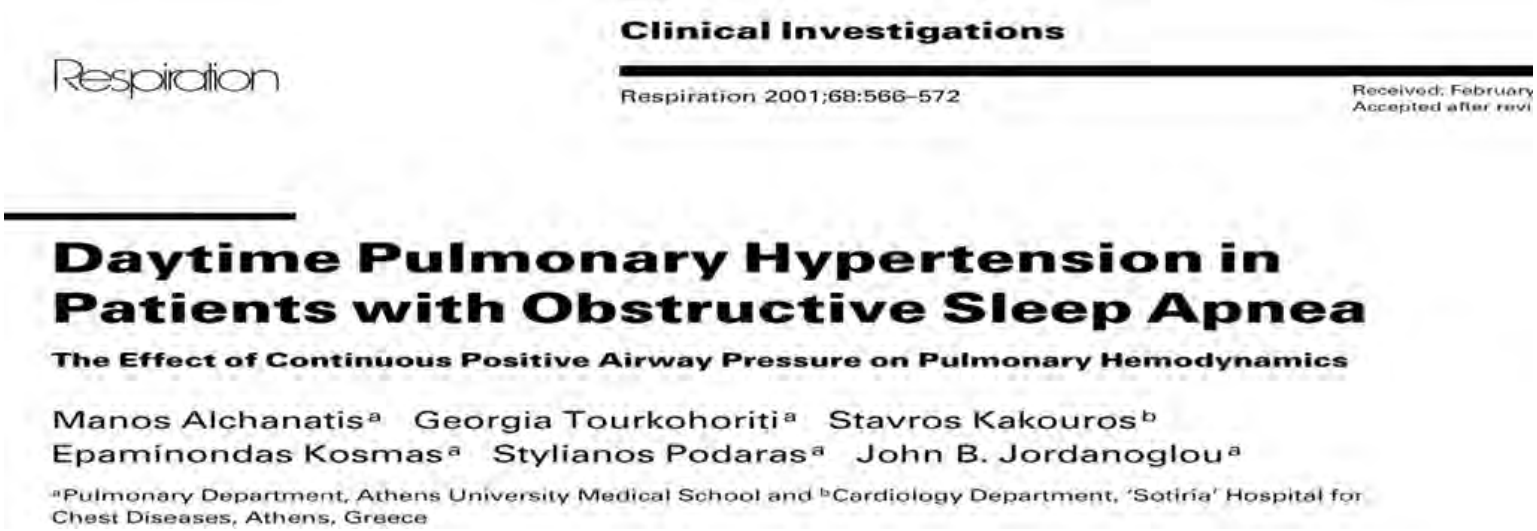
Treatment Effects

- Tracheostomy/ Supp. O_2– ↓ PAP in patients with COPD and nocturnal hypoxemia.

- Initial reports - Approximate 50% ↓ in PAP in 6patients with OSA who underwent tracheostomy, some of whom may have had comorbid disease.

Motta J et al. Ann Intern Med 1978;89:454–458.

- Very limited data on the effects of CPAP treatment of OSA on PAP



Respiration

Clinical Investigations

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Accepted after revi

Daytime Pulmonary Hypertension in Patients with Obstructive Sleep Apnea

The Effect of Continuous Positive Airway Pressure on Pulmonary Hemodynamics

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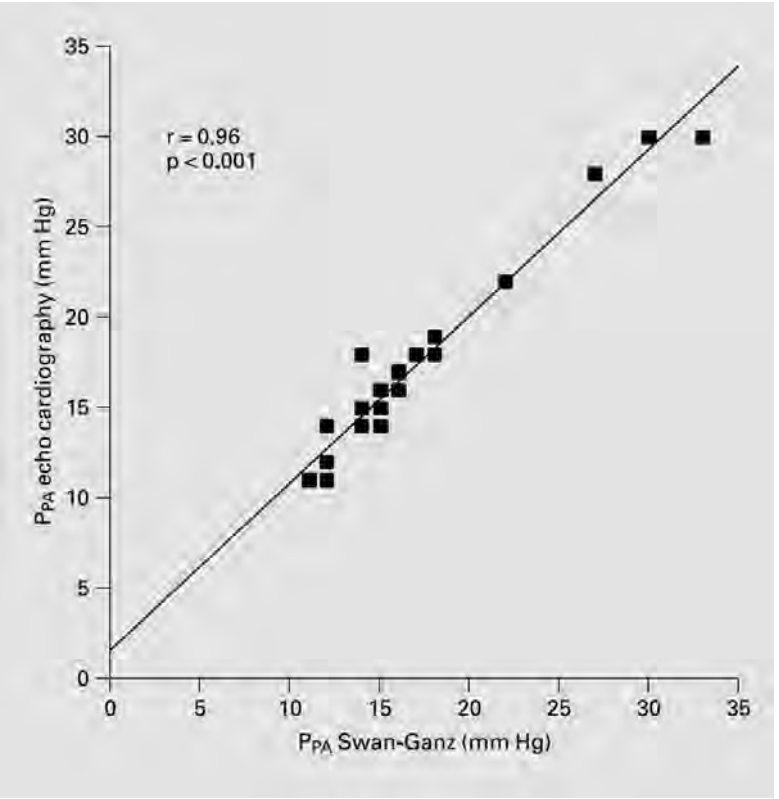
- To investigate whether OSA patients without any other cardiac or lung disease develop PH.
- To assess the effect of CPAP treatment on PA pressure.
- 29 pts – Age 51±10 years with OSA, 12 controls.
- PA pressure before and after 6-month effective treatment with CPAP.

	OSA patients (n = 29)	Control subjects (n = 12)	p value
Age, years	51 ± 10	53 ± 6	NS
BMI, kg/m^2	34 ± 6	30 ± 3	NS
FEV_1, % pred.	92 ± 13	91 ± 5	NS
FVC, % pred.	91 ± 12	88 ± 6	NS
FEV_1/FVC, %	79 ± 4	84 ± 6	NS
P_aO_2, mm Hg	90 ± 10	90 ± 4	NS
P_aCO_2, mm Hg	40 ± 4	39 ± 3	NS
AHI, events/h	54 ± 19	9 ± 2	<0.001
Doppler P_{PA}, mm Hg	17.2 ± 5.2 (11–30)	12.1 ± 1.9 (8–22)	<0.001
Swan-Ganz P_{PA}, mm Hg	16.9 ± 5.4 (11–33)		
Wedge pressure, mm Hg	6.8 ± 2.0 (5–11)		

Table 2. Anthropometric, lung function, polysomnographic and hemodynamic data in OSA patients with (PH group) and without pulmonary hypertension (non-PH group)

	PH group (n = 6)	Non-PH group (n = 23)	p value
Age, years	62 ± 4	48 ± 15	<0.05
BMI, kg/m^2	41 ± 7	32 ± 4	<0.02
FEV_1, % pred.	86 ± 15	93 ± 13	NS
FVC, % pred.	86 ± 16	92 ± 13	NS
FEV_1/FVC, %	76 ± 2	83 ± 8	NS
P_aO_2, mm Hg	81 ± 9	92 ± 9	<0.05
P_aCO_2, mm Hg	43 ± 4	40 ± 4	NS
AHI, events/h	63 ± 18	51 ± 19	NS
Lowest S_pO_2, %	60 ± 11	63 ± 12	NS
S_pO_2 drops > 4%	280 ± 41	222 ± 109	NS
Doppler P_{PA}, mm Hg	25.6 ± 4.0	14.9 ± 2.2	<0.002



	Mean P_{PA} before CPAP treatment mm Hg	Mean P_{PA} after CPAP treatment mm Hg	p value
OSA patients (n = 29)	17.2 ± 5.2	13.2 ± 3.8	<0.001
PH group (n = 6)	25.6 ± 4.0	19.5 ± 1.6	<0.001
Non-PH group (n = 23)	14.9 ± 2.2	11.5 ± 2.0	<0.001

Continuous Positive Airway Pressure Treatment Improves Pulmonary Hemodynamics in Patients with Obstructive Sleep Apnea

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- 20 patients with OSA (without coexistent pulmonary or cardiac disease) - 4 months of CPAP therapy.
- 5 patients - Met criteria for PH.
- To assess the reversibility of PH - PAP measured by Echo at three levels of fiO_2 (50, 21, and 11%).
- After 4 months of CPAP therapy - PAP (for all patients) ↓- Mean 13.9 mm Hg.
- CPAP may also affect vasoreactivity - PA pressor response to hypoxia was attenuated.

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doi:10.1093/eurheartj/ehi807

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Clinical research
Hypertension

Pulmonary hypertension in obstructive sleep apnoea: effects of continuous positive airway pressure

A randomized, controlled cross-over study

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- Randomized cross-over trial of CPAP/sham CPAP -12 weeks -23 patients with OSA.

- 10 patients with PH - More obese, had more ventilatory limitation (reduced FVC), and more severe sleep apnea (by AHI and mean oxygen saturation) than the 13 patients without PH.

- CPAP therapy ↓ PASP in all patients - More so in those with PH at baseline (mean reductions, 8.5 vs. 2.6mmHg).

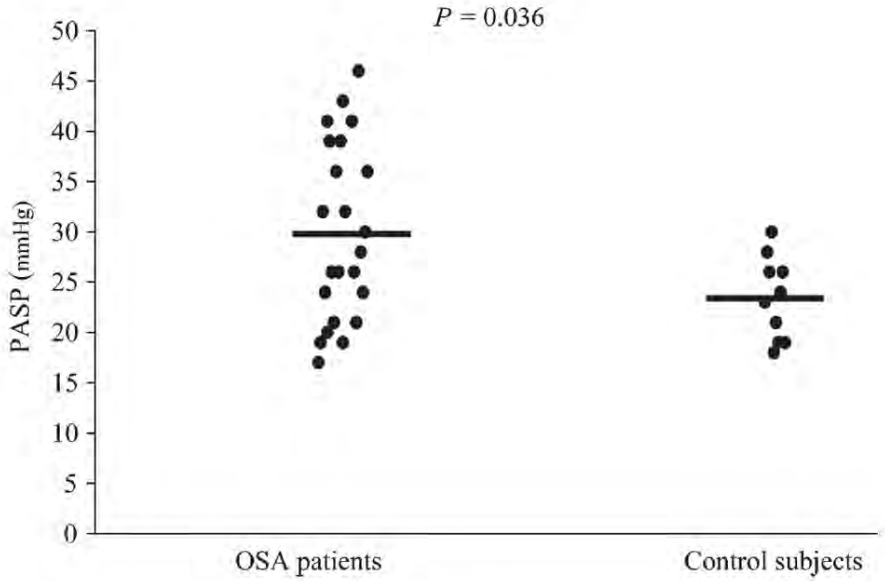

Figure 2 Individual values for the PASP in OSA patients and control subjects.

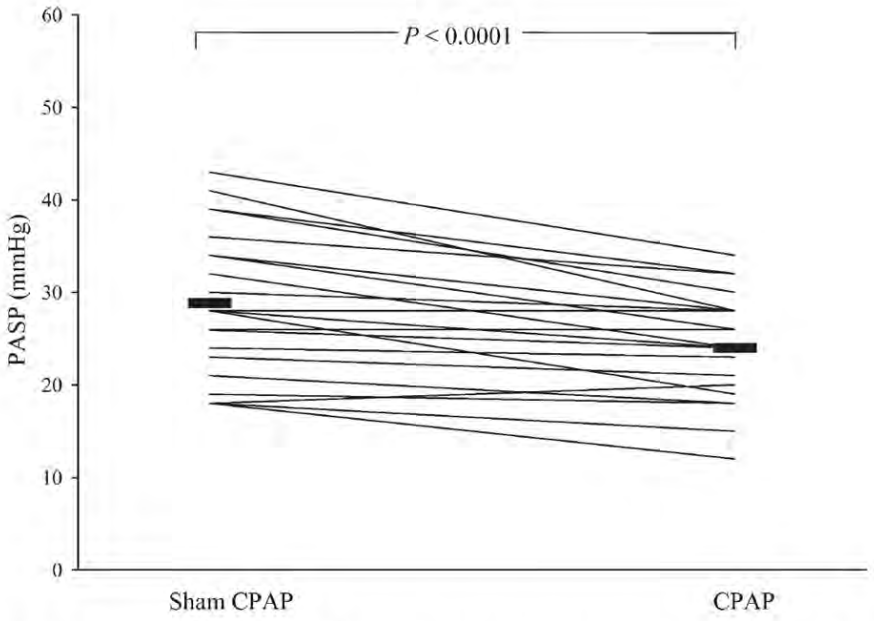

Figure 3 Individual values for the PASP after both sham and effective CPAP treatment in OSA patients.

Baseline differences in obesity and lung function between groups - Preclude the attribution of PH to OSA alone.

First to show, in a placebo-controlled fashion, the positive impact of CPAP therapy on PH in a small group of patients with OSA.

Further research is needed to assess the durability of CPAP therapy on PAP and right heart function

An ever increasing arsenal of pharmacologic treatments for PH

SYNDROME Z – OSA + Metabolic Syndrome (1990's)

- NCEP ATP III – 5 variables
- HTN, **insulin resistance**, low serum HDL cholesterol, elevated serum TG's, and **abdominal obesity**.
- 3/5 – Metabolic Syndrome.

- Growing experimental and clinical evidence - Independent contribution of OSA toward the development and/or severity of MS.

- MS and its components may have conductive influence on the development of sleep apnea.

- OSA itself may well be a ''metabolic disorder'' and a component of MS

OSA, MS & Cardiovascular outcomes – Very scanty Data

- 89 subjects with OSA treated with CPAP.
- 50 % patients had MS at baseline.
- Less CVD events in those with MS than those without MS (Mean period - 22 months).
- CPAP compliance data did not modify the outcome.

Ambrosetti M, Lucioni AM, Conti S, Pedretti RF, Neri M. Metabolic syndrome in obstructive sleep apnea and related cardiovascular risk. J Cardiovasc Med (Hagerstown) 2006;7:826–829.

- Limitations - Details of pharmacotherapy for metabolic control during the follow-up period were not available.

- Prospective studies with longer follow-up and rigorous characterization of subjects needed to address this issue.

OSA & Glucose Metabolism

- MS – “Insulin resistance syndrome”
- Insulin resistance – DM.
- Any independent contribution of OSA toward insulin resistance and/or glucose homeostasis would have a magnifying effect on the clinical outcomes.
- OSA, MS & Insulin resistance closely linked to obesity.
- Many further implications on the manifestations and sequelae of OSA.

Important to address Obesity as a confounder

- Visceral fat - Metabolically active tissue.
- Large amounts of proinflammatory or vasoactive substances.
- Central obesity is considered to be a very important determinant of MS
- OSA may well modulate the expression of adipose tissue–derived mediators.
- Determine the development of various features in MS as well as cardiovascular diseases.

OSA & Insulin resistance - What is the evidence ??

- Large no. Of studies - Presence and/or severity of OSA are linked to alterations in glucose metabolism independently of the degree of obesity.

- Most - Cross-sectional data, prospective studies very few.

- Additional studies with prospective and/or interventional designs are needed to address causation.

- To establish association -Investigators have explored changes in glucose metabolism after treatment of OSA with CPAP.

- Effects of CPAP treatment on glucose metabolism – Considerable disagreement.

OSA & Neuropsychological Impairment

- Cognitive function and neuropsychological testing - Assessed in numerous studies.

- Differences in sampling and study design.
- Varying characteristics of study populations.
- Most obvious source of variation - Severity of OSA.

- Effect size of cognitive impairment in OSA correlated highly with AHI.
- Severity also influenced the type of cognitive impairment observed.

Engleman HM et al. Cognitive function in the sleep apnea/hypopnea syndrome (SAHS). Sleep 2000;23:S102 –8.

Other factors affecting assessment

- Daytime CO_2 retention and hypoxemia - May play a role in the genesis of cognitive dysfunction independent of sleep apnea.
- Psychological state of subjects, particularly the degree of depression.
- Age and baseline cognitive function of subjects.
- Individuals with high baseline function – Compensatory ability.
- Comparison groups - Published normative data, healthy controls, and other groups like insomniacs ,other hypersomnolence disorders , and patients with treated COPD.
- Array of neuropsychological instruments.

- **Neuropsychological domains impaired in OSA patients**
- General intellectual function
- Attention/vigilance/concentration.
- Memory (working/episodic/procedural) and learning.
- Executive and motor function.

- **Treatment and reversibility**
- Numerous uncontrolled studies show improvement in cognitive function after initiation of CPAP.

- The results of placebo-controlled investigations do not provide unequivocal support for the hypothesis that this change is directly attributable to CPAP.

- **Association of depression with OSA.**

SUMMARY

- Sleep apnea is a disorder with widespread systemic manifestations.
- Cardiovascular complications have a strong association with sleep apnea.
- Metabolic syndrome and OSA link has increasingly been recognised.
- Neropsychological manifestations of sleep apnea can affect a number of cognitive domains.
- CPAP has shown to consistently ameliorate sleep disturbances in OSA but systemic effects are not always consistent.

SLEEP APNEA IS MUCH MORE THAN A SLEEP DISORDER.