

The Importance of Non-Anatomic Factors in the Pathogenesis of Obstructive Sleep Apnoea

by

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ABSTRACT

Obstructive sleep apnoea (OSA) is a common condition characterized by recurrent complete and partial upper airway obstruction. OSA sufferers have been shown to have a significantly smaller upper airway lumen compared to non-OSA sufferers. However, non-anatomical factors of sleep stage, arousability and neuromechanical responses to airway occlusion and chemosensitivity are likely to play a significant part in influencing OSA severity across the night. An exploration of these non-anatomical factors forms the basis for the experiments in this thesis.

In the first experimental chapter presented in this thesis, a detailed retrospective epoch by epoch analysis of nocturnal polysomnography in 253 patients referred to a clinical sleep service was performed to examine differences in sleep apnoea severity and arousal indices across the different stages of sleep, while controlling for posture. Both patients with and without OSA demonstrated significant reductions in respiratory and arousal event frequencies from stage 1 to 4 with intermediate frequencies in REM sleep. Lateral posture was also associated with significant improvements in OSA and arousal frequencies, with an effect size comparable to that of sleep stage. The majority of patients showed significant reductions in OSA severity during slow wave sleep. In non-REM sleep, there was a strong correlation between OSA severity and arousal frequency. These results confirm in a large group of patients, a strong sleep stage dependence of both OSA and arousal frequencies.

The second study in this thesis explores the development of a CO₂ stabilising or 'clamp' device to enable the provision of positive airway pressure, and by proportional rebreathing, the maintenance of relatively constant end-tidal CO₂ despite significant hyperventilation. Healthy volunteers performed brief periods of significant voluntary hyperventilation at 2 levels of CPAP with the rebreathing function off and with active CO₂ clamping in randomized order. Compared to CPAP alone, the device substantially attenuated hypocapnia associated with hyperventilation.

The third study of the thesis was designed to investigate if increasing and stabilizing end-tidal CO₂ could improve obstructive breathing patterns during sleep. 10 patients with severe OSA underwent rapid CPAP dialdown from therapeutic to a sub-therapeutic level to experimentally induce acute, partial upper airway obstruction over 2 minute periods repeated throughout the night. The CO₂ clamp device developed and validated in Study 2 was used to determine whether during periods of partial upper airway obstruction with severe flow limitation, (1) increased end-tidal CO₂ resulted in improved airflow and ventilation and (2) clamping end-tidal CO₂ lessened post-arousal ventilatory undershoot. Three conditions were studied in random order: no clamping of CO₂, clamping of end-tidal CO₂ 3-4 mmHg above eucapnic levels during the pre-dialdown baseline period only, and clamping of CO₂ above eucapnia during both baseline and dialdown periods. Elevated CO₂ in the baseline period alone or in the baseline and dialdown periods together resulted in significantly higher peak inspiratory flows and ventilation compared to the no clamp condition. Breath-by-breath analysis immediately pre- and post-arousal showed

higher end-tidal CO₂ despite hyperventilation immediately post-arousal and attenuation of ventilatory undershoot in CO₂ versus non-CO₂ clamped conditions. These results support that modulation of ventilatory drive by changes in pre- and post-arousal CO₂ are likely to importantly influence upper airway and ventilatory stability in OSA.

The fourth study was designed to explore several possible pathophysiological mechanisms whereby obstructive sleep apnoea is improved in stages 3 & 4 (slow wave) versus stage 2 sleep. 10 patients with severe OSA who demonstrated significant reductions in OSA frequency during slow wave sleep on diagnostic investigation were studied. Patients underwent rapid dialdowns from therapeutic CPAP to 3 different pre-determined sub-therapeutic pressures to induce partial airway obstruction and complete airway occlusions in a randomised sequence during the night in both stage 2 and slow wave sleep. Partial airway obstructions and complete occlusions were maintained until arousal occurred or until 2 minutes had elapsed, whichever came first. After airway occlusions, time to arousal, peak pre-arousal negative epiglottic pressure and the rate of ventilatory drive augmentation were significantly greater, suggesting a higher arousal threshold and ventilatory responsiveness to respiratory stimuli during slow wave compared to stage 2 sleep. Post dialdowns, the likelihood of arousal was lower with less severe dialdowns and in slow wave compared to stage 2 sleep. Respiratory drive measured by epiglottic pressure progressively increased post-dialdown, but did not translate into increases in peak flow or ventilation pre-arousal and was not different between sleep stages. These data suggest that while arousal time and propensity

following respiratory challenge are altered by sleep depth, there is little evidence to support that upper airway and ventilatory compensation responses to respiratory load are fundamentally improved in slow wave compared to stage 2 sleep.

In summary, sleep stage, arousal threshold and chemical drive appear to strongly influence upper airway and ventilatory stability in OSA and are suggestive of important non-anatomical pathogenic mechanisms in OSA.

PUBLICATIONS

Submitted for publication

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Ratnavadivel R, Stadler D, Windler S, Bradley J, Paul D, McEvoy RD, Catcheside PG. Upper airway function and arousability to ventilatory challenge in slow wave versus stage 2 sleep in obstructive sleep apnoea. Thorax 2008 (In review)

Published abstracts

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DECLARATION

This work contains no material which has been accepted for the award of any other degree or diploma in any university or tertiary institution and, to the best of my knowledge and belief, contains no material previously published or written by another person, except where due reference has been made in the text.

I give consent to this copy of my thesis, when deposited in the University Library, being available for loan and photocopying.

A handwritten signature in blue ink, consisting of a large, stylized 'R' followed by a series of connected loops and a final flourish.

Rajeev Ratnavadivel

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· கற்றது கைம்மண் அளவு கல்லாதது உலகளவு

“Known is a drop, unknown is an ocean”

Tamil proverb - Owaya