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IRB Lleida
Institut de Recerca Biomèdica

ciberes
Centro de Investigación Biomédica en Red
Enfermedades Respiratorias

Síndrom de apneas del son, risc cardiovascular i insuficiencia cardiaca

Ferran Barbé

Institut de Recerca Biomedica. IRBLleida

CIBERES. Instituto de Salud Carlos III. Madrid.

Definiciones

- **APNEA: Ausencia de flujo superior a 10 segundos**
- **HYPOPNEA: Reduccion de flujo que induce desaturacion o *arousal***
- **AHI: Nº de apneas + nº hipopneas por hora**

Prevalence

Workers 30-60 yr (Young et al. NEJM 1993)

	Men (n=1670)		Women (n=1843)	
AHI	%	(CI 95%)	%	(CI 95%)
≥ 5	24.0	(19-28)	9.0	(6-12)
≥ 10	15.0	(12-19)	5.0	(2-8)
≥ 15	9.1	(6-11)	4.0	(1-7)
SAHS	4.0	-	2.0	-

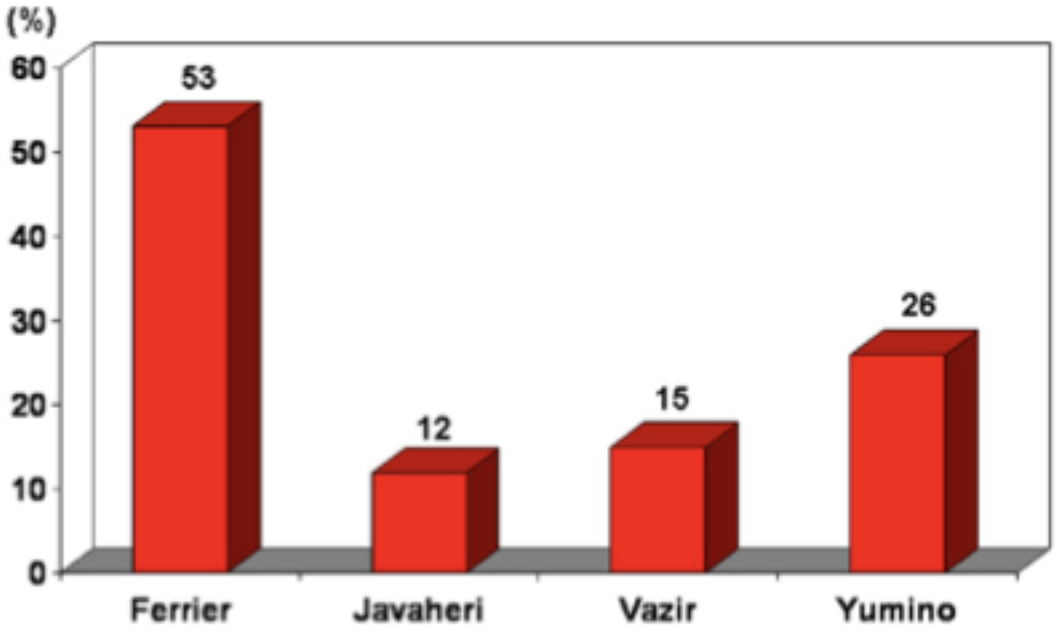


Figure 3 **The Prevalences of OSA Reported in 4 Studies**

The prevalences of OSA reported in 4 studies involving unselected patients with HF who underwent overnight polysomnography. Ferrier et al. (73) used an apnea-hypopnea index cutoff of ≥10 whereas the others used ≥15. Abbreviations as in Figure 2.

Bradley et al JACC 2011

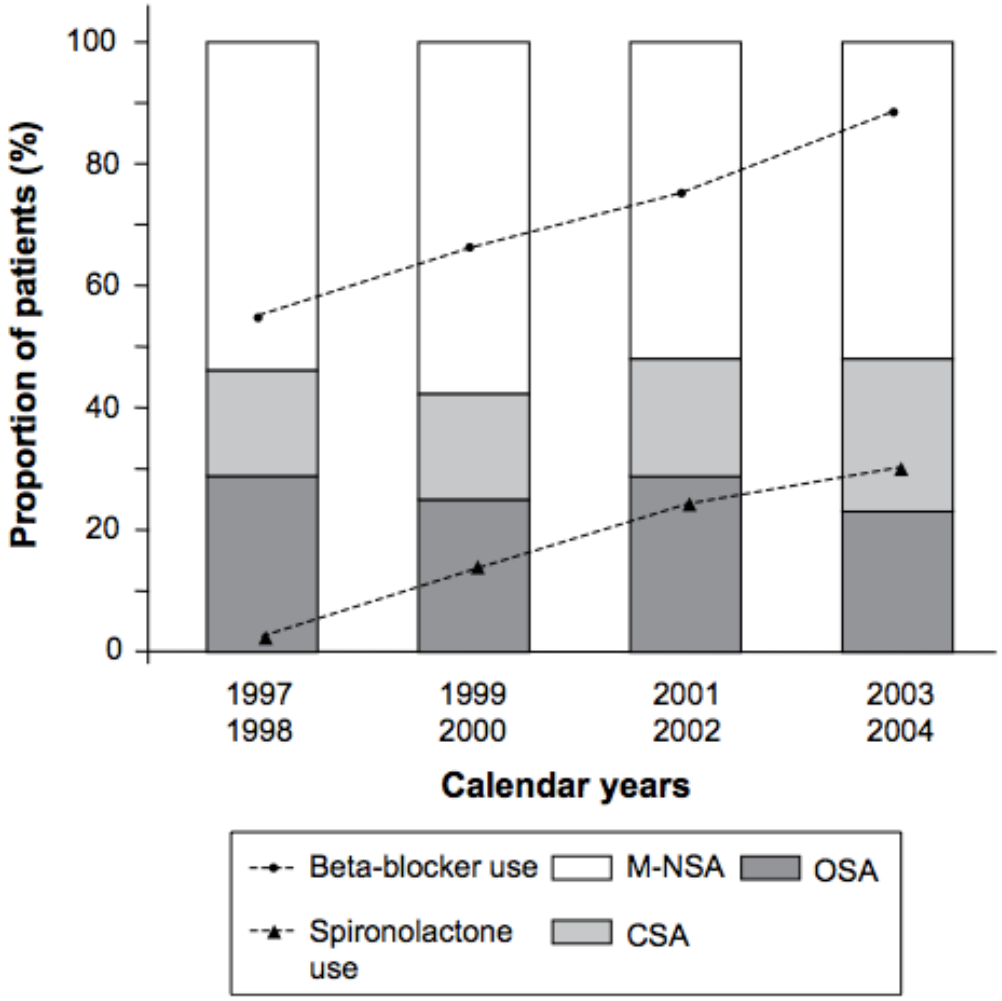
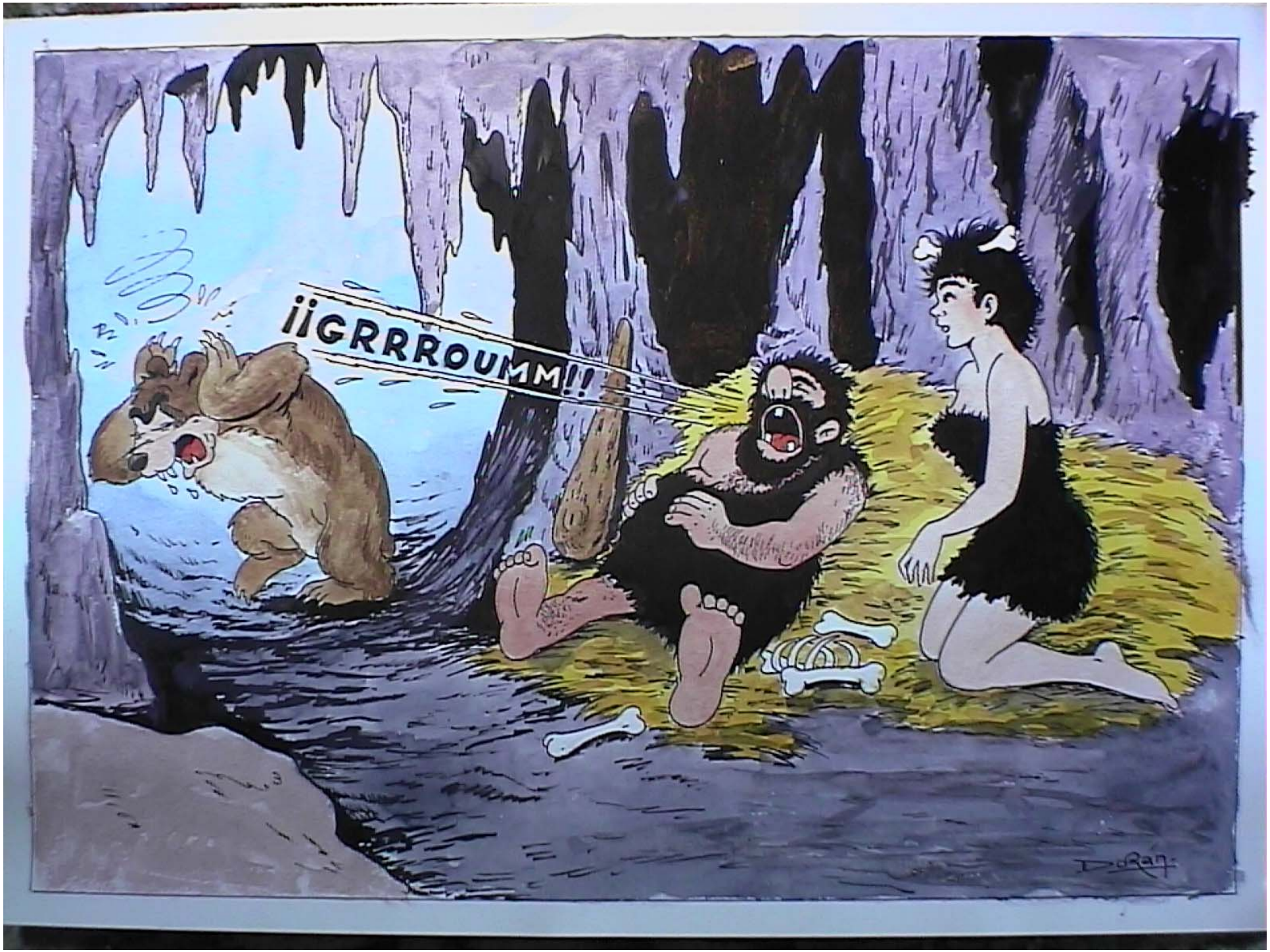
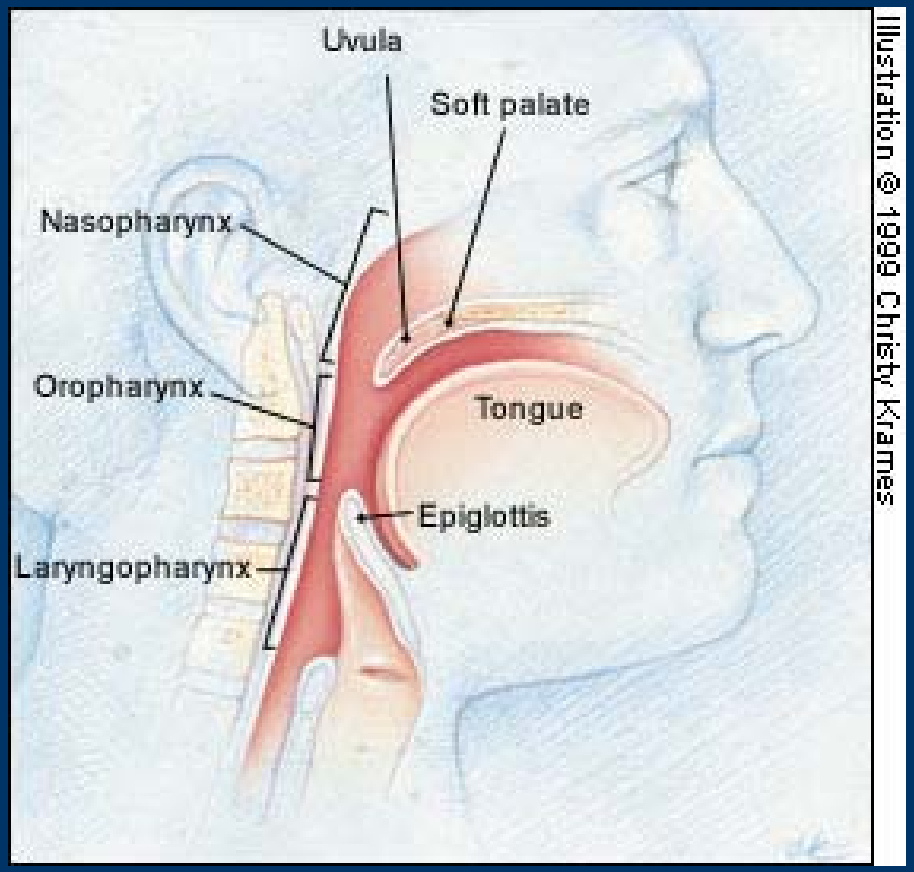
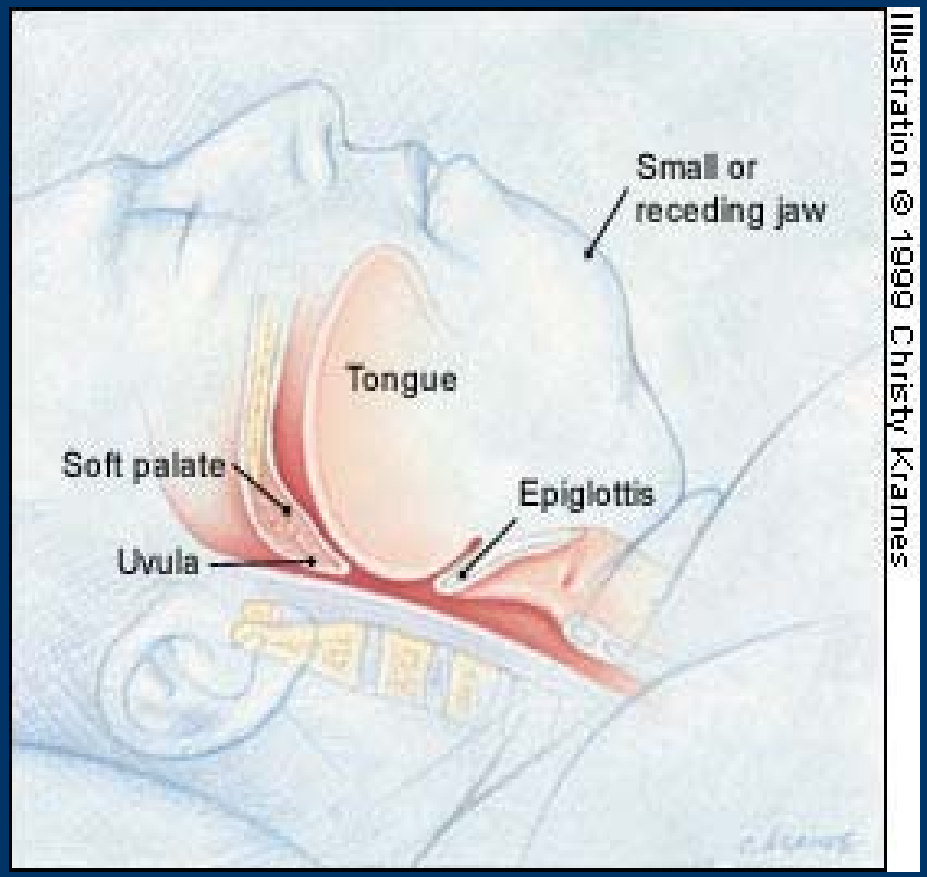


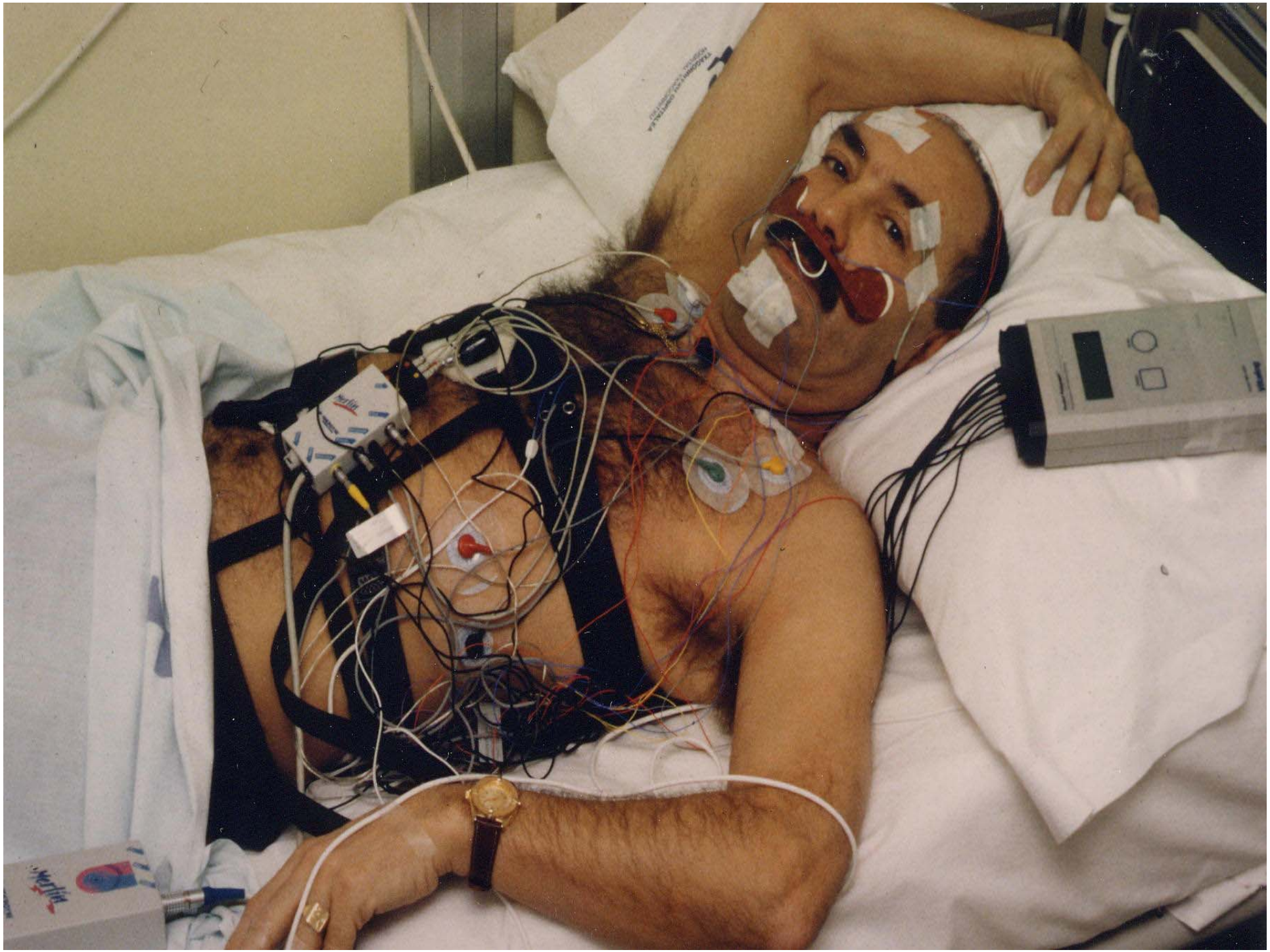
Fig. 1. Trends in the prevalences of sleep apnea, OSA and CSA, and of β-blocker and spironolactone use between the years 1997-1998 and 2003-2004. Although the percentage of subjects receiving β-blockers and spironolactone use increased progressively during this period, the prevalences of sleep apnea, OSA, and CSA remained unchanged. CSA, central sleep apnea; M-NSA, mild or no sleep apnea; OSA, obstructive sleep apnea.

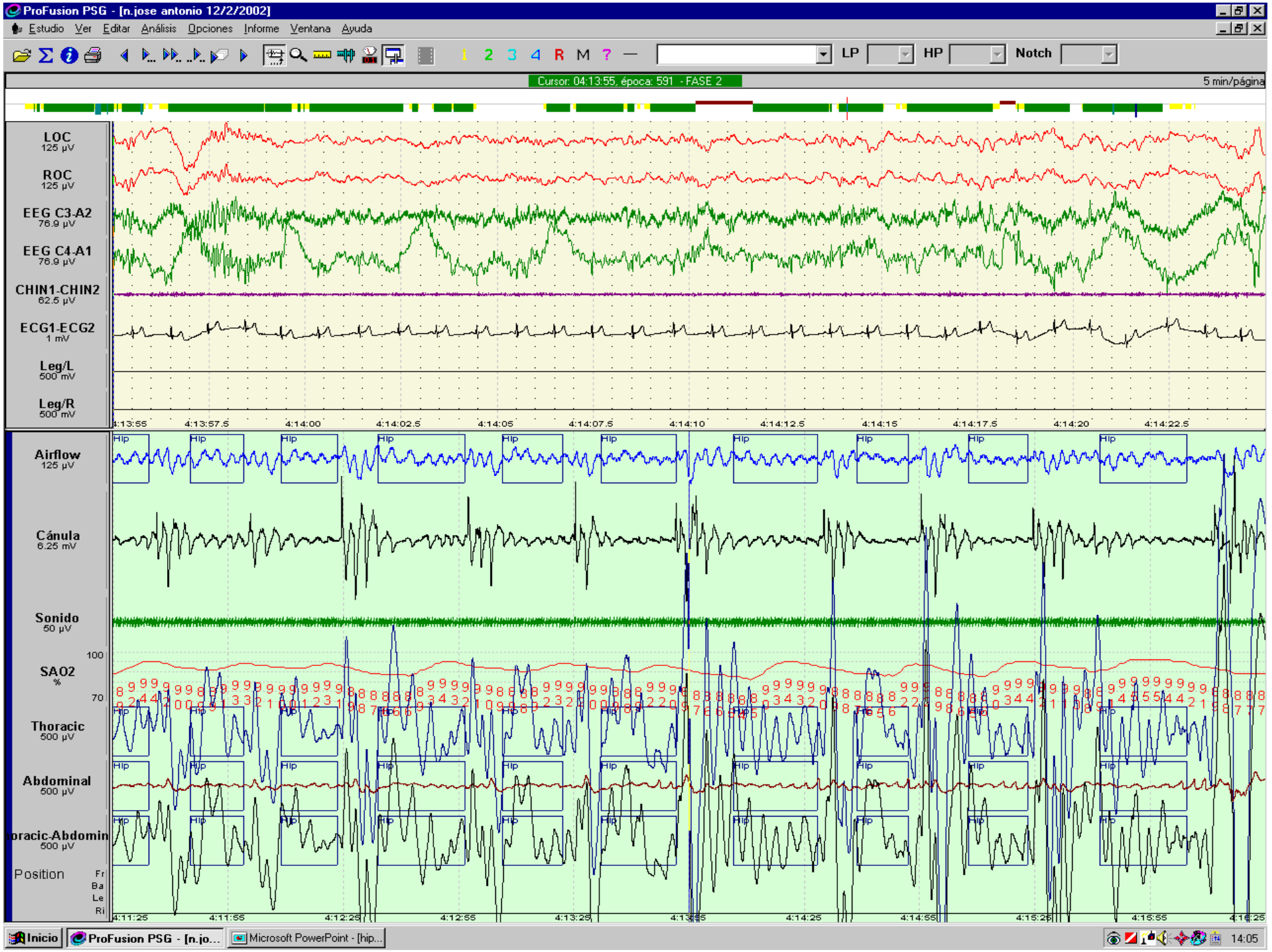

¡¡GRRROUMM!!


YONKIS.COM
Adena por la conservacion de la fauna ibérica


Uvula
Soft palate
Nasopharynx
Oropharynx
Tongue
Epiglottis
Laryngopharynx
Illustration © 1999 Christy Krames


Small or receding jaw
Tongue
Soft palate
Epiglottis
Uvula
Illustration © 1999 Christy Krames




ProFusion PSG - [n.jose antonio 12/2/2002]
Estudio Ver Editar Análisis Opciones Informe Ventana Ayuda
LP HP Notch
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5 min/página
LOC 125 µV
ROC 125 µV
EEG C3-A2 76.9 µV
EEG C4-A1 76.9 µV
CHIN1-CHIN2 62.5 µV
ECG1-ECG2 1 mV
Leg/L 500 mV
Leg/R 500 mV
4:13:55 4:13:57.5 4:14:00 4:14:02.5 4:14:05 4:14:07.5 4:14:10 4:14:12.5 4:14:15 4:14:17.5 4:14:20 4:14:22.5
Airflow 125 µV
Cánula 6.25 mV
Sonido 50 µV
SAO2 %
100
70
Thoracic 500 µV
Abdominal 500 µV
Thoracic-Abdomin 500 µV
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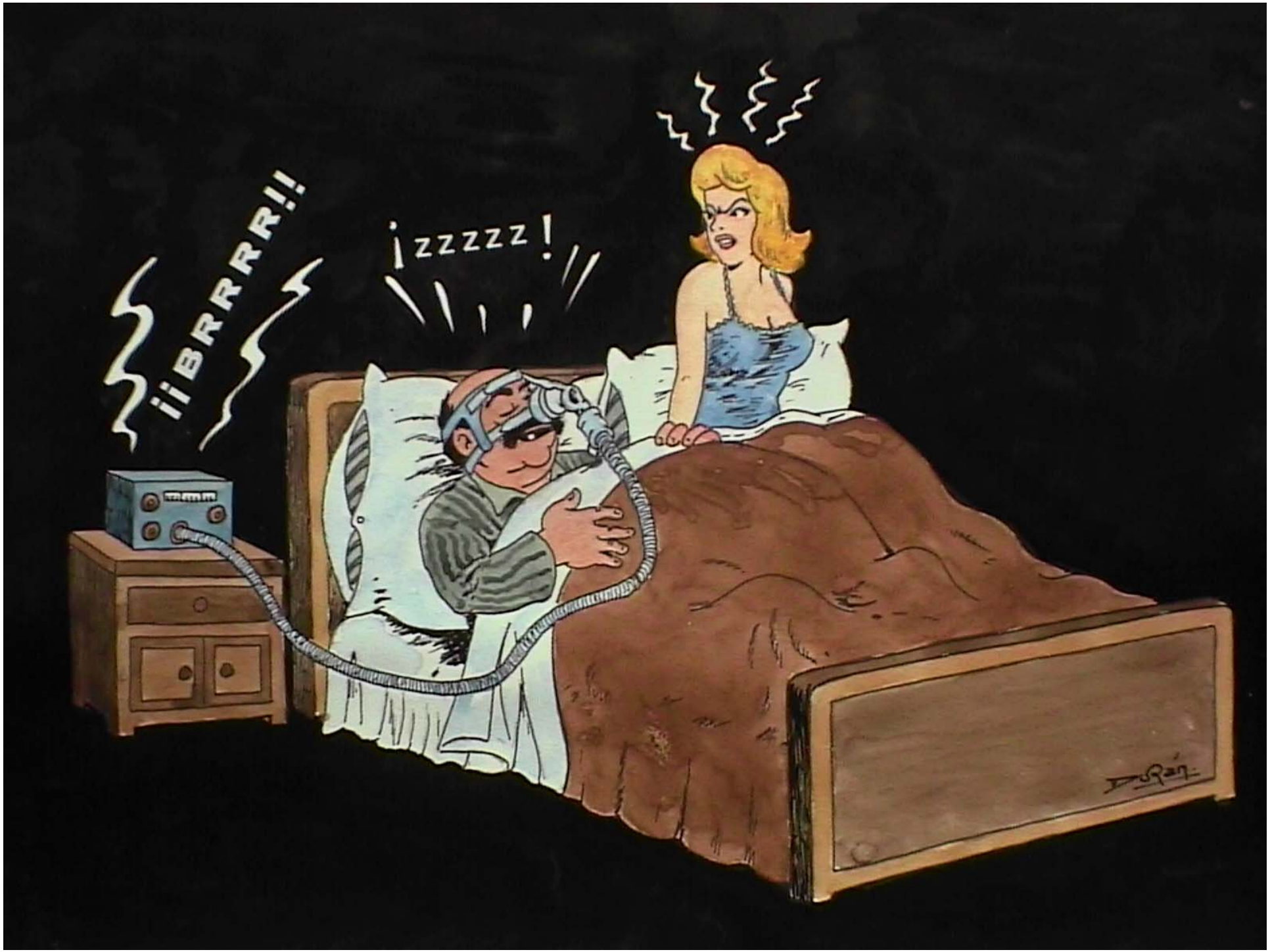
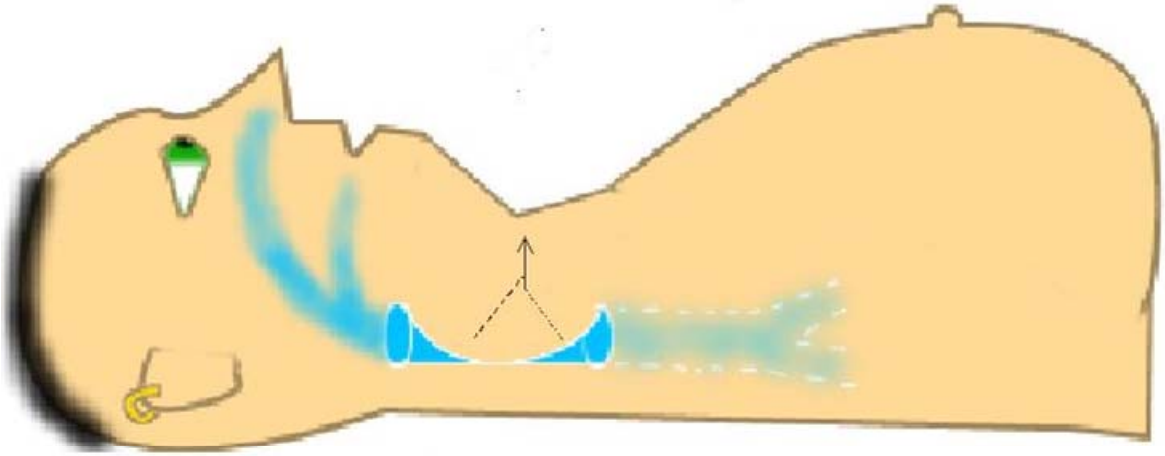
14:05


¡GRRRRR!...
¡GRRROUM!
¡GRRR!

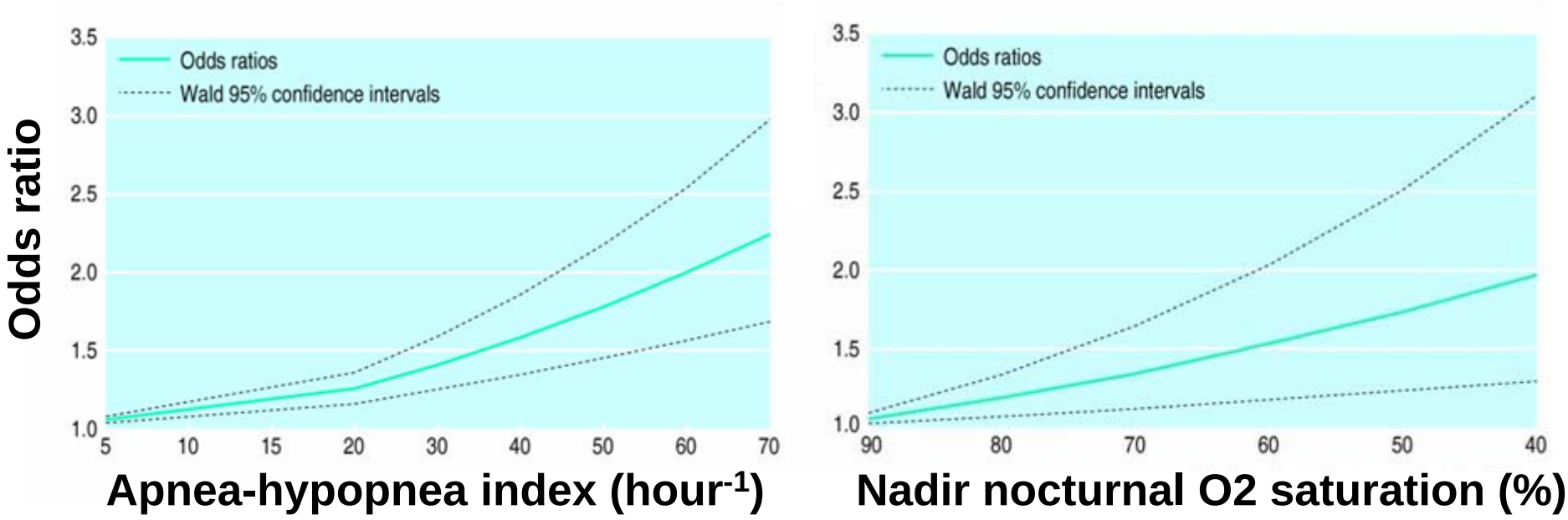

¡¡BRRRR!!
¡zzzzz!

Principales consecuencias del sd. apneas del sueño



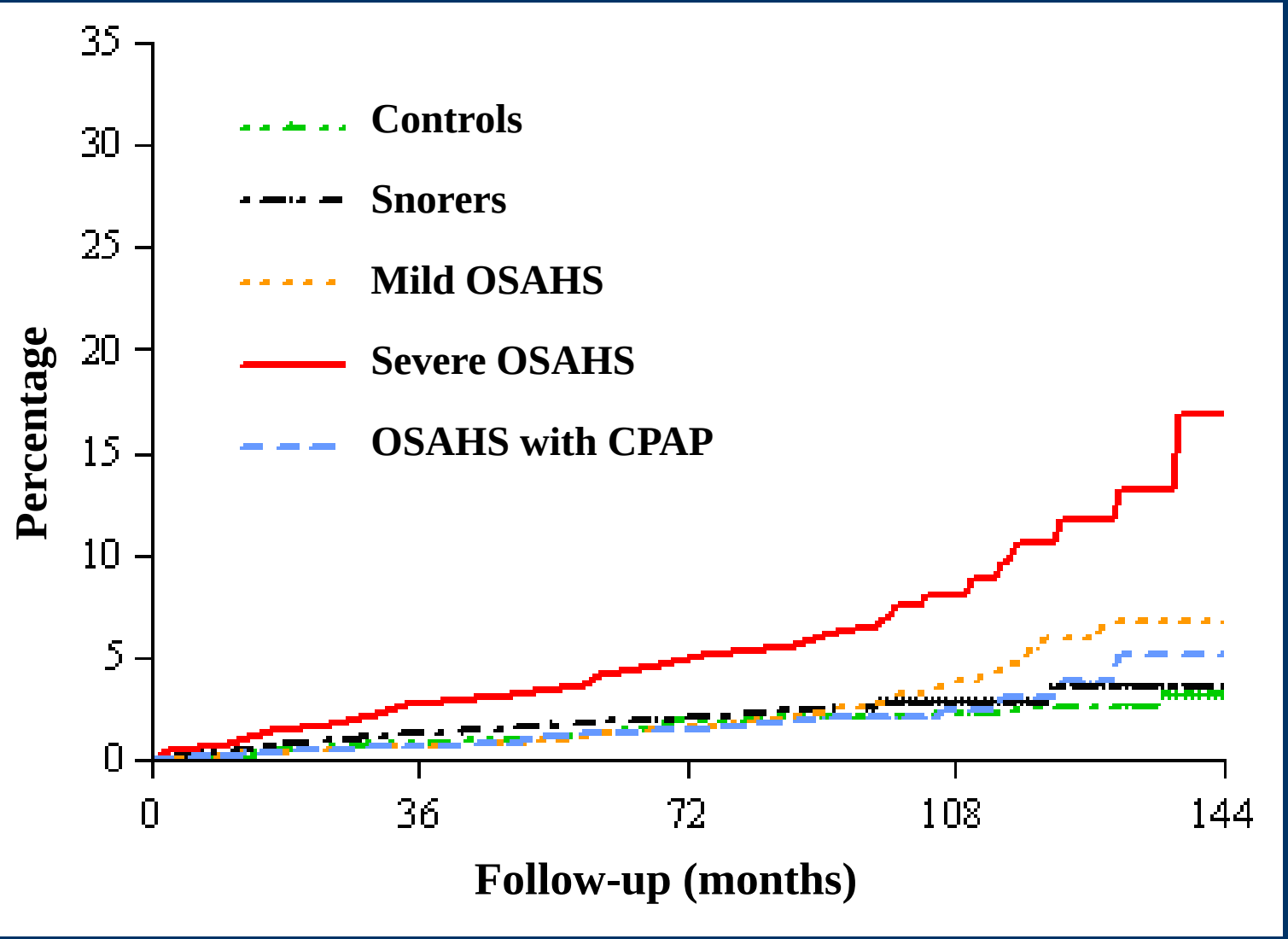
Obstructive sleep apnoea syndrome as a risk factor for hypertension: population study

Lavie P *et al. Brit.Med.J.* 2000; 320: 479-82



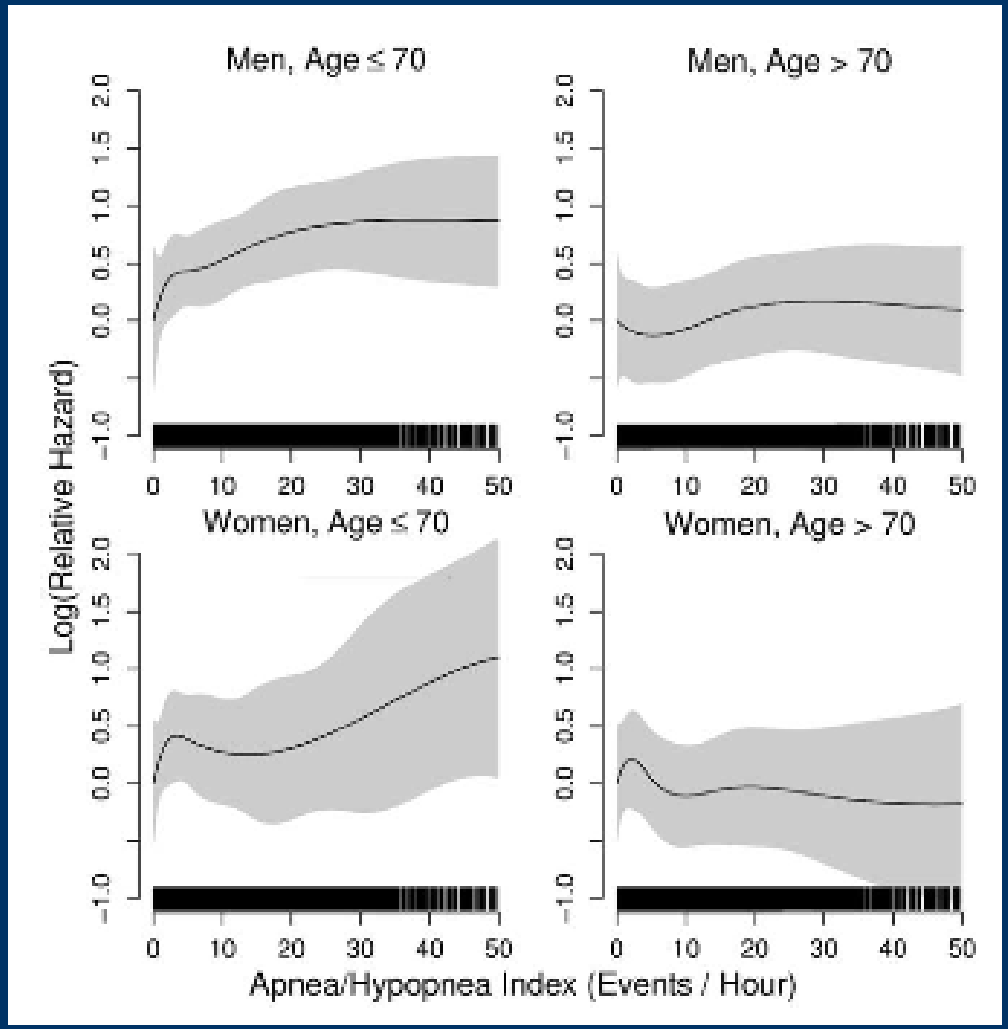
Cumulative incidence of fatal CV events

Marin JM *et al. Lancet* 2005



SDB and Mortality

Punjabi et al *Plos Med* 2010



Cardiologist looking at sleep

Barbe et al *Never Pub* 2010

Primary prevention of ischemic stroke
Circulation 2006, Stroke 2006

- **Nonmodifiable risk factors: age, sex, low birth weight, race/ethnicity, and genetic factors**
- **Well-documented and modifiable risk factors include hypertension, exposure to cigarette smoke, diabetes, atrial fibrillation and certain other cardiac conditions, dyslipidemia, carotid artery stenosis, sickle cell disease, postmenopausal hormone therapy, poor diet, physical inactivity, and obesity and body fat distribution.**
- **Less well-documented modifiable risk factors include the metabolic syndrome, alcohol abuse, drug abuse, oral contraceptive use, sleep-disordered breathing, migraine headache, hyperhomocysteinemia, elevated lipoprotein(a), elevated lipoprotein-associated phospholipase, hypercoagulability, inflammation, and infection**

Conditions for a risk factor

- The association between the factor and the risk must to be:
  - Statistically significant
  - Progressive
  - Temporally related
  - Must be present in most studies
  - Independent from other risk factors
  - Predictive real value
  - Pathogenic bases

SAS and cardiovascular disease

- Is there an association between SAS and CVD?
- Which are the pathogenic mechanisms?
- Recent studies and future challenges

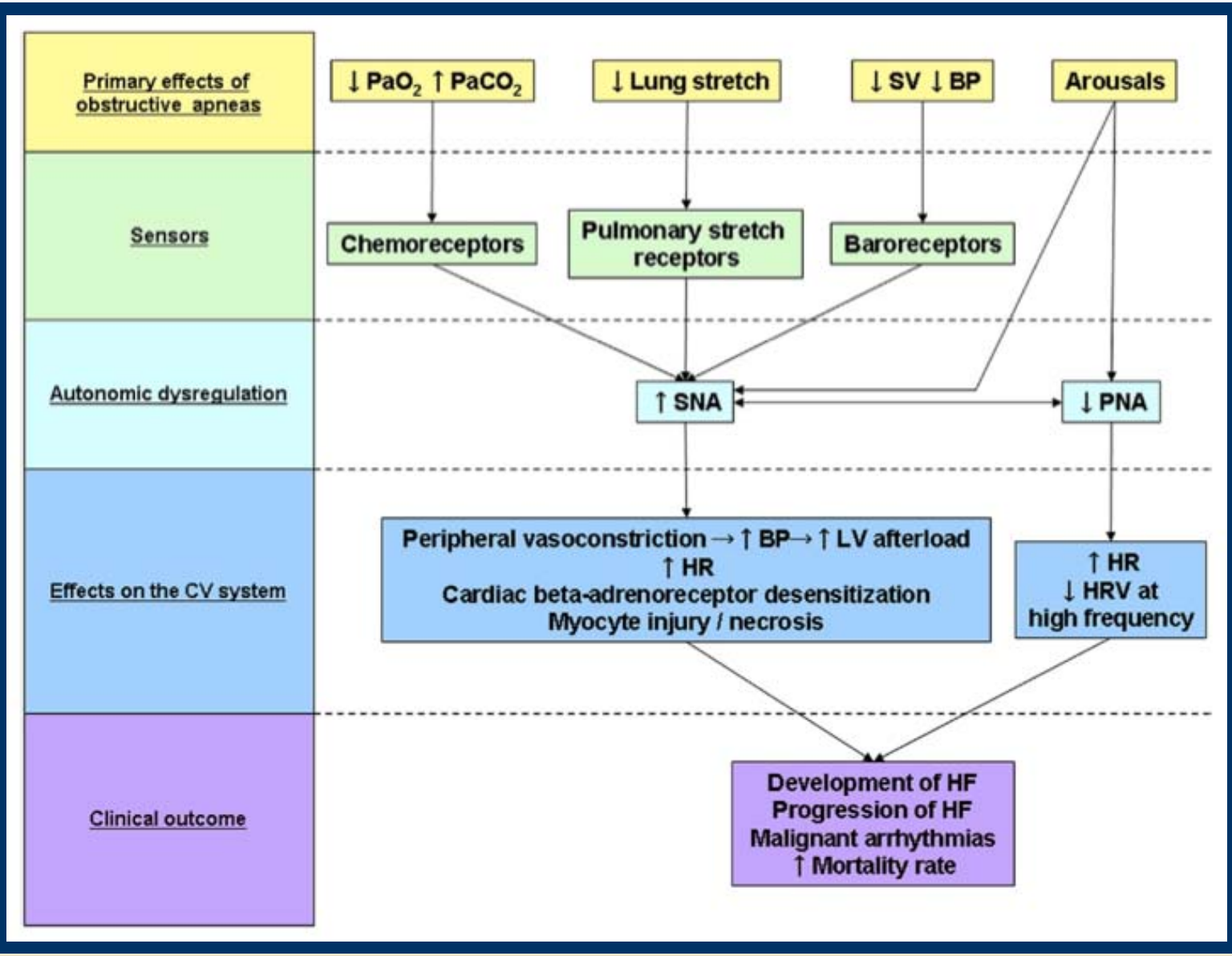
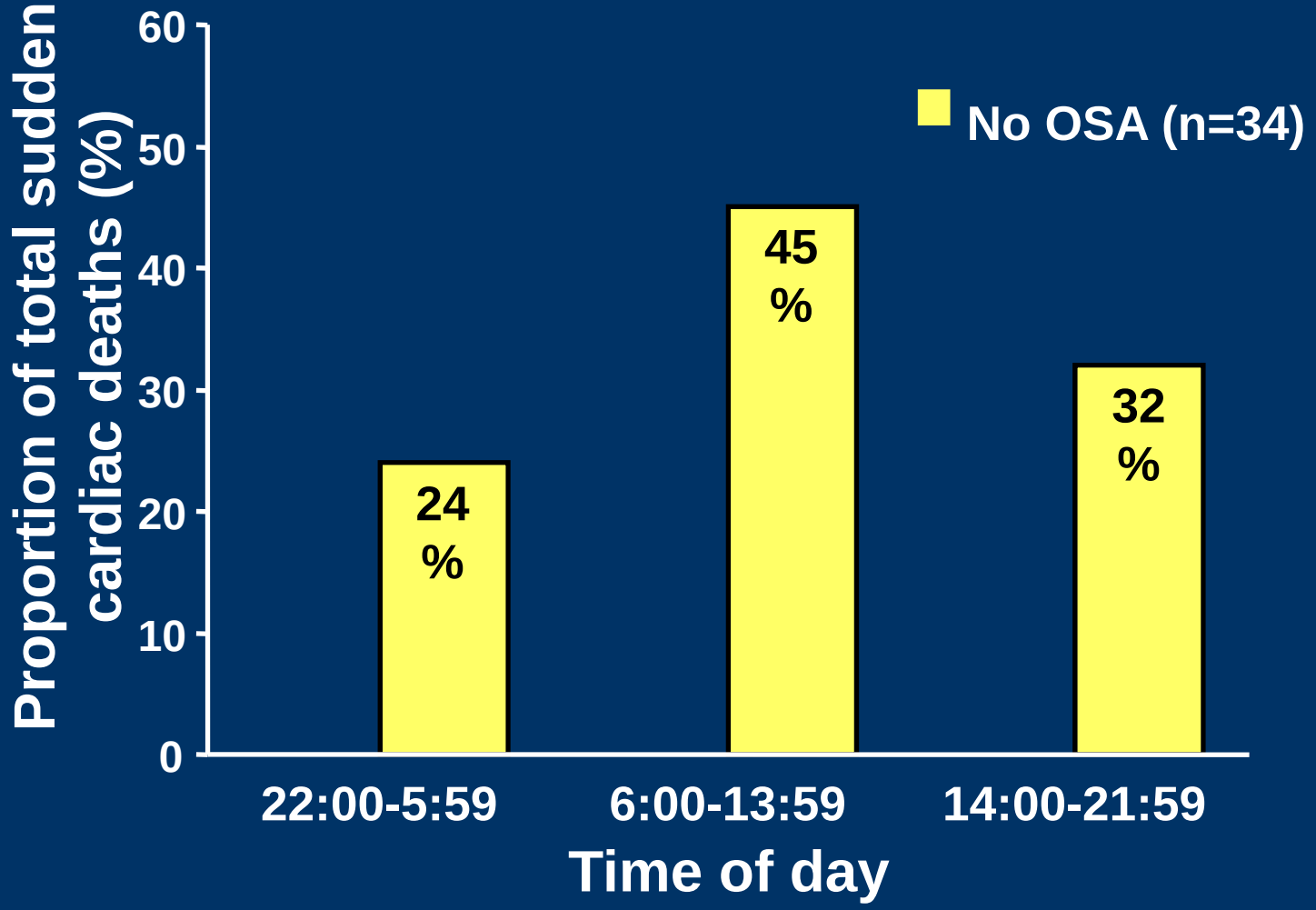


Figure 2 **Cardiovascular Autonomic Effects of OSA**

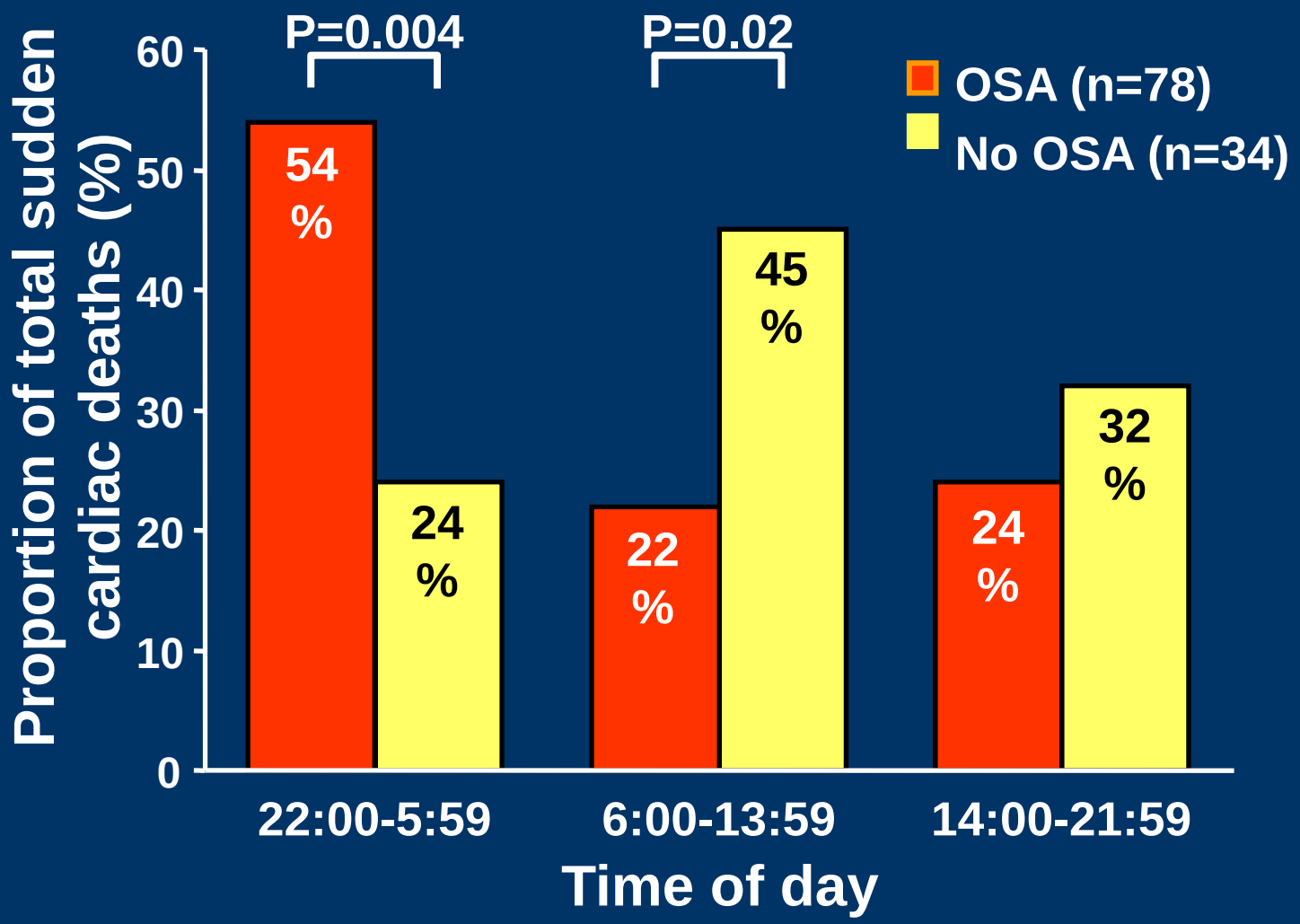
This diagram illustrates a number of mechanisms by which obstructive sleep apnea (OSA) augments sympathetic and diminishes parasympathetic activity. BP = blood pressure; CV = cardiovascular; HF = heart failure; HR = heart rate; HRV = heart rate variability; PNA = parasympathetic nervous system activity; SNA = sympathetic nervous system activity; SV = stroke volume.

Usual Sleep-Wake Cycles

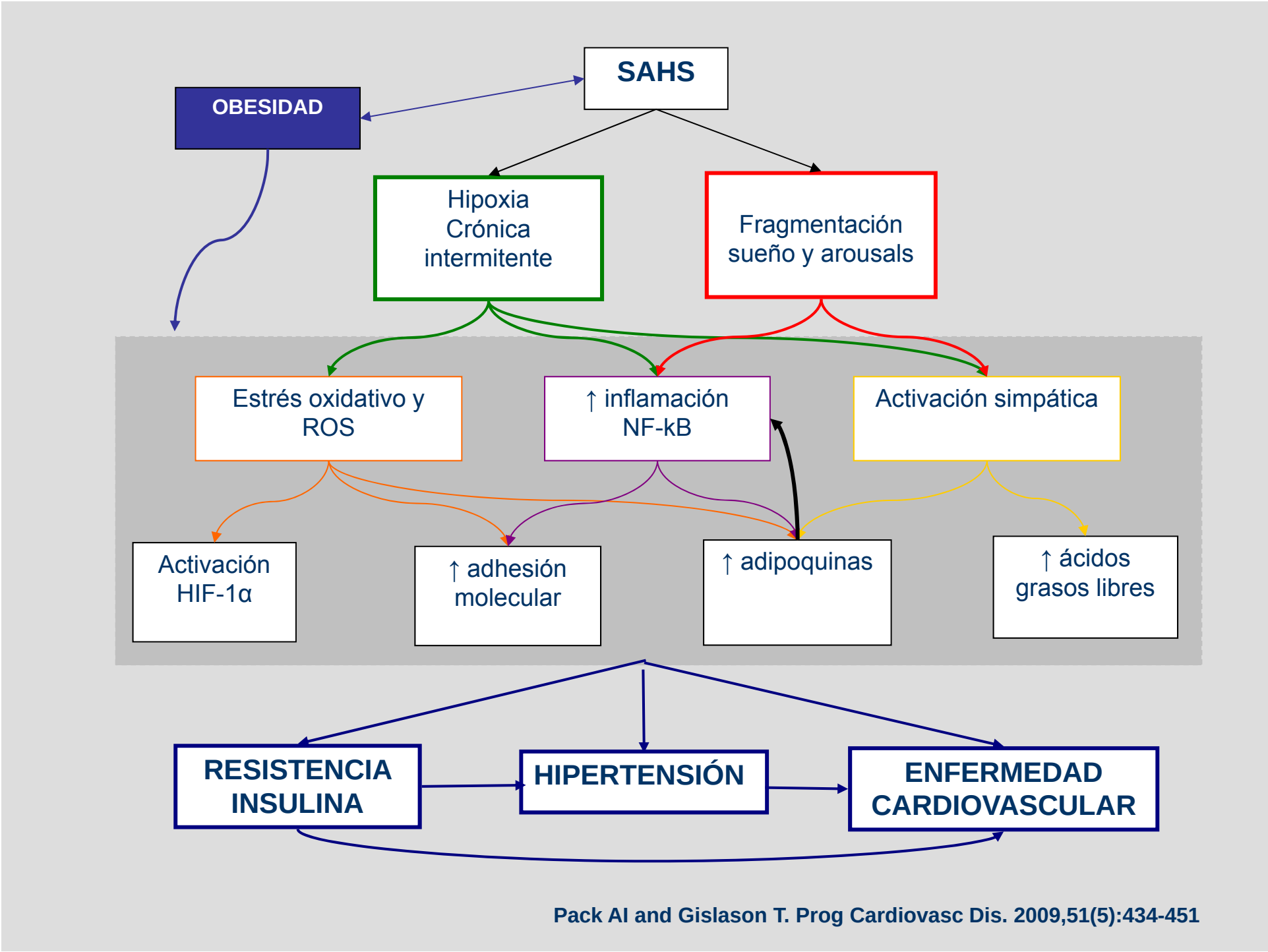


Gamiet al, NEJM 2005

Usual Sleep-Wake Cycles



Gamiet al, NEJM 2005

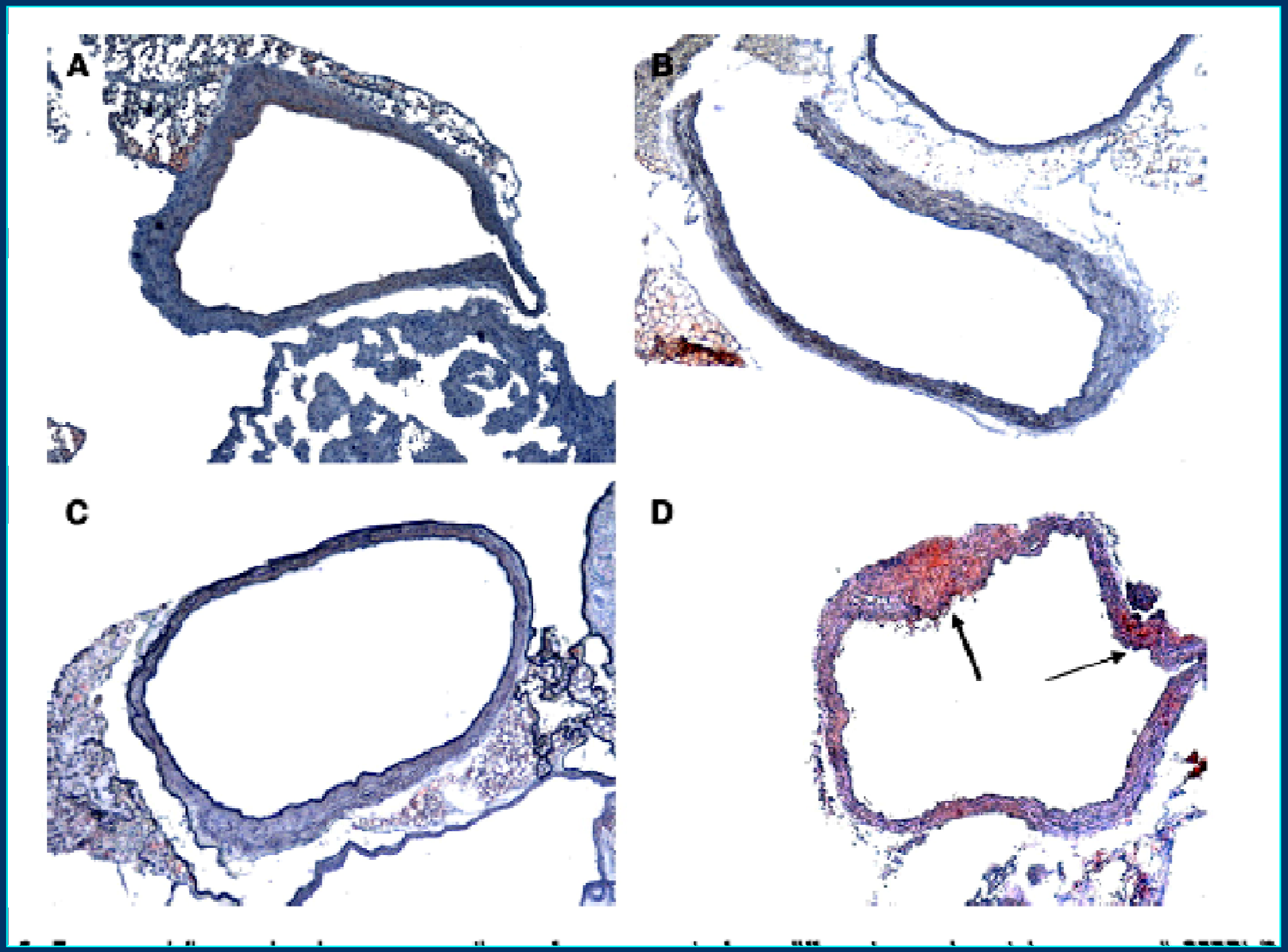


Pack AI and Gislason T. Prog Cardiovasc Dis. 2009,51(5):434-451

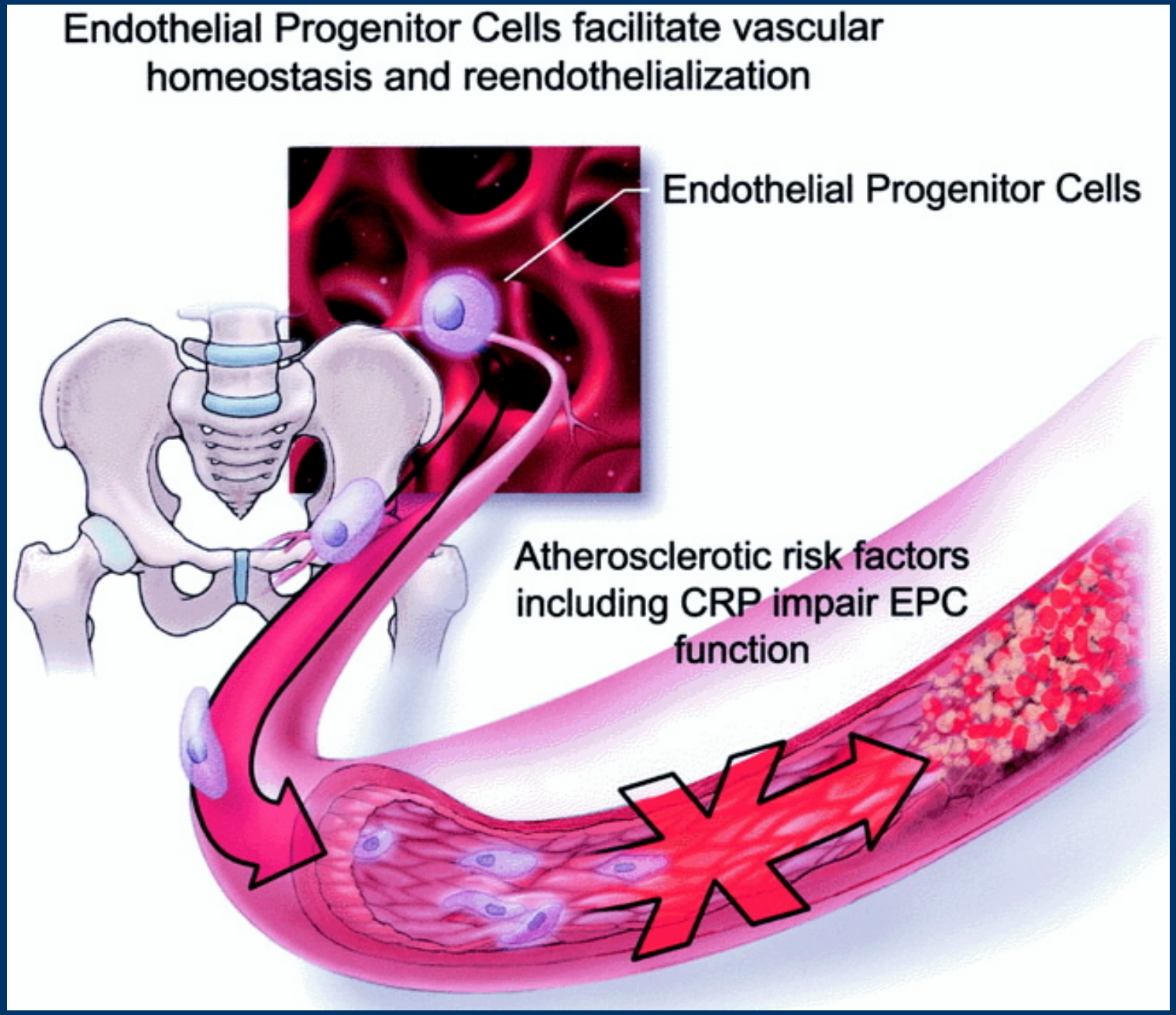
OSAHS and CV disease

Potential Mechanisms

- Oxidative stress
- Systemic inflammation
- Metabolic abnormalities
- Increased sympathetic tone
- Coagulation abnormalities
- Endothelial dysfunction
- Genetic background

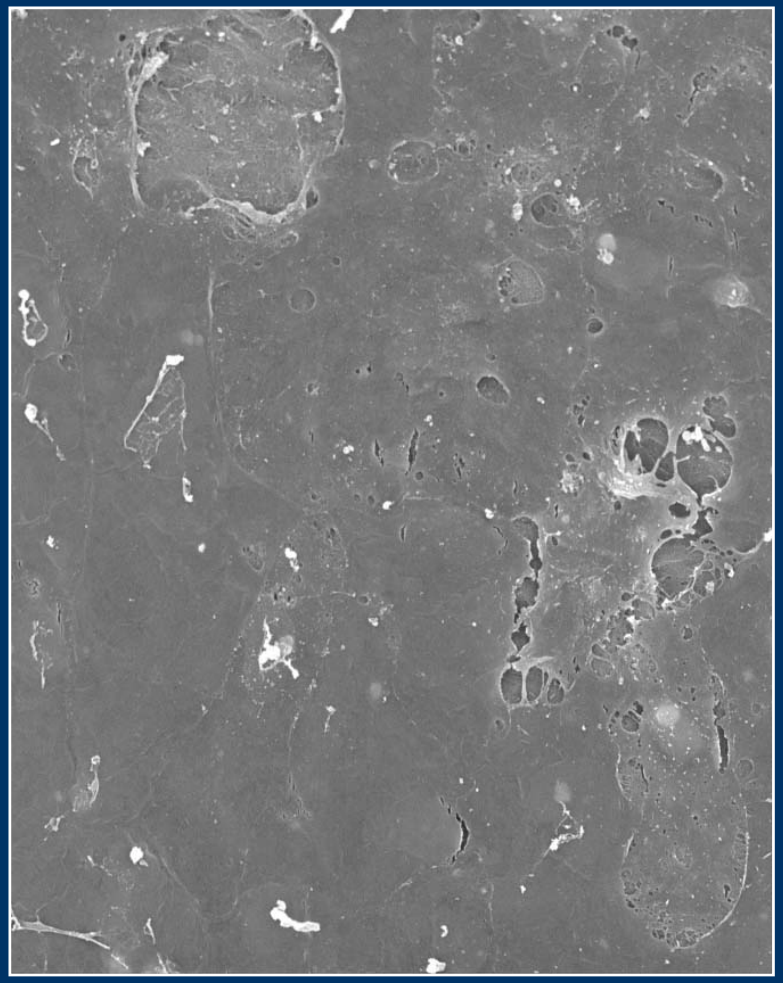


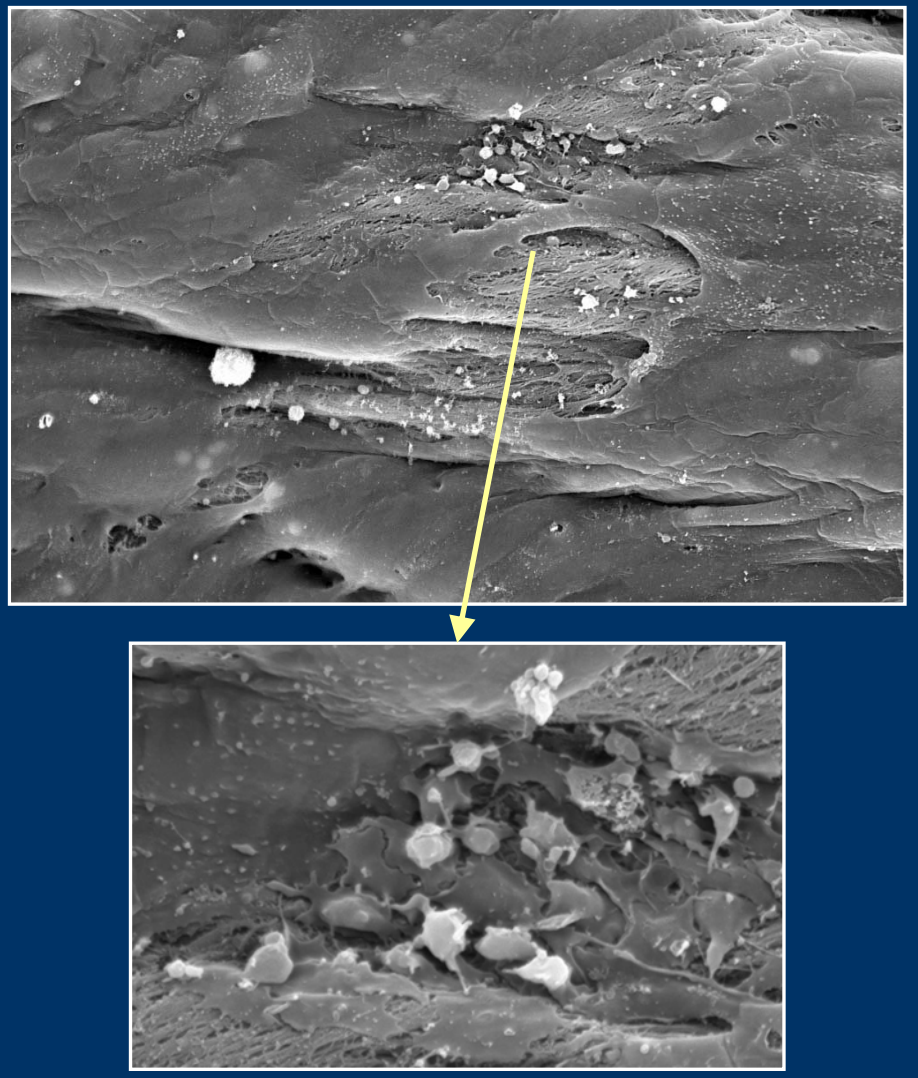
Polotsky AJRCCM 2009



Szmitko et al. *Circulation* 03; 108: 1917-23

Areas denudadas del endotelio vascular

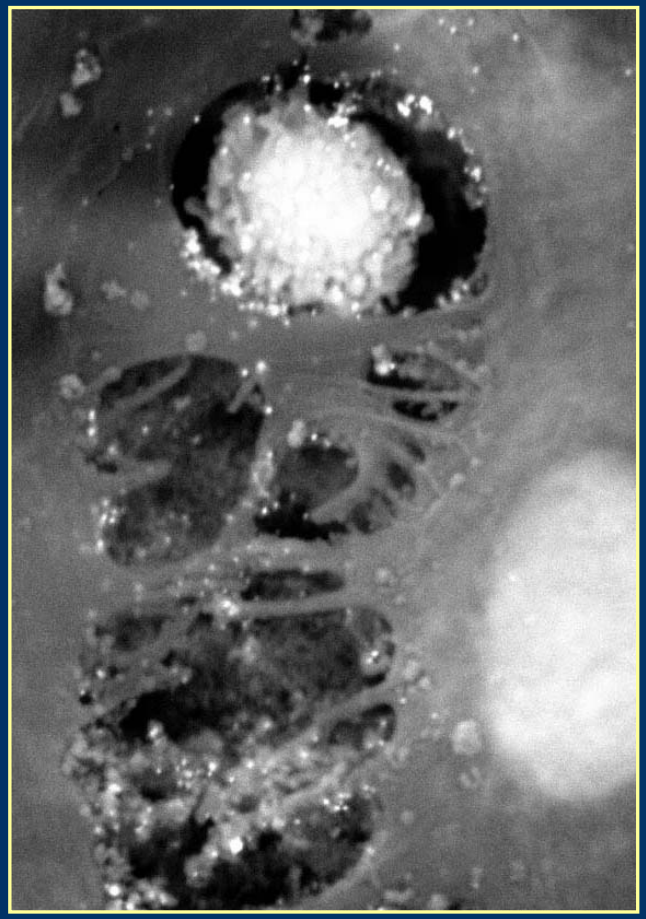


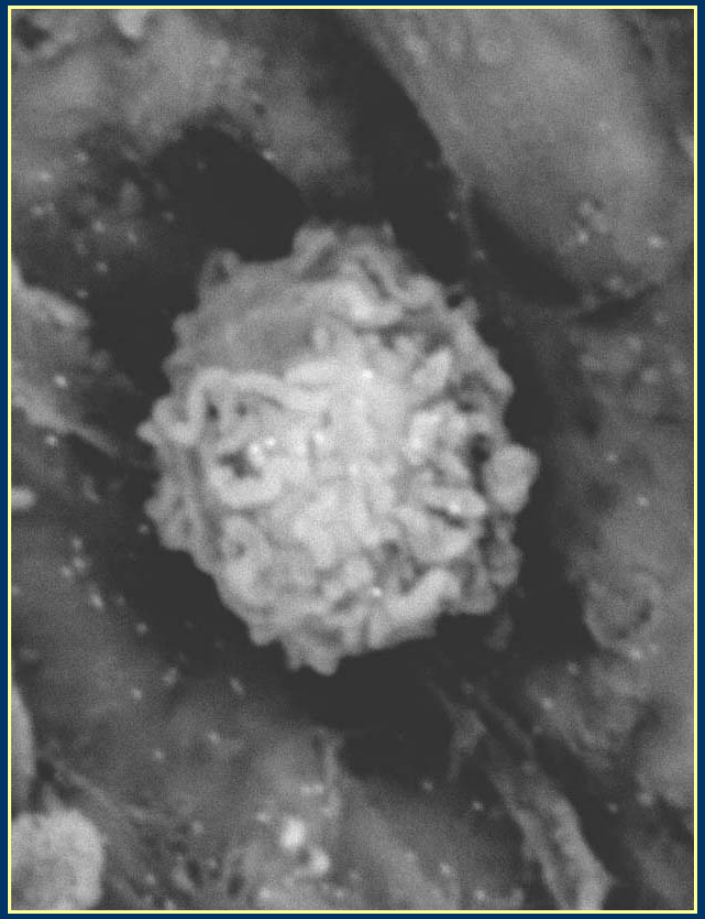


Peinado et al. ERJ 2004;24:435s

Células progenitoras endoteliales ($CD133^+$)

(técnica de inmunogold)





Peinado et al. ERJ 2004;24:435s

Endothelial progenitor cells in OSAHS

	SAHS n = 13	Control n = 13
Age (yr)	45±9	44±9
BMI ($kg.m^{-2}$)	28±2	27±3
$AHIh^{-1}$)	49±18	2±2
CD34 + (% linph)	0.11±0.01	0.13±0.01
EPCs (% CD34)	0.62±0.1	1.1±0.3
EPCs (% linphx$10^{(-3)}$)	0.59±0.07	1.2±0.26*

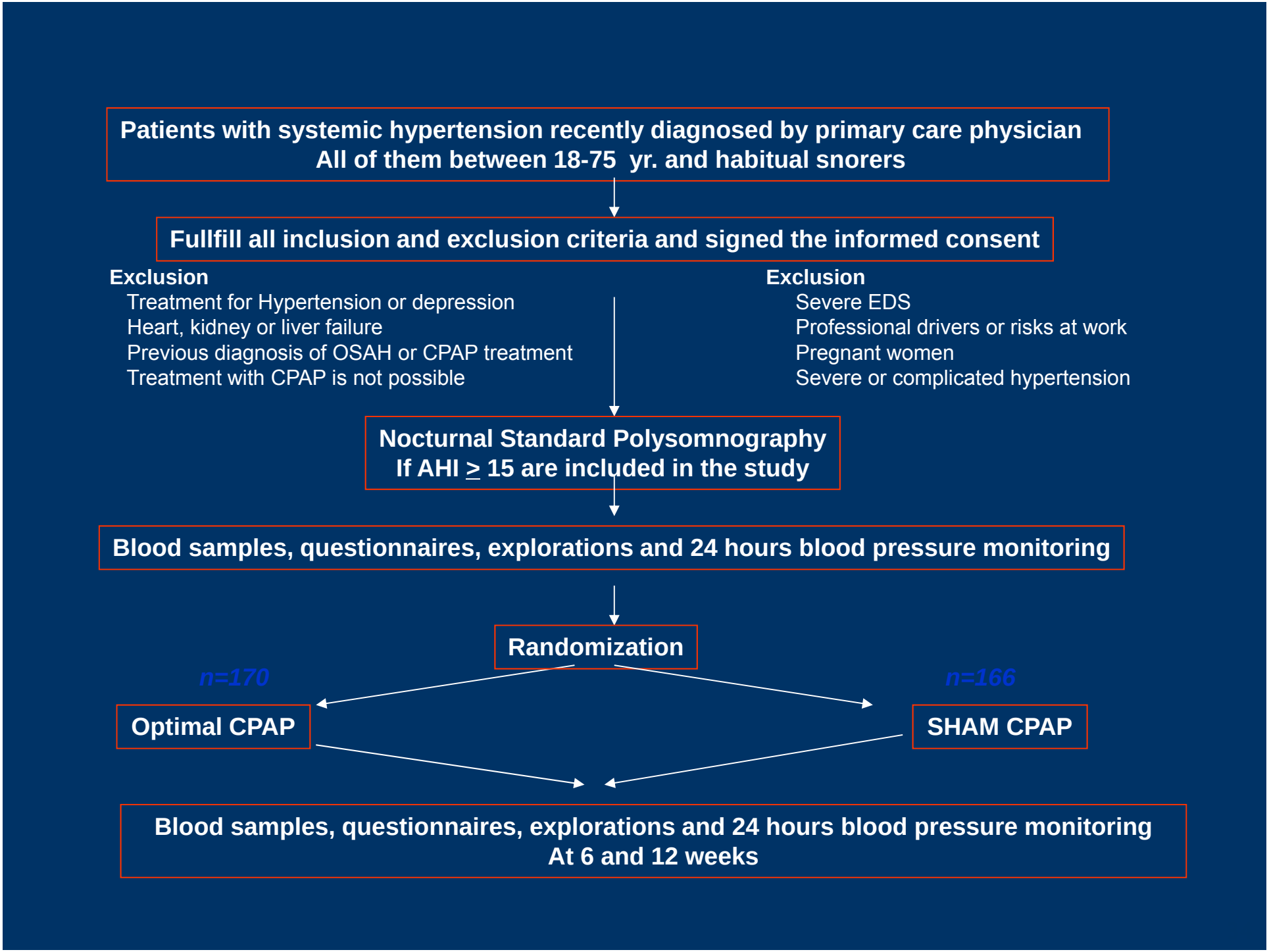
de la Peña Respiration 2007

SAS and cardiovascular disease

- Is there an association between SAS and CVD?
- Which are the pathogenic mechanisms?
- Recent studies and future challenges

- Objective: **To explore the effects of CPAP on systemic blood pressure in subjects with hypertension (new diagnostic) and have an apnea-hypoapnea index >15 h^{-1}**

- Design: **RCT, placebo control**


Patients with systemic hypertension recently diagnosed by primary care physician
All of them between 18-75 yr. and habitual snorers
Fullfill all inclusion and exclusion criteria and signed the informed consent
Exclusion
Treatment for Hypertension or depression
Heart, kidney or liver failure
Previous diagnosis of OSAH or CPAP treatment
Treatment with CPAP is not possible
Exclusion
Severe EDS
Professional drivers or risks at work
Pregnant women
Severe or complicated hypertension
Nocturnal Standard Polysomnography
If AHI ≥ 15 are included in the study
Blood samples, questionnaires, explorations and 24 hours blood pressure monitoring
Randomization
n=170
n=166
Optimal CPAP
SHAM CPAP
Blood samples, questionnaires, explorations and 24 hours blood pressure monitoring
At 6 and 12 weeks

Characteristics of the population

VARIABLE	SHAM	CPAP	*p*
n = 273	n = 135	n = 138	
Gender (% males)	84	80	0.3
Age (yr.)	52.3 ± 10.9	53.1 ± 9.6	0.5
BMI (Kg/m2)	32.0 ± 4.9	33.0 ± 6.3	0.2
Epworth	9.9 ± 4.4	10.4 ± 4.2	0.3
AHI	43.1 ± 24.8	43.0 ± 25.4	0.7
Diurnal SBP (mm Hg)	133.1 ± 10.7	134.4 ± 11.0	0.3
Nocturnal SBP (mm Hg)	122.2 ± 14.0	123.6 ± 12.2	0.3
Diurnal DBP (mm Hg)	85.3 ± 8.4	85.3 ± 8.1	0.9
Nocturnal DBP (mm Hg)	76.4 ± 10.4	76.4 ± 8.2	0.9
CPAP compliance (hr.)	4.3 ± 1.8	4.5 ± 1.7	0.3

Results of 24 hr. BPM

VARIABLE	BLOOD PRESSURE		Difference	P
	Basal	3 month		
SHAM CPAP				
Diurnal SBP	133 ± 11	132 ± 13	-0.8 ± 8.1	0.2
Nocturnal SBP	122 ± 14	121 ± 15	-0.8 ± 9.6	0.3
Diurnal DBP	85 ± 8	85 ± 9	-0.2 ± 2.4	0.7
Nocturnal DBP	76 ± 10	76 ± 10	-0.9 ± 7.2	0.1
OPTIMAL CPAP				
Diurnal SBP	134 ± 11	132 ± 12	-2.7 ± 9.7	0.001
Nocturnal SBP	124 ± 12	119 ± 13	-4.6 ± 12.5	<0.001
Diurnal DBP	85 ± 8	84 ± 9	-1.5 ± 6.2	0.006
Nocturnal DBP	76 ± 8	74 ± 9	-2.7 ± 7.6	<0.001

BMJ

RESEARCH

Continuous positive airway pressure as treatment for systemic hypertension in people with obstructive sleep apnoea: randomised controlled trial

Joaquín Durán-Cantolla, respiratory physician,[1,2] Felipe Aizpuru, epidemiologist,[3,4] Jose María Montserrat, respiratory physician,[5,6] Eugeni Ballester, respiratory physician,[5,6] Joaquín Terán-Santos, respiratory physician,[6,7] Jose Ignacio Aguirregomoscorta, respiratory physician,[8] Mónica Gonzalez, respiratory physician,[9] Patricia Lloberes, respiratory physician,[6,10] Juan Fernando Masa, respiratory physician,[6,11] Mónica De La Peña, respiratory physician,[6,12] Santiago Carrizo, respiratory physician,[6,13] Mercedes Mayos, respiratory physician,[14] Ferrán Barbé, respiratory physician,[2,6] on behalf of the Spanish Sleep and Breathing Group

Duran-Cantolla J, BMJ 24 Nov 2010

- Title: **Effect of CPAP on the incidence of hypertension and cardiovascular events in patients with sleep apnea and no daytime sleepiness (NCT 00127348)**

- Design: **RCT. 725 patients**

Patients description

	CPAP n= 349	Conservative n= 361
Age (yrs)	56 ± 10	55 ± 10
Male	85%	82%
AHI (h^{-1})	46 ± 21	37 ± 17*
BMI ($K.m^{-2}$)	31 ± 5	31 ± 5
Epworth	6.5 ± 2	6.5 ± 2
SBP (mmHg)	131 ± 17	132 ± 17
DPB (mmHg)	80 ± 11	80 ± 11
Hypertensive (%)	51	50
Compliance (h)	4.2 ± 2	-

CARDIAC FUNCTION IMPROVEMENT WITH CPAP THERAPY IN CHRONIC HEART FAILURE AND SLEEP APNOEA.

Carlos J Egea, MD[1] , Jose A Pinto, MD[2], Jose M Ayuela, MD[3], Eugeni Ballester, MD [4], Carlos Zamarrón MD [5], Agustin Sojo MD [6] and Ferran Barbe MD [7]

On behalf of the Spanish Group of Sleep Breathing Disorders:

Vanessa Zorrilla[1], Ramon Rubio[1], Angel Alonso[1] , Felipe Aizpuru[1], Jose L Lobo[1] , Joaquin Duran-Cantolla[1] , Julia Cortés[8], Antonio Jiménez[2], Jose Cifrián [2], M Ortega [2], Rosario Carpizo[2], A Sánchez [2], Joaquin Terán[3], L Iglesias [3],Carmen Fernández [3], Mari L. Alonso[3], J Cordero [3], Josep M Montserrat [4], Eulalia Roig [4], Felix Pérez [4,] Africa Muxi[4] , Francisco Gude[5], Antonio Amaro[5], Uxio Calvo[5], Juan F. Masa [6], Isabel Utrabo [6], Yolanda Porras[6], Isabel Lanchas[6], E Sánchez[6].

Centers

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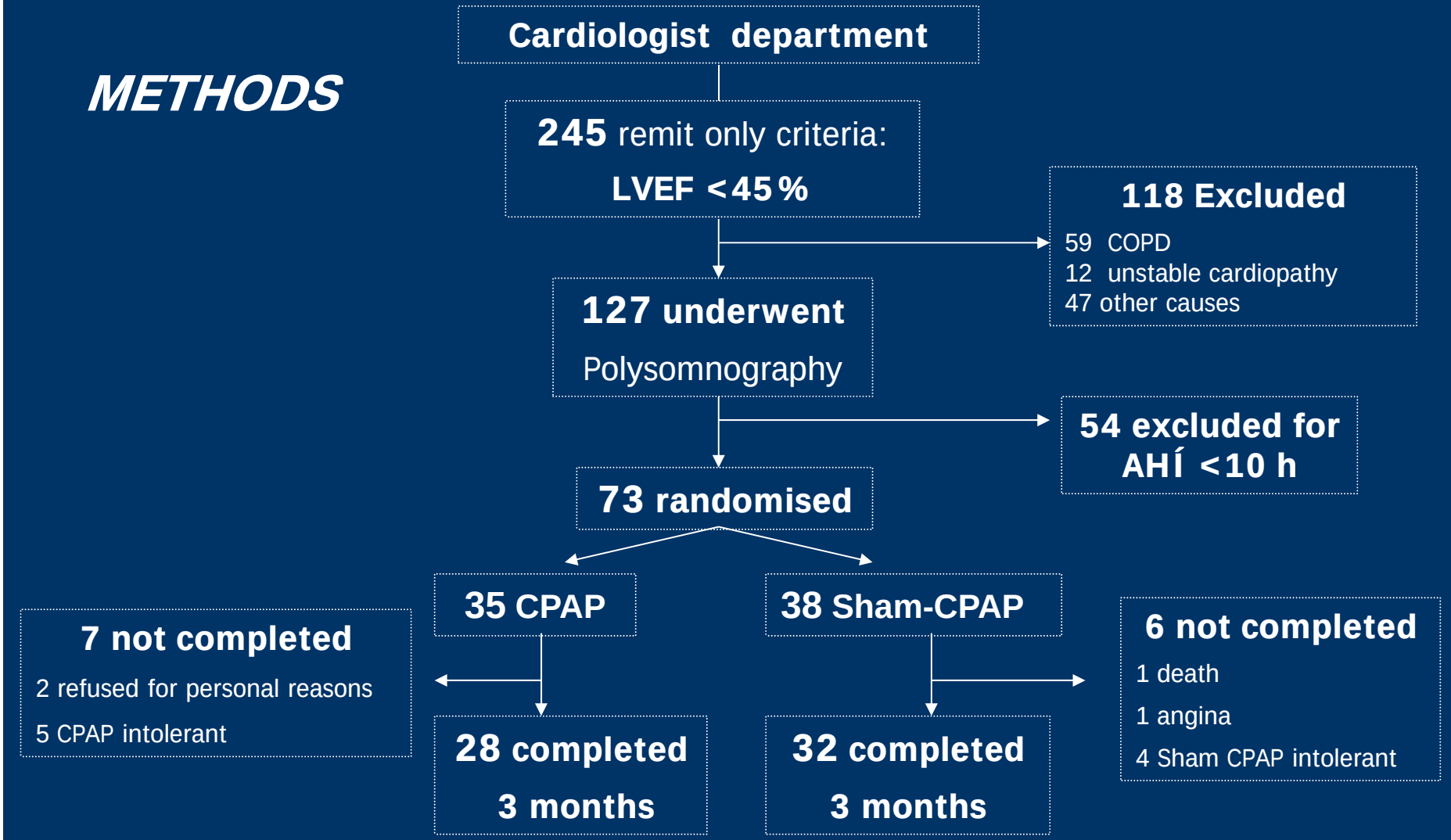
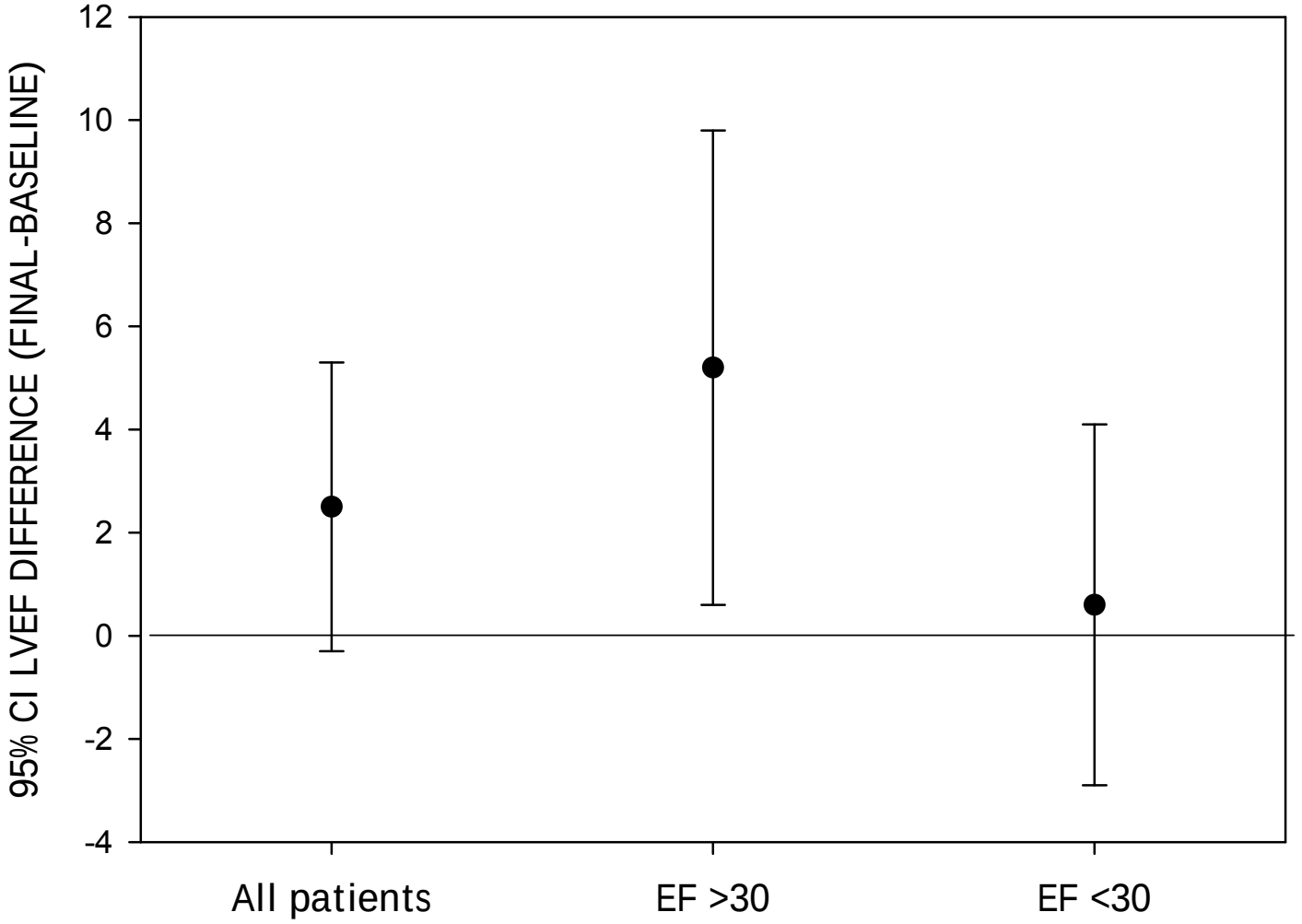
4 Hospital Clínic (Barcelona)
5 Hospital Universitario Compostela (Compostela)
6 Hospital San Pedro de Alcántara (Cáceres)
7 Hospital Son Dureta (Mallorca)
8 Hospital Santiago Apóstol (Vitoria)

METHODS


Cardiologist department
245 remit only criteria:
LVEF <45%
118 Excluded
59 COPD
12 unstable cardiopathy
47 other causes
127 underwent
Polysomnography
54 excluded for
AHÍ <10 h
73 randomised
35 CPAP
38 Sham-CPAP
7 not completed
2 refused for personal reasons
5 CPAP intolerant
6 not completed
1 death
1 angina
4 Sham CPAP intolerant
28 completed
3 months
32 completed
3 months

	Patients at baseline (n=73)		
	CPAP (n=35)	Sham CPAP (n=38)	p-value
Age (yr.)	62 (10)	63 (9)	0.525
Sex (% male)	91	90	0.777
BMI (Kg m-²)	29.0 (4.2)	28.5 (4.5)	0.619
Daily snoring (%)	84	68	0.158
Snoring 3 or more times/week (%)	90	74	0.113
Epworth scale	8.7 (4.0)	7.5 (4.5)	0.225
Minimum SaO2 (%)l	78.1 (10.2)	77.5 (11.6)	0.819
AHÍ	40 (22)	42 (30)	0.843



Egea, Sleep Med 2008

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Continuous Positive Airway Pressure for Central Sleep Apnea and Heart Failure

T. Douglas Bradley, M.D., Alexander G. Logan, M.D., R. John Kimoff, M.D., Frédéric Sériès, M.D., Debra Morrison, M.D., Kathleen Ferguson, M.D., Israel Belenkie, M.D., Michael Pfeifer, M.D., John Fleetham, M.D., Patrick Hanly, M.D., Mark Smilovitch, M.D., George Tomlinson, Ph.D., and John S. Floras, M.D., D. Phil., for the CANPAP Investigators*

N Engl J Med 2005;353:2025

Bradley T.D. N Engl J Med 2005

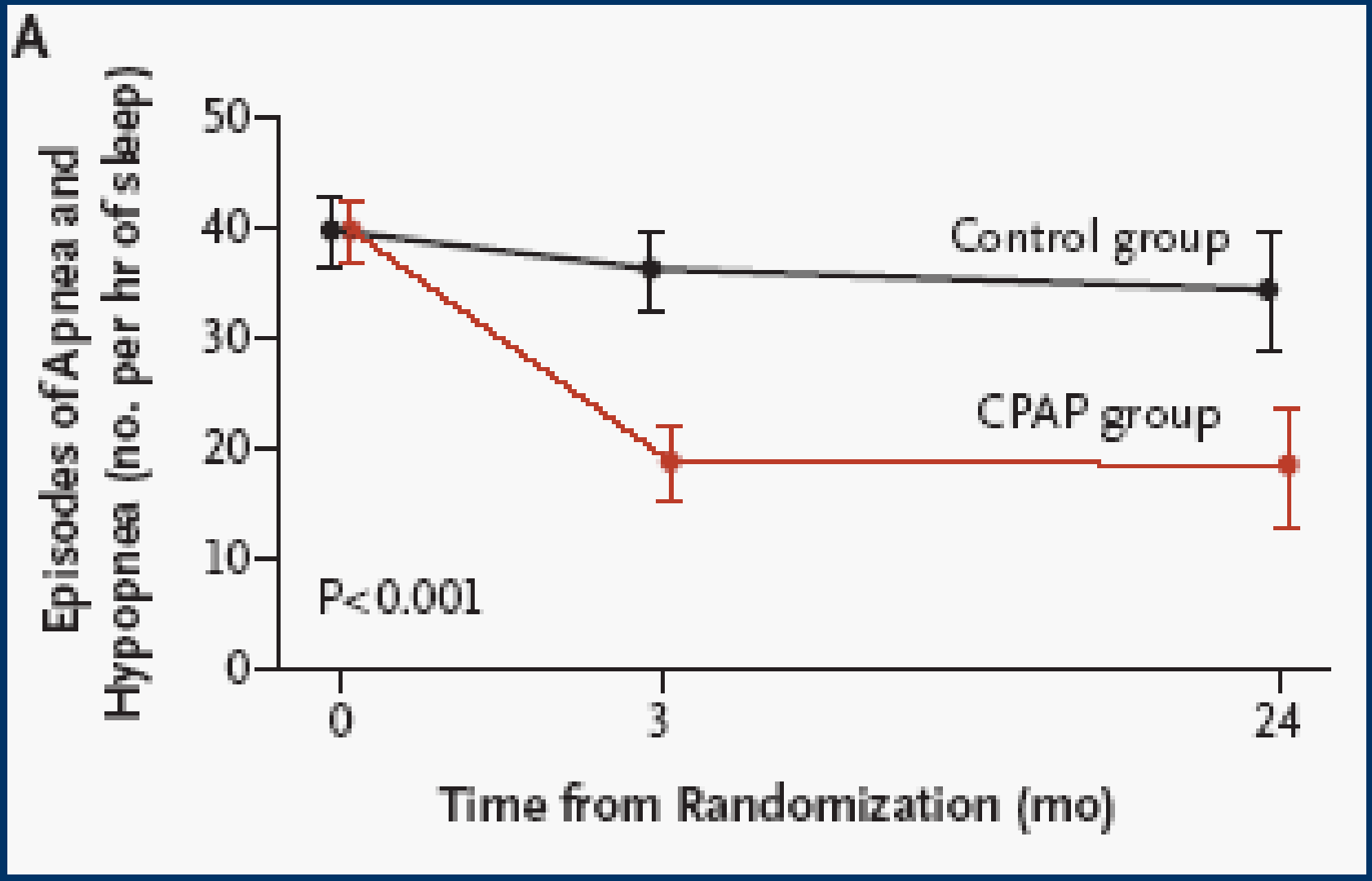
- Design: randomized parallel trial
- Main outcome: survival rate
- Secondary outcomes:
  - Ejection fraction
  - Exercise capacity
  - Quality of live
  - Neurohormones
- Inclusion criteria:
  - LVEF < 40%
  - AHI > 15 (> 50% central)

Baseline characteristics of the patients

Characteristic	Control Group (N=130)	CPAP Group (N=128)
Age — yr	63.5±9.8	63.2±9.1
Male sex — no. (%)	123 (95)	125 (98)
White race — no. (%)	123 (95)	121 (95)
Body-mass index†	29.3±6.5	28.8±5.5
Left ventricular ejection fraction — %	24.2±7.6	24.8±7.9
Arousals from sleep — no./hr of sleep	28±23	29±23
Apnea–hypopnea index — no./hr of sleep	40±17	40±15
Central apnea and hypopnea — %	87±14	91±12
Mean SaO_2 during sleep — %	93.1±3.1	93.2±3.7
Lowest SaO_2 during sleep — %	81.7±6.5	82.1±8.2

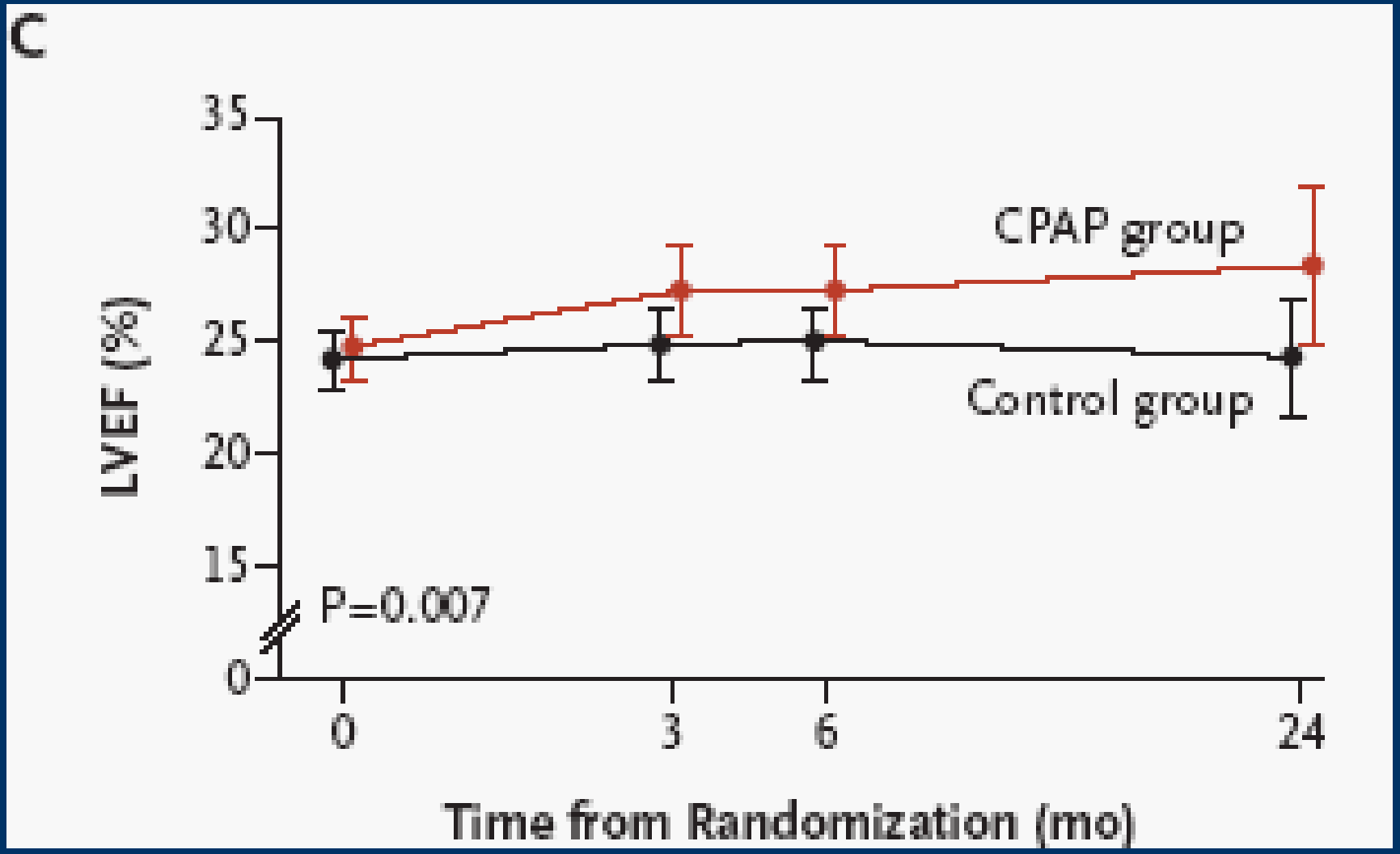
Bradley T.D. N Engl J Med 2005

Number of episodes of apnea and hypopnea/h



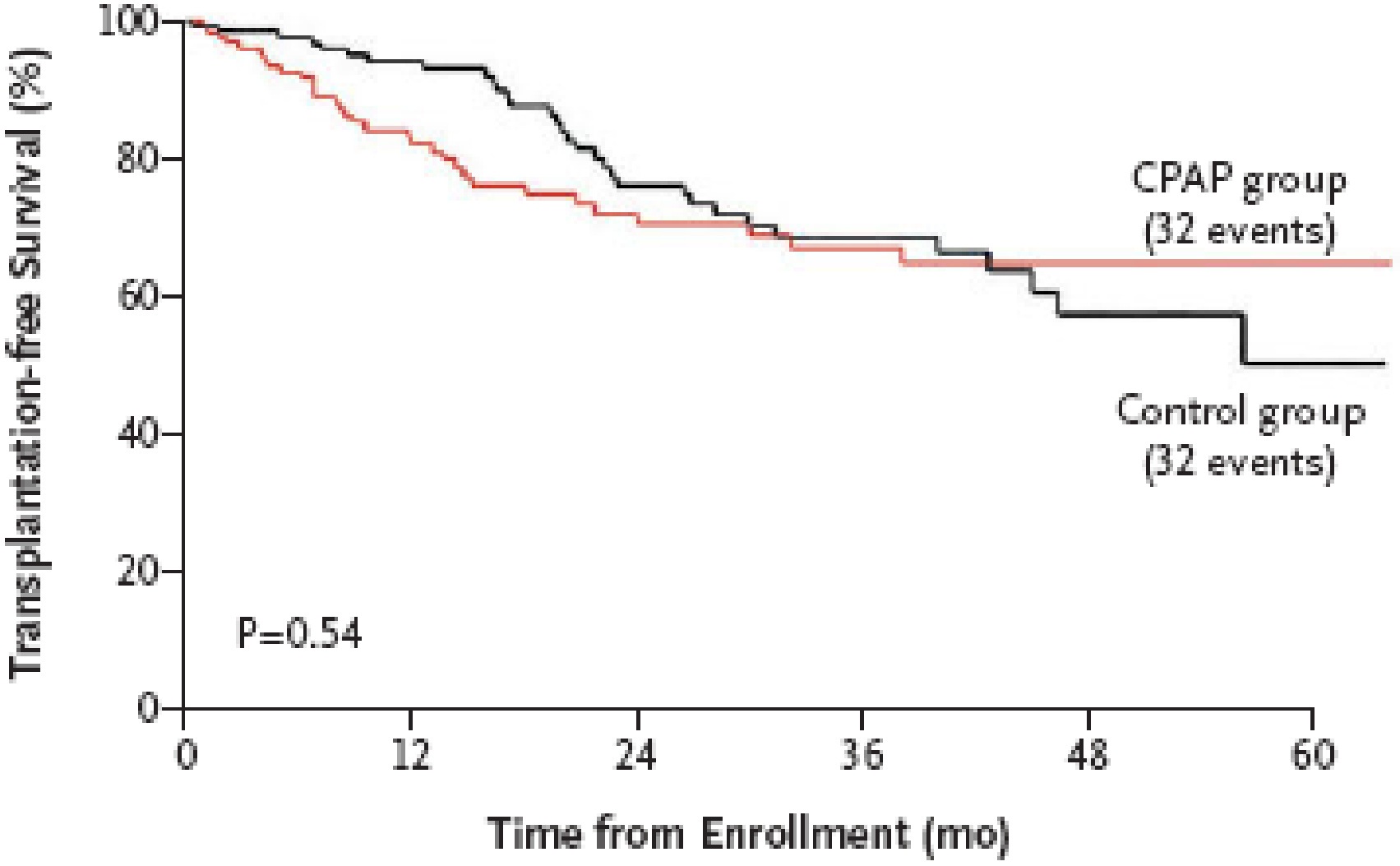
Bradley T.D. N Engl J Med 2005

Left ventricular ejection fraction (%)



Bradley T.D. N Engl J Med 2005

Transplantation-free survival (%)



Bradley T.D. N Engl J Med 2005

Conclusion: Although NIV attenuates central sleep apnea, improves nocturnal oxygenation, increases the ejection fraction and lowers catecholamines levels, it did not affect either survival or quality of live. Avaible data does not support the use of NIV to exten live in patients who suffer from central apneas and heart failure.

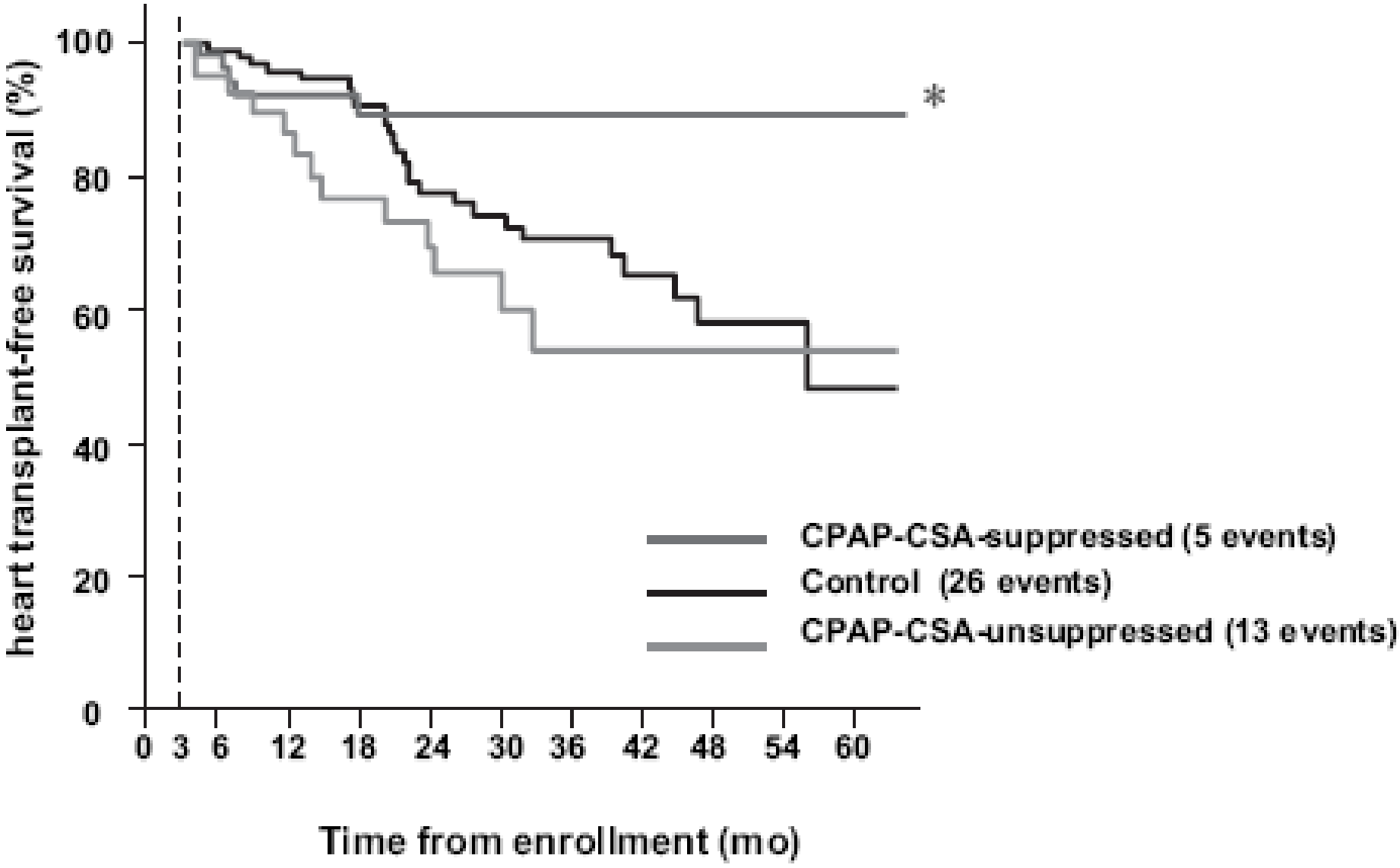
Modified from Bradley T.D. N Engl J Med 2005

Suppression of Central Sleep Apnea by Continuous Positive Airway Pressure and Transplant-Free Survival in Heart Failure

A Post Hoc Analysis of the Canadian Continuous Positive Airway Pressure for Patients With Central Sleep Apnea and Heart Failure Trial (CANPAP)

Michael Arzt, MD; John S. Floras, MD, DPhil; Alexander G. Logan, MD; R. John Kimoff, MD; Frederic Series, MD; Debra Morrison, MD; Kathleen Ferguson, MD; Israel Belenkie, MD; Michael Pfeifer, MD; John Fleetham, MD; Patrick Hanly, MD; Mark Smilovitch, MD; Clodagh Ryan, MD; George Tomlinson, PhD; T. Douglas Bradley, MD; for the CANPAP Investigators

Circulation 2007



Arzt Circulation 2007

CONCLUSIONS: These results suggest that in heart failure patients, CPAP might improve both left ventricular ejection fraction and heart transplant-free survival if CSA is suppressed soon after its initiation

Arzt Circulation 2007

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N Engl J Med 2005

CONCLUSIONS: These results suggest that in heart failure patients, CPAP might improve both left ventricular ejection fraction and heart transplant-free survival if CSA is suppressed soon after its initiation

Circulation 2007

CPAP for central apneas and CHF

Improves	
Central sleep apnea	
Nocturnal oxygenation	
LVEF	
Norepinephrine levels	

Bradley T.D. N Engl J Med 2005

CPAP for central apneas and CHF

Improves	Not improves
Central sleep apnea	**Survival**
Nocturnal oxygenation	**Quality of live**
LVEF	**Number of hospitalizations**
Norepinephrine levels	**6’ walking test**

Bradley T.D. N Engl J Med 2005

Toronto Rehab
Everything Humanly Possible

Estudio Multicéntrico, aleatorizado para evaluar los efectos de Ventilación Servo-adaptativa (ASV) sobre la Supervivencia y Frecuencia de Ingresos Hospitalarios Cardiovasculares (CV) en Pacientes con Fallo Cardiáco (HF) y Síndrome de Apnea del Sueño (SAS)

(ADVENT-HF Trial)

Canadian Institutes of Health Research (CIHR) y Philips-Respironics Inc.

Conclusions I

- **OSAHS is significantly associated to CV morbidity and mortality.**
- **Multiple mechanisms link OSAHS and CV disease.**
- **CPAP therapy effectively abolishes OSAHS and improves CV outcomes,**

Conclusions II

The challenge of “non-clinic” population:

- 40% of the hypertensive patients who snore show an AHI > 15 h.
- CPAP reduce blood pressure in these subjects
- CPAP decreases the incidence of CVE and HT in OSAS patients

Spanish Sleep and Breathing Network