Institut Català de la Salut
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IRB Lleida
Institut de Recerca Biomèdica

ciberes
Centro de Investigación Biomédica en Red
Enfermedades Respiratorias

Síndrome de apneas del sueño y riesgo cardiovascular

Ferran Barbé

Institut de Recerca Biomedica. IRBLleida

CIBERES. Instituto de Salud Carlos III. Madrid.

Definición SAHS

- Cuadro de somnolencia excesiva, trastornos cognitivo-conductuales, respiratorios, cardíacos, metabólicos o inflamatorios secundarios a episodios repetidos de obstrucción de la VAS durante el sueño.

GRUPO ESPAÑOL DE SUEÑO (GES) 2005

Definiciones

- **APNEA: Ausencia de flujo superior a 10 segundos**
- **HYPOPNEA: Reduccion de flujo que induce desaturacion o *arousal***
- **AHI: Nº de apneas + nº hipopneas por hora**

Factores de riesgo

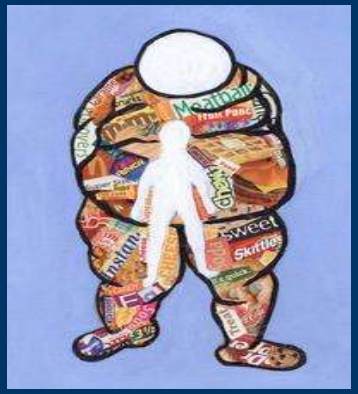
EDAD Y SEXO

OBESIDAD

FACTORES GENÉTICOS

MALFORMACIONES FACIALES

ALGUNAS ENFERMEDADES



Factores agravantes

IRRITANTES (Alcohol, tabaco)

DEPRESORES RESPIRATORIOS

POSICIÓN AL DORMIR (Decúbito-supino)

Prevalence

Workers 30-60 yr (Young et al. NEJM 1993)

	Men (n=1670)		Women (n=1843)	
AHI	%	(CI 95%)	%	(CI 95%)
≥ 5	24.0	(19-28)	9.0	(6-12)
≥ 10	15.0	(12-19)	5.0	(2-8)
≥ 15	9.1	(6-11)	4.0	(1-7)
SAHS	4.0	-	2.0	-

Sintomas asociados

- Ronquido
- Somnolencia diurna excesiva
- Apneas presenciadas

Menos frecuentes

- Nocturnos (nicturia, asfixia..)
- Diurnos (cefalea, irritabilidad…)


¡¡GRRROUMM!!

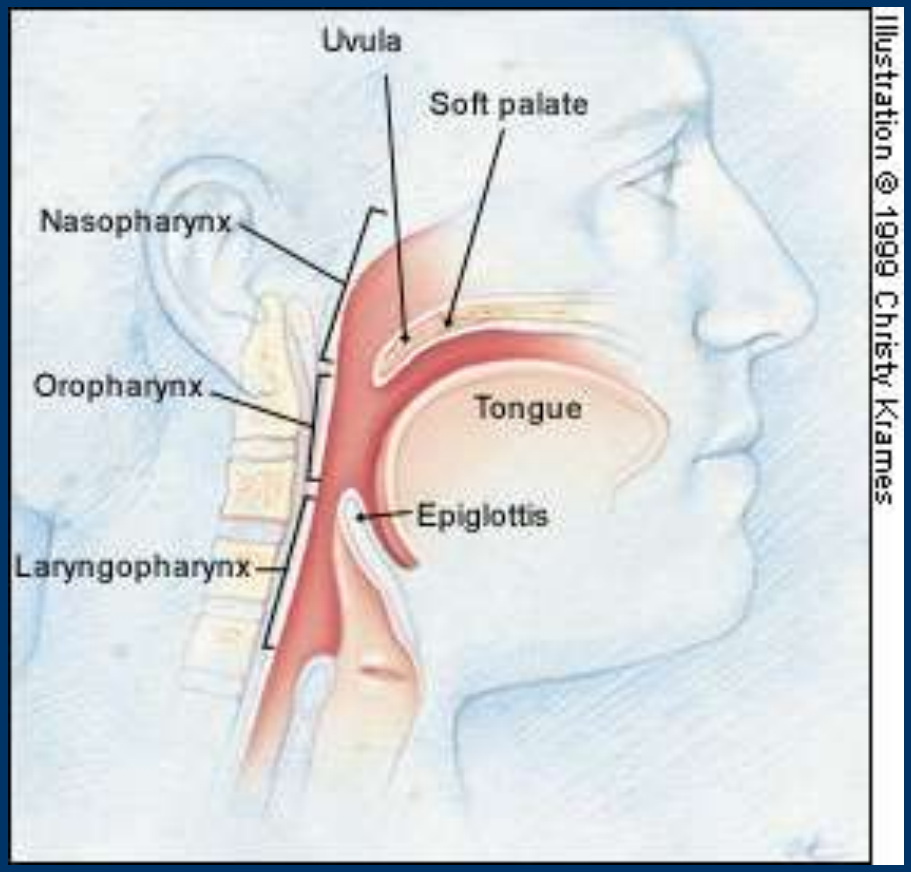
Evaluacion somnolencia diurna

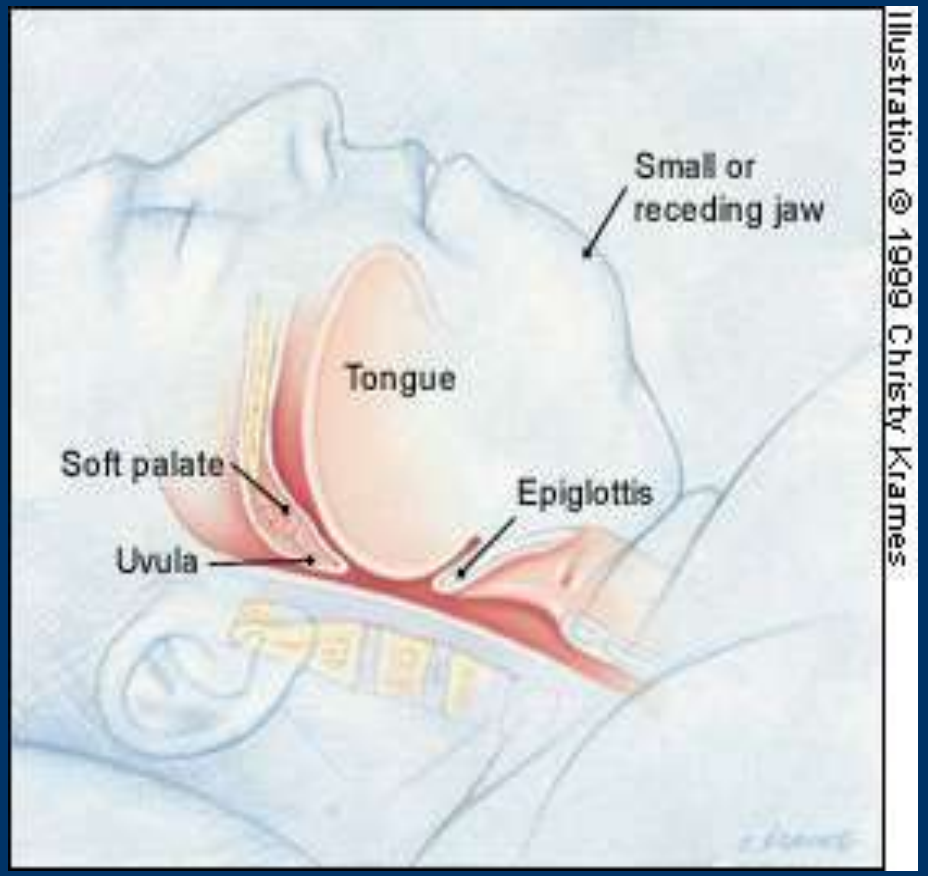
TEST DE EPWORTH

1. SENTADO LEYENDO …..
2. VIENDO LA TELEVISIÓN …..
3. SENTADO INACTIVO EN UN LUGAR PÚBLICO (cine, reunión) …….
4. COMO PASAJERO EN UN COCHE DURANTE 1 HORA …..
5. DESCANSANDO ECHADO POR LA TARDE …..
6. SENTADO CHARLANDO …..
7. SENTADO DESPUÉS DE COMER …..
8. EN EL COCHE AL PARARSE UNOS MINUTOS POR EL TRÁFICO ….

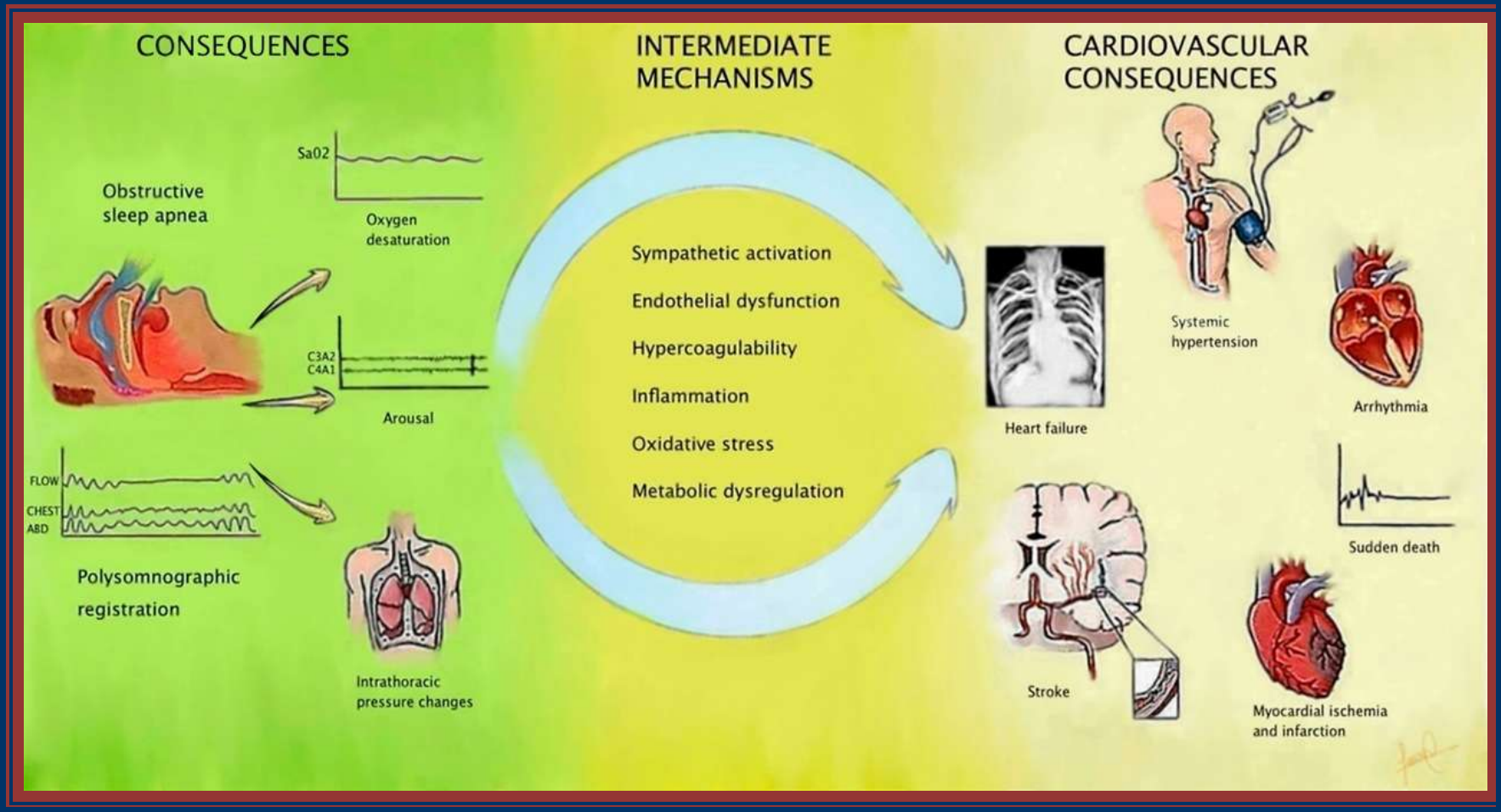
EPWORTH>10 ES PATOLÓGICO Y >12 CLARAMENTE PATOLÓGICO


YONKIS.COM
Adena por la conservacion de la fauna ibérica

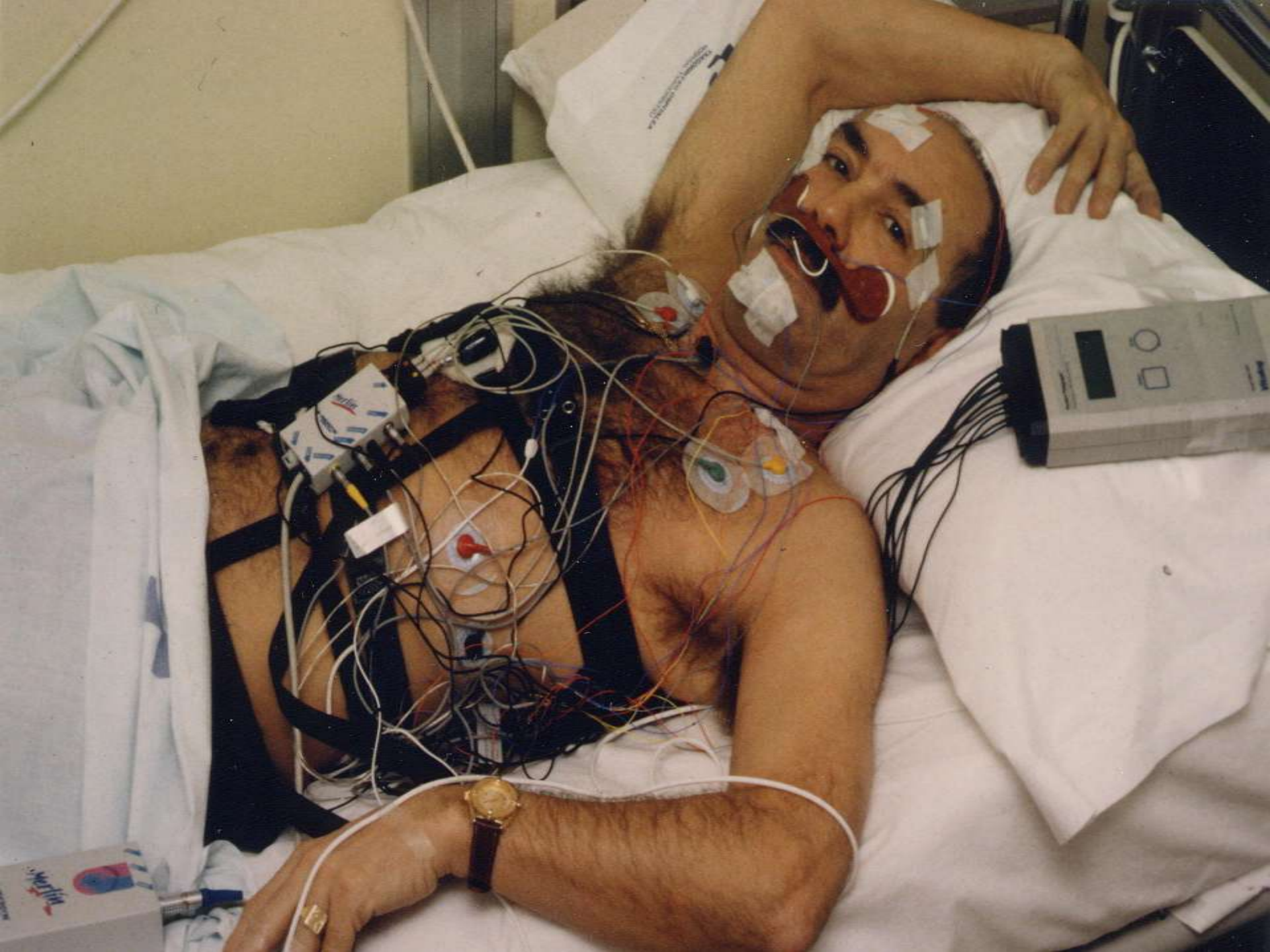

Uvula
Soft palate
Nasopharynx
Oropharynx
Tongue
Epiglottis
Laryngopharynx
Illustration © 1999 Christy Krames

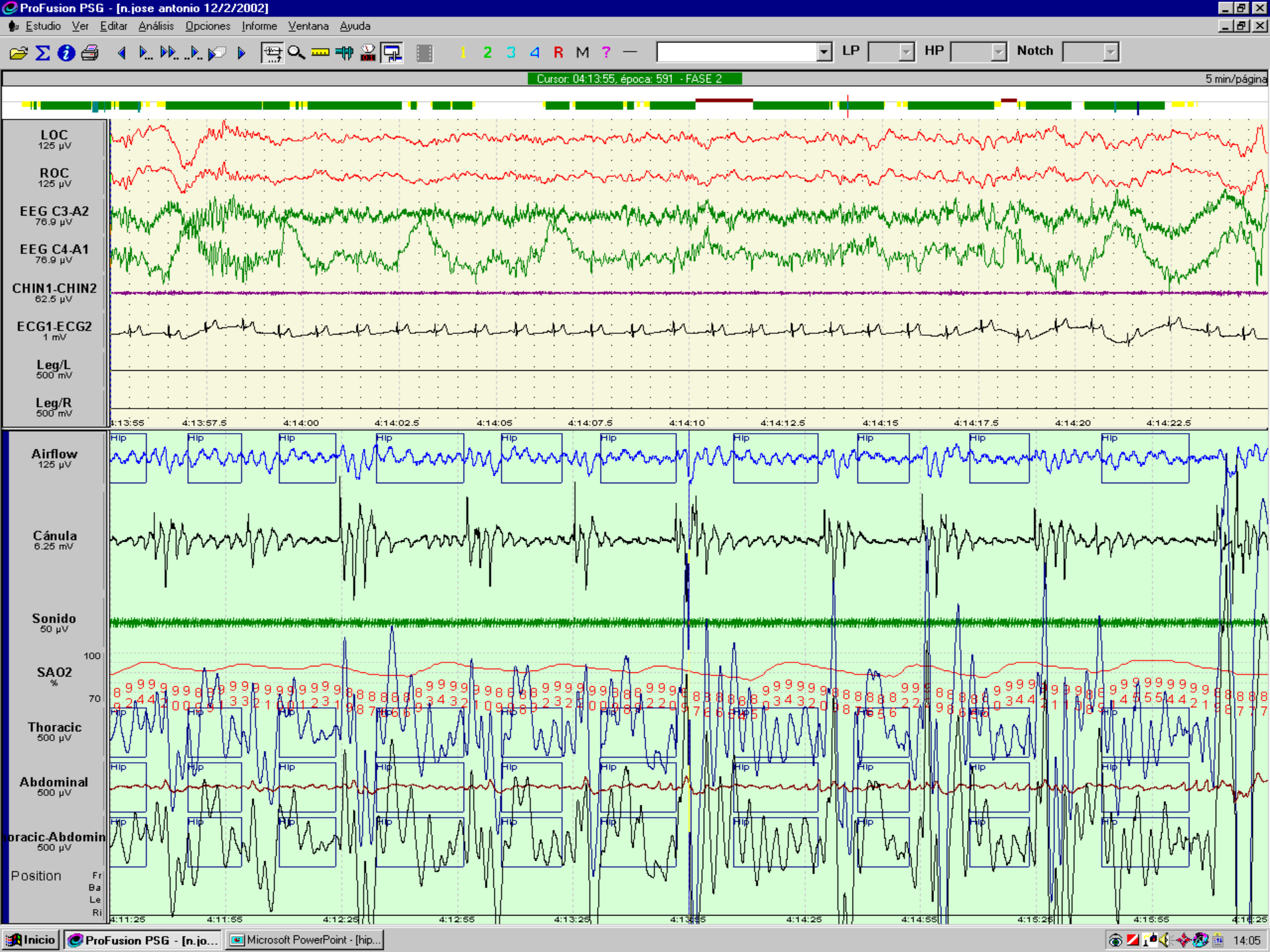

Small or receding jaw
Tongue
Soft palate
Epiglottis
Uvula
Illustration © 1999 Christy Krames

SÍNDROME DE APNEA-HIPOPNEA DEL SUEÑO (SAHS)



Sánchez-de-la-Torre M. Lancet Respir Med 2013




ProFusion PSG - [n.jose antonio 12/2/2002]
Estudio Ver Editar Análisis Opciones Informe Ventana Ayuda
LP HP Notch
Cursor: 04:13:55, época: 591 - FASE 2
5 min/página
LOC 125 µV
ROC 125 µV
EEG C3-A2 76.9 µV
EEG C4-A1 76.9 µV
CHIN1-CHIN2 62.5 µV
ECG1-ECG2 1 mV
Leg/L 500 mV
Leg/R 500 mV
4:13:55 4:13:57.5 4:14:00 4:14:02.5 4:14:05 4:14:07.5 4:14:10 4:14:12.5 4:14:15 4:14:17.5 4:14:20 4:14:22.5
Airflow 125 µV
Cánula 6.25 mV
Sonido 50 µV
SAO2 %
100
70
Thoracic 500 µV
Abdominal 500 µV
oracic-Abdomin 500 µV
Position
Fr
Ba
Le
Ri
Hip
4:11:25 4:11:55 4:12:25 4:12:55 4:13:25 4:13:55 4:14:25 4:14:55 4:15:25 4:15:55 4:16:25
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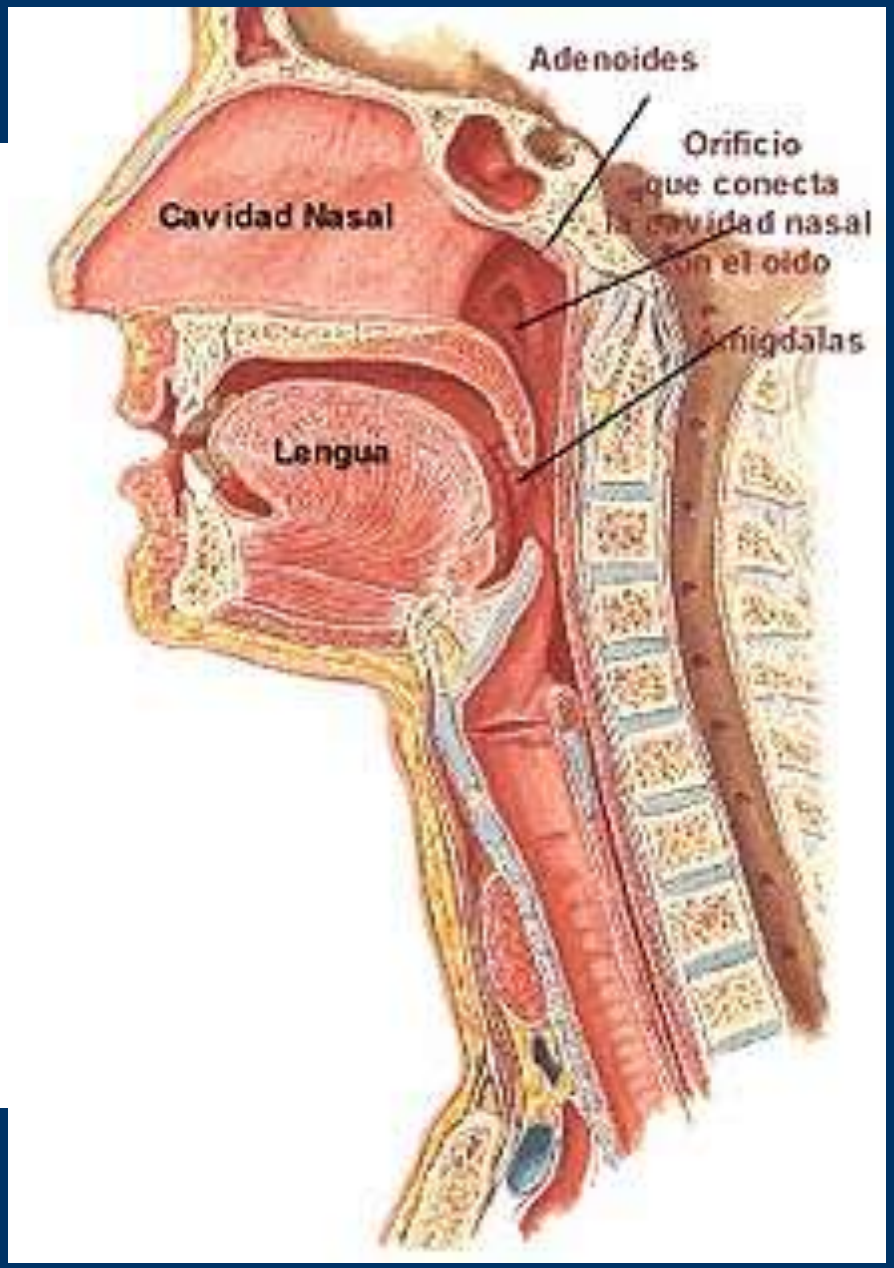
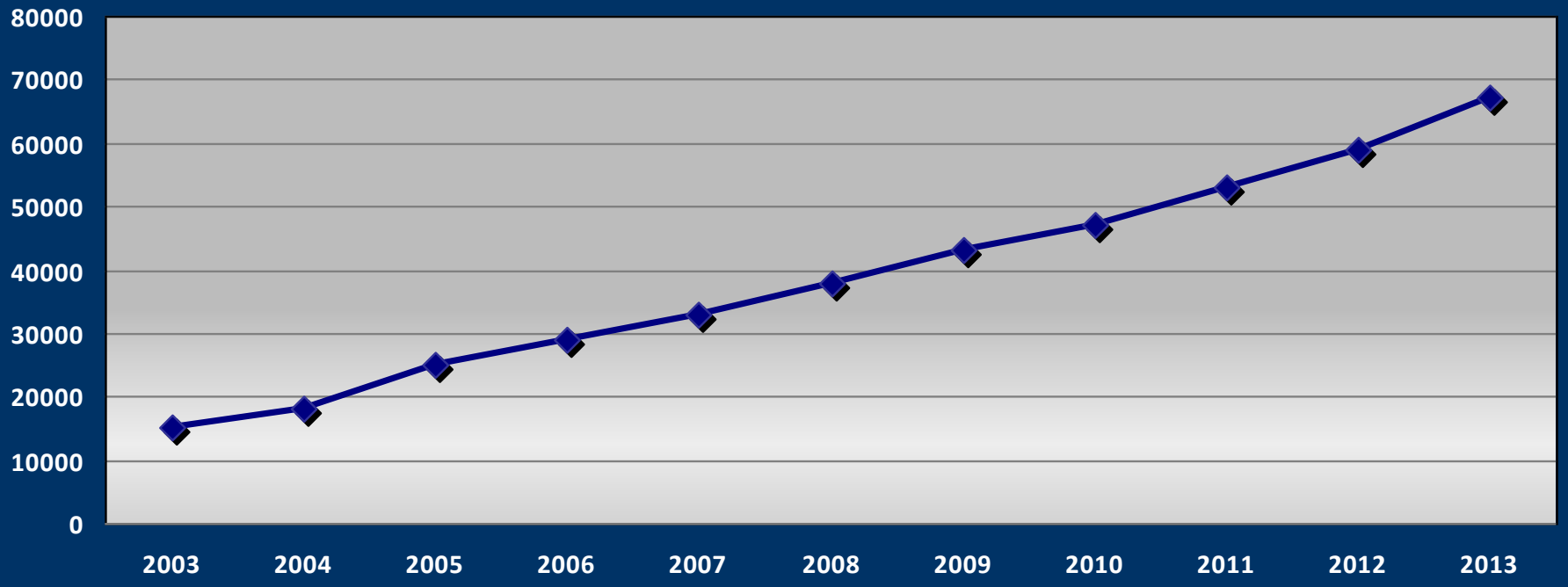
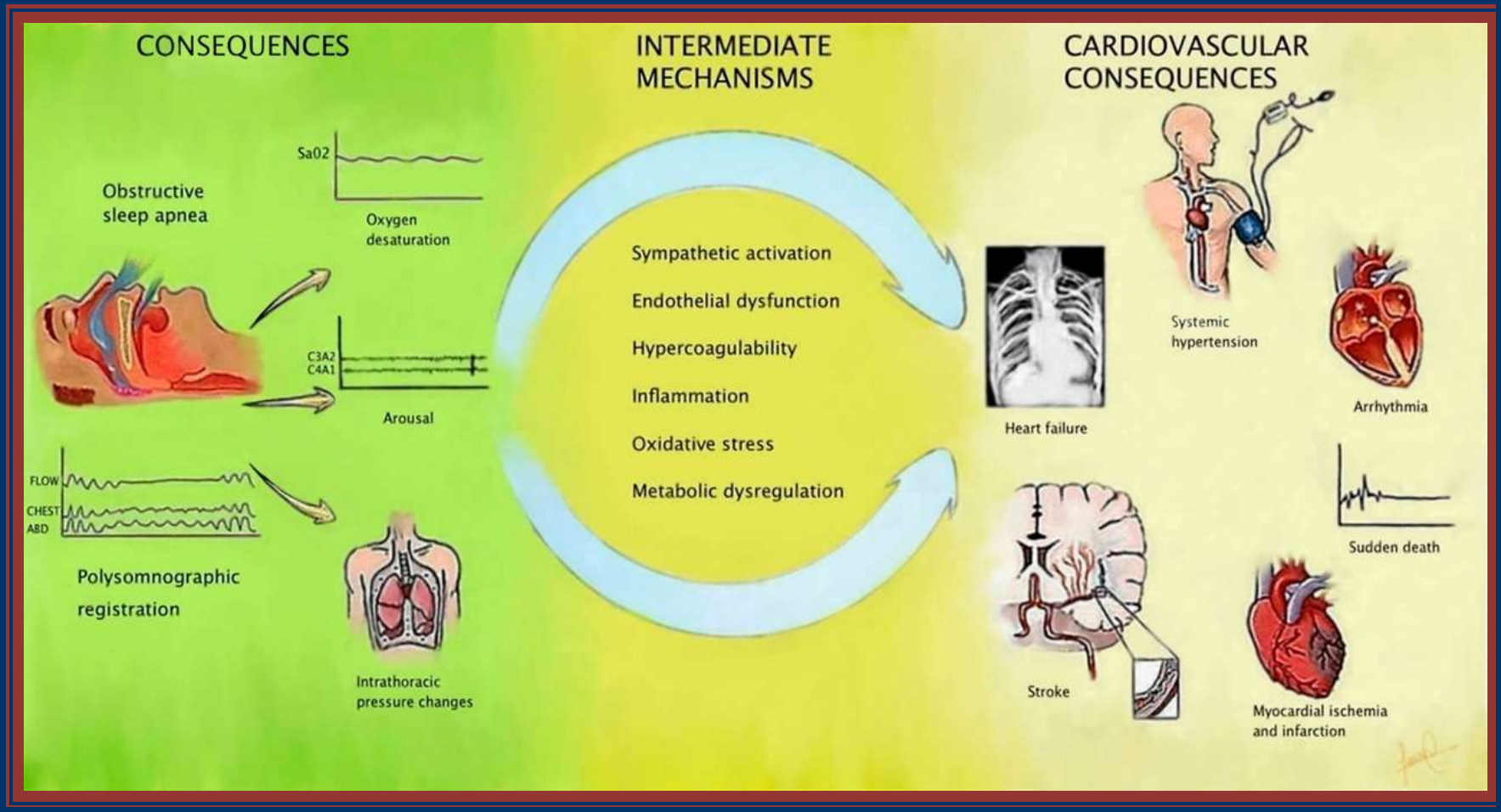

Adenoides
Orificio
que conecta
la cavidad nasal
con el oído
Cavidad Nasal
Amigdalas
Lengua

Pacients en tractament amb CPAP a Catalunya



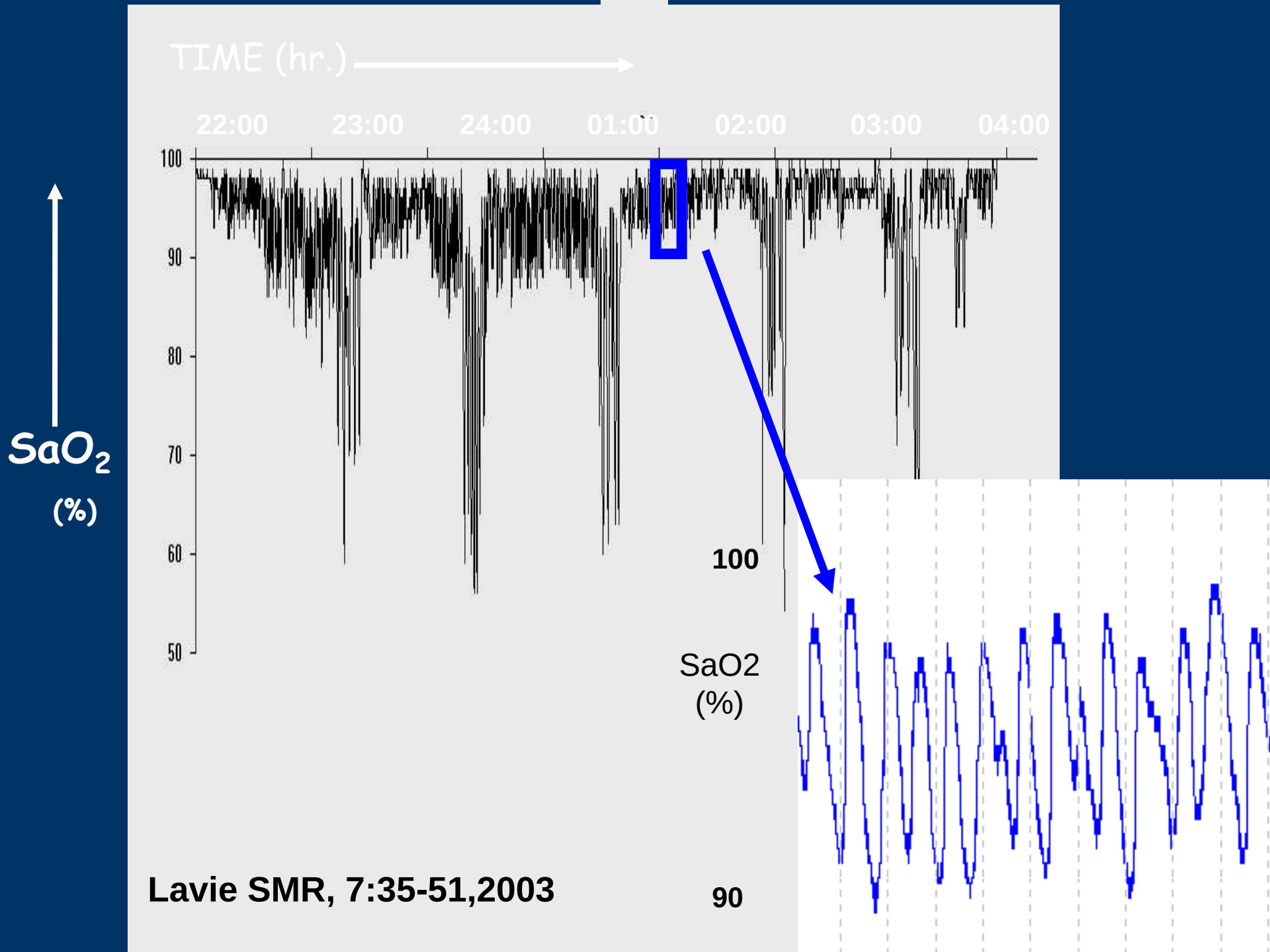
SÍNDROME DE APNEA-HIPOPNEA DEL SUEÑO (SAHS)



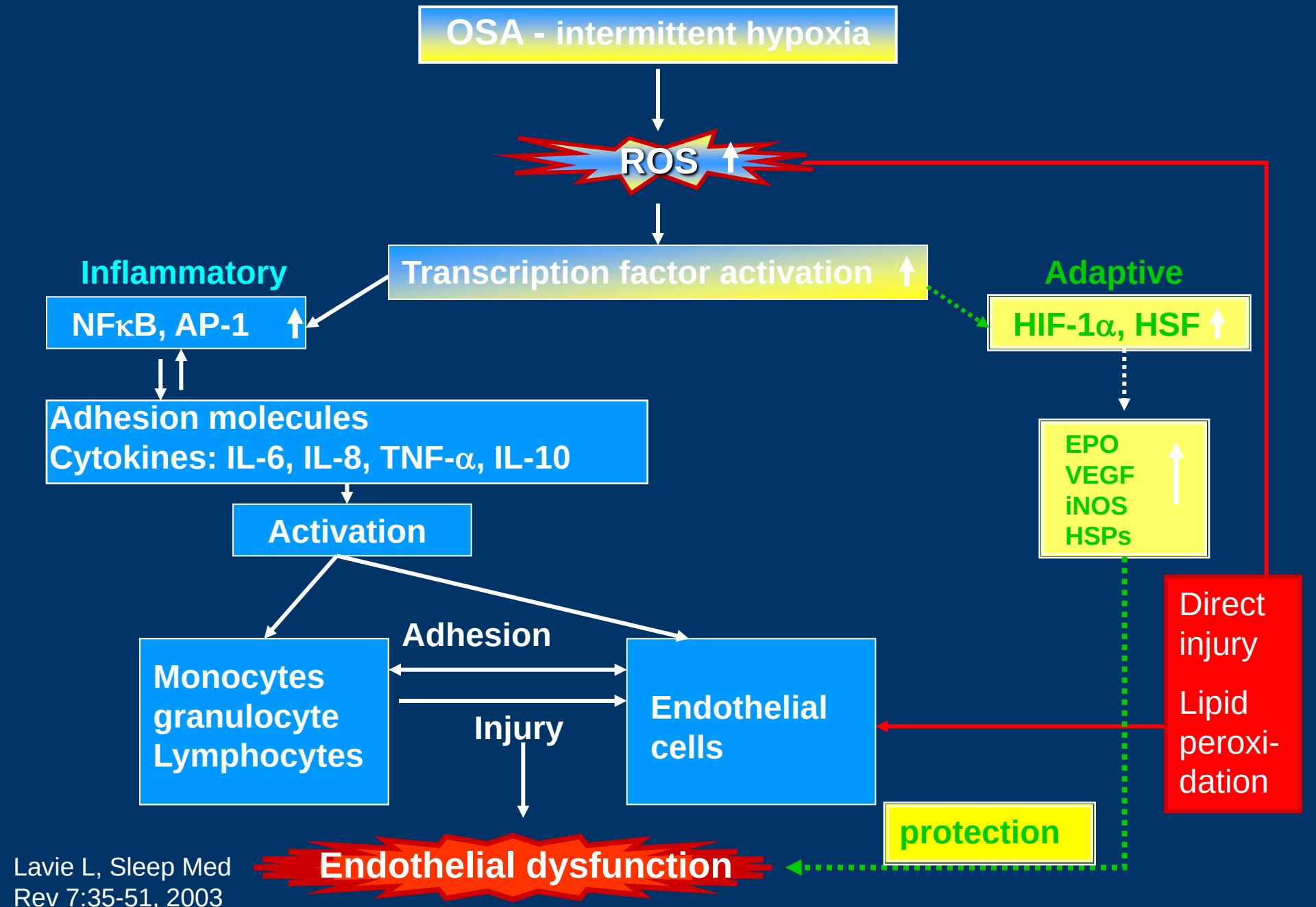
Sánchez-de-la-Torre M. Lancet Respir Med 2013

OSAHS and CV disease
Potential Mechanisms

- Oxidative stress
- Systemic inflammation
- Metabolic abnormalities
- Increased sympathetic tone
- Coagulation abnormalities
- Endothelial dysfunction
- Genetic background



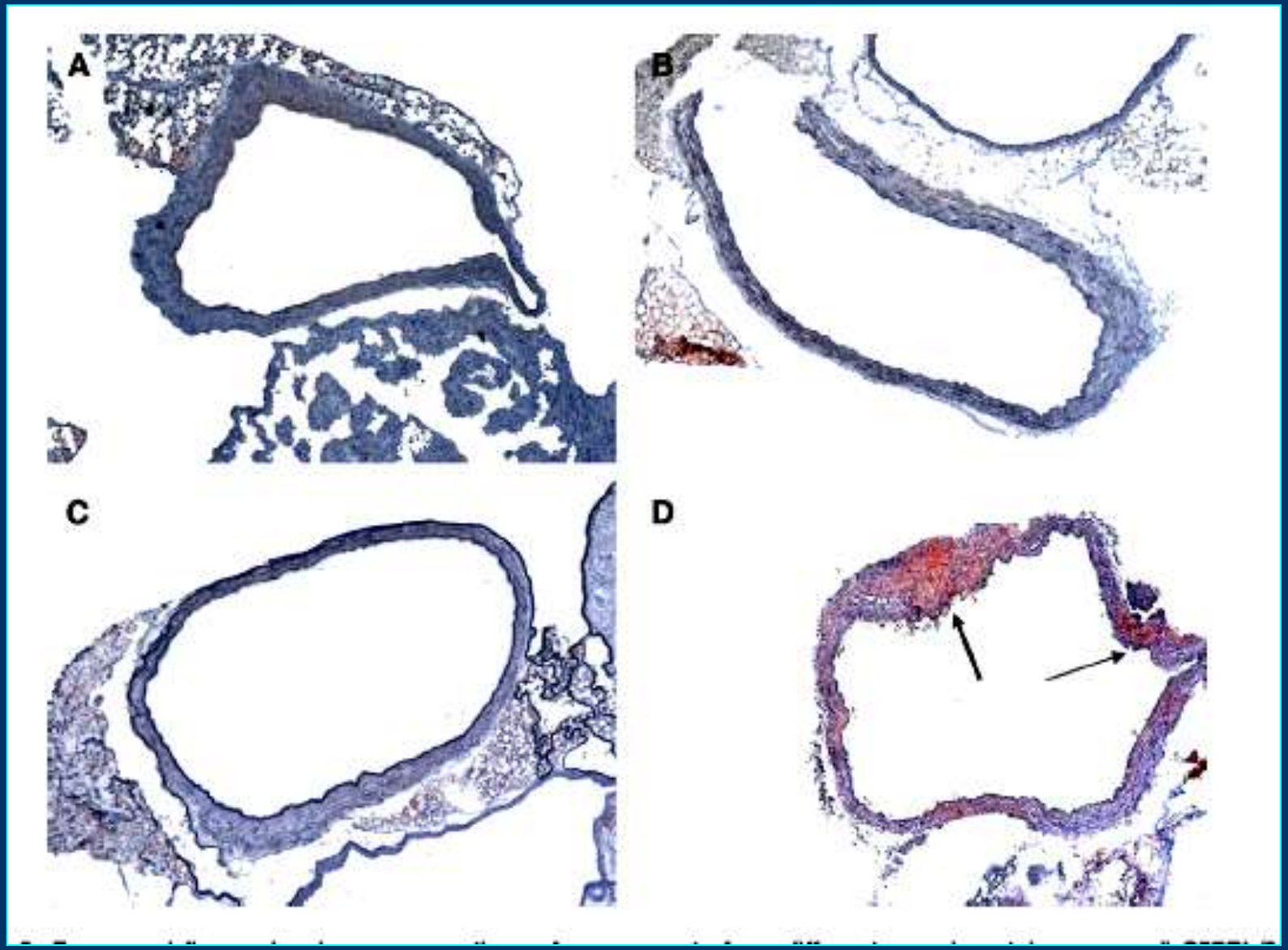
Lavie SMR, 7:35-51,2003



Lavie L, Sleep Med Rev 7:35-51, 2003

Control

Intermittent hypoxia



Fat diet

Fat diet + IH

Savransky AJRCCM 2007

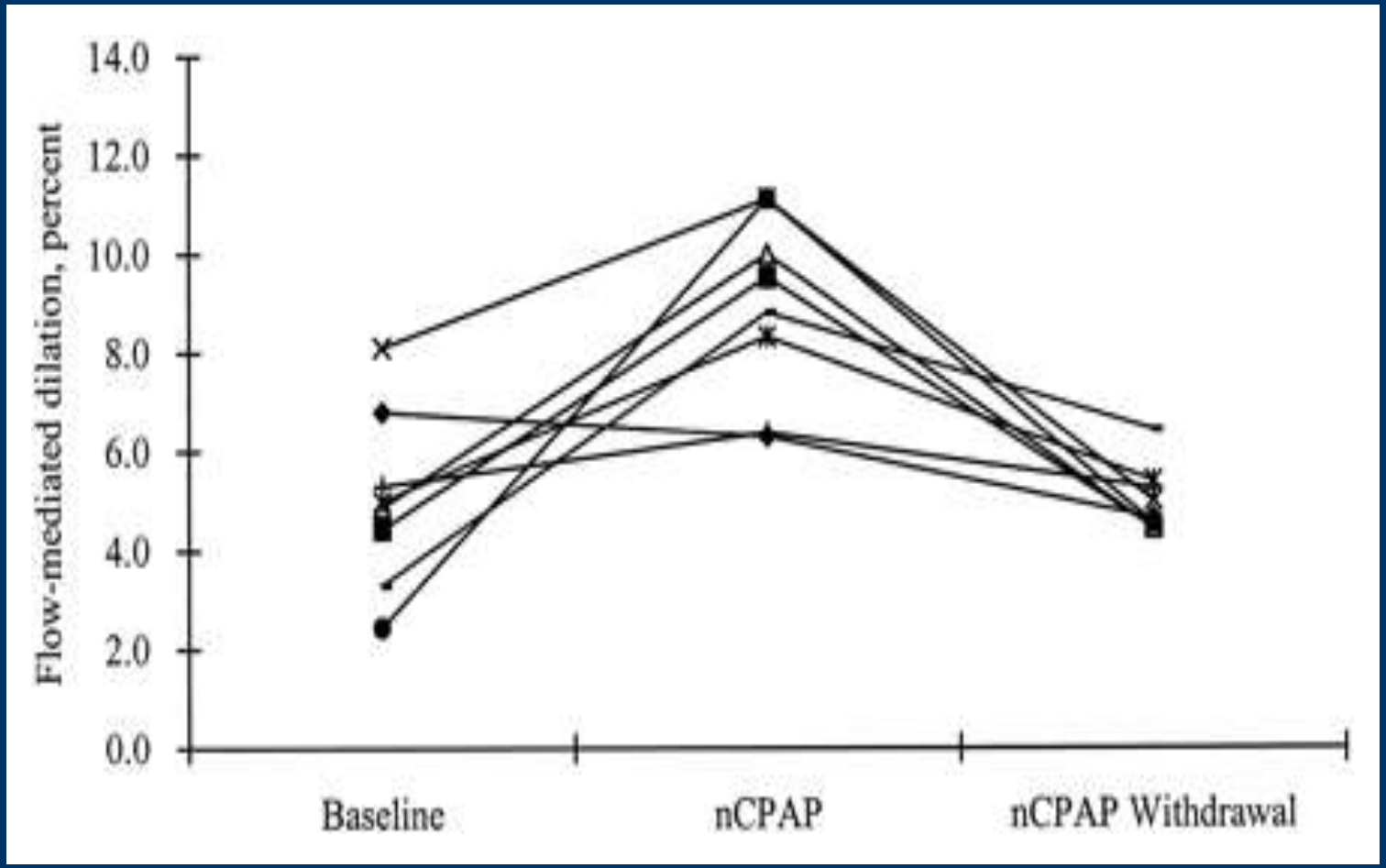
OSAHS and CV disease

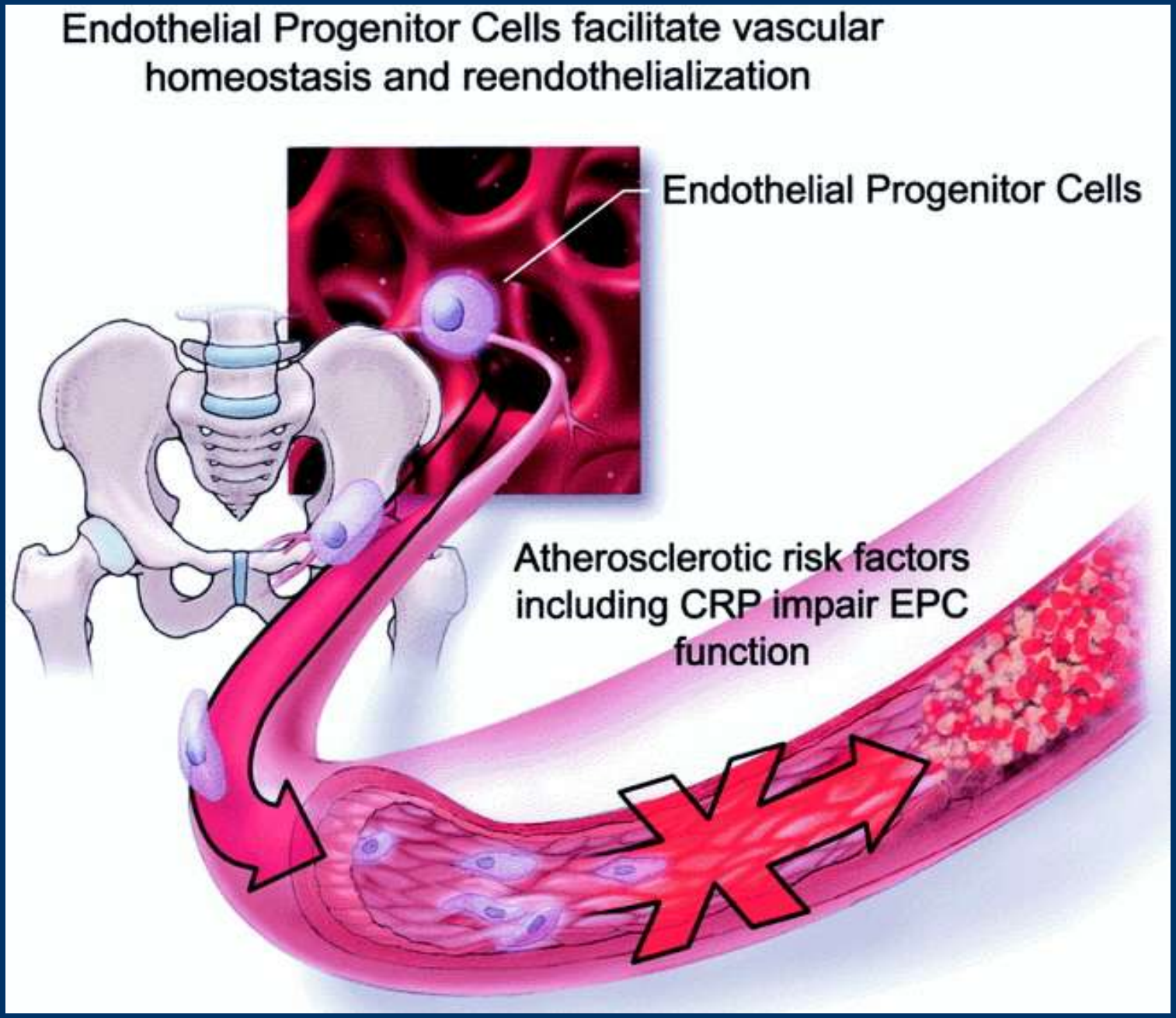
Potential Mechanisms

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

Endothelial function in OSAHS and response to treatment

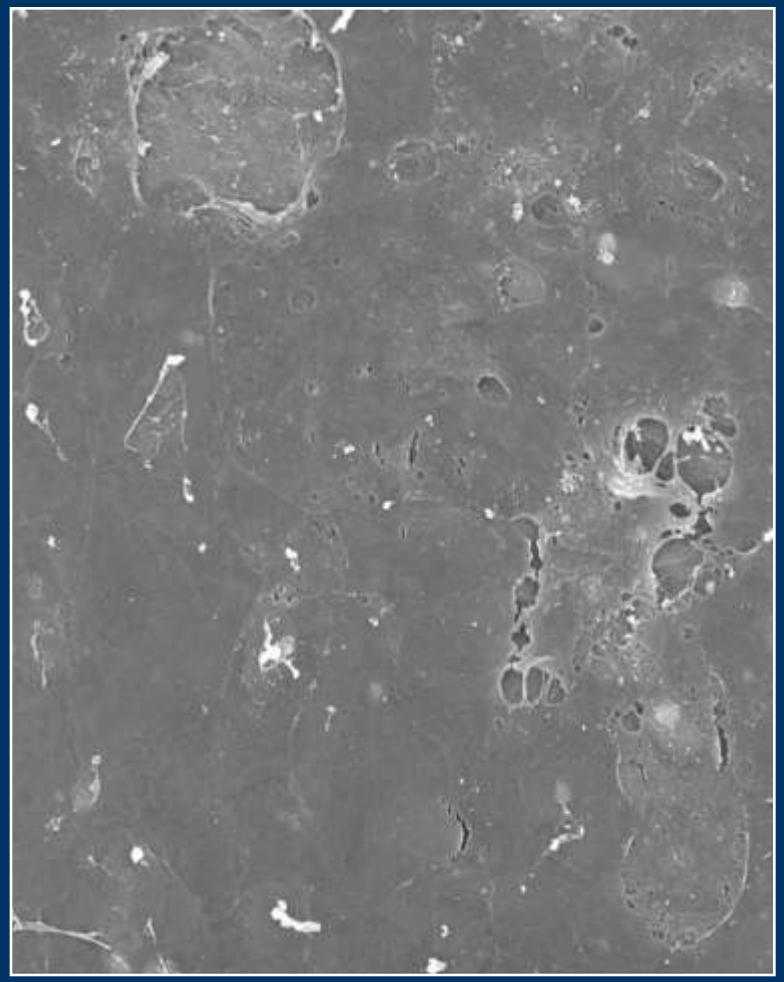
Ip MS *et al. AJRCCM* 2004; 169: 348-53

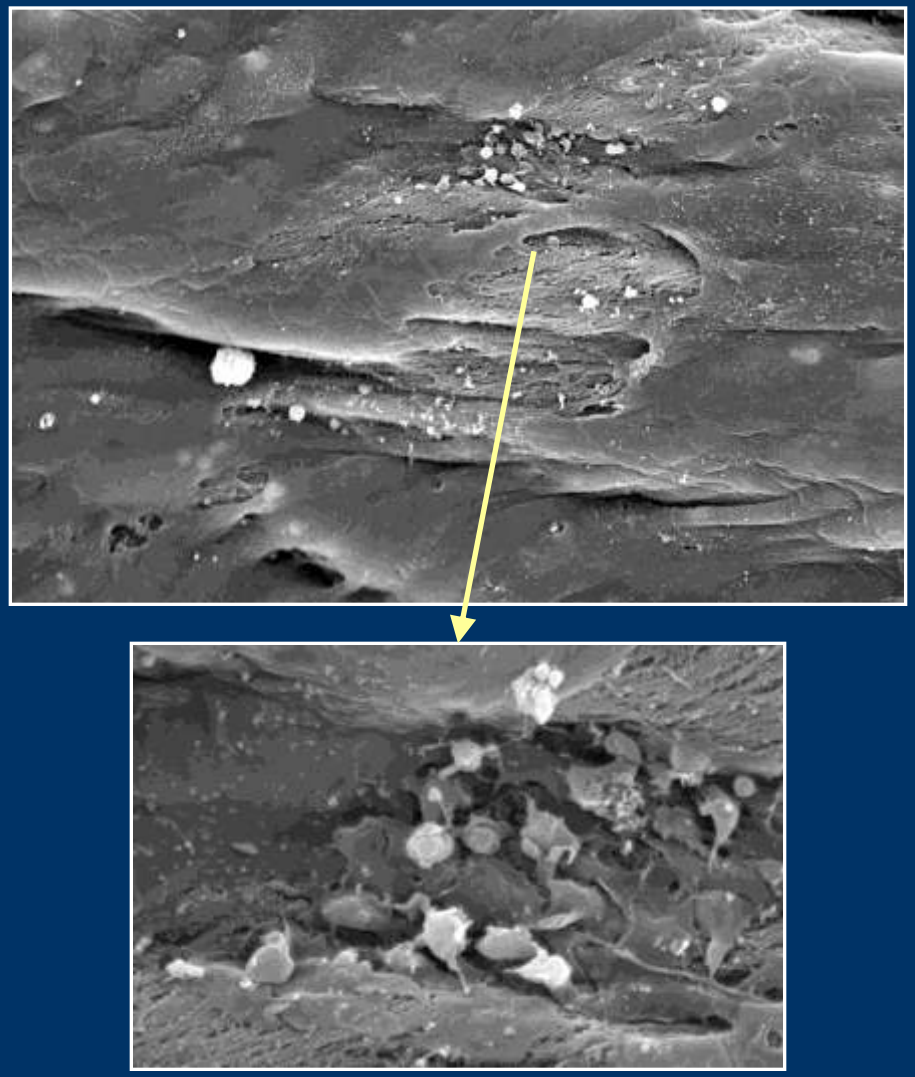




Szmitko et al. *Circulation* 03; 108: 1917-23

Areas denudadas del endotelio vascular





Peinado et al. ERJ 2004;24:435s

Células progenitoras endoteliales ($CD133^+$)

(técnica de inmunogold)

Peinado et al. ERJ 2004;24:435s

Endothelial progenitor cells in OSAHS

	SAHS n = 13	Control n = 13
Age (yr)	45±9	44±9
BMI ($kg.m^{-2}$)	28±2	27±3
$AHIh^{-1}$)	49±18	2±2
CD34 + (% linph)	0.11±0.01	0.13±0.01
EPCs (% CD34)	0.62±0.1	1.1±0.3
EPCs (% linphx$10^{(-3)}$)	0.59±0.07	1.2±0.26*

de la Peña Respiration 2007

OSAHS and CV disease

Potential Mechanisms

- Oxidative stress
- Systemic inflammation
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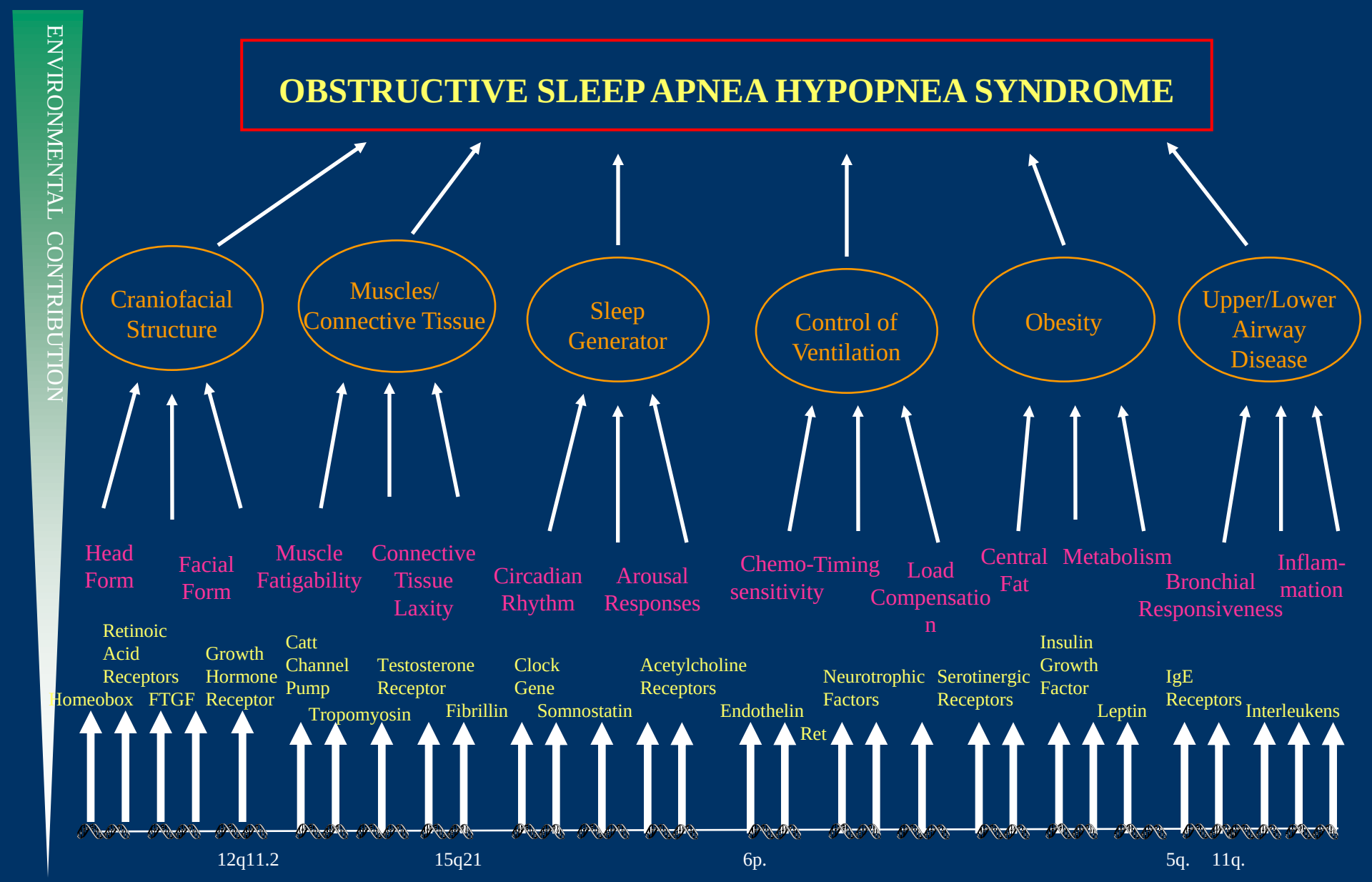
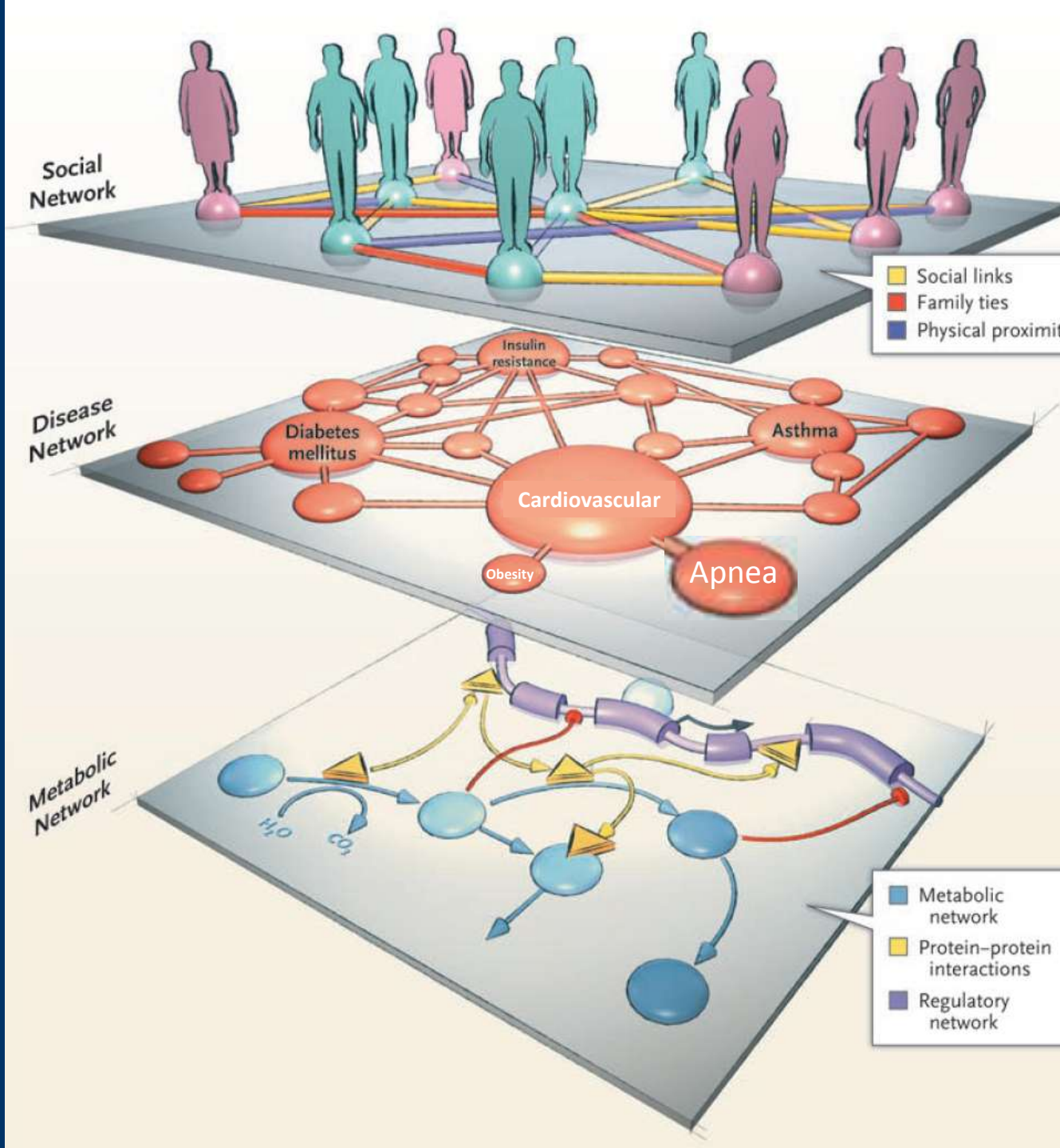
- Increased sympathetic tone
- Coagulation abnormalities
- Endothelial dysfunction
- Genetic background



Courtesy Dr Palmer

System biology

A new perspective: holism instead of reduction



AL Barabási. Network medicine.

From obesity to the diseasome

N Engl J Med, 2007

SYSTEMS BIOLOGY ANALYSES OF GENE EXPRESSION AND GENOME WIDE ASSOCIATION STUDY DATA IN OBSTRUCTIVE SLEEP APNEA

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Liu Y et al. Pac Symp Biocomput. 2011:14-25

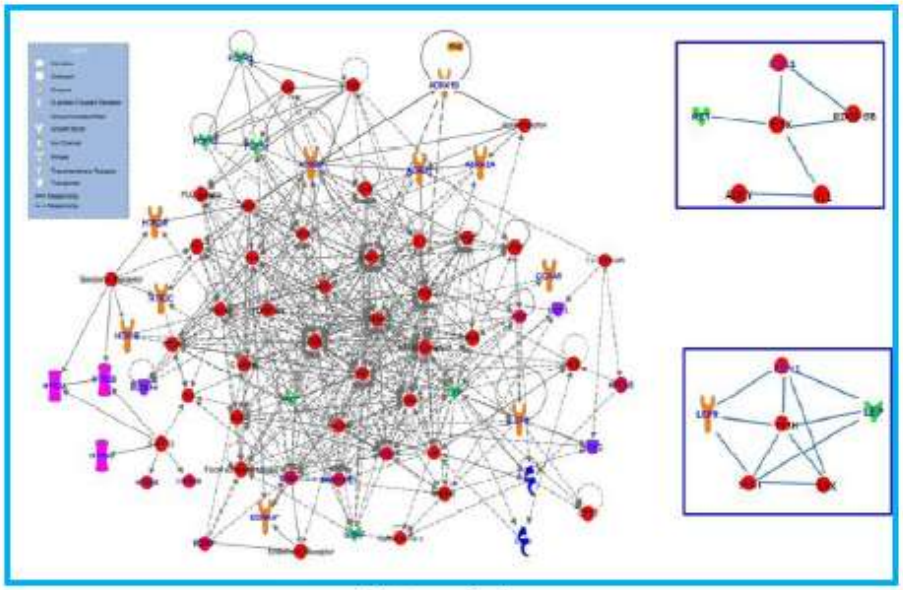
Systms biology of gene expresion and GWA in OSA.

Liu Y et al. Pac Symp Biocomput. 2011:14-25

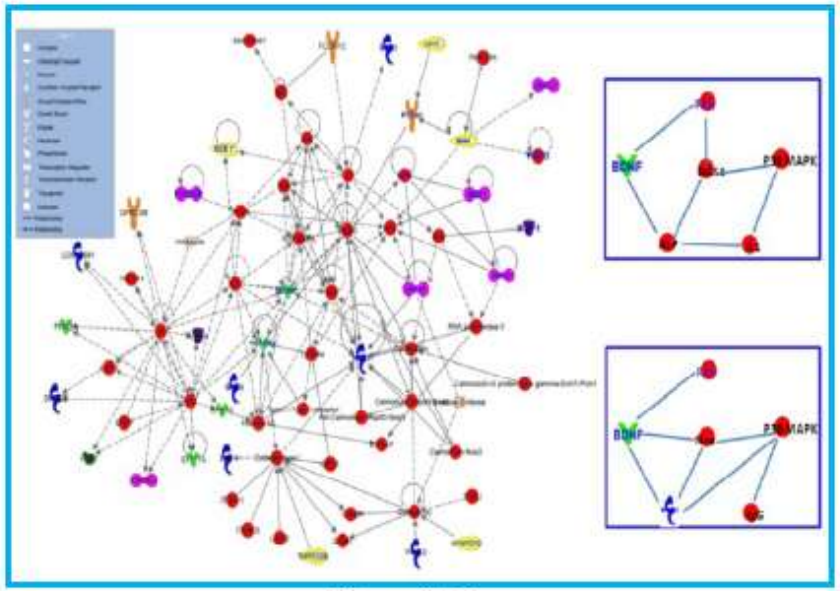
Mediante microarrays se estudiaron genes relacionados con el tejido adiposo.

Se estudio la interaccion de 56 proteinas relacionadas con OSA y sus comorbilidades

Se construye un "**interactoma**" entre las dos redes



Network 1



Network 2

Fig. 1 Networks generated using IPA with highest score (proteins name in blue indicates seed proteins), subnetworks with 6 nodes are identified by MI scores for subcutaneous and visceral fat tissues. Larger and high resolution picture can be found at http://proteomics.case.edu/news_events. aspx?newsid=38

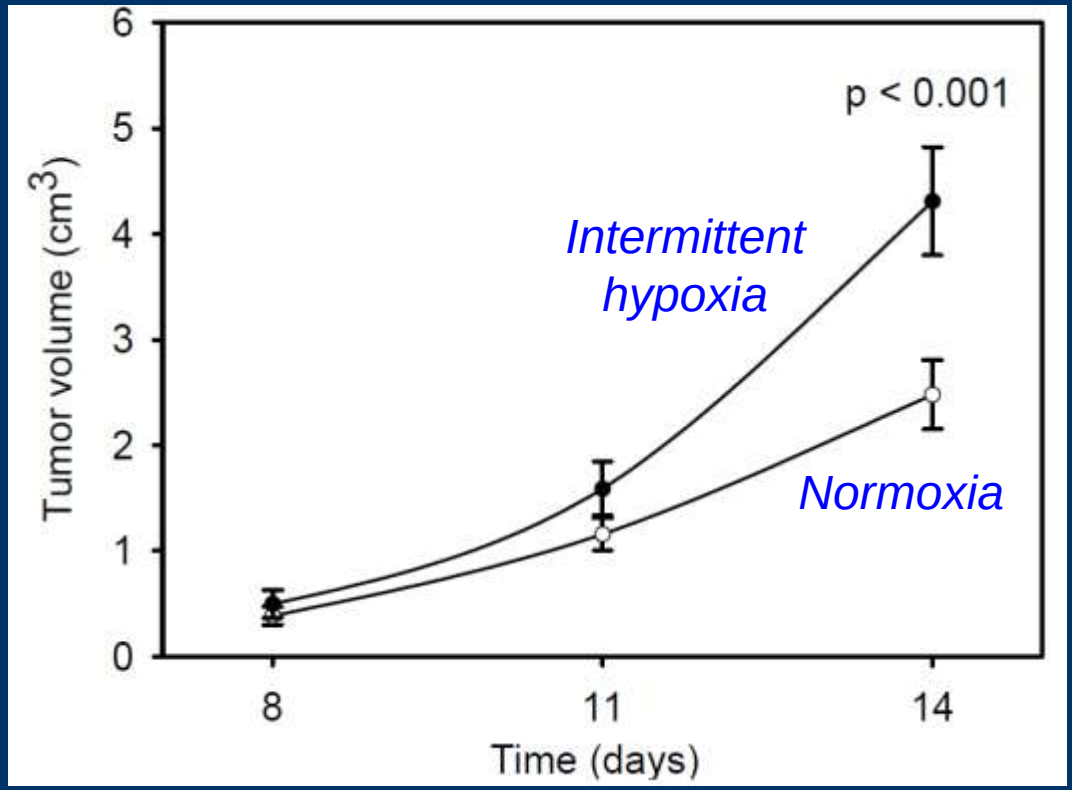
Liu Y et al. Pac Symp Biocomput. 2011:14-25

Systms biology of gene expresion and GWA in OSA.
Liu Y et al. Pac Symp Biocomput. 2011:14-25

- **The results of this preliminary study suggest that the P13K, the STAT protein family, and the insulin signaling may be associated with OSA**

Intermittent hypoxia and tumor growth

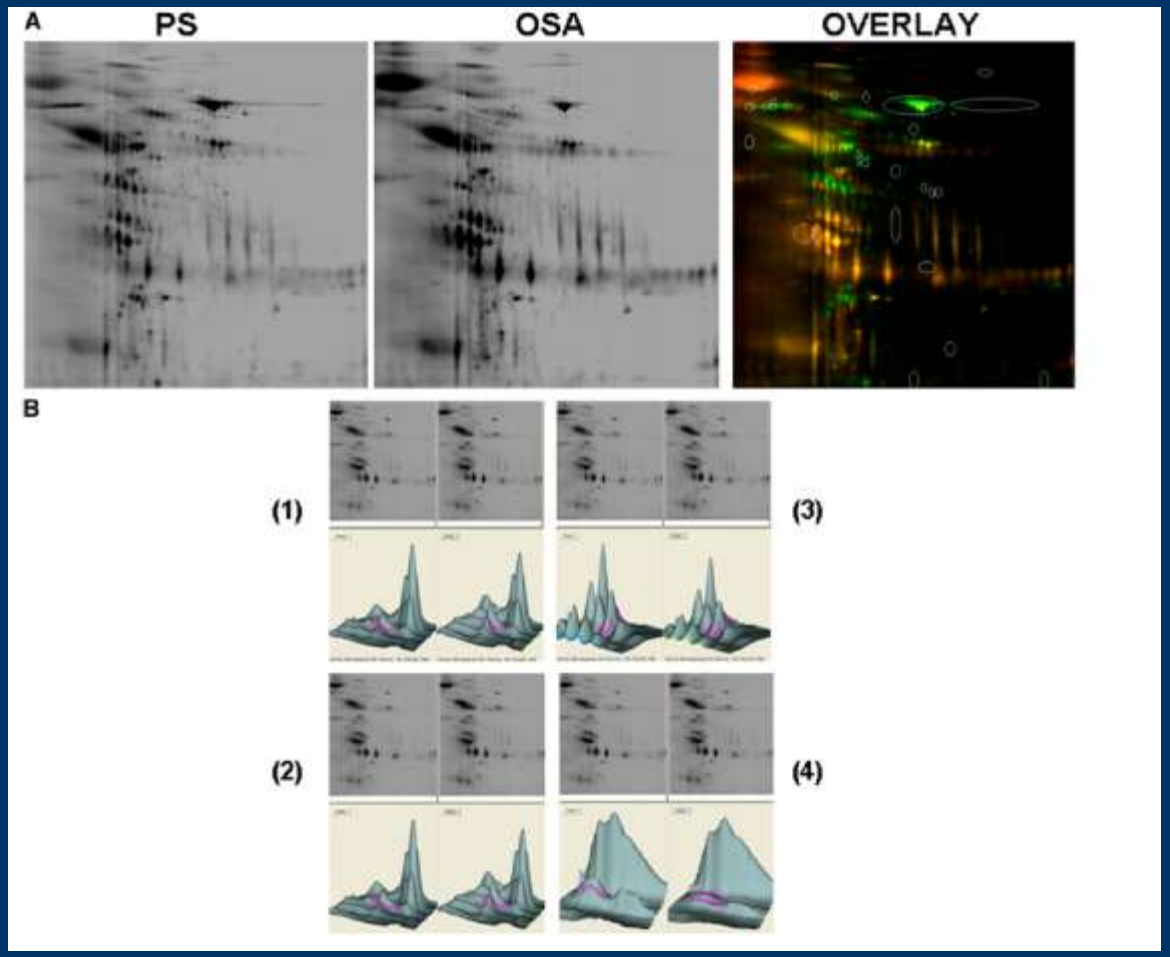
Tumor volume



Almendros et al. Eur Respir J 2012; 39: 215-217

Urine proteomic biomarkers in OSA

Gozal et al AJRCCM 2009



713-789 proteins

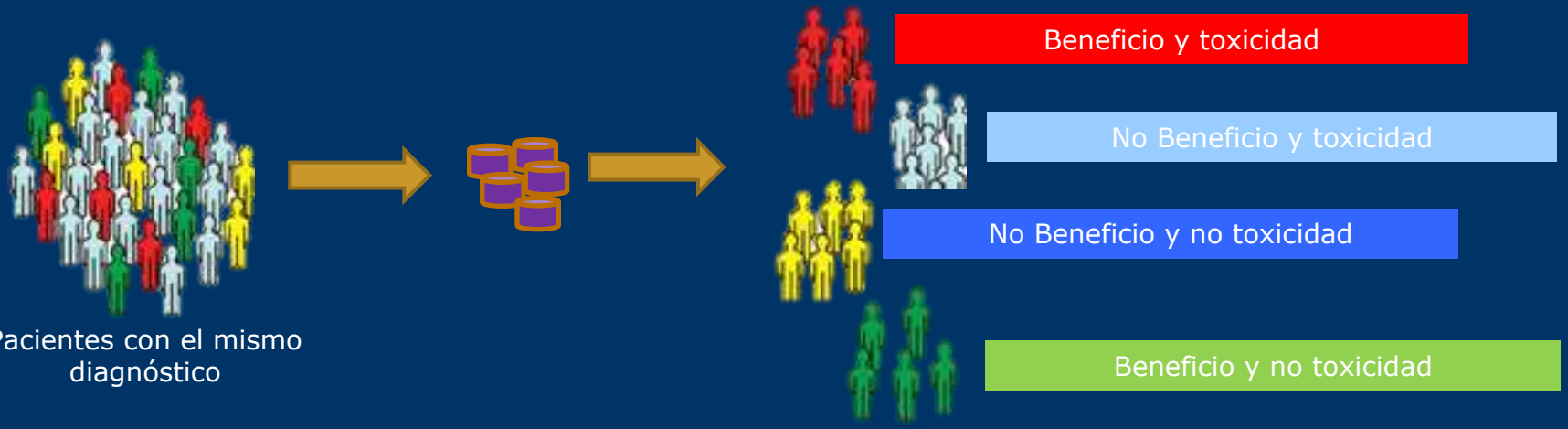
Urine proteomic biomarkers in OSA

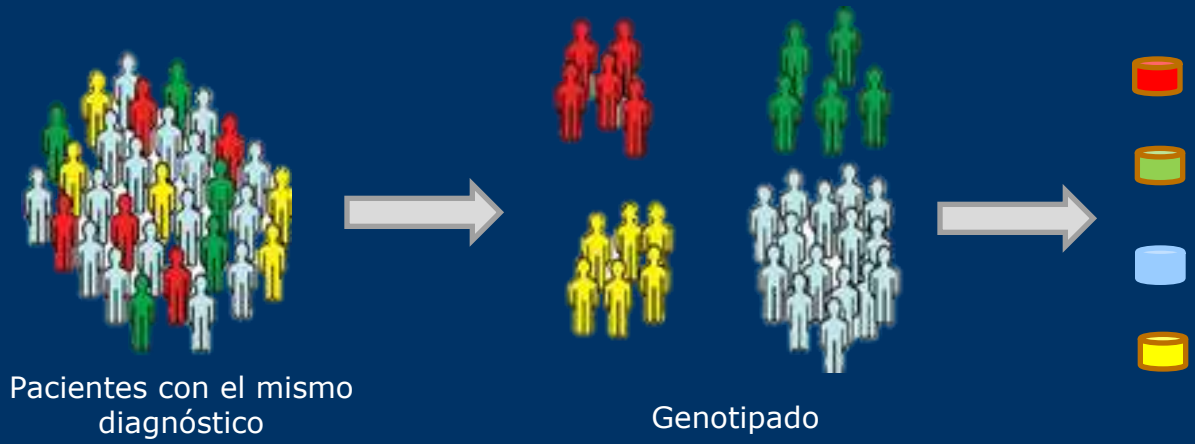
Gozal et al AJRCCM 2009

TABLE 3. URINARY PROTEINS ALTERED IN PEDIATRIC OBSTRUCTIVE SLEEP APNEA

Increased	Decreased
Uromodulin	Kallikrein
Urocortin-3	Zinc finger protein-81
Bikunin	Zinc finger protein-36/1
Tenascin	
Human Tribbles homolog-2	
Orosomucoid-2	
α_1-Microglobulin	
PCAF histone acetylase	
Prolyl hydroxylase domain	

MEDICINA PERSONALIZADA

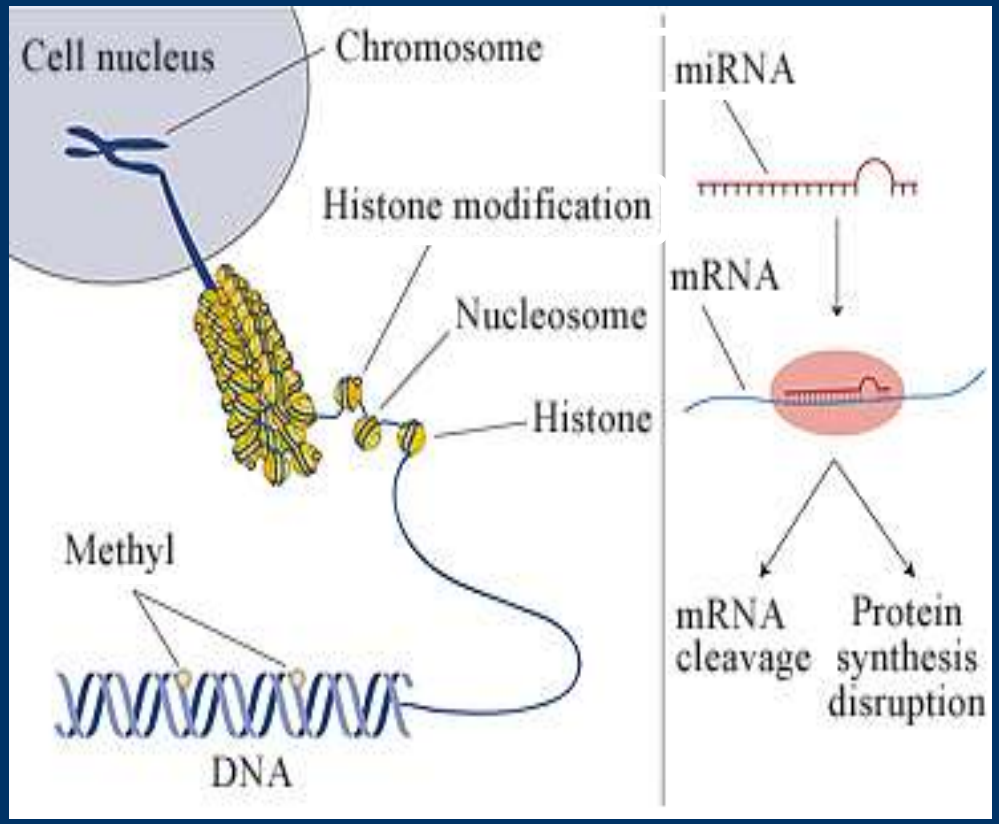




ANÁLISIS DE EXPRESIÓN GÉNICA EN ENFERMEDADES CARDIOVASCULARES

MECANISMOS EPIGENÉTICOS DE REGULACIÓN GÉNICA

- **Metilación del DNA**
- **Modificación de histonas**
- **microRNAs (miRNAs)**



PERFIL MOLECULAR DE RESPUESTA AL TRATAMIENTO CON CPAP

ANÁLISIS DEL PERFIL DE EXPRESIÓN DE miRNAs

Cambios en la presión arterial tras 3 meses de tratamiento con CPAP

Pacientes sin cambios en la TA post CPAP

PACIENTES NO RESPONDEDORES

Pacientes con descenso en la TA post CPAP

PACIENTES RESPONDEDORES

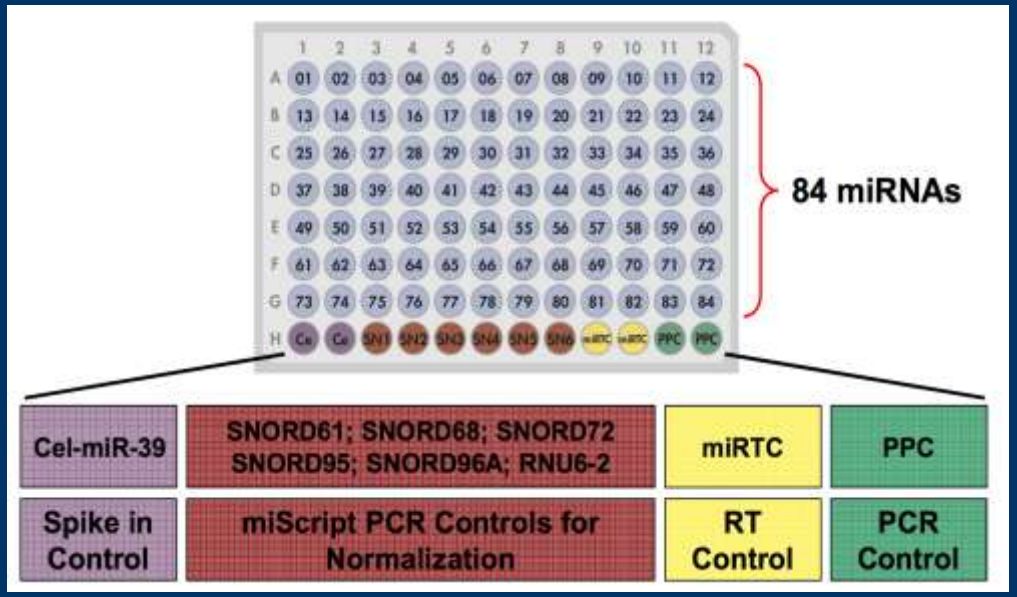
MicroRNAs (miRNAs):

- **Son pequeñas secuencias de material genético que regulan la expresión génica.**
- **Están implicados en la manifestación de distintos fenotipos y enfermedades.**
- **Expresión anormal de miRNAs ➔ procesos patológicos**

SELECCIÓN DE PACIENTES

12 PACIENTES NO RESPONDEDORES

12 PACIENTES RESPONDEDORES



miRNA PCR array para cuantificar 84 miRNAs relacionados con enfermedad cardiovascular

Conclusions

- OSAS is a common disorder
- The collapse of the UA induce, intermittent hypoxia, arousal and oscillations in the intra-pleural pressure
- OSAS is significantly associated to CV morbidity and mortality.
- The diagnostic always requires an objective evaluation
- CPAP therapy effectively abolishes OSAS and improves CV outcomes,
- Multiple mechanisms link OSAHS and CV disease
- The development of system medicine represents a challenge in the diagnostic and treatment paradigms

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- **Gonzalo Cao.** Farmaceútico.
- **Nuria Roure.** PhD.
- **Mª Jesús Muniesa,** MD.
- **Sandra Serra,** MD.
- **Nuria Nadal,** MD.
- **Alicia Sanchez,** biologa.
- **Grupo 35** del **CIBERes** (Madrid).

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- **Olga Minguez,** Técnico de Sueño.
- **Lydia Pacual,** Enfermera.

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Agradecimientos:
- **Antonia Barceló,** MD (Hospital Son Espases. Palma de Mallorca)