ABSTRACTS

001

CPAP adherence and compliance in elderly patients with Obstructive Sleep Apnea
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Rationale: The incidence of obstructive sleep apnea syndrome (OSAS) increases with age. In elderly patients adherence and compliance with CPAP could be worse than in younger patients.

Methods: We reviewed our database of patients with OSAS older than 70 years treated by CPAP for at least one year. We assessed the relationship between age and compliance in all patients. We then divided the cohort into those patients having started CPAP before (“young”) and after (“old”) 70 years old. We compared the compliance between the two groups. To define adherence to CPAP, we analyzed the fate of all patients older than 70 years diagnosed during a period of one year.

Results: We included 124 patients (23 female), mean + SD age 76.5 + 4.89 Y, BMI 32 + 5 kg/m2, oxygen desaturation index (ODI) 45 + 20/hour slept, microarousal index (MAI) 43 + 15/hour slept. Mean age at diagnosis was 68 years. Mean compliance was 396 + 93 min. There was no relationship between age and compliance for the whole group. According to age of start of CPAP therapy, 63 and 61 patients respectively pertained to the “young” and “old” groups. The mean follow-up time was 11 and 4 years respectively. There was no difference in compliance between the two groups (388 and 404 min/day respectively; p< 0.3) During a period of one year out of a total of 218 patients diagnosed with OSAS we found 32 patients (4 female) older than 70 years. Mean age was 74 + 4 years, BMI 28.5 + 5.2, ODI 32 + 21; MAI 37.7 + 11. Twenty eight patients actually are treated by CPAP. The adherence rate is thus 84 %.

Conclusion: Old age does not represent a limit to adherence and good compliance with CPAP in patients with OSAS.

002

Association of Nocturnal Sub-nuchal Fluid Sequestration in Women, with Lower Severity of Obstructive Sleep Apnea than in Men with Heart Failure.
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Background: Obstructive sleep apnea (OSA) is common in patients with heart failure (HF). We reported that nocturnal rostral fluid displacement from the legs was associated with an increase in the neck circumference (NC) and the severity of OSA in men with HF. However, it is not known whether nocturnal rostral fluid shift relates to OSA in women with HF. Because the prevalence of OSA is higher in men than in women, we hypothesized that in women with HF, the pattern of overnight rostral fluid displacement would differ from men such that less fluid would shift into the neck in association with a lower AHI.

Methods: In 22 men and 21 women with medically stable HF (ejection fraction ≤45%), we measured change in NC and leg fluid volume (LFV) by bioelectrical impedance before and after polysomnography (PSG). The severity of OSA was assessed by the apnea-hypopnea index (AHI).

Results: Although the mean overnight change in LFV was similar in men and women (-154±115 versus -161±99 ml, P=0.547), in women, the 0.4 cm, P=0.9 vs 0.2± overnight change in NC was smaller (1.0<0.001), 22.4, P=0.019). Furthermore, although change in LFV correlated inversely with the change in NC and AHI in men, this was not the case in women (Figures 1 and 2).

Conclusions: In women with HF, for the same overnight fluid displacement from the legs, less accumulates in the neck than in men. Unlike men, there is no relationship between change in LFV and either change in NC or AHI. These findings suggest a protective mechanism of subnuchal fluid sequestration that contributes to the lower severity of OSA in women than in men with HF.

Inverse relationship between subjective daytime sleepiness and sympathetic nervous system activity in patients with heart failure and obstructive sleep apnea.
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Background: We previously showed that patients with heart failure (HF) and obstructive sleep apnea (OSA) are less sleepy than non-HF patients with OSA, for a given apnea-hypopnea index (AHI). Furthermore, whereas in the non-HF population, the degree of daytime sleepiness was directly related to the AHI, in the HF population, it was not. The sympathetic nervous system plays a critical role in alertness. HF and OSA both independently increase sympathetic nervous system activity (SNA), and patients with HF and OSA have higher muscle SNA (MSNA) during wakefulness than patients with OSA or HF alone. We therefore hypothesized that in HF patients with OSA, the degree of subjective daytime sleepiness will be inversely related to SNA rather than to the AHI.
Methods: Polysomnography (PSG) and daytime MSNA recordings were performed in 27 HF patients (left ventricle ejection fraction, LVEF <45%) with OSA (AHI>15 events/hour). Subjective daytime sleepiness was assessed by the Epworth Sleepiness Scale (ESS).

Results: We studied 27 patients with HF and OSA (♀= 2; mean age, 50±13 years; body mass index [BMI], 31.7±6.1 kg/m2, LVEF, 25.9±7.9%, AHI, 39±18 events/hour, arousal index, 35±18 events/hour, and minimum SaO2, 79±10%). The mean ESS score of 6.4±3.3 was within normal limits, and mean MSNA was 75±17 bursts/100 heart beats. The ESS score was inversely related to MSNA (r= -0.63, p<0.001), but not to the AHI, arousal index or indices of oxygen desaturation.

Conclusions: In patients with HF and OSA, the degree of subjective daytime sleepiness is inversely related to MSNA, but not to the AHI, arousal index, or degree of nocturnal desaturation. This association is likely through activation of adrenergic central nervous system alerting mechanisms. These findings help to explain the previously reported lack of daytime hypersomnolence in patients with HF and OSA.

Supported by CIHR

CPAP acceptance and resting breathing irregularity during wakefulness in obstructive sleep apnea
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Rationale: Mixed apneas are often present in those with “complex” sleep apnea. Our prior report found that breathing irregularity before sleep onset is greater in mixed apnea dominant compared to obstructive apnea dominant obstructive sleep apnea, indicative of an underlying unstable controller.

Objectives: The purpose was to evaluate whether awake breathing irregularity might predict CPAP acceptance in obstructive sleep apnea (OSA).

Methods: Among the OSA patients who had a diagnostic polysomnography (PSG) from 2007 to 2010, the patients who could not tolerate CPAP within 6 months despite of having no nasal symptoms were extracted (Group A; n = 27). A group for good acceptance and compliance for CPAP (more than 90% of days use and more than 5 hrs use per night, Group B; n = 22) was randomly extracted from a pool of subjects in the same database. Five minutes of stable respiratory signal during wakefulness was examined using respiratory inductance plethysmography prior to the diagnostic PSG in both Groups. The coefficients of variation (CV) for the breath-to-breath respiratory duration (Ttot) and tidal volume (TV) were compared.
Results: In both groups, the respiratory events were obstructive apnea, not mixed apnea. AHI and BMI were significantly lower in Group A than in Group B (46 ± 18 vs. 66 ± 21 /hr, and 25.2 ± 3.2 vs. 29.1 ± 4.5 kg/m², respectively; p<0.01). Although age, the Epworth Sleepiness Scale, and CV values for Ttot were not different between groups, CV values for TV were significantly greater in Group A than in Group B (31 ± 8 vs. 24 ± 9 %, respectively, p<0.01). Logistic regression showed that CV values for TV as well as BMI were the independent predictors of CPAP acceptance.

Conclusions: Breathing irregularity expressed by high CV value for TV is one of the parameters to predict CPAP acceptance.

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Both heavy snoring and sleep apnea predict subclinical cardiovascular disease in community-dwelling young adults.

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Rationale: Self-reported snoring, a surrogate for sleep apnea (OSA) is associated with cardiovascular disease (CVD). Snoring may be a discrete insult that damages the carotid artery. We sought to determine if objectively measured snoring and OSA were associated with carotid intima media thickness (cIMT), in young adults.

Methods: A total of 61 young adults in a lifestyle intervention study underwent home sleep apnea testing (Apnealink® (ResMed) at the final visit of the study. The respiratory disturbance index (RDI) and oxygen desaturation index (ODI) were measured using a nasal pressure transducer and oximetry. Snoring vibration was identified from the airflow signal and analyzed as a 0-100 Hz waveform. A snore was defined as a frequency oscillation of 6% amplitude lasting 0.5-3 seconds. Snores were indexed to time in hours for a snoring index (SI). The cIMT was measured as the mean of six sites, and was compared in those with OSA (ODI≥5) and without. A median split of the SI was used to divide those without OSA to yield 3 groups: Normal (≤50% SI), Heavy Snoring (>50% SI) and OSA. A linear model was used to test for trend across categories with age, sex and BMI adjustment. Linear regression modeled the cIMT as a function of snoring (SI) and OSA (ODI).

Results: The mean age was 39.3±6, BMI was 32±5 and 82% were women. An ODI≥5 was present in 36%. The cIMT of those with OSA was greater than those without, 0.68±0.09 vs. 0.59±0.07 mm (p<0.0001). The figure shows a significant trend (p=0.001) for greater cIMT across categories, adjusted for age, sex and BMI. In an age-adjusted model, both the SI (p=0.05) and ODI (p=0.003) were significant predictors of cIMT.

Conclusions: Heavy snoring in the absence of OSA, and OSA are associated with subclinical CVD in young obese adults.
Growth and Sleep Impairment are related to Reduced Hypothalamic Growth Hormone Releasing Hormone in Chronic Upper Airway Loading Juvenile Rats.
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Introduction
Growth retardation is a significant morbidity in children with sleep-disordered breathing (SDB). The reduction of serum insulin-like growth factor-1 (IGF-1) in children with SDB is related to reduction of slow wave sleep (SWS). Chronic airway loading (CAL) in juvenile rats, a model of SDB, is associated with impaired longitudinal growth attributed to impaired growth hormone (GH)/IGF-1 axis. In the present study we explored whether CAL affects hypothalamic growth hormone releasing hormone (GHRH) that regulates both sleep and GH homeostasis.

Methods
The tracheae of 22-day-old rats were obstructed by tracheal banding (n=20 sham controls, n=21 CAL), and animals were returned to their cages for 12:12 h light dark cycle, lights on at 09:00. Sixteen days after CAL surgery animals were sacrificed. Sleep architecture, serum GH, IGF-1, and hypothalamic GHRH mRNA were analyzed using telemetric transmitters (DSI, St. Paul, MN), ELISA, and real time PCR, respectively.

Results
In the CAL group inspiratory swings in esophageal pressure increased (250%, p<0.001), respiratory rate decreased (30%, p<0.01), and tracheal resistance increased (50%, p<0.02). Body weight, and tibia and tail length gains were all 30% to 40% less (p<0.0001) in the CAL group. Serum GH and IGF-1 levels decreased by 38% (p<0.05) and 32% (p<0.001), respectively, in CAL animals. Hypothalamic GHRH mRNA levels decreased in CAL rats by 22% (p=0.06). CAL led to sleep fragmentation, i.e., there was 25% elevation in wakefulness and 15% reduction of SWS duration during 12 hrs light onset. EEG power density during the first 3 hrs of light on was 40% lower in the CAL group in the range of 0.5–4 Hz (p<0.001).

Conclusion
CAL impairs sleep architecture and the GH/IGF-1 axis, and is associated with somatic growth retardation. Underlying mechanisms may involve reduction of hypothalamic GHRH that regulates both GH level and sleep architecture/consolidation.

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Role of GHRH in Sleep and Growth Induced by Upper Airway Obstruction in Rats.
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Introduction
Chronic upper airway obstruction (UAO) can lead to abnormal growth hormone homeostasis and growth retardation in children and animals by unclear mechanisms. We explored the effect of UAO on hypothalamic growth hormone releasing hormone (GHRH) that has a role in both sleep and growth hormone regulation.

Methods
The tracheae of 22-day-old rats were narrowed; UAO and sham-operated animals were sacrificed 16 days post-surgery. To stimulate slow wave sleep and growth hormone secretion rats were treated with 5-HT2 receptor antagonist (ritanserin). Sleep was measured with telemetric system. Hypothalamic GHRH, hypothalamic GHRH and growth hormone receptors, and orexin were analyzed using ELISA, real-time PCR, and Western immunoblot.

Results
UAO decreased hypothalamic GHRH, GHRH and growth hormone receptors levels, while orexin mRNA increased (p<0.01). In UAO rats the duration of wakefulness was elevated and the duration of slow wave sleep (SWS), paradoxical sleep, and slow wave activity were reduced (p<0.001). Ritanserin alleviated these effects, i.e., normalized hypothalamic GHRH content, decreased wake duration, increased duration and depth of SWS and attenuated growth impairment (p<0.001).

Here we present evidence that growth retardation in UAO is associated with a reduction in hypothalamic GHRH content.

Conclusion
Our findings show that the abnormalities in GHRH/ growth hormone axis underlie both growth retardation and SWS disorder UAO.
Supported by the Israel Science Foundation (award number 164/06) to Y.S. and A.T.

Effect of sleep apnea on the 24-hour metabolic hormones profile.
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Introduction: Obstructive sleep apnea (OSA) has been related to metabolic disorders. The effect of OSA throughout a 24-hour period secretion of metabolic hormones has not been explored.

Objectve: To evaluate the effect of the sleep apnea in the secretion of ghrelin, leptin, resistin and adiponectin metabolic hormones throughout a 24-hour period.

Population and Methods: We have included 37 patients with OSA with and apnea-hypopnea index (AIH)>19 h-1, and 11 controls without OSA with and AIH<10h-1. In each subject, six different samples were obtained during 24 hours (22h, 2h, 6h, 10h, 14h, 18h). Ghrelin, leptin,
resistin and adiponectin levels were measured in plasma by immunoassay. Statistical analysis was performed using a nonparametric test to explore the differences in the area under the curve (AUC; acumulative concentration along follow-up of each hormone) between the two groups.

Results: The group of patients presented severe OSA as assessed by the AHI (mean±SD, 46±26 h-1) whereas control group presented an AHI of 6±3 h-1. Body mass index was similar between the OSA and control groups (28±4 vs. 26±4 kg•m-2, p=0.28). OSA patients were older than the control group (42±9 vs. 33±9, p=0.012). All subjects included in the study were male. The AUC for ghrelin was (OSA group vs. control group) 14212 vs. 15249 pg•ml-1•h (p=0.64), for leptin was 136 vs. 113 ng•ml-1•h (p=0.15), for resistin was 106 vs. 132 ng•ml-1•h (p=0.76), and for adiponectin was 96463 vs. 96766 ng•ml-1•h. Differences in metabolic hormones between the groups analyzed not reached statistical significance at any point of evaluation.

Conclusions: The results of this study suggest that OSA do not influence the 24h profile of ghrelin, leptin, resistin and adiponectin.

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Effects of Inhaled Fluticasone Treatment on Upper Airway Collapsibility during Sleep in Asthma Patients.
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Rationale: Asthma or inhaled corticosteroid therapy (ICS) could affect upper airway collapsibility increasing the risk for OSA in individuals with asthma. We assessed the associations of critical closing pressure (Pcrit) with asthma control indices, and effects of inhaled fluticasone (FP) on Perit.

Methodology: Pcrit was measured during sleep, before and after 4-month treatment with high dose (1,760 mcg/day) inhaled FP. Pcrit was derived from the pressure-inspiratory flow relationship in the flow limited range. Spirometry and the Asthma Control Questionnaire (ACQ—version with symptoms and rescue bronchiodilator use) were collected before and after treatment. The validated ACQ cut-point of ≥1.5 differentiated between ‘well’ and ‘not well-controlled’ asthma.

Results: Eleven steroid-naïve sleep-disordered breathing free subjects (9 females, mean [±s.d.] age 27±7 yrs, BMI 26±5 kg/m2) with well-controlled asthma (ACQ 1.15±0.55, FEV1 [%predicted] 87±9 and FVC [%predicted] 96±13) had a normal Pcrit at baseline (-10±7 cmH2O, range -21.8 to -0.6 cmH2O). There were no significant associations between Pcrit and: ACQ (Spearman rho=−0.06, p-value=0.87), FEV1% (rho=−0.32, p=0.37), or FVC% (rho=−0.35, p=0.43). Nine subjects completed the 4-month treatment trial with 89±8% adherent days. There were significant improvements in ACQ (1.26±0.51 vs 0.35±0.29,
p=0.0001) and FEV1 % predicted (88±10 vs 93±10%, p=0.03), but no change in FVC (97±12 vs 96±11% predicted, p=0.32) or BMI (25.8±5.7 vs 26.0±5.9 kg/m², p=0.46). There was no significant change in Pcrit following treatment (-12±6 vs -16±9 cmH₂O, p=0.07). No relationships of Pcrit change emerged with baseline FEV1% (p=0.45) or ACQ (p=0.57).

Conclusions: In this sample of young subjects with well-controlled asthma and stiff upper airways, no relationships between Pcrit and asthma control indices were found. Treatment with high dose FP for four months did not worsen Pcrit. Further testing in patients with a broader continuum of less negative Pcrit and more severe lower airway obstruction is required.

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SIMPLIFIED POLYSOMNOGRAPHY FOR THE DIAGNOSIS OF THE SLEEP APNEA-HYPOPNEA SYNDROME.
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INTRODUCTION
Full Nocturnal Polysomnography (PSG) is the gold standard to diagnose Sleep apnea-ypopnea syndrome (SAHS). However, given the high prevalence of SAHS, simpler, portable diagnostic devices are needed. Cardiorespiratory polygraphy is accepted system to evaluate SAHS but sleep efficiency and respiratory events related to arousals can not be determined.

OBJECTIVE
To evaluate a portable device (Somte, Compumedics, Australia), which incorporates 2 neurophysiological channels (electroencephalography and electrooculography) to cardiorespiratory monitoring, in the diagnosis of SAHS.

METHODS
PSG and Somte recordings were simultaneously performed in 68 patients. Data were blindly analysed by 2 scorers. Paired T-test was used to compare the sleep and respiratory parameters. Interscorer agreement, ROC curves and Bland and Altman plots were obtained.

RESULTS
The 68 patients (M39/F29) completed the protocol and all studies were considered valid for analysis. The mean apnea-hypopnea index (AHI) was 55.9(14.5), body mass index 28.5 (4.8) Kg/m² and Epworth sleepiness scale 8.6(9.5)
A good agreement between both methods in sleep efficiency was observed [68.8% (18.4) with PSG vs 68% (19.1) with Somte (p: n.s.) for scorer 1, and 67.5% (19.1) vs 68.4% (18.5) (p:n.s.) for scorer 2]. The AHI obtained with Somte was lower than with PSG: 19(17.8) vs 21.7(19) (p<0.001) for scorer 1, and 16.6(16.7) vs 20(18.8) (p<0.001) for scorer 2. The
sensitivity of Somte for a PSG-AHI $\geq 5$ was 91% for scorer 1 and 90% for scorer 2, while the specificity was 77% and 90% respectively. The areas under the receiver operating curve for different PSG-AHI cutoff points ($\geq 5$, $\geq 15$ and $\geq 30$) were 0.81, 0.90 and 0.86 respectively for scorer 1, and 0.90, 0.88 and 0.83 for scorer 2. The $K$ coefficients of agreement between the two scorers for these cutoff points were 0.66, 0.70 and 0.85 respectively.

CONCLUSIONS
These data suggest that Somte is an effective device to identify sleep and respiratory variables in patients with suspected SAHS.

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Cardiovascular mortality in females with Obstructive Sleep Apnea. Long-term effect of continuous positive airway pressure treatment.
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Background: Obstructive sleep apnea (OSA) is a risk factor for cardiovascular mortality in males, but its effects in females are unknown. The aims of this study were to investigate whether OSA is a risk factor for cardiovascular mortality and to assess the effect of treatment with continuous positive airway pressure (CPAP) on a large unselected female cohort with a long-term follow-up.

Methods: We performed an observational follow-up study of a female cohort consecutively studied for OSA suspicion between 1998-2007 at two sleep clinics, and followed-up until December 2009. Females with an apnea-hypopnea index (AHI)$<10$ comprised the control group. OSA was diagnosed when the AHI was $\geq 10$ (mild-moderate [AHI 10-29]; severe [AHI $\geq 30$]). OSA patients were classified as treated with CPAP (objective compliance $\geq 3$ hours/day) or non-treated (compliance <3 hours/day or CPAP not prescribed). We used the log-rank test to compare survival curves and the adjusted multivariate Cox regression analysis to identify independent predictors of cardiovascular mortality.

Results: A total of 1116 females were studied (follow-up 71.5±24.8 months, range 1-132). Cumulative survival rates were lower in both non-treated groups compared with the control group (severe OSA, $p<0.0005$; mild-moderate OSA, $p=0.02$). Fully adjusted Cox regression analysis showed that only non-treated severe OSA significantly increased the risk of cardiovascular mortality (HR 3.37; 95%CI 1.17-9.65). Mortality in severe OSA treated with CPAP showed no differences with the control group (HR 0.55; 95%CI 0.17-1.73).

Conclusions: Severe OSA is an independent risk factor for cardiovascular mortality in females. CPAP treatment reduces this excess of mortality to the level of the control group without OSA.
Predictors of Incident Sleep-disordered Breathing in a Baseline Cohort Free of Sleep-disordered Breathing: the Wisconsin Sleep Cohort Study.
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INTRODUCTION: Accurate assessment of sleep-disordered breathing (SDB) is challenging due to night-to-night SDB variability and measurement error; failure to account for this can lead to inflated estimates of SDB incidence. Thus, we used two serial baseline polysomnography studies to precisely determine a sub-cohort of Wisconsin Sleep Cohort subjects initially free of SDB. These were then followed-up to estimate predictors of risk of new-onset SDB.

METHODS: Our baseline employed population-based sample comprises 1524 subjects (30-60 years old) at initial sleep study. Subjects are restudied every 4 years. To ensure a baseline cohort free of SDB (apnea-hypopnea index [AHI]<5 events/hour) we identified subjects with two consecutive studies with AHI<5. Poisson regression estimated relative risks of the relationship between new-onset mild or worse SDB (new cases of AHI $\geq 5$ measured during 8 years of follow-up) and age, gender, overweight, and other variables. We also estimated the risk of new-onset SDB in persons who were (and remained) normal weight to characterize the natural history of SDB in a population entirely free of obesity.

RESULTS: 519 subjects were initially free of SDB. The probability of developing new-onset SDB over an 8-year period in men was 25% (95% CI=14-42%); the risk in women was 15% (95% CI=8-26%). Male to female relative risk was 1.7 (95% CI=1.1-2.5). Older age, smoking and alcohol use were not significantly associated with relatively higher risk of new-onset SDB. We estimate that, had the baseline cohort been (and remained) normal weight, the risk of new-onset SDB would have been approximately half the risk observed in the cohort: in men the 8-year risk would have been 13% (95% CI=7-26%), and in women, 8% (95% CI=4-15%).

CONCLUSION: Adults, especially those who are male, overweight, or who gain weight, are at high risk for new-onset SDB. All examined ages were at comparable risk for new-onset SDB.

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The Impact of Pulmonary Rehabilitation on Sleep Quality in Chronic Obstructive Pulmonary Disease.
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RATIONALE: Sleep-related disorders are common in patients with chronic obstructive pulmonary disease (COPD). In other populations, exercise has been shown to improve sleep health. In patients with chronic lung disease, pulmonary rehabilitation (PR) produces important health benefits in symptoms, exercise tolerance, and quality of life (QOL). However, the effect of PR on sleep quality in patients with COPD has not been studied. The aims of this observational study were to characterize sleep quality in COPD patients and evaluate the effect of PR on sleep quality.

METHODS: Sixty-three moderate to severe COPD patients enrolled in our PR program completed questionnaires related to symptoms, QOL, and sleep quality before and after an 8-week comprehensive PR program. Outcome measures reported here included: SF-36 Physical (PCS) and Mental (MCS) Component Scores; and Pittsburgh Sleep Quality Index (PSQI).

RESULTS: There were 28 (44%) males and 35 (56%) females; Baseline spirometry [mean(SD)] demonstrated moderate to severe COPD with an FEV1 % predicted = 46 (17), FVC % predicted = 76 (18), and FEV1/FVC % = 46 (13). 25 (40%) used long-term oxygen; 7 (11%) had been diagnosed with obstructive sleep apnea. Before PR 52% reported poor sleep quality (PSQI>5). There was improvement after PR in respiratory symptoms (p<0.005) and QOL (p<0.002). The number of patients with poor sleep quality was reduced to 41% (p<0.001) and mean PSQI decreased from 6.9 (4.2) to 5.5 (3.6) after PR (p<0.019).

CONCLUSIONS: Sleep quality in patients with moderate to severe COPD enrolled in our PR program was poor. PR had a significant positive impact on QOL and overall sleep quality, suggesting that PR maybe an effective non-pharmacologic treatment for improving sleep quality in these patients.

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Reversed Frequency-Dependence of Chemoreflex Gain Measured using Oscillatory Carbon Dioxide.
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Background
High chemoreflex gain in heart failure may result in periodic breathing (oscillations in cardiorespiratory parameters with a period of about a minute). Clinical research generally separates chemoreflexes into central and peripheral components for measurement, and makes the assumption that responses are independent of stimulation frequency. It is however the total ventilatory response to an oscillatory carbon dioxide (CO2) stimulus with a cycle time of one minute that is physiologically-relevant in heart failure.

Design
We tested the hypothesis that chemoreflex gain, like other physiological reflexes, is frequency-dependent: i.e. with increasing stimulus administration frequency, the response increases.
We administered oscillations of inspired CO2 at stimulus periods of 30-240 seconds, to
measure chemoreflex gain in 28 subjects (heart failure and age-matched controls), and compared this to rebreathing in a subset.

Results
Chemoreflex gain increased linearly with stimulus period (r=0.99, p<0.0001). This oscillatory gain correlated with the values obtained using the Modified Rebreathing method (r=0.96, p=0.0001), although the latter were higher (161±54 v 752±405 L/min/atm). We confirmed that chemoreflex gain is greater in heart failure patients with periodic breathing than in those with stable breathing measured using both oscillatory CO2 (261±37 v 144±23 L/min/atm, p=0.009)) and Modified Rebreathing (1278±356 v 526±76 L/min/atm, p=0.0004).

Conclusions
Over these clinically-relevant timescales, the chemoreflex has a greater gain when the cycle time of the oscillatory CO2 stimuli is longer, in contrast to other physiological reflexes, meaning that the Modified Rebreathing method may not measure the gain relevant to periodic breathing in heart failure.

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Novel Pacemaker-Mediated Therapy for Alleviation of Ventilatory Oscillations in Periodic Breathing in Heart Failure Subjects.
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Background
Periodic breathing in heart failure is associated with increased morbidity and mortality and is characterised by oscillations in carbon dioxide (CO2) and ventilation with a period of about a minute. An ideal dynamic therapy would therefore apply counteracting oscillations to these parameters.

We have shown previously that repetitive alternations in cardiac output, using a cardiac pacemaker, can modulate respiratory gas transport through the circulation sufficiently to elicit oscillations in respiratory variables.

In this study we use an experimental model of periodic breathing (using oscillatory inhaled CO2) to test whether dynamic cardiac output alternations using pacemakers can attenuate respiratory oscillations.

Methods
We administered oscillatory inhaled CO2 fraction with period one minute and magnitude 4.25±1.8% to fourteen patients with cardiac pacemakers, to induce oscillations in end-tidal CO2 (ETCO2) and ventilation. Using real-time Fourier transformation of the ventilation signal, we could detect the peak and magnitude of the induced oscillations, allowing prediction of the optimal timing for dynamic cardiac output programming. We programmed changes in paced rate and/or atrioventricular delay to elicit oscillations in cardiac output to counteract the oscillations in ETCO2 and ventilation.
Results
When peak cardiac output was programmed to coincide with peak ventilation, the induced oscillations in ETCO2 were reduced by 43% (standard deviation[SD]/mean ETCO2 untreated versus treated 0.08±0.02 v 0.05±0.02, p<0.001). Induced ventilatory oscillations were also attenuated by 55% (SD/mean ventilation untreated versus treated 0.13±0.06 v 0.09±0.05, p<0.01).

Conclusion
Dynamic cardiac pacemaker reprogramming can produce oscillations in cardiac output which can be used to deliberately induce oscillations in respiratory gases and ventilation. The resulting oscillations are predictable both in timing and magnitude, and therefore can be used to counteract intrinsic respiratory oscillations.
Dynamic pacemaker-induced cardiac output modulation is therefore a potential novel therapy for ventilatory conditions characterised by their oscillatory nature, such as periodic breathing in heart failure.

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INTRODUCTION. Despite its fast penetration in many fields, the application of information and communication technologies in the clinical practice is still very limited, especially in respiratory medicine. The availability of tools such as the Internet has grown rapidly and, although the web-based information is easily accessible on various aspects of health, it is rarely considered as an option for therapeutic support. The Obstructive Sleep Apnea Syndrome (OSAS) is a disease in which, because of its prevalence and chronic nature, telemedicine has a great potential.

OBJECTIVE. To develop and to assess the feasibility of a web-based follow-up of continuous positive pressure airway pressure (CPAP) therapy in patients with OSAS.

METHODS. A personal easy-structured web site was created for this study and each patient was given access to his/her own data exclusively. By visiting the web site, patients could answer to a weekly questionnaire about symptoms, sleep quality, potential CPAP side effects, physical activity and body weight, having the patient access to continuously updated temporal trends in graphical format. Moreover, informative documents about OSAS and CPAP therapy were available to free download.
RESULTS. On a total of 163 consecutive patients of the Sleep Clinic, 66 reported minimum knowledge of the Internet and agreed to participate. After 12 weeks of monitoring, the participation rate was high (82%). In addition, patients responded to a satisfaction survey through the website itself, showing a level of agreement to the statement “Overall I am satisfied with the web service” of 4.3 ± 0.58 points (1 = I strongly disagree, 5 = I strongly agree) and their potential interest in participating in a long-term web-based monitoring.

CONCLUSIONS. The results of this pilot study show the potential usefulness of the Internet as a tool to support home monitoring of CPAP treatment in OSAS.

The impact of intermittent hypoxia on the apnea/hypopnea index before and after administration of an antioxidant cocktail.
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Purpose: To determine the impact of intermittent hypoxia (IH) on apnea severity before and after administration of an antioxidant cocktail (AOX).

Methods: Two studies were completed. 13 participants with OSA completed study 1 while eight participants completed study 2. For both studies, a baseline sleep study was completed initially. During Study 1 participants were exposed to IH (12 – 4 minute episodes of hypoxia) each day for ten consecutive days. On days 1 and 10, the participants completed a sleep study after exposure to IH. During Study 2 participants were exposed to IH during two visits. Each exposure was followed immediately by a sleep study. During visits 2 and 3 of study 2 participants were administered either an AOX or Placebo (PLB) cocktail in a randomized blinded fashion. Breathing events were scored during the initial 3 hours of sleep.

Results: Study 1 – The apnea/hypopnea index (AHI) after exposure to IH was greater on day 1 compared to baseline (42.0 ± 5.9 vs. 26.6 ± 3.8 events/hr, p < 0.04). The AHI on day 10 (39.0 ± 6.2) was also greater than baseline (p < 0.04); however the AHI was similar to that measured on day 1. On days 1 and 10, the AHI was correlated to the hypoxic ventilatory response measured during the last episode of the IH protocol (r = 0.65, p < 0.0004). Study 2 - Similar results were observed when the AHI during PLB was compared to baseline (48.5 ± 8.2 vs. 29.9 ± 5.6 events/hr, p = 0.005). Moreover, the AHI during the PLB trial was greater compared to the AHI following AOX administration (48.5 ± 8.2 vs. 38.1 ± 8.5 events/hr, p = 0.02).

Conclusions: Exposure to acute IH may lead to an increase in the AHI while administration of an antioxidant cocktail may mitigate the increase.

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Intermittent hypoxia enhances cancer progression in a mouse model of sleep apnea.
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BACKGROUND: A hypoxic environment enhances the proliferation of cancer cells and tumor progression. However, it is not known whether the intermittent hypoxia experienced by patients with the obstructive sleep apnea (OSA) syndrome promotes cancer progression. AIM: The aim of this experimental work was to test the hypothesis that tumor growth is enhanced by a pattern of intermittent hypoxia mimicking the one found in OSA patients.

METHODS: A melanoma tumor was induced in twenty-two male C57BL/6J mice by subcutaneous injection of B16F10 cells in their left flank region. Seven animals were chronically subjected to intermittent hypoxia with a pattern mimicking OSA: 20 s of 5%O2 and 40 s of room air (6 h/day for 14 days). A control group of 8 animals were kept under normoxia. The tumors’ progression was assessed by estimating its volume at days 8, 11 and 14. At day 14 the tumors were excised and weighed. Tumor necrosis was assessed by hematoxilyn-eosin tumor preparations.

RESULTS: Tumor volume progressively increased with time for both groups and the increase was higher in the intermittent hypoxia group (p < 0.001). Tumor weight at day 14 was almost 2-fold greater (p = 0.012) in the intermittent hypoxia group (3.10 ± 0.42 g) compared to the normoxia group (1.66 ± 0.29 g). Tumor necrosis was 2-fold greater in the animals subjected to intermittent hypoxia than in those subjected to normoxia (29.1±6.2% and 14.5±4.7%, respectively; p = 0.08).

CONCLUSION: These data strongly suggest that intermittent hypoxia could contribute to cancer progression in OSA.

Sources of support: Ministerio de Ciencia e Innovación (SAF2009-02991, PI081908, PI080277).

Keywords: Sleep apnea, intermittent hypoxia and cancer.
Sponsor: Ramon Farré.

A Simplified Model of Screening Questionnaire and Home Monitoring for Obstructive Sleep Apnea in Primary Care.
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Introduction: To address the escalating burden of disease and growing demand for sleep services, we aimed to develop and validate a simplified, 2-step method for identifying patients in primary care with symptomatic obstructive sleep apnea (OSA) consisting of a screening questionnaire followed by home sleep monitoring.

Methods: 157 patients aged 25 to 70 years attending their primary care physician for any reason at 6 primary care clinics in rural and metropolitan regions of South Australia participated. The first 79 patients formed the development group and the next 78 patients the validation group. A screening questionnaire was developed from factors identified from sleep surveys, demographic and anthropometric data to be predictive of moderate-to-severe OSA. Receiver operating characteristic (ROC) curve analysis was used to validate the two-channel ApneaLink (ResMed) device against full polysomnography. The diagnostic accuracy of the overall two-stage model was then evaluated.

Results: Snoring, waist circumference, witnessed apneas & age were predictive of OSA and incorporated into a screening questionnaire (ROC area under curve (AUC)=0.84 [95%CI:0.75–0.94], p<0.001). Oximetry was highly predictive of OSA (3% dip rate ROC AUC=0.95 [0.90-1.00], p<0.001). The two-stage diagnostic model showed a sensitivity of 0.97 [0.81-1.00] and specificity of 0.87 [0.74-0.95] in the development group, and sensitivity of 0.88 [0.60-0.98] and specificity of 0.82 [0.70-0.90] in the validation group.

Conclusion: A two-stage model of screening questionnaire followed by home oximetry can accurately identify patients with OSA in primary care, and has the potential to expedite care for patients with this common sleep disorder.

Funded by the National Health and Medical Research Council of Australia; ApneaLink monitors donated by ResMed

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Cardiometabolic and Sleep Effects of Testosterone Therapy in Obese men with Obstructive Sleep Apnea: a randomized placebo controlled trial.

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Introduction: Testosterone therapy is increasingly used in the community despite poorly documented benefits and important risks including worsening sleep apnea (SA) in elderly men. Obese men with SA have both lower testosterone concentrations and worse cardiometabolic outcomes compared with normal individuals. The cardiometabolic and sleep effects of testosterone therapy in obese men with SA have not been studied.

Methods: 67 obese men with SA received at random intramuscular injections of 1000mg testosterone undecanoate or placebo at 0, 6 and 12 weeks with a weight loss program. Anthropometry, body composition abdominal and liver fat insulin sensitivity arterial stiffness, blood lipids and SA were measured before, during and after the 18-week treatment period.

Results: Testosterone, as compared with placebo, increased total lean muscle mass by 1.6kg (0.73kg to 2.5kg 95%CI, p=0.0005) and decreased arterial stiffness by 2.8% (-5.58% to -0.09%, p=0.04) after 18 weeks. The decrease in total and abdominal fat, total weight and body
Impact Of Obstructive Sleep Apnea On Metabolic Dysfunction In Severe Obesity.
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Rationale: It has been suggested that Obstructive Sleep Apnea (OSA) worsens the effect of obesity on cardio-metabolic impairment. Whether OSA may add deleterious metabolic consequences in morbid obesity is unknown.

Objectives: To examine whether OSA is associated with Metabolic Syndrome (MetS) in morbidly obese patients, independently of cofactors.

Methods: A prospective multi-centre cross-sectional study was conducted in consecutive morbidly obese individuals undergoing bariatric surgery. OSA was defined as apnea-hypopnea index (AHI) ≥15 following full overnight polysomnography. Fasting blood samples were obtained the morning after PSG. MetS was defined according to the National Cholesterol Educational Panel ATP III modified criteria.

Main Results: 159 patients (72% female) were studied; mean age 43±10 years, BMI 46.1±5.8 Kg/m2, mean Epworth sleepiness scale 8±5, and 72% had OSA. MetS prevalence was 70% in OSA vs 36% in non-OSA (p<0.001). The prevalence of each MetS component was also higher in OSA comparing to non-OSA: HTA (41% vs 76%, p<0.001), HiperGlu (48% vs 65%, p=0.044), HiperTAG (16% vs 37%, p=0.009) and hipoHDL (41% vs 27%, p=0.112). As OSA severity increased, the metabolic profile progressively worsened. AHI was independently associated with systolic and diastolic blood pressure, triglycerides and the
percentage of glycosylated hemoglobin (HbA1c). OSA prevalence was higher in patients with MetS than in patients without MetS (83% vs 56%, p < 0.001). After adjusting for age, gender and BMI, the presence of OSA (AHI ≥ 15) increased the odds ratio of having MetS by 2.84 (95% CI 1.30 – 6.22, p=0.009).

Conclusions: OSA is associated to an increase of MetS also in morbidly obese patients, independently of main cofactors and irrespectively of gender, suggesting an important role of OSA in the pathogenesis of MetS associated with obesity.

Keywords: obstructive sleep apnea, metabolic syndrome, metabolic index, morbid obesity.


022

A new induced and reversible animal model of obstructive sleep apnea.
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Introduction: The mechanisms underlying obstructive sleep apnea (OSA) are not fully understood and the identification of new pharmacological agents for OSA management is limited by the lack of animal models available for pharmacological screening. OSA is characterized by repetitive pharyngeal collapse during sleep in patients with a narrowed upper airway (UA). Flexion of the neck has been shown to increase UA collapsibility and the supine position is usually associated with substantially more severe OSA. We therefore hypothesized that combining these changes in body and head positions would generate OSA in cats.

Methods: We developed a conditioning restraining device in order to investigate the effect of combining two body positions, prone (P) or supine (S), and two head positions, with the neck flexed at right angles to the body (90°) or in extension in line with the body (180°), during sleep. Polysomnography was performed twice in each of 6 cats in each of the four sleeping positions P180, S180, P90, and S90. Before each daily recording, instrumental deprivation of rapid eye movement (REM) sleep was performed to promote sleep during recording sessions. The effect of continuous positive airway pressure (CPAP) treatment was then investigated in 2 cats under the most severe OSA condition.

Results: Compared to P180, S90 generated the highest apnea-hypopnea 2, p±1 vs 25±index (AHI) (3<3, p±0.001), while V90 (18<0.001) and 5, p±S180 (13<0.01) had a lesser effect. In position S90, an increase 3%, p±3% vs 22±in slow wave sleep stage 1 (28<0.05) and a decrease 2%, p±2% vs 18±in REM sleep (10<0.001) were also observed. CPAP 2, p±3 vs 8±resulted in a reduction in the AHI (22<0.01), with the added benefit of sleep consolidation.

Conclusion: To our knowledge, this is the first description of a non-anesthetized animal model in which OSA is induced by mimicking human sleeping conditions.
Sources of support: This work was supported by INSERM-U628 and Université Claude Bernard Lyon-1. We thank ADIR (Aides à Domicile aux Insuffisants Respiratoires, Isneauville, France) and ANTADIR (Association Nationale pour les Traitements à Domicile, les Innovations et la Recherche, Paris, France) and Weinmann (Hamburg, Germany) for fellowships.

023

Model based differentiation of cardiovascular dynamics during apneas
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The quantification of excessive daytime sleepiness and the apnea-hypopnea-index are common markers stratifying the risk of cardiovascular diseases and other complications caused by sleep disordered breathing. Based on these markers about thirty percent of the population in industrial countries suffer from sleep apnea. Using model based and coupling analyses, we were able to reveal significant different cardiovascular mechanisms not only between the deep sleep and the other sleep stages but also between healthy subjects and patients with obstructive sleep apnoea syndrome (p<0.05, Kruskal-Wallis test, 18 normotensive and 10 hypertensive patients, 10 controls). The question however is can we distinguish between more or less serious apneas? An answer by means of the common classification (obstructive, central, and mixed) is not possible.

As a first step to answer this question we plan to analyse the cardiovascular response to apnea. This investigation will be based on polysomnographic measurements and nocturnal continuous blood pressure records of 70 untreated patients suffering from moderate obstructive sleep apnea. The transient dynamics of heart rate, systolic and diastolic blood pressure during and after apnea will be quantified by minimal non-linear models. They are used to detect the couplings and to quantify their strength in the sense of Granger causality. A quantification of the cardiovascular regulation and dynamics may allow a clustering of the apneas in relation to their influence on heart rate and blood pressure and thus to their severity.

024

Correlates of Central (Aortic) Pressure Profiles in Obese Patients with Obstructive Sleep Apnea (OSA)
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Background: Arterial systolic (SP) and pulse (PP) pressures differ between the aorta and the brachial artery despite similar diastolic and mean pressures. Given the increased risk of heart failure and stroke in OSA, central pressures are important cardiovascular phenotypes because the heart and the brain are exposed to central, rather than brachial pressures.

Methods: We studied 70 obese subjects with moderate-to-severe OSA demonstrated by a full diagnostic polysomnogram (mean apnea hypopnea index=43.7±25 events/hr; mean
age=43.7±11 years; mean body mass index=38.7±7.7 kg/m2; 54% male; 47% white; 29% African-American). Central pressures were measured with high-fidelity radial applanation tonometry and a validated generalized transfer function. We analyzed the correlates of central pressure profiles in this population using linear regression.

Results: The ratio of aortic/brachial pulse pressure was associated with older age (standardized β=0.29; P=0.006), heart rate (standardized β=-0.48; P<0.0001) and African American ethnicity (standardized β=0.25; P=0.01), independent of waist circumference, C-reactive protein, measures of atherogenic dyslipidemia and other relevant covariates. For any given brachial pressures, age, gender, heart rate, waist circumference, body mass index and apnea hypopnea index, central PP and SP were, on average, 1.50 mmHg greater among African-American subjects. African-Americans demonstrated greater late systolic pressure augmentation (from wave reflections in the peripheral arterial tree), as quantified by the augmentation index (second/first systolic pressure peaks). The effect of African-American ethnicity on the augmentation index was quantitatively important and equivalent to that of ~13 years of aging of the arterial tree in this population.

Conclusions: African Americans with OSA demonstrate greater aortic SP and PP relative to their white counterparts, after adjustment for OSA severity, obesity and other relevant confounders. These findings should be taken into account when designing studies to assess hypertensive phenotypes in multiethnic populations with OSA.

Sources of Support: National Heart, Lung and Blood Institute RO1-HL080076 (J.A.C) and American Heart Association National Research Award 0885031N (J.A.C).

The utility of acetazolamide as a treatment for obstructive sleep apnea
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Background
Obstructive sleep apnea (OSA) likely results from the interaction of several traits including: poor pharyngeal anatomy, poor upper-airway muscle function, high ventilatory response to a change in ventilation (high loop gain), and a low arousal threshold. While continuous positive airway pressure (CPAP) is effective, it is often poorly tolerated, making pharmacological strategies an attractive potential alternative. Acetazolamide has been minimally studied in this context and little is known as to how it affects the traits causing OSA. Using a novel technique for measuring these four OSA traits, we aimed to (1) investigate the effect of acetazolamide on OSA traits and (2) determine how alterations in these traits alter OSA severity.

Methods
Thirteen OSA subjects underwent 4 nights of polysomnography to assess the effect of 7 days of acetazolamide (500mg twice daily) on OSA traits and AHI. To measure the traits, multiple 3-minute “drops” from therapeutic CPAP were performed. Each CPAP-drop reduced ventilation and increased ventilatory drive (determined by turning CPAP back to therapeutic levels and measuring the ventilatory overshoot). Loop gain was defined as the ratio of the ventilatory overshoot to the preceding reduction in ventilation. Pharyngeal collapsibility was
quantified as the ventilation at CPAP=0. Upper-airway responsiveness was taken as the ratio of increase in ventilation to the increase in ventilatory drive across the drop. Arousal threshold was quantified as the level of ventilatory drive (L/min) associated with arousal.

Results
Acetazolamide significantly reduced the median (interquartile range) AHI from 50 (35-57) to 24 (14-42) events/hr. However, AHI increased in two subjects. Acetazolamide significantly reduced loop gain from 3.6 (2.4-5.6) to 2.0 (1.4-3.5), but did not importantly alter pharyngeal collapsibility, upper-airway responsiveness, or arousal threshold.

Conclusions
Our data suggest that administration of acetazolamide can improve OSA severity, primarily due to reductions in the sensitivity of the ventilatory control feedback loop.

Clinical information followed by portable sleep studies identifies severe sleep apnea syndrome in outpatients with hypertension
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Background: A strategy to screen outpatients with hypertension for severe obstructive sleep apnea syndrome (s-OSAS) is needed; OSA may lead to hypertension, and its treatment may lower blood pressure in this group.

Objective: To validate single- and two-stage(1) strategies to screen for s-OSAS (apnea-hypopnea index ≥30/h with Epworth score >10).

Subjects: Outpatients with hypertension at internal medicine practice at VA Medical Center and University-hospital-based hypertension clinic.

Interventions:
1) Clinical variables: body mass index (BMI), neck circumference (NC), gender, apnea symptom frequency (Sx). We averaged the frequency of self-reported snoring, choking/gasping during sleep and witnessed apneas, on a scale of 0 (never) to 3 (often) to compute Sx(2).
2) In-home sleep-recordings: airflow, SaO2, and respiratory effort (ResMed AutoSet PDS);
3) We validated combinations of (1) and (2) against 12-channel, in-laboratory polysomnography.

Measurements:
1) For clinical variables, using logistic regression (SAS), we computed risk of having s-OSAS, (0=no risk and 1=high risk)(1).
2) We found cutpoints for these risk scores that minimized missed-case rates, and computed sensitivity, specificity, negative post-test probability and area-under-receiver-operating-characteristic curves (AUC).
3) We repeated this for two-stage models, using the clinical risk scores for the first stage, followed by in-home studies in an intermediate-risk subset(1).

Results: Of 250 subjects, 198 had polysomnography; 15/198=7.6% had s-OSAS. Sx+BMI+gender in all, followed by portable studies in a subset performed best (see Table). Sx+BMI+gender or Sx+NC used alone performed better than in-home studies alone (AUC=0.759).
Cutpoint Sensitivity Specificity Post-test Probability AUC
Sx+BMI+gender 0.75 88% 73% 1.3% 0.796
Sx+NC 0.70 88% 63% 1.5% 0.776
Portable sleep study 16e/h 80% 68% 2.1% 0.759
Sx+BMI+gender, then portable study 30e/h
for risk score between 0.5 & 0.8 100% 77% 0% 0.883

Conclusion: In-home sleep studies identified s-OSAS more accurately when combined with symptoms+BMI+gender than when used alone.

References:
2 SLEEP 1995; 18,158-66.
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Upper Airway Sensory and Motor Function in Obstructive Sleep Apnea.
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Background: The role of upper-airway sensory/motor impairment in obstructive sleep apnea pathogenesis/disease progression is debated. Theoretically, inadequate upper-airway sensation or impairment due to mechanical trauma and/or hypoxemia may reduce reflex-modulated motor output and contribute to sleep apnea pathophysiology/disease progression. If so, detectable changes in upper-airway sensory/motor function should be present during wakefulness.

Objective: To compare upper-airway sensory/motor function in obstructive sleep apnea patients with controls.

Methods: We performed a battery of upper-airway sensory and motor function tasks including assessment of: 1) the P1 component of the respiratory-related evoked potential, 2) genioglossus and tensor palatini negative pressure reflexes, 3) epiglottic pressure versus genioglossus activity during entrained iron lung ventilation, and 4) tongue protrusion force and fatigability in 12 awake obstructive sleep apnea patients and compared the results to 13 controls.

Results: Measures of sensori-motor integrity were not different between patients and controls including: the P1 component of the respiratory-related evoked potential (latency 25±2 vs. 24±1ms, p=0.61 and amplitude 3.9±0.6 vs. 3.8±0.6µV, p=0.87), upper-airway dilator muscle reflexes (e.g. genioglossus onset latency 20±1 vs. 19±2, p=0.82 and amplitude 473±108 vs. 317±51% baseline, p=0.19), and the slope epiglottic pressure versus genioglossus activity during iron lung ventilation (-0.68±1.0 vs. -0.80±2.0, p=0.59). Conversely, maximal tongue
protrusion force was greater in sleep apnea patients versus controls (35±2 vs. 27±2N, p<0.01), but task failure occurred more rapidly (149±24 vs. 254±23s, p<0.01).

Conclusions: These data do not support systematic impairment of upper-airway sensory/motor function as measured by the P1 component of the respiratory-related evoked potential and dilator muscle reflex responses in sleep apnea patients during wakefulness. Rather, consistent with a muscle training effect, tongue protrusion force is increased, not decreased, in untreated sleep apnea patients. However, obstructive sleep apnea patients may be more vulnerable to upper-airway dilator muscle fatigue which could contribute to disease progression.

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Disclosure Details
YLL and JPS have no personal potential conflicts to declare. DJE and ASJ are consultants for Apnex Medical. DPW is Chief Medical officer for Philips Respironics. AM has received consulting and/or research income from Philips, Medtronic, Apnicure, Apnex, Itamar Ethicon, Pfizer, Separacor, Merck, Cephalon, SGS and SHC. While a number of the authors have some industry affiliations related to the treatment of apnea, we do not see these as relevant to this physiological investigation that was funded via peer review grant mechanisms.

Automated pause frequency estimation to assess the risk of Postoperative Apnea in infants.
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Purpose: To evaluate the relation of short pause and thoraco-abdominal asynchrony (TAA) events to Postoperative Apnea (POA) in infants using an automated scoring system.

Methods: We recruited sixteen infants who underwent elective herniorrhaphy and were at risk of POA (median postconceptional age 42.8 [38.8 – 47.0] wk; median weight 3.6 [2.0 – 5.7] kg). Respiratory inductive plethysmograph (RIP) signals from the ribcage and abdomen, finger plethysmograph and blood oxygen saturation were recorded for 6 to 12 hours after arrival at the postanesthesia care unit. The recordings were scored by our automated scoring system described in [1], which uses RIP signals to assign the respiratory state at each time to one of four categories: Pause, TAA, Movement Artifact and Quiet Breathing. For each subject, we computed the Pause and TAA average frequencies dividing the total number of events longer than 2 s by the hours of the recording. Subjects were classified into two groups: Apnea and Control. Nine infants who exhibited at least one pause longer than 10 s were assigned to the Apnea group, and the rest to the Control group. The differences between the two groups in Postconceptional Age (PCA) and weight, as well as in Pause and TAA average frequencies, were assessed with the Wilcoxon rank-sum test.

Results: The average Pause frequency was significantly higher (p < 0.01) in the Apnea group (median 27.4 [18.7 – 39.2] pauses/hr), compared to the Control group (median 12.6 [6.4 – 16.3] pauses/hr). This variable correctly discriminated 100% of the cases. There were no significant differences in PCA, weight or average TAA frequency between the groups.
Discussion: Our findings suggest that the frequency of pauses longer than 2 s identified with our automated scoring system can be used to assess the risk of long pauses (> 10 s) on infants on the postoperative period.

References

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029

Diagnostic Accuracy of Heart Rate Variability and Pulse Oximetry for Detection of Sleep-Disordered Breathing in Chronic Heart Failure
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Introduction: Sleep-disordered breathing (SDB) occurs frequently in chronic heart failure (CHF) but is often underdiagnosed. Simple screening tests may improve detection of SDB in CHF. In this study, we tested the hypotheses that measurement of heart rate variability (HRV) or pulse oximetry can be used to diagnose SDB in CHF.

Methods: CHF patients attending cardiology clinics were invited to participate, irrespective of clinical suspicion of SDB. All patients provided written informed consent and were studied with polysomnography, synchronous ambulatory electrocardiography and pulse oximetry. SDB was defined as AHI >15.0/hour. The %VLFI component of HRV was measured from the electrocardiogram, with a cutoff >2.23% to diagnose SDB. The >3% oxygen desaturation index (ODI) was measured by pulse oximetry, with a cutoff of >7.5 desaturations/hour to diagnose SDB. Diagnostic accuracy of %VLFI and ODI>3% were assessed, using the polysomnogram as reference standard for diagnosis of SDB.

Results: 311 CHF patients were approached; 180 consented to participate. 7 patients were excluded due to insufficient sleep (<200 minutes). 173 patients were included in the analysis with mean (SD) age 66.9 (13.2) years; 86% male; Epworth Sleepiness Scale 7.5 (4.3); NYHA 2.1 (0.6); Left ventricular ejection fraction 42 (16)%; median (IQR) BNP 118 (55 - 239)pg/ml. SDB was present in 77 (45%) patients. HRV was measurable in 78 (45%) of CHF patients; cardiac pacing, atrial fibrillation and frequent ectopy prevented measurement in the remainder.

Diagnostic Accuracy of %VLFI and ODI>3% for detection of SDB in CHF patients
%VLFI ODI>3%
Sensitivity 0.53 0.97
Specificity 0.44 0.32
Positive Predictive Value 0.45 0.53
Negative Predictive Value 0.51 0.94
Positive Likelihood ratio 0.94 1.42
Negative Likelihood ratio 1.08 0.08
Area under Receiver Operating Characteristic curve 0.49 0.92

Conclusion: The %VLFI component of HRV has inadequate sensitivity or specificity to diagnose SDB in CHF, and could be measured in less than half of all patients in this study. In contrast, the ODI>3% has a very high sensitivity and low negative likelihood ratio for SDB diagnosis. Therefore, pulse oximetry is a valuable test to rule out SDB in patients with CHF. This study was funded by the British Heart Foundation

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Increased recruitment and function of endothelial progenitor cells in patients with acute myocardial infarction and sleep apnea
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Introduction and objectives: Obstructive sleep apnea (OSA), characterized by recurrent episodes of intermittent hypoxia (IH), can lead to endothelial dysfunction, atherosclerosis, and cardiovascular morbidity. However, endothelial progenitor cells (EPCs) can repair the endothelium by homing to ischemic sites and promoting neovascularization.

Preliminary data from our laboratory show that 44% of AMI patients were diagnosed with sleep-disordered breathing having an AHI>20. However, the presence of OSA did not confer an increased risk of mortality.

Several studies reported on higher numbers of EPCs in AMI patients, but the mechanisms inducing increased recruitment remain unclear. Therefore, this study is aimed at defining the numbers and functions of circulating EPCs in AMI patients with OSA (AMI-OSA) and without OSA (AMI-only).

Methods: AMI was diagnosed according to the Joint European Society of Cardiology/American College of Cardiology criteria. EPCs, Angiogenic T cells and VEGF expression by peripheral monocytes were determined by Flow Cytometry. Functional capacities of EPCs were measured by endothelial cell colony-forming units (EC-CFUs) assay.

Results: Blood was obtained from 17 male AMI-OSA patients (age=58.6±4.3 years; BMI=28.2±1.6 Kg/m2; AHI=21.3±3.8 events/h) and 17 matched male AMI-only patients (age=58.4±6.88 years; BMI=26.9±2.8 Kg/m2; AHI 8±2 events/h). Circulating EPCs (0.018±0.0072 vs. 0.0047±0.0016%; p<0.05) and angiogenic T cells (24.69±3.70 vs.18.6±2.7%; p<0.05) were markedly higher in AMI-OSA as compared with AMI-only patients. Additionally, EC-CFUs numbers were significantly higher in AMI-OSA patients than in AMI-only patients (79.1±7.6 vs. 28.8±14.1 colonies/field; p<0.05). Also, monocytes from AMI-OSA patients expressed higher intracellular VEGF levels (684.9±80.8 vs. 472.1±81.7 Mean fluorescence intensity; p<0.05). Oxidative stress and inflammatory markers did not differ between the groups.
Conclusions: Our findings demonstrate that the presence of OSA in AMI patients increases EPCs recruitment and function and monocyte VEGF expression. Activation of such mechanisms in AMI-OSA patients may improve endothelial function and provide a compensatory response in the setting of AMI.

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Arterial Hypertension In A Murine Model Of Sleep Apnea – Role Of NADPH Oxidases
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Rationale:
Obstructive sleep apnea (OSA) is a risk factor of arterial hypertension and it is linked to oxidative stress. In the present study, we aimed to investigate whether NADPH oxidases (NOX) a major source of free oxygen radicals, contribute to the emergence of arterial hypertension in a murine model of sleep apnea.

Methods:
C57BL/6J mice were exposed to chronic intermittent hypoxia (CIH) for 6 weeks (5 days per week, 8 hours per day, alternating cycles of hypoxia and normoxia, each lasting 120 sec., nadir FiO2: 7%). Blood pressure was monitored by telemetric catheters implanted in the femoral artery. Pharmacological inhibition of NOX by apocynin and NADPH oxidase subunit NOX2-deficient mice were used to assess the role of NOX in arterial hypertension induced by CIH.

Measurements and results: When compared to room air conditions, wild-type mice showed significant blood pressure elevations after exposure to CIH. This response was attenuated after treating animals with apocynin and in gp91 phox knock-out mice.

Conclusion:
Our data suggest that the OSA-associated arterial hypertension may at least partly be mediated by an increased oxidative stress derived from gp91 phox-containing NOX.

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Image-based Computational Fluid Dynamics Methods to Study Mechanical Properties of the Airway in Children with Obstructive Sleep Apnea
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Image-based computational fluid dynamics (CFD) models were applied to better understand the correlations between the anatomical, functional, and mechanical properties of the upper airway in children with obstructive sleep apnea (OSA). At first, CFD was applied based on static magnetic resonance (MR) imaging, anterior rhinomanometry, and flow measurement, to compute internal pressure and flow resistance in 12 children with OSA and 12 matched controls. Mean pharyngeal flow resistance was significantly higher in subjects with OSA (0.77±0.98 vs. 0.22±0.17 kPa/L/s, p < 0.05), and minimum internal airway pressure at peak flow (Pmin) was significantly lower (-6.7±7.3 vs. -1.7±1.3 cmH2O, p < 0.02). The above
model based on static MR imaging demonstrated that restricted upper airway anatomy can
drive low internal airway pressure, and may be useful to identify children who will most
benefit from adeno-tonsillectomy. We later used CFD to measure the functional compliance
of the airway in an OSA child and a matched control using a dynamic model. MR images
were gated to respiratory phases using abdominal bellows and acquired at 10%, 30%, 50%,
70%, and 90% of tidal volume on inspiration and exhalation. The internal pressure
distribution at each volume increment was calculated using CFD. Airway compliance (cross-
sectional area vs. pressure) was essentially zero in the control subject, but positive in the OSA
subject and higher in the oropharynx (1.028 mm2/Pa) than the nasopharynx (0.449 mm2/Pa).
The theoretical limiting flow rate, derived from compliance and airway cross-section area,
was consistently lower in the oropharynx than nasopharynx (minimum flow rates 24.1 and
50.4 ml/s respectively), indicating that the more compliant oropharynx was the flow-limiting
section of the airway. Thus, respiratory-gated MR imaging with CFD is capable to identify
airway segments or anatomical structures most associated with upper airway collapsibility and
high Pcrit in individual patients with OSA.

Oxygen profiles in metabolically active tissues during different hypoxic exposures in lean and
obese mice.
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Introduction
Intermittent hypoxia (IH) is widely used as a model of obstructive sleep apnea. There are
different paradigms, but 2 important issues remain unknown:
1) The pattern of hypoxic exposures in different tissues.
2) Effects of different hypoxic paradigms on inflammation, oxidative stress and metabolism.

Methods
C57BL6 mice (~25 weeks old) were exposed for 12hr overnight (fasting) to either IH (FiO2
21-5%, 60/h or FiO2 5% for 15s, 12/h), sustained hypoxia (SH, FiO2 10%) or control (FiO2
20.9%). Tissue pO2 in liver, muscle and epididymal fat was measured during the different
hypoxic regimens using an oxygen microelectrode (OX-50, Unisense A/S, Denmark)
simultaneously with pulse oximetry (Starr Life Sciences, Oakmont, PA) under urethane
anesthesia. In a second set of mice, inflammation, oxidative stress and metabolic outcomes
were measured.

Results
In lean mice, IH induced swings of pO2 in liver and muscle tissue, which were in phase with
SaO2 changes, whereas adipose tissue exhibited steady hypoxia without fluctuations; all 3
types of hypoxia caused lipid peroxidation in liver and increased blood glucose without
changes in insulin; hypoxia significantly increased plasma leptin, especially in the SH group
(44-fold); IH, but not SH, induced a 2.5-3-fold increase in cytokine secretion by adipocytes.
In obese mice, IH induced similar changes in tissue pO2; there were significantly higher
baseline levels of glucose, leptin, lipid peroxidation and adipocyte cytokines, compared to
lean mice, which were not affected by hypoxia.
Conclusions
During IH, adipose tissue shows steady hypoxia, whereas liver and muscle show an intermittent pattern. In lean mice, all types of hypoxia induced oxidative stress and metabolic dysfunction, but adipose inflammation was observed only in IH. In obese mice, oxidative stress, metabolic dysfunction and inflammation were present at baseline and were not accentuated by hypoxia.

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ALL-CAUSE AND CARDIOVASCULAR MORTALITY IN ELDERLY PATIENTS WITH SLEEP APNEA. ROLE OF CPAP TREATMENT.
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Objective. Our objective was to analyse the impact of OSA and CPAP treatment on long-term mortality in a large cohort of elderly patients.

Methods. Multicenter observational study of 939 consecutive elderly (65 years) subjects referred for OSA suspicion between 1999-2007 and followed-up until December-2009. Four groups were established: 1. Control group without OSA (AHI <15), (n=160); 2. Mild-moderate OSA without (or non-compliant with) CPAP treatment (AHI 16-29), (n=104); 3. Severe OSA (AHI ≥30) without (or non-compliant with) CPAP treatment, and 4. OSA of any severity with adequate (more than 3 hours/day) CPAP treatment, (n=505). Complete general, sleep study and cardiovascular history data were recorded. Mortality data were obtained from death certificates. Fatal cardiovascular events included stroke, heart failure (HF) and ischemic heart disease (IHD). Full-adjusted Cox proportional analysis was used to identify independent risk factors for all-cause and cardiovascular mortality.

Results. Mean age was 70.6 years (64.7% males). Median follow-up: 69 months. Mean AHI: 42.2 and BMI: 34.4 Kg/m2. During follow-up, 191 (20%) subjects died (101 cardiovascular; 28 strokes; 32 IHD; 38 HF). Non-treated severe OSA (but not non-treated mild-moderate OSA) was independently associated with all-cause (HR 1.74 [1.1-2.7]; p=0.016) and cardiovascular mortality (HR 2.33 [1.2-4.4]; p=0.016), as well as stroke (HR 3.85 [1.1-13.7]; p=0.043) and HF mortality (HR 3.14 [1.03-9.5]; p=0.043), but not with IHD (HR 1.23 [0.4-3.7]; p=ns). CPAP treatment reduced this excess of mortality in OSA patients.

Conclusions. In elderly patients, severe non-treated OSA is a risk factor for all-cause and cardiovascular mortality. Within the cardiovascular sphere, severe non-treated OSA increases the risk of stroke and HF mortality but not of IHD mortality. Treatment with CPAP was effective in normalizing this excess of mortality.

Funding and Conflict of Interest: None
Driving simulator performance and cortical responses remain abnormal in severe obstructive sleep apnoea patients after treatment with continuous positive air-way pressure

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Obstructive sleep apnoea (OSA) is linked to neurobehavioural abnormalities, poor driving performance and elevated motor vehicle accident (MVA) risk. Until recently, continuous positive air-way pressure (CPAP) was thought to completely correct OSA related neurobehavioral abnormalities. However, recent evidence suggests that sleepiness and cognitive dysfunction may persist in some patients despite treatment. The aim of this study was to evaluate the effectiveness of CPAP in improving driving simulator performance and task related cortical activation in severe OSA patients compared with age/gender matched controls. Driving simulator performance and event related potentials (ERP) were assessed in severe OSA patients and age/gender matched controls at baseline and 3 months follow-up, with patients treated with CPAP during this period. In contrast to previous studies we chose to simulate long distance 90min driving to capture performance deficits characteristic of fall asleep MVAs and to evaluate both early (sensory) and late (cognitive) ERP to more completely examine cortical responses in severe OSA. Main outcome measures were steering deviation and ERP components N1, P2, N2, P3. At baseline, OSA subjects demonstrated significantly greater steering deviation, delayed P2, N2 and P3 latencies, and significantly different P2 and P3 amplitudes (group effect, all p<0.05). Following ~3 months of CPAP treatment (Mean±SD 6.0±1.6 h/night), steering deviation in OSA subjects improved by an average of 3.1 [CI 1.4-4.9] cm, p<0.001 and P3 latency shortened by 21.1 [7.7-34.4] ms (p<0.01) with no change in other ERP components. However, despite the improvements, steering deviation and all ERP components remained abnormal in OSA patients compared to controls. These results add to the growing body of evidence that neuro-behavioural deficits in severe OSA patients may not always be fully reversed by treatment. Further studies are needed to assess causes of these residual impairments, and to determine whether this is associated with a persistently high accident risk and impaired cognition.

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(PAP) device for treatment is increasingly utilized. However, the effectiveness studies of ambulatory vs. standard laboratory management (LAB) of OSA have focused on comparison of change in disease severity indices, short-term symptom improvement, and treatment adherence. We examined the comparative effects of LAB vs. AMB management of OSA on blood pressure and glucose homeostasis.

Methods A retrospective cohort study of veterans (LAB, n=150; AMB, n=77) using administrative databases and clinical records review in 2005-2006. Inclusion criteria were: i) a new diagnosis of OSA; ii) Continuous PAP (LAB) or Autotitrating PAP (AMB) treatment; iii) co-morbid systemic hypertension or diabetes. Outcomes were changes in a) blood pressure (BP; mean of 3 highest recordings; systolic and diastolic) in patients with hypertension and b) glycemic control (mean of 3 highest fasting glucose and hemoglobinA1C) in type 2 diabetics at 3-6 months compared to pre-treatment.

Results: The AMB group had higher Body Mass Index (BMI; 35.91 + 5.70 vs. 33.89 + 6.28, p=0.04), higher severity of OSA (defined by apnea-hypopnea or respiratory-disturbance indices; p=0.001), and higher fasting glucose (132.7 + 47.91 vs. 117.6 + 38.00; p=0.02) at baseline. A generalized estimating equation (GEE model) was used with adjustment for potential confounders (demographics, BMI, Charlson co-morbidity index, and pharmacologic treatment adherence for hypertension and diabetes). Systolic (LAB= -7.44, CI -10.76 to -4.11; AMB –7.17, CI -10.86 to -3.48) and diastolic BP improved within both groups (LAB= -3.27, CI -5.19 to -1.34; AMB -2.70, CI -5.01 to –0.40). Fasting glucose and hemoglobinA1C did not change with OSA treatment in either group.

Conclusions: The ambulatory vs. the standard laboratory management may have differential effects on intermediate markers of cardiovascular risk and should be systematically examined.

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Effects of Adenotonsillectomy and Obesity on Upper Airway Properties during Sleep in Children as Assessed by Routine Polysomnography.
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Objective: Adenotonsillar hypertrophy (ATH) and obesity are risk factors for pediatric obstructive sleep apnea (OSA). They impose mechanical loads on the upper airway (UA), which are likely to predominate during REM sleep when neuromuscular activity wanes. We hypothesize that adenotonsillectomy will decrease UA obstruction in REM but not NREM sleep and that obesity will decrease responses to surgery.

Methods: Polysomnography before and after adenotonsillectomy was performed in children with OSA. To characterize the degree of UA obstruction during sleep, maximal inspiratory airflow (VImax) was measured during flow limited inspirations as a percentage of VImax during non flow limited breaths during NREM sleep, and responses were compared in lean and obese children (BMI z-score < or > 2).
Results: Seventeen children (age 6±1.4 years, M:F 9:8) were studied. Seven were non-obese (age 5±2.1 years, BMI z-score 0.4±0.1) and ten were obese (age 6±1.9 years, BMI z-score 3.0±1.0). In all children, the total AHI following adenotonsillectomy decreased (from 18±7 to 4±1 events/hour, p=0.03) predominantly due to a fall in the REM AHI (from 38±11 to 11±5 events/hour, p< 0.01). At baseline, the %VImax was lower during REM than NREM (66±6 vs. 85±5%, p= 0.01). Following adenotonsillectomy, the %VImax increased during REM (from 66±6 to 83±6, p=0.04), but no change was exhibited during NREM (85±5 vs. 83±4%, p=0.6). The %VImax increased during REM in lean (from 69±5 to 90±8, p=0.04), but not obese children (63±10 to 78±9, p=0.3).

Conclusion: Mechanical effects of adenotonsillectomy improve UA patency during REM but not NREM sleep, and responses are greater in lean than obese OSA children. Our findings imply that vigorous neuromuscular responses offset mechanical pharyngeal loads of ATH in NREM sleep. We speculate that obesity increases surrounding tissue pressure and/or decreases caudal traction, which attenuates improvements following adenotonsillectomy.

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Noradrenergic Activation of Hypoglossal (XII) Motoneurons in Rats Subjected to Chronic Intermittent Hypoxia (CIH)
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In obstructive sleep apnea patients, upper airway muscles are hyperactive during wakefulness and protect the airway against occlusions. Rats subjected to CIH have increased density of noradrenergic terminals and increased \( \alpha_1 \)-adrenoceptor immunoreactivity in the hypoglossal (XII) nucleus (Rukhadze et al., Am. J. Respir. Crit. Care Med. 182:1321-29, 2010). We investigated whether the increased noradrenergic innervation following CIH is associated with increased sensitivity of XII motoneurons to noradrenergic excitation.

Adult, male Sprague-Dawley rats were subjected to CIH for 10 h/day for 35 days, with O2 levels oscillating between 24% and 7% with 3 min period. They were then anesthetized with urethane, vagotomized, paralyzed and artificially ventilated. Dorsal medulla was exposed and phenylephrine (2 mM, 10 nl), and then \( \alpha_1 \)-adrenergic receptor antagonist, prazosin (0.2 mM, 3×40 nl), were microinjected into the XII nucleus while recording XII nerve activity. The area under integrated XII nerve activity was measured over 1 min intervals before and after microinjections.

During the first minute after injection, phenylephrine similarly increased XII nerve activity in CIH (median: 247% of the pre-injection level, min-max: 129-500%, n=8) and sham-treated (median: 246%, min-max: 172-908%, n=13; Kruskal-Wallis, p=0.61) rats, with the effect lasting less than 15 min. Prazosin injections reduced spontaneous XII nerve activity to 21±7%(SE) of the pre-injection level in CIH rats (n=7) and to 40±8% in sham-treated rats (n=10; Holm-Sidak, p=0.048) when measured 45 min after injections. The decline developed gradually, always being stronger in CIH than sham-treated rats. The effects were not associated with any significant changes in central respiratory rate, arterial blood pressure or heart rate.
Exposure to CIH is associated with increased noradrenergic innervation of the XII nucleus and, when tested under anesthesia, prazosin injections reveal a stronger endogenous noradrenergic excitatory drive to XII motoneurons in CIH than sham-treated rats.

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Imaging of functional residual capacity and upper airway dimensions by MRI during application of nasal expiratory positive airway pressure in patients with sleep disordered breathing.

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Nasal expiratory positive airway pressure (nEPAP) delivered with a disposable device (Provent™ Ventus) has been shown to improve sleep disordered breathing (SDB) in some subjects (JCSM 2009; 5:532). One possible mechanism of action is increased functional residual capacity (FRC) producing tracheal traction and reducing upper airway (UA) collapsibility. A second mechanism is passive dilatation of the airway by the expiratory pressure, carrying over into inspiration. Using MRI, we directly assessed change in FRC and ventilation as well as in cross sectional area of the UA in awake subjects breathing on and off the nEPAP device.

Ten patients with SDB (RDI 4.1-69.9/hr) underwent nocturnal polysomnography and separate MRI imaging with and without nEPAP. Simultaneous images were obtained of the lung and UA at 6 images/sec during wake. Image sequences were obtained during mouth and nose breathing with/without the nEPAP device in place. FRC was estimated from sagittal section of the right lung and UA transverse section was obtained at the level of the pharynx above the epiglottis. The nEPAP device produced an end expiratory pressure of 5-17 cmH20 and end-tidal PCO2 rose from 40 to 47 mmHg (p<0.01).

MRI FRC was correlated to N2 washout FRC (r=0.73, p=.03). nEPAP caused a consistent increase in FRC (46±29%, p<0.001) and a decrease in ventilation (50±15%, p<0.001) with no change in frequency. UA cross sectional area at end expiration showed a trend to increase.

During wakefulness nEPAP caused significant hyperinflation, consistent with an increase of tracheal traction and decreased UA collapsibility. Direct imaging effects on the UA were less consistent, but there was a trend to dilatation suggesting a second mechanism of action.

Finally, we showed significant hypoventilation and a rise in PCO2 during use of the nEPAP device during wake and sleep. Thus, at least three potential mechanisms of action appear to contribute to therapeutic effect of the nEPAP device on SDB.

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Prediction of cardiovascular risk from nocturnal pulse wave signal using the autonomic state indicator technology.

Dirk Sommermeyer1, 2, Ding Zou1, Derek N. Eder1, Jan Hedner1 on behalf of the ASIC Multi Center Study Group: Joachim Ficker3, Winfried Randerath4, Thomas Penzel5, Bernd Sanner6 and Ludger Grote1

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Introduction
Analysis of multiple continuous physiological signals obtained during sleep may provide a novel method to assess cardiovascular (CV) risk. The novel autonomic state indicator (ASI) algorithm combines information from arterial oxygen saturation (SpO2) and a photoplethysmographic pulse wave signal and computes a CV risk index.

Methods
Subjects (n=327, 227 male, age 55.1±13.6 yrs, BMI 30.1±6.4 kg/m2) referred to five sleep centers in Germany and Sweden were studied. The occurrence of CV risk factors was assessed and subjects were classified by four established CV risk matrixes (Framingham, EU-Score, PROCAM and ESC/ESH). Peripheral pulse wave was measured by overnight digital photoplethysmography. The ASI algorithm extracted patterns of the peripheral pulse wave and SpO2 signal by amplitude and time/frequency analysis. Five derived parameters (hypoxic variation, vascular augmentation, cardio acceleration, cardio-respiratory coupling and pulse wave amplitude) were used to determine the final ASI score (range 0-1).

Results
The computed ASI CV risk index was significantly associated with the ESH/ESC risk matrix (r=0.48, p<0.0001), the Framingham risk score (r=0.42, p<0.001, the PROCAM score (r=0.45, p<0.001) and the EU-Score (r=0.36, p<0.001). Moreover, the ASI CV risk index was elevated in patients with an already established CV endpoint (MI and/or stroke, n=29) compared with the remaining patients (0.72±0.43 vs. 0.47±0.38, p=0.002).

Conclusions
The ASI technique appears to provide a possibility to recognize subjects with increased CV risk based on recording of physiological signals. Interestingly, the sleep period appears to be a particularly useful window for assessment. This technique – based on a modified pulse oximeter – may be useful in both sleep and cardiovascular medicine.

The study was supported by Weinmann GMBH, the Swedish Heart and Lung Foundation and the University of Gothenburg.
THE EFFECT OF PROLONGED INTERMITTENT HYPOXIA EXPOSURE ON CARDIAC FUNCTION IN LEAN C57BL/6J MICE. R. Rodriguez and C.P. O’Donnell. Department of Medicine, University of Pittsburgh, Pittsburgh, USA.

INTRODUCTION: Rodent models of intermittent hypoxia (IH) mimic many of the pathological features of patients with obstructive sleep apnea (OSA). Although the majority of rodent studies report an increase in blood pressure, the effects of IH on cardiac function in mice are somewhat equivocal, but potentially dependent on time of exposure. Thus, the purpose of the current study was to determine if there were time-related changes in cardiac function in lean healthy mice exposed to IH over a range from one to eight weeks. Specifically, we hypothesized that with prolonged IH exposure there would be an eventual decline in cardiac output and ejection fraction.

METHODS: 52 adult male 10 week old C57BL/6J mice were exposed to 1 week (n=8), 4 weeks (n=14) and 8 weeks (n=6) of IH (nadir FIO2=0.05-0.06 at 60 cycles/hr for 12 hr during the light period only), or 1 week (n=7), 4 weeks (n=13) and 8 weeks (n=6) of IA (intermittent air for 12 hr). At the end of exposure periods, mice were anesthetized and underwent closed-chest pressure-volume loop analyses using a Millar conductance catheter inserted into the left ventricle (LV) via the common carotid artery.

RESULTS: The end-systolic pressure (107±2.0 vs 100±2 mmHg; p<0.05) was significantly elevated after one week of IH, but parameters of LV function remained unchanged compared to IA control. At four weeks, dPdtmax, a measure of cardiac contractility (13153±352 vs 8635±371 mmHg/sec; p<0.05), was elevated by IH and there was a weak trend for ejection fraction to increase (59.0±3.5 vs 53.3±1.8%; p=0.18). At eight weeks, stroke volume (8.3±1.0 vs 12.3±0.8 uL; p<0.05) and cardiac output (4868±630 vs 6900±583 uL/min; p<0.05) were significantly decreased by IH, and ejection fraction exhibited a strong trend to be reduced compared to IH at four weeks (46.4±5.9 vs 59.0±3.5 %; p=0.06). However, a trend remained for dPdtmax (12013±1269 vs 9704±823 mmHg/sec; p=0.150) to be elevated even after 8 weeks of IH.

CONCLUSION: Prolonged, eight week exposure to IH in lean mice induces deterioration in cardiac output and ejection fraction, in the presence of sustained contractility, consistent with the development of LV hypertrophy. Potentially, longer IH exposures, or the presence of co-morbidities, could accelerate progression from LV hypertrophy to LV failure.

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Reliability of a single, objective test to assess sleepiness in commercial drivers
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University of Pennsylvania, Philadelphia, United States of America.

INTRODUCTION: Commercial drivers are at risk for obstructive sleep apnea (OSA), a condition associated with sleepiness and driving accidents. A single, objective measure of sleepiness is preferred to subjective or repeated objective testing.

STUDY OBJECTIVE: To evaluate reliability of a single administration of the multiple sleep latency test (MSLT), psychomotor vigilance test (PVT) and divided attention driving task (DADT) in assessing sleepiness.
Method: From 4,826 community-drawn commercial drivers, we oversampled those at higher OSA risk. N=372 drivers completed polysomnography followed by 4-nap MSLT, with PVT and DADT one hour before each MSLT nap opportunity. We computed Intraclass Correlation Coefficients (ICC) of single- versus multiple-test administrations for: 1) sleep latency (MSLT), 2) response time and lapses (PVT), 3) tracking error (DADT). We compared ICC for drivers with severe OSA (AHI >30) against controls (AHI <5), after adjusting for age, race, BMI and time-of-day. We explored measures as continuous and binary.

RESULTS: The group was largely male (94.1%) and Caucasian (85.1%), with mean age 45.7 years, mean BMI 30.2 kg/m2 and mean+SD apnea-hypopnea index (AHI) 5.3+9.8/h (65.6% AHI <5/h, 5.9% AHI>30/h). As continuous measures, ICC were: 10-min DADT tracking error 0.87, PVT response time 0.69, PVT number of lapses 0.51, MSLT 0.45. ICC was highest for DADT and increased with OSA severity (0.85 AHI <5/h, 0.95 AHI >30/h). As binary measures, ICC were: 10-min DADT 0.95, PVT lapses 0.85, MSLT 0.63. Time-of-day effects were seen for MSLT and PVT (p<0.001) but not DADT (p=0.135).

CONCLUSION: A single DADT reliably identifies sleepiness, especially in drivers with severe OSA, without susceptibility to time-of-day effects, and is more reliable than PVT. A single MSLT administration can discriminate individuals with mean sleep latency <8 minutes. Single administration of objective tests may be suitable for assessing sleepiness in commercial drivers being evaluated for OSA.

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A novel non-invasive technique to discriminate central from obstructive hypopneas in patients with sleep disordered breathing.
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Sleep Disordered Breathing (SDB) events conceptually separate into “obstructive” and “central.” Whereas apneas can be classified by presence/absence of non-invasive effort signals, hypopneas require invasive esophageal manometry for definitive classification. Inspiratory flow limitation (FL) is predictive of high resistance (Condos et.al., AJRCCM 1994) but absence of FL within hypopnea may not imply low resistance. The aim of the present study was to develop and validate markers derived from the nasal cannula flow signal alone to classify hypopnea.

40 subjects with obstructive or central sleep apnea underwent full night diagnostic polysomnography including nasal cannula and esophageal manometry. Hypopneas were defined as being obstructive if the relative resistance of the smallest breaths was >200% of the resistance of reference breaths within 30 seconds. Each hypopnea was defined visually as FL or non-FL. A development set was created using 10 non-FL and 5FL randomly selected hypopneas in each of 20 subjects (289 hypopneas) and analyzed for relative Ti, Ti/Ttot, I/E and resistance. The best parameter and cut-off were identified for predicting relative resistance. An evaluation was performed prospectively for this parameter on a test set of 20
new subjects (257 hypopneas).
Absence of FL was not a reliable indicator of low resistance. In the development set, the best classification of hypopneas for high/low resistance was obtained with relative Ti using a cut-off of 110%. In the test set, classification analysis yielded sensitivity=72%, specificity=77% PPV=64% and NPV=83%. Similar numbers were obtained for classification of hypopneas based on presence of FL alone, but when either relative Ti or presence of FL were used to define high resistance, sensitivity=84%, specificity=74%, PPV=65%, NPV=89%.

Relative prolongation of Ti is a good non-invasive predictor of high resistance in a dataset with both FL and frequent non-FL hypopneas, and the combination of FL and relative Ti improves this classification. Utilization of relative Ti is particularly relevant to datasets containing many non-FL events.

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Determined Upper Airway Collapsibility Utilizing Quantitative Airflow Measurements at Atmospheric Pressure
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Critical collapsing pressure (Pcrit) is a standard method for determining upper airway patency during sleep, however is labor intensive and prohibits large-scale studies. Based on previously published data indicating RUS does not significantly vary between groups, our aim was to develop an approach to estimate the Pcrit from airflow at atmospheric pressure (V atm).

Methods: Using the Starling Resistor pressure-flow relationship: Where Pn= nasal pressure, V=airflow and Rus=upstream resistance
Pn=V·Rus+Pcrit – equation 1.

In a dataset of 126 subjects, where Pcrit and Rus were measured using standard techniques. We then determined the minimum sample size required to estimate the Rus mean and variance by utilizing a bootstrap procedure (30 times for n=3 to 126). We first estimated the minimum number of subjects needed for obtaining a group for a two-tailed (z=1.96) standard error for Rus in the population. Then in 75 individuals, quantitative estimates of airflow were obtained at atmospheric pressure. Using the estimated RUS and atmospheric V, we determined an estimated Pcrit from equation 1. Bland-Altman plots were generated to determine the agreement between the measured Pcrit and Pcrit.

Results: For the entire population the mean±SEM Rus was 23±1cmH2O/L/s (±95% CI: 21, 25). 39 subjects represent the minimum sample required to estimate the population variance within ±2 SEM. In the subsample with atmospheric flow measurements, a linear regression model (Pcrit [cmH2O]= V[@Pn=0][L/s]x-23 [cmH2O/L/s]), Pcrit ranged from 0 to -9.6cmH2O. In the Bland-Altman analysis there was no mean difference between the
measured $P_{crit}$ and $C_{Pcrit}$ ($-0.01\text{cmH}_2\text{O}; p=0.8$) with upper and lower limits of agreement at $\pm 2.3\text{cmH}_2\text{O}$.

Conclusions: The variance of upstream resistance approaches a constant value in groups with approximately 40 subjects. Utilizing a fixed up-stream resistance to estimate $P_{crit}$ from the airflow at atmospheric pressure agrees with the measured values. These data suggest that measurements of quantitative airflow during standard polysomnography can be used to determine upper airway properties in large cohorts.

045

The initial peak in inspiratory flow is not a transient
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Rationale: Clinical sleep studies often show an initial peak in flow at the start of inspiratory flow limitation. A benchside model suggested that the initial peak was not a transient phenomenon, as rapid reductions in downstream pressure did not produce a larger initial peak than slow reductions. We sought to recapitulate our benchside model in the passive human airway.

Methods: Subjects with and without obstructive sleep apnea (OSA) were instrumented with an epiglottic catheter (to measure downstream pressure), magnetometers (to measure change in EELV), and a nasal mask/pneumotachograph connected to a CPAP/BiPAP machine. After administration of zolpidem 10mg, subjects slept supine in a head-out iron lung in which the extra-thoracic pressure could be lowered. During stable NREM sleep, subjects were hyperventilated using BiPAP to create a central apnea. During the central apnea, pressure in the iron lung was decreased to create inspiratory flow. The rate of decrease in iron lung pressure was modulated to simulate fast and slow inspirations. Flow and downstream pressure were analyzed during flow limited breaths.

Results: 2 controls have been studied to date. Some flow limited inspirations showed a marked decrease (~50%) in flow as downstream pressure increased. As in the benchside model, fast inspirations did not produce a larger initial peak than slow ones.

Conclusion: The initial peak is not a transient phenomenon during passive flow in the human airway, indicating that the reduction in flow from the initial peak to the “plateau” could be due to negative effort dependence. Ongoing study will assess inter-subject variability, and the effect of OSA. Further studies are needed to explain the cause of such profound negative effort dependence observed in some individuals.

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Relative importance of the different phenotypic traits causing Obstructive Sleep Apnea
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Introduction: OSA is a multifactorial disorder due to: 1) collapsible upper airway, 2) poor pharyngeal muscle responsiveness, 3) large change in ventilatory drive for a given change in ventilation (high loop gain), and 4) low respiratory arousal threshold. A collapsible upper airway is generally regarded as the most important factor. The relative importance of the other factors is poorly understood. This study aims to define the relative importance of the different pathogenic traits.

Methods: The 4 variables were measured by dropping CPAP from therapeutic to various subtherapeutic pressures for 3-minute intervals during supine-NREM sleep. Passive pharyngeal “anatomy” was quantified as the ventilation at zero nasal pressure (V0). Pharyngeal muscle responsiveness (upper airway response) was quantified as the increase in ventilation from the beginning of the drop to the end of the drop, divided by the increase in ventilatory drive across the drop. The increase in ventilatory drive across the drop was determined by returning CPAP to the therapeutic level at the end of the drop (thereby opening the airway) and measuring the ventilatory overshoot above eupnea. Loop gain was calculated by dividing the increase in ventilatory drive across the drop by the reduction in ventilation below eupnea across the drop. Arousal threshold was quantified as the ventilatory drive at arousal. The factors were incorporated into a physiologic model of OSA to illustrate their relative importance.

Results: 40 individuals (33 with OSA, defined as AHI > 10) have been analyzed. 14/33 OSA patients had relatively normal “anatomy” (V0 > 50% of eupneic ventilation), with other factors playing a prominent pathogenic role. 3/7 individuals without OSA had abnormal anatomy (V0 < 50% of eupneic ventilation); non-anatomic factors were important in preventing OSA.

Conclusions: The mechanisms preventing or causing OSA vary considerably between individuals. Non-anatomic factors play an important role in many patients.

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Association of the Apnea-Hypopnea Index with Severity of the ARES (Apnea Risk Evaluation System) Questionnaire in Retired National Football League Players. Albuquerque FN, Calvin AD, Roberts AJ, Somers VK. Division of Cardiovascular Diseases, Mayo Clinic, Rochester-MN, Living Heart Foundation, Hospital of Saint Raphael, Yale School of Medicine, New Haven-CT, United States.
INTRODUCTION – Sleep-disordered breathing (SDB) is linked to several cardiovascular diseases including hypertension, coronary artery disease and arrhythmias. SDB is highly prevalent in retired National Football League (NFL) players and further screening tools to assess the severity of the SDB are also needed. We therefore sought to investigate the correlation of the SDB severity measured by the ARES (Apnea Risk Evaluation System) questionnaire compared to the apnea-hypopnea index (AHI) in a group of retired NFL players.

METHODS- We performed a cross-sectional study of retired NFL players who were consecutively assigned to undergo an unattended limited-channel portable sleep study and completed the ARES questionnaire. The ARES questionnaire has been validated in certain populations as a predictor of SDB severity and in patients at high risk of SDB it stratifies the severity into mild, moderate and severe. Linear regression analysis was used to assess the correlation of the ARES questionnaire and AHI and a p-value was calculated using ANOVA.

RESULTS- We studied 156 retired NFL players, mean age was 54±12 years, BMI was 31.8±4.1 kg/m², neck circumference was 17.5 inches, 53 %were African-Americans, and mean AHI was 14.5±14 events/hour. Former NFL players considered to have mild, moderate and severe SDB by the ARES questionnaire had a mean AHI of 8.2±2.9, 11.9±1.6, and 18.9±1.6 events/hour respectively. Severity measured by the ARES questionnaire was strongly associated with the AHI (p<0.001).

CONCLUSION- Severity of the SDB measured by the ARES questionnaire is strongly associated with the AHI in retired NFL players. The ARES questionnaire appears to be a useful tool to predict SDB severity and may help to guide referral for sleep studies in this particular population.

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The Forced Oscillation Technique and the Upper Airway in Patients with and without Asthma
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Rationale: The forced oscillation technique (FOT) provides a non-invasive assessment of airway and tissue properties. There have been few FOT measurements done during sleep without positive pressure and total resistance has not been separated into its upper and lower airway components. We aimed to separate both upper and lower airway resistance using FOT with an epiglottic pressure transducer during sleep and to assess differences of the upper airway between control subjects and those with asthma.

Methods: Overweight and obese subjects with and without asthma were studied during sleep. FOT was used to measure respiratory system resistance (Rrs) and reactance (Xrs) during sleep. An epiglottic pressure transducer was placed to separate Rrs and Xrs into upper airway (Rup, Xup) and lower airway (Rlow, Xlow) components. Resistance and reactance were quantified at end inspiration and end expiration over the entire sleep opportunity and averaged over each sleep stage.

Results: 8 (6 M) controls and 10 (2 Male) asthmatic subjects have been studied. Rrs, Rup, and Rlow were increased in asthma subjects as compared to controls, independent of sleep stage.
(2-way anova, p<0.02). From wake to NREM sleep Rup increased in controls from 0.99 ± 0.7 to 1.4 ± 0.9cmH2O/L/s and in asthma subjects Rup increased from 1.7 ± 0.9 to 2.7 ± 1.5cmH2O/L/s. No significant differences were seen in reactance measurements between asthma and controls. Xup was negatively correlated with increasing BMI in the asthma group during NREM sleep (R²=0.63).

Conclusions: It is possible to separate upper and lower airway components of respiratory system impedance using an epiglottic pressure catheter. Based on FOT measurements, both upper and lower airway resistance is increased in asthma subjects as compared to controls, particularly during NREM sleep. Differences in reactance of the upper airway with BMI may indicate changes in airway tissue properties upon sleep onset.

Influence of carbon dioxide breathing on upper airway muscles and diaphragm corticomotor responses assessed by transcranial magnetic stimulation in awake healthy men
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Rationale: During inspiration, the functional interaction between upper airway (UA) dilator muscles and diaphragm plays a crucial role in the maintenance of UA patency. This interaction could be altered with increasing respiratory drive. Cortical magnetic stimulation provides a mean to assess corticomotor responsiveness of these muscles. The aim of this study was to compare the effects of hypercapnic stimulation on corticomotor response of the diaphragm, genioglossus and alae-nasi in normal awake men.

Methods: 10 self-reported healthy men (age = 27±4 years; BMI = 23±3 kg.m-2) breathed, in random order, room air, 5% and 7% CO2 both balanced with pure O2. Cortical (vertex Cz) magnetic stimulations were applied during early inspiration and expiration at a stimulation intensity 20% above motor threshold. Ventilatory variables, isoflow (300mL.s-1) UA resistance and diaphragm, genioglossus, and alae nasi motor evoked compounds were recorded in each condition.

Results: Compared to room air, CO2 inhalation significantly increased minute ventilation, maximal inspiratory flow, tidal volume and mean inspiratory flow ratio. UA resistance remained unchanged with CO2 inhalation. During 7% CO2 breathing, the diaphragm motor threshold decreased 9.6±10.1% and genioglossus motor threshold increased 7.2±9%. CO2 – induced ventilatory stimulation led to an increase in diaphragm MEP amplitude during inspiration (156±232.8%) but not during expiration. During inspiration, the increase in diaphragm MEP amplitude was positively correlated with changes in Vt/Ti (R²=0.56, p<0.01). Diaphragm MEP latencies remained unchanged both in inspiration and expiration. Genioglossus and alae nasi motor evoked compounds were recorded in each condition.

Conclusion: In awaked healthy subjects, CO2-induced hyperventilation is associated with an increase in the diaphragmatic response to cortical magnetic stimulation without changing the cortico-motor responses of the genioglossus or alae nasi. Such imbalance suggests that CO2 may affect differently the central brain stem generators that govern diaphragm and upper airway dilator muscles.
The genioglossus has increased inspiratory phasic single motor unit activity in slow wave compared to stage 2 sleep
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Rationale: Slow wave sleep (SWS) is associated with more stable breathing and less obstructive apneas (OSA) than other stages. Characterizing single motor unit (SMU) activity in the genioglossus (the chief upper airway dilator) provides insight into the brainstem’s neuronal inputs. We sought to determine a mechanism by which SWS protects against OSA. We hypothesized that the number of inspiratory phasic (IP) SMUs would increase in SWS compared to stage 2 sleep.

Methods: 22 human subjects were studied (14 with OSA). Genioglossus activity was measured using intramuscular electrodes and analyzed for SMU activity. Initial data analysis identified 5 IP SMUs (from 4 subjects) that remained active during Stage 2 and the following SWS epoch. The onset, peak and end of SMU firing times (expressed as percentage of inspiratory time, %Ti) and the onset, peak and end discharge frequencies of the SMUs were compared between the 2 sleep stages. The total number of SMU action potentials per phasic burst of activity was calculated. All measurements for each individual IP unit were made in 3 consecutive breaths in each sleep stage. Therefore there were 15 values for each of the above measurements (e.g. onset SMU firing time) in each sleep stage.

Results: The duration of SMU phasic firing (mean±SEM) trended to be longer in SWS (119.4± 6.5%Ti) than stage 2 sleep (102.8± 5.0%Ti) (P=0.053). The onset, peak and end discharge frequencies were not significantly different between the 2 stages. The number of SMU action potentials occurring per phasic inspiratory burst was significantly greater in SWS (28.8±1.2) compared to stage 2 (22.4±1.5) (P=0.003).

Conclusion: During SWS the number of SMU action potentials per inspiratory phasic burst of activity was greater than during stage 2. This finding may explain why SWS protects against apneas.

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Critical closing pressure and upper airway anatomy
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INTRODUCTION: The passive critical closing pressure (Pcrit) evaluates upper airway collapsibility and is considered to reflect the anatomical contribution to airway obstruction in patients with obstructive sleep apnea (OSA). Anatomy of the upper airway is influenced by bony structures and obesity. However, only a few previous studies have explored the relationship between Pcrit and upper airway anatomy; these have revealed relatively weak correlations. How obesity contributes to upper airway collapsibility is unclear. We therefore aimed to examine the relationship between 1) Pcrit versus anthropometric and cephalometric variables and 2) markers of obesity and cephalometric measurements in patients with a wide range of OSA severity.

METHODS: Eighteen male patients, age=55±10 (range, 38-69 yrs), body mass index (BMI) = 29.8±4.0 (range, 24.4-38.6kg/m2), waist circumference=103±10 (range, 91-124cm), neck circumference = 42±4 (range, 37-48.5 cm) with OSA, apnea-hypopnea index (AHI) = 44±26 (9-93 events/h) have been studied thus far. Pcrit was determined during stable NREM sleep after sleep induction with midazolam by a rapid reduction of CPAP for 3-5 breaths as well as head and neck CT scan.

RESULTS: Pcrit of the group was -0.63±3.0 (-6.3 to +4.5cmH2O). Pcrit correlated with OSA severity (AHI) (r=0.58, p=0.012). Pcrit did not correlate with classical measurements of obesity, including BMI, waist, and neck circumference. In contrast, Pcrit correlated significantly with several cephalometric measurements, including airway length (AL) (r=-0.48,p=0.045), hyoid to mandibular plane (MPH) (r=0.51,p=0.032), cranial base angle (NSBa) (r=-0.52,p=0.046) and approached significance for cranial base length (NS) (r=-0.48,p=0.067). A multiple linear regression revealed that AL, NSBa and NS were independent predictors of Pcrit (r=0.84, p=0.003). AL correlated with waist (r=0.55,p=0.018) and neck circumference (r=0.47,p=0.047).

CONCLUSIONS: Pcrit reflects the anatomical component, at least in part, of obstruction in patients with OSA and can be reasonably predicted by simple cephalometric measurements. How obesity influences pharyngeal mechanics is unclear.

Physiological Network Structure Prediction in Sleep Disordered Breathing
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Motivated by the hypothesis that sleep disordered breathing is, in part, due to dysfunctional feedback control among several physiological systems, we propose a method to predict the onset of abnormal breathing using a complex systems approach that leverages techniques from nonlinear time series and social network analysis. First, we represented the temporal dynamics of polysomnographic data as a stream of edges between vertices, where vertices represent physiological signals and edges represent interactions at some time. To define an interaction, we decomposed each signal using empirical mode decomposition, which aims to
adaptively decompose data into a set of nearly orthogonal intrinsic mode functions (IMFs), each of which characterizes an intrinsic time/frequency scale embedded within the original signal. Furthermore, instantaneous phase is well defined on IMFs. An interaction was defined as any five second subsegment in which significant phase synchrony occurred between two IMFs. The edge stream also included edges representing abnormal respiratory events. We then applied an algorithm designed to adaptively learn and predict the dynamical evolution of network processes. First, the most frequently occurring subgraphs in a training set were discovered. Next, probability density functions were constructed for each frequent subgraph pair. Prediction estimators were then generated to predict in a test set when an abnormal breathing edge was expected to occur.

Preliminary results reveal the most frequently occurring sub-network of interactions involved electrooculography, electroencephalography (EEG), and submental electromyography. The interactions that most reliably predicted obstructive apnea, hypopnea, and upper airway resistance, respectively, were phase synchrony between nasal pressure (NP) and heart rate variability (HRV); EEG and NP; and HRV and thermistry. To the extent that this method can accurately and reliably predict abnormal breathing during sleep, we might not only improve conventional therapies, but also gain insight into the precise dynamical mechanisms that initiate and sustain sleep disordered breathing.

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Novel brain activity markers of neurocognitive deficits and sleepiness during 40 hours of extended wakefulness.
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Introduction: Chronic sleep restriction is a common problem that impairs neurocognitive functioning. Changes in waking electroencephalographic (EEG) activity following sleep deprivation have been correlated to sleepiness and worsening performance. We evaluate the use of detrended fluctuation analysis (DFA) of the resting EEG as a novel marker of impaired neurocognitive performance.

Methods: Healthy controls and obstructive sleep apnea patients attended the sleep laboratory and completed a 3-day/night protocol that included two nights of polysomnography (night 1 = 8h time in bed baseline; night 3 = recovery) and 40hrs of extended wakefulness in between. Every 2-hours subjects underwent performance and sleepiness assessments (psychomotor vigilance task (PVT), simulated driving task (AusEd) and subjective sleepiness rating (Karolinska sleepiness scale). Resting awake EEG was recorded during a Karolinska drowsiness test (KDT) prior to each 2-hourly assessment. The EEG (Cz/A1 derivation) of the KDT was analysed by DFA. DFA quantifies fluctuations in the EEG and yields scaling exponents (SeE) as a measure of the alertness level of the subject at the time of the test.
Results: We assessed 9 controls (8 male, age 28±4 yrs, BMI 23±3 kg/m2) and 8 OSA patients (8 male, age 45±8 yrs, BMI 33±5 kg/m2). In both groups, we found significant within-subject correlations between DFA ScE (eyes-closed) and the reciprocal slowest 10% of reaction times on the PVT (Controls: r=-0.49, p=<0.0001 / OSA: r=-0.31, p=0.0001); steering deviation during the simulated drive (Controls: r=0.62, p=<0.0001 / OSA: r=0.36, p=<0.0001); and subjective sleepiness (Controls: r=0.39, p=<0.0001 / OSA: r=0.32, p=<0.0001).

Discussion: Increased DFA ScE was correlated with worse performance and greater sleepiness in these subjects during 40hrs of extended wakefulness. DFA may provide a useful EEG marker of neurocognitive performance, explain the inter-individual variability in response to sleep loss, and identify those individuals at greater risk of vigilance failure such as impaired driving.

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Markers of liver dysfunction in patients with obstructive sleep apnea
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Increased liver enzymes in serum have been found in patients with obstructive sleep apnea (OSA), but the prevalence of liver dysfunction in OSA is poorly defined. In 75 consecutive patients (14 females) without serological evidence of viral hepatitis or any history of alcohol-induced liver disease, who underwent nocturnal respiratory monitoring for diagnosis of OSA, we measured alanine (ALT) and aspartate (AST) aminotransferase, and gamma-glutamyltransferase (GGT) in serum, together with the HOMA Index and the lipid profile. Mean age and BMI were 55±13 (SD) yr, and 37.3±8.8 kg/m2, respectively. OSA was moderate to severe (mean AHI 48±22/h, lowest SaO2 70.3±12.4%). Increased ALT or AST (≥41 IU/L) was found in 10 and 7 patients (13% and 9%), respectively. Compared to patients with normal ALT levels, patients with elevated ALT were significantly younger (43.8±5.4 vs 57.0±13.5 yr, p<0.005 by unpaired t-test) and showed higher HOMA index values (8.96±5.38 vs 3.74±2.66, p<0.005) and triglyceride level (238±201 vs 137±75 mg/dL, p<0.005). Elevated AST levels were significantly associated with high HOMA index. No association was found between OSA severity or the degree of obesity assessed as BMI and increased liver enzymes. Increased GGT (≥51 IU/L) occurred in 7 patients (9%) but showed no association with any of the variables tested. Our results suggest that increased liver enzymes are associated with more severe insulin resistance, but are not directly linked with obesity or OSA severity.

*presenting author

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Effectiveness of a nasal airway stent on obstructive sleep apnea.
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We report promising preliminary findings regarding the clinical effectiveness of a novel nasal airway stent (NAS) that was developed for the treatment of obstructive sleep apnea (OSA). The device is constructed using resilient semi-rigid silicone rubber and was designed to be safely and comfortably inserted into the upper airway. The NAS contains an expandable distal end, located within the nasopharynx and retropalatal oropharinx, that is encapsulated by a nontoxic water-soluble material. Following device placement, the distal end of the device is released and expands to maintain an air flow passageway of 5-10 mm in diameter.

Effectiveness of the NAS on sleep disordered breathing was assessed by polysomnographic studies before and during placement of the device in four patients with OSA. The NAS did not normalize the disordered breathing, but significantly improved the apnea hypopnea index (from 35.2±24.7 to 17.4±17.9), 3% oxygen desaturation index (from 30.3±27.4 to 14.3±16.7) and arousal index (from 31.9±19.1 to 19.5±11.5). None of the patients experienced traumatic side effects such as nasal bleeding, pain, or discomfort following placement of the device. The NAS appears to be a useful alternative or additive treatment for patients with OSA. The device may be used as an immediate therapeutic tool while a patient undertakes a weight loss program or as an alternative for patients who cannot tolerate a nasal continuous positive airway pressure treatment. The NAS affects obstruction of nasopharynx and partly oropharynx but not of hypopharynx, therefore the combination of the NAS and an oral appliance may provide additional benefits. Further studies are necessary to confirm our preliminary results.

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Radiofrequency catheter ablation for persistent atrial fibrillation improves sleep disordered breathing.
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Background: Recent studies have suggested an emerging link between sleep apnea and atrial fibrillation (AF). Radiofrequency (RF) catheter ablation is becoming an effective therapeutic option for drug-refractory AF. However, the effect of RF catheter ablation on sleep-disordered breathing has not been sufficiently clarified.

Methods: This study included 19 patients (18 men and 1 woman; 62±6 years) with central or obstructive sleep apnea who underwent extensive encircling pulmonary vein isolation for radiofrequency catheter ablation.
Results: The baseline apnea/hypopnea index (AHI) and arousal index were 29±23 and 41±21, respectively. The patients had a higher obstructive apnea index (21±22) than central apnea index (2±4; p<0.001). In 16 patients in whom sinus rhythm could be restored and maintained after the ablation, the AHI (27±18 to 15±10; p<0.005) and arousal index (37±15 to 29±9; p<0.01) improved after the ablation. However, in the remaining 3 patients with a failed ablation, the AHI did not improve after the ablation (p=0.2). This reduction of AHI depends on the decrease of obstructive apnea episodes not on those of central. Furthermore, plasma level of the B-type natriuretic peptide (BNP) were also reduced after the ablation (570±502 vs. 134±104 [pg/ml]; p<0.05). There was a positive correlation between the %change in the AHI and %change in the plasma BNP level (r=0.519, p=0.02).

Conclusions: In patients with sleep apnea syndrome and persistent AF, RF catheter ablation significantly reduces the number of episodes of obstructive sleep apnea without reducing the total sleep time.

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difference in mean AHI (7.2 in female and 13.4 in male) and PLMI (4.9 in female and 10.7 in male). 145 subjects (28.9%) an AHI >5 \leq 15 and 117 subjects (23.1%) had an AHI>15. Among the subjects with AHI > 15 are 29 (25%) female and 88 (75%) male. Interactions between severity of sleep apnea, clinical symptoms, age, gender, BMI, cardiovascular risk factors and other comorbidities are in the focus of this study.

The prevalence for arterial hypertension is much higher in Germany (55%) than in the USA (28%). In Germany we have a north-south divide with a higher prevalence in the north. According to the high prevalence of arterial hypertension in Pomerania (SHIP) we expect a much higher prevalence of sleep apnea in Pomerania than in southern Germany and in the US as the first results could confirm.

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Induced Snoring Reduces Carotid Artery Blood Flow and Wall Shear Stress in an Animal Model.
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Heavy snoring has been associated with carotid atherosclerosis but mechanisms remain unclear. Low arterial wall shear stress (WSS), associated with reduced blood flow, promotes endothelial dysfunction and favours atherogenic plaque accumulation. Using an established animal model, we tested the hypothesis that during snoring, negative pleural pressure-mediated cardio-respiratory interactions reduce peak carotid artery blood flow (CBF), thus creating a potential pro-atherogenic, low WSS environment within the carotid artery lumen. Methods: Right carotid CBF was measured in 8 supine, anaesthetised (ketamine, xylazine), male NZ White rabbits using a peri-vascular ultrasound probe (Transonic). A pressure transducer-tipped catheter (Millar) monitored oesophageal pressure. One-minute steady state snoring periods (3 runs) were induced by external compression of the neck/upper airway. Peak WSS was calculated from CBF values using the Hagen-Pouiseille equation, assuming carotid diameter=1.9 mm and blood viscosity=0.04 dyn.s/cm2. Data were expressed as group mean±SD. Comparisons were performed using a paired t test. Linear regression analysis was used to examine relationships between pleural pressure and CBF changes. Results: Snoring reduced mean peak inspiratory pleural pressure from -5.5 ±2.2 (tidal breathing) to -10.0±3.4 cmH2O (p<0.001). Correspondingly, peak inspiratory CBF fell from 75.7±7.7 ml/min to 73.8±7.7 ml/min (p<0.01) with a significant positive linear relationship between change in pleural pressure and CBF change (slope=0.694, r2=0.49, p<0.0001). Calculated WSS values fell from 14.85±0.19 to 14.46±0.19 dyn/cm2 (p<0.01). Conclusions: Snoring decreased CBF in accordance with the level of intra-pleural pressure generated with associated falls in CBF sufficient to reduce calculated WSS values, in this proof-of-concept study, by up to ~8%. Cardio-respiratory interactive effects may provide a potential pathophysiological linkage between snoring and development of a pro-atherogenic low WSS environment in the carotid artery.
Pre-treatment Characteristics of Sleepy and Non-sleepy Patients with Obstructive Sleep Apnea
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Study Objectives: To describe differences in patient characteristics, sleep duration, and sleep quality that may contribute to variability in sleepiness between sleepy and non-sleepy OSA patients.

Participants: Ninety-nine sleepy and 79 non-sleepy, middle-aged (47.6 yrs±8.8), newly-diagnosed OSA patients (AHI 33.9±31.6 events/hr; 29.2±26.2 events/hr, respectively; NS), referred to a sleep center.

Design and Methods: Preliminary analysis of data from an ongoing, prospective study (SCOR Project 01) seeking to explain a biologic basis for differential sleepiness among OSA patients with similar disease. After diagnostic polysomnogram (AHI>5), one week of pre-treatment actigraphy and sleep diary record were completed followed by a battery of measures, including Epworth Sleepiness Scale (ESS) and psychomotor vigilance task (PVT) was collected. Concordance on two administrations of ESS [subjective](< 11=non-sleepy; or ≥ 11=sleepy) and four trials of PVT [objective](< 2 lapses=non-sleepy; or ≥ 2 lapses=sleepy) defined sleepy and non-sleepy subjects. Descriptive statistics were used to explore differences between sleepy and non-sleepy OSA patients.

Results: Sleepy subjects had overall lower sleep quality than non-sleepy subjects (PSQI global score 11.22±4.24 vs. 7.32±3.22, respectively; p<0.001) and more sleep-related complaints as measured by the MAP (apnea symptoms, difficulty sleeping, daytime sleepiness, and narcolepsy-like symptoms, p<0.001). Sleepy subjects (n=90) had less total sleep time/24hrs than non-sleepy subjects (n=73)(492.3±135.4 vs. 549.4±153.0 minutes/24hrs, respectively; p=0.01), shorter nocturnal sleep duration (362.7±81.5 vs. 409.5±53.9 minutes/sleep period, respectively; p<0.001), and spent more time awake during nocturnal sleep period (101.3±55.8 vs. 77.6±29.1 minutes/sleep period, respectively; p=0.001). Sleepy subjects also had significantly more functional impairment than non-sleepy subjects as measured by both the FOSQ and MOS-SF36 (all subscales, p<0.001).

Conclusions: Differences in the state of sleepiness in OSA patients may be due to behavioral factors leading to shorter sleep duration and poorer overall sleep quality. This contributes to greater functional impairment and quality of life.

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Diagnosis of Obstructive Sleep Apnea by voice analysis. Preliminary results.
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OBJECTIVE: To develop a new tool for the diagnosis of Obstructive Sleep Apnea (OSA) using voice analysis.

METHODS: A multicenter, randomized, prospective, cross-over study of 750 adults, both sexes, older than 18 yr. (250 patients with suspected OSA; 250 habitual snorers and 250 non-snorers healthy subjects) were designed. All subjects underwent a clinical evaluation and a validated sleep study (polysomnography and/or respiratory poligraphy) according international recommendations. Clinical variables were applied using decision trees. For voice analysis we used the structure of glottal pulse and the voice formants of patients with OSA and we compared them with healthy individuals and snorers. We created a diagnosis algorithm using a neural networks on the basis of the information from the formants, the glottal pulse and clinical variables and we evaluate the accuracy of the model. Finally, we performed a sensitivity analysis.

RESULTS: Up to date 639 subjects (67% men) have been included (317 having OSA and 322 were healthy or habitual snorers). The characteristic of the population were: age 46.6 yr. (SD 14.5); body mass index 29.0 Kg/m2 (SD 6.1) and Epworth sleepiness scale 9.4 (SD 5.3). We analyzed 252 variables of voice and 7 clinic variables. Final analysis were done with 7 variables of voice and 4 clinic variables (sex, age, body mass index and Epworth sleepiness scale). The correct rate of classification of OSA (an Apnea Hypopnea Index (IAH) > or < 10) were 82.7%. The majority of false positive of false negative were at border area. Sensibility was 0.88 (CI 95% 0.78-0.98); specificity 0.75 (CI 95% 0.62-0.88); Predictive Positive Value 0.78 (CI 95% 0.66-0.90); Predictive Negative Value 0.86 (CI 95% 0.75-0.97).

CONCLUSIONS: Voice analysis could be a useful tool for diagnosis of patients with suspected OSA.

ASSOCIATION BETWEEN OBSTRUCTIVE SLEEP APNEA-HYPOPNEA AND SYSTEMIC HYPERTENSION IN THE GENERAL POPULATION
The Vitoria Sleep Cohort
Irene Cano-Pumarega

Rationale: Obstructive sleep apnea-hypopnea (OSAH) and systemic hypertension (SH) are highly prevalent. Although their association has been suggested in cross-sectional studies, conflicting evidence has emerged from longitudinal studies.
Objectives: To assess the association between OSAH and SH in the general population.

Methods: We included 2,148 subjects in a longitudinal study from the Vitoria Sleep Cohort (Spain), a general population sample aged 30-70 years. Of the 1,557 subjects who completed the 7-8 year follow-up, 304 were excluded for having SH at baseline. The odds ratios (OR) for the incidence of SH according to the respiratory disturbance index (RDI), were estimated in 1,253 subjects (585 men and 668 women) after adjustment for age, sex, body mass index, neck circumference, alcohol, tobacco and coffee consumption and fitness activity. The RDI was divided into quartiles (0-2.9, 3-6.9, 7-13.9 y ≥14), using the first quartile (RDI 0-2.9) as reference.

Results: For men, followed-up for 8.0 ± 0.8 years, the adjusted OR for stage-1 SH incidence increased with higher RDI category, but lost significance after adjustment. However, OR significantly increased for stage-2 SH [OR for an RDI ≥14 was 2.22 (95% CI 1.05-4.68), overall p trend = 0.035]. In women, after a follow-up of 7.1 ± 0.4 years, there was no significant trend in the incidence of SH.

Conclusions: There is a dose-response association between OSAH and the incidence of SH in middle-aged men. In women, there is no significant association, although there seems to be a dose-response effect in more severe forms of SH (stage 2).