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de Pneumologie

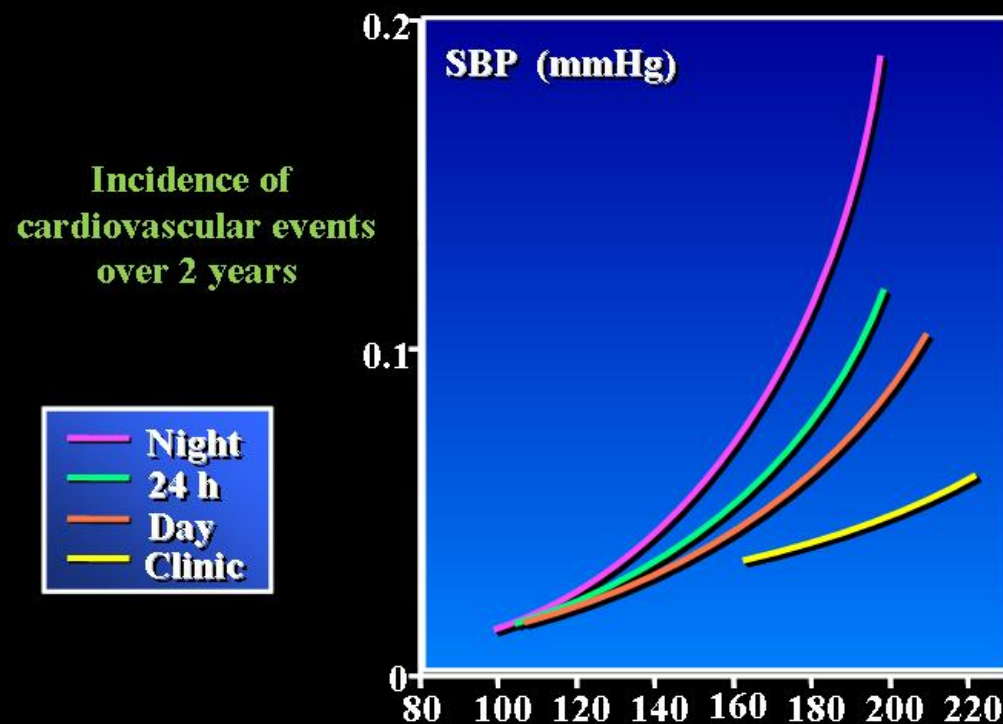


14ème Rencontre
SORRENTE 4-8 avril 2018

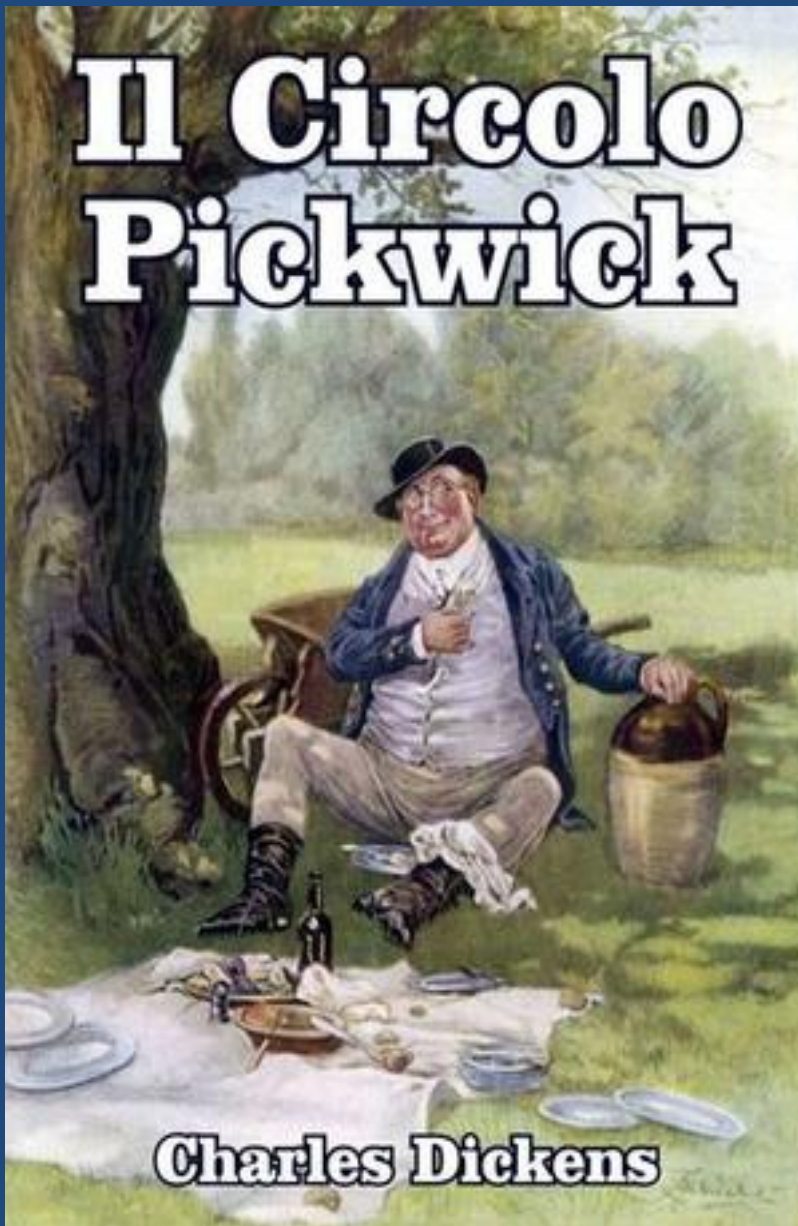
OBSTRUCTIVE SLEEP APNEA AND ARTERIAL HYPERTENSION

Dott. Carolina Lombardi
Head of Sleep Disorders Centre
Department of Cardiology,
University of Milano Bicocca
Istituto Auxologico Italiano IRCCS
Milan, ITALY

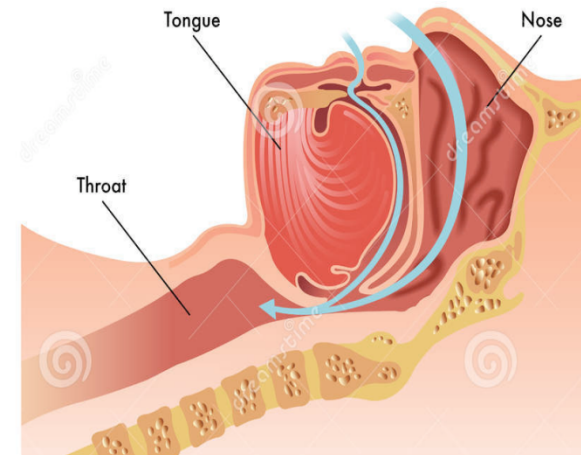
**CLINIC, 24 H, DAYTIME AND NIGHT-TIME SBP AT ENTRY
AS PREDICTORS OF CARDIOVASCULAR EVENT INCIDENCE OVER 2 YEARS
IN THE PLACEBO GROUP**



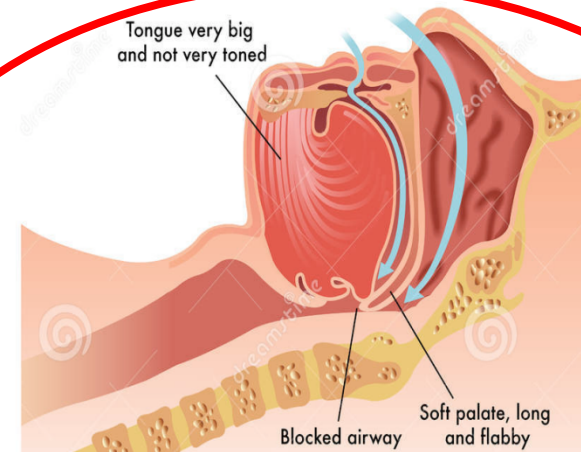
Il Circolo Pickwick



Charles Dickens



Normal breathing during sleep

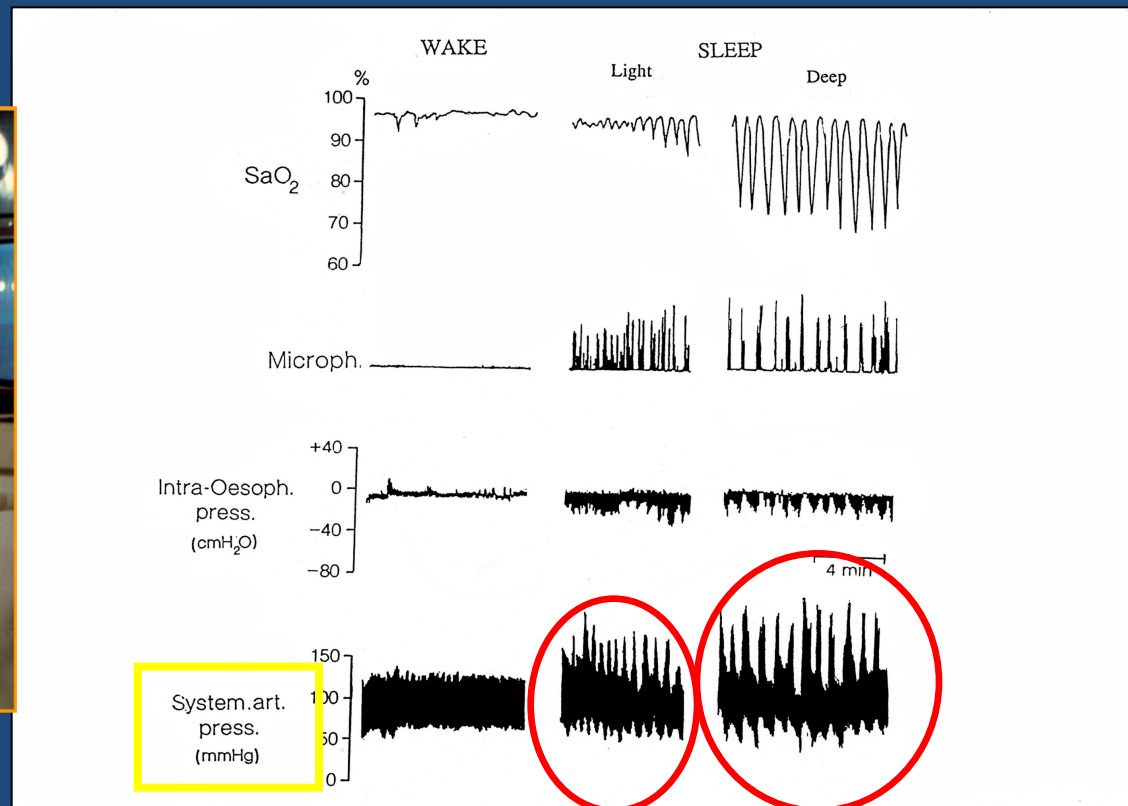


Obstructive sleep apnea



Continuous recording of the pulmonary and systemic arterial pressure during sleep in syndromes of hypersomnia with periodic breathing.

Coccagna G, Mantovani M, Brignani F, Parchi C, Lugaresi E.



PubMed search results for "sleep and hypertension".

Search bar: **sleep and hypertension** (highlighted in red)

Buttons: Create RSS, Create alert, Advanced

Format: Summary | Sort by: Most Recent | Per page: 20

Best matches for sleep and hypertension:

- [Hypertension and sleep: overview of a tight relationship.](#)
Pepin JL et al. **Sleep** Med Rev. (2014)
- [A review of evidence for the link between sleep duration and hypertension.](#)
Gangwisch JE et al. Am J Hypertens. (2014)
- [Relationship between Duration of Sleep and Hypertension in Adults: A Meta-Analysis.](#)
Wang Y et al. J Clin **Sleep** Med. (2015)

Switch to our new best match sort order

Search results

Items: 1 to 20 of 8549 (highlighted in red)

Page 1 of 428

Results by year (highlighted in red):

1968 (highlighted in blue)

2017 (highlighted in yellow)

PMC Images search for sleep and hypertension

Obstructive Sleep Apnea and Hypertension

David A. Calhoun

OSAS



Prevalence of hypertension= 50%.



Hypertension



Prevalence of OSA= 30-40%

Obstructive sleep apnoea syndrome as a risk factor for hypertension: population study

Lavie P, Herer P, Hoffstein V

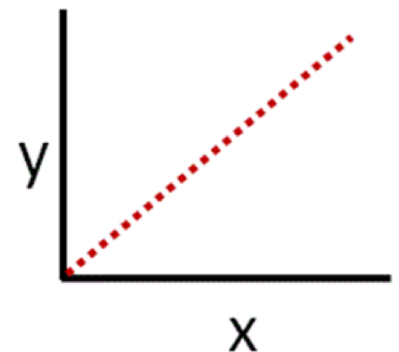
BMJ 2000 Feb 19;320(7233):479-82

Association of sleep-disordered breathing, sleep apnea and hypertension in a large community-based study; Sleep Heart Health Study

Nieto FJ, Young TB, Lind BK, Sharar E, Samet JM, Redline S, D'Agostino RB, Newman AB, Lebowitz MD, Pickering TG

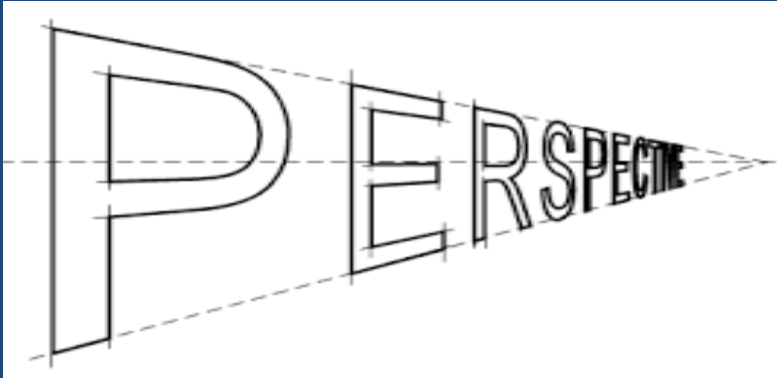
JAMA 2000 Apr 12;283(14):1829-39

There is a linear relationship between AHI and prevalence and severity of hypertension
The more severe the OSA, the higher the risk of having hypertension of increasing severity.



risk of having arterial hypertension.....

LONGITUDINAL STUDIES



**STILL
CONTROVERSIAL!!!**

several important differences among the studies:

type of the population investigated

1. homogenous working cohort (WSCS),
2. patients referred for evaluation of sleep-disordered breathing (Marin)
3. geographically and racially diverse population (SHHS),
4. a random sample from a specific region in Spain (Cano-Pumarega)

different BMIs

29 +/- 6 kg/m²
28.7 +/- 3.9
27.9 +/- 5,
25.5 +/- 3.7

different reference group to calculate odds ratio

AHI = 0 in WSCS
AHI = 0–4.9 in SHHS and Marin
RDI = 0–2.9 events/h in Cano-Pumarega

different ages at baseline

47 +/- 8
49.7 +/- 11.3
59.6 +/- 10.3
47.4 +/- 10.4

follow-up period

4 years
5 years
7.5 years
11.3 years

Different methodologies

in-laboratory polysomnography in WSCS
in-home polysomnography in SHHS and Marin
in-home polygraphy in Cano-Pumarega

How to diagnose Hypertension in OSA patients?

- Office?
- Home?
- ABPM?

Position paper on the management of patients with obstructive sleep apnea and hypertension: Joint recommendations by the European Society of Hypertension, by the European Respiratory Society and by the members of European COST (COoperation in Scientific and Technological research) ACTION B26 on Obstructive Sleep Apnea

Gianfranco Parati^{a,b}, Carolina Lombardi^b, Jan Hedner^c, Maria R. Bonsignore^d, Ludger Grote^c, Ruzena Tkacova^e, Patrick Levy^f, Renata Riha^g, Claudio Bassetti^h, Krzysztof Narkiewiczⁱ, Giuseppe Mancia^a, Walter T. McNicholas^j, on behalf of the EU COST ACTION B26 members

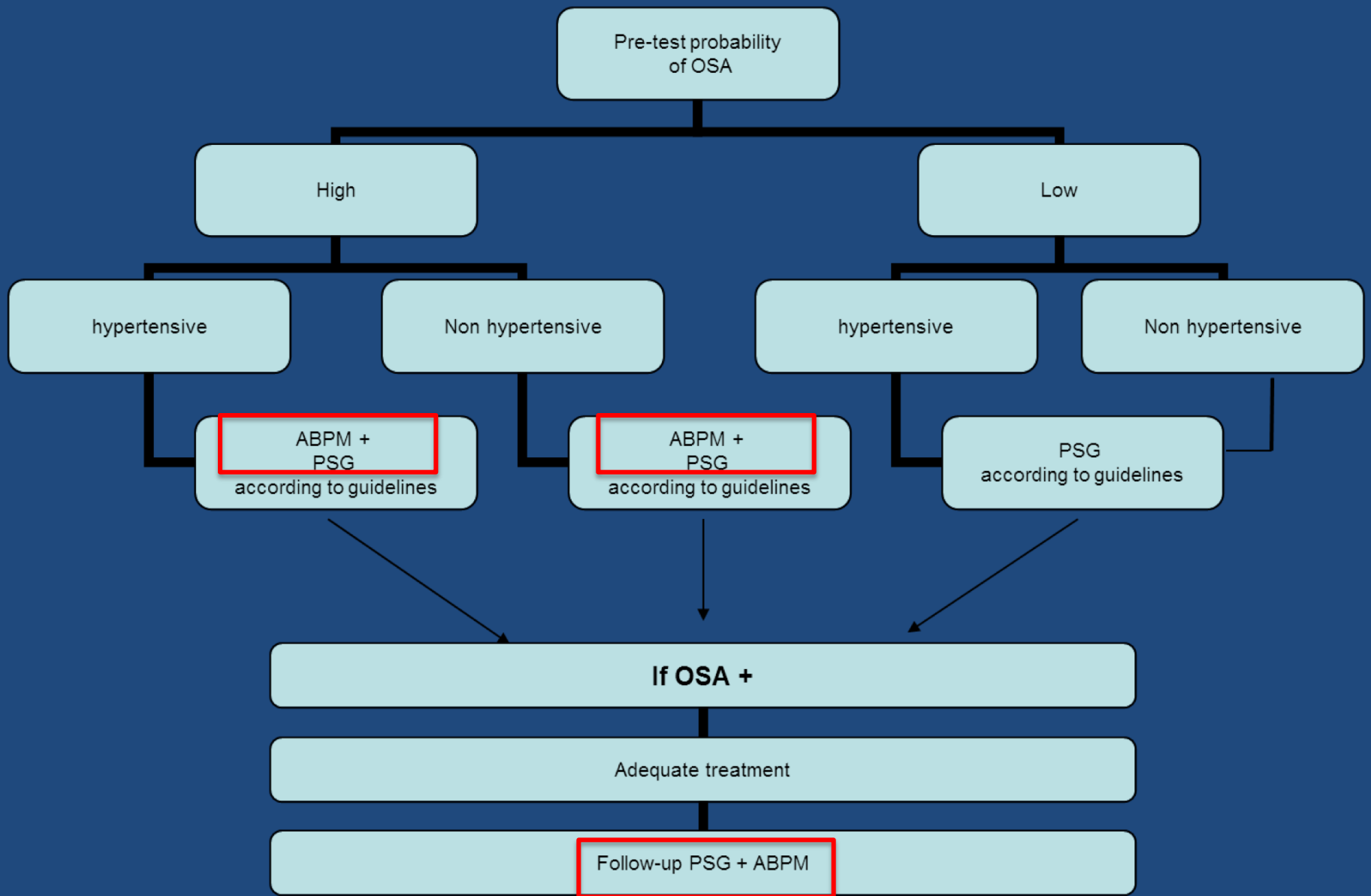
Eur Respir J 2013; 41: 523–538
DOI: 10.1183/09031936.00226711
Copyright©ERS 2013



ERS/ESH TASK FORCE REPORT

Recommendations for the management of patients with obstructive sleep apnoea and hypertension

Gianfranco Parati, Carolina Lombardi, Jan Hedner, Maria R. Bonsignore, Ludger Grote, Ruzena Tkacova, Patrick Lévy, Renata Riha, Claudio Bassetti, Krzysztof Narkiewicz, Giuseppe Mancia and Walter T. McNicholas on behalf of the EU COST Action B26 members



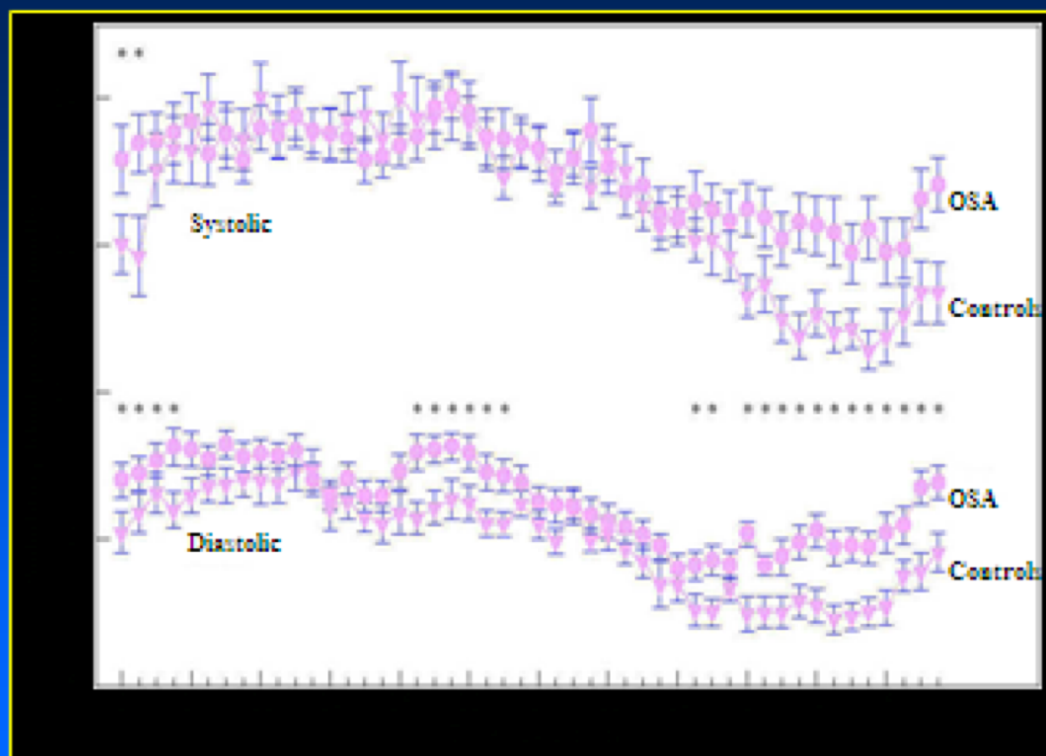
NON DIPPING



OSA



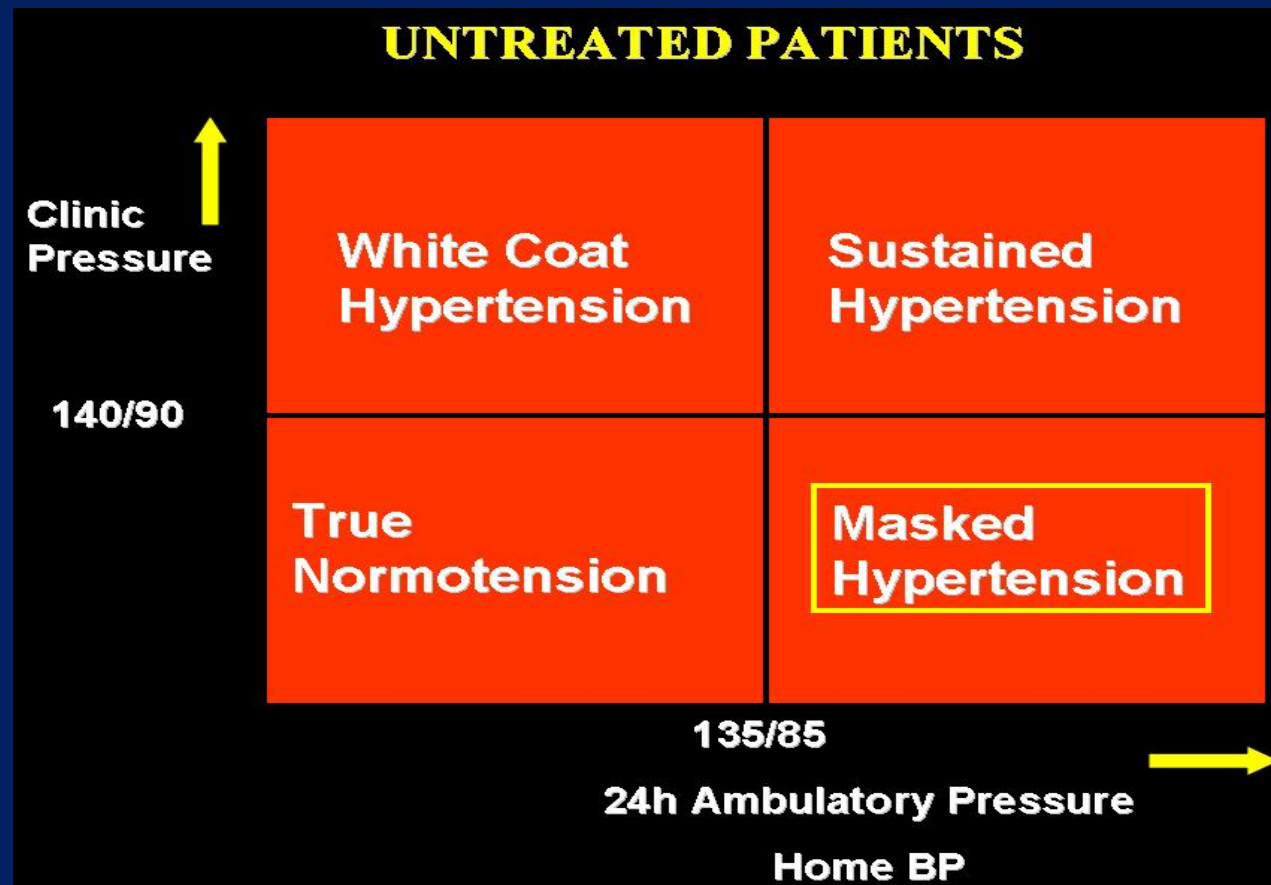
Ambulatory BP Profiles for Sleep Apnoea Subjects (n = 45) compared to Closely Matched Control Subjects (n = 45)



Davies et al., Thorax 2000; 55: 736-740

Masked hypertension in obstructive sleep apnea syndrome

Jean-Philippe Baguet^{a,b}, Patrick Lévy^{c,d}, Gilles Barone-Rochette^a,
Renaud Tamisier^{c,d}, Hélène Pierre^a, Marie Peeters^{c,d}, Jean-Michel Mallion^a
and Jean-Louis Pépin^{c,d}



High prevalence of unrecognized sleep apnoea in drug-resistant hypertension

Alexander G. Logan^{a,c}, Sandra M. Perlikowski^a, Andrew Mente^a, Andras Tisler^a, Ruzena Tkacova^b, Mitra Niroumand^b, Richard S.T. Leung^b and T. Douglas Bradley^{b,c}

Hypertension Research (2014) 37, 601–613
© 2014 The Japanese Society of Hypertension. All rights reserved 0916-9636/14
www.nature.com/htr



REVIEW SERIES

Obstructive sleep apnea syndrome as a cause of resistant hypertension

Gianfranco Parati^{1,2}, Juan Eugenio Ochoa^{2,3}, Grzegorz Bilo², Paola Mattaliano^{2,3}, Paolo Salvi², Kazuomi Kario⁴ and Carolina Lombardi²

Data are mean $\pm$ SEM. * $P < 0.05$, Fisher's exact test; † $P < 0.05$, unpaired t -test.

OSA was defined as AHI ≥ 10 and resistant HT as clinic BP $> 140/90$ mmHg, while taking a sensible combination of ≥ 3 antihypertensive drugs, titrated to maximally recommended doses.

The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure

The JNC 7 Report

Aram V. Chobanian, MD

George L. Bakris, MD

Henry R. Black, MD

William C. Cushman, MD

Lee A. Green, MD, MPH

Joseph L. Izzo, Jr. MD

Daniel W. Jones, MD

Barry J. Materson, MD, MBA

Suzanne Oparil, MD

Jackson T. Wright, Jr. MD, PhD

Edward J. Roccella, PhD, MPH

and the National High Blood Pressure Education Program Coordinating Committee

Box 3. Causes of Resistant Hypertension

Improper blood pressure in
Volume overload and pseudohypertension
Excess sodium intake
Volume retention from kidney disease
Inadequate diuretic therapy
Drug-induced or other causes
Nonadherence
Inadequate doses
Inappropriate combinations
Nonsteroidal anti-inflammatory drugs; cyclooxygenase 2 inhibitors
Cocaine, amphetamines, other illicit drugs
Sympathomimetics (decongestants, anorectics)
Oral contraceptives
Adrenal steroids
Cyclosporine and tacrolimus
Erythropoietin
Licorice (including some chewing tobacco)
Selected over-the-counter dietary supplements and medicines (eg, ephedra, ma huang, bitter orange)
Associated conditions
Obesity
Excess alcohol intake
Identifiable causes of hypertension (see Box 2)

Box 2. Identifiable Causes of Hypertension

Sleep apnea

Drug-induced or drug-related
(see Box 3)

Chronic kidney disease

Primary aldosteronism

Renovascular disease

Chronic steroid therapy and
Cushing syndrome

Pheochromocytoma

Coarctation of the aorta

Thyroid or parathyroid disease

JAMA. 2003

May 21;289(19):2560-72.

2007 Guidelines for the Management of Arterial Hypertension

The Task Force for the Management of Arterial Hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC)

Box 20 Causes of resistant hypertension

- Poor adherence to therapeutic plan
- Failure to modify lifestyle including:
 - weight gain
 - heavy alcohol intake (NB: binge drinking)
- Continued intake of drugs that raise blood pressure (liquorice, cocaine, glucocorticoids, non-steroid anti-inflammatory drugs etc.)
- Obstructive sleep apnea
- Unsuspected secondary cause
- Irreversible or scarcely reversible organ damage
- Volume overload due to:
 - inadequate diuretic therapy
 - progressive renal insufficiency
 - high sodium intake
 - hyperaldosteronism

Causes of spurious resistant hypertension:

- Isolated office (white-coat) hypertension
- Failure to use large cuff on large arm
- Pseudohypertension

**ESH-ESC GUIDELINES
J.Hypertension 2007,
25:1105–1187**



WHY?





Intermediary Mechanisms

Sympathetic Activation

Vasoconstriction

Increased Catecholamines

Tachycardia

Impaired CV Variability

Endothelial Dysfunction

Vascular Oxidative Stress

Inflammation

Increased Coagulation

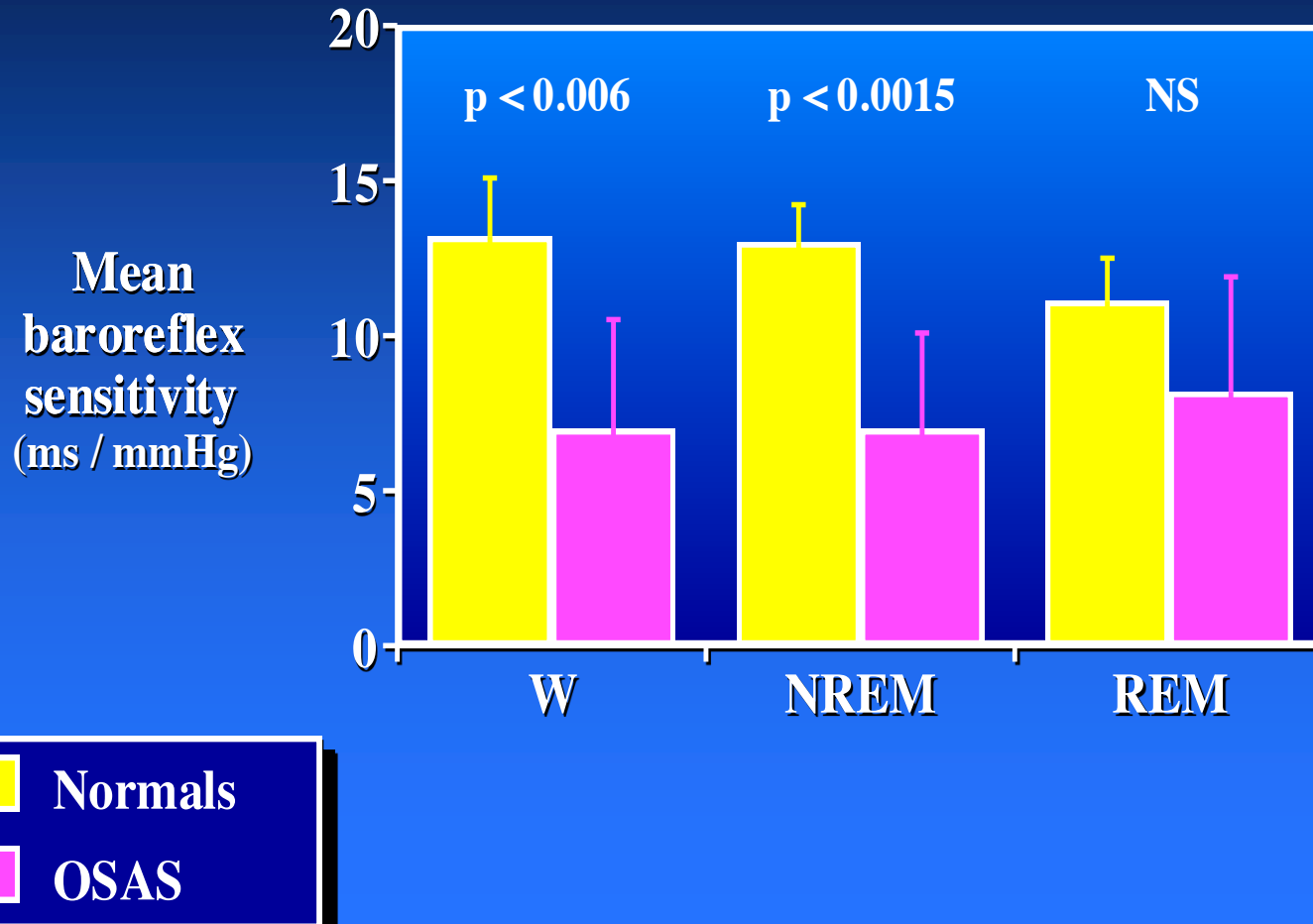
Metabolic Dysregulation

Leptin Resistance

Obesity

Insulin Resistance

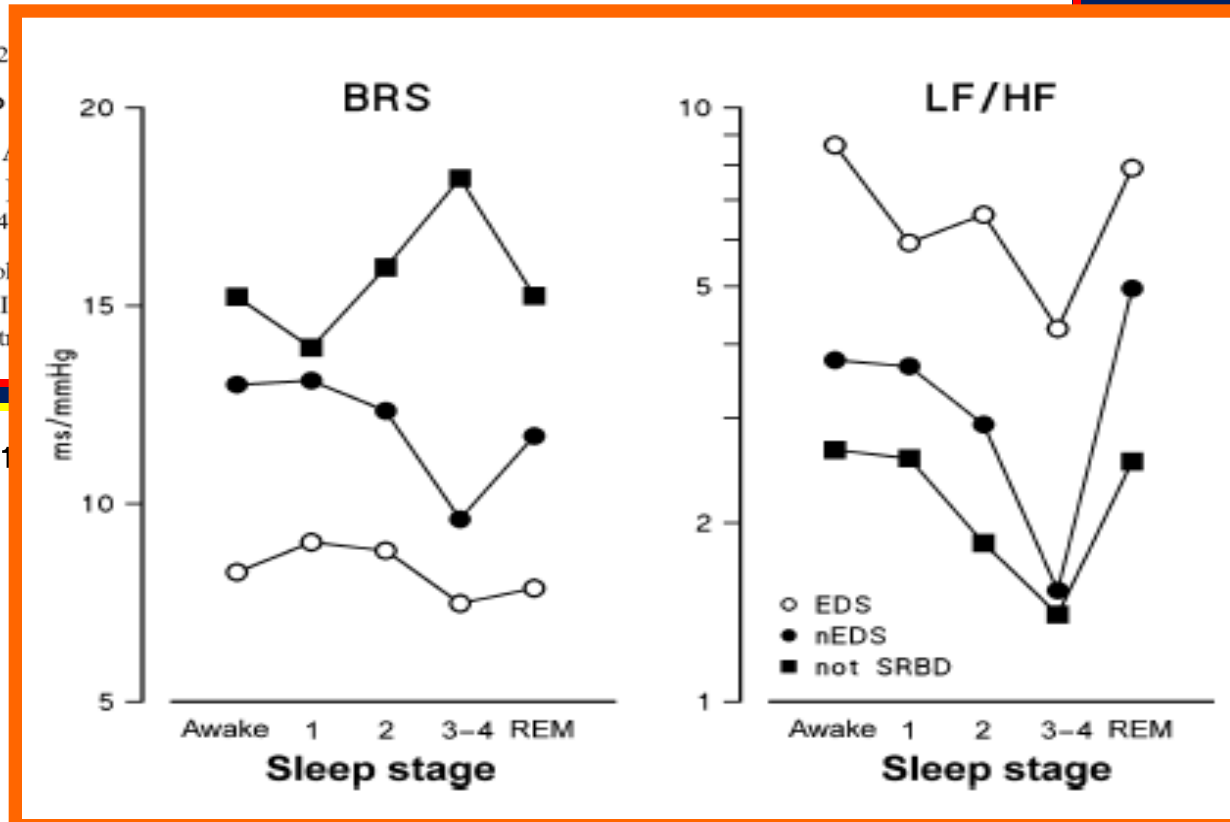
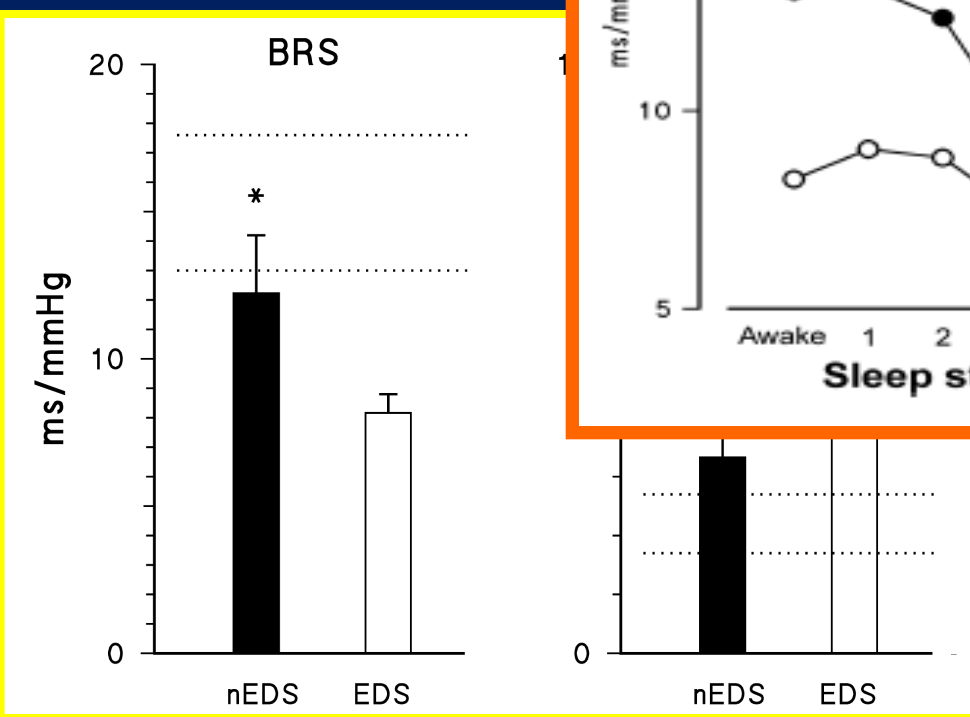
Spontaneous baroreflex sensitivity (BRS) during sleep is lower in OSAS patients than in normals in all sleep stages



Daytime sleepiness and neural cardiac modulation in sleep-related breathing disorders

CAROLINA LOMBARDI^{1,2},
CORTELLI¹, FEDERICA P.
GIUSEPPE PLAZZI¹, LUC
ELIO LUGARES¹, GIUSE
and PAOLO CASTIGLIONI⁴

¹Center for Sleep Disorders, Department of Neuro
Prevention, University of Milano-Bicocca, Milan, I
⁴Polo Tecnologico, Biomedical Technology Depart



Obstructive Sleep Apnea

Obstructive Sleep Apnea With Objective Daytime Sleepiness Is Associated With Hypertension

Rong Ren,* Yun Li,* Jihui Zhang, Junying Zhou, Yuanfeng Sun, Lu Tan, Taomei Li,
Yun-Kwok Wing, Xiangdong Tang

(*Hypertension*. 2016;68:1264-1270.

Table 3. Adjusted ORs and 95% CIs for the Association of Hypertension With OSA and MSLT

Predictors	n	OR (95% CI)		
		Model 1	Model 2	Model 3
Primary snoring				
MSLT >8 min	353	Reference	Reference	Reference
5 min≤MSLT≤8 min	85	1.03 (0.61–1.75)	1.08 (0.64–1.84)	1.13 (0.66–1.92)
MSLT <5 min	46	0.88 (0.44–1.80)	0.94 (0.46–1.80)	1.00 (0.40–2.04)
OSA				
MSLT >8 min				
5 min≤MSLT≤8 min				
MSLT <5 min				

SO.....SLEEPINESS AND NOT ONLY SLEEP IS A NEW CARDIOVASCULAR FRONTIER??

Probably yes

**SO.....SLEEPINESS AND NOT ONLY SLEEP IS A NEW
CARDIOVASCULAR FRONTIER??**

Probably yes

He's listening.

inTREATMENTSM

One doctor. Five sessions. Five nights a week.



LAURA
MONDAY 9:30



ALEX
TUESDAY 9:30



SOPHIE
WEDNESDAY 9:30



JAKE & AMY
THURSDAY 9:30



GINA
FRIDAY 9:30

MONDAY-FRIDAY AT 9:30PM. SERIES PREMIERE JAN. 28
HALF-HOUR SESSIONS AVAILABLE ON YOUR SCHEDULE

HBO



ON HBO
Catch up with back-to-back
episodes every Sunday



ON DEMAND
Watch episodes
whenever you want



ONLINE
Stream select episodes
at HBO.com



ON THE GO
Download select episodes
for free on iTunes

BENEFIT IS NOT THE SAME FOR EVERYONE



EFFECTS OF CPAP ON BP

Table 1 Summary of meta-analyses of randomized controlled CPAP trials

Study	Number of trials/patients	BP end point	Minimum CPAP duration	Outcome
• COMPLIANCE!!! • EXCESSIVE DAYTIME SLEEPINESS? • SLEEP COMORBIDITIES, PLMS? • TARGET ORGAN DAMAGE?				
Mo and He [28]	7/471	Ambulatory	4 wk	24-h SBP: -0.95 mm Hg (not significant) 24-h DBP: -1.78 mm Hg

BMI body mass index, *BP* blood pressure, *CPAP* continuous positive airway pressure, *DBP* diastolic blood pressure, *OSA* obstructive sleep apnea, *SBP* systolic blood pressure

Position paper on the management of patients with obstructive sleep apnea and hypertension: Joint recommendations by the European Society of Hypertension, by the European Respiratory Society and by the members of European COST (COoperation in Scientific and Technological research) ACTION B26 on Obstructive Sleep Apnea

Gianfranco Parati^{a,b}, Carolina Lombardi^b, Jan Hedner^c, Maria R. Bonsignore^d, Ludger Grote^c, Ruzena Tkacova^e, Patrick Levy^f, Renata Riha^g, Claudio Bassetti^h, Krzysztof Narkiewiczⁱ, Giuseppe Mancia^a, Walter T. McNicholas^j, on behalf of the EU COST ACTION B26 members

Journal of Hypertension 2012, 30:633–646

Continuous positive airway pressure treatment in obstructive sleep apnea patients with hypertension

Many studies have assessed the impact of active therapy of OSA on BP levels both in normotensive and hypertensive patients with variable results (see Table S1).

The various reports have employed widely different methodologies, ranging from short-term placebo-controlled protocols to long-term observational studies. Despite the widely differing methodologies, the overall findings of these reports is that CPAP therapy in OSAS results in a lowering of BP levels, which is most pronounced when assessed by ABPM and in patients with severe OSA that regularly use CPAP every night for at least 5 h per night, and who have preexisting hypertension. The benefit affects both SBP and DBP and is evident both during wakefulness and sleep.

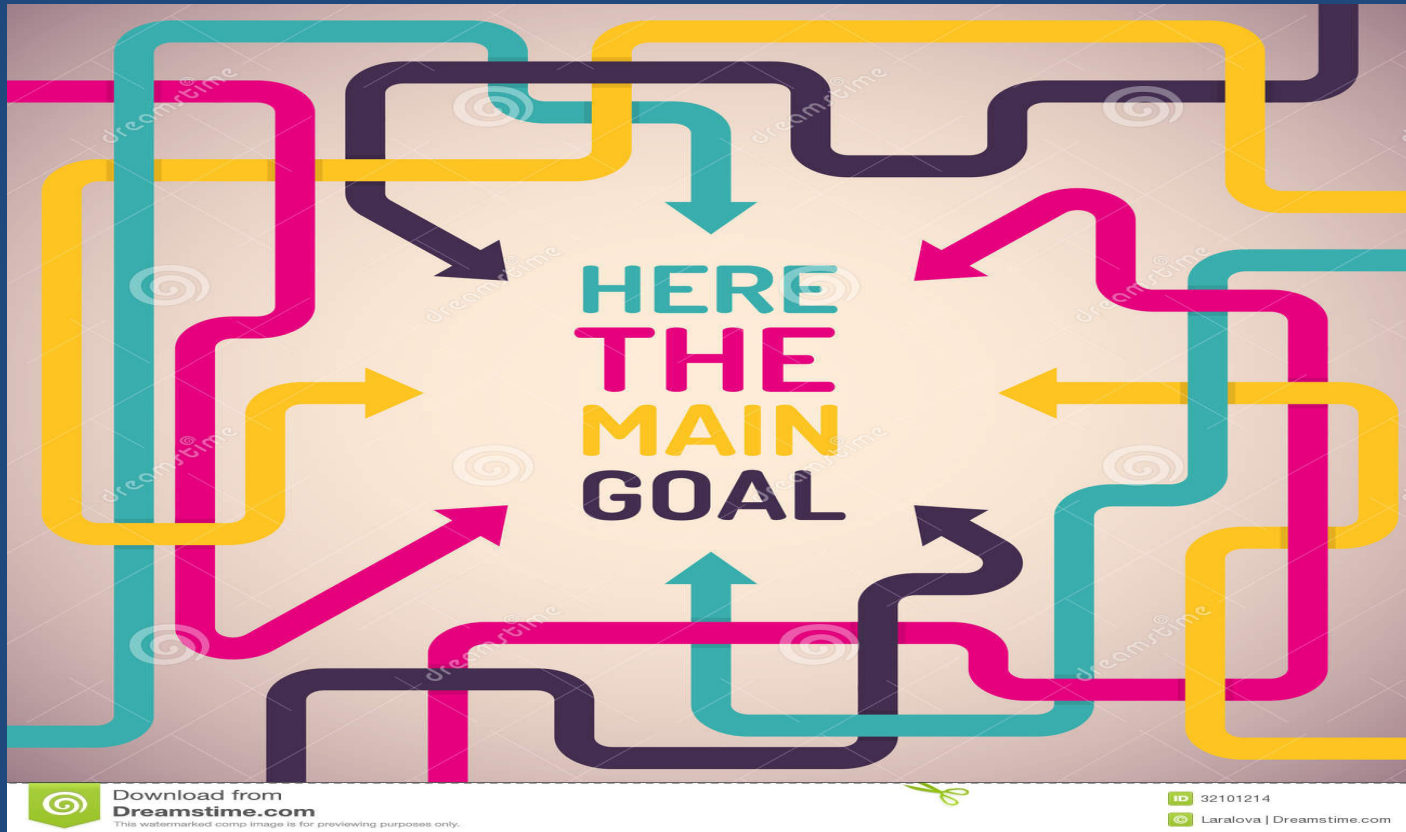


Key Points

- Diagnosis methodology
 - EDS/ non EDS
 - Treatment Adherence, Titration, Auto/fixed
 - Hypertension/non hypertension at baseline, Masked hypertension, Uncontrolled/controlled hypertension, Resistant hypertension
 - Target organ damage
- PRIMARY PREVENTION!!!!**



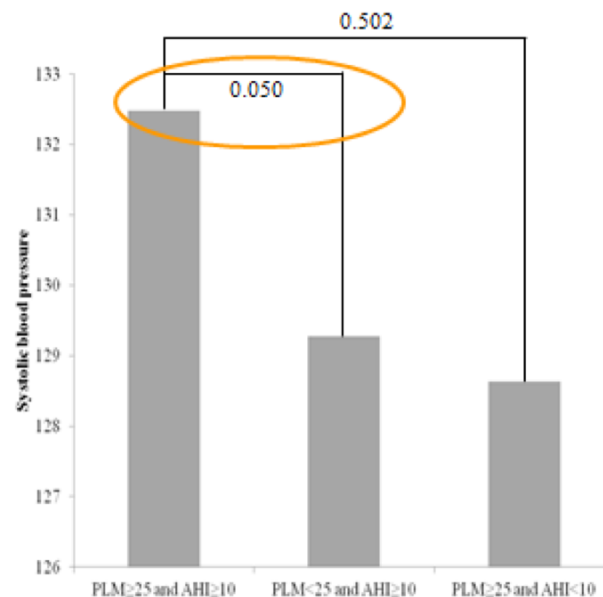
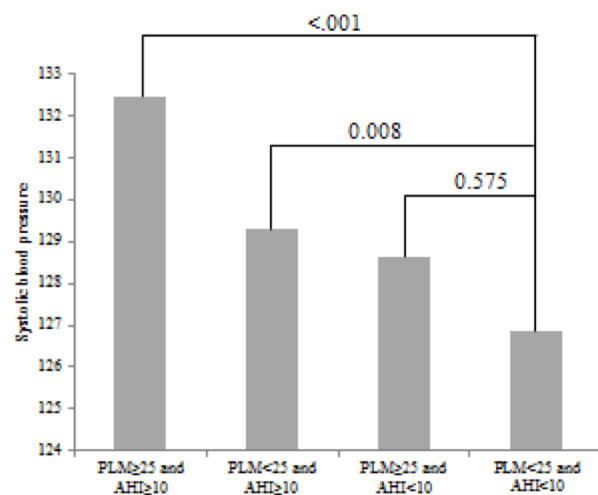
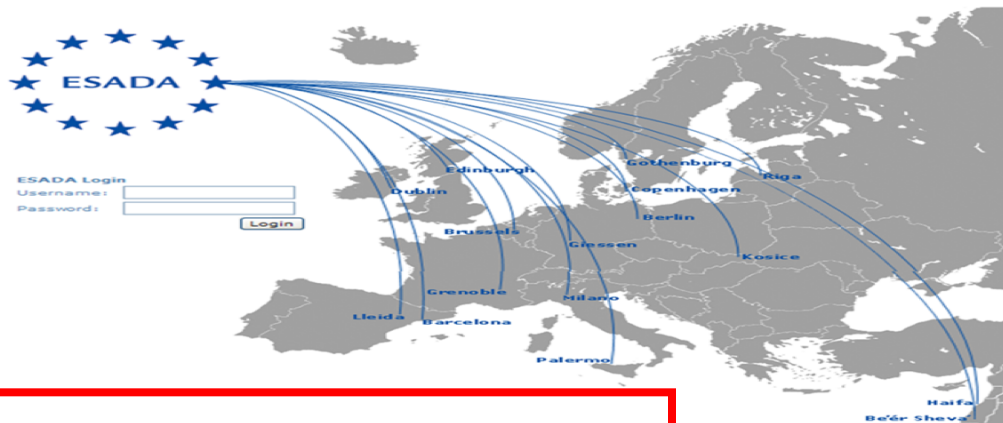
BEST PHENOTYPING



Predictors?

"Our goal is to generate a pan European sleep laboratory database for cross-sectional and for outcome research in sleep apnea"

The Esada project uses a web based platform for collection of clinical data from patients referred to European sleep laboratories. Specific sub cohort protocols linked to the database deal with pathophysiology, genetic mechanism, neurocognitive, impairment and cardiovascular disease in obstructive sleep apnea.



INSOMNIA



Circadian Sleep Disorders and Social JetLag

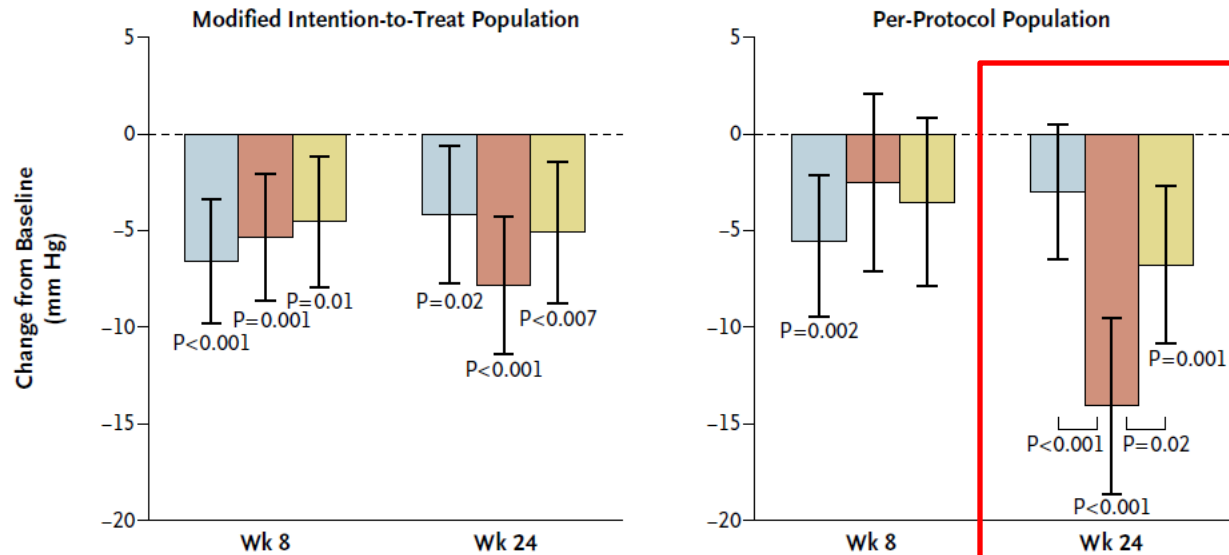
6 AM	10 AM
A blue stick figure standing upright, representing a person who is awake at 6 AM on other weekdays.	A blue stick figure lying in bed, representing a person who is sleeping at 10 AM on weekends. The text "ZZ" and "medchrome.com" are above the figure. An alarm clock is shown ringing with yellow lightning bolts.
Other Weekdays	Weekend (Go to hell you circadian rhythm)

«global treatment» of OSA

CPAP, Weight Loss, or Both for Obstructive Sleep Apnea

CPAP alone Weight loss+CPAP Weight loss alone

C Change in Systolic Blood Pressure





Which place of pharmacological approaches beyond continuous positive airway pressure to treat vascular disease related to obstructive sleep apnea? ☆

Elodie Gautier-Veyret ^{a,*}, Jean-Louis Pépin, Françoise Stanke-Labesque

^a Univ. Grenoble Alpes, HP2, F-38041 Grenoble, France

INSERM U1042, 38041 Grenoble, France

Centre hospitalier Universitaire Grenoble Alpes, 38043 Grenoble, France

Table 2
Studies investigating vascular effects of drugs in OSA patients.^a

Drug	Mode of action	Treatment modalities	Study design	Study population	Effects on vascular parameters ^a
Losartan	Angiotensin II receptor antagonist	50 mg/d for 6 weeks	Open randomized parallel-design trial: losartan alone (n = 23) vs. losartan + CPAP (n = 25)	Newly diagnosed hypertensive and OSA patients	↓ BP without any additive effect with CPAP, except in adherent patients (Thunström et al., 2016)
Spironolactone	Mineralocorticoid receptor antagonist	20 mg/d (up to 40 mg/d if required at week 4) for 12 weeks	Open blank-controlled randomized trial: usual hypertensive therapy vs. usual hypertensive therapy + spironolactone (n = 15 in each arm)	Moderate to severe OSA patients with resistant hypertension	↓ BP (Yang et al., 2016)
Eplerenone	Mineralocorticoid receptor antagonist	50 mg/d for 3 months	Observational uncontrolled trial (n = 31)	Moderate to severe OSA patients with resistant hypertension	↓ BP, PWV, aortic AIHR75, and AI (Krašífska et al., 2016)
Bosentan	Mixed endothelin receptor antagonist (ET _A and ET _B)	125 mg/d for 4 weeks	RCT cross-over design: bosentan vs. CPAP (n = 16)	Mildly hypertensive patients with severe OSA	↓ BP with a trend for a greater effect than CPAP (Joyeux-Faure et al., 2016)
Carbocysteine	Antioxidant	1500 mg/d (500 mg tid) for 6 weeks	Observational uncontrolled trial ^b (n = 40)	Moderate to severe OSA patients	↓ IMT ↔ FMD (Wu et al., 2016)
Vitamin C	Antioxidant	Single intravenous injection of 0.5 g	Case-control study (n = 10 cases)	Untreated severe OSA patients	↔ FMD (Grebe et al., 2006)
Vitamin C	Antioxidant	Single intra-arterial infusion of 625 mg	Case-control study (n = 11 cases)	Male moderate to severe OSA patients	↔ Ach-induced FBF (Büchner et al., 2011)
Allopurinol	Antioxidant (xanthine oxidase inhibitor)	300 mg/d for 2 weeks	RCT cross-over design: allopurinol vs. placebo (n = 12)	Moderate to severe OSA not treated	↔ FMD (El Solh et al., 2006)
Atorvastatin	HMG-CoA reductase inhibitor	40 mg/d for 12 weeks	RCT parallel-design: atorvastatin (n = 25) vs. placebo (n = 26)	Severe OSA patients	↓ BP ↔ PAT, PWV and carotid atherosclerosis (IMT and luminal diameter) (Joyeux-Faure et al., 2014)
Testosterone	Androgenic hormone	1000 mg at 0, 6, and 12 weeks	RCT parallel-design: testosterone (n = 33) vs. placebo (n = 34), both combined with lifestyle modification program	Obese OSA men	↓ aortic AI by 3.2% (Hoyos et al., 2012)
Liraglutide	Glucagon-like peptide-1 analog	3 mg for 32 weeks combined with diet and exercise	Double blind RCT: liraglutide (n = 180) vs. placebo (n = 179)	Obese moderate to severe OSA patients	↓ systolic BP ↔ diastolic BP (Blackman et al., 2016)
Phentermine + topiramate	Phentermine: sympathomimetic amine Topiramate: inhibitor of carbonic anhydrase ^d	15 mg/d of phentermine + extended release topiramate 92 mg/d for 28 weeks	Double blind RCT: phentermine + topiramate (n = 22) vs. placebo (n = 23), both combined with lifestyle-modification counseling	Obese moderate to severe OSA patients	↓ systolic BP (Winslow et al., 2012)

«SLEEP TEAM»

Prof. Parati Gianfranco



Dott.ssa Mattaliano

Dott.ssa Laccu

Dott. Pengo

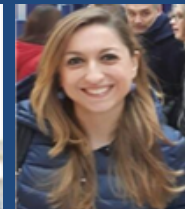


Students and fellows:

Davide

Valentina

Federica



TNFP

- Barbara Riccardi
- Francesca Gregorini
- Anna Motta
- Valeria De Stefano



Ing. Faini Andrea

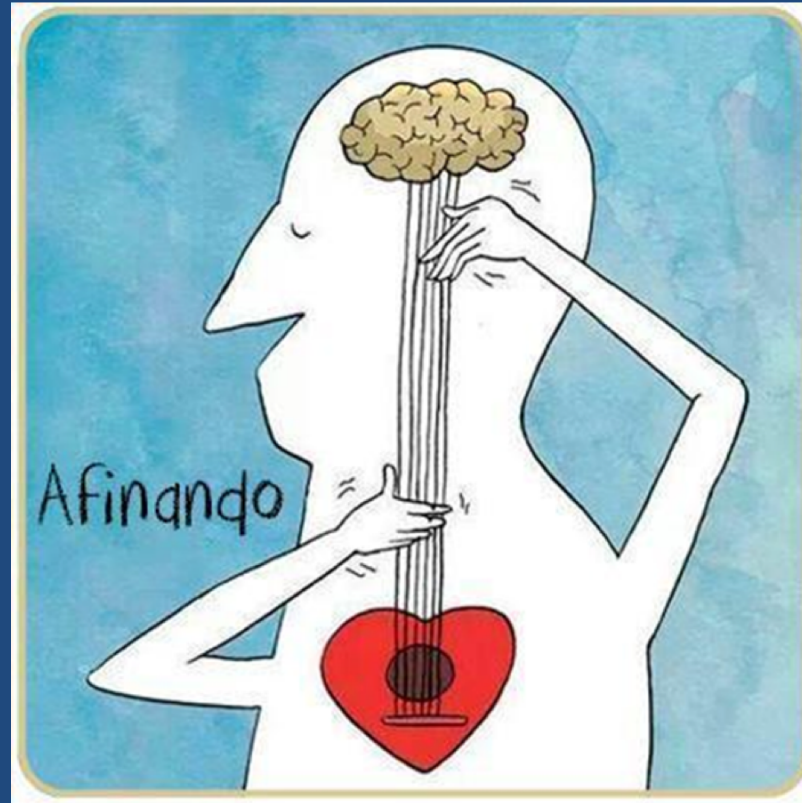
Ing.Castiglioni Paolo

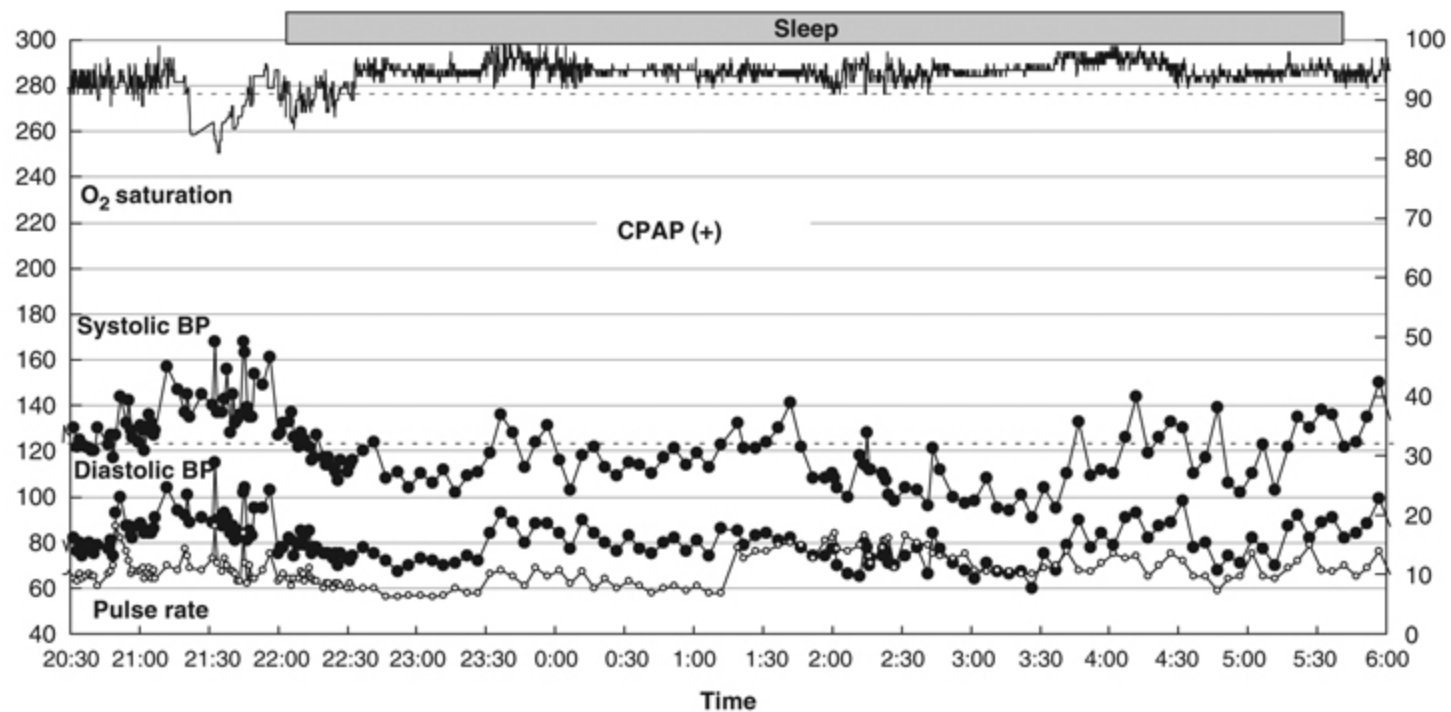
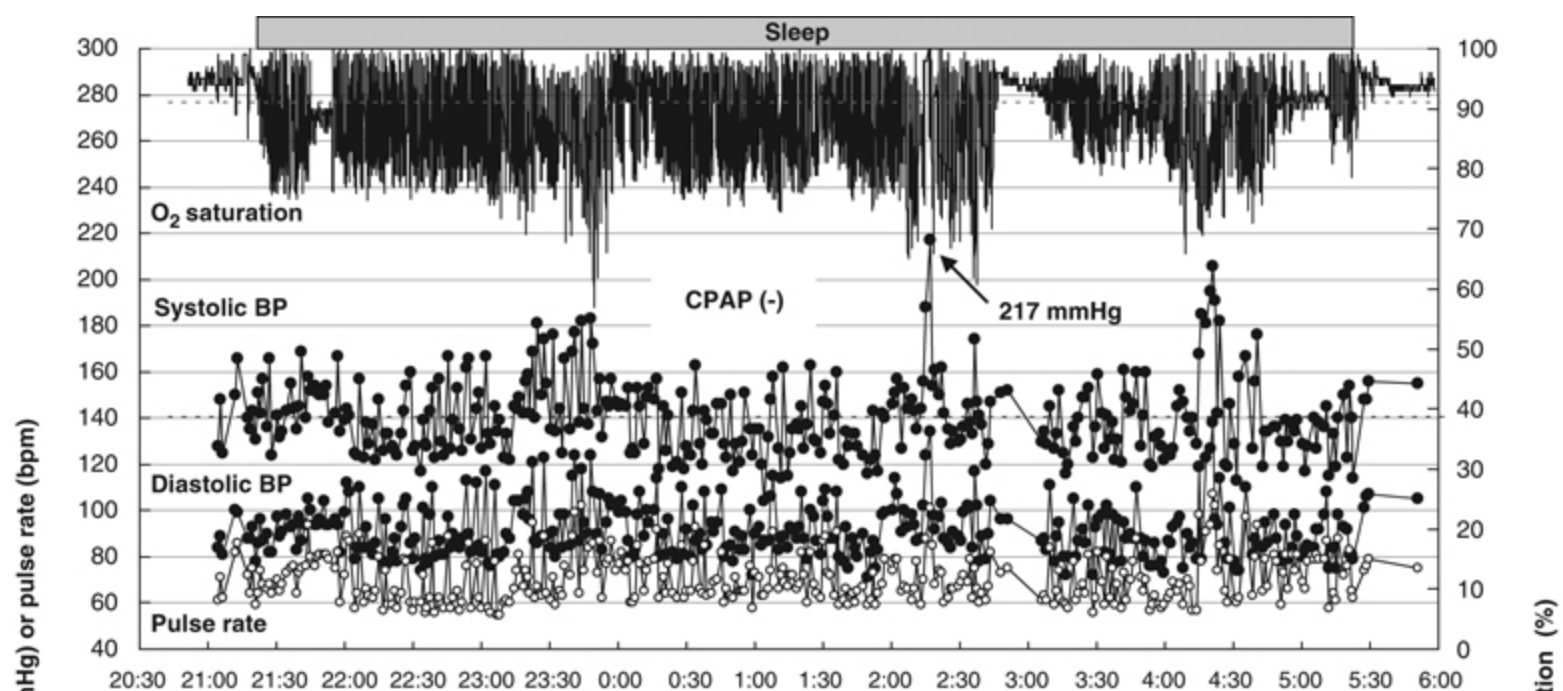


Thank you for your attention



THANK YOU FOR YOUR ATTENTION





Systolic BP (mmHg)

