

Journal Scan

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1. J Obes. 2012;2012:483135.

Nonalcoholic fatty liver disease and cardiovascular disease: has the time come for cardiologists to be hepatologists?

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ABSTRACT

Non-alcoholic fatty liver disease (NAFLD) is prevalent in people with the metabolic syndrome and type 2 diabetes and is present in up to one-third of the general population. Evidence is now accumulating that NAFLD is associated with obesity and diabetes and may serve as a predictor of cardiovascular disease (CVD). The possible mechanisms linking NAFLD and CVD include inflammation and oxidative stress, hyperlipidaemia, insulin resistance, and direct impact of NAFLD on coronary arteries and left ventricular dysfunction. In addition, several studies suggest that NAFLD is associated with high risk of CVD and atherosclerosis such as carotid artery wall thickness and lower endothelial flow-mediated vasodilation independently of classical risk factors and components of the metabolic syndrome. It is not yet clear how treatment of NAFLD will modulate the risk of CVD. Furthermore, studies are urgently needed to establish (i) the pathophysiology of CVD with NAFLD and (ii) the benefit of early diagnosis and treatment of CVD in patients with

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NAFLD. In the absence of biochemical markers, it is crucial that screening and surveillance strategies are adopted in clinical practice in the growing number of patients with NAFLD and at risk of developing CVD. Importantly, the current evidence suggests that statins are safe and effective treatment for CVD in individuals with NAFLD.

2. Heart Fail Rev. 2012 Dec 25. [Epub ahead of print]

Co-morbidities in heart failure.

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ABSTRACT

Heart failure is a clinical syndrome characterized by poor quality of life and high morbidity and mortality. Co-morbidities frequently accompany heart failure and further decrease in both quality of life and clinical outcome. We describe that the prevalence of co-morbidities in patients with heart failure is much higher compared to age-matched controls. We will specifically address the most studied organ-related co-morbidities, that is, renal dysfunction, cerebral dysfunction, anaemia, liver dysfunction, chronic obstructive pulmonary disease, diabetes mellitus and sleep apnoea. The pathophysiologic processes underlying the interaction between heart failure and co-morbid conditions are complex and remain largely unresolved. Although common risk factors are likely to contribute, it is reasonable to believe that factors associated with heart failure might cause other co-morbid conditions. Inflammation, neurohumoral pathway activation and hemodynamic changes are

potential factors. We try to provide explanations for the observed association between co-morbidities and heart failure, as well as its impact on survival.

3. *Sleep Breath. 2012 Dec 14. [Epub ahead of print]*

Toll-like receptor activity in patients with obstructive sleep apnea.

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ABSTRACT

BACKGROUND: Obstructive sleep apnea (OSA) has been linked to chronic inflammation and cardiovascular diseases. Considerable evidence suggests that innate immunodefense mechanisms might interact with proinflammatory pathways and contribute to atherogenesis. We hypothesized that the classical pathogen recognition receptors of the innate immune response, Toll-like receptors, are involved in modulating the inflammatory response in OSA.

METHODS: Expression of TLR2 and TLR4 on circulating monocytes from 29 subjects with documented OSA and 18 controls were compared with the use of flow cytometry and reverse transcription-polymerase chain reaction at baseline and after 8 weeks of continuous positive airway pressure (CPAP).

RESULTS: There was a significant increase in both TLR2 and TLR4 surface expression and mRNA levels on monocytes after adjustment for age, body mass index, and waist-to-hip ratio. This was paralleled by enhanced nuclear factor- κ B nuclear binding and an increased release of IL-6, INF- α , and TNF- α in OSA versus control subjects. Following 8 weeks of treatment, continuous positive airway pressure downregulated TLR2 and TLR4 expression and abrogated the release of inflammatory cytokines.

CONCLUSION: OSA is associated with enhanced expression and signaling events downstream of TLR2 and TLR4 in circulating monocytes. These observations are mitigated by CPAP therapy, which suggest that TLR2 and TLR4 activation may be involved as a signaling mechanism in immune-mediated progression of atherosclerosis in OSA.

4. *Cell BiochemBiophys. 2012 Dec 14. [Epub ahead of print]*

Intermittent Hypoxia-Induced NF- κ B and HO-1 Regulation in Human Endothelial EA.hy926 Cells.

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ABSTRACT

Intermittent hypoxia (IH) is a hallmark feature in obstructive sleep apnea (OSA) which is increasingly recognized as an independent risk factor for atherosclerosis. Oxidative stress, inflammation, and cell apoptosis are major pathological events initiating or accelerating atherogenesis. This study addressed whether IH would affect these proatherogenic factors in endothelial cells and the mechanistic pathways involved. EA.hy926 cells were exposed to intermittent normoxia or IH for different numbers of cycles (32, 64, or 96). IH exposure time-dependently raised cellular GSSG/GSH ratio, increased production of IL-6 and IL-8, and accelerated cell apoptosis and death, concurrent with activation of NF- κ B and inhibition of Nrf2/HO-1 pathways. At 64 cycles, inhibition of NF- κ B attenuated IH-induced cellular oxidative stress and accumulation of inflammatory cytokines in cell culture medium but aggravated IH-induced cell apoptosis, while stimulation of HO-1 suppressed IH-induced cellular oxidative stress and cell apoptosis without affecting accumulation of inflammatory cytokines in cell culture medium. We demonstrated that early stage of exposure to IH-induced oxidative and inflammatory stresses leading to acceleration of cell apoptosis via NF- κ B and Nrf2/HO-1 pathways in endothelial cells, suggesting the potential mechanisms for IH-induced vascular pathogenesis, in resemblance to OSA.

5. *Mediators Inflamm.* 2012;2012:879419. doi: 10.1155/2012/879419. Epub 2012 Nov 26.

Simulating sleep apnea by exposure to intermittent hypoxia induces inflammation in the lung and liver.

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ABSTRACT

Sleep apnea is a breathing disorder that results from momentary and cyclic collapse of the upper airway, leading to intermittent hypoxia (IH). IH can lead to the formation of free radicals that increase oxidative stress, and this mechanism may explain the association between central sleep apnea and nonalcoholic steatohepatitis. We assessed the level of inflammation in the lung and liver tissue from animals subjected to intermittent hypoxia and simulated sleep apnea. A total of 12 C57BL/6 mice were divided into two groups and then exposed to IH (n = 6) or a simulated IH (SIH) (n = 6) for 35 days. We observed an increase in oxidative damage and other changes to endogenous antioxidant enzymes in mice exposed to IH. Specifically, the expression of multiple transcription factors, including hypoxia inducible factor (HIF-1 α), nuclear factor kappa B (NF- κ B), and tumor necrosis factor (TNF- α), inducible NO synthase (iNOS), vascular endothelial growth factor (VEGF), and cleaved caspase 3 were shown to be increased in the IH group. Overall, we found that exposure to intermittent hypoxia for 35 days by simulating sleep apnea leads to oxidative stress, inflammation, and increased activity of caspase 3 in the liver and lung.

6. *J Thorac Dis.* 2012 Dec;4(6):608-16. doi: 10.3978/j.issn.2072-1439.2012.10.07.

Excessive daytime sleepiness in sleep disorders.

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ABSTRACT

Excessive daytime sleepiness is a significant public health problem, with prevalence in the community estimated to be as high as 18%. Sleepiness is caused by abnormal sleep quantity or sleep quality. Amongst others, multiple neurological, psychological, cardiac and pulmonary disorders may contribute. Risk factors for excessive sleepiness include obesity, depression, extremes of age and insufficient sleep. In the clinical setting, two of the most commonly encountered causes are obstructive sleep apnoea and periodic limb movement disorder. There is continuing discussion of the mechanisms by which these disorders cause daytime symptoms, with intermittent nocturnal hypoxia, sleep fragmentation and autonomic dysregulation identified as important factors. The increased prevalence of obstructive sleep apnoea in obese subjects does not fully account for the increased rates of daytime sleepiness in this population and there is evidence to suggest that it is caused by metabolic factors and chronic inflammation in obese individuals. Sleepiness is also more common in those reporting symptoms of depression or anxiety disorders and significantly impacts their quality of life. Clinicians should be aware of factors which put their patients at high risk of daytime sleepiness, as it is a debilitating and potentially dangerous symptom with medico-legal implications. Treatment option should address underlying contributors and promote sleep quantity and sleep quality by ensuring good sleep hygiene. However, stimulant medication may be indicated in some cases to allow for more normal daytime functioning.

7. *Med Sci Monit.* 2012 Dec;18(12):CR747-51.

Effect of CPAP treatment on endothelial function and plasma CRP levels in patients with sleep apnea.

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ABSTRACT

BACKGROUND: Continuous positive airway pressure (CPAP) is the most effective method for treating obstructive sleep apnea syndrome (OSAS) and alleviating symptoms. Improved sleep quality with effective CPAP therapy might also contribute to attenuated systemic inflammation and improved endothelial function, with subsequent reduction of cardiovascular risk. The aim of this study was to assess the effect of 3-month CPAP therapy on brachial artery flow-mediated dilation (FMD) and plasma C-reactive protein (CRP) levels in patients with OSAS.

MATERIAL/METHODS: Our study group consisted of 38 male patients with no prior history of cardiovascular disease. Twenty patients with an Apnea-Hypopnea Index (AHI) ≥ 15 were assigned to receive CPAP treatment and 18 subjects with an AHI < 5 were included in the control group. Six patients failed to comply with the CPAP treatment. Measurement of FMD and blood analysis was performed at baseline and 3 months after CPAP therapy.

RESULTS: Baseline FMD values were negatively correlated with age, BMI, AHI, DSI, % of time $< 90\%$ SaO₂, and CRP ($p < 0.05$). Plasma CRP values were positively correlated with BMI, AHI, DSI and % of time $< 90\%$ SaO₂ ($p < 0.05$). In the group of patients who complied with the CPAP treatment, there was a significant increase in the FMD values (9.18 ± 0.55 vs. 6.27 ± 0.50) and a decrease in the levels of CRP (0.67 ± 0.15 vs. 0.84 ± 0.18) ($p < 0.05$).

CONCLUSIONS: Appropriate CPAP therapy improved both CRP and FMD values, suggesting its potentially beneficial role in reducing cardiovascular risk in OSAS patients.

8. *Diabetes Metab Syndr Obes.* 2012;5:395-401.

Obstructive sleep apnea and bone mineral density in obese patients.

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ABSTRACT

CONTEXT: Obesity and its co-morbidities may adversely affect bone mineral density (BMD). Obstructive sleep apnea (OSA) is a major complication of obesity. To date, the effects of OSA on BMD in obese patients have been poorly studied.

OBJECTIVE: To examine whether the severity of OSA independently correlates with BMD in obese patients.

METHODS: One hundred and fifteen obese subjects with OSA (Apnea/Hypopnea Index [AHI] ≥ 5 events per hour) were included in the study. BMD was measured at lumbar spine, total hip, and femoral neck by dual energy X-ray absorptiometry. Body mass index, lean mass, and representative measures of metabolic syndrome (waist circumference, fasting plasma glucose, blood pressure, HDL-cholesterol, triglycerides) and inflammation (ESR, CRP, fibrinogen) were also evaluated.

RESULTS: BMD did not differ among obese individuals regardless of OSA severity. Correlation coefficient analysis for all the covariates showed a lack of association between AHI and BMD that was strongly influenced by age and weight.

CONCLUSION: Our study does not support an independent association between AHI and BMD in obese patients. Controlled studies involving a greater number of patients are warranted.

9. *Expert Rev Respir Med.* 2012 Nov;6(5):557-66. doi: 10.1586/ers.12.44.

Morbidities associated with obstructive sleep apnea.

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ABSTRACT

Obstructive sleep apnea (OSA)-induced biological changes include intermittent hypoxia, intermittent hypercapnia, intrathoracic pressure changes, sympathetic activation and sleep fragmentation. OSA can cause metabolic dysregulation, endothelial dysfunction, systemic inflammation, oxidative stress and

hypercoagulation, and neurohumoral changes. There is evidence suggesting that OSA is independently associated with metabolic syndrome. OSA has been shown to increase the risk for systemic hypertension, pulmonary vascular disease, ischemic heart disease, cerebral vascular disease, congestive heart failure and arrhythmias. Although there are evidences accumulating that there may be a causal relationship between OSA and cardiovascular disorders, there is a need for more data from randomized controlled intervention trials to confirm this relationship. Many risk factors of OSA (age, male gender and obesity) are also known risk factors for cardiovascular disease. Severe OSA-hypopnea significantly increases the risk of fatal and nonfatal cardiovascular events in both men and women, and continuous positive airway pressure treatment reduces this risk in both.

Neurocognitive consequences of OSA include daytime sleepiness, loss of alertness, memory deficit, reduced vigilance, impaired executive function, increased risk for automobile and occupational accidents, and decreased quality of life.

10. *Eur Respir J.* 2012 Oct 25.

Detection of obstructive sleep apnoea by an electronic nose.

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ABSTRACT

Diagnosis of obstructive sleep apnoea syndrome (OSAS) is technically demanding, cost-intensive and time-consuming. The measurement of volatile organic compounds by an electronic nose is an innovative method that determines distinct molecular patterns of exhaled breath in different patient groups. We addressed the following questions: What is the diagnostic accuracy of an electronic nose in the detection of OSAS and the ability to detect effects of standard therapy in patients with OSAS? Are these results related to changes in distinct markers of airway inflammation and extracellular remodelling? We included 40 OSAS patients and 20 healthy controls. Exhaled breath of all participants was analysed

using the Cyranose 320™. Pharyngeal washings were performed to sample the upper airway compartment. For statistical analysis linear discriminant analysis was employed. We identified a Linear Discriminant function separating OSAS from control ($p < 0.0001$). The corresponding area under the Receiver Operating Curve was 0.85 (95% CI 0.75-0.96; sensitivity 0.93; specificity 0.7). In pharyngeal washing fluids of OSAS patients we observed higher levels of alpha-1-antitrypsin and markers of extracellular remodelling compared to controls. The electronic nose can distinguish between OSAS patients and controls with high accuracy.

11. *J Transl Med.* 2012 Oct 22;10:211.

Bax/Mcl-1 balance affects neutrophil survival in intermittent hypoxia and obstructive sleep apnea: effects of p38MAPK and ERK1/2 signaling.

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ABSTRACT

BACKGROUND: Prolonged neutrophil survival is evident in various cardiovascular and respiratory morbidities, in hypoxic conditions in-vitro and in patients with obstructive sleep apnea (OSA) characterized by nightly intermittent hypoxia (IH). This may lead to persistent inflammation, tissue injury and dysfunction. We therefore investigated by a translational approach the potential contribution of the intrinsic stress-induced mitochondrial pathway in extending neutrophil survival under IH conditions. Thus, neutrophils of healthy individuals treated with IH in-vitro and neutrophils of OSA patients undergoing nightly IH episodes in-vivo were investigated. Specifically, the balance between pro-apoptotic Bax and anti-apoptotic Mcl-1 protein expression, and the potential involvement of p38MAPK and ERK1/2 signaling pathways in the control of Mcl-1 expression were investigated.

METHODS: Purified neutrophils were exposed to IH and compared to normoxia and to sustained hypoxia (SH) using a BioSpherix-OxyCycler C42 system. Bax

and Mcl-1 levels, and p38MAPK and ERK1/2 phosphorylation were determined by western blotting. Also, Bax/Mcl-1 expression and Bax translocation to the mitochondria were assessed by confocal microscopy in pre-apoptotic neutrophils, before the appearance of apoptotic morphology. Co-localization of Bax and mitochondria was quantified by LSM 510 Carl Zeiss Micro Imaging using Manders Overlap Coefficient. Paired two-tailed t test, with Bonferroni correction for multiple comparisons, was used for statistical analysis.

RESULTS: Compared to normoxia, IH and SH up-regulated the anti-apoptotic Mcl-1 by about 2-fold, down-regulated the pro-apoptotic Bax by 41% and 27%, respectively, and inhibited Bax co-localization with mitochondria before visible morphological signs of apoptosis were noted. IH induced ERK1/2 and p38MAPK phosphorylation, whereas SH induced only p38MAPK phosphorylation. Accordingly, both ERK and p38MAPK inhibitors attenuated the IH-induced Mcl-1 increase. In SH, only p38MAPK inhibition decreased Mcl-1 expression. Similar to neutrophils of healthy subjects exposed to IH (0.97 ± 0.2), in OSA neutrophils, Bax/Mcl-1 ratio was significantly lower compared to normoxic controls (1.0 ± 0.5 vs. 1.99 ± 0.3 , $p=0.015$), and Bax did not co-localize with mitochondria.

CONCLUSIONS: These findings suggest that decreased Bax/Mcl-1 balance promotes neutrophil survival in IH in-vitro as well as in OSA patients. Moreover, Bax/Mcl-1 protein function in IH and SH might be regulated by different signal transduction pathways, highlighting a novel regulatory function through ERK1/2 signaling in IH.

12. Front Neurol. 2012;3:149.

Obstructive sleep apnea and non-alcoholic fatty liver disease: is the liver another target?

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ABSTRACT

Obstructive sleep apnea (OSA) is recurrent obstruction of the upper airway during sleep leading to intermittent

hypoxia (IH). OSA has been associated with all components of the metabolic syndrome as well as with non-alcoholic fatty liver disease (NAFLD). NAFLD is a common condition ranging in severity from uncomplicated hepatic steatosis to steatohepatitis (NASH), liver fibrosis, and cirrhosis. The gold standard for the diagnosis and staging of NAFLD is liver biopsy. Obesity and insulin resistance lead to liver steatosis, but the causes of the progression to NASH are not known. Emerging evidence suggests that OSA may play a role in the progression of hepatic steatosis and the development of NASH.

Several cross-sectional studies showed that the severity of IH in patients with OSA predicted the severity of NAFLD on liver biopsy. However, neither prospective nor interventional studies with continuous positive airway pressure treatment have been performed. Studies in a mouse model showed that IH causes triglyceride accumulation in the liver and liver injury as well as hepatic inflammation. The mouse model provided insight in the pathogenesis of liver injury showing that (1)

IH accelerates the progression of hepatic steatosis by inducing adipose tissue lipolysis and increasing free fatty acids (FFA) flux into the liver; (2) IH up-regulates lipid biosynthetic pathways in the liver; (3) IH induces oxidative stress in the liver; (4) IH up-regulates hypoxia inducible factor 1 alpha and possibly HIF-2 alpha, which may increase hepatic steatosis and induce liver inflammation and fibrosis. However, the role of FFA and different transcription factors in the pathogenesis of IH-induced NAFLD is yet to be established. Thus, multiple lines of evidence suggest that IH of OSA may contribute to the progression of NAFLD but definitive clinical studies and experiments in the mouse model have yet to be done.

13. PLoS One. 2012;7(10):e47387.

Non-motor symptoms in patients with Parkinson's disease - correlations with inflammatory cytokines in serum.

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ABSTRACT

BACKGROUND: Parkinson's Disease (PD) is the second most common neurodegenerative disorder of the central nervous system. Motor symptoms are the focus of pharmacotherapy, yet non-motor features of the disease (e.g. fatigue, mood disturbances, sleep disturbances and symptoms of anxiety) are both common and disabling for the patient. The pathophysiological mechanisms behind the non-motor symptoms in PD are yet to be untangled. The main objective of this study was to investigate associations between pro-inflammatory substances and non-motor symptoms in patients with PD.

METHODS AND MATERIALS: We measured C-reactive protein, interleukin (IL)-6, soluble IL-2 receptor (sIL-2R) and tumor necrosis factor- α (TNF- α) in blood samples from PD patients (n=86) and healthy controls (n=40). Symptoms of fatigue, depression, anxiety and sleeping difficulties were assessed using the Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT), the Hospital Anxiety and Depression Scale (HAD), and the Scales for Outcome in PD-Sleep Scale respectively.

RESULTS: IL-6 was significantly higher in PD patients than in healthy controls. Compared to healthy controls, PD patients displayed significantly higher mean scores on HAD and lower scores on FACIT, thus indicating more severe symptoms as measured with these scales. Within the PD sample, high levels of both sIL-2R and TNF- α were significantly associated with more severe symptoms assessed by means of FACIT and HAD (depression and anxiety subscales). sIL-2R levels were able to significantly predict FACIT and HAD scores after the effects of age, gender, anti-parkinsonian medications, and severity of motor symptoms were controlled for.

DISCUSSION: We suggest that non-motor symptoms in PD patients, such as fatigue and depressive symptoms, might be generated via inflammatory mechanisms. This knowledge might contribute to the development of novel treatment options in PD, specifically targeting non-motor symptoms.

14. *Eur Respir J.* 2012 Oct 11. [Epub ahead of print]

Intermittent hypoxia activated cyclooxygenase pathway: role in atherosclerosis.

Gautier E, Arnaud C, Bäck M, Pépin JL, Petri MH, Baguet JP, Tamisier R, Lévy P, Stanke-Labesque F.

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ABSTRACT

Intermittent hypoxia (IH), the main stimulus of obstructive sleep apnoea (OSA), induces inflammation, leading to early atherosclerosis. Whether the cyclooxygenase (COX) pathway contributes to IH-induced atherosclerosis remains to be determined. We studied the effects of 8 week-IH exposure on COX-pathway gene expression and atherosclerosis, and the influence of COX-1 inhibition by SC-560 on atherosclerosis progression in aortas of ApoE(-/-) mice. Urinary 11-dehydrothromboxane B2 (11-dTXB2) was assessed in 50 OSA free of cardiovascular risk factor (CVRF) matched for age and body mass index with 25 controls, and 56 OSA with CVRF. IH significantly increased atherosclerotic lesion sizes, mRNA levels of COX-1 and thromboxane synthase (TXBS). Lesion sizes correlated to COX-1 ($r=0.654$, $p=0.0003$) and TXBS ($r=0.693$, $p<0.0001$) mRNA levels. COX-1 inhibition reduced lesion progression in IH mice only ($p=0.04$). Urinary 11-dTXB2 was similar in OSA free of CVRF and controls, but was increased by 13% ($p=0.007$) in OSA with CVRF compared to OSA without. Although OSA itself was not associated to increased urinary 11-dTXB2 concentration, COX-1 pathway was activated in IH exposed mice and in OSA presenting CVRF, and may contribute to IH-induced atherogenesis. COX-1 inhibition could be of clinical interest in the prevention of cardiovascular morbidity in OSA.

15. *Best Pract Res Clin Anaesthesiol.* 2012 Sep;26(3):355-66.

Delirium: is sleep important?

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ABSTRACT

Delirium and poor sleep quality are common and often co-exist in hospitalised patients. A link between these disorders has been hypothesised but whether this link is a cause-and-effect relationship or simply an association resulting from shared mechanisms is yet to be determined. Potential shared mechanisms include abnormalities of neurotransmitters, tissue ischaemia, inflammation and sedative exposure. Sedatives, while decreasing sleep latency, often cause a decrease in slow wave sleep and stage rapid eye movement (REM) sleep and therefore may not provide the same restorative properties as natural sleep. Mechanical ventilation, an important cause of sleep disruption in intensive care unit (ICU) patients, may lead to sleep disruption not only from the discomfort of the endotracheal tube but also as a result of ineffective respiratory efforts and by inducing central apnoea events if not properly adjusted for the patient's physiologic needs. When possible, efforts should be made to optimise the patient-ventilator interaction to minimise sleep disruptions.

16. *J Hypertens.* 2012 Dec;30(12):2345-51.

Circulating anandamide and blood pressure in patients with obstructive sleep apnea.

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ABSTRACT

OBJECTIVE: Obstructive sleep apnea chronically increases blood pressure through sympathetic nervous system activation. In animals, hypertension and sympathetic activity are restrained by cannabinoid receptor activation. Therefore, we hypothesized that increased blood pressure in patients with obstructive sleep apnea is associated with increased circulating endocannabinoid concentrations.

METHODS: Arterial oxygen saturation and apnea/hypopnea episodes were recorded in 29 patients with normal glucose tolerance, 26 patients with type 2 diabetes mellitus, and 21 obese subjects without sleep apnea. We determined seated blood pressure, insulin, glucose, and high-sensitive C-reactive protein in the morning, and insulin sensitivity by euglycemic-hyperinsulinemic clamp the next day. Anandamide, the sum of 1-arachidonoylglycerol and 2-arachidonoylglycerol, and oleoylethanolamide were measured in plasma by liquid chromatography-tandem mass spectrometry.

RESULTS: Endocannabinoid concentrations in sleep apnea patients were increased compared to obese individuals without disordered nocturnal breathing. Correction for variables of obesity and insulin resistance almost completely abrogated this difference in endocannabinoids. Anandamide strongly correlated with blood pressure in sleep apnea patients ($r = 0.60$ for SBP and $r = 0.58$ for DBP, $P < 0.001$). In multivariate regression analysis, anandamide was a stronger determinant of blood pressure than sleep apnea severity, obesity, insulin resistance, and inflammation.

CONCLUSION: Obstructive sleep apnea patients show positive correlations between blood pressure and venous anandamide concentrations independent of confounding factors. Our data suggest a previously not recognized role of the endocannabinoid system for blood pressure regulation in patients with high risk for hypertension and cardiovascular disease.

17. *Nat Rev Cardiol.* 2012 Dec;9(12):679-88.

Mechanisms of cardiac dysfunction in obstructive sleep apnea.

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ABSTRACT

Obstructive sleep apnea (OSA) is associated with cardiovascular morbidity and mortality, largely as a result of myocardial anomalies. Numerous mechanisms cause OSA-related myocardial damage. The majority are initiated as a result of OSA-induced, chronic, intermittent hypoxia. The most-important mechanisms that lead to myocardial damage are increased sympathetic activity, endothelial dysfunction, systemic inflammation, oxidative stress, and metabolic anomalies. All these mechanisms promote the development of hypertension, which is common in patients with OSA. Hypertensive cardiomyopathy and coronary heart disease, as well as obesity-related, diabetic, and tachycardia-induced cardiomyopathies, are also associated with OSA. Left ventricular hypertrophy, myocardial fibrosis, atrial dilatation, and left ventricular systolic and diastolic dysfunction in patients with OSA explain the association of the disease with these clinical outcomes. The gold-standard treatment for OSA, nasal continuous positive airway pressure (CPAP), might improve cardiac symptoms and hemodynamic parameters in patients with the disease. However, large clinical trials are required to improve our understanding of the cardiac consequences of OSA, and determine the effect of treatment, particularly CPAP, on myocardial damage in symptomatic patients and primary prevention of cardiovascular disorders.

18. *CurrCardiol Rev.* 2012 Nov;8(4):265-72.

Sleep apnea and atrial fibrillation; 2012 update.

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ABSTRACT

Atrial fibrillation (AF) and obstructive sleep apnea (OSA) are very prevalent diseases in modern society. Recent years have seen the emergence of a wide body of literature suggesting an important association between these two diseases. This review will provide a summary of this evidence as it currently exists. First, it will review the literature suggesting an association between AF and OSA by highlighting the prevalence of AF in OSA, the correlation of AF prevalence with OSA severity and the trend towards increased AF recurrence in patients with OSA after treatment for AF. Second, it will identify the possible pathophysiologic mechanisms for this association. In doing so, it will discuss the investigated effects of intrathoracic pressure changes, autonomic instability and atrial remodeling. Finally, it will review the evidence of the effect of treatment of OSA on AF, highlighting the role of continuous positive airway pressure (CPAP) in the treatment of OSA and its impact on AF prevalence and recurrence.

19. *CurrOpinPulm Med.* 2012 Nov;18(6):541-5.

Can sleep deprivation studies explain why human adults sleep?

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ABSTRACT

PURPOSE OF REVIEW: This review will concentrate on the consequences of sleep deprivation in adult humans. These findings form a paradigm that serves to demonstrate many of the critical functions of the sleep states.

RECENT FINDINGS: The drive to obtain food, water, and sleep constitutes important vegetative appetites throughout the animal kingdom. Unlike nutrition and hydration, the reasons for sleep have largely remained speculative. When adult humans are nonspecifically sleep-deprived, systemic effects may include defects in cognition, vigilance, emotional stability, risk-taking, and, possibly, moral reasoning. Appetite (for foodstuffs) increases and glucose intolerance may ensue. Procedural, declarative, and emotional memory are affected. Widespread alterations of immune function and inflammatory regulators can be observed, and functional MRI reveals profound changes in regional cerebral activity related to attention and memory. Selective deprivation of rapid eye movement (REM) sleep, on the contrary, appears to be more activating and to have lesser effects on immunity and inflammation.

SUMMARY: The findings support a critical need for sleep due to the widespread effects on the adult human that result from nonselective sleep deprivation. The effects of selective REM deprivation appear to be different and possibly less profound, and the functions of this sleep state remain enigmatic.

20. Metab Syndr Relat Disord. 2012 Oct;10(5):331-6. Epub 2012 Jun 29.

The effect of sleep apnea and insomnia on blood levels of leptin, insulin resistance, IP-10, and hydrogen sulfide in type 2 diabetic patients.

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ABSTRACT

INTRODUCTION: Sleep deficits associated with sleep apnea and insomnia increase the risk of vascular inflammation and insulin resistance. This study examined the hypothesis that inflammation markers are higher in those diabetic patients who experience sleep deficits compared with those without any history of a sleep disorder.

METHODS: Fasting blood was obtained after written informed consent, and sleep disorder histories were obtained from type 2 diabetic patients (n=81) attending clinics of the Louisiana State University Health Sciences Center.

RESULTS: There was a significant correlation between body weight and leptin, and leptin in turn was significantly correlated with 10-kDa interferon- α -induced protein (IP-10) levels and insulin resistance in type 2 diabetic patients. Fasting blood levels of leptin, IP-10, and insulin resistance were significantly elevated in patients with sleep deficits compared with diabetics with normal sleep patterns. There were no differences in glycosylated hemoglobin (HbA1c) or fasting glucose in patients with sleep deficits compared with those with normal sleep patterns. Sleep deficits increase circulating levels of leptin, IP-10, and insulin resistance compared to levels seen in patients with diabetes who reported no difficulty with sleep. Patients with sleep apnea had significantly lower hydrogen sulfide (H₂S) levels compared with patients with normal sleep patterns or patients with insomnia. Low levels of circulating H₂S could contribute to higher vascular inflammation in patients with sleep apnea.

CONCLUSIONS: These results suggest that sleep apnea is associated with a decrease in circulating H₂S and sleep disorders increase the risk of inflammation and insulin resistance, which can contribute to the increased risk of vascular disease in subjects with type 2 diabetes.

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Obstructive sleep apnea and diabetic neuropathy: a novel association in patients with type 2 diabetes.

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ABSTRACT

RATIONALE: Diabetic peripheral neuropathy is common and causes significant morbidity. Obstructive sleep apnea (OSA) is also common in patients with type 2 diabetes. Because OSA is associated with inflammation and oxidative stress, we hypothesized that OSA is associated with peripheral neuropathy in type 2 diabetes.

OBJECTIVES: To assess the relationship between OSA and peripheral neuropathy in patients with type 2 diabetes.

METHODS: A cross-sectional study of adults with type 2 diabetes recruited randomly from the diabetes clinic of two UK hospitals.

MEASUREMENTS AND MAIN RESULTS: Peripheral neuropathy was diagnosed using the Michigan Neuropathy Screening Instrument. OSA (apnea-hypopnea index \geq 5 events/h) was assessed using home-based, multichannel respiratory monitoring. Serum nitrotyrosine was measured by ELISA, lipid peroxide by spectrophotometer, and microvascular function by laser

speckle contrast imaging. Two hundred thirty-four patients (mean [SD] age, 57 [12] yr) were analyzed. OSA prevalence was 65% (median apnea-hypopnea index, 7.2; range, 0-93), 40% of which were moderate to severe. Neuropathy prevalence was higher in patients with OSA than those without (60% vs. 27%, $P < 0.001$). After adjustment for possible confounders, OSA remained independently associated with diabetic neuropathy (odds ratio, 2.82; 95% confidence interval, 1.44-5.52; $P = 0.0034$). Nitrotyrosine and lipid peroxide levels ($n = 102$, 74 with OSA) were higher in OSA and correlated with hypoxemia severity. Cutaneous microvascular function ($n = 71$, 47 with OSA) was impaired in OSA.

CONCLUSIONS: We describe a novel independent association between diabetic peripheral neuropathy and OSA. We identified increased nitrosative/oxidative stress and impaired microvascular regulation as potential mechanisms. Prospective and interventional studies are needed to assess the impact of OSA and its treatment on peripheral neuropathy development and progression in patients with type 2 diabetes.