Aspectes moleculars de la SAHS

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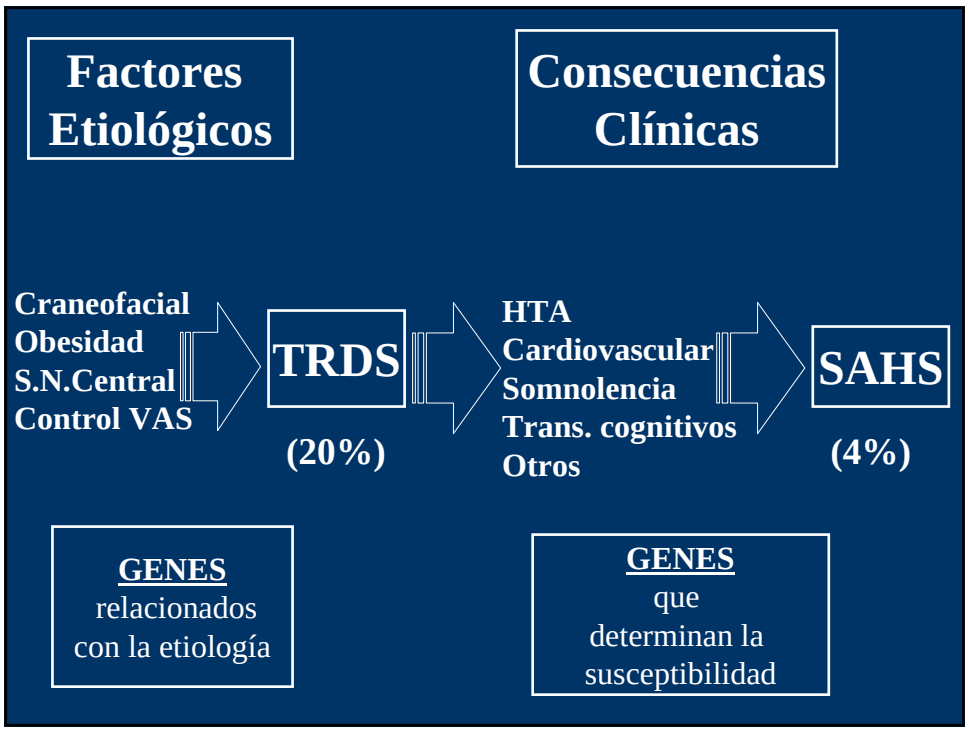
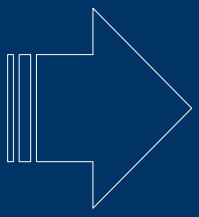


Factores Etiológicos

Craneofacial
Obesidad
S.N.Central
Control VAS



TRDS

(20%)

GENES
relacionados
con la etiología

Genetics in SAHS

Candidate chromosomes:

- **SAHS: 1p, 2p, 12p, 19p**
- **Obesity: 2p, 7p, 12p**

Palmer et al, *Am J Hum Genet* 2003

Genetics in SAHS

Candidate chromosomes in African-American:

- **SAHS: 8q**
- **Obesity: 4q, 8q**

Palmer et al, *AJRCCM* 2004

Consecuencias Clínicas

TRDS

(20%)

HTA
Cardiovascular
Somnolencia
Trans. Cognitivos
Otros

SAHS

(4%)

GENES que determinan la susceptibilidad

Genetics in OSAS

- Positive association
  Apo E ϵ 4. *JAMA* 2001
- No association
  PAI-I (Barceló *Res Med* 2002)
  ACE (Barceló *Eur Resp J* 2001)

OSAHS and CV disease
Potential Mechanisms

- **Metabolic abnormalities (obesity)**
- **Increased sympathetic tone**
- **Oxidative stress**
- **Systemic inflammation**
- **Coagulation abnormalities**
- **Endothelial dysfunction**
- **Genetic background**

Metabolic abnormalities in OSAHS

- **Obesity** is a known cardiovascular risk factor often present in patients with OSAHS
- Patients with OSAHS show metabolic abnormalities:
  - **Insulin resistance**
    - Ip et *al, Am J Respir Crit Care Med* 02; 165:670-6
    - Punjabi *et al, Am J Respir Crit Care Med* 02; 165: 677-82
    - Barceló *et al, Am J Med* 04
  - **Increased plasma leptin levels**
    - Chin *et al, Circulation* 99; 100: 706-12
    - Ip *et al, Chest* 00; 118: 580-6

Increased sympathetic activity in OSAHS

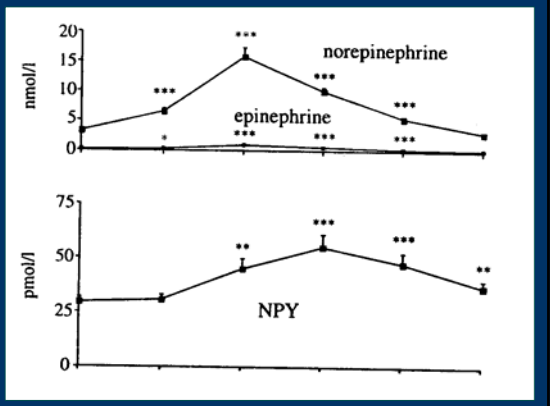
- Fletcher et al, *Sleep* 1987; 10:35-44
- Carlson et al, *Chest* 1993; 103: 1763-8
- Narkiewicz et al, *Circulation* 1999; 100: 2332-5
- Heitmann et al, *Eur Respir J* 2004; 23: 255-62

Increased sympathetic activity in obesity

- Spraul et al, *J Clin Invest* 1993; 92: 1730-5
- Scherrer et al, *Circulation* 1994; 89: 2634-40
- Grassi et al, *Hypertension* 1995; 25: 560-3
- Alvarez et al, *Circulation* 2002; 106: 2533-6

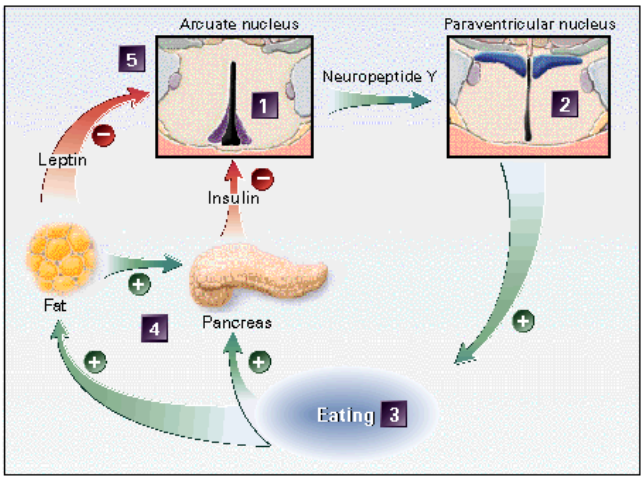
SYMPATHETIC ACTIVITY MARKERS

- NOREPINEPHRINE
- NEUROPEPTIDE Y



Gullestad et al, Circulation 2000

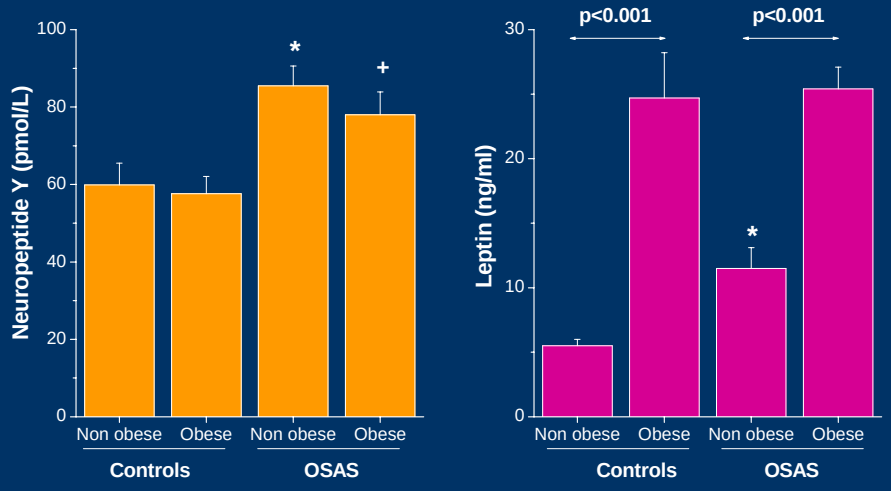
NEUROPEPTIDE Y



Schwartz and Seeley, N Engl J Med, 97; 336(25)

Neuropeptide Y and Leptin in Patients with OSAHS: Role of Obesity

Barcelo A *et al. AJRCCM* 2005; 171: 183-7



Neuropeptide Y and Leptin in Patients with OSAHS: Role of Obesity

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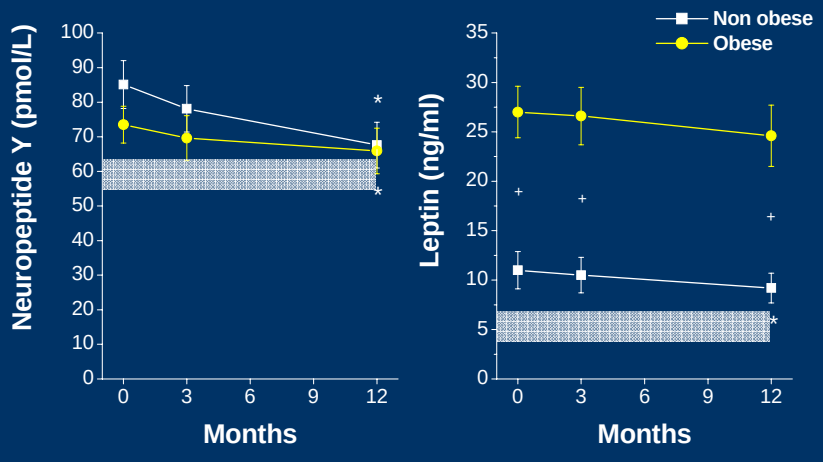
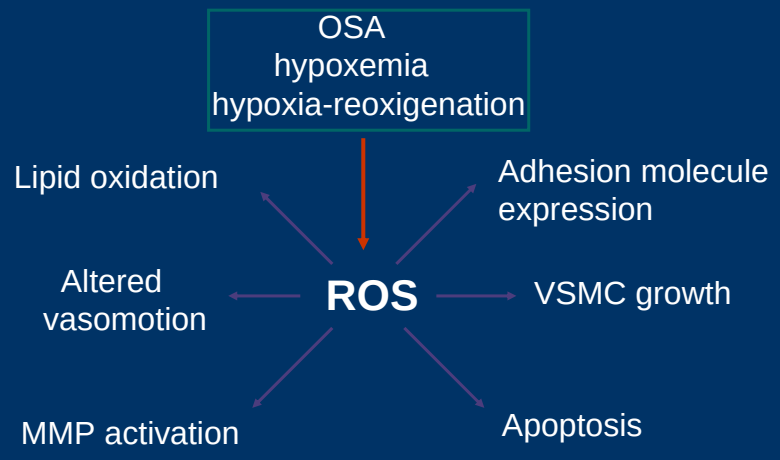


Oxidative stress and cardiovascular risk



Harrison et al; Am J Cardiol 03, 91: 7A-11A

Role of oxidative modifications in atherosclerosis.

Stocker R, Keaney JF Jr.

Physiol Rev. 2004 Oct;84(4):1381-478.

1112. **Zou MH, Shi C, and Cohen RA.** Oxidation of the zinc-thiolatecomplex and uncoupling of endothelial nitric oxide synthase byperoxynitrite. *J Clin Invest* 109: 817–826, 2002.

Oxidative stress and OSA

- **Direct markers:**

  -Increased ROS production
  -Increased plasma lipid peroxidation

- **Indirect markers:**

  - Activation of redox sensitive gene expression: VEGF, endothelin
  - Reduced NO availability
  - Hyperhomocysteinaemia
  - Reduced levels of antioxidants

Oxidative stress in OSAHS

- **Increased ROS production**

  Schultz *et al. AJRCCM* 00; 162: 566-70

  Dyugovskaya *et al. AJRCCM* 02; 165: 934-9

- **Lipoprotein oxidation**

  Saarelainen *et al. Clin Chem Lab Med* 99; 37:517-20

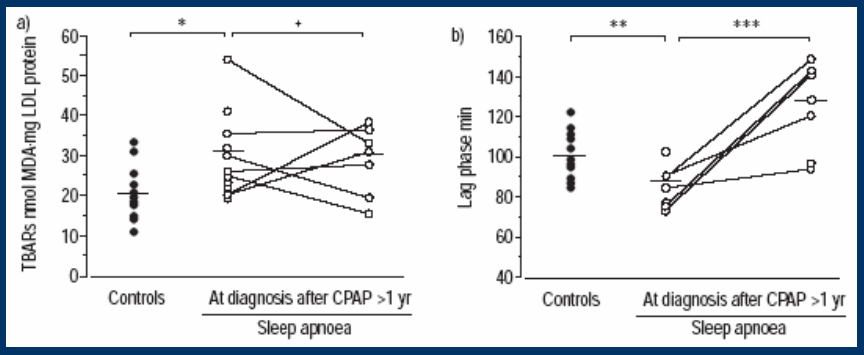
  Barceló *et al. Eur Respir J* 00; 16: 644-47

- **Plasma homocistein levels**

  Lavie *et al. Chest* 01; 120: 900-908

Abnormal lipid peroxidation in patients with OSAHS

Barceló A *et al. Eur Respir J.* 2000; 16: 644-7



Antioxidant status in patients with sleep apnoea and impact of continuous positive airway pressure treatment.

A. Barceló, F. Barbé, M. de la Peña, M. Vila, G. Pérez, J. Piérola, J. Duran and A.G.N. Agustí´

Eur Respir J 2006; 27: 756–760

TABLE 1 Clinical characteristics of patients and healthy subjects

	Controls	OSAS
Subjects n	37	47
Age yrs	46±9	48±9
BMI kg·m^{-2}	29.6±5.0	30.2±5.2
SBP mmHg	128±12	132±16
DBP mmHg	77±8	85±10***
Current smokers %	0	19 (40)***
Hypertension %	0	15 (31)***
AHI events·h^{-1}	2±1	49±16***
Mean sat O_2 %	93±1.6	92±2.7
Epworth scale	3±1	13±6***

Data are presented as mean±SD, n or n (%). OSAS: obstructive sleep apnoea syndrome; BMI: body mass index; SBP: systolic blood pressure; DBP: diastolic blood pressure; AHI: apnoea–hypopnoea index. ***: p<0.001 *versus* healthy controls.

OXIDATIVE STRESS

	Controls (n=37)	OSA (n=47)
TAS (mmol/L)	1.50±0.02	1.40±0.02*
GPX (U/L)	798±19	844±19
GGT (U/L)	32±2.9	42±3.3*
Vit A (ug/dL)	74±3	64±3*
Vit E (ug/dL)	1774±85	1525±73*
Folic ac (ng/mL)	9.5±0.6	10.1±0.5
Vit B12 (pg/mL)	474±51	501±81
Hcy (nmol/L)	11.8±1	10.8±0.6

TABLE 4 Effects of continuous positive airway pressure (CPAP) treatment

	OSAS patients	
	Pre-CPAP	Post-CPAP
HDLc mg·dL^{-1}	44±9	49±9***
TAS mmol·L^{-1}	1.39±0.10	1.50±0.13***
GGT U·L^{-1}	36±15	30±14*
Vitamin A μg·dL^{-1}	64±20	67±20
Vitamin E μg·dL^{-1}	1538±529	1549±397

Data are presented as mean±SD. HDLc: high-density lipoprotein cholesterol; TAS: total antioxidant status; GGT: γ-glutamyltransferase. n=27; *: $p<0.05$; ***: $p<0.001$ *versus* pre-CPAP.

European Heart Journal (2005) **26**, 2435–2439
doi:10.1093/eurheartj/ehi440

Clinical research

Oxidative stress in obstructive sleep apnoea

Anna Svatikova, Robert Wolk, Lilach O. Lerman, Luis A. Juncos, Eddie L. Greene, Joseph P. McConnell, and Virend K. Somers*

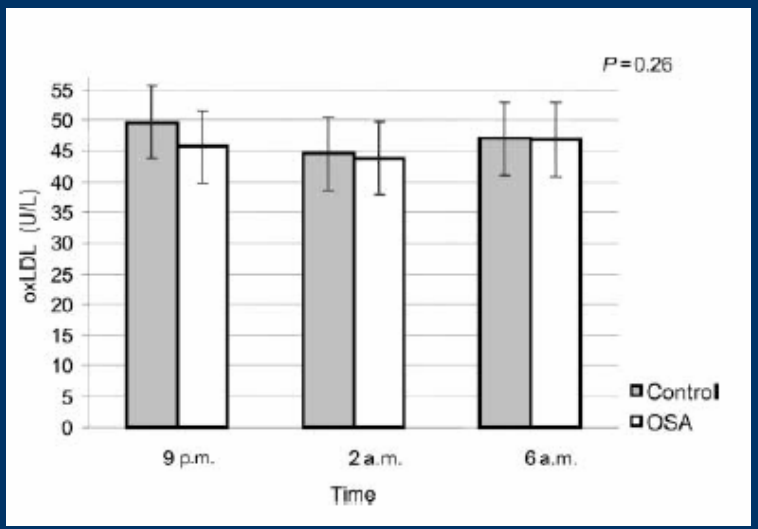
Mayo Clinic College of Medicine, Rochester, MN 55905, USA

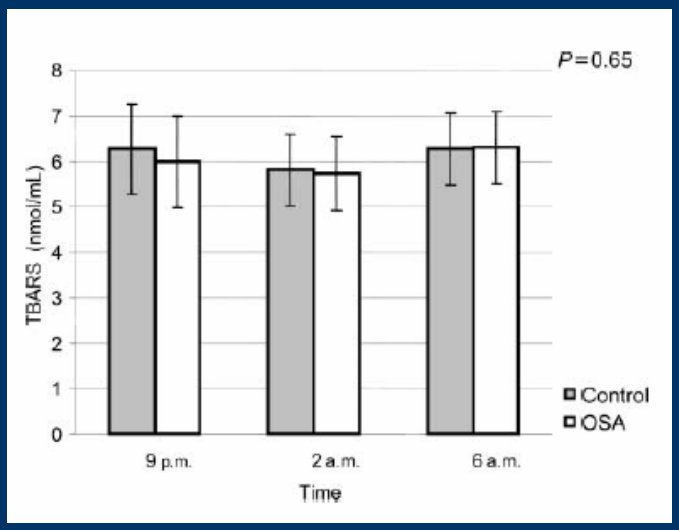
Received 29 March 2005; revised 16 June 2005; accepted 7 July 2005; online publish-ahead-of-print 16 August 2005

Table 1 Baseline characteristics of OSA patients and controls

	Moderate-severe OSA patients ($n = 41$)	Controls ($n = 35$)	P-value
Demographics			
Age (years)	47 ± 2	47 ± 2	0.96
BMI (kg/m^2)	33 ± 1	31 ± 1	0.06
Systolic BP (mmHg)	132 ± 2	133 ± 2	0.66
Diastolic BP (mmHg)	79 ± 2	79 ± 2	0.94
Heart rate (b.p.m.)	74 ± 2	70 ± 2	0.13
Biochemical measurements			
HDL (mg/dL)	40 ± 2	42 ± 2	0.56
LDL (mg/dL)	111 ± 8	114 ± 8	0.77
Triglycerides (mg/dL)	225 ± 40	258 ± 40	0.62
Creatinine (mg/dL)	1.2 ± 0.1	1.0 ± 0.05	0.08
Glucose (mg/dL)	99 ± 3	102 ± 3	0.41
Diagnostic sleep study			
AHI (events/h)	47 ± 3	4 ± 3	<0.0001
Arousal index (events/h)	51 ± 4	22 ± 4	<0.0001

Values are mean ± SEM.

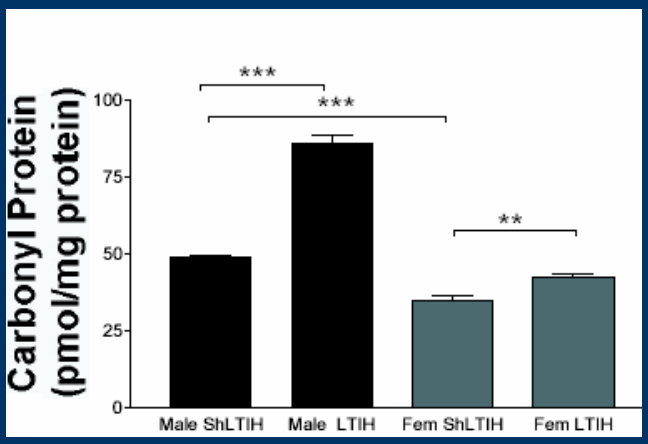




Sex Differences in Susceptibility to Oxidative Injury and Sleepiness From Intermittent Hypoxia

Benjamin Sanfilippo-Cohn1; Saien Lai1; Guanxia Zhan MD1; Polina Fenik MS1; Domenico Pratico PhD2; Emilio Mazza MD, PhD1; Sigrid C Veasey, MD.

SLEEP 2006;29(2): 152-159.



Sanfilippo-Cohn *Sleep* 2006;29:152

Somnolencia diurna y polisomnografia

	EDS n = 24	No EDS n = 21	p value
TST (min)	401 ± 41	379 ± 61	ns
Sleep latency (min)	11 ± 16	18 ± 16	0.03
Sleep efficiency (%)	90 ± 7	83 ± 12	0.03
Awake (min)	37 ± 29	63 ± 51	0.04
Arousal index	64±21	60±23	ns
Respiratory arousals	58 ± 20	53 ±23	ns
Phase 1 + 2 (%)	80±13	75±12	ns
Phase 3 + 4 (%)	7±9	9±6	ns
REM (%)	13 ± 6	15 ± 7	ns
Min Sat (%)	69 ± 12	78 ± 10	0.007
Mean Sat (%)	86 ± 6	90 ± 5	0.03

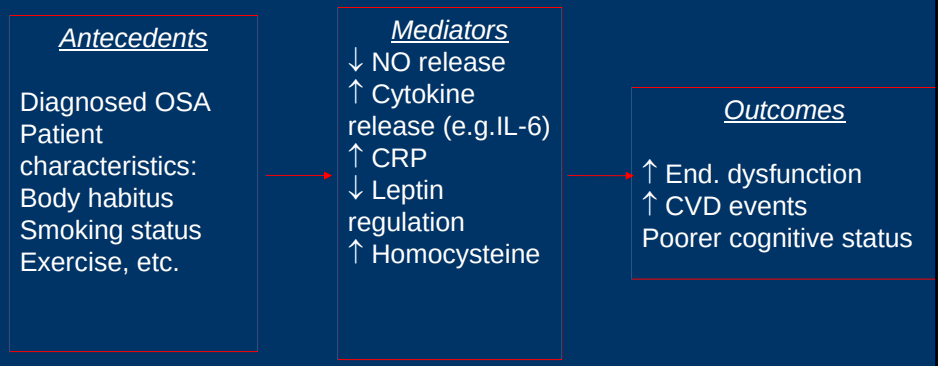
O Mediano ERJ 2007

Oxidative stress and OSA

- **Abnormal lipid peroxidation**
- **Reduced antioxidant defenses**
- **CPAP treatment: benefit on oxidative state**
- **Effects of antioxidants on cardiovascular morbidity. Sex may be important.**

Hypothetical model of OSA pathophysiology.

Carol M. Baldwin, SMR 2005



Hypothetical model of OSA pathophysiology.

Carol M. Baldwin, SMR 2005

Antecedents

Diagnosed OSA
Patient characteristics:
Body habitus
Smoking status
Exercise, etc.

Mediators

↓ NO release
↑ Cytokine release (e.g.IL-6)
↑ CRP
↓ Leptin regulation
↑ Homocysteine

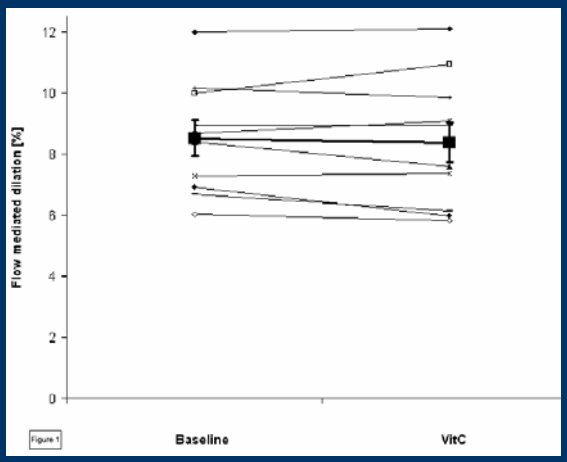
Outcomes

↑ End. dysfunction
↑ CVD events
Poorer cognitive status

Moderators

Antioxidant nutrient (↑ fruit or vegetable) and/or supplement intake (e.g., folate, B12, B6, C, and E)

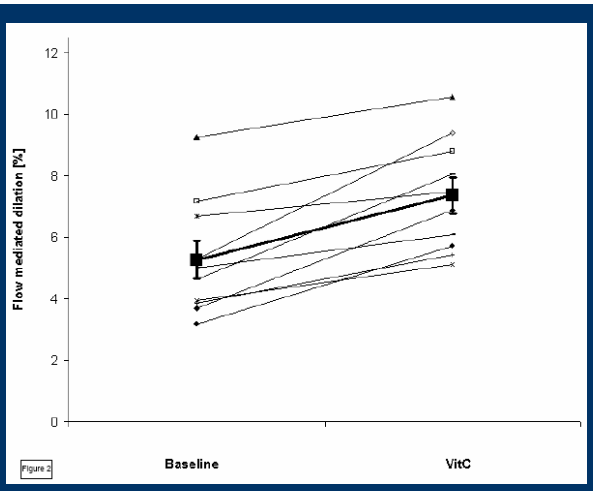
Antioxidant vitamin C improves endothelial function in obstructive sleep apnea



Controls

AJRCCM Articles in Press. Published on January 26, 2006

Antioxidant vitamin C improves endothelial function in obstructive sleep apnea



Patients

AJRCCM Articles in Press. Published on January 26, 2006

C-reactive protein and OSAHS

- **Positive association**

  Shamsuzzaman et al. *Circulation* 2002; 105: 2462-4
  Yokoe et al. *Circulation* 2003; 107: 1129-34

- **No association**

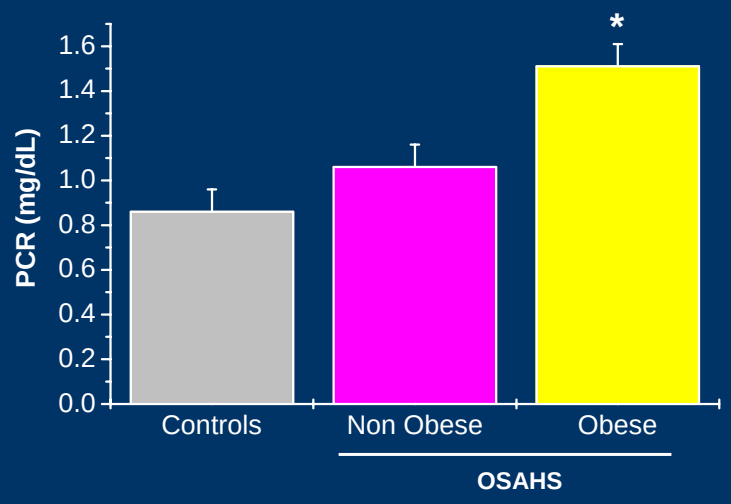
  Chin K et al. *Am J Med* 2000; 109: 562-7

C-reactive protein and obesity

- Visser et al. *JAMA* 1999; 282: 2131-5
- Frölich et al. *Diabetes Care* 2000; 3: 1835-9
- Escobar et al. *Diabetologia* 2003; 46: 625-33
- Aronson et al. *Int J Obes Relat Metab* 2004; 28: 674

Effects of obesity on C-reactive protein level and metabolic disturbances in male patients with OSAHS

Barcelo A *et al. Am.J Med* 2004; 117: 118-21



Coagulation abnormalities in OSAHS

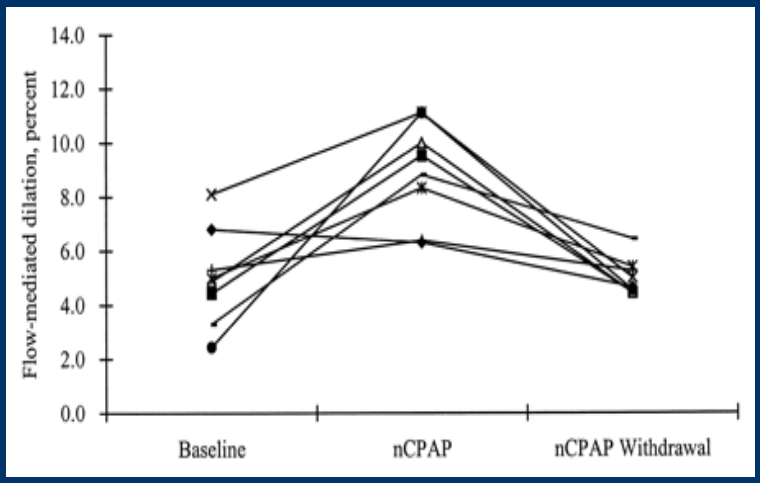
- **Increased Platelet Aggregation**
  - Bokinsky *et al. Chest* 95; 108: 625-30
  - Eisensehr *et al. Neurology* 98; 51: 188-95
  - Sanner *et al. Eur Respir J* 00; 16: 648-52
  - Geiser *et al. Respiration* 02; 69: 229-34
- **Increased Fibrinogen & Factor Vii Levels**
  - Chin K *et al. AJRCCM* 96; 153: 1972-76
  - Wessendorf T *et al. AJRCCM* 00;162: 2039-42
  - Chin K *et al. QJM* 98; 91(9): 627-33
- **Abnormal Fibrinolysis**
  - Rangermak *et al. Sleep* 95; 18:188-94
  - von Kanel *et al. J Hypertension* 01; 19:1445-51

Endothelial dysfunction in OSAHS

- **Nitric Oxide**
  - Ip et al. Am J Respir Crit Care Med 2000; 162: 2166-71
  - Schulz et al. Thorax 2000; 55: 1046-51
  - Lavie et al. J Mol Neurosci 2003; 21: 57-64
- **Endothelin-1**
  - Saarelainen et al. Endothelium 1997; 5: 115-8
  - Phillips et al. J Hypertens 1999; 17: 61-6

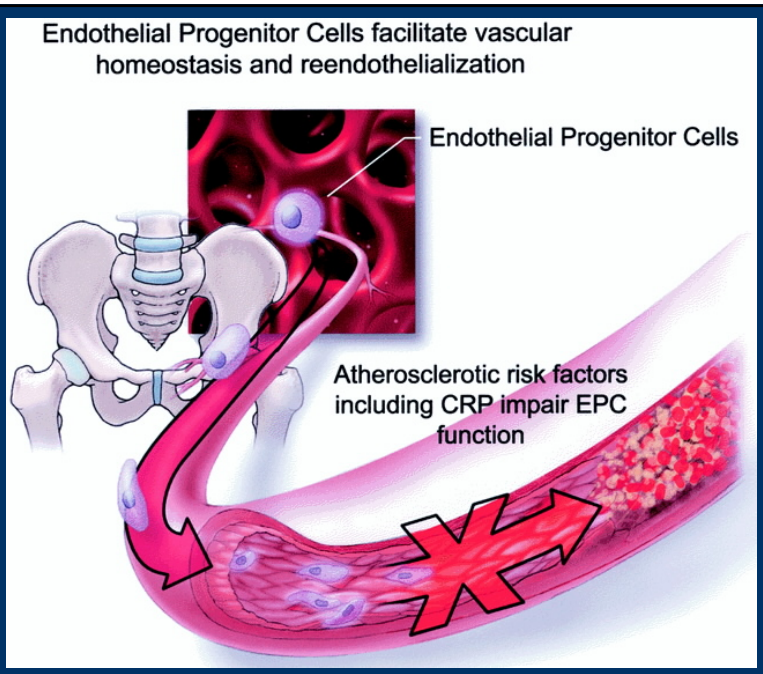
Endothelial function in OSAHS and response to treatment

Ip MS *et al. AJRCCM* 2004; 169: 348-53



Increased circulating levels of VEGF in OSAHS

- Imagawa *et al*. *Blood* 2001; 98: 1255-7
- Schulz *et al*. *AJRCCM* 2002; 165: 67-70
- Gozal *et al*. *Sleep* 2002; 25: 59-65
- Lavie *et al*. *AJRCCM* 2002; 165: 1624-8
- Teramoto *et al*. *Intern Med* 2003; 42: 681-5



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

Obstructive sleep apnoea: time for a radical change?

C.L. Phillips, and R.R. Grunstein. Eur Respir J 2006

… it is probably simplistic to link intermittent hypoxaemia in obstructive sleep apnoea to cardiovascular endpoints as a direct cause–effect relationship.

Certain obstructive sleep apnoea patients may will be more susceptible to cardiovascular disease, and methods for the detection of these patients need to be developed.

Obstructive sleep apnoea: time for a radical change?

C.L. Phillips, and R.R. Grunstein. Eur Respir J 2006

Large intervention studies will be required that are beyond the resources of one centre and will require multinational initiatives.

Such studies may include factorial designs with continuous positive airway pressure, sham continuous positive airway pressure and, indeed, dietary antioxidant supplementation, and collect data on genetic factors.

Obstructive sleep apnoea: time for a radical change?

C.L. Phillips, and R.R. Grunstein. Eur Respir J 2006

.... it is probably time for the sleep apnoea field to move away from small mechanistic studies and make the radical change to implement such a research programme.

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