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Mechanisms underlying the supine related phenotype of obstructive sleep apnoea

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GENERAL DECLARATION

Monash University, Monash Research Graduate School
Declaration for thesis based or partially based on conjointly published or unpublished work

In accordance with Monash University Doctorate Regulation 17.2 Doctor of Philosophy and Research Master's regulations the following declarations are made:

I hereby declare that this thesis contains no material which has been accepted for the award of any other degree or diploma at any university or equivalent institution and that, to the best of my knowledge and belief, this thesis contains no material previously published or written by another person, except where due reference is made in the text of the thesis.

This thesis includes 3 original papers published in peer-reviewed journals and 1 paper that has been accepted for publication in a peer-reviewed journals. The core theme of the thesis is the pathogenesis of supine related obstructive sleep apnoea. The ideas, development and writing up of all the papers in the thesis were the principal responsibility of myself, the candidate, working within the Ritchie Centre, Monash Institute of Medical Research – Prince Henry's Institute, under the supervision of Dr Philip Berger and Dr Garun Hamilton.

The inclusion of co-authors reflects the fact that the work came from active collaboration between researchers and acknowledges input into team-based research.

In the case of chapters 1, 2, 3 and 4 my contribution to the work involved the following:

Thesis chapter	Publication title	Publication Status	Nature and extent of candidate's contribution
1	Supine position	Published	For this chapter I performed the literature

	related obstructive sleep apnea in adults: pathogenesis and treatment		review, wrote the manuscript and submitted for publication. The extent of my contribution was 90%.
2	Night-to-Night Repeatability of Supine-related Obstructive Sleep Apnea	Published	For this chapter I was responsible for hypothesis generation, data analysis, interpretation of results and manuscript preparation. The extent of my contribution was 80%.
3	Evaluation of the role of lung volume and airway size and shape in supine predominant obstructive sleep apnoea patients	Published	For this chapter I was responsible for hypothesis generation, data collection, data analysis, interpretation of results and manuscript preparation. The extent of my contribution was 80%.
4	The effect of body position on four physiological traits causing obstructive sleep apnea	Accepted for Publication	For this chapter I was responsible for hypothesis generation, data collection, data analysis, interpretation of results and manuscript preparation. The extent of my contribution was 80%.

I have renumbered sections of submitted papers in order to generate a consistent presentation within the thesis. Published papers are presented in their published format with an additional page number consistent with the thesis numbering.

Signed: ……

Date: ……

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SUMMARY

Obstructive sleep apnoea (OSA) is a common medical disorder that affects up to 24% of men and 9% of women (Young, Palta et al. 1993). Between 50 - 60% of patients with OSA who present to sleep clinics for overnight polysomnography experience twice as many respiratory events in supine sleep compared to lateral sleep (Pevernagie and Shepard 1992, Oksenberg, Silverberg et al. 1997, Richard, Kox et al. 2006, Joosten, Hamza et al. 2012), while approximately 25-30% of the same population experience respiratory events exclusively in the supine position (Mador, Kufel et al. 2005, Gillman, Roebuck et al. 2012, Joosten, Hamza et al. 2012). The cause of the observed preponderance of respiratory events in the supine sleeping position remains elusive. Certainly several studies have demonstrated a less collapsible airway in the lateral compared to the supine position in male OSA patients (Boudewyns, Punjabi et al. 2000, Penzel, Moller et al. 2001, Ong, Touyz et al. 2011); that is, a more negative pressure needs to be applied to the airway lumen to cause the airway to collapse when lateral – with the collapsing pressure referred to as the pharyngeal critical closing pressure (Pcrit).

However, the reason for the fall in Pcrit is unclear with a postulated role for upper airway size and shape changes with body position. Recent advances in the understanding of OSA pathogenesis have revealed that non-anatomical factors such as ventilatory control instability and arousal threshold play an important role in airway obstruction in a significant proportion of OSA patients (Eckert, White et al. 2013). Importantly, there are no studies that examine the role of body position on ventilatory control instability, arousal threshold or active Pcrit (the pharyngeal critical closing pressure when airway muscles are activated) and there are no studies that examine upper airway size and shape, and lung volume in supine related OSA patients compared to matched controls.

For patients with supine related OSA, the use of positional therapy can be an effective treatment. A number of positional modification devices have been demonstrated to be efficacious in preventing supine sleep and thus reducing the overall apnoea and hypopnoea index (AHI) (Jokic, Klimaszewski et al. 1999, Loord and Hultcrantz 2007, Permut, Diaz-Abad et al. 2010, Bignold, Mercer et al. 2011). Indeed, the use of

positional modification devices for supine related OSA constitutes the most common form of individualised treatment for OSA sufferers. Despite the common occurrence of supine related OSA, and a seemingly cheap and readily available treatment, there remain a number of important unanswered questions that this thesis addresses.

Selecting patients for the use of positional modification devices

The use of positional modification devices in the treatment of supine related OSA relies on three assumptions. Firstly, that the supine AHI is high from night-to-night (i.e. that there is a problem that warrants intervention), secondly, and partly related, that supine sleep time remains sufficient from night-to-night to warrant treatment, and thirdly that the lateral AHI remains low from night-to-night (i.e. that the intervention will be effective ongoing). Because these assumptions have never been tested, and because there is a recognised variability in the AHI from night-to-night (Le Bon, Hoffmann et al. 2000, Bittencourt, Suchecki et al. 2001) coupled with poor treatment compliance with traditional discomfort based treatments the take-up of positional modification by clinicians is poor. Chapter 2 delivers important information that will help guide clinicians' use of positional modification devices. We demonstrate for the first time that male subjects with four times as many respiratory events in supine sleep compared to lateral sleep have a repeatable phenotype of supine related OSA. In addition, we show that a low lateral AHI is repeatable from night-to-night, thus giving clinicians confidence when using positional modification in selected patients.

Upper airway shape and lung volume

The observed fall in passive Pcrit (the Pcrit when upper airway muscles are relaxed) when subjects move from the supine to lateral position is frequently attributed to less favourable airway shape and size in the supine position. However, many studies show no significant change in upper airway cross-sectional area when subjects move from supine to lateral (Jan, Marshall et al. 1994, Martin, Marshall et al. 1995, Pevernagie, Stanson et al. 1995, Walsh, Leigh et al. 2008), whilst there are conflicting results on the effect of body position on airway shape. Importantly, no studies compare patients with supine related OSA to controls matched for key potential confounders such as age, gender, degree of obesity and body mass distribution. Another potential mechanism by which

passive Pcrit may be reduced in lateral sleep is a change in lung volume. Previous studies have demonstrated that a reduced lung volume raises the Pcrit (Stanchina, Malhotra et al. 2003, Jordan, White et al. 2009) and that body position can affect lung volume with a reduced lung volume in the supine position in normal subjects. Chapter 3 clarifies some of the confusion present in the upper airway imaging literature. We have demonstrated that there are no significant differences between supine OSA patients and matched controls with regard to airway cross sectional area and shape when moving from supine to lateral position. However, there was a significant improvement in lung volume in the lateral position. This suggests that lung volume is likely to, at least in part, explain the consistently observed fall in passive Pcrit in the lateral position in OSA patients.

The effect of body position on active Pcrit, ventilatory control stability and arousal threshold

Recent advances in the understanding of OSA pathogenesis have highlighted a number of important contributors including: the ability of the upper airway muscles to stiffen and dilate the airway (McGinley, Schwartz et al. 2008, Edwards and White 2011), ventilatory control instability (i.e. a high loop gain) (Wellman, Jordan et al. 2004) and arousal threshold (Younes 2004). Despite the clear contribution of these factors to OSA, how they are affected by body position is not known. By applying a recently developed method for measuring these parameters in a non-invasive manner (Wellman, Edwards et al. 2013) we have been able to demonstrate that lateral positioning improves the ability of the airway to stiffen and dilate with no significant effect on arousal threshold or ventilatory control instability. The important findings in Chapter 4 highlight the enticing prospects for combination treatments for OSA that could include positional modification to improve passive Pcrit and the ability of the upper airway to stiffen and dilate, together with treatments that improve ventilatory control instability and arousal threshold, such as acetazolamide (Edwards, Sands et al. 2012) and non-muscle relaxant sedatives (Eckert, Owens et al. 2011).

Conclusions and future directions

The work in this doctoral thesis demonstrates that there is a sub-population of OSA patients with a repeatable form of supine related OSA and a reliably low lateral AHI who

are likely to benefit from positional modification. We have shed light on the mechanism by which lateral positioning reduces Pcrit by showing that supine related OSA patients have an improvement in lung volume in the lateral position compared to matched controls, without any significant differences in upper airway size and shape. By applying a recently developed method for measuring the traits contributing to OSA we have demonstrated important improvements in the passive and active airway anatomy in the lateral position, with no significant improvement in ventilatory control instability or arousal threshold. This raises the possibility of future treatments that combine positional treatment with treatments known to reduce loop gain and raise the arousal threshold.

LIST OF ABBREVIATIONS

AHI	Apnoea and hypopnoea index
AASM	American academy of sleep medicine
ASA	Australasian sleep association
B.C.	Before Christ
BMI	Body mass index
CO_2	Carbon dioxide
CPAP	Continuous positive airway pressure
CSA	Cross-sectional area
CSF	Cerebrospinal fluid
EEG	Electroencephalogram
EELV	End-expiratory lung volume
EMG	Electromyogram
ERV	Expiratory reserve volume
FRC	Functional residual capacity
GABA	Gamma-aminobutyric acid
H+	Hydrogen ions
NREM	Non-rapid eye movement
OSA	Obstructive sleep apnoea
O_2	Oxygen
Pa_{CO_2}	Arterial pressure of carbon dioxide
Pa_{O_2}	Arterial pressure of oxygen
Pcrit	Pharyngeal critical closing pressure
REM	Rapid eye movement
RV	Residual volume
siOSA	Supine isolated obstructive sleep apnoea
spOSA	Supine predominant obstructive sleep apnoea
TLC	Total lung capacity
TV	Tidal volume
VC	Vital capacity

ABSTRACTS PRESENTED AT NATIONAL CONFERENCES

Joosten SA, Sands SA, Turton A, Ong CW, Skuza EM, Berger PJ, Hamilton GS. Physiological phenotypes of OSA. Upper Airway Symposium, Victor Harbour, February 8-10, 2012.

Joosten SA, Sands SA, Turton A, Ong CW, Skuza EM, Berger PJ, Hamilton GS. Positional changes in lung volume and airway shape in supine dependent versus rapid eye movement obstructive sleep apnoea. 24th Annual Scientific Meeting of the Australasian Sleep Association. Darwin, October 10-13, 2012.

Joosten SA, Sands SA, Turton A, Ong CW, Skuza EM, Berger PJ, Hamilton GS. Positional changes in lung volume and airway shape in supine dependent versus rapid eye movement obstructive sleep apnoea. Upper Airway Symposium, Margaret River, February 20-22, 2013.

Joosten SA, Hamza K, Churchward TJ, O'Donoghue FJ, Barnes M, Rochford PD, Berger PJ, Hamilton GS. Repeatability of supine related OSA phenotypes. 25th Annual Scientific Meeting of the Australasian Sleep Association. Brisbane, October 17-19, 2013.

Joosten SA, Edwards BA, Turton A, Skuza EM, Berger PJ, Hamilton GS. Physiological trait changes in obstructive sleep apnoea patients in supine and lateral sleep. 25th Annual Scientific Meeting of the Australasian Sleep Association. Brisbane, October 17-19, 2013.

Joosten SA, Edwards BA, Turton A, Skuza EM, Berger PJ, Hamilton GS. Physiologic phenotypic traits of OSA in the supine compared to lateral positions. Upper Airway Symposium, Mornington Peninsula, February 19-21, 2014.

Joosten SA, Edwards BA, Wellman A, Turton A, Samarasinghe T, Skuza EM, Berger PJ, Hamilton GS. Airway physiology changes moving from lateral to supine sleeping position in OSA patients. 25th Annual Scientific Meeting of the Australasian Sleep Association. Perth, October 9-11, 2014.

ABSTRACTS PRESENTED AT INTERNATIONAL CONFERENCES

Joosten SA, Sands SA, Skuza EM, Ong CW, Lau KP, Berger PJ, Hamilton GS. Positional Changes in Lung Volume and Airway Shape in Supine Based versus Rapid Eye Movement Based Obstructive Sleep Apnoea. American Thoracic Society Annual Scientific Meeting. Philadelphia, USA, May 17-22, 2013.

Joosten SA, Edwards BA, Wellman A, Turton A, Samarasinghe T, Skuza EM, Berger PJ, Hamilton GS. Obstructive sleep apnoea phenotypic trait changes from supine to lateral position. American Thoracic Society Annual Scientific Meeting. San Diego, USA, May 16-21, 2014.

PUBLISHED PAPERS

The following papers were accepted for publication during PhD candidature and form the basis of this thesis:

Joosten SA, O'Driscoll DM, Berger PJ, Hamilton GS (2014). Supine position related obstructive sleep apnea in adults: pathogenesis and treatment. *Sleep Medicine Reviews*. **18**(1), 7-17.

Joosten SA, O'Donoghue FJ, Rochford PD, Barnes M, Hamza K, Churchward TJ, Berger PJ, Hamilton GS (2014). Night-to-night repeatability of supine-related obstructive sleep apnea. *Annals of the American Thoracic Society*. **11**(5), 761-769.

Joosten SA, Sands SA, Edwards BA, Hamza K, Turton A, Lau KK, Crossett M, Berger PJ, Hamilton GS (2015). Evaluation of the role of lung volume and airway size and shape in supine predominant obstructive sleep apnoea patients. Respirology. Accepted for publication 16/2/2015.

Joosten SA, Edwards BA, Wellman A, Turton A, Skuza EJ, Berger PJ, Hamilton GS (2015). The effect of body position on physiological factors that contribute to obstructive sleep apnea. *Sleep*. Accepted for publication 1/2/2015.

The following papers were accepted for publication during PhD candidature but are not presented in this thesis:

Joosten SA, Hamza K, Sands S, Turton A, Berger P, Hamilton G (2012). Phenotypes of patients with mild to moderate obstructive sleep apnoea as confirmed by cluster analysis. *Respirology*. **17**(1), 99-107.

Joosten SA, MacDonald M, Lau KK, Bardin P, Hamilton G (2012). Excessive dynamic airway collapse co-morbid with COPD diagnosed using 320-slice dynamic CT scanning technology. *Thorax*. **67**(1), 95-96.

Joosten SA, Hannan L, Heroit G, Boerner E, Irving L (2012). Penicillium marneffei presenting as an obstructing endobronchial lesion in an immunocompetent host. *Eur Respir J*. **39**(6), 1540-1543.

Jennings BR, Millward MJ, Amanuel B, Mulrennan S, Joosten SA, Phillips MJ (2012). Role of endobronchial ultrasound in diagnosis and molecular assessment of metastatic melanoma. *Respirology.* **17**(6), 991-996.

Pirakalathanan J, Lau KK, Joosten SA (2013). Chest radiographic appearances in adult inpatients admitted with swine flu infection: local experience in Melbourne. *J Med Imaging Radiat Oncol.* **57**(1), 50-56.

Wallbridge PD, Hannan LM, Joosten SA, Irving LB, Steinfort DP (2013). Clinical utility of sequential venous blood gas measurement in the assessment of ventilatory status during physiological stress. *Intern Med J.* **43**(10), 1075-1080.

Lafontaine N, Joosten SA, Steinfort D, Irving L, Hew M (2014). Differential implementation of special society pleural guidelines according to craft-group: impetus toward cross-specialty guidelines? *Clin Med.* **14**(4), 361-366.

CHAPTER 1

REVIEW OF THE LITERATURE

1

Review of the Literature

Parts of this chapter have been published in *Sleep Medicine Reviews* and the published version can be found in Appendix 1 (page 168).

Respiration, the process by which nutrients are converted into energy, usually through the consumption of oxygen (O_2) and production of carbon dioxide (CO_2), maintains cellular function and life and is critically dependent upon an adequate and continuous level of breathing to replenish O_2 and to remove metabolic CO_2. Breathing is a repetitive process with both volitional and automated control pathways, as well as complex mechanical and chemical feedback that ensure ventilation and gas exchange occur efficiently and at a level to meet the metabolic demands of the organism. During sleep, the volitional control of respiration is removed and breathing is controlled in an automated fashion. Additionally, the sleep state affects a number of important processes critical for the maintenance of ventilation, especially airway patency. To our scientific forebears, who believed that sleep was an "intermediate state between wakefulness and death" (Macnish 1834), the idea of automated breathing at sleep onset would have had teleological appeal. However, just as we have come to understand that the sleep state is an active and dynamic process, we now also have begun to appreciate the complex pathways involved in maintaining ventilation during sleep. Over the past three decades many gains have been made in understanding how breathing and sleep interact. One of the catalysts behind these discoveries has been the need to understand apnoea, or breathing cessation, because apnoea during sleep appears to play a causative role in long-term diseases that damage the health of millions of people and consume billions of health dollars worldwide.

The most common form of sleep apnoea is obstructive sleep apnoea (OSA). In this condition, breathing during sleep is temporarily reduced (or halted) by a partial (or complete) obstruction of the upper airway. OSA has long been recognised as a disease entity, with the most famous of the early descriptions being that of Joe "the fat boy" by Charles Dickens in his novel The Posthumous Papers of the Pickwick Club (Dickens, Seymour et al. 1837). In the more recent past the effect of body position on OSA has been noted by both researchers (Cartwright 1984) and relatives of patients (Anon. 1984) with the condition. The following sections review the current understanding of the mechanisms that underlie the generation of upper airway obstruction during sleep and how these mechanisms are altered by body position.

1.1 THE EFFECT OF SLEEP ON RESPIRATION

The sleep state has a number of important effects on the process of respiration. In neuroanatomical terms, sleep is initiated when sleep promoting ventro-lateral preoptic neurons become active and inhibit a number of wake promoting neurons such as the pedunculopontine and laterodorsal tegmental nuclei, the locus coeruleus, ventral periaqueductal grey and the tuberomamillary nucleus (Fuller, Gooley et al. 2006). Because the wake promoting nuclei have an extensive and complex network of projections to respiratory related neurons, a number of feed-forward respiratory drives are lost at sleep onset and remain absent throughout consolidated sleep. In particular, changes in the control of breathing, lung volume and upper airway control are pertinent to maintaining adequate ventilation during sleep.

1.1.1 Changes to the control of breathing during sleep

The respiratory control system is composed of a number of feedback loops that integrate information from a number of sources. Chemoreceptors feedback to ensure maintenance of blood gas tensions and mechanoreceptors feedback to help manage energy expenditure. The respiratory pacemaker, which provides the signal for the rhythm of breathing, resides in the medulla and is composed of the pre-Botzinger complex and the retrotrapezoid nucleus/parafacial respiratory group (Feldman and Del Negro 2006). The pacemaker fires rhythmically to maintain respiration and can do so in experimental conditions even in the absence of sensorial input. During sleep the respiratory pacemaker receives inputs from a number of sources that modulate its output including chemical and mechanical signals.

Chemical signalling to the respiratory pacemaker

Chemical input to the respiratory pacemaker occurs both centrally and peripherally. The regulation of respiration in response to changes in CO_2 is primarily regulated through central chemoreceptors (although peripheral chemoreceptors also sense CO_2). Animal experiments had previously led authors to conclude that the central chemoreceptors were located in the ventro-lateral medulla (Mitchell, Loeschcke et al. 1963, Fukuda and Loeschcke 1977) although more recent opinion has chemoreception occurring at multiple

sites within the brainstem (Ballantyne and Scheid 2000, Putnam, Filosa et al. 2004). The putative mechanism of this signal was thought to arise from a decrease in pH (rise in hydrogen ions, H+) following diffusion of CO_2 across the blood-brain-barrier into the cerebrospinal fluid (CSF). However, the neuronal response to increased CSF CO_2 and H+ more probably involves multiple cellular signals with a variety of ion channels involved that result in increased firing of chemosensitive neurons (Putnam, Filosa et al. 2004).

The regulation of respiration in response to changes in O_2 occurs primarily through peripheral chemoreceptors found in the carotid and aortic bodies. Although both the aortic and carotid bodies are excited by a decline in arterial O_2, an increase in arterial CO_2 and an increase in H+ (Lahiri and Forster 2003), the carotid bodies have the dominant role in respiratory control (Altose and Kawakami 1999).

The ventilatory response to hypercapnia is blunted during sleep. Several studies have demonstrated that the slope of the ventilation–CO_2 response line falls in non-rapid eye movement (NREM) sleep versus wakefulness (Douglas, White et al. 1982, Berthon-Jones and Sullivan 1984, Gleeson, Zwillich et al. 1989) and that it is lowest during rapid eye movement (REM) sleep (Douglas, White et al. 1982, Berthon-Jones and Sullivan 1984). The end result is that the partial pressure of CO_2 in the arterial blood normally rises 2-3 torr during NREM sleep and a further 2-3 torr in REM sleep. The fall in central chemosensitivity to CO_2 at sleep onset is likely the result of activation of the sleep promoting ventro-lateral preoptic neurons which promote release of gamma-Aminobutyric acid (GABA) (Gallopin, Fort et al. 2000) and consequent inhibition of the respiratory centres. In addition to the GABAergic inhibition of respiratory related neurons, the loss of excitation to these areas from the reticular activating system likely contributes to the decrease in the sensitivity of central chemoreceptors to CO_2. With the relatively recent discovery of multiple chemosensitive sites in the brainstem, the effect of descending sleep-promoting GABAergic inhibitory pathways on these multiple sites has made understanding the effect of sleep on control of breathing more complicated. Indeed, it appears that the separate chemosensitive centres may vary in their response to CO_2

depending on the state of consciousness, with some sites contributing more during wakefulness and others during NREM sleep (Nattie 2001).

The ventilatory response to hypoxia also falls during NREM sleep compared to wakefulness, with the response further attenuated during REM sleep (Berthon-Jones and Sullivan 1982, Douglas, White et al. 1982). The mechanism by which peripheral chemosensitive signals are attenuated by sleep is not completely understood. One of the main reasons why this process has proved difficult to elucidate is that peripheral signals are integrated with central respiratory chemoreceptors such as the retrotrapezoid nucleus, medullary raphe, nucleus of the solitary tract and locus coeruleus. Animal models demonstrate that carotid body afferents synapse with nuclei in the nucleus of the solitary tract (Donoghue, Felder et al. 1985) and retrotrapezoid nucleus (Takakura, Moreira et al. 2006), which renders these signals susceptible to descending influences of the sleep promoting GABAergic ventro-lateral preoptic neurons.

Mechanical signals to respiratory centres

Information about the mechanical load of breathing is sensed by mechanoreceptors located throughout the respiratory tract (Widdicombe 2001). Because the larynx is the most compliant region of the upper airway, pressure receptors in the larynx are ideally placed to detect collapsing forces and initiate reflex mechanisms to maintain airway patency. Laryngeal afferent fibres travel in the recurrent laryngeal nerve (for areas below the glottis) and the superior laryngeal nerve (for areas above the glottis) (Sant'Ambrogio and Mathew 1988). The central projections of these nerves synapse within the nucleus of the solitary tract (Sant'Ambrogio, Tsubone et al. 1995) and there is a prominent respiratory modulation of the afferent firing in the superior laryngeal nerve.

Much of the information we have regarding the role of laryngeal mechanoreceptor afferents and reflexes in the homeostasis of breathing comes from the study of upper airway muscle responses to inspiratory load challenges. In particular, the response of genioglossus to negative pressure stimuli has been extensively investigated. Genioglossus is a large muscle in the upper airway whose main action is to protrude the tongue. It has multiple functions including roles in speech, swallowing and maintenance

of airway patency. The majority of studies have demonstrated that genioglossus exhibits an excitatory response to a negative pressure stimulus (Malhotra, Pillar et al. 2000, Fogel, Malhotra et al. 2001) and that the reflex is attenuated during NREM (Wheatley, Mezzanotte et al. 1993, Horner, Innes et al. 1994) and REM sleep (Shea, Edwards et al. 1999). However, it has become apparent that the genioglossus may play a more complex role than simply increasing its activity in response to negative pressure with the reflex waning during sleep. Eckert et al. discovered an initial excitatory response in genioglossus to negative pressure stimulus followed by an inhibitory response with the reflex action not diminished by NREM sleep (Eckert, McEvoy et al. 2007). The authors postulate that the negative pressure reflex may be threshold dependent, with an excitatory response of genioglossus to small negative pressure changes (such as may occur during tidal breathing) and in response to larger negative pressure stimuli there is an inhibition of genioglossus. The reflex inhibition reported in genioglossus is not observed in tonic muscles of the upper airway (muscles in which discharge frequency is not modulated by respiration) such as tensor palatini (Eckert, Saboisky et al. 2010). Tensor palatini is a small muscle located behind the soft palate whose main role is to stiffen the soft palate and facilitate its elevation by levator palatini. Interestingly, the lack of diminution in genioglossus activity during NREM sleep observed by Eckert et al. may have a postural explanation (Malhotra, Trinder et al. 2004); this will be discussed in detail later.

Reflex inhibition to increasing load has been observed in a number of other phasic respiratory related muscles, in particular respiratory pump muscles (e.g. diaphragm and intercostal muscles). Probably the best studied of these reflexes is the Hering-Breuer reflex. The reflex describes a response to lung inflation with afferent fibres arising from pulmonary parenchymal stretch receptors and travelling with vagal afferents. The efferent arm of the reflex response is inhibition of pulmonary pump muscles such as the diaphragm (Larrabee and Knowlton 1946, Widdicombe 1954). The reflex remains intact during sleep (Hamilton, Winning et al. 1988). In addition to the intra-pulmonary stretch receptors involved in the Hering-Breuer reflex, inspiratory muscle afferents are also involved in reflex inhibition to inspiratory load. In lung transplant patients (in whom pulmonary vagal afferents had been cut during transplantation), Butler et al. demonstrated reflex inhibition of parasternal intercostal and scalene muscles to brief inspiratory

occlusion (Butler, McKenzie et al. 1997). This finding implies the presence of a spinal reflex with afferents arising from the respiratory muscles themselves. Importantly, the authors demonstrated a central latency of approximately 15ms, which is compatible with a supraspinal contribution to the inhibition. This raises the possibility that reflex inhibition of respiratory pump muscles to inspiratory load may be centrally influenced/co-ordinated for the purpose of avoiding aspiration or economising inspiratory effort in the face of a collapsing upper airway (e.g. avoidance of so-called negative effort dependence – where increasing inspiratory effort from pump muscles induces greater negative intraluminal upper airway pressure because of dynamic airway narrowing).

1.1.2 The effect of sleep on lung volume and minute ventilation

Lung volume is an important determinant of respiratory homeostasis. The capacity for gas exchange is influenced by the tidal volume and frequency of breathing. Additionally, lung volume influences upper airway performance through the degree of tracheal traction and unloading of upper airway tissue pressures.

Minute ventilation (the volume of inhaled gas per minute of breathing) is reduced during sleep (Douglas, White et al. 1982, Skatrud and Dempsey 1985, Stradling, Chadwick et al. 1985) with a subsequent elevation of alveolar CO_2, arterial CO_2 and fall in arterial blood pH (Robin, Whaley et al. 1958, Birchfield, Sieker et al. 1959). The level of ventilation falls as patients move from awake to NREM sleep and decreases further in REM sleep (Douglas, White et al. 1982, Stradling, Chadwick et al. 1985). The fall in minute ventilation in these experiments appears explained by an observed decrease in tidal volume with the respiratory rate seen to increase (Douglas, White et al. 1982) or remain largely unchanged by the sleep state (Stradling, Chadwick et al. 1985). Functional residual capacity (FRC) also declines in sleep, with gas dilution estimating 3.14L awake, 2.95L in stage 2 NREM sleep and 2.86L in slow wave sleep and REM sleep (Hudgel and Devadatta 1984); plethysmography shows an approximate 0.5L fall from awake to consolidated sleep (Ballard, Irvin et al. 1990).

The fall in lung volume and minute ventilation during sleep is likely due to a combination of increasing upper airway resistance, as the activity of airway dilator muscles falls at sleep onset, as well as the response of respiratory pump muscles to the increasing respiratory load. The removal of the awake stimulus and reduced chemosensitivity to CO_2 have important feed-forward effects on upper airway and respiratory pump muscles. In normal subjects at sleep onset there is an initial drop in genioglossus, tensor palatini, diaphragmatic and intercostal muscle electromyographic (EMG) activity (Worsnop, Kay et al. 1998, Stadler, McEvoy et al. 2010) and a fall in end expiratory lung volume (EELV) (Stadler, McEvoy et al. 2010). As sleep progresses there is some recovery in the activity of phasic upper airway dilators, but not tonic dilators such as tensor palatini (Tangel, Mezzanotte et al. 1992) so that upper airway resistance remains elevated during consolidated sleep. The activity of respiratory pump muscles also recovers as sleep progresses, most probably in response to the increased resistive load, but also to rising CO_2 (Henke, Dempsey et al. 1991), with the subsequent reduction in minute ventilation and elevation in CO_2 a product of both the incomplete compensation of the pump muscles to upper airway resistance and the permissive effect of reduced central chemosensitivity to CO_2.

An inextricable link between upper and lower airway function is highlighted by the fact that the fall in lung volume during sleep, which is probably at least in part due to increasing upper airway resistance, also increases upper airway collapsibility during sleep. Thus reducing EELV by approximately 0.5L during consolidated NREM sleep leads to increased collapsibility of the upper airway in normal subjects (Stanchina, Malhotra et al. 2003). Animal models suggest that the effect is probably mediated by changes in caudal tracheal traction and reduction of upper airway tissue pressures (Van de Graaff 1988, Rowley, Permutt et al. 1996, Kairaitis, Byth et al. 2007). Conversely, increasing EELV by approximately 0.5L decreases upper airway collapsibility (Owens, Malhotra et al. 2010). As discussed later, the link between reductions in lung volume and upper airway collapsibility is important when considering the role of obesity in OSA.

1.1.3 The effect of sleep on upper airway function

The upper airway lies between the airway opening at the nares and mouth and the trachea. It serves a number of functions including speech, co-ordination of swallowing and the warming and moistening of inhaled air. During sleep the primary function of the upper airway is to conduct inspired air to the lungs and expired gases out to the atmosphere to eliminate CO_2. Whilst the nose, larynx and trachea are supported by cartilage, parts of the pharynx are highly deformable soft tissue structures that rely on muscle activity to maintain patency.

The pharynx is divided into three sections; the nasopharynx, which runs from the nasal turbinates to the hard palate; the oropharynx, which runs from the hard palate to the epiglottis and is subdivided into the retropalatal oropharynx (lying posterior to the soft palate, also referred to as the velopharynx) and the retroglossal oropharynx (lying posterior to the tongue, and which some authors confusingly refer to also as the oropharynx); and the hypopharynx, which runs from the base of the epiglottis to the larynx (see Figure 1.1) (White and Younes 2012). The cross-sectional shape of the airway varies along its length, with the pharyngeal airway typically narrowest at the level of the retropalatal oropharynx (Isono, Remmers et al. 1997). Although the section of the airway with the highest resistance is the nose, this section of the airway is supported primarily by cartilaginous structures and it is therefore largely non-collapsible.

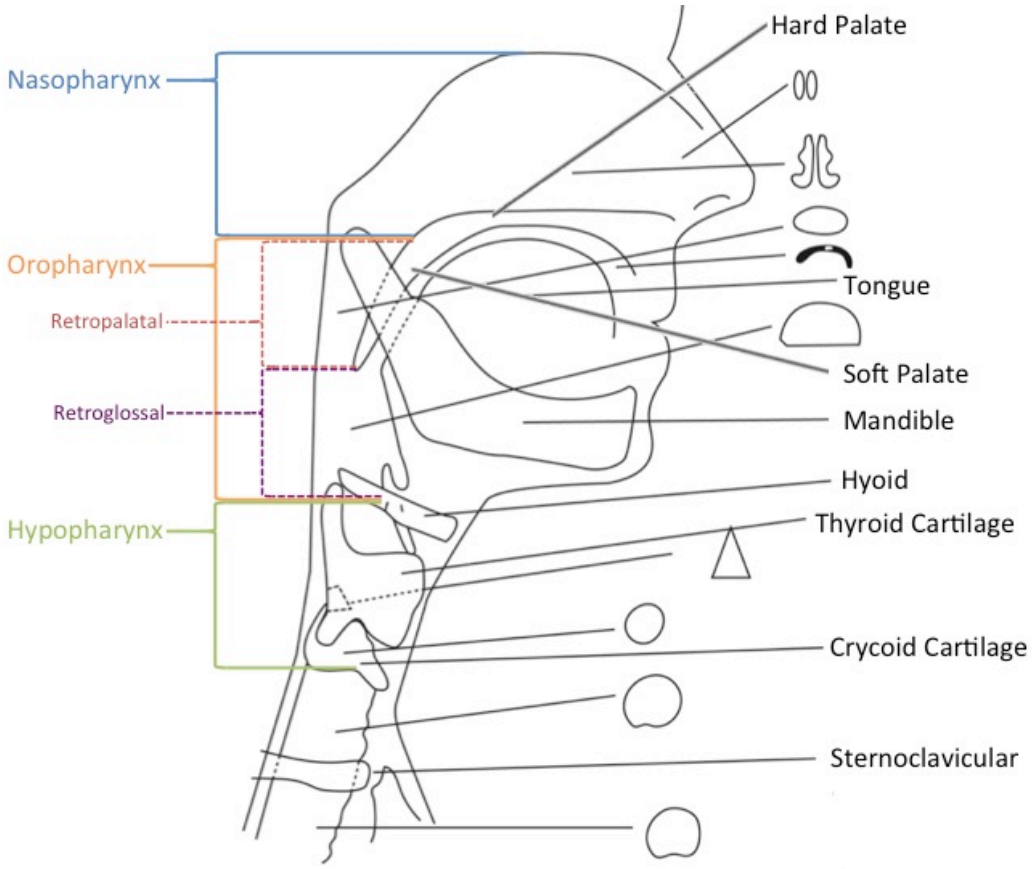

Figure 1.1 A schematic diagram of the upper airway demonstrating important structures, regional boundaries and the cross-sectional shape of the airway at different levels. Adapted from (Strohl, Butler et al. 2012)

The upper airway of normal subjects remains patent during sleep because the forces tending to collapse the upper airway are balanced by forces that dilate or stiffen the upper airway. One potential model for understanding how these forces affect the upper airway is the Starling resistor (Smith, Wise et al. 1988). The model has limitations in its application, including an inability to explain the phenomenon of negative effort dependence (Owens, Edwards et al. 2014, Wellman, Genta et al. 2014). However, it is a useful construct when considering the net effect of collapsing and dilating forces on the upper airway.

The Starling resistor displays classic collapsible tube behaviour. It is characterised by flow that increases with driving pressure until a critical pressure is reached, above which there is a plateau of flow despite increasing driving pressure (flow limitation). The

maximal flow through the tube is determined by upstream resistance (i.e. nasal) and the transmural pressure across the collapsible segment. The transmural pressure is dependent on the pressure of tissues surrounding the upper airway and the intra-luminal pressure (see Figure 1.2). An estimation of upper airway surrounding tissue pressures can be made by calculating the pharyngeal critical closing pressure (Pcrit), which will be discussed in detail in a later section. Countering the effects of tissue pressure and negative intraluminal pressure (during inspiration) are the effects of muscles that stiffen and dilate the upper airway and which can decrease resistance.

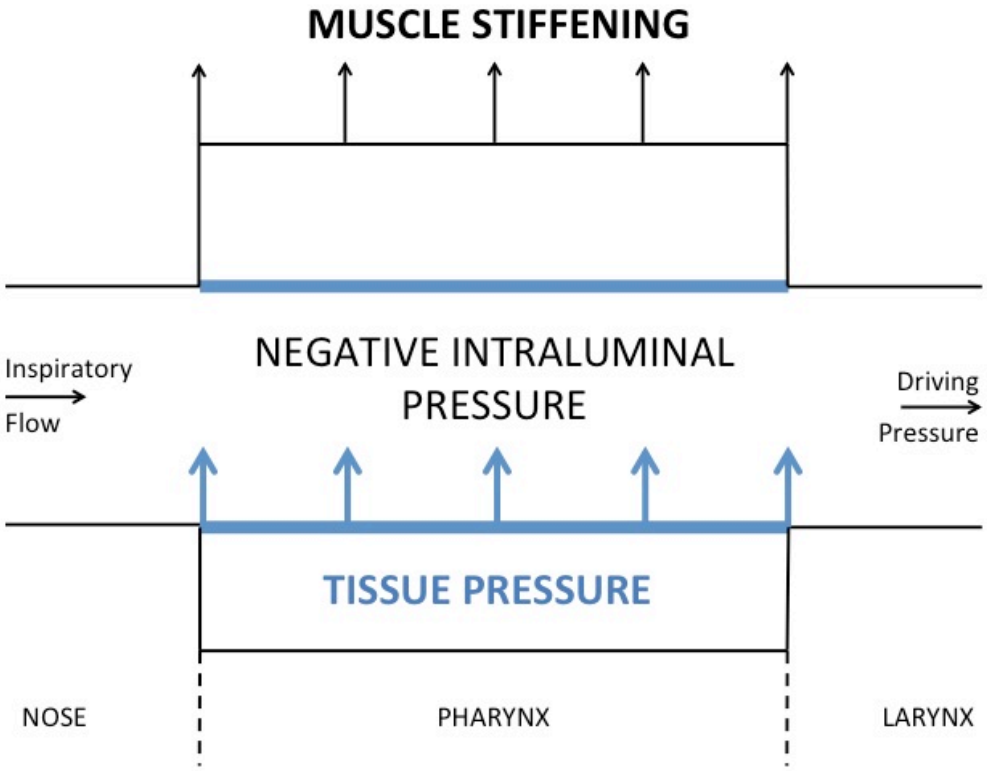

Figure 1.2 – The balance of collapsing and dilating forces in the upper airway. Adapted from (Kryger, Roth et al. 2011).

Upper airway resistance is increased in normal subjects during sleep (Hudgel and Hendricks 1988, Wiegand, Zwillich et al. 1989, Wiegand, Latz et al. 1990) and so the balance between collapsing and dilating/stiffening forces must be changed by sleep onset. A number of collapsing forces are largely unchanged by sleep. Nasal resistance increases only slightly (or not at all) during sleep (Hudgel and Hendricks 1988, Wheatley, Tangel et

al. 1993, Miljeteig, Cole et al. 1995), the amount of soft tissue surrounding the airway remains static and fluid redistribution to the upper airway in euvolaemic normal subjects is likely to contribute very little given that application of leg pressure cuffs has an insignificant effect on airway cross-sectional area (Shepard, Pevernagie et al. 1996). The upper airway muscles that help stiffen and dilate, especially genioglossus and tensor palatini, are significantly affected by sleep (Wheatley, Tangel et al. 1993, Horner, Innes et al. 1994, Lo, Jordan et al. 2007). With mechanical and respiratory influences minimised, and with a passive ventilation strategy, the EMG activity of both genioglossus and tensor palatini is reduced at sleep onset and remains reduced in NREM and REM sleep compared to wakefulness (Lo, Jordan et al. 2007).

In addition to the loss of the wakefulness stimulus to genioglossus and tensor palatini, a number of other factors influence the hypoglossal motor nucleus and therefore many upper airway muscles in sleep. These other factors include: 1) Mechanoreceptor feedback – as discussed earlier, negative upper airway luminal pressure influences the activity of genioglossus and it is known that mechanoreceptor input is independent of central drive and is more important than chemical input (Malhotra, Pillar et al. 2002); 2) Respiratory pacemaker – the pre-Botzinger complex influences the hypoglossal motor nucleus with monosynaptically connected interneurons identified in cats (Bianchi, Grelot et al. 1988), and the presence of pre-activation of the hypoglossal nerve prior to diaphragmatic firing suggesting a similar influence in humans (Strohl, Hensley et al. 1980); 3) Chemoreceptive input – rising CO_2 increases genioglossus activity in awake (Onal, Lopata et al. 1981) and asleep subjects (Lo, Jordan et al. 2006); 4) Specific neurotransmitters – a number of specific neurotransmitter networks provide input into the hypoglossal motor nucleus including cholinergic, histaminergic, serotonergic, orexinergic and adrenergic (Horner 2001).

1.2 THE EFFECT OF AROUSAL ON RESPIRATION

The arousal system constitutes the neural networks required for the maintenance of wakefulness and consciousness. The seminal works of Maruzzi and Magoun localised the consciousness stimulus to the reticular formation by creating precise small brain lesions that induced coma and by showing that electrical stimulation of the same area in intact animals produces electroencephalogram (EEG) changes identical to those of arousal (Moruzzi and Magoun 1949). Subsequent studies confirm that the subcortical regions essential for maintaining the arousal state are the basal forebrain and parabrachial complex (Fuller, Sherman et al. 2011). In particular, the parabrachial complex seems well situated to mediate arousal in response to respiratory stimuli as it is part of both the arousal and central respiratory systems (Chamberlin 2004). Additionally, research in rat models shows that the parabrachial complex receives input from the nucleus of the solitary tract and the retrotrapezoid nucleus (Ricardo and Koh 1978, Rosin, Chang et al. 2006), both of which receive input from peripheral chemoreceptors as discussed earlier.

It is clear that a number of respiratory stimuli can lead to arousal from sleep including mechanical stimuli (Gleeson, Zwillich et al. 1990), elevated CO_2 (Douglas, White et al. 1982, Berthon-Jones and Sullivan 1984) and reduced O_2 (Berthon-Jones and Sullivan 1982, Douglas, White et al. 1982). The early studies exploring the effect of hypoxia and hypercapnia on respiratory arousal from sleep originally focussed on establishing respiratory arousal threshold values for arterial O_2 and CO_2. However, in the absence of airway occlusion, the level of hypoxia required to stimulate arousal is inconsistent (Berry and Gleeson 1997) and although hypercapnia is a more potent stimulus to arousal than hypoxia (Douglas, White et al. 1982, Berthon-Jones and Sullivan 1984), there is still a wide individual variation in arousal response to rising levels of CO_2 (Berry and Gleeson 1997). Gleeson and colleagues significantly advanced our understanding of the process of respiratory arousal by demonstrating that regardless of whether respiratory arousal was triggered by inspiratory resistance, hypoxia or hypercapnia, the level of oesophageal pressure at which arousal occurred was consistent (Gleeson, Zwillich et al. 1990). The idea that respiratory effort (as measured by peak negative intrathoracic pressure) may well underlie the primary trigger for respiratory arousal (Vincken, Guilleminault et al.

1987, Gleeson, Zwillich et al. 1990) is further supported by observations in OSA patients (Berry and Light 1992, Berry, Mahutte et al. 1993). Another possibility, however, is that respiratory effort could be a surrogate for the integrated central signal generated by CO_2 and O_2 levels (at the carotid bodies and centrally in the CSF) and mechanoreceptor signals generated by a collapsing upper airway. That is, by measuring blood gas tensions we do not adequately assess the tissue levels of CO_2 and O_2 and so we do not know their level of input to the arousal system at a given point. Rather, the measurement we currently make of the integrated chemosensory and mechanoreceptor signal is the resultant output in respiratory effort. In this way, respiratory effort may simply be the best surrogate signal of the integrated effect of CO_2, O_2 and a collapsing upper airway on the respiratory and arousal systems.

Arousal from sleep was previously thought to be a protective mechanism, preventing the perpetuation of apnoea. However, many respiratory events are terminated in the absence of arousal (Younes 2004). Additionally, Worsnop and colleagues demonstrated in healthy males volunteers that the EMG activity of genioglossus, tensor palatini and diaphragm muscles as well as minute ventilation were reduced when transitioning from wake to sleep. Importantly, when transitioning from sleep to wake (i.e. when arousing from sleep), the magnitudes of the EMG and minute ventilation increases were greater than the decrement when falling asleep (Worsnop, Kay et al. 1998). The cause of the overshoot is not clear but may be due to the combination of the wakefulness stimulus and the added effect of increased sensitivity to CO_2 leading to increased respiratory drive. An additional factor may be that of an arousal reflex that produces a transient burst of activity above that which occurs with normal wakefulness(Trinder, Allen et al. 2003). Regardless, arousal clearly stimulates respiration and can do so above the normal waking level. The potential for the ventilatory overshoot to contribute to repetitive apnoea will be discussed in detail in a subsequent section.

1.3 OBSTRUCTIVE SLEEP APNOEA

For clinicians who have treated patients suffering from OSA, the absence of the condition from medical literature prior to the mid twentieth century is striking. Dickens aside, there are scant descriptions of the condition prior to this time. Kryger reports early descriptions attributed to Dionysius (360B.C.) of "an unusually fat man… choked by his fat" (Kryger 1983), while Lavie recounts reports to the Clinical Society of London by Caton and Morison of patients with "narcolepsy" who almost certainly suffered from OSA (Lavie 1984). Lavie also quotes 19th century physician W.H. Broadbent, who recognised the importance of body position to sleep disordered breathing, "When a person… is lying on his back in heavy sleep and snoring loudly, it very commonly happens that every now and then the inspiration fails to overcome the resistance in the pharynx" (Lavie 1984).

In the mid 1950s respiratory physicians began to recognise patients with obesity and breathing difficulties. The classic description from this period, by Burwell and colleagues, describes a morbidly obese patient with somnolence and polycythaemia (Bickelmann, Burwell et al. 1956). However, the link between these symptoms and disturbance of breathing during sleep was not established fully until the 1960s, when researchers pioneering the use of polysomnographic techniques demonstrated that the somnolence of morbidly obese patients was not related to blood gas abnormalities but rather to disturbance of sleep (Jung and Kuhlo 1965).

Since the mid 1960s there has been an explosion in literature regarding OSA and the condition is now recognised as constituting a significant health burden that consumes considerable resources. The illness is associated with excessive sleepiness (Gottlieb, Whitney et al. 1999), depression (Peppard, Szklo-Coxe et al. 2006), motor vehicle accident (Teran-Santos, Jimenez-Gomez et al. 1999), systemic hypertension (Nieto, Young et al. 2000, Peppard, Young et al. 2000), the metabolic syndrome (Coughlin, Mawdsley et al. 2004), insulin resistance (Ip, Lam et al. 2002) and subsequent cardiac ischemia and arrhythmias (Shahar, Whitney et al. 2001, Shamsuzzaman, Gersh et al. 2003, Mehra, Benjamin et al. 2006).

The following sections will focus on the definition, epidemiology and pathogenesis of OSA and supine related OSA.

1.3.1 Definition of OSA and supine related OSA

Obstructive sleep apnoea is characterised by repetitive upper airway obstruction leading to partial or complete cessation of airflow through the upper airway. The clinical entity of "OSA syndrome" is present when there is evidence of airway obstruction with the added feature of hypersomnolence or limitations in daily function resultant from severely disturbed sleep.

Because polysmnography is the most often utilised technique to diagnose OSA, the condition is invariably described in terms of its polysomnographic appearance. The apnoea and hypopnoea index (AHI) is the metric used to quantify the degree of airway obstruction. Loosely defined, an apnoea occurs when there is complete cessation of flow, while a hypopnoea is present when there is a reduction in the amplitude of flow (of a certain magnitude from baseline) in association with oxygen desaturation or arousal from sleep (Guilleminault, Tilkian et al. 1976, Block, Boysen et al. 1979, Gould, Whyte et al. 1988). How an apnoea or hypopnoea should be defined has been the source of ongoing debate for the better part of two decades with various groups (e.g. researchers, clinicians, health care providers) advocating along the lines of their interest. Apnoea and hypopnoea definitions influence treatment thresholds (Ruehland, Rochford et al. 2009), prevalence estimates (Young, Peppard et al. 2002) and the establishment of associations between OSA and co-morbid conditions (Redline and Sanders 1997).

The widely followed practice in Australia, through the recommendations of the Australasian Sleep Association (ASA), is to follow the prescribed definitions for scoring respiratory events of the American Academy of Sleep Medicine (AASM). Although the AASM released an update of the definitions in 2012 (Berry, Budhiraja et al. 2012), at the time of writing these have not yet been universally adopted in Australia, although the ASA has recently recommended a switch to these rules. For the duration of this research project, the 2007 edition of the AASM (recommended) rules were applied at our sleep

centre (Iber and American Academy of Sleep Medicine. 2007). In addition to the frequently changing definition, the AHI shows significant night-to-night variability, which will be discussed shortly.

Several different patterns of OSA have been described on the basis of the AHI (Joosten, Hamza et al. 2012). The most common pattern of sleep apnoea is one where the majority of events are observed in the supine sleeping position (see Figure 1.3), which is usually defined as being present when the AHI is greater than 5 events/hr and respiratory events occur at twice the frequency in the supine sleeping position compared to the non-supine sleeping positions (Cartwright 1984, Oksenberg, Silverberg et al. 1997) (see Figure 1.3).

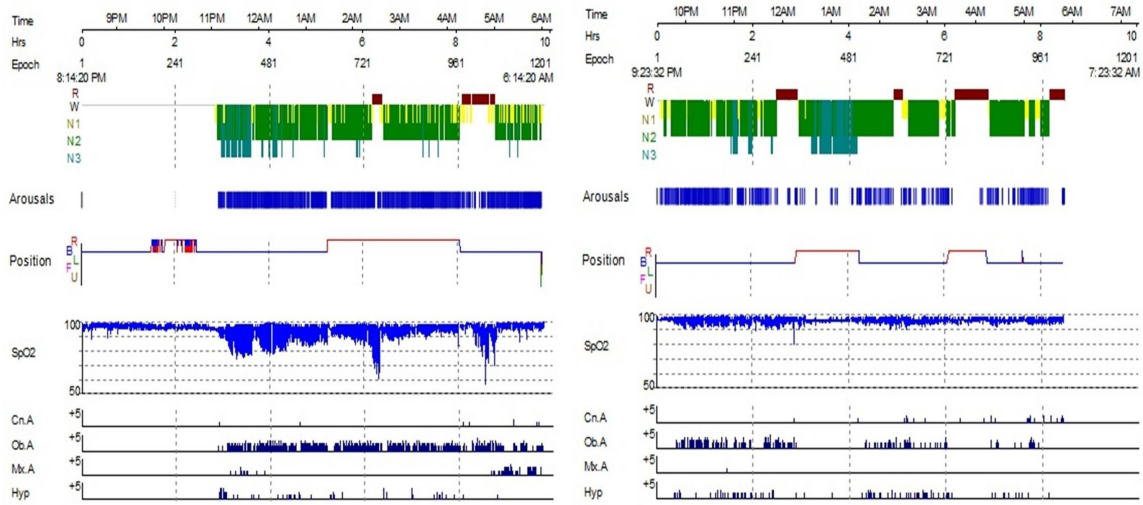

Figure 1.3 – A polysomnogram montage of a non-positional OSA patient (left) and a positional OSA patient (right). The montage demonstrates that the patient on the left has obstructive respiratory events regardless of body position (in this case supine or right lateral decubitus). On the right montage we can see that the patient only has obstructive respiratory events when lying supine, with no events when lying in the right lateral decubitus position. SpO_2 – percent oxygen saturation of arterial blood, CnA – central apnoea, ObA – obstructive apnoea, MxA – mixed apnoea, Hyp – obstructive hypopnoea. Body position abbreviations, R – right lateral decubitus, B – supine, L – left lateral decubitus, F – prone, U – unknown.

In an alternative definition of supine OSA (Mador, Kufel et al. 2005) the ratio of events in the supine position to the non-supine positions must be greater than two to one and the AHI in the non-supine positions must be less than 5 events/hr. Mador and colleagues felt this definition was more clinically relevant given that avoidance of the supine sleeping

position by patients who fit this description would result in normalisation of the AHI and relief of the symptoms of OSA. The Mador definition has been adopted and modified for use in some studies of treatment of positional OSA with supine sleep avoidance techniques (Loord and Hultcrantz 2007, Bignold, Mercer et al. 2011).

For clarity, in this chapter we will use the following definitions:

1. Supine predominant obstructive sleep apnoea (spOSA):
   - Overall AHI is greater than 5 events/hr, and,
   - The supine AHI is greater than two times the non-supine AHI.
2. Supine isolated obstructive sleep apnoea (siOSA):
   - Overall AHI is greater than 5 events/hr, and,
   - The supine AHI is greater than two times the non-supine AHI and,
   - Non-supine AHI is less than 5 events/hr.

Variability and repeatability of the measurement of AHI

One potential issue in using the AHI to classify patients relates to the repeatability or variability of the metric. Several different statistical techniques have been employed to assess the variability or repeatability of the AHI. One frequently applied method is to compare the correlation of the AHI on a given test night with the AHI on a subsequent test night(s). The Pearson product-moment correlation coefficient has been frequently applied to data sets exploring AHI reliability. It is an interclass correlation that tests the strength and direction of the linear relationship between two variables. A number of studies utilising the Pearson correlation coefficient have found a strong correlation in AHI across test night(s) in elderly patients (Mosko, Dickel et al. 1988, Aber, Block et al. 1989) and patients referred to a sleep clinic for further management and investigation (Dealberto, Ferber et al. 1994, Mendelson 1994, Le Bon, Hoffmann et al. 2000, Bittencourt, Suchecki et al. 2001). Counter to these studies, research by Levandowski and colleagues demonstrated a poor Pearson correlation coefficient in overall AHI (0.44, $p > 0.05$) in a small sample of 20 patients drawn from a larger study.

Using correlations has been criticised as a method for assessing repeatability. Bland and Altman emphasise that correlations detect the strength of a relationship between two

variables, not the agreement between them (Bland and Altman 1986). This issue helps to explain why many of the aforementioned studies demonstrate a strong correlation, but when they categorise or stratify their patients according AHI cut-offs, many of the patients change categorisation across night(s) (Mosko, Dickel et al. 1988, Bliwise, Benkert et al. 1991, Chediak, Acevedo-Crespo et al. 1996). That is, the correlation co-efficient does not take into account the individual variability in AHI from night-to-night. Two studies have performed a Bland Altman analysis on their data to explore the individual variability in overall AHI from night-to-night. Bittencourt and colleagues demonstrated a large variability in AHI across nights on Bland Altman plots (Bittencourt, Suchecki et al. 2001) (see Figure 1.4). Le Bon and colleagues did not publish their Bland Altman plots but also reported poor repeatability (Le Bon, Hoffmann et al. 2000).

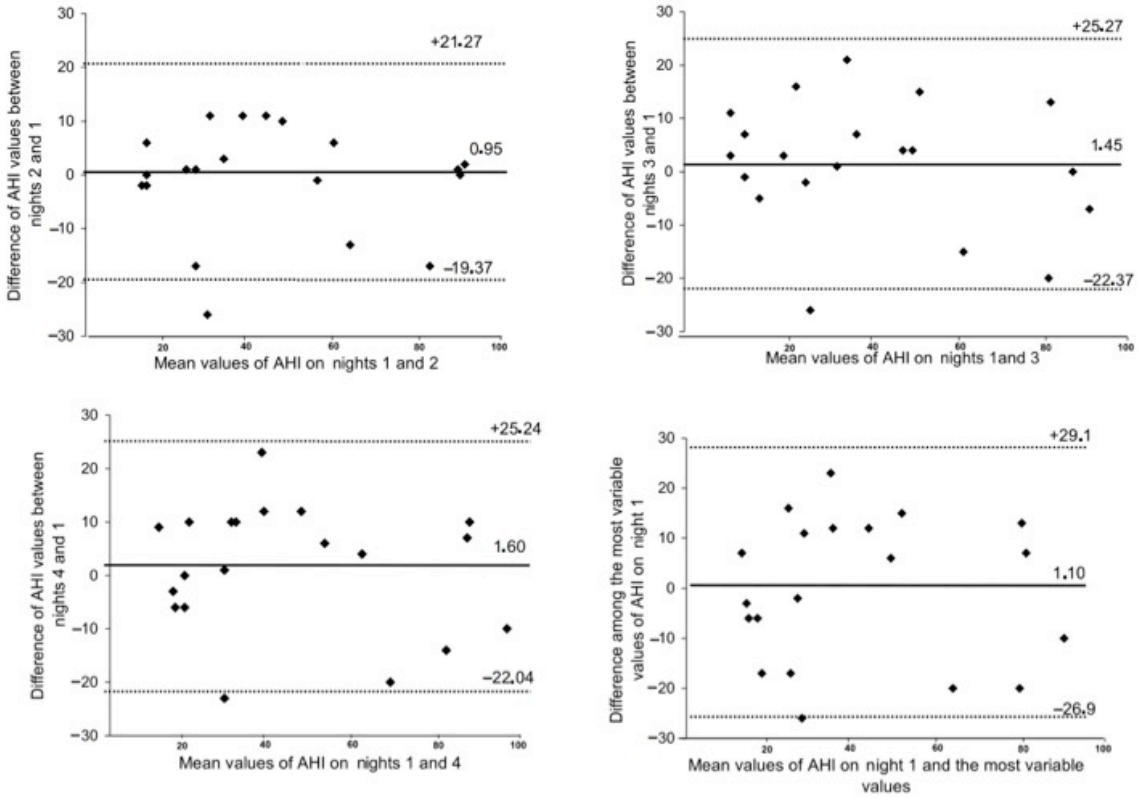

Figure 1.4 Bland Altman plots demonstrating a high individual variability across nights in overall AHI (Bittencourt, Suchecki et al. 2001).

The issue of AHI variability across nights is of critical importance to the classification and treatment of patients with spOSA and siOSA. Positional treatment for spOSA and

siOSA, where patients are prevented from sleeping on their back, has been reported as a viable alternative to CPAP therapy (Jokic, Klimaszewski et al. 1999). Treating patients with positional modification based on a single overnight AHI measurement makes three inherent assumptions. Firstly, that the supine predominant phenotype is reproducible from night-to-night, secondly and partly related, that supine sleep time remains sufficient from night-to-night to warrant treatment, and thirdly, that the lateral AHI is consistently low so that preventing patients from sleeping on their back will be consistently effective at reducing the total AHI. These assumptions have not been tested.

1.3.2 Epidemiology of OSA and supine related OSA

The prevalence of the obstructive sleep apnoea syndrome in Western countries is 5% of the population (Davies and Stradling 1996, Lindberg and Gislason 2000). The presence of polysomnographically defined OSA is now likely to be higher than the 9% in women and 24% in men from North America (Young, Palta et al. 1993) or the 4.7% of women and 8.5% of men from Australia (Bearpark, Elliott et al. 1993) on account of the increasing levels of obesity in Western society. Indeed, more recent studies suggest that 20% of adults have mild OSA (defined as AHI 5-15 events/hr) and approximately 7% have moderate or severe OSA (defined as AHI >15 events/hr) (Young, Peppard et al. 2002).

Many risk factors for OSA have been identified in population studies. The strongest contributor to risk for OSA is excess weight (Young, Skatrud et al. 2004), with the putative contribution to airway obstruction thought to be a narrowing of the upper airway due to fatty deposits and a reduction in lung volume and tracheal traction secondary to increased transdiaphragmatic pressure (these mechanisms will be discussed in detail in a subsequent section). Other important risk factors include male gender (Young, Palta et al. 1993), increasing age (Bixler, Vgontzas et al. 1998, Bixler, Vgontzas et al. 2001), the presence of snoring (Duran, Esnaola et al. 2001), facial skeletal characteristics (Cistulli 1996, Lee, Sutherland et al. 2010), familial predispositions (Redline and Tishler 2000) and anatomical obstruction of the upper airway (adenotonsillar hypertrophy).

The prevalence of spOSA is variably reported as between 50 - 60% of patients who present to sleep clinics for overnight polysomnography (Pevernagie and Shepard 1992, Oksenberg, Silverberg et al. 1997, Richard, Kox et al. 2006, Joosten, Hamza et al. 2012), whereas approximately 25-30% of the same population may be classified as having siOSA (Mador, Kufel et al. 2005, Gillman, Roebuck et al. 2012, Joosten, Hamza et al. 2012). The prevalence of spOSA in the Asian population is higher than for Caucasians at between 67-75% (Mo, Lee et al. 2011, Teerapraipruk, Chirakalwasan et al. 2012). There are no reports giving the prevalence of either condition in the general population.

Time Spent Supine:

The time in which a subject sleeps supine is an important determining factor of the overall AHI in patients with spOSA and siOSA. Having spOSA or siOSA does not influence the amount of time spent supine as these patients appear to spend as much time in the supine position as unselected patients with OSA (Joosten, Hamza et al. 2012), ranging from 32-42.7% of total sleep time (Pevernagie and Shepard 1992, Richard, Kox et al. 2006, Chung, Enciso et al. 2010, Joosten, Hamza et al. 2012) for spOSA, 40-48.1% for siOSA (Mador, Kufel et al. 2005, Gillman, Roebuck et al. 2012) and 27-48% of total sleep time for patients with non-positional obstructive events (Pevernagie and Shepard 1992, Richard, Kox et al. 2006, Chung, Enciso et al. 2010, Gillman, Roebuck et al. 2012, Joosten, Hamza et al. 2012).

Age and gender also do not influence the time spent supine. With increasing age, fewer position shifts are made over the course of the night (De Koninck, Lorrain et al. 1992), but a small cross-sectional study showed that the time spent supine did not change markedly across a series of age ranges (apart from early childhood) (De Koninck, Lorrain et al. 1992). Likewise, being male or female appears not to affect the amount of time supine during sleep (O'Connor, Thornley et al. 2000). The amount of time spent in supine sleep in unselected general populations is not known.

1.3.3 The effect of body position on the pathogenesis of OSA

Many important pathophysiological processes have been identified as contributing to airway obstruction in OSA, including unfavourable airway anatomy (Schwab, Gefter et al. 1993), an inability of the upper airway muscles to open or stiffen the airway during sleep (McGinley, Schwartz et al. 2008, Edwards and White 2011), a low lung volume (Jordan, White et al. 2009), a low respiratory arousal threshold (Younes 2004) and an oversensitive ventilatory control system (Wellman, Jordan et al. 2004). Given that many patients experience an improvement in airway obstruction when asleep in the lateral position compared to the supine position, it follows that one or more of the mechanisms involved in airway obstruction are also altered by body position.

Airway anatomy

A number of anatomical features of the upper airway contribute to obstruction in OSA patients. Ultimately, airway lumen size and shape and anatomical propensity to collapse are determined by the interaction between a number of factors such as the size of the bony enclosure (mandible, maxilla, cervical spine) (Isono, Tanaka et al. 2002), the size of the soft tissues (tongue, soft palate, lateral pharyngeal fat pads) (Schwab, Pasirstein et al. 2003) and the shape and folding characteristics of the airway (Amatoury, Kairaitis et al. 2010).

The narrowest site of the airway in normal subjects and OSA patients is generally accepted to be the velopharynx (Schwab, Gupta et al. 1995, Ciscar, Juan et al. 2001). Contributors to narrowing of the velopharynx in OSA subjects include the tongue, soft palate and lateral pharyngeal fat pads (Schwab, Pasirstein et al. 2003). Given the propensity for collapse in the supine sleeping position, several studies have imaged the upper airway in the seated, lateral and supine position in order to examine the effect of gravity on the soft tissue structures.

Studies in awake normal subjects (Jan, Marshall et al. 1994) and awake OSA patients (Jan, Marshall et al. 1994, Martin, Marshall et al. 1995, Pevernagie, Stanson et al. 1995, Walsh, Leigh et al. 2008) show no significant change in airway cross-sectional area

(CSA) when moving from the supine to lateral position. Studies in anaesthetised patients, however, demonstrate a small but significant change, with a larger airway CSA in the lateral position (Ono, Otsuka et al. 2000, Isono, Tanaka et al. 2002). The discrepancy in CSA changes from supine to lateral between anaesthetised and awake patients may lie in the effect of anaesthetic on genioglossus activity. That is, in awake OSA studies, an increased genioglossus activity in the supine position (in an effort to protect the airway) negates the effect of gravity on the bulk soft tissue structures that lie anteriorly (see Figure 1.5) in that position so that CSA is preserved. In support of this idea, it has been shown in sleeping OSA patients that genioglossus activity is indeed increased in the supine position compared to the lateral position (Malhotra, Trinder et al. 2004).

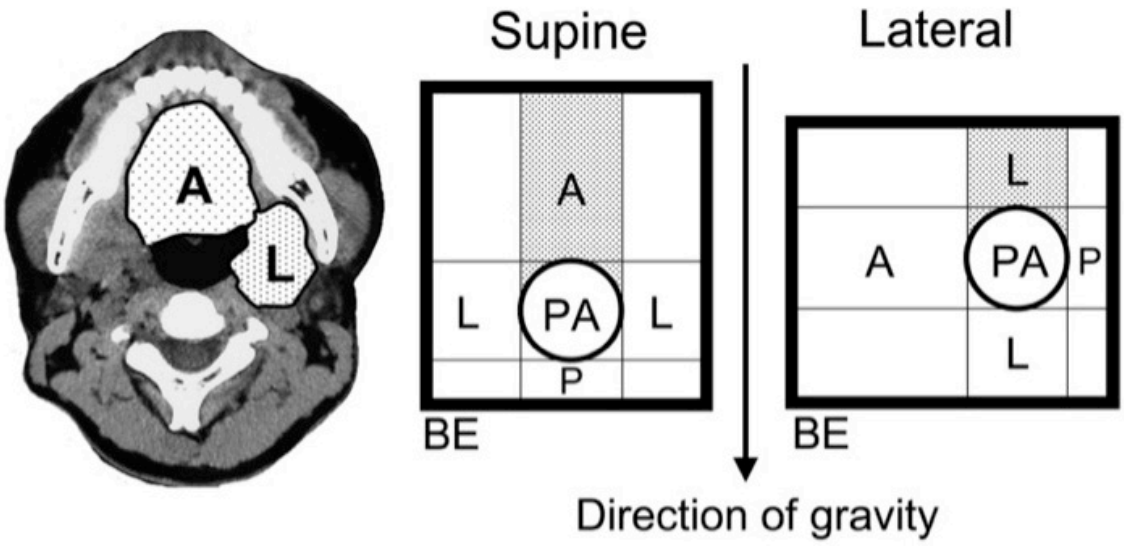

Figure 1.5 – Schematic representation of the axial structural arrangements while the patient is in the supine and lateral positions. BE – bony enclosure, PA – pharyngeal airway, A – mass of soft tissues, which lie anteriorly when supine, L – mass of soft tissues located laterally when the patient lies supine, P – mass of soft tissues located posteriorly when the patient lies supine. From (Isono, Tanaka et al. 2002).

The literature regarding airway shape changes from lateral to supine is somewhat conflicting, which is likely to represent differences in methodologies regarding imaging modality and acquisition of orthogonal images, head and neck position, controlling for phase of respiration, sleep state of the subjects and the population under examination. Both positional (Pevernagie, Stanson et al. 1995) and non-positional sleep apnoea patients

(Ryan and Love 1996, Ciscar, Juan et al. 2001, Walsh, Leigh et al. 2008) have been shown to have an elliptically shaped airway in the supine position with the long axis oriented laterally (see Figure 1.6). By contrast, there is evidence that some patients with severe non-positional OSA have an elliptically shaped airway that is oriented in the antero-posterior direction (Schwab, Gefter et al. 1993, Fogel, Malhotra et al. 2003). Importantly, no imaging studies have selected for spOSA or siOSA subjects and used matched controls.

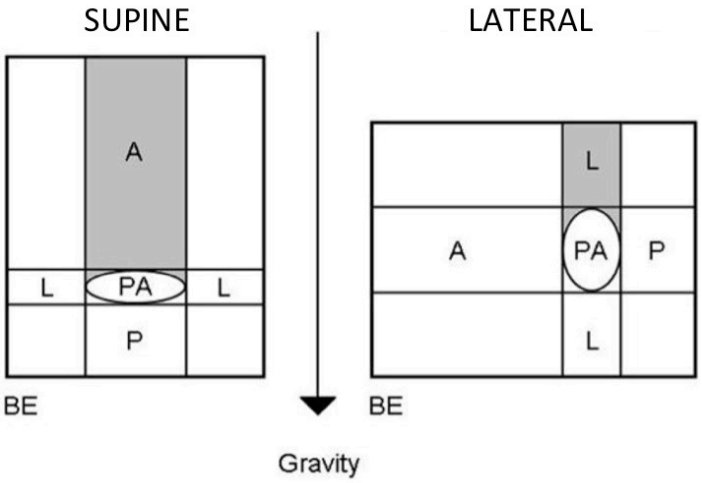

Figure 1.6 – Schematic of airway lumen shape in OSA patients when lying supine (left) and lateral (right) demonstrating a more ellipsoid shape with a narrower antero-posterior diameter in the supine position. BE – bony enclosure, A – anterior soft tissue mass, P – posterior soft tissue mass, L – lateral soft tissue mass. From (Walsh, Leigh et al. 2008).

The size and shape of the bony enclosure of the upper airway is an important determinant for how the soft tissues of the upper airway contribute to lumen narrowing (Isono, Tanaka et al. 2002). Clearly, the starting configuration of the bony enclosure as encompassed by the size and orientation of the maxilla, mandible and cervical spinal column are important. Patients with supine OSA (defined as supine AHI greater than two times lateral AHI and lateral AHI less than 15/hr, in this case) have been shown to have a relatively small craniofacial volume on three-dimensional magnetic resonance imaging (MRI) modelling compared to age and BMI matched non-positional patients (Saigusa, Suzuki et al. 2009). Saigusa and colleagues also demonstrated that the small volume

likely results from the lower facial height and more backward position of the jaw in positional patients. The relationship between bony structures enclosing the upper airway may change through either alteration in neck flexion (see Figure 1.7) or mandibular opening in order to change patency of the lumen. In anaesthetised individuals with a diagnosis of sleep apnoea, neck flexion and jaw opening decrease the oropharyngeal airway size and increase the closing pressure of the velopharynx (Isono, Tanaka et al. 2004). Although movement of the mandible during sleep has been studied, somewhat surprisingly, sleep stage rather than body position was found to have a larger effect on mandibular opening in normal subjects (Miyamoto, Ozbek et al. 1998). Importantly, the degree of neck flexion and mandibular opening are not measured as part of the standard polysomnographic setup and are therefore overlooked in the majority of literature relating to the effect of body position on OSA.

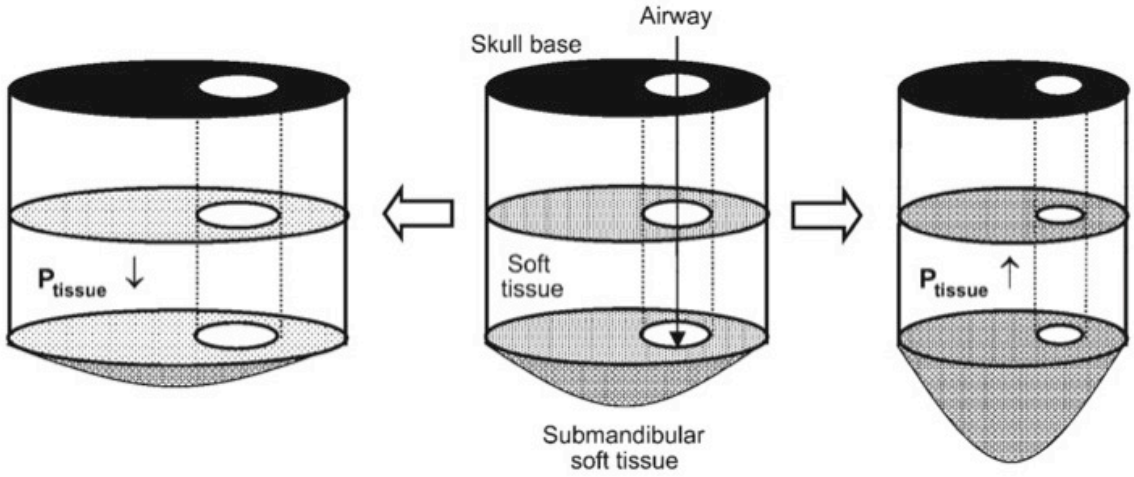

Figure 1.7 – 3-dimensional mechanical model of the upper airway explaining the effect of neck extension. Neck extension (left) results in increase in bony box size with displacement of soft tissue into the box and lengthening of the airway with resultant decrease in tissue pressure. Neck flexion (right) reduces the size of the bony box resulting in displacement of soft tissue out of the box with resultant increase in tissue pressure. From (Isono, Tanaka et al. 2004).

From a purely anatomical perspective, differences in airway shape rather than CSA may be more important in the generation of airway obstruction in the supine rather than the lateral sleeping position in patients with spOSA and siOSA. Advanced models of the upper airway utilising flow-field computation analysis, and modified Starling-resistor models where tissue compliance is accounted for, may help to explain this observation

(Amatoury, Kairaitis et al. 2010, Lucey, King et al. 2010). Amatoury et al. report that the airway folding characteristics may be more important than CSA in causing obstruction (Amatoury, Kairaitis et al. 2010). In terms of geometry, flow-field computation analysis has demonstrated that changes in soft palate displacement and side wall deformation (e.g. with the more elliptical airway shape of the supine position) may generate altered pressure gradients in the velopharynx and therefore increase its propensity to collapse (Lucey, King et al. 2010). This modelling is particularly interesting as it not only demonstrates how shape may predispose to collapse, but also supports the observation that increasing lateral pharyngeal fat pad size increases OSA risk (Schwab, Pasirstein et al. 2003) as lateral low pressure areas are steepened as the airway is narrowed by enlarging the side walls (Lucey, King et al. 2010).

Pharyngeal critical closing pressure (Pcrit)

The Pcrit quantifies airway mechanics or the collapsibility of a subject's airway and, as such, provides a functional measurement that is more clinically relevant than image based airway anatomical measures. Unfavourable airway anatomy as measured by a Pcrit of less than -2cmH2O is present in 80% of OSA patients and improvements in airway collapsibility (as measured by Pcrit) have been demonstrated with weight loss (Schwartz, Gold et al. 1991), upper airway surgery (Schwartz, Schubert et al. 1992) and mandibular advancement (Isono, Tanaka et al. 1995) on OSA patients.

The measurement of Pcrit can be made in a passive airway, in which upper airway dilator muscles are quiescent, by performing a series of rapid CPAP pressure drops from optimal CPAP (Schwartz, Smith et al. 1988, Gleadhill, Schwartz et al. 1991, Gold and Schwartz 1996, Patil, Punjabi et al. 2004). The maximal flow achieved, during flow limited breathing of a CPAP pressure drop (using the third, fourth or fifth breath) is then plotted against mask pressure. A linear regression is performed to determine pressure at flow = zero L/min and this is the passive Pcrit (Figure 1.8).

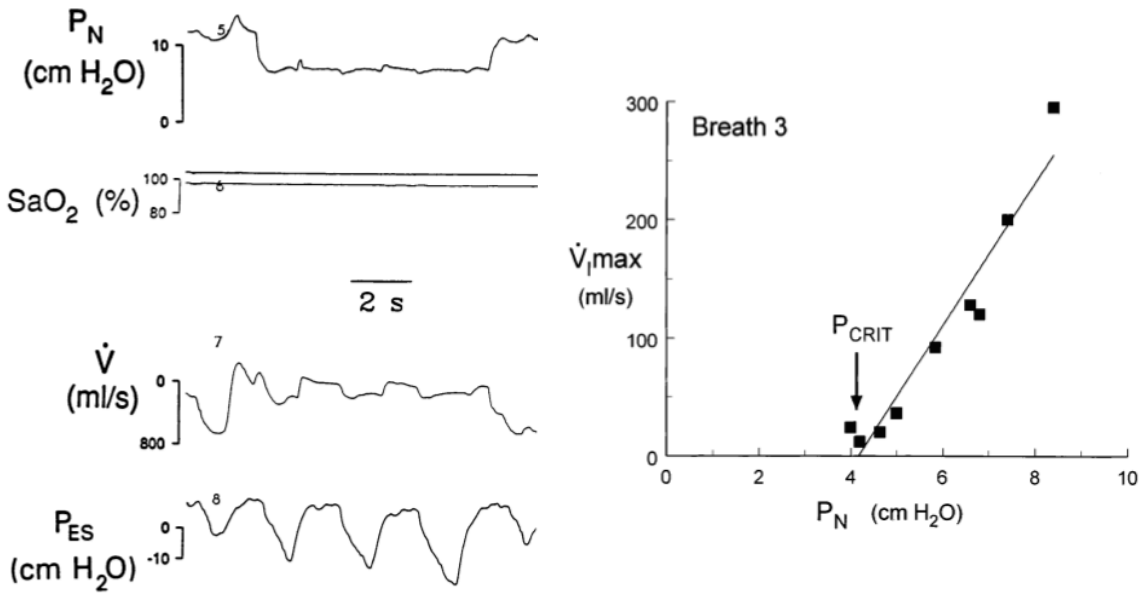

Figure 1.8 – The left panel demonstrates mask pressure (P_N), oxygen saturation (SaO_2), flow($\dot{V}$) and oesophageal pressure (P_{ES}) during a rapid CPAP dial-down from 12cmH_2O to 8cmH_2O for three breaths. The right panel demonstrates plots of maximal flow versus mask pressure for a series of CPAP drops with a regression line plotted. The intersection with the x-axis (where flow = zero) is the Pcrit. Adapted from (Schwartz, Smith et al. 1988).

The Pcrit measurement can also be performed in an active airway, in which the upper airway dilator muscles are activated in an effort to maintain airway patency (Jordan, Wellman et al. 2007, Patil, Schneider et al. 2007, McGinley, Schwartz et al. 2008). The technique involves reducing CPAP pressure gradually (usually in 1-2cmH_2O increments) over longer periods of time (usually periods of 5-10min) than used in the passive measurement (see Figure 1.9). The active Pcrit quantitatively assesses a subject's ability to compensate for a collapsing airway via increased neuromuscular drive in the face of flow limitation and a collapsing airway.

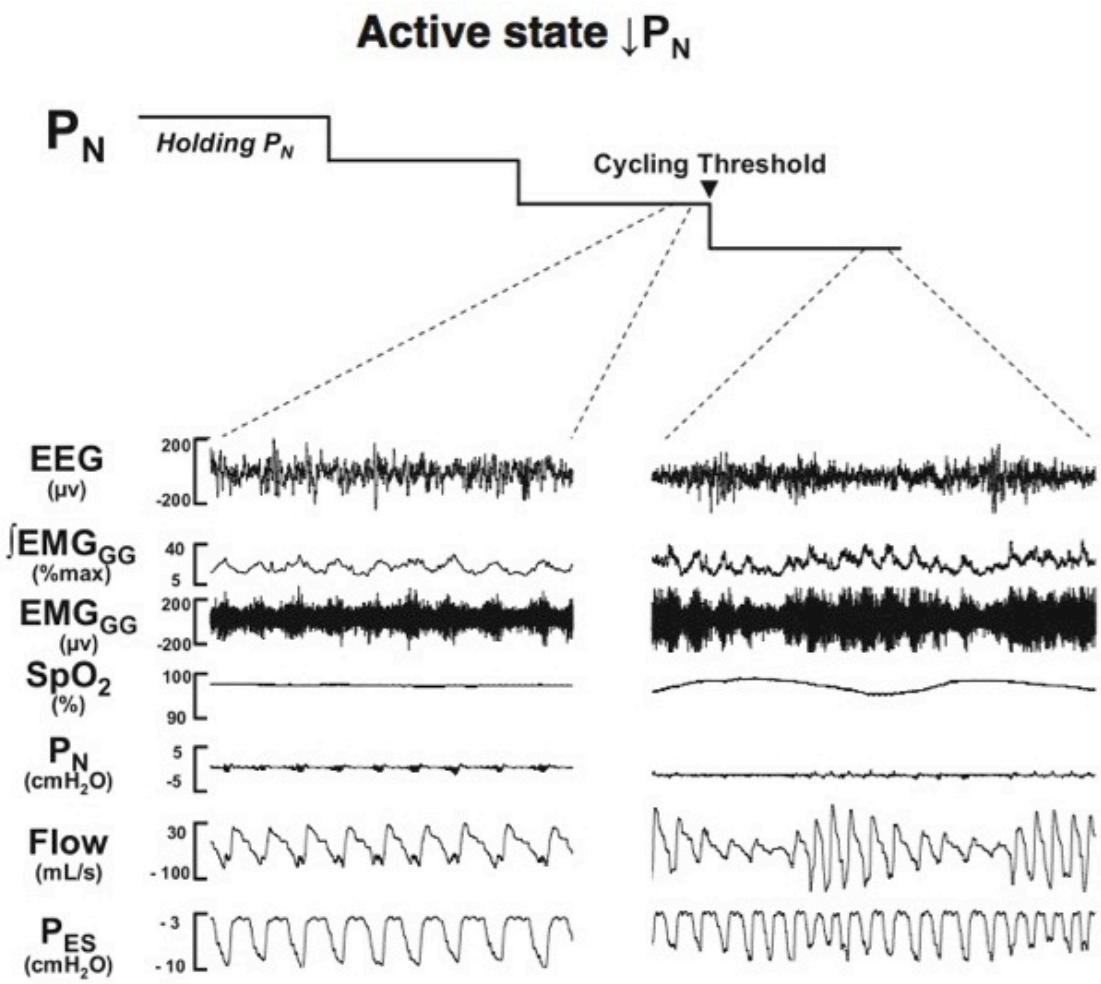

Figure 1.9 – Method for performing active Pcrit measurement. P_N – mask pressure, EEG – electroencephalogram, EMG_{GG} – electromyographic recording from genioglossus, SpO_2 – oxygen saturation of arterial blood, P_{ES} – oesophageal pressure. From (McGinley, Schwartz et al. 2008).

In contrast to the imaging literature, the Pcrit literature is more consistent when examining changes from the supine to lateral body position. Several studies have demonstrated a more negative passive Pcrit (and therefore less collapsible airway) in the lateral position compared to the supine position in male OSA patients (Boudewyns, Punjabi et al. 2000, Penzel, Moller et al. 2001, Ong, Touyz et al. 2011). The positional difference in Pcrit is typically in the order of 2.2-2.9cmH_2O higher in the supine position in OSA patients in NREM sleep, although a larger difference was found in anaesthetised OSA patients (Isono, Tanaka et al. 2002). Importantly, there are no published data on how Pcrit changes from lateral to supine specifically in spOSA or siOSA patients compared to non-positional OSA patients. Furthermore, there are no published data on

the effect of body position on the effectiveness of neuromuscular compensation (active Pcrit).

Upper airway dilator muscle activity

As discussed earlier, the ability of upper airway dilator muscles, in particular genioglossus, to compensate/activate in the face of collapsing forces is a key determinant of upper airway patency. Patients with OSA have increased baseline genioglossus activity when awake (Mezzanotte, Tangel et al. 1992, Fogel, Trinder et al. 2005), most likely compensating for unfavourable upper airway mechanics with a greater negative pressure in OSA patients on inspiration (Fogel, Malhotra et al. 2001). There is a greater fall in genioglossus activity at sleep onset in OSA patients compared with controls (Mezzanotte, Tangel et al. 1996) even though genioglossus activity remains higher overall than in matched controls (Fogel, Trinder et al. 2005). The greater fall may be due to a combination of the loss of the wakefulness drive (Lo, Jordan et al. 2007) and a diminished negative pressure reflex activity of genioglossus (as discussed earlier).

Views differ as to how sleep affects the genioglossus response to negative pressure in the upper airway, with some studies reporting a reduced response (Wheatley, Mezzanotte et al. 1993, Horner, Innes et al. 1994) whilst others report an enhanced response from sleep onset to stable NREM sleep (Berry, McNellis et al. 1997, Worsnop, Kay et al. 1998). Two explanations suggest themselves: first, different levels of stimulus (i.e. negative pressure pulse, or the "natural" condition of a collapsing airway at tidal volumes) elicit enhanced or reduced genioglossus activation as discussed earlier (Eckert, McEvoy et al. 2007) or second, body position has an effect on the activity of genioglossus. As Malhotra and colleagues discuss, many of the existing studies record genioglossus in the lateral sleeping position and this is problematic because genioglossus activity is augmented in the supine compared to the lateral position (Otsuka, Ono et al. 2000, Malhotra, Trinder et al. 2004). The augmentation of genioglossus activity when supine may also explain some of the discordance in the literature regarding chemical activation of upper airway dilator muscles during sleep. For example, Badr et al. showed that hypercapnia increased genioglossus activity in supine NREM sleep in normal subjects (Badr, Skatrud et al. 1991), while other studies, in which patients were positioned laterally during sleep,

demonstrated no increased activity of genioglossus with hypercapnia (Pillar, Malhotra et al. 2000, Stanchina, Malhotra et al. 2002).

The mechanism by which genioglossus is able to increase its activity in response to supine positioning has not been fully elucidated. It may be that the muscle responds to increased mechanical and chemical stimulus as the passive collapsibility of the upper airway is increased in the supine position. Additionally, the observed increase in genioglossus activity in the supine position may involve feedback from the vestibular apparatus. Supporting this, Otsuka et al. have demonstrated that when lying supine, with the head rotated to the side, the activity of genioglossus is not different to lying with the trunk and head oriented laterally so that in both positions the vestibular apparatus is oriented in the same plane (Otsuka, Ono et al. 2000). Furthermore, in cats stimulation of the vestibular apparatus results in augmented genioglossus EMG activity (Anker, Ali et al. 2003).

Lung volume

Lung volume is an important variable in sleep apnoea as it influences upper airway stability in normal subjects (Series, Cormier et al. 1990, Stanchina, Malhotra et al. 2003) and in OSA patients (Bradley, Brown et al. 1986), via caudal tracheal displacement and subsequent changes in upper airway tissue pressure, as demonstrated in dog, cat and rabbit models (Van de Graaff 1988, Rowley, Permutt et al. 1996, Kairaitis, Byth et al. 2007).

A number of studies have examined the effects of changes in lung volume on upper airway stability in subjects lying supine during sleep (Stanchina, Malhotra et al. 2003, Heinzer, Stanchina et al. 2006, Tagaito, Isono et al. 2007, Jordan, White et al. 2009, Squier, Patil et al. 2010). In 19 young normal subjects, reductions of 600mL in EELV, as measured with magnetometers, increased Pcrit by 1.1cmH_2O (rendering the airway more collapsible) despite an increased activation of genioglossus (Stanchina, Malhotra et al. 2003). Tagiato et al. demonstrated similar interactions between lung volume and Pcrit with increased lung volume. In 7 OSA patients, Tagiato et al. increased lung volume by 720mL which resulted in a fall in Pcrit by 1.2cmH_2O (Tagaito, Isono et al. 2007);

importantly this effect was independent of upper airway neuromuscular input as patients were anaesthetised and paralysed.

One of the mechanisms by which lung volume may be reduced in the supine posture in OSA patients is secondary to increasing abdominal fat distribution and increasing intra-abdominal pressure, which has been shown to influence FRC in anaesthetised obese individuals (Pelosi, Croci et al. 1997). Use of a pressure cuff to increase intra-abdominal pressure in obese male OSA patients while sleeping in the supine position caused EELV to fall by 530mL and upper airway closing pressure to increase by 1.4cmH_2O (Stadler, McEvoy et al. 2009). This paper demonstrates an interaction between increasing BMI, decreasing lung volume and increasing collapsibility of the upper airway.

Body position changes have relatively predictable effects on lung volumes in normal weight individuals, where lung volume is significantly reduced by a change in body posture from seated to supine and from lateral to supine. However, the effect that a change in body position has on lung volume is dependent on the BMI of the subject being examined. As shown in Figure 1.10, when normal subjects move from upright to supine there is a fall in functional residual capacity (FRC) (Ibanez Juve, Garcia Moris et al. 1979, Kauppinen-Walin, Sovijarvi et al. 1980, Behrakis, Baydur et al. 1983, Navajas, Farre et al. 1988), total lung capacity (TLC), expiratory reserve volume (ERV) and vital capacity (VC) without a change in residual volume (RV) (Navajas, Farre et al. 1988). Few studies address the effect of lateral positioning on lung volume, but in normal subjects ERV (Behrakis, Baydur et al. 1983) and FRC (Barnas, Campbell et al. 1992, Barnas, Green et al. 1993) increase and dynamic lung compliance decreases (Tanskanen, Kytta et al. 1997) when moving from the supine to the lateral position.

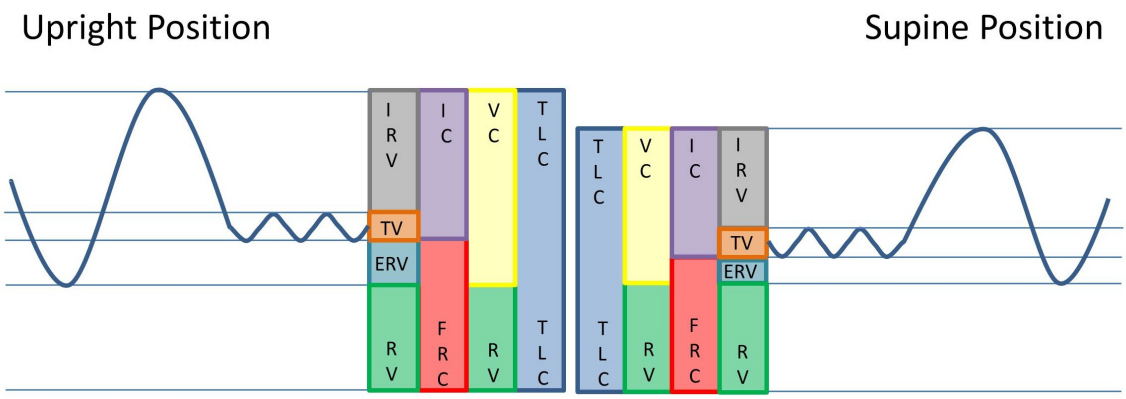

Figure 1.10 - Lung volume changes from upright to supine. IRV – inspiratory reserve volume, TV – tidal volume, ERV – expiratory reserve volume, RV – residual volume, IC – inspiratory capacity, FRC – functional residual capacity. From (Joosten, O'Driscoll et al. 2014).

In overweight (BMI 25 – 29.99kg/m^2) and in obese (class I, BMI 30 – 34.99kg/m^2; class II 35 – 40kg/m^2; class III >40kg/m^2) (World Health Organization. 2000) patients, the effect of body position on lung volume is more complex. A cross-sectional study of seated lung volumes demonstrated a linear decrease in TLC with increasing BMI (Jones and Nzekwu 2006). However, ERV and FRC decreased exponentially with increasing BMI over the 25-35kg/m^2 range (Jones and Nzekwu 2006) with a plateau in the decrease of ERV and FRC in the obese class III BMI range, see Figure 1.11. That is, once patients are in the obese class III BMI bracket, ERV and FRC remain relatively static in the face of further increases in BMI, probably because ERV approaches zero and FRC approximates RV.

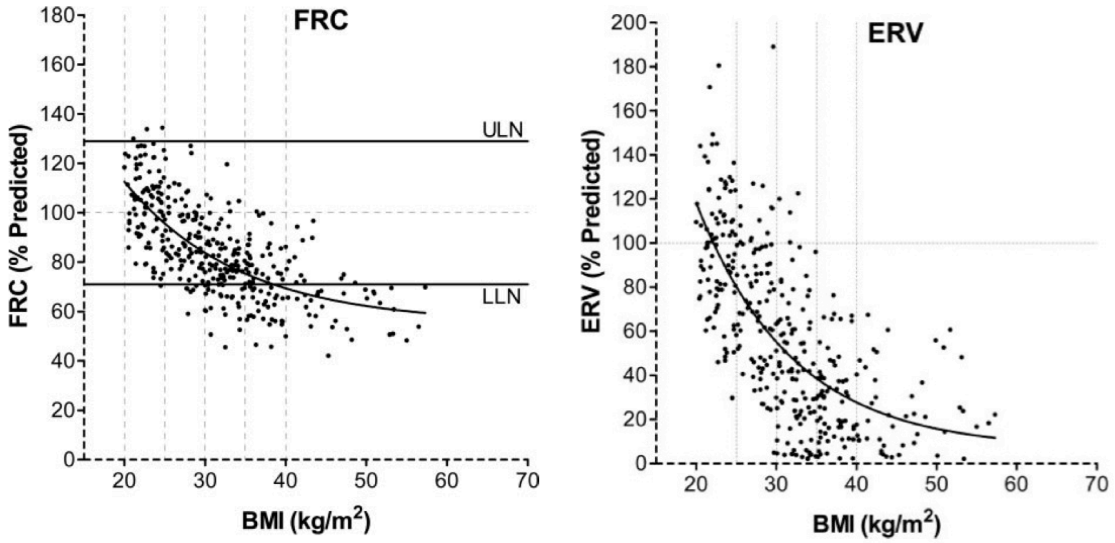

Figure 1.11 – The effect of increasing body-mass index (BMI) on functional residual capacity (FRC) and expiratory reserve volume (ERV). From (Jones and Nzekwu 2006).

In overweight and obese class I patients with OSA, FRC falls when moving from upright to supine (Shore and Millman 1984), as does forced vital capacity and other lung function measurements (Shepard and Burger 1990). These patients lie on the rapidly falling portion of the curve in the Jones study (see Figure 1.11) and still have capacity to lose FRC without reaching RV when moving from the seated to supine position.

In contrast to the overweight and obese class I BMI population, the FRC does not fall in the obese class II and III (BMI >35kg/m^2) when moving from upright to supine (Yap, Watson et al. 1995, Watson and Pride 2005). The balance of elastic forces of the lung and chest wall in these patients gives rise to lower lung volumes. As a result, FRC and ERV (Ferretti, Giampiccolo et al. 2001) are smaller than predicted in the seated posture, but change less compared to non-obese controls when adopting the supine position (Yap, Watson et al. 1995, Watson and Pride 2005) as these patients are already breathing at, or near, RV in the upright posture (i.e. FRC and RV are approximately equal).

In summary, the effects of body position changes on lung volume appear greatest for those patients with BMI <35kg/m^2. Moving from seated to supine does not change lung volume in those with BMI >35kg/m^2 most probably because their lung volume is already reduced to the point that FRC approximates RV and any further reductions would impact

TV. Importantly, patients with mild-moderate spOSA typically have a BMI in the obese range (BMI 30-35kg/m^2) (Joosten, Hamza et al. 2012). There are no published studies that investigate the effect of moving from the supine to lateral on lung volumes, either in OSA patients in general or in selected OSA phenotypes such as spOSA and siOSA.

Arousal

The role of arousal in the pathogenesis of OSA has received a great deal of attention over the last decade. Up until 10 years ago it was generally accepted that arousal from sleep was a necessary protective mechanism which enabled resolution of obstructive respiratory events and re-establishment of ventilation (Remmers, deGroot et al. 1978). However, a number of observations have led to the argument that an oversensitive arousal response (i.e. low arousal threshold) increases sleep disruption and predisposes to OSA in certain individuals.

Firstly, many respiratory events terminate without arousal (Carlson, Onal et al. 1995, Rees, Spence et al. 1995, Berry and Gleeson 1997), probably because of an effective recruitment of upper airway dilator muscles prior to the development of arousal (Onal, Lopata et al. 1982, Carlson, Onal et al. 1995, Berry, McNellis et al. 1997). Secondly, patients with OSA experience periods of stable breathing during the night with only 35% of the variability accounted for by mechanical load (Younes 2003). Thirdly, stable breathing in OSA patients often occurs in delta sleep (Ratnavadivel, Chau et al. 2009), when arousal threshold is at its highest level (Berry, Asyali et al. 1998). Fourthly, arousal from sleep can result in an overshoot in ventilation above eupneic ventilatory demand (Worsnop, Kay et al. 1998) with resultant hypocapnia and destabilisation of breathing (Onal, Burrows et al. 1986, Hudgel, Chapman et al. 1987), although this mechanism is disputed (Jordan, Eckert et al. 2011). And fifth, elevation of the arousal threshold with pharmacological intervention reduces the AHI in certain patients (Eckert, Owens et al. 2011).

The key initiating stimulus to arousal in OSA is thought to be respiratory effort, as measured by oesophageal pressure (Gleeson, Zwillich et al. 1990). Recent data demonstrate that there is an increase in oesophageal pressure when moving from the

seated to supine position in awake obese and normal weight individuals (Owens, Campana et al. 2012) and it would seem that respiratory effort would have to be greater in the supine position to overcome the unfavourable physiology of that position. Oesophageal pressure also changes significantly from lateral to supine but with the changes of a smaller magnitude than upright to supine, as demonstrated in normal weight subjects (Milic-Emili, Mead et al. 1964) and even when taking lung volume changes into account (Washko, O'Donnell et al. 2006). As such, and if the arousal threshold was not altered by body position, one might expect to see more rapid and frequent arousal from sleep in the supine position compared to the lateral position as pleural pressures (approximated by oesophageal pressure) and, therefore, respiratory effort is higher. However, respiratory events in supine sleep are more severe than in lateral sleep with an increased apnoea duration, increased desaturation and increased arousal length (Oksenberg, Khamaysi et al. 2000). The combination of increased respiratory effort but more severe respiratory events in the supine posture compared to the lateral position suggests that arousal threshold may be raised in the supine position. There are no published data exploring the effect of body position on arousal threshold.

Ventilatory control instability and loop gain

If chemical drive is to continually maintain upper airway patency in an upper airway susceptible to collapse, any washing out of CO_2, as would occur in the context of increased ventilation above eupneic ventilatory demand (ventilatory overshoot), may result in a fall in chemical drive below the level required to maintain airway patency. We know that ventilatory responses following airway opening (both with and without arousal from sleep) in patients with OSA exceed eupneic ventilatory demand (Worsnop, Kay et al. 1998, Younes 2004), i.e. they are excessive and likely to result in a fall in chemical drive below the eupneic drive level. In this way OSA represents a state of ventilatory control instability in which excessive ventilatory responses following airway opening result in a fall in chemical drive to pump and resistance muscles, which in turn may perpetuate recurrent upper airway obstruction.

Loop gain is a useful way of conceptualising the contribution of ventilatory control instability to the development of apnoea in both obstructive and central sleep apnoea.

Loop gain is simply the ratio of response (i.e. change in ventilatory drive) to an initial disturbance in ventilation. If the ratio is >1, the response will itself create a disturbance that is greater than the initial disturbance and the following response will be even greater. Such a scenario (see Figure 1.12) would promote large swings in ventilation with recurrent ventilatory overshoot, reductions in gas tensions (and therefore chemical drive) and resultant ventilatory undershoot (or upper airway obstruction and obstructive apnoea once chemical drive falls below the threshold necessary to keep the upper airway patent in OSA). In this way, respiratory instability may be precipitated by anything that increases the ventilatory sensitivity to hypoxia and/or hypercapnia (controller gain), or results in underdamping of responses in blood gases to changes in ventilation such as reductions in lung volume or an elevation in the efficiency of gas exchange (plant gain), or changes to the transit time of blood from the lungs to the chemoreceptors (most relevant in central sleep apnoea).

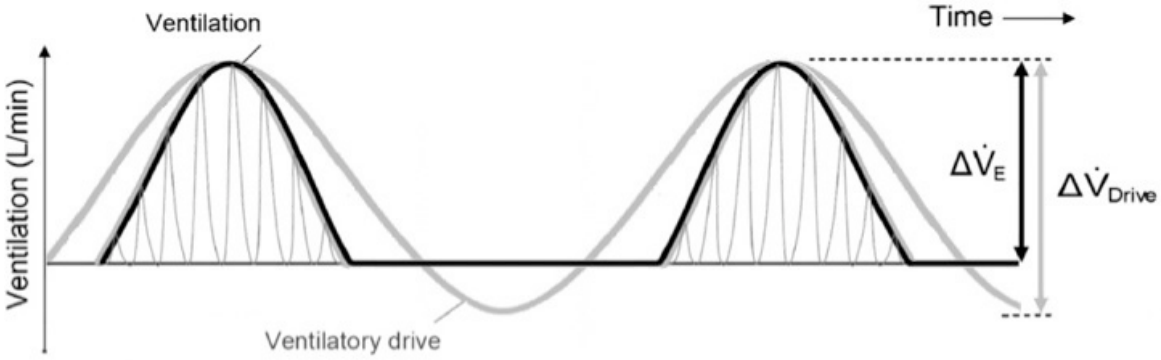

Figure 1.12 – Relationship of ventilation to ventilatory drive. Once ventilatory drive falls below the level required to maintain patency in an upper airway susceptible to collapse, upper airway obstruction and apnoea occur. $\Delta\dot{V}_E$ – disturbance, $\Delta\dot{V}_{DRIVE}$ - response. Adapted and modified from (Sands, Edwards et al. 2011).

A number of studies have assessed controller gain in patients with OSA. The reported ventilatory response in awake OSA patients to either hypercapnia or hypoxia is variable depending on the study chosen. Some have demonstrated that the response to increasing CO_2 is higher than in normal subjects (Hudgel, Gordon et al. 1998), while others have demonstrated an elevated ventilatory response in awake OSA patients to a hypoxic stimulus, but not to a hypercapnic stimulus (Narkiewicz, van de Borne et al. 1999). The source of variability in the literature on this issue may be a combination of the awake state of the patients and the nature of the stimulus used. Most of the studies assess either

hypercapnia or hypoxia in isolation (when in OSA both occur simultaneously) and usually allow the gas stimulus to accumulate over several minutes (usually via a re-breathing technique). Younes et al. demonstrated that the ventilatory response to a hypoxic (11% or 15% O2) and hypercapnic (3% CO2) gas mixture (administered rapidly over a 30 second interval, in order to mimic the effects of OSA) in asleep OSA patients is thought to be excessive at 134 ± 77% of eupneic ventilatory levels (Younes, Ostrowski et al. 2007). The ventilatory response to the hypoxic and hypercapnic gas mixture in the same patients was attenuated by the use of CPAP, suggesting that the elevated controller gain present in these patients is acquired during the course of developing OSA (Loewen, Ostrowski et al. 2009). Further evidence that elevated controller gain is an important contributor to OSA in certain patients comes from studies that attempt to pharmacologically manipulate loop gain. Wellman and colleagues demonstrated that the administration of supplemental oxygen to OSA patients with a high loop gain lowered the AHI significantly (Wellman, Malhotra et al. 2008) most probably through an improvement in controller gain. In addition, administration of 500mg of Acetazolamide twice daily to subjects with treated OSA reduced the NREM AHI by 50% (Edwards, Sands et al. 2012). It is not clear whether Acetazolamide's primary action is to improve plant gain or controller gain with several conflicting studies on the topic (Edwards, Sands et al. 2012). Acetazolamide may have additional modes of action and it has been found to exert an influence on post-arousal ventilatory overshoot (Edwards, Connolly et al. 2013).

In the past 20 years a number of methods have been developed to measure loop gain in sleeping patients. Using a ventilation strategy known as proportional assist ventilation, in which tidal volume is augmented in order to increase controller gain and therefore loop gain until breathing becomes unstable, it has been shown that loop gain is higher in OSA patients (Younes, Ostrowski et al. 2001, Wellman, Jordan et al. 2004) than normal subjects (Wellman, Malhotra et al. 2003). Because in these studies both OSA patients and normals have a loop gain <1, an elevated loop gain, secondary to increased controller gain, cannot be the only cause of OSA. Indeed, Wellman and colleagues demonstrated that in subjects with a very positive Pcrit (> +1cmH2O) loop gain did not correlate well with AHI, suggesting that anatomical factors are the predominant contributor to airway obstruction in this group. However, in those with a peri-atmospheric Pcrit (-1 to

+1cmH2O) loop gain was strongly correlated with AHI, suggesting that in those patients with a vulnerable airway loop gain may act as an important inciting factor to airway obstruction (Wellman, Jordan et al. 2004, Eckert, White et al. 2013).

The effect of body position on ventilatory control instability in OSA patients has not been studied. However, with respect to central sleep apnoea a number of studies have demonstrated a worsening of Cheyne-Stokes respiration when patients lie in the supine position compared to the lateral position (Sahlin, Svanborg et al. 2005, Szollosi, Roebuck et al. 2006). Reduced lung volume (increased plant gain) with adoption of the supine position has been postulated as the cause of the high loop gain and subsequent respiratory instability (Sahlin, Svanborg et al. 2005, Szollosi, Roebuck et al. 2006), although change in lung volume in this patient group has not been directly measured and is disputed (Soll, Yeo et al. 2009).

The overall contribution of ventilatory control instability to the generation of obstructive respiratory events in the supine compared to lateral position is not known. It may be that the reduced lung volume seen in the supine position contributes to ventilatory instability via an increased plant gain in some OSA patients, but this remains to be proven.

1.3.4 Modelling and measuring the pathophysiological contributors to OSA

Many pathophysiological factors contribute to airway obstruction in OSA, in particular: upper airway collapsibility, the ability of the upper airway dilator muscles to stiffen and prevent collapse, respiratory control instability and a low arousal threshold. Measuring these traits individually is technically challenging, expensive and often involves patient discomfort above and beyond that experienced during standard polysomnographic techniques. Thus we have not been able to measure these factors in a clinical context, which in turn hinders the applicability of information regarding these factors and their implications for individualised treatment for individual patients.

Recent advances in measuring the physiological traits that contribute to OSA have overcome some of the aforementioned technical difficulties. Wellman and colleagues

have created an innovative method that measures upper airway collapsibility, the ability of the upper airway muscles to stiffen and dilate the airway, loop gain and arousal threshold in an individual patient (Wellman, Eckert et al. 2011, Wellman, Edwards et al. 2013). The technique can be performed using standard polysomnographic methods with the simple addition of the measurement of exhaled O_2 and CO_2 and the use of a pneumotachograph to measure flow. Importantly, there is no need for uncomfortable or painful instrumentation with intramuscular electrodes or oesophageal pressure cannulae.

In more detail, the technique involves a series of controlled pressure drops in a patient receiving therapeutic CPAP. CPAP is altered during sleep to measure 4 different ventilations and loop gain: i) eupneic ventilatory demand, ii) ventilation off CPAP (pressure = 0 cmH_20) when the upper airway dilator muscles are quiescent, iii) the ventilation at which respiratory arousals begin to occur and iv) ventilation off CPAP (pressure = 0 cmH_20) when the upper airway dilator muscles are activated during sleep, v) loop gain assessed by the ratio of the ventilatory drive response to a disturbance in ventilation. The method for measuring the factors is summarised in Figure 1.13.

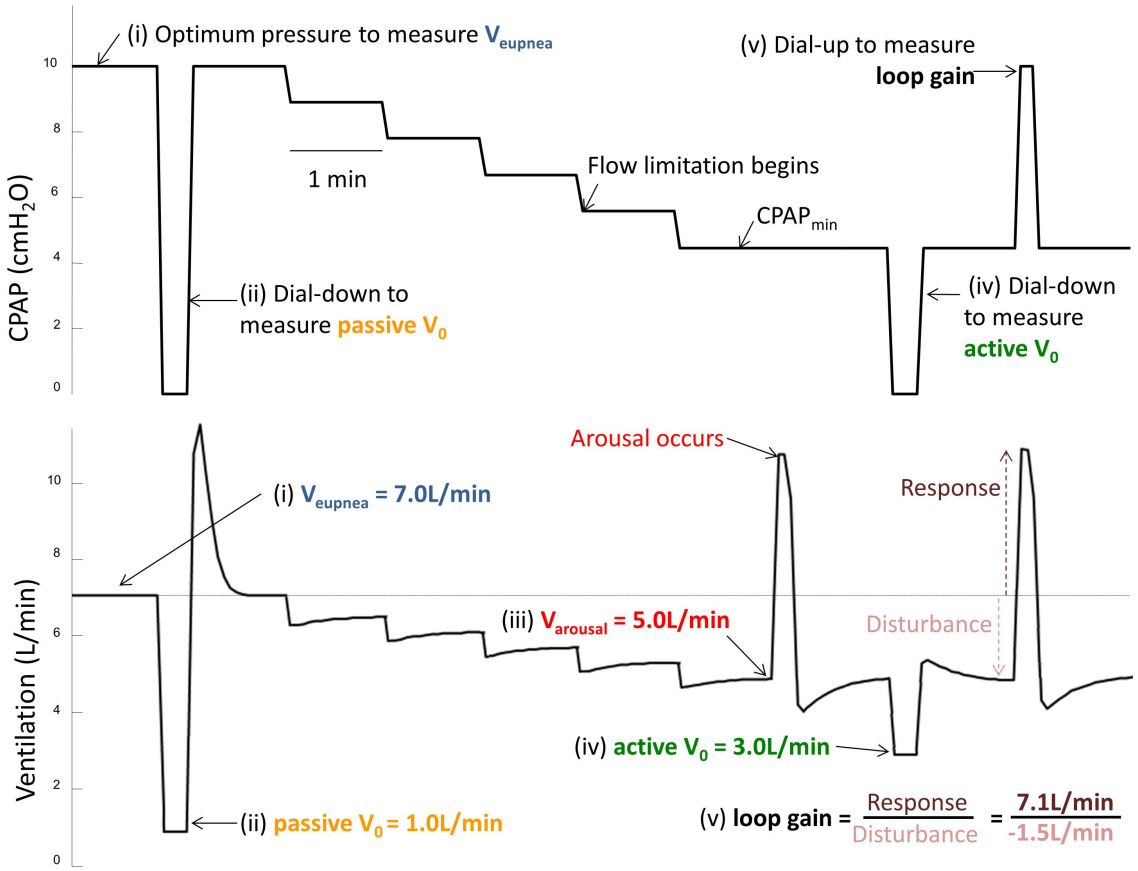

Figure 1.13 - CPAP dial-down method for measuring phenotypic traits. V_{eupnea} – ventilation at optimal CPAP with no evidence of snoring or flow limited breathing, Passive V_0 – ventilation at CPAP = 0cmH_2O with completely relaxed pharyngeal muscles, $V_{arousal}$ – the ventilation just prior to a respiratory-induced arousal, Active V_0 – ventilation at CPAP = 0cmH_2O with maximally activated pharyngeal muscles, Loop Gain – is the ratio of ventilatory overshoot (response) above V_{eupnea} when returning to optimal CPAP pressure from a period of sub-optimal CPAP with reduced ventilation (disturbance). Adapted from (Wellman, Edwards et al. 2013)

Wellman plots the various ventilations and calculates upper airway gain and arousal threshold on a ventilation versus ventilatory drive graph, enabling a visual analysis of the pathophysiological traits as demonstrated in Figure 1.14.

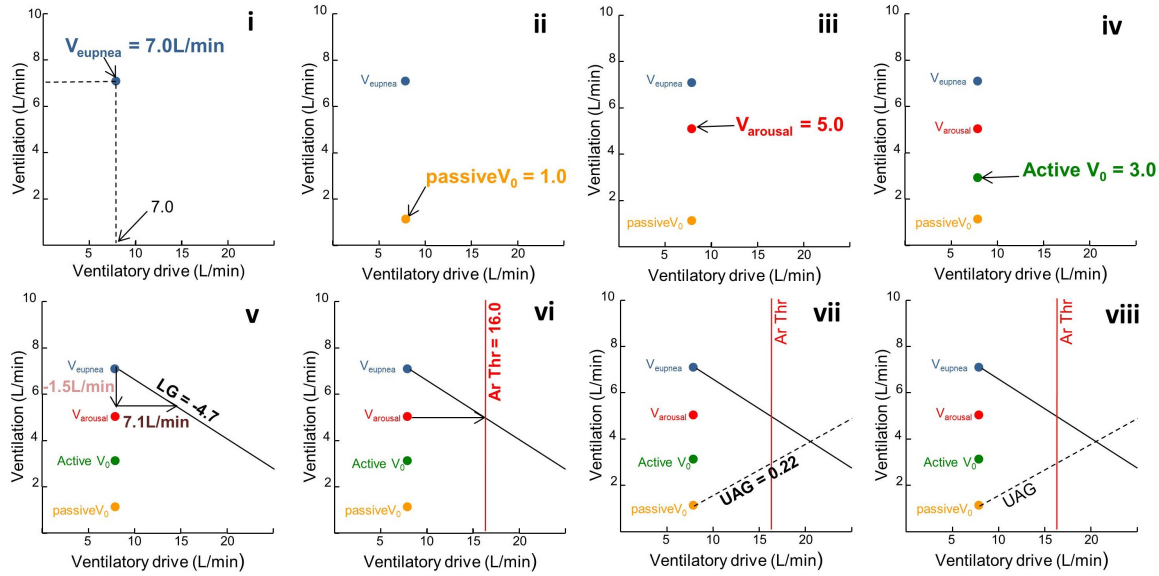

Figure 1.14 – Plotting the phenotypic trait variables. UAG – upper airway gain, ArThr – arousal threshold. Adapted from (Wellman, Edwards et al. 2013).

The model enables a visual assessment that can help predict OSA as demonstrated in Figure 1.15. If the upper airway gain line and loop gain line intersect to the left of the arousal threshold line then steady state ventilation can be achieved without arousal. However, if the upper airway gain line and loop gain line intersect to the right of the arousal threshold line then the patient will arouse before steady state ventilation can be achieved.

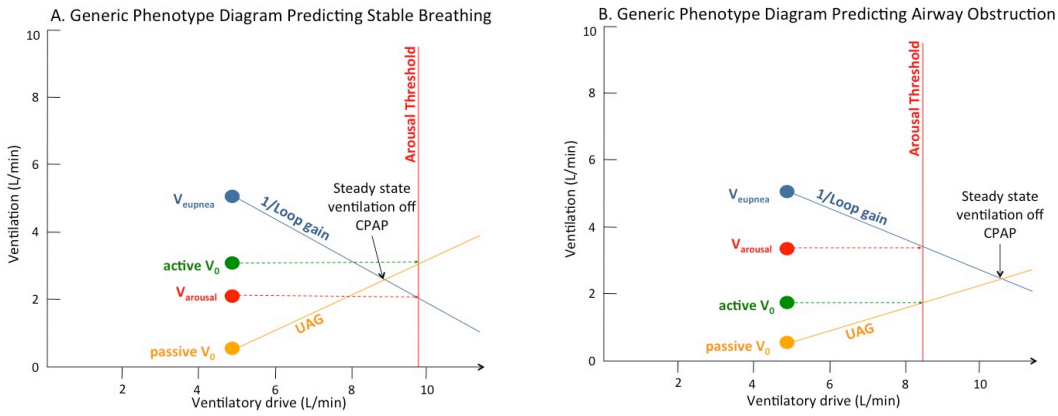

Figure 1.15 – Generic phenotype diagram demonstrating steady state ventilation (left panel) and arousal before steady state ventilation can be achieved (right panel). UAG – upper airway gain, CPAP – continuous positive airway pressure.

This method is an important advance in identifying the contributors to OSA in an individual. If treatment advances are to be made involving individualised therapy (for example administering a non-muscle relaxant sedative to a patient with a high arousal threshold, or acetazolamide to a patient with a high loop gain) then measurement of these traits in a clinical setting needs to be simplified further.

1.3.5 Treatment of OSA and positional OSA

For the past 30 years the gold standard of treatment for patients suffering from OSA has been CPAP therapy. The treatment was developed as a way of preventing upper airway collapse by Sullivan and colleagues (Sullivan, Issa et al. 1981). It most likely prevents upper airway obstruction by pneumatically splinting the pharynx so that the collapsing forces of the surrounding tissues are overcome (Alex, Aronson et al. 1987) although another putative mechanism is an increase in lung volume with subsequent caudal tracheal traction and relief of pharyngeal transmural tissue pressures (Squier, Patil et al. 2010).

CPAP is recommended as first line treatment for patients with moderate to severe OSA (Kushida, Littner et al. 2006) and for patients with mild-moderate OSA who are symptomatic (Weaver, Mancini et al. 2012). The use of CPAP therapy results in improvements in daytime sleepiness (Patel, White et al. 2003), quality of life (Avlonitou, Kapsimalis et al. 2012), risk of motor vehicle accidents (George 2001), hypertension (Martinez-Garcia, Gomez-Aldaravi et al. 2007) and stroke (Martinez-Garcia, Campos-Rodriguez et al. 2012). CPAP treatment is also cost effective (Ayas, FitzGerald et al. 2006).

However, many patients prescribed CPAP therapy fail to use the treatment for 4 or more hours per night (Weaver and Grunstein 2008) which is the threshold above which most patients will experience subjective improvements in sleepiness (Weaver, Maislin et al. 2007). The difficulty that many patients have with CPAP treatment has driven the exploration of alternative therapies for OSA. In this context, understanding the pathophysiological contributors to airway collapse in a given patient offers the prospect

of individualised treatment for OSA. The most obvious form of individualised therapy for OSA is the use of positional modification devices in the treatment of supine related OSA. A number of positional modification devices have been demonstrated to be efficacious in preventing supine sleep and thus reducing the overall AHI (Jokic, Klimaszewski et al. 1999, Loord and Hultcrantz 2007, Permut, Diaz-Abad et al. 2010, Bignold, Mercer et al. 2011). However, the selection of patients for the use of these devices remains an unresolved issue. Clearly choosing patients with a high supine AHI and a low non-supine AHI is important, but there are no current data assessing the repeatability of the non-supine AHI from night-to-night. Thus, advising patients regarding this form of treatment remains somewhat arbitrary.

Understanding the degree to which a certain pathophysiological process (e.g. ventilatory control instability) contributes to airway obstruction in a given patient could help direct individualised treatment for that patient. We know that OSA is a heterogeneous disorder with unfavourable airway anatomy the main contributor, but with other non-anatomical factors contributing to airway collapse in many patients (Eckert, White et al. 2013). In a similar way, understanding how a given treatment affects the pathogenesis of OSA will also help direct therapy. For instance, we know that the administration of oxygen improves ventilatory control instability (loop gain) (Wellman, Malhotra et al. 2008) or that the use of non-muscle relaxant sedatives reduces AHI in patients with a low arousal threshold by elevating the arousal threshold (Eckert, Owens et al. 2011). If we are able to easily identify patients with abnormalities in loop gain or arousal threshold then a theoretical pathway for individualised treatment exists.

However, despite most patients favouring the lateral sleeping position (Joosten, Hamza et al. 2012), we do not know the effect of lateral positioning on the ability of the airway to stiffen and dilate or how it affects the non-anatomical contributors to OSA (i.e. loop gain and arousal threshold). Given that positional modification treatments have already been tested and applied in a clinical setting (Jokic, Klimaszewski et al. 1999, Bignold, Mercer et al. 2011) they have an advantage over other proposed individualised therapies, which have not been tested in clinical trials (such as non-muscle relaxant sedatives). If positional

therapy is to find a place in the individualised treatment of OSA then understanding its effects on the pathogenesis of the condition is crucial.

1.4 RATIONALE FOR THE STUDY

Obstructive sleep apnoea is a common medical disorder affecting over 5% of the population (Davies and Stradling 1996, Lindberg and Gislason 2000). The condition is associated with serious adverse outcomes including excessive sleepiness (Gottlieb, Whitney et al. 1999), depression (Peppard, Szklo-Coxe et al. 2006), motor vehicle accident (Teran-Santos, Jimenez-Gomez et al. 1999), systemic hypertension (Nieto, Young et al. 2000, Peppard, Young et al. 2000), the metabolic syndrome (Coughlin, Mawdsley et al. 2004), insulin resistance (Ip, Lam et al. 2002) and subsequent cardiac ischemia and arrhythmias (Shahar, Whitney et al. 2001, Shamsuzzaman, Gersh et al. 2003, Mehra, Benjamin et al. 2006). Most people with OSA experience a preponderance of respiratory events in the supine sleeping position (Pevernagie and Shepard 1992, Oksenberg, Silverberg et al. 1997, Richard, Kox et al. 2006, Joosten, Hamza et al. 2012), with up to 25% of patients experiencing airway obstruction exclusively in the supine position (Mador, Kufel et al. 2005, Gillman, Roebuck et al. 2012, Joosten, Hamza et al. 2012). In addition, most patients spend an average of 40% of the night lying in the supine position (Joosten, Hamza et al. 2012). As a result, defining the pathological contributors to supine OSA and understanding how positional modification devices affect the process of airway obstruction in supine OSA patients could have a significant impact on individualised therapy for OSA.

The existing definitions of supine OSA (i.e. spOSA and siOSA) are arbitrary. The definition of siOSA is appealing from a clinical perspective, however, it is yet to be established which patients will benefit from avoiding supine sleep. The assumption underlying positional modification treatment is that if a patient has a lower AHI in the lateral position, as observed on a single overnight polysomnogram, restricting their sleep to the lateral position should reduce the number of respiratory events. However, we do not know if the lateral AHI and supine sleep time are repeatable measures from night-to-night and, therefore, if positional modification will have the desired impact on breathing. Furthermore, the justification for intervening in supine OSA is the assumption that the supine AHI will remain elevated from night-to-night, which has not been proven to date.

The clear importance of the supine sleeping position to the generation of obstructive events in most patients belies the paucity of data regarding the effect of body position on the pathogenesis of OSA. The literature regarding upper airway shape and size is conflicting and confusing, largely because of the different imaging modalities utilised, but also because there are no studies that examine patients with spOSA or siOSA and compare them to matched controls. Whilst the data pertaining to passive airway properties (i.e. passive Pcrit) are more consistent, there are no data regarding the effect of body position on the ability of the airway to stiffen and dilate in response to collapsing pressures (i.e. active Pcrit). Despite the well-established role of lung volume (Jordan, White et al. 2009), ventilatory control instability (Wellman, Jordan et al. 2004) and arousal threshold (Younes 2004) in the pathogenesis of OSA, there is a striking lack of evidence regarding the effect of body position on these factors.

This thesis aimed to determine the mechanisms underlying the supine predominance of OSA and to test whether patients truly can be categorised as having a supine form of the disease that manifests from night to night. A related aim was to clarify the definition of supine related OSA and the effect of body position on airway size and shape. By recruiting patients who suffer OSA we were able to directly examine the pathogenesis of the condition. Access to the latest in imaging technology and the use of recently developed non-invasive methods for measuring the traits known to contribute to OSA (Wellman, Edwards et al. 2013) allowed for the application of cutting edge research techniques to aid our exploration of the outlined gaps in the current literature regarding supine related OSA.

1.5 AIMS AND HYPOTHESES:

These aims resulted in three studies, each presented in its own chapter and published in the literature as separate manuscripts:

Aim 1

To investigate the repeatability of traditionally defined supine predominant OSA on consecutive polysomnographic recordings.

To investigate if the repeatability of supine predominant OSA can be improved by systematically altering the definition.

To investigate the night-to-night repeatability of a low non-supine AHI.

Hypotheses

The traditional definition of supine predominant OSA has poor night-to-night repeatability.

The definition of supine related OSA can be altered to produce a more clinically relevant outcome, whereby it delivers a phenotype in which patients experience respiratory events in the supine position consistently from night-to-night and have a consistently low non-supine AHI.

Aim 2

To investigate the effect of body position on lung volume, airway size and airway shape in patients with supine related OSA.

To compare lung volume, airway size and airway shape in the supine and lateral position in patients with supine related OSA to matched controls.

Hypotheses

Patients with supine related OSA demonstrate an improvement in lung volume, airway size and airway shape in the lateral position.

Patients with supine related OSA demonstrate a greater improvement in lung volume airway size and airway shape in the lateral position compared to matched controls.

Aim 3

To investigate the influence of body position on passive upper airway anatomy, upper airway gain, loop gain and arousal threshold in patients with severe OSA.

To compare passive upper airway anatomy, upper airway loop gain and arousal threshold in patients with supine related OSA to non-positional OSA patients.

Hypotheses

Patients with severe OSA demonstrate an improvement in passive upper airway anatomy and upper airway gain in the lateral position with no improvement in loop gain and arousal threshold.

Patients with supine related OSA demonstrate a greater improvement in passive upper airway anatomy and upper airway gain compared to non-positional OSA patients.

CHAPTER 2

NIGHT-TO-NIGHT REPEATABILITY OF SUPINE RELATED OBSTRUCTIVE SLEEP APNOEA

2.1 DECLARATION FOR THESIS CHAPTER 2

Declaration by candidate

In the case of Chapter 2, the nature and extent of my contribution to the work was the following:

Nature of contribution	**Contribution**
For this chapter I was responsible for hypothesis generation, data analysis, interpretation of results and manuscript preparation.	80%

The following co-authors contributed to the work. If co-authors are students at Monash University, the extent of their contribution in percentage terms must be stated:

Name	**Nature of contribution**	**Contribution % (student co-authors only)**
Dr FJ O'Donoghue	Aided in manuscript preparation.	
Mr PD Rochford	Aided in data collection and manuscript preparation.	
Dr M Barnes	Aided in manuscript preparation.	
A/Prof. K Hamza	Aided in data analysis.	
Mr T Churchward	Aided in data collection.	
Dr PJ Berger	Aided in hypothesis generation, data analysis and manuscript preparation.	
Dr GS Hamilton	Aided in hypothesis generation, data analysis and manuscript preparation.	

The undersigned hereby certify that the above declaration correctly reflects the nature and extent of the candidate's and co-authors' contributions to this work*.

Candidate's		**Date**

Signature		

Main Supervisor's Signature		**Date**

2.2 INTRODUCTION TO CHAPTER

As discussed in Chapter 1, several different patterns of OSA have been described on the basis of the AHI (Joosten, Hamza et al. 2012). The most common pattern of sleep apnoea is one where the majority of events are observed in the supine sleeping position, which is usually defined as being present when the AHI is greater than 5 events/hr and respiratory events occur at twice the frequency in the supine sleeping position compared to the non-supine sleeping positions (Cartwright 1984, Oksenberg, Silverberg et al. 1997). An alternative definition of supine OSA has been proposed (Mador, Kufel et al. 2005) whereby the ratio of events in the supine position to the non-supine positions must be greater than two to one and the AHI in the non-supine positions must be less than 5 events/hr. The definitions were proposed in an ad hoc fashion with the underlying idea that positional modification (avoidance of supine sleep) could be used as a treatment for those patients that experienced the majority of respiratory events when lying supine.

One potential issue in using the AHI to classify patients relates to the repeatability or variability of the metric. Although a number of studies demonstrate a strong correlation in AHI across nights (Mosko, Dickel et al. 1988, Aber, Block et al. 1989, Dealberto, Ferber et al. 1994, Mendelson 1994, Le Bon, Hoffmann et al. 2000, Bittencourt, Suchecki et al. 2001), when patients are categorized according to their AHI several authors have found that patients will change categorization across nights (Mosko, Dickel et al. 1988, Bliwise, Benkert et al. 1991, Chediak, Acevedo-Crespo et al. 1996). The use of statistical techniques, such as the Bland-Altman plot, has helped elucidate the seeming contradiction of a strong correlation and yet a frequent change of classification across nights. By interrogating the individual repeatability of a test, the Bland-Altman plot revealed a large individual variability in AHI from night-to-night despite the presence of a strong correlation in the population data (Le Bon, Hoffmann et al. 2000, Bittencourt, Suchecki et al. 2001).

The issue of AHI variability across nights is of critical importance to the classification and treatment of patients with spOSA and siOSA. Positional treatment for spOSA and siOSA, where patients are prevented from sleeping on their back, has been reported as a

viable alternative to CPAP therapy (Jokic, Klimaszewski et al. 1999). Treating patients with positional modification based on a single overnight AHI measurement makes three inherent assumptions. Firstly, that the supine predominant phenotype is reproducible from night-to-night and secondly, and partly related, that supine sleep time remains sufficient from night-to-night to warrant treatment, and thirdly that the lateral AHI is consistently low so that preventing patients from sleeping on their back will be effective at reducing the total AHI.

Our results demonstrate that the current definitions used to classify patients as having spOSA or siOSA have poor repeatability from night-to-night. We have demonstrated that the optimal definition of supine related OSA, in terms of night-to-night repeatability, is one that incorporates a supine AHI to non-supine AHI ratio of greater than 4 to 1. There is no optimal definition for female subjects, who have poor repeatability regardless of the definition applied. Bland-Altman analysis demonstrates high repeatability for a non-supine AHI of less than 10 events/hr. We conclude that male patients with a supine to non-supine AHI ratio of greater than 4 to 1 and a non-supine AHI of less than 10 events/hr are most likely to benefit from treatment with positional modification.

As per Monash University guidelines for thesis by publication, the following chapter is presented as a PDF as it has been published.

2.3 NIGHT-TO-NIGHT REPEATABILITY OF SUPINE RELATED OBSTRUCTIVE SLEEP APNOEA

Joosten SA, O'Donoghue FJ, Rochford PD, Barnes M, Hamza K, Churchward TJ, Berger PJ, Hamilton GS

Annals of the American Thoracic Society. **11**(5), 761-769, 2014.

ORIGINAL RESEARCH

Night-to-Night Repeatability of Supine-related Obstructive Sleep Apnea

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Abstract

Rationale: Patients with obstructive sleep apnea (OSA) experience respiratory events with greater frequency and severity while in the supine sleeping position. Postural modification devices (PMDs) prevent supine sleep, although there is a paucity of guidance to help clinicians decide when to use PMDs for their patients. In order for PMDs to treat OSA effectively, patients must experience respiratory events in the supine sleeping position consistently from night to night and must have a low nonsupine apnea and hypopnea index (AHI_{NS}).

Objectives: To document the repeatability of traditionally defined supine predominant OSA on consecutive polysomnography, to determine whether the consistency of the supine-predominant phenotype can be improved by altering the definition of it, and to determine whether a low AHI_{NS} is repeatable from night to night.

Methods: We recruited 75 patients for polysomnography on two separate nights. Patients were classified as having supine OSA on each night on the basis of traditional and novel definitions, and the classification systems used were compared on the basis of agreement from night to night.

Measurements and Main Results: The definition of supine OSA with the highest level of agreement from night to night incorporates a supine AHI (AHI_S) to AHI_{NS} ratio $\geq$4:1. In addition, agreement exists for males, but there is poor agreement for female patients, regardless of the definition applied. An AHI_{NS} $<$10 events/hour is highly repeatable from night to night.

Conclusions: Males with an AHI_S:AHI_{NS} ratio $\geq$4:1 and an AHI_{NS} $<$10 events/hour represent a consistent supine-predominant OSA phenotype from night to night. This patient group is likely to benefit from treatment with PMD.

Keywords: sleep-disordered breathing; diagnosis; sleep-disordered breathing; management

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Author Contributions: S.A.J.: conception, hypothesis delineation, data analysis, manuscript preparation. F.J.O.: conception, data acquisition, manuscript preparation. P.D.R.: conception, data acquisition, manuscript preparation. M.B.: conception, data acquisition, manuscript preparation. K.H.: data analysis, manuscript preparation. T.C.: data analysis, manuscript preparation. P.J.B.: hypothesis delineation, manuscript preparation. G.S.H.: conception, hypothesis delineation, data analysis, manuscript preparation.

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Continuous positive airway pressure (CPAP) remains the gold standard for treating obstructive sleep apnea (OSA). In patients with OSA, CPAP improves neurocognitive function (1), blood pressure, and quality of life (2) and reduces the risk of motor vehicle accidents (3). It may also reduce the frequency of cardiovascular events (4). Despite these benefits, many patients cannot tolerate CPAP and either reject it outright or are only partially compliant (5, 6). Research continues to focus on finding alternative treatments for this important disease.

A prominent strategy now being adopted by many researchers is to develop new treatments that are based on classifying patients with OSA according to shared anatomical and physiological features (7–10). Once a patient has been phenotyped, it should be possible to design a treatment that overcomes the phenotypic features that predispose the patient to developing sleep apnea. One large category that has been identified is made up of patients whose OSA is most severe while in the supine sleeping position (11). To be assigned to the

supine predominant OSA group, the most common definition requires the ratio of the apnea and hypopnea index (AHI) in supine sleep (AHI_S) to the AHI in nonsupine sleep (AHI_{NS}) to be >2. Although this definition is somewhat arbitrary, supine-predominant OSA thus defined afflicts between 50–60% of the entire OSA population (12, 13) and has a marked male predominance (13, 14), and patients with it are younger and have a lower body mass index (BMI) than with non–position-related patients with OSA (12, 15, 16). The clinical importance of recognizing supine-predominant OSA is that avoidance of the supine posture in sleep through the use of a postural modification device (PMD) in these patients may produce a significant improvement in OSA severity (17) and could even abolish sleep-disordered breathing altogether (18).

There are two inherent assumptions underlying the decision to treat supine-predominant OSA with a PMD. First, the supine-predominant phenotype is reproducible from night to night, and, second, the AHI_{NS} is consistently low, so that preventing patients from sleeping in the supine position will be consistently effective at lowering the total AHI. To our knowledge, these assumptions have never been tested. The aims of this study therefore were to document the repeatability of traditionally defined supine-predominant OSA on consecutive PSGs, to determine if the consistency of the supine-predominant phenotype can be improved by altering this definition, and to determine if a low AHI_{NS} is repeatable from night to night.

Methods

Patients were enrolled through the Institute for Breathing and Sleep at Austin Health in Melbourne, Australia. Ethics approval for the conduct of this research was obtained from the Human Research Ethics Committee of Austin Health. Each Monday during the study period, a database of OSA referrals was interrogated for all patients awaiting diagnostic polysomnography. The list order of patients was randomized, and the first patients were recruited. This "quasi-consecutive" strategy was employed because referrals outstripped the capacity to perform research studies. The exclusion criteria were (*1*) inability to provide informed consent, (*2*) domicile more than 75 km from Austin Health, and (*3*) not meeting the PSG result inclusion criteria described forth below.

Patients were studied on two nights with no more than 4 days intervening. PSG recordings were performed per the American Academy of Sleep Medicine (AASM) recommendations (19) using Compumedics E-Series equipment (Compumedics, Abbotsford, Australia). Body position was recorded with a body position sensor (part number 7000-0104-02; Compumedics) placed over the sternum and attached to the thoracic inductance band with Velcro (Hallam, Australia) and tape and verified by video monitoring, with manual correction as appropriate. The sensor uses a series of gravity-referenced switches to output a signal indicating one of four possible positions: supine, left lateral, right lateral, or prone.

Deidentified PSGs were staged and scored by an experienced sleep scientist participating in internal and external quality assurance programs in accordance with AASM guidelines (19).

Included patients were required to have OSA (AHI >5 events/h) on both PSGs, experience ⩾30 minutes supine and ⩾30 minutes nonsupine sleep on both PSGs. We then classified patients as having supine-related OSA on the basis of the following two published definitions (11, 15): (*1*) supine-predominant OSA (spOSA), in which the AHI_S to AHI_{NS} ratio is ⩾2 to 1; and (*2*) supine-isolated OSA (siOSA), in which the AHI_S to AHI_{NS} ratio is ⩾2 to 1 *and* the AHI_{NS} is <5 events/hour. Data were collated using Microsoft Excel 2010 software (Microsoft Corp., Redmond, WA) and analyzed using IBM SPSS software (2011, Release 20.0.0; IBM Corp., Chicago, IL).

The stability of PSG phenotypic classification across nights was analyzed using the raw agreement and the κ statistic because of the categorical nature of the classification system. The raw agreement was calculated as the number of subjects who were classified in the same way on both study nights divided by the total number of subjects (including both "positive hits" and "negative hits," i.e., patients classified as meeting the criteria on both nights or as not meeting the criteria on both nights). The kappa (κ) value was used because it takes into account chance agreement. The strength of the association as determined by the κ value was judged according to the scale established by Landis and coworkers (20). Although the statistical significance of the κ value is reported in terms of a *P* value, this value is not representative of the strength of the agreement, but rather that the reported κ value is not due to chance alone.

We explored the effect of altering the definitions by iteratively increasing the AHI_S:AHI_{NS} ratio. We increased the ratio from 2 to 2.5, 3, 3.5, 4, 4.5, and 5 and explored the effect of each ratio on the agreement of the classification system across nights. Given the known sex difference in prevalence of spOSA and siOSA, we stratified the results according to sex. Finally, the variability in AHI_{NS} across study nights was analyzed by charting a Bland-Altman plot (21). All results are given as mean (±SD) unless otherwise stated. A *P* value <0.05 was accepted as statistically significant.

Results

Seventy-five subjects were enrolled, and forty-four met the PSG inclusion criteria (*see* Table 1 for demographic data, which were obtained on Night 1). Patients were classified as spOSA or siOSA on both Night 1 and Night 2. The raw agreement and the κ statistic were then calculated (Table 2).

Table 2 demonstrates that, for spOSA, the κ value is 0.35, which means the proportion of raw agreement of 0.71 is better than expected by 35% due to chance alone, and the difference due to chance agreement is significant (*P* = 0.02). For siOSA, the κ value is 0.32, which means the proportion of raw agreement of 0.73 is better than expected by 26% due to chance alone, and the difference due to chance agreement is significant (*P* = 0.03). For spOSA, overall agreement between studies was only fair (20) (κ = 0.35, *P* = 0.02); however, there was a considerable effect regarding sex, with moderate agreement (20) for males (κ = 0.47, *P* = 0.02) and no significant agreement for females above what one would expect due to chance. For siOSA, the agreement improved slightly for males (κ = 0.56, *P* = 0.005), but remained nonsignificant for females.

We iteratively tested the agreement for novel definitions of spOSA and siOSA with increasing AHI_S:AHI_{NS} ratios, which were

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Table 1. Study participant demographics and Study Night 1 parameters

Patient Demographics (*N* = 44)	Males, median (IQR)	Females, median (IQR)	Significance (Mann-Whitney *U* test)
Number	24	20	
Age, yr	48.5 (14.8)	52.5 (14.8)	0.36
BMI, kg/m^2	28.5 (9.8)	32.9 (11.9)	0.16
Epworth Sleepiness Score	9 (5.3)	7.5 (8.3)	0.46
Neck circumference, cm	42.3 (7.3)	38.3 (4)	0.003
AHI, events/h	25.6 (48.3)	13 (16.8)	0.02
AHI_S, events/h	47.3 (59.1)	23(22.8)	0.003
AHI_{NS}, events/h	16.7 (47.6)	9.6 (16)	0.21
AHI_S:AHI_{NS} Ratio	3 (3.2)	2 (3.1)	0.28

Definition of abbreviations: AHI = apnea and hypopnea index; AHINS = apnea and hypopnea index in the nonsupine position; AHIS = apnea and hypopnea index in the supine position; BMI = body mass index; IQR = interquartile range.

stratified according to sex. The results of raw agreement, prevalence, and κ values are graphed against the AHI_S:AHI_{NS} ratios for each of the spOSA definitions in Figure 1.

Across all definitions for males (except AHI_S:AHI_{NS} ratio = 2.5:1), the difference from chance agreement is significant. There was no definition for females that had a significant difference from chance agreement. The definition with maximum agreement for males was an AHI_S:AHI_{NS} ratio ⩾4:1. With this definition, the proportion of raw agreement of 0.83 is better than expected by 60% due to chance, and the difference from chance agreement is significant (P = 0.003). The same iterative analysis was applied using siOSA definitions, as shown in Figure 2.

The difference from chance agreement is significant across all definitions for males, with the optimum agreement again seen for a definition of AHI_S:AHI_{NS} ratio ⩾4:1. With this definition, the proportion of raw agreement of 0.92 is better than expected by 75% due to chance alone, and the difference to chance agreement is highly significant (P = 0.0001). This is considered a substantial agreement (20). For females, none of the tested definitions demonstrated a significant difference from chance agreement.

We assessed the repeatability of the AHI_{NS} and AHI_S using Bland-Altman analysis.

The mean value of the difference between measurements is not significantly different from zero. The limits of agreement shown are 26.7 to −22.1 for the AHI_{NS} plot. Figure 3 demonstrates that the repeatability for AHI_{NS} values <10 events/hour is excellent. Similarly, for the AHI_S plot (*see* Figure 4), the repeatability is better for lower AHI_S values, although it is not as good as for AHI_{NS}. The limits of agreement shown are 40.8 and −32.1, and the mean value of the difference between measurements is not significantly different from zero.

We applied the AHI_{NS} cutoff of <10 events/hour to the iteratively increased AHI_S:AHI_{NS} ratios as described above. The optimal definition for males remained a ratio ⩾4:1 (κ = 0.56, P = 0.01), and there were no significant κ values for females (*see* Part 1 of the online supplement for full table of values).

Discussion

There are a number of important findings of this study. First, the agreement on consecutive PSGs of traditionally defined groups of supine-predominant OSA and supine-isolated OSA is considered only fair (20) and is not elevated much above that expected by chance alone. Second, there is no repeatability for the supine phenotype in females, regardless of how the definition is altered. Third, the agreement on consecutive PSGs of traditionally defined groups of supine OSA in males is moderate (20), and the agreement is improved by altering the definition used. On the basis of these findings, the previously used arbitrary definitions of supine OSA should be reviewed.

Our results provide a basis for establishing the existence of a supine-predominant class of patients who can be identified reliably on the basis of an AHI_S:AHI_{NS} ratio ⩾4:1. Additionally, with the high repeatability of an AHI_{NS} <10 events/hour, we propose that male subjects are likely to benefit from treatment with a PMD, where they have a single PSG demonstrating an AHI_S:AHI_{NS} ratio ⩾4:1 and an AHI_{NS} <10 events/hour. Given that there is a paucity of recommendations regarding the use of postural modification in the treatment of OSA, the results of this study will help guide clinicians in the application of an important non-CPAP therapy.

In a previously published patient database (13), 27% of patients with mild to moderate OSA were males with an AHI_S:AHI_{NS} ratio ⩾4:1 and an AHI_{NS} <10/hour. Many of these patients cannot use CPAP, and therefore alternative treatment is

Table 2. Night-to-night agreement of supine-predominant and supine-isolated OSA phenotypes by sex

Definition		*n* (Night 1)	*n* (Night 2)	Raw Agreement	κ	*P* Value
Supine-Predominant OSA:AHI_S: AHI_{NS} = 2:1	Female (*n* = 20)	10	9	0.65	0.18	0.46
	Male (*n* = 24)	15	15	0.75	0.47	0.02
	Combined (*N* = 44)	25	24	0.71	0.35	0.02
Supine-Isolated OSA:AHI_S: AHI_{NS} = 2:1 and AHI_{NS} <5	Female	5	7	0.60	0.06	0.8
	Male	5	7	0.83	0.56	0.005
	Combined	10	14	0.73	0.32	0.03

Definition of abbreviations: AHI = apnea and hypopnea index; AHINS = apnea and hypopnea index in the nonsupine positions; AHIS = apnea and hypopnea index in the supine position.

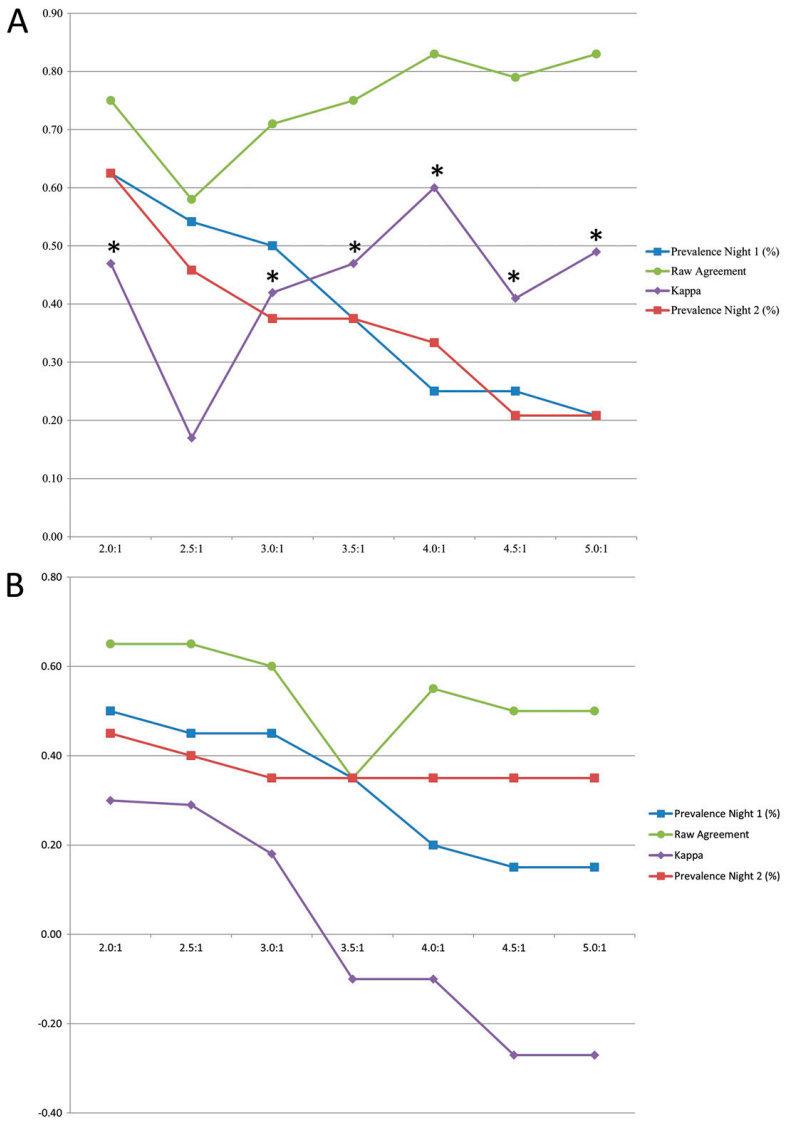

Figure 1. Raw agreement and κ value for each of the definitions of spOSA. (*A*) Values for males. (*B*) Values for females. Prevalence of spOSA on Night 1 and Night 2 according to each definition is expressed as a percentage. Asterisk denotes that the difference from chance agreement is significant.

required. A number of different PMDs have been proven to be efficacious in preventing supine sleep (18, 22, 23). Although many factors determine long-term adherence to PMDs, such as patient comfort (24), a crucial requirement for success is that the therapy be consistently effective. For this to occur, spOSA needs to be of a stable phenotype (i.e., problem present from night

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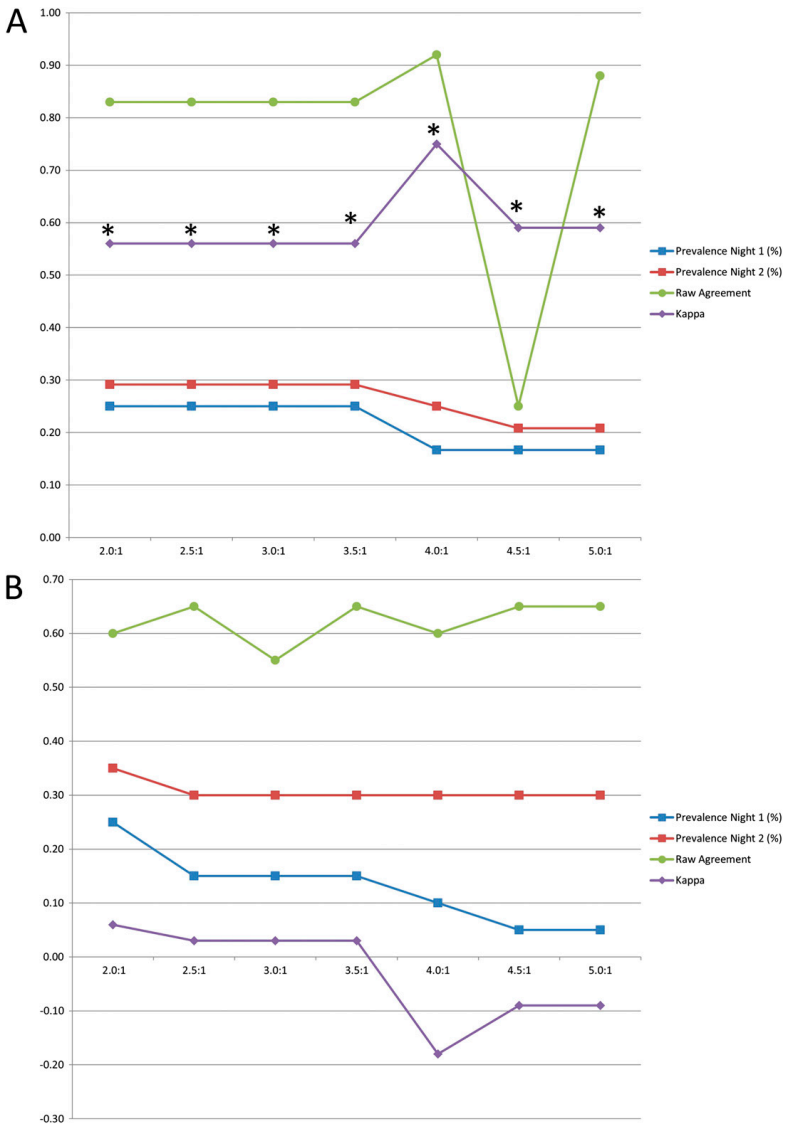

Figure 2. Raw agreement and κ value for each of the definitions of siOSA. (*A*) Values for males. (*B*) Values for females. Prevalence of siOSA on Night 1 and Night 2 according to each definition is expressed as a percentage. Asterisk denotes that the difference from chance agreement is significant.

to night) and the AHI_{NS} needs to be consistently low from night to night. Previous studies have documented that there is considerable night-to-night variability in total AHI (25, 26), raising the possibility that the supine-predominant phenotype is not stable. Our data are therefore novel and can help guide patient selection for PMD.

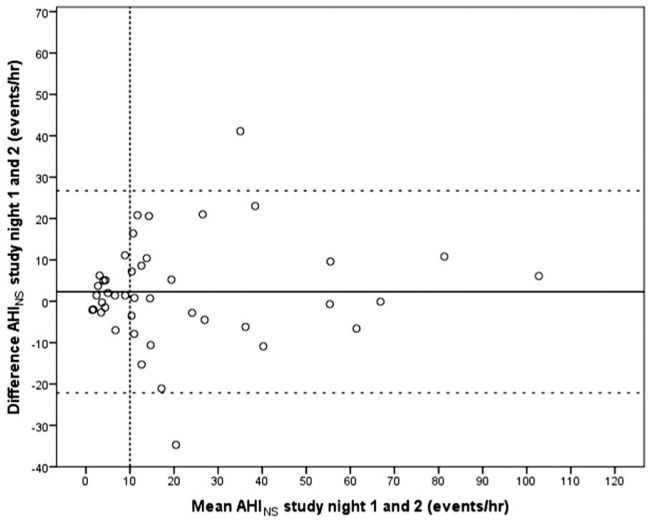

Figure 3. Bland-Altman plot of the AHI_{NS} (events/h). The line drawn at AHI_{NS} = 10/hour highlights the low variability between nights when AHI_{NS} <10 events/hour compared with high variability when AHI_{NS} >10 events/hour. Horizontal dashed lines are drawn at the limits of agreement.

Positional OSA has traditionally been divided into supine-predominant OSA (spOSA; AHI_S:AHI_{NS} ⩾2:1) and supine-isolated OSA (siOSA; AHI_S:AHI_{NS} ⩾2:1 with AHI_{NS} <5 events/h) (11, 12, 15). Our results show that, although raw agreement between study nights appears reasonable at 71% and 73%, respectively, when one takes into account the potential for agreement occurring due to chance, there is only moderate consistency in spOSA and siOSA from night to night in men and no consistent phenotype in women. We propose that this level of variability in supine OSA over time does not support the use of these definitions, either for clinical practice or for research purposes.

Why Might the Supine OSA Phenotype Be Variable in Some Patients, but Not Others?

There may be physiological reasons for night-to-night variability in the classification of supine OSA. Factors such as upper-airway passive collapsibility, airway dilator muscle activity, loop gain and arousal threshold fluctuate in a given patient (27). Most researchers who have assessed these factors have studied patients lying in the supine position. There is evidence, however, that some of these physiological traits more strongly promote upper-airway collapsibility while the patient is in the supine position compared with the lateral position. For example, pharyngeal critical closing pressure is more positive in supine compared with lateral sleep in male OSA patients (28). This may be due to lung volume influences, because functional residual capacity is reduced when nonobese patients move from the lateral to supine position (29, 30). Conversely, genioglossus activity is more pronounced while the patient is in the supine position than in the lateral position (31, 32), and the effect of body position on loop gain and arousal threshold is unknown. Knowing how these physiological traits interact in a given individual is critical to determining whether OSA ensues, and the relative importance of each trait varies between individuals (33). There are currently no data that indicate how the interaction of these traits is affected by alterations in body position. On the basis of the results of our study, we speculate that those OSA subjects with a strong supine-predominant phenotype (AHI_S:AHI_{NS} ratio ⩾4:1 and AHI_{NS} <10 events/h) have trait interactions that sit well above the threshold for obstruction while supine and well below the threshold while lateral. In this case, slight variability in the traits from night to night will not influence the supine-predominant phenotype in such patients. Conversely, for those patients with less difference noted in AHI between positions, the trait interactions may sit closer to the OSA threshold, which means that night-to-night variations in the traits will also lead to variability in the extent of positional OSA.

Sleep state also has an effect on upper-airway collapsibility. OSA severity is frequently observed to be increased during REM sleep (34) secondary to a decrease in motor output to pharyngeal dilator muscles (35). The proportion of supine sleep that coincides with REM sleep will therefore have an effect on AHI_S. We accounted for this by reanalyzing our data after introducing requirements that all patients in both studies have at least 30 minutes of supine and nonsupine sleep and that they have at least 15 minutes of REM sleep. A total of 41 patients fulfilled these criteria, and the results were not altered from those presented (*see* Part 2 of the online supplement). In addition, we analyzed our data with an extra requirement that patients have a minimum of 10 minutes of REM sleep while in the supine position (*see* Part 3 of the online supplement). Although only 19 patients fulfilled these extra criteria, the raw agreement and κ statistics remained optimal for definitions with an AHI_S:AHI_{NS} ratio ⩾4:1.

There may also be aspects related to measurement of body position that influence the repeatability of the supine-predominant OSA phenotype. The technique with which position is detected and recorded in the laboratory and the handling of position as a categorical variable may introduce a degree of variability into the AHI_S.

The AASM manual for the scoring of sleep and associated events contains a paucity of information on the technique for scoring body position (19). Because of the lack of recommendations regarding the recording of body position during PSGs, the methods and standards are likely to vary across laboratories. In our study, we used a sensor attached to the thoracic impedance bands with Velcro and tape. Slippage of the sensor can move it into an orientation that does not reflect the true orientation of the chest; therefore, we used

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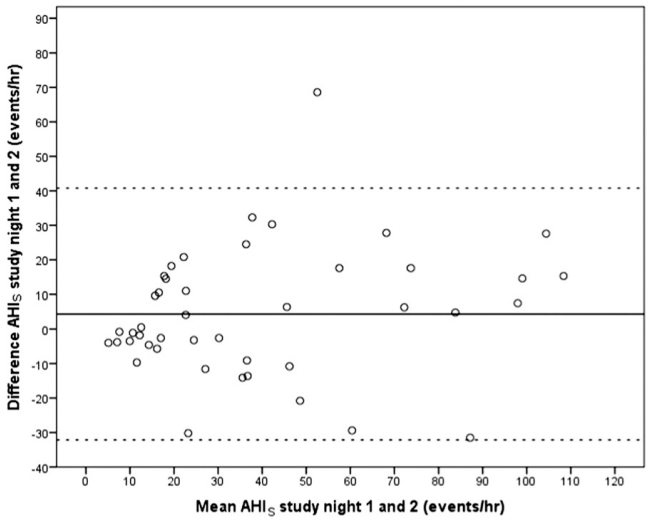

Figure 4. Bland-Altman plot of the AHI_S (events/h). Horizontal dashed lines are drawn at the limits of agreement, and the solid line represents the mean difference in AHI_S from Study Night 1 to Study Night 2.

a video monitoring system to correct and verify the sensor output.

Both automatic position sensors and video monitoring lead to body position being defined as a categorical variable rather than a continuous 360° variable. This does not reflect the physiological impact of various body positions on the collapsibility of the upper airway (23), and there is likely to be a continuous relationship between the degree of supine or lateral trunk position and AHI (36). Furthermore, simply recording trunk position does not account for the effect of head (37), neck (38), and jaw positions (39) on upper-airway collapsibility. For example, head and neck position can influence the AHI independently of trunk position (40). Until there is a schema for classifying sleeping position that takes these factors into account, there will likely be a degree of inherent variability in AHI_S and AHI_{NS}.

Why Do Females Have Poor Repeatability of the Supine OSA Phenotype?

The repeatability of the supine-related OSA phenotype is poor for females. There are a number of important differences between male and female patients with supine-related OSA. In our present study, we noted that males had a significantly larger neck circumference and higher AHI than females. Similar to our study results, van Kesteren and colleagues demonstrated that females spend significantly more time with the head and trunk in the supine position than males do, but that the AHI_S for females is less than that in males (40).

The differences in prevalence and repeatability of supine related OSA in males and females are likely due to sex differences in pathophysiological interactions which lead to upper airway collapse, particularly anatomical factors. Females have a more favorable pharyngeal critical closing pressure in supine non-REM sleep compared with males matched on body mass index, but no significant difference in loop gain (41). The differences observed in upper-airway collapsibility in males and females may also be due to more favorable genioglossus activation in females (42). Given that the protective action of genioglossus is increased in females and that the action of the muscle is augmented in the supine position compared with the lateral position (32), we speculate that this may be an explanation for why females less frequently experience supine-related OSA and have it more variably from night to night.

Limitations

There are a number of limitations in our study. Our study includes a relatively small number of patients ($N = 44$) because of the requirements that patients have OSA and ⩾30 minutes supine sleep in both studies. Nevertheless, our numbers compare favorably with the number of subjects included in several other published studies that addressed the night-to-night variability of total AHI (25, 43–45). Importantly, all patients in our study were from a single center, and therefore we recommend replicating the findings in another cohort of OSA patients to confirm the generalizability of the data.

Conclusions

The currently accepted definitions for supine-related OSA have only moderate repeatability for males and no consistent repeatability for females, other than what would be expected due to chance. The stability of the supine OSA phenotype from night to night can be improved substantially for males when the definition is altered to require an AHI_S: AHI_{NS} ratio ⩾4:1. Additionally, we have demonstrated that when the AHI_{NS} is <10 events/hour, it remains consistently low from night to night. Our results identify a supine-predominant class of patients who can be selected reliably on the basis of a single PSG: male subjects with an AHI_S:AHI_{NS} ratio ⩾4:1 and an AHI_{NS} <10 events/hour. This finding has important implications for researchers studying the pathophysiological causes of supine OSA, as well as for clinicians, who can now reliably recommend postural modification treatment for this class of patient. ■

Author disclosures are available with the text of this article at www.atsjournals.org.

References

1 Engleman HM, Martin SE, Deary IJ, Douglas NJ. Effect of continuous positive airway pressure treatment on daytime function in sleep apnoea/hypopnoea syndrome. *Lancet* 1994;343: 572–575.
2 Giles TL, Lasserson TJ, Smith BH, White J, Wright J, Cates CJ. Continuous positive airways pressure for obstructive sleep apnoea in adults. *Cochrane Database Syst Rev* 2006;(3):CD001106.
3 Tregear S, Reston J, Schoelles K, Phillips B. Continuous positive airway pressure reduces risk of motor vehicle crash among drivers with obstructive sleep apnea: systematic review and meta-analysis. *Sleep* 2010;33:1373–1380.
4 Shamsuzzaman AS, Gersh BJ, Somers VK. Obstructive sleep apnea: implications for cardiac and vascular disease. *JAMA* 2003;290: 1906–1914.
5 Kribbs NB, Pack AI, Kline LR, Smith PL, Schwartz AR, Schubert NM, Redline S, Henry JN, Getsy JE, Dinges DF. Objective measurement of patterns of nasal CPAP use by patients with obstructive sleep apnea. *Am Rev Respir Dis* 1993;147:887–895.
6 Reeves-Hoche MK, Meck R, Zwillich CW. Nasal CPAP: an objective evaluation of patient compliance. *Am J Respir Crit Care Med* 1994; 149:149–154.
7 Eckert DJ, White DP, Jordan AS, Malhotra A, Wellman A. Defining phenotypic causes of obstructive sleep apnea: identification of novel therapeutic targets. *Am J Respir Crit Care Med* 2013;188: 996–1004.
8 Younes M. Role of arousals in the pathogenesis of obstructive sleep apnea. *Am J Respir Crit Care Med* 2004;169:623–633.
9 Younes M, Ostrowski M, Thompson W, Leslie C, Shewchuk W. Chemical control stability in patients with obstructive sleep apnea. *Am J Respir Crit Care Med* 2001;163:1181–1190.
10 Jordan AS, Wellman A, Heinzer RC, Lo YL, Schory K, Dover L, Gautam S, Malhotra A, White DP. Mechanisms used to restore ventilation after partial upper airway collapse during sleep in humans. *Thorax* 2007;62:861–867.
11 Cartwright RD. Effect of sleep position on sleep apnea severity. *Sleep* 1984;7:110–114.
12 Oksenberg A, Silverberg DS, Arons E, Radwan H. Positional vs nonpositional obstructive sleep apnea patients: anthropomorphic, nocturnal polysomnographic, and multiple sleep latency test data. *Chest* 1997;112:629–639.
13 Joosten SA, Hamza K, Sands S, Turton A, Berger P, Hamilton G. Phenotypes of patients with mild to moderate obstructive sleep apnoea as confirmed by cluster analysis. *Respirology* 2012;17: 99–107.
14 O'Connor C, Thornley KS, Hanly PJ. Gender differences in the polysomnographic features of obstructive sleep apnea. *Am J Respir Crit Care Med* 2000;161:1465–1472.
15 Mador MJ, Kufel TJ, Magalang UJ, Rajesh SK, Watwe V, Grant BJB. Prevalence of positional sleep apnea in patients undergoing polysomnography. *Chest* 2005;128:2130–2137.
16 Pevernagie DA, Shepard JW Jr. Relations between sleep stage, posture and effective nasal CPAP levels in OSA. *Sleep* 1992;15: 162–167.
17 Skinner MA, Kingshott RN, Filsell S, Taylor DR. Efficacy of the 'tennis ball technique' versus nCPAP in the management of position-dependent obstructive sleep apnoea syndrome. *Respirology* 2008; 13:708–715.
18 Bignold JJ, Mercer JD, Antic NA, McEvoy RD, Catcheside PG. Accurate position monitoring and improved supine-dependent obstructive sleep apnea with a new position recording and supine avoidance device. *J Clin Sleep Med* 2011;7:376–383.
19 Iber C, American Academy of Sleep Medicine. AASM manual for the scoring of sleep and associated events: rules, terminology and technical specifications. Westchester, IL: American Academy of Sleep Medicine; 2007.
20 Landis JR, Koch GG. The measurement of observer agreement for categorical data. *Biometrics* 1977;33:159–174.
21 Bland JM, Altman DG. Statistical methods for assessing agreement between two methods of clinical measurement. *Lancet* 1986;1: 307–310.
22 Loord H, Hultcrantz E. Positioner—a method for preventing sleep apnea. *Acta Otolaryngol* 2007;127:861–868.
23 Joosten SA, O'Driscoll DM, Berger PJ, Hamilton GS. Supine position related obstructive sleep apnea in adults: pathogenesis and treatment. *Sleep Med Rev* 2014;18:7–17.
24 Bignold JJ, Deans-Costi G, Goldsworthy MR, Robertson CA, McEvoy D, Catcheside PG, Mercer JD. Poor long-term patient compliance with the tennis ball technique for treating positional obstructive sleep apnea. *J Clin Sleep Med* 2009; 5:428–430.
25 Bittencourt LR, Suchecki D, Tufik S, Peres C, Togeiro SM, Bagnato MC, Nery LE. The variability of the apnoea-hypopnoea index. *J Sleep Res* 2001;10:245–251.
26 Levendowski DJ, Zack N, Rao S, Wong K, Gendreau M, Kranzler J, Zavora T, Westbrook PR. Assessment of the test-retest reliability of laboratory polysomnography. *Sleep Breath* 2009;13: 163–167.
27 Younes M. Contributions of upper airway mechanics and control mechanisms to severity of obstructive apnea. *Am J Respir Crit Care Med* 2003;168:645–658.
28 Penzel T, Möller M, Becker HF, Knaack L, Peter JH. Effect of sleep position and sleep stage on the collapsibility of the upper airways in patients with sleep apnea. *Sleep* 2001;24: 90–95.
29 Barnas GM, Campbell DN, Mackenzie CF, Mendham JE, Fahy BG, Runcie CJ, Mendham GE. Lung, chest wall, and total respiratory system resistances and elastances in the normal range of breathing. *Am Rev Respir Dis* 1992;145:110–113.
30 Barnas GM, Green MD, Mackenzie CF, Fletcher SJ, Campbell DN, Runcie C, Broderick GE. Effect of posture on lung and regional chest wall mechanics. *Anesthesiology* 1993;78: 251–259.
31 Otsuka R, Ono T, Ishiwata Y, Kuroda T. Respiratory-related genioglossus electromyographic activity in response to head rotation and changes in body position. *Angle Orthod* 2000;70: 63–69.
32 Malhotra A, Trinder J, Fogel R, Stanchina M, Patel SR, Schory K, Kleverlaan D, White DP. Postural effects on pharyngeal protective reflex mechanisms. *Sleep* 2004;27:1105–1112.
33 Wellman A, Edwards BA, Sands SA, Owens RL, Nemati S, Butler JP, Passaglia CL, Jackson AC, Malhotra A, White DP. A simplified method for determining phenotypic traits in patients with obstructive sleep apnea. *J Appl Physiol* 2013;114: 911–922.
34 Anch AM. Sleep: a scientific perspective. Englewood Cliffs, NJ: Prentice Hall; 1988.
35 Fenik VB, Davies RO, Kubin L. REM sleep-like atonia of hypoglossal (XII) motoneurons is caused by loss of noradrenergic and serotonergic inputs. *Am J Respir Crit Care Med* 2005;172: 1322–1330.
36 Tiotiu A, Mairesse O, Hoffmann G, Todea D, Noseda A. Body position and breathing abnormalities during sleep: a systematic study. *Pneumologia* 2011;60:216–221.
37 Isono S, Tanaka A, Tagaito Y, Ishikawa T, Nishino T. Influences of head positions and bite opening on collapsibility of the passive pharynx. *J Appl Physiol (1985)* 2004;97:339–346.
38 Walsh JH, Maddison KJ, Platt PR, Hillman DR, Eastwood PR. Influence of head extension, flexion, and rotation on collapsibility of the passive upper airway. *Sleep* 2008;31:1440–1447.
39 Ayuse T, Inazawa T, Kurata S, Okayasu I, Sakamoto E, Oi K, Schneider H, Schwartz AR. Mouth-opening increases upper-airway collapsibility without changing resistance during midazolam sedation. *J Dent Res* 2004;83:718–722.
40 van Kesteren ER, van Maanen JP, Hilgevoord AAJ, Laman DM, de Vries N. Quantitative effects of trunk and head position on the apnea hypopnea index in obstructive sleep apnea. *Sleep* 2011;34: 1075–1081.
41 Jordan AS, Wellman A, Edwards JK, Schory K, Dover L, MacDonald M, Patel SR, Fogel RB, Malhotra A, White DP. Respiratory control stability and upper airway collapsibility in men and women with obstructive sleep apnea. *J Appl Physiol (1985)* 2005;99: 2020–2027.

42 Popovic RM, White DP. Influence of gender on waking genioglossal electromyogram and upper airway resistance. *Am J Respir Crit Care Med* 1995;152:725–731.
43 Levendowski D, Steward D, Woodson BT, Olmstead R, Popovic D, Westbrook P. The impact of obstructive sleep apnea variability measured in-lab versus in-home on sample size calculations. *Int Arch Med* 2009;2:2.
44 Lord S, Sawyer B, O'Connell D, King M, Pond D, Eyland A, Mant A, Holland JT, Hensley MJ, Saunders NA. Night-to-night variability of disturbed breathing during sleep in an elderly community sample. *Sleep* 1991;14:252–258.
45 Mosko SS, Dickel MJ, Ashurst J. Night-to-night variability in sleep apnea and sleep-related periodic leg movements in the elderly. *Sleep* 1988;11:340–348.

CHAPTER 3

EVALUATION OF THE ROLE OF LUNG VOLUME AND AIRWAY SIZE AND SHAPE IN SUPINE PREDOMINANT OBSTRUCTIVE SLEEP APNOEA PATIENTS

3.1 DECLARATION FOR THESIS CHAPTER 3

Declaration by candidate

In the case of Chapter 3, the nature and extent of my contribution to the work was the following:

Nature of contribution	**Contribution**
For this chapter I was responsible for hypothesis generation, data collection, data analysis, interpretation of results and manuscript preparation. The extent of my contribution was 80%.	80%

The following co-authors contributed to the work. If co-authors are students at Monash University, the extent of their contribution in percentage terms must be stated:

Name	**Nature of contribution**	**Contribution % (student co-authors only)**
Dr SA Sands	Aided in data analysis and manuscript preparation.	
Dr BA Edwards	Aided in manuscript preparation.	
A/Prof. K Hamza	Aided in data analysis.	
Mr A Turton	Aided in data collection.	
A/Prof. KK Lau	Aided in data collection – interpretation of CT scan images.	
Mr M Crossett	Aided in data collection – performing CT scan images.	
Dr PJ Berger	Aided in hypothesis generation, data analysis, interpretation of results and manuscript preparation.	
Dr GS Hamilton	Aided in hypothesis generation, data analysis, interpretation of results and	

	manuscript preparation.	

The undersigned hereby certify that the above declaration correctly reflects the nature and extent of the candidate's and co-authors' contributions to this work*.

Candidate's Signature		**Date**

Main Supervisor's Signature		**Date**

3.2 INTRODUCTION TO CHAPTER

A number of anatomical features of the upper airway contribute to obstruction in OSA patients. Ultimately, airway lumen size and shape and anatomical propensity to collapse are determined by the interaction between a number of factors such as the size of the bony enclosure (mandible, maxilla, cervical spine) (Isono, Tanaka et al. 2002), the size of the soft tissues (tongue, soft palate, lateral pharyngeal fat pads) (Schwab, Pasirstein et al. 2003) and the shape and folding characteristics of the airway (Amatoury, Kairaitis et al. 2010).

Studies in awake normal subjects (Jan, Marshall et al. 1994) and awake OSA patients (Jan, Marshall et al. 1994, Martin, Marshall et al. 1995, Pevernagie, Stanson et al. 1995, Walsh, Leigh et al. 2008) show no significant change in cross-sectional area (CSA) when moving from the supine to lateral position. The literature regarding how airway shape changes from lateral to supine is conflicting because of the various imaging methodologies employed. Both positional (Pevernagie, Stanson et al. 1995) and non-positional OSA patients (Ryan and Love 1996, Ciscar, Juan et al. 2001, Walsh, Leigh et al. 2008) have been shown to have an elliptically shaped airway in the supine position with the long axis oriented laterally. By contrast, there is evidence that some patients with severe non-positional OSA have an elliptically shaped airway that is oriented in the antero-posterior direction (Schwab, Gefter et al. 1993, Fogel, Malhotra et al. 2003). Importantly, none of these studies select for spOSA or siOSA subjects for comparison with appropriately matched controls.

Lung volume is an important variable in OSA as it is known to influence upper airway stability in normal subjects (Series, Cormier et al. 1990, Stanchina, Malhotra et al. 2003) and OSA patients (Bradley, Brown et al. 1986), via caudal tracheal displacement and subsequent changes in upper airway tissue pressure, as demonstrated in animal models (Van de Graaff 1988, Rowley, Permutt et al. 1996, Kairaitis, Byth et al. 2007). There are no published studies that investigate the effect of moving from the supine to lateral position on lung volumes, either in OSA patients in general or in selected OSA phenotypes such as spOSA and siOSA.

According to the gaps highlighted in the current literature, we designed a study to explore the effect of body position on lung volume and airway size and shape in supine OSA patients compared to matched controls. We have demonstrated that there is no significant difference in CSA when moving from the supine to lateral position in supine OSA patients compared to matched controls. All groups demonstrated a significant shape change in the supine position so that the airway adopted a more laterally oriented ellipse in the supine position. The major finding, however, was a significant increase in lung volume when supine OSA patients moved from supine to lateral compared to the control groups. We conclude that an improvement in lung volume in the lateral position in supine OSA patients may be an important contributing factor to the improvement in OSA in lateral sleep seen in these patients.

As per Monash University guidelines for thesis by publication, the following chapter is presented as a PDF as it has been published.

3.3 EVALUATION OF THE ROLE OF LUNG VOLUME AND AIRWAY SIZE AND SHAPE IN SUPINE PREDOMINANT OBSTRUCTIVE SLEEP APNOEA PATIENTS

Joosten SA, Sands SA, Edwards BA, Hamza K, Turton A, Lau KK, Crossett M, Berger PJ, Hamilton GS

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Respirology 20

ORIGINAL ARTICLE

Evaluation of the role of lung volume and airway size and shape in supine-predominant obstructive sleep apnoea patients

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ABSTRACT

Background and objective: **This study aimed to evaluate the involvement of airway cross-sectional area and shape, and functional residual capacity (FRC), in the genesis of obstructive sleep apnoea (OSA) in patients with supine-predominant OSA.**
Methods: **Three groups were recruited: (i) supine OSA, defined as a supine apnoea–hyponoea index (AHI) at least twice that of the non-supine AHI; (ii) rapid eye movement (REM) OSA, defined as REM AHI at least twice the non-REM AHI and also selected to have supine AHI less than twice that of the non-supine AHI (i.e. to be non-positional); and (iii) no OSA, defined as an AHI less than five events per hour. The groups were matched for age, gender and body mass index. Patients underwent four-dimensional computed tomography scanning of the upper airway in the supine and lateral decubitus positions. FRC was measured in the seated, supine and lateral decubitus positions.**
Results: **Patients with supine OSA demonstrated a significant decrease in FRC of 340 mL ($P = 0.026$) when moving from the lateral to supine position compared to controls with no OSA, and REM OSA patients. We found no differences between groups in upper airway size and shape. However, all groups showed a significant change in airway shape with the velopharyngeal airway adopting a more elliptoid shape (with the long axis laterally oriented), with reduced anteroposterior diameter in the supine position.**
Conclusions: **A fall in FRC when moving lateral to supine in supine OSA patients may be an important triggering factor in the generation of OSA in this patient group.**

Key words: apnoea, functional residual capacity, lung volume measurement, sleep, supine position.

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SUMMARY AT A GLANCE

There is a significant reduction in lung volume when moving from the lateral to supine position in supine-predominant obstructive sleep apnoea patients, which may be an important triggering factor in their airway obstruction. Additionally, the upper airway is more elliptoid in shape when supine in both sleep apnoea patients and controls.

Abbreviations: AHI, apnoea–hyponoea index; ANOVA, one-way analysis of variance; AP, anteroposterior; BMI, body mass index; CSA, cross-sectional area; CT, computed tomography; FRC, functional residual capacity; OSA, obstructive sleep apnoea; REM, rapid eye movement.

INTRODUCTION

Obstructive sleep apnoea (OSA) is due to repetitive collapse of the upper airway during sleep. The majority of patients with OSA have mild–moderate disease[1] with intermittent periods of OSA mixed with periods of stable breathing, which may be driven by a change in body position. Supine-predominant OSA, when defined as more than twice the number of respiratory events in supine compared with non-supine positions, is present in approximately 60% of the OSA population.[2,3]

An obvious inference from the existence of supine-predominant OSA is that at least one of the underlying mechanisms of airway collapse is worsened in the supine position. A number of pathogenic factors may predispose to OSA, including unfavourable airway anatomy,[4] an inability of muscles to open or stiffen the airway during sleep,[5,6] an oversensitive ventilatory control system (i.e. high loop gain),[7] a low respiratory arousal threshold[8] and a low lung volume.[9] Importantly, unfavourable airway anatomy (pharyngeal critical closing pressure, Pcrit, less than –2 cmH_2O) is

seen in over 80% of patients with OSA.[10] The propensity to collapse is related to airway size or airway shape (elliptical vs circular). According to Laplace's law a more rounded airway is inherently more stable than an elliptically shaped one as the transmural pressure gradient required to collapse the airway varies inversely with the radius of curvature. Furthermore, the orientation of an elliptically shaped airway is important, as collapse is most likely to occur at the end segments of the long axis.[11,12]

Although airway size and shape are affected by body position, there is disagreement as to how they are altered. Studies in awake OSA patients consistently report no significant change in pharyngeal cross-sectional area (CSA) moving from lateral to supine.[13–16] The majority of airway shape studies in awake OSA patients demonstrate that the velopharyngeal shape approximates a laterally oriented ellipse in the supine position,[13,14,17,18] whereas others suggest the shape is more circular when supine.[4,19] Limiting their value, existing studies have not always used controls, and only one matched subjects for age, gender and body mass index (BMI).[13] Crucially, only one existing study has targeted patients with supine-predominant OSA[14] and no studies to date have assessed differences in CSA and shape when moving from the lateral to supine position in supine-predominant versus non-position dependent OSA patients and matched controls.

A key determinate of airway shape is lung volume (in particular functional residual capacity, FRC), which influences airway collapsibility[20] through caudal tracheal displacement and subsequent upper airway tissue pressure changes.[21] Both BMI and body position have been shown to influence FRC. The interaction between BMI and FRC is complex and the BMI of a subject will influence how much lung volume changes with changing body position, at least in the non-obese range of BMIs.[22] In normal BMI subjects without OSA, FRC falls significantly when moving from the lateral to supine position,[23,24] but this is unlikely to be the case in the morbidly obese (BMI >35 kg/m^2) as there is no change when moving from the sitting to the supine position.[25] Patients with supine OSA more commonly have a BMI in the overweight range (25–30 kg/m^2)[3] compared with non-positional OSA patients who are more likely to have a BMI in the obese range (>30 kg/m^2)[3]; however, there are no published data investigating the effect of body position changes on lung volume in OSA patients.

Given the current literature, we performed a study to test three hypotheses to explain the existence of supine-predominant OSA. We hypothesize that when supine-predominant OSA patients assume the supine position they will experience (i) a decrease in airway CSA; (ii) a deformation of the upper airway into a more elliptoid shape; and (iii) a decrease in FRC. To evaluate the involvement of airway CSA, airway shape and FRC in the genesis of supine-predominant OSA we compared each factor in subjects with supine-predominant OSA to those in two matched control groups: one with non-positional OSA and one comprising normal controls without OSA.

METHODS

Ethics approval was obtained from the Human Research Ethics Committee of Monash Health. Patients were recruited based on polysomnogram results (polysomnograms staged and scored in accordance with American Academy of Sleep Medicine guidelines),[26] if they experienced >30 min supine sleep, >30 min non-supine sleep and >15 min of rapid eye movement (REM) sleep and had an apnoea and hypopnoea index (AHI) more than five events per hour. Subjects were recruited into three groups:

1 Supine-predominant OSA patients:
- – Supine AHI (AHI_S) to non-supine AHI (AHI_{NS}) ratio greater than 2:1. Additionally, patients were required to have REM AHI (AHI_{REM}) to non-REM AHI (AHI_{NREM}) ratio of less than 2:1 to ensure there was no sleep stage effect.
- – During the recruitment of this study we published data demonstrating that the definition of supine OSA with the greatest level of repeatability from night-to-night is one which incorporates a supine AHI to non-supine AHI of >4:1.[27] Although we set out initially to recruit subjects with a ratio of >2:1 for this study, all subjects included, in fact, also have a supine to non-supine ratio of >4:1.

2 Control patients without OSA:
- – Overall AHI less than five per hour. Patients were also required to have an AHI less than five per hour in supine sleep, in non-supine sleep, in REM sleep and in non-REM sleep.

3 REM-based OSA patients with no body positionality to their respiratory events:
- – Required to have the AHI_S to AHI_{NS} ratio <2:1. Additionally, patients were required to have an AHI in REM sleep (AHI_{REM}) to AHI in NREM sleep (AHI_{NREM}) ratio of greater than 2:1.

Patients were selected this way to provide a group of OSA patients (REM OSA) who were likely to have a different combination of pathogenic mechanisms to the supine OSA group given that they displayed no positionality in their airway obstruction and they had REM-specific OSA, with no significant OSA in NREM sleep.

Patients were excluded if they were <18 years, pregnant, had abnormal spirometry, had heart disease or renal disease, or if they had previous upper airway surgery.

Statistical analysis

Data were collated in Excel (2010, Microsoft Corporation, Redmond, WA, USA) and analysed using IBM SPSS 20 (2011, IBM Corporation). Demographic variables were compared with a one-way analysis of variance (ANOVA). We applied a repeated measures ANOVA to compare differences in mean values for airway parameters and lung volumes between the lateral/supine position and across groups. We examined both absolute lung volumes and positional lung volume expressed as a percentage of seated lung volume in order to reduce variability. All results are given as mean ± standard deviation unless otherwise stated. A P-value of <0.05 was accepted as statistically significant.

Anthropomorphic measurements

Weight was measured with electronic scales (Seca 703, Hamburg, Germany) and height with a stadiometer (Seca 264) in order to determine BMI. Circumferential measurements were performed at the neck just inferior to the cricoid cartilage, the chest at the level of the third intercostal space, the waist at the smallest girth between the iliac crest and the costal margin and the hip at the level of its largest dimension over the buttocks.

Lung volume and pulmonary function

Lung volume was measured twice in each of the seated, supine and lateral positions (with the order randomized) using a nitrogen gas washout method[28] with the average of the two measurements used subsequently. The patient's head and neck position were controlled in the supine and lateral position as described below. Patients breathed through a mouthpiece (with a noseclip in place) that facilitated the measurement of ventilation and carbon dioxide (CO_2) (NICO Cardiopulmonary Management System) and oxygen (O_2) (Ametek S-3A/I, Ametek Process Instruments, Pittsburgh, PA, USA). Fractional expired nitrogen was calculated from the fractional O_2 and CO_2 levels ($FN_2 = 1 - FO_2 - FCO_2$). Once patients were acclimatized (~2–3 min), we switched the inspired gas from room air (79% nitrogen, N_2) to 100% oxygen (0% nitrogen, N_2), facilitated by a low resistance non-rebreathing valve (Medium T shape 2-Way NRBV, Hans-Rudolph, Kansas City, MO, USA). When a steady-state expired FN_2 was achieved, participants were switched back to room air ('wash-in' phase) until a steady state was reached (constant FN_2 within 1.5% between breaths, ~5–7 min). The time course of the rise in N_2 was used to measure FRC according to the equation $FRC = \Delta VolN_2/\Delta FN_2$, where $\Delta VolN_2$ is the change in alveolar N_2 volume from the start to end of the test (area under the curve of expired FN_2 vs cumulative expired volume; see Fig. 1), and ΔFN_2 is the change in alveolar N_2 concentration during this time (final FN_2 – initial FN_2). The wash-in phase of the test, rather than the 'washout' phase, was used to avoid the transient reduction in ventilation that can occur with a rapid rise in PO_2 at the onset of the washout.

Computed tomography upper airway

Computed tomography (CT) scans were performed using the Toshiba Aquilion-One CT (Toshiba Medical Systems, Tokyo, Japan) with 320 multi-detector rows. Patients were positioned in the CT scanner in supine and lateral decubitus positions with the scanner bed in the horizontal position. When lying supine, foam pads were used to position the head and neck in the Frankfort plane perpendicular to the bed. When lateral, the Frankfort plane was aligned with the craniocaudal axis of the body, perpendicular to the long axis of the bed. Again, foam pads were used to support the head to eliminate neck flexion/rotation. The technique employed for the scan has been described previously[29] and can be found in full in Supplementary Appendix S1.

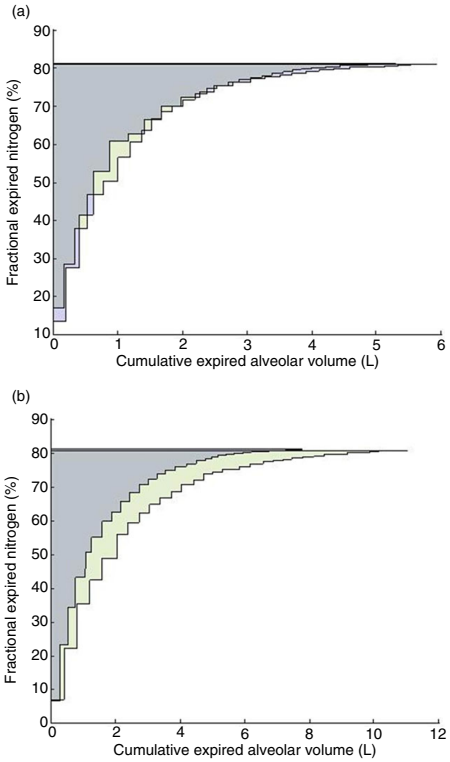

Figure 1 (a,b) Expired FN_2 versus cumulative expired volume graphs for a control patient (a) and a supine obstructive sleep apnoea patient (b). The darker (purple/blue) shaded area is the graph for when the patient is lying in the supine position and the lighter (green) graph is for the lateral washout.

RESULTS

Lung volume and pulmonary function

Patients were matched for age, gender (equal male : female) and BMI. The supine AHI (34.2 ± 9.9 events per hour) and REM AHI (40.5 ± 16.9 events per hour) were similar between the supine OSA and REM OSA groups, respectively. Demographics, anthropomorphics and sleep study parameters are displayed in Table 1. No significant differences were detected in demographic and anthropomorphic features. The positional FRC values are demonstrated in Table 2.

Repeated measures ANOVA demonstrated that the absolute value (L) of FRC was significantly different between the group conditions ($P = 0.026$) and trended to a significant difference between the lateral/supine body positions ($P = 0.059$). Repeated measures ANOVA of the FRC expressed as a percentage of the

Table 1 Demographics of recruited patients

	Control—No OSA	Supine OSA	REM OSA	ANOVA
Number	*N* = 8 (4M, 4F)	*N* = 8 (4M, 4F)	*N* = 8 (4M, 4F)	
AHI—total	0.7 ± 0.6	17.2 ± 6.8	9.6 ± 3.7	<0.01
AHI—state specific		34.2 ± 9.9	40.5 ± 16.9	0.38
Total sleep time (min)	366.9 ± 84.7	365.1 ± 47.9	377.0 ± 80.2	0.94
Stage 1 time (min)	40.4 ± 40.3	45.6 ± 38.6	26.3 ± 15.5	0.50
Stage 2 time (min)	172.1 ± 60.9	212.6 ± 44.7	191.6 ± 62.2	0.37
Stage 3 and 4 time (min)	79.7 ± 51.5	77.9 ± 45.8	61.9 ± 25.4	0.43
REM time (min)	74.8 ± 34.7	45.1 ± 17.1	67.1 ± 14.7	0.06
Nadir oxygen (min)	89.3 ± 2.6	87.3 ± 3.4	78.8 ± 9.3	0.004
Baseline awake O_2 (%)	96.4 ± 1.1	95.8 ± 1.2	94.8 ± 2.0	0.11
Age (years)	43.6 ± 18.3	55.3 ± 15.4	58.8 ± 10.4	0.13
BMI (kg/m^2)	33.7 ± 5.2	31.9 ± 5.4	36.4 ± 4.2	0.21
Neck circ (cm)	40.1 ± 3.6	40.4 ± 2.3	40.4 ± 3.8	0.98
Chest circ (cm)	109.8 ± 9.0	111.0 ± 9.3	115.5 ± 7.7	0.40
Waist circ (cm)	107.1 ± 9.8	107.5 ± 8.7	116.9 ± 11.1	0.11
Hip circ (cm)	113.6 ± 9.9	113.3 ± 11.2	121.4 ± 12.6	0.29
FEV1 (L)	3.3 ± 1.2	3.2 ± 1.2	2.3 ± 0.6	0.13
FVC (L)	4.3 ± 1.4	4.1 ± 1.3	3.0 ± 0.8	0.08
FRC (L)	3.3 ± 0.9	3.3 ± 0.4	3.0 ± 0.8	0.68
TLC (L)	5.9 ± 1.2	5.7 ± 1.0	5.0 ± 1.0	0.28
RV (L)	2.0 ± 0.6	2.3 ± 0.4	2.2 ± 0.8	0.58

AHI, apnoea and hypopnoea index; ANOVA, analysis of variance; BMI, body mass index; Circ, circumference; FEV1, forced expiratory volume; FRC, functional residual capacity; FVC, forced vital capacity; OSA, obstructive sleep apnoea; REM, rapid eye movement; RV, residual volume; TLC, total lung capacity; Washout, multibreath nitrogen washout.

Table 2 Lung volume measurements

	Control—No OSA	Supine OSA	REM OSA
FRC washout seated (L)	2.178 ± 0.617	2.340 ± 1.040	2.043 ± 0.670
FRC washout lateral (L)	1.844 ± 0.709	2.384 ± 1.249	1.800 ± 0.400
FRC washout supine (L)	1.845 ± 0.692	2.045 ± 0.980	1.808 ± 0.488
Lateral lung volume (as percentage of seated lung volume)	83.3 ± 11.6	100.9 ± 13.6	93.2 ± 20.5
Supine lung volume (as percentage of seated lung volume)	83.5 ± 12.0	87.8 ± 14.4	92.7 ± 20.9

FRC, functional residual capacity; OSA, obstructive sleep apnoea; REM, rapid eye movement.

seated value revealed a significant difference in percentage FRC across the group condition ($P = 0.016$) and between lateral/supine body position ($P = 0.028$). Despite the fact that we matched for demographic factors, there are differences (although not significant) between the study groups in BMI, chest circumference and waist circumference. We performed an analysis of covariance, adjusting for BMI, waist and chest circumference. After adjusting for these factors, there remains a significant difference between study groups in terms of the change in FRC when moving from the supine to lateral position ($P = 0.027$). Figure 2 illustrates the change in FRC with change in body position, expressed as a percentage of seated FRC. Patients with supine OSA do not lose volume when moving from seated to lateral recumbent position, but lose a significant volume when moving from lateral to supine.

CT upper airway

We calculated the CSA, anteroposterior (AP) diameter, lateral diameter and AP diameter to lateral diameter ratio for the narrowest section of the velopharynx, oropharynx and hypopharynx during both the inspiratory phase and the expiratory phase. Although the mean value for velopharyngeal CSA during inspiration is less than the mean value for expiration, within-subject values reveal several instances where the inspiratory value exceeds the expiratory value (i.e. expiratory narrowing), a phenomenon described previously.[30]

The airway parameters in the supine and lateral position are displayed in Table 3. A significant difference between the two body positions was detected for each of the characteristics: AP diameter ($P = 0.03$), lateral diameter ($P = 0.004$) and AP to lateral ratio ($P < 0.001$), while this difference was not significantly affected by the group condition ($P = 0.078$, $P = 0.749$, $P = 0.138$, respectively). Figure 3, which is a schematic representation of the mean airway dimensions for each group, reveals a characteristic change to a more circular shape on adopting the lateral position. No significant differences were detected between the supine and lateral positions or across the group

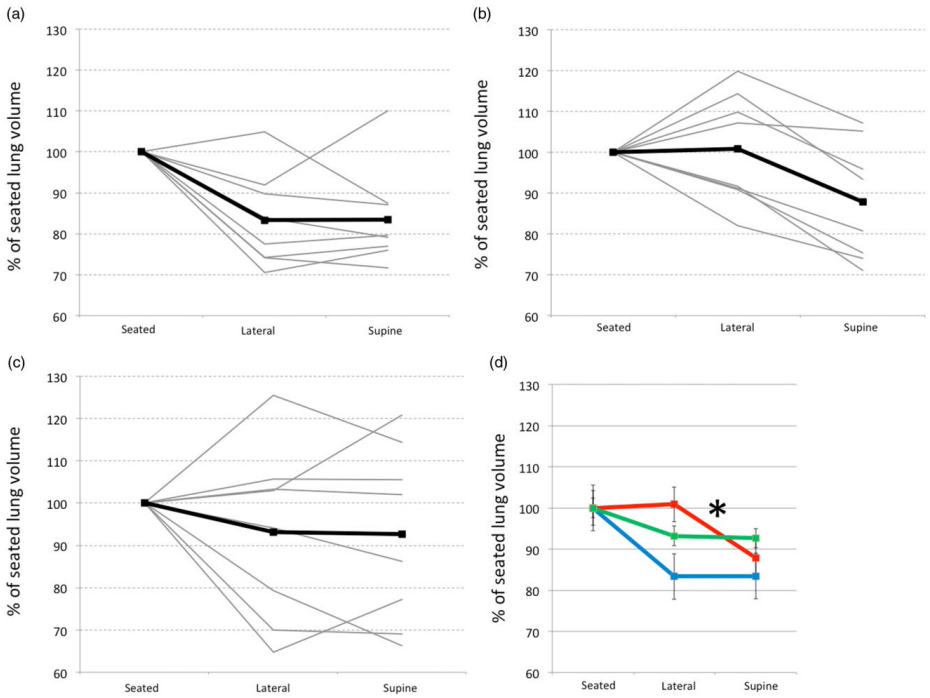

Figure 2 Change in nitrogen washout lung volume (functional residual capacity) expressed as a percentage of the seated lung volume. (a) Control patients, (b) supine obstructive sleep apnoea (OSA) patients, (c) rapid eye movement (REM) OSA patients, (d) mean values for each category, * denotes $P < 0.05$, the error bars in figure (d) are standard error. (▬) Control patients, (▬) supine OSA patients, (▬) REM OSA patients.

Table 3 Between-group analysis of minimal velopharyngeal airway characteristics during inspiration in each of the three groups

Velopharynx during inspiration	Lateral		
	Control	Supine OSA	REM OSA
AP diam (mm)	8.2 ± 2.5	7.1 ± 2.5	9.6 ± 4.8
Lateral diam (mm)	13.4 ± 2.8	14.4 ± 4.4	11.8 ± 3.6
AP to lat ratio	0.7 ± 0.3	0.5 ± 0.2	0.9 ± 0.5
CSA (mm^2)	79.8 ± 39.4	78.3 ± 33.8	86.4 ± 61.7
Velopharynx during inspiration	Supine		
	Control	Supine OSA	REM OSA
AP diam (mm)	7.1 ± 2.9	6.6 ± 2.2	6.4 ± 3.6
Lateral diam (mm)	16.4 ± 3.2	19.1 ± 6.1	14.7 ± 6.8
AP to lat ratio	0.5 ± 0.3	0.4 ± 0.2	0.5 ± 0.2
CSA (mm^2)	86.6 ± 36.4	118.0 ± 43.6	98.5 ± 85.9

AP, anteroposterior; CSA, cross-sectional area; Diam, diameter; OSA, obstructive sleep apnoea; REM, rapid eye movement.

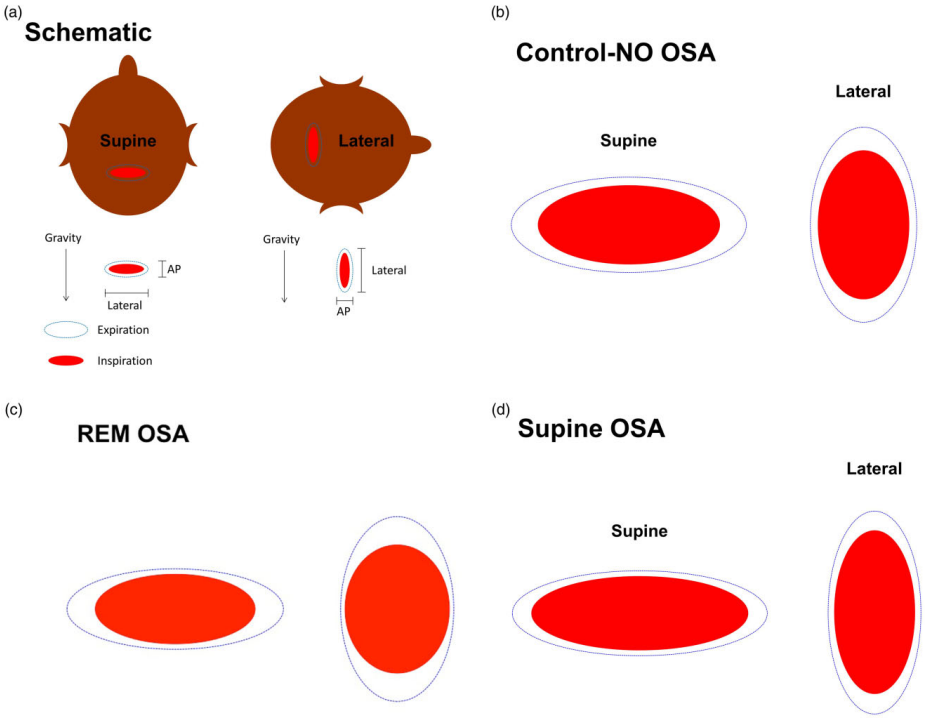

Figure 3 (a–d) A schematic diagram of upper airway shape and dimensions in inspiration (red) and expiration (blue) for each of the study groups. AP, anteroposterior; OSA, obstructive sleep apnoea; REM, rapid eye movement.

conditions for airway CSA. These results are replicated in the analysis of the velopharynx during the expiratory phase (see Supplementary Appendix S2). Analysis of the remaining airway levels during inspiration and expiration revealed a significant difference between body position in the AP diameter of the hypopharynx in both inspiration and expiration, whereas no significant differences were detected at the other airway levels.

Role of gender

There were significant differences between males and females with regard to lung volume and airway shape measurements with males predictably having larger absolute values. Importantly, there are no significant gender differences in repeated measures and multivariate analysis did not demonstrate any influence of gender on repeated measures of lung volume or airway parameters.

DISCUSSION

Our principal finding is that supine OSA patients experience a significant decrease in FRC when moving from lateral to supine, whereas no such decrease occurs in matched controls without OSA or with REM-based OSA. The size of the velopharyngeal airway (determined by CSA) was not significantly different between the two body positions or across the three groups. The shape of the velopharynx (determined by AP and lateral diameter) was significantly different, with a reduced AP diameter and more elliptoid shape when moving from lateral to supine. The difference was not affected by the group condition. Our results suggest that for supine OSA patients, the changes to FRC brought about by moving from the lateral to supine position are an important predisposing factor in generation of upper airway obstruction in that position. However, given that the FRC is reduced from sitting to supine in the control group (without OSA), it cannot be the sole explanation for the generation of obstruction, instead it may act as a triggering factor in those patients with supine-predominant OSA when they move from lateral to supine.

Our study demonstrated a significant FRC fall of 340 mL (13%) in the supine OSA group when moving from lateral to supine, whereas there was no change in the REM OSA and control groups. The fall in FRC

occurs despite the groups being matched for BMI and for hip and waist circumference.

Changes in FRC are known to impact upper airway function. A fall in FRC is known to influence upper airway collapsibility via caudal tracheal displacement with resultant changes in upper airway tissue pressure.[21,31,32] A fall in end expiratory lung volume of 600 mL increases the pharyngeal critical closing pressure (Pcrit) by 1.1 cmH_2O.[20] Similarly, an increase of 720 mL in end expiratory lung volume in anaesthetized patients decreased Pcrit by 1.2 cmH_2O.[33] We found that supine OSA subjects lose 340 mL in FRC when they move from the lateral to supine position. Such a loss of lung volume could be expected to raise Pcrit by approximately 0.5 cmH_2O, which may be sufficient to trigger upper airway obstruction in a vulnerable airway. In addition, a reduced lung volume increases the loop gain of the ventilatory control system during sleep by reducing lung oxygen and carbon dioxide stores[34,35] and this may therefore contribute to breathing instability in the supine sleeping position. Given that a lateral to supine positional shift did not change lung volume in the other two groups, our findings suggest that reduced lung volume in the supine-predominant OSA group may be a key pathological mechanism that predisposes to airway obstruction in the supine position.

The interaction between obesity, body position and lung volume is complex and dependent on the magnitude of the BMI and distribution of excess adipose tissue. Central obesity is thought to contribute to OSA by increasing transdiaphragmatic pressure, reducing lung volume and subsequently reducing caudal tracheal traction to increase upper airway collapsibility.[36] Therefore, one postulated mechanism explaining the supine predisposition to airway collapse in supine-predominant patients is excess abdominal obesity with abdominal obesity in the supine position increasing transdiaphragmatic pressure greater than when lying in the lateral position. However, in our study we observed a significant decrease in FRC between the groups when moving from lateral to supine without any difference between the groups in terms of BMI or waist circumference. In our cohort, the fall in FRC in the supine-predominant group is not explained by a difference in BMI or body mass distribution as measured by waist and chest circumference.

The small increase in FRC when moving from seated to lateral in nine of our individual patients (see Fig. 2) is an interesting observation. It is important to initially highlight that when looking at the FRC of all patients included in our study there is, in fact, a significant *fall* when moving from the seated to the lateral position 2.19 ± 0.77 versus 2.01 ± 0.87 L, $P = 0.032$. Additionally, when analysed according to group, none of the groups demonstrate an increase in mean FRC when moving from seated to lateral. These overall findings are in keeping with several other studies that have demonstrated obese subject experience no significant fall in FRC when moving from seated to supine.[25,37] Watson and Pride demonstrate that obese subjects have no significant change in FRC when moving from seated to supine.[25] The finding of individuals with a small increase in FRC when moving from the seated to lateral position is important because this small increase may have a protective effect for some patients in lateral sleep and this finding requires further investigation. We compared those patients with an increase in FRC from seated to lateral in order to explore potential causes for the increase. There were no significant differences in demographic or anthropomorphics in the nine patients with an increase FRC from seated to lateral compared with others. A larger cohort powered to explore the potential causes of an increase in FRC from seated to lateral in some OSA patients is warranted.

Our study is the first to compare the size and shape of the upper airway in both the lateral and supine position in patients classified according to their OSA phenotype and compared with matched controls. We found no significant differences in awake upper airway characteristics between the groups, but a significant difference in airway shape when moving from lateral to supine was observed in all three groups. Airway size (CSA) did not change significantly when moving from lateral to supine. Importantly, the AP diameter was reduced in the supine position in all study groups, meaning the airway assumes a more laterally oriented elliptical shape when supine and there is less distance for the airway to collapse posteriorly in this position.

Previous imaging studies of OSA patients have methodological limitations including no matched controls, the method of image acquisition including breath holding, reconstruction of two-dimensional images and recording of orthogonal images. We addressed these problems using novel CT technology to obtain real-time four-dimensional images across the tidal breathing cycle, without the need for image reconstruction or breath holding. We also focused our study on those with purely supine positional OSA, who by definition have a clear difference in airway collapsibility in the lateral and supine positions.

Our finding that the velopharyngeal airway adopts a more elliptoid shape (with a reduced AP diameter) in the supine position across all groups suggests that this is not the differentiating factor mediating airway collapse in the supine sleeping position in supine OSA patients. Although a more elliptoid airway shape makes the airway inherently more collapsible, our data point to changes in FRC in the supine OSA group as a predisposing factor for airway collapse in the supine position. We postulate that changes in airway shape on adoption of the supine sleeping position in all groups bring the airway closer to the threshold for collapse, and that changes in FRC (likely in combination with other predisposing factors) are enough to tip patients with supine OSA into having airway collapse in this position. It is also possible that the genioglossus and other airway dilator muscles are not as effective at maintaining airway patency when supine during sleep in supine OSA patients compared with those without position dependent obstruction. In our study we did not measure upper airway dilator muscle activity and this hypothesis requires testing with future studies.

The main limitation of our study is the measurement of FRC and airway shape in the awake state. Although we know that lung volume[38] and airway shape[17] are not altered to a large degree by sleep onset in OSA patients in general, it may be that sleep-induced changes in these parameters are important in sleep state and body position-specific airway collapse.

In conclusion, we present the first study of upper airway size, shape and FRC in patients with a phenotype of purely supine-predominant OSA. Patients with supine-predominant OSA demonstrate a significant decrease in FRC of 340 mL when moving from the lateral to supine position when compared with age, gender and BMI-matched controls with no OSA, and controls with REM (but non-positional) OSA. We found no significant differences between groups in upper airway size and shape. Airway shape changed to a more laterally oriented ellipse when moving from the lateral to supine body position (which makes the airway more inherently collapsible), but this shape change was not specific to those with supine-predominant OSA. We conclude that a fall in FRC when moving from lateral to supine in supine OSA patients may be an important precipitating pathological factor in the generation of upper airway obstruction in this patient group.

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REFERENCES

1 Young T, Palta M, Dempsey J, Skatrud J, Weber S, Badr S. The occurrence of sleep-disordered breathing among middle-aged adults. *N. Engl. J. Med.* 1993; **328**: 1230–5.
2 Oksenberg A, Silverberg DS, Arons E, Radwan H. Positional vs nonpositional obstructive sleep apnea patients: anthropomorphic, nocturnal polysomnographic, and multiple sleep latency test data. *Chest* 1997; **112**: 629–39.
3 Joosten SA, Hamza K, Sands S, Turton A, Berger P, Hamilton G. Phenotypes of patients with mild to moderate obstructive sleep apnoea as confirmed by cluster analysis. *Respirology* 2012; **17**: 99–107.
4 Schwab RJ, Gefter WB, Hoffman EA, Gupta KB, Pack AI. Dynamic upper airway imaging during awake respiration in normal subjects and patients with sleep disordered breathing. *Am. Rev. Respir. Dis.* 1993; **148**: 1385–400.
5 McGinley BM, Schwartz AR, Schneider H, Kirkness JP, Smith PL, Patil SP. Upper airway neuromuscular compensation during sleep is defective in obstructive sleep apnea. *J. Appl. Physiol.* 2008; **105**: 197–205.
6 Edwards BA, White DP. Control of the pharyngeal musculature during wakefulness and sleep: implications in normal controls and sleep apnea. *Head Neck* 2011; **33**(Suppl. 1): S37–45.
7 Wellman A, Jordan AS, Malhotra A, Fogel RB, Katz ES, Schory K, Edwards JK, White DP. Ventilatory control and airway anatomy in obstructive sleep apnea. *Am. J. Respir. Crit. Care Med.* 2004; **170**: 1225–32.
8 Younes M. Role of arousals in the pathogenesis of obstructive sleep apnea. *Am. J. Respir. Crit. Care Med.* 2004; **169**: 623–33.
9 Jordan AS, White DP, Lo Y-L, Wellman A, Eckert DJ, Yim-Yeh S, Eikermann M, Smith SA, Stevenson KE, Malhotra A. Airway dilator muscle activity and lung volume during stable breathing in obstructive sleep apnea. *Sleep* 2009; **32**: 361–8.
10 Eckert DJ, White DP, Jordan AS, Malhotra A, Wellman A. Defining phenotypic causes of obstructive sleep apnea. Identification of novel therapeutic targets. *Am. J. Respir. Crit. Care Med.* 2013; **188**: 996–1004.
11 Kuna ST, Bedi DG, Ryckman C. Effect of nasal airway positive pressure on upper airway size and configuration. *Am. Rev. Respir. Dis.* 1988; **138**: 969–75.
12 Schwab RJ, Pack AI, Gupta KB, Metzger LJ, Oh E, Getsy JE, Hoffman EA, Gefter WB. Upper airway and soft tissue structural changes induced by CPAP in normal subjects. *Am. J. Respir. Crit. Care Med.* 1996; **154**: 1106–16.
13 Walsh JH, Leigh MS, Paduch A, Maddison KJ, Armstrong JJ, Sampson DD, Hillman DR, Eastwood PR. Effect of body posture on pharyngeal shape and size in adults with and without obstructive sleep apnea. *Sleep* 2008; **31**: 1543–9.
14 Pevernagie DA, Stanson AW, Sheedy PF 2nd, Daniels BK, Shepard JW Jr. Effects of body position on the upper airway of patients with obstructive sleep apnea. *Am. J. Respir. Crit. Care Med.* 1995; **152**: 179–85.
15 Martin SE, Marshall I, Douglas NJ. The effect of posture on airway caliber with the sleep-apnea/hypopnea syndrome. *Am. J. Respir. Crit. Care Med.* 1995; **152**: 721–4.
16 Jan MA, Marshall I, Douglas NJ. Effect of posture on upper airway dimensions in normal human. *Am. J. Respir. Crit. Care Med.* 1994; **149**: 145–8.
17 Ciscar MA, Juan G, Martinez V, Ramon M, Lloret T, Minguez J, Armengot M, Marin J, Basterra J. Magnetic resonance imaging of the pharynx in OSA patients and healthy subjects. *Eur. Respir. J.* 2001; **17**: 79–86.
18 Ryan CF, Love LL. Mechanical properties of the velopharynx in obese patients with obstructive sleep apnea. *Am. J. Respir. Crit. Care Med.* 1996; **154**: 806–12.
19 Fogel RB, Malhotra A, Dalagiorgou G, Robinson MK, Jakab M, Kikinis R, Pittman SD, White DP. Anatomic and physiologic predictors of apnea severity in morbidly obese subjects. *Sleep* 2003; **26**: 150–5.
20 Stanchina ML, Malhotra A, Fogel RB, Trinder J, Edwards JK, Schory K, White DP. The influence of lung volume on pharyngeal mechanics, collapsibility, and genioglossus muscle activation during sleep. *Sleep* 2003; **26**: 851–6.
21 Kairaitis K, Byth K, Parikh R, Stavrinou R, Wheatley JR, Amis TC. Tracheal traction effects on upper airway patency in rabbits: the role of tissue pressure. *Sleep* 2007; **30**: 179–86.
22 Joosten SA, O'Driscoll DM, Berger PJ, Hamilton GS. Supine position related obstructive sleep apnea in adults: pathogenesis and treatment. *Sleep Med. Rev.* 2014; **18**: 7–17.
23 Barnas GM, Campbell DN, Mackenzie CF, Mendham JE, Fahy BG, Runcie CJ, Mendham GE. Lung, chest wall, and total respiratory system resistances and elastances in the normal range of breathing. *Am. Rev. Respir. Dis.* 1992; **145**: 110–13.
24 Barnas GM, Green MD, Mackenzie CF, Fletcher SJ, Campbell DN, Runcie C, Broderick GE. Effect of posture on lung and regional chest wall mechanics. *Anesthesiology* 1993; **78**: 251–9.
25 Watson RA, Pride NB. Postural changes in lung volumes and respiratory resistance in subjects with obesity. *J. Appl. Physiol.* 2005; **98**: 512–17.
26 Iber C, American Academy of Sleep Medicine. *The AASM Manual for the Scoring of Sleep and Associated Events: Rules, Terminology, and Technical Specifications*. American Academy of Sleep Medicine, Westchester, IL, 2007.
27 Joosten SA, O'Donoghue FJ, Rochford PD, Barnes M, Hamza K, Churchward TJ, Berger PJ, Hamilton GS. Night-to-night repeatability of supine-related obstructive sleep apnea. *Ann. Am. Thorac. Soc.* 2014; **11**: 761–9.
28 Wanger J, Clausen JL, Coates A, Pedersen OF, Brusasco V, Burgos F, Casaburi R, Crapo R, Enright P, van der Grinten CP *et al.*

Standardisation of the measurement of lung volumes. *Eur. Respir. J.* 2005; **26**: 511–22.
29 Low K, Lau KK, Holmes P, Crossett M, Vallance N, Phyland D, Hamza K, Hamilton G, Bardin PG. Abnormal vocal cord function in difficult-to-treat asthma. *Am. J. Respir. Crit. Care Med.* 2011; **184**: 50–6.
30 Morrell MJ, Arabi Y, Zahn B, Badr MS. Progressive retropalatal narrowing preceding obstructive apnea. *Am. J. Respir. Crit. Care Med.* 1998; **158**: 1974–81.
31 Van de Graaff WB. Thoracic influence on upper airway patency. *J. Appl. Physiol.* 1988; **65**: 2124–31.
32 Rowley JA, Permutt S, Willey S, Smith PL, Schwartz AR. Effect of tracheal and tongue displacement on upper airway airflow dynamics. *J. Appl. Physiol.* 1996; **80**: 2171–8.
33 Tagaito Y, Isono S, Remmers JE, Tanaka A, Nishino T. Lung volume and collapsibility of the passive pharynx in patients with sleep-disordered breathing. *J. Appl. Physiol.* 2007; **103**: 1379–85.
34 Edwards BA, Sands SA, Feeney C, Skuza EM, Brodecky V, Wilkinson MH, Berger PJ. Continuous positive airway pressure reduces loop gain and resolves periodic central apneas in the lamb. *Respir. Physiol. Neurobiol.* 2009; **168**: 239–49.
35 Sands SA, Edwards BA, Kee K, Turton A, Skuza EM, Roebuck T, O'Driscoll DM, Hamilton GS, Naughton MT, Berger PJ. Loop gain as a means to predict a positive airway pressure suppression of Cheyne-Stokes respiration in patients with heart failure. *Am. J. Respir. Crit. Care Med.* 2011; **184**: 1067–75.
36 Stadler DL, McEvoy RD, Sprecher KE, Thomson KJ, Ryan MK, Thompson CC, Catcheside PG. Abdominal compression increases upper airway collapsibility during sleep in obese male obstructive sleep apnea patients. *Sleep* 2009; **32**: 1579–87.
37 Yap JC, Watson RA, Gilbey S, Pride NB. Effects of posture on respiratory mechanics in obesity. *J. Appl. Physiol.* 1995; **79**: 1199–205.
38 Stadler DL, McEvoy RD, Bradley J, Paul D, Catcheside PG. Changes in lung volume and diaphragm muscle activity at sleep onset in obese obstructive sleep apnea patients vs. healthy-weight controls. *J. Appl. Physiol.* 2010; **109**: 1027–36.

Supplementary Information

Additional Supplementary Information can be accessed via the *html* version of this article at the publisher's web-site.

Appendix S1 Methods.

Appendix S2 Repeated measures analysis of variance—velopharynx in expiration.

SUPPLEMENT 1:

CT Upper Airway

CT scans were performed using the Toshiba Aquilion-One CT (Toshiba Medical Systems, Tokyo, Japan) with 320 multi-detector rows. Patients were positioned in the CT scanner in supine and lateral decubitus positions with the scanner bed in the horizontal position. When lying supine, foam pads were used to position the head and neck in the Frankfort plane perpendicular to the bed. When lateral, the Frankfort plane was aligned with the cranio-caudal axis of the body, perpendicular to the long axis of the bed. Again, foam pads were used to support the head to eliminate neck flexion/rotation. Patients were asked to "breathe through the nose with the tongue relaxed and behind the front teeth". The scanning parameters were 80kVp, 250-350mA with automatic exposure, 0.5mm collimation, 0.35 second gantry rotation and scan range from the level just above hard palate extending inferiorly over a z-axis of 16 cm. Patients were instructed via an automated system to breathe normally in and out and images were acquired over a full cycle of ventilation in each of the supine and lateral decubitus positions. Scanning commences at the start of inspiration and runs through expiration until early inspiration on the second breath. This procedure usually takes approximately 5 seconds. The respiratory phase is confirmed on the scanned images by movement of the larynx and clavicles. That is, when the patient inhales (as instructed by the CT scanner) the clavicles are observed to move upwards, forwards and outwards.(Pitts, Patel et al. 2013) The movement of the clavicles in this way is later used by the radiologist to confirm that the patient is inhaling at the start of the scan when reviewing the images. Without the need for table movement, and with just a short period of continuous scanning, this CT technique enabled dynamic 4-dimensional (4-D) image displays of moving body structures to be generated over a 16cm anatomical length during the entire respiratory cycle. From this CT data set it is possible to obtain multiplanar images (including 3 orthogonal planes to the airway), 3 dimensional images and 3-dimensional cine images of the entire airway. Integrated CT software programs generate dynamic axial, sagittal and coronal multiplanar images of the nasopharynx, oropharynx and hypopharynx – from the tip of the nose to the level of the vocal cords. The images acquired in the supine and the lateral positions were interrogated by a senior radiologist blinded to the patient group to

generate a minimum cross sectional area (CSA), antero-posterior diameter and lateral diameter at each of the velopharynx, oropharynx and hypopharynx. (Velopharynx defined as from the level of the posterior hard palate to the base of the uvula, oropharynx as from the base of the uvula to the tip of the epiglottis, and hypopharynx as from the tip of the epiglottis to the base of the epiglottis). Linear measurements were performed manually while CSA was calculated from an outline traced at the interface of soft tissue and air and each of the aforementioned levels of the airway. A minimum CSA was determined for both the inspiratory phase and the expiratory phase. The cumulative CT radiation doses in these patients were low and ranged from 0.8 to 2mSv. The radiation dose was primarily dependent on the volume of soft tissue in the neck.

SUPPLEMENT 2:

Repeated Measures Analysis of Variance – Velopharynx in Expiration

General Linear Model – Velopharynx in Expiration CSA

Descriptive Statistics

	CONTROL_0_REMISO_1_SUPISO_2	Mean	Std. Deviation	N
VEL_LAT_EXP_CSA	.000	120.22500	63.442634	8
	1.000	136.71250	91.144633	8
	2.000	121.16250	52.894800	8
	Total	126.03333	68.297066	24
VEL_SUP_EXP_CSA	.000	140.15000	48.141785	8
	1.000	162.18750	128.483967	8
	2.000	164.36250	41.722037	8
	Total	155.56667	79.901144	24

Multivariate Tests[a]

Effect		Sig.
VelExpCSA	Pillai's Trace	.060
	Wilks' Lambda	.060
	Hotelling's Trace	.060
	Roy's Largest Root	.060
VelExpCSA * CONTROL_0_REMISO_1_SUPISO_2	Pillai's Trace	.801
	Wilks' Lambda	.801
	Hotelling's Trace	.801
	Roy's Largest Root	.801

Tests of Within-Subjects Effects

Source		F	Sig.
VelExpCSA	Sphericity Assumed	3.964	.060
	Greenhouse-Geisser	3.964	.060
	Huynh-Feldt	3.964	.060
	Lower-bound	3.964	.060
VelExpCSA * CONTROL_0_REMISO_1_SUPISO_2	Sphericity Assumed	.224	.801
	Greenhouse-Geisser	.224	.801
	Huynh-Feldt	.224	.801
	Lower-bound	.224	.801
Error(VelExpCSA)	Sphericity Assumed		
	Greenhouse-Geisser		
	Huynh-Feldt		
	Lower-bound		

Tests of Within-Subjects Contrasts

Source	VelExpCSA	Sig.
VelExpCSA	Linear	.060
VelExpCSA * CONTROL_0_REMISO_1_SUPISO_2	Linear	.801
Error(VelExpCSA)	Linear	

Tests of Between-Subjects Effects

Source	Type III Sum of Squares	df	Mean Square	F	Sig.
Intercept	951582.720	1	951582.720	102.777	.000

CONTROL_0_REMISO_1_SUPISO_2	3060.785	2	1530.393	.165	.849
Error	194433.855	21	9258.755		

General Linear Model – Velopharynx Expiration AP Diameter

Descriptive Statistics

	CONTROL_0_REMISO_1_SUPISO_2	Mean	Std. Deviation	N
VEL_LAT_EXP_A_P	.000	9.75000	2.877002	8
	1.000	10.41250	3.899977	8
	2.000	8.23750	2.786158	8
	Total	9.46667	3.221081	24
VEL_SUP_EXP_A_P	.000	8.58750	2.871255	8
	1.000	7.43750	4.202359	8
	2.000	7.53750	2.135374	8
	Total	7.85417	3.090938	24

Multivariate Tests[a]

Effect		Sig.
VelExpAP	Pillai's Trace	.002
	Wilks' Lambda	.002
	Hotelling's Trace	.002
	Roy's Largest Root	.002
VelExpAP * CONTROL_0_REMISO_1_SUPISO_2	Pillai's Trace	.115
	Wilks' Lambda	.115
	Hotelling's Trace	.115
	Roy's Largest Root	.115

Tests of Within-Subjects Effects

Source		F	Sig.
VelExpAP	Sphericity Assumed	12.948	.002
	Greenhouse-Geisser	12.948	.002
	Huynh-Feldt	12.948	.002
	Lower-bound	12.948	.002
VelExpAP * CONTROL_0_REMISO_1_SUPISO_2	Sphericity Assumed	2.400	.115
	Greenhouse-Geisser	2.400	.115
	Huynh-Feldt	2.400	.115
	Lower-bound	2.400	.115
Error(VelExpAP)	Sphericity Assumed		
	Greenhouse-Geisser		
	Huynh-Feldt		
	Lower-bound		

Tests of Within-Subjects Contrasts

Source	VelExpAP	Sig.
VelExpAP	Linear	.002
VelExpAP * CONTROL_0_REMISO_1_SUPISO_2	Linear	.115
Error(VelExpAP)	Linear	

Tests of Between-Subjects Effects

Source	Type III Sum of Squares	df	Mean Square	F	Sig.
Intercept	3600.135	1	3600.135	198.231	.000
CONTROL_0_REMISO_1_SUPISO_2	14.813	2	7.406	.408	.670

Error	381.387	21	18.161		

General Linear Model – Velopharynx in Expiration Width

Descriptive Statistics

	CONTROL_0_REMISO_1_SUPISO_2	Mean	Std. Deviation	N
VEL_LAT_EXP_Width	.000	17.56250	2.286568	8
	1.000	17.00000	4.725916	8
	2.000	17.91250	5.538550	8
	Total	17.49167	4.227541	24
VEL_SUP_EXP_Width	.000	21.23750	4.440379	8
	1.000	19.92500	6.710280	8
	2.000	22.50000	5.500130	8
	Total	21.22083	5.483174	24

Multivariate Tests[a]

Effect		Sig.
VelExpWidth	Pillai's Trace	.005
	Wilks' Lambda	.005
	Hotelling's Trace	.005
	Roy's Largest Root	.005
VelExpWidth * CONTROL_0_REMISO_1_SUPISO_2	Pillai's Trace	.849
	Wilks' Lambda	.849
	Hotelling's Trace	.849
	Roy's Largest Root	.849

Tests of Within-Subjects Effects

Source		F	Sig.
VelExpWidth	Sphericity Assumed	9.900	.005
	Greenhouse-Geisser	9.900	.005
	Huynh-Feldt	9.900	.005
	Lower-bound	9.900	.005
VelExpWidth * CONTROL_0_REMISO_1_SUPISO_2	Sphericity Assumed	.164	.849
	Greenhouse-Geisser	.164	.849
	Huynh-Feldt	.164	.849
	Lower-bound	.164	.849
Error(VelExpWidth)	Sphericity Assumed		
	Greenhouse-Geisser		
	Huynh-Feldt		
	Lower-bound		

Tests of Within-Subjects Contrasts

Source	VelExpWidth	Sig.
VelExpWidth	Linear	.005
VelExpWidth * CONTROL_0_REMISO_1_SUPISO_2	Linear	.849
Error(VelExpWidth)	Linear	

Tests of Between-Subjects Effects

Source	Type III Sum of Squares	df	Mean Square	F	Sig.
Intercept	17983.892	1	17983.892	525.507	.000
CONTROL_0_REMISO_1_SUPISO_2	24.371	2	12.186	.356	.705
Error	718.662	21	34.222		

General Linear Model – Velopharynx in Expiration AP – Lat Ratio

Descriptive Statistics

	CONTROL_0_REMISO_1_SUPISO_2	Mean	Std. Deviation	N
VEL_LAT_EXP_AP_LAT_ratio	.000	.55919	.155359	8
	1.000	.64841	.312212	8
	2.000	.50640	.218800	8
	Total	.57133	.234876	24
VEL_SUP_EXP_AP_LAT_ratio	.000	.43106	.194445	8
	1.000	.37226	.152970	8
	2.000	.36822	.183030	8
	Total	.39051	.172293	24

Multivariate Tests[a]

Effect		Sig.
VelExpAPLRatio	Pillai's Trace	.000
	Wilks' Lambda	.000
	Hotelling's Trace	.000
	Roy's Largest Root	.000
VelExpAPLRatio * CONTROL_0_REMISO_1_SUPISO_2	Pillai's Trace	.233
	Wilks' Lambda	.233
	Hotelling's Trace	.233
	Roy's Largest Root	.233

Tests of Within-Subjects Effects

Source	F	Sig.

VelExpAPLRatio	Sphericity Assumed	22.416	.000
	Greenhouse-Geisser	22.416	.000
	Huynh-Feldt	22.416	.000
	Lower-bound	22.416	.000
VelExpAPLRatio * CONTROL_0_REMISO_1_SUPISO_2	Sphericity Assumed	1.563	.233
	Greenhouse-Geisser	1.563	.233
	Huynh-Feldt	1.563	.233
	Lower-bound	1.563	.233
Error(VelExpAPLRatio)	Sphericity Assumed		
	Greenhouse-Geisser		
	Huynh-Feldt		
	Lower-bound		

Tests of Within-Subjects Contrasts

Source	VelExpAPLRatio	Sig.
VelExpAPLRatio	Linear	.000
VelExpAPLRatio * CONTROL_0_REMISO_1_SUPISO_2	Linear	.233
Error(VelExpAPLRatio)	Linear	

Tests of Between-Subjects Effects

Source	Type III Sum of Squares	df	Mean Square	F	Sig.
Intercept	11.102	1	11.102	157.333	.000
CONTROL_0_REMISO_1_SUPISO_2	.048	2	.024	.337	.718
Error	1.482	21	.071		

CHAPTER 4

THE EFFECT OF BODY POSITION ON PHYSIOLOGICAL FACTORS THAT CONTRIBUTE TO OBSTRUCTIVE SLEEP APNOEA

4.1 DECLARATION FOR THESIS CHAPTER 4

Declaration by candidate

In the case of Chapter 4, the nature and extent of my contribution to the work was the following:

Nature of contribution	**Contribution**
For this chapter I was responsible for hypothesis generation, data collection, data analysis, interpretation of results and manuscript preparation. The extent of my contribution was 80%.	80%

The following co-authors contributed to the work. If co-authors are students at Monash University, the extent of their contribution in percentage terms must be stated:

Name	**Nature of contribution**	**Contribution % (student co-authors only)**
Dr BA Edwards	Aided in data collection, data analysis and manuscript preparation.	
Dr A Wellman	Aided in data analysis and manuscript preparation.	
Mr A Turton	Aided in data collection.	
Ms EM Skuza	Aided in data collection.	
Dr PJ Berger	Aided in hypothesis generation, data analysis, interpretation of results and manuscript preparation.	
Dr GS Hamilton	Aided in hypothesis generation, data analysis, interpretation of results and manuscript preparation.	

The undersigned hereby certify that the above declaration correctly reflects the nature and

extent of the candidate's and co-authors' contributions to this work*.

Candidate's Signature		**Date**

Main Supervisor's Signature		**Date**

4.2 INTRODUCTION TO CHAPTER

As outlined in Chapter 1, a number of important pathophysiological factors contribute to airway obstruction in OSA. In particular, upper airway collapsibility, the ability of the upper airway dilator muscles to stiffen and prevent collapse, respiratory control instability and a low arousal threshold are all considered important contributors. However, many of these factors have not been recorded in lateral sleep – despite the fact that most patients spend the majority of the night lying on their side.

One of the barriers to investigating the effect of body position on the aforementioned contributors to OSA is that many of the techniques employed in the past have been invasive, expensive and technically challenging. Recent advances in measuring the physiological traits known to contribute to OSA have overcome some of the previous barriers. Wellman and colleagues have devised a technique that allows the measurement of upper airway collapsibility, the ability of the upper airway muscles to stiffen and dilate the airway, loop gain and arousal threshold in an individual patient (Wellman, Eckert et al. 2011, Wellman, Edwards et al. 2013). The technique can be performed using standard polysomnographic methods with the simple addition of the measurement of exhaled O_2 and CO_2 and the use of a pneumotachograph to measure flow. Importantly, there is no need for uncomfortable or painful instrumentation with intramuscular electrodes or oesophageal pressure cannulae.

We utilised Wellman's method for measuring the effect of body position on upper airway collapsibility, the ability of the upper airway dilator muscles to stiffen and prevent collapse, respiratory control instability and arousal threshold. Our results indicate that the improvement in airway obstruction observed in lateral sleep in most OSA patients likely results from an improvement in passive airway anatomy, the ability of the airway to stiffen and dilate and an increase in lung volume in the lateral position. We found no significant effect on loop gain or arousal threshold by lateral positioning. These findings provide important insights into the potential effect of positional modification treatment on the pathogenesis of OSA. In particular, our finding raise the tantalizing possibility that

treatments that improve loop gain or arousal threshold may be combined with positional modification for the treatment of OSA.

As per Monash University guidelines for thesis by publication, the following chapter is presented as a PDF as it has been published.

4.3 THE EFFECT OF BODY POSITION ON PHYSIOLOGICAL FACTORS THAT CONTRIBUTE TO OBSTRUCTIVE SLEEP APNOEA

Joosten SA, Edwards BA, Wellman A, Turton A, Skuz EM, Berger PJ, Hamilton GS

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BODY POSITION EFFECTS ON PHYSIOLOGICAL FACTORS THAT CONTRIBUTE TO OSA

The Effect of Body Position on Physiological Factors that Contribute to Obstructive Sleep Apnea

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Study objectives: Obstructive sleep apnea (OSA) resolves in lateral sleep in 20% of patients. However, the effect of lateral positioning on factors contributing to OSA has not been studied. We aimed to measure the effect of lateral positioning on the key pathophysiological contributors to OSA including lung volume, passive airway anatomy/collapsibility, the ability of the airway to stiffen and dilate, ventilatory control instability (loop gain), and arousal threshold.

Design: Non-randomized single arm observational study.

Setting: Sleep laboratory.

Patients/participants: 20 (15M, 5F) CPAP-treated severe OSA patients.

Interventions: Supine vs. lateral position.

Measurements: CPAP dial-downs performed during sleep to measure: (i) V_{eupnea}: asleep ventilatory requirement, (ii) passive V_0: ventilation off CPAP when airway dilator muscles are quiescent, (iii) $V_{arousal}$: ventilation at which respiratory arousals occur, (iv) active V_0: ventilation off CPAP when airway dilator muscles are activated during sleep, (v) loop gain: the ratio of the ventilatory drive response to a disturbance in ventilation, (vi) arousal threshold: level of ventilatory drive which leads to arousal, (vii) upper airway gain (UAG): ability of airway muscles to restore ventilation in response to increases in ventilatory drive, and (viii) pharyngeal critical closing pressure (Pcrit). Awake functional residual capacity (FRC) was also recorded.

Results: Lateral positioning significantly increased passive V_0 (0.33 ± 0.76L/min vs. 3.56 ± 2.94L/min, P < 0.001), active V_0 (1.10 ± 1.97L/min vs. 4.71 ± 3.08L/min, P < 0.001), and FRC (1.31 ± 0.56 L vs. 1.42 ± 0.62 L, P = 0.046), and significantly decreased Pcrit (2.02 ± 2.55 cm H_2O vs. −1.92 ± 3.87 cm H_2O, P < 0.001). Loop gain, arousal threshold, $V_{arousal}$, and UAG were not significantly altered.

Conclusions: Lateral positioning significantly improves passive airway anatomy/collapsibility (passive V_0, Pcrit), the ability of the airway to stiffen and dilate (active V_0), and the awake FRC without improving loop gain or arousal threshold.

Keywords: sleep apnea, obstructive; supine position; airway obstruction; lung volume measurements; functional residual capacity.

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INTRODUCTION

Obstructive sleep apnea (OSA), a medical condition that affects up to 24% of men and 9% of women, is characterized by repetitive upper airway obstruction, oxygen desaturation, and sleep fragmentation. In the long term, OSA predisposes to poor cardiovascular outcome, neurocognitive dysfunction, metabolic dysfunction, and increased risk of motor vehicle accidents.[1–6] Current evidence demonstrates that patients with OSA experience varying severities of obstruction depending upon body position. Of all patients who have OSA, up to 60% have a preponderance of respiratory events when sleeping supine[7,8]; for approximately 20% of patients, upper airway obstruction occurs exclusively in the supine position.[8,9] An obvious inference from the existence of positional dependence of OSA is that the pathophysiological causes of upper airway obstruction manifest themselves variably with body position.

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Recent evidence has suggested that OSA is not simply due to poor upper airway anatomy,[10,11] but has other pathophysiological causes including (1) inability of the pharyngeal muscles to hold open or stiffen the airway during sleep (i.e., impaired upper airway gain),[12,13] (2) oversensitive ventilatory control system (i.e., high loop gain),[14,15] (3) low respiratory arousal threshold,[16,17] and (4) low lung volume.[18,19] Surprisingly, the only studies to have investigated the impact of body position on OSA have focused on just one trait—passive upper airway anatomy/collapsibility. These studies, which measured the pharyngeal critical closing pressure (Pcrit), demonstrated a 2.2–2.9 cm H_2O increase in Pcrit (i.e., airway more collapsible) when adopting the supine sleeping position.[20–22]

The current literature fails to assess why 20% of OSA patients have resolution of obstructive events in lateral sleep. Consequently, the aim of the current study was two-fold. Firstly, in patients with severe OSA, we aimed to measure how sleeping position (i.e. lateral versus supine) affects: (i) V_{eupnea}: eupneic ventilatory demand, (ii) passive V_0: ventilation off CPAP (pressure = 0 cm H_2O) when the upper airway dilator muscles are quiescent, (iii) $V_{arousal}$: the ventilation at which respiratory arousals begin to occur, (iv) active V_0: ventilation off CPAP (pressure = 0 cm H_2O) when the upper airway dilator muscles are activated during sleep, (v) loop gain: assessed by the ratio of the ventilatory drive response to a disturbance

in ventilation, (vi) arousal threshold: the level of ventilatory drive at which a patient will arouse from sleep, (vii) upper airway gain (UAG) the ability of the upper airway muscles to activate and restore ventilation in response to increases in ventilatory drive, and (vii) functional residual capacity (FRC). Secondly, we aimed to assess the physiological characteristics that differentiate OSA patients who have a reduced apnea and hypopnea index (AHI) in the lateral sleeping position compared to other OSA patients with severe OSA regardless of sleep position. We prespecified the definition of supine OSA based on previously published data from our group.[23] Preliminary results of this analysis have been published in abstract form.[24]

METHODS

Institutional ethics approval was obtained from the Monash Health Human Research Ethics Committee. Patients with severe OSA (AHI > 30 events/h) were identified from a hospital database. To be included, patients were required to have recorded > 30 min supine and > 30 min non-supine NREM sleep on their diagnostic study. Patients were required to be using CPAP for > 2 months and to be adherent for > 4h/night in the 30 days prior to enrolment. Patients were randomly selected from the included list, gave written informed consent to participate, and attended the Monash Sleep Centre for 2 overnight studies one week apart in order to measure the OSA traits (detailed below). Anthropomorphic and lung volume measurements were made prior to each overnight study. One overnight study was conducted with the subject in the supine position (with the head also supine). The other study was performed with the patient lying in the right lateral position with the head in the neutral position as comfort allowed. Patients were under continuous video monitoring and were repositioned if they moved from the prescribed position. The order of the position studied was randomized. We defined 2 groups of OSA patients for the purpose of this study based on our previously published work[23]: patients with a supine AHI to non-supine AHI ratio of > 4:1 on their diagnostic polysomnogram (PSG), whom we refer to as the supine OSA group, and patients with a supine AHI to non-supine AHI ratio of < 4:1, whom we refer to as the position-independent OSA group.

Anthropomorphic Measurements

Weight was measured with electronic scales (Seca 703, Hamburg, Germany) and height with a stadiometer (Seca 264, Hamburg, Germany) in order to determine BMI. Circumferential measurements were carried out upright with the tape measure in a plane parallel to the ground, completely surrounding the body without compressing the subcutaneous tissues; the neck was measured just inferior to the cricoid cartilage, the chest at the level of the third intercostal space, the waist at the smallest girth between the iliac crest and the costal margin, and the hips at the level of the largest dimension over the buttocks.

Lung Volume

Awake measurements of FRC were performed 4 times in each of the seated, supine, and lateral positions (with the order of measurement randomized in each patient) using a nitrogen gas washout method,[25] with the average of the 4 measurements used subsequently. The full description of the method used can be found in section 1 of the supplemental material.

Overnight Phenotyping

On the study night, patients were instrumented for a standard clinical PSG montage with electroencephalogram, submental and leg electromyogram, electrocardiogram, arterial oxygen saturation, and CPAP mask pressure. Additional respiratory measurements were made using a pneumotachograph, capnograph, and an oxygen analyzer. Exhaled CO_2 (NICO Cardiopulmonary Management System, Respironics Novametrix, Wallingford, CT) and exhaled O_2 (Ametek S-3A/I, Ametek Process Instruments, Pittsburgh, PA) were sampled via a cannula inserted through a port into the CPAP mask and under constant 0.1 L/min suction. The CPAP mask was sealed and connected to a pneumotachograph (model 3700A, Hans Rudolph, Kansas City, MO) with a vent inserted in the circuit distal to the pneumotachograph (i.e., with the pneumotachograph closer to the CPAP mask and the vent closer to the pressure source). The circuit was connected to a positive/negative pressure source (Resmed, New South Wales, Australia) that was used to control the level of CPAP delivered and was capable of delivering +20 cm H_2O to −20 cm H_2O pressure. Sleep state and arousals were scored by an experienced sleep scientist in accordance with standard criteria.[26] The scientist was blinded to the respiratory measurements and the position state of the patient. All signals were recorded and displayed overnight using Compumedics Profusion PSG 3 (Compumedics, Abbotsford, Australia). Data were exported from Profusion PSG3 in the European Data Format (EDF) and analyzed in Spike2 (Cambridge Electronic Design, Cambridge, UK) and MatLab (Mathworks, Natick, MA).

The method for measuring the contributory mechanisms for OSA has been described in detail previously[27] and is summarized in Figure 1 (with subsequent numbering corresponding to the numbering in Figure 1). In brief, CPAP was altered during sleep to measure 4 different ventilations and loop gain. Ventilation was determined from flow on a breath-by-breath basis. Subsequent analysis involved averaging of these breaths as described below. The ventilation measurements included (i) V_{eupnea}: the eupneic ventilatory demand or the subject's asleep ventilatory requirement (which is determined by dead space ventilation and ventilatory requirement), (ii) passive V_0: ventilation off CPAP (pressure = 0 cm H_2O) when the upper airway dilator muscles are quiescent, (iii) $V_{arousal}$: the ventilation at which respiratory arousals begin to occur, and (iv) active V_0: ventilation off CPAP (pressure = 0 cm H_2O) when the upper airway dilator muscles are activated during sleep, (v) loop gain: assessed by the ratio of the ventilatory drive response to a disturbance in ventilation.

Initially, the CPAP pressure was increased to eliminate snoring and flow limited breathing to obtain the measurement of V_{eupnea} (i). Then the mask pressure was rapidly dialled down to 0 cm H_2O for 5 breaths to obtain a measurement for passive V_0 (ii). The CPAP was then returned to optimal pressure and subsequently decreased slowly according to the algorithm presented in section 2 of the supplemental material. The pressure was decreased to achieve flow-limited breathing and then to determine the level of ventilation at which arousals begin

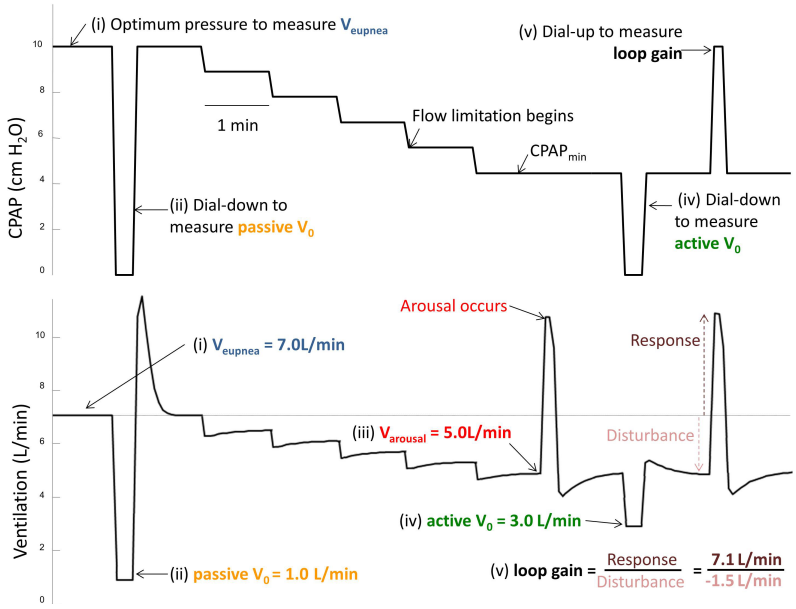

Figure 1—CPAP dial-down method for measuring phenotypic traits. **(i)** V_{eupnea}, ventilation at optimal CPAP with no evidence of snoring or flow limited breathing; **(ii)** passive V_0, ventilation at CPAP = 0 cm H_2O with completely relaxed pharyngeal muscles; **(iii)** $V_{arousal}$, the ventilation just prior to a respiratory-induced arousal; **(iv)** active V_0, ventilation at CPAP = 0 cm H_2O with maximally activated pharyngeal muscles; **(v)** loop gain, the ratio of ventilatory overshoot (response) above V_{eupnea} when returning to optimal CPAP pressure from a period of sub-optimal CPAP with reduced ventilation (disturbance).

to occur $V_{arousal}$ (iii). This level of pressure was termed the $CPAP_{min}$. At $CPAP_{min}$, during periods of relatively arousal-free breathing, a series of dial downs to 0 cm H_2O was performed to measure active V_0 (iv). An additional maneuver which involved a series of dial ups to the optimal CPAP level from the $CPAP_{min}$ was then performed in order to determine loop gain (v). If the patient experienced awakening (i.e., an increase in EEG activity > 15 sec) at any time such as at $CPAP_{min}$, during the slow decreases in CPAP or subsequent to a dial up or dial down from $CPAP_{min}$, the CPAP was returned to the optimal pressure, and once sleep was reinstated, the sequence was repeated. Several reduction sequences such as that demonstrated in Figure 1 were achieved across the night.

In order to model the interaction between the various traits to determine the predisposition to OSA, the 5 "ventilations": (i) V_{eupnea}, (ii) passive V_0, (iii) $V_{arousal}$, (iv) active V_0, and (v) loop gain; were plotted on a graph of ventilation (L/min) versus ventilatory drive (L/min). One advantage of this method is that it enables a normalization of the trait measurements to ventilatory drive. The graph also allows the calculation of (vi) arousal threshold, and (vii) upper airway gain (see Figure 2 with the sequential numbering matching that of Figure 1). First, V_{eupnea} was determined by averaging several minutes of ventilation on optimal CPAP, was plotted (Figure 2i and Figure 1i). The value was placed along the line of identity between ventilation and ventilatory drive, as it indicates that the patient's ventilatory demand is being fully met with the airway completely patent on optimal CPAP. Second, the passive V_0, which is the ventilation at CPAP = 0 cm H_2O when the upper airway muscles are passive, was plotted (Figure 2ii and Figure 1ii). This value was determined by averaging the ventilation of breaths 3 and 4 (without arousal) following a rapid dial down from optimal CPAP to 0 cm H_2O. Third, $V_{arousal}$, which is the ventilation that leads to a respiratory arousal, was plotted (Figure 2iii and Figure 1iii). This value was determined from the mean ventilation of the 5 breaths prior to a respiratory-induced arousal. Fourth, active V_0, which is the ventilation at CPAP = 0 cm H_2O when the pharyngeal muscles are active, was plotted (Figure 2iv and Figure 1iv). This value was determined by averaging the ventilation of breaths 3 and 4 following a dial down in CPAP pressure from $CPAP_{min}$ to 0 cm H_2O (if $CPAP_{min}$ is a negative pressure then the pressure is dialled "up" to 0 cm H_2O). Fifth, the reciprocal of loop gain line was plotted (Figure 2v and Figure 1v). The slope of the line was determined by calculating how much increased ventilatory drive (horizontal vector of the line) was created by a reduction in ventilation (vertical vector of line). That is, loop gain = response (increase or overshoot in ventilation above eupnea) ÷ disturbance (reduction in ventilation below eupnea)—in this case loop gain = 7.1L/min ÷ −1.5L/min = −4.7 (note that loop gain is dimensionless). The slope of the line plotted is 1/LG or in this case 1/−4.7.

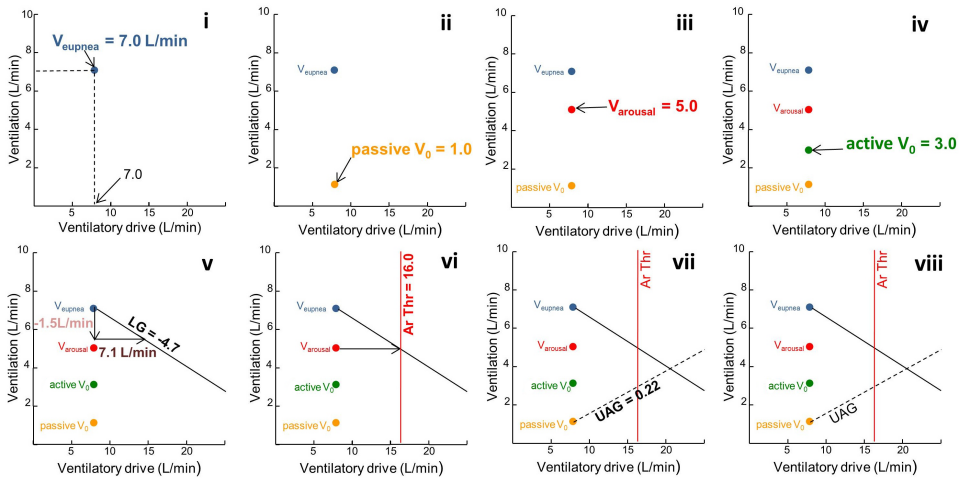

Figure 2—Plotting the phenotypic trait variables. Lower case roman numerals correspond with numbering in Figure 1.

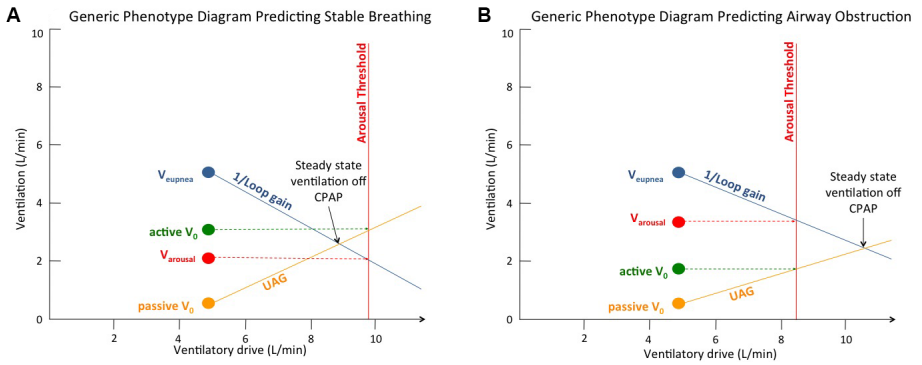

Figure 3—Generic phenotype diagram. **(A)** Model predicting stable breathing with loop gain line and UAG line intersecting to the left of the arousal threshold line. **(B)** Model predicting airway obstruction with the loop gain line and UAG line intersecting to the right of the arousal threshold line. UAG, upper airway gain.

Once the loop gain is known, the arousal threshold, which is the level of ventilatory drive at which a patient will arouse from sleep, could be determined from the intersection of a horizontal line through $V_{arousal}$ and the loop gain line (Figure 2vi). Lastly, the upper airway gain (UAG) was determined as follows (Figure 2vii): A horizontal line was drawn through the active V_0 and its intersection with the arousal threshold line. The passive V_0 point was then connected with this intersection point. The slope of this line is called the upper airway gain (UAG) (UAG = change in ventilation/change in ventilatory drive). The UAG represents the ability of the upper airway muscles to activate and restore ventilation in response to increases in ventilatory drive. Figure 2viii depicts visually how the traits interact and illustrates whether the combination predicts the presence or absence of OSA.[27] The generic phenotype diagram depicted in Figure 3 demonstrates how the model predicts airway obstruction. If a steady state ventilation off CPAP (determined by the intersection of the loop gain line and the upper airway gain line) is achieved below the arousal threshold (i.e., if the loop gain and UAG lines intersect to the left of the arousal threshold line [Figure 3A]), the patient will be able to achieve stable breathing, whereas if this intersection occurs to the right of the arousal threshold line (Figure 3B), the patient will experience a respiratory arousal, and thus OSA.

In addition to the measurements reported above, for consistency with previous data, we also measured the passive

Table 1—Patient demographics.

	All Patients (n = 20, 15M, 5F)	Supine OSA (n = 7)	Position-Independent OSA (n = 13)
Age (y)	54.9 ± 11.9	54.86 ± 14.90	54.85 ± 10.56
BMI (kg/m^2)	34.7 ± 6.3	32.63 ± 4.53	35.76 ± 7.01
Neck circumference (cm)	43.2 ± 3.1	42.29 ± 3.04	43.62 ± 3.07
Chest circumference (cm)	113.5 ± 8.6	108.57 ± 7.74	116.08 ± 8.03
Waist circumference (cm)	114.3 ± 13.8	108.43 ± 13.02	117.38 ± 13.58
Hip circumference (cm)	114.5 ± 14.0	109.29 ± 9.72	117.31 ± 15.50
AHI (events/h)	57.0 ± 23.8	48.54 (20.35)*	75.19 (50.14)*
Supine AHI (events/h)	69.9 ± 27.0	65.16 ± 21.91	72.38 ± 29.95
Non-supine AHI (events/h)	36.7 ± 31.9	4.52 (12.13)*,^	55.28 (47.82)*,^
Non-REM (events/h)	54.35 ± 24.31	42.57 ± 12.92	60.69 ± 20.99
REM AHI (events/h)	45.02 ± 27.88	22.05 ± 12.06^	57.39 ± 26.06^
Apnea index (events/h)	39.68 ± 26.07	23.99 ± 16.14°	48.12 ± 26.92°
Hypopnea index (events/h)	15.74 ± 8.92	18.40 ± 12.78	14.31 ± 6.16

*Values are nonparametric and are expressed as median (interquartile range). ^Significant difference between the supine OSA group and position-independent group with P < 0.01. °Significant difference between the supine OSA group and position independent group with P < 0.05. M, males; F, females; BMI, body mass index; AHI, apnea-hypopnea index; REM, rapid eye movement.

critical collapsing pressure or Pcrit.[28] In brief, while the patient was in NREM sleep receiving optimal CPAP, the mask pressure was rapidly reduced for 5 breaths before being returned to optimal CPAP. The reduction in mask pressure was performed in sequenced drops to a level of CPAP (positive or negative) that produced flow limitation. Each run of pressure drops included ≥ 3 drops that produced flow limitation. Flow was taken from breaths 3–5 in a drop in which flow limitation was observed. The data points were plotted on a flow vs mask pressure graph and a linear regression line was plotted. The intersection of the regression line with the x-axis gives the Pcrit.

Statistics

Data were collated on an Excel spreadsheet (2010, Version 14.0.6129.5000, Microsoft Corporation) and analyzed using IBM SPSS 22 (2013, Release 22.0.0, IBM Corporation). Positional changes were analyzed using a paired t-test. Mean values between 2 groups were analyzed using an unpaired t-test. We examined both the absolute lung volumes and the positional lung volume expressed as a percentage of the seated lung volume in order to standardize the magnitude of change. All results are given as mean ± standard deviation unless otherwise stated. A P value < 0.05 was considered statistically significant.

RESULTS

The patient demographics are listed in Table 1. The mean value for each phenotypic trait measurement was compared from the supine night to the lateral night, with the results presented in Table 2 and Figure 4.

There was a similar number of phenotype measurements made in each condition. There was a significant increase when moving from supine to lateral in the passive V_0 and active V_0, and a significant decrease in Pcrit. The remaining traits (V_{eupnea}, $V_{arousal}$, loop gain, AT, and UAG) were unaltered by a change in position. The awake FRC was also significantly increased in the lateral position by a mean of 110 mL (8%). The model of the group data (Figure 4) demonstrated that although there was an increase in passive V_0 and active V_0, the loop gain line and UAG line still intersected to the right of the arousal threshold line when the patients lay in the lateral position. Therefore the model predicted that although lateral sleep increased both the passive anatomy (passive V_0, Pcrit) and the achievable ventilation once the upper airway muscles are activated (active V_0), it still did not resolve OSA as the intersection of the loop gain and UAG lines lies to the right of the arousal threshold line. Such a prediction is in line with the mean lateral AHI being 36.7 ± 31.9 events/h. The individual phenotype diagrams for each of the 20 patients are included in section 3 of the supplemental material.

Table 2—Phenotype values from supine to lateral.

	Supine	Lateral	Paired t-test
V_{eupnea} (L/min)	6.84 ± 0.86	6.95 ± 1.03	0.490
Passive V_0 (L/min)	0.33 ± 0.76	3.56 ± 2.94	< 0.001
$V_{arousal}$ (L/min)	5.47 ± 1.09	6.16 ± 1.37	0.074
Active V_0 (L/min)	1.10 ± 1.97	4.71 ± 3.08	< 0.001
Loop gain	−2.29 ± 1.13	−2.70 ± 1.85	0.288
AT (L/min)	9.72 ± 2.27	8.60 ± 3.00	0.075
UAG	0.24 ± 1.20	0.54 ± 2.71	0.510
Pcrit (cm H_2O)	2.02 ± 2.55	−1.92 ± 3.87	< 0.001
FRC (L)	1.31 ± 0.56	1.42 ± 0.62	0.046
Percent FRC (%)	79.25 ± 13.24	87.05 ± 18.01	0.011

AT, arousal threshold; UAG, upper airway gain; FRC, functional residual capacity; Pcrit, pharyngeal critical closing pressure; Percent FRC, the FRC expressed as a percentage of the seated value.

We compared the phenotype trait values for patients who had supine OSA with those patients with position-independent OSA; the full results are listed in section 4 of the supplemental material.

There were 7 patients in the supine OSA group and 13 in the position-independent group. There were no significant

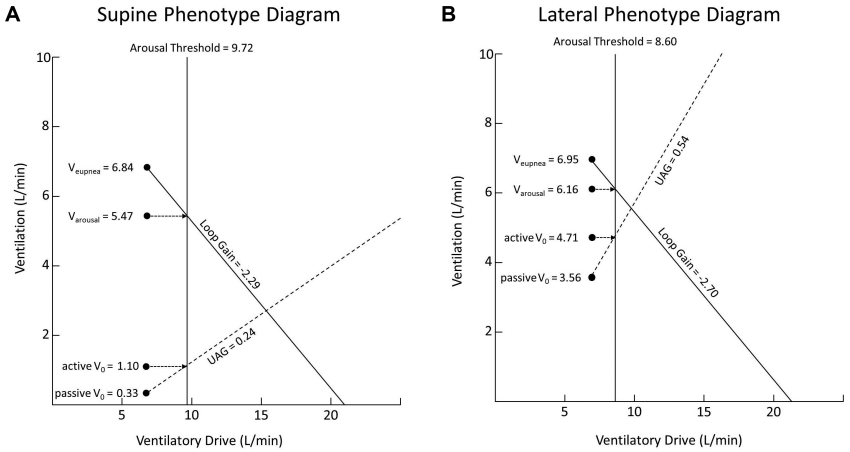

Figure 4—Summary phenotype diagrams for patients with severe OSA when moving from the supine sleeping position to the lateral sleeping position. UAG, upper airway gain.

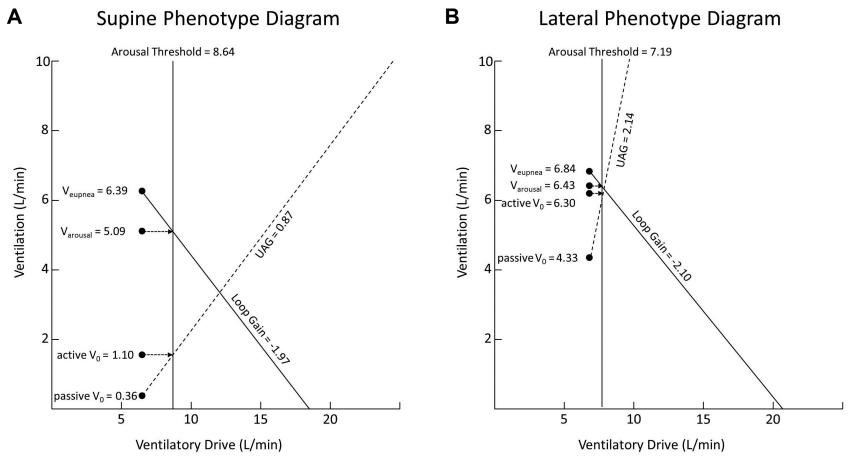

Figure 5—Phenotype diagrams for supine and lateral position in patients who have a supine to non-supine AHI ratio of > 4:1. UAG – upper airway gain.

differences in any of the anthropomorphic or demographic features between the 2 groups. The lateral UAG was significantly increased and the lateral Pcrit significantly decreased in the supine OSA group compared to the lateral UAG and Pcrit in the position-independent group (2.14 ± 2.53 vs −0.32 ± 2.48, P = 0.049 and −4.63 ± 3.33 cm H_2O vs −0.50 ± 3.40 cm H_2O, P = 0.02, respectively). There was also a strong trend to a significantly increased active V_0 in the lateral position in the supine OSA group compared to the position-independent group (6.30 ± 0.74 vs 3.85 ± 0.91, P = 0.052).

A within-group analysis of the supine OSA group demonstrated a significant improvement when moving from supine to lateral in passive V_0 (0.36 ± 0.94 L/min vs 4.33 ± 2.83 L/min, P = 0.007), active V_0 (1.56 ± 2.37 L/min vs 6.30 ± 0.74 L/min, P = 0.01), and Pcrit (3.00 ± 2.32 cm H_2O vs −4.63 ± 3.33 cm H_2O, P = 0.001). For patients with supine OSA, the increase in active V_0, passive V_0, and UAG brought the intersection of the loop gain line and UAG line very close to the arousal threshold (Figure 5). This is in keeping with the known low lateral AHI in this group of patients of 4.52 events/h (reported with an

interquartile range of 12.13, as these data were not normally distributed).

DISCUSSION

Our study demonstrates for the first time that when patients with severe OSA shift from the supine to lateral position, they experience a significant increase in awake FRC, passive V_0, and active V_0, and a significant decrease in Pcrit. On their own, these improvements are not large enough to prevent OSA in the lateral position in all patients because two other traits that predispose to OSA, loop gain and arousal threshold, are not altered by changes in body position. Furthermore, we demonstrate for the first time that the subgroup of OSA patients who have a supine predominant OSA (defined by a supine to non-supine AHI ratio of > 4:1) have significantly more favorable UAG and Pcrit, and a trend to significant improvement in active V_0 in the lateral position compared to other patients with OSA. This improvement is large enough to almost completely avert OSA in the lateral position in these patients. Our findings demonstrate that, in a subpopulation of OSA patients with supine OSA, the preservation of airway function in the lateral position arises from an ability to stiffen and dilate the airway more effectively (improved UAG and active V_0) than patients with position-independent OSA. Additionally, our findings suggest that patients with supine OSA exhibit a dynamic change in their collapsibility with positional changes. In a subset of patients who display a relatively less collapsible airway in the lateral position, we speculate that these individuals will be more likely to respond to therapies targeting the non-anatomical traits (i.e., loop gain and arousal threshold)—as those with position-independent OSA will need to have their anatomy altered before any non-anatomical therapy is likely to be of benefit.

The observed improvements in the passive and active V_0 observed in all patients in the lateral sleeping position likely result from a combination of: (1) a more effective airway dilatation in the lateral position, (2) improved caudal traction of the trachea secondary to improved lung volume, (3) the inherent folding qualities of the lateral pharyngeal walls, and (4) a change in the direction of gravity through upper airway structures.

The improvements observed in active V_0 in the lateral position indicate that the airway is able to stiffen or dilate more effectively in that position. In addition to the improvements of lateral positioning on passive characteristics of the airway listed above (i.e., improvement in passive V_0 and Pcrit), it may be that the function or effectiveness of pharyngeal dilator muscles is also improved in this position. Previous studies have demonstrated that the genioglossus muscle is at its most active when OSA patients and normal subjects lie in the supine sleeping position.[29,30] This is likely the result of the muscle having to work harder to overcome the unfavorable passive anatomy in the supine position (i.e., a higher Pcrit when supine). With the improvement in passive qualities and change in the direction of gravity through soft tissue structures it may be that the genioglossus has to work less to achieve greater stiffening and dilating in the lateral position. In our study, the subgroup of patients with supine-predominant OSA demonstrated a significant improvement in UAG and a trend towards a significant improvement ($P = 0.052$) in active V_0 in the lateral position, despite no significant differences in passive V_0. In this group of patients, the function of pharyngeal dilator muscles appears to be the main difference determining almost complete resolution of OSA in the lateral position.

In our patients, the awake FRC increased when they shifted from supine to lateral—an effect already reported[31] and shown to be associated with a reduced upper airway collapsibility that may result from an increase in caudal tracheal traction and reduced tissue pressures around the upper airway.[32–34] Whether the size of the volume change we observed (110 mL) is sufficient to explain an improved Pcrit of 3.9 cm H_2O (from 2.0 ± 2.5 cm H_2O supine to -1.9 ± 3.9 cm H_2O lateral) is questionable in view of earlier studies. For instance, Jordan et al. demonstrated that increasing end-expiratory lung volume by 500 mL improved the Pcrit from 2.2 ± 0.7 cm H_2O to -1.0 ± 0.5 cm H_2O. Of note, the improvement in Pcrit observed in our study of −3.9 cm H_2O in the lateral position is larger than that observed in previous studies (2.2–2.9 cm H_2O).[20–22] The most likely explanation for the larger Pcrit improvement observed in lateral sleep compared to previous reports is that the proportion of supine-related OSA patients in our cohort (7/20) is greater than in other cohorts of severe OSA patients.[9] A larger proportion of patients with supine-related OSA will bias the results to a greater improvement in Pcrit in the lateral position compared to previous studies.

The folding characteristics of the lateral pharyngeal airway may also play an important role in determining collapse in the supine sleeping position. With the airway adopting a laterally oriented ellipsoid shape with the patient supine,[35] collapse is most likely to occur initially at the lateral walls before propagating medially.[36,37] Modeling of the human airway, using both physical[38] and mathematical[39] models, indicates that the folding geometry of the lateral airway is critically important in determining collapsibility of the airway. When a patient with OSA lies in the lateral position, there is an opening up of the lateral portions of the airway, so that the overall shape of the velopharynx becomes more circular.[35] Coupled with a change in the direction of gravity through the upper airway soft tissues, the altered geometry of the lateral airway when the patient lies in the lateral position may explain part of the improvement seen in passive V_0 in that position.

When lying in the supine position, the bulk of the soft tissue structures such as the tongue and soft palate lie anterior to the velopharyngeal airway.[40] In this position, gravitational pull favors posterior collapse of the bulky soft tissue structures. With the patient lying in the lateral position, the tongue and soft palate now lie perpendicular to the gravitational pull (i.e., they now constitute the lateral wall of a 90° rotated airway). It is now the smaller volume of soft tissue that constitutes the lateral pharyngeal wall that lies in the anterior position, resulting in an airway that is less likely to collapse when passive and in the lateral position.[40]

Implication for an Alternative to CPAP Treatment of OSA

A number of strategies may be employed to prevent patients with OSA from sleeping in the supine position.[41] In certain patients, where the lateral AHI is low from night to night, and the propensity for supine airway collapse is repeatable,[23]

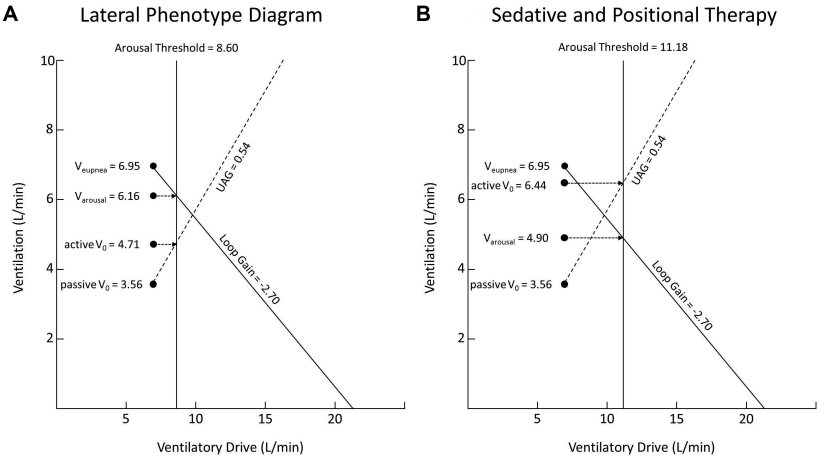

Figure 6—(A) Data of the 20 patients in our study in the lateral position. **(B)** Predicted effect of combination therapy with lateral positioning and non-muscle relaxant sedative to improve arousal threshold.

positional therapy could normalize the AHI.[42] Our study demonstrates why positional therapy does not work for all OSA patients. Only some patients improve their active (active V_0) and passive (passive V_0 and Pcrit) anatomy sufficiently when moving to the lateral position, particularly when considering the interaction between airway anatomy and the other physiological traits predisposing to OSA. We show for the first time that arousal threshold and loop gain are not significantly affected by moving to the lateral position and continue to predispose the airway to collapse.

Several studies have addressed the contribution of a high loop gain and low arousal threshold to OSA severity.[43–45] From these studies, it has been estimated that a low arousal threshold contributes to OSA in up to 50% of patients with the disease,[46] and that the administration of a non-muscle relaxant sedative can elevate the arousal threshold by 28% to 48%.[44,47] In addition, the administration of acetazolamide reduces the loop gain in OSA sufferers by 41% without altering any of the other pathophysiological traits measured.[45] Altering these traits has been shown to lead to a partial improvement in OSA.

Given that lateral sleep improves passive V_0 and active V_0 but not loop gain or arousal threshold, we considered the effect combining these treatments would have on patients with OSA (i.e., the effect of lateral positioning combined with treatment of loop gain or arousal threshold). By using our data demonstrating the phenotypic trait values of all 20 patients when lying in the lateral position (see Figure 6A, copied from Figure 4B above) and applying an improvement in arousal threshold of 30% (from previously published data) to our data, we can demonstrate that the model now predicts complete resolution of obstructive events (see Figure 6B). That is, in Figure 6A the model predicts obstructive events with the loop gain line and UAG line intersecting to the right of the arousal threshold line, while in Figure 6B, with the improvement in arousal threshold applied, the model predicts stable breathing with the loop gain line and arousal threshold line intersecting to the left of the arousal threshold line. By contrast, an improvement in loop gain of 40% applied on its own is not enough to resolve obstructive events (Figure 7). Figure 7A is the data from our 20 patients in the lateral position (again, copied from Figure 4B above), with the model predicting obstructive events. In this instance, the model still predicts obstructive events despite the applied improvement in loop gain (see Figure 7B where the loop gain line and UAG line still intersect to the right of the arousal threshold line).

This analysis suggests that the potential combination of positional modification and non-muscle relaxant sedatives as an alternative to CPAP therapy in severe OSA sufferers is a fruitful strategy for further investigation.

Limitations

The first limitation of our study is that it included only a small cohort of patients, all of whom had severe OSA, limiting its applicability to the OSA population as a whole, particularly patients of varying OSA severity.

For technical reasons, we limited our measurements of the pathophysiological traits to NREM sleep. The interaction of the variables measured in REM sleep and the effect of lateral position on the variables has not been demonstrated, although we know from previous studies that positional effects on the AHI do occur in REM sleep.[22,48]

The lung volume measurements we made were during wakefulness. Measurements of both supine and lateral lung volumes have not been made during sleep in individuals with OSA, and no studies have compared these values with awake values in the same postures. We therefore cannot be certain of how our awake measurements of FRC relate to the actual FRC during sleep, and this is a limitation of the data presented.

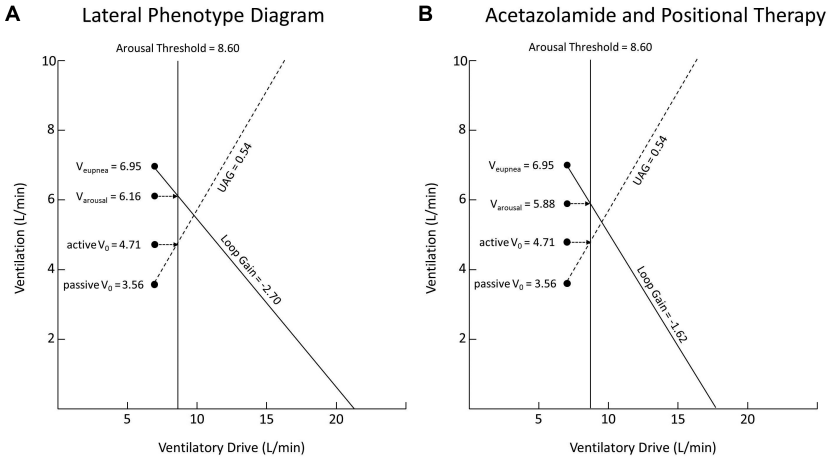

Figure 7—(A) Data of the 20 patients in our study in the lateral position. **(B)** Predicted effect of combination therapy with lateral positioning and acetazolamide treatment of ventilatory control instability (loop gain).

CONCLUSION

We have demonstrated for the first time that patients with severe OSA who move from the supine to lateral position have a significant improvement in awake FRC, passive upper airway collapsibility (passive V_0 and Pcrit), and the ability of the airway to dilate and stiffen (active V_0), but there is no significant change in the respiratory arousal threshold or loop gain. In a subgroup of OSA patients with supine OSA (a supine to non-supine AHI ratio > 4:1), the improvement in OSA in the lateral position appears to be the result of an improvement in the ability of the airway to stiffen and dilate in that position, possibly as a function of more effective pharyngeal dilation in that position (i.e., improved UAG and trend to significant improvement in active V_0). Our data suggest that, although positional therapy alone will not resolve obstruction in the majority of patients with severe OSA, it could be combined with treatments that improve arousal threshold and loop gain as an alternative to CPAP in patients with severe OSA.

DISCLOSURE STATEMENT

The dial-down CPAP machine used in this project was loaned for use by ResMed. Dr. Joosten is supported by a National Health and Medical Research Council (NHMRC) of Australia's Postgraduate Research Scholarship (1038124) and has been a paid speaker for Astra Zenica. Dr. Wellman is a consultant for Galleon and has received grant/research support from Philips/Respironics. Mr. Turton has consulted for Compumedics. Dr. Hamilton has received equipment for investigator lead research from ResMed. Dr. Edwards is supported by the NHMRC of Australia's CJ Martin Overseas Biomedical Fellowship (1035115). This was not an industry supported study. The other authors have indicated no financial conflicts of interest. Author Contribution: Concept and design: Drs. Joosten, Hamilton, Berger, Edwards, and Wellman. Data collection: Dr. Joosten, Mr. Turton, and Ms. Skuza. Data analysis: Dr. Joosten, Dr. Berger, and Mr. Turton. Manuscript preparation: Drs. Joosten, Hamilton, Berger, and Edwards.

REFERENCES

1. Peppard PE, Young T, Palta M, Skatrud J. Prospective study of the association between sleep-disordered breathing and hypertension. N Engl J Med 2000;342:1378–84.
2. Shamsuzzaman AS, Gersh BJ, Somers VK. Obstructive sleep apnea: implications for cardiac and vascular disease. JAMA 2003;290:1906–14.
3. Cheshire K, Engleman H, Deary I, Shapiro C, Douglas NJ. Factors impairing daytime performance in patients with sleep apnea/hypopnea syndrome. Arch Intern Med 1992;152:538–41.
4. Gottlieb DJ, Whitney CW, Bonekat WH, et al. Relation of sleepiness to respiratory disturbance index: the Sleep Heart Health Study. Am J Respir Crit Care Med 1999;159:502–7.
5. Coughlin SR, Mawdsley L, Mugarza JA, Calverley PM, Wilding JP. Obstructive sleep apnoea is independently associated with an increased prevalence of metabolic syndrome. Eur Heart J 2004;25:735–41.
6. Tregear S, Reston J, Schoelles K, Phillips B. Obstructive sleep apnea and risk of motor vehicle crash: systematic review and meta-analysis. J Clin Sleep Med 2009;5:573–81.
7. Oksenberg A, Silverberg DS, Arons E, Radwan H. Positional vs nonpositional obstructive sleep apnea patients: anthropomorphic, nocturnal polysomnographic, and multiple sleep latency test data. Chest 1997;112:629–39.
8. Joosten SA, Hamza K, Sands S, Turton A, Berger P, Hamilton G. Phenotypes of patients with mild to moderate obstructive sleep apnoea as confirmed by cluster analysis. Respirology 2012;17:99–107.
9. Mador MJ, Kufel TJ, Magalang UJ, Rajesh SK, Watwe V, Grant BJ. Prevalence of positional sleep apnea in patients undergoing polysomnography. Chest 2005;128:2130–7.
10. Isono S, Remmers JE, Tanaka A, Sho Y, Sato J, Nishino T. Anatomy of pharynx in patients with obstructive sleep apnea and in normal subjects. J Appl Physiol 1997;82:1319–26.
11. Schwab RJ. Upper airway imaging. Clin Chest Med 1998;19:33–54.
12. Eckert DJ, Lo YL, Saboisky JP, Jordan AS, White DP, Malhotra A. Sensorimotor function of the upper-airway muscles and respiratory sensory processing in untreated obstructive sleep apnea. J Appl Physiol 2011;111:1644–53.

13. Jordan AS, Wellman A, Heinzer RC, et al. Mechanisms used to restore ventilation after partial upper airway collapse during sleep in humans. Thorax 2007;62:861–7.
14. Wellman A, Jordan AS, Malhotra A, et al. Ventilatory control and airway anatomy in obstructive sleep apnea. Am J Respir Crit Care Med 2004;170:1225–32.
15. Wellman A, Malhotra A, Jordan AS, Stevenson KE, Gautam S, White DP. Effect of oxygen in obstructive sleep apnea: role of loop gain. Respir Physiol Neurobiol 2008;162:144–51.
16. Jordan AS, Eckert DJ, Wellman A, Trinder JA, Malhotra A, White DP. Termination of respiratory events with and without cortical arousal in obstructive sleep apnea. Am J Respir Crit Care Med 2011;184:1183–91.
17. Younes M. Role of arousals in the pathogenesis of obstructive sleep apnea. Am J Respir Crit Care Med 2004;169:623–33.
18. Stanchina ML, Malhotra A, Fogel RB, et al. The influence of lung volume on pharyngeal mechanics, collapsibility, and genioglossus muscle activation during sleep. Sleep 2003;26:851–6.
19. Jordan AS, White DP, Lo YL, et al. Airway dilator muscle activity and lung volume during stable breathing in obstructive sleep apnea. Sleep 2009;32:361–8.
20. Boudewyns A, Punjabi N, Van de Heyning PH, et al. Abbreviated method for assessing upper airway function in obstructive sleep apnea. Chest 2000;118:1031–41.
21. Ong JS, Touyz G, Tanner S, Hillman DR, Eastwood PR, Walsh JH. Variability of human upper airway collapsibility during sleep and the influence of body posture and sleep stage. J Sleep Res 2011;20:533–7.
22. Penzel T, Moller M, Becker HF, Knaack L, Peter JH. Effect of sleep position and sleep stage on the collapsibility of the upper airways in patients with sleep apnea. Sleep 2001;24:90–5.
23. Joosten SA, O'Donoghue FJ, Rochford PD, et al. Night-to-night repeatability of supine-related obstructive sleep apnea. Ann Am Thorac Soc 2014;11:761–9.
24. Joosten SA, Edwards BA, Wellman A, et al. Obstructive sleep apnea phenotypic trait changes from supine to lateral position [abstract]. Am J Respir Crit Care Med 2014;189:A3909.
25. Wanger J, Clausen JL, Coates A, et al. Standardisation of the measurement of lung volumes. Eur Respir J 2005;26:511–22.
26. Iber C, Ancoli-Israel S, Chesson A, and Quan SF for the American Academy of Sleep Medicine. The AASM manual for the scoring of sleep and associated events: rules, terminology, and technical specifications. Westchester, IL: American Academy of Sleep Medicine, 2007.
27. Wellman A, Edwards BA, Sands SA, et al. A simplified method for determining phenotypic traits in patients with obstructive sleep apnea. J Appl Physiol 2013;114:911–22.
28. Gold AR, Schwartz AR. The pharyngeal critical pressure. The whys and hows of using nasal continuous positive airway pressure diagnostically. Chest 1996;110:1077–88.
29. Otsuka R, Ono T, Ishiwata Y, Kuroda T. Respiratory-related genioglossus electromyographic activity in response to head rotation and changes in body position. Angle Orthod 2000;70:63–9.
30. Malhotra A, Trinder J, Fogel R, et al. Postural effects on pharyngeal protective reflex mechanisms. Sleep 2004;27:1105–12.
31. Tagaito Y, Isono S, Remmers JE, Tanaka A, Nishino T. Lung volume and collapsibility of the passive pharynx in patients with sleep-disordered breathing. J Appl Physiol 2007;103:1379–85.
32. Kairaitis K, Byth K, Parikh R, Stavrinou R, Wheatley JR, Amis TC. Tracheal traction effects on upper airway patency in rabbits: the role of tissue pressure. Sleep 2007;30:179–86.
33. Van de Graaff WB. Thoracic influence on upper airway patency. J Appl Physiol 1988;65:2124–31.
34. Rowley JA, Permutt S, Willey S, Smith PL, Schwartz AR. Effect of tracheal and tongue displacement on upper airway airflow dynamics. J Appl Physiol 1996;80:2171–8.
35. Walsh JH, Leigh MS, Paduch A, et al. Effect of body posture on pharyngeal shape and size in adults with and without obstructive sleep apnea. Sleep 2008;31:1543–9.
36. Schwab RJ, Pack AI, Gupta KB, et al. Upper airway and soft tissue structural changes induced by CPAP in normal subjects. Am J Respir Crit Care Med 1996;154:1106–16.
37. Kuna ST, Bedi DG, Ryckman C. Effect of nasal airway positive pressure on upper airway size and configuration. Am Rev Respir Dis 1988;138:969–75.
38. Amatoury J, Kairaitis K, Wheatley JR, Bilston LE, Amis TC. Onset of airflow limitation in a collapsible tube model: impact of surrounding pressure, longitudinal strain, and wall folding geometry. J Appl Physiol 2010;109:1467–75.
39. Lucey AD, King AJ, Tetlow GA, et al. Measurement, reconstruction, and flow-field computation of the human pharynx with application to sleep apnea. IEEE Trans Biomed Eng 2010;57:2535–48.
40. Isono S, Tanaka A, Nishino T. Lateral position decreases collapsibility of the passive pharynx in patients with obstructive sleep apnea. Anesthesiology 2002;97:780–5.
41. Joosten SA, O'Driscoll DM, Berger PJ, Hamilton GS. Supine position related obstructive sleep apnea in adults: pathogenesis and treatment. Sleep Med Rev 2014;18:7–17.
42. Bignold JJ, Mercer JD, Antic NA, McEvoy RD, Catcheside PG. Accurate position monitoring and improved supine-dependent obstructive sleep apnea with a new position recording and supine avoidance device. J Clin Sleep Med 2011;7:376–83.
43. Eckert DJ, White DP, Jordan AS, Malhotra A, Wellman A. Defining phenotypic causes of obstructive sleep apnea. Identification of novel therapeutic targets. Am J Respir Crit Care Med 2013;188:996–1004.
44. Eckert DJ, Owens RL, Kehlmann GB, et al. Eszopiclone increases the respiratory arousal threshold and lowers the apnoea/hypopnoea index in obstructive sleep apnoea patients with a low arousal threshold. Clin Sci (Lond) 2011;120:505–14.
45. Edwards BA, Connolly JG, Campana LM, et al. Acetazolamide attenuates the ventilatory response to arousal in patients with obstructive sleep apnea. Sleep 2013;36:281–5.
46. Edwards BA, Eckert DJ, McSharry DG, et al. Clinical predictors of the respiratory arousal threshold in patients with obstructive sleep apnea. Am J Respir Crit Care Med 2014;190:1293–300.
47. Heinzer RC, White DP, Jordan AS, et al. Trazodone increases arousal threshold in obstructive sleep apnoea. Eur Respir J 2008;31:1308–12.
48. Oksenberg A, Arons E, Nasser K, Vander T, Radwan H. REM-related obstructive sleep apnea: the effect of body position. J Clin Sleep Med 2010;6:343–8.

SUPPLEMENT 1:

Description of method for lung volume nitrogen gas washout method:

The patient's head and neck position were controlled in the supine and lateral position using a series of pillows. Briefly, patients breathed through a mouthpiece that facilitated the measurement of ventilation and carbon dioxide (CO_2) (NICO Cardiopulmonary Management System) and oxygen (O_2) (Ametek S-3A/I, Ametek Process Instruments, Pittsburgh, PA). Fractional expired nitrogen was calculated from the fractional expired O_2 and CO_2 levels (expired FN_2=1- expired FO_2- expired FCO_2). Once patients were acclimatized (~2-3 min) to the breathing circuit, we switched the inspired gas from room air (79% nitrogen, N_2) to 100% O_2 (0% N_2), facilitated by a low resistance non-rebreathing valve (*Medium* T *shape* 2-Way *NRBV, Hans-Rudolph*, Kansas City, MO). When a steady-state expired FN_2 was achieved, participants were switched back to room air ('wash-in' phase) until a steady state was reached (constant FiN_2 within 1.5% between breaths, ~5-7 min). The time course of the rise in N_2 was used to measure FRC according to the equation $FRC = \Delta VolN_2/\Delta FN_2$; where $\Delta VolN_2$ is the change in alveolar N_2 volume from the start to end of the test (area under the curve of expired FN_2 versus cumulative expired volume), and ΔFN_2 is the change in alveolar N_2 concentration during this time (final FN_2 − initial FN_2). The 'wash-in' phase of the test, rather than the 'washout' phase, was used to avoid the transient reduction in ventilation that can occur with a rapid rise in PO_2 at the onset of the washout.

SUPPLEMENT 2:

Algorithm For Performing CPAP Dial-down:

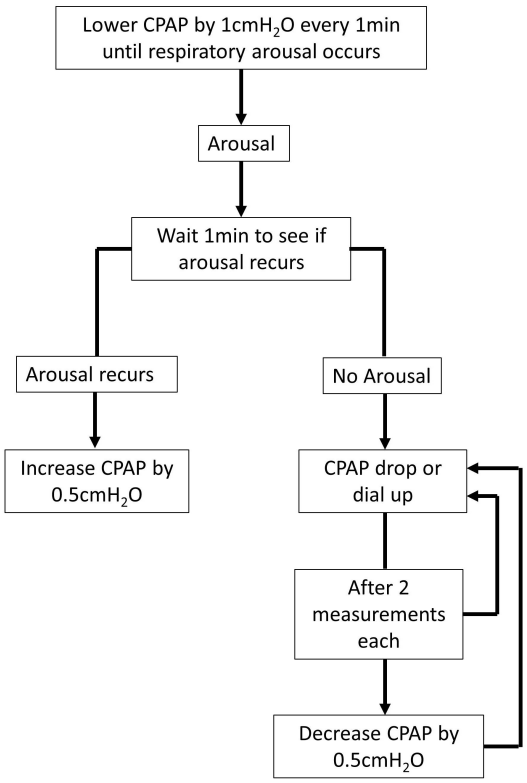

Figure 1 – Algorithm for measuring phenotypic traits.

SUPPLEMENT 3:

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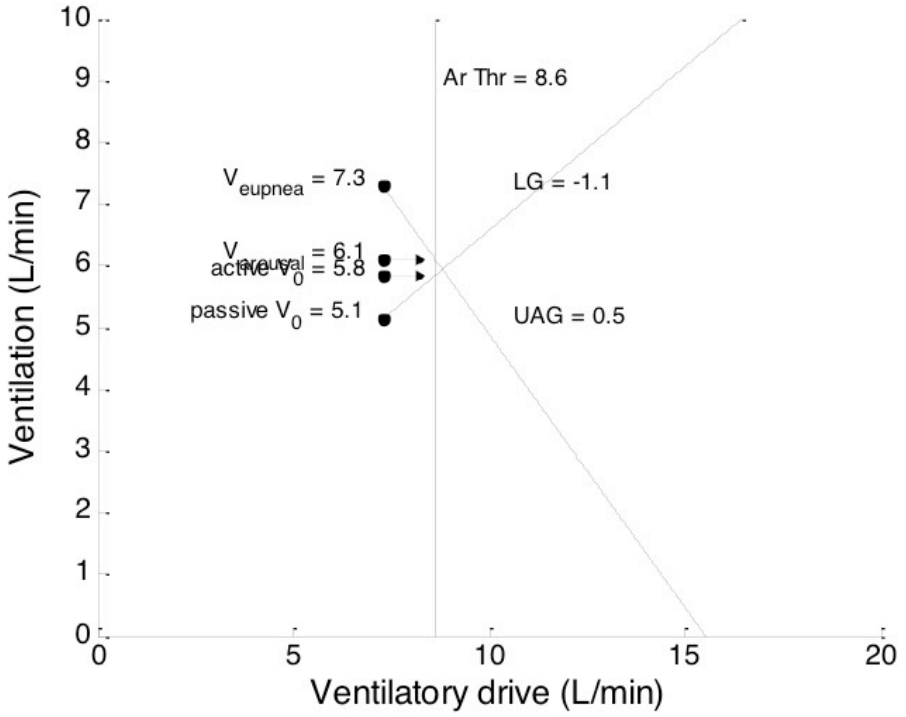

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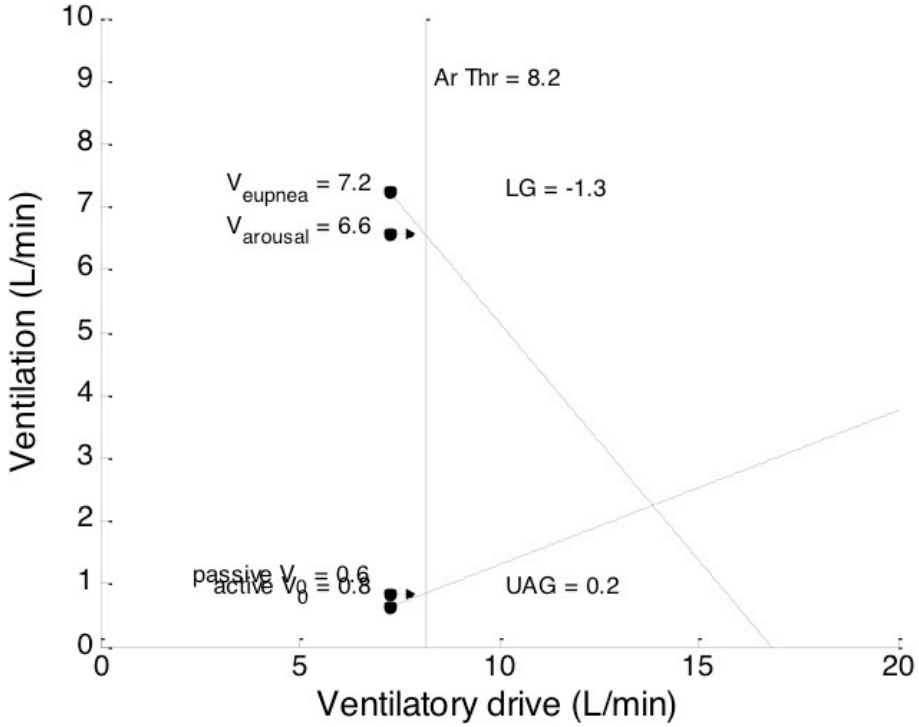

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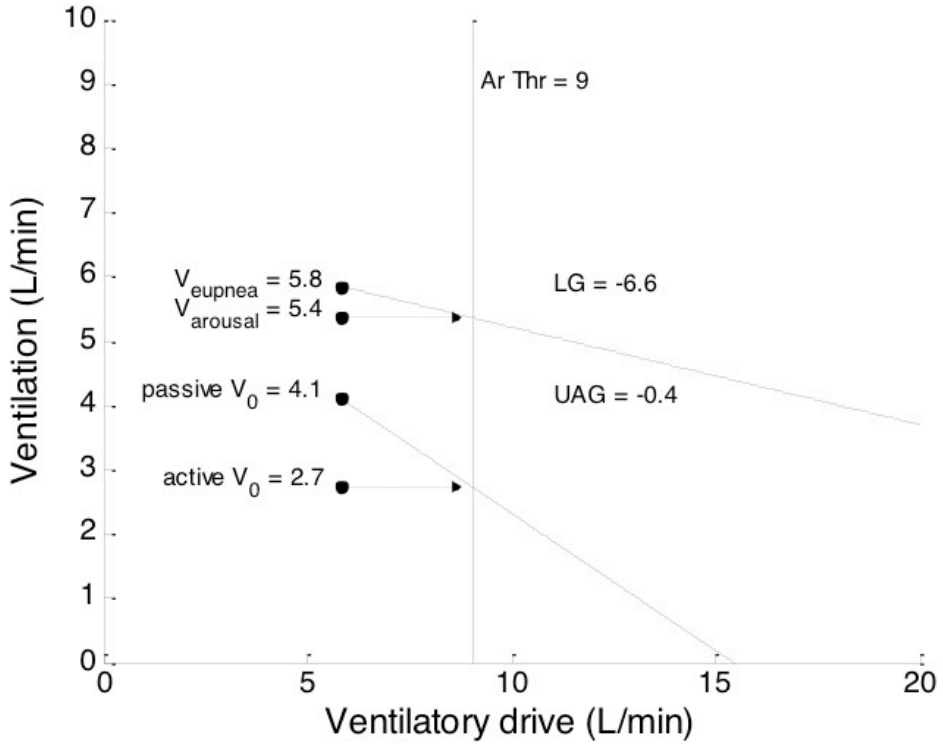

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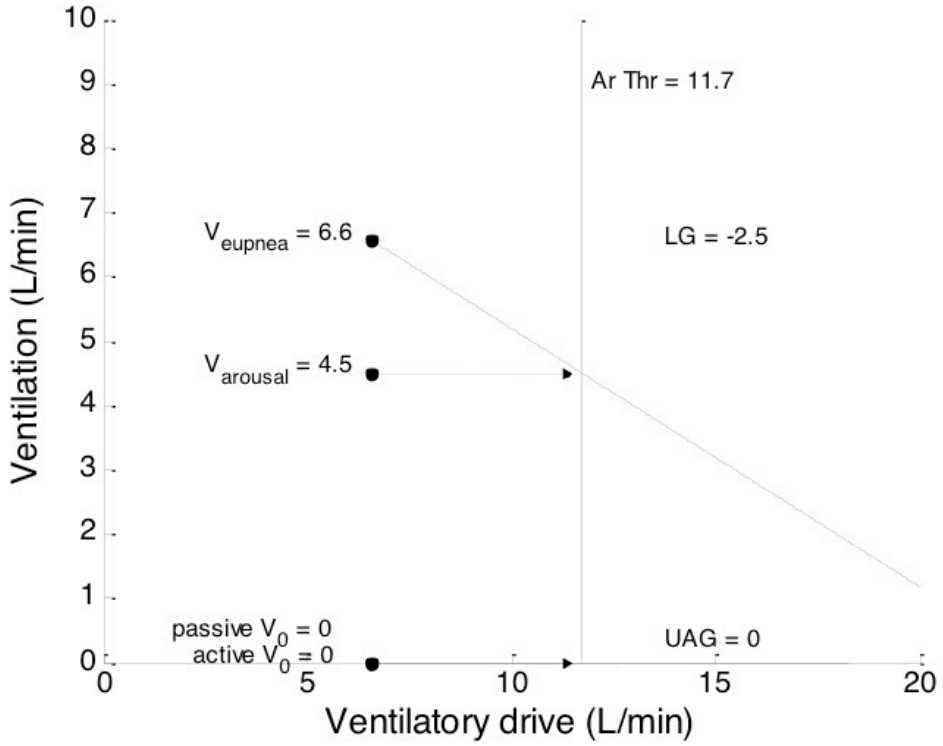

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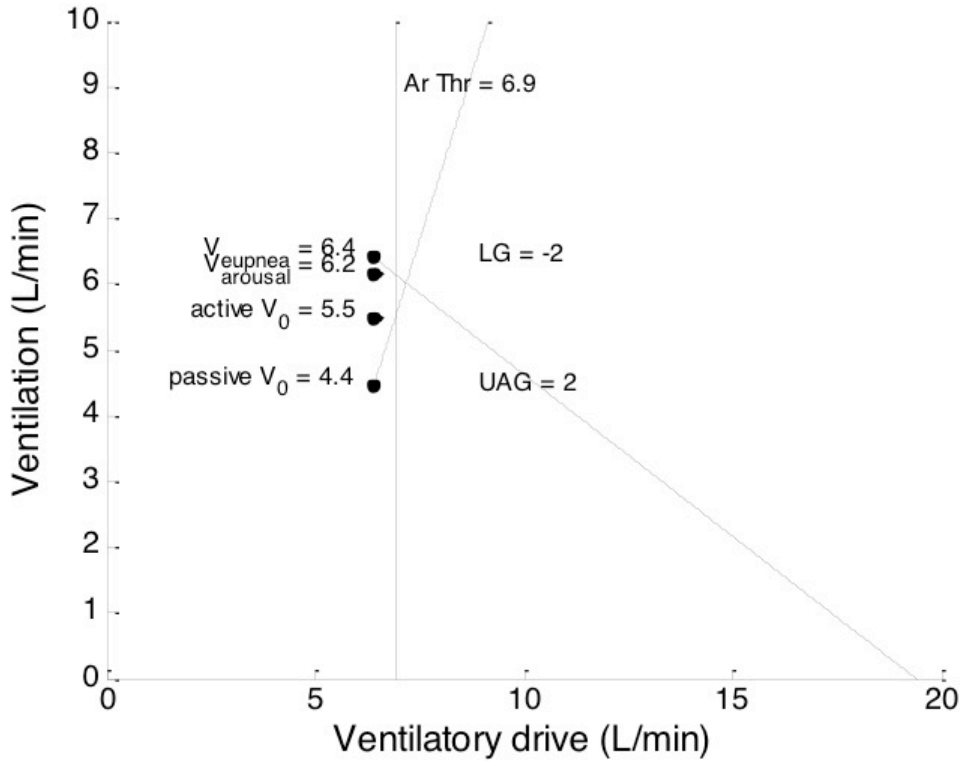

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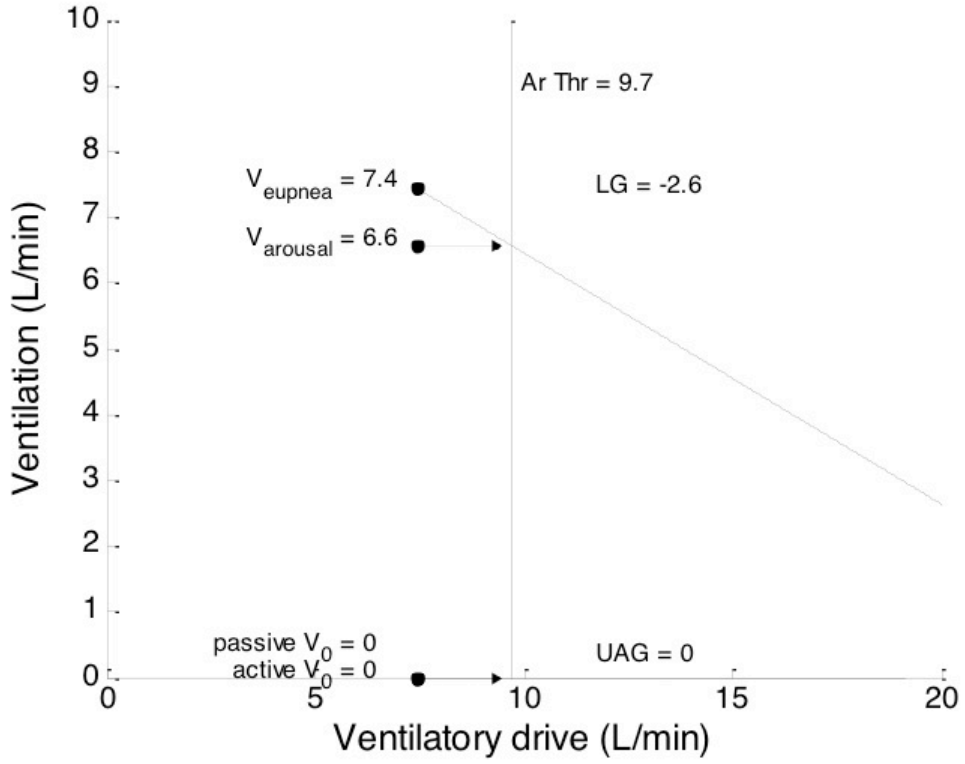

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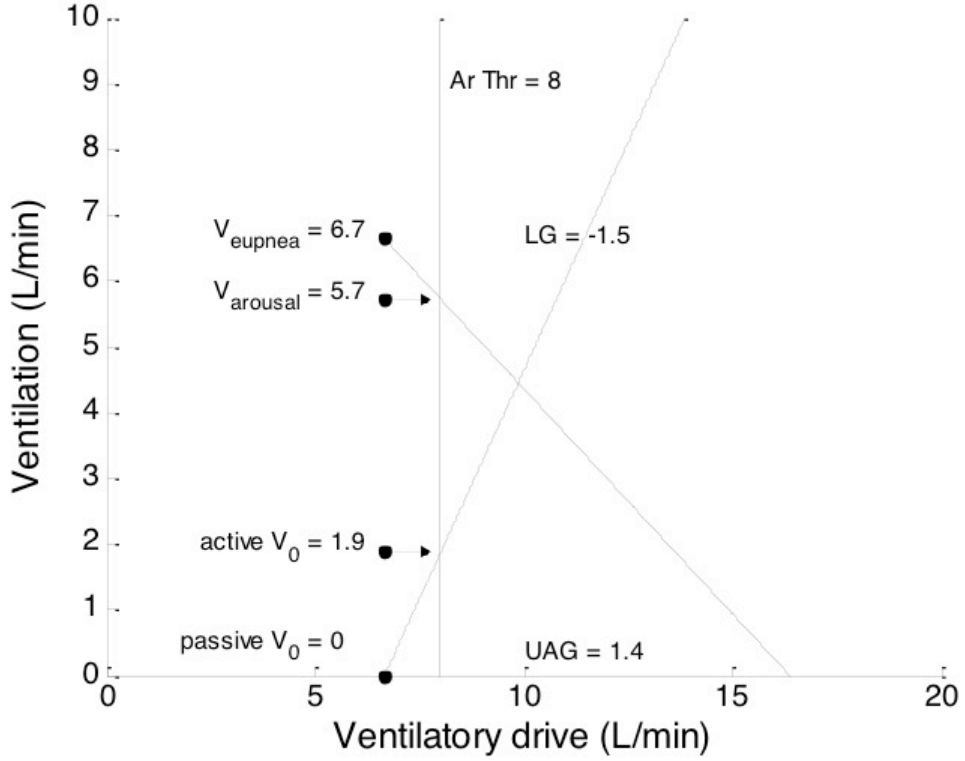

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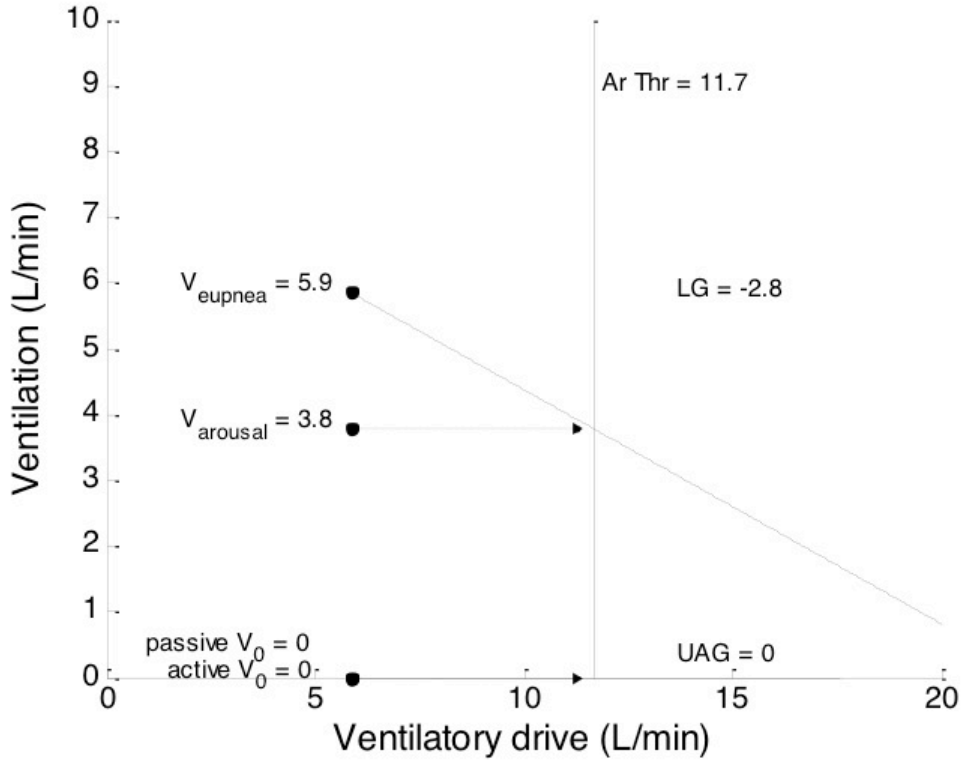

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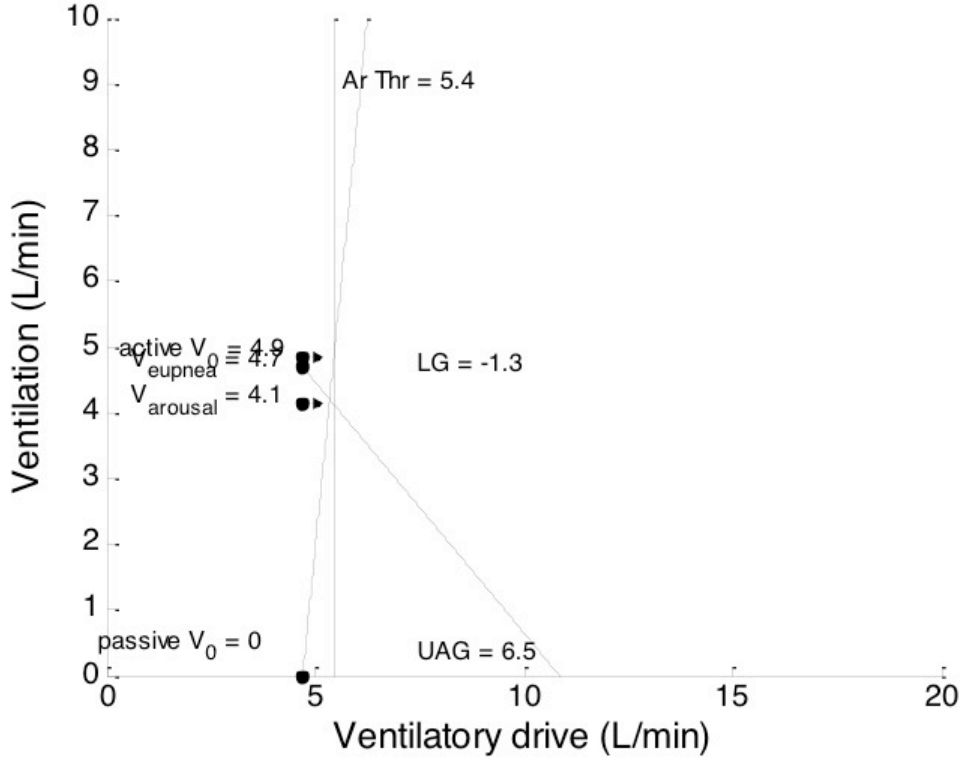

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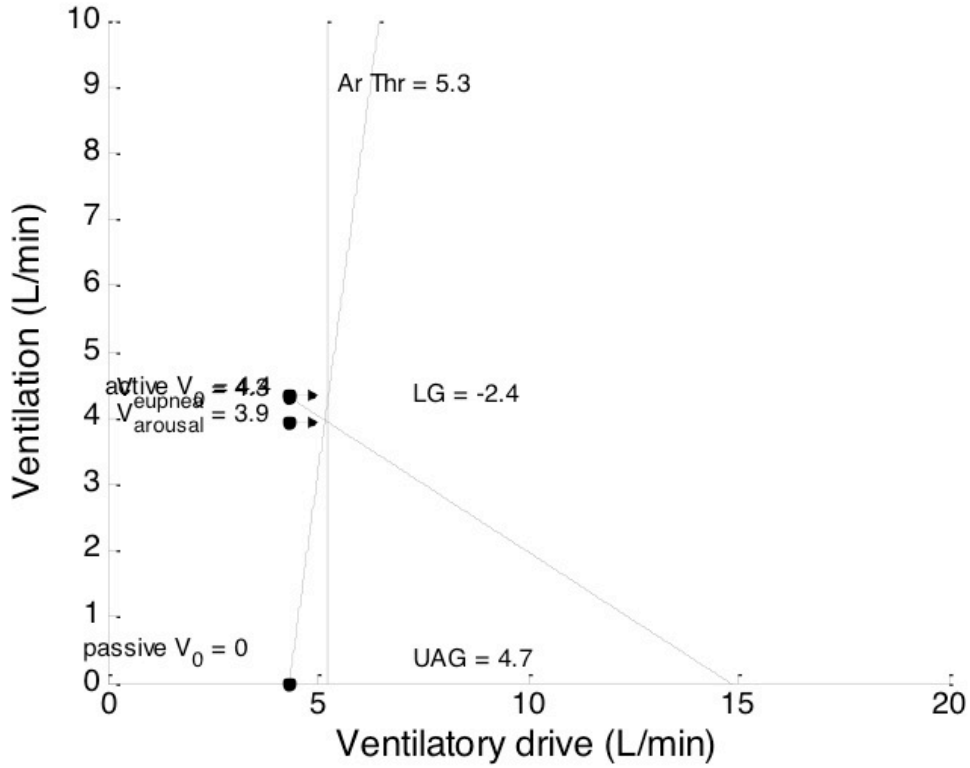

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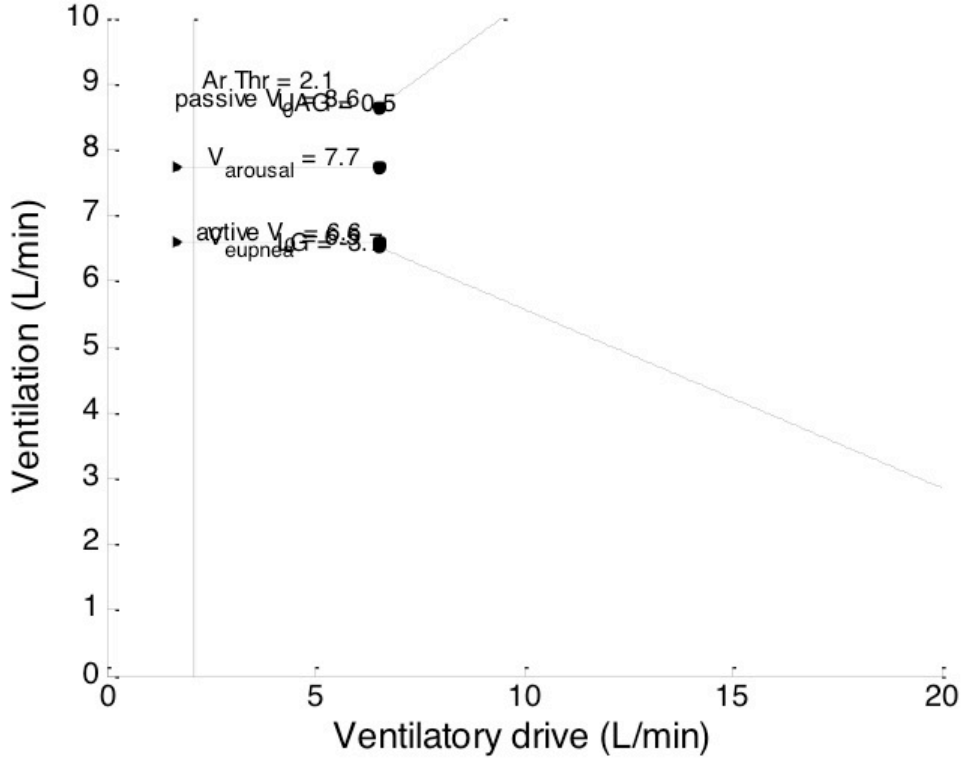

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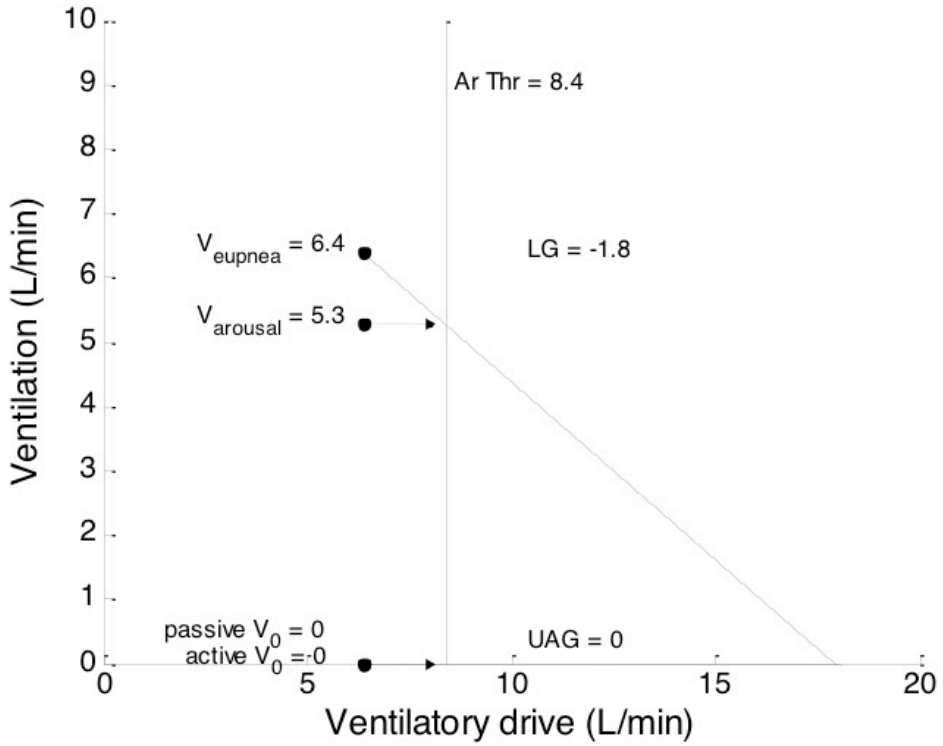

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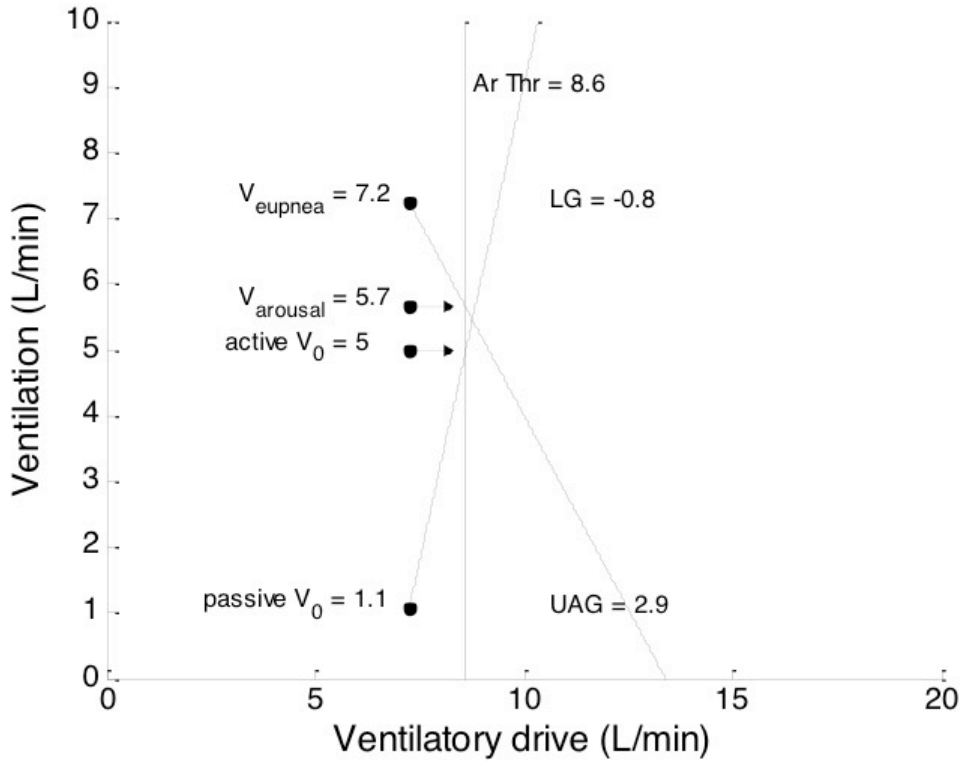

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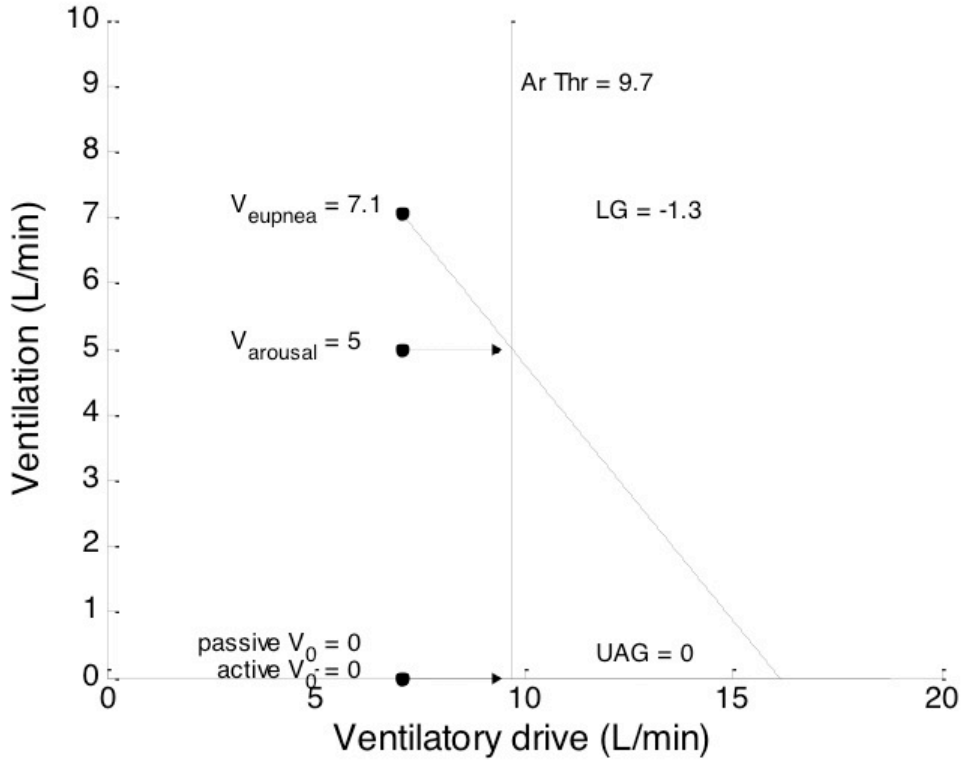

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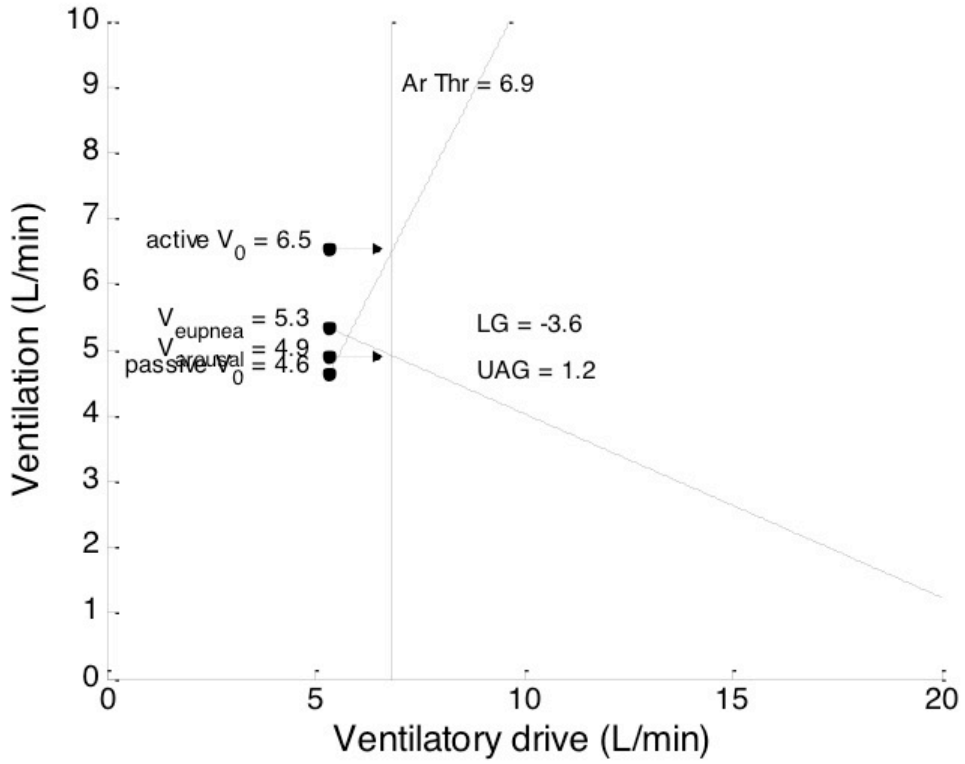

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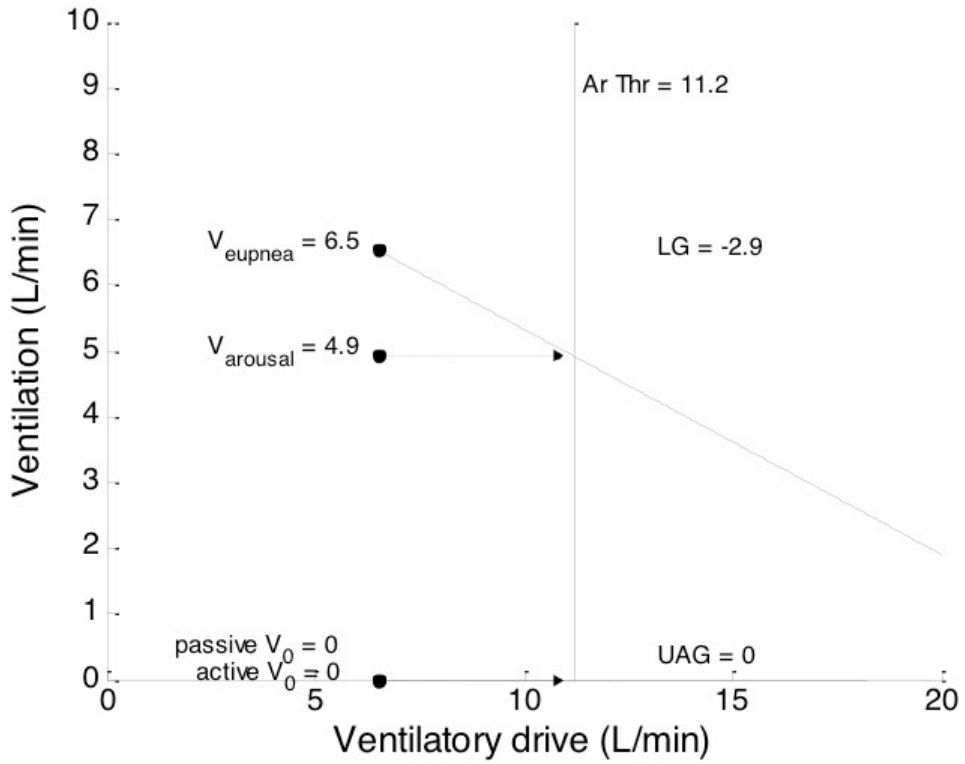

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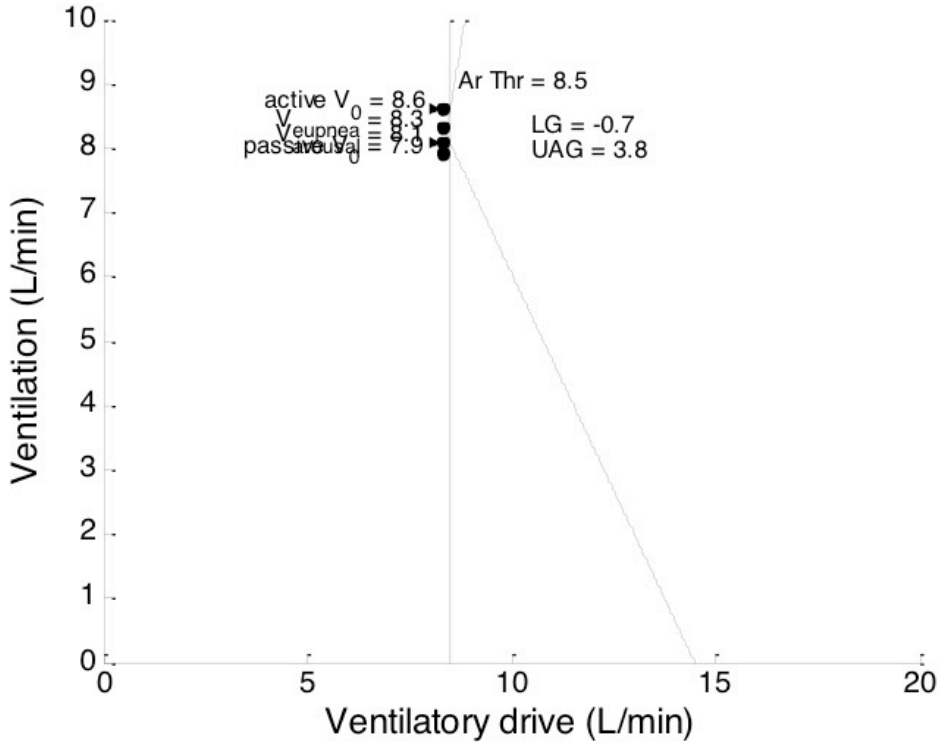

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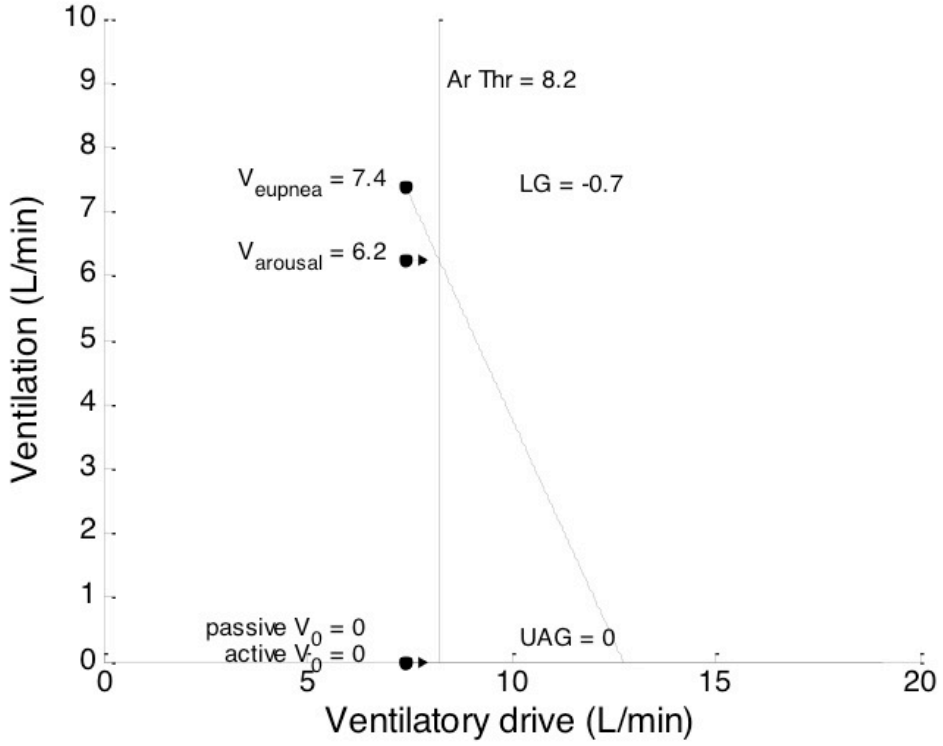

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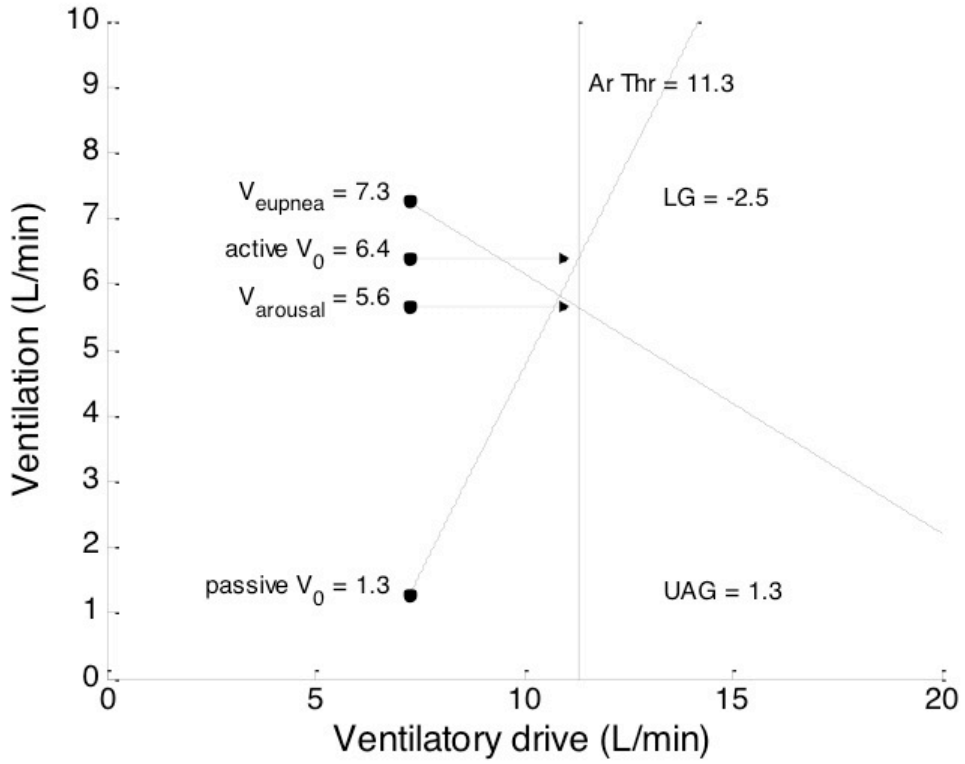

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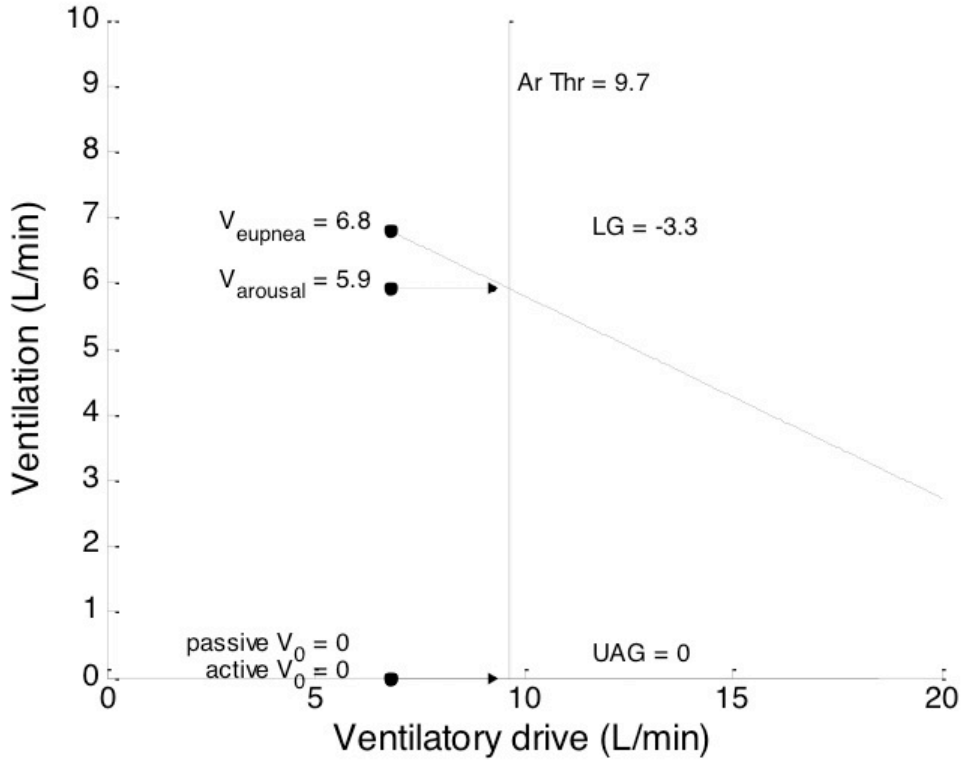

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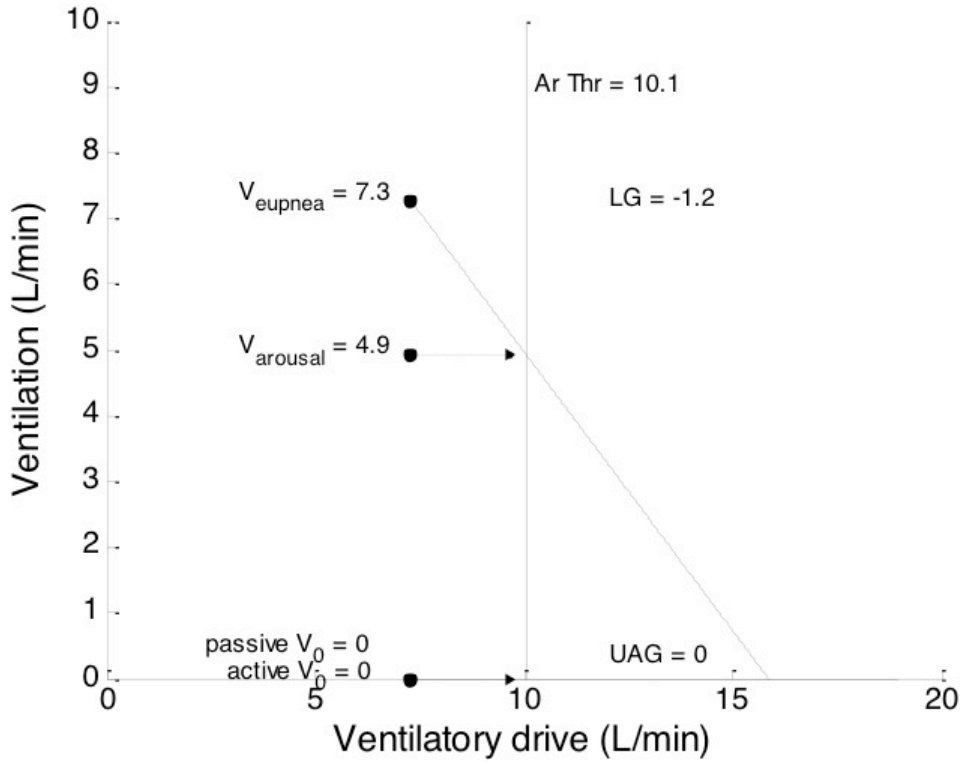

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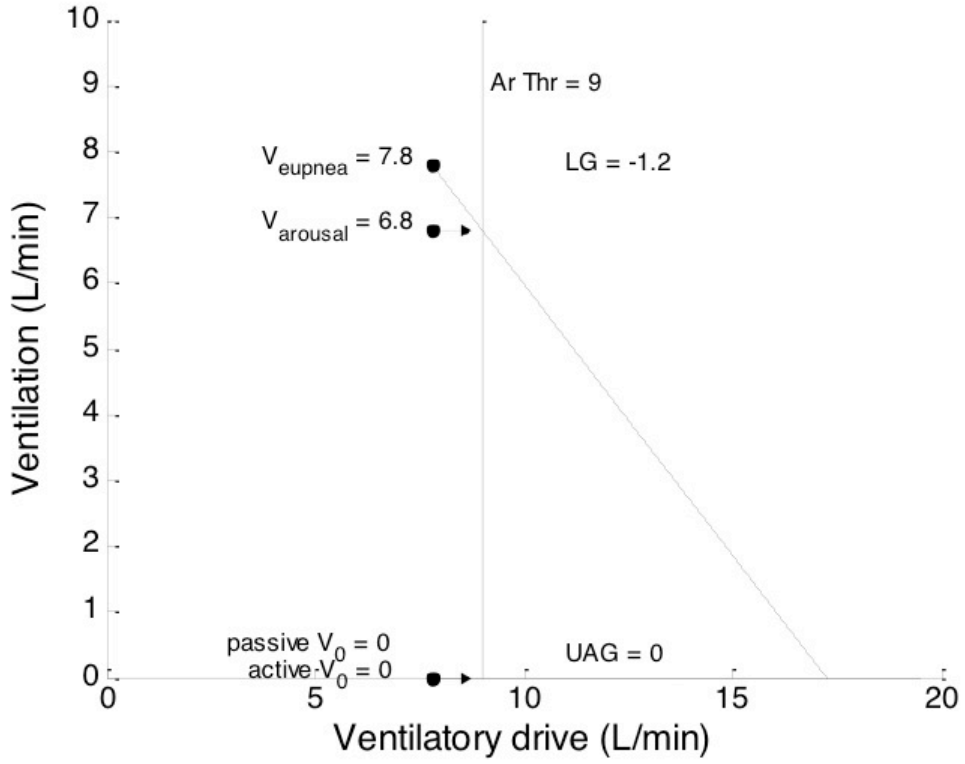

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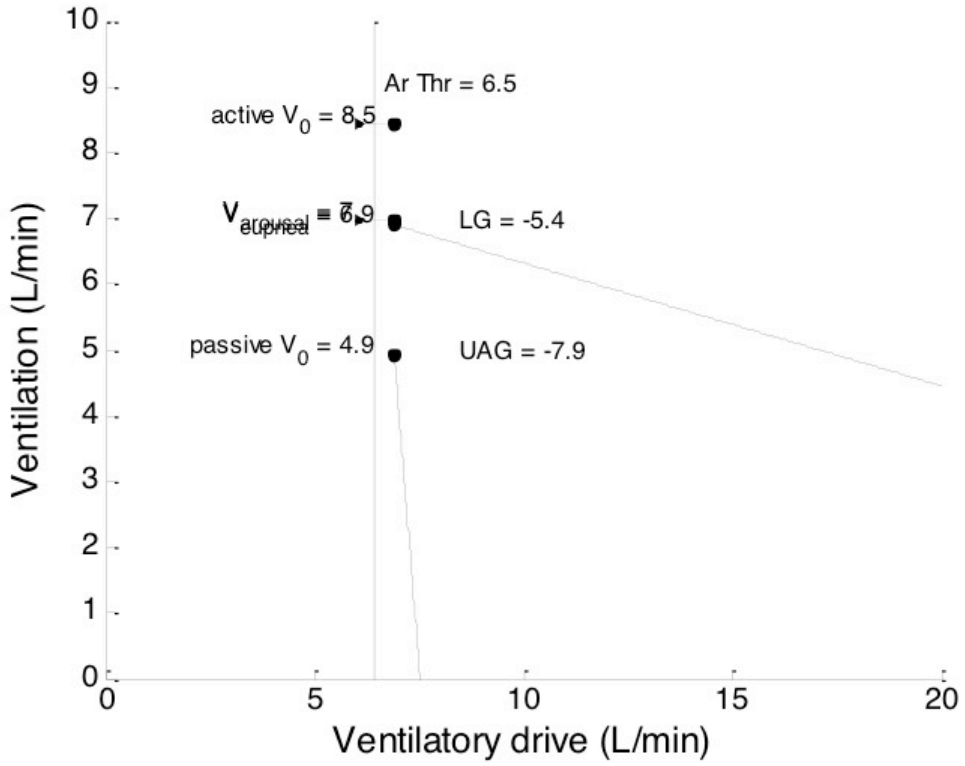

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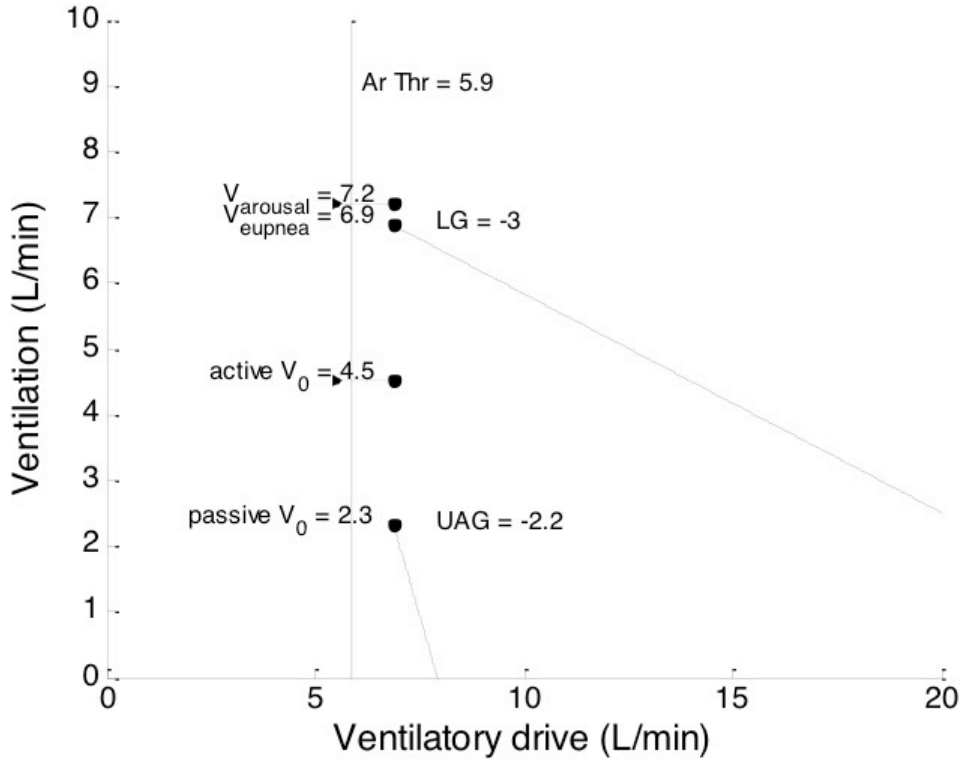

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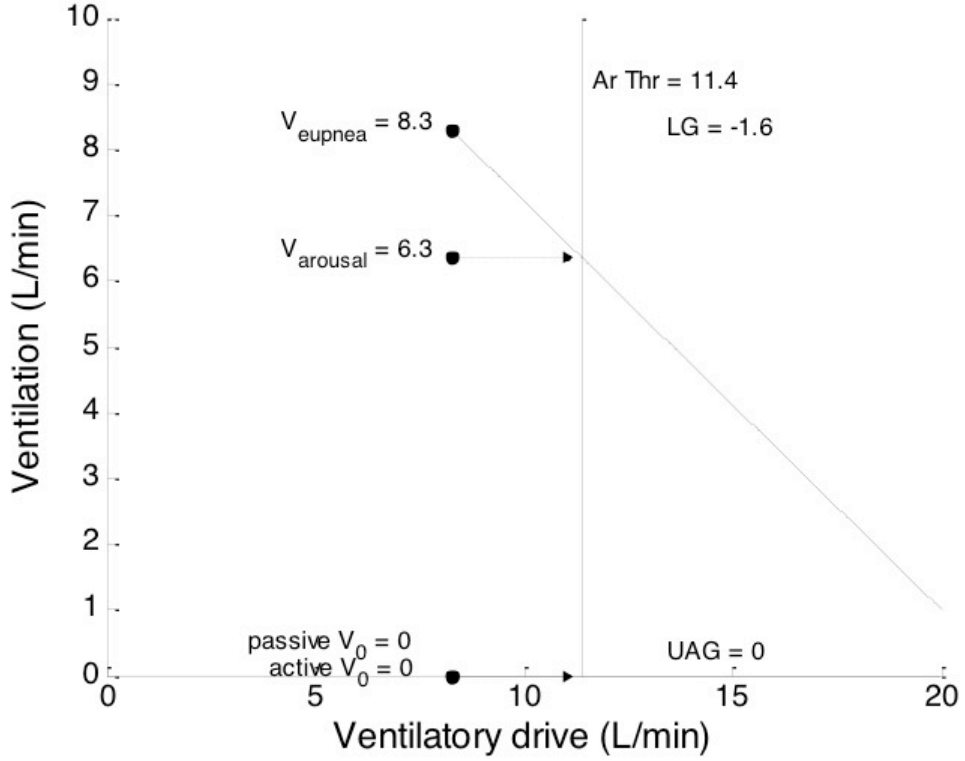

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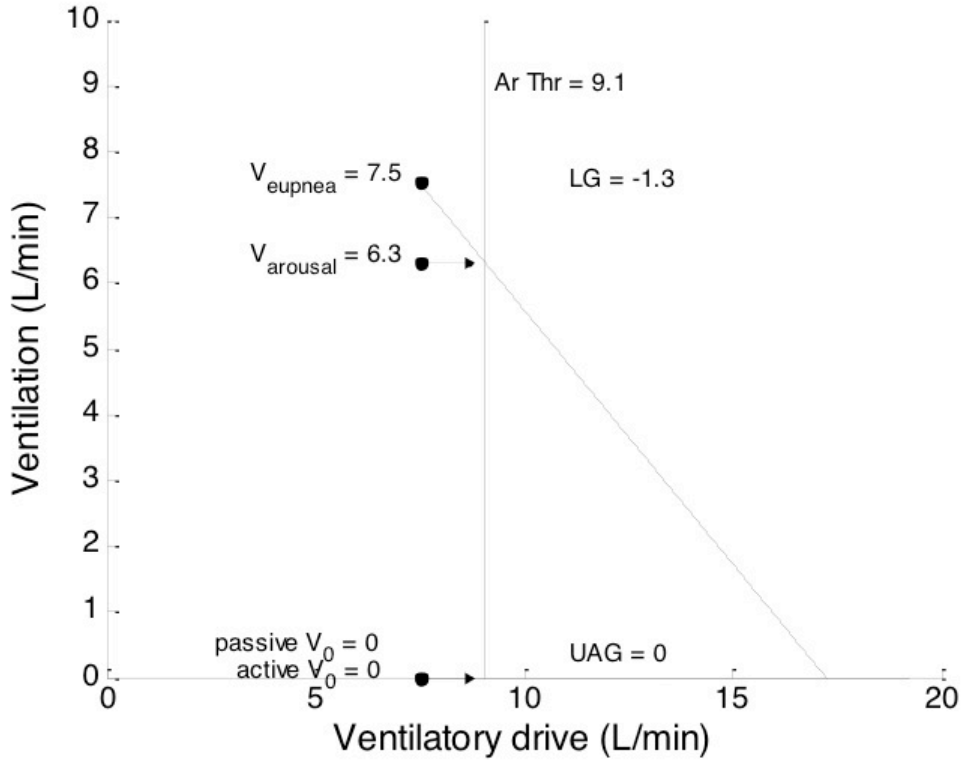

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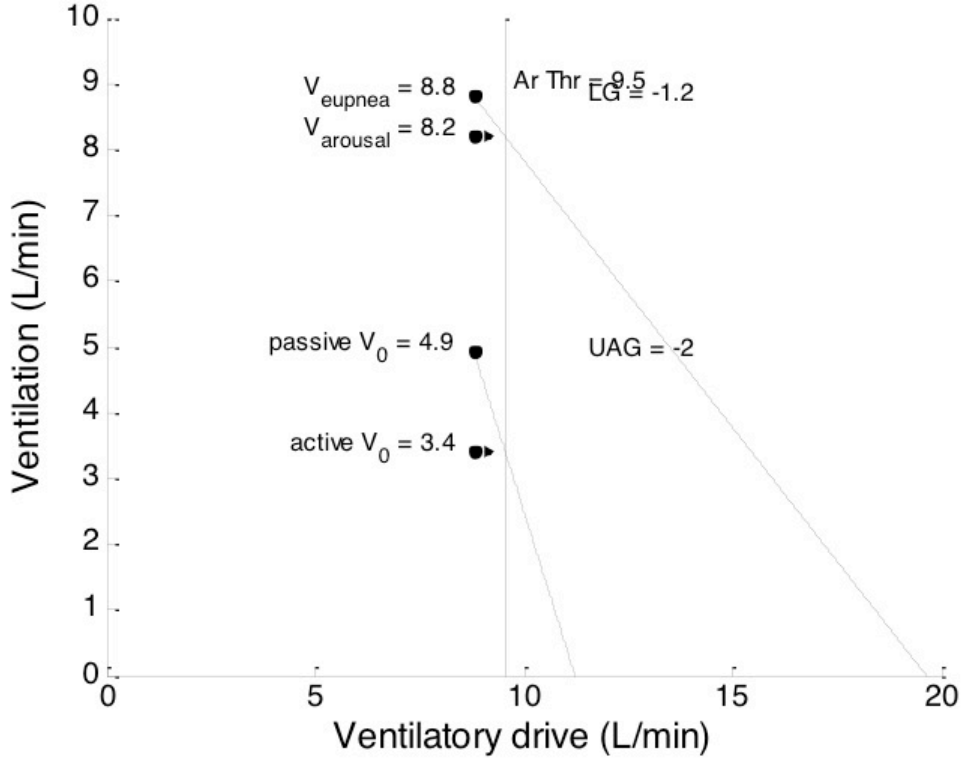

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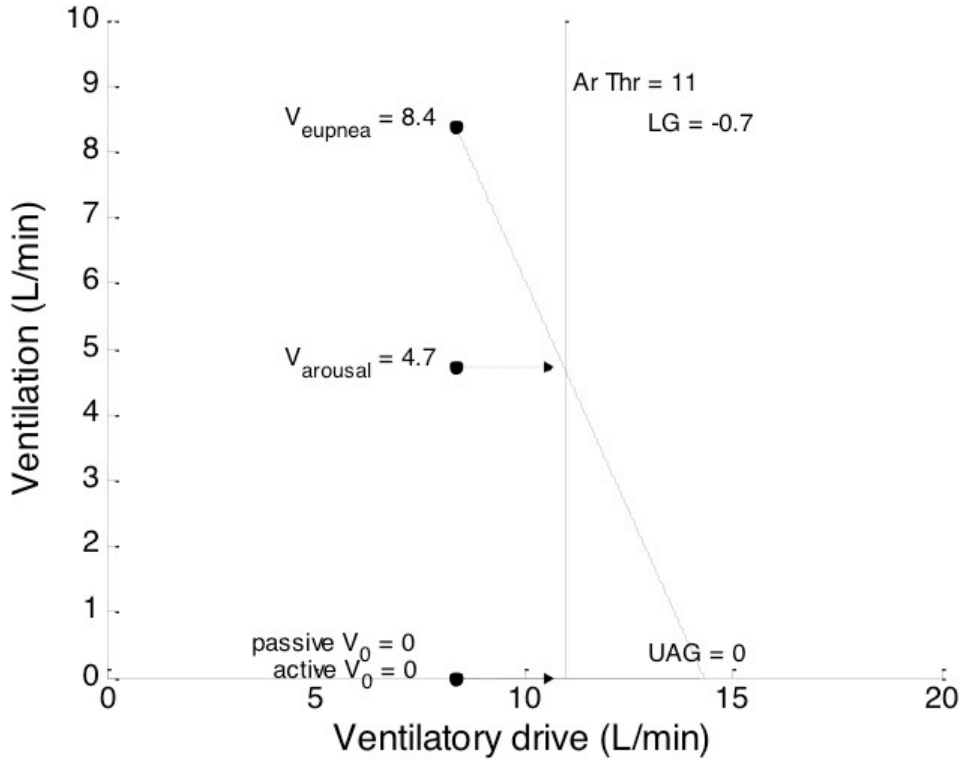

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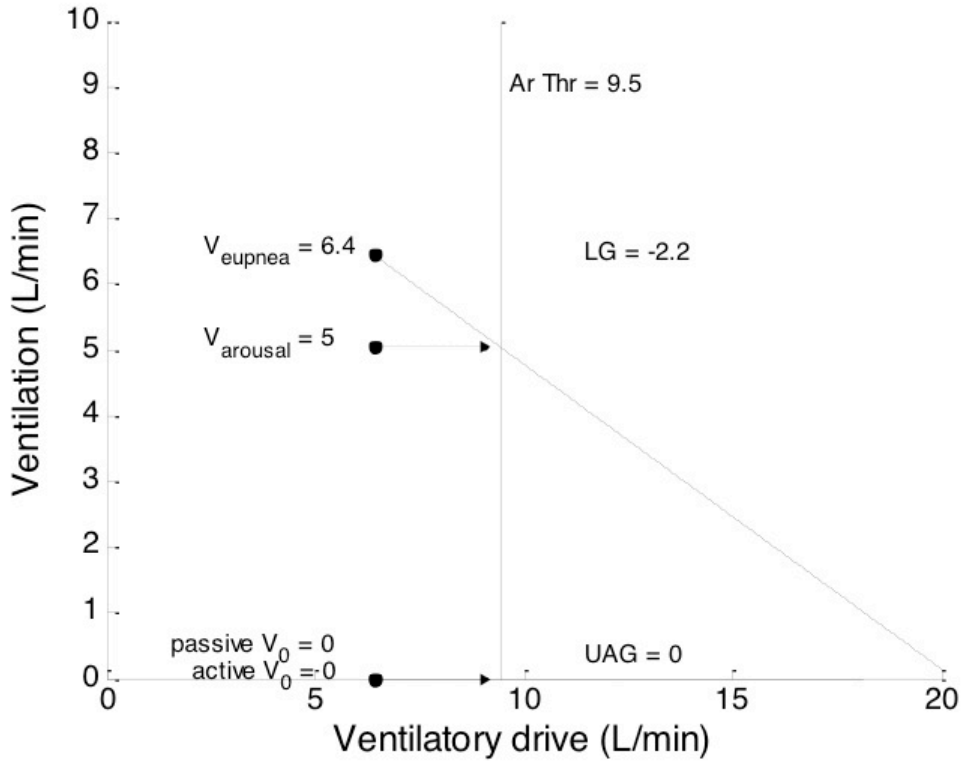

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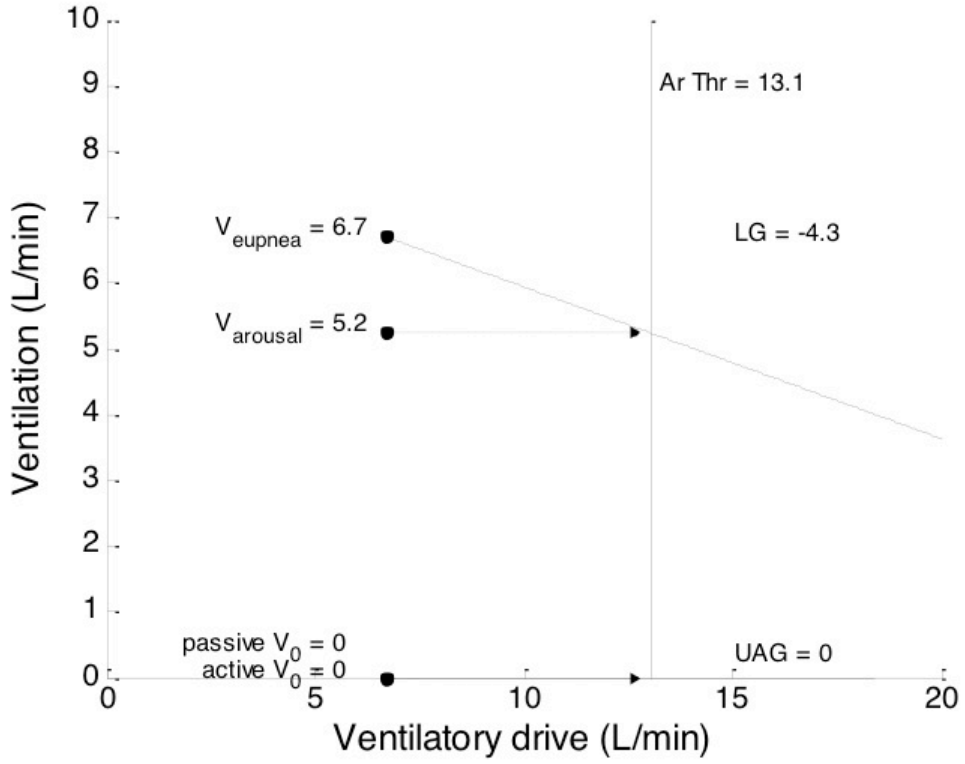

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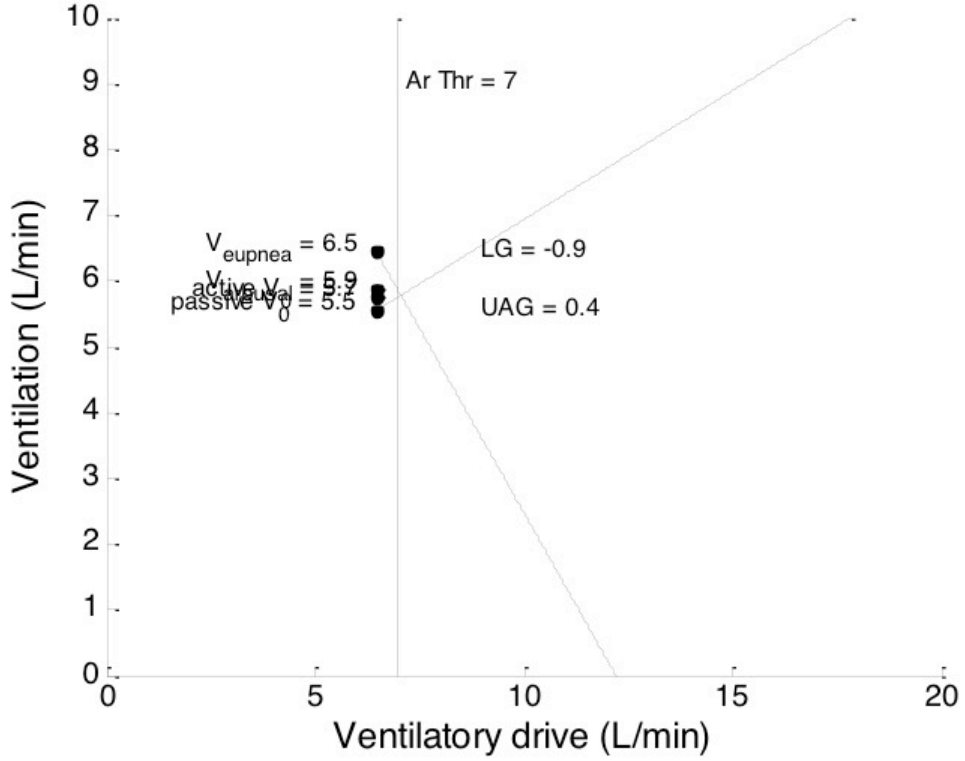

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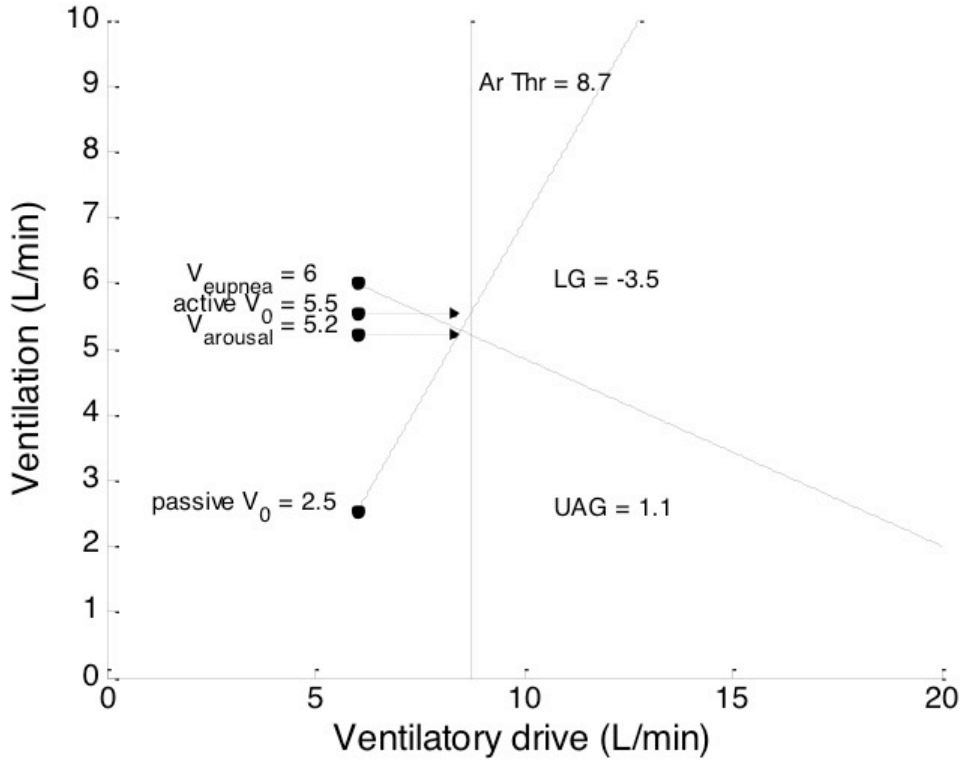

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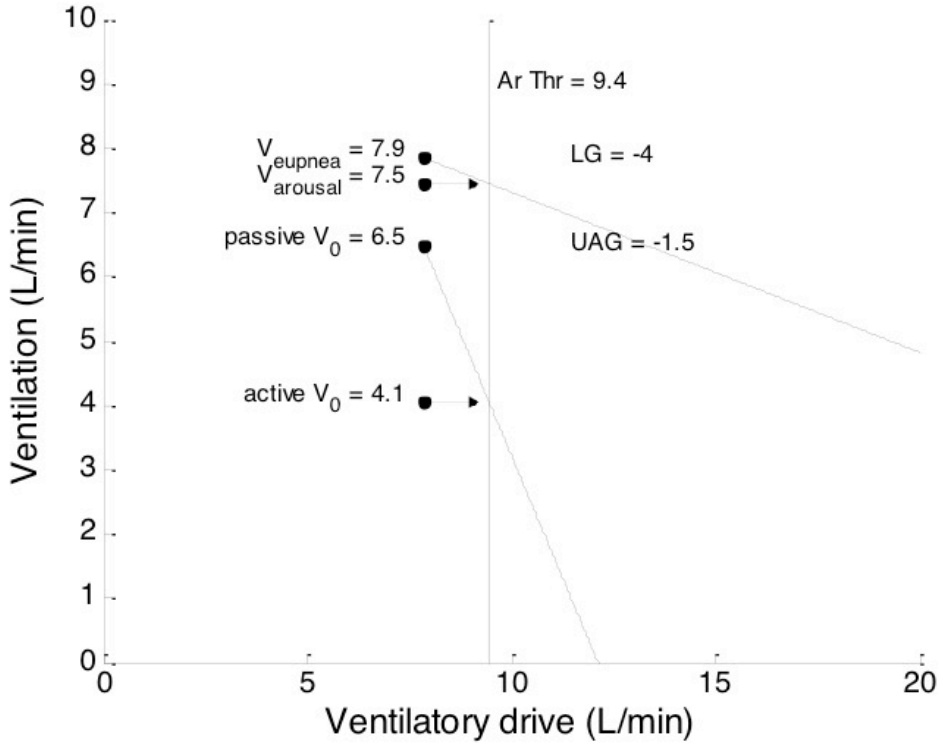

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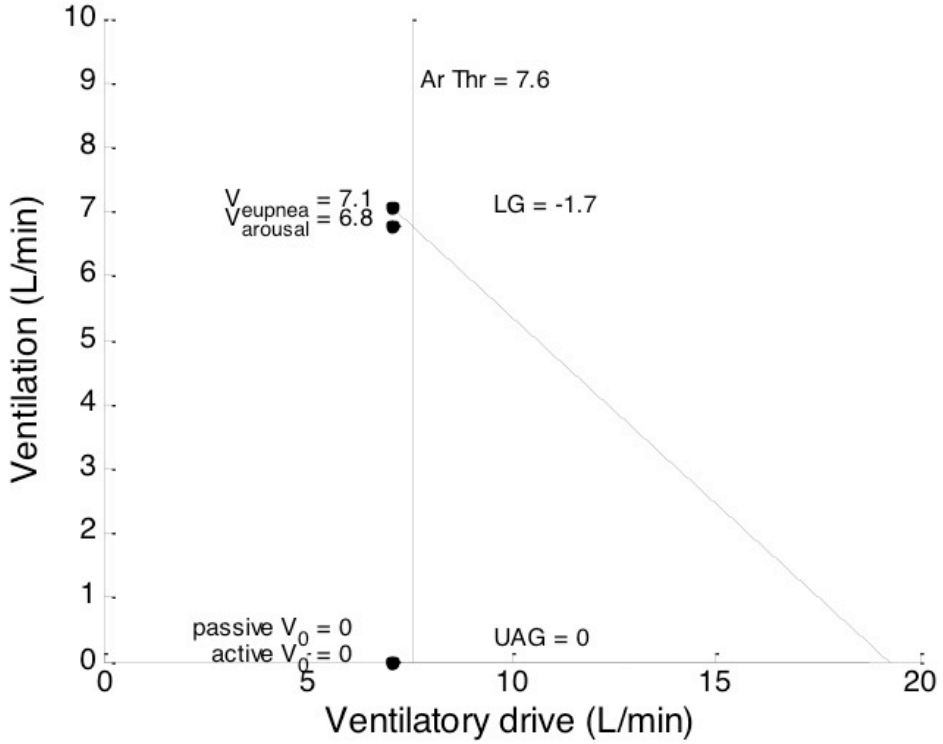

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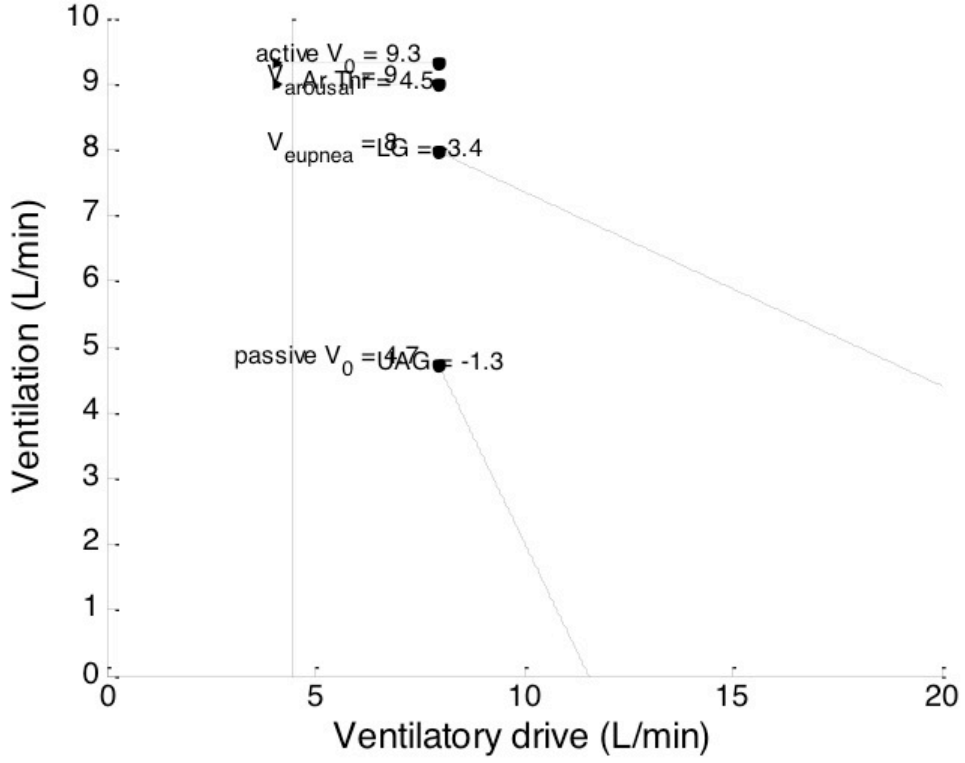

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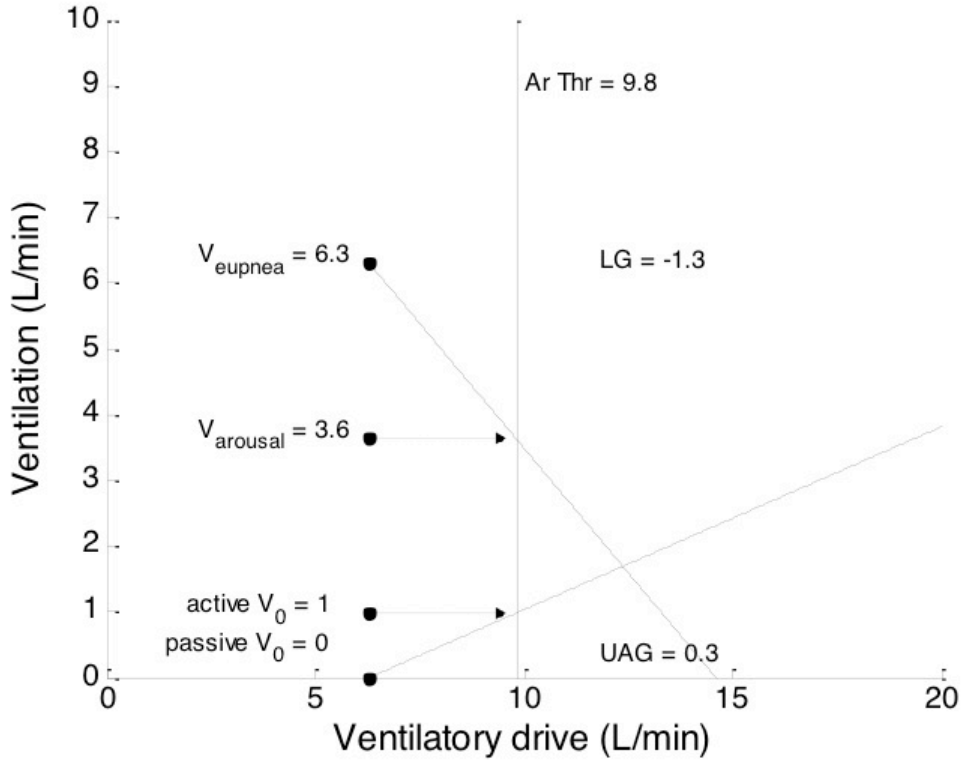

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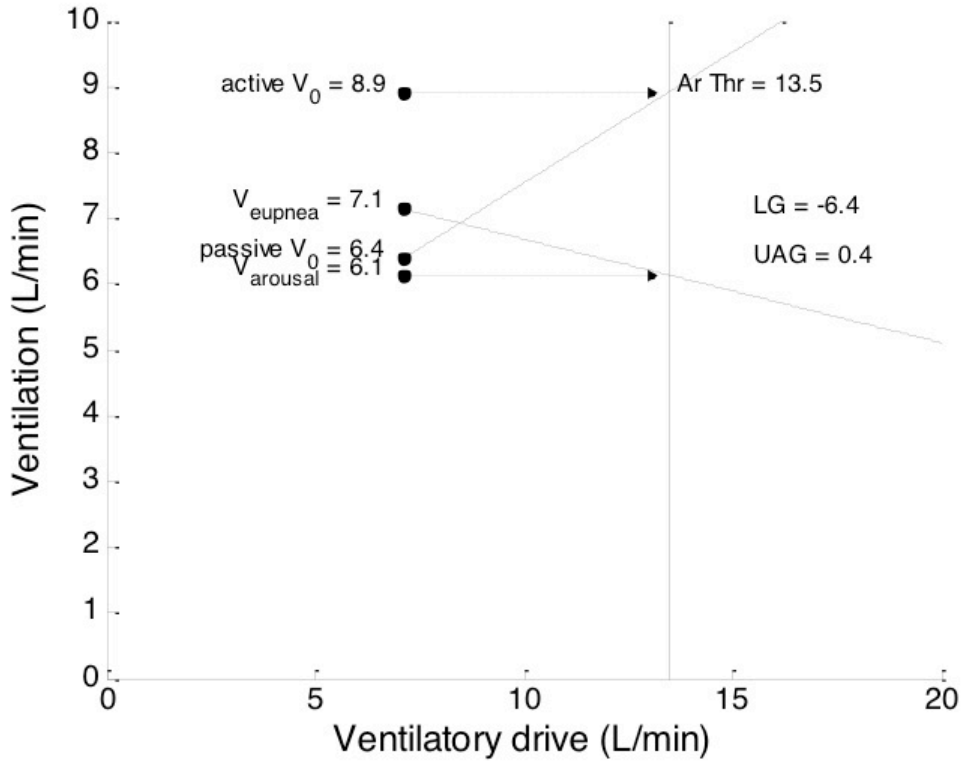

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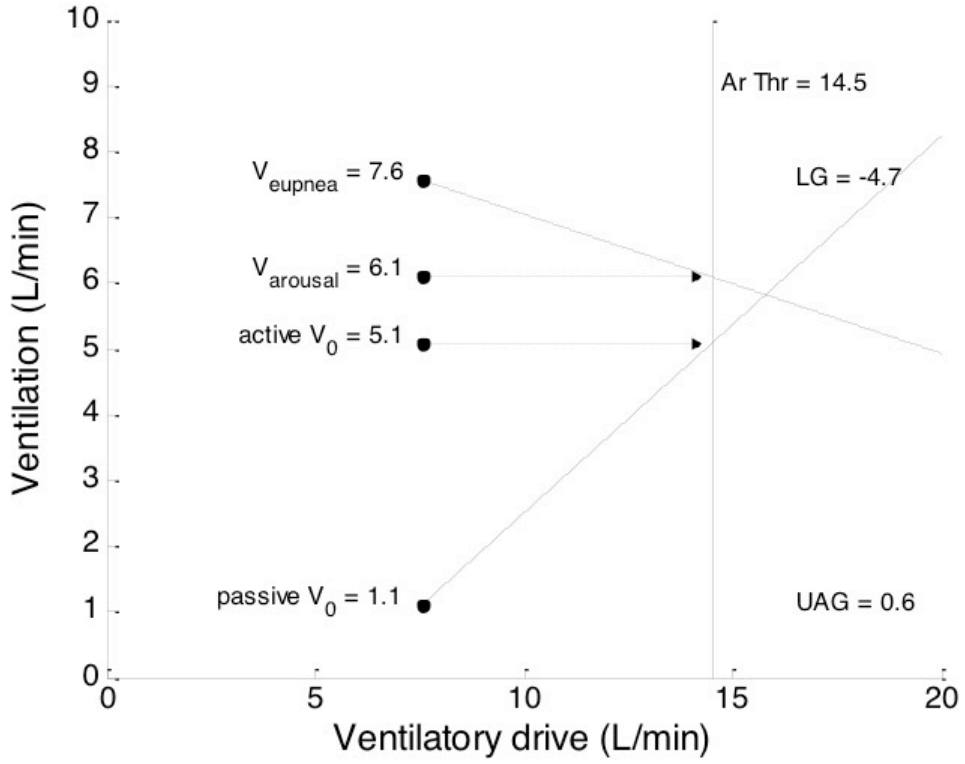

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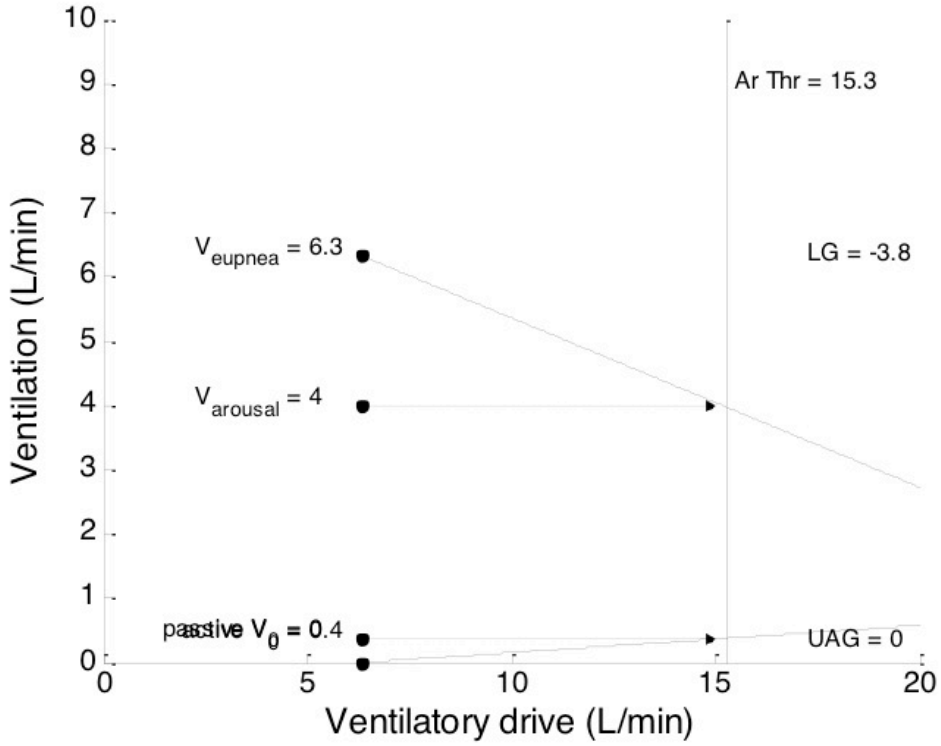

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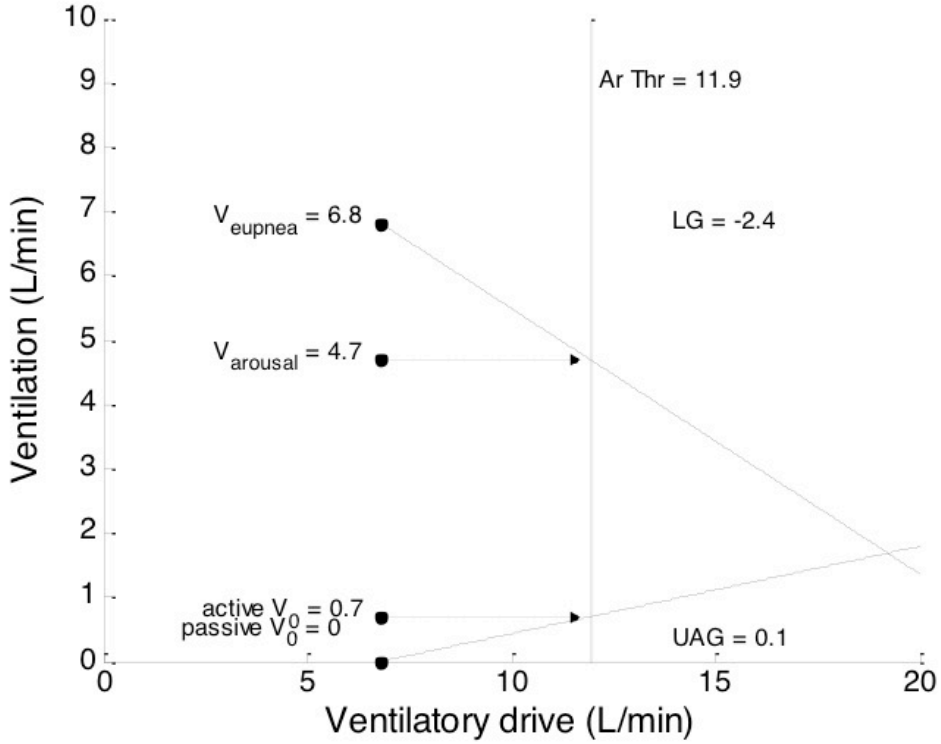

SUPPLEMENT 4:

Table 1. Comparison of supine OSA group and Position-independent OSA groups

	Supine OSA (n=7)		**Position-independent OSA (n=13)**		**P value (unpaired t-test)**	
Phenotype traits	**Supine**	**Lateral**	**Supine**	**Lateral**	**P value (supine vs supine)**	**P value (lateral vs lateral)**
V_{eupnea} (L/min)	6.39 ± 1.05	6.84 ± 1.40	7.08 ± 0.66	7.01 ± 0.83	0.09	0.743
Passive V_0 (L/min)	0.36 ± 0.94†	4.33 ± 2.83†	0.31 ± 0.68‡	3.14 ± 3.02‡	0.89	0.403
$V_{arousal}$ (L/min)	5.09 ± 1.14	6.43 ± 1.80	5.67 ± 1.04	6.02 ± 1.14	0.26	0.536
AT(L/min)	8.64 ± 1.89	7.19 ± 1.79	10.30 ± 2.30	9.36 ± 3.30	0.12	0.125
Active V_0 (L/min)	1.56 ± 2.37†	6.30 ± 0.74†	0.85 ± 1.78‡	3.85 ± 0.91‡	0.46	**0.052**
Loop Gain	-1.97 ± 1.00	-2.10 ± 1.49	-2.45 ± 1.20	-3.02 ± 1.99	0.38	0.302
UAG	0.87 ± 0.66	2.14 ± 2.53	-0.10 ± 0.18	-0.32 ± 2.48	0.20	**0.049**
Pcrit (cmH_2O)	3.00 ± 2.32†	-4.63 ± 3.33†	1.49 ± 2.60‡	-0.50 ± 3.40‡	0.22	**0.02**
FRC (L)	1.16 ± 0.51	1.27 ± 0.45	1.39 ± 0.58	1.51 ± 0.69	0.39	0.441
Percent FRC (%)	79.71 ± 14.85	89.71 ± 12.72	79.00 ± 12.93	85.62 ± 20.65	0.91	0.640

Supplemental table. Comparison of patients with supine to non-supine AHI ratio of >4:1 to all other patients. *denotes values that are non-parametric and are expressed as median

± interquartile range (IQR). BMI – body mass index, Circ. – circumference, AHI_{SUP} – supine AHI, AHI_{LAT} – non-supine AHI, Pcrit – pharyngeal critical closing pressure, FRC – functional residual capacity, Percent FRC – FRC expressed as a percentage of the seated FRC value, AHI – apnea and hypopnea index, AT – arousal threshold, UAG – upper airway gain. † Denotes a statistically significant paired t-test within the supine OSA subgroup comparing the supine mean value to the lateral mean value within that group. ‡ Denotes a statistically significant paired t-test within the position-independent OSA subgroup comparing the supine mean value to the lateral mean value within that group.

CHAPTER 5

GENERAL DISCUSSION

5

General Discussion

5.1 OVERVIEW

OSA is a common medical disorder that affects up to 24% of men and 9% of women (Young, Palta et al. 1993). The condition is associated with a number of poor health outcomes including excessive sleepiness (Gottlieb, Whitney et al. 1999), depression (Peppard, Szklo-Coxe et al. 2006), motor vehicle accident (Teran-Santos, Jimenez-Gomez et al. 1999), systemic hypertension (Nieto, Young et al. 2000, Peppard, Young et al. 2000), the metabolic syndrome (Coughlin, Mawdsley et al. 2004), insulin resistance (Ip, Lam et al. 2002) and subsequent cardiac ischemia and arrhythmias (Shahar, Whitney et al. 2001, Shamsuzzaman, Gersh et al. 2003, Mehra, Benjamin et al. 2006). The majority of OSA sufferers experience a preponderance of respiratory events in the supine sleeping position (Joosten, Hamza et al. 2012). Despite the prevalence of supine related OSA the exact mechanisms behind the improvement in airway obstruction in the lateral position are not known. Many of the factors known to contribute to OSA have not been studied in the lateral position, which hinders our understanding of why OSA improves in lateral sleep in so many patients. Furthermore, even though positional modification is a cheap and simple treatment that prevents patients from sleeping in the supine position there are no studies that guide clinicians in selecting patients likely to benefit from this intervention. This thesis adopted the simple proposition that the key to understanding positional OSA, and selecting which patients to treat with positional modification, lies in studying patients with OSA in both the supine and lateral sleeping positions.

The primary aim of this thesis was to examine the effect of body position on recently identified factors known to contribute to OSA (a reduced lung volume, unfavourable passive upper airway anatomy, an inability of the upper airway muscles to stiffen and dilate the airway, a low arousal threshold and ventilatory control instability). Additionally, we aimed to test the repeatability of the traditional definitions of supine OSA in order to determine whether there is a group of patients that will benefit from treatment with positional modification devices.

Our aim was to identify a population of supine related OSA patients on a single PSG night and to repeat measurements on a second night to assess night-to-night repeatability using standard and modified versions of the definition. Our ultimate goal was to have confidence in our selection of supine-related OSA patients on the basis of a single polysomnogram. We also applied state of the art 4-dimensional CT scanning techniques in order to image the upper airway of patients with supine OSA in both the supine and lateral position. The technology employed removed many of the methodological difficulties of upper airway imaging present in previous literature. In addition, the thesis probed the effect of body position on a number of important pathophysiological factors known to contribute to OSA by employing a non-invasive technique developed by Wellman and colleagues (Wellman, Eckert et al. 2011, Wellman, Edwards et al. 2013).

The thesis demonstrates that the definition of supine OSA that optimises repeatability (Chapter 2) incorporates a ratio of supine AHI to non-supine AHI of greater than 4 to 1. There was no definition that provided good repeatability in female patients. We demonstrated that in patients with supine OSA, airway shape and size are not significantly different to that of matched controls (Chapter 3). The main difference between the groups is found in lung volume, with supine OSA patients having a significantly greater improvement in lung volume when moving from supine to lateral compared to matched controls. The thesis also reveals the important effect of body position on a number of pathophysiological factors known to contribute to OSA (Chapter 4). In particular, with a move to the lateral position there is an improvement in passive airway anatomy, the ability of upper airway muscles to stiffen and dilate the airway and lung volume, but there was no effect on arousal threshold or loop gain.

5.2 IMPLICATIONS OF FINDINGS

5.2.1 A repeatable definition of supine OSA

In the past, OSA patients have been arbitrarily categorised as suffering from supine related OSA based on an observed preponderance of respiratory events when lying in the supine position, so that the supine AHI is at least twice that of the non-supine AHI (Cartwright 1984, Oksenberg, Silverberg et al. 1997). This definition of supine related OSA was modified by Mador and colleagues (Mador, Kufel et al. 2005) who believed that a definition that incorporated a low lateral AHI would have more clinical relevance. The implication of a low lateral AHI being that preventing supine sleep should normalise the overall AHI. It has never been demonstrated, however, either that patients categorised as suffering from supine OSA have the condition on repeat polysomnogram or that a low lateral AHI is repeatable from night-to-night. As such, we cannot say with certainty that patients with supine OSA have a night-to-night problem that requires intervention, or that the proposed intervention of positional modification would be successful.

The results of Chapter 2 demonstrate that, in males, the definition of supine related OSA that best identified those with night-to-night consistency of effect involved a supine to non-supine AHI ratio of >4:1. For females there was no definition that provided adequately identified patients with night-to-night consistency of effect. This finding helps guide clinicians as to which supine related OSA patients to select for positional modification therapy. The finding that a low lateral AHI is repeatable from night-to-night will give clinicians confidence that the application of positional modification devices in such patients is likely to be beneficial in reducing respiratory events. In previously published work we have demonstrated that approximately 27% of patients with mild-moderate OSA are males with a supine to non-supine ratio of >4:1 (Joosten, Hamza et al. 2012). As such, the findings of Chapter 2 help guide clinicians to consider positional modification as a viable primary treatment option for a large proportion of OSA patients.

5.2.2 Lung volume and airway shape in supine OSA patients

Airway size and shape and lung volume have been implicated as a major contributing factor to upper airway obstruction in OSA. These factors have both been demonstrated to change with body position. With regard to airway size, current literature demonstrates consistently that there is minimal change in CSA when moving from the supine to lateral position (Jan, Marshall et al. 1994, Martin, Marshall et al. 1995, Pevernagie, Stanson et al. 1995, Walsh, Leigh et al. 2008). However, no study selected patients specifically suffering from supine related OSA and compared them to matched controls. The literature regarding the effect of body position on airway shape is confusing and conflicting. The type of patients enrolled in these kinds of studies varies widely as does the method of imaging the upper airway (Schwab, Gefter et al. 1993, Pevernagie, Stanson et al. 1995, Ryan and Love 1996, Ciscar, Juan et al. 2001, Fogel, Malhotra et al. 2003, Walsh, Leigh et al. 2008). Again, no studies exist that match patients with supine related OSA to controls.

Although it has been shown that lung volume influences upper airway collapsibility (Tagaito, Isono et al. 2007, Jordan, White et al. 2009) and that lung volume changes with body position (Behrakis, Baydur et al. 1983, Barnas, Campbell et al. 1992, Barnas, Green et al. 1993), no studies have assessed whether lung volume changes with a shift in body position in supine related OSA patients compared to other OSA patients.

Based on these gaps in current knowledge, we crafted a study to explore the effect of body position on upper airway size and shape and on lung volume. The findings of Chapter 3 clarify the current literature relating to upper airway imaging in that we have confirmed that supine OSA patients do not have an increase in airway CSA when moving from supine to lateral. Airway shape as assessed by the ratio of AP to lateral diameter changes significantly with a move from supine to lateral across all groups. The change is similar in supine OSA patients and matched controls and demonstrates that the airway adopts a laterally oriented elliptical shape in the supine position and a more circular shape in the lateral position. These findings suggest that airway size and shape, when assessed in the awake state, are not the differentiating factor determining airway patency in the

lateral position or airway collapse in the supine position in patients who have supine related OSA.

However, the study demonstrates that lung volume is significantly reduced when moving from lateral to supine in the supine OSA group compared to matched controls. Given that a lower lung volume can increase upper airway collapsibility, the reduced lung volume observed in the supine position in supine OSA patients may be a triggering factor for airway collapse in that position.

The findings of this study implicate a lung volume loss in the supine position with respiratory events in supine OSA patients. Loss of lung volume in the supine position may be as a result of increased trans-diaphragmatic pressure resulting from abdominal adiposity (Stadler, McEvoy et al. 2010). Although our subjects were matched for BMI, and there were no significant differences in neck, chest, waist or hip circumference, further investigation is warranted to determine if the supine OSA group has a fat distribution that may favour loss of lung volume in the supine position. The use of more sophisticated measures of body fat distribution such as magnetic resonance imaging may be useful in shedding light on the cause for the observed reduction in lung volume in the supine position. Another possible avenue for further investigation is the potential impact of mediastinal volume on reduction in lung volume. Watson and colleagues have demonstrated that an increased mediastinal volume can reduce lung function in obese patients (Watson, Pride et al. 2010). We do not know how mediastinal volume is altered by body position in OSA patients and this may be another mechanism by which supine OSA patients experience a reduction in lung volume in the supine position.

5.2.3 The effect of body position on physiological mechanisms contributing to OSA

Although CPAP is the current gold standard treatment for patients suffering OSA, a number of patients have difficulty using it (Weaver and Grunstein 2008). The lack of acceptance and adherence to CPAP therapy has prompted a push to develop new treatments for OSA. Understanding that OSA is a heterogeneous disorder that results from the interplay of a number of pathophysiological processes raises the possibility of

individualised treatments that target the specific mechanisms at play in a given patient such as administering a non-muscle relaxant sedative (which elevates the arousal threshold) to patients with a low arousal threshold (Eckert, Owens et al. 2011).

Positional modification therapy represents the oldest individualised therapy for OSA and it has advantages over other proposed individualised treatments in that it has been studied in a clinical context and compares favourably with the currently most effective therapy, CPAP (Jokic, Klimaszewski et al. 1999). However, if positional modification is to play an important role in tailoring treatment to a patient's pathology then understanding the effect of lateral sleep on the pathophysiological traits known to contribute to OSA is crucial.

The data presented in Chapter 4 demonstrate that OSA patients have an improvement in passive airway anatomy (as assessed by passive Pcrit and passive V_0) and the ability of the airway to stiffen and dilate (as assessed by active V_0) when they move from the supine to lateral sleeping position. There are no significant changes in loop gain or arousal threshold when moving from supine to lateral.

The findings presented in this thesis have important implications for the application of positional modification. We know that anatomical factors are the major contributor to airway obstruction in OSA (Eckert, White et al. 2013) and so positional modification may have a role to play in the treatment of many patients with OSA. However, we also know that lateral sleep does not resolve OSA in many patients. Such patients continue to experience obstructive events in lateral sleep either because of the presence of non-anatomical factors (loop gain and arousal threshold) or because the beneficial effect of lateral positioning does not improve their anatomy enough to prevent airway collapse.

Studies in which loop gain and arousal threshold have been targeted by specific therapies (Eckert, Owens et al. 2011, Edwards, Sands et al. 2012) demonstrate that these treatments are effective in a proportion of patients in whom non-anatomical factors are a major contributor to airway obstruction. They do not resolve OSA in patients in whom poor airway anatomy is the main contributory factor. This raises the tantalizing prospect of

combining treatments that improve anatomy (e.g. positional modification therapy), with treatments that target non-anatomical traits (e.g. acetazolamide for loop gain and non-muscle relaxant sedatives for arousal threshold).

A stepwise treatment strategy that involves assessment of an individual patient's pathology, with the subsequent treatment or combination of treatments tailored to the situation, is the next step in the evolution of treatment for OSA.

REFERENCES

Aber, W. R., A. J. Block, D. W. Hellard and W. B. Webb (1989). "Consistency of respiratory measurements from night to night during the sleep of elderly men." Chest **96**(4): 747-751.

Alex, C. G., R. M. Aronson, E. Onal and M. Lopata (1987). "Effects of continuous positive airway pressure on upper airway and respiratory muscle activity." J Appl Physiol (1985) **62**(5): 2026-2030.

Altose, M. D. and Y. Kawakami (1999). Control of breathing in health and disease. New York, Marcel Dekker.

Amatoury, J., K. Kairaitis, J. R. Wheatley, L. E. Bilston and T. C. Amis (2010). "Onset of airflow limitation in a collapsible tube model: impact of surrounding pressure, longitudinal strain, and wall folding geometry." J Appl Physiol **109**(5): 1467-1475.

Anker, A. R., A. Ali, H. E. Arendt, S. P. Cass, L. A. Cotter, B. J. Jian, B. Tamrazi and B. J. Yates (2003). "Use of electrical vestibular stimulation to alter genioglossal muscle activity in awake cats." J Vestib Res **13**(1): 1-8.

Anon. (1984). "Patient's Wife Cures His Snoring." CHEST Journal **85**(4): 582-c.

Avlonitou, E., F. Kapsimalis, G. Varouchakis, C. I. Vardavas and P. Behrakis (2012). "Adherence to CPAP therapy improves quality of life and reduces symptoms among obstructive sleep apnea syndrome patients." Sleep Breath **16**(2): 563-569.

Ayas, N. T., J. M. FitzGerald, J. A. Fleetham, D. P. White, M. Schulzer, C. F. Ryan, R. Ghaeli, G. W. Mercer, P. Cooper, M. C. Tan and C. A. Marra (2006). "Cost-effectiveness of continuous positive airway pressure therapy for moderate to severe obstructive sleep apnea/hypopnea." Arch Intern Med **166**(9): 977-984.

Badr, M. S., J. B. Skatrud, P. M. Simon and J. A. Dempsey (1991). "Effect of hypercapnia on total pulmonary resistance during wakefulness and during NREM sleep." Am Rev Respir Dis **144**(2): 406-414.

Ballantyne, D. and P. Scheid (2000). "Mammalian brainstem chemosensitive neurones: linking them to respiration in vitro." J Physiol **525 Pt 3**: 567-577.

Ballard, R. D., C. G. Irvin, R. J. Martin, J. Pak, R. Pandey and D. P. White (1990). "Influence of sleep on lung volume in asthmatic patients and normal subjects." J Appl Physiol (1985) **68**(5): 2034-2041.

Barnas, G. M., D. N. Campbell, C. F. Mackenzie, J. E. Mendham, B. G. Fahy, C. J. Runcie and G. E. Mendham (1992). "Lung, chest wall, and total respiratory system resistances and elastances in the normal range of breathing." Am Rev Respir Dis **145**(1): 110-113.

Barnas, G. M., M. D. Green, C. F. Mackenzie, S. J. Fletcher, D. N. Campbell, C. Runcie and G. E. Broderick (1993). "Effect of posture on lung and regional chest wall mechanics." Anesthesiology **78**(2): 251-259.

Bearpark, H., L. Elliott, R. Grunstein, J. Hedner, S. Cullen, H. Schneider, W. Althaus and C. Sullivan (1993). "Occurrence and correlates of sleep disordered breathing in the Australian town of Busselton: a preliminary analysis." Sleep **16**(8 Suppl): S3-5.

Behrakis, P. K., A. Baydur, M. J. Jaeger and J. Milic-Emili (1983). "Lung mechanics in sitting and horizontal body positions." Chest **83**(4): 643-646.

Berry, R. B., M. A. Asyali, M. I. McNellis and M. C. Khoo (1998). "Within-night variation in respiratory effort preceding apnea termination and EEG delta power in sleep apnea." J Appl Physiol (1985) **85**(4): 1434-1441.

Berry, R. B., R. Budhiraja, D. J. Gottlieb, D. Gozal, C. Iber, V. K. Kapur, C. L. Marcus, R. Mehra, S. Parthasarathy, S. F. Quan, S. Redline, K. P. Strohl, S. L. Davidson Ward, M. M. Tangredi and M. American Academy of Sleep (2012). "Rules for scoring respiratory events in sleep: update of the 2007 AASM Manual for the Scoring of Sleep and Associated Events. Deliberations of the Sleep Apnea Definitions Task Force of the American Academy of Sleep Medicine." J Clin Sleep Med **8**(5): 597-619.

Berry, R. B. and K. Gleeson (1997). "Respiratory arousal from sleep: mechanisms and significance." Sleep **20**(8): 654-675.

Berry, R. B. and R. W. Light (1992). "Effect of hyperoxia on the arousal response to airway occlusion during sleep in normal subjects." Am Rev Respir Dis **146**(2): 330-334.

Berry, R. B., C. K. Mahutte and R. W. Light (1993). "Effect of hypercapnia on the arousal response to airway occlusion during sleep in normal subjects." J Appl Physiol **74**(5): 2269-2275.

Berry, R. B., M. I. McNellis, K. Kouchi and R. W. Light (1997). "Upper airway anesthesia reduces phasic genioglossus activity during sleep apnea." Am J Respir Crit Care Med **156**(1): 127-132.

Berthon-Jones, M. and C. E. Sullivan (1982). "Ventilatory and arousal responses to hypoxia in sleeping humans." Am Rev Respir Dis **125**(6): 632-639.

Berthon-Jones, M. and C. E. Sullivan (1984). "Ventilation and arousal responses to hypercapnia in normal sleeping humans." J Appl Physiol Respir Environ Exerc Physiol **57**(1): 59-67.

Bianchi, A. L., L. Grelot, S. Iscoe and J. E. Remmers (1988). "Electrophysiological properties of rostral medullary respiratory neurones in the cat: an intracellular study." J Physiol **407**: 293-310.

Bickelmann, A. G., C. S. Burwell, E. D. Robin and R. D. Whaley (1956). "Extreme obesity associated with alveolar hypoventilation; a Pickwickian syndrome." Am J Med **21**(5): 811-818.

Bignold, J. J., J. D. Mercer, N. A. Antic, R. D. McEvoy and P. G. Catcheside (2011). "Accurate position monitoring and improved supine-dependent obstructive sleep apnea with a new position recording and supine avoidance device." Journal of Clinical Sleep Medicine **7**(4): 376-383.

Birchfield, R. I., H. O. Sieker and A. Heyman (1959). "Alterations in respiratory function during natural sleep." J Lab Clin Med **54**: 216-222.

Bittencourt, L. R., D. Suchecki, S. Tufik, C. Peres, S. M. Togeiro, M. C. Bagnato and L. E. Nery (2001). "The variability of the apnoea-hypopnoea index." J Sleep Res **10**(3): 245-251.

Bixler, E. O., A. N. Vgontzas, H. M. Lin, T. Ten Have, J. Rein, A. Vela-Bueno and A. Kales (2001). "Prevalence of sleep-disordered breathing in women: effects of gender." Am J Respir Crit Care Med **163**(3 Pt 1): 608-613.

Bixler, E. O., A. N. Vgontzas, T. Ten Have, K. Tyson and A. Kales (1998). "Effects of age on sleep apnea in men: I. Prevalence and severity." Am J Respir Crit Care Med **157**(1): 144-148.

Bland, J. M. and D. G. Altman (1986). "Statistical methods for assessing agreement between two methods of clinical measurement." Lancet **1**(8476): 307-310.

Bliwise, D. L., R. E. Benkert and R. H. Ingham (1991). "Factors associated with nightly variability in sleep-disordered breathing in the elderly." Chest **100**(4): 973-976.

Block, A. J., P. G. Boysen, J. W. Wynne and L. A. Hunt (1979). "Sleep apnea, hypopnea and oxygen desaturation in normal subjects. A strong male predominance." N Engl J Med **300**(10): 513-517.

Boudewyns, A., N. Punjabi, P. H. Van de Heyning, W. A. De Backer, C. P. O'Donnell, H. Schneider, P. L. Smith and A. R. Schwartz (2000). "Abbreviated method for assessing upper airway function in obstructive sleep apnea." Chest **118**(4): 1031-1041.

Bradley, T. D., I. G. Brown, R. F. Grossman, N. Zamel, D. Martinez, E. A. Phillipson and V. Hoffstein (1986). "Pharyngeal size in snorers, nonsnorers, and patients with obstructive sleep apnea." N Engl J Med **315**(21): 1327-1331.

Butler, J. E., D. K. McKenzie, A. R. Glanville and S. C. Gandevia (1997). "Pulmonary afferents are not necessary for the reflex inhibition of human inspiratory muscles produced by airway occlusion." J Neurophysiol **78**(1): 170-176.

Carlson, D. M., E. Onal, D. W. Carley, M. Lopata and R. C. Basner (1995). "Palatal muscle electromyogram activity in obstructive sleep apnea." Am J Respir Crit Care Med **152**(3): 1022-1027.

Cartwright, R. D. (1984). "Effect of sleep position on sleep apnea severity." Sleep **7**(2): 110-114.

Chamberlin, N. L. (2004). "Functional organization of the parabrachial complex and intertrigeminal region in the control of breathing." Respir Physiol Neurobiol **143**(2-3): 115-125.

Chediak, A. D., J. C. Acevedo-Crespo, D. J. Seiden, H. H. Kim and M. H. Kiel (1996). "Nightly variability in the indices of sleep-disordered breathing in men being evaluated for impotence with consecutive night polysomnograms." Sleep **19**(7): 589-592.

Cheshire, K., H. Engleman, I. Deary, C. Shapiro and N. J. Douglas (1992). "Factors impairing daytime performance in patients with sleep apnea/hypopnea syndrome." Arch Intern Med **152**(3): 538-541.

Chung, J. W., R. Enciso, D. J. Levendowski, P. R. Westbrook and G. T. Clark (2010). "Patients with positional versus nonpositional obstructive sleep apnea: a retrospective study of risk factors associated with apnea-hypopnea severity." Oral Surgery Oral Medicine Oral Pathology Oral Radiology & Endodontics **110**(5): 605-610.

Ciscar, M. A., G. Juan, V. Martinez, M. Ramon, T. Lloret, J. Minguez, M. Armengot, J. Marin and J. Basterra (2001). "Magnetic resonance imaging of the pharynx in OSA patients and healthy subjects." Eur Respir J **17**(1): 79-86.

Cistulli, P. A. (1996). "Craniofacial abnormalities in obstructive sleep apnoea: implications for treatment." Respirology **1**(3): 167-174.

Coughlin, S. R., L. Mawdsley, J. A. Mugarza, P. M. Calverley and J. P. Wilding (2004). "Obstructive sleep apnoea is independently associated with an increased prevalence of metabolic syndrome." Eur Heart J **25**(9): 735-741.

Davies, R. J. and J. R. Stradling (1996). "The epidemiology of sleep apnoea." Thorax **51 Suppl 2**: S65-70.

De Koninck, J., D. Lorrain and P. Gagnon (1992). "Sleep positions and position shifts in five age groups: an ontogenetic picture." Sleep **15**(2): 143-149.

Dealberto, M. J., C. Ferber, L. Garma, P. Lemoine and A. Alperovitch (1994). "Factors related to sleep apnea syndrome in sleep clinic patients." Chest **105**(6): 1753-1758.

Dickens, C., R. Seymour and H. K. Browne (1837). The posthumous papers of the Pickwick club. London,, Chapman and Hall.

Donoghue, S., R. B. Felder, M. P. Gilbey, D. Jordan and K. M. Spyer (1985). "Post-synaptic activity evoked in the nucleus tractus solitarius by carotid sinus and aortic nerve afferents in the cat." J Physiol **360**: 261-273.

Douglas, N. J., D. P. White, C. K. Pickett, J. V. Weil and C. W. Zwillich (1982). "Respiration during sleep in normal man." Thorax **37**(11): 840-844.

Douglas, N. J., D. P. White, J. V. Weil, C. K. Pickett, R. J. Martin, D. W. Hudgel and C. W. Zwillich (1982). "Hypoxic ventilatory response decreases during sleep in normal men." Am Rev Respir Dis **125**(3): 286-289.

Douglas, N. J., D. P. White, J. V. Weil, C. K. Pickett and C. W. Zwillich (1982). "Hypercapnic ventilatory response in sleeping adults." Am Rev Respir Dis **126**(5): 758-762.

Duran, J., S. Esnaola, R. Rubio and A. Iztueta (2001). "Obstructive sleep apnea-hypopnea and related clinical features in a population-based sample of subjects aged 30 to 70 yr." Am J Respir Crit Care Med **163**(3 Pt 1): 685-689.

Eckert, D. J., Y. L. Lo, J. P. Saboisky, A. S. Jordan, D. P. White and A. Malhotra (2011). "Sensorimotor function of the upper-airway muscles and respiratory sensory processing in untreated obstructive sleep apnea." J Appl Physiol (1985) **111**(6): 1644-1653.

Eckert, D. J., R. D. McEvoy, K. E. George, K. J. Thomson and P. G. Catcheside (2007). "Genioglossus reflex inhibition to upper-airway negative-pressure stimuli during wakefulness and sleep in healthy males." J Physiol **581**(Pt 3): 1193-1205.

Eckert, D. J., R. L. Owens, G. B. Kehlmann, A. Wellman, S. Rahangdale, S. Yim-Yeh, D. P. White and A. Malhotra (2011). "Eszopiclone increases the respiratory arousal threshold and lowers the apnoea/hypopnoea index in obstructive sleep apnoea patients with a low arousal threshold." Clin Sci (Lond) **120**(12): 505-514.

Eckert, D. J., J. P. Saboisky, A. S. Jordan, D. P. White and A. Malhotra (2010). "A secondary reflex suppression phase is present in genioglossus but not tensor palatini in response to negative upper airway pressure." J Appl Physiol (1985) **108**(6): 1619-1624.

Eckert, D. J., D. P. White, A. S. Jordan, A. Malhotra and A. Wellman (2013). "Defining phenotypic causes of obstructive sleep apnea. Identification of novel therapeutic targets." Am J Respir Crit Care Med **188**(8): 996-1004.

Edwards, B. A., J. G. Connolly, L. M. Campana, S. A. Sands, J. A. Trinder, D. P. White, A. Wellman and A. Malhotra (2013). "Acetazolamide attenuates the ventilatory response to arousal in patients with obstructive sleep apnea." Sleep **36**(2): 281-285.

Edwards, B. A., D. J. Eckert, D. G. McSharry, S. A. Sands, A. Desai, G. Kehlmann, J. P. Bakker, P. R. Genta, R. L. Owens, D. P. White, A. Wellman and A. Malhotra (2014). "Clinical predictors of the respiratory arousal threshold in patients with obstructive sleep apnea." Am J Respir Crit Care Med **190**(11): 1293-1300.

Edwards, B. A., S. A. Sands, D. J. Eckert, D. P. White, J. P. Butler, R. L. Owens, A. Malhotra and A. Wellman (2012). "Acetazolamide improves loop gain but not the other physiological traits causing obstructive sleep apnoea." J Physiol **590**(Pt 5): 1199-1211.

Edwards, B. A., S. A. Sands, C. Feeney, E. M. Skuza, V. Brodecky, M. H. Wilkinson and P. J. Berger (2009). "Continuous positive airway pressure reduces loop gain and resolves periodic central apneas in the lamb." Respir Physiol Neurobiol **168**(3): 239-249.

Edwards, B. A. and D. P. White (2011). "Control of the pharyngeal musculature during wakefulness and sleep: implications in normal controls and sleep apnea." Head Neck **33 Suppl 1**: S37-45.

Feldman, J. L. and C. A. Del Negro (2006). "Looking for inspiration: new perspectives on respiratory rhythm." Nat Rev Neurosci **7**(3): 232-242.

Ferretti, A., P. Giampiccolo, A. Cavalli, J. Milic-Emili and C. Tantucci (2001). "Expiratory flow limitation and orthopnea in massively obese subjects." Chest **119**(5): 1401-1408.

Fogel, R. B., A. Malhotra, G. Dalagiorgou, M. K. Robinson, M. Jakab, R. Kikinis, S. D. Pittman and D. P. White (2003). "Anatomic and physiologic predictors of apnea severity in morbidly obese subjects." Sleep **26**(2): 150-155.

Fogel, R. B., A. Malhotra, G. Pillar, J. K. Edwards, J. Beauregard, S. A. Shea and D. P. White (2001). "Genioglossal activation in patients with obstructive sleep apnea versus control subjects. Mechanisms of muscle control." Am J Respir Crit Care Med **164**(11): 2025-2030.

Fogel, R. B., J. Trinder, D. P. White, A. Malhotra, J. Raneri, K. Schory, D. Kleverlaan and R. J. Pierce (2005). "The effect of sleep onset on upper airway muscle activity in patients with sleep apnoea versus controls." J Physiol **564**(Pt 2): 549-562.

Fukuda, Y. and H. H. Loeschcke (1977). "Effect of H+ on spontaneous neuronal activity in the surface layer of the rat medulla oblongata in vitro." Pflugers Arch **371**(1-2): 125-134.

Fuller, P. M., J. J. Gooley and C. B. Saper (2006). "Neurobiology of the sleep-wake cycle: sleep architecture, circadian regulation, and regulatory feedback." J Biol Rhythms **21**(6): 482-493.

Fuller, P. M., D. Sherman, N. P. Pedersen, C. B. Saper and J. Lu (2011). "Reassessment of the structural basis of the ascending arousal system." J Comp Neurol **519**(5): 933-956.

Gallopin, T., P. Fort, E. Eggermann, B. Cauli, P. H. Luppi, J. Rossier, E. Audinat, M. Muhlethaler and M. Serafin (2000). "Identification of sleep-promoting neurons in vitro." Nature **404**(6781): 992-995.

George, C. F. (2001). "Reduction in motor vehicle collisions following treatment of sleep apnoea with nasal CPAP." Thorax **56**(7): 508-512.

Gillman, A., T. Roebuck, S. Ho, E. van Braak and M. T. Naughton (2012). "Comparison of supine-only and REM-only obstructive sleep apnoea." Sleep Med **13**(7): 875-878.

Gleadhill, I. C., A. R. Schwartz, N. Schubert, R. A. Wise, S. Permutt and P. L. Smith (1991). "Upper airway collapsibility in snorers and in patients with obstructive hypopnea and apnea." Am Rev Respir Dis **143**(6): 1300-1303.

Gleeson, K., C. W. Zwillich and D. P. White (1989). "Chemosensitivity and the ventilatory response to airflow obstruction during sleep." J Appl Physiol (1985) **67**(4): 1630-1637.

Gleeson, K., C. W. Zwillich and D. P. White (1990). "The influence of increasing ventilatory effort on arousal from sleep." Am Rev Respir Dis **142**(2): 295-300.

Gold, A. R. and A. R. Schwartz (1996). "The pharyngeal critical pressure. The whys and hows of using nasal continuous positive airway pressure diagnostically." Chest **110**(4): 1077-1088.

Gottlieb, D. J., C. W. Whitney, W. H. Bonekat, C. Iber, G. D. James, M. Lebowitz, F. J. Nieto and C. E. Rosenberg (1999). "Relation of sleepiness to respiratory disturbance index: the Sleep Heart Health Study." Am J Respir Crit Care Med **159**(2): 502-507.

Gould, G. A., K. F. Whyte, G. B. Rhind, M. A. Airlie, J. R. Catterall, C. M. Shapiro and N. J. Douglas (1988). "The sleep hypopnea syndrome." Am Rev Respir Dis **137**(4): 895-898.

Guilleminault, C., A. Tilkian and W. C. Dement (1976). "The sleep apnea syndromes." Annu Rev Med **27**: 465-484.

Hamilton, R. D., A. J. Winning, R. L. Horner and A. Guz (1988). "The effect of lung inflation on breathing in man during wakefulness and sleep." Respir Physiol **73**(2): 145-154.

Heinzer, R. C., M. L. Stanchina, A. Malhotra, A. S. Jordan, S. R. Patel, Y. L. Lo, A. Wellman, K. Schory, L. Dover and D. P. White (2006). "Effect of increased lung volume on sleep disordered breathing in patients with sleep apnoea." Thorax **61**(5): 435-439.

Heinzer, R. C., D. P. White, A. S. Jordan, Y. L. Lo, L. Dover, K. Stevenson and A. Malhotra (2008). "Trazodone increases arousal threshold in obstructive sleep apnoea." Eur Respir J **31**(6): 1308-1312.

Henke, K. G., J. A. Dempsey, M. S. Badr, J. M. Kowitz and J. B. Skatrud (1991). "Effect of sleep-induced increases in upper airway resistance on respiratory muscle activity." J Appl Physiol (1985) **70**(1): 158-168.

Horner, R. L. (2001). "The neuropharmacology of upper airway motor control in the awake and asleep states: implications for obstructive sleep apnoea." Respir Res **2**(5): 286-294.

Horner, R. L., J. A. Innes, M. J. Morrell, S. A. Shea and A. Guz (1994). "The effect of sleep on reflex genioglossus muscle activation by stimuli of negative airway pressure in humans." J Physiol **476**(1): 141-151.

Hudgel, D. W., K. R. Chapman, C. Faulks and C. Hendricks (1987). "Changes in inspiratory muscle electrical activity and upper airway resistance during periodic breathing induced by hypoxia during sleep." Am Rev Respir Dis **135**(4): 899-906.

Hudgel, D. W. and P. Devadatta (1984). "Decrease in functional residual capacity during sleep in normal humans." J Appl Physiol **57**(5): 1319-1322.

Hudgel, D. W., E. A. Gordon, S. Thanakitcharu and E. N. Bruce (1998). "Instability of ventilatory control in patients with obstructive sleep apnea." Am J Respir Crit Care Med **158**(4): 1142-1149.

Hudgel, D. W. and C. Hendricks (1988). "Palate and hypopharynx--sites of inspiratory narrowing of the upper airway during sleep." Am Rev Respir Dis **138**(6): 1542-1547.

Ibanez Juve, J., S. Garcia Moris, P. Marse Milla, R. Abizanda Campos, M. Fiol Sala and J. M. Abadal Centellas (1979). "[Pulmonary function differences in healthy subjects according to postural changes (author's transl)]." Medicina Clinica **73**(4): 149-152.

Iber, C. and American Academy of Sleep Medicine. (2007). The AASM manual for the scoring of sleep and associated events : rules, terminology, and technical specifications. Westchester, IL, American Academy of Sleep Medicine.

Ip, M. S., B. Lam, M. M. Ng, W. K. Lam, K. W. Tsang and K. S. Lam (2002). "Obstructive sleep apnea is independently associated with insulin resistance." Am J Respir Crit Care Med **165**(5): 670-676.

Isono, S., J. E. Remmers, A. Tanaka, Y. Sho, J. Sato and T. Nishino (1997). "Anatomy of pharynx in patients with obstructive sleep apnea and in normal subjects." J Appl Physiol **82**(4): 1319-1326.

Isono, S., A. Tanaka and T. Nishino (2002). "Lateral position decreases collapsibility of the passive pharynx in patients with obstructive sleep apnea." Anesthesiology **97**(4): 780-785.

Isono, S., A. Tanaka, Y. Sho, A. Konno and T. Nishino (1995). "Advancement of the mandible improves velopharyngeal airway patency." J Appl Physiol **79**(6): 2132-2138.

Isono, S., A. Tanaka, Y. Tagaito, T. Ishikawa and T. Nishino (2004). "Influences of head positions and bite opening on collapsibility of the passive pharynx." Journal of Applied Physiology **97**(1): 339-346.

Jan, M. A., I. Marshall and N. J. Douglas (1994). "Effect of posture on upper airway dimensions in normal human." American Journal of Respiratory & Critical Care Medicine **149**(1): 145-148.

Jokic, R., A. Klimaszewski, M. Crossley, G. Sridhar and M. F. Fitzpatrick (1999). "Positional treatment vs continuous positive airway pressure in patients with positional obstructive sleep apnea syndrome." Chest **115**(3): 771-781.

Jones, R. L. and M. M. Nzekwu (2006). "The effects of body mass index on lung volumes." Chest **130**(3): 827-833.

Joosten, S. A., B. A. Edwards, A. Wellman, A. Turton, T. Samarasinghe, E. Skuza, P. Berger and G. S. Hamilton (2014). Obstructive Sleep Apnea Phenotypic Trait Changes From Supine To Lateral Position. B110. UPPER AIRWAY AND RESPIRATORY CONTROL DURING SLEEP, American Thoracic Society**:** A3909-A3909.

Joosten, S. A., K. Hamza, S. Sands, A. Turton, P. Berger and G. Hamilton (2012). "Phenotypes of patients with mild to moderate obstructive sleep apnoea as confirmed by cluster analysis." Respirology **17**(1): 99-107.

Joosten, S. A., F. J. O'Donoghue, P. D. Rochford, M. Barnes, K. Hamza, T. Churchward, P. J. Berger and G. S. Hamilton (2014). "Night-to-Night Repeatability of Supine-related Obstructive Sleep Apnea." Ann Am Thorac Soc.

Joosten, S. A., F. J. O'Donoghue, P. D. Rochford, M. Barnes, K. Hamza, T. J. Churchward, P. J. Berger and G. S. Hamilton (2014). "Night-to-Night Repeatability of Supine-related Obstructive Sleep Apnea." Ann Am Thorac Soc **11**(5): 761-769.

Joosten, S. A., D. M. O'Driscoll, P. J. Berger and G. S. Hamilton (2013). "Supine position related obstructive sleep apnea in adults: Pathogenesis and treatment." Sleep Med Rev.

Joosten, S. A., D. M. O'Driscoll, P. J. Berger and G. S. Hamilton (2014). "Supine position related obstructive sleep apnea in adults: pathogenesis and treatment." Sleep Med Rev **18**(1): 7-17.

Jordan, A. S., D. J. Eckert, A. Wellman, J. A. Trinder, A. Malhotra and D. P. White (2011). "Termination of respiratory events with and without cortical arousal in obstructive sleep apnea." Am J Respir Crit Care Med **184**(10): 1183-1191.

Jordan, A. S., A. Wellman, R. C. Heinzer, Y. L. Lo, K. Schory, L. Dover, S. Gautam, A. Malhotra and D. P. White (2007). "Mechanisms used to restore ventilation after partial upper airway collapse during sleep in humans." Thorax **62**(10): 861-867.

Jordan, A. S., D. P. White, Y.-L. Lo, A. Wellman, D. J. Eckert, S. Yim-Yeh, M. Eikermann, S. A. Smith, K. E. Stevenson and A. Malhotra (2009). "Airway dilator muscle activity and lung volume during stable breathing in obstructive sleep apnea." Sleep **32**(3): 361-368.

Jung, R. and W. Kuhlo (1965). "Neurophysiological Studies of Abnormal Night Sleep and the Pickwickian Syndrome." Prog Brain Res **18**: 140-159.

Kairaitis, K., K. Byth, R. Parikh, R. Stavrinou, J. R. Wheatley and T. C. Amis (2007). "Tracheal traction effects on upper airway patency in rabbits: the role of tissue pressure." Sleep **30**(2): 179-186.

Kauppinen-Walin, K., A. R. Sovijarvi, A. Muittari and A. Uusitalo (1980). "Determination of functional residual capacity with 133-xenon radiospirometry. Comparison with body plethysmography and helium spirometry. Effect of body position." Scandinavian Journal of Clinical & Laboratory Investigation **40**(4): 347-354.

Kryger, M. H. (1983). "Sleep apnea. From the needles of Dionysius to continuous positive airway pressure." Arch Intern Med **143**(12): 2301-2303.

Kryger, M. H., T. Roth and W. C. Dement (2011). Principles and practice of sleep medicine. Philadelphia, PA, Saunders/Elsevier.

Kuna, S. T., D. G. Bedi and C. Ryckman (1988). "Effect of nasal airway positive pressure on upper airway size and configuration." Am Rev Respir Dis **138**(4): 969-975.

Kushida, C. A., M. R. Littner, M. Hirshkowitz, T. I. Morgenthaler, C. A. Alessi, D. Bailey, B. Boehlecke, T. M. Brown, J. Coleman, Jr., L. Friedman, S. Kapen, V. K. Kapur, M. Kramer, T. Lee-Chiong, J. Owens, J. P. Pancer, T. J. Swick and M. S. Wise (2006). "Practice parameters for the use of continuous and bilevel positive airway pressure devices to treat adult patients with sleep-related breathing disorders." Sleep **29**(3): 375-380.

Lahiri, S. and R. E. Forster, 2nd (2003). "CO2/H(+) sensing: peripheral and central chemoreception." Int J Biochem Cell Biol **35**(10): 1413-1435.

Larrabee, M. G. and G. C. Knowlton (1946). "Excitation and inhibition of phrenic motoneurones by inflation of the lungs." Am J Physiol **147**: 90-99.

Lavie, P. (1984). "Nothing new under the moon. Historical accounts of sleep apnea syndrome." Arch Intern Med **144**(10): 2025-2028.

Le Bon, O., G. Hoffmann, J. Tecco, L. Staner, A. Noseda, I. Pelc and P. Linkowski (2000). "Mild to moderate sleep respiratory events: one negative night may not be enough." Chest **118**(2): 353-359.

Lee, R. W. W., K. Sutherland and P. A. Cistulli (2010). "Craniofacial Morphology in Obstructive Sleep Apnea: A Review." Clinical Pulmonary Medicine **17**(4): 189-195.

Lindberg, E. and T. Gislason (2000). "Epidemiology of sleep-related obstructive breathing." Sleep Med Rev **4**(5): 411-433.

Lo, Y. L., A. S. Jordan, A. Malhotra, A. Wellman, R. A. Heinzer, M. Eikermann, K. Schory, L. Dover and D. P. White (2007). "Influence of wakefulness on pharyngeal airway muscle activity." Thorax **62**(9): 799-805.

Lo, Y. L., A. S. Jordan, A. Malhotra, A. Wellman, R. C. Heinzer, K. Schory, L. Dover, R. B. Fogel and D. P. White (2006). "Genioglossal muscle response to CO2 stimulation during NREM sleep." Sleep **29**(4): 470-477.

Loewen, A., M. Ostrowski, J. Laprairie, R. Atkar, J. Gnitecki, P. Hanly and M. Younes (2009). "Determinants of ventilatory instability in obstructive sleep apnea: inherent or acquired?" Sleep **32**(10): 1355-1365.

Loord, H. and E. Hultcrantz (2007). "Positioner--a method for preventing sleep apnea." Acta Oto-Laryngologica **127**(8): 861-868.

Low, K., K. K. Lau, P. Holmes, M. Crossett, N. Vallance, D. Phyland, K. Hamza, G. Hamilton and P. G. Bardin (2011). "Abnormal vocal cord function in difficult-to-treat asthma." Am J Respir Crit Care Med **184**(1): 50-56.

Lucey, A. D., A. J. King, G. A. Tetlow, J. Wang, J. J. Armstrong, M. S. Leigh, A. Paduch, J. H. Walsh, D. D. Sampson, P. R. Eastwood and D. R. Hillman (2010). "Measurement, reconstruction, and flow-field computation of the human pharynx with application to sleep apnea." IEEE Trans Biomed Eng **57**(10): 2535-2548.

Macnish, R. (1834). The philosophy of sleep. n.p.

Mador, M. J., T. J. Kufel, U. J. Magalang, S. K. Rajesh, V. Watwe and B. J. B. Grant (2005). "Prevalence of positional sleep apnea in patients undergoing polysomnography." Chest **128**(4): 2130-2137.

Malhotra, A., G. Pillar, R. B. Fogel, J. Beauregard, J. K. Edwards, D. I. Slamowitz, S. A. Shea and D. P. White (2000). "Genioglossal but not palatal muscle activity relates closely to pharyngeal pressure." Am J Respir Crit Care Med **162**(3 Pt 1): 1058-1062.

Malhotra, A., G. Pillar, R. B. Fogel, J. K. Edwards, N. Ayas, T. Akahoshi, D. Hess and D. P. White (2002). "Pharyngeal pressure and flow effects on genioglossus activation in normal subjects." Am J Respir Crit Care Med **165**(1): 71-77.

Malhotra, A., J. Trinder, R. Fogel, M. Stanchina, S. R. Patel, K. Schory, D. Kleverlaan and D. P. White (2004). "Postural effects on pharyngeal protective reflex mechanisms." Sleep **27**(6): 1105-1112.

Martin, S. E., I. Marshall and N. J. Douglas (1995). "The effect of posture on airway caliber with the sleep-apnea/hypopnea syndrome." American Journal of Respiratory & Critical Care Medicine **152**(2): 721-724.

Martinez-Garcia, M. A., F. Campos-Rodriguez, J. J. Soler-Cataluna, P. Catalan-Serra, P. Roman-Sanchez and J. M. Montserrat (2012). "Increased incidence of nonfatal cardiovascular events in stroke patients with sleep apnoea: effect of CPAP treatment." Eur Respir J **39**(4): 906-912.

Martinez-Garcia, M. A., R. Gomez-Aldaravi, J. J. Soler-Cataluna, T. G. Martinez, B. Bernacer-Alpera and P. Roman-Sanchez (2007). "Positive effect of CPAP treatment on the control of difficult-to-treat hypertension." Eur Respir J **29**(5): 951-957.

McGinley, B. M., A. R. Schwartz, H. Schneider, J. P. Kirkness, P. L. Smith and S. P. Patil (2008). "Upper airway neuromuscular compensation during sleep is defective in obstructive sleep apnea." J Appl Physiol **105**(1): 197-205.

Mehra, R., E. J. Benjamin, E. Shahar, D. J. Gottlieb, R. Nawabit, H. L. Kirchner, J. Sahadevan, S. Redline and S. Sleep Heart Health (2006). "Association of nocturnal arrhythmias with sleep-disordered breathing: The Sleep Heart Health Study." Am J Respir Crit Care Med **173**(8): 910-916.

Mendelson, W. B. (1994). "Use of the sleep laboratory in suspected sleep apnea syndrome: is one night enough?" Cleve Clin J Med **61**(4): 299-303.

Mezzanotte, W. S., D. J. Tangel and D. P. White (1992). "Waking genioglossal electromyogram in sleep apnea patients versus normal controls (a neuromuscular compensatory mechanism)." J Clin Invest **89**(5): 1571-1579.

Mezzanotte, W. S., D. J. Tangel and D. P. White (1996). "Influence of sleep onset on upper-airway muscle activity in apnea patients versus normal controls." Am J Respir Crit Care Med **153**(6 Pt 1): 1880-1887.

Milic-Emili, J., J. Mead and J. M. Turner (1964). "Topography of Esophageal Pressure as a Function of Posture in Man." J Appl Physiol **19**: 212-216.

Miljeteig, H., P. Cole and J. S. Haight (1995). "Nasal resistance in recumbency and sleep." Rhinology **33**(2): 82-83.

Mitchell, R. A., H. H. Loeschcke, W. H. Massion and J. W. Severinghaus (1963). Respiratory responses mediated through superficial chemosensitive areas on the medulla.

Miyamoto, K., M. M. Ozbek, A. A. Lowe, T. T. Sjoholm, L. L. Love, J. A. Fleetham and C. F. Ryan (1998). "Mandibular posture during sleep in healthy adults." Archives of Oral Biology **43**(4): 269-275.

Mo, J. H., C. H. Lee, C. S. Rhee, I. Y. Yoon and J. W. Kim (2011). "Positional dependency in Asian patients with obstructive sleep apnea and its implication for hypertension." Archives of otolaryngology--head & neck surgery **137**(8): 786-790.

Morrell, M. J., Y. Arabi, B. Zahn and M. S. Badr (1998). "Progressive retropalatal narrowing preceding obstructive apnea." Am J Respir Crit Care Med **158**(6): 1974-1981.

Moruzzi, G. and H. W. Magoun (1949). "Brain stem reticular formation and activation of the EEG." Electroencephalogr Clin Neurophysiol **1**(4): 455-473.

Mosko, S. S., M. J. Dickel and J. Ashurst (1988). "Night-to-night variability in sleep apnea and sleep-related periodic leg movements in the elderly." Sleep **11**(4): 340-348.

Narkiewicz, K., P. J. van de Borne, C. A. Pesek, M. E. Dyken, N. Montano and V. K. Somers (1999). "Selective potentiation of peripheral chemoreflex sensitivity in obstructive sleep apnea." Circulation **99**(9): 1183-1189.

Nattie, E. E. (2001). "Central chemosensitivity, sleep, and wakefulness." Respir Physiol **129**(1-2): 257-268.

Navajas, D., R. Farre, M. M. Rotger, J. Milic-Emili and J. Sanchis (1988). "Effect of body posture on respiratory impedance." Journal of Applied Physiology **64**(1): 194-199.

Nieto, F. J., T. B. Young, B. K. Lind, E. Shahar, J. M. Samet, S. Redline, R. B. D'Agostino, A. B. Newman, M. D. Lebowitz and T. G. Pickering (2000). "Association of

sleep-disordered breathing, sleep apnea, and hypertension in a large community-based study. Sleep Heart Health Study." JAMA **283**(14): 1829-1836.

O'Connor, C., K. S. Thornley and P. J. Hanly (2000). "Gender differences in the polysomnographic features of obstructive sleep apnea." Am J Respir Crit Care Med **161**(5): 1465-1472.

Oksenberg, A., E. Arons, K. Nasser, T. Vander and H. Radwan (2010). "REM-related obstructive sleep apnea: the effect of body position." Journal of Clinical Sleep Medicine **6**(4): 343-348.

Oksenberg, A., I. Khamaysi, D. S. Silverberg and A. Tarasiuk (2000). "Association of body position with severity of apneic events in patients with severe nonpositional obstructive sleep apnea." Chest **118**(4): 1018-1024.

Oksenberg, A., D. S. Silverberg, E. Arons and H. Radwan (1997). "Positional vs nonpositional obstructive sleep apnea patients: anthropomorphic, nocturnal polysomnographic, and multiple sleep latency test data." Chest **112**(3): 629-639.

Onal, E., D. L. Burrows, R. H. Hart and M. Lopata (1986). "Induction of periodic breathing during sleep causes upper airway obstruction in humans." J Appl Physiol (1985) **61**(4): 1438-1443.

Onal, E., M. Lopata and T. O'Connor (1982). "Pathogenesis of apneas in hypersomnia-sleep apnea syndrome." Am Rev Respir Dis **125**(2): 167-174.

Onal, E., M. Lopata and T. D. O'Connor (1981). "Diaphragmatic and genioglossal electromyogram responses to CO2 rebreathing in humans." J Appl Physiol Respir Environ Exerc Physiol **50**(5): 1052-1055.

Ong, J. S. L., G. Touyz, S. Tanner, D. R. Hillman, P. R. Eastwood and J. H. Walsh (2011). "Variability of human upper airway collapsibility during sleep and the influence of body posture and sleep stage." Journal of Sleep Research **20**(4): 533-537.

Ono, T., R. Otsuka, T. Kuroda, E. Honda and T. Sasaki (2000). "Effects of head and body position on two- and three-dimensional configurations of the upper airway." Journal of Dental Research **79**(11): 1879-1884.

Otsuka, R., T. Ono, Y. Ishiwata and T. Kuroda (2000). "Respiratory-related genioglossus electromyographic activity in response to head rotation and changes in body position." Angle Orthodontist **70**(1): 63-69.

Owens, R. L., L. M. Campana, L. Hess, D. J. Eckert, S. H. Loring and A. Malhotra (2012). "Sitting and supine esophageal pressures in overweight and obese subjects." Obesity (Silver Spring) **20**(12): 2354-2360.

Owens, R. L., B. A. Edwards, S. A. Sands, J. P. Butler, D. J. Eckert, D. P. White, A. Malhotra and A. Wellman (2014). "The classical Starling resistor model often does not predict inspiratory airflow patterns in the human upper airway." J Appl Physiol (1985) **116**(8): 1105-1112.

Owens, R. L., A. Malhotra, D. J. Eckert, D. P. White and A. S. Jordan (2010). "The influence of end-expiratory lung volume on measurements of pharyngeal collapsibility." J Appl Physiol **108**(2): 445-451.

Patel, S. R., D. P. White, A. Malhotra, M. L. Stanchina and N. T. Ayas (2003). "Continuous positive airway pressure therapy for treating sleepiness in a diverse population with obstructive sleep apnea: results of a meta-analysis." Arch Intern Med **163**(5): 565-571.

Patil, S. P., N. M. Punjabi, H. Schneider, C. P. O'Donnell, P. L. Smith and A. R. Schwartz (2004). "A simplified method for measuring critical pressures during sleep in the clinical setting." Am J Respir Crit Care Med **170**(1): 86-93.

Patil, S. P., H. Schneider, J. J. Marx, E. Gladmon, A. R. Schwartz and P. L. Smith (2007). "Neuromechanical control of upper airway patency during sleep." J Appl Physiol (1985) **102**(2): 547-556.

Pelosi, P., M. Croci, I. Ravagnan, M. Cerisara, P. Vicardi, A. Lissoni and L. Gattinoni (1997). "Respiratory system mechanics in sedated, paralyzed, morbidly obese patients." Journal of Applied Physiology **82**(3): 811-818.

Penzel, T., M. Moller, H. F. Becker, L. Knaack and J. H. Peter (2001). "Effect of sleep position and sleep stage on the collapsibility of the upper airways in patients with sleep apnea." Sleep **24**(1): 90-95.

Peppard, P. E., M. Szklo-Coxe, K. M. Hla and T. Young (2006). "Longitudinal association of sleep-related breathing disorder and depression." Arch Intern Med **166**(16): 1709-1715.

Peppard, P. E., T. Young, M. Palta and J. Skatrud (2000). "Prospective study of the association between sleep-disordered breathing and hypertension." N Engl J Med **342**(19): 1378-1384.

Permut, I., M. Diaz-Abad, W. Chatila, J. Crocetti, J. P. Gaughan, G. E. D'Alonzo and S. L. Krachman (2010). "Comparison of positional therapy to CPAP in patients with positional obstructive sleep apnea." Journal of Clinical Sleep Medicine **6**(3): 238-243.

Pevernagie, D. A. and J. W. Shepard, Jr. (1992). "Relations between sleep stage, posture and effective nasal CPAP levels in OSA." Sleep **15**(2): 162-167.

Pevernagie, D. A., A. W. Stanson, P. F. Sheedy, 2nd, B. K. Daniels and J. W. Shepard, Jr. (1995). "Effects of body position on the upper airway of patients with obstructive sleep apnea." American Journal of Respiratory & Critical Care Medicine **152**(1): 179-185.

Pillar, G., A. Malhotra, R. B. Fogel, J. Beauregard, D. I. Slamowitz, S. A. Shea and D. P. White (2000). "Upper airway muscle responsiveness to rising PCO(2) during NREM sleep." J Appl Physiol **89**(4): 1275-1282.

Pitts, D. G., M. K. Patel, P. O. Lang, A. J. Sinclair and R. Aspinall (2013). "A respiratory monitoring device based on clavicular motion." Physiol Meas **34**(8): N51-61.

Putnam, R. W., J. A. Filosa and N. A. Ritucci (2004). "Cellular mechanisms involved in CO(2) and acid signaling in chemosensitive neurons." Am J Physiol Cell Physiol **287**(6): C1493-1526.

Ratnavadivel, R., N. Chau, D. Stadler, A. Yeo, R. D. McEvoy and P. G. Catcheside (2009). "Marked reduction in obstructive sleep apnea severity in slow wave sleep." J Clin Sleep Med **5**(6): 519-524.

Redline, S. and M. Sanders (1997). "Hypopnea, a floating metric: implications for prevalence, morbidity estimates, and case finding." Sleep **20**(12): 1209-1217.

Redline, S. and P. V. Tishler (2000). "The genetics of sleep apnea." Sleep Med Rev **4**(6): 583-602.

Rees, K., D. P. Spence, J. E. Earis and P. M. Calverley (1995). "Arousal responses from apneic events during non-rapid-eye-movement sleep." Am J Respir Crit Care Med **152**(3): 1016-1021.

Remmers, J. E., W. J. deGroot, E. K. Sauerland and A. M. Anch (1978). "Pathogenesis of upper airway occlusion during sleep." J Appl Physiol **44**(6): 931-938.

Ricardo, J. A. and E. T. Koh (1978). "Anatomical evidence of direct projections from the nucleus of the solitary tract to the hypothalamus, amygdala, and other forebrain structures in the rat." Brain Res **153**(1): 1-26.

Richard, W., D. Kox, C. den Herder, M. Laman, H. van Tinteren and N. de Vries (2006). "The role of sleep position in obstructive sleep apnea syndrome." European Archives of Oto-Rhino-Laryngology **263**(10): 946-950.

Robin, E. D., R. D. Whaley, C. H. Crump and D. M. Travis (1958). "Alveolar gas tensions, pulmonary ventilation and blood pH during physiologic sleep in normal subjects." J Clin Invest **37**(7): 981-989.

Rosin, D. L., D. A. Chang and P. G. Guyenet (2006). "Afferent and efferent connections of the rat retrotrapezoid nucleus." J Comp Neurol **499**(1): 64-89.

Rowley, J. A., S. Permutt, S. Willey, P. L. Smith and A. R. Schwartz (1996). "Effect of tracheal and tongue displacement on upper airway airflow dynamics." J Appl Physiol **80**(6): 2171-2178.

Ruehland, W. R., P. D. Rochford, F. J. O'Donoghue, R. J. Pierce, P. Singh and A. T. Thornton (2009). "The new AASM criteria for scoring hypopneas: impact on the apnea hypopnea index." Sleep **32**(2): 150-157.

Ryan, C. F. and L. L. Love (1996). "Mechanical properties of the velopharynx in obese patients with obstructive sleep apnea." Am J Respir Crit Care Med **154**(3 Pt 1): 806-812.

Sahlin, C., E. Svanborg, H. Stenlund and K. A. Franklin (2005). "Cheyne-Stokes respiration and supine dependency." European Respiratory Journal **25**(5): 829-833.

Saigusa, H., M. Suzuki, N. Higurashi and K. Kodera (2009). "Three-dimensional morphological analyses of positional dependence in patients with obstructive sleep apnea syndrome." Anesthesiology **110**(4): 885-890.

Sands, S. A., B. A. Edwards, K. Kee, A. Turton, E. M. Skuza, T. Roebuck, D. M. O'Driscoll, G. S. Hamilton, M. T. Naughton and P. J. Berger (2011). "Loop gain as a means to predict a positive airway pressure suppression of Cheyne-Stokes respiration in patients with heart failure." Am J Respir Crit Care Med **184**(9): 1067-1075.

Sant'Ambrogio, G. and O. P. Mathew (1988). Respiratory function of the upper airway. New York, Dekker.

Sant'Ambrogio, G., H. Tsubone and F. B. Sant'Ambrogio (1995). "Sensory information from the upper airway: role in the control of breathing." Respir Physiol **102**(1): 1-16.

Schwab, R. J. (1998). "Upper airway imaging." Clin Chest Med **19**(1): 33-54.

Schwab, R. J., W. B. Gefter, E. A. Hoffman, K. B. Gupta and A. I. Pack (1993). "Dynamic upper airway imaging during awake respiration in normal subjects and patients with sleep disordered breathing." Am Rev Respir Dis **148**(5): 1385-1400.

Schwab, R. J., K. B. Gupta, W. B. Gefter, L. J. Metzger, E. A. Hoffman and A. I. Pack (1995). "Upper airway and soft tissue anatomy in normal subjects and patients with sleep-disordered breathing. Significance of the lateral pharyngeal walls." Am J Respir Crit Care Med **152**(5 Pt 1): 1673-1689.

Schwab, R. J., A. I. Pack, K. B. Gupta, L. J. Metzger, E. Oh, J. E. Getsy, E. A. Hoffman and W. B. Gefter (1996). "Upper airway and soft tissue structural changes induced by CPAP in normal subjects." Am J Respir Crit Care Med **154**(4 Pt 1): 1106-1116.

Schwab, R. J., M. Pasirstein, R. Pierson, A. Mackley, R. Hachadoorian, R. Arens, G. Maislin and A. I. Pack (2003). "Identification of upper airway anatomic risk factors for obstructive sleep apnea with volumetric magnetic resonance imaging." Am J Respir Crit Care Med **168**(5): 522-530.

Schwartz, A. R., A. R. Gold, N. Schubert, A. Stryzak, R. A. Wise, S. Permutt and P. L. Smith (1991). "Effect of weight loss on upper airway collapsibility in obstructive sleep apnea." Am Rev Respir Dis **144**(3 Pt 1): 494-498.

Schwartz, A. R., N. Schubert, W. Rothman, F. Godley, B. Marsh, D. Eisele, J. Nadeau, L. Permutt, I. Gleadhill and P. L. Smith (1992). "Effect of uvulopalatopharyngoplasty on upper airway collapsibility in obstructive sleep apnea." Am Rev Respir Dis **145**(3): 527-532.

Schwartz, A. R., P. L. Smith, R. A. Wise, A. R. Gold and S. Permutt (1988). "Induction of upper airway occlusion in sleeping individuals with subatmospheric nasal pressure." J Appl Physiol **64**(2): 535-542.

Series, F., Y. Cormier, J. Couture and M. Desmeules (1990). "Changes in upper airway resistance with lung inflation and positive airway pressure." J Appl Physiol **68**(3): 1075-1079.

Shahar, E., C. W. Whitney, S. Redline, E. T. Lee, A. B. Newman, F. J. Nieto, G. T. O'Connor, L. L. Boland, J. E. Schwartz and J. M. Samet (2001). "Sleep-disordered

breathing and cardiovascular disease: cross-sectional results of the Sleep Heart Health Study." Am J Respir Crit Care Med **163**(1): 19-25.

Shamsuzzaman, A. S., B. J. Gersh and V. K. Somers (2003). "Obstructive sleep apnea: implications for cardiac and vascular disease." JAMA **290**(14): 1906-1914.

Shea, S. A., J. K. Edwards and D. P. White (1999). "Effect of wake-sleep transitions and rapid eye movement sleep on pharyngeal muscle response to negative pressure in humans." J Physiol **520 Pt 3**: 897-908.

Shepard, J. W., Jr. and C. D. Burger (1990). "Nasal and oral flow-volume loops in normal subjects and patients with obstructive sleep apnea." Am Rev Respir Dis **142**(6 Pt 1): 1288-1293.

Shepard, J. W., Jr., D. A. Pevernagie, A. W. Stanson, B. K. Daniels and P. F. Sheedy (1996). "Effects of changes in central venous pressure on upper airway size in patients with obstructive sleep apnea." Am J Respir Crit Care Med **153**(1): 250-254.

Shore, E. T. and R. P. Millman (1984). "Abnormalities in the flow-volume loop in obstructive sleep apnoea sitting and supine." Thorax **39**(10): 775-779.

Skatrud, J. B. and J. A. Dempsey (1985). "Airway resistance and respiratory muscle function in snorers during NREM sleep." J Appl Physiol (1985) **59**(2): 328-335.

Smith, P. L., R. A. Wise, A. R. Gold, A. R. Schwartz and S. Permutt (1988). "Upper airway pressure-flow relationships in obstructive sleep apnea." J Appl Physiol **64**(2): 789-795.

Soll, B. A. G., K. K. Yeo, J. W. Davis, T. B. Seto, I. J. Schatz and E. N. Shen (2009). "The effect of posture on Cheyne-Stokes respirations and hemodynamics in patients with heart failure." Sleep **32**(11): 1499-1506.

Squier, S. B., S. P. Patil, H. Schneider, J. P. Kirkness, P. L. Smith and A. R. Schwartz (2010). "Effect of end-expiratory lung volume on upper airway collapsibility in sleeping men and women." J Appl Physiol **109**(4): 977-985.

Stadler, D. L., R. D. McEvoy, J. Bradley, D. Paul and P. G. Catcheside (2010). "Changes in lung volume and diaphragm muscle activity at sleep onset in obese obstructive sleep apnea patients vs. healthy-weight controls." Journal of Applied Physiology **109**(4): 1027-1036.

Stadler, D. L., R. D. McEvoy, K. E. Sprecher, K. J. Thomson, M. K. Ryan, C. C. Thompson and P. G. Catcheside (2009). "Abdominal compression increases upper airway collapsibility during sleep in obese male obstructive sleep apnea patients." Sleep **32**(12): 1579-1587.

Stanchina, M. L., A. Malhotra, R. B. Fogel, N. Ayas, J. K. Edwards, K. Schory and D. P. White (2002). "Genioglossus muscle responsiveness to chemical and mechanical stimuli during non-rapid eye movement sleep." Am J Respir Crit Care Med **165**(7): 945-949.

Stanchina, M. L., A. Malhotra, R. B. Fogel, J. Trinder, J. K. Edwards, K. Schory and D. P. White (2003). "The influence of lung volume on pharyngeal mechanics, collapsibility, and genioglossus muscle activation during sleep." Sleep **26**(7): 851-856.

Stradling, J. R., G. A. Chadwick and A. J. Frew (1985). "Changes in ventilation and its components in normal subjects during sleep." Thorax **40**(5): 364-370.

Strohl, K. P., J. P. Butler and A. Malhotra (2012). "Mechanical properties of the upper airway." Compr Physiol **2**(3): 1853-1872.

Strohl, K. P., M. J. Hensley, M. Hallett, N. A. Saunders and R. H. Ingram, Jr. (1980). "Activation of upper airway muscles before onset of inspiration in normal humans." J Appl Physiol Respir Environ Exerc Physiol **49**(4): 638-642.

Sullivan, C. E., F. G. Issa, M. Berthon-Jones and L. Eves (1981). "Reversal of obstructive sleep apnoea by continuous positive airway pressure applied through the nares." Lancet **1**(8225): 862-865.

Szollosi, I., T. Roebuck, B. Thompson and M. T. Naughton (2006). "Lateral sleeping position reduces severity of central sleep apnea / Cheyne-Stokes respiration." Sleep **29**(8): 1045-1051.

Tagaito, Y., S. Isono, J. E. Remmers, A. Tanaka and T. Nishino (2007). "Lung volume and collapsibility of the passive pharynx in patients with sleep-disordered breathing." J Appl Physiol **103**(4): 1379-1385.

Takakura, A. C., T. S. Moreira, E. Colombari, G. H. West, R. L. Stornetta and P. G. Guyenet (2006). "Peripheral chemoreceptor inputs to retrotrapezoid nucleus (RTN) CO2-sensitive neurons in rats." J Physiol **572**(Pt 2): 503-523.

Tangel, D. J., W. S. Mezzanotte, E. J. Sandberg and D. P. White (1992). "Influences of NREM sleep on the activity of tonic vs. inspiratory phasic muscles in normal men." J Appl Physiol **73**(3): 1058-1066.

Tanskanen, P., J. Kytta and T. Randell (1997). "The effect of patient positioning on dynamic lung compliance." Acta Anaesthesiologica Scandinavica **41**(5): 602-606.

Teerapraipruk, B., N. Chirakalwasan, R. Simon, P. Hirunwiwatkul, N. Jaimchariyatam, T. Desudchit, N. Charakorn and C. Wanlapakorn (2012). "Clinical and polysomnographic data of positional sleep apnea and its predictors." Sleep & breathing = Schlaf & Atmung **16**(4): 1167-1172.

Teran-Santos, J., A. Jimenez-Gomez and J. Cordero-Guevara (1999). "The association between sleep apnea and the risk of traffic accidents. Cooperative Group Burgos-Santander." N Engl J Med **340**(11): 847-851.

Tregear, S., J. Reston, K. Schoelles and B. Phillips (2009). "Obstructive sleep apnea and risk of motor vehicle crash: systematic review and meta-analysis." J Clin Sleep Med **5**(6): 573-581.

Trinder, J., N. Allen, J. Kleiman, V. Kralevski, D. Kleverlaan, K. Anson and Y. Kim (2003). "On the nature of cardiovascular activation at an arousal from sleep." Sleep **26**(5): 543-551.

Van de Graaff, W. B. (1988). "Thoracic influence on upper airway patency." J Appl Physiol **65**(5): 2124-2131.

Vincken, W., C. Guilleminault, L. Silvestri, M. Cosio and A. Grassino (1987). "Inspiratory muscle activity as a trigger causing the airways to open in obstructive sleep apnea." Am Rev Respir Dis **135**(2): 372-377.

Walsh, J. H., M. S. Leigh, A. Paduch, K. J. Maddison, J. J. Armstrong, D. D. Sampson, D. R. Hillman and P. R. Eastwood (2008). "Effect of body posture on pharyngeal shape and size in adults with and without obstructive sleep apnea." Sleep **31**(11): 1543-1549.

Wanger, J., J. L. Clausen, A. Coates, O. F. Pedersen, V. Brusasco, F. Burgos, R. Casaburi, R. Crapo, P. Enright, C. P. van der Grinten, P. Gustafsson, J. Hankinson, R. Jensen, D. Johnson, N. Macintyre, R. McKay, M. R. Miller, D. Navajas, R. Pellegrino and G. Viegi (2005). "Standardisation of the measurement of lung volumes." Eur Respir J **26**(3): 511-522.

Washko, G. R., C. R. O'Donnell and S. H. Loring (2006). "Volume-related and volume-independent effects of posture on esophageal and transpulmonary pressures in healthy subjects." J Appl Physiol (1985) **100**(3): 753-758.

Watson, R. A. and N. B. Pride (2005). "Postural changes in lung volumes and respiratory resistance in subjects with obesity." Journal of Applied Physiology **98**(2): 512-517.

Watson, R. A., N. B. Pride, E. L. Thomas, J. Fitzpatrick, G. Durighel, J. McCarthy, S. X. Morin, P. W. Ind and J. D. Bell (2010). "Reduction of total lung capacity in obese men: comparison of total intrathoracic and gas volumes." Journal of Applied Physiology **108**(6): 1605-1612.

Weaver, T. E. and R. R. Grunstein (2008). "Adherence to continuous positive airway pressure therapy: the challenge to effective treatment." Proc Am Thorac Soc **5**(2): 173-178.

Weaver, T. E., G. Maislin, D. F. Dinges, T. Bloxham, C. F. George, H. Greenberg, G. Kader, M. Mahowald, J. Younger and A. I. Pack (2007). "Relationship between hours of CPAP use and achieving normal levels of sleepiness and daily functioning." Sleep **30**(6): 711-719.

Weaver, T. E., C. Mancini, G. Maislin, J. Cater, B. Staley, J. R. Landis, K. A. Ferguson, C. F. George, D. A. Schulman, H. Greenberg, D. M. Rapoport, J. A. Walsleben, T. Lee-Chiong, I. Gurubhagavatula and S. T. Kuna (2012). "Continuous positive airway pressure treatment of sleepy patients with milder obstructive sleep apnea: results of the CPAP Apnea Trial North American Program (CATNAP) randomized clinical trial." Am J Respir Crit Care Med **186**(7): 677-683.

Wellman, A., D. J. Eckert, A. S. Jordan, B. A. Edwards, C. L. Passaglia, A. C. Jackson, S. Gautam, R. L. Owens, A. Malhotra and D. P. White (2011). "A method for measuring and modeling the physiological traits causing obstructive sleep apnea." J Appl Physiol **110**(6): 1627-1637.

Wellman, A., B. A. Edwards, S. A. Sands, R. L. Owens, S. Nemati, J. P. Butler, C. L. Passaglia, A. C. Jackson, A. Malhotra and D. P. White (2013). "A simplified method for determining phenotypic traits in patients with obstructive sleep apnea." J Appl Physiol.

Wellman, A., P. R. Genta, R. L. Owens, B. A. Edwards, S. A. Sands, S. H. Loring, D. P. White, A. C. Jackson, O. F. Pedersen and J. P. Butler (2014). "Test of the Starling resistor model in the human upper airway during sleep." J Appl Physiol (1985): jap 00259 02014.

Wellman, A., A. S. Jordan, A. Malhotra, R. B. Fogel, E. S. Katz, K. Schory, J. K. Edwards and D. P. White (2004). "Ventilatory control and airway anatomy in obstructive sleep apnea." American Journal of Respiratory & Critical Care Medicine **170**(11): 1225-1232.

Wellman, A., A. Malhotra, R. B. Fogel, J. K. Edwards, K. Schory and D. P. White (2003). "Respiratory system loop gain in normal men and women measured with proportional-assist ventilation." J Appl Physiol **94**(1): 205-212.

Wellman, A., A. Malhotra, A. S. Jordan, K. E. Stevenson, S. Gautam and D. P. White (2008). "Effect of oxygen in obstructive sleep apnea: role of loop gain." Respir Physiol Neurobiol **162**(2): 144-151.

Wheatley, J. R., W. S. Mezzanotte, D. J. Tangel and D. P. White (1993). "Influence of sleep on genioglossus muscle activation by negative pressure in normal men." Am Rev Respir Dis **148**(3): 597-605.

Wheatley, J. R., D. J. Tangel, W. S. Mezzanotte and D. P. White (1993). "Influence of sleep on alae nasi EMG and nasal resistance in normal men." J Appl Physiol (1985) **75**(2): 626-632.

Wheatley, J. R., D. J. Tangel, W. S. Mezzanotte and D. P. White (1993). "Influence of sleep on response to negative airway pressure of tensor palatini muscle and retropalatal airway." J Appl Physiol (1985) **75**(5): 2117-2124.

White, D. P. and M. K. Younes (2012). "Obstructive sleep apnea." Compr Physiol **2**(4): 2541-2594.

Widdicombe, J. (2001). "Airway receptors." Respir Physiol **125**(1-2): 3-15.

Widdicombe, J. G. (1954). "Respiratory reflexes excited by inflation of the lungs." J Physiol **123**(1): 105-115.

Wiegand, D. A., B. Latz, C. W. Zwillich and L. Wiegand (1990). "Upper airway resistance and geniohyoid muscle activity in normal men during wakefulness and sleep." J Appl Physiol **69**(4): 1252-1261.

Wiegand, L., C. W. Zwillich and D. P. White (1989). "Collapsibility of the human upper airway during normal sleep." J Appl Physiol (1985) **66**(4): 1800-1808.

World Health Organization. (2000). Obesity : preventing and managing the global epidemic : report of a WHO consultation. Geneva, World Health Organization.

Worsnop, C., A. Kay, R. Pierce, Y. Kim and J. Trinder (1998). "Activity of respiratory pump and upper airway muscles during sleep onset." J Appl Physiol (1985) **85**(3): 908-920.

Yap, J. C., R. A. Watson, S. Gilbey and N. B. Pride (1995). "Effects of posture on respiratory mechanics in obesity." Journal of Applied Physiology **79**(4): 1199-1205.

Younes, M. (2003). "Contributions of upper airway mechanics and control mechanisms to severity of obstructive apnea." American Journal of Respiratory & Critical Care Medicine **168**(6): 645-658.

Younes, M. (2004). "Role of arousals in the pathogenesis of obstructive sleep apnea." Am J Respir Crit Care Med **169**(5): 623-633.

Younes, M., M. Ostrowski, R. Atkar, J. Laprairie, A. Siemens and P. Hanly (2007). "Mechanisms of breathing instability in patients with obstructive sleep apnea." J Appl Physiol (1985) **103**(6): 1929-1941.

Younes, M., M. Ostrowski, W. Thompson, C. Leslie and W. Shewchuk (2001). "Chemical control stability in patients with obstructive sleep apnea." Am J Respir Crit Care Med **163**(5): 1181-1190.

Young, T., M. Palta, J. Dempsey, J. Skatrud, S. Weber and S. Badr (1993). "The occurrence of sleep-disordered breathing among middle-aged adults." N Engl J Med **328**(17): 1230-1235.

Young, T., P. E. Peppard and D. J. Gottlieb (2002). "Epidemiology of obstructive sleep apnea: a population health perspective." Am J Respir Crit Care Med **165**(9): 1217-1239.

Young, T., J. Skatrud and P. E. Peppard (2004). "Risk factors for obstructive sleep apnea in adults." JAMA **291**(16): 2013-2016.

APPENDIX 1

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CLINICAL REVIEW

Supine position related obstructive sleep apnea in adults: Pathogenesis and treatment

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SUMMARY

The most striking feature of obstructive respiratory events is that they are at their most severe and frequent in the supine sleeping position: indeed, more than half of all obstructive sleep apnea (OSA) patients can be classified as supine related OSA. Existing evidence points to supine related OSA being attributable to unfavorable airway geometry, reduced lung volume, and an inability of airway dilator muscles to adequately compensate as the airway collapses. The role of arousal threshold and ventilatory control instability in the supine position has however yet to be defined. Crucially, few physiological studies have examined patients in the lateral and supine positions, so there is little information to elucidate how breathing stability is affected by sleep posture.

The mechanisms of supine related OSA can be overcome by the use of continuous positive airway pressure. There are conflicting data on the utility of oral appliances, while the effectiveness of weight loss and nasal expiratory resistance remains unclear. Avoidance of the supine posture is efficacious, but long term compliance data and well powered randomized controlled trials are lacking. The treatment of supine related OSA remains largely ignored in major clinical guidelines.

Supine OSA is the dominant phenotype of the OSA syndrome. This review explains why the supine position so favors upper airway collapse and presents the available data on the management of patients with supine related OSA.

Introduction

Obstructive sleep apnea (OSA) affects almost one fifth of the adult population[1] in whom it is associated with excessive sleepiness,[2] depression,[3] systemic hypertension,[4,5] the metabolic syndrome,[6] insulin resistance[7] and subsequent cardiac ischemia and arrhythmias.[8]

Within the OSA spectrum, the condition is particularly severe when subjects adopt the supine sleeping position and may occur almost exclusively in this position. Despite important and comprehensive reviews of supine sleep apnea,[9] how the supine position interacts with upper airway anatomy, lung volume, function of upper airway dilator muscles, arousal threshold and ventilatory control instability to bring about upper airway collapsibility is poorly understood. Very few of these physiological parameters have been studied comprehensively in both the lateral and supine sleeping positions to see how they may be affected by moving position.

The high prevalence and severity of OSA in the supine sleeping position has led to the development of a number of treatment strategies for this phenotype of the OSA syndrome. Treatments may be similar to those used in the general sleep apnea population or focus on methods to discourage sleeping supine.

There are still a number of areas where our understanding of supine related OSA is lacking. Longitudinal studies of the effects of supine OSA versus non-supine OSA on morbidity and mortality, physiological studies that observe patients in both the lateral and supine position, and adequately powered randomized controlled trials for the treatment of the condition, are potential foci for future research.

Aim

We review the available evidence relating to the pathogenesis and treatment of supine related obstructive sleep apnea.

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Definitions

The definition used to classify patients with a preponderance of respiratory events in the supine position has varied. Many authors consider that supine OSA is present when the apnea and hypopnea index (AHI) is greater than 5 events/h and respiratory events occur at twice the frequency in the supine sleeping position compared to the non-supine sleeping positions.[10,11] A majority of the papers focusing on the diagnosis and treatment of supine related OSA have adopted this definition.

Mador et al.[12] proposed an alternative definition of supine OSA whereby the ratio of events in the supine position to the non-supine positions must be greater than two to one and the AHI in the non-supine positions must be less than 5 events/h. The authors felt this definition was more clinically relevant given that avoidance of the supine sleeping position by patients who fit this description would result in normalization of the AHI and subsequent relief of symptoms of OSA. The Mador definition has been adopted and modified for use in some studies of treatment of positional OSA by avoidance of supine sleep.[13,14]

For clarity in this paper we will use the following definitions:

1) Supine predominant obstructive sleep apnea (spOSA):
   - Overall AHI is greater than 5 events/h, and,
   - The supine AHI is greater than two times the non-supine AHI.
2) Supine isolated obstructive sleep apnea (siOSA):
   - Overall AHI is greater than 5 events/h, and,
   - The supine AHI is greater than two times the non-supine AHI and,
   - Non-supine AHI is less than 5 events/h.

The time that a patient spends in a specific body position can have an important effect on the AHI in that position.[15,16] The vast majority of the papers in the published literature relating to supine OSA describe a minimum time required in the supine position as an inclusion/exclusion criterion. Typically the minimum time required in the supine and non-supine positions to be included in these studies is between 15 and 30 min.[11–13,17,18] The decision to have a time cut off for the definition of supine sleep apnea is an arbitrary one and the effect of changing the definition to shorter or longer time periods is not known.

Both of the aforementioned definitions are widely used throughout the literature regarding supine OSA. Neither definition, however, acknowledges the potentially confounding role of rapid eye movement (REM) sleep in the generation of obstructive events. It is already well established that the supine AHI rises in REM sleep compared with non-rapid eye movement (NREM) sleep.[19] It follows then, that a disproportionate time spent in the supine sleeping position in REM sleep will increase the likelihood of a patient being classified as having spOSA even if the ratio of events in NREM sleep (which makes up the majority of the night) is less than two to one. This may be an important distinction to make if the mechanisms involved in obstruction in REM sleep are different to those in supine sleep.

Epidemiology

Prevalence

The prevalence of spOSA is variably reported as between 50 and 60% of patients who present to sleep clinics for overnight polysomnography,[11,17,18,20] whereas approximately 25–30% of the same population may be classified as having siOSA.[12,17,21] The prevalence of spOSA in the Asian population is higher than for Caucasians at between 67 and 75%.[22,23] There are no reports of the prevalence of either condition in the general population.

Time spent supine

The time in which a subject sleeps supine is an important determining factor of the overall AHI in patients with spOSA and siOSA. Having spOSA or siOSA does not influence the amount of time spent supine as these patients appear to spend as much time in the supine position as unselected patients with OSA,[17] ranging from 32 to 42.7% of total sleep time[17,18,20,24] for spOSA, 40–48.1% for siOSA[12,21] and 27–48% of total sleep time for patients with non-positional obstructive events.[17,18,20,21,24]

Age and gender also do not influence the time spent supine. With increasing age, fewer position shifts are made over the course of the night,[25] although the time spent supine in a small cross-sectional study did not change markedly across a series of age ranges (apart from early childhood).[25] O'Connor et al. demonstrated that men and women spend a similar amount of time supine during sleep.[26] The amount of time spent in supine sleep in unselected general populations is not known.

The published studies relating to the classification and polysomnographic features of supine OSA are largely based on single night observations. Although the correlation of overall AHI across nights is strong,[27] there is a considerable individual variability in overall AHI using Bland-Altman analysis.[28] It is unclear how much variability in time spent supine contributes to this night-to-night variability in total AHI. Several studies have explored the possible contributors to night-to-night variability in overall AHI,[29–31] including various polysomnographic and demographic features. Although the mean AHI in specific body positions and sleep stages does not change significantly across nights,[28] the individual variability of the position specific AHI from night-to-night has not been reported.

Clinical features

Like OSA in general, spOSA is more likely to be seen in men than women. The male to female ratio is 11.1:1 for all severities of OSA,[26] and 2.6:1 in mild-moderate OSA,[17] with the discrepancy between these figures likely arising from the increased male prevalence of severe OSA.[26]

Patients with spOSA differ from non-positional patients: their body mass index (BMI) is less at 29.3–31.6 kg/m^2 [11,12,17] versus 31.9–38 kg/m^2,[11,12,18] and their ages differ at 49.5 - 52.9 y[11,17] versus 54.9-59.2 y.[11,12] These differences in BMI and age hold true for siOSA patients compared to non-positional patients,[12] even when controlling for the lower overall AHI found in the siOSA group.[17]

One of the most common presentations to the sleep physician is loud snoring. It has long been recognized by patients and their partners that the loudness of snoring is worse when supine.[32] As distinct from OSA, simple snoring without apnea is louder and more frequent in the supine sleeping position.[33] The distinction between simple snoring and spOSA and siOSA is an important one in the context of body position and the goals of treatment. As discussed in the treatment section of this article, positional therapies for siOSA and spOSA may not reduce complaints of snoring,[13] unless the snoring is louder or occurs predominantly in the supine position.

Supine predominant patients have been reported as subjectively more sleepy[17] than other OSA patients, whereas with siOSA patients no differences are reported.[12] Conversely, with regard to objective determinants of sleepiness, multiple sleep latency test (MSLT) data from Oksenberg et al.[11] demonstrate a trend toward reduced sleepiness in spOSA patients compared to non-positional

OSA patients, although these data are confounded by the fact that the non-positional patients had more severe OSA (respiratory disturbance index in the non-positional group of 44.0 events/h versus 27.8 events/h in the spOSA group, $p < 0.05$).

Obstructive events observed on polysomnographic recordings are more severe in the supine position.[34] In patients with severe non-positional OSA, apnea duration and degree of oxygen desaturation are both more severe when the patients are observed in the supine sleeping position.[34] The typical polysomnographic features of non-positional and positional OSA patients are demonstrated in Fig. 1.

Recording of position

Despite the clear influence of the supine position on OSA, there are surprisingly few data as to how body position is recorded and the accuracy of body position sensors is unknown. Early studies on the effect of body position on sleep disordered breathing used direct observation and recording overnight[10,18] and video recording with manual recording of position.[25] Using video recording it has been shown that the time spent supine may be over-estimated in a sleep laboratory because of the restriction on movement by the polysomnographic instrumentation used.[35] Later studies use position sensors with or without correction using video monitoring. The American Academy of Sleep Medicine manual for the scoring of sleep and associated events contains little information on the scoring of body position during sleep. The sole recommendation is for a signal acquisition frequency of 1 Hz.[36] Very few studies have compared the accuracy of the various trunk position sensors in use with video monitoring. Furthermore, head and neck position can influence AHI independent of trunk position,[37] and there is likely to be a continuous relationship between the degree of supine versus lateral trunk position and AHI[38] – two additional factors which are not recorded by standard trunk position sensors, which tend to treat body position as a categorical variable. The issue here is that handling all possible trunk sleeping positions as either supine or non-supine ignores the likely graded effect of trunk rotation from supine to lateral on the collapsibility of the upper airway.

Pathogenesis

OSA is characterized by recurrent obstruction of the upper airway during sleep. Several mechanisms have been identified in the generation of upper airway obstruction, including passive airway characteristics as determined by anatomical structures and the pharyngeal critical closing pressure (PCrit), the role of lung volume and tracheal tug, the action of airway dilator muscles such as genioglossus, ventilatory control instability and arousal threshold (see Fig. 2). These factors may be understood as interacting to varying degrees in patients across the night.[39] By evaluating the effect of the supine body position on each of these factors it may be possible to understand why a given patient obstructs more frequently and with greater severity in the supine compared to the lateral position. It is important to acknowledge that the majority of data presented here has been collected from male subjects, which is a deficit in the OSA literature in general.

Gravity

Before discussing each of the pathogenic mechanisms of supine related OSA it is important to recognize the effect of gravity on the respiratory system. A change of body position from lateral to supine results in a 90° long axis shift in the directional effect of gravity on the structures of the respiratory system which is likely to underpin many of the physiological changes observed when moving from one position to another. This is supported by a small study of weightlessness on the AHI in astronauts.[40] During this study it was observed that the AHI in zero gravity was lower than when recordings were made in standard gravity. The authors of this paper attributed the observation to changes of zero gravity on upper airway structures rather than lung volume and this is supported by a later study demonstrating that lung volume does not change significantly in zero gravity compared to standard gravity.[41] Interestingly, this study demonstrated a significant change in lung volume when changing position from upright to supine or 30° tilt under the conditions of standard gravity.

Airway anatomy

A number of anatomical features of the upper airway contribute to obstruction in OSA patients. Ultimately, airway lumen size and shape and anatomical propensity to collapse are determined by the interaction between a number of factors such as the size of the bony enclosure (mandible, maxilla, cervical spine),[42] the size of the soft tissues (tongue, soft palate, lateral pharyngeal fat pads)[43] and the shape and folding characteristics of the airway.[44]

The narrowest site of the airway in normals and OSA patients is generally accepted to be the velopharynx.[45,46] Contributors to narrowing of the velopharynx in OSA subjects include the tongue, soft palate and lateral pharyngeal fat pads.[43] Given the propensity for collapse in the supine sleeping position several studies have imaged the upper airway in detail in the seated, lateral and supine

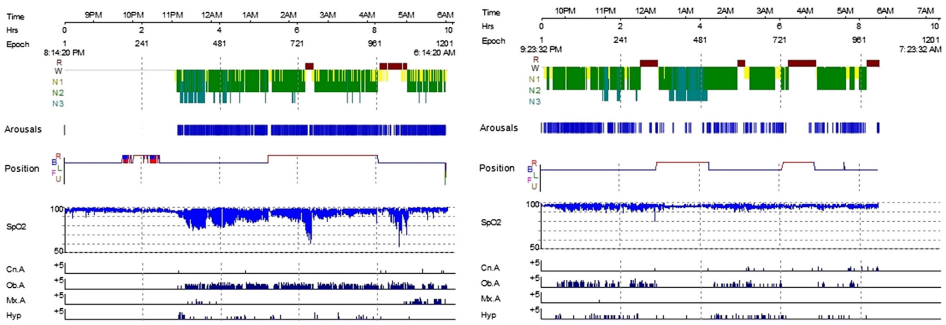

Fig. 1. PSG montage of non-positional (left) and positional (right) patients.

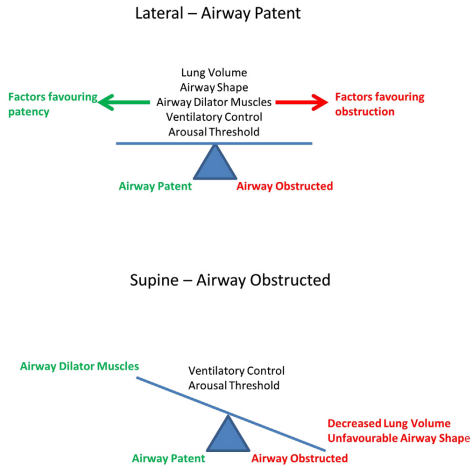

Fig. 2. Physiological changes from the lateral sleeping position to the supine sleeping position. This figure demonstrates the decrease in total lung capacity when moving from the upright to supine position. The decrease is largely a result of a fall in vital capacity and expiratory reserve volume. Abbreviations: ERV, expiratory reserve volume; IRV, inspiratory reserve volume; RV; residual volume; TLC, total lung capacity; TV, tidal volume; VC vital capacity.

position in order to examine the effect of gravity on the soft tissue structures and relationship of the bony enclosures. The literature is somewhat conflicting with regard to anatomical changes from lateral to supine, which is likely to represent differences in methodologies regarding imaging modality and acquisition of orthogonal images, head and neck position, controlling for phase of respiration, sleep state of the subjects and the population under examination.

Normal subjects have a significant decrease in pharyngeal cross-sectional area (CSA) when moving from seated to supine but not from lateral to supine.[47] When unselected OSA patients move from lateral to supine some studies demonstrate no significant change in CSA,[47–50] while others show a small but significant change.[42,51] Technical differences are likely to explain the different findings including the use of anesthetic, ventilation of the patients, and direct endoscopic examination with conversion of maximal CSA images to measurements based on pixel sizes[42] and the averaging of CSA over a number of breaths.[51] Both positional and non-positional sleep apnea patients have an elliptically shaped airway in the supine position with the long axis oriented laterally.[46,48,49,52] By contrast, there is evidence that some patients with severe non-positional OSA have an elliptically shaped airway that is oriented in the antero-posterior direction.[53,54] Once again, the patients selected, the imaging modalities utilized and the methodology applied were widely varied across papers. Importantly, studies that select for spOSA or siOSA subjects, use matched controls, or image subjects both supine and lateral while asleep are lacking. Controlling for the phase of respiration is also important.

The relationship of the bony enclosure of the upper airway is an important determinant for how the soft tissues of the upper airway contribute to lumen narrowing.[42] Clearly the starting configuration of the bony enclosure as encompassed by size and orientation of the maxilla, mandible and cervical spinal column are important. Patients with supine OSA (defined as supine AHI greater than two times lateral AHI and lateral AHI less than 15 events/h in this case) have been shown to have a relatively small craniofacial volume on three-dimensional magnetic resonance imaging (MRI) modeling compared to age and BMI matched non-positional patients.[55] The small volume likely results from the lower facial height and more backward position of the jaw in positional patients.[55] The relationship between bony structures enclosing the upper airway may change through either alteration in neck flexion or mandibular opening in order to change patency of the lumen.[56] Although movement of the mandible during sleep has been studied, somewhat surprisingly, sleep stage rather than body position was found to have a larger effect on mandibular opening in normal subjects.[57] Further investigation of the dynamic jaw and neck movements of patients with spOSA and siOSA during supine and lateral sleep are required to clarify the contribution of the bony enclosure to these forms of OSA.

From a purely anatomical perspective, differences in airway shape rather than CSA may be more important in generation of airway obstruction in the supine rather than the lateral sleeping position in patients with spOSA and siOSA. Advanced models of the upper airway utilizing flow-field computations analysis, and modified Starling-resister models where tissue compliance is accounted for, may help to explain this observation.[44,58] Amatoury et al. report that the airway folding characteristics may be more important than CSA in causing obstruction.[44] In terms of geometry, flow-field computation analysis has demonstrated that changes in soft palate displacement and side wall deformation (e.g., with the more elliptical airway shape of the supine position) may generate altered pressure gradients in the velopharynx and therefore increase the propensity to collapse.[58] This modeling is particularly interesting as it not only demonstrates how shape may predispose to collapse, but also supports the observation that increasing lateral pharyngeal fat pad size increases risk of OSA[43] – lateral low pressure areas are steepened as the airway is narrowed by enlarging the side walls.[58] Another avenue by which airway shape may affect airway function is through modulation of the effectiveness of upper airway muscles such as genioglossus[59] – the function of which is examined subsequently.

Pharyngeal critical closing pressure (PCrit)

The PCrit of the upper airway quantifies the overall collapsibility of the upper airway in a given patient[60] and is widely considered a superior measurement to static imaging and measurements of resistance. The measurement can be made while patients are asleep and can be repeated over the course of the night in different body positions.[61] The technique of PCrit measures the pressure of the upper airway at which collapse and obstruction occur, with a more positive measurement indicating a more collapsible airway.

In contrast to the imaging literature, the PCrit literature is more consistent when examining changes from lateral to supine body position. Several studies have demonstrated a more positive PCrit (and therefore more collapsible airway) in the supine position compared to the lateral position in male OSA patients.[61–64] The difference in PCrit is typically in the order of 2.2–2.9 cmH_2O in OSA patients in NREM sleep,[61,63,64] although a larger difference was found in anesthetized OSA patients.[42] Importantly, there are no published data on how PCrit changes from lateral to supine specifically in spOSA patients or siOSA compared to non-positional OSA patients or controls. It seems highly likely these patients would have an even greater positional change in PCrit compared to unselected OSA patients. Factors leading to the decrement in PCrit in the supine position are a less favorable airway shape (as discussed above) and a reduced lung volume.[65]

The influence of head, neck and jaw position on PCrit and the severity of OSA in spOSA and siOSA patients are unknown. As there

is no standardized way of recording head, neck and jaw position on overnight polysomnography these parameters are largely ignored, despite their known effect on the collapsibility of the upper airway in normal subjects.[62,66,67]

Lung volume

Lung volume is an important variable in sleep apnea as it is known to influence upper airway stability, in normal subjects[68,69] and OSA patients,[70] via caudal tracheal displacement and subsequent changes in upper airway tissue pressure, as demonstrated in dog, cat and rabbit models.[71–73]

Lung volume is reduced significantly both with increasing BMI and on adopting the supine position. When normal subjects move from upright to supine there is a fall in functional residual capacity (FRC),[74–77] total lung capacity (TLC), expiratory reserve volume (ERV) and vital capacity (VC) without a change in residual volume (RV),[77] see Fig. 3. Few studies address the effect of lateral positioning on lung volume, but in normal subjects ERV[75] and FRC[78,79] fall and dynamic lung compliance increases[80] when moving from the lateral to the supine position.

When moving from upright to supine FRC falls in overweight patients with OSA.[81] A cross-sectional study of seated lung volumes demonstrated a linear decrease of TLC with increasing BMI,[82] although the values did not lie outside the predicted range. However, ERV and FRC decreased exponentially with increasing BMI over the 25–30 kg/m^2 range,[82] which corresponds closely to the mean BMI of supine predominant OSA patients.[17] This study supports the possibility of a BMI dependent interaction with lung volume in subjects up to a BMI of 30 kg/m^2. The lung volume changes within this range of BMIs may be secondary to increasing abdominal fat distribution and increasing intra-abdominal pressure, which has been shown to influence FRC in anesthetized obese individuals.[83] By contrast, the FRC does not fall in the morbidly obese (BMI $>$ 40 kg/m^2) when moving from upright to supine.[84,85] The balance of elastic forces of the lung and chest wall in these patients gives rise to lower lung volumes. As a result, FRC and ERV[86] are smaller than predicted in the seated posture, but change less compared to non-obese controls when adopting the supine position[84,85] as the morbidly obese are already breathing at, or near, RV in the upright posture. Lung volume changes when moving from lateral to supine in the obese have not been studied.

A number of studies have examined the effects of changes in lung volume on upper airway stability in subjects lying supine during sleep.[65,69,87–89] In 19 young normal subjects, reductions of 600 mL in end expiratory lung volume (EELV), as measured with magnetometers, increase PCrit by 1.1 cmH_2O (rendering the airway more collapsible) despite an increased activation of genioglossus.[69] Tagaito et al. demonstrated the same interaction between lung volume and PCrit in reverse. In seven OSA patients Tagaito et al. increased lung volume by 720 mL which resulted in a fall in PCrit by 1.2 cmH_2O[89]; importantly this effect was independent of upper airway neuromuscular input as patients were anesthetized and paralyzed. Stadler et al.[90] increased the intra-abdominal pressure in 15 obese (BMI 34.5 kg/m^2) male OSA patients while sleeping in the supine position by inflating a pressure cuff around the abdomen. As a result, EELV fell by 530 mL and PCrit increased by 1.4 cmH_2O. This paper ties in the potential interaction between increasing BMI, decreasing lung volume and increasing collapsibility of the upper airway.

There are no published studies that investigate the effect of moving from the lateral to the supine body position on the *interaction* between EELV and PCrit, either in OSA patients in general or in selected OSA phenotypes such as spOSA.

Upper airway dilator muscle function

The ability of upper airway dilator muscles, in particular genioglossus, to compensate in the face of collapsing forces is a key determinant of upper airway patency. Patients with OSA have increased baseline genioglossus activity,[91] most likely in compensation for unfavorable airway size and shape and reduced lung volume with resultant increased PCrit. The activity of genioglossus decreases at sleep onset[92] and subsequent increases in its activity while asleep can help protect against obstruction.[88] The variable activity of genioglossus while asleep helps explain why some patients experience obstructive events at different times during the night.[93]

Body position is known to have a significant influence on the function of genioglossus, as does the route of breathing.[94] Takahashi et al. demonstrated that genioglossus activity was increased in oral as compared to nasal breathing. Genioglossus activity is greater in the supine compared to both the upright[94–97] and the lateral position in both normals[97] and OSA patients.[98] The magnitude of this compensatory response has not been quantified in patients with spOSA or siOSA compared to other OSA patients or controls.

Thus the activity of genioglossus is increased in the supine position to protect the airway when it is at its most vulnerable and when the muscle is likely to have maximal beneficial effect; that is, when lying supine, tongue protrusion secondary to genioglossus contraction will maximally enhance upper airway caliber. The responsible mechanism by which genioglossus is activated in the supine position is not entirely clear, but stimulating the vestibular apparatus results in augmented genioglossus electromyogram (EMG) activity in cats.[99] Additionally, when the subjects in the Otsuka et al. study lay with the trunk supine but with the head rotated laterally the genioglossus EMG activity was not significantly different from when the subjects were lying in the lateral

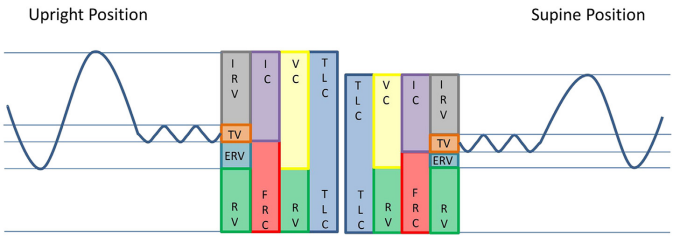

Fig. 3. Lung volume changes from upright to supine.

recumbent position (both head and trunk oriented laterally).[97] In both of these positions the vestibular apparatus is oriented in the same plane, and the observed muscle response is of similar magnitude.

It is not clear if the genioglossus response in patients lying supine is attenuated in spOSA compared to other forms of OSA or controls, as no studies have addressed this particular group. It may be that the muscle does not activate sufficiently to compensate for other unfavorable physiology in the supine position and it would be possible to measure this by comparing the genioglossus EMG response to a position change from lateral to supine.

Ventilatory control

Disturbances of the ventilatory control system could contribute to the pathogenesis of OSA by creating excessive responses in pump and resistance muscles to respiratory disturbances. Such high loop gain states create oscillations in drive to the respiratory muscles and thereby favor upper airway collapse when drive is at its minimum. Ventilatory control instability will predispose to obstruction in patients with a susceptible airway, for instance one with a PCrit close to atmospheric pressure.[100]

The effect of body position on ventilatory control instability in OSA patients has not been studied. However, with respect to central sleep apnea a number of studies have demonstrated a worsening of Cheyne-Stokes respiration in patients with cardiac disease when lying in the supine position compared to the lateral position.[101,102] Reduced lung volume with adoption of the supine position has been postulated as the cause of the high loop gain and subsequent respiratory instability,[101,102] although change in lung volume in this patient group has not been directly measured and is disputed by some.[103]

The overall contribution of ventilatory control instability to the generation of obstructive respiratory events in the supine compared to lateral position is not known. It may be that the reduced lung volume seen in the supine position contributes to ventilatory instability via an increased plant gain in some OSA patients, but this remains to be proven.

Arousal threshold

Arousal from sleep is protective in OSA as it allows resolution of obstructive respiratory events and re-instatement of ventilation. However, given that a significant proportion of patients are able to achieve stable flow limited breathing through recruitment of upper airway dilator muscles,[93] arousal from sleep is not essential to terminate an obstructive event. In patients with a low arousal threshold the arousal response itself may potentially be maladaptive as it can exacerbate instability and worsen OSA. Pharmacological manipulation of the arousal threshold is now being considered as a means to improve the severity of sleep disordered breathing in these patients.[104]

The key initiating stimulus to arousal in OSA is thought to be respiratory effort, as measured by esophageal pressure (Pes).[105] One may hypothesize that a higher Pes is generated in supine sleep as the subject tries to overcome the reduced lung volume in the supine position, however the threshold response to rising Pes has also not been compared in the lateral and supine position. It has been observed that respiratory events are more severe in the supine position both in duration and level of oxygen desaturation. Whether it simply takes longer to overcome the unfavorable physiology of the supine position or if arousal threshold rises in the supine position to permit more severe OSA is not clear. More basic research is required to elucidate the effect of body position on arousal threshold in OSA patients.

Treatment

The treatment of spOSA and siOSA can be divided into two broad categories: treatments that focus on avoidance of the supine sleeping position and treatments that have been used generally in the management of OSA. Although a number of papers have addressed the efficacy of these various treatment forms, the studies are generally underpowered and long term efficacy and follow-up data are lacking. In addition, some studies are weakened by a lack of control of the time spent supine in pre- and post-treatment sleep studies and the subsequent effect this has on overall AHI, which is often used as an outcome measure.

Supine sleep avoidance

If sleep disordered breathing is worse in the supine position then it follows that avoidance of supine sleep should improve the AHI, especially if the non-supine AHI is not elevated (for example, in patients with siOSA). Several strategies have been tested in aiding avoidance of supine sleep with varying success as reviewed recently.[106] Determinants of effectiveness include efficacy at avoiding the supine position and the lateral AHI of the subjects selected. However, the extent of lateral trunk rotation achieved by the treatment, as well as the head and neck position are further important factors which are often overlooked. Using response surface analysis, Lee et al.[107] have shown that in 25 spOSA patients that the optimal position for avoidance of spOSA is greater than 40° lateral rotation with greater than 70 mm of cervical heat tilt support and an elevation underneath the scapula of 30 mm.

The "tennis-ball technique" is often reported by clinicians as a relatively simple and cost-effective method of supine sleep avoidance. In this strategy a tennis ball is held over the patient's back either with a sling, a pocket sewn into a t-shirt or cloth belt. The rationale is that whenever patients roll onto their back the discomfort of lying on the tennis-ball forces them to roll onto their side. Oksenberg et al.[108] recruited 12 spOSA patients who had refused continuous positive airway pressure (CPAP) therapy and applied a cloth belt which held a tennis ball in the middle of the subjects' back and repeated the polysomnogram with the device in situ. Time spent supine reduced from 79% on the diagnostic night to 12.3% on the treatment night – leading to a reduction in overall AHI from 46.5 events/h to 17.5 events/h. Interestingly, the average of 79% supine sleep in the diagnostic study is much higher than in most other reported studies[17,18,20,21,24] and may have led to an overstatement of the treatment effect. In another study, Skinner et al.[109] conducted a randomized cross-over trial comparing a modified tennis-ball technique to CPAP in 20 positional OSA patients. The patients were diagnosed with mild-moderate OSA and selected on the basis of twice as many events in the supine sleeping position and a non-supine AHI of <10 events/h. Although there were no differences in Epworth sleepiness scores (ESS) or Functional Outcomes of Sleep Questionnaire, CPAP was more effective at reducing the AHI (from a mean of 22.9 events/h in both groups prior to treatment to 4.9 events/h versus 12.0 events/h). In this study, the modified technique reduced supine sleeping from 34.4% to 6.3%. In addition to reducing time spent supine, the "tennis-ball technique" has been shown to reduce 24-h blood pressure in a small sample of patients with spOSA.[110] Thus long term treatment of supine related OSA could improve cardiovascular outcomes, although findings need to be replicated in a larger sample with a longer follow-up period.

The main problem with the simple "tennis ball technique" is poor short and long term adherence to treatment, primarily due to discomfort. In the Berger et al. study[110] 5/18 selected patients were unable to comply with the treatment over a one month period for

various reasons and in the Oksenberg et al. study,[108] only 38% of responders reported ongoing use of the technique at 6 mo. In another study of long term compliance with the tennis-ball technique, less than 10% of patients continued treatment after an average follow-up time of 30 mo.[111]

Because of the discomfort associated with the tennis-ball technique, and its variants, a number of other strategies to avoid supine sleep have been explored and have shown reasonably good short term success. Jokic et al.[112] conducted a randomized crossover trial comparing a positioning device with CPAP for a trial period of 2 wk each. The study included 13 patients with siOSA and the device consisted of a back pack with a large 30 cm semi-rigid foam cushion inside. The device prevented supine sleep in all patients although the authors report semi-supine sleep in some of the subjects. Both CPAP and the positional therapy were effective in reducing the overall AHI in these selected subjects, with CPAP being more effective. ESS, maintenance of wakefulness test (MWT) results, cognitive performance and mood were not significantly different between CPAP and positional therapy, although with small numbers a type 2 error cannot be excluded. Seven of the 13 patients preferred CPAP therapy. Loord and Hultcrantz[14] used a device called "the Positioner" in 23 patients with siOSA. The device consisted of a horizontal board placed under a pillow to which the patient is physically strapped by way of a tight fitting vest. Although effective at preventing supine sleep, five of the 23 could not tolerate the treatment. Interestingly, recordings of noise while using "the Positioner" in situ demonstrated an increase in snoring, the cause of which was not clear. In a similarly designed study, Zuberi et al.[113] demonstrated in 22 patients (19 of whom had mild-moderate OSA) that the use of a pillow that prevents supine sleep resulted in a reduction in AHI and snoring. Use of other simple pillows to avoid the supine position is likely to be quite prevalent but no data are available as to their effectiveness and comfort.

Permut et al.[114] recruited 38 siOSA patients and randomly assigned them to a night of CPAP or a positional device followed by a second night utilizing the other treatment. The device was worn around the chest and comprised a foam block embedded in a synthetic belt: its use reduced supine sleep from 40% to 0% and resulted in a reduced AHI that was equivalent to that achieved with CPAP usage. On a single night the device was very effective, however no long term compliance or efficacy data was collected. A less bulky device able to record time spent supine via an internal position-sensitive tilt switch was tested by Bignold et al.[13] The device is embedded within a belt strapped around the chest and whenever the patient moves supine a vibration is delivered to the sternum that alerts the patient and allows them to move to the lateral position. The device reduced the percentage of sleeping time spent supine from 36.4% to approximately 1% in positional OSA patients with a subsequent 45% reduction in AHI. The recording capabilities of the device allowed for objective measurements of compliance and demonstrated over a 3-wk period that the device was worn 85% of the time. Snoring was not reduced and bed partners reported increased disturbance. This raises an important issue that is likely to affect long-term compliance of all positioning devices – if the trigger to seek medical attention is disruptive snoring rather than other OSA symptoms, ongoing snoring (despite adequately treated OSA) is likely to lead to patient dissatisfaction with the treatment.

In summary, in selected patients with mild-moderate siOSA a number of body positioning devices are efficacious in the short term at reducing the time spent supine and, subsequently, the overall AHI. Some of these devices appear equivalent to CPAP in their ability to improve daytime symptoms of OSA and the overall AHI, but patient numbers in these studies have been very small. The devices used vary significantly in patient comfort and cost, do not resolve residual snoring in the lateral position, and there is no evidence of good long term compliance for any of the devices. Further research into the ongoing effectiveness and, in particular, long term compliance of body positioning devices is needed before their use could become more widespread.

Effect of general OSA treatments on supine OSA

A number of treatments developed for OSA have been trialled in the context of patients suffering from supine OSA. CPAP, oral appliances, nasal expiratory resistance therapy, surgery and weight loss have all been studied in the context of OSA and their application to the spOSA and siOSA population is reviewed here.

Continuous positive airways pressure

CPAP is the recommended first line treatment for moderate to severe OSA.[115] As discussed above, CPAP therapy has been compared to a number of positional therapies for spOSA. It is superior to most positional therapies at reducing the overall AHI, it resolves all snoring and has beneficial effects on a number of sleepiness and quality of life metrics. CPAP is preferred by patients to positioning devices in some studies[112] although the finding is not universal.[114] With regard to implementing fixed pressure CPAP therapy, it is critically important that patients are observed in the supine position while titrating the CPAP therapy in those with spOSA and siOSA. This enables a pressure to be selected which will treat the periods of most significant upper airway obstruction. An alternative approach to commencing CPAP therapy is to use ambulatory auto-titrating positive airway pressure (auto-PAP) therapy. Although no more effective than fixed pressure CPAP in unselected OSA patients,[116,117] auto-PAP may lead to better outcomes in spOSA.[118] Series and Marc[119] studied the effect of auto-PAP versus fixed pressure CPAP on patients with body specific or sleep stage dependent OSA. The outcomes studied were ESS, MWT and compliance. Over a 3-wk period, patients with sleep stage or supine predominant OSA treated with auto-PAP therapy performed better on MWT and ESS. Although the treatment period was short and a proportion of the data was historical, using the lowest possible CPAP pressure for each sleep stage or body position could lead to better treatment tolerance. However, this issue requires confirmation with further research before auto-PAP can be widely recommended ahead of fixed pressure CPAP for spOSA.

Oral appliances

A number of studies have demonstrated that oral appliances are particularly effective at treating obstructive events that occur in the supine position.[120–123] Supine dependent OSA is a predictor of treatment success with oral appliances in men[124] and patients with spOSA respond better to oral appliances compared with non-positional patients even when controlling for the overall AHI.[125] The mechanisms by which oral appliances improve supine OSA are likely related to improving the shape and size of the velopharynx[126–129] and augmenting the inspiratory related activity of the genioglossus muscle.[130] The finding of improvement in supine related respiratory events with application of oral appliances is not universal, however.[131] Potential sources of outcome differences include the criteria by which events were scored, the nature of the oral appliance and how it affected route of breathing and mouth opening and jaw position. As noted earlier, mouth opening can increase upper airway collapsibility.[62] Further research on the effect of oral appliances on supine OSA will need to account for these factors so that it may be

determined if certain types of oral appliance are more effective for supine sleep than others.

Weight loss

Significant weight loss has been associated with large improvements in AHI[132–134] although many of the published studies do not analyze the effect of weight loss on obstructive events occurring in the supine sleeping position. Kansanen et al.[135] demonstrated a significantly reduced oxygen desaturation index in the supine position without a significant change in the respiratory disturbance index in the supine position in a cohort of 15 overweight patients with severe OSA who undertook a three-month course of very low caloric intake. In a prospective randomized trial of weight loss in overweight patients with mild OSA, Tuomilehto et al.[136] demonstrated that the overall AHI was improved by weight loss. However, when analyzed according to body position the supine AHI did not change significantly with weight loss. Indeed, it was the non-supine AHI that reduced significantly and largely accounted for the change in overall AHI. This finding is supported by recent data from Oksenberg et al. who found that weight loss reduces the non-supine AHI while, conversely, weight gain increases the non-supine AHI.[137] These studies raise the likelihood that weight loss in patients with OSA preferentially reduces the non-supine AHI. Further work is needed to elucidate the mechanisms underlying this selective improvement in OSA.

Nasal expiratory resistance therapy

The application of a nasal expiratory resistance device has recently been shown to be efficacious in the treatment of OSA[138] and is effective in reducing the supine AHI.[139] Although it has not been applied specifically to patients with spOSA or siOSA it may be that patients with positional OSA respond more favorably to this form of treatment.[140] Given that the device is thought to increase end expiratory lung volume[141] it seems plausible that patients whose lung volume falls when supine may benefit the most from this sort of treatment. Further research of this new therapy in spOSA and siOSA phenotypes is needed to address this question.

Upper airway surgery

The importance of supine related obstructive events in the surgical literature has been noted[142] but there are few data published regarding the effect of upper airway surgery on the development of obstructive respiratory events in the supine sleeping position. Kwon et al.[143] have demonstrated that a uvula preserving uvulopalatopharyngeoplasty reduced the AHI in the supine position in patients with moderate and severe OSA, but further work is needed. Indeed, current recommendations by the American Academy of Sleep Medicine (AASM) highlight the lack of rigorous examination of the effectiveness of various surgical modalities in treating OSA overall.[144]

Combination treatment

The possibility of combining various treatment modalities has not been explored in the form of randomized controlled trials. The idea appeals in that supine avoidance and a second modality may benefit those patients with spOSA who have a residual non-supine AHI greater than 5 events/h or in whom residual snoring is an issue.

Conclusion

Many patients with OSA spend a substantial proportion of time sleeping in the supine position. Obstructive events are commonly more severe and frequent in the supine sleeping position and up to 60% of OSA patients can be classified as having supine predominant OSA. Given that spOSA and siOSA patients comprise the majority of patients with OSA it is surprizing that the long term sequelae of this patient cohort is unknown.

The mechanisms underlying the increased frequency and severity of OSA in the supine position are likely to be a combination of unfavorable airway geometry with an increase in collapsibility, reduced lung volume and an inability of the airway dilator muscles to adequately compensate. The role of arousal threshold and ventilatory control instability in the supine position remains to be elucidated. Most of the reported physiological data pertains to male subjects and there is a deficit of information on the pathogenesis of spOSA and siOSA in women. There is a paucity of studies examining the effect of the lateral position on a number of physiological parameters and, as such, it remains to be seen which of the contributing factors is most important in causing obstruction when moving from the lateral to the supine position.

The effectiveness of positional treatment of supine OSA is dependent on the ability of the method to maintain comfortable non-supine sleep and the subject's non-supine AHI. In the right circumstances it may be equivalent to CPAP therapy on a number of end points, but data on long term success and compliance is either lacking or suggests that adherence to treatment is poor. The application of oral appliances favorably alters upper airway geometry and dilator muscle function and may be beneficial for a proportion of patients suffering spOSA. Although weight loss appears beneficial at reducing OSA severity overall, benefit seems to be preferentially limited to non-supine sleep and may therefore have limited success in supine predominant OSA. There is minimal evidence that upper airway surgery has a beneficial effect on the generation of supine related obstructive events. The role that new therapies such as nasal expiratory resistance therapy play in the specific management of supine predominant OSA remains unclear at this stage.

In conclusion, supine predominant and supine isolated OSA are important and common phenotypes of the OSA syndrome. Further research is required to fully elucidate the contributory mechanisms at play and to determine the best way to treat patients who present with this condition.

Practice points

1) Supine predominant obstructive sleep apnea (spOSA) is defined as:
   - Overall AHI is greater than 5 events/h, and,
   - The supine AHI is greater than two times the non-supine AHI.
2) Supine isolated obstructive sleep apnea (siOSA) is defined as:
   - Overall AHI is greater than 5 events/h, and,
   - The supine AHI is greater than two times the non-supine AHI and,
   - Non-supine AHI is less than 5 events/h.
3) spOSA is present in approximately 50–60% and siOSA in 25–30% of patients who undergo diagnostic polysomnography.
4) There are important clinical and pathophysiological differences between spOSA and siOSA patients and unselected or non-positional OSA patients.
5) Treatment of spOSA and siOSA needs to be tailored to the individual patient but may comprise positional therapy or a number of general OSA treatments such as CPAP or oral appliances.

Research agenda

1) Develop an industry standard for the measurement of body position in the sleep laboratory setting.
2) Measurement of sleeping position in a normal population and including head, neck and trunk position.
3) Longitudinal data exploring the effect of supine obstructive events on the many conditions associated with OSA.
4) Physiological studies aimed at elucidating the mechanisms of OSA that examine subjects in both the lateral and supine position.
5) Adequately powered, randomized controlled trial data exploring the treatment options for spOSA and siOSA.
6) Long term compliance data for the common treatments employed in spOSA and siOSA.

Conflict of interest

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References

1. Young T, Peppard PE, Gottlieb DJ. Epidemiology of obstructive sleep apnea: a population health perspective. *Am J Respir Crit Care Med* 2002;**165**:1217–39.
2. Gottlieb DJ, Whitney CW, Bonekat WH, Iber C, James GD, Lebowitz M, et al. Relation of sleepiness to respiratory disturbance index: the Sleep Heart Health Study. *Am J Respir Crit Care Med* 1999;**159**:502–7.
3. Peppard PE, Szklo-Coxe M, Hla KM, Young T. Longitudinal association of sleep-related breathing disorder and depression. *Arch Intern Med* 2006;**166**:1709–15.
4. Nieto FJ, Young TB, Lind BK, Shahar E, Samet JM, Redline S, et al. Association of sleep-disordered breathing, sleep apnea, and hypertension in a large community-based study. Sleep Heart Health Study. *J Am Med Assoc* 2000;**283**:1829–36.
5. Peppard PE, Young T, Palta M, Skatrud J. Prospective study of the association between sleep-disordered breathing and hypertension. *N Engl J Med* 2000;**342**:1378–84.
6. Coughlin SR, Mawdsley L, Mugarza JA, Calverley PM, Wilding JP. Obstructive sleep apnoea is independently associated with an increased prevalence of metabolic syndrome. *Eur Heart J* 2004;**25**:735–41.
7. Ip MS, Lam B, Ng MM, Lam WK, Tsang KW, Lam KS. Obstructive sleep apnea is independently associated with insulin resistance. *Am J Respir Crit Care Med* 2002;**165**:670–6.
8. Shamsuzzaman AS, Gersh BJ, Somers VK. Obstructive sleep apnea: implications for cardiac and vascular disease. *J Am Med Assoc* 2003;**290**:1906–14.
9. Oksenberg A, Silverberg DS. The effect of body posture on sleep-related breathing disorders: facts and therapeutic implications. *Sleep Med Rev* 1998;**2**:139–62.
10. Cartwright RD. Effect of sleep position on sleep apnea severity. *Sleep* 1984;**7**:110–4.
*11. Oksenberg A, Silverberg DS, Arons E, Radwan H. Positional vs nonpositional obstructive sleep apnea patients: anthropomorphic, nocturnal polysomnographic, and multiple sleep latency test data. *Chest* 1997;**112**:629–39.
12. Mador MJ, Kufel TJ, Magalang UJ, Rajesh SK, Watwe V, Grant BJB. Prevalence of positional sleep apnea in patients undergoing polysomnography. *Chest* 2005;**128**:2130–7.
*13. Bignold JJ, Mercer JD, Antic NA, McEvoy RD, Catcheside PG. Accurate position monitoring and improved supine-dependent obstructive sleep apnea with a new position recording and supine avoidance device. *J Clin Sleep Med* 2011;**7**:376–83.
14. Loord H, Hultcrantz E. Positioner – a method for preventing sleep apnea. *Acta Otolaryngol* 2007;**127**:861–8.
15. Eiseman NA, Westover MB, Ellenbogen JM, Bianchi MT. The impact of body posture and sleep stages on sleep apnea severity in adults. *J Clin Sleep Med* 2012;**8**:655–66.
16. Sunnergren O, Brostrom A, Svanborg E. Positional sensitivity as a confounder in diagnosis of severity of obstructive sleep apnea. *Sleep Breath* 2012. [E-pub ahead of print].
17. Joosten SA, Hamza K, Sands S, Turton A, Berger P, Hamilton G. Phenotypes of patients with mild to moderate obstructive sleep apnoea as confirmed by cluster analysis. *Respirology* 2012;**17**:99–107.
*18. Pevernagie DA, Shepard Jr JW. Relations between sleep stage, posture and effective nasal CPAP levels in OSA. *Sleep* 1992;**15**:162–7.
19. Oksenberg A, Arons E, Nasser K, Vander T, Radwan H. REM-related obstructive sleep apnea: the effect of body position. *J Clin Sleep Med* 2010;**6**:343–8.
20. Richard W, Kox D, den Herder C, Laman M, van Tinteren H, de Vries N. The role of sleep position in obstructive sleep apnea syndrome. *Eur Arch Otorhinolaryngol* 2006;**263**:946–50.
21. Gillman A, Roebuck T, Ho S, van Braak E, Naughton MT. Comparison of supine-only and REM-only obstructive sleep apnoea. *Sleep Med* 2012;**13**:875–8.
22. Mo JH, Lee CH, Rhee CS, Yoon IY, Kim JW. Positional dependency in Asian patients with obstructive sleep apnea and its implication for hypertension. *Arch Otolaryngol Head Neck Surg* 2011;**137**:786–90.
23. Teerapraipruk B, Chirakalwasan N, Simon R, Hirunwiwatkul P, Jaimchariyatam N, Desudchit T, et al. Clinical and polysomnographic data of positional sleep apnea and its predictors. *Sleep Breath* 2012;**16**:1167–72.
24. Chung JW, Enciso R, Levendowski DJ, Westbrook PR, Clark GT. Patients with positional versus nonpositional obstructive sleep apnea: a retrospective study of risk factors associated with apnea-hypopnea severity. *Oral Surg Oral Med Oral Pathol Oral Radiol Endodontics* 2010;**110**:605–10.
25. De Koninck J, Lorrain D, Gagnon P. Sleep positions and position shifts in five age groups: an ontogenetic picture. *Sleep* 1992;**15**:143–9.
26. O'Connor C, Thornley KS, Hanly PJ. Gender differences in the polysomnographic features of obstructive sleep apnea. *Am J Respir Crit Care Med* 2000;**161**:1465–72.
27. Stepnowsky Jr CJ, Orr WC, Davidson TM. Nightly variability of sleep-disordered breathing measured over 3 nights. *Otolaryngol Head Neck Surg* 2004;**131**:837–43.
28. Bittencourt LR, Suchecki D, Tufik S, Peres C, Togeiro SM, Bagnato MC, et al. The variability of the apnoea-hypopnoea index. *J Sleep Res* 2001;**10**:245–51.
29. Pittsley M, Gehrman P, Cohen-Zion M, Stepnowsky C, Marler M, Ancoli-Israel S. Comparing night-to-night variability of sleep measures in elderly African Americans and Whites. *Behav Sleep Med* 2005;**3**:63–72.
30. Maestri R, La Rovere MT, Robbi E, Pinna GD. Night-to-night repeatability of measurements of nocturnal breathing disorders in clinically stable chronic heart failure patients. *Sleep Breath* 2011;**15**:673–8.
31. Zheng H, Sowers M, Buysse DJ, Consens F, Kravitz HM, Matthews KA, et al. Sources of variability in epidemiological studies of sleep using repeated nights of in-home polysomnography: SWAN Sleep Study. *J Clin Sleep Med* 2012;**8**:87–96.
32. Patient's wife cures his snoring. *Chest* 1984;**85**:582-c.
33. Nakano H, Ikeda T, Hayashi M, Ohshima E, Onizuka A. Effects of body position on snoring in apneic and nonapneic snorers. *Sleep* 2003;**26**:169–72.
34. Oksenberg A, Khamaysi I, Silverberg DS, Tarasiuk A. Association of body position with severity of apneic events in patients with severe nonpositional obstructive sleep apnea. *Chest* 2000;**118**:1018–24.
35. Metersky ML, Castriotta RJ. The effect of polysomnography on sleep position: possible implications on the diagnosis of positional obstructive sleep apnea. *Respiration* 1996;**63**:283–7.
36. Iber C, American Academy of Sleep Medicine. *The AASM manual for the scoring of sleep and associated events: rules, terminology, and technical specifications*. Westchester, IL: American Academy of Sleep Medicine; 2007.
37. van Kesteren ER, van Maanen JP, Hilgevoord AAJ, Laman DM, de Vries N. Quantitative effects of trunk and head position on the apnea hypopnea index in obstructive sleep apnea. *Sleep* 2011;**34**:1075–81.
38. Tiotiu A, Mairesse O, Hoffmann G, Todea D, Noseda A. Body position and breathing abnormalities during sleep: a systematic study. *Pneumologia* 2011;**60**:216–21.
39. Wellman A, Eckert DJ, Jordan AS, Edwards BA, Passaglia CL, Jackson AC, et al. A method for measuring and modeling the physiological traits causing obstructive sleep apnea. *J Appl Physiol* 2011;**110**:1627–37.
40. Elliott AR, Shea SA, Dijk DJ, Wyatt JK, Riel E, Neri DF, et al. Microgravity reduces sleep-disordered breathing in humans. *Am J Respir Crit Care Med* 2001;**164**:478–85.

* The most important references are denoted by an asterisk.

41. Bettinelli D, Kays C, Bailliart O, Capderou A, Techoueyres P, Lachaud JL, et al. Effect of gravity and posture on lung mechanics. *J Appl Physiol* 2002;**93**: 2044–52.
42. Isono S, Tanaka A, Nishino T. Lateral position decreases collapsibility of the passive pharynx in patients with obstructive sleep apnea. *Anesthesiology* 2002;**97**:780–5.
43. Schwab RJ, Pasirstein M, Pierson R, Mackley A, Hachadoorian R, Arens R, et al. Identification of upper airway anatomic risk factors for obstructive sleep apnea with volumetric magnetic resonance imaging. *Am J Respir Crit Care Med* 2003;**168**:522–30.
*44. Amatoury J, Kairaitis K, Wheatley JR, Bilston LE, Amis TC. Onset of airflow limitation in a collapsible tube model: impact of surrounding pressure, longitudinal strain, and wall folding geometry. *J Appl Physiol* 2010;**109**: 1467–75.
45. Schwab RJ, Gupta KB, Gefter WB, Metzger LJ, Hoffman EA, Pack AI. Upper airway and soft tissue anatomy in normal subjects and patients with sleep-disordered breathing. Significance of the lateral pharyngeal walls. *Am J Respir Crit Care Med* 1995;**152**:1673–89.
*46. Ciscar MA, Juan G, Martinez V, Ramon M, Lloret T, Minguez J, et al. Magnetic resonance imaging of the pharynx in OSA patients and healthy subjects. *Eur Respir J* 2001;**17**:79–86.
47. Jan MA, Marshall I, Douglas NJ. Effect of posture on upper airway dimensions in normal human. *Am J Respir Crit Care Med* 1994;**149**:145–8.
*48. Walsh JH, Leigh MS, Paduch A, Maddison KJ, Armstrong JJ, Sampson DD, et al. Effect of body posture on pharyngeal shape and size in adults with and without obstructive sleep apnea. *Sleep* 2008;**31**:1543–9.
49. Pevernagie DA, Stanson AW, Sheedy 2nd PF, Daniels BK, Shepard Jr JW. Effects of body position on the upper airway of patients with obstructive sleep apnea. *Am J Respir Crit Care Med* 1995;**152**:179–85.
50. Martin SE, Marshall I, Douglas NJ. The effect of posture on airway caliber with the sleep-apnea/hypopnea syndrome. *Am J Respir Crit Care Med* 1995;**152**:721–4.
51. Ono T, Otsuka R, Kuroda T, Honda E, Sasaki T. Effects of head and body position on two- and three-dimensional configurations of the upper airway. *J Dent Res* 2000;**79**:1879–84.
52. Ryan CF, Love LL. Mechanical properties of the velopharynx in obese patients with obstructive sleep apnea. *Am J Respir Crit Care Med* 1996;**154**: 806–12.
53. Fogel RB, Malhotra A, Dalagiorgou G, Robinson MK, Jakab M, Kikinis R, et al. Anatomic and physiologic predictors of apnea severity in morbidly obese subjects. *Sleep* 2003;**26**:150–5.
54. Schwab RJ, Gefter WB, Hoffman EA, Gupta KB, Pack AI. Dynamic upper airway imaging during awake respiration in normal subjects and patients with sleep disordered breathing. *Am Rev Respir Dis* 1993;**148**: 1385–400.
55. Saigusa H, Suzuki M, Higurashi N, Kodera K. Three-dimensional morphological analyses of positional dependence in patients with obstructive sleep apnea syndrome. *Anesthesiology* 2009;**110**:885–90.
56. Ono T, Lowe AA, Ferguson KA, Fleetham JA. Associations among upper airway structure, body position, and obesity in skeletal Class I male patients with obstructive sleep apnea. *Am J Orthod Dentofacial Orthop* 1996;**109**:625–34.
57. Miyamoto K, Ozbek MM, Lowe AA, Sjoholm TT, Love LL, Fleetham JA, et al. Mandibular posture during sleep in healthy adults. *Arch Oral Biol* 1998;**43**: 269–75.
58. Lucey AD, King AJ, Tetlow GA, Wang J, Armstrong JJ, Leigh MS, et al. Measurement, reconstruction, and flow-field computation of the human pharynx with application to sleep apnea. *IEEE Trans Biomed Eng* 2010;**57**: 2535–48.
59. Leiter JC. Analysis of pharyngeal resistance and genioglossal EMG activity using a model of orifice flow. *J Appl Physiol* 1992;**73**:576–83.
60. Schwartz AR, Smith PL, Wise RA, Gold AR, Permutt S. Induction of upper airway occlusion in sleeping individuals with subatmospheric nasal pressure. *J Appl Physiol* 1988;**64**:535–42.
61. Boudewyns A, Punjabi N, Van de Heyning PH, De Backer WA, O'Donnell CP, Schneider H, et al. Abbreviated method for assessing upper airway function in obstructive sleep apnea. *Chest* 2000;**118**:1031–41.
62. Isono S, Tanaka A, Tagaito Y, Ishikawa T, Nishino T. Influences of head positions and bite opening on collapsibility of the passive pharynx. *J Appl Physiol* 2004;**97**:339–46.
63. Ong JSL, Touyz G, Tanner S, Hillman DR, Eastwood PR, Walsh JH. Variability of human upper airway collapsibility during sleep and the influence of body posture and sleep stage. *J Sleep Res* 2011;**20**:533–7.
64. Penzel T, Moller M, Becker HF, Knaack L, Peter JH. Effect of sleep position and sleep stage on the collapsibility of the upper airways in patients with sleep apnea. *Sleep* 2001;**24**:90–5.
65. Squier SB, Patil SP, Schneider H, Kirkness JP, Smith PL, Schwartz AR. Effect of end-expiratory lung volume on upper airway collapsibility in sleeping men and women. *J Appl Physiol* 2010;**109**:977–85.
66. Walsh JH, Maddison KJ, Platt PR, Hillman DR, Eastwood PR. Influence of head extension, flexion, and rotation on collapsibility of the passive upper airway. *Sleep* 2008;**31**:1440–7.
67. Ayuse T, Inazawa T, Kurata S, Okayasu I, Sakamoto E, Oi K, et al. Mouth-opening increases upper-airway collapsibility without changing resistance during midazolam sedation. *J Dent Res* 2004;**83**:718–22.
68. Series F, Cormier Y, Couture J, Desmeules M. Changes in upper airway resistance with lung inflation and positive airway pressure. *J Appl Physiol* 1990;**68**:1075–9.
*69. Stanchina ML, Malhotra A, Fogel RB, Trinder J, Edwards JK, Schory K, et al. The influence of lung volume on pharyngeal mechanics, collapsibility, and genioglossus muscle activation during sleep. *Sleep* 2003;**26**:851–6.
70. Bradley TD, Brown IG, Grossman RF, Zamel N, Martinez D, Phillipson EA, et al. Pharyngeal size in snorers, nonsnorers, and patients with obstructive sleep apnea. *N Engl J Med* 1986;**315**:1327–31.
71. Rowley JA, Permutt S, Willey S, Smith PL, Schwartz AR. Effect of tracheal and tongue displacement on upper airway airflow dynamics. *J Appl Physiol* 1996;**80**:2171–8.
72. Kairaitis K, Byth K, Parikh R, Stavrinou R, Wheatley JR, Amis TC. Tracheal traction effects on upper airway patency in rabbits: the role of tissue pressure. *Sleep* 2007;**30**:179–86.
73. Van de Graaff WB. Thoracic influence on upper airway patency. *J Appl Physiol* 1988;**65**:2124–31.
74. Ibanez Juve J, Garcia Moris S, Marse Milla P, Abizanda Campos R, Fiol Sala M, Abadal Centellas JM. Pulmonary function differences in healthy subjects according to postural changes [Diferencias en la funcion pulmonar de sujetos sanos secundarias al cambio postural]. *Med Clin* 1979;**73**:149–52.
75. Behrakis PK, Baydur A, Jaeger MJ, Milic-Emili J. Lung mechanics in sitting and horizontal body positions. *Chest* 1983;**83**:643–6.
76. Kauppinen-Walin K, Sovijarvi AR, Muittari A, Uusitalo A. Determination of functional residual capacity with 133-xenon radiospirometry. Comparison with body plethysmography and helium spirometry. Effect of body position. *Scand J Clin Lab Invest* 1980;**40**:347–54.
77. Navajas D, Farre R, Rotger MM, Milic-Emili J, Sanchis J. Effect of body posture on respiratory impedance. *J Appl Physiol* 1988;**64**:194–9.
78. Barnas GM, Green MD, Mackenzie CF, Fletcher SJ, Campbell DN, Runcie C, et al. Effect of posture on lung and regional chest wall mechanics. *Anesthesiology* 1993;**78**:251–9.
79. Barnas GM, Campbell DN, Mackenzie CF, Mendham JE, Fahy BG, Runcie CJ, et al. Lung, chest wall, and total respiratory system resistances and elastances in the normal range of breathing. *Am Rev Respir Dis* 1992;**145**:110–3.
80. Tanskanen P, Kytta J, Randell T. The effect of patient positioning on dynamic lung compliance. *Acta Anaesthesiol Scand* 1997;**41**:602–6.
81. Shore ET, Millman RP. Abnormalities in the flow-volume loop in obstructive sleep apnoea sitting and supine. *Thorax* 1984;**39**:775–9.
82. Jones RL, Nzekwu MM. The effects of body mass index on lung volumes. *Chest* 2006;**130**:827–33.
83. Pelosi P, Croci M, Ravagnan I, Cerisara M, Vicardi P, Lissoni A, et al. Respiratory system mechanics in sedated, paralyzed, morbidly obese patients. *J Appl Physiol* 1997;**82**:811–8.
84. Yap JC, Watson RA, Gilbey S, Pride NB. Effects of posture on respiratory mechanics in obesity. *J Appl Physiol* 1995;**79**:1199–205.
85. Watson RA, Pride NB. Postural changes in lung volumes and respiratory resistance in subjects with obesity. *J Appl Physiol* 2005;**98**:512–7.
86. Ferretti A, Giampiccolo P, Cavalli A, Milic-Emili J, Tantucci C. Expiratory flow limitation and orthopnea in massively obese subjects. *Chest* 2001;**119**: 1401–8.
87. Heinzer RC, Stanchina ML, Malhotra A, Jordan AS, Patel SR, Lo YL, et al. Effect of increased lung volume on sleep disordered breathing in patients with sleep apnoea. *Thorax* 2006;**61**:435–9.
88. Jordan AS, White DP, Lo Y-L, Wellman A, Eckert DJ, Yim-Yeh S, et al. Airway dilator muscle activity and lung volume during stable breathing in obstructive sleep apnea. *Sleep* 2009;**32**:361–8.
89. Tagaito Y, Isono S, Remmers JE, Tanaka A, Nishino T. Lung volume and collapsibility of the passive pharynx in patients with sleep-disordered breathing. *J Appl Physiol* 2007;**103**:1379–85.
90. Stadler DL, McEvoy RD, Sprecher KE, Thomson KJ, Ryan MK, Thompson CC, et al. Abdominal compression increases upper airway collapsibility during sleep in obese male obstructive sleep apnea patients. *Sleep* 2009;**32**:1579–87.
91. Mezzanotte WS, Tangel DJ, White DP. Waking genioglossal electromyogram in sleep apnea patients versus normal controls (a neuromuscular compensatory mechanism). *J Clin Invest* 1992;**89**:1571–9.
92. Fogel RB, Trinder J, White DP, Malhotra A, Raneri J, Schory K, et al. The effect of sleep onset on upper airway muscle activity in patients with sleep apnoea versus controls. *J Physiol* 2005;**564**:549–62.
93. Younes M. Contributions of upper airway mechanics and control mechanisms to severity of obstructive apnea. *Am J Respir Crit Care Med* 2003;**168**: 645–58.
94. Takahashi S, Ono T, Ishiwata Y, Kuroda T. Effect of changes in the breathing mode and body position on tongue pressure with respiratory-related oscillations. *Am J Orthod Dentofacial Orthop* 1999;**115**:239–46.
95. Pae EK, Lowe AA, Sasaki K, Price C, Tsuchiya M, Fleetham JA. A cephalometric and electromyographic study of upper airway structures in the upright and supine positions. *Am J Orthod Dentofacial Orthop* 1994;**106**:52–9.
96. Douglas NJ, Jan MA, Yildirim N, Warren PM, Drummond GB. Effect of posture and breathing route on genioglossal electromyogram activity in normal subjects and in patients with the sleep apnea/hypopnea syndrome. *Am Rev Respir Dis* 1993;**148**:1341–5.

97. Otsuka R, Ono T, Ishiwata Y, Kuroda T. Respiratory-related genioglossus electromyographic activity in response to head rotation and changes in body position. *Angle Orthod* 2000;**70**:63–9.
98. Malhotra A, Trinder J, Fogel R, Stanchina M, Patel SR, Schory K, et al. Postural effects on pharyngeal protective reflex mechanisms. *Sleep* 2004;**27**: 1105–12.
99. Anker AR, Ali A, Arendt HE, Cass SP, Cotter LA, Jian BJ, et al. Use of electrical vestibular stimulation to alter genioglossal muscle activity in awake cats. *J Vestib Res* 2003;**13**:1–8.
100. Wellman A, Jordan AS, Malhotra A, Fogel RB, Katz ES, Schory K, et al. Ventilatory control and airway anatomy in obstructive sleep apnea. *Am J Respir Crit Care Med* 2004;**170**:1225–32.
101. Sahlin C, Svanborg E, Stenlund H, Franklin KA. Cheyne-Stokes respiration and supine dependency. *Eur Respir J* 2005;**25**:829–33.
102. Szollosi I, Roebuck T, Thompson B, Naughton MT. Lateral sleeping position reduces severity of central sleep apnea/Cheyne-Stokes respiration. *Sleep* 2006;**29**:1045–51.
103. Soll BAG, Yeo KK, Davis JW, Seto TB, Schatz IJ, Shen EN. The effect of posture on Cheyne-Stokes respirations and hemodynamics in patients with heart failure. *Sleep* 2009;**32**:1499–506.
104. Eckert DJ, Owens RL, Kehlmann GB, Wellman A, Rahangdale S, Yim-Yeh S, et al. Eszopiclone increases the respiratory arousal threshold and lowers the apnoea/hypopnoea index in obstructive sleep apnoea patients with a low arousal threshold. *Clin Sci (Lond)* 2011;**120**:505–14.
105. Gleeson K, Zwillich CW, White DP. The influence of increasing ventilatory effort on arousal from sleep. *Am Rev Respir Dis* 1990;**142**:295–300.
106. Ravesloot MJ, van Maanen JP, Dun L, de Vries N. The undervalued potential of positional therapy in position-dependent snoring and obstructive sleep apnea – a review of the literature. *Sleep Breath* 2012. [E-pub ahead of print].
107. Lee JB, Park YH, Hong JH, Lee SH, Jung KH, Kim JH, et al. Determining optimal sleep position in patients with positional sleep-disordered breathing using response surface analysis. *J Sleep Res* 2009;**18**:26–35.
108. Oksenberg A, Silverberg D, Offenbach D, Arons E. Positional therapy for obstructive sleep apnea patients: a 6-month follow-up study. *Laryngoscope* 2006;**116**:1995–2000.
109. Skinner MA, Kingshott RN, Filsell S, Taylor DR. Efficacy of the 'tennis ball technique' versus nCPAP in the management of position-dependent obstructive sleep apnoea syndrome. *Respirology* 2008;**13**:708–15.
110. Berger M, Oksenberg A, Silverberg DS, Arons E, Radwan H, Iaina A. Avoiding the supine position during sleep lowers 24 h blood pressure in obstructive sleep apnea (OSA) patients. *J Hum Hypertens* 1997;**11**:657–64.
111. Bignold JJ, Deans-Costi G, Goldsworthy MR, Robertson CA, McEvoy D, Catcheside PG, et al. Poor long-term patient compliance with the tennis ball technique for treating positional obstructive sleep apnea. *J Clin Sleep Med* 2009;**5**:428–30.
112. Jokic R, Klimaszewski A, Crossley M, Sridhar G, Fitzpatrick MF. Positional treatment vs continuous positive airway pressure in patients with positional obstructive sleep apnea syndrome. *Chest* 1999;**115**:771–81.
113. Zuberi NA, Rekab K, Nguyen HV. Sleep apnea avoidance pillow effects on obstructive sleep apnea syndrome and snoring. *Sleep Breath* 2004;**8**:201–7.
114. Permut I, Diaz-Abad M, Chatila W, Crocetti J, Gaughan JP, D'Alonzo GE, et al. Comparison of positional therapy to CPAP in patients with positional obstructive sleep apnea. *J Clin Sleep Med* 2010;**6**:238–43.
115. Kushida CA, Littner MR, Hirshkowitz M, Morgenthaler TI, Alessi CA, Bailey D, et al. Practice parameters for the use of continuous and bilevel positive airway pressure devices to treat adult patients with sleep-related breathing disorders. *Sleep* 2006;**29**:375–80.
116. d'Ortho MP, Grillier-Lanoir V, Levy P, Goldenberg F, Corriger E, Harf A, et al. Constant vs. automatic continuous positive airway pressure therapy: home evaluation. *Chest* 2000;**118**:1010–7.
117. Hudgel DW, Fung C. A long-term randomized, cross-over comparison of auto-titrating and standard nasal continuous airway pressure. *Sleep* 2000;**23**:645–8.
*118. Oksenberg A, Silverberg DS, Arons E, Radwan H. The sleep supine position has a major effect on optimal nasal continuous positive airway pressure: relationship with rapid eye movements and non-rapid eye movements sleep, body mass index, respiratory disturbance index, and age. *Chest* 1999;**116**:1000–6.
119. Series F, Marc I. Importance of sleep stage- and body position-dependence of sleep apnoea in determining benefits to auto-CPAP therapy. *Eur Respir J* 2001;**18**:170–5.
120. Itasaka Y, Miyazaki S, Tada H, Ishikawa K, Togawa K. Effectiveness of prosthetic mandibular advancement for obstructive sleep apnea: analysis by sleep position. *Psychiatry Clin Neurosci* 1998;**52**:225–7.
121. Yoshida K. Influence of sleep posture on response to oral appliance therapy for sleep apnea syndrome. *Sleep* 2001;**24**:538–44.
122. Neill A, Whyman R, Bannan S, Jeffrey O, Campbell A. Mandibular advancement splint improves indices of obstructive sleep apnoea and snoring but side effects are common. *N Z Med J* 2002;**115**:289–92.
123. Marklund M, Persson M, Franklin KA. Treatment success with a mandibular advancement device is related to supine-dependent sleep apnea. *Chest* 1998;**114**:1630–5.
*124. Marklund M, Stenlund H, Franklin KA. Mandibular advancement devices in 630 men and women with obstructive sleep apnea and snoring: tolerability and predictors of treatment success. *Chest* 2004;**125**:1270–8.
125. Chung JW, Enciso R, Levendowski DJ, Morgan TD, Westbrook PR, Clark GT. Treatment outcomes of mandibular advancement devices in positional and nonpositional OSA patients. *Oral Surg Oral Med Oral Pathol Oral Radiol Endodontics* 2010;**109**:724–31.
126. Gale DJ, Sawyer RH, Woodcock A, Stone P, Thompson R, O'Brien K. Do oral appliances enlarge the airway in patients with obstructive sleep apnoea? A prospective computerized tomographic study. *Eur J Orthod* 2000;**22**: 159–68.
127. Ryan CF, Love LL, Peat D, Fleetham JA, Lowe AA. Mandibular advancement oral appliance therapy for obstructive sleep apnoea: effect on awake calibre of the velopharynx. *Thorax* 1999;**54**:972–7.
128. Tsuiki S, Lowe AA, Almeida FR, Kawahata N, Fleetham JA. Effects of mandibular advancement on airway curvature and obstructive sleep apnoea severity. *Eur Respir J* 2004;**23**:263–8.
129. Tsuiki S, Hiyama S, Ono T, Imamura N, Ishiwata Y, Kuroda T, et al. Effects of a titratable oral appliance on supine airway size in awake non-apneic individuals. *Sleep* 2001;**24**:554–60.
130. Tsuiki S, Ono T, Kuroda T. Mandibular advancement modulates respiratory-related genioglossus electromyographic activity. *Sleep Breath* 2000;**4**:53–8.
131. Fransson AM, Tegelberg A, Leissner L, Wenneberg B, Isacsson G. Effects of a mandibular protruding device on the sleep of patients with obstructive sleep apnea and snoring problems: a 2-year follow-up. *Sleep Breath* 2003;**7**: 131–41.
132. Kajaste S, Brander PE, Telakivi T, Partinen M, Mustajoki P. A cognitive-behavioral weight reduction program in the treatment of obstructive sleep apnea syndrome with or without initial nasal CPAP: a randomized study. *Sleep Med* 2004;**5**:125–31.
133. Schwartz AR, Gold AR, Schubert N, Stryzak A, Wise RA, Permutt S, et al. Effect of weight loss on upper airway collapsibility in obstructive sleep apnea. *Am Rev Respir Dis* 1991;**144**:494–8.
134. Smith PL, Gold AR, Meyers DA, Haponik EF, Bleecker ER. Weight loss in mildly to moderately obese patients with obstructive sleep apnea. *Ann Intern Med* 1985;**103**:850–5.
135. Kansanen M, Vanninen E, Tuunainen A, Pesonen P, Tuononen V, Hartikainen J, et al. The effect of a very low-calorie diet-induced weight loss on the severity of obstructive sleep apnoea and autonomic nervous function in obese patients with obstructive sleep apnoea syndrome. *Clin Physiol* 1998;**18**:377–85.
136. Tuomilehto HP, Seppa JM, Partinen MM, Peltonen M, Gylling H, Tuomilehto JO, et al. Lifestyle intervention with weight reduction: first-line treatment in mild obstructive sleep apnea. *Am J Respir Crit Care Med* 2009;**179**:320–7.
137. Oksenberg A, Dynia A, Nasser K, Gadoth N. Obstructive sleep apnoea in adults: body postures and weight changes interactions. *J Sleep Res* 2012;**21**:402–9.
138. Berry RB, Kryger MH, Massie CA. A novel nasal expiratory positive airway pressure (EPAP) device for the treatment of obstructive sleep apnea: a randomized controlled trial. *Sleep* 2011;**34**:479–85.
139. Kryger MH, Berry RB, Massie CA. Long-term use of a nasal expiratory positive airway pressure (EPAP) device as a treatment for obstructive sleep apnea (OSA). *J Clin Sleep Med* 2011;**7**:449B–53B.
140. Patel AV, Hwang D, Masdeu MJ, Chen GM, Rapoport DM, Ayappa I. Predictors of response to a nasal expiratory resistor device and its potential mechanisms of action for treatment of obstructive sleep apnea. *J Clin Sleep Med* 2011;**7**:13–22.
141. Braga CW, Chen Q, Burschtin OE, Rapoport DM, Ayappa I. Changes in lung volume and upper airway using MRI during application of nasal expiratory positive airway pressure in patients with sleep-disordered breathing. *J Appl Physiol* 2011;**111**:1400–9.
142. Lee CH, Shin H-W, Han DH, Mo J-H, Yoon I-Y, Chung S, et al. The implication of sleep position in the evaluation of surgical outcomes in obstructive sleep apnea. *Otolaryngol Head Neck Surg* 2009;**140**:531–5.
143. Kwon M, Jang YJ, Lee B-J, Chung Y-S. The effect of uvula-preserving palatopharyngoplasty in obstructive sleep apnea on globus sense and positional dependency. *Clin Exp Otorhinolaryngol* 2010;**3**:141–6.
144. Aurora RN, Casey KR, Kristo D, Auerbach S, Bista SR, Chowdhuri S, et al. Practice parameters for the surgical modifications of the upper airway for obstructive sleep apnea in adults. *Sleep* 2010;**33**:1408–13.