THE EFFECTS OF HYPOXIA ON RESPIRATORY SENSATION AND REFLEXES IN HEALTHY SUBJECTS: Implications for Sleep and Respiratory Disease

By

Danny Joel Eckert

BAppSc (Human Movement, University of South Australia, 2000) &

BSc (Hons) (Physiology, University of Adelaide, 2002)

A thesis submitted for the degree of

DOCTOR OF PHILOSOPHY

June, 2006

Discipline of Physiology
School of Molecular &
Biomedical Science
University of Adelaide
South Australia, 5005.

Adelaide Institute for Sleep Health
Repatriation General Hospital
South Australia, 5041.

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ABSTRACT

Hypoxia is a common feature of many respiratory disorders including acute severe asthma, chronic obstructive pulmonary disease and pneumonia. Hypoxia also occurs during sleep-disordered breathing in conditions such as sleep hypoventilation syndrome and sleep apnea. In most respiratory diseases hypoxia is coupled with increased respiratory load. Compensatory protective mechanisms are activated to oppose these impediments to respiration. However, hypoxia is associated with impaired neurocognitive function and recent studies have demonstrated that hypoxia suppresses respiratory load perception in healthy individuals and asthma patients. These recent findings raise the possibility that a variety of protective physiological reflex responses to increased respiratory load may be impaired during periods of hypoxia. The effects of hypoxia on several of these protective responses and possible mechanisms of respiratory sensory depression by hypoxia are explored in the experiments outlined in this thesis.

In the first study, the respiratory related evoked potential (RREP) was used to investigate the mechanisms underlying hypoxia-induced suppression of respiratory load sensation in healthy individuals. As a positive control the effects of hypoxia on respiratory load perception to inspiratory resistive loads were also measured. The amplitude of the first and second positive peaks (P1 and P2) of the RREP were significantly reduced during hypoxia. P1 is thought to reflect the arrival of the ascending respiratory signals to the somatosensory area of the cortex. The perceived magnitude of externally applied inspiratory resistive loads was also

reduced during hypoxia. These data provide further support that hypoxia suppresses respiratory load perception and suggest that this is mediated, at least in part, by suppression of respiratory afferent information prior to its arrival at the cortex.

In the second study, the effects of acute sustained hypoxia on the cough reflex threshold and cough tachyphylaxis to inhaled capsaicin were explored in healthy individuals. Acute sustained hypoxia suppressed cough reflex sensitivity to inhaled capsaicin. This finding raises the possibility that the cough reflex, important for protecting the lungs from inhalation or aspiration of potentially injurious substances and for clearing excess secretions, may be impaired during acute exacerbations of hypoxic-respiratory disease.

In the third study, reflex responses of the genioglossus and scalene muscles to brief pulses of negative airway pressure were compared between hypoxia and normoxia during wake and sleep in healthy males in the supine position. Cortical RREPs to the same stimuli were also examined under these conditions. The genioglossus is the largest upper airway (UA) dilator muscle and can be reflexively augmented in response to negative UA pressure. A diminished response of this muscle during sleep has been postulated to be a contributing mechanism to obstructive sleep apnea (OSA) in individuals with an anatomically narrow UA. Cortical activation (i.e. arousal) to sudden airway narrowing in OSA is an important protective response to help restore ventilation during an obstructive event. In this study, genioglossus reflex responses to negative pressure pulse stimuli were

maintained during mild overnight hypoxia. Conversely, reflex inhibition of the scalene muscle to the same stimuli was prolonged during hypoxia. In addition, a previously undescribed morphology of the genioglossus negative pressure reflex consisting of activation followed by suppression was observed with greater suppression during sleep than wake. The amplitude of the P2 component of the RREP was also significantly reduced during hypoxia.

In summary, the potential mechanisms underlying hypoxia-induced suppression of respiratory load sensation and the effects of hypoxia on several protective respiratory responses have been investigated in healthy subjects. The potential implications of these findings for patients with hypoxic-respiratory disease are discussed.

PUBLICATIONS

The following are publications that have arisen from work conducted towards this thesis:

Journal Articles:

Eckert DJ, Catcheside PG, McEvoy RD. Blunted sensation of dyspnoea and near fatal asthma. *Eur Respir J* (Invited Editorial) 2004;24:197-9.

Eckert DJ, Catcheside PG, McDonald R, Adams AM, Webster KE, Hlavac MC, McEvoy RD. Sustained hypoxia depresses sensory processing of respiratory resistive loads. *Am J Respir Crit Care Med* 2005;172:1047-54.

Eckert DJ, Catcheside PG, Stadler D, McDonald R, Hlavac MC, McEvoy RD. Acute sustained hypoxia suppresses the cough reflex in healthy subjects. *Am J Respir Crit Care Med* 2006;173:506-11.

Published Abstracts:

Eckert DJ, McDonald R, Catcheside PG, Webster KE, Hlavac MH, McEvoy RD. Targeted hyperventilation for matching respiratory related evoked potential stimuli during hypoxia and normoxia. *Respirology* 2004;9:A67.

Eckert DJ, Catcheside PG, McDonald R, Adams AM, Webster KE, Hlavac MC, McEvoy RD. Evoked potential differences and blunted perception to respiratory stimuli with hypoxia*. Intern Med J* 2005;35(3):A21.

Eckert DJ, Catcheside PG, McDonald R, Adams AM, Hlavac MC, Webster KE, McEvoy RD. Decreased amplitude in early respiratory related evoked potential components and impaired perception of respiratory load with hypoxia. *Respirology* 2005;10:A18.

Eckert DJ, Catcheside PG, McDonald R, Adams AM, Hlavac MC, Webster KE, McEvoy RD. Amplitude Reductions in Early RREP Components and Blunted Perception of Respiratory Load with Hypoxia. *Proceedings of the American Thoracic Society* 2005;2:A6

Eckert DJ, Catcheside PG, Stadler DL, McDonald R, Hlavac MC, McEvoy RD. Acute Sustained Hypoxia Depresses Cough Reflex Sensitivity in Healthy Individuals. *Respirology* 2006;11:A17.

Published Abstracts (continued):

Eckert DJ, Catcheside PG, George K, Thompson K, Webster KE, McEvoy RD. Sustained Hypoxia Decreases Sensory Processing to Brief Pulses of Negative Upper Airway Pressure During NREM Sleep. *Sleep* 2006;29:A591.

Unpublished Conference Proceedings:

Eckert DJ, Catcheside PG, McDonald R, Adams AM, Hlavac MC, Webster KE, McEvoy RD. Amplitude reductions in early evoked potential components and impaired perception of respiratory load with hypoxia. *International Union of Physiological Sciences Congress. Dyspnea: Mechanisms and Management two-day satellite meeting.* San Diego, United States of America. 2005;A18.

Eckert DJ, Catcheside PG, George K, Thompson K, McEvoy RD. Evidence for Reflex Inhibition of the Genioglossus Muscle to Brief Pulses of Negative Upper Airway Pressure during Wake and Sleep. *Australian Society for Medical Research Annual Scientific Meeting*, *South Australian Branch*, Adelaide, Australia. 2006.

This citation not included in the original print copy of thesis

Published Abstract:

Eckert, D.J., McEvoy, R.D., George, K.E., Thomson, K.J. and Catcheside, P.G. Genioglossus reflex inhibition to upper-airway negative-pressure stimuli during wakefulness and sleep in healthy males.
J Physiol. 2007 Jun 15;581(Pt 3):1193-205

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 made available in all forms of media, now or hereafter known.

Danny Eckert

Date: Wednesday, 16 June 2006

ACKNOWLEDGEMENTS

Firstly, I would like to thank Professor Doug McEvoy for providing me the opportunity to carry out this Ph.D. in his laboratory. I am exceptionally grateful for his incredible insight, commitment to research and for his continual support, encouragement and mentorship.

I would also like to sincerely thank Dr Peter Catcheside for his invaluable scientific input and assistance with study designs, the collection, analysis and interpretation of the data, for proof reading and most importantly for his friendship, careful explanations and support.

I am very appreciative to all the Adelaide Institute for Sleep Health Research Assistants and co-workers that have assisted with the data collection, provided valuable technical assistance and camaraderie during these studies including: Rachel McDonald, Amanda Adams, Daniel Stadler, Michael Hlavac, Kate George and Kieron Thompson.

I am very grateful to Dr Kate Webster for her expertise and collaboration in establishing the techniques used to measure and interpret respiratory related evoked potential recordings for studies 1 and 3.

Dr Stuart Mazzone provided valuable insight and advice into the sensory physiology of the cough reflex for experiment 2.

I am very grateful to all of the Adelaide Institute for Sleep Health staff at the Repatriation General Hospital, in particular Samantha Windler for staging the sleep

studies for experiment 3 and Jeremy Mercer and Mark Jurisevic for their assistance with laboratory issues.

Professor Tim Miles provided valuable assistance and advice regarding the EMG recordings in experiment 3.

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

Proof reading of this thesis was provided by Ruth Eckert and Murray Bramwell.

Finally, a big thank you to my brothers, Jamie, Cary and Tom, my partner Hoa-han and my dad Paul for their great support and understanding. Similarly, my mother Polly who despite losing her battle with cancer in 2002, has been a continual inspiration throughout my Ph.D. studies and life.

GLOSSARY OF ABBREVIATIONS

ARDS	Acute respiratory distress syndrome
BMI	Body mass index ($kg \cdot m^{-2}$)
CNS	Central nervous system
COPD	Chronic obstructive pulmonary disease
CSA	Central sleep apnea
ECG	Electrocardiogram
EEG	Electroencephalogram
EMG_{DI}	Diaphragm electromyogram
EMG_{GG}	Genioglossus electromyogram
EMG_{IC}	Parasternal intercostal electromyogram
EMG_{SC}	Scalene electromyogram
EOG	Electrooculogram
ERP	Event related potential
GABA	γ-aminobutyric acid
IC	Inspiratory capacity (l)
F_B	Breathing frequency ($breath \cdot min^{-1}$)
F_ICO_2	Fraction of inspired carbon dioxide concentration (%)
F_IO_2	Fraction of inspired oxygen concentration (%)
FEV_1	Forced expiratory volume in 1 second (% predicted)
FRC	Functional residual capacity (l)
FVC	Forced vital capacity (% predicted)
LTF	Long-term facilitation
NREM	Non rapid eye movement sleep
N1 & N2	First and second negative peaks of the ERP respectively
Nf	Negative frontal peak of the RREP
NTS	Nucleus tractus solitarius

OSA	Obstructive sleep apnea
P1,P2 & P3	First, second and third positive peaks of the ERP respectively
P_{CHO}	Choanal pressure (cmH_2O)
$PaCO_2$	Partial pressure of arterial carbon dioxide (mmHg)
PaO_2	Partial pressure of arterial oxygen (mmHg)
P_{EPI}	Epiglottic pressure (cmH_2O)
$PETCO_2$	End-tidal partial pressure of carbon dioxide (mmHg)
PIF	Peak inspiratory flow ($l \cdot min^{-1}$)
PIP	Peak inspiratory pressure (cmH_2O)
P_{MASK}	Mask pressure (cmH_2O)
RDI	Respiratory disturbance index (events$\cdot hr^{-1}$ sleep)
REM	Rapid eye movement sleep
RREP	Respiratory related evoked potential
R	Resistance ($cmH_2O \cdot l^{-1} \cdot sec$)
RV	Residual volume (l)
SaO_2	Arterial oxygen saturation (%)
SEM	Standard error of the mean
SOL	Sleep onset latency (minutes)
TLC	Total lung capacity (l)
TST	Total sleep time (minutes)
UA	Upper Airway
VC	Vital capacity (l)
V_{TI}	Inspiratory tidal volume (l)
$\dot{V}_I$	Inspiratory minute ventilation ($l \cdot min^{-1}$)
ψ	Perceived magnitude of externally applied resistive loads