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## 154. Physiology and cardiometabolic comorbidities in obstructive sleep apnoea

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### Late-breaking abstract: Nocturnal intermittent hypoxia strongly predicts systemic hypertension in the European Sleep Apnoea Cohort Study

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**Background:** Systemic hypertension is independently associated with obstructive sleep apnoea syndrome (OSAS). The underlying mechanisms of this association are incompletely understood. A collaborative European network of 22 sleep centres facilitated the establishment of a European Sleep Apnoea Database (ESADA), designed to evaluate associations between OSAS and cardiovascular diseases. The present study employed ESADA to study associations between OSAS and systemic hypertension.

**Methods:** 5103 adult subjects evaluated for suspected OSAS underwent overnight sleep studies. The association of prevalent hypertension with OSAS was examined and adjusted for relevant covariates such as age, smoking, obesity, dyslipidaemia and diabetes. We compared the predictive value of the apnoea-hypopnoea index (AHI) and oxygen desaturation index (ODI) for the presence of hypertension.

**Findings:** Patients were 72% male; 29% were >60 years; 79.4% had AHI >5 and 42.9% had systemic hypertension. Both AHI and ODI were related to prevalent hypertension after adjustment for relevant covariates ( $P < 0.001$  for linear trend across quartiles of severity (Q) for both variables). However, in multiple regression analysis with both ODI and AHI in the model, ODI was, whereas AHI was not, independently associated with hypertension (odds ratio and 95% confidence intervals for Q4 vs Q1 for ODI were 2.39 (1.58 - 3.63) and for AHI, 0.97 (0.65 - 1.47);  $P < 0.001$  and  $P = 0.902$  respectively).

**Interpretation:** These findings support ODI as an important predictor of systemic hypertension in OSAS patients and chronic intermittent hypoxia as a central pathophysiological mechanism.

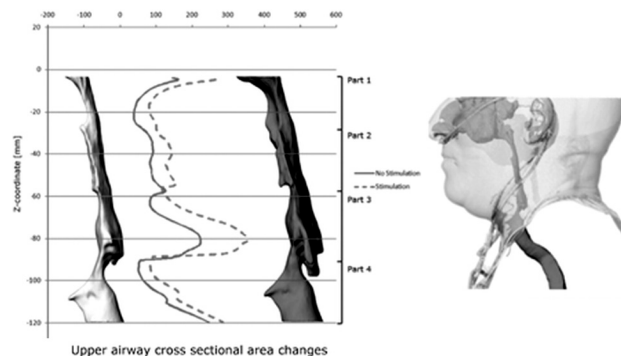
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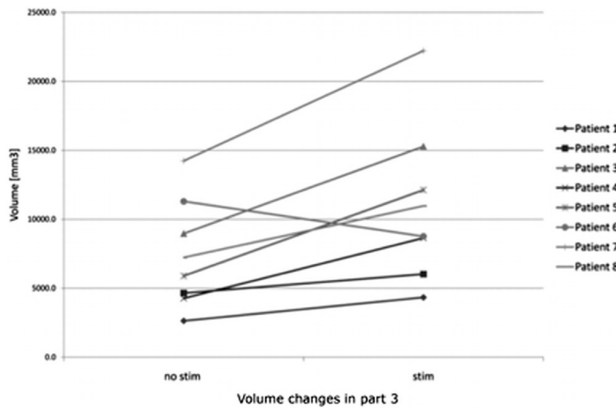
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### Functional imaging using computational fluid dynamics to assess effect of stimulation of the hypoglossal nerve on upper airway morphology: A pilot study

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This study assessed the in-vivo effect of stimulation of the hypoglossal nerve on the upper airway morphology using imaging techniques in combination with computational fluid dynamics (CFD) tools. In 8 patients the upper airway was imaged using CT before and during stimulation of the hypoglossal nerve. Changes in airway volume and resistance were determined using segmentation and CFD. A statistically significant ( $p = 0.035$ ) enlargement of the volume for the upper airway at the level of the tongue-base was observed. A significant correlation ( $R^2 = 0.89$ ,  $p = 0.002$ ) was found between the change in hydraulic radius and the volume changes at the level of the palate. The distance from the tongue base to





the mandibula measured just above the epiglottis correlated significantly with the change in upper airway resistance ( $R^2=0.91, p=0.014$ ). It could be concluded that stimulating the hypoglossal nerve changes the upper airway morphology. A relatively complex motion of the tongue is observed with an enlargement of the airway lumen predominantly near the tongue base. Depending on the volume of the oral cavity, the enlargement is homogeneous or a decrease in cross sectional area occurs at the palatal level. The distance between the tongue base and the mandibula appears to be a good surrogate for changes in upper airway resistance.

**1424 Mechanical response to electrical- and neuro-stimulation of the genioglossus (GG) in propofol-sedated OSA patients**

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Pharyngeal collapsibility during sleep is believed to increase primarily due to decline in dilator muscle activity. However, it is well documented that GG-EMG increases during apneas and hypopneas. The magnitude of increase is limited, however, as arousal terminates the respiratory disturbance. In the present study we prevented arousal by “drug-induced sleep” with propofol. We induced prolonged hypopneas in 17 patients with OSA by lowering CPAP after discontinuation of propofol, and monitored GG-EMG, flow and the area (CSA) at the site of collapse (pharyngoscopy) until arousal. Prolonged hypopnea triggered a dramatic increase in GG-EMG. The mechanical response to this physiological drive to the GG was compared to baseline condition (after lowering CPAP from holding pressure), electrical stimulation (ES) of the GG, and after arousal.

	“Drug-induced sleep”			Awake
	baseline	GG-ES	pre-arousal	post arousal
CSA (mm <sup>2</sup> )	25.1±28.9	66.3±75.5	11.8±8.2	80.4±83.5
flow (l/min)	11.5±6.5	18.6±9.2	11.4±6.4	25.1±8.3
GG-EMG (% max)				
tonic	4.4±3.8	-	15.7±12.2	9.1±6.1
phasic	13.0±10.7	-	62.2±32.7	17.7±10.2

Before arousal from sedation, flow remained unchanged despite the large increase in GG-EMG activity, while inspiratory CSA decreased. ES of GG, however, increased CSA and flow. Arousal resulted in fast enlargement of CSA and restoration of unobstructed flow, associated with marked reduction in GG EMG. We conclude that during propofol-induced sedation (and presumably also during sleep), pharyngeal collapse is due to inadequate mechanical response to activation of the GG, which occurs despite the well preserved mechanical response of this muscle to ES.

**1425 Sleep apnea increases sympathetic activity independent of decreased neurovascular transduction**

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**Introduction:** Patients with obstructive sleep apnea (OSA) have elevated sympathetic outflow independent of obesity or hypertension. However, greater outflow may not result in reduced limb blood flow, suggesting lower sympathetic neurovascular transduction that may cause elevated outflow for appropriate hemodynamic control.

**Aims:** We tested the hypothesis that greater resting sympathetic activity in OSA would relate to lesser sympathetic neurovascular transduction.

**Methods:** We assessed resting sympathetic outflow and sympathetic neurovascular transduction in newly diagnosed OSA without comorbidities (N=10) and in age-matched (N=10) and young (N=10) healthy controls. Sympathetic activity was directly measured (microneurography) at rest and in response to sustained isometric handgrip exercise. Neurovascular transduction was derived from the relationship of sympathetic activity and blood pressure to leg blood flow during exercise.

**Results:** Sympathetic activity in OSA was almost 2x the age-matched and 3x the younger controls. Neurovascular transduction was not different between OSA and age-matched controls, but was lower in both compared to younger controls. Among all subjects, resting activity was related to transduction ( $r^2 0.12, p=0.04$ ), however this relation was much stronger without those with OSA ( $r^2 0.55, p<0.01$ ).

**Conclusions:** Greater sympathetic activity in OSA does not appear to derive solely from lesser neurovascular transduction. Hence, other potential mechanisms associated with OSA per se likely result in greater sympathetic outflow. However, elevated outflow without lesser transduction may underlie the prevalent development of hypertension in this population.

**1426 Chronic intermittent hypoxia is a major trigger for non-alcoholic fatty liver disease**

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**Backgrounds and aims:** Morbid obesity is frequently associated with low grade systemic inflammation, increased macrophage accumulation in adipose tissue (AT), obstructive sleep apnea (OSA) and nonalcoholic fatty liver disease (NAFLD). It has been suggested that chronic intermittent hypoxia (CIH) resulting from OSA could be an independent factor for early stage of NAFLD in addition to other well-recognized factors (dyslipidemia, insulin resistance). Moreover, macrophage accumulation in AT is associated with local hypoxia in fat tissue. We hypothesized that the association between CIH and morbid obesity could exert additional specific deleterious effects both in liver and adipose tissues.

**Methods:** 101 morbidly obese subjects were prospectively recruited and underwent bariatric surgery during which a liver biopsy as well as subcutaneous and omental AT biopsies were obtained. Oxygen desaturation index (ODI) quantified the severity of nocturnal CIH.

**Results:** Liver biopsies analysis demonstrated that NAFLD lesions (ballooning of hepatocytes, lobular inflammation), NAFLD activity score (NAS) and fibrosis were more severe in patients with the highest ODI tertile (p values  $\leq 0.001$  for all hepatic lesions). In multivariate analysis, after adjustment for age, obesity and insulin resistance status, CIH remained independently associated with hepatic fibrosis, fibroinflammation and NAS. By contrast, no association was found between CIH, macrophage accumulation and adipocytes size in both subcutaneous and omental adipose tissue.

**Conclusions:** In morbidly obese patients, CIH was strongly associated with more severe liver injuries but did not worsen obesity induced macrophage accumulation in adipose tissue depots.

**1427 The impact of obstructive sleep apnea syndrome on superoxide dismutase-1 activity in erythrocytes of high risk for type 2 diabetes (pre-diabetic) males**

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**Introduction:** The relationships between obstructive sleep apnea syndrome (OSAS) and cardiovascular risk factors are under wide-world interest.

The aim of the study was to analyze superoxide dismutase-1 activity in erythrocytes of high risk for type 2 diabetes (pre-diabetic) males, due to a severity of OSAS diagnosis.

**Methods:** OSA suspected males with no acute or severe chronic disease were enrolled. Non-smoking Caucasians aged 30-63, with BMI 25-39 kg/m<sup>2</sup>, submitted clinical, biochemical and polysomnographic examinations. EMBLA device was used to establish the severity of apnea episodes. The results of oral glucose tolerance test allowed to select pre-diabetic males. Apnea/hypopnea index (AHI) categorized patients for: OSAS0 (n=14, aged 53±7, AHI 0-4.9), OSAS1 (n=14, aged 55±8, AHI 5-15); OSAS2 (n=14, aged 56±5, AHI 16-30); OSAS3 (n=14, aged 55±7, AHI≥31). Plasma glucose, fasting lipid profile (T-C, HDL-C, LDL-C, TG), uric acid were estimated. Fasting serum insulin (ELISA BioSource, Sunrise

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Tekan) and erythrocyte Cu,Zn-superoxide dismutase activity, SOD-1 (Randox, Statfax™ 1904 Plus) were determined. Statistical analysis was performed using STATISTICA 6.0 for Windows. Data are shown as means  $\pm$  SD.

**Results:** 1. The studied groups did not differ in their age, BMI, blood pressure, and routine metabolic parameters.

2. Kruskal-Wallis Test revealed increased SOD-1 in OSAS1 group and the lowest in OSAS3 group (from OSAS0 to OSAS3:  $1174 \pm 404$  vs  $1432 \pm 476$  vs  $1248 \pm 495$  vs  $944 \pm 298$  U/gHGB;  $p=0,038$ ).

**Conclusion:** In the studied pre-diabetic males only OSAS1 persons seem to present some native mechanisms for cardiovascular prevention.

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#### CPAP effects on leptin and visceral fat in patients with sleep apnea:

##### Double-blind, randomized, controlled trial

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**Rationale:** Obstructive sleep apnea (OSA) is common in obesity. Leptin plays an important role in controlling appetite, energy expenditure, and body fat deposition. Studies investigating the effect of continuous positive airway pressure (CPAP) on leptin have conflicting results. The major confounder is the visceral obesity.

**Objectives:** We tested the stored blood from a double-blind, randomized, placebo-controlled trial aimed to (1) determine the CPAP effect on leptin and visceral fat (2) investigate if changes of visceral fat after CPAP correlated with leptin in OSA patients.

**Methods:** Ninety-six patients were randomized to 12-week therapeutic (n=48) or subtherapeutic (n=48) CPAP. We measured the levels of leptin from stored blood and measured visceral fat with abdominal MRI. Results were analyzed with the intention to treat. The multiple linear regression was used to measure correlation between changes of visceral fat with changes of leptin.

**Results:** Eighty patients completed the study and 16 withdrew. 12-week therapeutic CPAP did not modify leptin and visceral fat compared to subtherapeutic group although significant improvement of objective sleepiness. The regression analysis identified that changes of visceral fat independently correlated with changes of leptin (coefficient 1.531,  $P<0.001$ , 95% CI 0.690 to 2.305).

**Conclusions:** 12-week CPAP treatment does not modify leptin and visceral fat and changes in visceral fat independently correlate with changes of leptin. CPAP therapy should be combined with other measures that can reduce visceral fat when managing OSA patients.

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#### Predictors of recurrence in patients undergoing cryoballoon ablation for treatment of atrial fibrillation: The independent role of sleep disordered breathing

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**Introduction:** In patients with atrial fibrillation (AF) undergoing pulmonary vein isolation, cryoballoon technique (cryoPVI) has been adopted in many centers. This study aimed to evaluate predictors of AF recurrence including impact of sleep disordered breathing (SDB).

**Methods:** In 82 patients consecutively assigned to cryoPVI cardiorespiratory screening for SDB, assessment of medical history, ECG, echocardiography, standard laboratory measurement, and blood gas analysis were performed prior to intervention. After 3 months blanking period 7-days Holter ECG was performed at 3, 6 and then every 6 months to determine AF recurrence.

**Results:** 75 patients (69 paroxysmal AF, 6 persistent AF, 22 female, age  $60 \pm 9$  years) completed at least 6 month follow-up. Median follow-up of 12 months (interquartile range 6 to 18 months) confirmed maintenance of sinus rhythm in 69.4% of these patients. Stepwise forward regression model revealed moderate to severe SDB (cut-off apnea-hypopnea-index (AHI)  $\geq 15/h$ ; Hazard Ratio (HR) 2.95,  $p=0.04$ ), early recurrence of atrial fibrillation (HR 8.74,  $p<0.001$ ), persistent atrial fibrillation (HR 7.16,  $p<0.001$ ), pre-procedural class III-antiarrhythmic drug treatment (HR 3.63,  $p=0.02$ ), but not SDB per se (AHI  $\geq 5/h$ ) as independent predictors for AF recurrence.

**Conclusion:** Moderate to severe SDB is a treatable condition that independently predicts AF recurrence in patients undergoing cryoPVI. Screening for SDB and adequate treatment may improve long-term success of cryoPVI.