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Sleep Medicine in the APSR Respiratory Updates Series

by

Dr Jyoti Prasad MBBS, Sleep and Respiratory Medicine Registrar, Department of Allergy, Immunology and Respiratory Medicine, The Alfred Hospital, Melbourne, VIC, Australia

and

Professor Matthew T Naughton, MBBS MD FRACP, Head General Respiratory and Sleep Medicine, Department of Allergy, Immunology and Respiratory Medicine, The Alfred Hospital and Monash University, Melbourne, VIC, Australia

Upper Airway Stimulation for Obstructive Sleep Apnoea

Authors: Strollo PJ et al
Reference: N Eng J Med 2014; 370:139-49
URL: http://www.nejm.org/doi/full/10.1056/NEJMoa1308659
Comment: Hypoglossal nerve stimulation by pacemakers, either uni- or bilateral and either tonically or phasically with respiration have been long considered a possible therapy for OSA. This multicentre trial used unilateral phasic pacing in 126 obese (mean BMI ~28.4 kg/m2) middle aged (mean 54.5yrs) patients with moderate to severe obstructive sleep apnoea (AHI 20-50) who had either difficulty accepting or adhering to CPAP therapy. 17% had had a previous UPPP. Following pacemaker insertion, upper airway stimulation was shown to reduce median AHI by 68% from 29.3 events per hour to 9.0 events with a 70% decrease in ODI score from 25.4 events per hour to 7.4 events per hour over 12 months. Significant improvements in FOSQ score (mean change by 2.9) and Epworth Sleepiness Scale (normalised to <10) compared to baseline were also observed. Sleep time with oxygen saturation <90% also decreased from 5.4% to 0.9%. During treatment withdrawal phase the AHI was significantly higher in group where therapy was withdrawn for one week (25.8 vs 7.6 events per hour, p<0.001). The authors concluded that upper airway stimulation is an option for management of selected patients with moderate to severe OSA and intolerant of CPAP. Sleep state and body position data were not provided. Although 33 serious adverse events were reported, only 2% were classed as directly related to the pacemaker. These changes in AHI with unilateral hypoglossal nerve phasic pacing are similar to the Australian study by Eastwood et al (Sleep 23011;34:1479-1486), although rates of device complication and need for removal were lower in the Strollo paper. Precise mechanisms by which pacing may work in OSA, and the longer term sequelae, remain to be determined.

Comparison of Pregabalin with Pramipexole for Restless Legs Syndrome

Authors: Allen RP et al
Reference: N Eng J Med 2014; 370:621-31
URL: http://www.nejm.org/doi/full/10.1056/NEJMoa1303646
Comment: This industry sponsored randomised controlled double blind study compared 300mg pregabalin (an α2δ ligand analgesic and antiepileptic) with two doses of dopamine agonist pramipexol (0.25 and 0.5mg) or placebo in 719 participants with moderate to severe Restless Legs Syndrome (RLS) over a period of 52 weeks. Placebo duration was 12 weeks only

then followed by randomization to one of three active arms. Over the initial 12 weeks, the improvement in mean scores on the RLS scale (0 to 40, high number indicating worse symptoms) was statistically greater among participants receiving pregabalin than among those receiving placebo (~7 vs 11 point reduction, P<0.001), and the proportion of patients with symptoms that were very much improved or much improved was also greater with pregabalin than with placebo (71.4% vs. 46.8%, P<0.001). Pregabalin was also shown to cause a greater reduction in RLS in a non inferiority assessment compared to pramipexole at dose of 0.25mg but not 0.5mg. The rate of augmentation over a period of 40 or 52 weeks was significantly lower with 300mg pregabalin than with 0.5mg pramipexole (2.1% vs. 7.7%, P = 0.001) but not at the 0.25mg dose (2.1% vs. 5.3%, P = 0.08). Although pregabalin had lower rates of GI adverse events and headaches, it was associated with a higher rate of suicidal ideation, dizziness, somnolence and weight gain. Discontinuation of drug was greater for pregabalin (27.5%) than for pramipexol (18.5% for 0.25mg and 23.9% for 0.5mg dose). These factors may limit the long term use of pregabalin. A major limitation was that iron levels and previous iron therapy (well known to alleviate RLS), were not included in the trial. This study highlights that augmentation is an iatrogenic phenomenon and casts doubt on the theory that RLS is primarily due to doperminergic abnormality. Further studies with Pregabalin will be required to determine whether this effect holds true in larger groups and over a longer periodic of time.

Obstructive Sleep Apnoea in Patients With Typical Atrial Flutter- Prevalence and Impact on Arrhythmia Control Outcome

Authors: Bazan V et al
Reference: Chest 2013;143 :1277-83
URL: http://journal.publications.chestnet.org/article.aspx?articleid=1388066

Comment: 56 patients undergoing cavotricuspid isthmus (CTI) radiofrequency ablation of atrial flutter were prospectively recruited to assess the impact of CPAP in reducing the occurrence of atrial fibrillation (AF) after CTI ablation over a 12 month follow up period. This study demonstrated a high prevalence of OSA of any degree and severe OSA in this non selected group of patients with AF (82% and 45% respectively). It also demonstrated that treatment of severe OSA with CPAP in patients undergoing CTI for AF was associated with reduction in incidence of new onset AF during the follow up period (from 46% to 6%). However, presence of AF prior to CTI ablation was the crucial factor on recurrence post CTI ablation and CPAP therapy

did not provide any protective role in this group. External validity of this study will have to be assessed with further multicentre trials. However, the study concludes that as part of clinical strategy for better arrhythmia control after CTI ablation, consideration should be given to screening of OSA and management with CPAP. This study confirms a similar observational study by Kanagala et al (Circulation 2003;107:2589-2594) in which patients with OSA treated with CPAP had a lower recurrence rate of AF following cardioversion. There is a desperate need for longer term randomised controlled trials in this field.

Association between Obstructive Sleep Apnoea and Cancer Incidence in a Large Multicentre Spanish Cohort

Authors: Campos-Rogriguez F
Reference: Am J Respir Crit Care Med, 2013;187: 99-105
URL: http://www.atsjournals.org/doi/pdf/10.1164/rccm.201209-1671OC

Comment: Intermittent hypoxemia and re-oxygenation associated with sleep fragmentation may up regulate reactive oxygen species and pro-angiogenic mediators involved in carcinogenesis, tumour vasculature and thereby accelerate tumour growth as seen in animal models (Liu et al. J Cell Biochem, 2010;111:554-563). A prospective multicentre analysis of 4910 participants undergoing assessment of obstructive sleep apnoea (OSA) with either a standard polysomnography or validated respiratory polygraphy for median of 4.5 years was undertaken to assess the incidence of cancer. This was undertaken as OSA has been associated with increased cancer mortality but whether it is associated with cancer incidence is unknown. Severity of OSA was determined by the AHI as well as percent of time spent with oxygen saturation less than 90% (TSat90). By the end of the follow up period, 5.3% of patients had received a diagnosis of cancer. The most frequent locations were bowel and prostate. Cancer incidence was observed to increase with increasing AHI and TSat90 categories, however adjusted analysis did not show AHI as an association with cancer incidence. In comparison to AHI, the adjusted hazard ratio for cancer incidence for increasing categories of TSat90 compared to <1.2%, was 1.58, for 1.2-12% and 2.33 for TSat90 greater than 12%. Hence overnight hypoxia, as a surrogate of OSA severity, was associated with increased incidence of cancer. This association appeared to be limited to younger patients(< 65 years) and male patients. Despite the limitations (low female sample size, confounders such as diet and exercise, malignancy type and location plus ability to access CPAP therapy) a larger prospective trial is suggested, and may be a by product of larger trials already underway such as the SAVE trial.

Sleep- Disordered Breathing and Postoperative Outcomes After Elective Surgery- Analysis of the Nationwide Inpatient Sample

Authors: Mokhlesi B, et al
Reference: Chest 2013;144: 903- 14
URL: http://journal.publications.chestnet.org/article.aspx?articleid=1672183

Comment: This retrospective analysis of ~ 1 million surgical inpatients in USA from Nationwide Inpatient Database on postoperative outcomes following orthopaedic, prostate, abdominal or cardiovascular surgery was undertaken to assess impact of sleep disordered breathing (SDB) on postoperative outcomes. SDB was independently associated with increased rates of emergent endotracheal intubation and mechanical ventilation, CPAP/NIV use and respiratory failure, with the new independent association of atrial fibrillation also being shown across all 4 surgical groups. These results confirm similar findings by Memtsuodis (Anesth Analg 2011;112:113–21) who reported outcomes of ~ 6 million post operative complications following orthopaedic and general surgery between 1998-2007. Mokhlesi reported no increase in in-hospital mortality, length of stay or total charges as an inpatient. As upper airway complications were proposed as the main cause for respiratory failure in SDB group, a lower threshold for intubation in SDB group was thought to be the reason for patients without SDB being intubated later, having a higher mortality rate, longer length of stay and higher cost. Main limitations of this study is that data was obtained retrospectively from a large database which could be prone to recording and coding errors. Also SDB diagnosis and adherence to treatment (even CPAP and NIV use in hospital) was not recorded.

Obstructive Sleep Apnoea and the Risk of Sudden cardiac Death: A Longitudinal Study of 10, 701 Adults

Authors: Gami AS, et al
Reference: J Am Coll Cardiol 2013;62:610-6
URL: http://www.sciencedirect.com/science/article/pii/S0735109713022511

Comment: The study was designed to determine whether OSA is associated with sudden cardiac death (SCD). A retrospective analysis of 10, 701 patients undergoing a polysomnogram between 1987-1993 in a single US centre with mean follow-up of 5.3 years was undertaken. The baseline mean demographics of the entire group were as follows: age 53years, BMI 34kg/

m2, 68% male, 57% smokers, 41% hypertensive, 14% diabetes, 14% pre-existing coronary artery disease, 6% heart failure and 5% past TIA or stroke. The annual risk of SCD (0.27%) was greater than their state average of 0.1-0.2% reflecting the population studied were of high cardiovascular risk. Although a prior diagnosis of OSA was excluded at entry point, CPAP therapy initiated post polysomnogram was not measured nor controlled for in this retrospective study. Despite these limitations, univariate predictors of SCD were age > 60years (Hazards ratio [HR] = 5.53), AHI>20 (HR=1.6), minimum overnight SpO2 <78% (HR=2.6) and mean overnight SpO2 < 93% (HR=2.93). Multivariate predictors of SCD were age, hypertension, coronary artery disease, ventricular ectopy included minimum SpO2 < 78%. An obvious limitation to this study was the precise oximeter setting (eg averaging time and sampling frequency) which are well known to influence readings (Pretto et al Respirology 2014;19:38-46). However similar to the large US Sleep Heart Health Study (Punjabi NM et al, PlosMed. 2009;6 (8):e1000132), overnight oximetry values are indicative of increased cardiovascular disease.

Sleep Drive Metabolite Clearance from the Adult Brain

Authors: Xie L et al
Reference: Science 2013:342:372- 377
URL: http://www.sciencemag.org/content/342/6156/373.long

Comment: This article demonstrates the critical function that sleep plays in turning on the glymphatic system to clear toxic proteins from the cerebrospinal fluid. Sleep deprivation has been shown to reduce learning, impair performance in cognitive tests, prolong reaction time and reduce seizure threshold. In extreme cases, continuous sleep deprivation kills rodents and flies within days to weeks. In humans, fatal or sporadic insomnia is a cause of rapid development of dementia and death. Toxic proteins linked to neurodegenerative disease (ie βamyloid, α-synuclein and tau) are present in the interstitial space surrounding the brain. As the brain lacks a lymphatic system, cerebrospinal fluid (CSF) exchanges with interstitial fluid to remove toxic waste, via a glymphatic system. This group of investigators demonstrated (a) an increase in CSF flux by 95% while asleep with two tracers (fluorescein isothiocyanate (FITC)–dextran) and (Texas red dextran) in mice. A reduction in interstitial fluid was also demonstrated using real-time iontophoretic tetramethylammonium (23±2% in sleep vs 14±2% in awake state), similar to

sleep effect seen in anesthetized mice. (23±1%). Finally, to assess if βamyloid is cleared most effectively during sleep, radiolabelled 125I-ABi-40 was injected intracortically in 3 groups of mice; awake, naturally sleeping and anesthetized. Brains, harvested 10 to 240 minutes later, showed a twofold increase in the clearance of βamyloid while asleep or anesthetized compared to wake. These findings suggest sleep is not only "restorative" but is an important functional state in which toxic waste products within the CSF are cleared.

Diagnostic Predictors of Obesity- Hypoventilation Syndrome in Patients Suspected of Having Sleep Disordered Breathing

Authors: Macavei V, et al
Reference: J Clin Sleep Med 2013; 9 :879-84
URL: *http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3746715/*

Comment: Obesity Hypoventilation Syndrome (OHS) is a combination of obesity (BMI> 30kg/m2) and daytime hypercapnia (pCO2 >45mmHg) in the absence of other known causes of alveolar hypoventilation. If left undiagnosed and untreated, there is significant morbidity (invasive mechanical ventilation and longer hospital stay) and mortality (23% at 18 months). In this retrospective study, data from 525 patients who attended a UK sleep clinic were evaluated using a specifically designed protocol. Patients underwent limited or full PSG with capillary blood gas (CBG) sampling. Sleep parameters including presence and severity of OSA, severity of hypoxia and body position were recorded. Obese patient with a BMI > 30kg/m2 were divided into 3 groups: BMI 30-35, 35-40 and >40kg/m2. OSA prevalence among obese patients was 80% and of OHS was 22% in OSAHS group. Prevalence of daytime hypercapnia increased from 11%in mild obesity group (BMI 30-35) to 30% in morbid (BMI>40) obesity group. Univariate analysis showed a significant relationship between PaCO2 and BMI, FEV1, FVC, AHI, mean SpO2, min nocturnal SpO2, time spent with SpO2 below 90% , PaO2 and calculated HCO3 (all with p- values < 0.01).Multiple regression analysis revealed that PaO2 and calculated HCO3 were independent predictors of OHS. Logistic regression analysis showed that a calculated bicarbonate threshold of 27mmol/L was most effective in detecting obesity hypoventilation syndrome with 86% sensitivity and 90% specificity. Study concluded that a normal HCO3 value may exclude daytime hypercapnia and should be used as a screening tool in obese patients to assess their risk of OHS.

Impact of Different Backup Rates on the Efficacy of Noninvasive Positive Pressure Ventilation in Obesity Hypoventilation Syndrome

Authors: Contal O et al
Reference: Chest. 2013;143: 37-46
URL: http://journal.publications.chestnet.org/article.aspx?articleid=1216043

Comment: A randomized trial of 10 patients with obesity hypoventilation syndrome with associated severe obstructive sleep apnoea was undertaken to study the impact of backup respiratory rate (BURR) on the efficacy of positive pressure ventilation and the quality of sleep in stable patients on long term bilevel ventilation treatment. Patients underwent three sleep studies on separate nights with the only change made being in the BURR mode of ventilation. These were spontaneous "S" mode (no BURR), and S/T mode with a low BURR (set at 2 points below the average nocturnal respiratory rate) and a high BURR (set at 95% of respiratory rate). Results showed that total AHI, central AHI and mixed AHI were higher in S than S/T modes. All respiratory events were lowest in the high BURR S/T mode sleep study. Sleep latency was longer in S (~ 20 minutes) than S/T modes (4-8 minutes), perhaps suggesting that patients found it more difficult to trigger and cycle the ventilator. Total sleep time and wake after seep onset, arousal and micro arousal as well as percentage of TST spent in N1, N2 and N3 were not statistically significant between the three settings. REM sleep was lowest in S/T mode with a high BURR. Oxygen desaturation index was statistically higher in S mode although PtcCO2 remained similarly stable across the three groups. Patients perceived low BURR ventilation better for sleep quality. Low sample size made it difficult to draw a definitive conclusion but have raised doubts regarding use of S mode for bilevel ventilation in patient with obesity hypoventilation on long term therapy.

Effect of CPAP on Blood Pressure in Patients With Obstructive Sleep Apnoea and Resistant Hypertension: The HIPARCO Randomized Clinical Trial

Authors: Martinez-Garcia M et al
Reference: JAMA. 2013;310:2407- 2415
URL: http://jama.jamanetwork.com/article.aspx?articleid=1788459

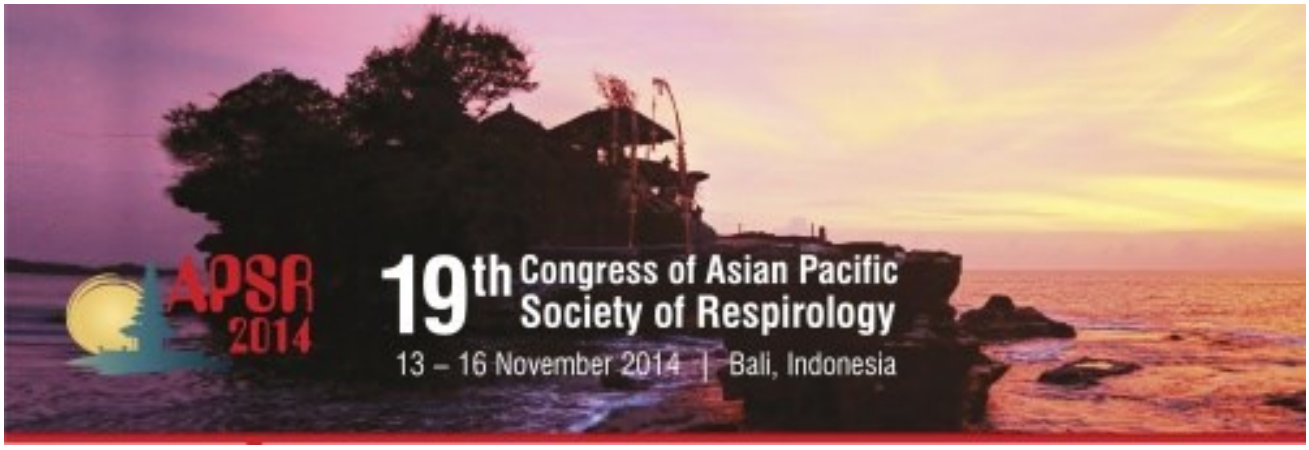
Comment: A, randomized clinical trial of 12 weeks CPAP therapy for OSA on 24 hour ambulatory blood pressure in 194 patients with drug resistant hypertension Mean patient de-

mographics were 56years, BMI=34, 69% male, AHI=40 kg/m2, mean 3.8 antihypertensive drugs with 26% being overnight “dippers” of BP defined by >10% fall in BP overnight. Mean adherence to CPAP was 5.2 hrs per night with 72% using CPAP >4 hours per night. Patients with CPAP therapy had a greater decrease in their mean 24 hours blood pressure (3.1 mmHg, CI 0.6-5.6 mmHg) and diastolic blood pressure but not in their systolic blood pressure. Confining the analysis to the CPAP adherent group, significant reductions in systolic (4.9mmHg) and diastolic BP (4.1mmHg) were observed. Greater percentage of patients in the CPAP group had an overnight “dipper” pattern of blood pressure (36% vs 22%). There was also a positive correlation between the hours of CPAP used and the fall in mean 24 hour blood pressure, systolic and diastolic blood pressure. Study concluded that CPAP in patient with resistant hypertension with OSA led to a significant decrease in mean 24 hour blood pressures and a rise in the number of patients with a “dipper” blood pressure pattern.

Effects of maternal obstructive sleep apnoea on fetal growth: a prospective cohort study

Authors: Fung et al.
Reference: Plos One 8(7):e68057
URL: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3722214/

Comment: Identification of factors that lead to intra-uterine growth retardation (IUGR) are of paramount importance as IUGR impacts upon foetal survival and long term health. Current data suggests maternal hypertension, hypobaric hypoxia and cardiovascular disease may contribute. Studies regarding OSA as an independent contributor of IUGR have been conflicting. This prospective cohort study included 371 pregnant women who had screening questionnaires for OSA symptoms, from which 51 had home polysomnography during 2nd trimester, from which 14 had confirmed OSA (AHI >5) and 27 were controls (AHI <5). OSA was associated with IUGR, based upon serial ultrasounds, across the third trimester (43 vs 11%). Logistic regression suggested OSA to be equally significant with body mass index to predict IUGR. These findings highlight the need for cross fertilization of research findings, easy access to sleep diagnostic services and most importantly the potential to identify new diagnoses in a maternity population. The impact of treating the OSA upon foetal health remains to be clarified.



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Articles selected and commented on by Dr Jyoti Prasad MBBS, Sleep and Respiratory Medicine Registrar, Department of Allergy, Immunology and Respiratory Medicine, The Alfred Hospital, Melbourne, VIC, Australia and Professor Matthew T Naughton, MBBS MD FRACP, Head General Respiratory and Sleep Medicine, Department of Allergy, Immunology and Respiratory Medicine, The Alfred Hospital and Monash University, Melbourne, VIC, Australia

Coordinator: Dr David CL Lam, Department of Medicine, University of Hong Kong, Hong Kong, China

Compiled by Dr Christel Norman, Respirology Editorial Office, Perth, Australia