Syndrome d'Apnée du Sommeil et Syndrome Métabolique

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Définition

Syndrome d'apnée du sommeil

- Hypersomnolence diurne
- Au moins deux des symptômes suivants
  - Sommeil non récupérateur
  - Éveils multiples
  - Étouffements nocturnes
  - Fatigue
  - Troubles de la concentration
- > 5 événements obstructifs/h de sommeil en PSMG ou PV

Syndrome métabolique (3/5)

- Obésité abdominale
  - Tour de taille > 88 cm (80cm) femme
  - Tour de taille > 102 cm (94cm) homme
- TG≥ 1,5g/L
- HTA ≥ 130/85 mmHg
- HDL-C < 0,4g/ homme >0,5g/L femme
- Glycémie ≥ 1,1g/L

SAS et syndrome métabolique

- Une épidémiologie croisée
- Un risque cardiovasculaire accru
- Lien de causalité probable entre le SAS et les différentes composantes du SM
  - des données cliniques
  - des données thérapeutiques
  - des données physiopathologiques
- Implications en pratique clinique

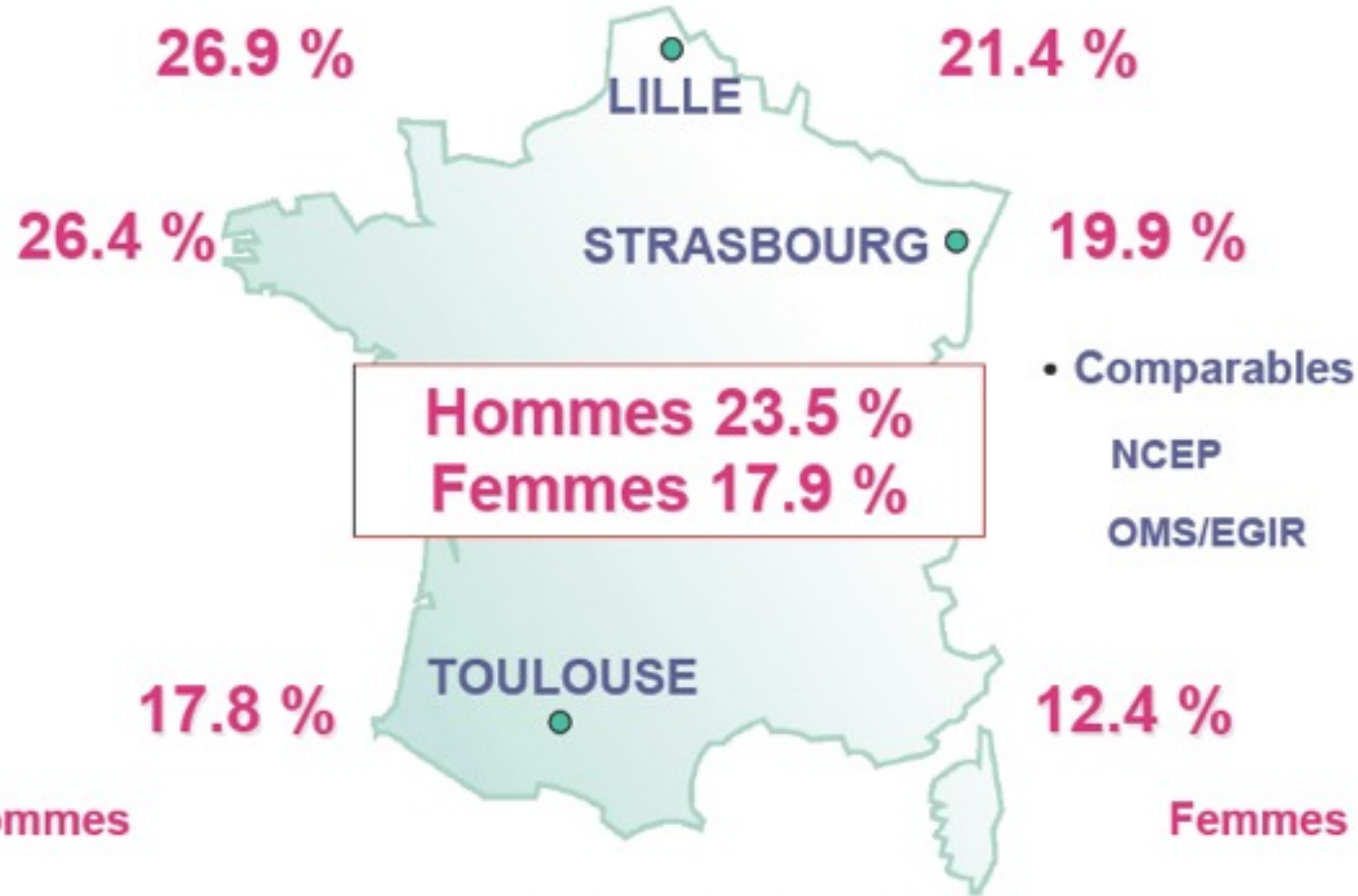
Lien étroit SAS et obésité

- 5615 sujets de 45 à 98 ans
- 18% de SAS si IAH> 15/h

	Poids normal	Surcharge pondérale	Obésité modérée	Obésité sévère	Obésité morbide
IMC	< 25	25 - 30	30 - 35	35 - 40	> 40
SAS (%)	12	17	32	38	42

Young T et al Arch Int Med, 2002

Prévalence du Syndrome Métabolique en France (défini par les critères de NCEP)



Résultats en pourcentage pour des sujets âgés de 35 à 64 ans

2007

Le SAS: un facteur de risque cardio vasculaire majeur

1522 patients avec SAS
suivis pendant 18 ans

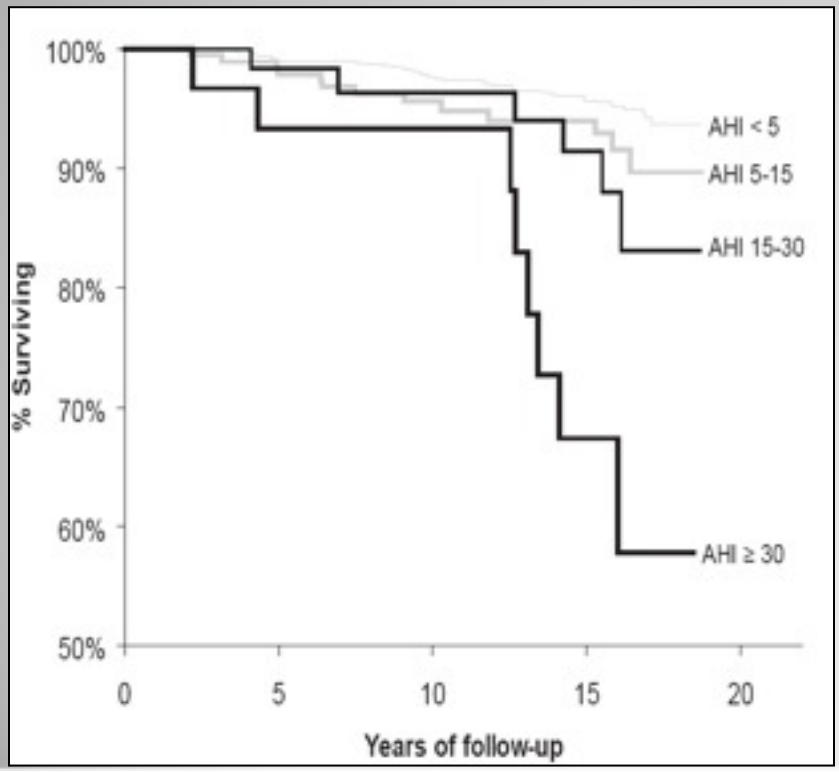


Table 6—Mortality Risk* With Untreated Sleep-Disordered Breathing (n = 1396)**

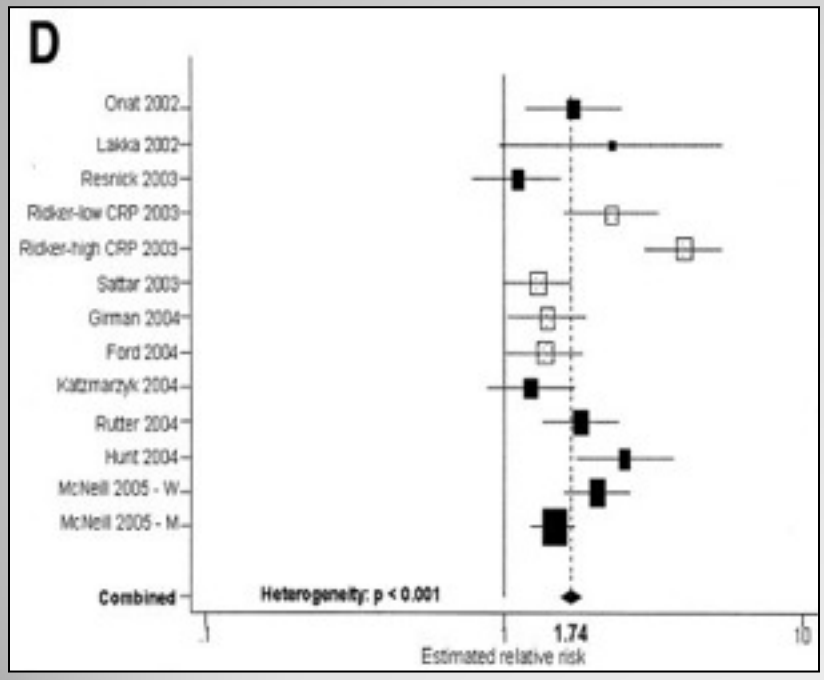
Baseline AHI category	All-cause mortality Hazard Ratio (95% CI)	Cardiovascular mortality Hazard Ratio (95% CI)
None: 0 - < 5	Reference	Reference
Mild: 5 - < 15	1.4 (0.7, 2.6)	1.3 (0.4, 4.1)
Moderate: 15 - < 30	1.7 (0.7, 4.1)	1.5 (0.3, 7.3)
Severe: ≥30	3.8 (1.6, 9.0)	5.2 (1.4, 19.2)
	P trend = 0.004	P-trend = 0.03

*Hazard ratios adjusted for age, age^2, sex, body mass index, and body mass index^2
**126 persons who reported usual use of continuous positive air pressure (CPAP) ≥ 4 nights per week were excluded from sample
AHI denotes number of apnea and hypopnea events per hour of sleep, CI denotes confidence interval

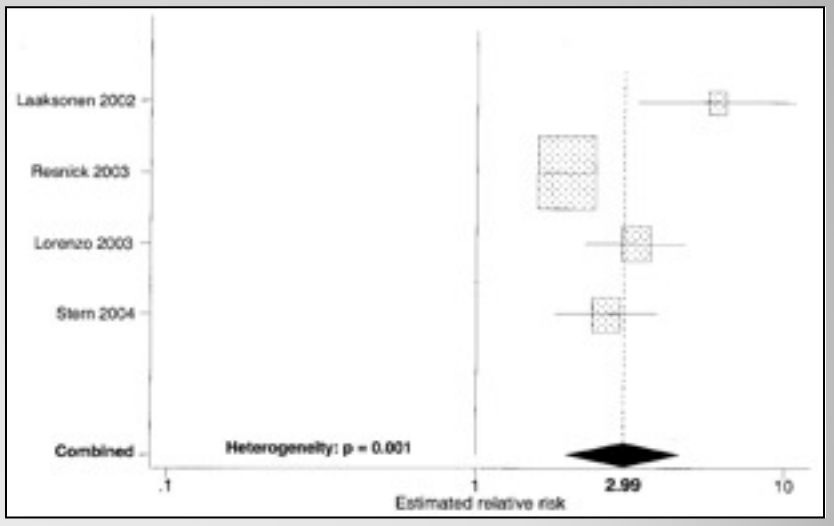
Young T et al, Sleep, 2008

Le SM : un facteur de risque cardiovasculaire et de diabète

Evénements cardio-vasculaires



Diabète



Etudes prospectives
juillet 1998 à Aout 2004

Ford F et al, Diabetes Care, 2005

Association indépendante du SAS aux différentes composantes du SM

Table 2—*Metabolic Characteristics of Patients With and Without OSAS**

Characteristics	OSAS (n = 42)	Non-OSAS (n = 52)	p Value
Systolic BP, mm Hg	131 ± 3	125 ± 1	< 0.05
Diastolic BP, mm Hg	77 ± 2	77 ± 1	NS
Subjects with high BP	19/42 (45.2)	8/52 (15.4)	< 0.01
Serum triglycerides (range), mg/dL†	126 (35–271)	117 (40–244)	NS
Serum TC, mg/dL	182 ± 5	189 ± 4	NS
Serum HDL-C, mg/dL	50 ± 2	55 ± 2	NS
Subjects with dyslipidemia	20/42 (47.6)	13/52 (25.0)	< 0.05
FPG, mg/dL	111 ± 6	93 ± 3	< 0.05
Subjects with hyperglycemia	14/42 (33.3)	5/52 (9.6)	< 0.01
HOMA-R	3.7 ± 0.4	2.5 ± 0.2	< 0.05
Subjects with at least two of the following: hypertension, hyperglycemia, and dyslipidemia	8/42 (19.0)	2/52 (3.8%)	< 0.05

*Data are presented as mean ± SE or No./total (%) unless otherwise indicated. See Table 1 for expansion of abbreviation.
†Data are presented as median (range).

Kono M et al, Chest, 2007

Le risque de SM est 9 fois + important chez les patients ayant un SAS

- 61 hommes avec SAS
- 41 sujets contrôle

Table 3 The association of obstructive sleep apnoea with components of the metabolic syndrome

Dependent variable	β Coefficient (95% CI)	p
Systolic blood pressure (mmHg) $F_{6,97} = 7.00$, $p < 0.0001$. Adj R^2 26%, SE estimate = 13.71	6.8 (0.8, 12.9)	0.0281
Diastolic blood pressure (mmHg) $F_{6,97} = 3.75$, $p = 0.0021$. Adj R^2 14%, SE estimate = 8.42	4.3 (0.5, 8.0)	0.0257
Mean arterial blood pressure (mmHg) $F_{6,97} = 6.22$, $p < 0.0001$. Adj R^2 23%, SE estimate = 8.92	5.1 (1.2, 9.1)	0.0118
Fasting glucose (mmol/l) $F_{6,97} = 1.55$, $p = 0.1691$. Adj R^2 3%, SE estimate = 0.45	0.1 (−0.1, 0.3)	0.5256
Fasting insulin (pmol/l)[a] $F_{6,96} = 6.68$, $p < 0.0001$. Adj R^2 25%, SE estimate = 0.61	1.5 (1.1, 1.9)	0.0137
HOMA IR $F_{6,97} = 5.36$, $p < 0.0001$. Adj R^2 20%, SE estimate = 2.01	0.8 (−0.1, 1.7)	0.0763
Cholesterol (mmol/l) $F_{6,96} = 3.14$, $p = 0.0075$. Adj R^2 12%, SE estimate = 0.96	0.3 (−0.2, 0.7)	0.2018
Triglyceride (mmol/l)[a] $F_{6,96} = 1.88$, $p = 0.0914$. Adj R^2 5%, SE estimate = 0.47	1.3 (1.1, 1.6)	0.0138
HDL (mmol/l) $F_{6,96} = 5.26$, $p < 0.0001$. Adj R^2 20%, SE estimate = 0.27	−0.2 (−0.3, −0.1)	0.0006
LDL (mmol/l) $F_{6,92} = 1.89$, $p = 0.0905$. Adj R^2 5%, SE estimate = 0.89	0.3 (−0.1, 0.7)	0.0951
Cholesterol:HDL $F_{6,93} = 4.65$, $p = 0.0004$. Adj R^2 18%, SE estimate = 1.16	1.1 (0.5, 1.6)	0.0001
Metabolic syndrome (n)[b] Hosmer and Lemeshow test, $p = 0.6789$	9.1 (2.6, 31.2)	<0.0001

Coughlin et al, European Heart Journal, 2004

La prévalence SM augmente avec la sévérité du SAS

Table 2 Clinical identification of the metabolic syndrome.

Metabolic parameters	(%) Fulfilling metabolic criteria			
	AHI < 5 ($n = 160$)	AHI ⩾ 5 ($n = 95$)	Odds ratio (CI)	*P*-value
Waist circumference	60 (38)	63 (66)	3.3 (1.9–5.6)	< 0.001
Systolic blood pressure	56 (35)	53 (56)	2.41(1.43–4.08)	0.001
Diastolic blood pressure	34 (21)	42 (44)	3.0 (1.72–5.25)	< 0.001
HDL-cholesterol	72 (45)	60 (63)	2.1 (1.25–3.53)	0.006
Triglycerides	40 (25)	42 (44)	2.4 (1.39–4.08)	0.002
Fasting glucose	15 (9)	22 (23)	2.9 (1.43–5.95)	0.003
Metabolic syndrome (Any 3 risk factors or more)	33 (21)	55 (58)	5.3 (3.03–9.26)	< 0.001

Number of subjects (% in the group).
By the Chi-square test.

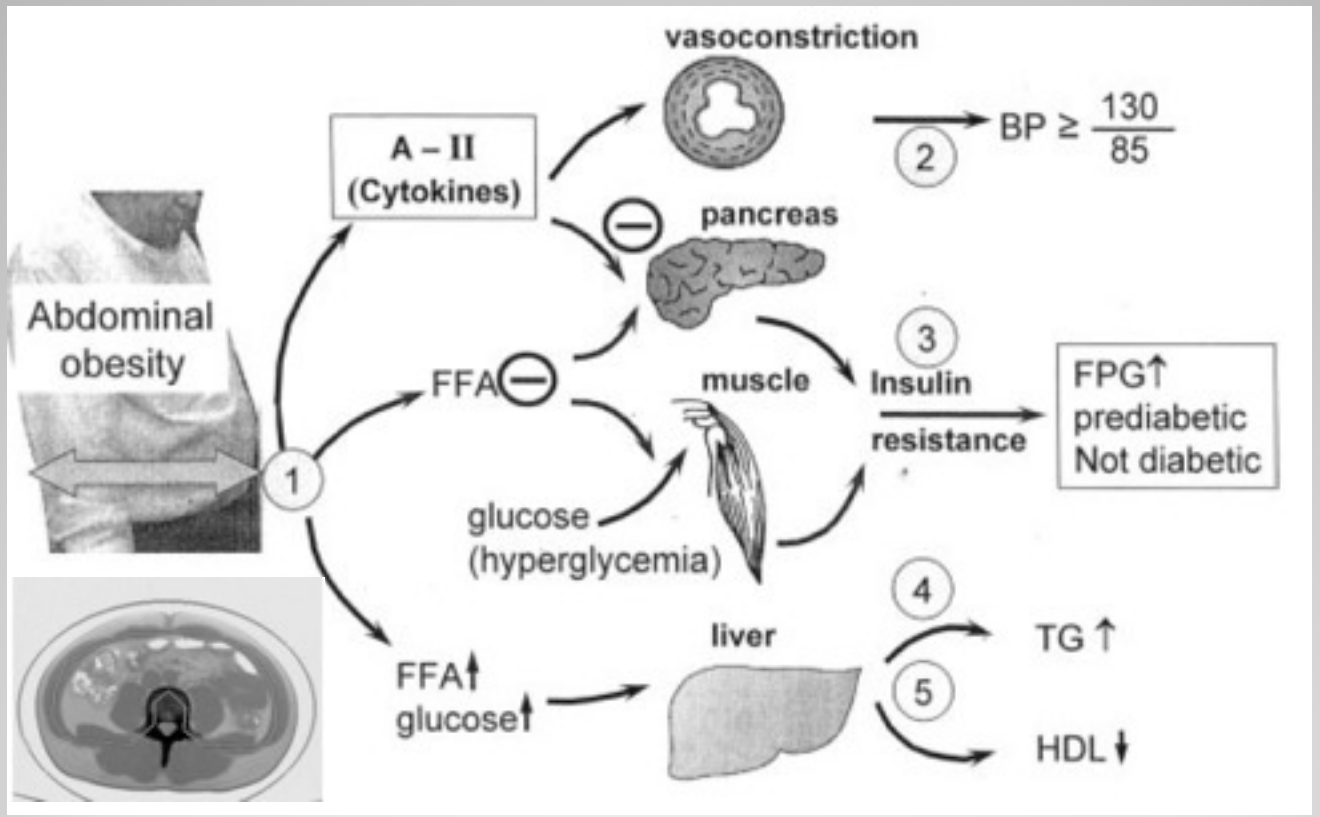
Table 3 Association of OSA and the metabolic syndrome (stratified by AHI).

AHI	< 5	5–14.9	15–29.9	⩾ 30	
Number of subjects	160	48	27	20	*P*-value
Metabolic syndrome, number (%)	33 (21)	26 (54)	15 (56)	14 (70)	0.001

Number of subjects (% in the group).
By analysis of variance.

LAM JC et al, Respir Med, 2006

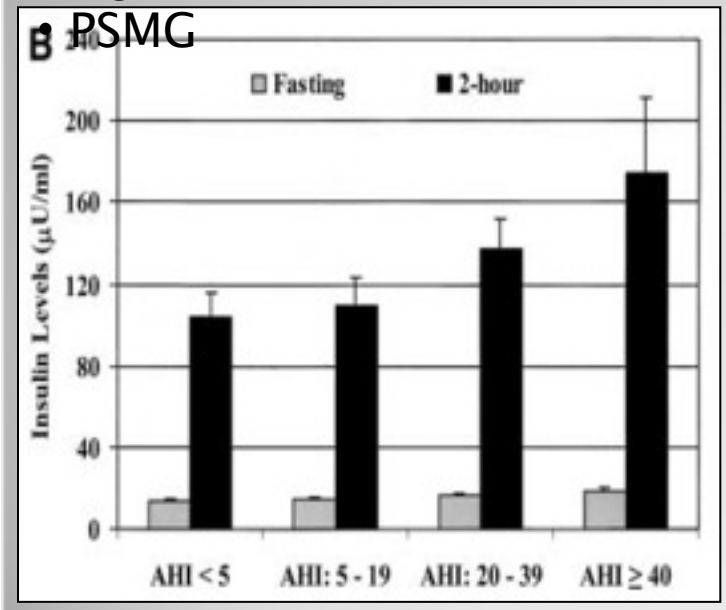
L'obésité viscérale: un rôle déterminant dans le SM



Opie L, Circulation 2007

Association indépendante du SAS à la résistance à l'insuline

- 150 sujets non diabétiques, IMC =30
- HGPO : Glycémie de la 2eme heure <2g/L
- PSMG



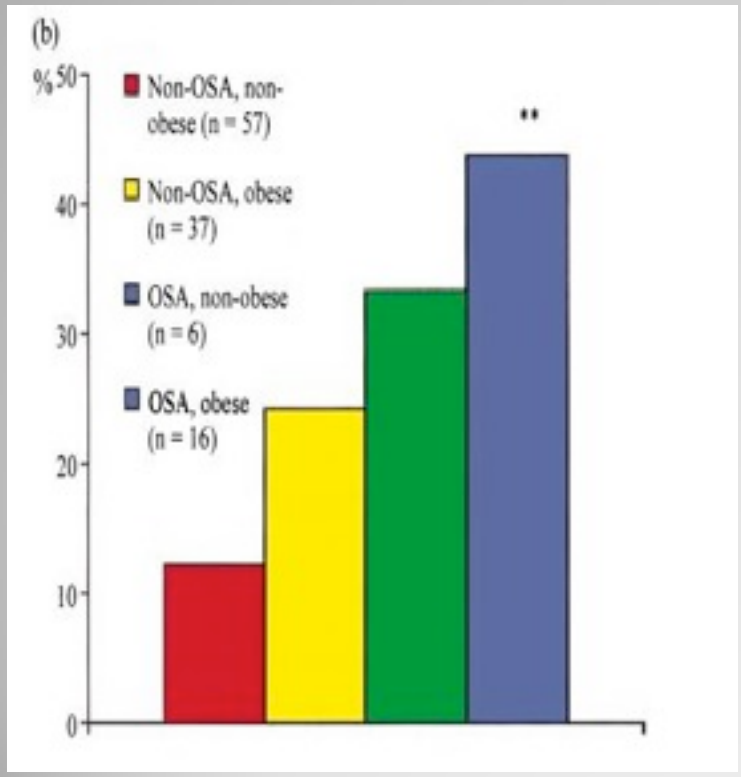
	Adjusted Odds Ratio (95% Confidence Interval)	
Predictor Variable	Model 1*	Model 2†
AHI ≥ 5, events/h	2.15 (1.05–4.38)	1.37 (0.61–3.09)
BMI, kg/m^2	1.20 (1.04–1.38)	1.15 (1.00–1.33)
Percent body fat, %	1.00 (0.92–1.09)	1.02 (0.94–1.12)
ΔSa_{O_2},‡ %	—	1.99 (1.11–3.56)

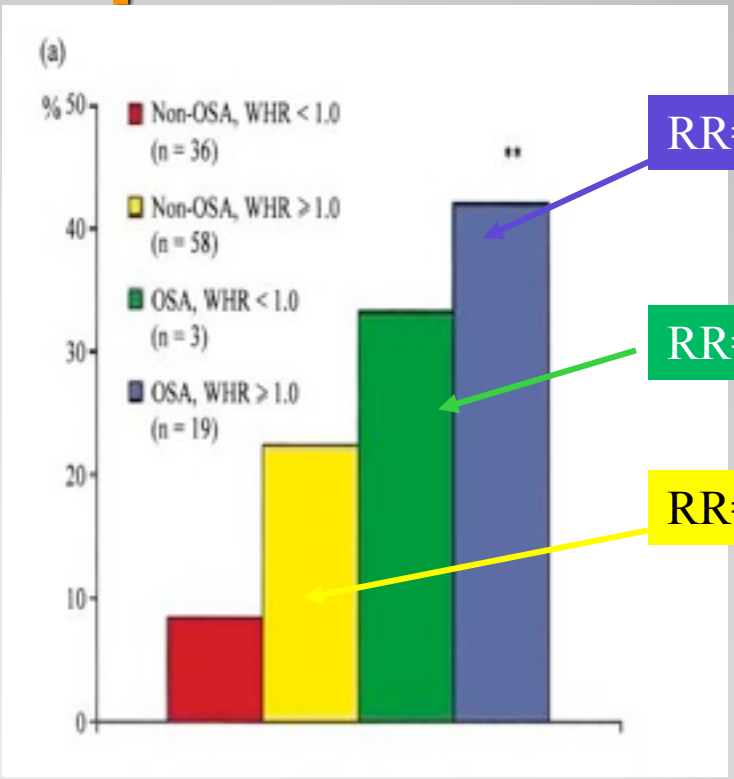
* Model 1 includes AHI, body mass index (BMI), and percent body fat.
† Model 2 includes AHI, body mass index (BMI), percent body fat, and oxyhemoglobin desaturation (ΔSa_{O_2}).
‡ Odds ratio for a 4% change in ΔSa_{O_2}.

Punjabi NM, Am J Respir Crit Care Med, 2002

SM et SAS : un risque accru de DT2

Obésité BMI > 27 **obésité abdominale > 100**





(n=150)

(Elmasry et al, *J Intern Med* 2001)

Effet du traitement du SAS sur les composantes du SM

- Un effet positif démontré sur la pression artérielle
- Un effet moindre sur les composantes métaboliques
- Des données contradictoires sur la résistance à l'insuline

Effet de la PPC sur le SM

Eur Respir J 2007; 29: 720–727
DOI: 10.1183/09031936.00043306
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Cardiovascular and metabolic effects of CPAP in obese males with OSA

S.R. Coughlin, L. Mawdsley, J.A. Mugarza, J.P.H. Wilding and P.M.A. Calverley

Sujets	Intervention	Evaluation
n= 34 (non diabétiques) - AHI 39.7 ± 13.8 - BMI 36.1 ± 7.6	6 sem PPC vs Placebo appareil (cross-over)	- Glycémie à jeun, insulinémie - HOMA - Syndrome métabolique

Coughlin SR et al. Eur Respir J 2007

Effet de la PPC sur le SM

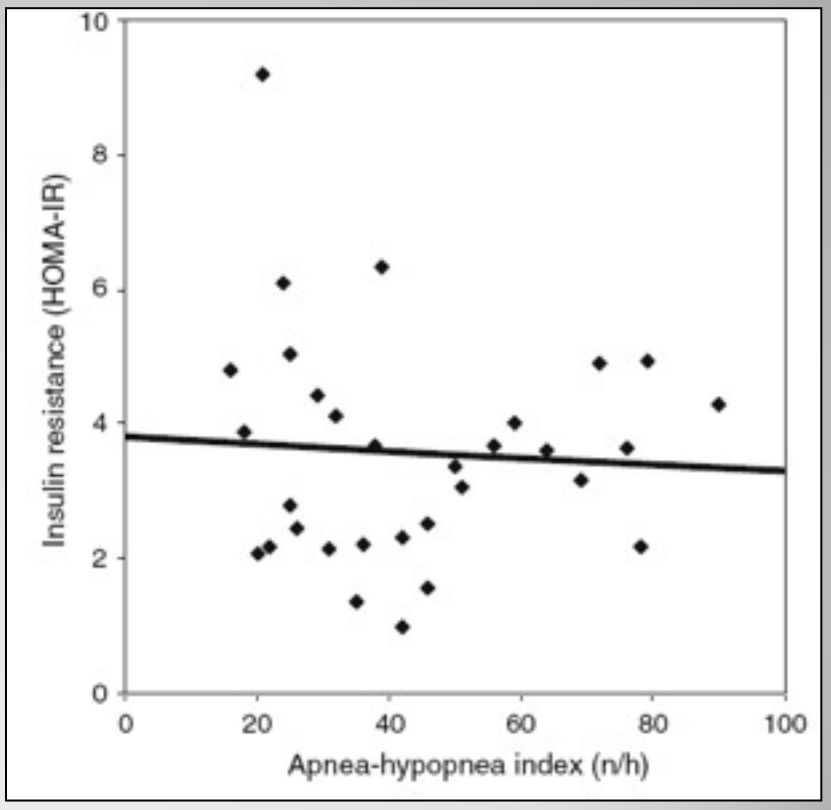
	CPAP	Placebo	Difference (95% CI)	p-value
Subjects n	34	34		
ESS	9.4±0.9	12.5±0.9	-3.1 (-4.5– -1.7)	<0.01
BP mmHg				
Systolic	135.7±2.0	142.4±2.4	-6.7 (-10.1– -3.3)	<0.01
Diastolic	86.8±0.15	91.7±1.6	-4.9 (-8.0– -1.8)	<0.01
Mean arterial	103.1±1.5	108.6±1.7	-5.5 (-8.2– -2.8)	<0.01
BRS ms·mmHg^{-1}	5.5±0.5	4.5±0.4	1.0 (-0.1–2.2)	0.07
Fasting glucose mmol·L^{-1}	4.7±0.1	4.8±0.1	-0.1 (-0.3–0.03)	0.11
Fasting insulin pmol·L^{-1}	15.5±1.6	18.1±2.0	-2.6 (-5.9–0.8)	0.13
HOMA IR	3.3±0.4	3.9±0.5	-0.6 (-1.3–0.1)	0.08

Coughlin SR et al.. Eur Respir J 2007

Pas de corrélation entre insulino résistance et sévérité du SAS

Variable	Mean ± SD	Range
Age (year)	53.9 ± 9.7	28–76
BMI (kg/m^2)	32.3 ± 4.7	26–44
ESS score	11.2 ± 5.7	3–24
AHI (h^{-1})	43 ± 21	16–90
ODI (h^{-1})	44 ± 25	9–113

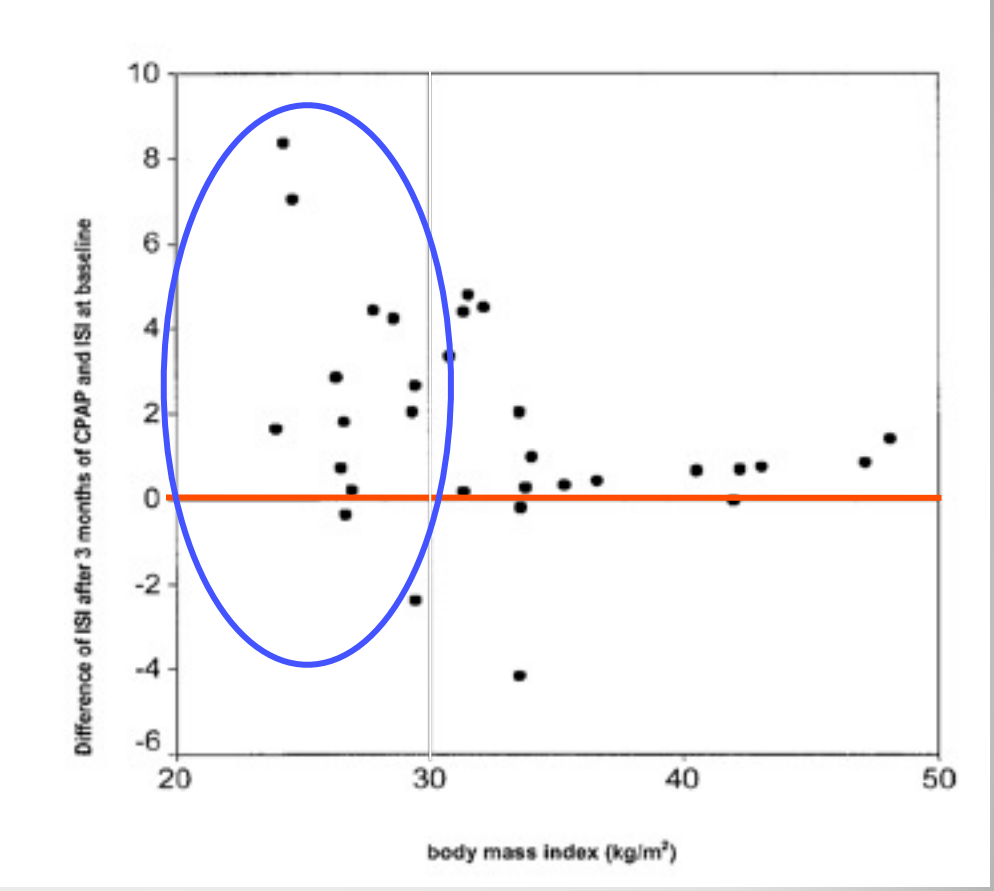
ESS Epworth Sleepiness Scale, *AHI* apnea-hypopnea index, *ODI* oxyhemoglobin desaturation index



Cuhadaroglu C et al, Lung 2009

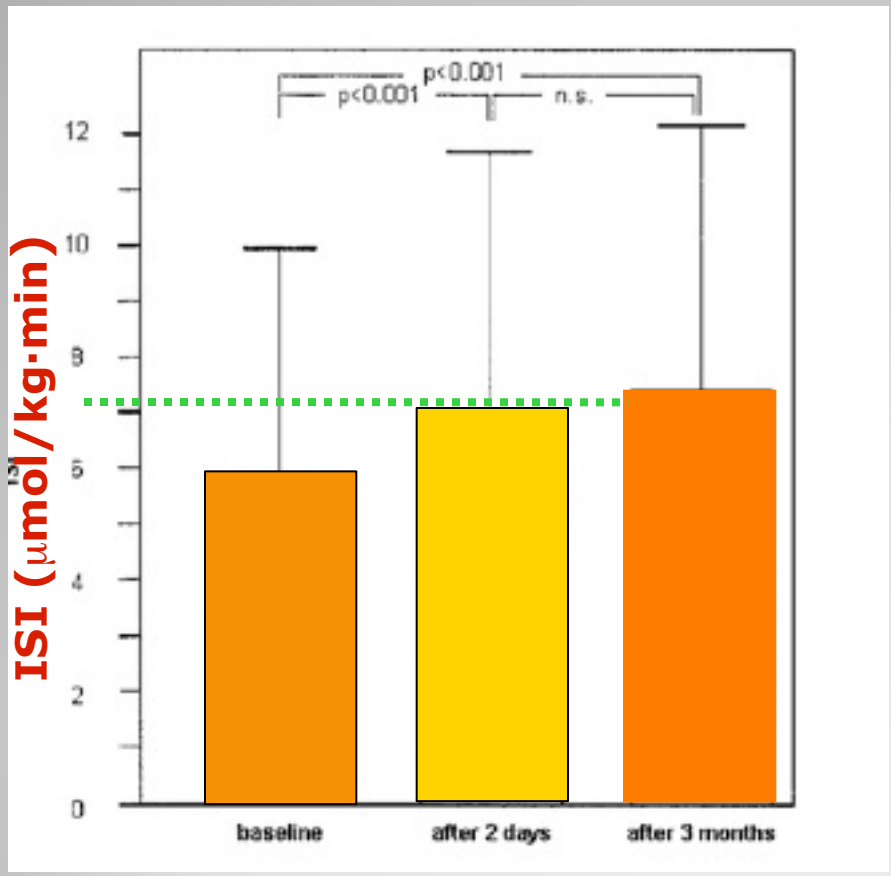
Amélioration de la sensibilité à l'insuline chez les patients à IMC < 30

- 40 patients avec SAS
- IAH >20
- PPC pendant 3 mois
- Clamp euglycémique hyperinsulinique



Harsch et al *AJCCRM* 2004

Amélioration la sensibilité à l'insuline après traitement par PPC (n=31)



L'amélioration rapide de la sensibilité à l'insuline suggère un impact majeur sur l'activité sympathique

Harsch et al *AJCCRM* 2004

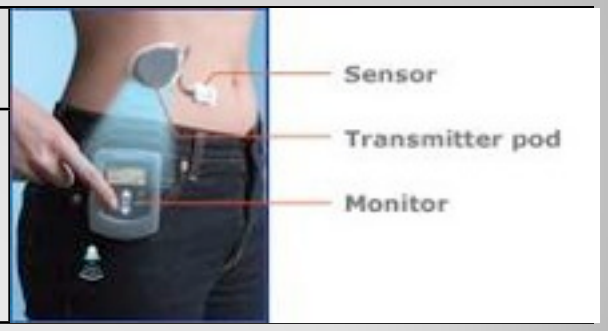
Effet de la PPC sur la glycémie

ORIGINAL INVESTIGATION

Type 2 Diabetes, Glycemic Control, and Continuous Positive Airway Pressure in Obstructive Sleep Apnea

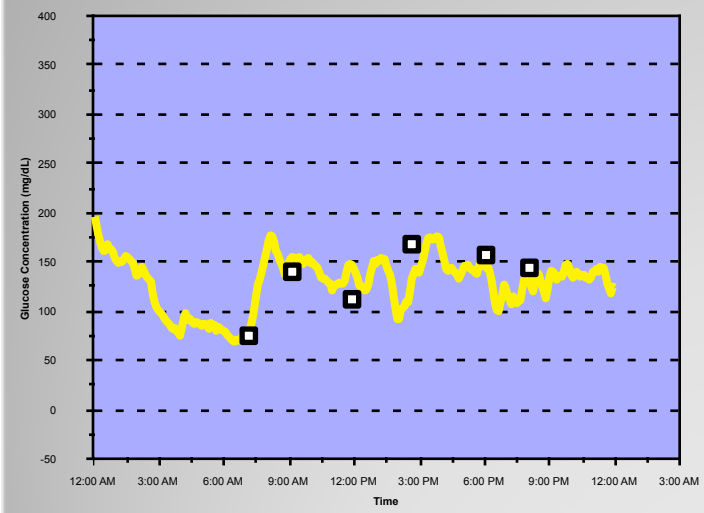
Ambika R. Babu, MD; James Herdegen, MD; Leon Fogelfeld, MD; Susan Shott, PhD; Theodore Mazzone, MD

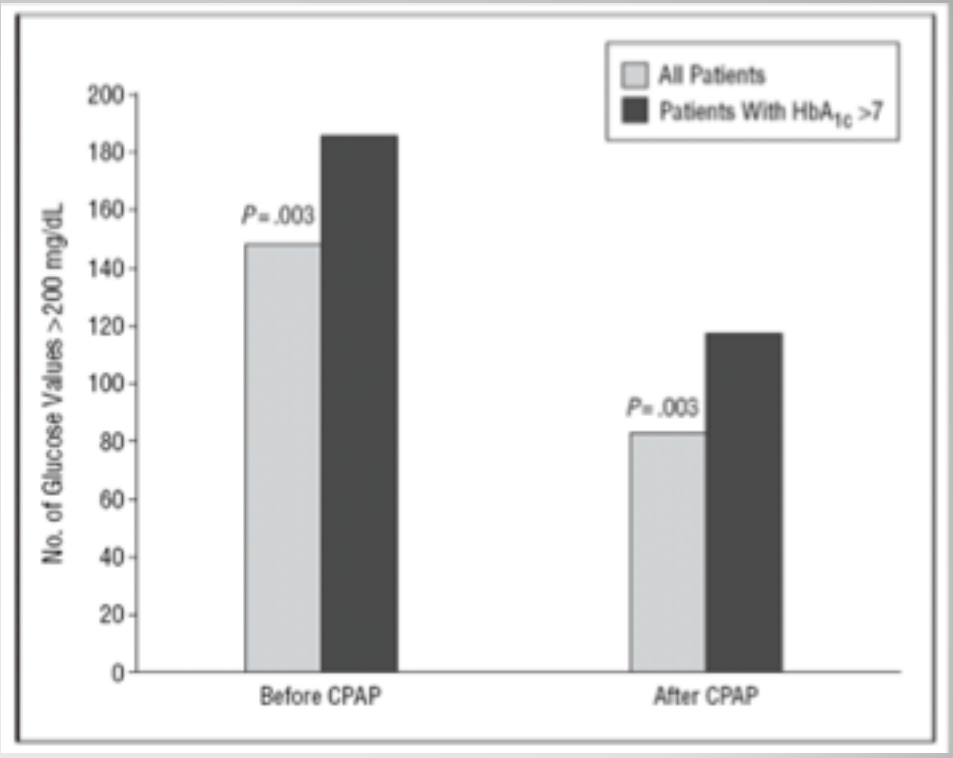
Sujets	intervention	outcome
n=25 - type 2 diabetes - BMI 42.7 ± 8.7 - AHI 56 ± 37	PPC pendant 80 ± 5 days	-72h continuous glucose monitoring - HbA1c



Arch Intern Med 2005;165:447–452

Effet de la PPC sur les glycémies





Babu et al. Arch Intern Med 165: 447–452, 2005

Etude prospective randomisée pour la PPC sur 3 mois chez le DT2 avec SAS

Table 1 Baseline measurements and changes from baseline in subjects randomised to therapeutic and placebo CPAP

	Baseline		Change from baseline (Δ)			
	Therapeutic CPAP (n=20)	Placebo CPAP (n=22)	Therapeutic CPAP (n=19)	Placebo CPAP (n=21)	95% CI between groups	p Value (for Δ)
Age (years)	57.8 (10.4)	54.5 (9.4)				
>4% SaO_2 dips/h	33.1 (21.6)	39.1 (24.8)				
ESS	14.7 (3.5)	13.6 (3.5)	−6.6 (4.5)	−2.6 (4.9)	−7.0 to −0.9	0.01
MWT (Osler) (min)	21.9 (12.8)	32.0 (10.8)	+10.6 (13.9)	−4.7 (11.8)	+6.5 to +23.9	0.001
BMI (kg/m^2)	36.6 (4.9)	36.8 (4.6)	−0.2 (1.0)	−0.2 (1.1)	−0.6 to +0.7	1.0
SAQLI	4.3 (1.1)	4.4 (0.9)	+0.8 (1.0)	+0.03 (1.2)	−1.5 to +0.04	0.04
Neck size (cm)	46.2 (2.6)	47.0 (2.6)	+0.04 (1.2)	−0.06 (1.4)	−0.7 to +0.9	0.8
Waist to hip ratio	1.0 (0.06)	1.1 (0.06)	0 (0.3)	0 (0.4)	−0.03 to +0.02	0.5
Impedance	426.4 (91.3)	404.9 (39.5)	−3.8 (28.4)	+9.3 (31.2)	−32.6 to +6.4	0.2
Fasting glucose (mmol/l)	10.1 (3.6)	10.0 (4.5)	+0.3 (2.1)	−0.2 (2.1)	−0.9 to +1.8	0.5
HbA1c (%)	8.5 (1.8)	8.4 (1.9)	−0.02 (1.5)	+0.1 (0.7)	−0.6 to +0.9	0.7
Fasting plasma insulin (pmol/l)	93.3 (52.2)*	100.0 (71.5)*	+1.3 (1.6)	+1.1 (1.7)	−0.2 to +0.09	0.4
HOMA-%S	47.9 (1.6)*	44.7 (1.7)*	−1.5 (2.3)*	−1.1 (1.8)*	−0.3 to +0.08	0.2
M/I: euglycaemic damp (l/kg/min^{1000})	26.5 (14.4)	27.8 (17.9)	+1.7 (14.1)	−5.7 (14.8)	−1.8 to +0.3	0.2
Adiponectin (μg/ml)	3.7 (2.2)*	2.8 (1.5)*	−1.1 (1.2)*	−1.1 (1.3)*	−0.7 to +0.6	0.2

CPAP, continuous positive airway pressure; SaO_2, oxygen saturation; ESS, Epworth sleepiness score; MWT, Maintenance of Wakefulness test; BMI, body mass index; SAQLI, Sleep Apnea Quality of Life Index; HbA1c, glycosylated haemoglobin; HOMA, homeostatic model assessment; M/I, quantity of glucose metabolised per unit of plasma insulin concentration (a measure of insulin sensitivity).
Data are shown as mean (SD).
*Geometric mean (SD).
There was no significant difference in any of the baseline data between the groups (p=0.3–0.9) except for MWT (p<0.01) and adiponectin (p=0.05).

West SD, Thorax 2007

Le traitement par PPC augmente le HDL- cholestérol

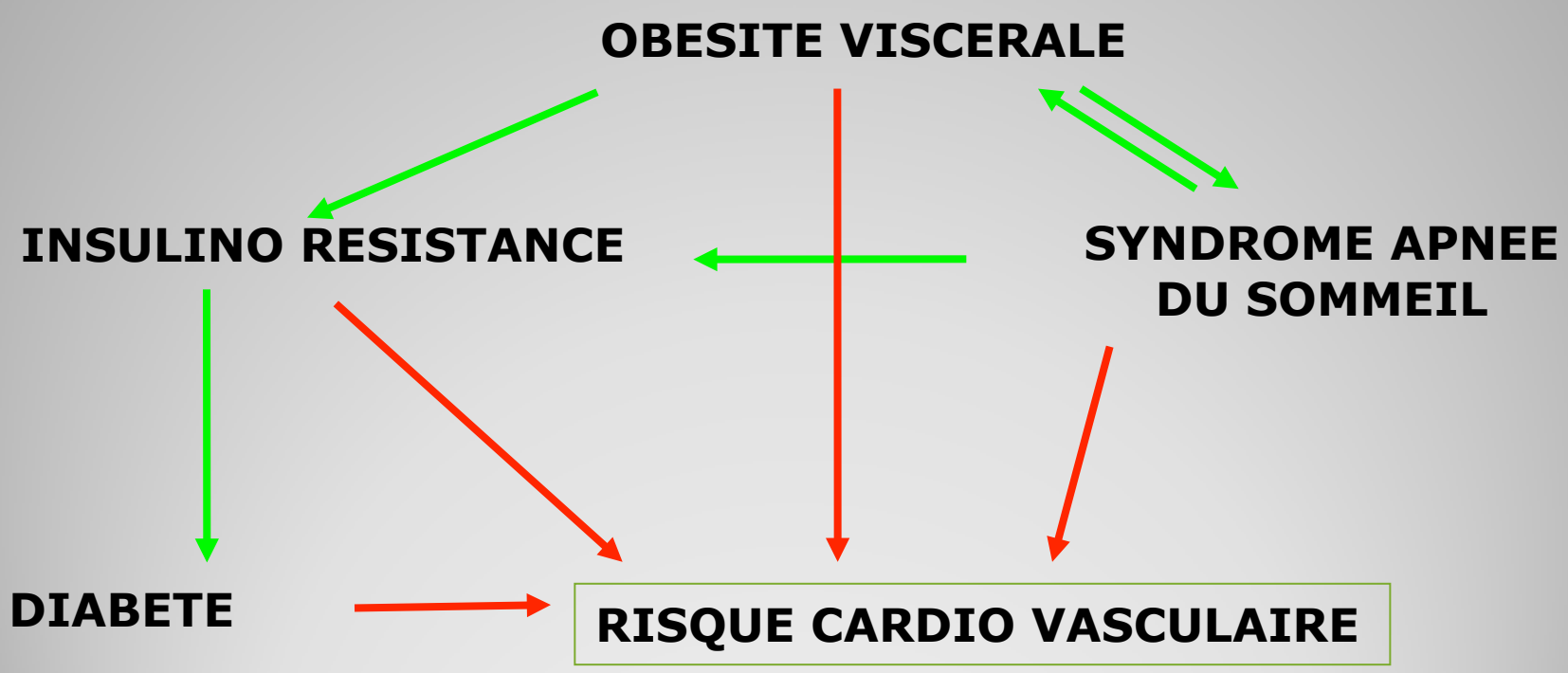
TABLE 3 Effect of Bi-/CPAP therapy on polysomnographic data, lipids and body mass index (BMI) in patients with obstructive sleep apnoea

	Untreated OSA	After 6 months of Bi-/CPAP therapy	Mean difference (95% CI)	p-value
Polysomnography				
AHI events·h^{-1}	32.9±21.5	2.2±2.3	-30.7 (-26.8– -34.6)	<0.001
Mean O_2 saturation	91.4±5.4	93.9±1.9	2.8 (3.5–1.5)	<0.001
Maximum O_2 desaturation	79.8±10.6	88.0±7.1	8.1 (10.5–5.8)	<0.001
Arousal index	19.1±8.0	7.9±6.1	-11.2 (-6.1– -16.3)	<0.001
Sleep efficiency	86.7±11.3	86.3±13.6	-0.4 (2.9– -3.9)	0.784
Lipids				
Total cholesterol	223.5±41.4	220.30±39.4	-3.4 (3.6– -10.0)	0.351
Triglycerides	175.1±102.3	166.2±87.77	-8.6 (6.2– -23.5)	0.116
HDL-C	46.9±15.8	49.6±15.25	2.7 (4.9–0.6)	0.013
LDL-C	144.5±37.8	138.99±37.1	-5.5 (2.0– -13.0)	0.151
BMI	31.6±5.9	31.4±5.4	-0.9 (0.15– -0.6)	0.229

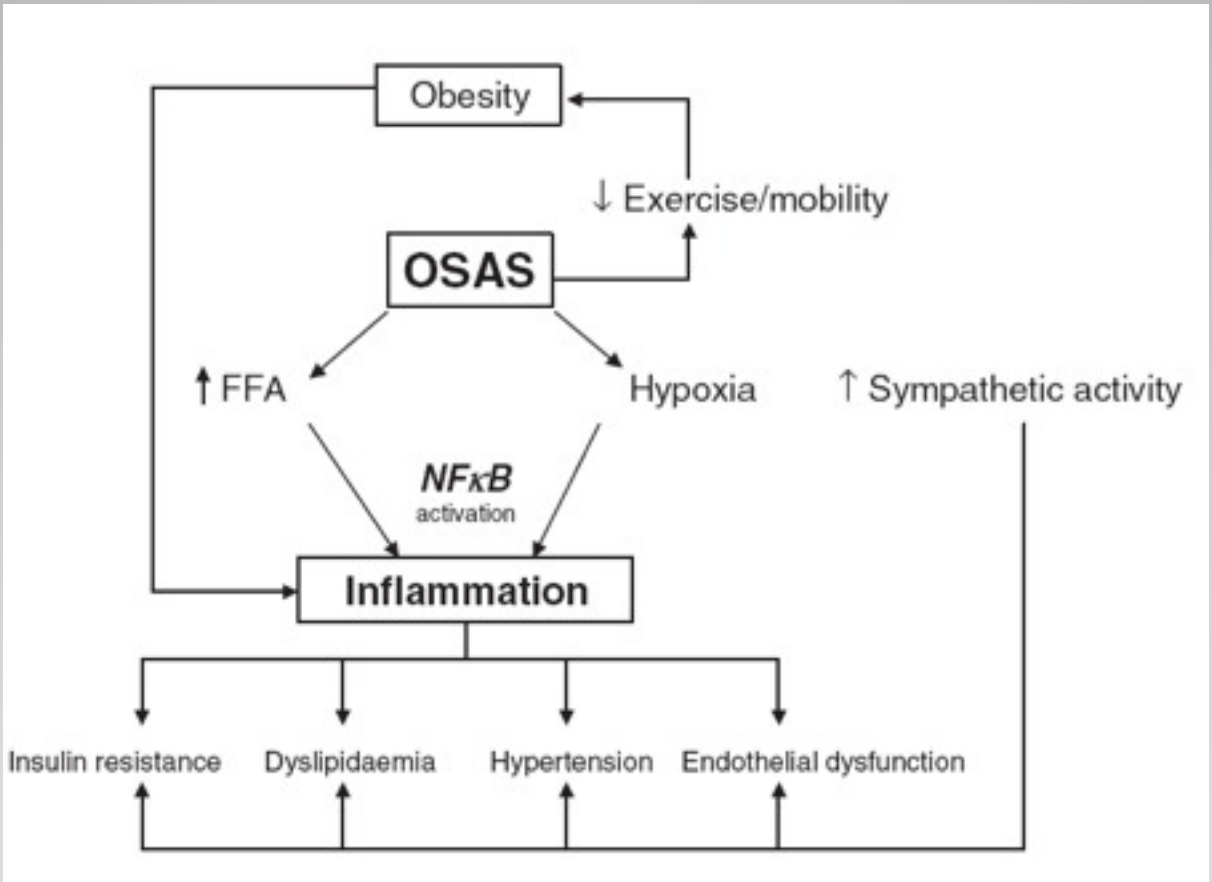
Data are presented as mean±SD unless otherwise stated. Bi-/CPAP: bilevel or continuous positive airway pressure; CI: confidence interval; AHI: apnoea–hypopnoea index; HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol.

Borgel J et a, Eur Respir J, 2006

Relation entre SAS et SM

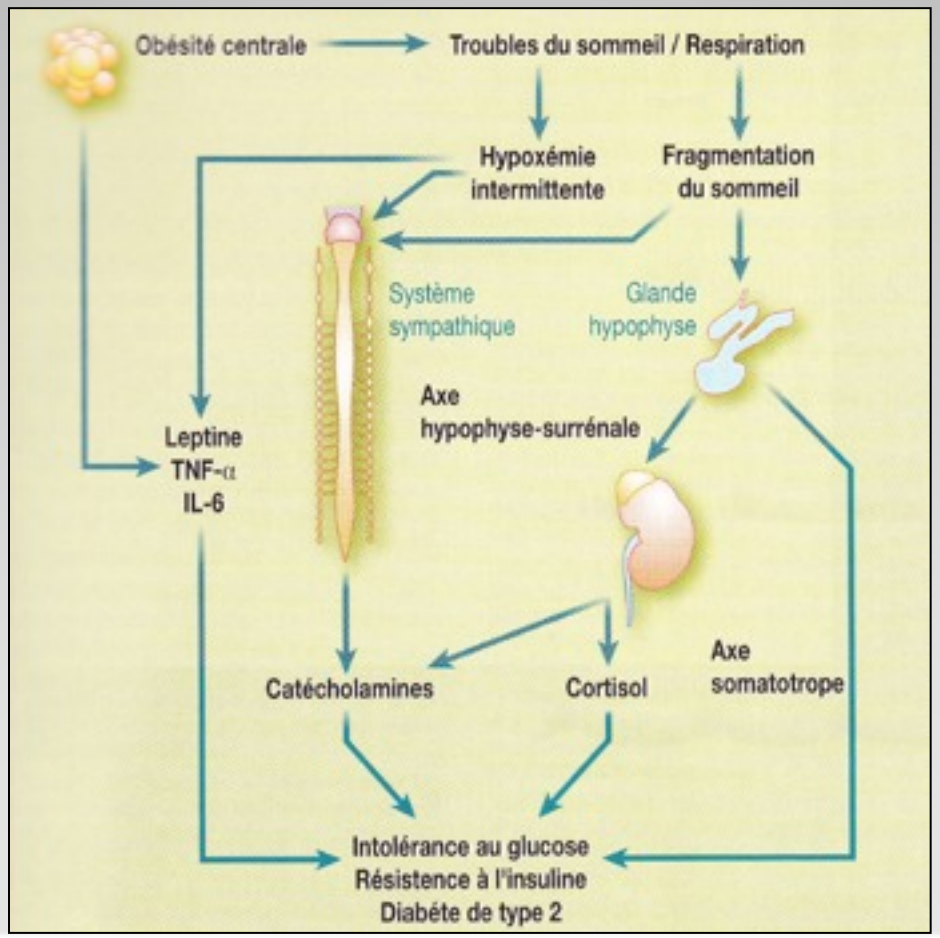


SAS et SM: tous les deux des états pro inflammatoires



Alam I et al, Obesity review, 2006

Mécanisme physiopathologique de l'insulino résistance au cours du SAS

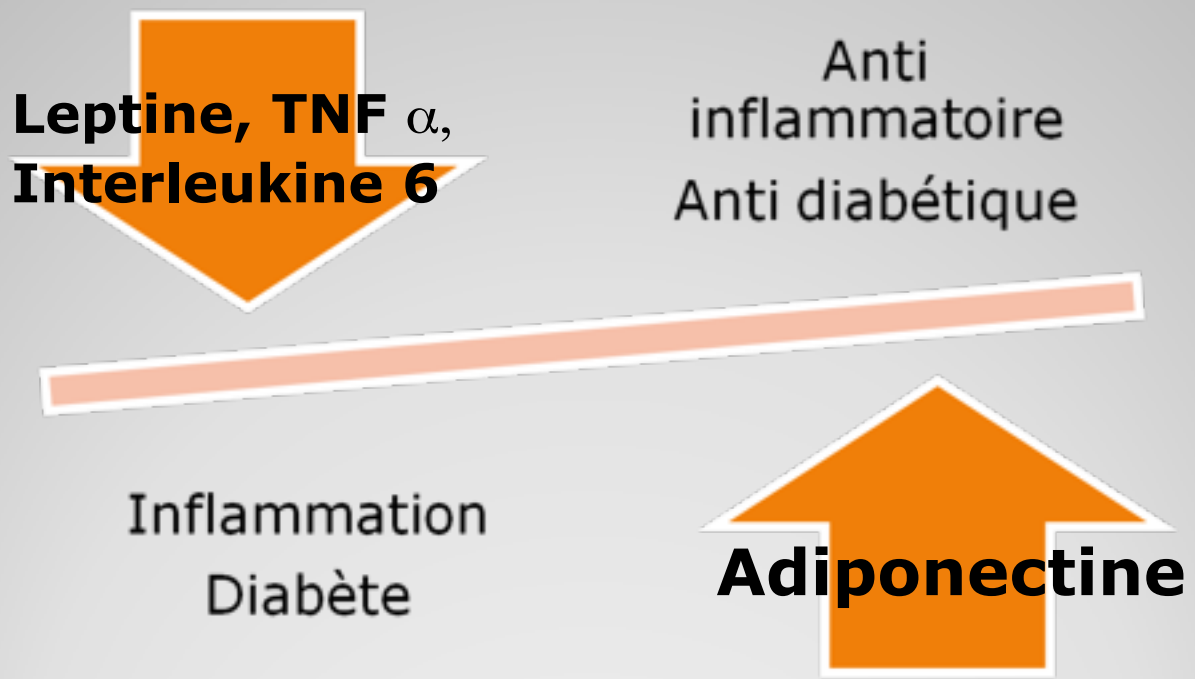


(Punjabi NM et al, J Appl Physiol 2005)

Le tissu adipeux une cible commune au SAS et SM

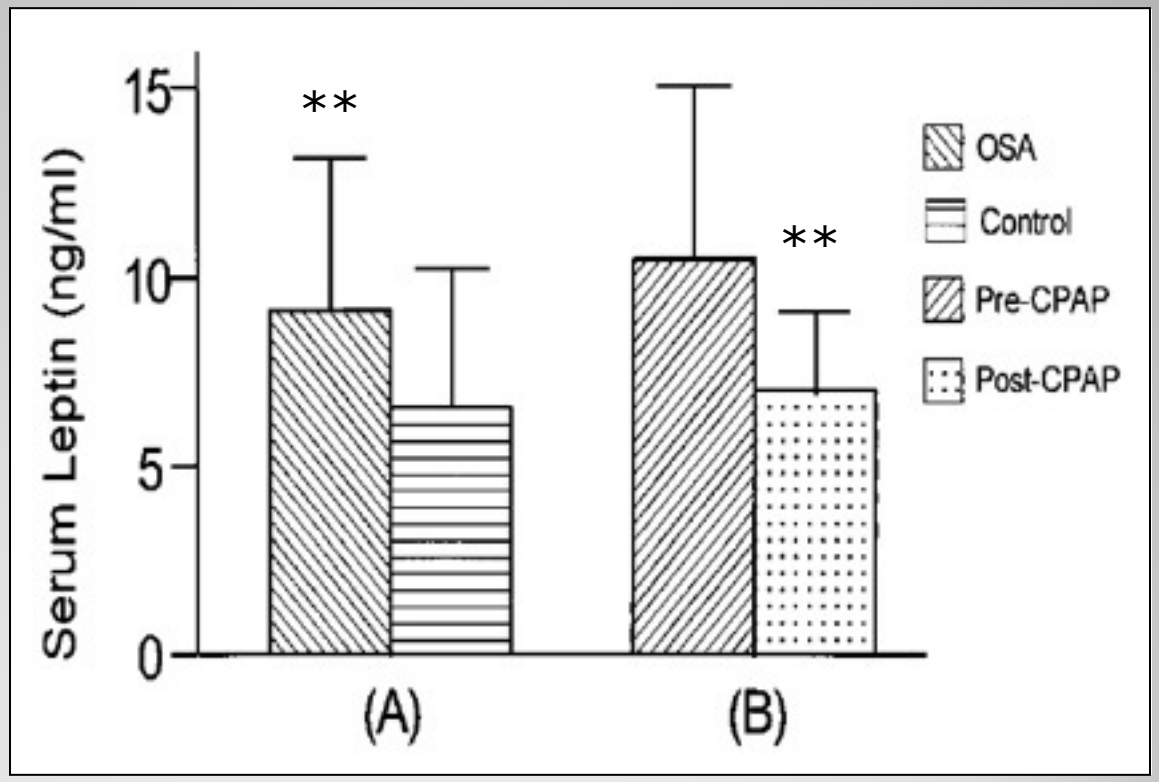
- Rôle endocrine du tissu adipeux
  - Leptine
  - Adiponectine
- Inflammation et stress oxydant du tissu adipeux
- Rôle de l'hypoxie intermittente

Le tissu adipeux: une structure endocrine du contrôle de l'inflammation



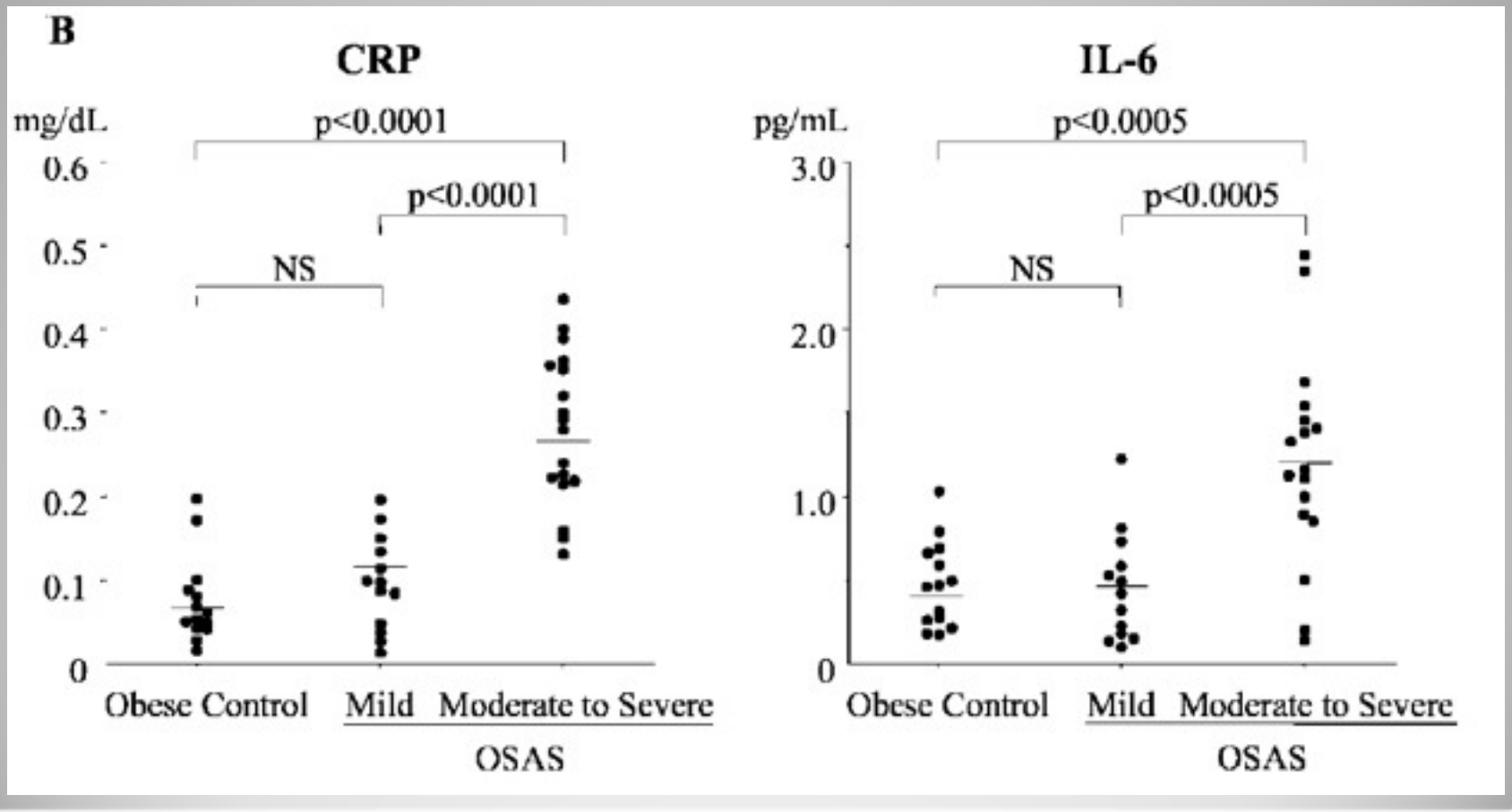
Augmentation de la leptine au cours du SAS influencée par la PPC

- 30 sujets
- IMC=28
- 6 mois de PPC



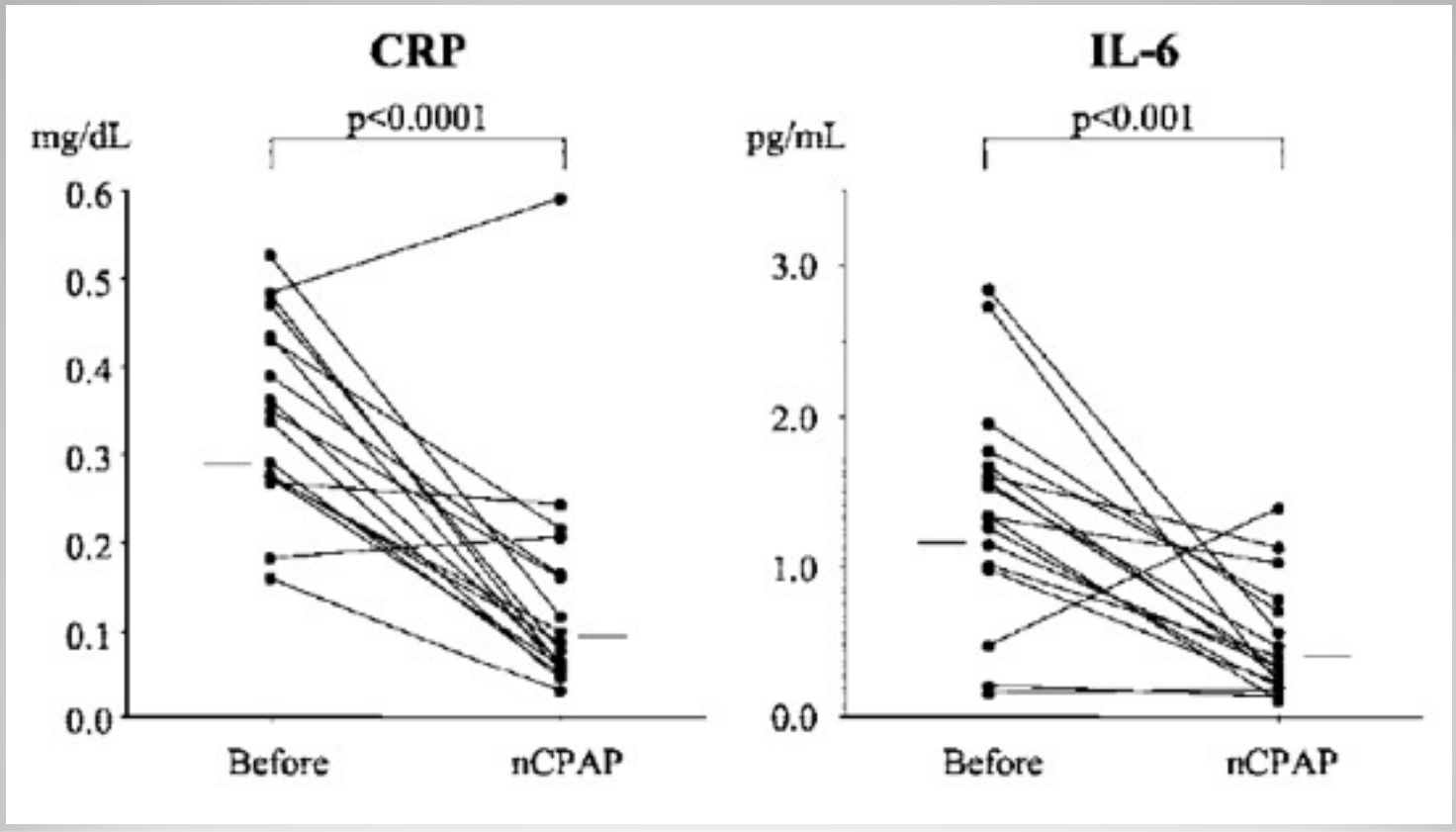
Ip MS et al, Chest, 2000

Augmentation de la CRP et IL-6 au cours du SAS



Yokoe T et al, Circulation, 2003

Diminution de la CRP et IL-6 après 3 mois de PPC



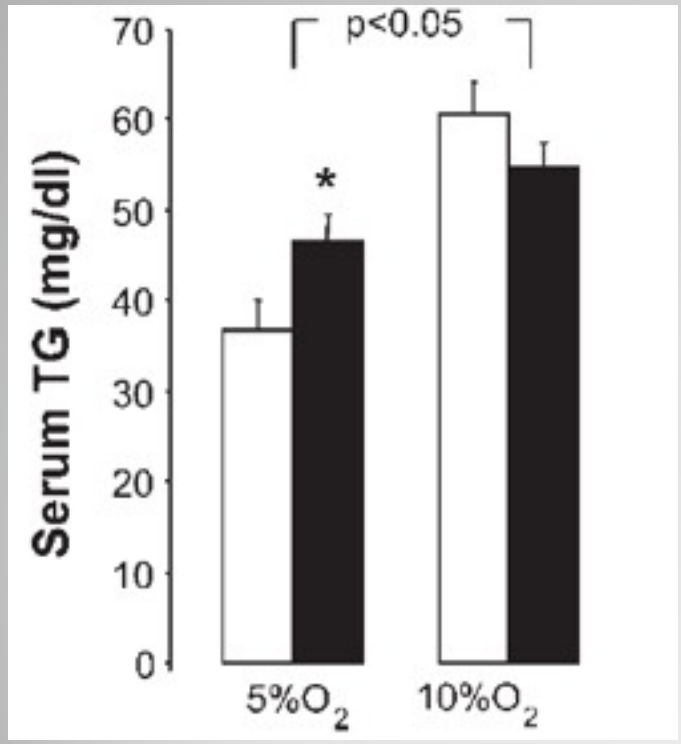
Yokoe T et al, Circulation, 2003

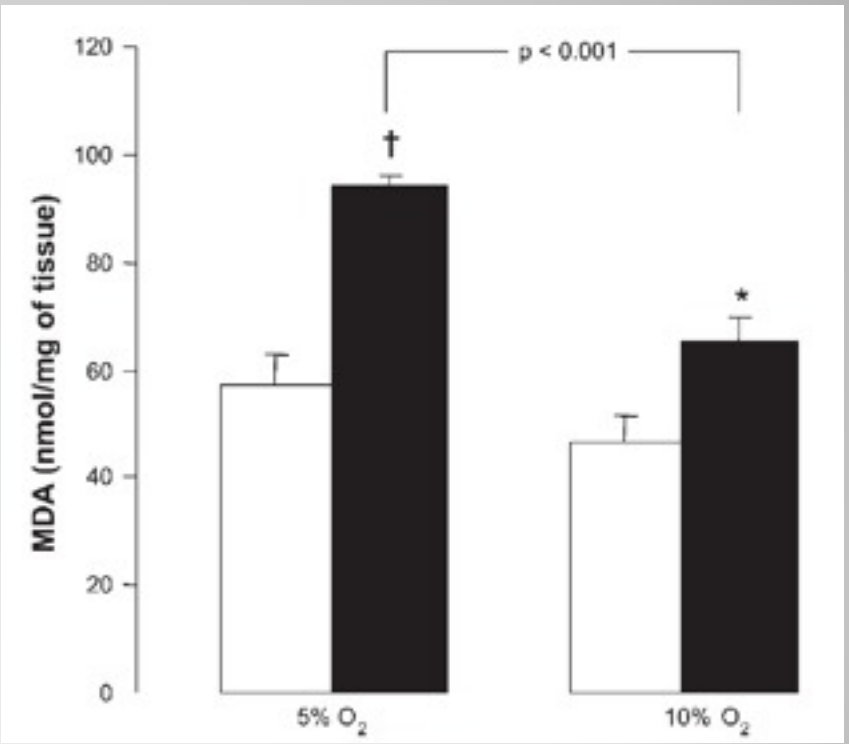
Rôle de l'hypoxie intermittente

	Severe CIH (F_{IO_2} Nadir 5%)	
	IA	CIH
n	8	8
Body weight, g		
Day 0	24.2±0.4	24.2±0.5
Day 7	22.8±0.3‡	22.4±0.3‡
Day 28	24.7±0.5	22.5±0.4*†‡
Food intake, g/day		
Day 7	2.7±0.1	3.3±0.1*†
Day 28	3.6±0.1§	3.9±0.1§
Serum leptin, ng/ml	1.0±0.2	2.5±0.6*
Fasting serum insulin, ng/ml	0.29±0.03	0.27±0.02
Liver cholesterol content, mg/g of tissue	0.89±0.05	0.79±0.07
Liver triglyceride content, mg/g of tissue	6.1±0.3	6.3±0.4
Liver phospholipid content, mg/g of tissue	8.2±0.2	7.2±0.8

Li J et al, A Appl Physiol, 2006

Augmentation des TG et de la peroxydation hépatique des lipides au

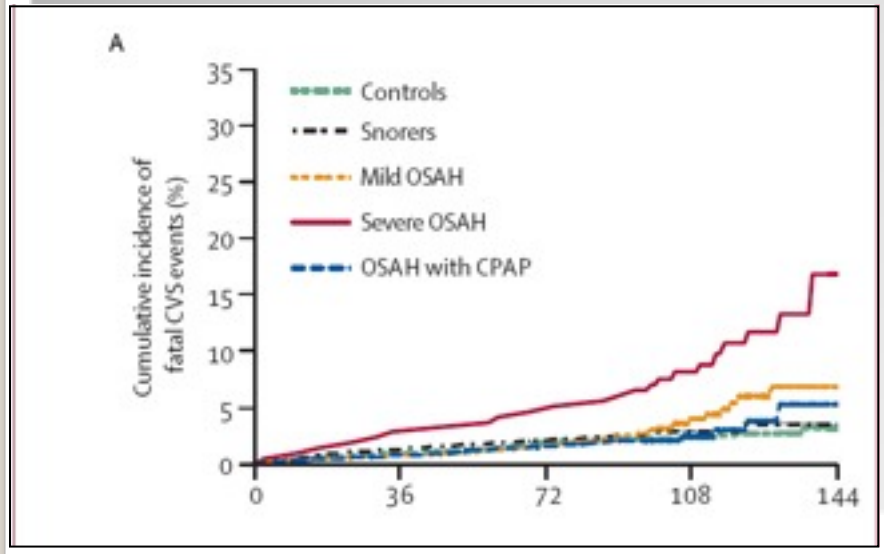


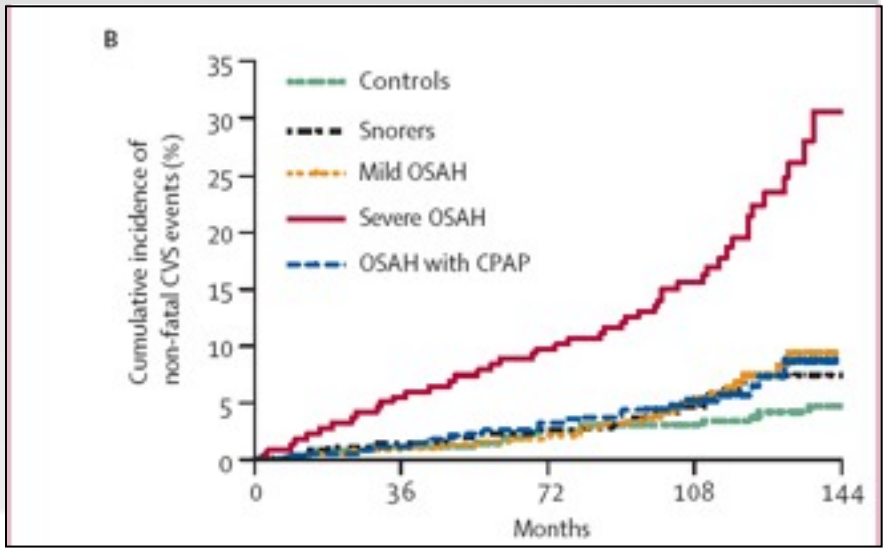


Li J et al, A Appl Physiol, 2006

Le traitement par PPC diminue les accidents CV mortels chez le patient

	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†
Apnoea-hypopnoea index	1·2 (0·3)	3·5 (0·8)	18·2 (3·5)*	43·3 (5·7)*	42·4 (4·9)*





Lancet, Marin J, 2005

En Conclusion

- SAS et Syndrome métabolique sont tous deux des facteurs de risque cardiovasculaire
- Leur effet semble médié par une action pro inflammatoire au niveau du tissu adipeux
- Le traitement par PPC
  - permet de contrôler la TA
  - améliore la survie des patients
  - semble diminuer l'inflammation du tissu adipeux
- L'obésité est le principal facteur confondant expliquant l'effet limité du traitement du SAS sur le métabolisme

En Pratique

- Il convient de rechercher un SAS chez tout patient ayant un syndrome métabolique pour
  - Quantifier son risque cardio vasculaire
  - Mettre en route un traitement par PPC