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Inside this issue: APSR Update in Respiratory Sleep Medicine

Articles selected and commented on by: Dr Hamna Sahi[1],Dr Timothy Cheung[2], A/Prof Darren Mansfield[3]and Associate Professor Garun Hamilton MBBS, FRACP, PhD[4]

[1]Sleep Fellow, Monash Lung and Sleep Department, [2]Respiratory and Sleep Registrar, Monash Lung and Sleep, Monash Health, [3]Deputy Director Monash Lung and Sleep, Head Sleep Service Monash Health, Director Epworth Sleep Centre, Consortia Director of Physician Training Monash Health Consultant Respiratory and Sleep Physician, [4]Director Sleep Medicine Research at Monash Health, Dept of Lung and Sleep, Adjunct Clinical Associate Professor, School of Clinical Sciences, Monash University, Monash Medical Centre

To advertise, subscribe a colleague or to unsubscribe please contact : Secretariat, Asian Pacific Society of Respirology, 2F, UK's Bldg. 2-29-3 Hongo, Bunkyo-ku, Tokyo 113-0033 Japan. Email: apsrinfo@theapsr.org

CPAP for Prevention of Cardiovascular events in OSA

Author: R.Doug McEvoy, MD
URL: http://www.nejm.org/doi/full/10.1056/NEJMoa1606599

Prior observational studies have shown significantly fewer cardiovascular events in patient's adherent to CPAP than in those who are non-adherent. In this international, multicentre, randomized, parallel-group, open-label trial, with blinded end-point assessment study, 2717 eligible adults with moderate to severe OSA and coronary or cerebrovascular disease were randomly assigned to receive CPAP therapy plus usual care or usual care alone. In the CPAP group the mean duration of therapy was 3.3 hours per night with mean improvement in AHI from 29 events/hr to 3.7/hr on machine download. After a mean follow up of 3.7 years, CPAP did not result in a lower rate of pre-specified primary end points (a composite of death from cardiovascular causes, MI, stroke or hospitalisation for unstable angina, heart failure or TIA). CPAP therapy did, however, have a beneficial impact on quality of life, mood, daytime sleepiness and work productivity.

It is possible that the results were negative because the usage of CPAP was insufficient to derive cardiovascular benefits. It is also possible that CPAP therapy has a beneficial effect, but that the effect size is much smaller than that suggested by the observational studies, thus the study may have been underpowered. Finally, it is also possible that although associated with cardiovascular disease (CVD), OSA may not in fact be a reversible risk factor for CVD.

Notwithstanding these arguments, based on results from this trial, there is insufficient evidence to support the use of CPAP for the sole purpose of reducing cardiovascular events in patients with moderate to severe sleep apnoea and established cardiovascular disease. A trial of CPAP should be offered to these patients, however, as many may receive symptomatic benefit. It can be argued that although cardiovascular risk attributable to OSA is not established however the diagnosis may be an important opportunity to modify risk factors that both contribute to OSA as well as pose additional risks to cardiovascular health e.g. obesity

CPAP in patients with OSA and resistant Hypertension: Meta- analysis of Randomised Controlled Trials

Author: Liping Liu et al.
Reference: J Clin Hypertens (Greenwich). 2016 Feb;18(2):153-8.
URL: http://onlinelibrary.wiley.com/doi/10.1111/jch.12639/abstract

This meta- analysis of RCT's investigated the impact of CPAP therapy on Blood pressure in patients with moderate to severe OSA and treatment resistant hypertension. The search of various major databases identified 5 RCT's that were suitable for analysis. A total of 446 patients were studied across the trials and the duration of CPAP use ranged from 3 to 6 months. The analysis showed that CPAP treatment resulted in pooled reduction in 24- hour systolic blood pressure of 4.78 mmHg and diastolic blood pressure of 2.95 mmHg. Furthermore, the effect of CPAP on nocturnal diastolic blood pressure was favourable.
These results, focusing on a group of the most severely hypertensive patients, demonstrate a greater magnitude of benefit of blood pressure reduction compared to previous meta-analyses which included all-comers.
OSA is extremely common in treatment resistant hypertension with different studies quoting a prevalence of OSA anywhere between 63% to 83% in patients with treatment resistant hypertension, moreover severity of

OSA is directly associated with the degree of blood pressure elevation. This analysis provides further evidence that CPAP treatment in patients with OSA and resistant hypertension can result in improved blood pressure control. A 24 hour or ambulatory BP measurement is considered superior in predicting end organ damage and cardiovascular mortality. Furthermore, nocturnal BP levels are a better predictor of cardiovascular risk than daytime BP levels. Although the improvements in blood pressure may appear small, these results translate into large benefits in terms of cardiovascular and cerebrovascular risk reduction. These findings suggest that physicians may need to be more aggressive with screening for sleep apnoea and at measures to optimise CPAP adherence in patients with resistant hypertension.

Irregular sleep/wake patterns are associated with poorer academic performance and delayed circadian and sleep/wake timing

Author: Andrew J. K. Phillips

Reference: Scientific reports 7, Article number: 3216(2017)

URL: http://www.nature.com/articles/s41598-017-03171-4

Previous research has shown that short sleep duration is associated with cognitive impairment, motor vehicle accidents and increased risk of metabolic disorders. However, given that sleep is complex and multidimensional, sleep pattern and composition may be equally important for an individual's health and wellbeing. It is known that composition of sleep varies depending on circadian phase and the time of day at which sleep occurs. In this study, researchers objectively measured sleep and circadian rhythms and association to academic performance in 61 college students, finding that irregular sleep/wake pattern or rhythm (Form of circadian rhythm sleep disorder characterized by numerous naps throughout the 24-hour period, no main night-time sleep episode and irregularity from day to day) and light exposure patterns are associated with delayed circadian rhythms and lower academic performance. It was noted that irregular sleepers, perceived their sleep to be of poorer quality in comparison to regular sleepers, but had the same total sleep time as regular sleepers by sleeping more during the day. Causal relationship between sleep patterns and academic performance however could not be established as sleep irregularity may be an indicator of irregularity in other aspects of daily living and schedules (including the irregular routine conflicting with early class schedules). Nevertheless, this study does highlight sleep regularity as a potentially important and modifiable factor – independent from sleep duration– in determining academic performance and circadian timing.

Obstructive sleep apnoea: the effect of bariatric surgery after 12 months. A prospective multicentre trial

Author: P. Peromaa-Haavisto et al

URL: http://www.sleep-journal.com/article/S1389-9457(17)30004-7/fulltext

The rise in obesity, world-wide, is associated with a proportionate increase in related comorbidities including obstructive sleep apnoea. Weight loss appears to confer benefits on obstructive sleep apnoea (OSA) severity and vice versa (A 10% weight loss was associated with a 26% reduction in apnoea hyponoea index [AHI] while 10% weight gain was observed to be associated with a 32% increase in AHI).

Unfortunately, weight loss through conservative strategies is hard to achieve and maintain. Bariatric surgery is known to contribute to a more sustained weight loss and favourable effects on related comorbidities. This uncontrolled prospective multi- centre study investigated the effect of a laparoscopic Roux-en- Y gastric bypass (LRYGB) on OSA severity one year after surgery. Anthropometric measurements (weight, body mass index (BMI), and waist and neck circumference) improved (p<0.001) 12 months post procedure form baseline. All patients lost weight varying from 6 kg to 82 kg (mean of 32 kg) with mean BMI reduced from 43.9 to 33 kg/m2. It was noted that 90 % of patients had resolution or improvement in OSA. Of 187 patients with completed baseline data, 132 (71%) were demonstrated to have OSA (AHI>5events/h) on baseline cardiorespiratory recording (Embletta®- level III polysomnography investigation). Of 119 patients that undertook follow-up cardiorespiratory recordings 12 months post LRYGB, the prevalence of OSA and total AHI decreased from 71% to 44% and 27.8 events /h to 9.9 events/h (p <0.001) respectively. The improvement was more pronounced in participants in the severe OSA category in which the prevalence fell from 22% to 7% (P<0.001).) Sleep symptom questionnaire also indicated improvement (p <0.001) and a clear trend towards improvements in the Obesity/ OSA- related comorbidities (Hypertension, DMII/with insulin, Hyperlipidaemia) was also observed.

This study corroborates the previously known effect of bariatric surgery on AHI however, although well-designed, is limited by the possibility of systematic bias and effects of regression to the mean, due to lack of a comparative group and randomisation. Furthermore a longer follow-up time may have captured the effects of ongoing weight loss that potentially may have occurred beyond the 12 month study period. Although it would not have altered the outcome measures, this study utilized type 3 polygraphy pre and post-procedure, for practical and financial reasons and resultant lack of EEG data meant sleep time and staging could not be confirmed objectively, additionally data regarding the possible change in body position was not evaluated.

Notwithstanding above limitations, this study confirms that laparoscopic Roux-en- Y gastric bypass (LRYGB) procedure does result in significant weight loss and improvement in obesity related comorbidities, including OSA, at least in the short.

Effect of Home Non-invasive Ventilation with Oxygen Therapy vs Oxygen Therapy Alone on Hospital Readmission or Death After an Acute COPD Exacerbation: A Randomised Clinical Trial

Authors: Murphy PB et al

Reference: JAMA. 2017 Jun 6;317(21):2177-2186

URL: https://jamanetwork.com/journals/jama/fullarticle/10.1001/jama.2017.4451

Previous studies into the usefulness of non-invasive ventilation in the home to prevent COPD exacerbations have yielded conflicting results. In this multi-centre open-label trial, 116 patients with persistent hypercapnia following admission to hospital with acute decompensated type 2 respiratory failure requiring acute NIV were randomized to receive either home oxygen alone or high-pressure non-invasive positive pressure ventilation (median IPAP 24, IQR 22- 26; median EPAP 4 , IQR 4 -5) in addition to home oxygen. Patients with clinically significant obstructive sleep apnoea were excluded from the trial. 69% of patients had a history of prior use of long term oxygen therapy. At the end of the 12 month follow up period, there was a significant reduction in time to readmission or death in the intervention group (adjusted HR 0.49 (95% CI 0.31 – 0.788); P=0.002). There was good overall adherence

(mean 7.6hr/night at 12 months). A reduction in the frequency of COPD exacerbations was also observed (adjusted risk ratio 0.66 (95% CI, 0.44 – 0.94; P=0.02). All-cause mortality was not significantly different. Although there was early benefit in Health Related Quality of Life and mean between-group difference in reduction of PaCO2 at 6 weeks, the differences were not significant by the end of the study period. The authors concluded that the results of the study support screening for persistent hypercapnia in COPD patients who have required acute non-invasive ventilation for consideration of home non-invasive ventilation. Note that in this study, 2021 patients were screened in order to randomise 116, highlighting that in this patient group many will be unsuitable for long term NIV. Nevertheless, selected patients are likely to benefit and those with recurrent exacerbations are perhaps those who have most to gain.

A randomised controlled trial of CPAP versus non-invasive ventilation for initial treatment of obesity hypoventilation syndrome

Authors: Howard ME, et al
Reference: Thorax. 2017 May;72(5):437-444
URL: http://thorax.bmj.com/content/early/2016/11/15/thoraxjnl-2016-208559

Untreated ventilatory failure related to morbid obesity increases risk for cardiopulmonary complications and mortality. The optimal modality of positive airway pressure (PAP) to treat obesity hypoventilation has not been established. In this multicentre Australian study, sixty patients with a primary diagnosis of obesity hypoventilation syndrome were randomised to receive nocturnal bi-level PAP (Bi-PAP) or continuous PAP (CPAP) for a period of 3 months. There was no limit on the degree of hypoxaemia or hypercapnia for inclusion into the trial. Bi-PAP was delivered in spontaneous-timed mode to minimise suboptimal treatment with this mode due to failure to trigger the machine into inspiratory phase. A slightly greater proportion in the CPAP group had a history of prior PAP use (67.7% vs 44.8%). At the end of the study period, there was no significant difference in the primary end-point (between-group difference 1.5% (95% CI -16.6% to 19.6%,), p-0.87), which comprised of a composite of hospital admission, persistent ventilatory failure or non-adherence to treatment. There was a non-significant trend in the CPAP group for having persistently elevated PaCO2 early at 1 month, but overall the improvements in PaCO2 and PaO2 were similar between groups at 3 months. Treatment adherence was comparable between Bi-PAP and CPAP (5.3 hours / night vs 5.0 hours / night). The authors also found sleepiness and health-related quality of life improved on both treatments with no significant differences between groups. The findings support the data from a previous randomised controlled trial by Piper et al (Thorax 2008;63:395–401) suggesting similar improvements in ventilatory failure and symptoms between CPAP and bi-level PAP. These results suggest that most patients with obesity hypoventilation syndrome should begin treatment with CPAP, with Bi-PAP considered for those who with uncontrolled or the most severe ventilatory failure.

Effect of Continuous Positive Airway Pressure on Glycemic Control in Patients with Obstructive Sleep Apnea and Type 2 Diabetes

Authors: Shaw JE et al

Reference: Am J Respir Crit Care Med. 2016 Aug 15;194(4):486-92

URL: http://www.atsjournals.org/doi/abs/10.1164/rccm.201511-2260OC

Type 2 diabetes and OSA are both highly prevalent conditions. Observational studies have suggested that OSA is an independent risk factor for the development of Type 2 diabetes. A previous study by Babu et al (Arch Intern Med. 2005 Feb 28;165(4):447-52) reported improvement in glycaemic control after treatment of OSA with positive airway pressure (PAP).

In this multicentre randomised control trial, 416 participants with reasonably well controlled type 2 diabetes screened positive either for moderate-severe OSA (AHI ≥ 15/hr) or, in the United States only, OSA (AHI ≥ 5/hr) with clinical sequelae. To harmonise the entry conditions across all sites, the inclusion criteria was redefined after study commencement to a centrally scored oxygen desaturation index (ODI 3%) > 15/hr. The authors concede that the resultant withdrawal of 118 participants may have left the study underpowered. The remaining 298 participants were randomised to receive PAP therapy plus usual care or usual care alone. There was no significant difference between the groups for the primary outcome of change in HbA1c from baseline after 6 months of follow up despite reasonable adherence to PAP (mean 4.9 hours per night) and control of OSA (residual AHI 6.2/hr). Daytime sleepiness significantly improved and a trend towards greater fall in diastolic fall in diastolic pressure (-3.5 mm Hg vs. -1.5 mm Hg; P = 0.07) was observed for the PAP group.

The findings of this study do not support the observational data and add to the already varied findings from smaller prospective studies. A prior study by West et al (Thorax 2007;62:969–974) found no benefit of CPAP on HbA1c in men with OSA and type 2 diabetes but a subsequent study by Martínez-Cerón (Am J Respir Crit Care Med. 2016 Aug 15;194(4):476-85) demonstrated improved glycaemic control and insulin resistance with CPAP treatment. The authors of this study speculate that OSA may be more important in the development of glucose intolerance rather than glycaemic control among people with established type 2 diabetes. The question of whether PAP has a positive effect on glycaemic control in selected patients, such as those with severe OSA or poorly controlled type 2 diabetes, remains unanswered. Nevertheless, there is insufficient evidence at this stage to support routine screening for OSA in patients with type 2 diabetes.

Validation of the System One RemStar Auto A-Flex for Obstructive Sleep Apnea Treatment and Detection of Residual Apnea-Hypopnea Index: A European Randomized Trial

Authors: Gagnadoux F et al
Reference: J Clin Sleep Med. 2017 Feb 15;13(2):283-290
URL: http://www.aasmnet.org/jcsm/ViewAbstract.aspx?pid=30951

Attended manually titrated CPAP during in-laboratory polysomnography (PSG) has been the gold standard for CPAP implementation for many years. Automatically adjusted positive airway pressure (APAP) devices have been developed to overcome the resource intensive limitations of in-laboratory CPAP titration. Although previous randomized controlled trials have found comparable efficacy between APAP and CPAP in treatment of moderate to severe OSA, the algorithm for detection of residual respiratory events is device-dependent and has not been well validated against the established standard.

This double-blinded randomised cross-over study evaluated the efficacy of the System One RemStar Auto A-Flex device in APAP mode compared to fixed CPAP using the same device set at the optimal pressure determined by manual titration. Fifty-three adult patients with recently diagnosed moderate to severe OSA (mean AHI 45.9 ± 23) underwent a CPAP titration PSG and completed two further PSGs on consecutive nights either with APAP set at 4-20cmH2O followed by CPAP fixed at the optimal pressure determined by the initial titration study or vice-versa. All PSGs were centrally scored by automated analysis followed by expert review according to American Academy of Sleep Medicine (AASM) 2007 scoring criteria.

No significant differences between mean or median 90th percentile pressure / fixed CPAP pressure, total arousal index or respiratory arousal index was observed between APAP and fixed CPAP. Both groups had effective treatment of their OSA with PSG-derived AHI values (mean ± standard deviation) of (4.3 ± 5.9 vs 6.7 ± 11.9 respectively, P=0.063). Significant differences between groups in total apnoea index (2.8 ± 0.8 vs 5.3 ± 11.5, p = 0.004) and percentage of N1 sleep were small and thought not to be clinically relevant.

There was a tendency for the device to slightly overestimate AHI, however residual AHIs computed by the device were strongly correlated with AHI automated scored on PSG (intraclass correlation coefficient 0.956, $p < 0.001$). Using an AHI cut-off of ≥ 10/hr, the area under the receiver operating characteristic curve was 0.988.

The results support the use of this APAP device as a reasonable alternative to manual CPAP titration and therapy at a fixed pressure for treatment of moderate to severe OSA. The proprietary algorithm of the RemStar device delivered a 90th percentile pressure similar to the PSG-derived optimal pressure without an increase in arousal indexes. Clinicians may also have greater confidence in the machine-derived AHI as a reliable surrogate of the AHI determined from polysomnography.

Screening for Obstructive Sleep Apnea in Adults: Evidence Report and Systematic Review for the US Preventive Services Task Force

Authors: Jonas DE et al.

Reference: JAMA. 2017;317(4):415-433
URL: http://dx.doi.org/10.1001/jama.2016.19635

Obesity is a major risk factor for OSA. With the increasing prevalence of obesity in the United States, there may be a greater population at risk of severe OSA and its complications. The authors hypothesised that primary care screening for OSA in asymptomatic individuals would lead to improved health outcomes. This systematic review of 110 English-language randomised controlled trials (n = 46 118), performed by two independent reviewers under the auspices of the US Preventive Services Task Force, sought to review the evidence for OSA screening in improving health outcomes. The accuracy of existing screening strategies, diagnostic test accuracy, benefits and harms of screening and treatment, and the association between AHI and health outcomes were also examined.

No studies were identified that directly compared screening with no screening for health outcomes.

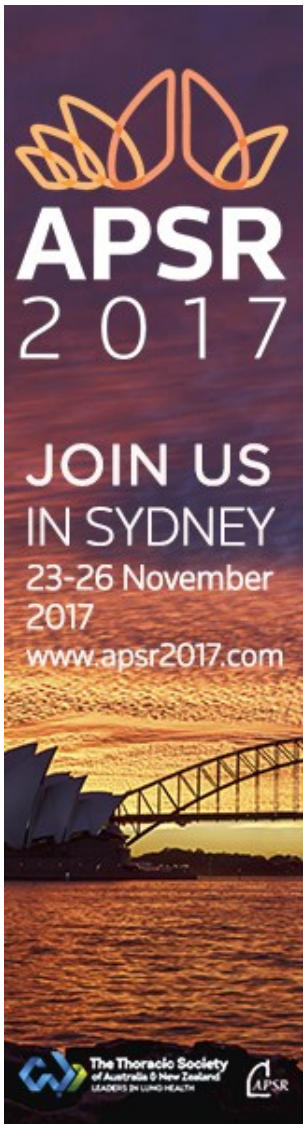
Three studies looked at the accuracy of existing clinical prediction tools or screening questionnaires including the Berlin Questionnaire and The Multi-Variable Apnoea Predictor (MVAP) score. MVAP score combined with an in-home portable monitoring study was found to have reasonable discrimination in predicting severe OSA syndrome in two trials [AUC 0.80 (95% CI, 0.78 to 0.82) and 0.83 (95% CI, 0.77 to 0.90)]. However, there was selection bias towards more symptomatic patients in both studies.

Seventy-six RCTs evaluated OSA treatment on intermediate outcomes, however none of the trials included patients that were detected by screening in primary care. Meta-analysis found that CPAP, when compared to sham, significantly improved AHI (weighted mean difference [WMD], −33.8 [95% CI, −42.0 to −25.6]; 13 trials, 543 participants), daytime sleepiness (ESS WMD, −2.0 [95% CI, −2.6 to −1.4]; 22 trials, 2721 participants) and blood pressure (systolic BP WMD, −2.4 points [95% CI, −3.9 to −0.9]; 15 trials, 1190 participants). There was a modest benefit found for sleep-related quality of life. AHI and ESS were also improved by Mandibular Advancement Devices and weight loss interventions but to a lesser degree.

An association between AHI and all-cause mortality was supported by prospective cohort studies. Participants with severe untreated OSA had a hazard ratio for death of 2.07 (95% CI, 1.48 to 2.91) compared with controls when pooling data from multivariable analyses of six studies.

No studies were found that looked at harms associated with screening or diagnostic testing for OSA. Reporting of harms associated with treatment were sparse, although common reported adverse effects of CPAP included oral or nasal dryness, eye or skin irritation and pain.

The results of this systematic review formed the basis of the Recommendation Statement for Screening for OSA in Adults issued by the US Preventive Services Task Force (JAMA. 2017;317(4):407- 414). The task force concluded that there was insufficient evidence to assess the balance of benefits and harms of screening for OSA in asymptomatic adults (I statement). Further study is needed to answer the overarching question of whether screening asymptomatic individuals for OSA improves health outcomes. Meanwhile, clinicians should not be dissuaded from using the available tools to assess symptomatic individuals at high risk given the heavy disease burden of severe OSA.



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[1]Sleep Fellow, Monash Lung and Sleep Department, [2]Respiratory and Sleep Registrar, Monash Lung and Sleep, Monash Health, [3]Deputy Director Monash Lung and Sleep, Head Sleep Service Monash Health, Director Epworth Sleep Centre, Consortia Director of Physician Training Monash Health Consultant Respiratory and Sleep Physician, [4]Director Sleep Medicine Research at Monash Health, Dept of Lung and Sleep, Adjunct Clinical Associate Professor, School of Clinical Sciences, Monash University, Monash Medical Centre

Editor in chief: Dr David CL Lam, Department of Medicine, University of Hong Kong, Hong Kong, China

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