11th Annual Cardiology Summit
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The most accurate predictors of arterial hypertension in patients with Obstructive Sleep Apnea Syndrome

Natsios Georgios

University Hospital of Larissa, Greece

Definitions

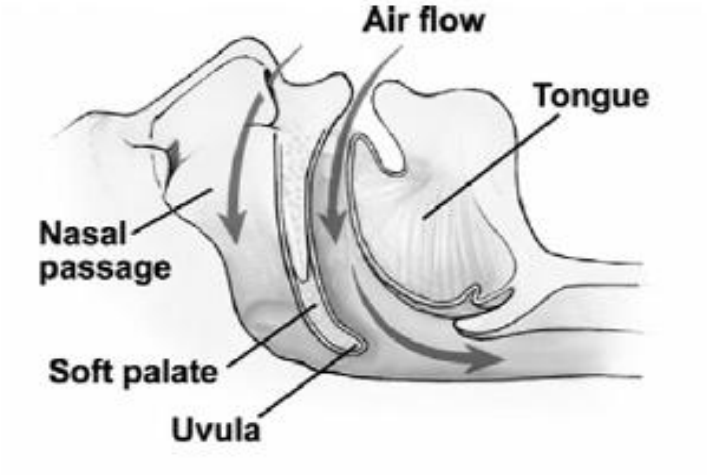
- **Obstructive Sleep Apnea (OSA)**

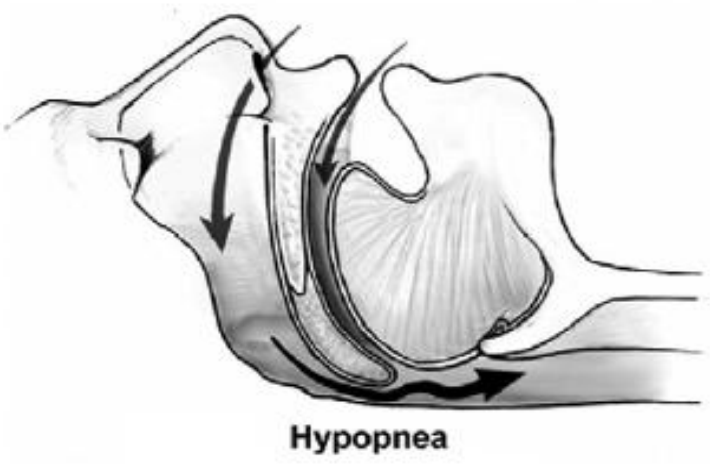
  complete upper airways obstruction (≥ 90% loss of airflow) for at least 10 sec with preserved respiratory effort

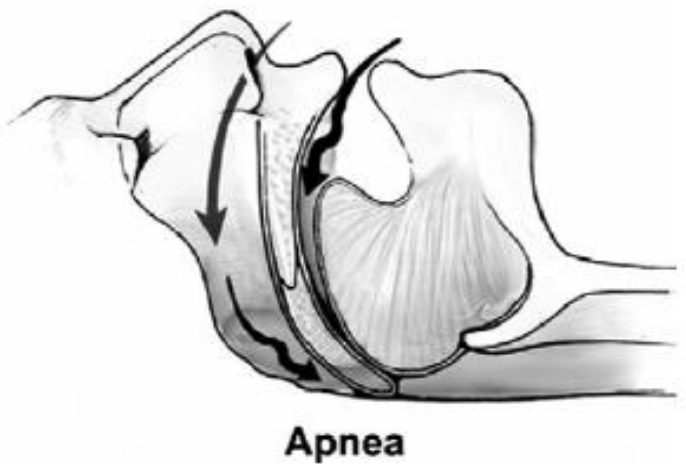
- **Obstructive Sleep Hypopnea**
  - >50% reduction in airflow
  - <50% reduction in airflow associated with a desaturation of >3%
  - a moderate reduction in airflow with associated arousal by electroencephalography *(Chicago Criteria)*

AASM Task Force. Sleep 1999:22:667-89

Obstructive Sleep Apnea & Hypopnea

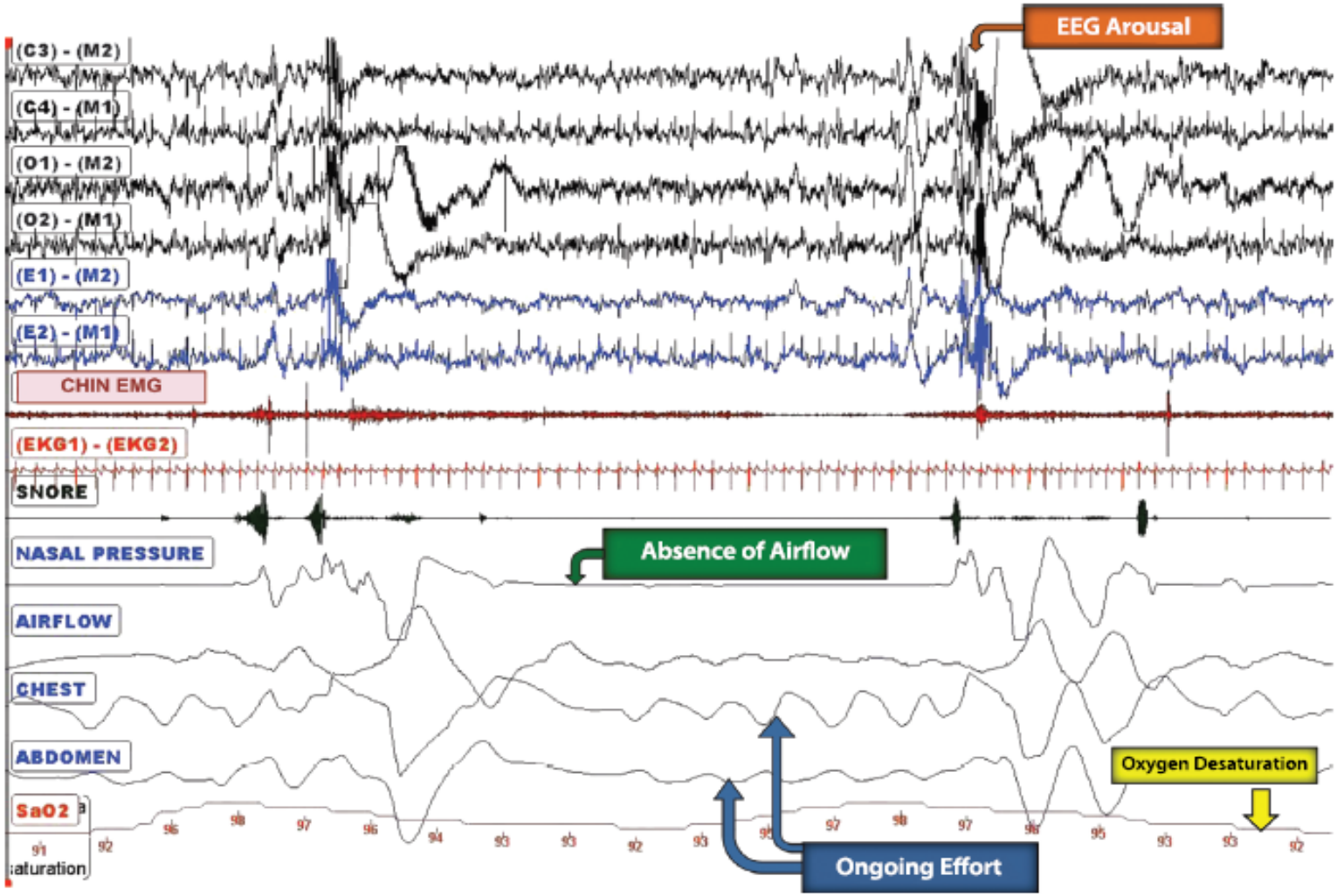






J Am Coll Cardiol 2008;52:686–717

Polysomnographic example of obstructive apnea



Continuum (Minneap Minn) 2013;19(1):86–103

Definitions

- **Apnea-Hypopnea Index (AHI)**

✓ the number of apneas and hypopneas per hour of sleep

✓ the measure used to define the severity of the OSA syndrome

- **Oxygen Desaturation Index (DI)**

the number of > 3% arterial oxygen desaturations per hour of sleep

Mayo Clin Proc 2011;86:549-55

Definitions

- **Respiratory Effort Related Arousal (RERA)**

  events characterised by increased respiratory effort during sleep caused by flow limitation in the upper airways which is terminated by an arousal from sleep.

- **Respiratory Disturbance Index (RDI)**

  summarises both the AHI and the RERA indices together.

J Clin Sleep Med 2012;8(5):597-619

Definitions

- **Obstructive Sleep Apnea Syndrome (OSAS)**

➢ AHI > 5 and associated symptoms

(excessive daytime sleepiness, chocking or gasping during sleep, recurrent awakenings from sleep, unrefreshing sleep, daytime fatigue, impaired concetration)

or

➢ AHI ≥ 15 regardless of associated symptoms

- **Mild** = AHI between 5 and below 15
- **Moderate** = AHI between 15 and below 30
- **Severe** = AHI above 30

Mayo Clin Proc 2011;86:549-55

Epidemiology - OSA

- in 5% to 10% of the general population, regardless of race and ethnicity. *Proc Am Thorac Soc 2008;5:136–143*
- The prevalence of OSA is increasing in developed countries in parallel with the increasing prevalence of obesity. *CHEST 2015; 148 (3): 824 - 832*
- AHI ≥ 15 occurs in 6% to 13% of the adult population affecting more than 20 million Americans.
- Among middle-aged adults, the prevalence of OSA is 24% to 26% in men and 17% to 28% in women.

Am J Epidemiol 2013; 177 (9): 1006 - 1014

Clinical symptoms, characteristics and objective findings suggesting a high probability for OSAS

1) OSA related symptoms and clinical signs

Night-time

Witnessed apnoeas
Loud, frequent and intermittent snoring
Dry mouth
Thirsty during the night
Nocturnal diuresis
Choking; dyspnoea
Disturbed sleep
Sweating; nasal congestion (preferably night-time)
Family history of snoring and sleep apnoea

Daytime

Increased daytime sleepiness
Daytime fatigue
Concentration difficulties
Monotony intolerance
Morning pain in the throat
Headache (preferably in the morning hours)

2) Frequent clinical characteristics

- Male sex
- Post-menopausal females
- Overweight, preferably central obesity (linkage between history of obesity and snoring/witnessed apnoeas/sleepiness)
- History of cardiovascular disease (ischaemic heart disease, stroke or heart failure, probability of OSA 30% to >50%)
- Upper airway anatomic abnormalities (enlarged tonsils and uvula, adenoids and macroglossia, according to Friedman classification stage III)
- Retrognathia

3) Objective findings in the cardiovascular/metabolic risk assessment of hypertensive patients

- Refractory hypertension (likelihood of OSA 50% to >80%)
- Nocturnal non-dipping of 24-h blood pressure
- Left ventricular hypertrophy
- Generalised atherosclerotic disease
- Holter ECG (nocturnal bradycardia/tackycardia, SA and AV blocks during the sleep period, increased occurrence of SVES/VES during sleep period, atrial fibrillation, paroxysmal nocturnal atrial fibrillation)
- Metabolic disease like diabetes mellitus

ERS/ESH TASK FORCE REPORT
Eur Respir J 2013; 41: 523–538

OSA & Hypertension

- There is a high prevalence of OSA in hypertensive individuals (30%-40%).

Am J Cardiol 2010;105:1135–1139

- If we consider only patients with resistant hypertension, then an increase in prevalence, reaching 83%, is observed. *CHEST 2015; 148 (3): 824 - 832*

- 50% to 56% of OSA patients have hypertension.

Am J Cardiol 2010;105:1135–1139

OSA & Hypertension

- An association between OSA and hypertension has been observed since the early description of OSA in the 1970s.

Annu Rev Med 1976;27:465–484

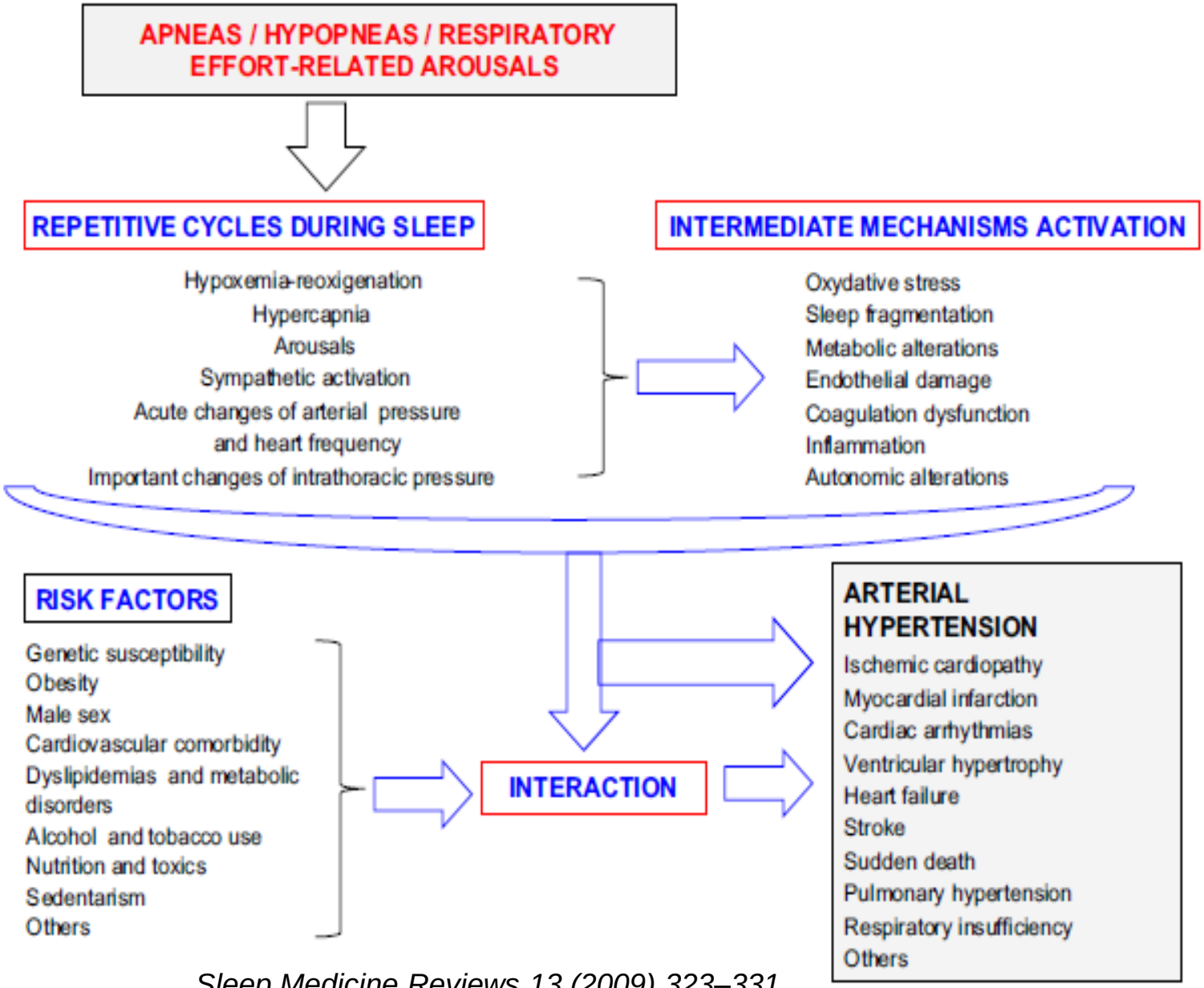
Lancet 1984;2:1005–1008

- Whether OSA is truly an independent risk factor for hypertension has yet to be definitively established.

- Patients with hypertension and patients with OSA have common risk factors such as age, sex, obesity, smoking, and alcohol abuse.

Hypertension 2014;63:203–209

Physiopathological mechanisms involved in the etiology of hypertension



Sleep Medicine Reviews 13 (2009) 323–331

OSA & Hypertension

- In recent years, the majority of studies performed to examine the relationship between OSA and hypertension have focused on the role of AHI.
- The results of these studies were controversial.

- Data from some studies support a dose-response relationship of OSA at baseline and the cumulative incidence of hypertension. *N Engl J Med 2000;342:1378-84*

  JAMA 2012;307:2169-76

- In contrast, other studies have reported that the unadjusted risk of hypertension increases in concert with AHI, but this association was not significant after adjustment for potential confounding variables. *Am J Respir Crit Care Med 2009;179:1159-64*

  Am J Respir Crit Care Med 2011;184:1299-304

The New England Journal of Medicine

VOLUME 342 MAY 11, 2000 NUMBER 19

PROSPECTIVE STUDY OF THE ASSOCIATION BETWEEN SLEEP-DISORDERED BREATHING AND HYPERTENSION

PAUL E. PEPPARD, PH.D., TERRY YOUNG, PH.D., MARI PALTA, PH.D., AND JAMES SKATRUD, M.D.

TABLE 3. ADJUSTED ODDS RATIOS FOR HYPERTENSION AT A FOLLOW-UP SLEEP STUDY, ACCORDING TO THE APNEA–HYPOPNEA INDEX AT BASE LINE.*

BASE-LINE APNEA–HYPOPNEA INDEX	ODDS RATIO, ADJUSTED FOR BASE-LINE HYPERTENSION STATUS	ODDS RATIO, ADJUSTED FOR BASE-LINE HYPERTENSION STATUS AND NONMODIFIABLE RISK FACTORS (AGE AND SEX)	ODDS RATIO, ADJUSTED FOR BASE-LINE HYPERTENSION STATUS, NONMODIFIABLE RISK FACTORS, AND HABITUS (BMI AND WAIST AND NECK CIRCUMFERENCE)	ODDS RATIO, ADJUSTED FOR BASE-LINE HYPERTENSION STATUS, NONMODIFIABLE RISK FACTORS, HABITUS, AND WEEKLY ALCOHOL AND CIGARETTE USE
	odds ratio (95% confidence interval)			
0 events/hr†	1.0	1.0	1.0	1.0
0.1–4.9 events/hr	1.66 (1.35–2.03)	1.65 (1.33–2.04)	1.42 (1.14–1.78)	1.42 (1.13–1.78)
5.0–14.9 events/hr	2.74 (1.82–4.12)	2.71 (1.78–4.14)	2.03 (1.29–3.19)	2.03 (1.29–3.17)
≥15.0 events/hr	4.54 (2.46–8.36)	4.47 (2.37–8.43)	2.89 (1.47–5.69)	2.89 (1.46–5.64)
P for trend‡	<0.001	<0.001	0.002	0.002

American Heart Association

Hypertension. 2003;42:1206–1252.

SEVENTH REPORT OF THE JOINT NATIONAL COMMITTEE ON PREVENTION, DETECTION, EVALUATION, AND TREATMENT OF HIGH BLOOD PRESSURE

Aram V. Chobanian, George L. Bakris, Henry R. Black, William C. Cushman, Lee A. Green, Joseph L. Izzo, Jr, Daniel W. Jones, Barry J. Materson, Suzanne Oparil, Jackson T. Wright, Jr, Edward J. Roccella, and the National High Blood Pressure Education Program Coordinating Committee

TABLE 7. Identifiable Causes of Hypertension

Chronic kidney disease
Coarctation of the aorta
Cushing syndrome and other glucocorticoid excess states including chronic steroid therapy
Drug-induced or drug-related (see Table 18)
Obstructive uropathy
Pheochromocytoma
Primary aldosteronism and other mineralocorticoid excess states
Renovascular hypertension
Sleep apnea
Thyroid or parathyroid disease

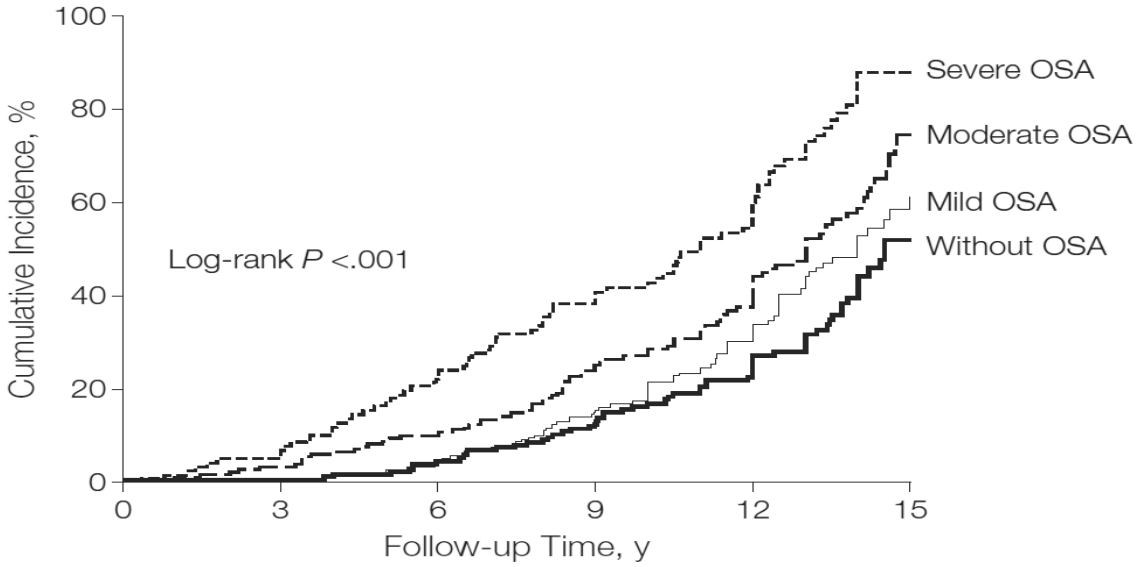
✓ The WSCS results impacted the American guidelines for the management of hypertension, and OSA was recognized as the first secondary cause of hypertension.

JAMA. 2012 May 23; 307(20): 2169–2176. doi:10.1001/jama.2012.3418.

Association Between Treated and Untreated Obstructive Sleep Apnea and Risk of Hypertension

José M. Marin, MD, Alvar Agusti, MD, Isabel Villar, PhD, Marta Forner, PhD, David Nieto, MD, Santiago J. Carrizo, MD, Ferran Barbé, MD, Eugenio Vicente, MD, Ying Wei, PhD, F. Javier Nieto, MD, PhD, and **Sanja Jelic, MD**

➢ **Kaplan-Meier survival function for new-onset hypertension in Participants Without OSA and in Untreated Patients with OSA**



No. at risk						
Severe OSA	199	184	141	119	62	37
Moderate OSA	258	222	202	162	114	67
Mild OSA	298	289	260	194	127	59
Without OSA	310	306	269	211	152	72

Cox Proportional Hazards Regression Models of Incident Hypertension in Patients With OSA With Multiple Imputations[a]

		Patients With OSA			
	Controls (n = 310)	Ineligible for CPAP Therapy (n = 462)	Declined CPAP Therapy (n = 195)	Nonadherent to CPAP Therapy (n = 98)	Treated With CPAP Therapy (n = 824)
Baseline AHI, mean (SD)	2.6 (1.3)	14.2 (6.6)	37.1 (16.3)	31.3 (13.4)	41.2 (19.9)
		Hazard Ratio (95% CI)			
Model 1, adjusted for AHI, age, and sex	1 [Reference]	1.63 (1.25–2.12)	2.89 (2.18–3.84)	2.70 (1.90–3.83)	1.47 (1.24–1.88)
Model 2, adjusted for model 1 + SBP and DBP	1 [Reference]	1.57 (1.20–2.05)	2.78 (2.08–3.70)	2.50 (1.75–3.56)	1.17 (0.90–1.51)
Model 3, adjusted for model 2 + BMI	1 [Reference]	1.46 (1.12–1.91)	2.54 (1.90–3.39)	2.20 (1.90–3.39)	1.01 (0.78–1.31)
Model 4, adjusted for model 3 + baseline covariates[b]	1 [Reference]	1.39 (1.06–1.82)	2.23 (1.36–3.01)	1.96 (1.36–2.83)	0.83 (0.63–1.11)
Model 5, adjusted for model 4 + change in BMI	1 [Reference]	1.33 (1.01–1.75)	1.96 (1.44–2.66)	1.78 (1.23–2.58)	0.71 (0.53–0.94)

JAMA. 2012 May 23; 307(20): 2169–2176. doi:10.1001/jama.2012.3418.

AMERICAN JOURNAL OF RESPIRATORY AND CRITICAL CARE MEDICINE VOL 179 2009 pp 1159–1164, 2009

Prospective Study of Sleep-disordered Breathing and Hypertension

The Sleep Heart Health Study

George T. O'Connor[1], Brian Caffo[2], Anne B. Newman[3], Stuart F. Quan[4,5], David M. Rapoport[6], Susan Redline[7], Helaine E. Resnick[8], Jonathan Samet[2], and Eyal Shahar[9]

Obesity

TABLE 2. ADJUSTED ODDS RATIOS* OF INCIDENT HYPERTENSION AT FOLLOW-UP IN RELATION TO BASELINE APNEA-HYPOPNEA INDEX AMONG 2,470 SLEEP HEART HEALTH STUDY SUBJECTS WITHOUT HYPERTENSION AT BASELINE

Baseline AHI	n	Model 1†	Model 2‡	Model 3§
0–4.9	1,511	—	—	—
5–14.9	629	1.13 (0.90–1.43)	0.92 (0.72–1.17)	0.94 (0.73–1.22)
15–29.9	234	1.54 (1.12–2.11)	1.12 (0.80–1.56)	1.09 (0.77–1.54)
≥30	97	2.19 (1.39–3.44)	1.51 (0.93–2.47)	1.50 (0.91–2.46)

Definition of abbreviations: AHI = apnea-hypopnea index; BMI = body mass index.

* Estimated by generalized estimating equation models with each subject contributing one or two follow-up intervals.

Values are odds ratio (95% confidence interval) or n.

† Adjusted for age, sex, race, and time since baseline.

‡ Adjusted for factors in model 1 plus BMI.

§ Adjusted for factors in model 2 plus waist/hip ratio and neck girth.

AMERICAN JOURNAL OF RESPIRATORY AND CRITICAL CARE MEDICINE VOL 184 2011 pp 1299–1304

Obstructive Sleep Apnea and Systemic Hypertension

Longitudinal Study in the General Population: the Vitoria Sleep Cohort

Irene Cano-Pumarega[1*‡], Joaquín Durán-Cantolla[2,3,7*‡], Felipe Aizpuru[4,8‡], Erika Miranda-Serrano[4], Ramón Rubio[2,7‡], Cristina Martínez-Null[2,7‡], Javier de Miguel[5], Carlos Egea[2,7‡], Laura Cancelo[2‡], Ainhoa Álvarez[2‡], Marta Fernández-Bolaños[2], and Ferrán Barbé[6,7‡]

TABLE 3. ODDS RATIO AND 95% CONFIDENCE INTERVAL FOR INCIDENCE OF SYSTEMIC HYPERTENSION IN MEN AND WOMEN AFTER A FOLLOW-UP OF 7.5 ± 0.8 YEARS, ACCORDING TO THE RDI*

RDI by Quartiles (*n* = 1180)	No. of Events	Model 1†	Model 2‡	Model 3§	Model 4‖	Model 5¶	Model 6**
0–2.9 (n = 367)	93 (25.3%)	1.00	1.00	1.00	1.00	1.00	1.00
3–6.9 (n = 417)	140 (33.6%)	1.49 (1.09–2.03)	1.18 (0.85–1.64)	1.16 (0.83–1.61)	1.09 (0.78–1.52)	1.10 (0.78–1.53)	1.08 (0.77–1.52)
7–13.9 (n = 247)	95 (38.5%)	1.84 (1.30–2.61)	1.22 (0.84–1.77)	1.10 (0.75–1.60)	0.94 (0.64–1.39)	0.95 (0.64–1.41)	0.90 (0.61–1.34)
≥14 (n = 149)	70 (47%)	2.61 (1.75–3.89)	1.57 (1.02–2.40)	1.28 (0.83–1.99)	1.00 (0.63–1.57)	1.02 (0.65–1.61)	0.98 (0.62–1.57)
P_{trend}		<0.001	0.051	0.342	0.803	0.885	0.708

Definition of abbreviation: RDI = respiratory disturbance index per hour.

Systemic hypertension was defined as systolic blood pressure greater than or equal to 140 mm Hg or diastolic blood pressure greater than or equal to 90 mm Hg or use of antihypertensive medication.

*All subjects with systemic hypertension at baseline were excluded.

†Model 1: Unadjusted model (crude odds ratio).

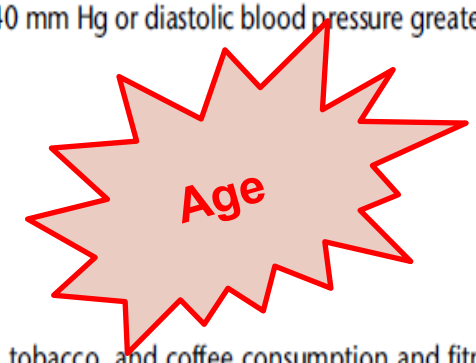
‡Model 2: Adjusted for age.

§Model 3: Adjusted for age and sex.

‖Model 4: Adjusted for age, sex, and body mass index.

¶Model 5: Adjusted for age, sex, body mass index, and neck circumference.

**Model 6: Adjusted for age, sex, body mass index, neck circumference, and alcohol, tobacco, and coffee consumption and fitness level.



Eur Respir J 2014; 44: 931–941 | DOI: 10.1183/09031936.00225113

Nocturnal intermittent hypoxia predicts prevalent hypertension in the European Sleep Apnoea Database cohort study

Ruzena Tkacova[1,2], Walter T. McNicholas[3], Martin Javorsky[1,2], Ingo Fietze[4], Pawel Sliwinski[5], Gianfranco Parati[6,7], Ludger Grote[8] and Jan Hedner[8], on behalf of the European Sleep Apnoea Database study collaborators[9]

ABSTRACT Systemic hypertension is associated with obstructive sleep apnoea syndrome (OSAS) but the pathophysiological mechanisms are incompletely understood. A collaborative European network of 24 sleep centres established a European Sleep Apnoea Database to evaluate cardiovascular morbidity associated with OSAS.

11 911 adults referred with suspected OSAS between March 2007 and September 2013 underwent overnight sleep studies, either cardiorespiratory polygraphy or polysomnography. We compared the predictive value of the apnoea–hypopnoea index (AHI) and 4% oxygen desaturation index (ODI) for prevalent hypertension, adjusting for relevant covariates including age, smoking, obesity, dyslipidaemia and diabetes.

Among patients (70% male, mean±SD age 52±12 years), 78% had AHI >5 events·h^{-1} and 41% systemic hypertension. Both AHI and ODI independently related to prevalent hypertension after adjustment for relevant covariates ($p<0.0001$ for linear trend across quartiles (Q) of severity for both variables). However, in multiple regression analysis with both ODI and AHI in the model, ODI was, whereas AHI was not, independently associated with prevalent hypertension: odds ratios (95% CI) for Q4 *versus* Q1 regarding ODI were 2.01 (1.61–2.51) and regarding AHI were 0.92 (0.74–1.15) ($p<0.0001$ and $p=0.3054$, respectively).

This cross sectional study suggests that chronic intermittent hypoxia plays an important role in OSAS-related hypertension.

The Journal of Clinical Hypertension Vol 18 | No 2 | February 2016

ORIGINAL PAPER

Age, Body Mass Index, and Daytime and Nocturnal Hypoxia as Predictors of Hypertension in Patients With Obstructive Sleep Apnea

Georgios Natsios, MD;[1] Chaido Pastaka, MD, PhD;[1,2] Georgios Vavougios, MD;[1] Sotirios G. Zarogiannis, MPH, PhD;[3] Vasiliki Tsolaki, MD;[1] Andreas Dimoulis, MD;[1] Georgios Seitanidis, MSc;[2] Konstantinos I. Gourgoulianis, MD, PhD[1,2]

From the Respiratory Medicine Department;[1] Sleep Laboratory, University Hospital of Larissa;[2] and Department of Physiology, University of Thessaly Medical School, Larissa, Greece[3]

A growing body of evidence links obstructive sleep apnea (OSA) with hypertension. The authors performed a retrospective cohort study using the University Hospital of Larissa Sleep Apnea Database (1501 patients) to determine predictors of in-laboratory diagnosed OSA for development of hypertension. Differences in continuous variables were assessed via independent samples *t* test, whereas discrete variables were compared by Pearson's chi-square test. Multivariate analysis was performed via discriminant function analysis. There were several significant differences between hypertensive and normotensive patients. Age, body mass index, comorbidity, daytime oxygen saturation, and indices of hypoxia during sleep were deemed the most accurate predictors of hypertension, whereas apnea-hypopnea index and desaturation index were not. The single derived discriminant function was statistically significant (Wilk's lambda=0.771, χ^2=289.070, P<.0001). Daytime and nocturnal hypoxia as consequences of chronic intermittent hypoxia play a central role in OSA-related hypertension and should be further evaluated as possible severity markers in OSA. *J Clin Hypertens (Greenwich).* 2016;18:146–152.

TABLE II. Univariate Analysis Between Hypertension and Demographic, Respiratory, and Sleep Apnea Characteristics

	Hypertensive Patients	Normotensive Patients	Hypertension *P* Value
Age, y	57.2±11.2	45.8±15.8	<.0001
BMI, kg/m^2	33.3±6.3	30.3±5.8	<.0001
CCI	1.8±2	0.5±1.1	<.0001
ESS	10.1±9.9	8.5±4.9	<.0001
FEV_1, %	86.3±18.5	95.9±41.5	<.0001
FVC, %	87.1±16.6	96.3±15.1	<.0001
FEV_1/FVC	79.9±8.3	81.2±6.2	.003
Daytime SaO_2, %	96.6±2	97.5±1.6	<.0001
Mean SaO_2, %	87.7±5.5	89.2±5.3	<.0001
Minimum SaO_2, %	75.5±11.8	80.2±11.1	<.0001
REM mean SaO_2, %	89.8±5.7	92.3±6.2	<.0001
NREM mean SaO_2, %	93.3±39.8	93±3.1	.848
DI	42±29.3	32.1±31.5	<.0001
AHI	36.5±26.6	28.7±28.6	<.0001
Apneas/h	14.4±18	12.2±18.5	.023
Hypopneas/h	22.3±17.9	17.3±17.3	<.0001
AI	39.7±36.2	35.4±24.4	.019

TABLE IV. Structure Matrix Displaying the Correlation of Each Predictor With the Discriminant Function

Predictors of Hypertension	Discriminant Loadings
Age	0.692
CCI	0.667
BMI	0.446
Daytime SaO_2	−0.426
Minimum SaO_2	−0.386
REM mean SaO_2	−0.350
Mean SaO_2	−0.326
DI	0.284
Hypopneas/h	0.275
AHI	0.243
ESS	0.241
Wilk's lambda=0.771, χ^2=289.070, P<.0001	

Cut off = I0.30I

The Journal of Clinical Hypertension Vol 18 | No 2 | February 2016

Burns RB, Burns RA (eds). Business Research Methods and Statistics Using SPSS. London: SAGE Publications Ltd, 2009.

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- Several statistically significant differences between individuals with hypertension and those without hypertension.

- Age, BMI, Comorbidity, daytime SaO_2, and indices of hypoxia during sleep were estimated to be the most precise predictors for hypertension.

- Although AHI and DI were independent predictive factors for hypertension, both were not included in the most accurate predictors for development of hypertension.

- AHI and DI are more complex measures reflecting the degree of intermittent hypoxia, and therefore are susceptible to variability in the clinical setting.

- Hypoxemia (daytime and nocturnal) as consequences of chronic intermittent hypoxia play a central role in OSA-related hypertension.

- The shift from chronic intermittent hypoxia to daytime and nocturnal hypoxia may represent a direct prelude to the development of hypertension.

- Daytime SaO_2 and indices of hypoxia during sleep should be further evaluated as possible severity markers in OSAS patients.

Conclusions

- There is a significant association between OSA and hypertension.
- Several well-known risk factors for OSA such as age and obesity are also risk factors for hypertension.
- Age, BMI, Comorbidity, and daytime and nocturnal Hypoxia are the most accurate predictive factors for development of hypertension.


Thank you for your Attention
Olympus (2918m), Greece