Sleep Apnea:

…the heart suffers even while sleeping…

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Cosme Argerich Hospital Symposium
November 2010

Sleep Apnea and Cardiovascular Disease

1. Definitions and clinical symptoms
2. Epidemiology
3. Pathophysiology
4. The link between SA and cardiovascular disease
5. Diagnostic yield
6. Brief summary of management
7. Areas of investigation

Sleep Apnea
Definitions

1. SA: a history of excessive sleepiness, frequent episodes of obstructing breathing during sleep, snoring, morning headaches, “arousals” + polysomnography showing apneic episodes longer than 10 seconds (at least 5 per hour)
2. Apnea: cessation of air flow, 0_2 saturation reduction ≥ 4%
   - ► Central: alteration at CNS level
   - ► Obstructive: alteration at the upper respiratory way
3. Hypopnea: air flow reduction ≥ 30%, 02 saturation reduction ≥ 4%
4. AHI (Apnea/hypopnea index): amount of apneas & hypopneas per hour

Sleep Apnea: Pathophysiology

Progress in Cardiovascular Diseases

Vol. 41, No. 5
March/April 1999

Pathogenesis of Obstructive Sleep Apnea

M. Safwan Badr

Mechanisms of obstruction of airways during sleep:

1. Sub-atmospheric intraluminal pressure
2. Expiratory narrowing
3. Ventilatory-motor reduction
4. Mixed theory: central + obstructive

The link between SA and cardiovascular morbidity

Cardiovascular Morbidity in Obstructive Sleep Apnea

J. Woodrow Weiss, Sandrine H. Launois, Amit Anand, and Erik Garpestad

Progress in Cardiovascular Diseases, Vol. 41, No. 5 (March/April), 1999: pp 367-376

1. Physiological changes during sleep

a. In NREM stage: BP and HR reduction (10-20%): ↓ of CO and TPR, ↓ sympathetic tone in phase 4 of NREM

b. In REM stage: vasoconstriction + fluctuation of CO and HR

2. Acute changes during SA

a. HR: there are 2 possible patterns:
   - Bradycardia at the onset of apnea, acceleration during SA (chemoreceptors) and acceleration peak at the end of apnea and arousal *(more frequent)*
   - Progressive bradycardia along the apnea

b. BP: increase at the end of apnea (> desaturation, ↑ sympathetic tone by arousal)

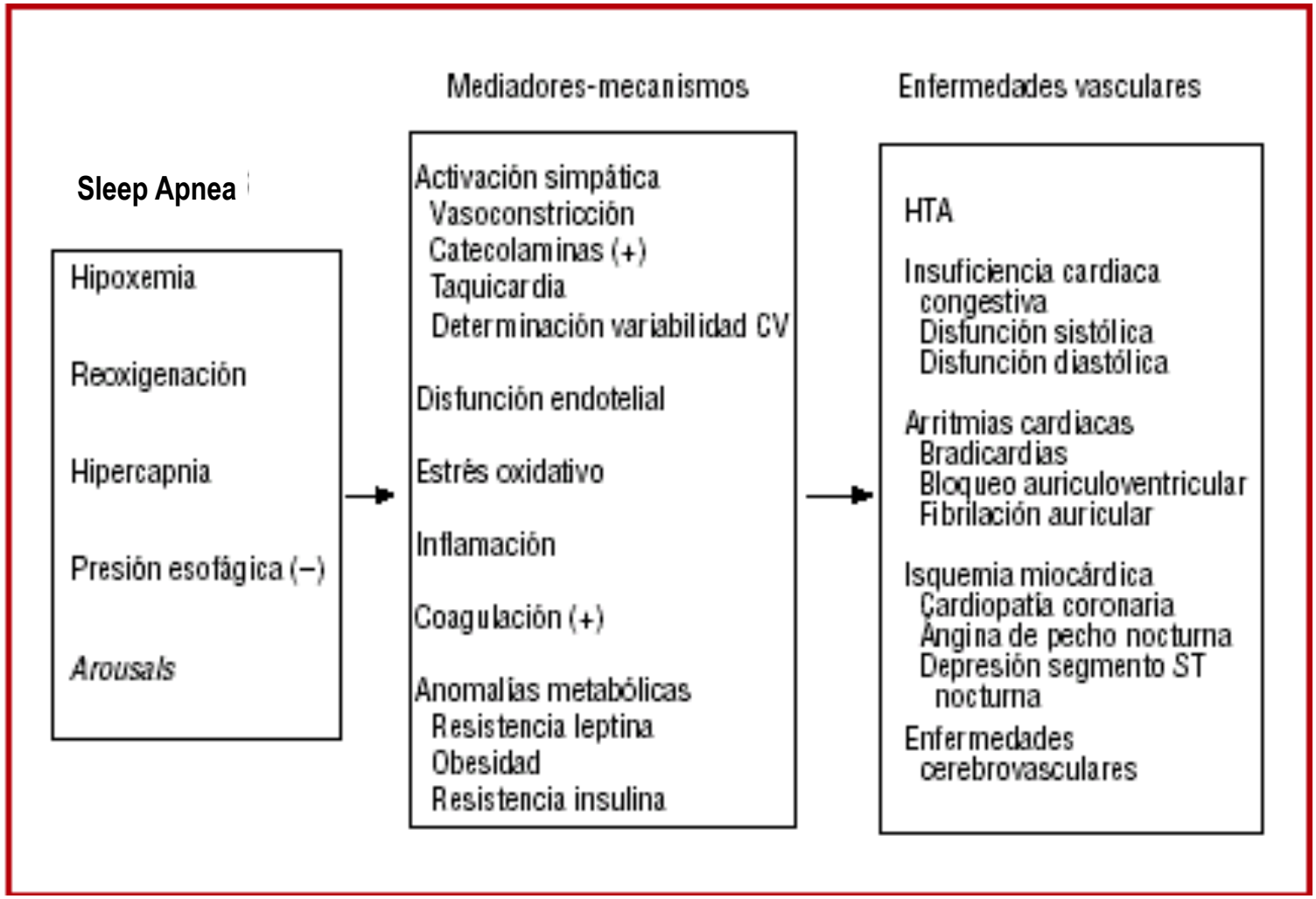
c. Cardiac Output: ↓ ejection volume during apnea along with intrapleural negative pressure

Pathophysiologic mechanisms of cardiovascular morbidity

Síndrome de apneas-hipopneas durante el sueño y corazón

Joaquín Terán Santos[a], M. Luz Alonso Álvarez[a], José Cordero Guevara[b], José María Ayuela Azcárate[c] y José María Monserrat Canal[d]

Rev Esp Cardiol. 2006;59(7):718-24



In summary…

Cardiovascular Morbidity in Obstructive Sleep Apnea

J. Woodrow Weiss, Sandrine H. Launois, Amit Anand, and Erik Garpestad

Progress in Cardiovascular Diseases, Vol. 41, No. 5 (March/April), 1999: pp 367-376

SA

Fluctuations of BP, HR and cardiac putput + Desaturation 0_2

Cardiovascular morbidity

Acute changes

- Arrhythmias
- Myocardial infarction
- Stroke

Chronic changes

- CHF
- HTN
- Pulmonary HTN
- LVH

Sleep Apnea:
SA and Arrhythmias

1. Bradyarrhythmias

   - Sinus arrest

   - AV block

2. Tachyarrhythmias

   - Atrial fibrillation

   - Ventricular arrhythmias

What is the available evidence?

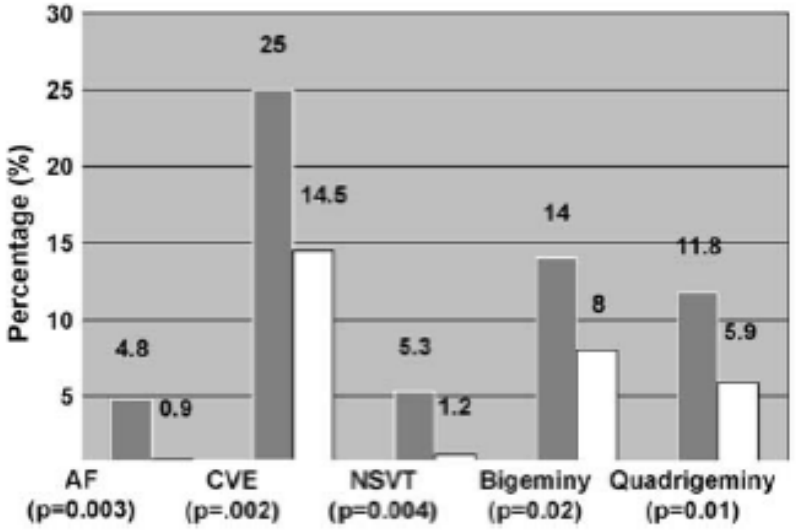
Sleep Apnea:
SA and Arrhythmias

Association of Nocturnal Arrhythmias with Sleep-disordered Breathing

The Sleep Heart Health Study

AMERICAN JOURNAL OF RESPIRATORY AND CRITICAL CARE MEDICINE VOL 173 2006

	SDB, % (*n* = 228)	No SDB, % (*n* = 338)	Pearson's χ^2 p Value
Ventricular Arrhythmias			
Premature Ventricular Contraction (≥ 5/h)	35.1	21.3	0.0003
Bigeminy	14.0	8.0	0.02
Trigeminy	9.2	5.6	0.10
Quadrigeminy	11.8	5.9	0.01
Nonsustained ventricular tachycardia	5.3	1.2	0.004
Complex ventricular ectopy*	25	14.5	0.002
Supraventricular Arrhythmias			
Premature atrial contraction (≥ 5/h)†	33.8	24.3	0.001
Atrial fibrillation	4.8	0.9	0.003
Supraventricular tachycardia	14.9	14.5	0.89
Conduction Delay Arrhythmias			
Sinus pause (≥ 3 s)	11.0	8.6	0.34
First-degree atrioventricular block	25.0	22.5	0.49
Second-degree atrioventricular block type 1	1.8	0.3	0.07
Second-degree atrioventricular block type 2	2.2	0.9	0.20
Intraventricular conduction delay	8.9	5.3	0.11

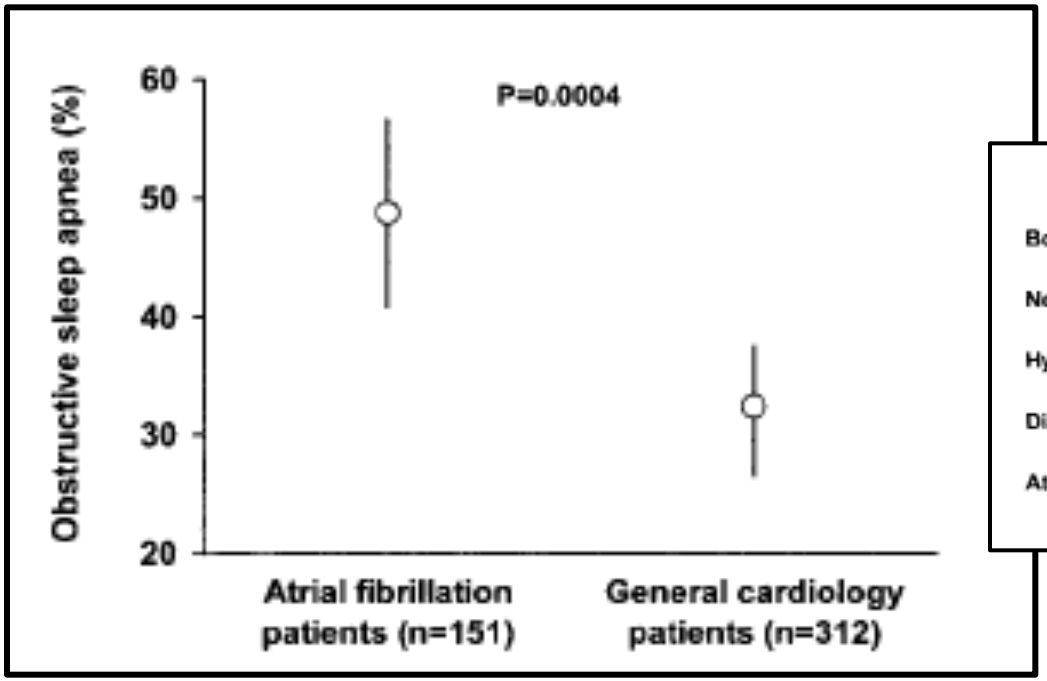


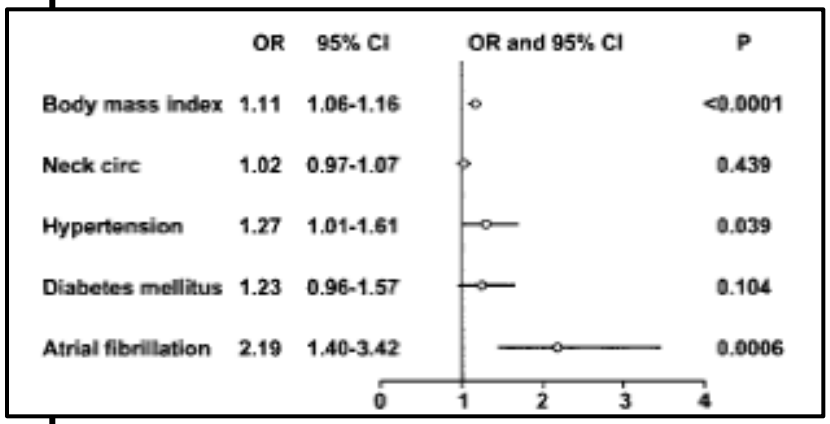
The association between SA and AF is highly significant. SA is also associated to ventricular arrhythmias.

Sleep Apnea:
SA and AF

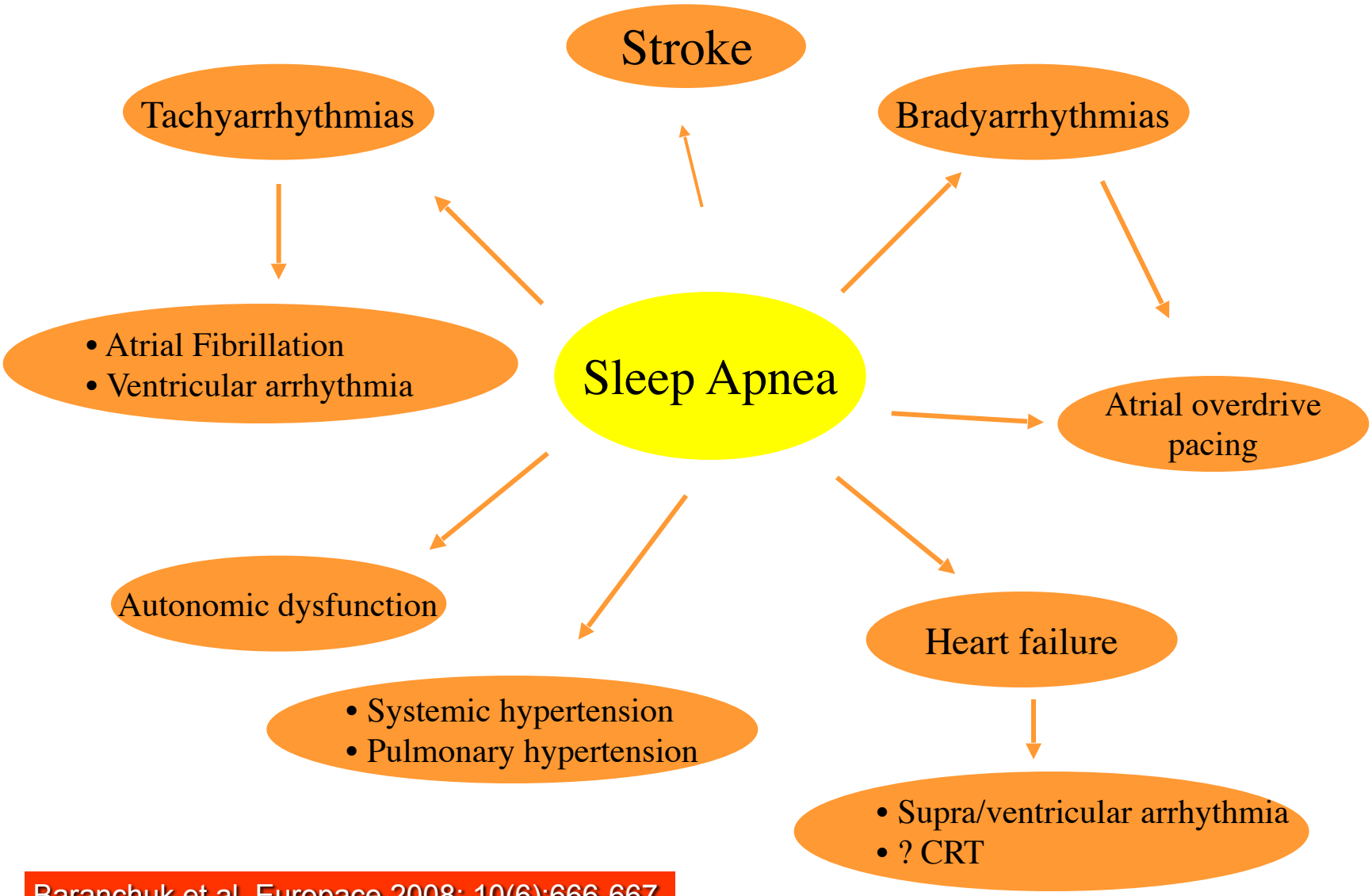
Association of Atrial Fibrillation and Obstructive Sleep Apnea

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





It's time to wake up!: sleep apnea and cardiac arrhythmias



Baranchuk et al. Europace 2008; 10(6):666-667

Sleep Apnea :
SA and Arrhythmias

It's time to wake up!: sleep apnea and cardiac arrhythmias

(i) Impaired autonomic nervous control has been demonstrated in patients with OSA, manifesting as increased sympathetic tone and/or decreased parasympathetic tone. Decreased baroreflex sensitivity, reduced vagal input, and impairment of the parasympathetic components of the heart rate variability have been demonstrated in patients with OSA.[22,23]

(ii) A persistent increase in sympathetic tone, as occurring in OSA, has been shown to generate abnormal electrical remodelling of the atrium, facilitating supraventricular arrhythmias, and AF in particular.[24] Specifically, electrical remodelling may create some degree of interatrial block, contributing to the genesis of atrial arrhythmias.[25]

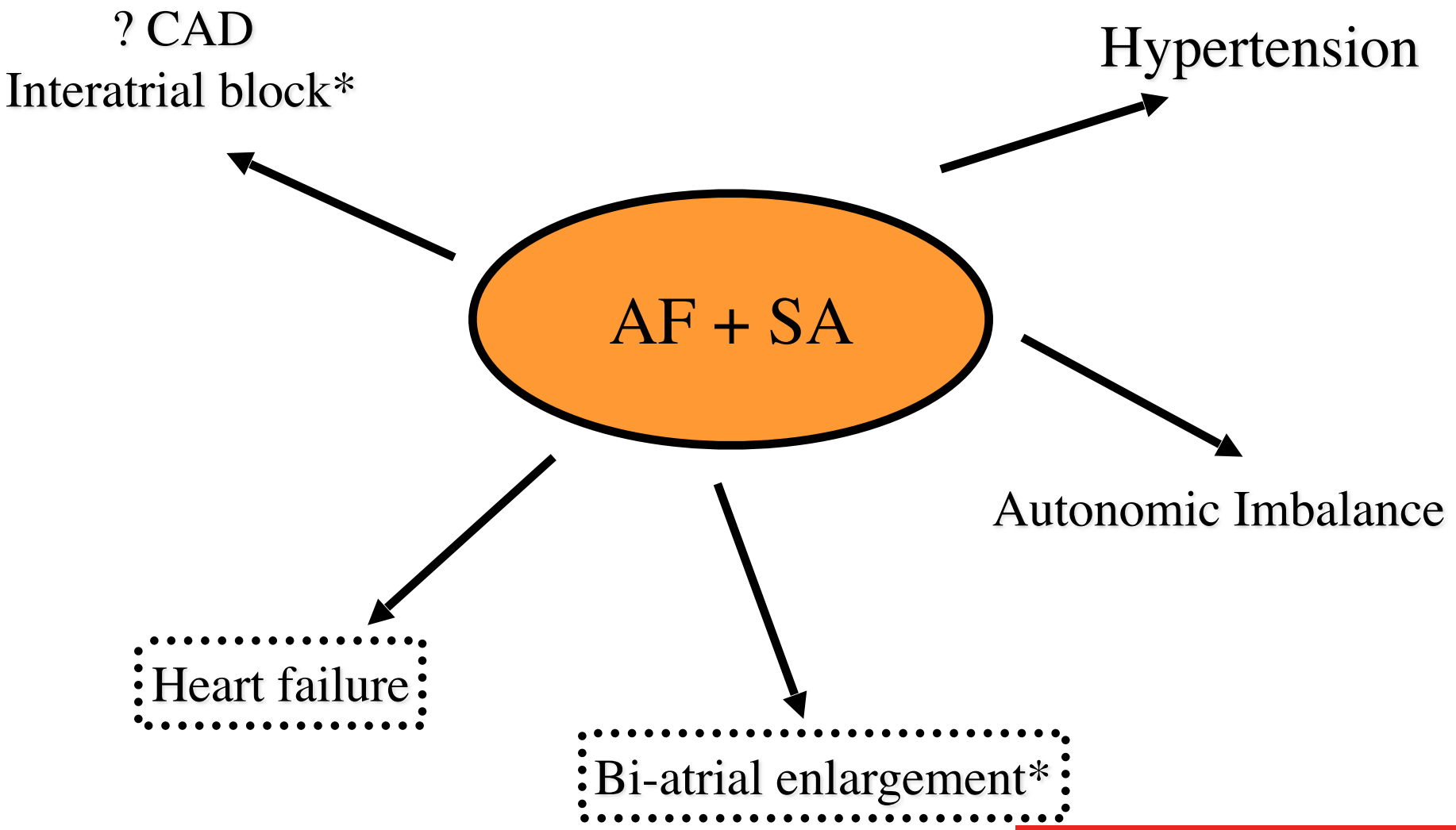
(iii) A strong association between OSA and hypertension has been reported extensively.[6,26] As well, the association between hypertension and AF is well recognized.[27,28] Although purely speculative, the link

Baranchuk et al. Europace 2008; 10(6):666-667

EDITORIAL COMMENTARY

Understanding the association between sleep apnea & cardiac arrhythmias

Adrian Baranchuk MD FACC[1], Christopher S. Simpson MD FACC FRCPC[1], Damian P. Redfearn MB ChB MRCPI[1], Kevin Michael MD[1], Mike Fitzpatrick MD FRCPI, FRCPC, D.ABSM[2]



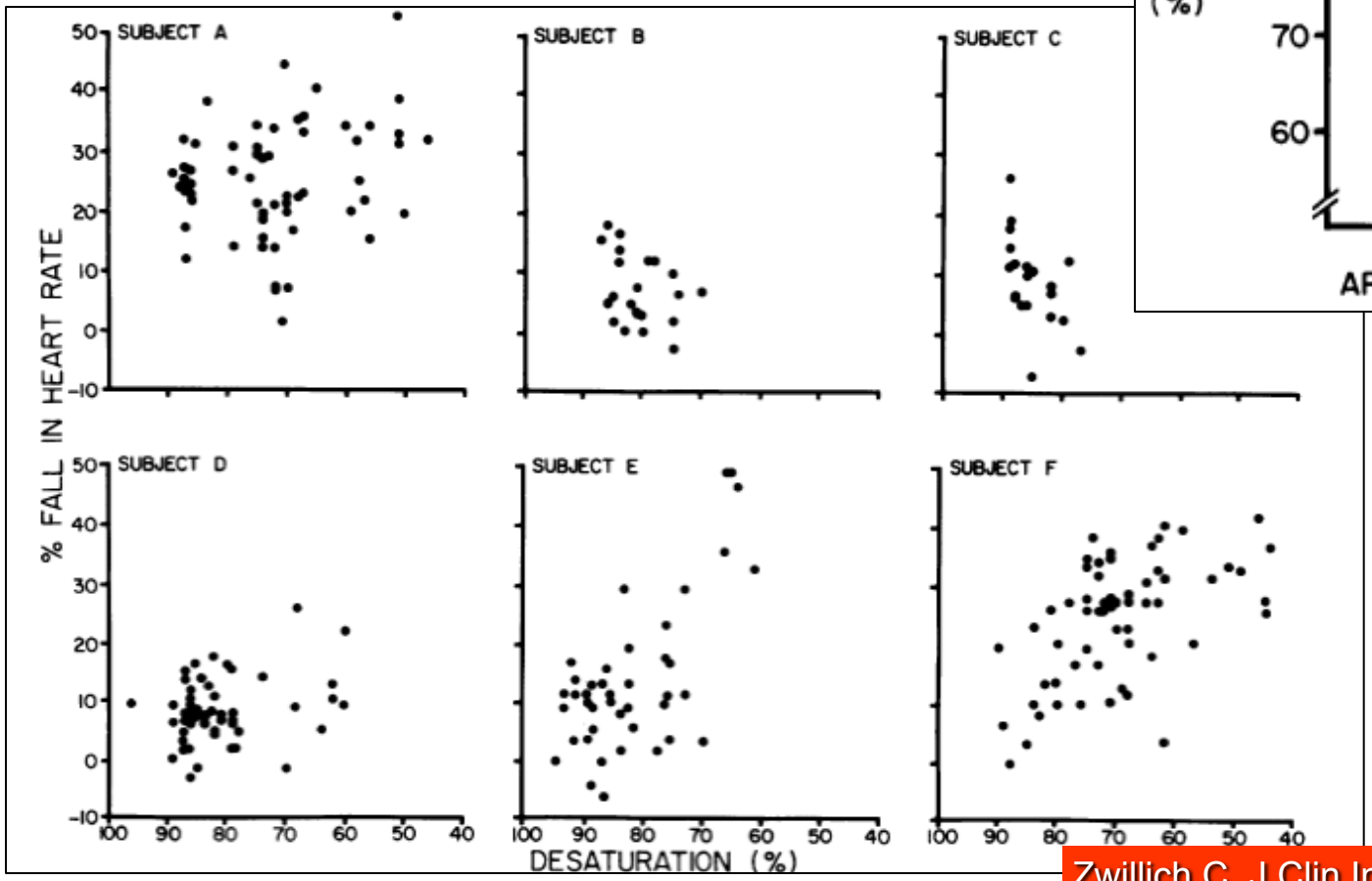
Baranchuk A et al. Rev Electrofisol y Arrit 2008;1:5-6

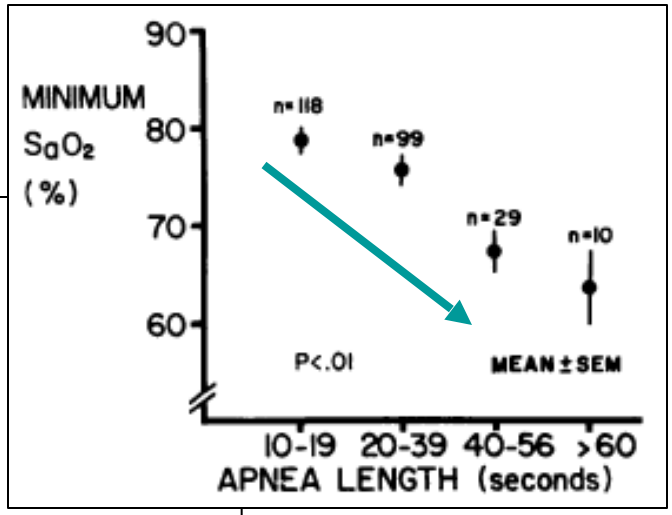
*Interatrial Block in Patients with OSA Baranchuk et al Cardiol J 2010; in Press)

Sleep Apnea:
SA and Arrhythmias

Bradycardia during Sleep Apnea

CHARACTERISTICS AND MECHANISM



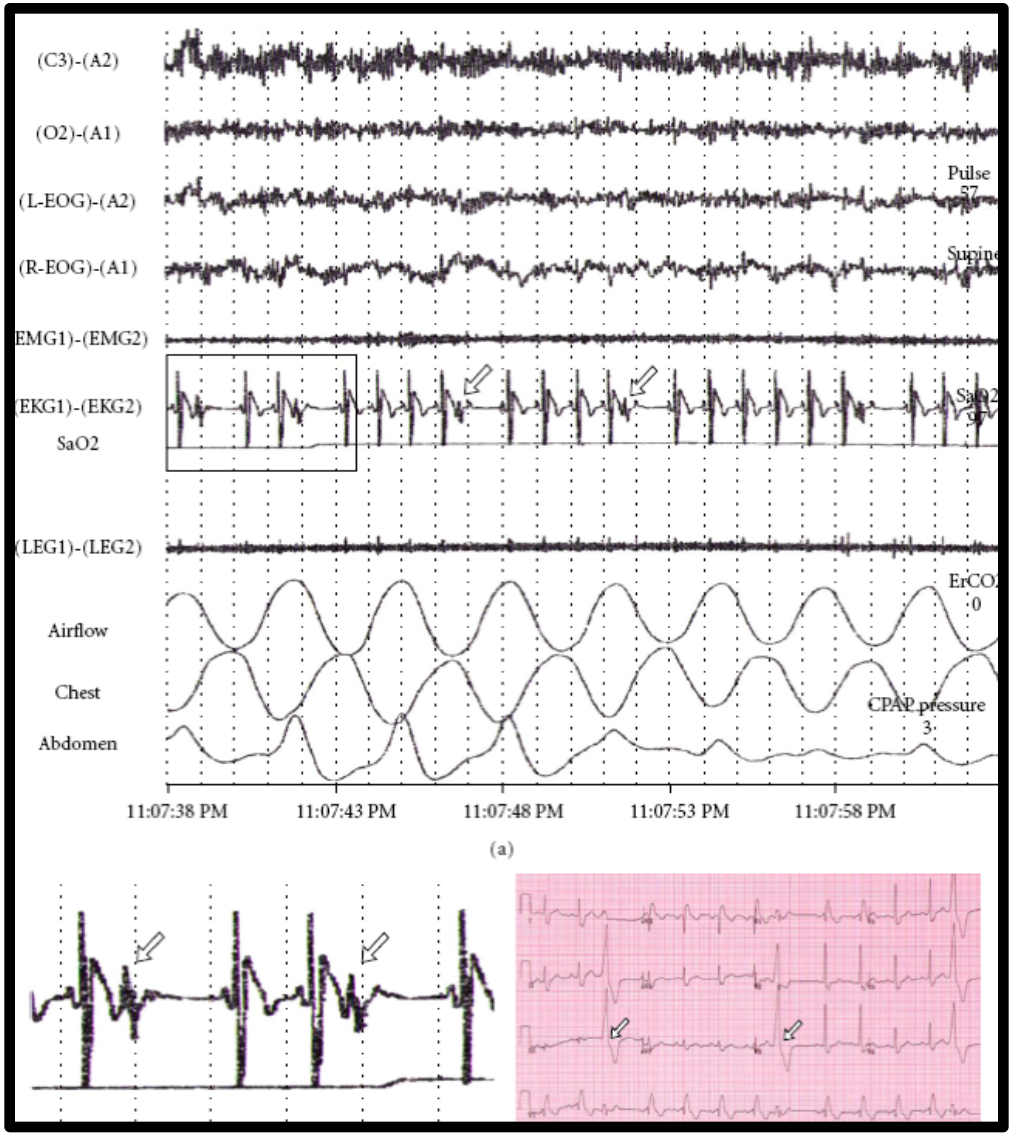


- Bradycardia during SA
- The longer the apnea, the longer the bradycardia
- No bradycardia in absence of SA

Zwillich C. J Clin Invest 1982;69:1286-92

Truths and Lies from the Polysomnography ECG Recording: An Electrophysiologist Perspective

Polysomnography ECG recording is represented by a single lead and at times, it can be confusing. In this case, the patient was referred due to 2:1 block and in fact, the patient presented RV outflow tract premature contractions.



Baranchuk et al. Case Reports Med 2009

Sleep Apnea:
Role for pacing

Physiologic Pacing in Patients With Obstructive Sleep Apnea

A Prospective, Randomized Crossover Trial

Andrew D. Krahn, MD,* Raymond Yee, MD,* Mark K. Erickson, BSc,† Toby Markowitz, BSEE,†
Lorne J. Gula, MD,* George J. Klein, MD,* Allan C. Skanes, MD,* Charles F. P. George, MD,*
Kathleen A. Ferguson, MD*

Parameter	Control	AAI Pacing	Difference (95% CI)	p Value
Apnea hypopnea index	42.1 ± 20.7	38.6 ± 20.5	−3.4 (−9.3 to 2.5)	0.23
Heart rate (beats/min)	65 ± 7	77 ± 1	12 (8 to 16)	0.001
Time in bed (min)	437 ± 45	417 ± 108	−19 (−87 to 48)	0.55
Minimum SaO_2 (%)	77 ± 11	75 ± 10	−2 (−9 to 4)	0.38
% time SaO_2 <90%	3.5 ± 4.3	3.8 ± 6.0	0.3 (−1.4 to 2.1)	0.70
Apnea hypopnea duration (s)	28.4 ± 4.7	33.1 ± 11.2	4.7 (0.7 to 8.7)	0.11
Circulatory time (s)	25.5 ± 4.4	23.4 ± 3.2	−2.1 (−4.7 to 0.4)	0.09

Physiologic pacing did not show benefits in patients with OSA

JACC 2006;47:379-83

Atrial overdrive pacing: 12 RCT since 2002…

Effects of physiological cardiac pacing on sleep-disordered breathing in patients with chronic bradydysrhythmias *Psychiatry and Clinical Neurosciences* (2001), 55, 257–258

Atrial Overdrive Pacing for the Obstructive Sleep Apnea–Hypopnea Syndrome
N Engl J Med 2005;353:2568-77.

Physiologic Pacing in Patients

- The benefits are not clear…

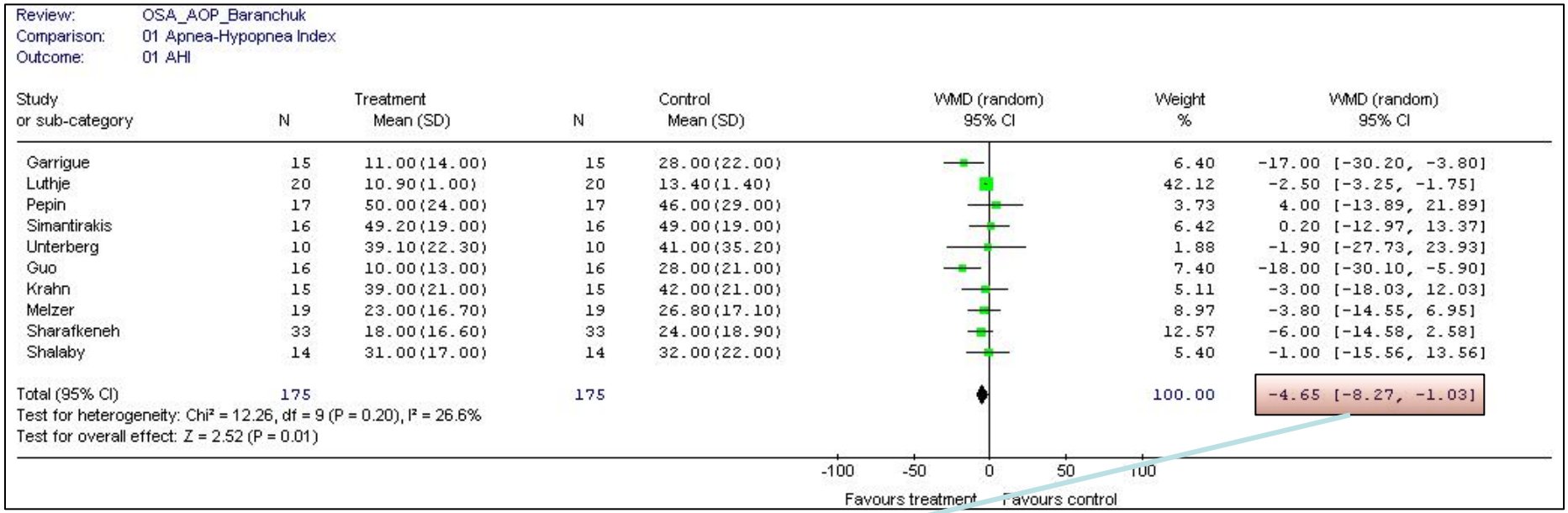
Atrial overdrive pacing compared to CPAP in patients with obstructive sleep apnoea syndrome
European Heart Journal (2005) 26, 2568–2575

Overdrive atrial pacing does not improve obstructive sleep apnoea syndrome
Eur Respir J 2005; 25: 343–347

Effect of atrial overdrive pacing on obstructive sleep apnea in patients with systolic heart failure ☆
Sleep Medicine 8 (2007) 31–36

Atrial overdrive pacing in sleep apnoea: a meta-analysis

Adrian Baranchuk[1]*, Jeff S. Healey[2], Christopher S. Simpson[1], Damian P. Redfearn[1], Carlos A. Morillo[2], Stuart J. Connolly[2], and Michael Fitzpatrick[1]

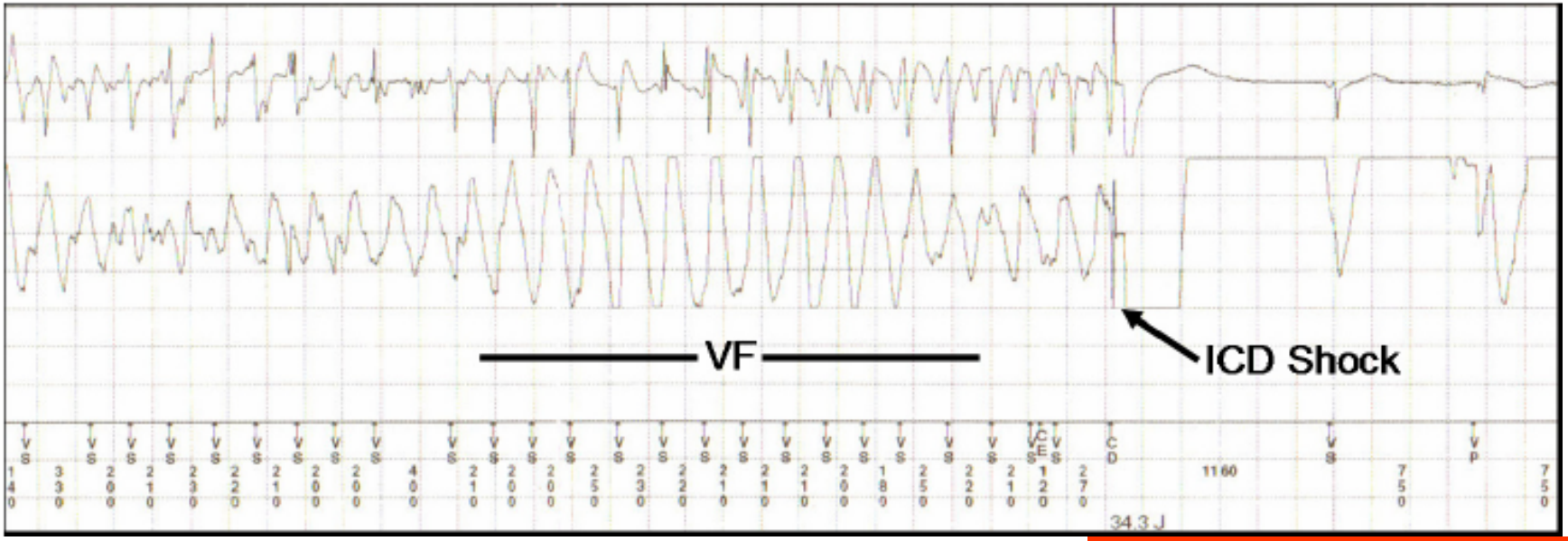


Reduction of AHI in 5 points:
Statistically significant but…
No clinical relevance!!!

Baranchuk et al. Europace 2009.

Sleep Disordered Breathing And Ventricular Arrhythmias: Mechanisms and Implications

	SA (N=26)	NO SA (N=106)	p
Incidence of Therapies			
Appropriate (%)	31	17	0.09
Inappropriate (%)	3.8	9.4	NS
Time to First Appropriate Therapy (months ± SD)	8.0 ± 5.2	11.89 ± 5.9	0.12
Incidence of Arrhythmias			
NSVT (%)	34.6	50.0	NS
SVT (%)	26.9	30.1	NS



Baranchuk et al. ICRJ 2008;2(1):10-13

Sleep Apnea:
Coronary Artery Disease

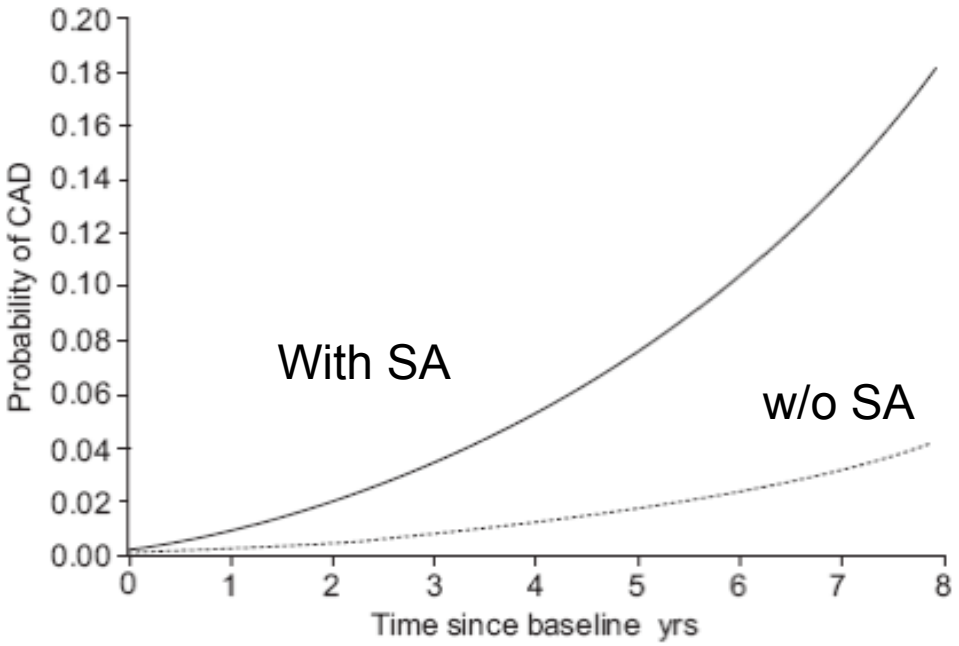
Increased incidence of coronary artery disease in sleep apnoea: a long-term follow-up

Eur Respir J 2006;28:596-602

(n=308)
Follow up: 7 years
SA: AHI ≥ 30

	β	RR (95% CI)	p-value
Constant	-22.84		
OSA at baseline	1.53	4.60 (1.83–11.6)	0.001
Time since baseline yrs	0.19	1.21 (1.01–1.45)	0.043
SBP at baseline mmHg	0.04	1.03 (1.01–1.05)	<0.001
Current age yrs	0.06	1.06 (1.02–1.11)	0.007
Sa,O_2,min at baseline %	0.11	1.11 (1.02–1.22)	0.019

BASAL	OSA	Non-OSA	p-value[#]
Subjects n	105	203	
Age yrs	51.8±8.9	47.6±10.2	<0.001
BMI $kg \cdot m^{-2}$	28.6±4.0	25.9±3.7	<0.001
SBP mmHg	138.4±16.3	130.1±17.9	<0.001
DBP mmHg	82.2±9.4	78.6±10.3	0.003
OD events·6 h^{-1}	94.1±86.0	8.9±8.3	<0.001
ODI events·h^{-1}	17.8±15.1	1.6±1.7	<0.001
Sa,O_2,min %	80.5±7.8	88.6±4.2	<0.001
Males	91 (86.7)	154 (75.9)	0.026
Hypertension	30 (28.6)	33 (16.3)	0.011
Diabetes mellitus	2 (1.9)	2 (1.0)	NS
Smokers	35 (34.0)	80 (41.5)	NS
CAD incidence	17 (16.2)	11 (5.4)	0.003
Cardiovascular death	8 (7.6)	1 (0.5)	<0.001



Sleep Apnea:
Coronary Artery Disease

Sleep-disordered Breathing and Cardiovascular Disease

Cross-sectional Results of the Sleep Heart Health Study

AMERICAN JOURNAL OF RESPIRATORY AND CRITICAL CARE MEDICINE VOL 163 2001

(n=6424)
AHI divided into quartiles
Multivariate analysis and adjusted by co-variables

	Quartile				
	I	II	III	IV	p Value†
Coronary heart disease					
Full model	1.0	1.01 (0.77–1.32)	1.20 (0.92–1.57)	1.22 (0.93–1.59)	0.08
Parsimonious model	1.0	0.92 (0.71–1.20)	1.20 (0.93–1.54)	1.27 (0.99–1.62)	0.004
Heart failure					
Full model	1.0	1.19 (0.56–2.53)	1.96 (0.99–3.90)	2.20 (1.11–4.37)	0.008
Parsimonious model	1.0	1.13 (0.54–2.39)	1.95 (0.99–3.83)	2.38 (1.22–4.62)	0.002
Stroke					
Full model	1.0	1.24 (0.76–2.01)	1.38 (0.86–2.83)	1.55 (0.96–2.50)	0.06
Parsimonious model	1.0	1.15 (0.72–1.83)	1.42 (0.91–2.21)	1.58 (1.02–2.46)	0.03

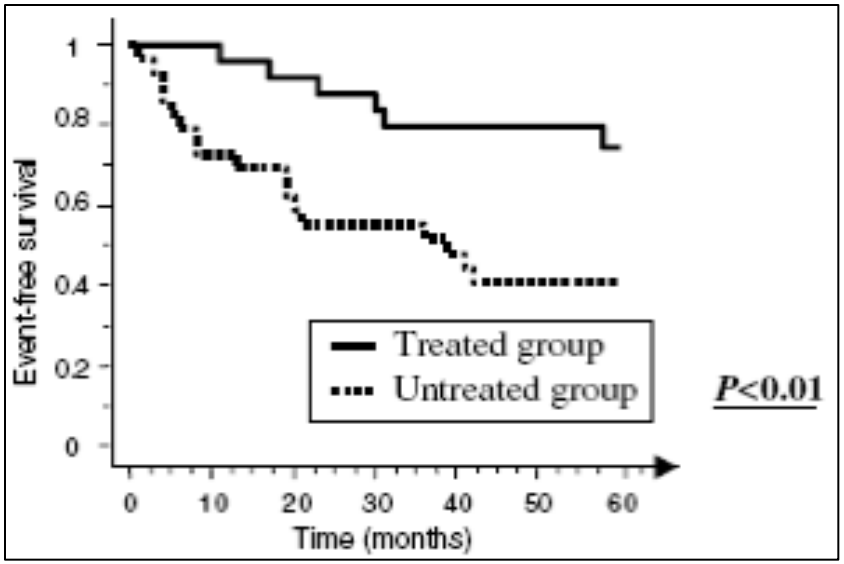
Associated mechanisms

1. Hypertension
2. Daytime sympathetic hyperactivity
3. Hypoxemia
4. ↑ platelet aggregation
5. Acute rupture of plaque
6. Pulmonary hypertension

Sleep Apnea : Coronary Artery Disease

Benefits of obstructive sleep apnoea treatment in coronary artery disease: a long-term follow-up study☆

- (n=54)
- Patients with SA + CAD
- CPAP/ surgery vs no treatment
- Composite end-point: cardiovascular mortality, ischemic event, hospitalization by CHF, revascularization



Treatment	No treatment
6/25 (24%)	17/29 (58%)

HR 0.24 (95% CI 0.09 – 0.62)
P<0.01

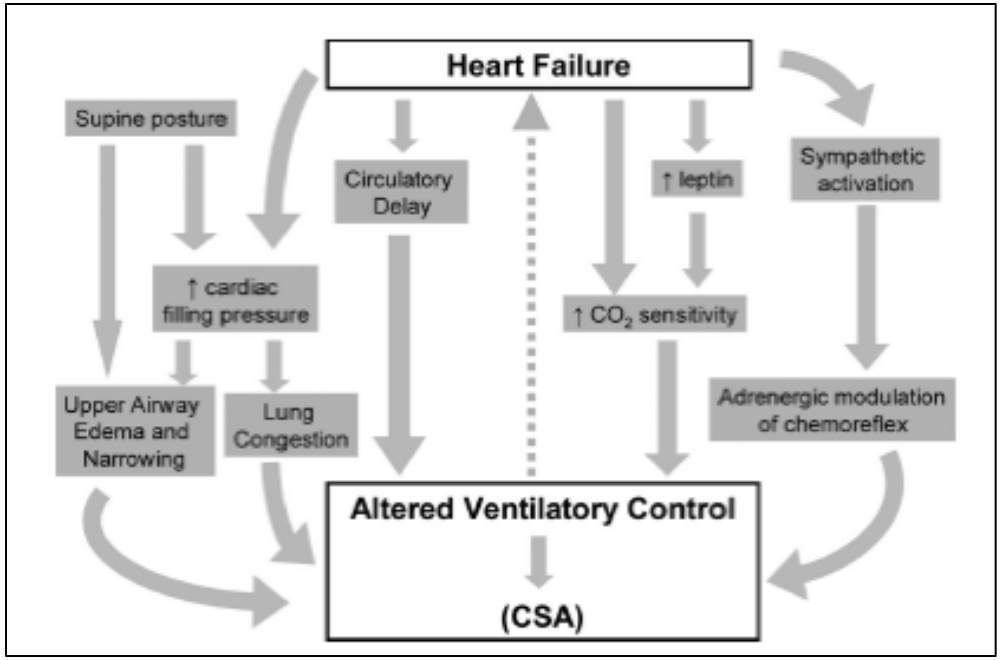
Who is interested in this topic…?

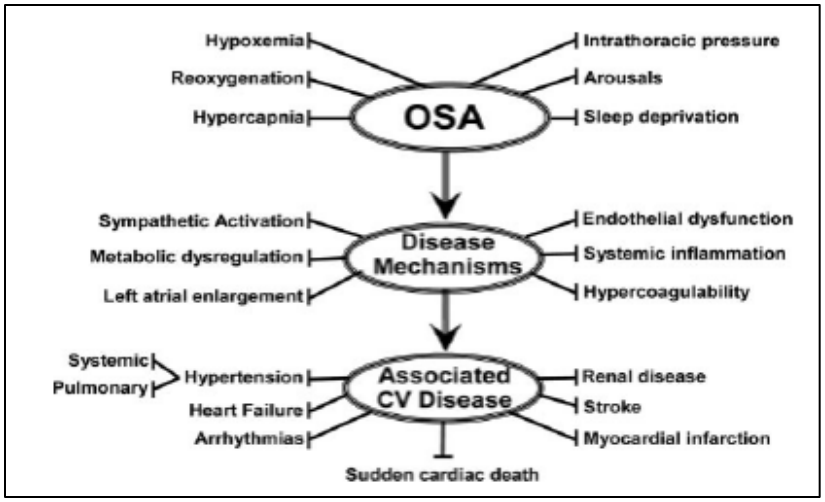
Milleron O. Eur H Journal 2004;25:728-734

Sleep Apnea and Cardiovascular Disease

An American Heart Association/American College of Cardiology Foundation Scientific Statement From the American Heart Association Council for High Blood Pressure Research Professional Education Committee, Council on Clinical Cardiology, Stroke Council, and Council on Cardiovascular Nursing Council

In Collaboration With the National Heart, Lung, and Blood Institute National Center on Sleep Disorders Research (National Institutes of Health)





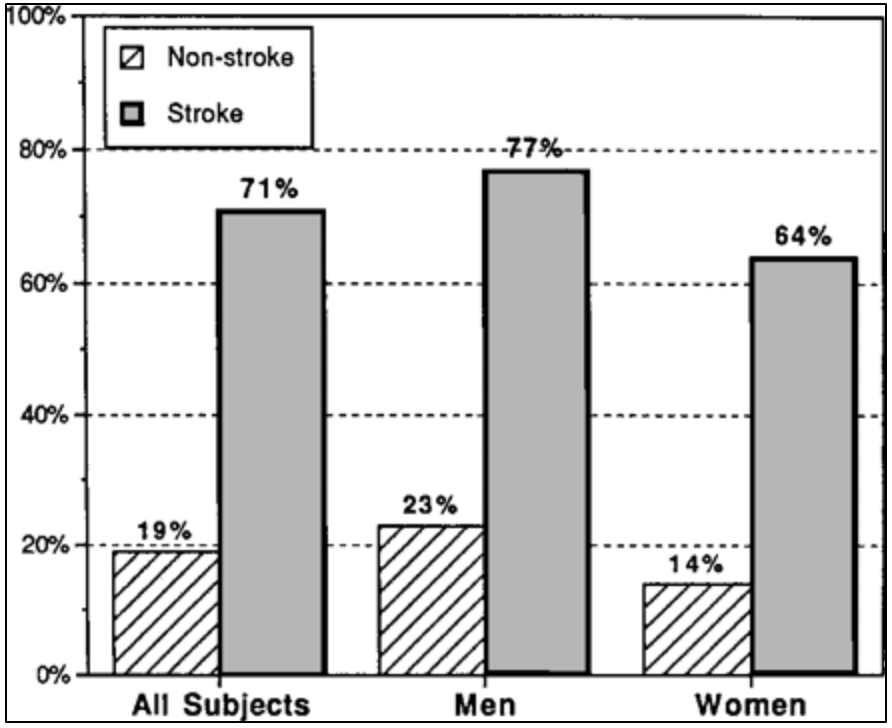
AUGUST 2008 (On-LINE)

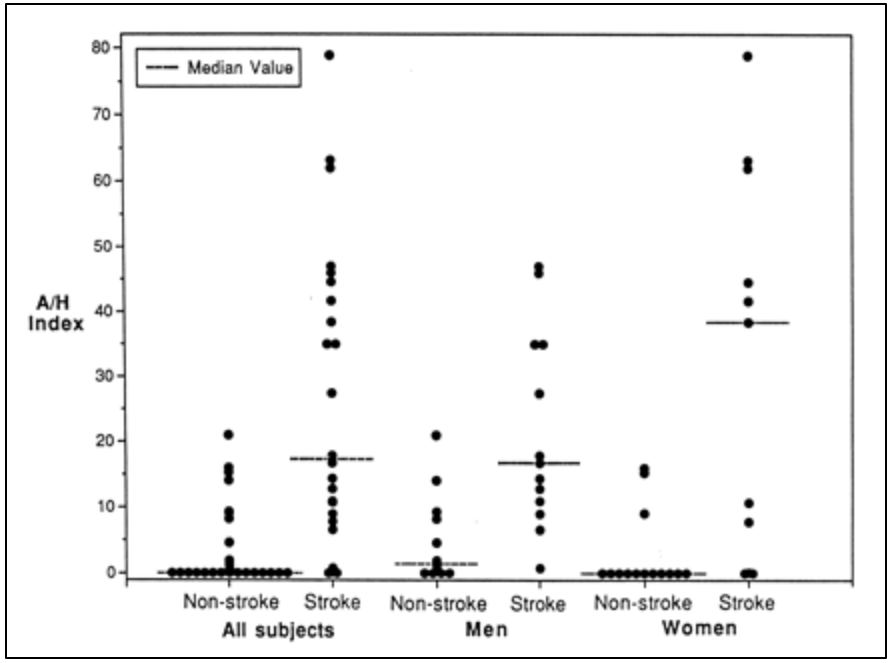
DOI: 10.1161/CIRCULATIONAHA.107.189420

Sleep Apnea: Stroke

Investigating the Relationship Between Stroke and Obstructive Sleep Apnea

Should we refine the $CHADS_2$ score?





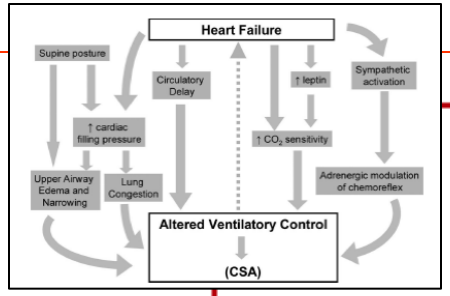
SA → stroke

?

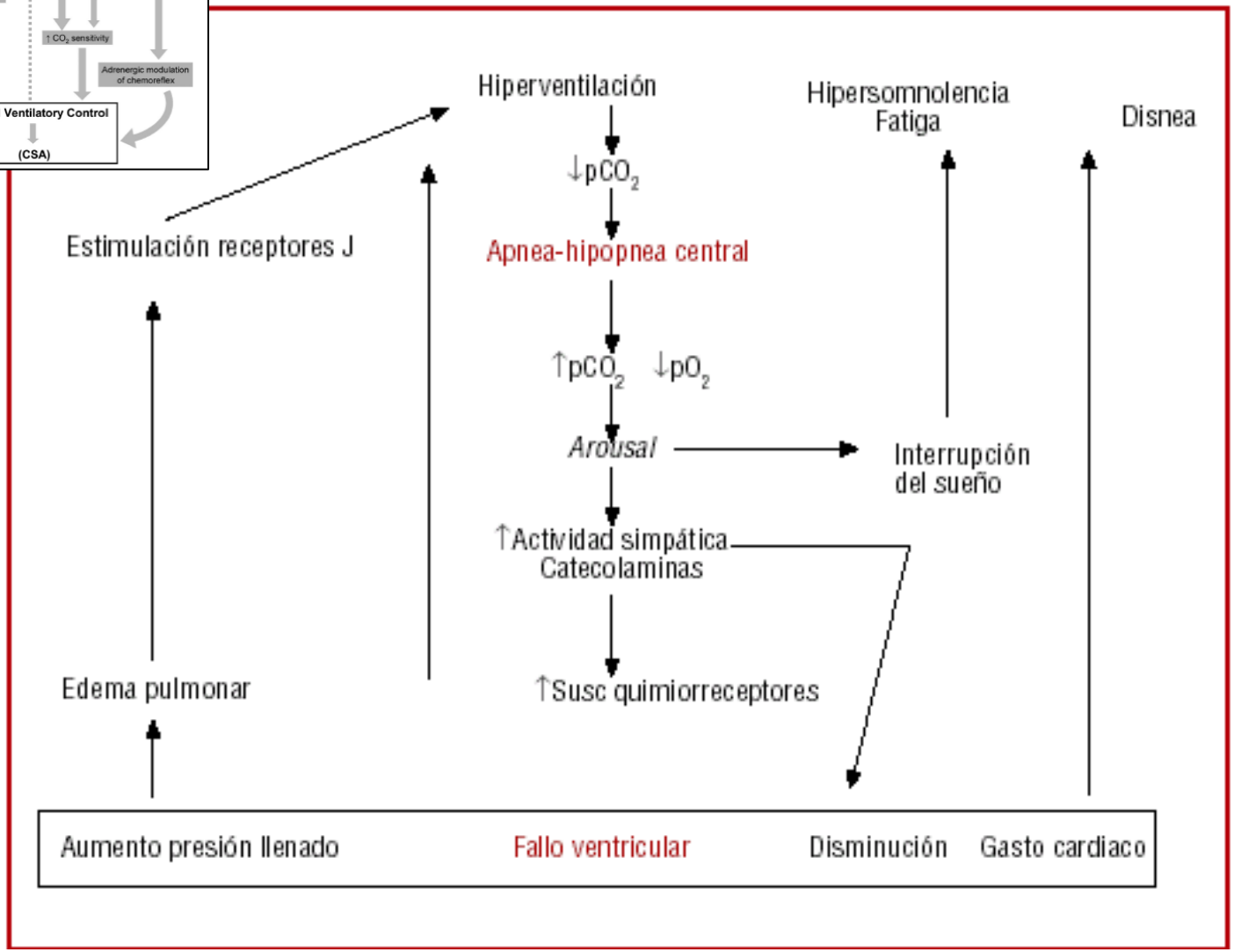
stroke → SA

Dyken ME. Stroke 1996;27:401-407

SA & Heart Failure
Mechanism of interaction



Rev Esp Cardiol. 2006;59(7):718-24



SA & Heart Failure
Clinical scenarios

1. Left ventricular dysfunction

(n=47)
EF < 40%
AHI > 15

Results

1. SA association: 55%
2. More frequent in CAD

Circulation 2003,197:727-732

Central Sleep Apnea in Left Ventricular Dysfunction
Prevalence and Implications for Arrhythmic Risk

Paola A. Lanfranchi, MD; Virend K. Somers, MD, PhD; Alberto Braghiroli, MD; Ugo Corra, MD; Ermanno Eleuteri, MD; Pantaleo Giannuzzi, MD

Background—The prevalence and characteristics of sleep-disordered breathing in patients with asymptomatic left ventricular (LV) dysfunction are unknown. Therefore, we evaluated the prevalence of sleep-disordered breathing in patients with LV dysfunction without overt heart failure and tested the hypothesis that sleep-disordered breathing is linked to greater hemodynamic and autonomic impairment.

Methods and Results—We studied 47 patients with LV ejection fractions ≤40% without any history of heart failure. Central sleep apnea (CSA), as defined by an apnea-hypopnea index ≥15/h, was present in 26 patients (55%), 17 (36%) of whom had severe CSA (apnea-hypopnea index ≥30/h). Obstructive sleep apnea was evident in 5 patients (11%). The prevalence and severity of CSA were higher in patients with ischemic cardiomyopathy than in patients with nonischemic cardiomyopathy ($P<0.05$). Exercise tolerance and echocardiographic indices of systolic and diastolic function were similar in patients without CSA, with mild CSA, and with severe CSA. Heart rate variability was markedly depressed in patients with CSA ($P<0.05$). Patients with severe CSA also had a higher incidence of nonsustained ventricular tachycardia ($P=0.05$).

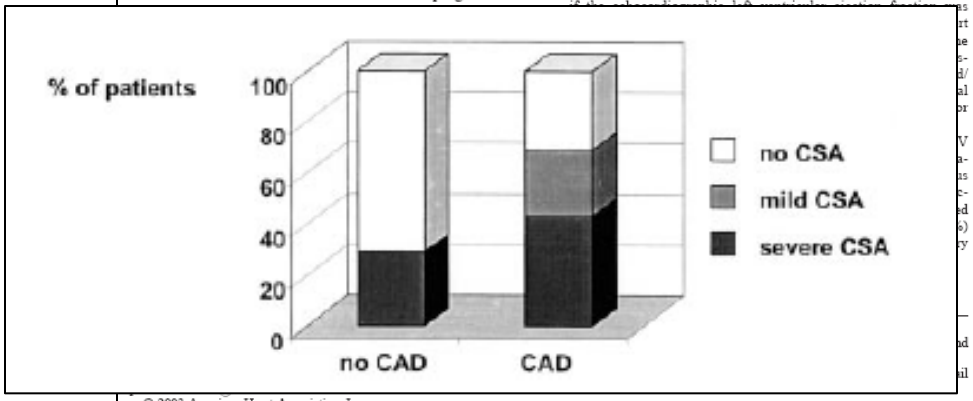
Conclusions—CSA is highly prevalent in patients with asymptomatic LV dysfunction. The severity of CSA may not be related to the severity of hemodynamic impairment. Severe CSA is associated with impaired cardiac autonomic control and with increased cardiac arrhythmias. (*Circulation*. 2003;107:727-732.)

Key Words: sleep ■ nervous system, autonomic ■ tachyarrhythmias ■ heart failure

In patients with overt heart failure, there is a high prevalence of nocturnal periodic breathing with central apneas (central sleep apnea: CSA).[1–4] CSA is associated with increased arrhythmic risk[3] and may indicate increased mortality in heart failure.[4] Autonomic responses to CSA may contribute to the adverse prognosis in these patients.[2,5] Patients with left ventricular (LV) dysfunction without heart failure also have neurohumoral activation and are at risk for progression to

Methods

We prospectively studied consecutive patients referred to the Cardiology Department of the Medical Center of Rehabilitation, Veruno, Italy, between January 1999 and December 2000 who were found to have LV systolic dysfunction due to either ischemic or nonischemic cardiomyopathy. Patients were referred for one of the following: (1) functional evaluation of asymptomatic LV dysfunction, (2) evaluation of chest pain, or (3) rehabilitation after myocardial infarction or cardiac surgery. They were eligible



SA & Heart Failure
Clinical scenarios

2. Congestive heart failure

(n=450)
EF 27.3±15%
NYHA II: 62%, NYHA III: 34%
AF: 15%
AHI > 20

Results

1. SA (AHI>20) association: 53%
2. More frequent in AF (p<0.01)

Am J Respir Crit Care Med 1999,160:1101-06

Risk Factors for Central and Obstructive Sleep Apnea in 450 Men And Women with Congestive Heart Failure

DON D. SIN, FABIA FITZGERALD, JOHN D. PARKER, GARY NEWTON, JOHN S. FLORAS, and T. DOUGLAS BRADLEY

Sleep Research Laboratory of the Toronto Rehabilitation Institute and the Departments of Medicine, The Toronto Hospital and Mount Sinai Hospital, University of Toronto, Toronto, Ontario, Canada

In previous analyses of the occurrence of central (CSA) and obstructive sleep apnea (OSA) in patients with congestive heart failure (CHF), only men were studied and risk factors for these disorders were not well characterized. We therefore analyzed risk factors for CSA and OSA in 450 consecutive patients with CHF (382 male, 68 female) referred to our sleep laboratory. Risk factors for CSA were male gender (odds ratio [OR] 3.50; 95% confidence interval [CI], 1.39 to 8.84), atrial fibrillation (OR 4.13; 95% CI 1.53 to 11.14), age > 60 yr (OR 2.37; 95% CI 1.35 to 4.15), and hypocapnia (Pco_2 < 38 mm Hg during wakefulness) (OR 4.33; 95% CI 2.50 to 7.52). Risk factors for OSA differed by gender: in men, only body mass index (BMI) was significantly associated with OSA (OR for a BMI > 35 kg/m², 6.10; 95% CI 2.86 to 13.00); whereas, in women, age was the only important risk factor (OR for age > 60 yr, 6.04; 95% CI 1.75 to 20.0). We conclude that historical information, supplemented by a few simple laboratory tests may enable physicians to risk stratify CHF patients for the presence of CSA or OSA, and the need for diagnostic polysomnography for such patients. **Sin DD, Fitzgerald F, Parker JD, Newton G, Floras JS, Bradley TD. Risk factors for central and obstructive sleep apnea in 450 men and women with congestive heart failure.** AM J RESPIR CRIT CARE MED 1999;160:1101–1106.

Obstructive sleep apnea (OSA) is an important risk factor for the development of hypertension, angina pectoris, myocardial infarction, and cor pulmonale (1–4). More recent data suggest that sleep apnea can also lead to the progression of cardiac dysfunction in patients with chronic congestive heart failure (CHF) (5, 6). This adverse effect on cardiac function probably arises from repetitive apneas causing arterial oxyhemoglobin desaturation, excessive stimulation of the sympathetic nervous system, and increases in systemic blood pressure (5–7).

The presence of central sleep apnea (CSA) in patients with CHF is associated with a significantly increased risk for death and cardiac transplantation (8, 9). In addition, fragmentation of sleep architecture by frequent arousals can also lead to the development of excessive daytime sleepiness and fatigue in CHF patients with either OSA or CSA (5, 6, 10). Treatments specifically aimed at OSA and CSA in patients with CHF have been shown to improve cardiovascular function and clinical status. For example, continuous positive airway pressure (CPAP) has been shown to alleviate both OSA and CSA, and to improve left ventricular ejection fraction (LVEF), decrease urinary and plasma norepinephrine concentrations, and improve symptoms of heart failure (5, 11, 12). Oxygen also alleviates CSA and reduces nocturnal urinary norepinephrine concentrations (13).

A recent report suggests that both CSA and OSA are common in the CHF population (14). The clinical characteristics of patients with CSA appear to differ from those with OSA, probably reflecting important differences in the underlying pathophysiologies of these two breathing disorders. In a study of men with CHF, Javaheri and coworkers found that those with OSA were heavier and had a higher prevalence of snoring than those with CSA or no sleep apnea (14). Patients with CSA, on the other hand, had a lower LVEF. However, because only 81 patients (of whom only nine had OSA) were evaluated in their study, other factors that distinguish risk for OSA from those for CSA or no sleep-related breathing disorder (SBD) may have escaped detection. More importantly, because only men were studied, risk factors for sleep apnea in women with CHF remain unknown. Indeed, risk factors for CSA in women either with or without CHF have not been reported. The purpose of our study, therefore, was twofold: first, to determine the overall risk factors for CSA and OSA in a large group of 450 patients with CHF referred to our sleep laboratory; and second, to determine whether there are differences in risk factors for CSA and OSA between men and women with chronic, stable CHF.

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Am J Respir Crit Care Med Vol 160. pp 1101–1106, 1999
Internet address: www.atsjournals.org

METHODS

Subjects

We conducted a retrospective analysis of 450 consecutive patients with CHF, referred to the Toronto Rehabilitation Institute Sleep Research Laboratory between July 1987 and November 1998. All patients were referred to the sleep laboratory by cardiologists. The crite-

SA & Heart Failure
Clinical scenarios

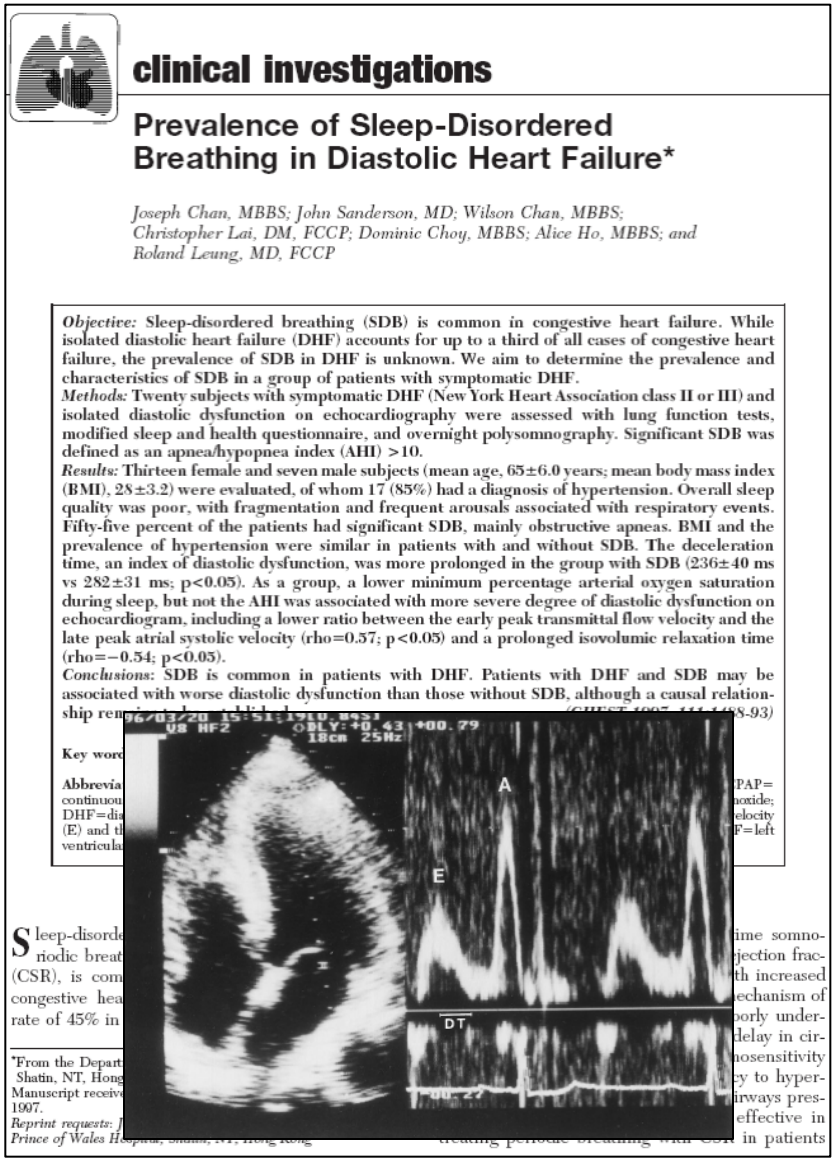
3. Diastolic dysfunction

(n=20)
NYHA II-III
AHI > 10

Results

1. SA (AHI>10) association: 55%
2. Time of deceleration (p<0.05)

Chest 1997,111:1488-93



clinical investigations

Prevalence of Sleep-Disordered Breathing in Diastolic Heart Failure*

Joseph Chan, MBBS; John Sanderson, MD; Wilson Chan, MBBS; Christopher Lai, DM, FCCP; Dominic Choy, MBBS; Alice Ho, MBBS; and Roland Leung, MD, FCCP

Objective: Sleep-disordered breathing (SDB) is common in congestive heart failure. While isolated diastolic heart failure (DHF) accounts for up to a third of all cases of congestive heart failure, the prevalence of SDB in DHF is unknown. We aim to determine the prevalence and characteristics of SDB in a group of patients with symptomatic DHF.
Methods: Twenty subjects with symptomatic DHF (New York Heart Association class II or III) and isolated diastolic dysfunction on echocardiography were assessed with lung function tests, modified sleep and health questionnaire, and overnight polysomnography. Significant SDB was defined as an apnea/hypopnea index (AHI) >10.
Results: Thirteen female and seven male subjects (mean age, 65±6.0 years; mean body mass index (BMI), 28±3.2) were evaluated, of whom 17 (85%) had a diagnosis of hypertension. Overall sleep quality was poor, with fragmentation and frequent arousals associated with respiratory events. Fifty-five percent of the patients had significant SDB, mainly obstructive apneas. BMI and the prevalence of hypertension were similar in patients with and without SDB. The deceleration time, an index of diastolic dysfunction, was more prolonged in the group with SDB (236±40 ms vs 282±31 ms; p<0.05). As a group, a lower minimum percentage arterial oxygen saturation during sleep, but not the AHI was associated with more severe degree of diastolic dysfunction on echocardiogram, including a lower ratio between the early peak transmittal flow velocity and the late peak atrial systolic velocity (rho=0.57; p<0.05) and a prolonged isovolumic relaxation time (rho=−0.54; p<0.05).
Conclusions: SDB is common in patients with DHF. Patients with DHF and SDB may be associated with worse diastolic dysfunction than those without SDB, although a causal relationship ren

SA & Cardiac Resynchronization Therapy

Cardiac Resynchronization Therapy Improves Central Sleep Apnea and Cheyne-Stokes Respiration in Patients With Chronic Heart Failure

Anil-Martin Sinha, MD, DPHIL,* Erik C. Skobel, MD,* Ole-Alexander Breithardt, MD,* Christine Norra, MD,† Kai U. Markus, MD,* Christian Breuer, MD,* Peter Hanrath, MD, FESC, FACC,* Christoph Stellbrink, MD, FESC*

Aachen, Germany

(n=24)

Non-randomized study

Ambulatory polysomnography

		All Patients (n = 24)	CSA (n = 14)	No CSA (n = 10)	p Value (CSA vs. No CSA)
Cardiorespiratory polygraph					
Duration of recording (h)	Pre	8 ± 2	8 ± 2	8 ± 3	NS
	CRT	8 ± 3	8 ± 3	8 ± 2	NS
AHI (per h)	Pre	11.9 ± 11.7 (1–42)	19.2 ± 10.3 (9–42)	1.7 ± 0.7 (1–3)	0.00001
	CRT	3.3 ± 3.8* (0–12)	4.6 ± 4.4* (0–12)	1.5 ± 1.6 (0–4)	NS
SaO_2min (%)	Pre	88 ± 5 (70–92)	84 ± 5 (70–90)	90 ± 2 (88–92)	<0.05
	CRT	90 ± 2* (85–93)	89 ± 2* (85–90)	91 ± 1 (90–93)	NS
PSQI	Pre	7.5 ± 4.2 (2–14)	10.4 ± 1.6 (8–14)	2.4 ± 0.5 (2–4)	<0.05
	CRT	3.5 ± 2.2* (2–10)	3.9 ± 2.4* (2–10)	2.6 ± 0.9 (2–4)	NS

1. Significant reduction of AHI (pre CRT vs post CRT)
2. Significant increment of SaO_2
3. Significant reduction of PSQI (Pittsburgh Sleep Quality Index)

JACC 2004,44:68-71

SA & Cardiac Resynchronization Therapy

Improvement in Cheyne-Stokes respiration following cardiac resynchronisation therapy

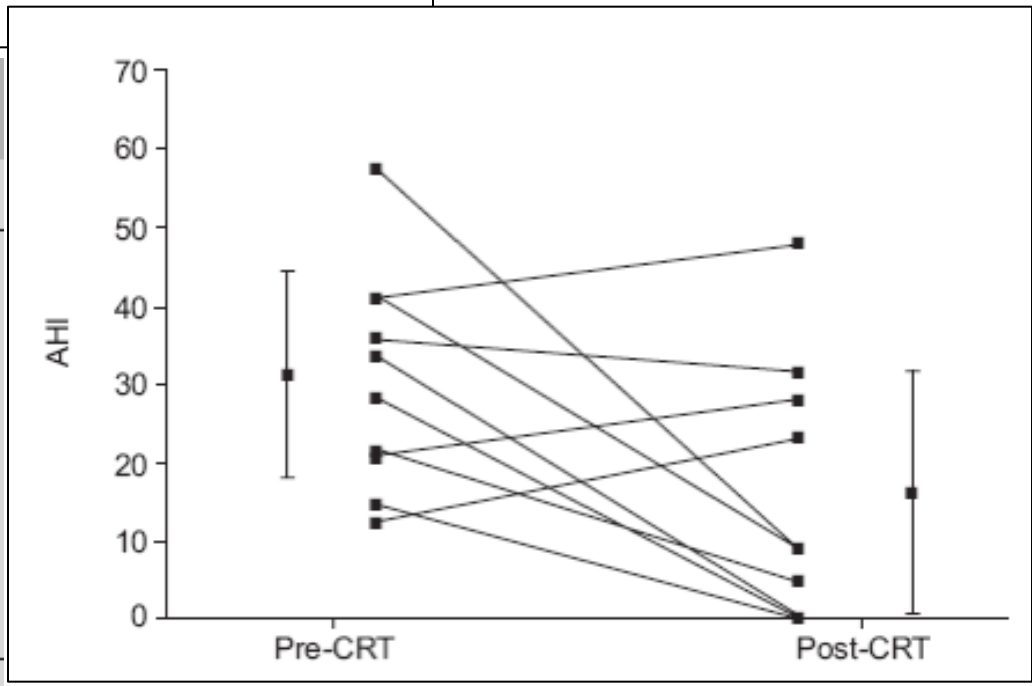
J.Y. Gabor, D.A. Newman, V. Barnard-Roberts, V. Korley, I. Mangat, P. Dorian and P.J. Hanly

1. uncontrolled
2. observational
3. small sample

TABLE 3 Sleep apnoea following 6 months of cardiac resynchronisation therapy (CRT)

	Pre-CRT	Post-CRT
Subjects n	10	10
Total AHI[¶] ·h^{-1}	42.7±9.1	30.8±18.7
CSR events ·h^{-1}*	30.6±14.0	15.3±16.5
Obstructive AHI ·h^{-1}	9.7±12.3	11.8±10.2
Mean Sa,O_2,awake %	93.6±1.0	93.9±0.7
Mean Sa,O_2,sleep %	93.3±1.1	93.3±1.1
Mean PCO_2,tc,awake mmHg	42.1±4.1	43.6±4.9
Mean PCO_2,tc,sleep mmHg	42.2±3.9	44.9±4.4
PB cycle length s	63.6±16.2	59.1±9.6
LFCT s	43.0±12.4	35.6±6.8#

Data are presented as mean±SD, unless otherwise stated. AHI: apnoea–hypopnoea index; CSR: Cheyne-Stokes respiration; Sa,O_2: arterial oxygen saturation; PCO_2,tc: transcutaneous partial pressure of carbon dioxide; PB: periodic breathing; LFCT: lung-to-finger circulation time. [¶]: includes mixed apnoeas in addition to CSR and obstructive apnoeas. *: $p<0.05$ *versus* pre-CRT; #: $p=0.09$.



6/10 have significantly reduced AHI
Two thirds have reduced CSR

Eur Respir J 2006,26:95-100

Sleep Apnea :
SA & Hypertension

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.

NEJM 2000;342:1378-84

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	HTN: ODDS RATIO, ADJUSTED FOR BASE-LINE HYPERTENSION STATUS AND NONMODIFIABLE RISK FACTORS (AGE AND SEX)	HTN + BMI: ODDS RATIO, ADJUSTED FOR BASE-LINE HYPERTENSION STATUS, NONMODIFIABLE RISK FACTORS, AND HABITUS (BMI AND WAIST AND NECK CIRCUMFERENCE)	HTN + BMI + Alc/smoking: 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=709)

SA & Hypertension
Large population studies

Wisconsin Sleep Study[1]: (n=709), follow up 8 years
Sleep Heart Health Study[2]: (n=6841), follow up 3 years

Wisconsin Sleep Study			Sleep Heart Health Study		
Punto de corte IAH	Prevalencia HTA (%)	OR* (IC del 95%)	Punto de corte IAH	Prevalencia HTA (%)	OR* (IC del 95%)
0	17	1	< 1,5	43	1
0,1-4,9	28	1,39 (1,04-1,84)	1,5-4,9	53	1,07 (0,91–1,26)
5-14,9	48	1,92 (1,09-3,39)	5-14,9	59	1,20 (1,01-1,42)
≥ 15	60	2,66 (1,13-6,25)	15-29,9	62	1,25 (1,00-1,56)
			≥ 30	67	1,37 (1,03-1,83)

The greater the severity of SA, the association with HTN increases

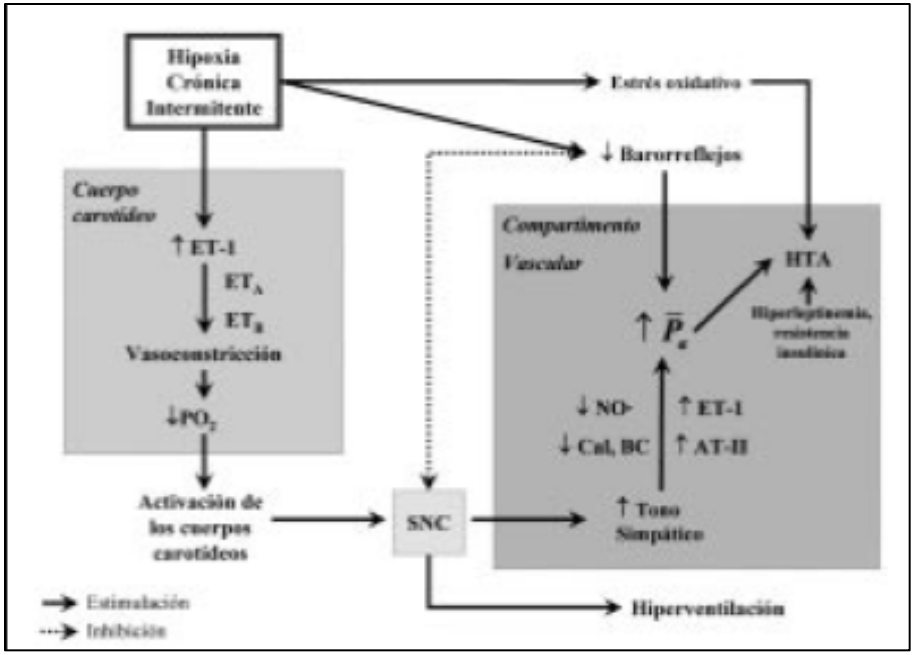
The question is: Is there any causality?

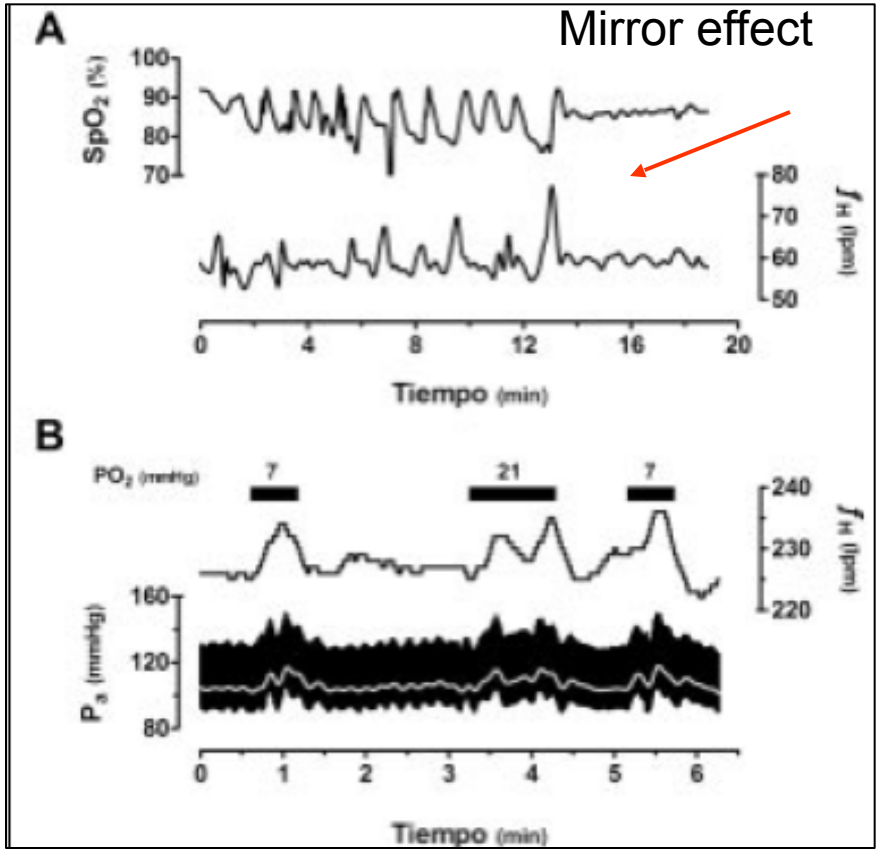
1. N Engl J Med 2000;342:1378-84
2. JAMA 2000;283:1829-36

SA & Hypertension Pathophysiology

Fisiopatología de la hipertensión asociada al síndrome de apnea obstructiva del sueño: Evidencia de estudios clínicos y modelos animales de hipoxia crónica intermitente

Rev Med Chile 2007; 135: 1333-1342





Rey et al. 2008

SA & Pulmonary Hypertension
The controversy remains…

Pulmonary Artery Hypertension and Sleep-Disordered Breathing*

ACCP Evidence-Based Clinical Practice Guidelines

Chest 2004;126;72-77

RECOMMENDATIONS

1. In the evaluation of pts with pulmonary HTN, evaluating SA is mandatory (evidence: low, yield: poor, class C)
2. In the evaluation of pts with pulmonary HTN by SA, polysomnography is indicated (evidence: expert's opinion, yield: intermediate, class B)
3. In the management of pts with SA, routine pulmonary HTN evaluation is *NOT* advised (evidence: low, yield: no, class I)
4. In pts with SA and pulmonary HTN, CPAP reduces pulmonary pressure (but does *NOT* normalize it) (evidence: low, yield: poor, class C)

Source	AHI or RDI, /h	BMI (or %IBW)‡	%COPD	Definition of PH	PAP Measurement Method	Prevalence of PH, No./Total (%)	Factors With Significant Association with PH
Alchanatis et al,[10] 2001	> 15	NR	NR	mPAP > 20 mm Hg	RH cath	6/29 (20.7)	Age ($p < 0.05$) BMI ($p < 0.02$) Daytime Po_2 ($p < 0.05$)
Apprill et al,[11] 1991	NR	NR	NR	mPAP ≥ 20 mm Hg	RH cath	9/46 (20)	Daytime Po_2 ($p < 0.001$) Daytime Pco_2 ($p < 0.001$) FVC and FEV_1 ($p < 0.001$)
Bady et al,[12] 2000	> 5	NR	Excluded	mPAP > 20 mm Hg	RH cath	12/44 (27)	Body weight ($p = 0.0002$) BMI ($p = 0.002$)
Chaouat et al,[13] 1996	> 20	NR	NR	mPAP ≥ 20 mm Hg	RH cath	37/200 (17)	FEV_1 ($p < 0.001$)† FEV_1/FVC ($p < 0.001$) Po_2 ($p < 0.001$) AHI ($p < 0.001$) Mean nocturnal Sao_2 ($p < 0.001$)† BMI ($p < 0.01$) FEV_1/FVC < 65% Pco_2†
				mPAP ≥ 20 mm Hg	RH cath	19/100 (19)	Po_2 ($p < 0.001$) Pco_2 ($p < 0.001$) TLC, FEV_1, FEV_1/FVC, %FVC ($p < 0.001$) AHI, apnea index ($p < 0.001$) Daytime Sao_2 ($p < 0.001$)
				mPAP ≥ 20 mm Hg	RH cath	42/100 (42)	Po_2 ($p < 0.001$)† Pco_2 ($p < 0.001$) FEV_1 ($p < 0.001$)† FEV_1/FVC ($p = 0.03$) Sao_2 ($p = 0.01$)
				mPAP > 20 mm Hg	RH cath	10/19 (52.6)	BMI ($p < 0.01$) Awake pH ($p < 0.05$) $Paco_2$ ($p < 0.05$) VC ($p < 0.01$) No difference in FEV_1/FVC, FRC %pred
				NS	RH cath	13/65 (20) 31/65 (48) with exercise	NR
				mPAP ≥ 20 mm Hg	Doppler echo	11/32 (34)	No difference in age, BMI, smoking history
				mPAP ≥ 20 mm Hg	RH cath	18/92 (20)	PCWP ($p < 0.005$) Sleep time with Spo_2 < 90% ($p < 0.05$)
%) patients				mPAP ≥ 20 mm Hg	RH cath	9/46 (20)	FVC, FVC %pred, FEV_1, FEV_1/FVC ($p < 0.001$) Pao_2 ($p < 0.001$) $Paco_2$ ($p < 0.001$)
				NR	Doppler echo	8/37 (22)	Minimum Spo_2 ($p = 0.051$)

ideal body weight; %COPD = percentage of patients with COPD; TLC = total reported; RH cath = right-heart catheterization; echo = echocardiography; FRC y; Sao_2 = arterial oxygen saturation; VC = vital capacity; NS = not significant; oximetric saturation; %pred = percentage of predicted.
ation with PH not only in univariable analysis, but also in multivariable analysis. dicated.

d on eral, PAP

in each of these studies was < 30 mm Hg; in most, it was < 25 mm Hg. Prevalence estimates of PH ranged from 17 to 53%.

Sleep Apnea & Left ventricular hypertrophy

Prevalence of Left Ventricular Hypertrophy in Persons With and Without Obstructive Sleep Apnea

(*Cardiology in Review* 2006;14: 170–172)

- (n=53)
- RDI > 5, severe > 30
- LVH: ♀ 110 g/m² / ♂ 134 g/m²

Variable	OSA (n = 40)	No OSA (n = 13)	*P*
Age (years)	51 ± 8	50 ± 8	NS
Men	24 (60%)	3 (23%)	<0.025
Women	16 (40%)	10 (77%)	<0.025
Hypertension	17 (43%)	5 (38%)	NS
Diabetes mellitus	9 (23%)	3 (23%)	NS
Body mass index ≥30 kg/m²	22 (55%)	7 (54%)	NS
Coronary artery disease	10 (25%)	4 (31%)	NS

	LVH
Moderate or severe OSA (n = 27)	21 (78%)
Mild OSA (n = 13)	6 (46%)
No OSA (n = 13)	3 (23%)

P < 0.001 comparing moderate or severe OSA with no OSA.
P < 0.05 comparing moderate or severe OSA with mild OSA.

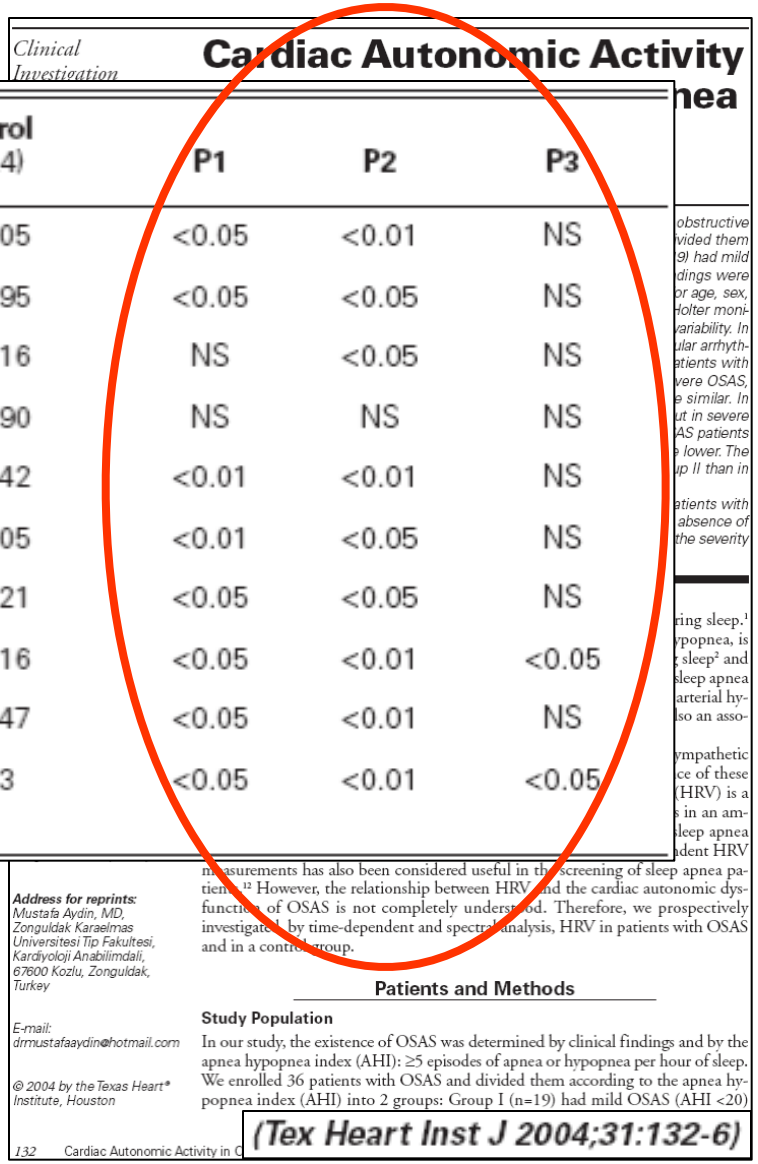
The link between SA and LVH could be *hypertension, however, children and teenagers with SA may develop LVH w/o having clinical HTN*

Sleep Apnea & Autonomic Nervous System

- (n=60)
- 3
- S
- 2
  - I
  -
- A

HRV Data	Mild OSAS (n=19)	Severe OSAS (n=17)	Control (n=24)	P1	P2	P3
SDNN (ms)	124.94	120.38	131.05	<0.05	<0.01	NS
SDANN (ms)	112.29	108.63	126.95	<0.05	<0.05	NS
RMSSD (ms)	35.11	31.54	44.16	NS	<0.05	NS
Triangular index*	33.88	32.33	36.90	NS	NS	NS
Total power (ms²)	1,405.35	1,695.63	1,290.42	<0.01	<0.01	NS
Ultra low frequency (ms²)	165.24	137.54	119.05	<0.01	<0.05	NS
Very low frequency (ms²)	582.77	633.71	510.21	<0.05	<0.05	NS
Low frequency (ms²)	432.12	476.58	411.16	<0.05	<0.01	<0.05
High frequency (ms²)	341.12	332.50	351.47	<0.05	<0.01	NS
Low-frequency/high-frequency ratio	1:4	1:4	1:3	<0.05	<0.01	<0.05

- ↓ parasympathetic tone
- ↑ sympathetic tone



Clinical Investigation

Cardiac Autonomic Activity

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Patients and Methods

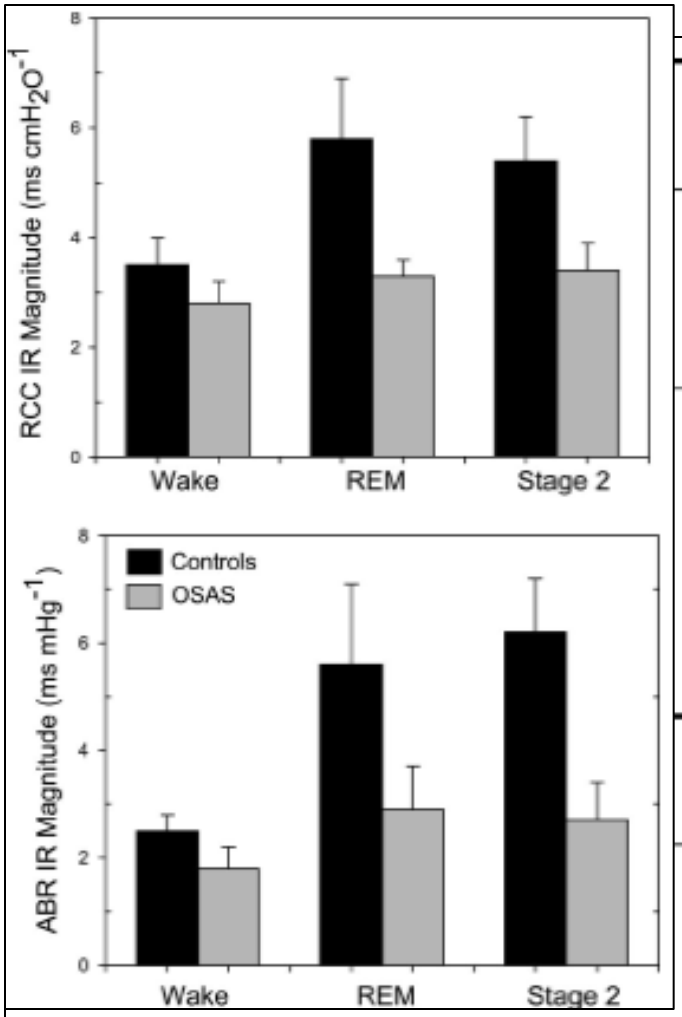
Study Population

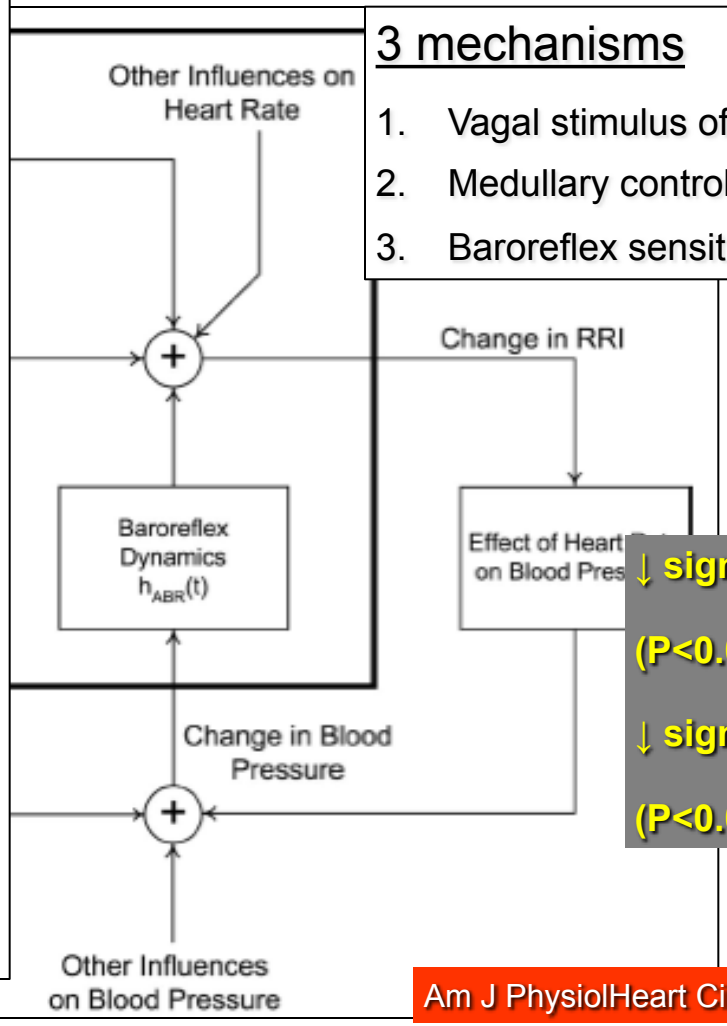
In our study, the existence of OSAS was determined by clinical findings and by the apnea hypopnea index (AHI): ≥5 episodes of apnea or hypopnea per hour of sleep. We enrolled 36 patients with OSAS and divided them according to the apnea hypopnea index (AHI) into 2 groups: Group I (n=19) had mild OSAS (AHI <20)

(Tex Heart Inst J 2004;31:132-6)

Sleep Apnea & HRV regulation

Determinants of heart rate variability in obstructive sleep apnea syndrome during wakefulness and sleep





3 mechanisms

1. Vagal stimulus of pulmonary receptors
2. Medullary control of respiratory centers
3. Baroreflex sensitivity (BRS)

↓ significant vagal afference (P<0.04)

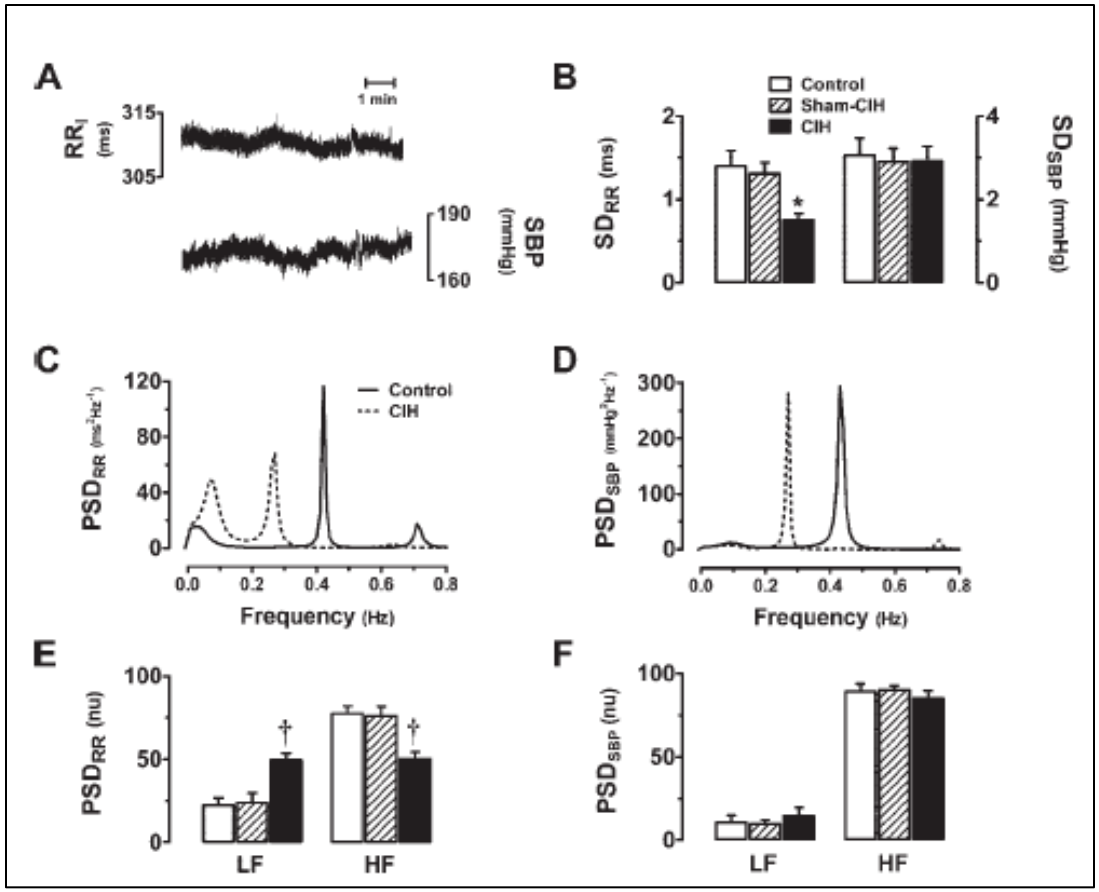
↓ significant BRS (P<0.03)

Am J PhysiolHeart Circ Physiol 2005;288:1103-12

Sleep Apnea & Regulation of HRV

Dynamic time-varying analysis of heart rate and blood pressure variability in cats exposed to short-term chronic intermittent hypoxia

Am J Physiol Regul Integr Comp Physiol 295: R28–R37, 2008.



Intermittent chronic hypoxia (8 H-4 days):

1. ↓ baroreflex sensitivity
2. ↓ Total HRV (LF predominant)

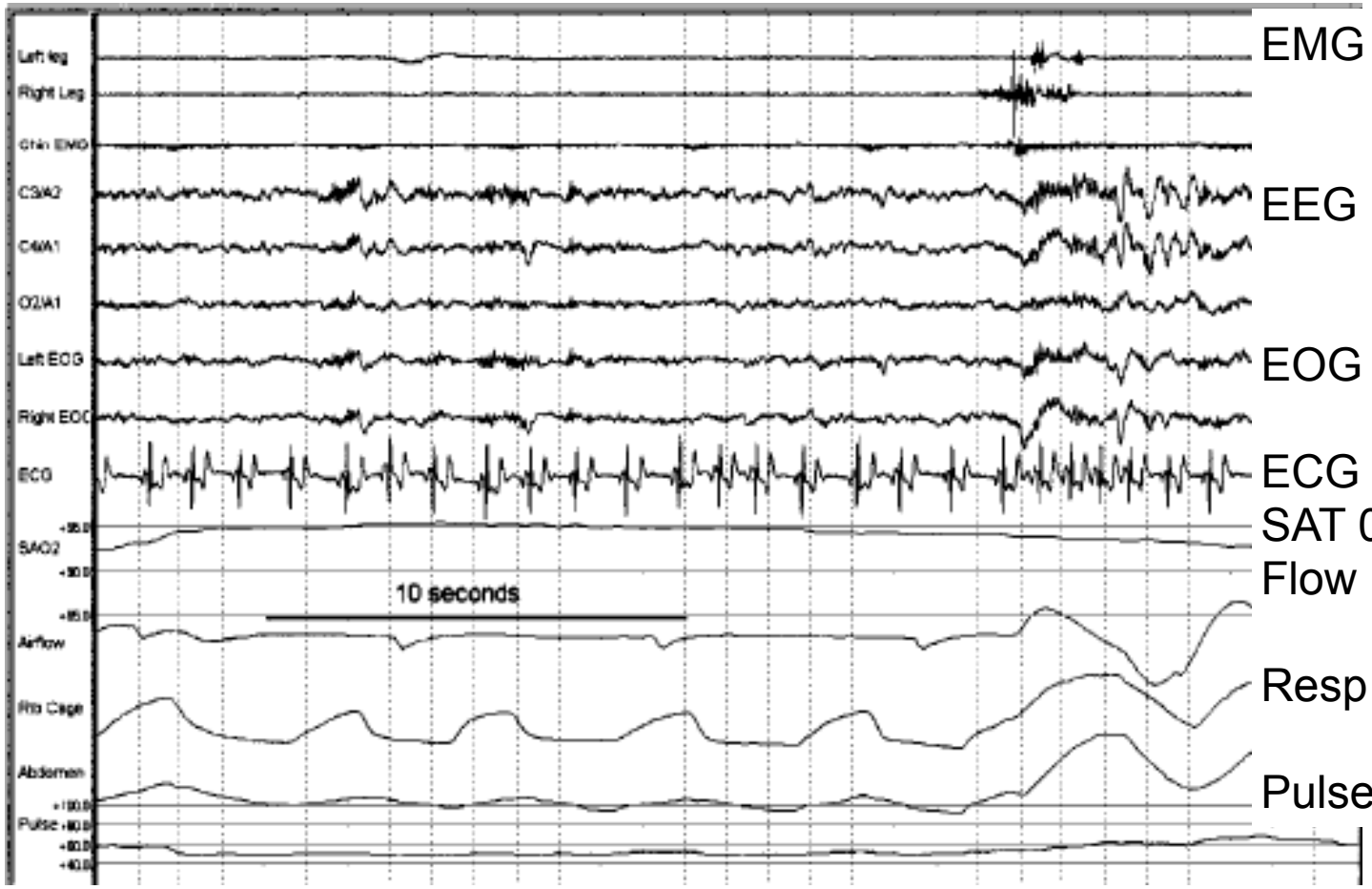
Rey et al. 2008

Sleep Apnea:
Diagnosis: Polysomnography

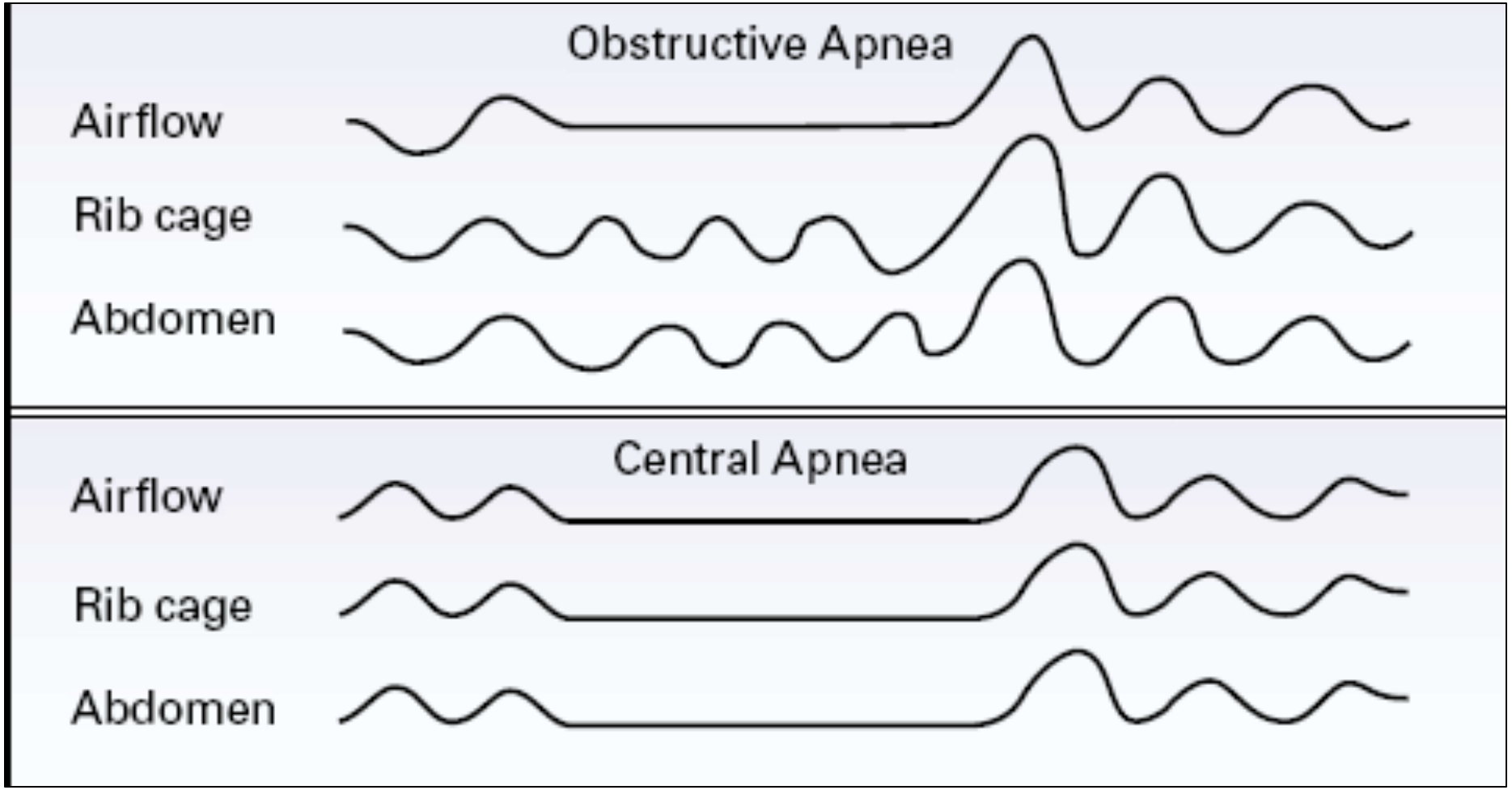
Diagnostic Techniques in Obstructive Sleep Apnea

Charles Frederick Petersen George

Progress in Cardiovascular Diseases, Vol. 41, No. 5 (March/April), 1999: pp 355-366



Differences between obstructive apnea and central apnea



N Engl J Med, Vol. 346, No. 6 · February 7, 2002

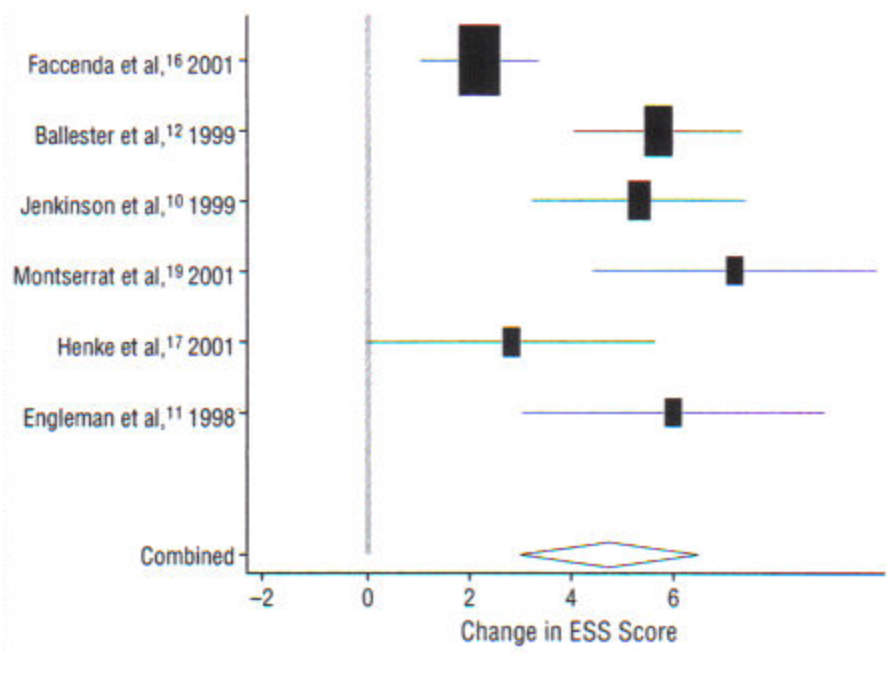
Sleep Apnea :
Treatment with CPAP

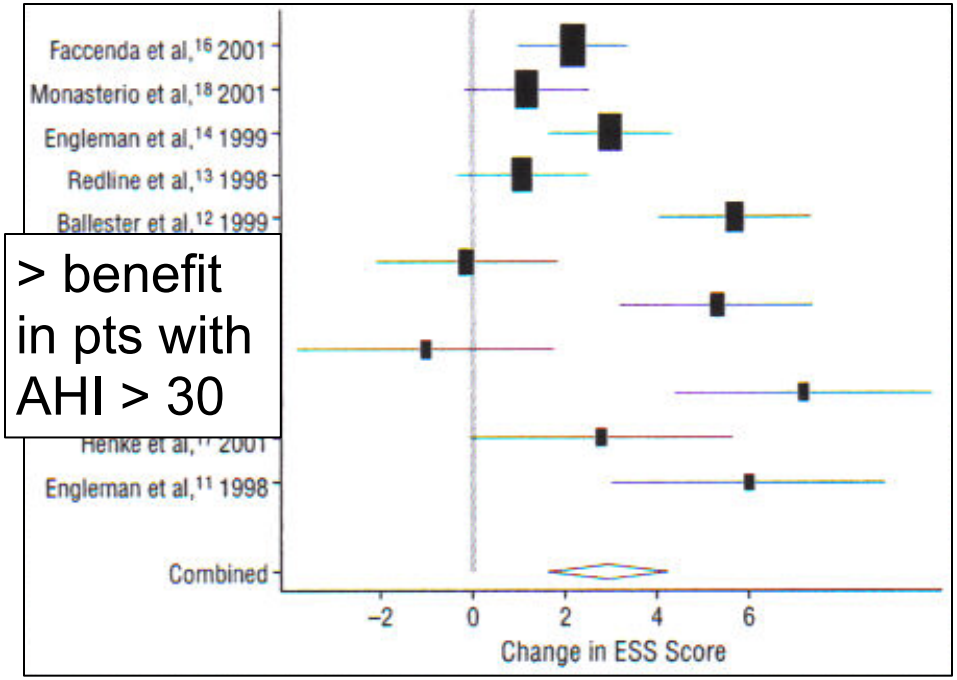
Continuous Positive Airway Pressure Therapy for Treating Sleepiness in a Diverse Population With Obstructive Sleep Apnea

Results of a Meta-analysis

Arch Intern Med. 2003;163:565-571

- 12 randomized studies
- End point: reduction in Epworth score





> benefit in pts with AHI > 30

CPAP better than placebo (OR 2.94, $p<0.001$)
Heterogeneity – $p<0.001$

Queen's University

Some Conclusions

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1. Sleep Apnea is highly prevalent.
2. Associated with cardiovascualr diseases such as CHF, HTN, Obesity and Metabolic Syndrome, Stroke, CAD, Autonomic Dysfunction, and Arrhythmias
3. Knowing the pathophysiological mechanisms permits starting multifactorial treatments (lose weight, control HTN, prevent arrhythmias and infarctions).
4. Identifying patients with SA allows treatment with C-PAP
5. Evidence indicates that rapid atrial pacing should NOT be universally recommended.
6. In patients with central sleep apnea, cardiac resynchronization remarkably improves apnea indices. This should be considered when recommending CRT.