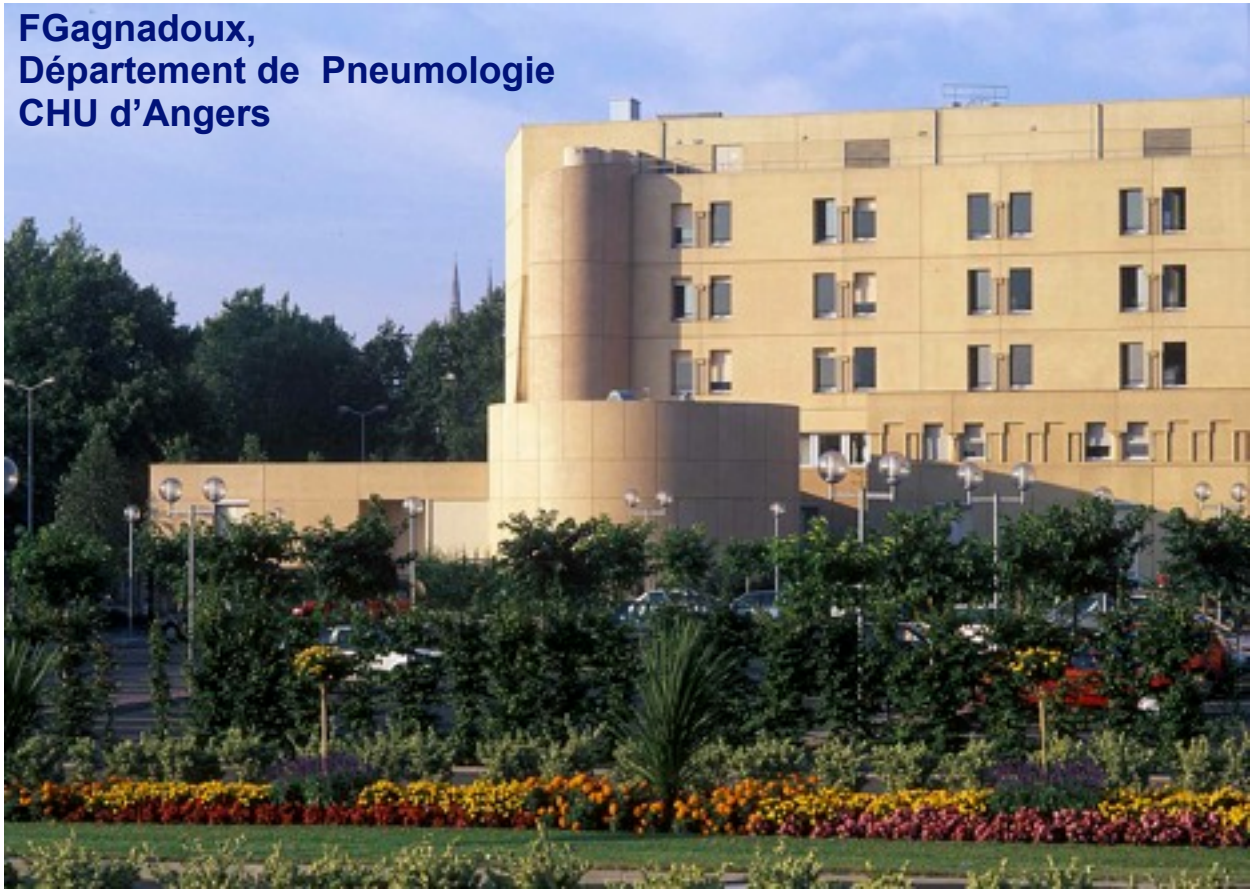
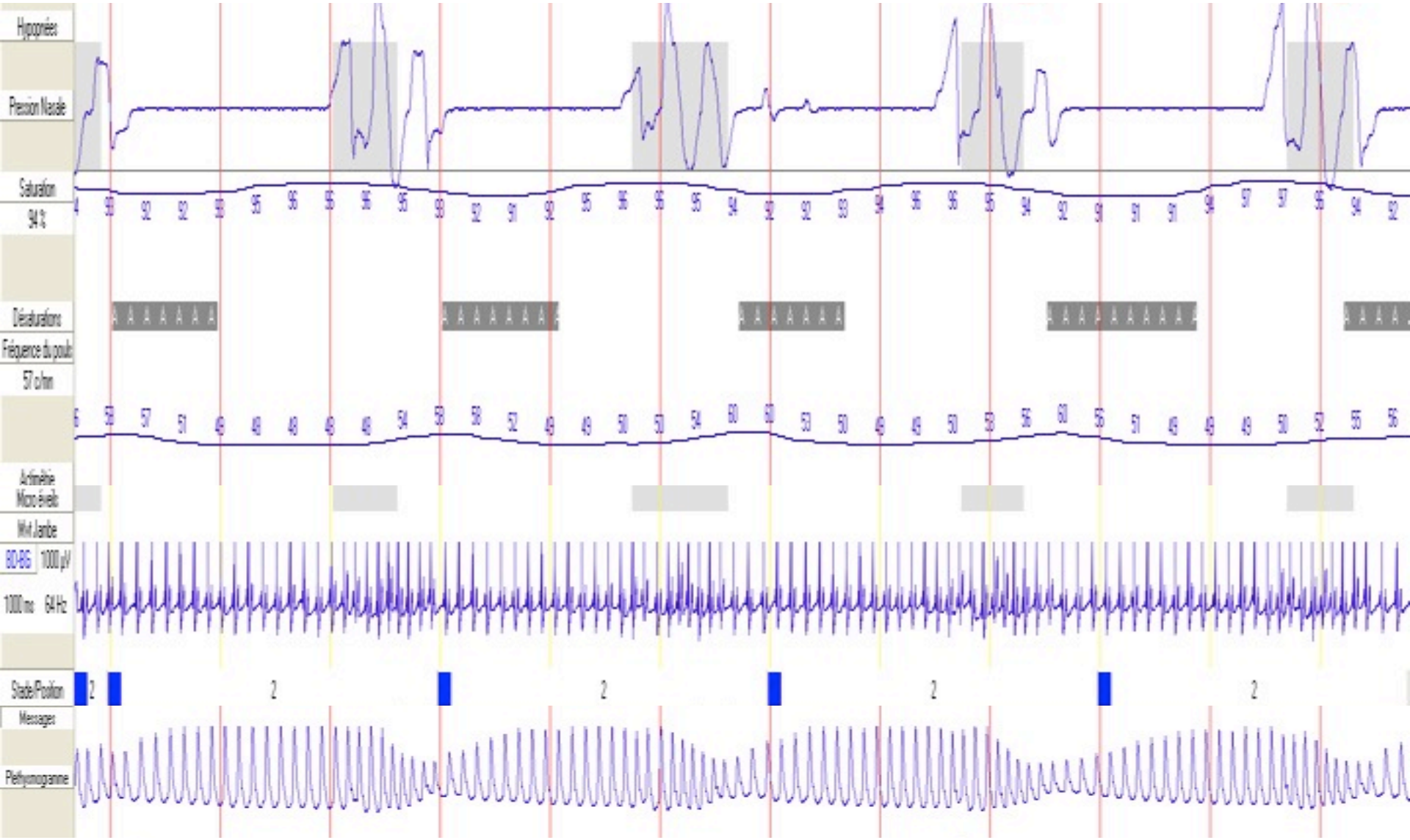
SAOS et risque cardiovasculaire



FGagnadoux,
Département de Pneumologie
CHU d'Angers

Conséquences hémodynamiques immédiates des apnées et hypopnées



Conséquences hémodynamiques immédiates des apnées et hypopnées

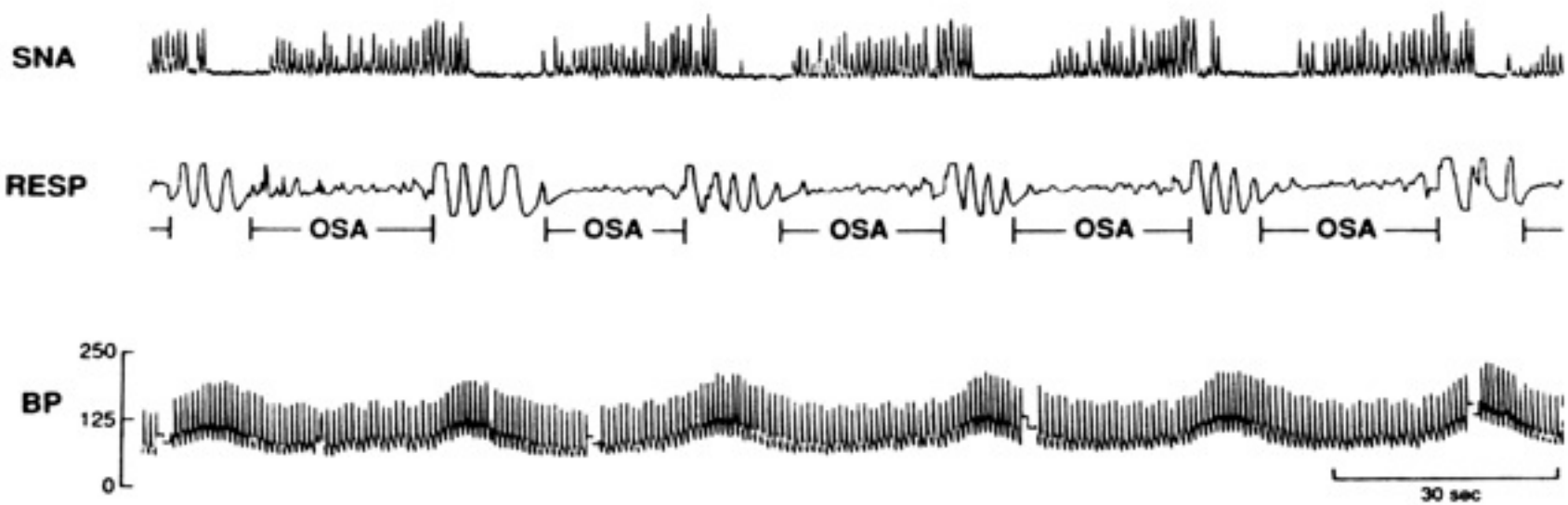
Hypoxie + µéveil

⇓

Activation du SNA

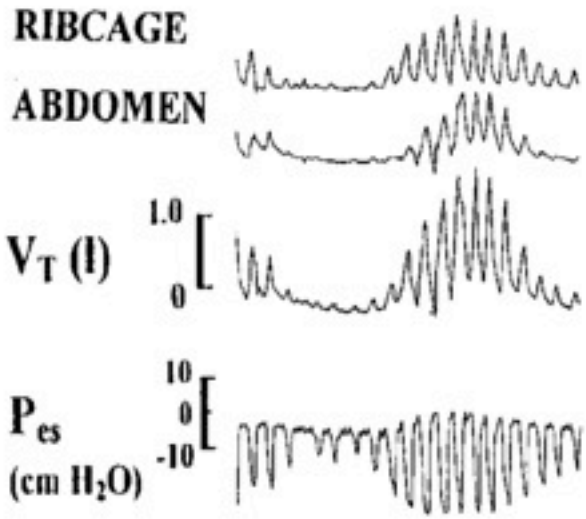
⇓

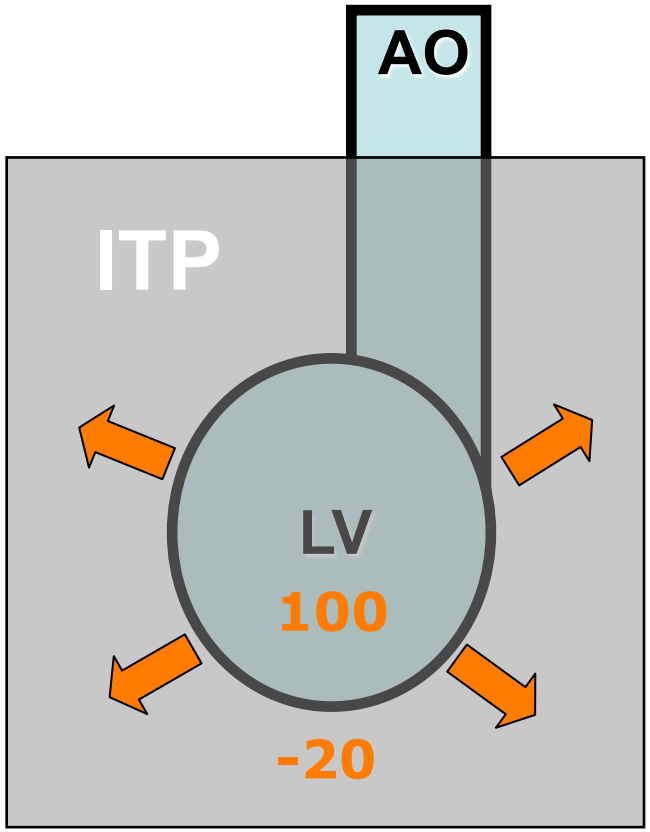
↗ FC + vasoconstriction ⇒ ↗ PA



Somers, JCI 1995

Conséquences hémodynamiques immédiates des apnées et hypopnées





↗ Effort ⇒ ↘ PIT ⇒ ↗ Ptm

⇓

↗ POST CHARGE VG

Ptm = 100-(-20) = 120

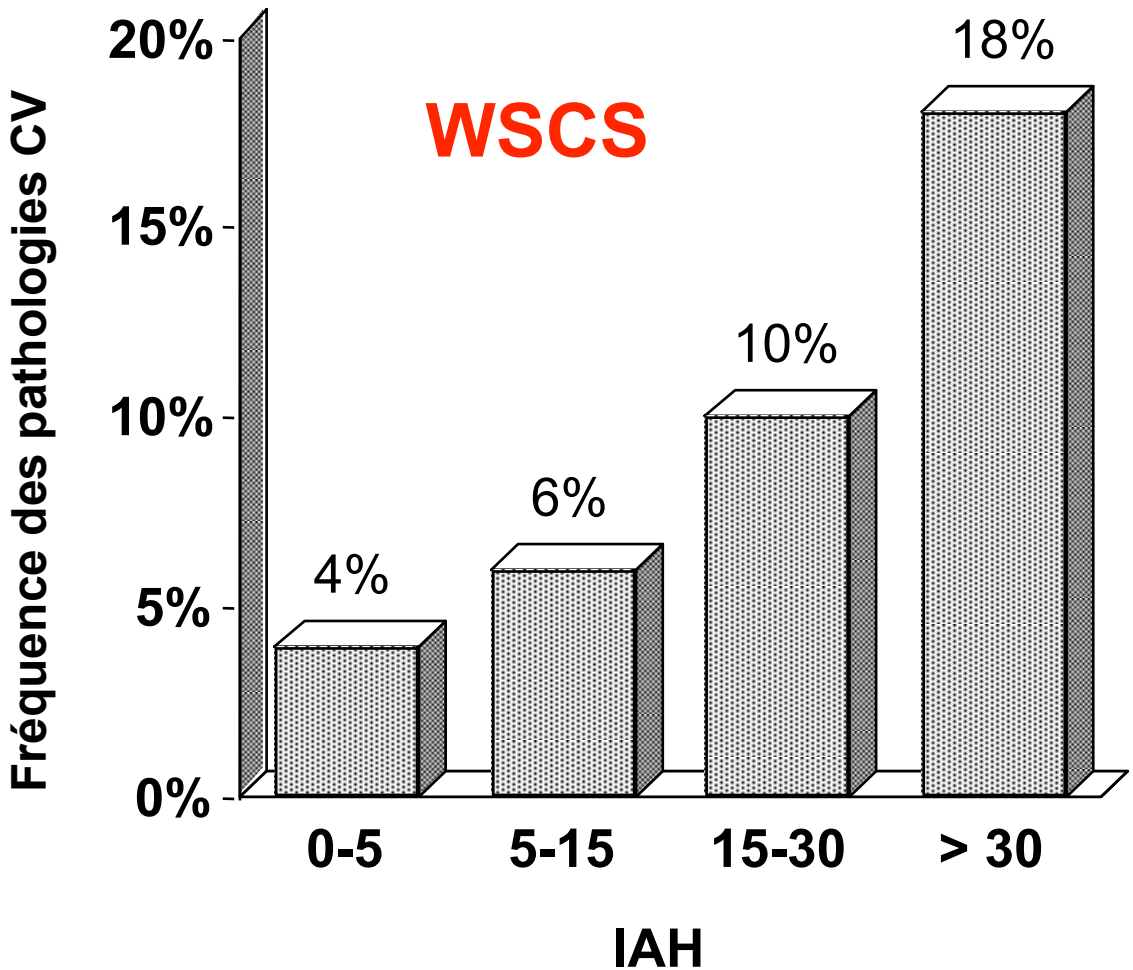
Circulation 2003;107;1671-1678

Un lien statistique évident entre SAOS et maladies CV

- **En populations cliniques** la prévalence du SAOS est élevée dans :
  - Hypertension (30-83%)
  - Insuffisance cardiaque (12-53%)
  - Cardiopathies ischémiques (30-58%)
  - AVC (43-91%)

Un lien statistique évident entre SAOS et maladies CV

- **En population générale** le SAOS est associé aux maladies CV



Young, Sleep 2000

Un lien statistique évident entre SAOS et maladies CV

- **LA QUESTION:** ce lien est-il indépendant, en faveur d'une relation de causalité ou lié à des **facteurs de confusion: age, sexe, IMC….?**

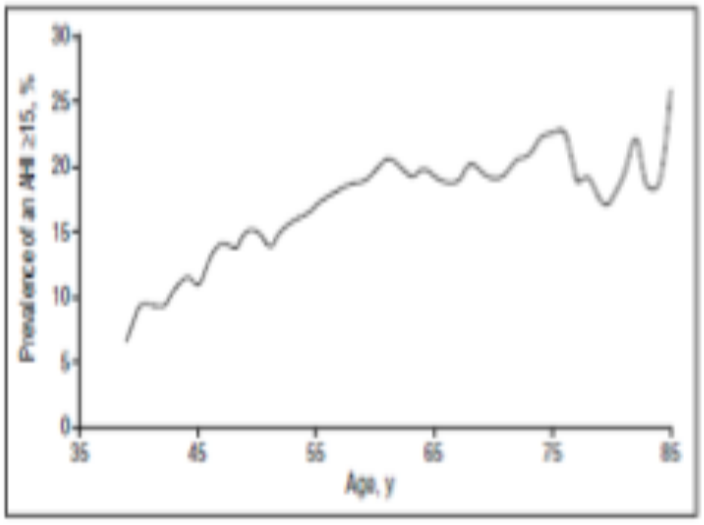


Figure 1. Smoothed plot (5-year moving average) of the prevalence of an apnea-hypopnea index (AHI) of 15 or greater by age.

Table 2. Estimated Percent Change in the AHI for Selected Decrements and Increments of Percent Body Weight*

Percent Change in Weight (vs No Change)	Estimated Percent Change in AHI (95% Confidence Interval)†
−20	−48 (−58 to −35)
−10	−26 (−34 to −18)
−5	−14 (−18 to −9)
+5	+15 (+10 to +21)
+10	+32 (+20 to +45)
+20	+70 (+42 to +104)

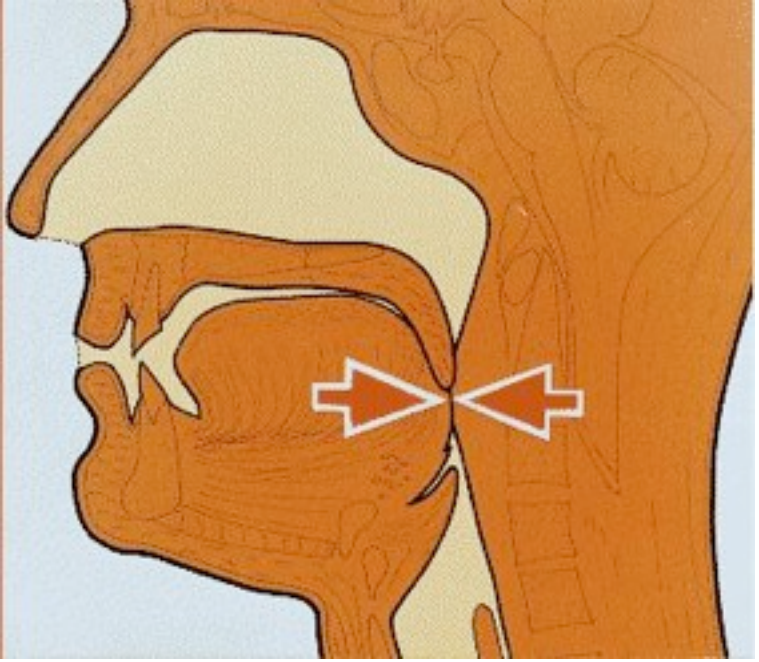
*AHI indicates apnea-hypopnea index. Adjusted for sex, change in cigarette packs/wk, baseline body mass index (kg/m²), and baseline age. All $P<.001$.
†In addition to change expected if weight remained stable.

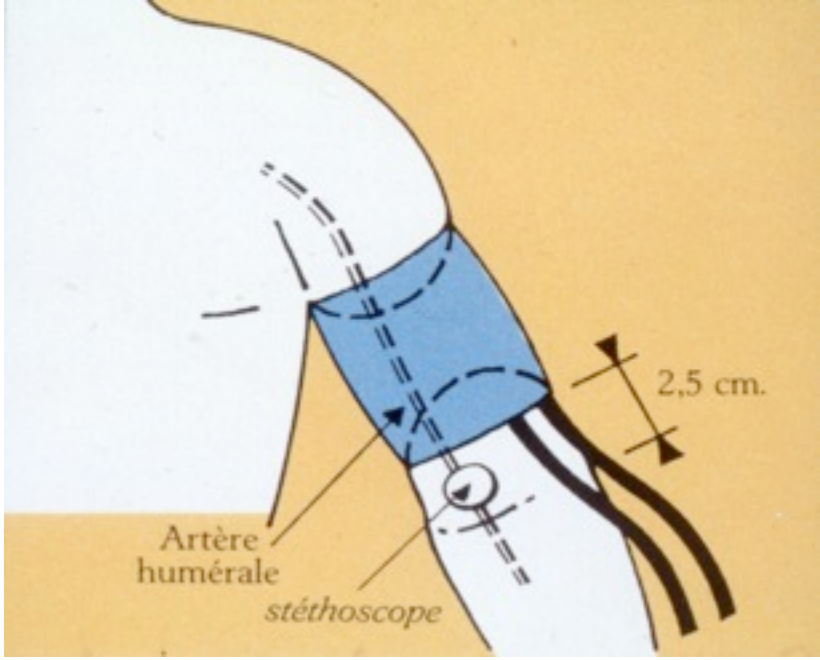
Young, Arch Intern Med 2002

Peppard, JAMA 2000

Un lien statistique évident entre SAOS et maladies CV

- **LES ELEMENTS DE REPONSE:**
  - Etudes multivariées des facteurs de risque:
    - Transversales / longitudinales
    - En population générale / populations cliniques
  - Relation temporelle entre les troubles respiratoires nocturnes et la morbi-mortalité cardiovasculaire
  - Données interventionnelles
  - Données expérimentales et mécanistiques

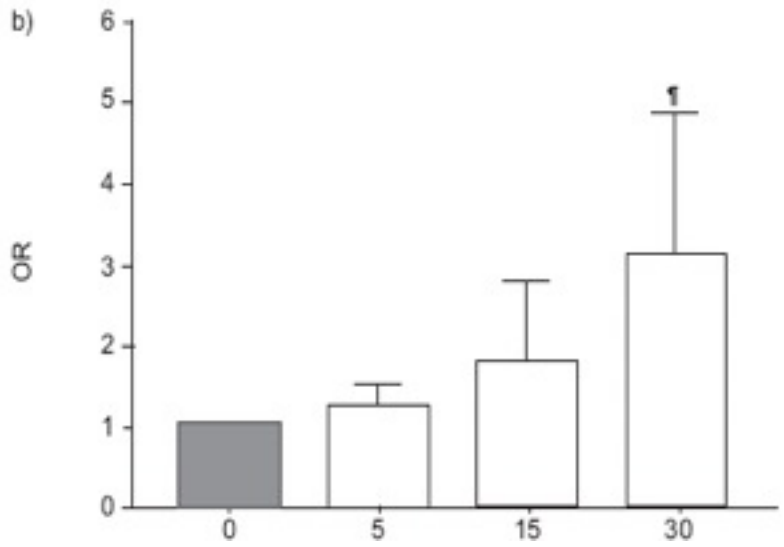




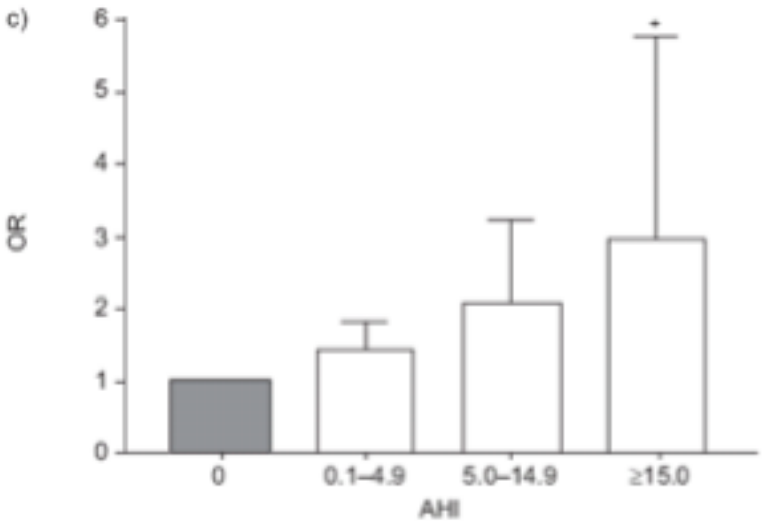
SAOS et HTA

SAOS – HTA : données épidémiologique

WISCONSIN SLEEP COHORTE STUDY: > 1000 SUJETS 30-60 ANS



A l'entrée

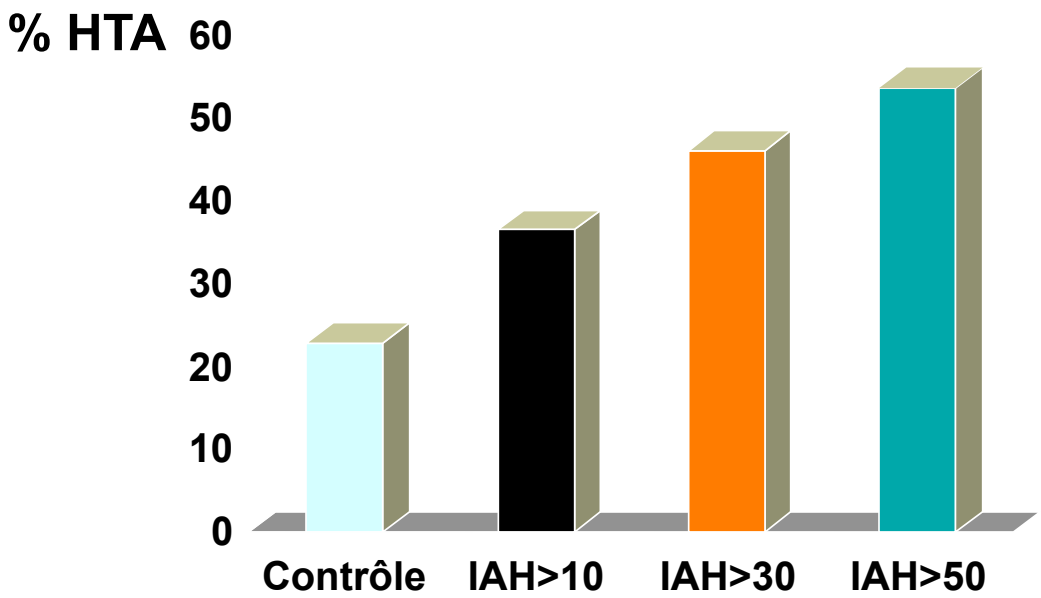


A 4 ans

Le risque de développer une HTA est x 3 à 4 ans si IAH > 15 indépendamment de la PA initiale et des autres facteurs de risque

Buyse, Eur Respir Rev 2007

SAOS – HTA : cohortes cliniques



IAH < 10 : HTA 1/5

IAH > 50 : HTA 1/2

2677 patients

suspects de SAOS

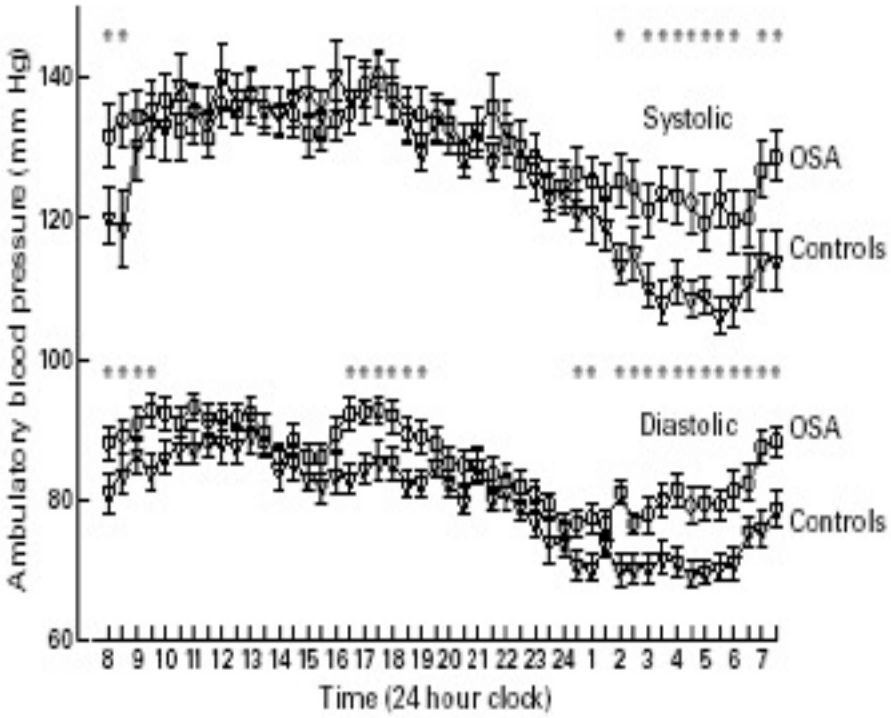
Toute augmentation d' un événement (apnée ou hypopnée) par heure de sommeil est associée, de façon indépendante de l'âge, du sexe et de l'IMC, à une élévation de 1% du RR d'HTA.

Toute diminution de 10% de la saturation nocturne en O2 augmente le risque d'HTA de 10%.

Lavie, BMJ 2000

Spécificités de l'HTA du SAOS

- Infraclinique et nocturne
  - 59 patients SAOS sans HTA connue
  - 42 % d'HTA clinique
  - 76 % d'HTA diagnostiquée par mesure ambulatoire
- Profil « non dipper »
- Profil diastolique



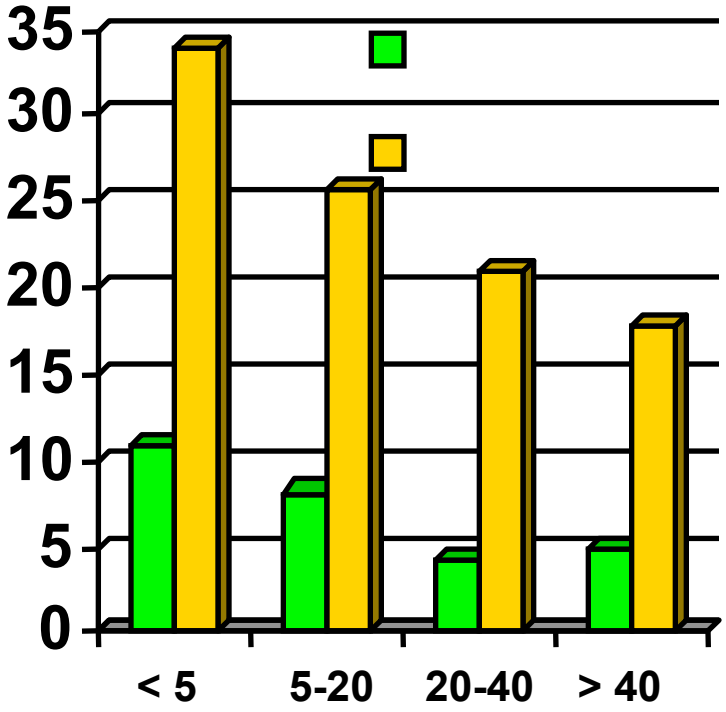
⇒ **Intérêt potentiel de la MAPA dans le SAOS**

Baguet, J Hypertens 2005

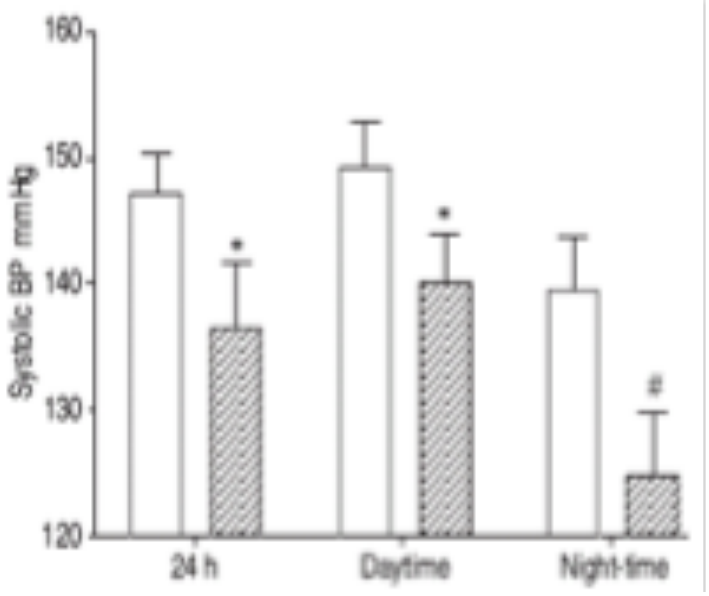
Davies, Thorax 2000

SAOS et HTA réfractaire

% HTA contrôlée

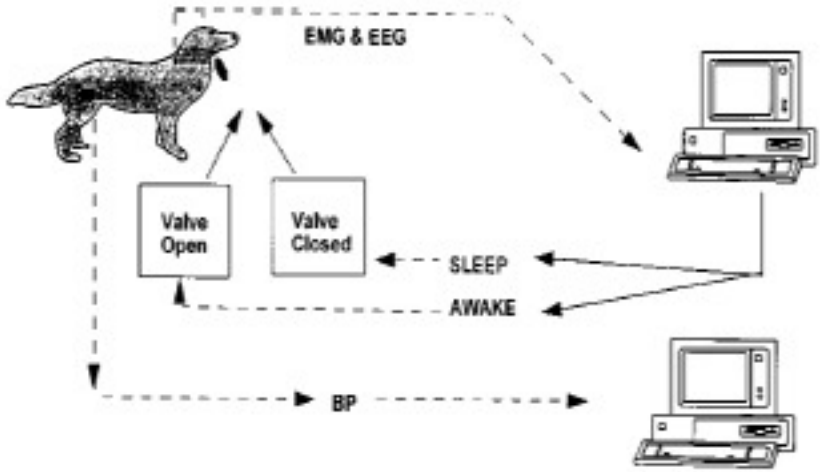


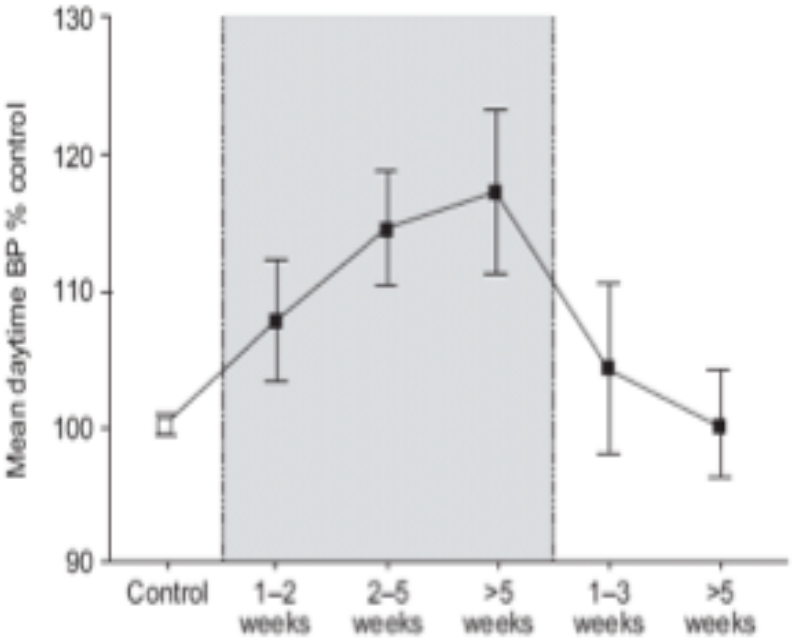
Le SAOS est un facteur d'HTA réfractaire (Logan, J Hypertens 2001)



Effet de la PPC sur l'HTA réfractaire (Logan, ERJ 2003)

SAOS – HTA: données expérimentales



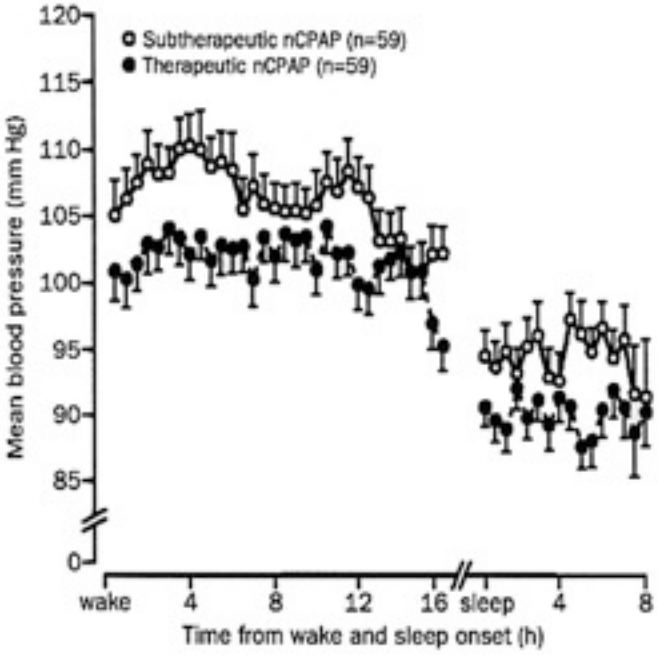


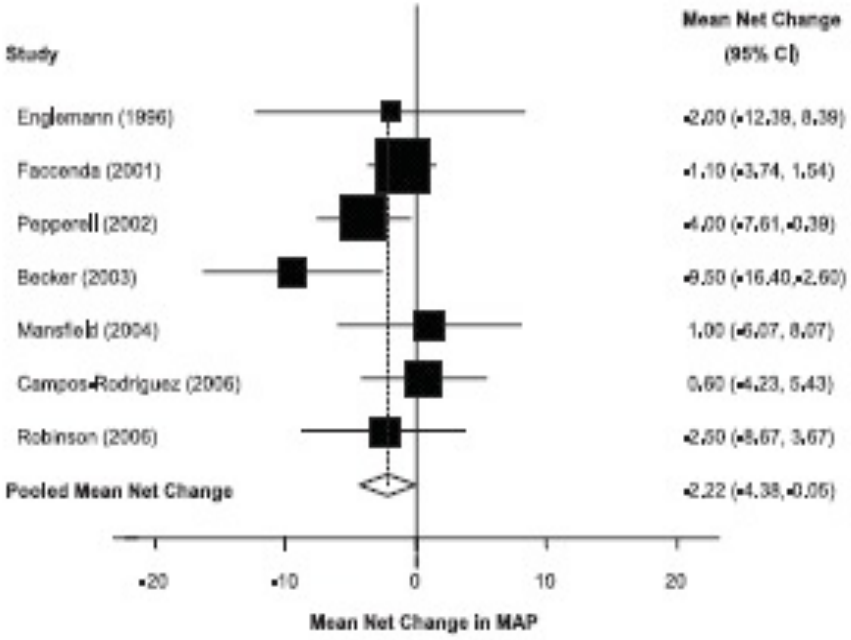
Après plusieurs semaines, il existe une augmentation de la PA diurne (15.7 ± 4.3 mmHg)

Des micro-éveils sans apnées n'entraînent pas d'augmentation de la PA diurne

Brooks JCI 1997

SAOS-HTA: données interventionnelles



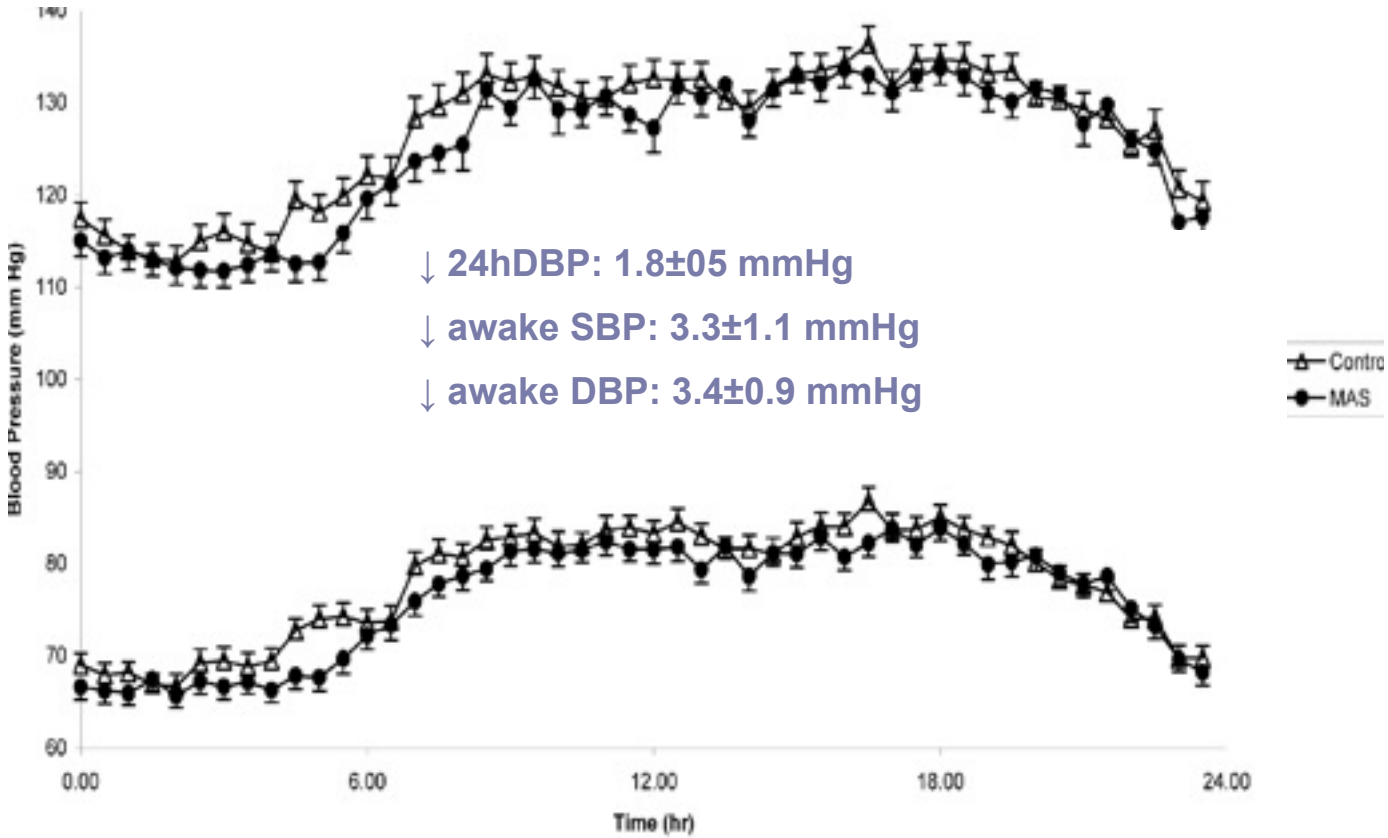


La PPC fait baisser la PA d'autant plus que le patient est: SEVERE, HYPERTENDU ET OBSERVANT+++

Peperell, Lancet 2002

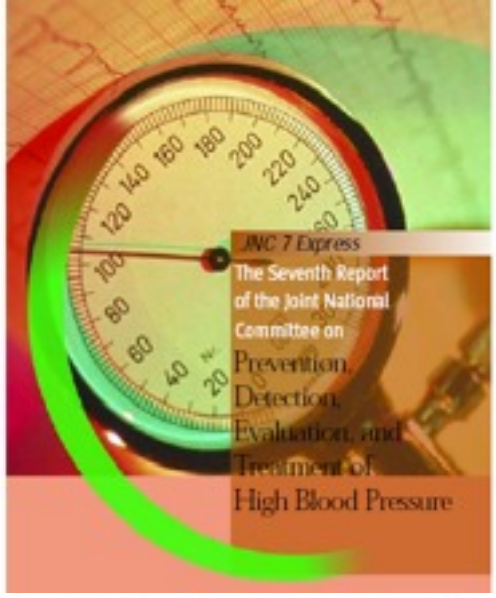
Bazzano, J Hypertens 2007

SAOS-HTA: données interventionnelles



Gotsopoulos, Sleep 2004.

La SAOS est entré dans les recommandations sur l'HTA



ANAES 2005

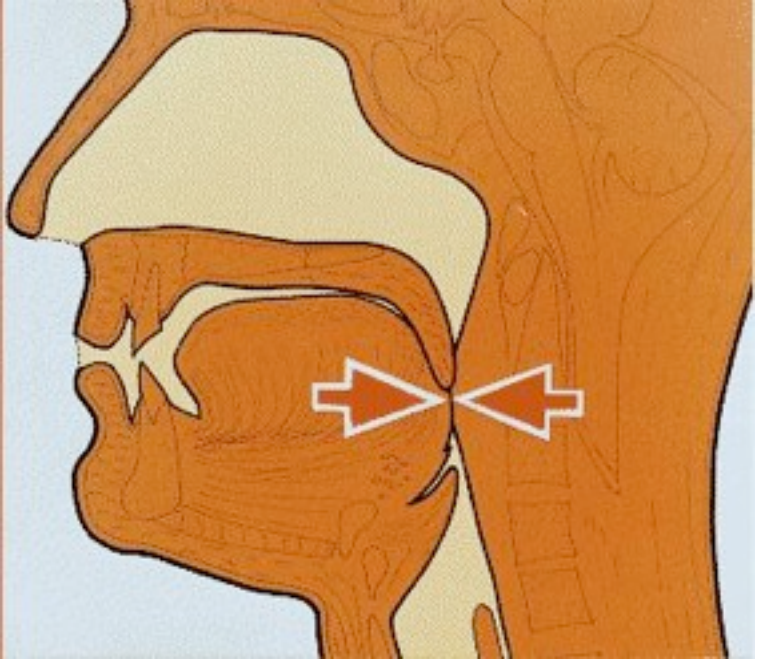
ESH-ESC 2007

NIH: National High Blood Pressure Education Program 2003

Table 4. Identifiable causes of hypertension

Sleep apnea
Drug-induced or related causes (see table 9)
Chronic kidney disease
Primary aldosteronism
Renovascular disease
Chronic steroid therapy and Cushing's syndrome
Pheochromocytoma
Coarctation of the aorta
Thyroid or parathyroid disease

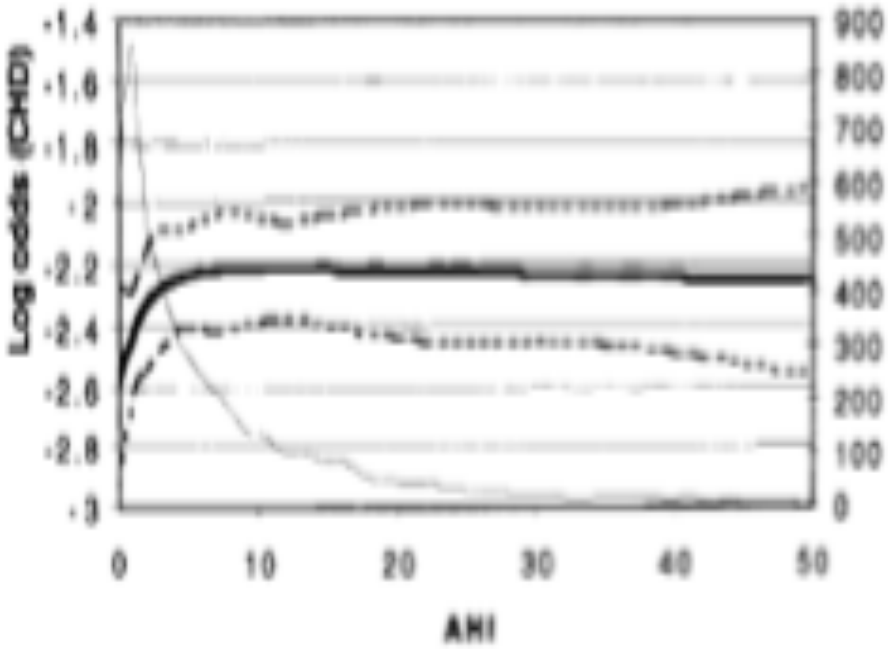
NIH Publication No. 03-5233
December 2003



SAOS ET INSUFFISANCE CORONARIENNE

SAOS = facteur de risque d'insuffisance coronarienne

Sleep Heart Health Study: 6132 SUJETS > 40 ANS

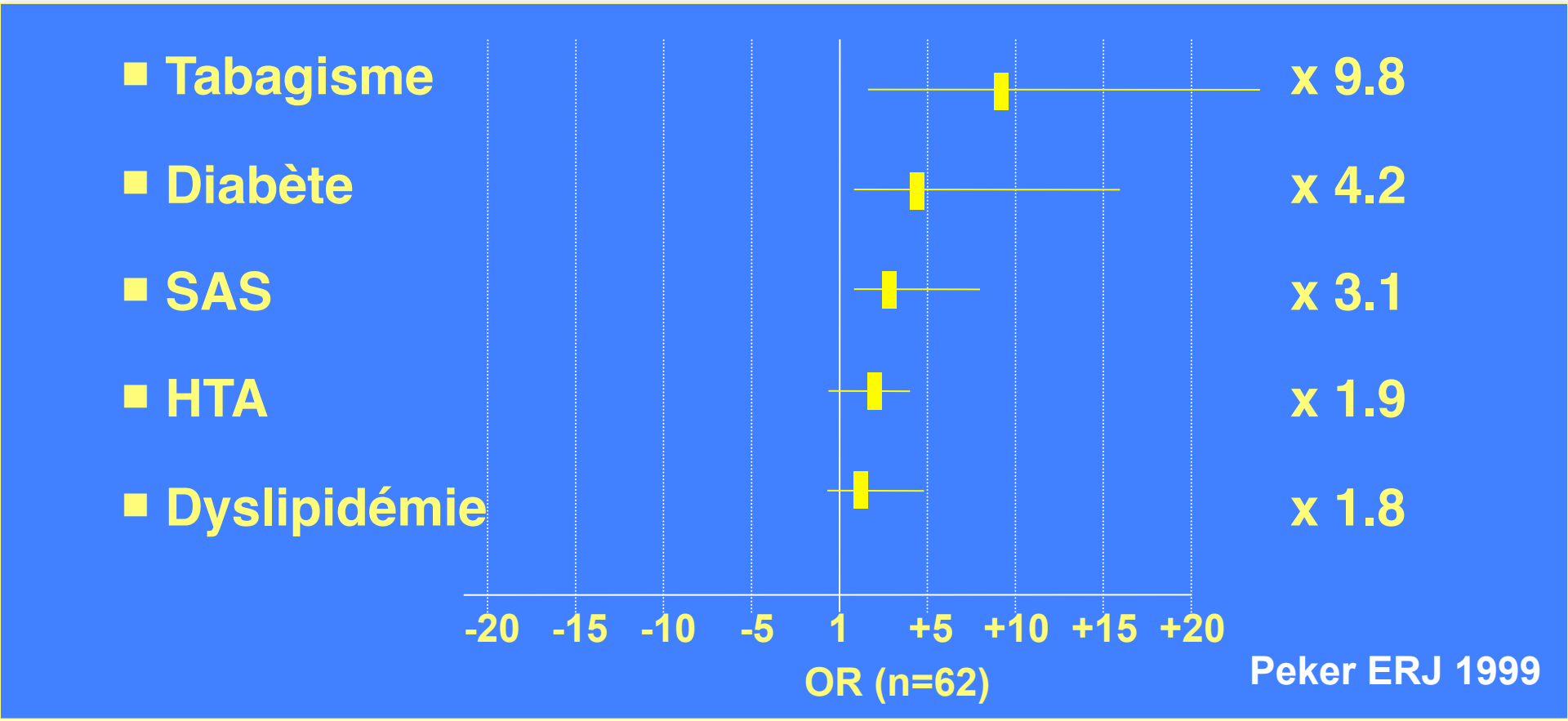


The relative odds (95% CI) of coronary heart disease (upper versus lower AHI quartile) was 1.27 (0.99–1.62)

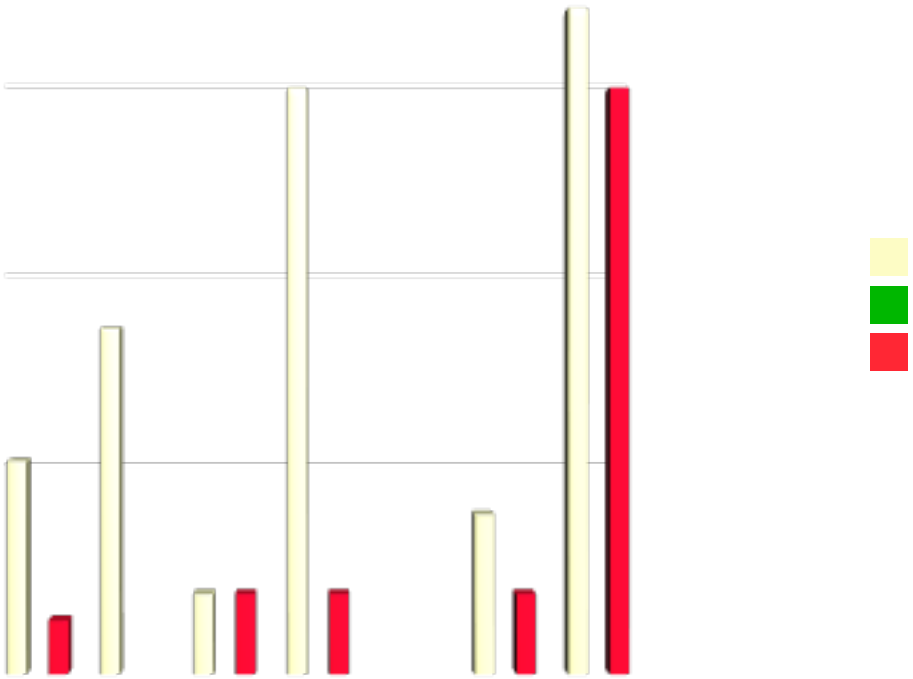
Shahar, AJRCCM 2001

SAOS = facteur de risque d'insuffisance coronarienne

62 patients avec insuffisances coronariennes (19 (30%) SAOS) et 62 témoins (8 (13%) SAOS) appariés / sexe, age, IMC



SAOS et ischémie myocardique nocturne



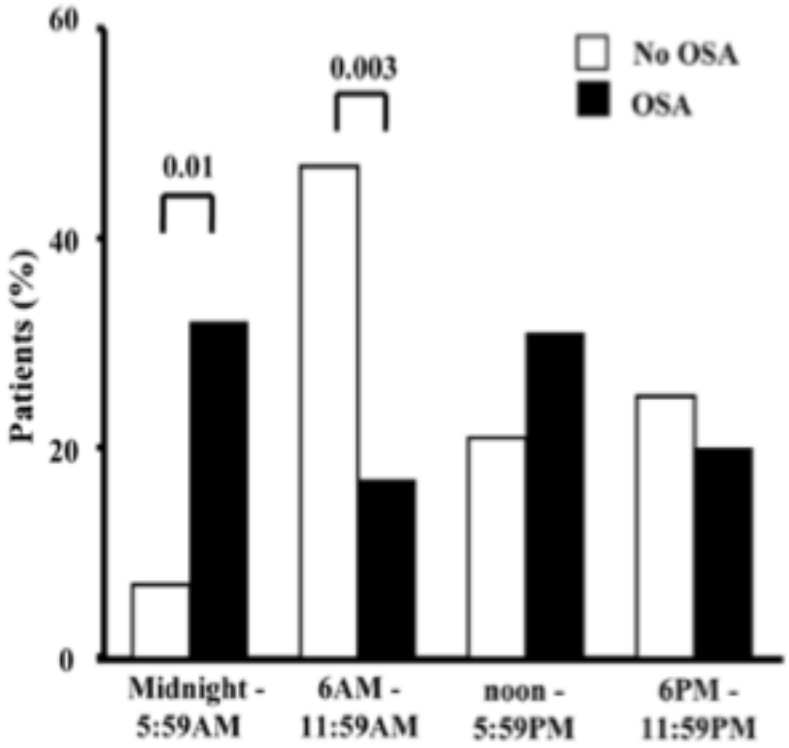
51 patients avec SOAS + insuff coronarienne et 17 contrôles

Ischémie nocturne chez 10 patients 0 contrôles

Peled, JACC 1999

SAOS et ischémie myocardique nocturne

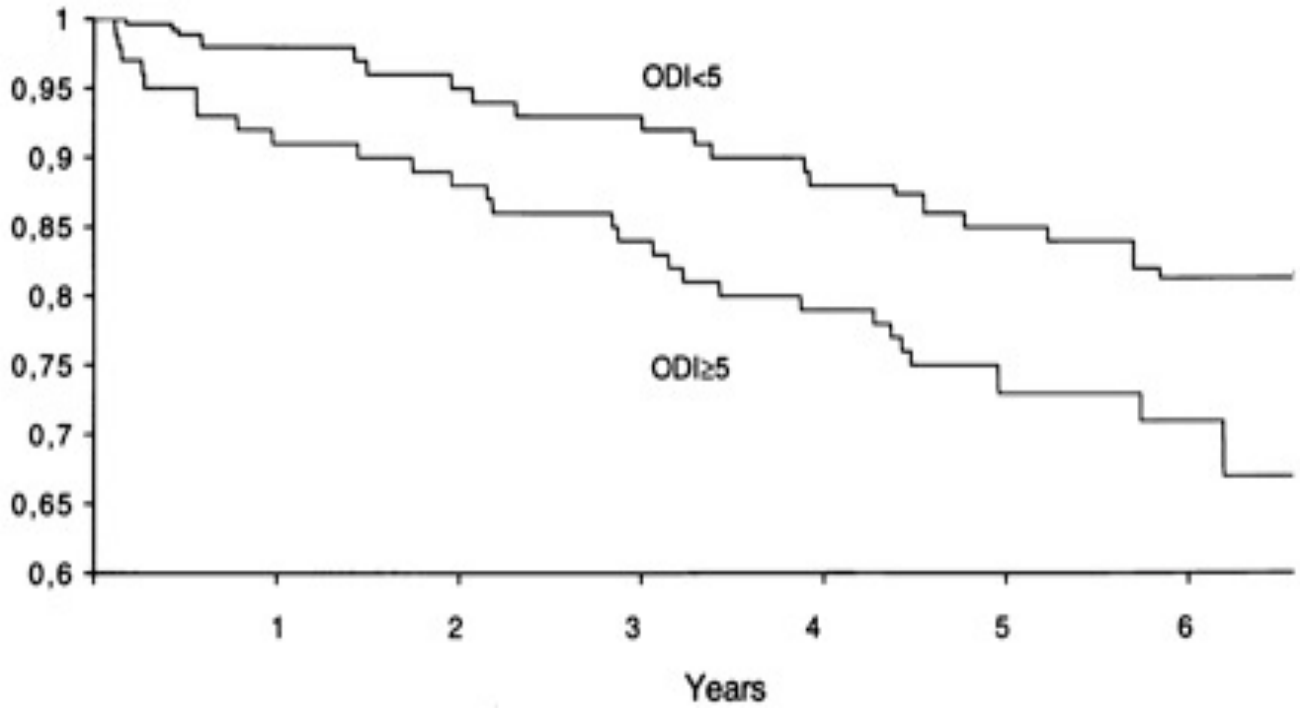
- 92 patients avec IDM dont l'heure de survenue est connue
- PSG: 70% de SAS (IAH≥5)
- **Le risque d'avoir un SAS est 6 fois plus élevé chez les patients dont l'IDM est survenu entre 00H00 et 06h00**



JACC 2008

SAOS = facteur pronostic défavorable dans l'insuffisance coronarienne

408 patients avec insuffisances coronariennes suivis 5 ans; survie sans évènement CV chez SAOS vs non SAOS



Mooe AJRCCM 2001

Impact de la PPC

371 patients avec insuffisances coronariennes traitée par angioplastie + SAOS (IAH ≥15); évolution des traités (n=175) vs non traités (n=196)

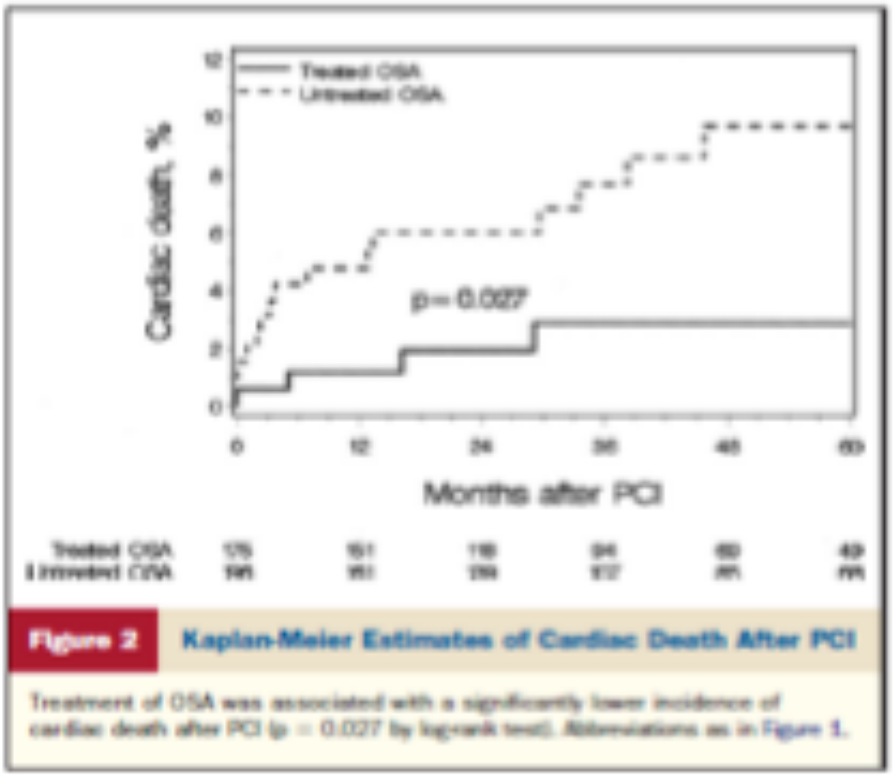
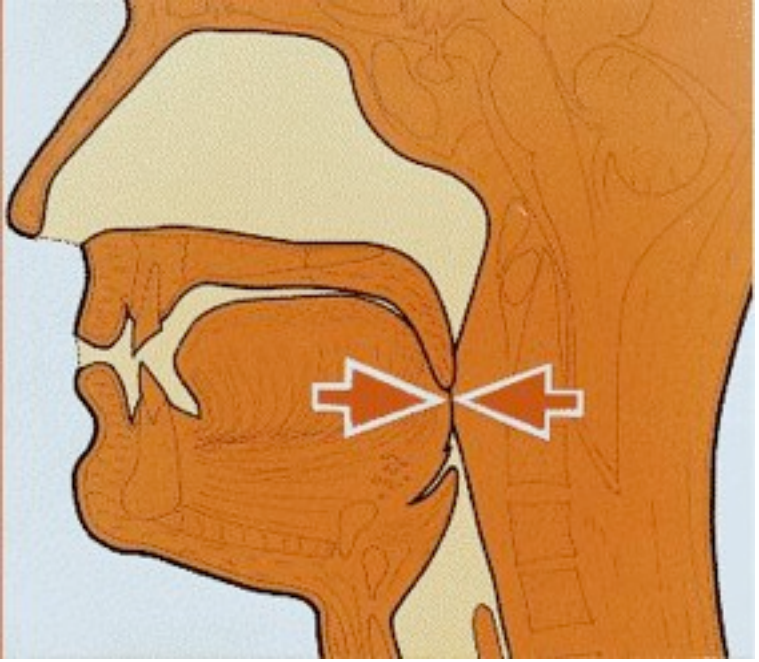


Figure 2 Kaplan-Meier Estimates of Cardiac Death After PCI

Treatment of OSA was associated with a significantly lower incidence of cardiac death after PCI (p = 0.027 by log-rank test). Abbreviations as in Figure 1.

Cassar, JACC 2007



SAOS ET TROUBLES DU RYTHME CARDIAQUE

SAOS et troubles du rythme nocturnes

2 à 4 x plus fréquents chez les SAOS après ajustement pour age, sex, IMC et prévalence de l'insuffisance coronarienne

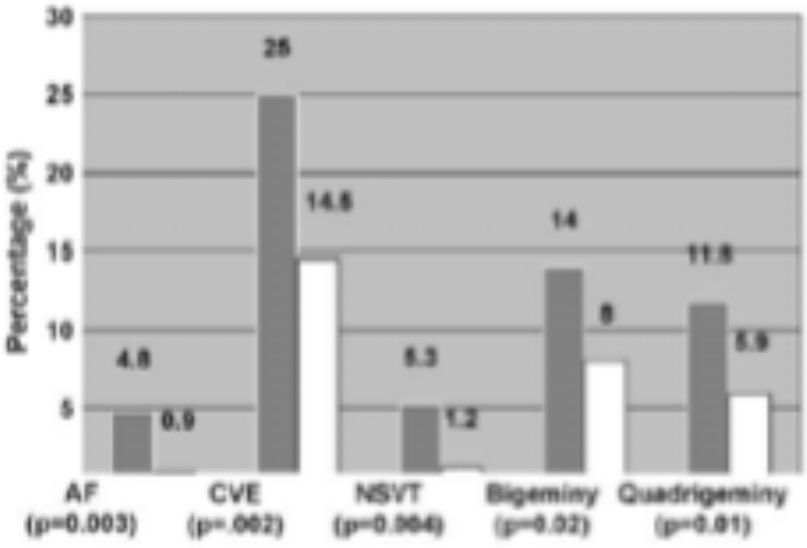
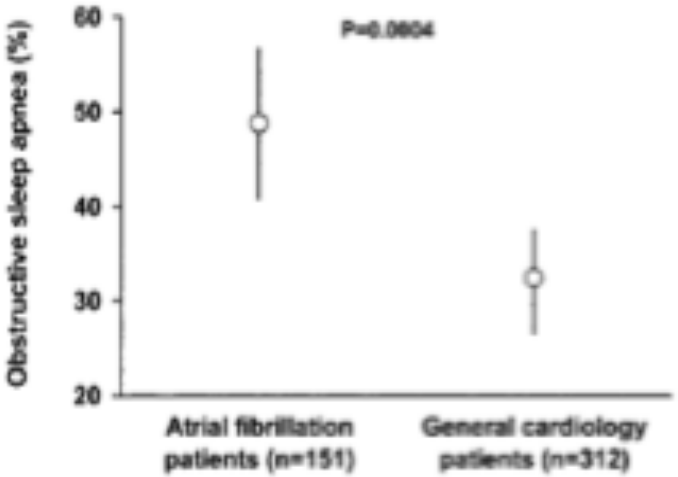


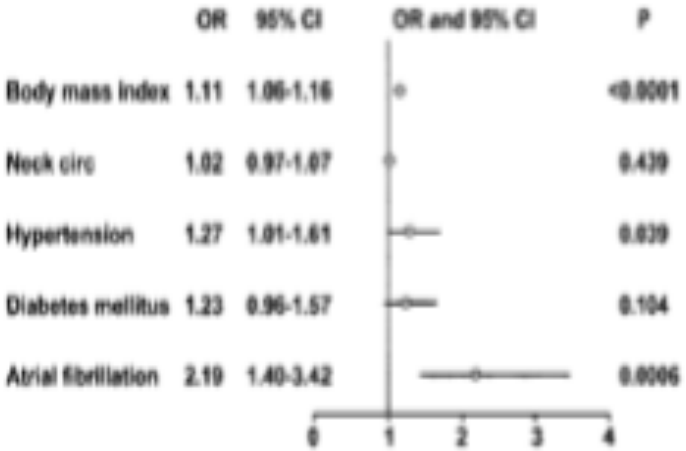
Figure 1. Arrhythmia prevalence (%) according to sleep-disordered breathing (SDB) status. *Shaded bars*, SDB; *open bars*, non-SDB. AF, atrial fibrillation; CVE, complex ventricular ectopy; NSVT, nonsustained ventricular tachycardia. n = 228 with SDB and n = 338 without SDB.

Mehra, AJRCCM 2006

SAOS et AC/FA

- 151 patients avec FA et 312 patients de cardiologie sans FA. Recherche de SAS par le questionnaire de Berlin



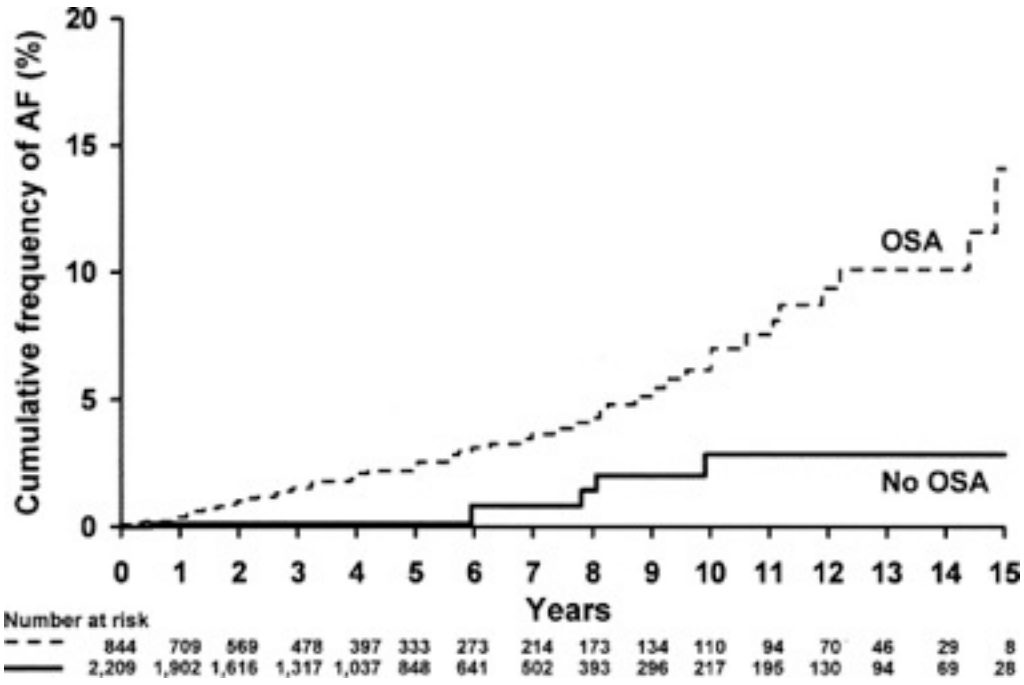


The adjusted odds ratio for the association between AF and OSA was 2.19 (95% CI 1.40 to 3.42, *P*0.0006).

Gami, Circulation 2004

SAOS et incidence de l'AC/FA

Etude rétrospective de 3542 patients sans ATCD d'AC/FA suivis 4,7 ans: incidence de l'ACFA chez SAOS versus non SAOS.



Gami AS, JACC 2007

Impact de la PPC sur la récidive d'AC/FA après cardioversion

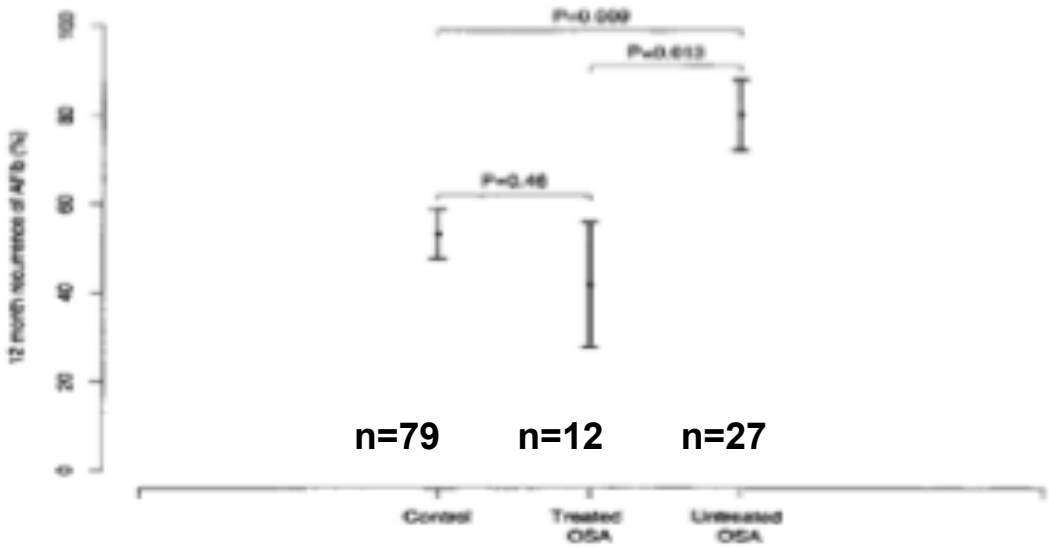
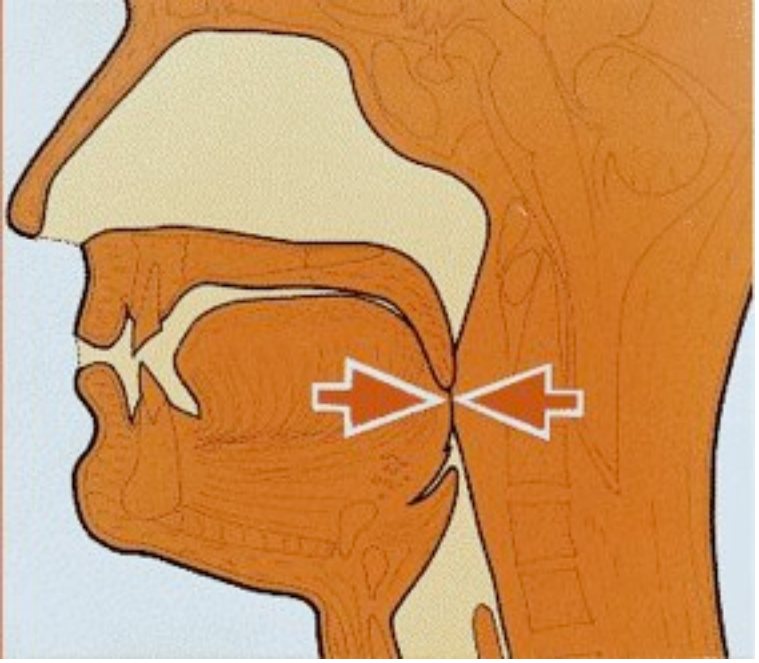


Figure 1. Recurrence of AF at 12 months comparing patients who did not have sleep studies (controls) with treated OSA patients and with untreated (including noncompliant) OSA patients (mean ± SD).

Patients with untreated OSA have a higher recurrence of AF after cardioversion than patients without OSA. Appropriate treatment with CPAP in OSA patients is associated with lower recurrence of AF.

Kanagala, Circulation 2003



SAOS ET AVC

Le SAOS est fréquent au décours de l'AVC

A LA PHASES AIGUE

	IAH ≥ 10	IAH ≥ 30
Dyken, 1996	70%	42%
Bassetti, 1996	63%	28%
Bassetti, 1999	63%	13%
Bassetti, 2000	55%	18%
Parra, 2000	72%	28%

Le SAOS est fréquent au décours de l'AVC

A DISTANCE DE L'AVC

	3 jours	45 jours
Age, ans	71,8 ± 9,3	71,8 ± 9,3
IMC, kg/m2	27,0 ± 4,3	26,8 ± 3,9
Epworth	4,8 ± 3,2	4,5 ± 2,8
IAH	22,4 ± 17,3	16,9 ± 13,8*
IAO	4,7 ± 8,6	4,6 ± 7,3
IAC	6,2 ± 10,2	3,3 ± 7,6*
AHI > 10	60 (69,6%)	53 (61,6%)
Cheyne-Stoke, n	17	6

SAOS = facteur de risque d' AVC ?

WSCS: 1475 SUJETS 30-60 ANS, 1189 SUIVIS 4 ANS

- Etude transversale :RR d'AVC pour un IAH > 20/h versus IAH < 5 = 4,33 (95%CI, 1.32-14.24; p=0.02)
- Etude longitudinal :

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

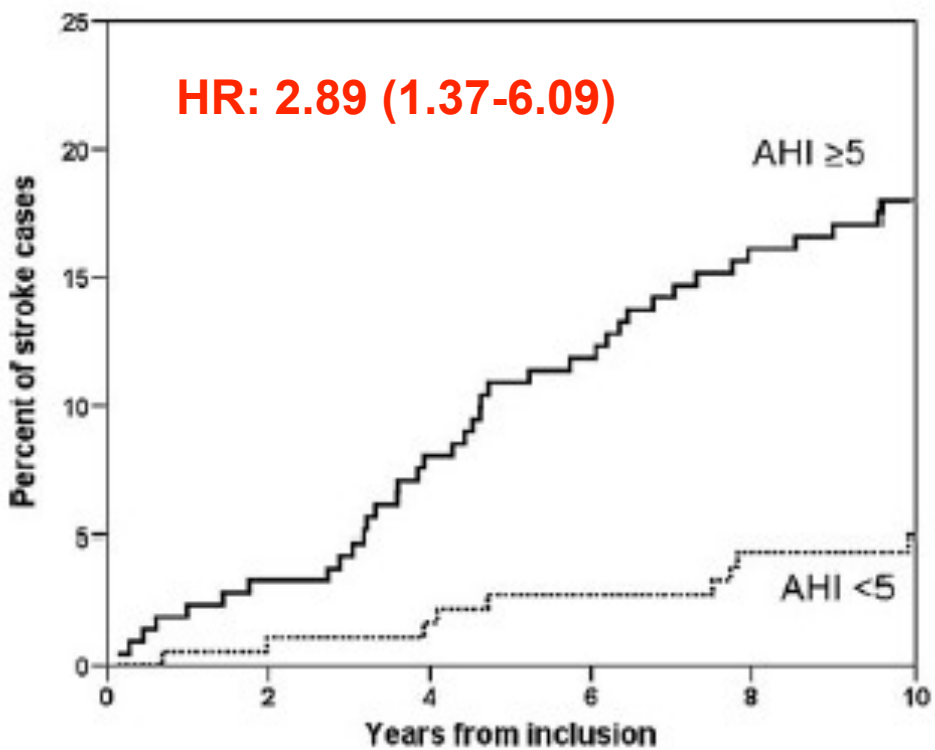
	Model 1B		Model 2B		Model 3B	
AHI (*events/h*)	OR (*95% CI*), unadjusted	p Value	OR (*95% CI*), adjusted for age, sex	p Value	OR (*95% CI*), adjusted for age, sex, and BMI	p Value
< 5*	1.0		1.0		1.0	
≥ 5 to < 20	0.40 (0.05–3.18)	0.39	0.35 (0.05–2.69)	0.31	0.29 (0.04–2.36)	0.25
≥ 20	4.31 (1.31–14.15)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

Arzt, AJRCCM 2005

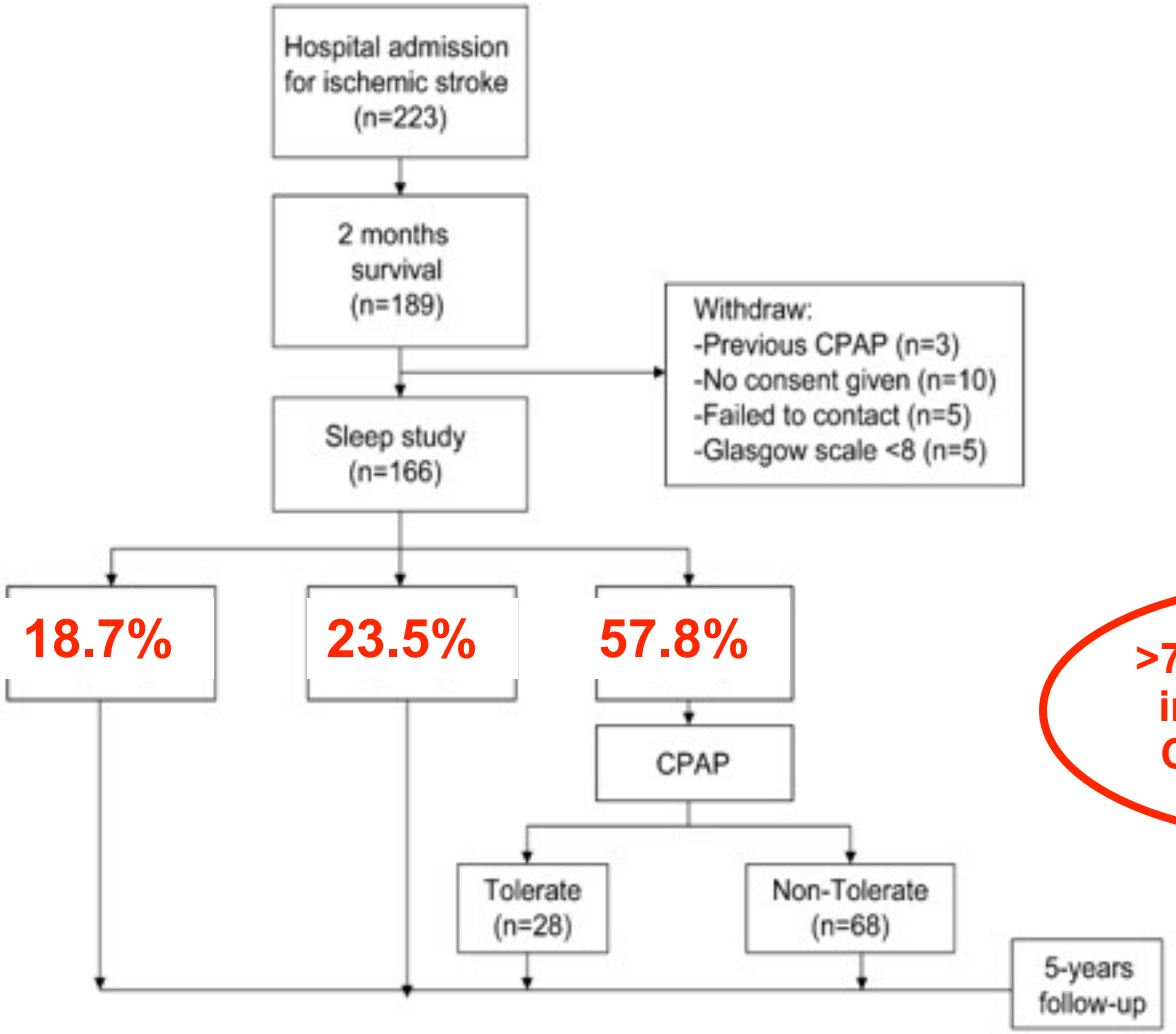
SAOS = facteur de risque d' AVC ?

- 392 explorés par coronarographie pour angor
- PSG: 54% de SAS (IAH≥5)
- **Risque d'AVC X 3 à 10 ans indépendamment de age, sexe, IMC, tabac, diabète, HTA, ATCD d' AVC, intervention coronarienne**



Valham, Circulation 2008

Impact de la PPC après l'AVC ?



>70% de patients intolérants à la CPAP à 5 ans !

Martinez Garcia AJRCCM 2009

Impact de la PPC après l'AVC ?

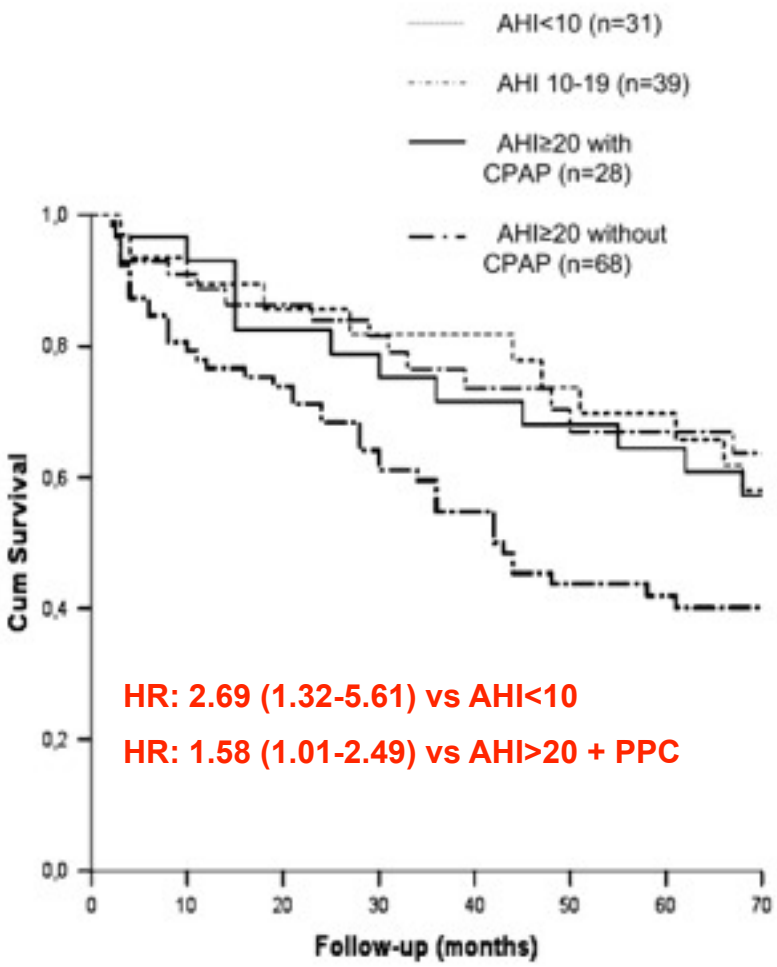
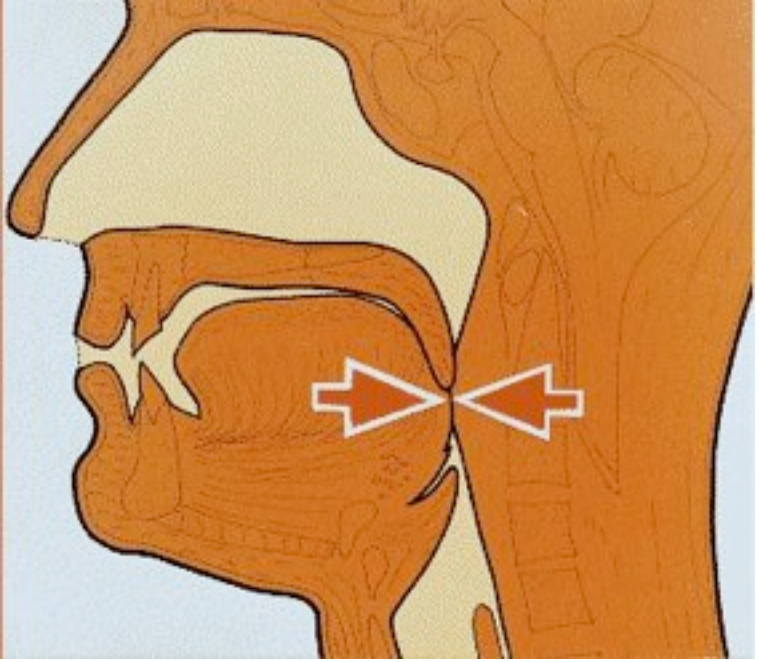


TABLE 2. COMPARISON OF THE CAUSES OF CARDIOVASCULAR AND NON-CARDIOVASCULAR DEATHS BETWEEN THE STUDIED GROUPS

	AHI (0–9)	AHI (10–19)	AHI ≥20 Without CPAP	AHI ≥20 With CPAP
n	31	39	68	28
Deaths, n (%)	11 (35.5)	15 (38.5)	43 (68.3)*	12 (49.6)
Cardiovascular deaths, n (%)	6 (54.5)	8 (53.3)	29 (67.4)*	6 (50)
Stroke deaths, n	5	5	21†	5
Ischemic stroke	4	4	17†	3
Hemorrhagic stroke	1	1	4	2
Cardiac deaths, n	1	2	8	1
Noncardiovascular deaths, n (%)	5 (45.5)	7 (46.7)	14 (32.6)*	6 (50)
Tumors, n	1	1	2	0
Infections, n	0	2	4	2
Lung disease, n	2	2	5	1
Other, n	2	2	3	3

Diminution des décès de causes CV (IDM, AVC) sous PPC

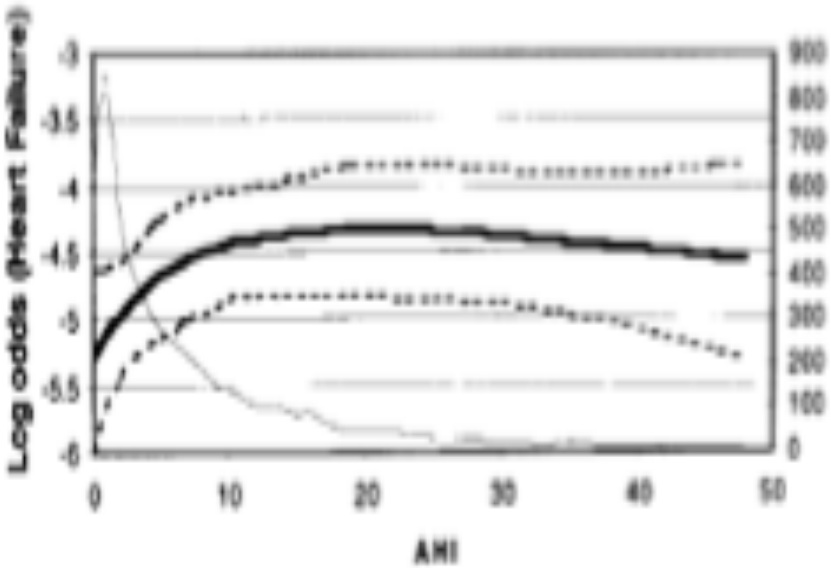
Martinez Garcia AJRCCM 2009



SAOS ET INSUFFISANCE CARDIAQUE

SAOS = facteur de risque d'insuffisance cardiaque ?

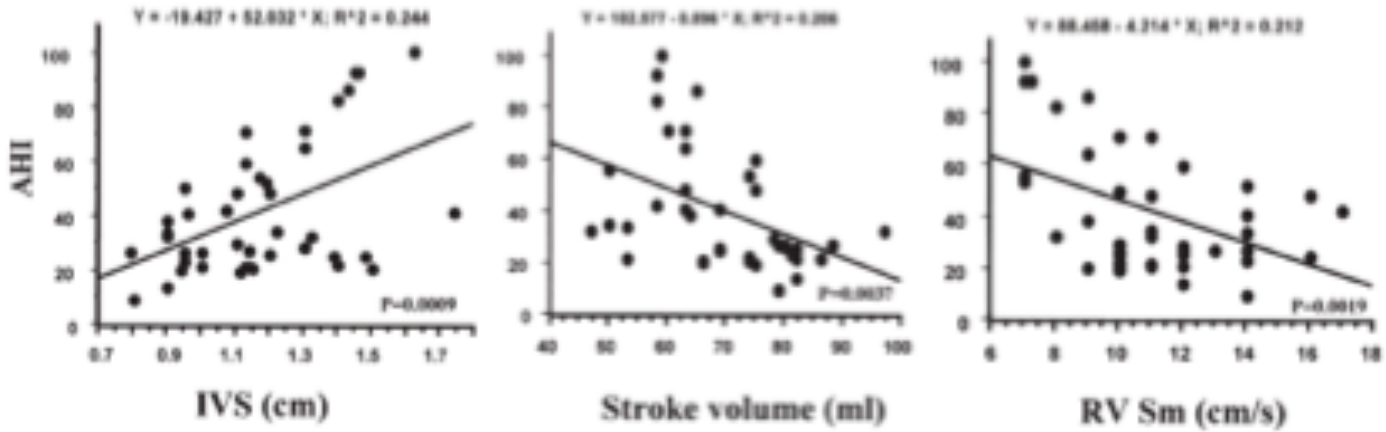
Sleep Heart Health Study: 6132 SUJETS > 40 ANS

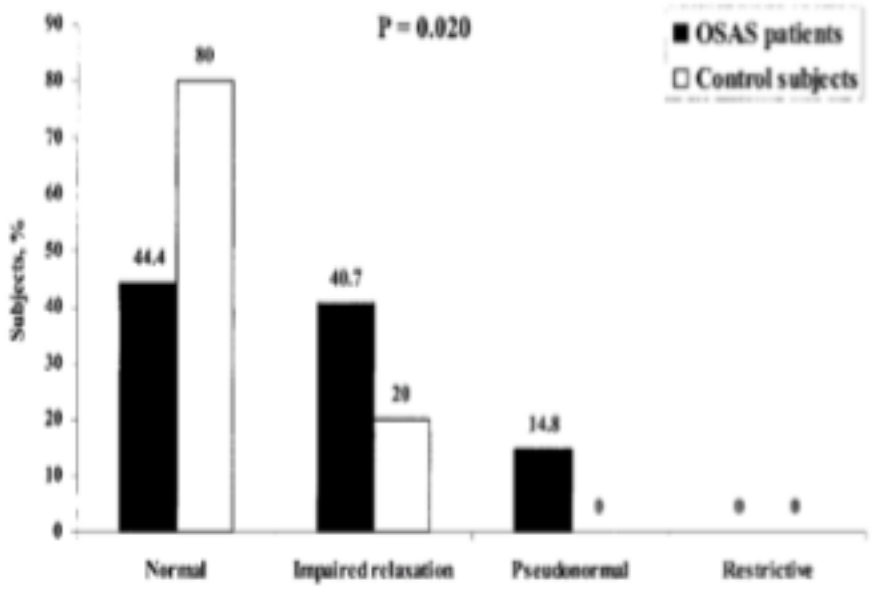


The relative odds (95% CI) of coronary heart disease (upper versus lower AHI quartile) was 2.38 (1.22–4.62),

Shahar, AJRCCM 2001

SAOS et mesures échographique de la fonction cardiaque systolique et diastolique



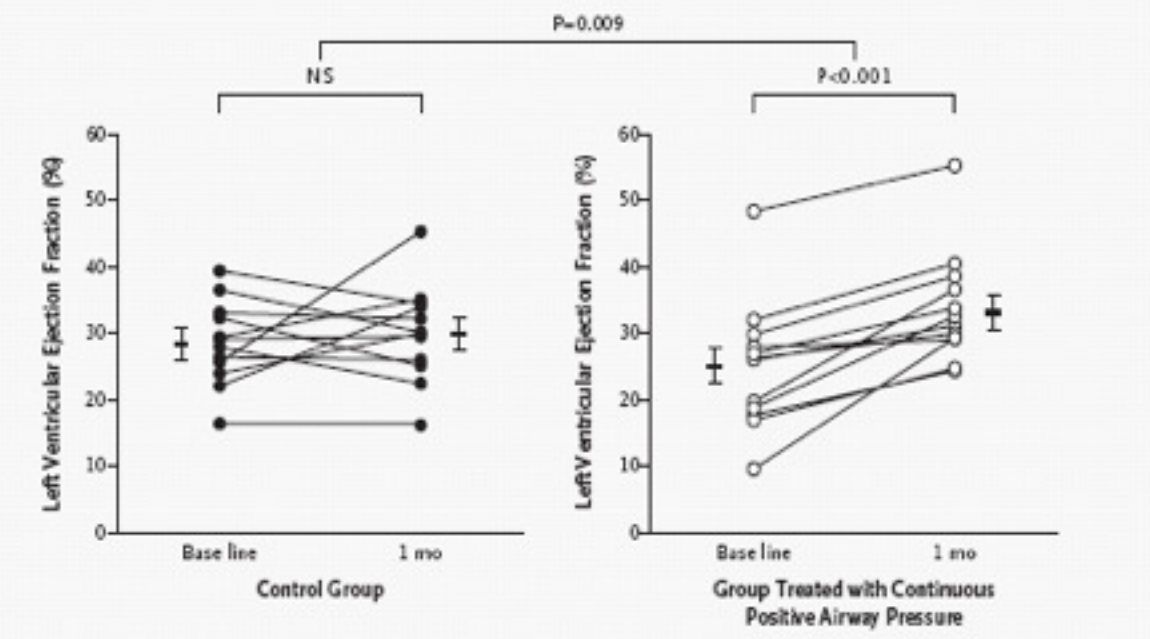


Shivalkar, JACC 2006

Arias, Circulation 2005

SAOS + insuffisance cardiaque: impact de la PPC

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



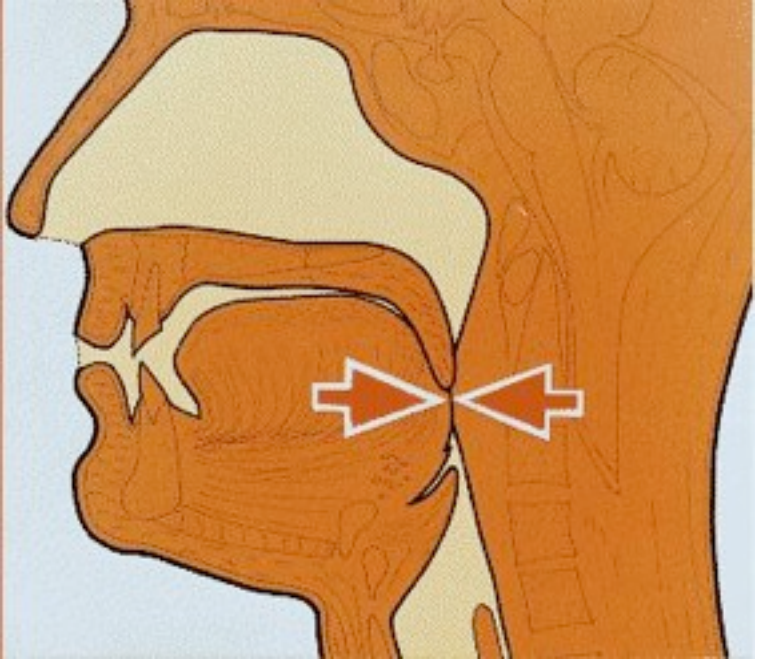
24 patients

ICG stable (FEVG < 45%) + SAOS

tt médical seul vs tt médical + PPC

1 mois

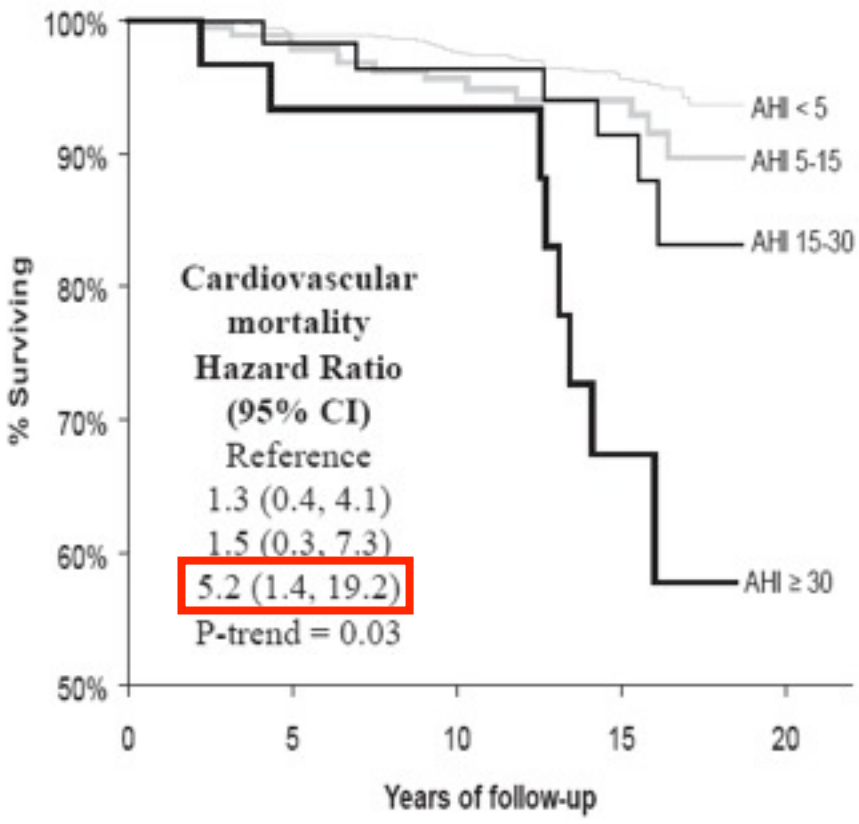
Kaneko, NEJM 2003



SAOS et MORTALITE CV

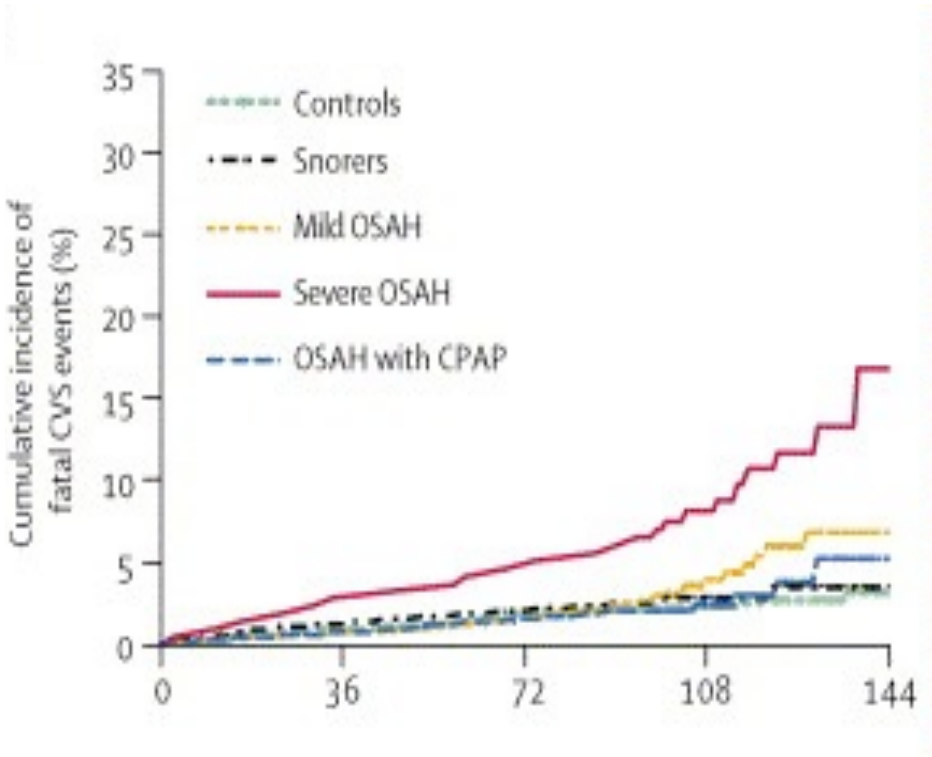
SAOS et mortalité CV

ETUDES EPIDEMIOLOGIQUES



WSCS: 1396 sujets suivis 13,8 ans

ETUDES CLINIQUES



> 1500 patients suivis > 10 ans

Young, Sleep 2008
Marin, Lancet 2005

SAOS et mortalité CV

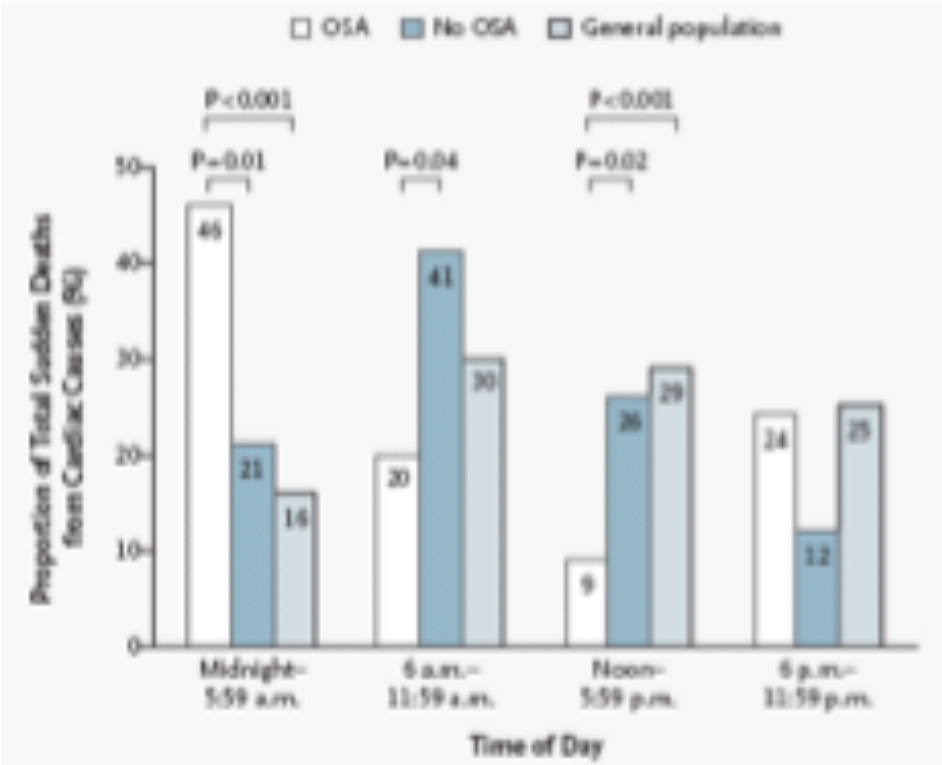
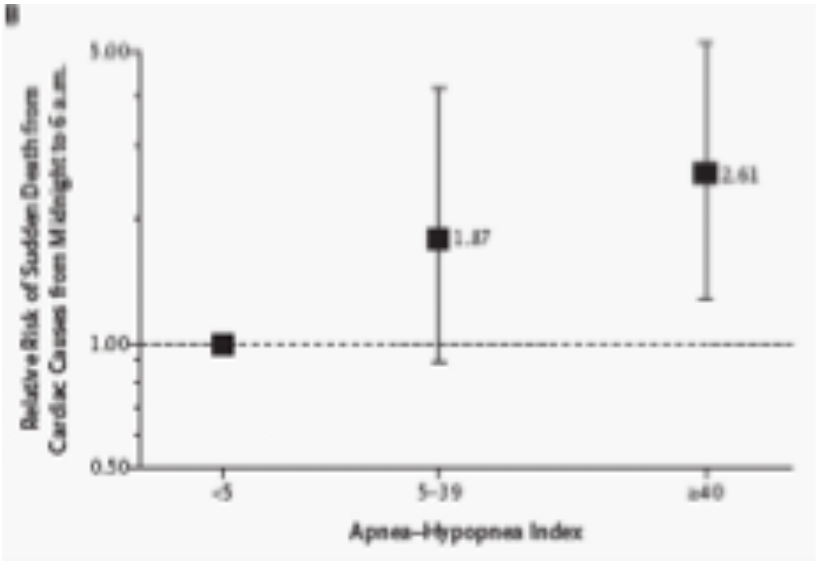


Figure 1. Day–Night Pattern of Sudden Death from Cardiac Causes in 78 Persons with and 34 Persons without Obstructive Sleep Apnea (OSA) and in the General Population.

Data for the general population were derived from Cohen et al.[8]

Augmentation du risque de mort subite CV au cours du sommeil



Somers, NEJM 2005

SAOS et mortalité CV

La surmortalité liée au SAOS décroît avec l'age

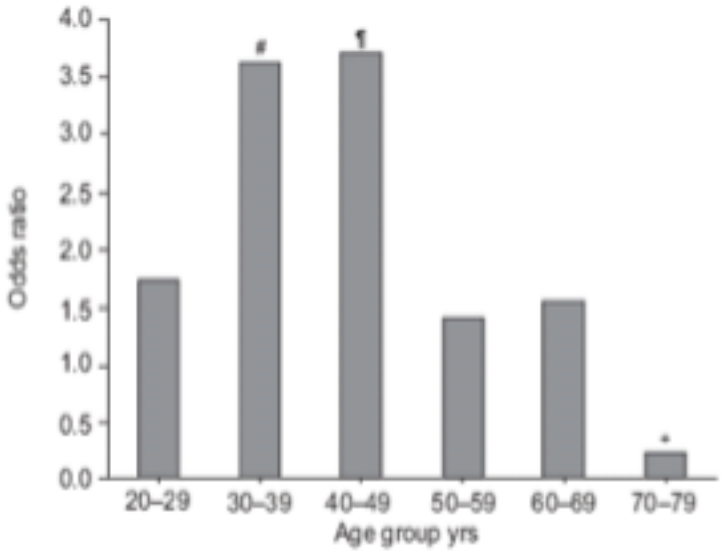


FIGURE 1. Odds ratios for mortality in males with sleep apnoea at different ages. #: p<0.002; ¶: p<0.0002; *: p<0.0007.

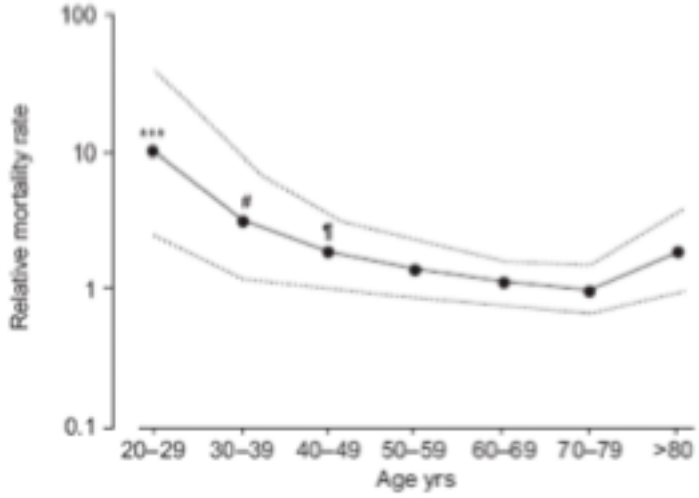
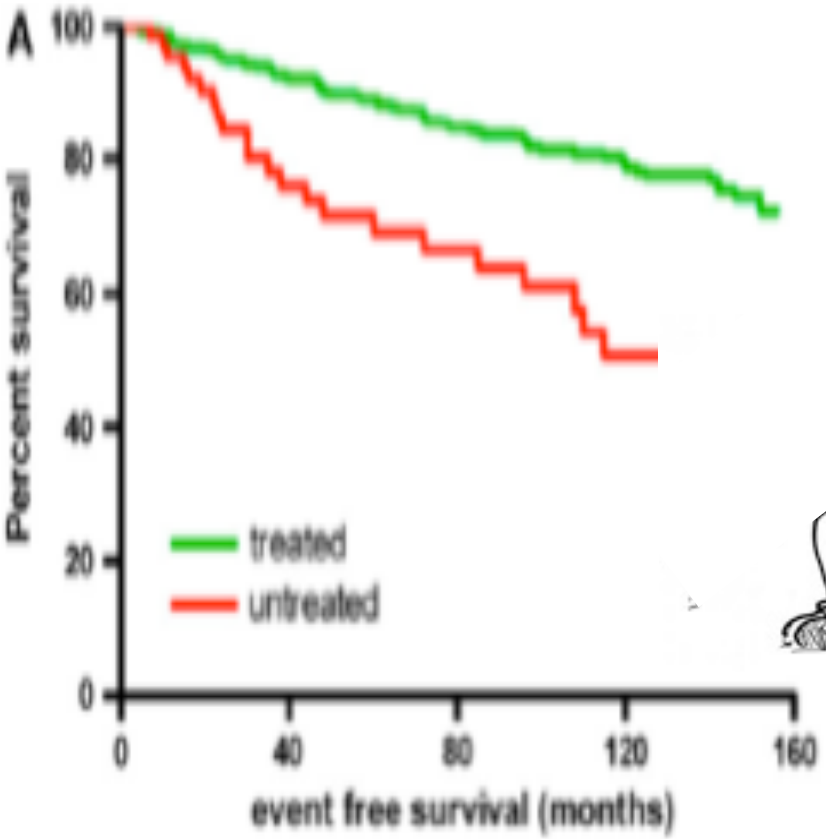


FIGURE 5. Relative rates (—) and 95% confidence intervals (----) of all cause mortality in males with severe sleep apnoea (apnoea/hypopnoea index >50 events·h⁻¹, median 75 events·h⁻¹) referenced to the corresponding rates in the general population. #: p<0.002; ¶: p<0.03. *** p<0.001. Reproduced from [14].

Lavie, ERR 2007

SAOS et mortalité CV: impact de la PPC



Biais potentiels ??

Buchner, AJRCCM 2007

SAOS et mortalité CV: impact de la PPC

ClinicalTrials.gov
A service of the U.S. National Institutes of Health

Continuous Positive Airway Pressure Treatment of Obstructive Sleep Apnea to Prevent Cardiovascular Disease (SAVE)

This study is currently recruiting participants.

Verified by Adelaide Institute for Sleep Health, May 2009

First Received: August 19, 2008 Last Updated: May 26, 2009

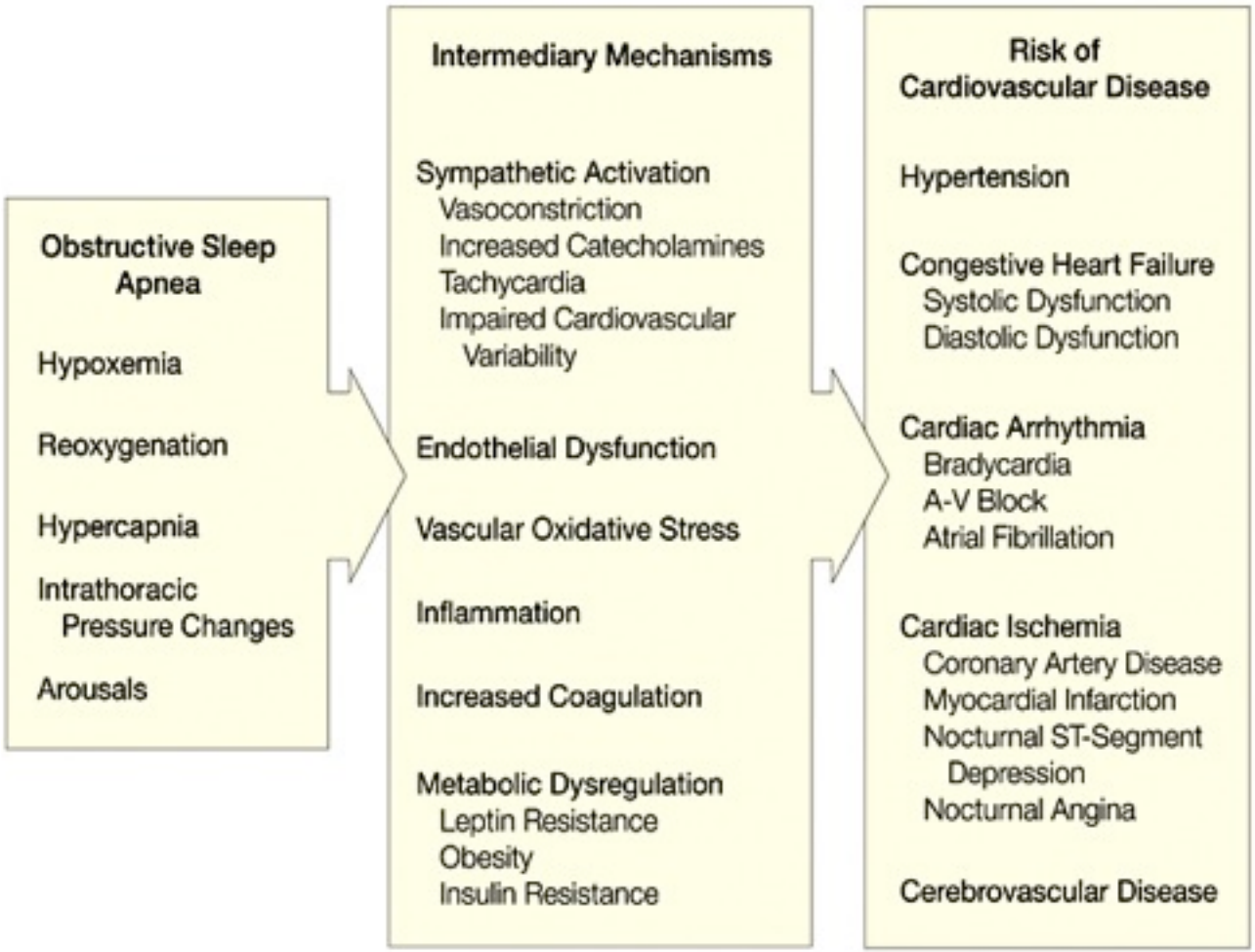
Condition	Intervention	Phase
Sleep Apnea Cardiovascular Disease	Device: Continuous Positive Airway Pressure (CPAP) Other: Standard care	Phase III

Primary Outcome Measures:

•**A composite of the CV endpoints of CV death**, non-fatal acute myocardial infarction, non-fatal stroke, hospital admission for heart failure, and new hospitalisation for unstable angina or transient ischaemic attack.

[Time Frame: Reviewed 6-monthly; average patient follow up, 4 years]

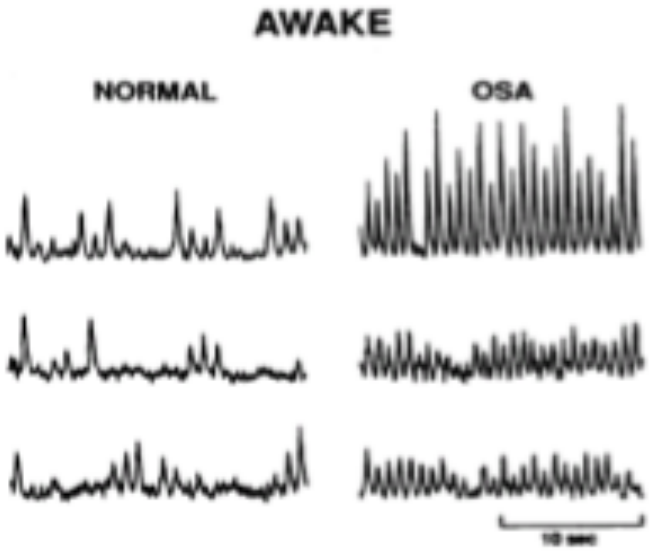
Quels mécanismes pour expliquer la morbidité CV associée au SAOS ?

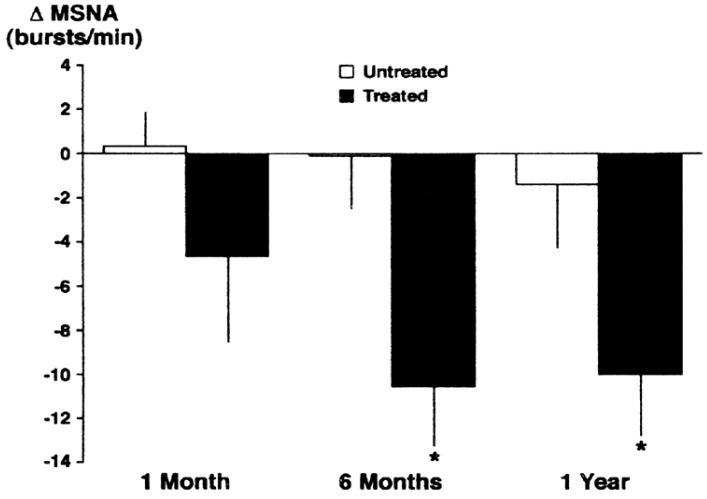


Shamsuzzaman, JAMA 2003

Intermediary Mechanisms

- Sympathetic Activation
  - Vasoconstriction
  - Increased Catecholamines
  - Tachycardia
  - Impaired Cardiovascular Variability
- Endothelial Dysfunction
- Vascular Oxidative Stress
- Inflammation
- Increased Coagulation
- Metabolic Dysregulation
  - Leptin Resistance
  - Obesity
  - Insulin Resistance





Somers, JCI 1995

Narkiewicz, Circulation 1999

Intermediary Mechanisms

Sympathetic Activation
- Vasoconstriction
- Increased Catecholamines
- Tachycardia
- Impaired Cardiovascular Variability

Endothelial Dysfunction

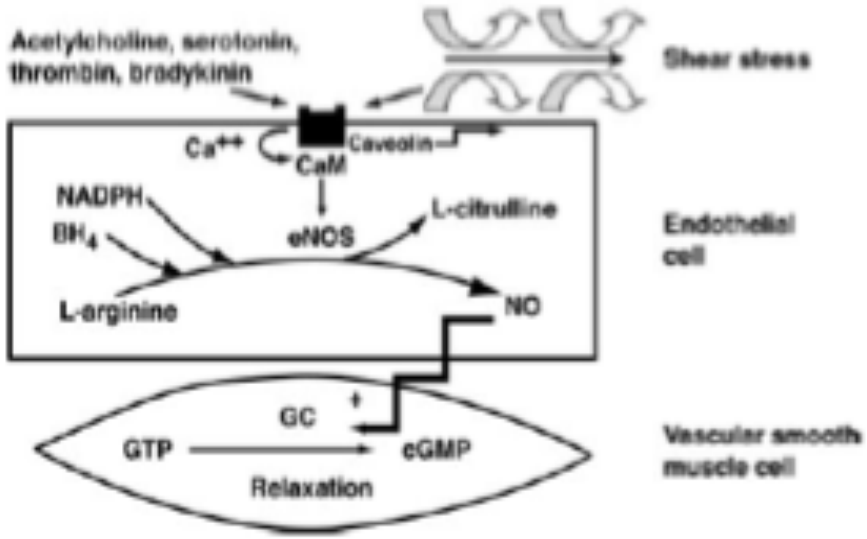
Vascular Oxidative Stress

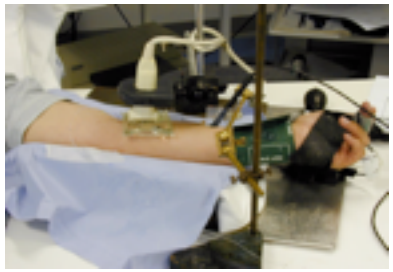
Inflammation

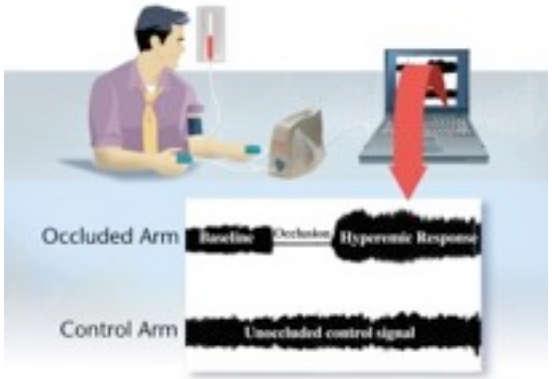
Increased Coagulation

Metabolic Dysregulation
- Leptin Resistance
- Obesity
- Insulin Resistance

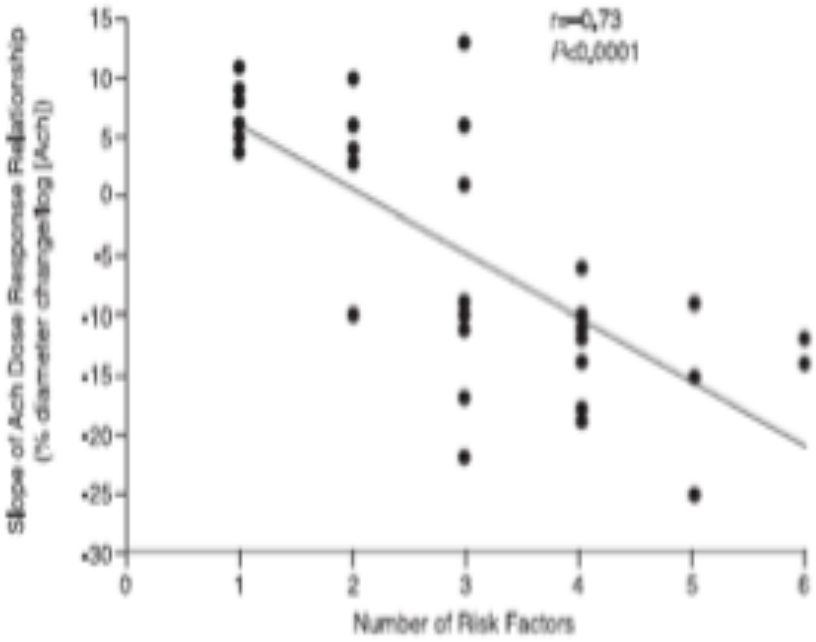
- **Perte de la vasodilatation à l'Ach ou à une épreuve d'hyperhémie**

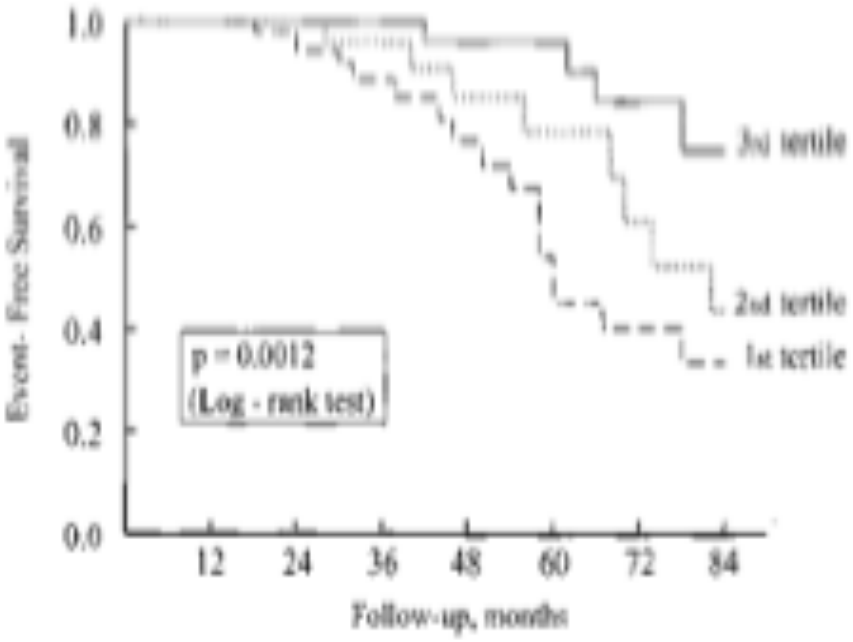






Dysfonction endothéliale: marqueur précoce d'athérome et facteur de risque CV en population à risque



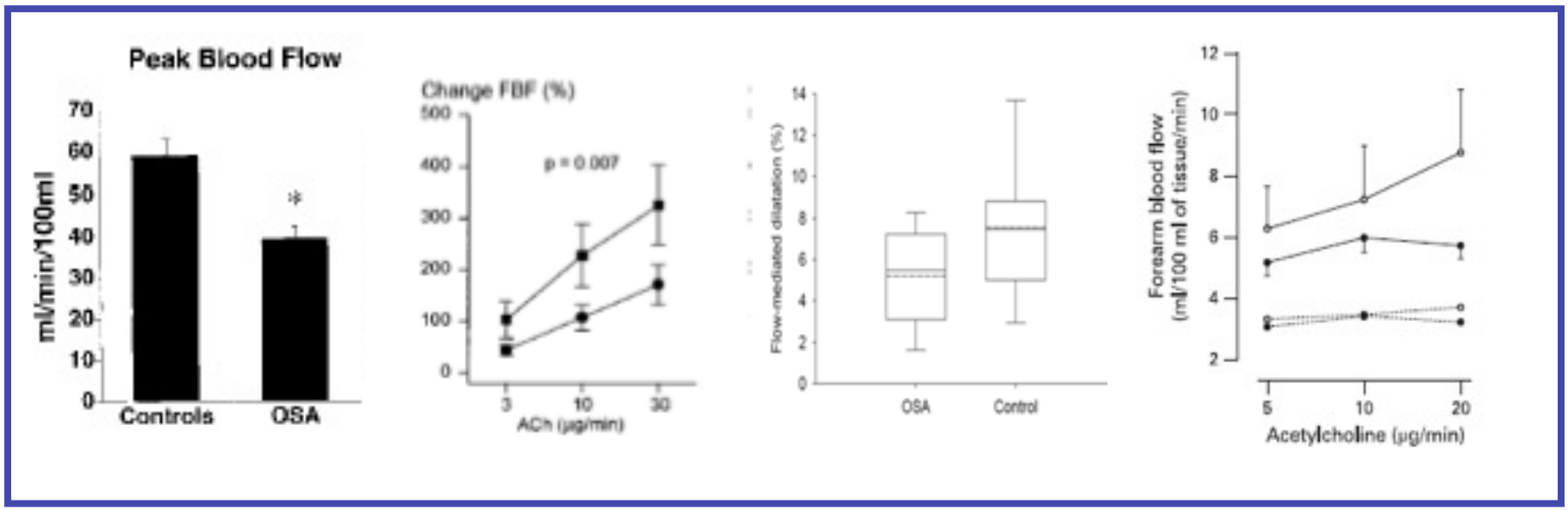


Vita, Circulation 1990

Perticone, Circulation 2001

SAOS et dysfonction endothéliale

La fonction endothéliale est altérée dans le SAOS par rapport à des sujets contrôles



Kato, Circulation 2000

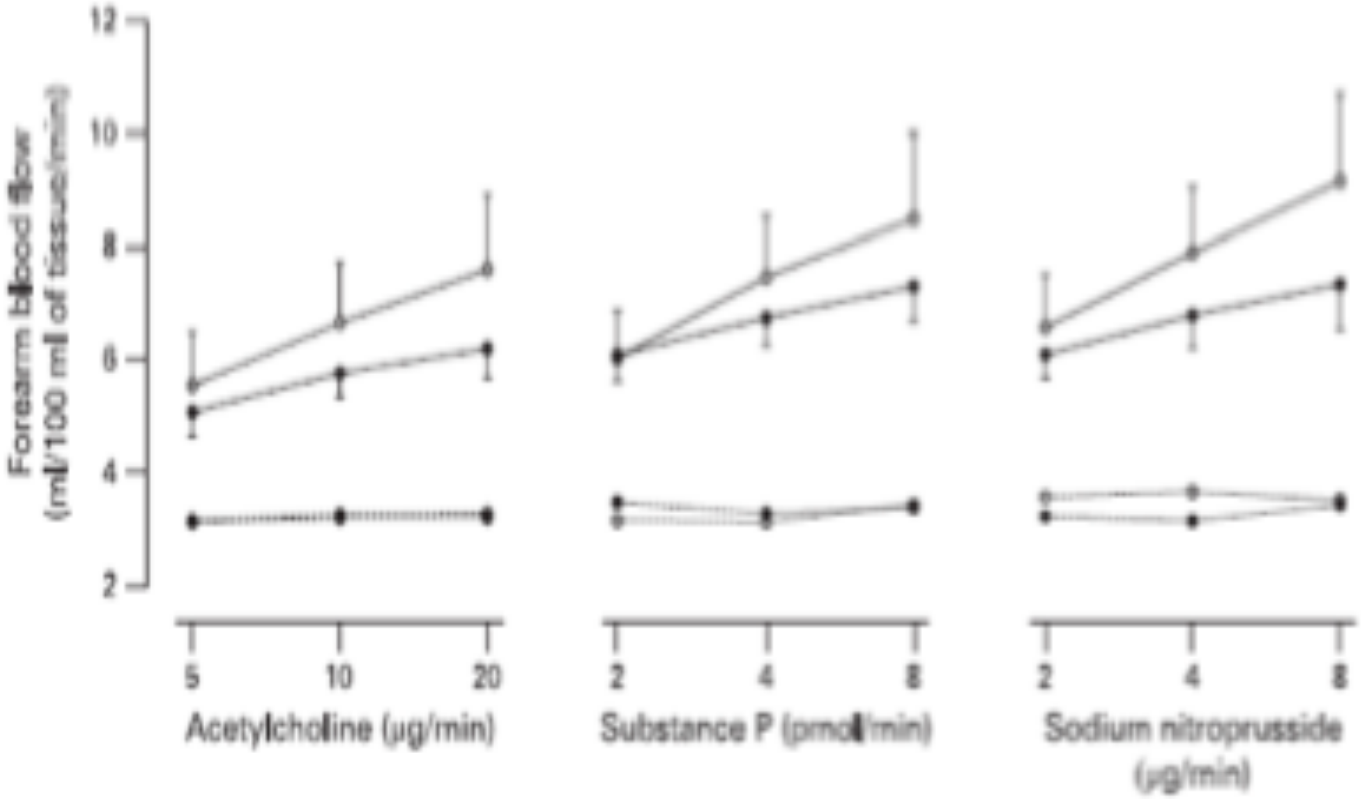
Imadojemu, AJRCCM 2002

Kohler, AJRCCM 2009

Cross, Thorax 2009

SAOS et dysfonction endothéliale

- **Amélioration de la fonction endothéliale après 6 semaines de PPC vs 6 semaines de sham PPC en cross over chez des SAOS désaturateurs nocturnes**



Thorax 2008

Intermediary Mechanisms

Sympathetic Activation
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- Increased Catecholamines
- Tachycardia
- Impaired Cardiovascular Variability

Endothelial Dysfunction

Vascular Oxidative Stress

Inflammation

Increased Coagulation

Metabolic Dysregulation
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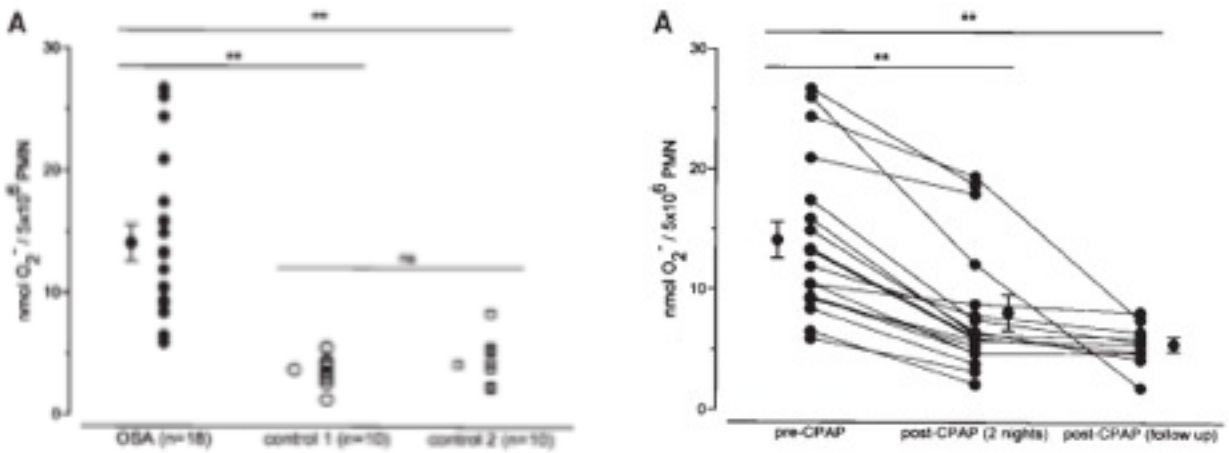

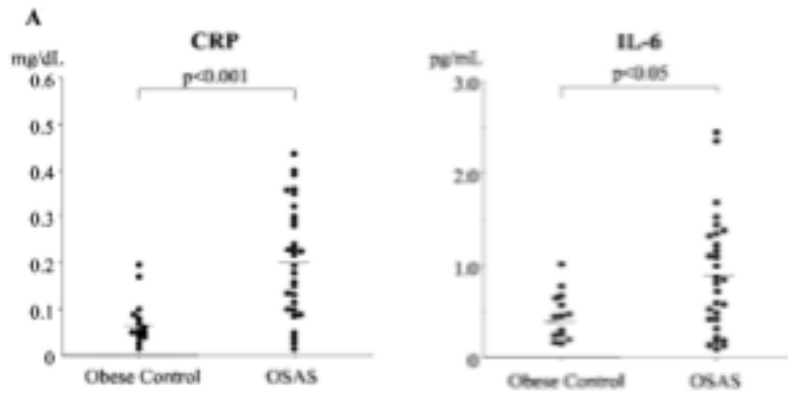

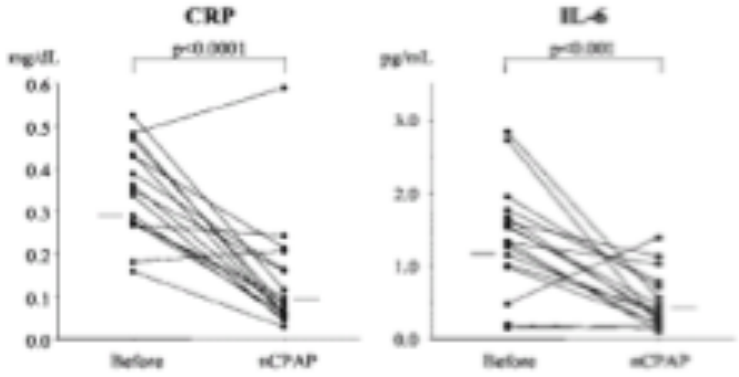

Yokoe, circulation 2003

Shultz, AJRCCM 2000

Intermediary Mechanisms

Sympathetic Activation
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- Increased Catecholamines
- Tachycardia
- Impaired Cardiovascular Variability

Endothelial Dysfunction

Vascular Oxidative Stress

Inflammation

Increased Coagulation

Metabolic Dysregulation
- Leptin Resistance
- Obesity
- Insulin Resistance

- *En population générale, le SAS est lié de façon indépendante à l'intolérance au glucose, l'insulino résistance, la prévalence (et non l'incidence) du diabète*
- *Les mécanismes intermédiaires suggérés par des données expérimentales et épidémiologiques sont l'hypoxémie intermittente et la ↘ TST et SLP*
- *L'impact du traitement par PPC sur le métabolisme glucidique demeure incertain: influence de la durée de traitement, du poids, du statut diabétique ou non ?*

Levy, ERJ 2009

CONCLUSIONS

- Données expérimentales, épidémiologiques et interventionnelles en faveur d'un lien de cause à effet entre SAOS et HTA.
- Données épidémiologiques en faveur d'une relation statistique indépendante entre SAOS et morbi-mortalité CV
- Données interventionnelles randomisées en faveur d'un bénéfice de la PPC sur les marqueurs précoce d'athérosclérose et la fonction cardiaque
- Données observationnelles en faveur d'un bénéfice de la PPC sur la morbi-mortalité CV….. Études randomisées en cours.
- Faut-il traiter le SAOS comme un facteur de risque CV chez un sujet non symptomatique ?
  - Probablement si IAH>30
  - IAH<30 ?
  - Problème d'acceptation de la PPC….nécessité d'évaluer d'autre approches thérapeutiques (OAM, médicaments……)

Une bonne lecture

Obstructive sleep apnoea and its cardiovascular consequences

T Douglas Bradley, John S Floras

Lancet 2009; 373: 82–93
Published Online October 30, 2008
DOI:10.1016/S0140-6736(08)61622-0

Obstructive sleep apnoea (OSA) is a common disorder in which repetitive apnoeas expose the cardiovascular system to cycles of hypoxia, exaggerated negative intrathoracic pressure, and arousals. These noxious stimuli can, in turn, depress myocardial contractility, activate the sympathetic nervous system, raise blood pressure, heart rate, and myocardial wall stress, depress parasympathetic activity, provoke oxidative stress and systemic inflammation, activate platelets, and impair vascular endothelial function. Epidemiological studies have shown significant independent associations between OSA and hypertension, coronary artery disease, arrhythmias, heart failure, and stroke. In randomised trials, treating OSA with continuous positive airway pressure lowered blood pressure, attenuated signs of early atherosclerosis, and, in patients with heart failure, improved cardiac function. Current data therefore suggest that OSA increases the risk of developing cardiovascular diseases, and that its treatment has the potential to diminish such risk. However, large-scale randomised trials are needed to determine, definitively, whether treating OSA improves cardiovascular outcomes.

MERCI POUR VOTRE ATTENTION