51. Diagnostics in OSA: from polygraphy to genetics and cancer

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The method for diagnosis matters in sleep apnea. A systematic analysis of polygraphy and polysomnography data in the European Sleep Apnea Database (ESADA)

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In the ESADA study, each of the 23 participating centers used its own routine clinical and diagnostic procedures for OSA detection. Alltogether, data from 8228 patients with suspected OSA (M or F, 18–80 yrs) were analysed in order to compare results obtained by polygraphy (PG) (n= 5032) or polysomnography (PSG) (n=3196). The AASM 2007 criteria have been used for visual scoring of apnoea/hypopnoea and in addition in a PSG study, an event with ≤50% flow reduction, associated with arousal was also classified as hypopnoea (Eur Respir J 2011; 38: 635–642).

AHI was higher by PSG (29.9±26 hr-1) than by PG (22.3±23 hr-1) ($p<0.001$). 66% of the patients had an AHI>15 by PSG whereas only 50% of patients were above this limit by PG ($p<0.001$). Although analyzed time (7.4±0.9 hr) by PG was higher than total sleep time (6.4±1.3 hr) by PSG ($p<0.0001$), oxygen desaturation index (ODI) (≥4%) was only marginally different: 21±24 hr^{-1} by PSG and 19±22 hr^{-1} by PG. Furthermore the difference between the AHI and ODI scores was higher by PSG (8.6±15.7) than by PG (1,1±10) ($p<0.0001$). The average number of events per recording was similar by PG (186±183) and by PSG (184±189) (NS) which rules out a significant time dilution effect to explain the higher AHI by PSG compared with PG.

In summary, the AHI is underestimated by PG leading to a lower rate of patients suffering from significant OSA than by PSG. This discrepancy is likely to relate to the scoring of hypopnea by arousal rather than the result of the time dilution effect.

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Real-time attended home-polysomnography through telematic data transmission

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Introduction: Home-polysomnography (HPSG) has been proposed as a cost-effective alternative for obstructive sleep apnea (OSA) diagnosis but its failure rate may be a drawback. We assessed in a feasibility study whether telematic transmission using the Dream® and SleepBox® technologies for HPSG (with Skype® intervention if required) was associated with low PSG failure rate.

Methods: 20 patients suspected of OSA were recruited. They underwent 1 HPSG (Dream®, Medatec®,Belgium) with the Sleepbox®, a wireless system containing an internet communication through a wifi/3G interface; equipped with a camera and a speaker for bidirectional audio/video communication via Skype®.

The sleep lab nurse performed a discontinue monitoring of the PSG. In case of defective signal, she called the patient who had previously been educated to replace the probes/electrodes.

Results:

Patients characteristics

	Mean ± SD
Male (%)	70
Female (%)	30
Age (y)	51±11
BMI (kg/m^2)	30±6
Epworth Sleepiness Scale	7±4
Neck Circumference (cm)	41±3
AHI	28±27

90% of the recordings were of excellent quality. We observed a 10% failure rate: 1 recording of poor quality and 1 failure of the Dream®. There were 2 successful Skype® interventions resulting in replacing the defective signals (nasal airway pressure and EEG). PSG signal visualisation was possible in 90% of cases but Skype® connection was problematic in 18% of cases. However, patients could be reached by phone to solve the problem.

Conclusion: Real-time attended HPSG through telematic data transmission is feasible and could be an interesting perspective to decrease the failure rate of home sleep studies even if some technical aspects need to be improved.

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Contribution of APO E allleles and ACE I/D polymorphism in the development of hypertension in sleep apnea-hipoapnea syndrome

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Sleep apnea/hypopnea syndrome (SAHS) is a common condition affecting approximately 0.3–4% of the middle-aged population and is defined on the basis of symptoms of daytime sleepiness and objective measures of disordered breathing during sleep. Several studies have identified SAHS as a risk factor for hypertension, but a direct etiologic link between these disorders has not been established definitively.

Aims: Evaluate the influence of polymorphisms on the APO E gene and the I/D polymorphism on ACEI in the presence of hypertension (HT) In Sleep Apnea – Hipoapnea Syndrome patients.

Methods: APO E and ACEI I/D genotypes were obtained from 99 controls and 114 patients with a diagnosis of sleep apnea-hipoapnea sindrome after polysomnography in the Sleep unit of the Rio Hortega Hospital.

Results: There were not any difference in the APO E alleles frequency between patients and controls, but SAHS patients carrying the APO E ε4 allele showed an increased frequency of HT 3,145 higher than ε3 homozygous and ε2 carriers (CI 1.269-7.79). These findings keep significant even after correction for sex. The ACE I/D genotypes were in Hardy-Weinberg equilibrium ($p<0.05$) and they seem don't have any influence on the development of HT in these patients (DD OR 0,478 (CI 0,21-1,08)

Conclusions: Our results demonstrate that the presence of the ε4 allele increases the probability to develop HT in Sleep Apnea patients. We suggested that this allele could be useful as a biological marker for identification of a subgroup of SAHS patients who are more likely to have HT.

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Independent impact of obstructive sleep apnea severity on glycated haemoglobin in adults without diabetes

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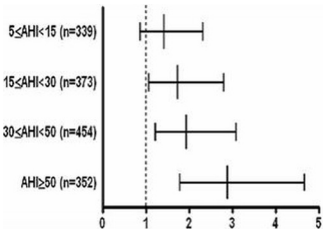
Hypothesis: There may be an independent association between obstructive sleep apnea (OSA) severity and glycated hemoglobin (HbA1c) in adults without known diabetes.

Methods: HbA1c was measured in 1,728 patients with no history of diabetes undergoing nocturnal recording for suspected OSA.

Results: A dose-response relationship was observed between apnea-hypopnea index (AHI) and percentage of patients with HbA1c>6.0% that increased from 13.8% for AHI<5 to 42.6% for AHI≥50. After adjustment for age, gender, smoking habits, body mass index (BMI), waist circumference (WC), cardiovascular morbidity, daytime sleepiness, depression, insomnia and sleep duration, odds ratios (95% confidence intervals) for HbA1c>6.0% were 1 (reference), 1.43 (0.88 to 2.33), 1.74 (1.08 to 2.81), 1.94 (1.22 to 3.09) and 2.89 (1.79 to 4.67) for AHI values ≤5, 5 to <15, 15 to <30, 30 to <50, and ≥50 respectively. Increasing hypoxemia during sleep was also independently associated with the odds of HbA1c >6.0%.



Conclusions: Among adults without known diabetes, increasing OSA severity is independently associated with impaired glucose metabolism that may expose to higher risks of diabetes and cardiovascular disease.

Odds ratio (95% confidence intervals) for HbA1c >6% according to AHI (AHI<5=reference) after adjustment for age, gender, smoking habits, BMI, WC, cardiovascular morbidity, daytime sleepiness, depression, insomnia and total sleep time.

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Prediction modeling and temporal validation of sleep disordered breathing from large community samples

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Aim: Common sleep apnea prediction tools (e.g. the STOP-BANG score) were derived using laboratory-based polysomnography in academic centers. In contrast, we assessed and temporally validated the sleep apnea risk factors in patients undergoing ambulatory screening and testing in community practice.

Methods: Two consecutive sets of 2000 ambulatory sleep monitor recordings referred for interpretation by community physicians and CPAP vendors were used for modeling and validation. With each study the patient's age, gender, mass, height, neck circumference, use of anti-hypertensive drugs, reported gasping awakenings, reported disruptive snoring and Epworth sleepiness score were reported. An estimated respiratory disturbance index (RDI) was derived from each study's signals. Modeling of the predicted RDI was done using linear regression and reduced error pruning tree methods on the first sample with temporal validation testing on the second sample (WEKA, v. 3.7.5).

Results: Linear regression modeling showed all risk factors significantly associated with RDI, however, the model's correlation coefficient was poor in both the training (0.3953) and validation (0.4604) samples. Tree modeling showed sequential cutoffs for neck circumference < 44 cm, Epworth score < 18.5 and mass < 107 kg best modeled the estimated RDI. The tree model's training (0.375) and validation (0.3015) correlation coefficients were, like the regression model values, also poor.

Conclusion: Common sleep apnea risk factors have poor statistical validity for predicting sleep disordered breathing in patients undergoing ambulatory screening and testing.

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Association between sleep apnoea and cancer incidence. Longitudinal study of a large multicenter Spanish cohort

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Background: The role of Sleep Apnoea (SA) in the development of cancer in humans has not yet been assessed.

Objective: To investigate whether SA is associated with increased cancer incidence.

Methods: We performed a multicenter, clinical cohort study, analyzing 8,961 patients referred to 8 Spanish Sleep Clinics for suspected SA. Subjects with an apnoea-hypopnoea index (AHI)<10 comprised the control group. SA was diagnosed when the AHI was≥10. We used the log-rank test to compare cancer incidence between groups, and the Cox proportional hazards model to calculate both unadjusted and adjusted HR and 95%CI for incident cancer.

Results: 8,542 (95.3%) patients were finally analyzed. The median follow-up of the cohort was 5.1 years (interquartile range 4.0 to 7.5). SA was associated with increased incidence of cancer in unadjusted analyses (HR 1.27, 95%CI 1.04-1.56). The cancer incidence density rate was also significantly higher in patients with SA compared to the control group (14.99 vs. 11.71 per 1,000 person-years; incidence density ratio 1.28 [95%CI 1.04-1.57], p=0.02). However, when these results were adjusted for age and gender, SA was no longer associated with cancer incidence (HR 0.96, 95%CI 0.78-1.18). Further adjustments for body mass index, smoking or alcohol intake did not modify these results. Cancer incidence was not associated with either mild-moderate SA (HR 1.02; 95%CI 0.81 to 1.28), or severe SA (HR 0.85; 95%CI 0.68 to 1.06) in the adjusted models.

Conclusions: Sleep Apnoea was associated with increased cancer incidence, but this association disappeared when the results were adjusted for confounders.

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Intermittent hypoxia increases melanoma metastasis to the lung in a mouse model of sleep apnea

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Background: Obstructive sleep apnea (OSA) is associated with an increased risk of cancer mortality in humans (Nieto et al., ATS Congress, 2012). Experimental data in mice have recently shown that application of a pattern of intermittent hypoxia similar to the one observed in OSA patients enhances the rate of tumor growth (Almendros et al., Eur Respir J. 2012; 39:215-7). However, whether intermittent hypoxia mimicking OSA also increases the metastatic potential of tumors is unknown.

Aim: To test the hypothesis that intermittent hypoxia enhances metastasis to the lung from a subcutaneous melanoma.

Methods: 28 male C57BL/6J mice were investigated. To induce a melanoma tumor in each mouse, one million of B16F10 cells were subcutaneously injected in the left flank region of the animal. Thirteen of these animals were then subjected to breathe intermittently hypoxic air with a pattern mimicking OSA: 20 s 5% O_2 followed by 40 s room air, for 6 h/day. The other 15 animals were breathing room air (controls). After 30 days the mice were sacrificed, their lungs were excised and hematoxilyn-eosin preparations were analyzed by a pathologist to quantify the number of metastases.

Results: The number of lung metastases in each mouse was significantly greater in the animals subjected to intermittent hypoxia (5.5±3.2) (mean ± SE) than in control mice (1.0±0.6) (p=0.028).

Conclusion: The data from this animal study strongly suggest that cancer metastasis could by enhanced in patients with OSA.

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Mortality and morbidity after sleep disordered breathing

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The long-term prognosis of obstructive sleep apnea (OSA) and obesity hypoventilation syndrome (OHS), as compared to age, gender and social controls, are incompletely described.

Using data from the Danish National Patient Registry (NPR) (1998-2010), 30278 individuals with a diagnosis of OSA (23208 men and 7070 women) and 1562 with a diagnosis OHS (1092 men and 470 women) were identified. For every patient, four ages-, sex- and social matched citizens were randomly selected from the Danish Civil Registration System, a total of 120506 OSA and 6241 HS controls. Morbidity and all-cause mortality was extracted from the NPR.

The 10 year survival of treated and untreated OSA patients was 90.7% compared to 92.4% (controls) and of OHS patients 63.9% compared to 85.5% (controls) (both: $p<0.0001$).

Commonly significant ($p<0.01$) observed morbidities in OSA patients OSA were related to respiratory (1.91 (1.82-2.01), nervous (1.65 (1.55-1.75), endocrine, metabolic, nutrietal (1.53 (1.54-1.75), ENT:1.39 (1.30-1.49), circulatory: 1.20 (1.16-1.27), musculoskeletal: 1,25 (1.20-1.30), digestive illnesses (1.09 (1.03-.14), and injuries 1.12 (10.8-1.16). Mental disease and neoplasm showed a lower occurrence: 0.90 (0.81-0.99) and 0.85 (0.80-0.95), respectively.

OHS showed higher morbidities to respiratory: 4.03 (3.21-5.07), nervous: 3.17 (2.43-4.15), endocrine, metabolic, nutrietal (4.65 (3.67-5.90), ENT:1.39 (1.30-1.49), circulatory: 1.84 (1.50-2.26), musculoskeletal: 1,25 (1.20-1.30) and digestive illnesses (1.09 (1.03-.14), and injuries 1.12 (10.8-1.16). Neoplasm occurred less often: 0.70 (0.50-0.97).

OSA and especially OHS present significant mortality. The morbidity includes a wide range of medical disorders beside cardiovascular complications.