

**The role of intermittent hypercapnic hypoxia
in the induction of high loop gain in
obstructive sleep apnoea pathophysiology**

by

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Bachelor of Science (Honours), 2007

A thesis submitted for the degree of

DOCTOR OF PHILOSOPHY

December, 2015

Discipline of Physiology

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ABSTRACT

Intermittent hypoxia (IH) and unstable breathing are key features of obstructive sleep apnoea (OSA), the most common respiratory sleep disorder. Unstable ventilatory control is characterised by high loop gain (LG), and likely contributes to the propagation of apnoeas by promoting airway collapse during periods of low ventilatory drive. Currently, the contribution of inherent versus induced traits causing high LG in OSA remains unclear. OSA patients exhibit abnormal chemoreflex control which contributes to increased LG. These abnormalities normalise with continuous positive airway pressure (CPAP) treatment, suggesting induced rather than inherent trait abnormalities. Experimental IH, mimicking OSA, increases hypoxic chemosensitivity and induces long-term facilitation; a sustained increase in ventilatory neural output which outlasts the original stimulus. These neuroplastic changes induce the same abnormalities in chemoreflex control as seen in OSA patients, suggesting that high LG in OSA is largely induced by IH, and is reversible.

IH protocols are typically conducted on a background of poikilocapnia or isocapnia, in contrast to combined hypoxia and hypercapnia experienced in OSA. The level of concomitant CO₂ is thought to be critical for both the induction and expression of IH induced neuroplasticity. To more accurately mimic OSA, the effects of intermittent hypercapnic hypoxia (IHH) on ventilatory neuroplasticity and LG were investigated in the first two experiments contained within this thesis. The effect of CPAP treatment on LG in untreated OSA patients was investigated in the third and final study of this thesis.

In the first study, whether IHH during sleep induces LTF or increases chemosensitivity in healthy males was investigated. A randomised, separate day of intermittent medical air served as control. Unlike previous reports using isocapnic IH during sleep in healthy males, IHH did not induce LTF of ventilation or genioglossal muscle activity. Also, there was no change in the magnitude or slope of the ventilatory response to IHH from the first exposure to the last, to indicate any change in chemosensitivity. These findings suggest the effects of IHH differ to those of IH during sleep in healthy males.

During wakefulness LTF in humans is only expressed during mild hypercapnia. In the second study, the effect of IHH on LG was investigated in healthy males during wakefulness using a CO₂ pseudorandom binary stimulation technique to measure LG on a background of mild hypercapnia. There was no change in chemosensitivity during IHH or ventilatory LTF following IHH. There was no change in LG and although there was a trend towards a change in the ventilatory impulse response to a sudden change in CO₂ following IHH, this was not statistically significant. These findings further support that the effects of IHH during wakefulness differ to those of IH in healthy males.

In the third study, the effect of 6 weeks CPAP treatment on LG in previously untreated OSA males was investigated. Participants matched for age, sex, height, weight and BMI were also studied as controls. Helium dilution was used to assess supine functional residual capacity (FRC) and LG was compared prior to

commencing CPAP treatment and at 2 and 6 weeks after starting treatment, and at the same time points but without CPAP treatment in controls. LG was higher in the OSA patients versus matched controls, but there was no effect of CPAP treatment on LG. There was also no difference between patients and controls in FRC or controller or plant gain components of LG, although given that LG is the product of controller and plant gains, this could reflect a type II error. Patients exhibited reduced FEV1 and FVC and also higher supine abdominal height which positively correlated with AHI. Thus, this study confirmed that LG is higher in OSA patients versus matched controls, and supported previous work suggesting that central adiposity contributes to upper airway collapse. However, given no effect of CPAP on LG, larger cohorts and potentially alternative measures may be required to determine mechanisms driving elevated LG in OSA patients.

Although IH has previously been shown to induce neuroplastic changes to chemoreflex control that mirror abnormalities associated with high LG in OSA patients, the findings in this thesis suggest the effects of acute IHH differ to those of IH, both during sleep and wakefulness in healthy males. Potential causes for this disparity, and relevance of experimental findings to OSA pathophysiology are discussed. The effects of CPAP treatment on LG and implications for treatment options and CPAP adherence outcomes are also discussed.

PUBLICATIONS

Publications arising from this thesis

1. **Deacon, N.L.**, Catcheside, P.G. The role of high loop gain induced by intermittent hypoxia in the pathophysiology of obstructive sleep apnoea. *Sleep Med Rev.*, <http://dx.doi.org/10.1016/j.smrv.2014.10.003>.

Editorialised: Mateika JH, The role of high loop gain induced by intermittent hypoxia in the pathophysiology of obstructive sleep apnea. *Sleep Med Rev.*, <http://dx.doi.org/10.1016/j.smrv.2015.02.001>.

Conference abstracts

1. Harmer L, Stadler D, **Deacon N**, McEvoy RD, Catcheside P. The effect of intermittent hypoxia on respiratory load perception and respiratory evoked potentials. *Sleep and Biological Rhythms* (2009) 7: A62.
2. **Deacon, N.**, McEvoy, D., Stadler, D., Catcheside, P. The effects of intermittent hypercapnic hypoxia during sleep in healthy males on long-term facilitation, respiratory and upper airway control. *Sleep and Biological Rhythms* (2010) 8(Suppl): OP19, A25.
3. Stadler, D., McEvoy, D.R., Paul, D., **Deacon, N.**, Catcheside, P. The effect of abdominal compression on obstructive sleep apnoea severity. *Sleep and Biological Rhythms* (2010) 8(Suppl): PO99, A63.
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5. D Stadler, R. Doug McEvoy, D Paul, **N Deacon**, P Catcheside. Abdominal Compression Increases Obstructive Sleep Apnoea Severity. *Am. Respir Crit Care Med* (2011); 183: A6160.
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8. **Deacon, N.**, McEvoy, D., Catcheside, P. The effects of intermittent hypercapnic hypoxia on loop gain in healthy males. *Sleep and Biological Rhythms* (2012) 10(Suppl 1) 128: 47.
9. **N Deacon**, D McEvoy, P Catcheside. The effect of intermittent hypercapnic hypoxia on loop gain in healthy males. *Am. Respir. Crit. Care Med.* (2013); 187: A5674.

Other refereed journal articles

1. **Deacon, N.L.**, Arnould, J.P.Y. Terrestrial apnoeas and the development of cardiac control in Australian fur seal (*Arctocephalus pusillus doriferus*) pups. *J Comp Physiol B* (2009) **179**:287-295.
2. Atul Malhotra, **Naomi Deacon**, Frank Powell, Eliot Katz. Adaptive responses using obstructive sleep apnea as the paradigm. *Physiology.* (2014) **29**(3): 153-155

DECLARATION

I certify that this work contains no material which has been accepted for the award of any other degree or diploma in my name, in any university or other 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. In addition, I certify that no part of this work will, in the future, be used in a submission in my name, for any other degree or diploma in any university or other tertiary institution without the prior approval of the University of Adelaide and where applicable, any partner institution responsible for the joint-award of this degree.

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Naomi Louise Deacon

Date: Monday, 21 December 2015

ACKNOWLEDGEMENTS

Firstly, I would like to thank Professor Doug McEvoy for providing me the opportunity to undertake my studies in his laboratory. I am extremely grateful for his insight, advice and ability to see to the core of an issue so sharply. He has taught me to avoid getting lost in the intricacies as we researchers often can, and to think first and foremost of the clinical relevance. I am also forever grateful that he sent me to the U.S. specifically to meet experts in the field, providing me with an invaluable learning experience which helped solidify my hypotheses early in my PhD.

I am extremely grateful to A. Prof. Peter Catcheside for allowing me to develop and execute my own hypotheses, even though he may not have wholly agreed with them. Although not particularly fruitful, the ability to have such full control over my research, from conceptualisation to completion, has provided me with possibly the greatest lesson I have learnt so far as a researcher. In addition to his wealth of knowledge of respiratory physiology, I am extremely grateful to have been trained by someone so exceptionally technically skilled in computing, electronics and analyses. I only wish I had absorbed more.

I am grateful to all the Research and technical staff at Adelaide Institute for Sleep Health who assisted with data collection and sleep study scoring including; Jeremy Mercer, Amanda McKenna, Marni Ahmer, Hiro Tojo, Denzil Paul, Lee Harmer, and most of all to Daniel Stadler, who trained me in the laboratory and who sat through countless overnight studies with me.

I am also very appreciative to the subjects who participated in the studies and to The University of Adelaide and the School of Medical Science, Discipline of Physiology for financial and educational assistance.

I am also forever grateful to my Nanna and my mum, who assisted me in buying my unit so I could live comfortably and stress free while I studied. This was a huge investment in my future on both their parts, and one I will never forget and hope to one day be able to repay.

GLOSSARY OF ABBREVIATIONS

| | |
|-------------------------------------|--|
| AG | abdominal girth |
| AHI | apnea hypopnea index (events·hr ⁻¹ sleep) |
| AIH | acute intermittent hypoxia |
| PaCO₂ | arterial CO ₂ partial pressure |
| F_B | breathing frequency |
| CIH | chronic intermittent hypoxia |
| CPAP | continuous positive airway pressure |
| CG | controller gain |
| EMG_{dia} | diaphragm electromyogram |
| diaLTF | diaphragm long-term facilitation |
| ECG | electrocardiogram |
| EEG | electroencephalogram |
| EMG | electromyogram |
| P_{ET}CO₂ | end tidal partial pressure of CO ₂ |
| Pepi | epiglottic pressure |
| T_E | expiratory time |
| FRC | functional residual capacity |
| FEV1 | forced expiratory volume in the first second |
| FVC | forced vital capacity |
| EMG_{gg} | genioglossal electromyogram |
| ggLTF | genioglossal long-term facilitation |
| HH | hypercapnic hypoxia |
| HCVR | hypercapnic ventilatory response |
| hLTF | hypoglossal long-term facilitation |
| HVR | hypoxic ventilatory response |

| | |
|------------------------------------|---|
| T_I | inspiratory time |
| P_ICO₂ | inspiratory partial pressure of CO ₂ |
| IHH | intermittent hypercapnic hypoxia |
| IH | intermittent hypoxia |
| LTF | long-term facilitation |
| LG | loop gain |
| P_{MASK} | mask pressure |
| MAP | mean arterial pressure |
| V_I | minute ventilation |
| OSA | obstructive sleep apnoea |
| PIF | peak inspiratory flow |
| pLTF | phrenic long-term facilitation |
| PG | plant gain |
| PSG | polysomnography |
| PRBS | pseudorandom binary stimulation |
| PA | progressive augmentation |
| SaO₂ | saturation of oxygen |
| sLTF | sensory long-term facilitation |
| V_T | tidal volume |
| T_{TOT} | total breath time |
| u_ALTF | upper airway long-term facilitation |
| R_{UA} | upper airway resistance |
| vLTF | ventilatory long-term facilitation |
| ROS | reactive oxygen species |
| SAH | supine abdominal height |