AIAC
Associazione Italiana Aritmologia e Cardiostimolazione

CORSI TEORICO-PRATICI
Sleep Apnea 2020

CORSO TEORICO-PRATICO
LA SLEEP APNEA
FATTORE DI RISCHIO CARDIOVASCOLARE
16 gennaio 2020
Hotel NH Bologna De La Gare, Bologna

SCOMPENSO CARDIACO ED APNEE NOTTURNE

DOTT. ERMINIO MAURO

Cardiologia Policlinico di Modena

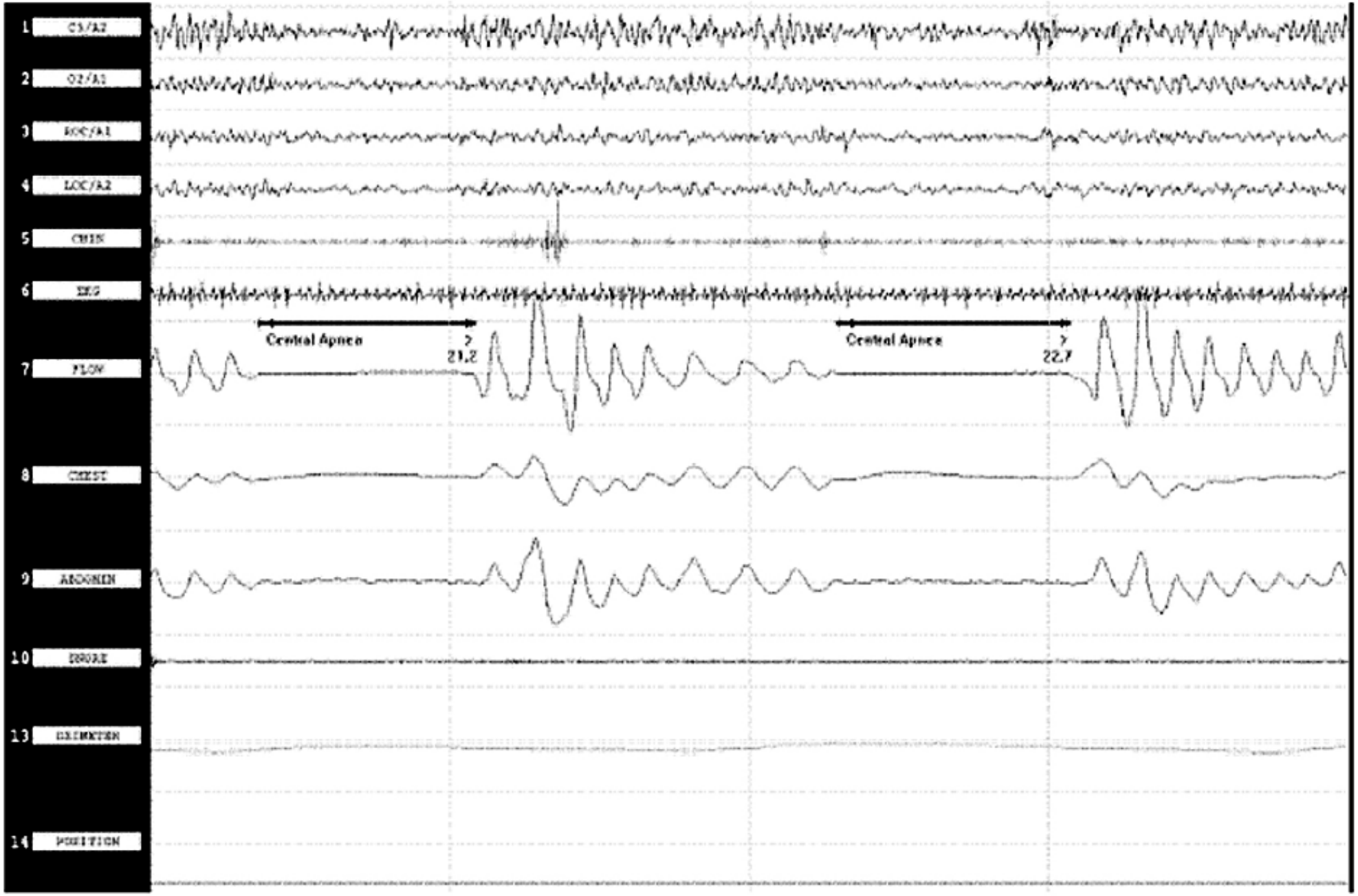
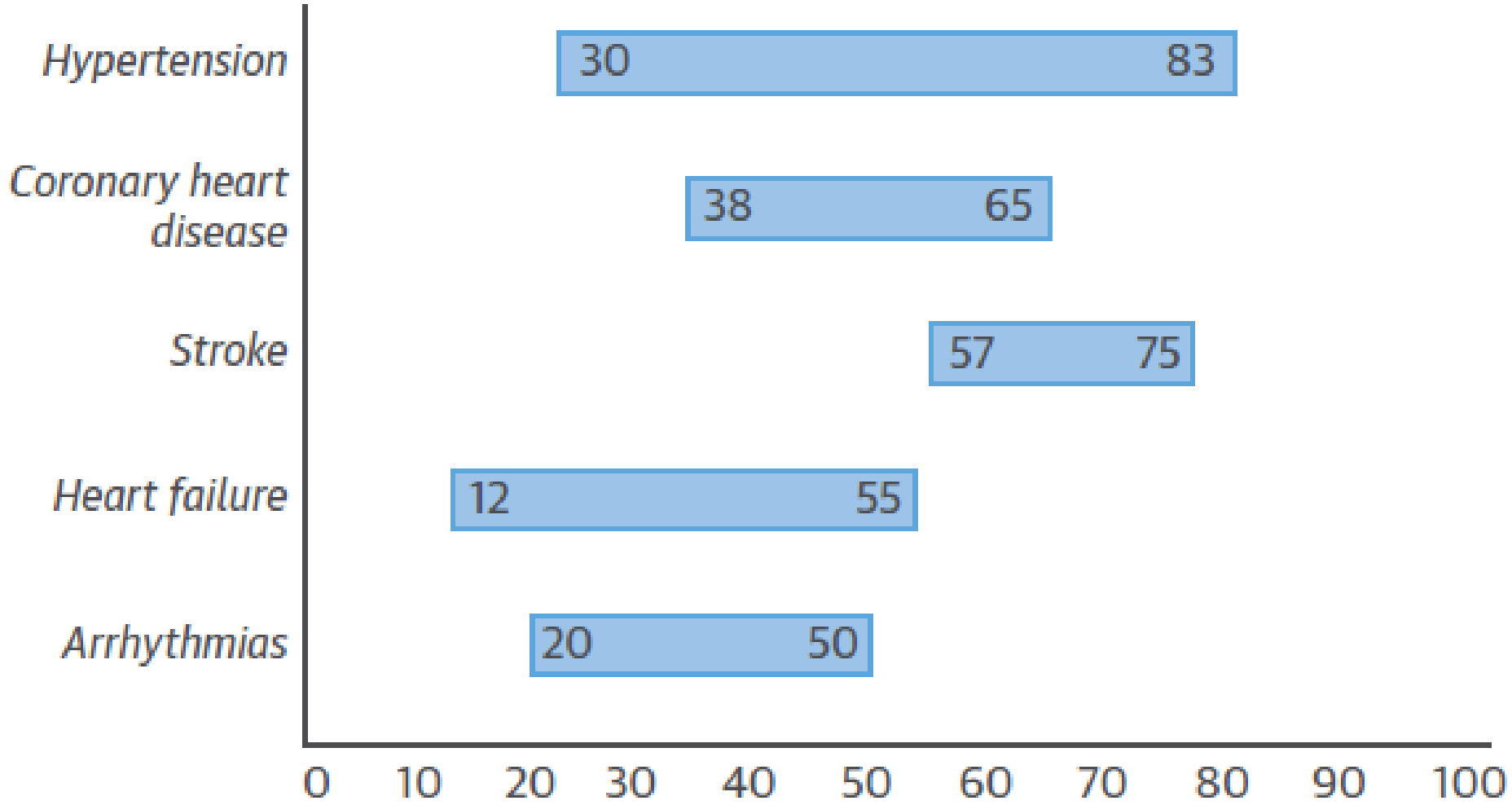

1
C3/A2
2
O2/A1
3
ROC/A1
4
LOC/A2
5
CHIN
6
ECG
7
FLOW
8
CHEST
9
ABDOMEN
10
SNORE
13
SATURATION
14
POSITION
Central Apnea
21.2
Central Apnea
22.7

FIGURE 5 Prevalence (%) of OSA in CVD



Box 2 | Epidemiology of sleep-disordered breathing

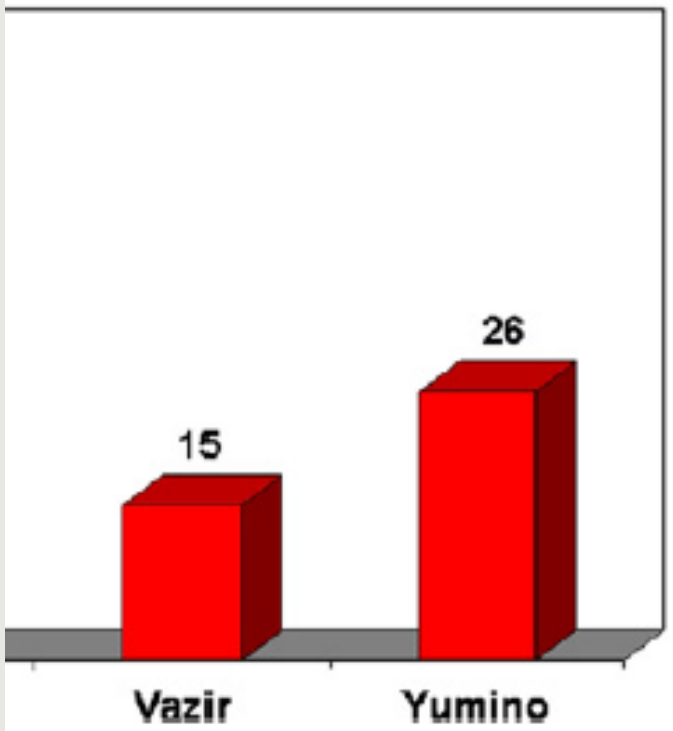
Prevalence of sleep disorders in patients with heart failure compared with the general population

Obstructive sleep apnoea[20,21,26,27]:
11–38% versus 2–26%

Central sleep apnoea/Cheyne–Stokes respiration[26–28,30–33,194]:
28–82% versus <5%

Chronic insomnia[2]:
33% versus 10–15%

NATURE REVIEWS | CARDIOLOGY



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.

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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

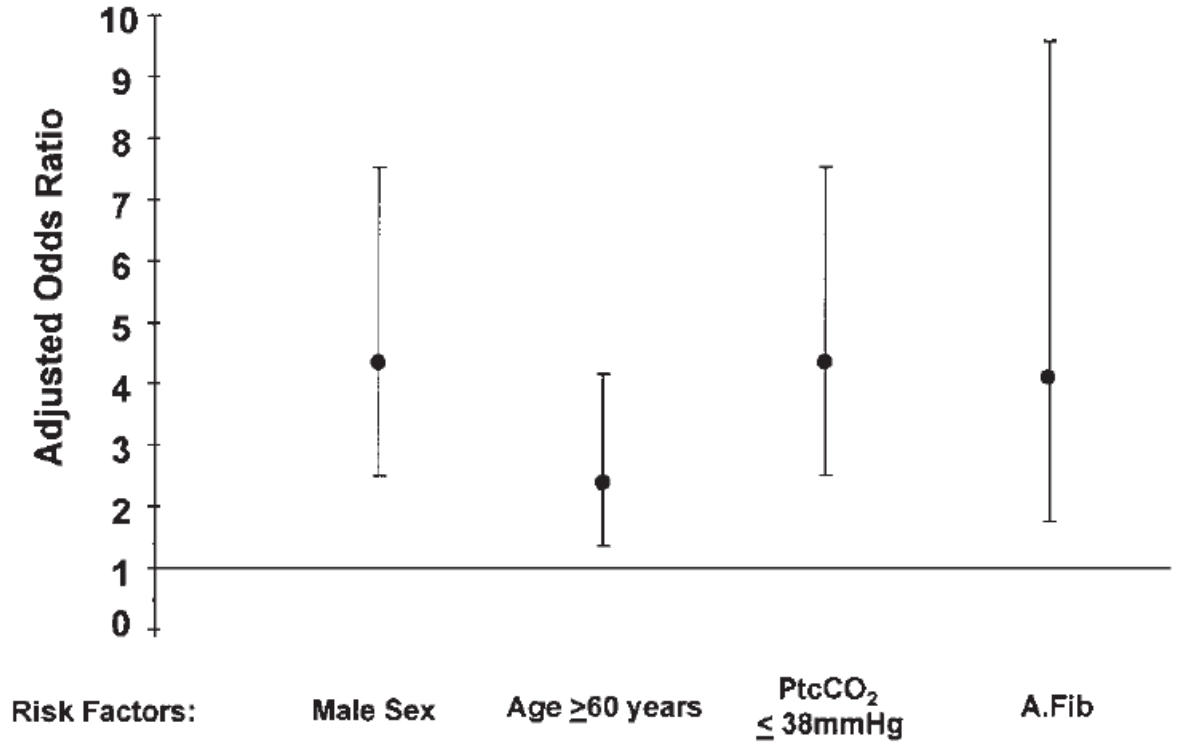


Figure 1. Adjusted relative OR for CSA in men and women. All categories are compared with women less than 60 yr of age with $PtcCO_2 > 38$ and without atrial fibrillation. Adjustments were made for BMI, LVEF, and all the variables listed in the figure. A.Fib = atrial fibrillation.

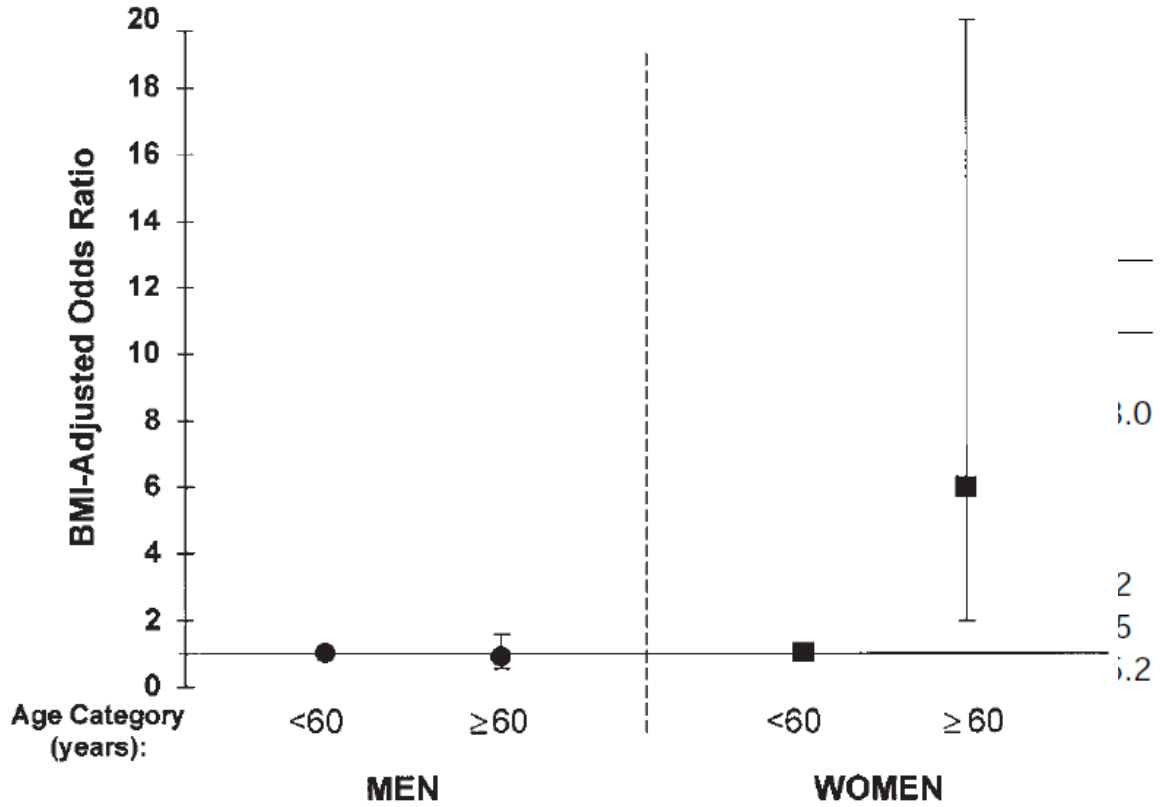


Figure 3. BMI-adjusted relative OR for OSA in men and women younger and older than 60 yr of age. For men and women, all age categories are compared with those younger than 60 yr of age. Adjustments were made for BMI, and cause of CHF.

Prevalence and Physiological Predictors of Sleep Apnea in Patients With Heart Failure and Systolic Dysfunction

DAI YUMINO, MD, PhD,[1,4] HANQIAO WANG, MD,[1,4] JOHN S. FLORAS, MD, DPhil,[2,3] GARY E NEWTON, MD, FACC,[2] SUSANNA MAK, MD, PHD,[2] PIMON RUTTANAUMPAWAN, MD,[1,4] JOHN D. PARKER, MD, FACC,[2,3] AND T. DOUGLAS BRADLEY, MD[1,3,4]

Table 3. Multivariable Odds Ratios for OSA and CSA

	OSA			CSA		
Variables	Adjusted Odds Ratio (95%CI)		*P* Value	Adjusted Odds Ratio (95%CI)		*P* Value
Age (per 10-y increase)	1.52	(1.08 – 2.14)	.017	1.48	(1.01 – 2.18)	.047
Male sex	4.95	(1.74 – 14.07)	.003	8.36	(2.38 – 29.38)	.001
Body mass index (per 5-kg/m^2 increase)	1.58	(1.08 – 2.33)	.019	0.99	(0.62 – 1.55)	.940
Atrial fibrillation	2.44	(0.56 – 10.55)	.231	7.93	(1.76 – 35.65)	.007
PCO_2, wake (per 1-mmHg decrease)	1.02	(0.94 – 1.11)	.569	1.27	(1.15 – 1.41)	<.001
Thiazide and loop diuretic use	2.25	(0.87 – 5.82)	.094	14.16	(2.70 – 74.28)	.002

Table 4. Sex-Specific Clinical Characteristics of Patients with Heart Failure

Variables	Men (n=168)	Women (n=50)
Sleep apnea, %	54	22*
OSA, %	30	12*
CSA, %	24	10*
Age, y	55.4±13.2	56.3±10.7
Body mass index, kg/m^2	29.1±5.2	29.5±5.8
Left ventricular ejection fraction, %	24.0±9.8	26.9±10.1
NYHA Class (III+IV), %	44	53
Ischemic heart failure, %	46	22*

Arch Intern Med. 2006;166:1716-1722

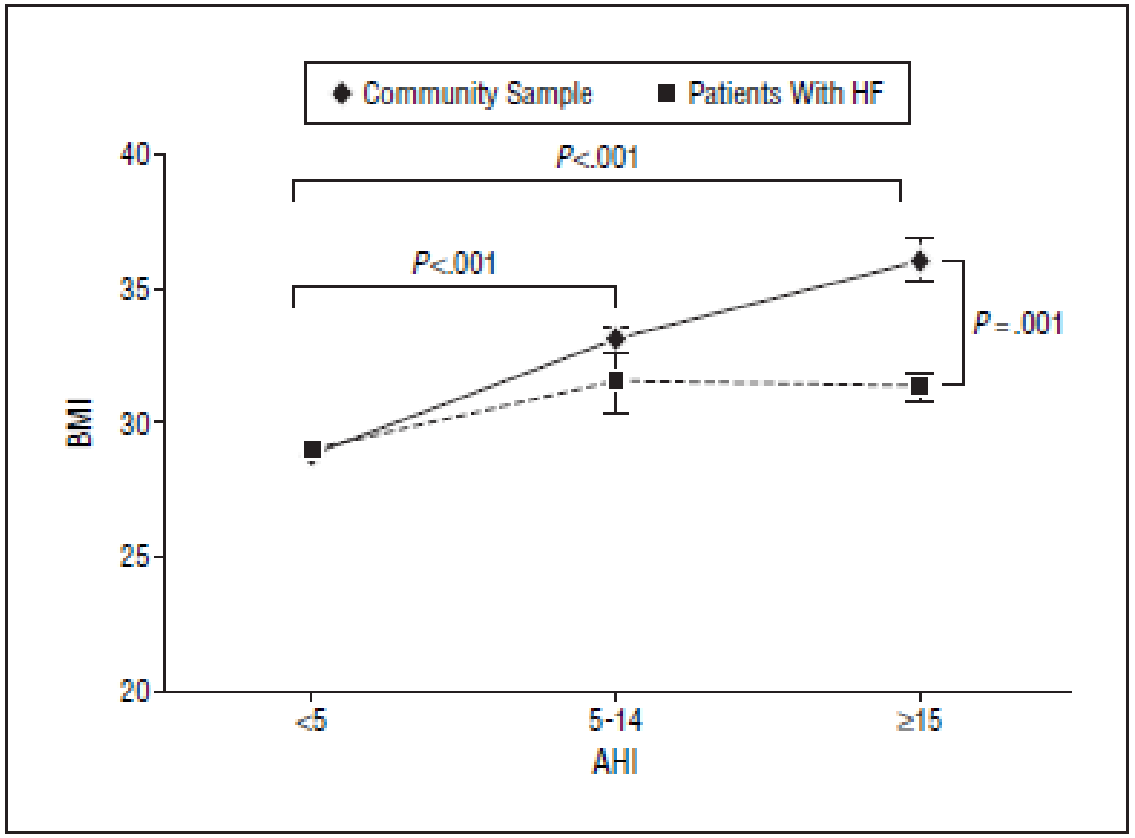
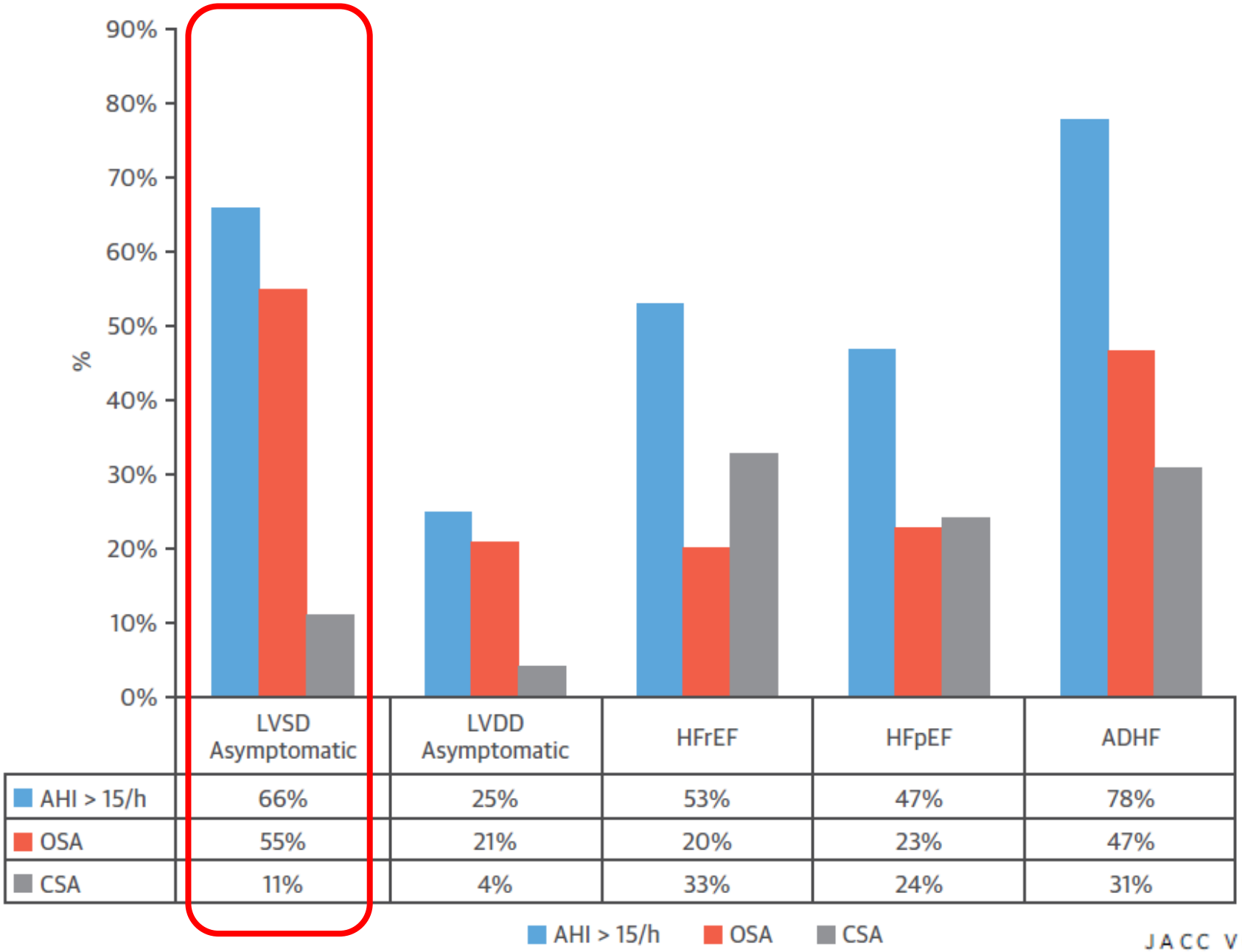


Figure 2. Body mass index (BMI) (calculated as weight in kilograms divided by the height in meters squared) by apnea-hypopnea index (AHI) categories (<5, 5-14, and ≥15). In the community sample, the AHI category increased significantly in association with increasing mean±SE BMI (28.9±0.2, 33.1±0.5, and 36.1±0.8, respectively). In contrast, in patients with heart failure (HF) there was no significant increase in the AHI category with increasing BMI (29.0±0.5, 31.5±1.1, and 31.3±1.2, respectively). In those with an AHI of 15 or higher, BMI was significantly greater in the community sample compared with the patients with HF.

FIGURE 9 Sleep Apnea is Prevalent in Left Ventricular Dysfunction

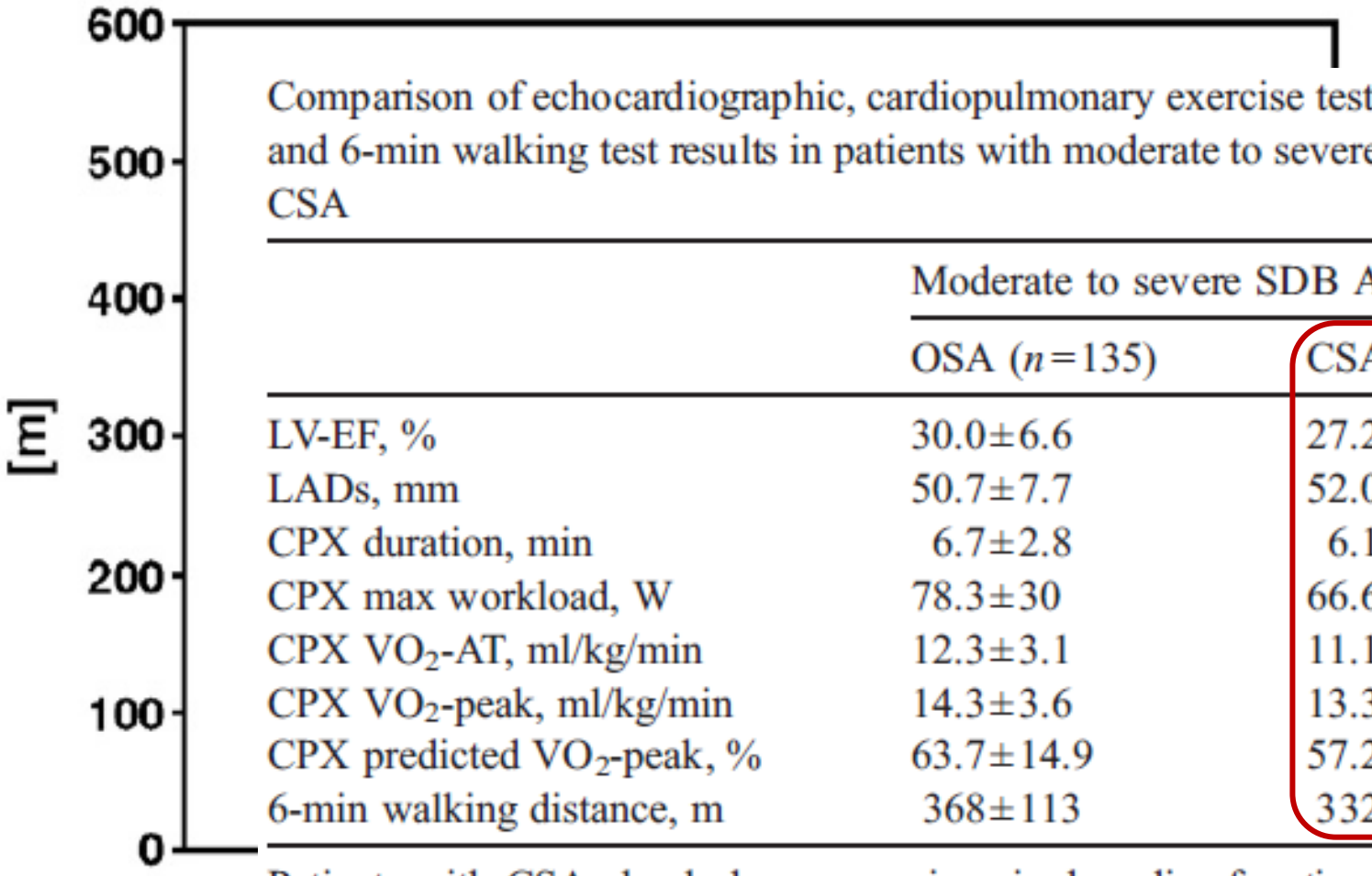


	LVSD Asymptomatic	LVDD Asymptomatic	HFrEF	HFpEF	ADHF
AHI > 15/h	66%	25%	53%	47%	78%
OSA	55%	21%	20%	23%	47%
CSA	11%	4%	33%	24%	31%

Demographic and clinical data for the CHF patients with moderate to severe SDB

nptomatic heart failure
icteristics of 700 patients

	Moderate to severe SDB	
	Echocardiographic parameters	
	No SDB	OSA	CSA
n (% of all patients)			
Age, years			
Sex, f/m			
Underlying disease			
DCM	LV-EF, %	28.2±7.3	29.3±2.6	27.4±6.6[a]
CAD	LADs, mm	47.4±8.4	51.0±8.0[b]	52.5±8.8[b]
CAD+VHD	LVEDD, mm	69.9±11.8	70.8±9.0	70.8±9.8
VHD	LVEDI, mm/m^2	23.6±4.5	23.5±3.5	23.4±3.5
NYHA class		3 (2.2%)	11 (4.7%)
BMI, kg/m^2		7 (5.2%)	9 (3.9%)
Diabetes		2.57±0.5	2.92±0.5[a]
Nycturia		28.6±4.4	26.3±3.6[a]
Rhythm		41%	30%
Sinus rhythm		1.7±0.9	2.1±1.0[a]
Atrial fibrillation			
Pacemaker		91 (67.4%)	131 (56.2%)
		30 (22.2%)	85 (36.5%)
		14 (10.4%)	17 (7.3%)



Comparison of echocardiographic, cardiopulmonary exercise testing (CPX) and 6-min walking test results in patients with moderate to severe OSA and CSA

	Moderate to severe SDB AHI ≥ 15/h	
	OSA (n=135)	CSA (n=233)
LV-EF, %	30.0±6.6	27.2±6.5[a]
LADs, mm	50.7±7.7	52.0±8.7
CPX duration, min	6.7±2.8	6.1±2.6
CPX max workload, W	78.3±30	66.6±28[a]
CPX VO_2-AT, ml/kg/min	12.3±3.1	11.1±3.4[a]
CPX VO_2-peak, ml/kg/min	14.3±3.6	13.3±3.9
CPX predicted VO_2-peak, %	63.7±14.9	57.2±16.3[a]
6-min walking distance, m	368±113	332±102[a]

Patients with CSA clearly have more impaired cardiac function compared to OSA patients: left-ventricular ejection fraction (LV-EF) is significantly lower, there is a clear trend towards more dilated left atria, whereas there is no difference in left ventricular diameters (data not shown). CSA patients had significantly lower results in cardiopulmonary exercise testing and 6-min walking distance.

[a] $p<0.05$ vs. OSA.

Fig. 2. Result
(331.2±111 m
OSA patients (3
†$p<0.01$).

EFFETTI MECCANICI

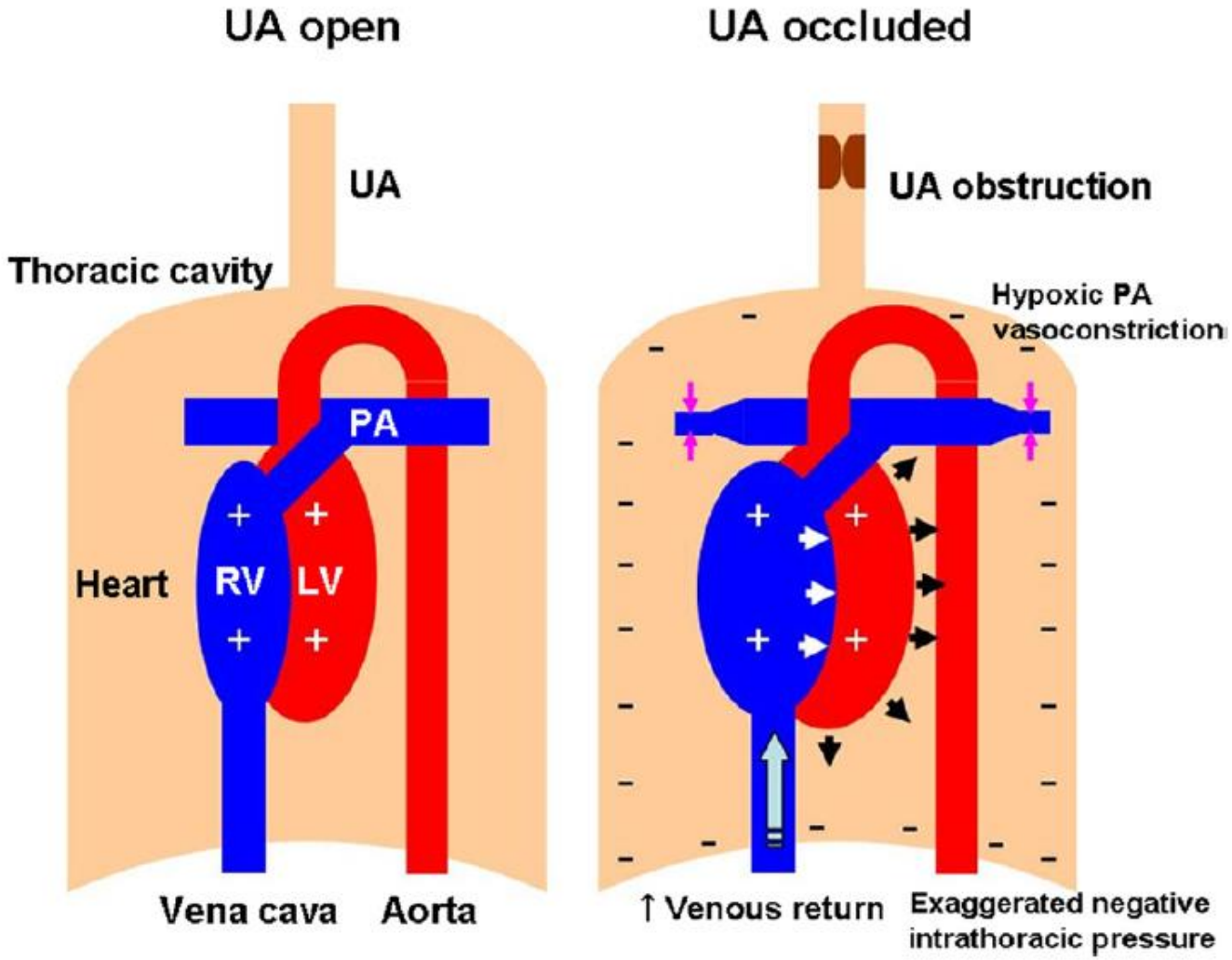


Figure 1 Effects of OSA on the RV and LV

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Eur Respir J. 1990 May;3(5):509-14.

The relationship between neck circumference, radiographic pharyngeal anatomy, and the obstructive sleep apr

Davies RJ[1], Stradling JR.

Author information

1 Sleep Clinic, Churchill Hospital, Headir

Abstract

We have studied the predictive importance
dimensions for obstructive sleep apnoea (
greater than 4% dips in arterial oxygen sat
95% confidence interval (C.I.) 0.46-0.76),
0.17-0.59), soft palate length (r = 0.31, 95
0.49), correlated significantly with saturatic
analysis (saturation dip rate as the depenc
independent correlates (total r2 = 0.42, 95
between general obesity, hyoid position, s
circumference.

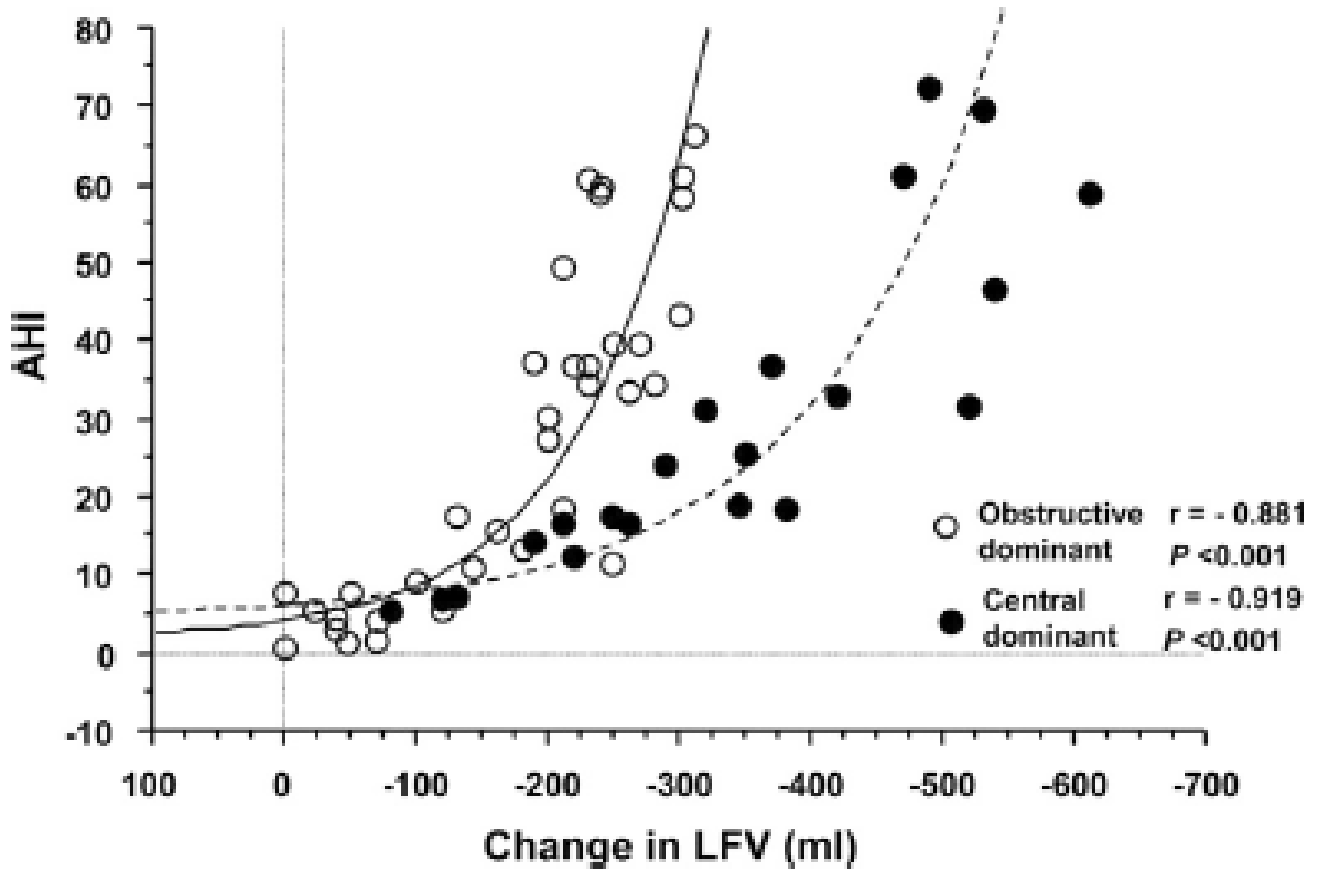
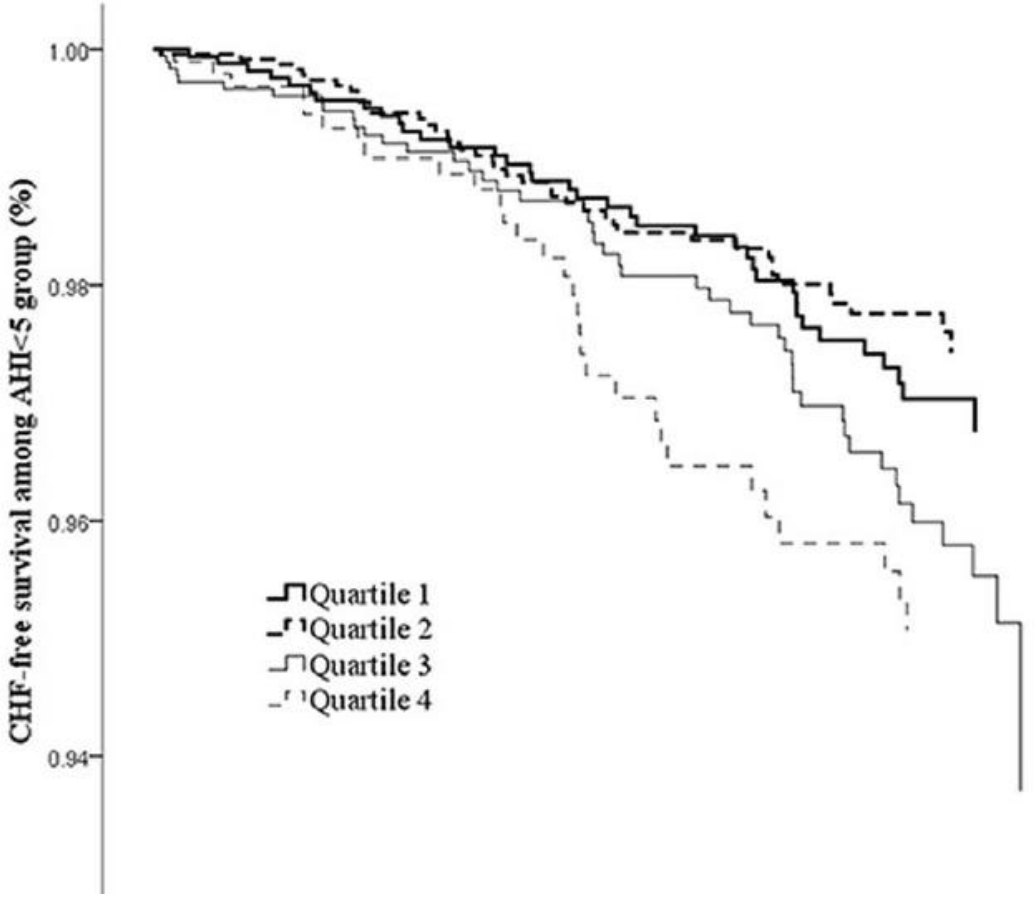
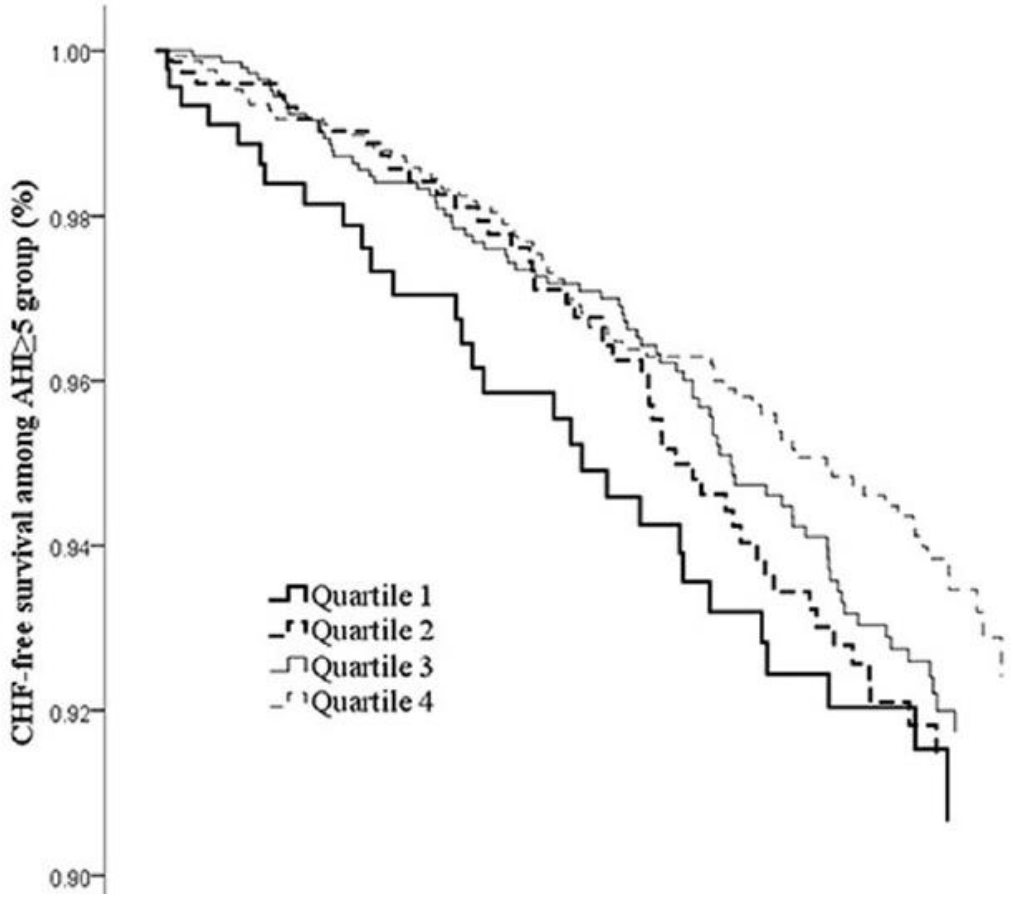


Figure 1. Relationship between overnight change in leg fluid volume (LFV) and apnea-hypopnea index (AHI) in heart failure patients with either predominantly obstructive or central sleep apnea. Reproduced from Yumino et al.[51] with permission from the American Heart Association.

Canadian Journal of Cardiology

The association of neck circumference with



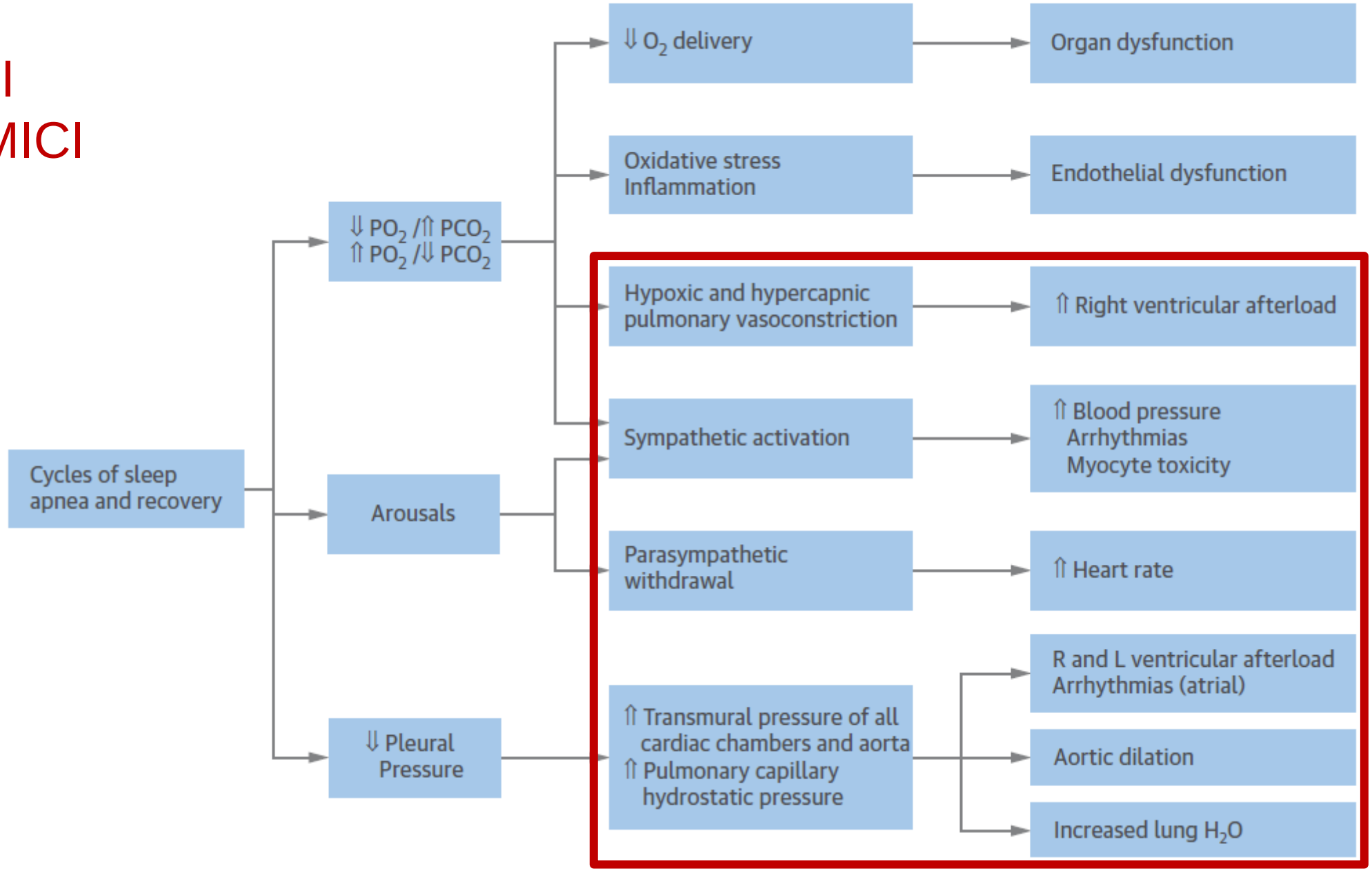


Conclusions: NC may correlate with CHF incidence and CHD mortality in population without SDB. NC measurement may help risk stratification for cardiovascular diseases.

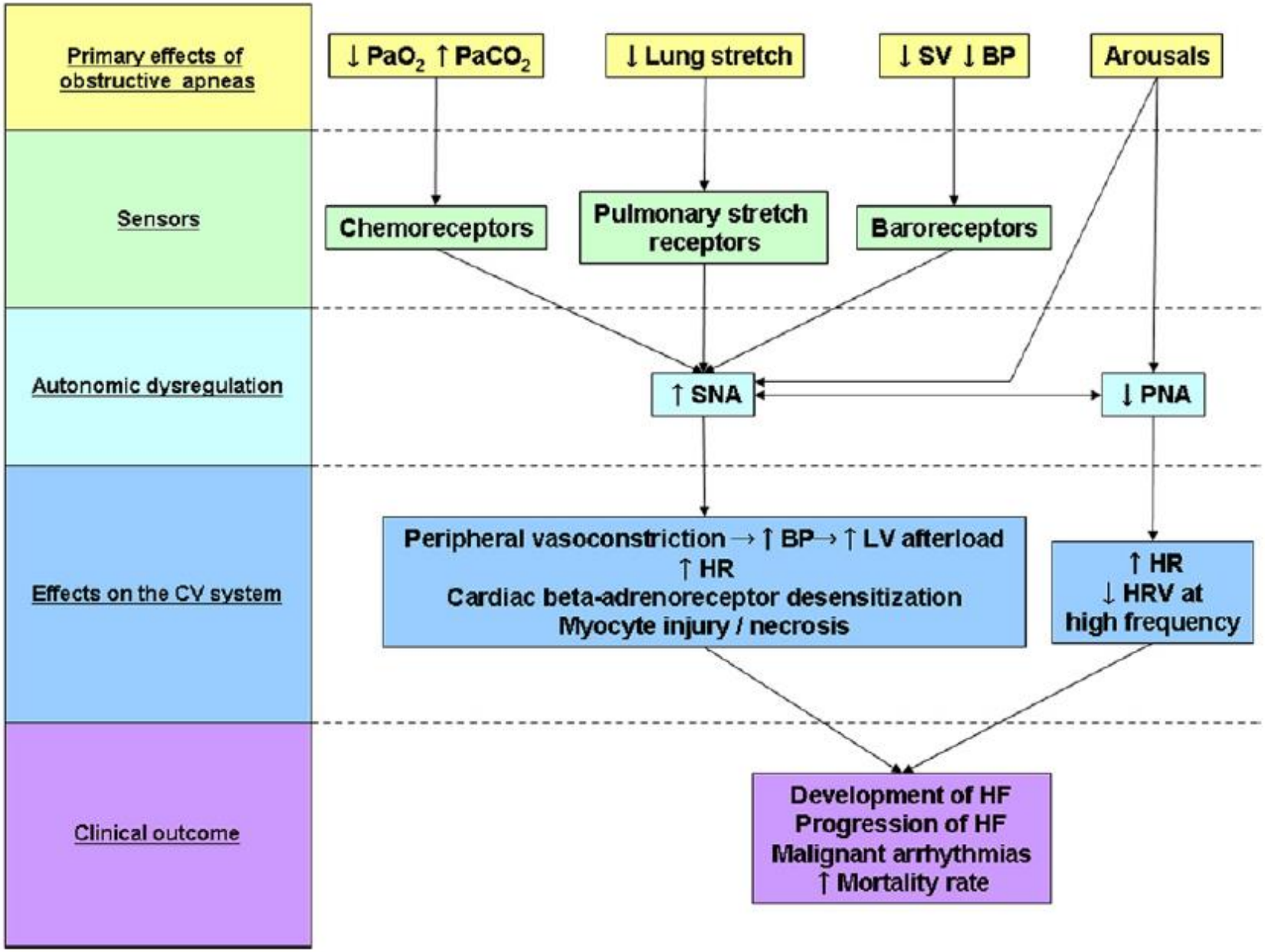
BMC Cardiovascular Disorders

EFFETTI EMODINAMICI

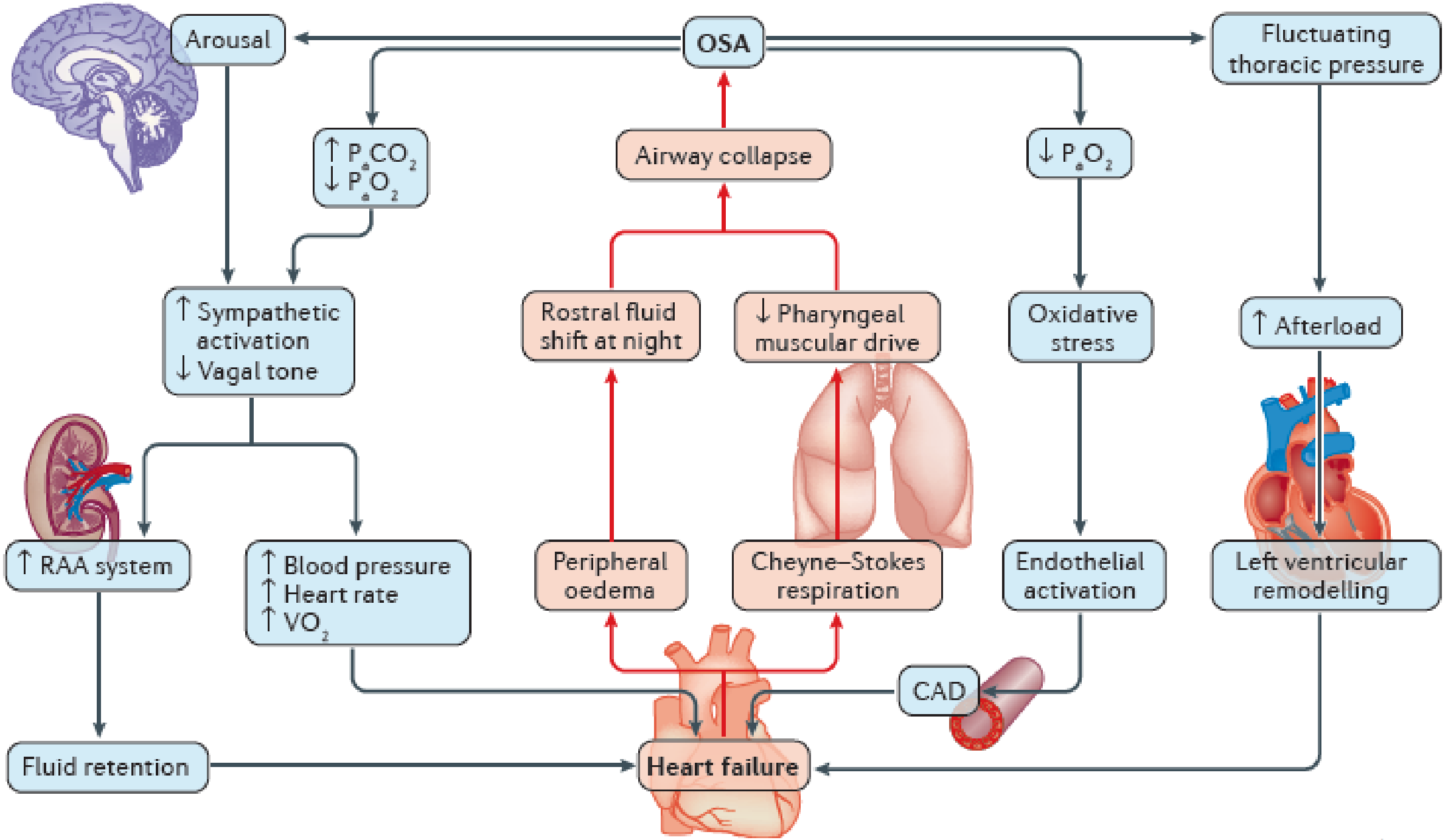
FIGURE 4 Pathophysiological Consequences of Sleep Apnea and Hypopnea



EFFETTI AUTONOMICI



Cardiovascular Autonomic Effects of OSA


Arousal
OSA
Fluctuating thoracic pressure
↑ P_aCO_2
↓ P_aO_2
Airway collapse
↓ P_aO_2
↑ Sympathetic activation
↓ Vagal tone
Rostral fluid shift at night
↓ Pharyngeal muscular drive
Oxidative stress
↑ Afterload
↑ RAA system
↑ Blood pressure
↑ Heart rate
↑ VO_2
Peripheral oedema
Cheyne–Stokes respiration
Endothelial activation
Left ventricular remodelling
CAD
Fluid retention
Heart failure

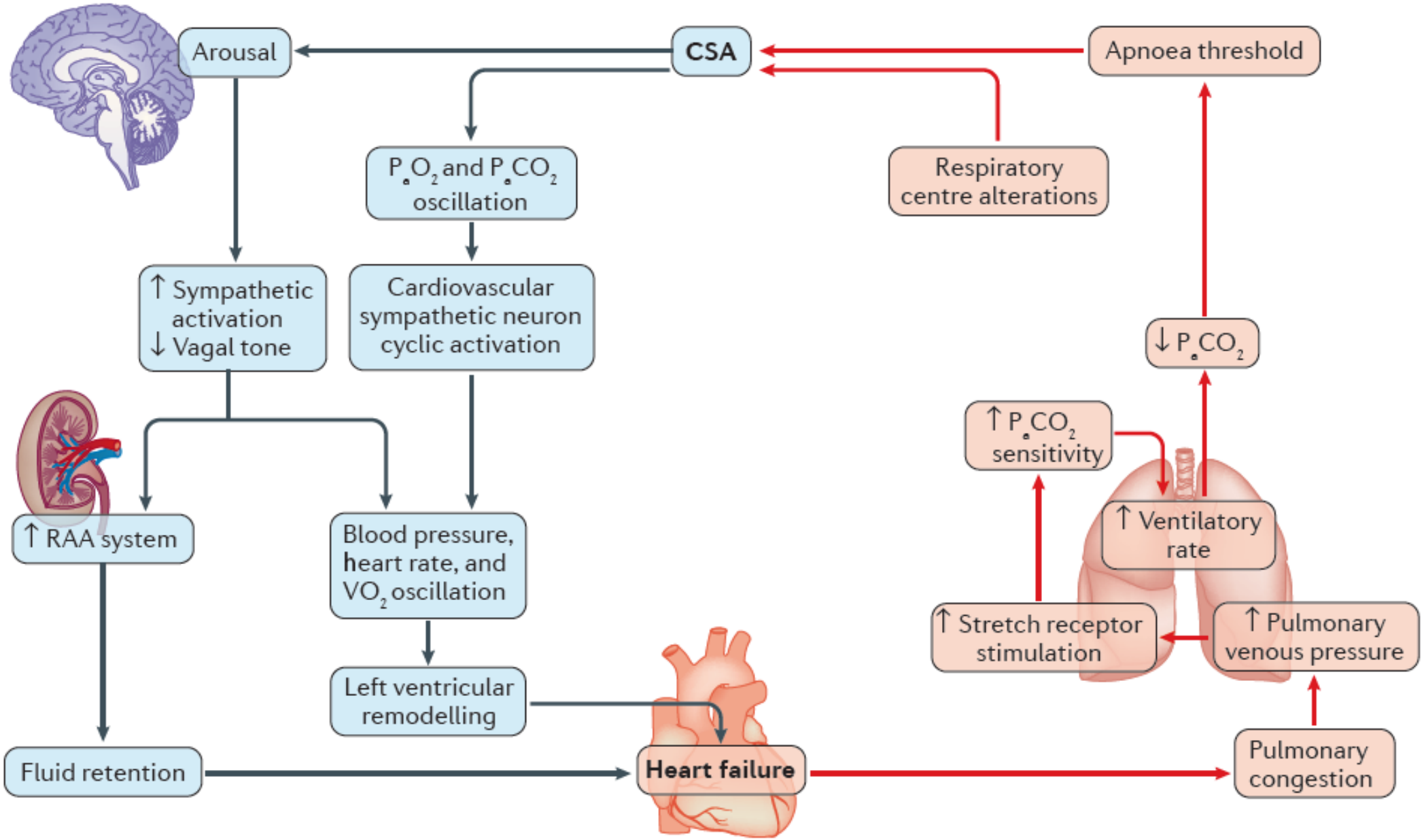
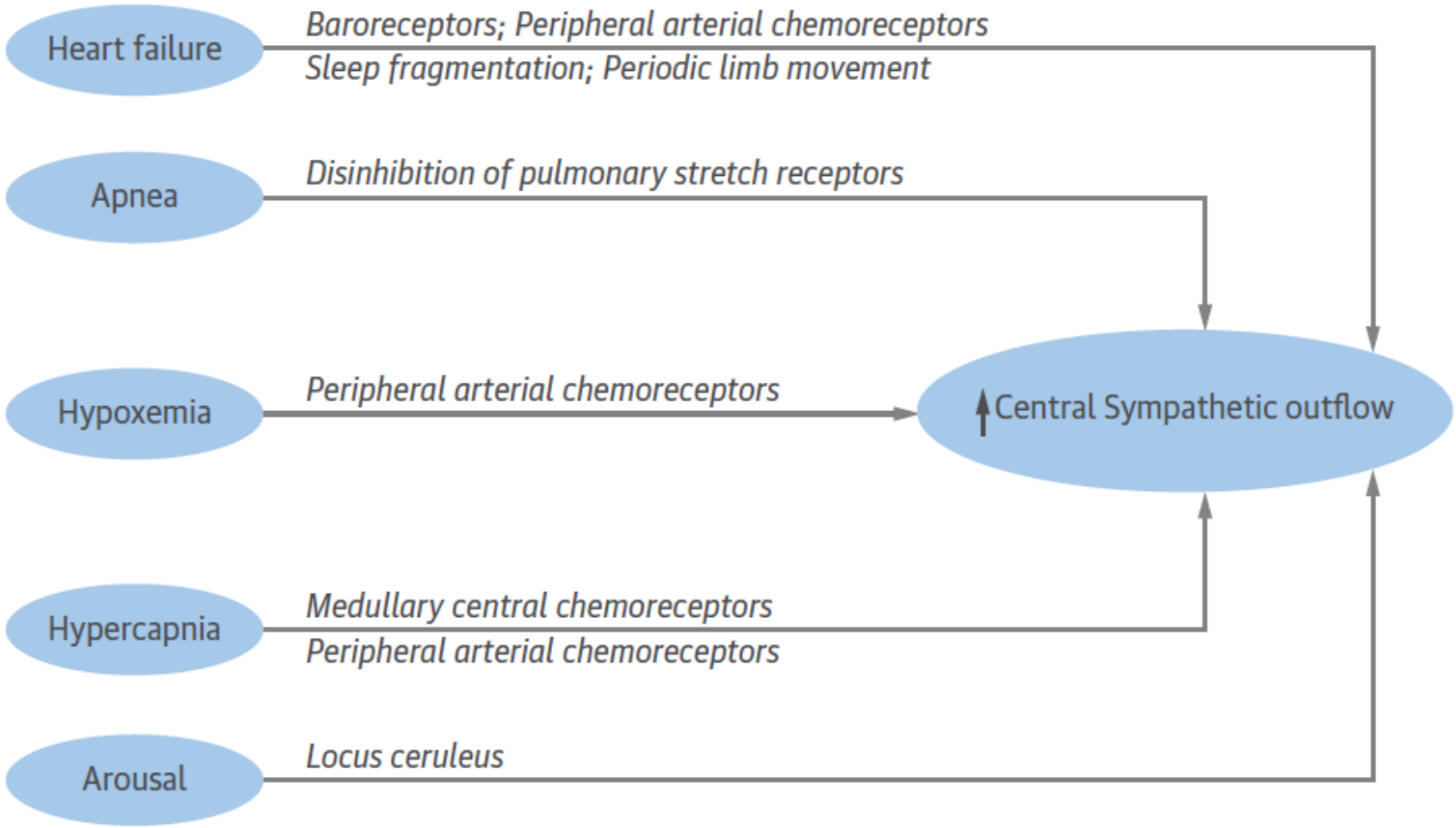


Figure 3 | **Relationship between central sleep apnoea (CSA) and heart failure.** Schematic representation of the mutual interaction between CSA and heart failure. P_aCO_2, arterial partial pressure of CO_2; P_aO_2, arterial pressure partial of O_2; RAA, renin–angiotensin–aldosterone; VO_2, oxygen consumption rate.

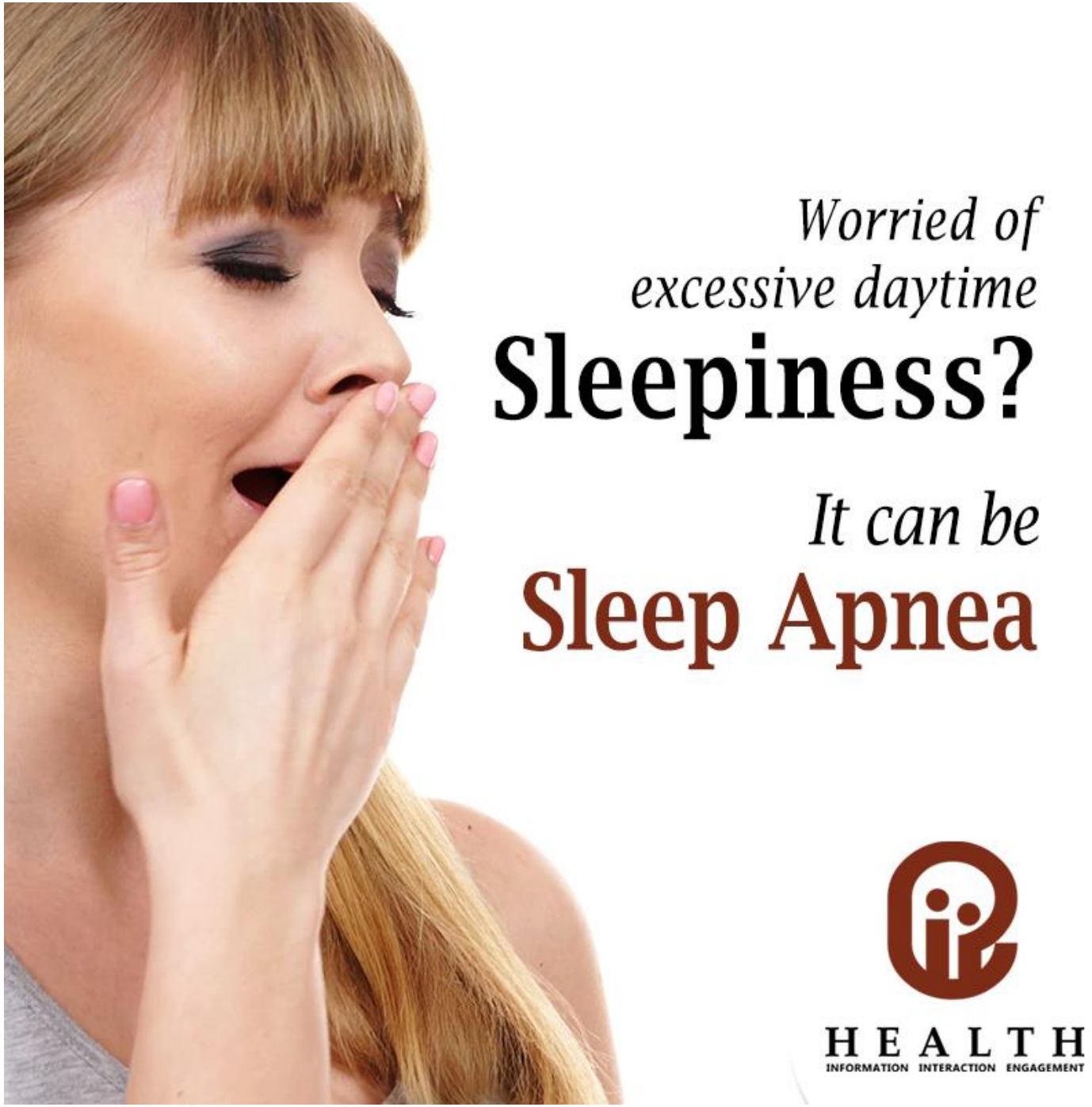
FIGURE 10 **Effects of Sleep Apnea and HF on Central Sympathetic Outflow**

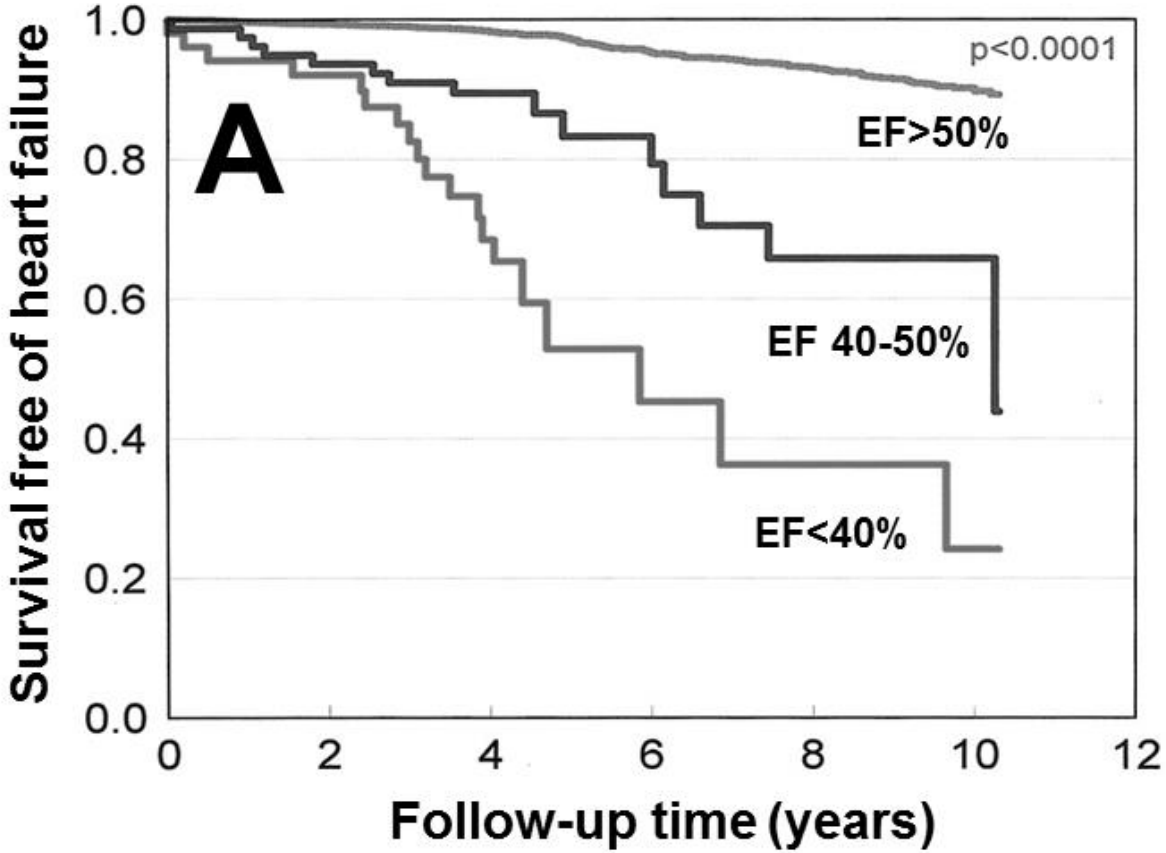


Heart failure is a hyperadrenergic state. Sleep apnea further contributes to increased central sympathetic outflow. Locus ceruleus is the brainstem arousal network, and norepinephrine is the neurotransmitter. HF = heart failure.

A QUESTO PUNTO, ATTENZIONE ALLA SONNOLENZA PERCHÉ ….

….POTREI ESSERE IO!!!!!!!!!





PLoS Medicine 2009

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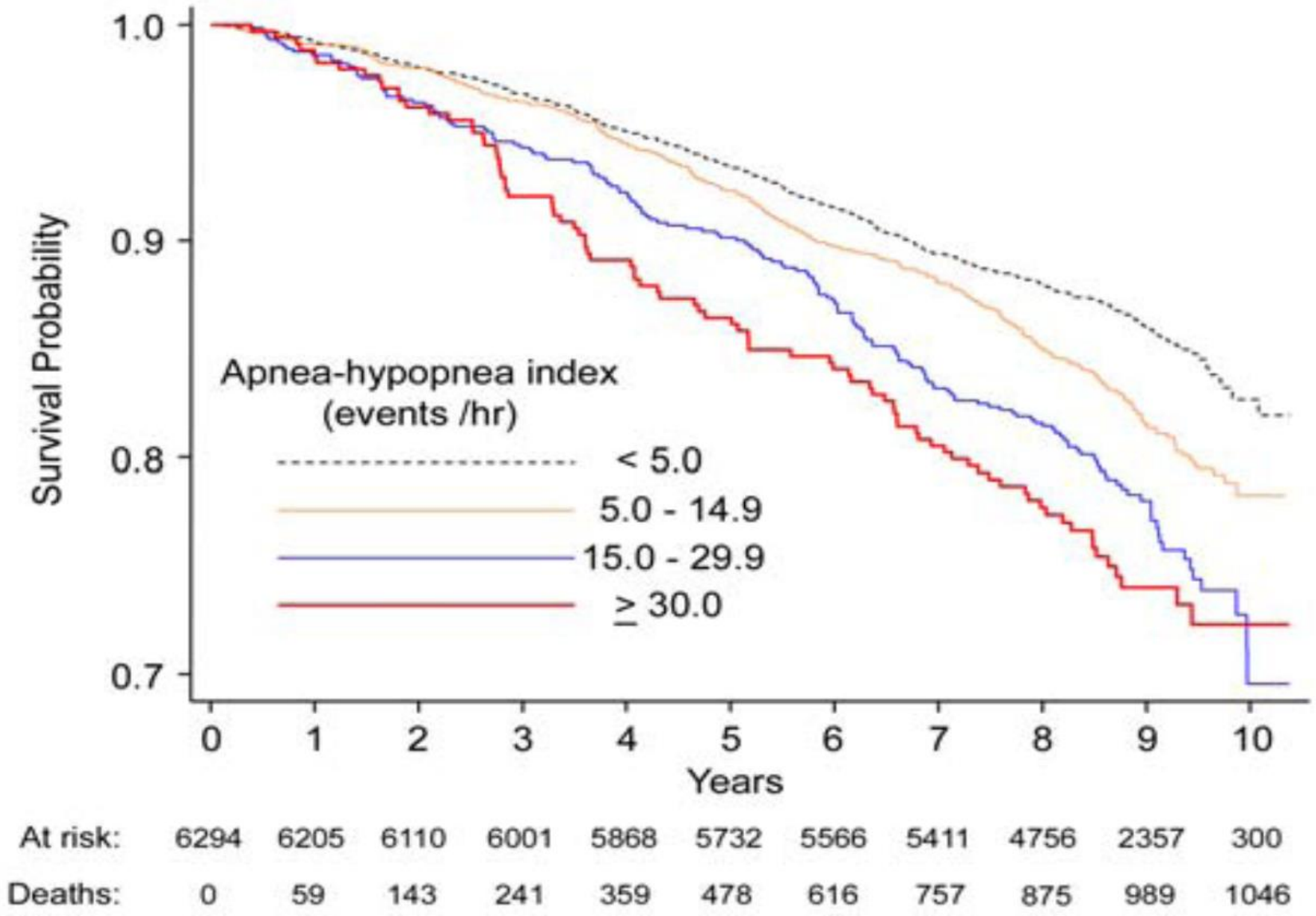
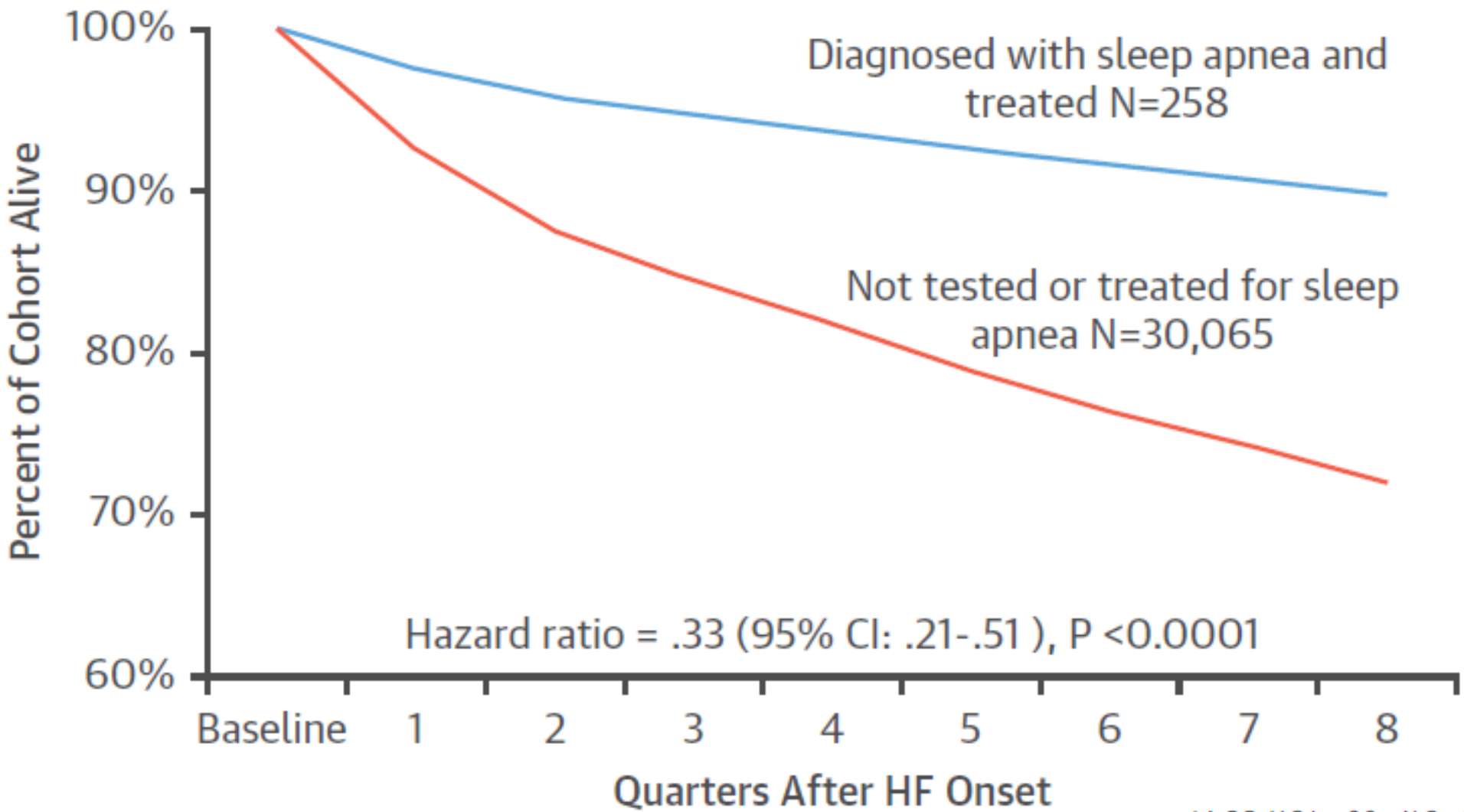


FIGURE 11 **Comparative Survival of 258 HF Patients Treated for Sleep Apnea and 30,000 Patients Not Tested for Sleep Apnea**



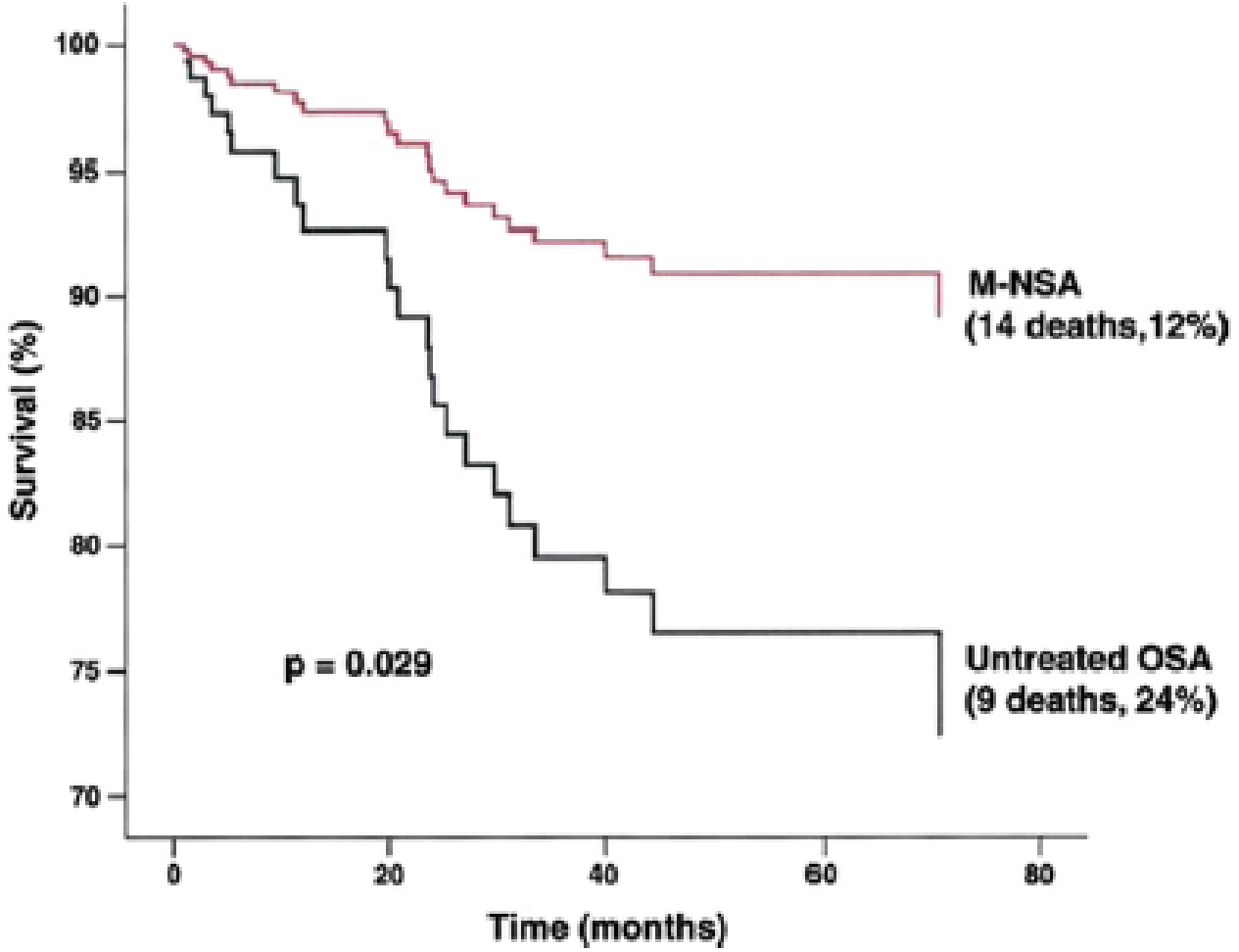


Figure 2. Multivariate Cox proportional hazards survival plots show worse survival of heart failure patients with untreated obstructive sleep apnoea (OSA) (apnea-hypopnea index $\geq$ 15) than in those with mild or no sleep apnea (M-NSA with apnea-hypopnea index <15) (hazard ratio: 2.81; $P = 0.029$), after adjusting for significant confounders (left ventricular ejection fraction, New York Heart Association functional class, and age). Reproduced from Wang et al.[83]

Table 2 | **Current and potential treatments for sleep-disordered breathing**

Treatment	Evidence	Refs
Central sleep apnoea		
Noninvasive positive airway pressure:		
• Continuous positive airway pressure	• Partly controversial evidence from small studies	58,170
• Bilevel positive airway pressure	• Partly controversial evidence from small studies	178,179
• Adaptive pressure support servo-ventilation	• Still under investigation	165
Acetazolamide and theophylline	Small observational studies	154–156
Supplemental O_2	Controversial evidence	163–165
Phrenic nerve stimulation	Pilot studies, efficacy to be proven	191
Cardiac pacing	Small studies, more evidence needed	185,186
Furosemide and spironolactone	Preliminary results	140
Hypoglossal nerve stimulation	Preliminary results	152
Cardiac pacing	Potential treatment, but negative results have been obtained	185,186

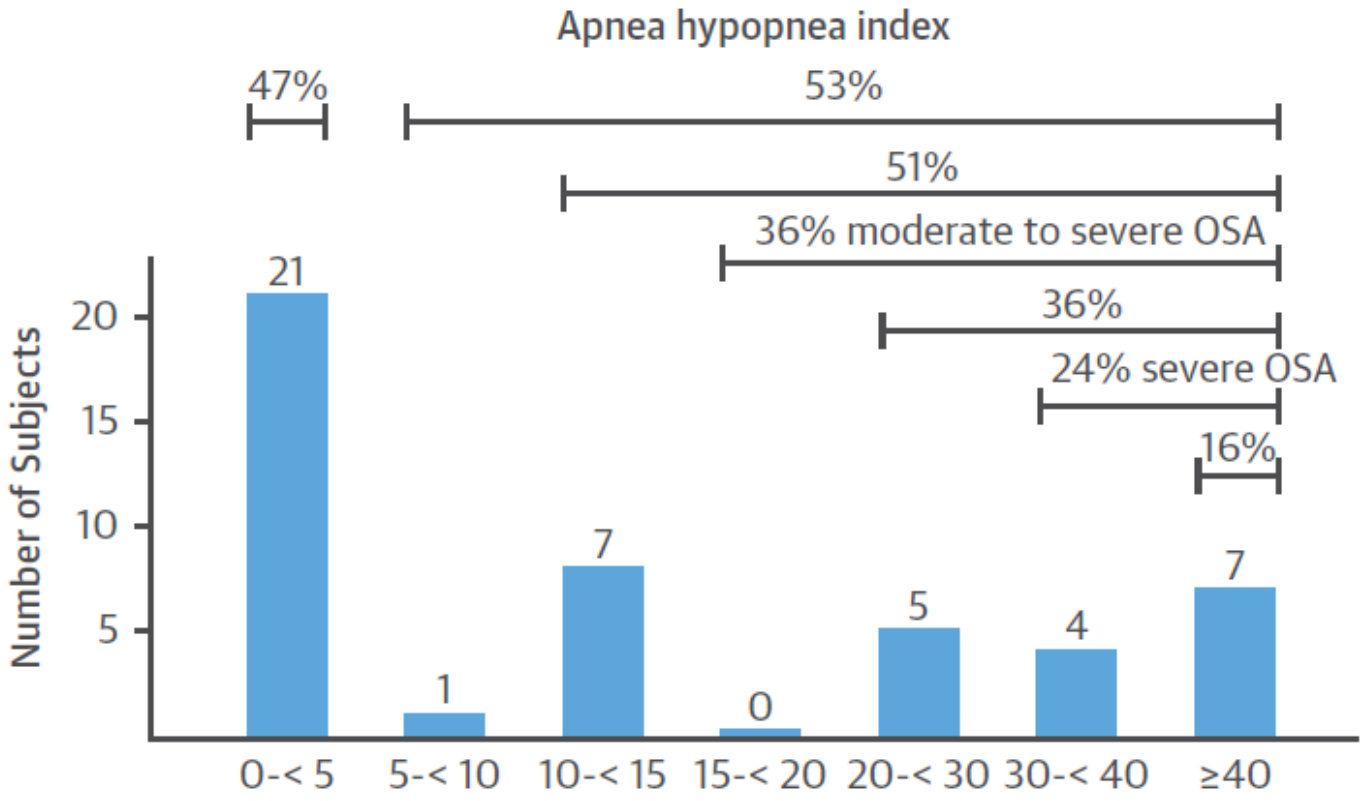
ASV ADAPTIVE-SERVO VENTILATION

Table 2. Results of short-term trials investigating effects of ASV in HF patients with CSA

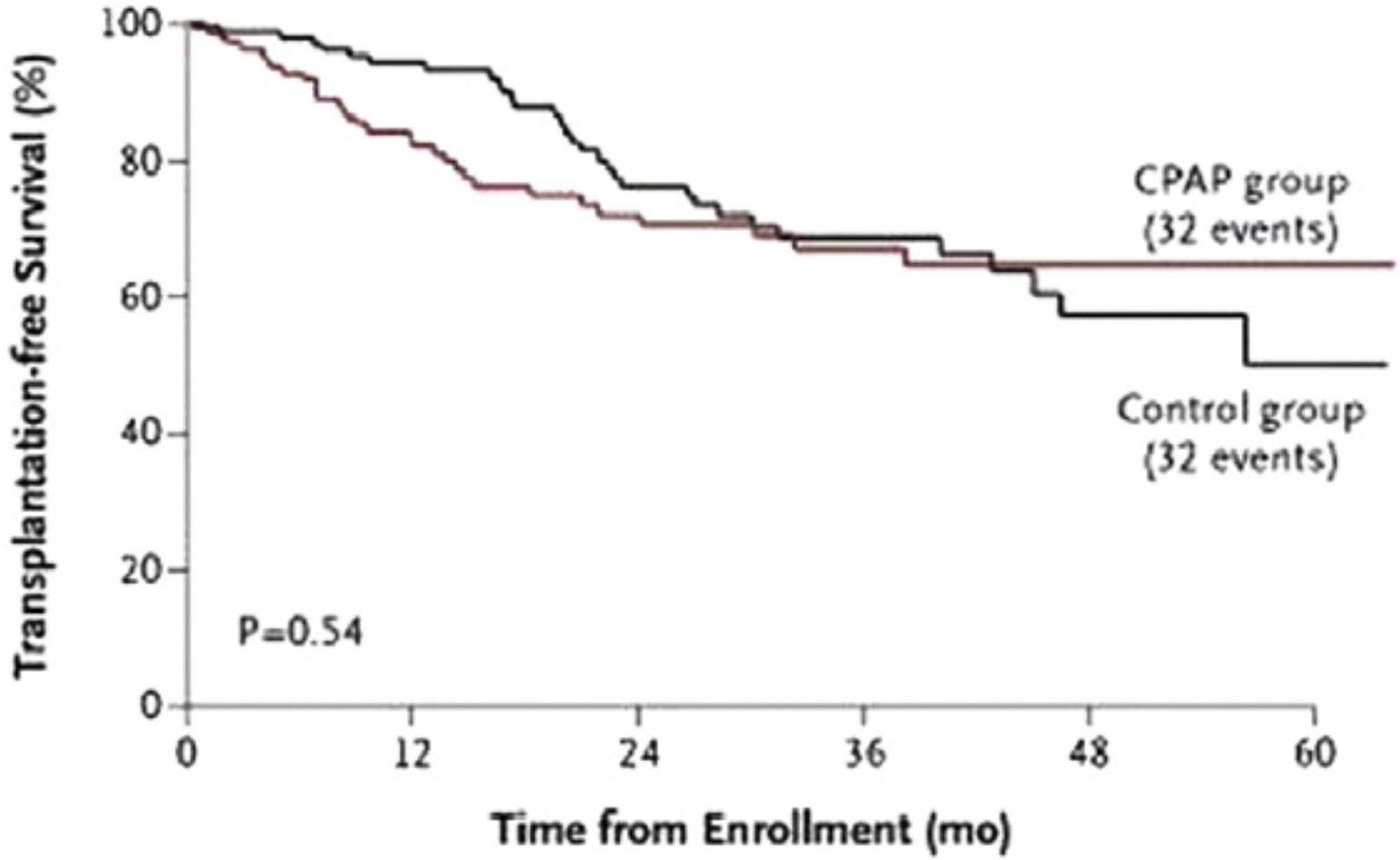
Reference	Study design	N*	Duration	Intervention	AHI, events per hour			LVEF, %		
					Before	After	*P*	Before	After	*P*
Pepperell et al.[119]	RCT	30	1 Month	ASV	21.9 ± 11.3	5.0 ± 1.4	< 0.001	36.5 ± 11.5	38.3 ± 3.3	0.7†
	Parallel			Sub-therapeutic ASV	17.7 ± 13.3	20.6 ± 2.3		35.7 ± 11.3	36.3 ± 3.8	
Philippe et al.[120]	RCT	25	6 Months	ASV	47.0	20.5	< 0.05†	29.0*	36.0*	< 0.05†
	Parallel			CPAP	40.5	2.0		30.0*	28.0*	
Fietze et al.[121]	RCT	30	6 Weeks	ASV	31.7 ± 9.8	11.2 ± 9.4	< 0.001	24.6 ± 7.9	26.5 ± 8.8	NS†
	Parallel			Bilevel pressure support	33.3 ± 34.0	12.4 ±15.0	< 0.01	25.5 ± 9.2	31.1 ± 10.5	
Kasai et al.[122,‡]	RCT	31	3 Months	ASV	36.3 ± 19.4	1.9 ± 2.1	< 0.01	35.7	26.6	< 0.05†
	Parallel			CPAP	38.6 ± 13.9	15.4 ±12.8	< 0.05	36.0	34.1	
Randerath et al.[123]	RCT	70	12 Months	ASV	46.8 ± 23.6	11.1 ±11.6	< 0.01	47.4 ± 15.9	45.5 ±16.0	NS†
	Parallel			CPAP	40.8 ± 17.1	17.0 ±17.9	< 0.01	43.2 ± 16.4	48.1 ±11.9	
Arzt et al.[124]	RCT	72	3 Months	ASV	48.0 ± 18.0	11.0 ± 10.0	< 0.001	29.9 ± 7.2	33.1 ± 8.6	0.728†
	Parallel			Medical therapy	47.0 ± 19.0	47.0 ± 22.0	0.733	29.4 ± 6.9	31.7 ± 8.9	

TREATMENT OF CSA: IMPACT OF THERAPY ON SYMPATHETIC ACTIVITY, LV MORTALITY. Intensive thera cotherapy and cardiac resync improve cardiac function, p CSA (5,73,84).

FIGURE 12 Prevalence of OSA in 45 of 60 Consecutive Cardiac Transplant Recipients



Those who developed sleep apnea had gained the most weight after transplantation. Adapted with permission from Javaheri et al. (95). CI = confidence interval; HF = heart failure; OSA = obstructive sleep apnea.



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

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doi:10.109

Cardiac

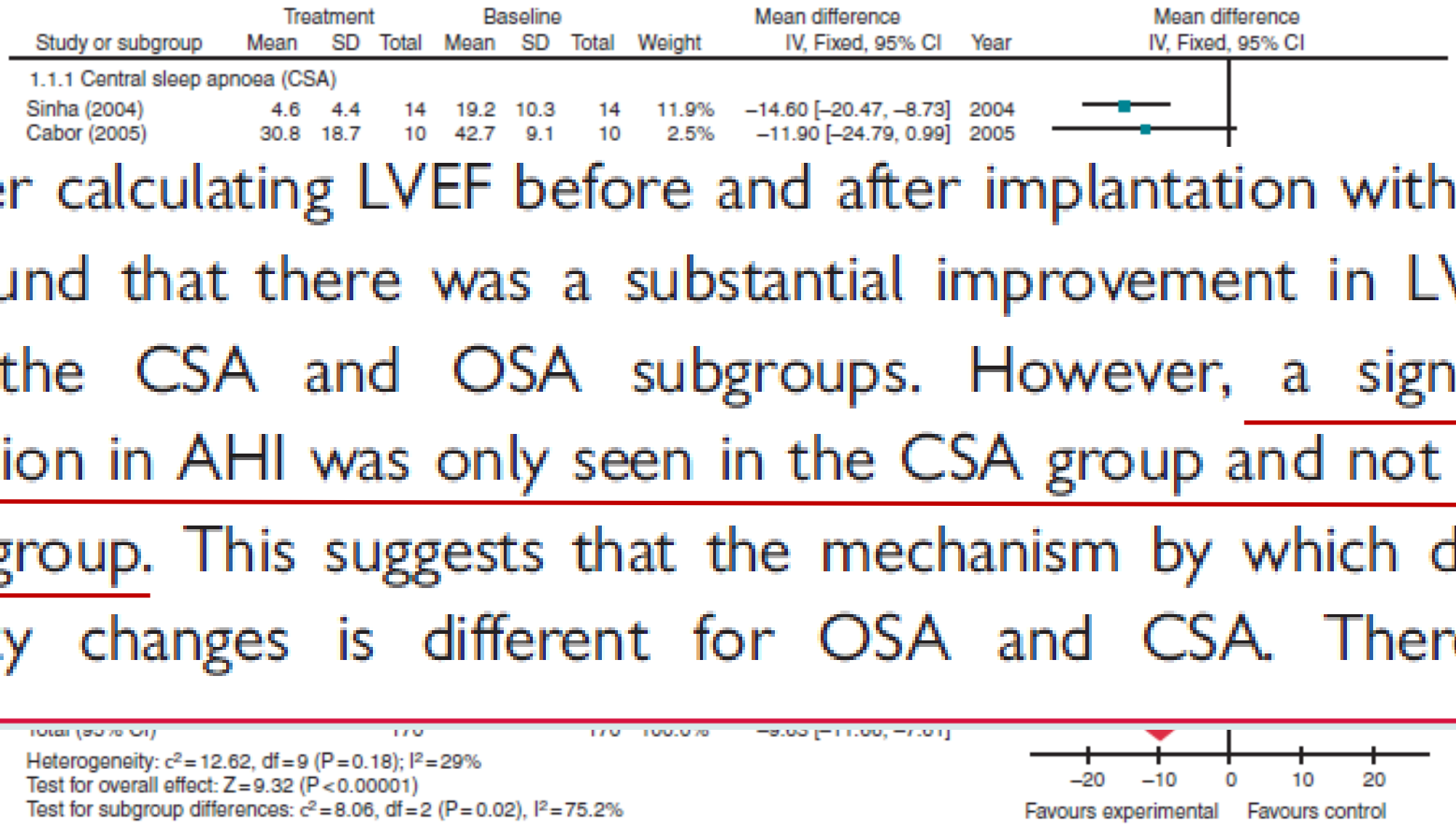


Figure 2 Reduction of sleep apnoea parameters with the use of cardiac resynchronization therapy. CI, confidence intervals; IV, inverse variance; SD, standard deviation.

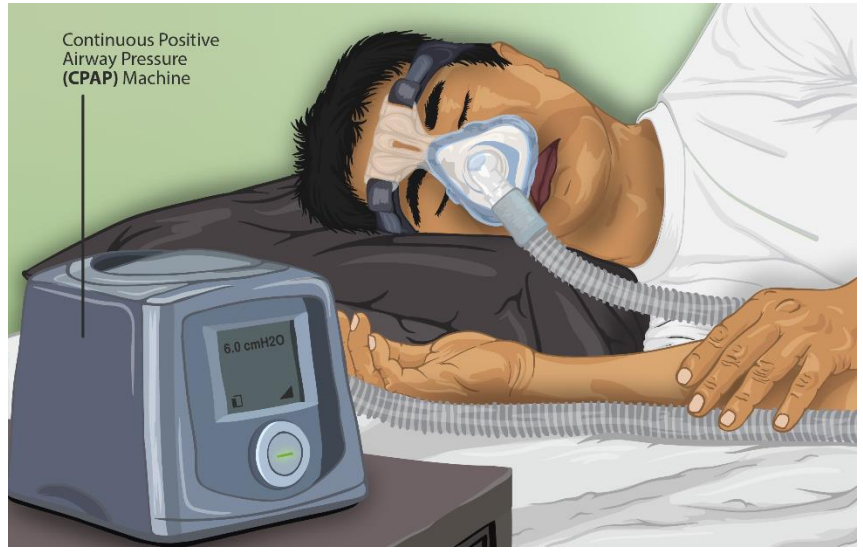
After calculating LVEF before and after implantation with CRT, we found that there was a substantial improvement in LVEF in both the CSA and OSA subgroups. However, a significant reduction in AHI was only seen in the CSA group and not in the OSA group. This suggests that the mechanism by which disease severity changes is different for OSA and CSA. There still

Table 1. Results of short-term trials that investigated effects of CPAP in HF patients with OSA

Reference	Study design	N	Duration	Intervention	AHI, events per hour			LVEF, %		
					Before	After	*P*	Before	After	*P*
Malone et al.[14]	Observational	19	1 month	CPAP	54.1 ± 7.2	1.0 ± 0.4	< 0.001	37 ± 4	49 ± 5	< 0.001
Kaneko et al.[95]	RCT	24	1 month	CPAP	37.1 ± 6.4	8.3 ± 2.8	0.002	25.0 ± 2.8	33.8 ± 2.4	0.009
				Control (no CPAP)	45.2 ± 5.3	44.7 ± 6.8		28.5 ± 1.8	30.0 ± 2.1	
Mansfield et al.[96]	RCT	40	3 months	CPAP	25.0 ± 4.1	2.9 ± 0.8	< 0.001	37.6 ± 2.5	42.6 ± 0.3	0.04
				Control (no CPAP)	26.6 ± 4.5	18.2 ± 2.8		33.6 ± 2.6	35.1 ± 3.1	
Ryan et al.[98]	RCT	18	1 month	CPAP	29.3 ± 4.8	6.1 ± 1.1	0.017	27.6 ± 3.4	29.6 ± 3.1	0.02
				Control (no CPAP)	57.9 ± 5.5	56.2 ± 5.3		34.1 ± 3.0	34.3 ± 2.8	
Smith et al.[101]	RCT Crossover	26	1 month	Auto-titrating CPAP	36 ± 23	NA	NA	29 ± 10	30 ± 10	0.56
				Sham CPAP	36 ± 23			29 ± 10	30 ± 10	
Gilman et al.[99]	RCT	19	1 month	CPAP	30 ± 15	7 ± 6	0.025	26 ± 10	35 ± 8	0.028
				Control (no CPAP)	41 ± 13	37 ± 18		30 ± 11	30 ± 6	

In the RCTs, *P* values refer to the difference between intervention and control groups.

AHI, apnea-hypopnea index; CPAP, continuous positive airway pressure; HF, heart failure; LVEF, left ventricular ejection fraction; NA, not applicable; OSA, obstructive sleep apnea; RCT, randomized control trial.



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)	Snorers (n=377)	Untreated mild-moderate OSAH (n=403)	Untreated severe OSAH (n=235)	OSAH treated with CPAP (n=372)
Age (years)	49·6 (8·1)	49·9 (9·1)	50·3 (8·1)	49·9 (7·2)	49·9 (8·5)
Body-mass index (kg/m²)	29·8 (4·4)	26·1 (3·6)*	27·5 (4·4)*	30·3 (4·2)	30·7 (4·4)†
Hypertension (%)	14·8	17·7	24·8‡	34·9*	35·1*
Diabetes (%)	6·1	7·5	8·5	9·9	11·3†
Lipid disorders (%)	6·8	7·2	7·4	7·7	7·9

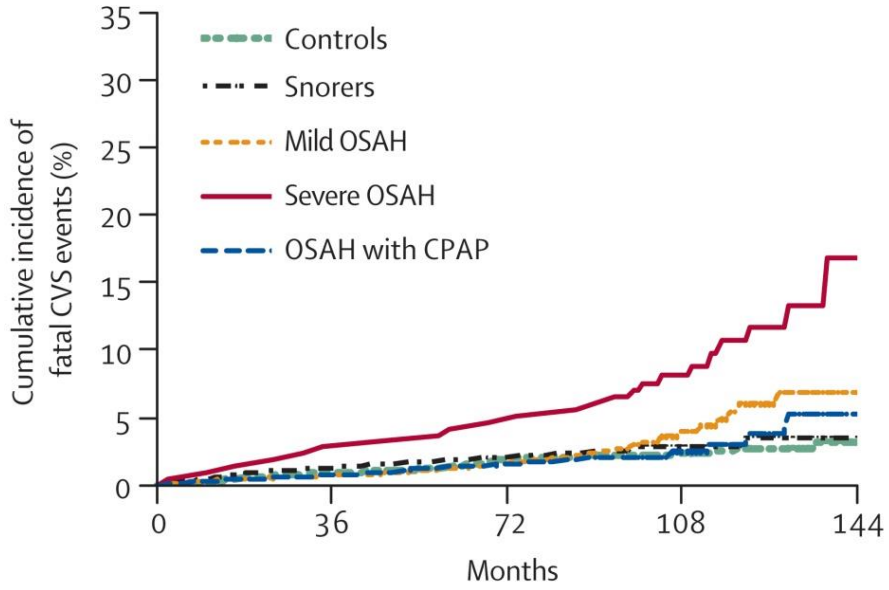
	Healthy men (n=264)	Simple snorers (n=377)	Untreated mild-moderate OSAH (n=403)	Untreated severe OSAH (n=235)	OSAH treated with CPAP (n=372)
Non-fatal cardiovascular events					
Number of events	12	22	36	50	24
Events per 100 person years	0·45	0·58	0·89	2·13*	0·64
Cardiovascular death					
Number of events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

A



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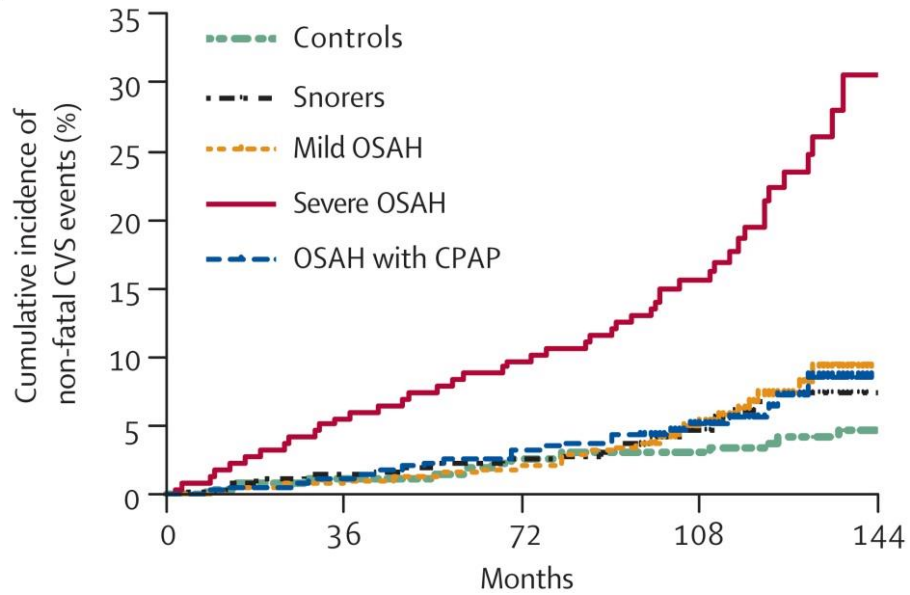

Numbers at risk

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

Lancet 2005; 365: 1046–53

Obstructive Sleep Apnea and Heart Failure

Pathophysiologic and Therapeutic Implications

Table 2 Observational Studies Assessing Efficacy of CPAP on Morbidity and Mortality in HF Patients With OSA

First Author (Ref. #) Year	n	Mean/Maximum Follow-Up (yrs)	Baseline Characteristics: Age (yrs)	BMI (kg/m²)	Male (%)	AHI	LVEF (%)	ICM (%)	Outcome
Wang et al. (78) 2007	Untreated: 37	2.9/7.3	58.5	30.1	87	32.8	25.9	41	Trend for reduced mortality in treated group (p = 0.07)
	Treated: 14		53.2	32.3	100	38.8	23.9	36	
Kasai et al. (94) 2008	Untreated: 65	2.1/4.8	59.8	24.9	83	38.1	35.0	30	Lower death and hospitalization risk in treated group (p = 0.03)
	Treated: 23		59.6	27.5*	95	45.1	36.2	22	

Smith et al. (93) 2007	RCT-double crossover									
	Sham ACPAP	23	1.5	36.0	29.0	10.0	NA	1.0	NA	−2.0
	ACPAP						NA	1.0	NA	−3.0†
Egea et al.‡ (91) 2008	RCT									
	Sham CPAP	25	3.0	35.0	27.2	6.9	−7.3	−0.5	−1.6/1.2	−1.7
	CPAP	20		44.0	28.8	8.6	−32.9	2.2†	0.0/0.4	−3.6

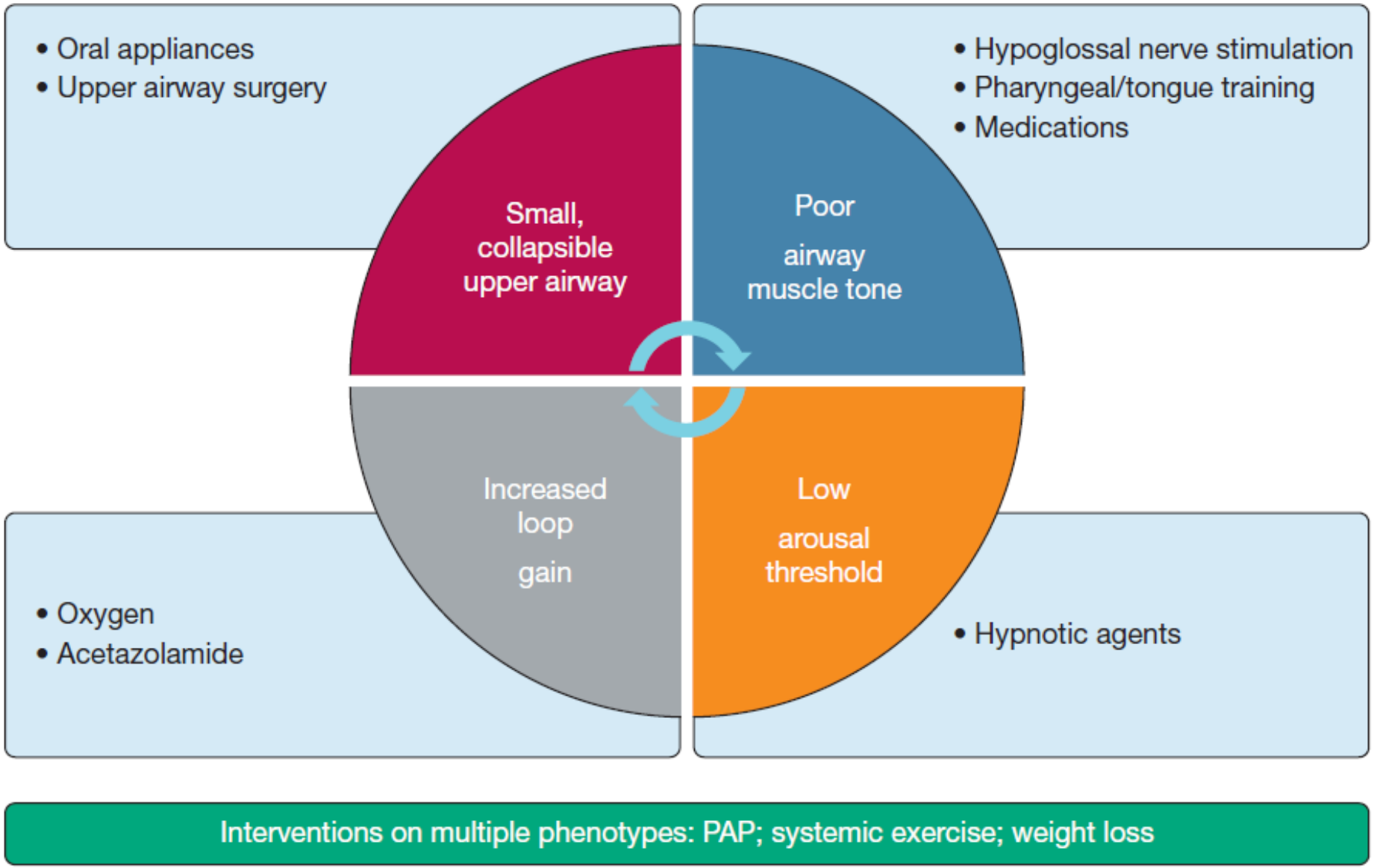

Figure 4 – *A conceptual approach to phenotype-guided treatment for OSA in patients with heart failure. PAP = positive airway pressure.*

Key points

- Patients with heart failure (HF) are characterized by relevant problems during sleep, including short sleep time, low sleep quality, and sleep-disordered breathing
- Approximately 33% of patients with HF have insomnia, potentially related to HF features, adverse effects of medications, or to conditions that often accompany chronic diseases such as mood disorders and psychological stress
- Sleep-disordered breathing is highly prevalent in patients with HF; both central and obstructive sleep apnoeas are frequently observed in these patients, and were shown to have an important added prognostic value
- Continuous positive airway pressure has a beneficial effect on left ventricular ejection fraction and is currently the best treatment option for obstructive sleep apnoeas in patients with HF
- At present, no consensus exists on whether central sleep apnoeas should be treated and what the optimal therapy in HF might be

Obstructive Sleep Apnea during REM Sleep and Cardiovascular Disease

R. Nisha Aurora[1], Ciprian Crainiceanu[2], Daniel J. Gottlieb[3,4], Ji Soo Kim[2], and Naresh M. Punjabi[1,5]

Table 1. Baseline Characteristics in Participants with a Non-REM Apnea–Hypopnea Index of less than 5 Events per Hour by Prevalent Cardiovascular Disease

	All Participants (*n* = 3,265)	Participants without CVD (*n* = 2,813)	Participants with CVD (*n* = 452)	*P* Value*
Age, yr, mean (SD)	62.0 (10.7)	61.0 (10.5)	68.6 (9.5)	<0.001
BMI, kg/m^2, mean (SD)	27.8 (5.0)	27.7 (4.9)	28.4 (5.2)	0.004
Waist girth, cm, mean (SD)	95.5 (13.8)	95.0 (13.8)	98.6 (13.0)	<0.001
Sex, %				
Women	63.1	65.2	49.8	<0.001
Men	36.9	34.8	50.2	
Race, %				
White	79.0	79.5	76.6	<0.001
African American	5.2	4.9	6.8	
Native American	9.6	8.6	15.3	
Other	6.2	7.0	1.3	
Smoking status, %				
Never	47.1	48.3	40.0	<0.001
Former	40.1	38.9	47.8	
Current	12.7	12.8	12.2	
Hypertension, %	44.7	39.6	76.1	<0.001
Diabetes, %	8.9	7.1	19.7	<0.001
CVD, %†	13.8	0.0	100.0	—
REM AHI, events/h				
<5.0, %	53.8	55.5	43.4	<0.001
5.0–14.9, %	27.7	27.5	29.0	
15.0–29.9, %	13.0	11.8	20.3	
≥30.0, %	5.5	5.2	7.3	

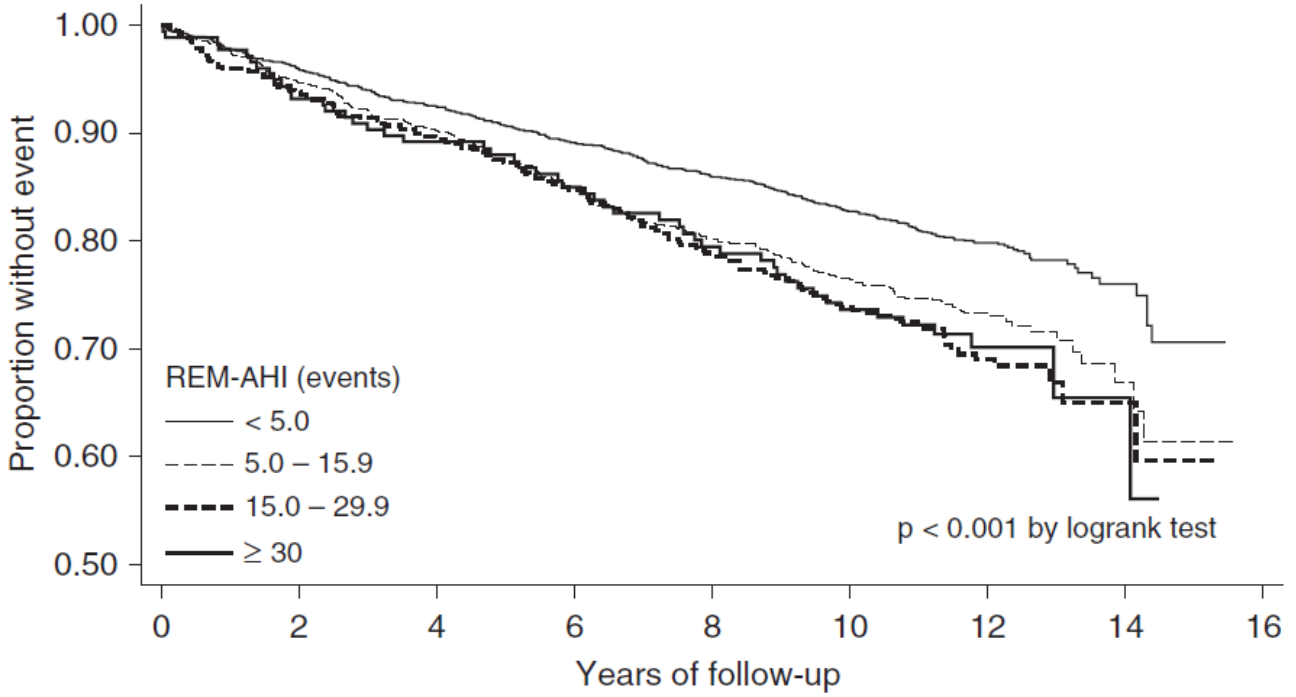

Figure 2. Kaplan-Meier survival curves across categories of REM apnea–hypopnea index (AHI).

Day-Night Pattern o
Sleep Apnea

Gami AS, Howard DE, Ol
2005;352:1206–14.

time of day

patients
den death

SA	General population
	16
	30
	29
	25