Journal Scan

U. C. Ojha
Senior Specialist & Head – Department of Respiratory Medicine, E.S.I Hospital, New Delhi

Indian J Sleep Med 2013; 8.2, 93-50

1. Chest 2012;142(6)1499-150

Is Sleep Apnea a Winter Disease?: Meteorologic and Sleep Laboratory Evidence Collected Over 1 Decade

Cristiane Maria Cassol, PT, MSc; Denis Martinez, MD, PhD; Fernando Augusto Boeira Sabino da Silva, MSc; Marcia Kraide Fischer, PT, MSc; Maria do Carmo Sfreddo Lenz, MD, PhD; Ângelo José Gonçalves Bós, MD, PhD

Background: The severity of obstructive sleep apnea increases by influence of conditions that are more frequent in winter. The hypothesis that the apnea-hypopnea index (AHI) of different patients undergoing polysomnography may be seasonally affected was tested.

Methods: The retrospectively analyzed database included 7,523 patients of both sexes who underwent in-laboratory baseline polysomnography to investigate any complaint of disordered sleep, during 1 decade, between January 2000 and December 2009. Data on climate and air pollution were obtained from official organizations. AHI was the main outcome variable. Cosinor analysis, a statistical method for the investigation of time series, was used to detect seasonality.

Results: The cosinor analysis confirmed the existence of a circannual pattern of AHI, with acrophase in winter and nadir during the summer. The seasonality is significant even after adjusting for sex, age, BMI, neck circumference, and relative air humidity. Median (25-75 interquartile range) AHI in the 6 months with colder weather was 17.8 (6.5-40.6/h), and in the warmer weather was 15.0 (5.7-33.2/h). The AHI correlated inversely with ambient temperature and directly with atmospheric pressure, relative air humidity, and carbon monoxide levels. Correlations with precipitation, particulate air matter < 10 ìm, sulfur dioxide, and ozone were nonsignificant.

Conclusions: More sleep-disordered breathing events were recorded in winter than in other seasons. Cosinor analysis uncovered a significant seasonal pattern in the AHI of different patients undergoing polysomnography, independent of sex, age, BMI, neck circumference, and relative air humidity. This finding suggests that obstructive sleep apnea severity may be associated with other seasonal epidemiologic phenomena.

Address for correspondence
Dr. U. C. Ojha
Senior Consultant and Head of the Department
Specialist & Head, Dept of Respiratory Medicine
E.S.I. Hospital, Basaidarapur, New Delhi
Email: ucojha@rediffmail.com

2. CHEST 2012; 142(1): 239 – 245

Biomarkers of Sleep Apnea

Sydney B. Montesi, MD; Ednan K. Bajwa, MD, MPH; and Atul Malhotra, MD.

Obstructive sleep apnea (OSA) is a condition of repetitive upper airway collapse, which occurs during sleep. Recent literature has emphasized the role of OSA in contributing to glucose intolerance, dyslipidemia, and hypertension. OSA is associated with the development of cardiovascular disease, although defi nitive data are sparse with regard to the prevention of cardiovascular disease and CPAP therapy. CPAP provides effective treatment for OSA, but patient adherence remains challenging. Aside from daytime symptom improvement, it is diffi cult to monitor the adequacy of treatment response. Thus, the search for a biomarker becomes critical. The discovery of an ideal biomarker for OSA has the potential to provide information related to diagnosis, severity, prognosis, and

response to treatment. In addition, because large-scale randomized controlled trials are both ethically and logistically challenging in assessing hard cardiovascular outcomes, certain biomarkers may be reasonable surrogate outcome measures. This article reviews the literature related to potential biomarkers of OSA with the recognition that an ideal biomarker does not exist at this time.

3. Eur Respir J 2012; 40: 1180–1190

Dose response of continuous positive airway pressure on nasal symptoms, obstruction and inflammation in vivo and in vitro

Mohammed D. Al Ahmari, Raymond J. Sapsford, Jadwiga A. Wedzicha and John R. Hurst

Obstructive sleep apnoea is a common condition associated with cardiovascular risk. Continuous positive airway pressure (CPAP) is an effective treatment but is associated with nasal side-effects, which hinder compliance and may result from inflammation. We investigated whether CPAP was pro-inflammatory to human subjects in vivo, and to cultured bronchial epithelial cells in vitro. In vivo, we further investigated whether induction of nasal inflammation was associated with the development of systemic inflammation, nasal symptoms and changes in nasal mucociliary clearance. In vitro, CPAP resulted in cytokine release from cultured BEAS-2B cells in a time- and dose (pressure)-dependent manner. In vivo, CPAP resulted in dose-dependent upregulation of nasal inflammatory markers associated with the development of nasal symptoms, and reduced mucociliary clearance. CPAP also upregulated selected markers of systemic inflammation.CPAP results in dose-dependent release of inflammatory cytokines from human epithelial cells in vitro and in vivo. In vivo responses were associated with systemic inflammation, reductions in nasal mucociliary function and the development of nasal symptoms. This emphasises the need for novel strategies to reduce nasal inflammation and therefore aid compliance.

4 . Immunology 2012, 13:1

Acute sleep deprivation has no lasting effects on the human antibody titer response following a novel influenza A H1N1 virus vaccination.

Christian Benedict, Maria Brytting, Agneta Markström, Jan-Erik Broman and Helgi Birgir Schiöth

Background: Experimental studies in humans have yielded evidence that adaptive immune function, including the production of antigen-specific antibodies, is distinctly impaired when sleep is deprived at the time of first antigen exposure. Here we examined the effects of a regular 24- hour sleep-wake cycle (including 8 hours of nocturnal sleep) and a 24-hour period of continuous wakefulness on the 7-week antibody production in 11 males and 13 females in response to the H1N1 (swine flu) virus vaccination. The specific antibody titer in serum was assayed by the hemagglutination inhibition test on the days 5, 10, 17, and 52 following vaccination. Results: In comparison to the sleep group, sleep-deprived males but not females had reduced serum concentration of H1N1-specific antibodies five days after vaccination, whereas antibody titers at later time points did not differ between the conditions.

Conclusions: These findings concur with the notion that sleep is a supportive influence in the very early stage of an adaptive immune response to a viral antigen. However, our results do not support the view that acute sleep deprivation has lasting effects on the human antibody titer response to influenza vaccination.

5. Eur Respir J 2012; 39: 1492–1500.

Carotid body inflammation and cardiorespiratory alterations in intermittent hypoxia

Rodrigo Del Rio, Esteban A. Moya, Marý´a J. Parga, Carlos Madrid and Rodrigo Iturriaga

ABSTRACT

Chronic intermittent hypoxia (CIH), a main feature of

obstructive sleep apnoea (OSA), increases hypoxic ventilatory responses and elicits hypertension, partially attributed to an enhance carotid body (CB) responsiveness to hypoxia. As inflammation has been involved in CIH induced hypertension and chemosensory potentiation, we tested whether ibuprofen may block CB chemosensory and cardiorespiratory alterations induced by CIH in a rat model of OSA. We studied the effects of ibuprofen (40 $mg.kg^{-1}.day^{-1}$) on immunohistochemical interleukin (IL)- 1b and tumour necrosis factor (TNF)-a levels in the CB, the number of c-fos-positive neurons in the nucleus tractus solitarii (NTS), CB chemosensory and ventilatory responses to hypoxia, and arterial blood pressure in male rats either exposed for 21 days to 5% O2 (12 episodes.h^{-1}, 8 h.day-1) or kept under sham condition. CIH increased CB TNF-a and IL-1b and c-fos-positive neurons in the NTS, enhanced carotid chemosensory and ventilatory hypoxic responses, and produced hypertension. Ibuprofen prevented CB cytokine overexpression and CIH-induced increases in c-fos-positive neurons in the NTS, the enhanced hypoxic ventilatory responses and hypertension, but failed to impede the CB chemosensory potentiation.

Results suggest that pro-inflammatory cytokines may contribute to the CIH-induced cardiorespiratory alterations, acting at several levels of the hypoxic chemoreflex and cardiovascular control pathways.

6. SLEEP 2012;35(1):97-101.

A Prospective Study of Sleep Duration and Pneumonia Risk in Women

Sanjay R. Patel, Atul Malhotra, Xiang Gao, Frank B. Hu, Mark I. Neuman; Wafaie W. Fawzi,

Study Objective: Experimental data suggest sleep deprivation may impair host immunity. We sought to assess the effect of poor sleep on pneumonia risk.

Design: Prospective, observational cohort study.

Participants: 56,953 female nurses (ages 37 to 57 years old) participating in the Nurses' Health Study II cohort free of cancer, cardiovascular disease, diabetes, and asthma with no prior history of pneumonia.

Measurements and Results: At baseline, participants reported their average sleep duration and whether this quantity was adequate for them.

Questionnaires ascertaining a new pneumonia diagnosis were mailed every 2 years. Cases required physician diagnosis and chest radiograph confirmation. Cox proportional hazards models were used to assess the relative risk for incident pneumonia over 4 years. Over 217,500 personyears, 977 cases of pneumonia were identified. Relative to 8-h sleepers, both short and long sleep durations were associated with elevated pneumonia risk. The age-adjusted relative risk for pneumonia was 1.70 (95% CI 1.30-2.23) in those sleeping d" 5 h and 1.49 (95% CI 1.12-1.98) in those sleeping e" 9 h. After adjusting for potential confounders, the relative risks were 1.39 (95% CI: 1.06-1.82) in those sleeping d" 5 h and 1.38 (95% CI 1.04-1.84) in those sleeping e" 9 h. Perceived inadequate sleep was also associated with pneumonia with a relative risk of 1.50 (95% CI 1.29-1.74) in multivariate models.

Conclusions: Both reduced and prolonged habitual sleep durations are associated with increased risk of pneumonia. Further research is needed to understand how sleep habits can influence immunity.

7. SLEEP 2012;35(6):783-790.

Sleep is associated with the metabolic syndrome in a multi-ethnic cohort of midlife women: the SWAN Sleep Study.

Hall MH; Okun ML; Sowers M; Matthews KA; Kravitz HM; Hardin K; Buysse DJ; Bromberger JT; Owens JF; Karpov I; Sanders MH.

Study Objectives: We evaluated associations among subjective and objective measures of sleep and the metabolic syndrome in a multi-ethnic sample of midlife women.

Design: Cross-sectional study.

Setting: Participants' homes.

Participants: Caucasian (n = 158), African American (n = 125), and Chinese women (n = 57); mean age = 51 years. Age range = 46-57 years.

Interventions: None.

Measurements and Results: Metabolic syndrome was measured in the clinic and sleep quality was assessed by self-report. Indices of sleep duration, continuity/ fragmentation, depth, and sleep disordered breathing were assessed by in-home polysomnography (PSG). Covariates included sociodemographics, menopausal status, use of medications that affect sleep, and self-reported health complaints and health behaviors known to influence metabolic syndrome risk. Logistic regression was used to test the hypothesis that the metabolic syndrome would be associated with increased subjective sleep complaints and PSG-assessed sleep disturbances. In univariate analyses, the metabolic syndrome was associated with decreased sleep duration and efficiency and increased NREM beta power and apnea-hypopnea index (AHI). After covariate adjustment, sleep efficiency (odds ratio [OR] = 2.06, 95% confidence interval [CI]: 1.08-3.93), NREM beta power (OR = 2.09, 95% CI: 1.09-3.98), and AHI (OR = 1.86, 95% CI: 1.40-2.48) remained significantly associated with the metabolic syndrome (odds ratio values are expressed in standard deviation units). These relationships did not differ by race.

Conclusions: Objective indices of sleep continuity, depth, and sleep disordered breathing are significant correlates of the metabolic syndrome in midlife women, independent of race, menopausal status and other factors that might otherwise account for these relationships.

8. SLEEP 2012;35(7):921-932.

The interaction of obstructive sleep apnea and obesity on the inflammatory markers c-reactive protein and interleukin-6: the Icelandic Sleep Apnea Cohort.

Arnardottir ES; Maislin G; Schwab RJ; Staley B; Benediktsdottir B; Olafsson I; Juliusson S; Romer M; Gislason T; Pack AI.

Study Objectives: To assess the relative roles and interaction of obstructive sleep apnea (OSA) severity and obesity on interleukin-6 (IL-6) and C-reactive protein (CRP) levels.

Design: Cross-sectional cohort.

Setting: The Icelandic Sleep Apnea Cohort.

Participants: 454 untreated OSA patients (380 males and 74 females), mean ± standard deviation age 54.4 ± 10.6 yr.

Interventions: N/A.

Measurements and Results: Participants underwent a sleep study, abdominal magnetic resonance imaging to measure total abdominal and visceral fat volume, and had fasting morning IL-6 and CRP levels measured in serum. A significantly higher correlation was found for BMI than visceral fat volume with CRP and IL-6 levels. Oxygen desaturation index, hypoxia time, and minimum oxygen saturation (SaO2) significantly correlated with IL-6 and CRP levels, but apnea-hypopnea index did not. When stratified by body mass index (BMI) category, OSA severity was associated with IL-6 levels in obese participants only (BMI > 30 kg/m2). A multiple linear regression model with interaction terms showed an independent association of OSA severity with IL-6 levels and an interaction between OSA severity and BMI, i.e., degree of obesity altered the relationship between OSA and IL-6 levels. An independent association of OSA severity with CRP levels was found for minimum SaO2 only. A similar interaction of OSA severity and BMI on CRP levels was found for males and postmenopausal women.

Conclusions: OSA severity is an independent predictor of levels of IL-6 and CRP but interacts with obesity such that this association is found only in obese patients.

9. *SLEEP* 2012;35(12):1667-1672.

Pain sensitivity and recovery from mild chronic sleep loss.

Roehrs TA; Harris E; Randall S; Roth T.

Study Objectives: To determine whether an extended bedtime in sleepy and otherwise healthy volunteers would increase alertness and thereby also reduce pain sensitivity.

Setting: Outpatient with sleep laboratory assessments.

Participants and Interventions: Healthy volunteers (n = 18), defined as having an average daily sleep latency on

the Multiple Sleep Latency Test (MSLT) < 8 min, were randomized to 4 nights of extended bedtime (10 hr) (EXT) or 4 nights of their diary-reported habitual bedtimes (HAB). On day 1 and day 4 they received a standard MSLT (10:00, 12:00, 14:00, and 16:00 hr) and finger withdrawal latency pain testing to a radiant heat stimulus (10:30 and 14:30 hr).

Results: During the four experimental nights the EXT group slept 1.8 hr per night more than the HAB group and average daily sleep latency on the MSLT increased in the EXT group, but not the HAB group. Similarly, finger withdrawal latency was increased (pain sensitivity was reduced) in the EXT group but not the HAB group. The nightly increase in sleep time during the four experimental nights was correlated with the improvement in MSLT, which in turn was correlated with reduced pain sensitivity.

Conclusions: These are the first data to show that an extended bedtime in mildly sleepy healthy adults, which resulted in increased sleep time and reduced sleepiness, reduces pain sensitivity.

10. Psychosom Med. 2011 ; 73(2): 142–150.

Sleep Variability, Health-Related Practices and Inflammatory Markers in a Community Dwelling Sample of Older Adults.

Michele L. Okun, Ph.D.1, Charles F. Reynolds III, M.D.1, Daniel J. Buysse, M.D.1, Timothy H Monk, D.Sc., Ph.D.1, Sati Mazumdar, Ph.D.2, Amy Begley, M.A.1, and Martica Hall, Ph.D.1

1. Sleep Medicine Institute and Department of Psychiatry, University of Pittsburgh School of Medicine, Pittsburgh, PA

2. Department of Biostatistics, University of Pittsburgh Graduate School of Public Health

Background: Low-grade chronic inflammation is an important risk factor for age-related morbidity. Health behaviors, including average aggregate measures of sleep, have been linked to increased inflammation in older adults. Variability in sleep timing may also be associated with increased inflammation. This study evaluated relationships among several health behaviors and circulating proinflammatory cytokines (IL-6 and TNF-á).

Method: Participants were community dwelling older adults >60 years (N = 222: 39 bereaved, 55 caregivers, 52 with insomnia, and 76 good sleepers). Mean values and intra-individual variability in sleep, as well as caffeine and alcohol use, exercise, and daytime napping were assessed by sleep diaries. Blood draws were obtained in the morning.

Results: Several interactions were noted between sleep behaviors, inflammatory markers, and participant group. Greater variability in wake time and time in bed was associated with higher IL-6 among good sleepers relative to caregivers and older adults with insomnia. Good sleepers who consumed moderate amounts of alcohol had the lowest concentrations of IL-6 compared to the other three groups who consumed alcohol. Insomnia subjects, but not good sleepers, showed increased concentrations of IL-6 associated with caffeine use. Caregivers showed increased concentrations of TNF-á with alcohol use relative to good sleepers. Greater variability in bedtime, later wake times and longer time in bed was associated with higher TNF-á regardless of group.

Conclusions: Moderation and regularity in the practice of certain health behaviors, including sleep practices, were associated with lower plasma levels of inflammatory markers in older adults.Life circumstances and specific sleep disorders may modify these associations.

11. PLoS ONE 2012;7(1): e30972

Association of Sleep Duration with Chronic Diseases in the European Prospective Investigation into Cancer and Nutrition (EPIC)-Potsdam Study.

von Ruesten A, Weikert C, Fietze I, Boeing H

Background: In view of the reduced number of hours devoted to sleep in modern western societies the question arises what effects might result from sleep duration on occurrence of chronic diseases.

Methods: Data from 23 620 middle-aged participants

of the European Prospective Investigation into Cancer and Nutrition (EPIC)-Potsdam study, that were recruited between 1994–1998, were analyzed by using Cox proportional hazard regression to examine the association between self-reported sleep duration at baseline and incidence of chronic diseases, such as diabetes, myocardial infarction, stroke, and cancer.

Results: During a mean follow-up period of 7.8 years 841 incident cases of type 2 diabetes, 197 cases of myocardial infarction, 169 incident strokes, and 846 tumor cases were observed. Compared to persons sleeping 7-,8 h/day, participants with sleep duration of ,6 h had a significantly increased risk of stroke (Hazard Ratio (HR) = 2.06, 95% confidence interval (CI): 1.18–3.59), cancer (HR = 1.43, 95% CI: 1.09–1.87), and overall chronic diseases (HR = 1.31, 95% CI: 1.10–1.55) in multivariable adjusted models. Self-reported daytime sleep at baseline was not associated with incident chronic diseases in the overall study sample. However, there had been an effect modification of daytime sleep by hypertension showing that daytime sleep was inversely related to chronic disease risk among non-hypertensive participants but directly related to chronic diseases among hypertensive.

Conclusion: Sleep duration of less than 6 h is a risky behavior for the development of chronic diseases, particularly stroke and cancer, and should be therefore addressed in public health campaigns.

12. Endocr Connect. 2012 Nov 19;2(1):23-31.

Circadian rhythm of salivary cortisol, plasma cortisol, and plasma ACTH in end-stage renal disease.

Raff H, Trivedi H

OBJECTIVE: Patients with end-stage renal disease (ESRD) can display the features of endogenous hypercortisolism but are difficult to evaluate for Cushing's syndrome. We evaluated the circadian rhythm of plasma compared with salivary cortisol in subjects with ESRD.

DESIGN: Plasma and salivary cortisol and plasma ACTH samples were drawn frequently over 24 h in an inpatient research unit in stable ESRD subjects on daytime chronic hemodialysis (n=16) vs controls (n=8).

METHODS: Plasma cortisol was measured every 2 h from 0800 to 0600 h the following day. Salivary cortisol was measured every 2 h, except between 2400 and 0400 h (sleep time). Plasma ACTH measured in a subset of samples and C-reactive protein (CRP) was measured as a marker of a subclinical inflammatory state in all subjects.

RESULTS: ESRD subjects had a discernable circadian rhythm in plasma and salivary cortisol, but with a significantly higher nadir (1800-2400 h) compared with the controls (P=0.016-<0.001). After excluding four ESRD subjects without a normal circadian rhythm, the ESRD subjects still had higher nadir plasma and salivary cortisol and plasma ACTH compared with controls. There was no difference in the correlation of salivary and plasma cortisol in control vs ESRD subjects. ESRD subjects had higher CRP levels compared with controls.

CONCLUSIONS: ESRD subjects had increased late-night plasma and salivary cortisol and plasma ACTH levels. Late-night salivary cortisol is a reliable index of plasma cortisol in ESRD patients.

13. Curr Aging Sci. 2012 Dec;5(3):195-202.

Cancer-related fatigue, inflammation and thyrotropin-releasing hormone.

Kamath J.
Department of Psychiatry, The Carol and Ray Neag Comprehensive Cancer Center University of Connecticut Health Center, USA.
JKAMATH@uchc.edu

Aging and aging related illnesses such as cancer have been associated with inflammatory changes. Cancer-related behavioral comorbidities such as fatigue, sleep disturbances, depression have also been associated with inflammation, hypothalamic-pituitary-adrenal (HPA) axis dysregulation and other neuroendocrine changes. From a clinical perspective, cancer-related fatigue demonstrates striking similarities with the cytokine-induced sickness phenomenon in animal models. Thyrotopin-releasing hormone (TRH) plays a homeostatic role in its interaction with several biological systems, including a critical role in its interactions with the immune system. Considerable evidence supports a pivotal role for TRH in the

inflammatory processes with specific relevance to the "cytokine-induced sickness behavior" paradigm. Additionally, TRH exerts arousing and analeptic effects in instances of behavioral depression. In a small proof-of-concept study conducted by our group, we investigated TRH administration as a treatment fatigue in cancer survivors in comparison with saline administration using a double-blind, crossover design. We also evaluated impact of TRH/saline administration on the inflammatory markers in these patients. TRH administration was associated with significant improvement ($p < 0.05$) in fatigue levels as measured by the Visual Analog Scale-Energy (VAS-E), was associated with significant ($p < 0.05$) improvement in sleep disturbances and improved quality of life. Notably, TRH administration was associated with decrease in C-reactive protein (CRP) levels, a marker of inflammation. This decrease in CRP level with TRH administration was associated with improvement in energy levels as measured by the VAS-E. The present review supports potential utility of TRH-based therapeutics in medical and psychiatric disorders with underlying inflammatory processes.

14. Sleep. 2012 Jul 1;35(7):921-32.

The interaction of obstructive sleep apnea and obesity on the inflammatory markers C-reactive protein and interleukin-6: the Icelandic Sleep Apnea Cohort.

Arnardottir ES, Maislin G, Schwab RJ, Staley B, Benediktsdottir B, Olafsson I, Juliusson S, Romer M, Gislason T, Pack AI.

Department of Respiratory Medicine and Sleep, Landspitali-The National University Hospital of Iceland, Reykjavik, Iceland.)

STUDY OBJECTIVES: To assess the relative roles and interaction of obstructive sleep apnea (OSA) severity and obesity on interleukin-6 (IL-6) and C-reactive protein (CRP) levels.

DESIGN: Cross-sectional cohort.

SETTING: The Icelandic Sleep Apnea Cohort.

PARTICIPANTS: 454 untreated OSA patients (380 males and 74 females), mean ± standard deviation age 54.4 ± 10.6 yr.

INTERVENTIONS: N/A.

MEASUREMENTS AND RESULTS: Participants underwent a sleep study, abdominal magnetic resonance imaging to measure total abdominal and visceral fat volume, and had fasting morning IL-6 and CRP levels measured in serum. A significantly higher correlation was found for BMI than visceral fat volume with CRP and IL-6 levels. Oxygen desaturation index, hypoxia time, and minimum oxygen saturation (SaO_2) significantly correlated with IL-6 and CRP levels, but apnea-hypopnea index did not. When stratified by body mass index (BMI) category, OSA severity was associated with IL-6 levels in obese participants only (BMI > 30 kg/m²). A multiple linear regression model with interaction terms showed an independent association of OSA severity with IL-6 levels and an interaction between OSA severity and BMI, i.e., degree of obesity altered the relationship between OSA and IL-6 levels. An independent association of OSA severity with CRP levels was found for minimum SaO_2 only. A similar interaction of OSA severity and BMI on CRP levels was found for males and postmenopausal women.

CONCLUSIONS: OSA severity is an independent predictor of levels of IL-6 and CRP but interacts with obesity such that this association is found only in obese patients.