OBESITY EFFECTS ON LUNG VOLUME, TRANSDIAPHRAGMATIC PRESSURE, UPPER AIRWAY DILATOR AND INSPIRATORY PUMP MUSCLE ACTIVITY IN OBSTRUCTIVE SLEEP APNOEA

by

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ABSTRACT

Obstructive sleep apnoea (OSA) is a common respiratory disorder characterised by repetitive periods of upper airway (UA) collapse during sleep. OSA is more common in males and the obese but the reasons why remain poorly understood. Abdominal obesity, particularly common in males, is likely to indirectly modulate the amount of tension (tracheal traction) exerted on the UA by the trachea and other intrathoracic structures, potentially leading to increased UA collapsibility. Other factors such as lung volume changes with obesity, altered drive to UA muscles and exaggerated arousal responses are also likely to contribute to UA instability. An investigation of these potential contributing factors forms the basis of this thesis.

In the first study, the effect of external abdominal compression on UA collapsibility during sleep was investigated in a group of obese male OSA patients. A large pneumatic cuff wrapped around the abdomen was inflated to increase intra-abdominal pressure, aiming to produce an upward force on the diaphragm, designed to reduce axial tension on the UA. Abdominal compression increased end-expiratory gastric (P_{GA}) and end-expiratory transdiaphragmatic (P_{DI}) pressure by ~50% and produced a significant rise in UA collapsibility compared to the cuff deflated condition. These data support that increased intra-abdominal pressure has a negative effect on UA function during sleep. This effect may help explain why obesity is the leading risk factor for OSA and why OSA affects men more than women, given that abdominal obesity is particularly common in obese males.

In the second study, differences in minimum expiratory (tonic) diaphragm activity during wakefulness were compared between 8 obese OSA patients and 8 healthy-weight controls. Changes in tonic diaphragm activity and lung volume following sleep onset were also compared between the two groups. There was no evidence of increased tonic diaphragmatic activity during wakefulness in obese OSA patients to support significant diaphragmatic compensation for abdominal compressive effects of obesity. There were small decrements in lung volume following sleep onset in both groups (<70 ml), with significantly greater lung volume and diaphragmatic EMG decrements when sleep onsets were immediately followed by respiratory events. While lung volume decrements at sleep onset were relatively small, this does not discount that UA function is not more sensitive to effects of reduced lung volume in obese OSA patients.

To more closely investigate the potential interactive effects of obesity on physiological variables likely influencing UA function, the third study investigated the temporal relationships between a comprehensive range of relevant physiological variables leading into and following the termination of obstructive apnoeas during sleep in 6 obese OSA patients. Prior to UA obstruction, diaphragm and genioglossus muscle activity decreased, while UA resistance increased. Lung volume and end-expiratory P_{GA} and end-expiratory P_{DI} also fell during this period, consistent with diaphragm ascent. There was a substantial increase in ventilation, muscle activity and lung volume immediately following the termination of obstructive events. Respiratory events and arousals occurred in close temporal proximity prior to and following obstructive apnoeas, supporting that cyclical respiratory events and arousals may both help to perpetuate further events. The

results from this study support that there is a ‘global’ loss in respiratory drive to UA dilator and pump muscles precipitating obstructive respiratory events. The associated decreases in UA dilator muscle activity and lung volume may therefore both contribute to the propensity for the UA to obstruct.

In summary, increased intra-abdominal pressure was shown to negatively impact UA airway collapsibility during sleep. A decrease in lung volume at sleep onset and prior to UA obstruction further support that lung volume decrement, coincident with a decline in overall respiratory drive, potentially contributes to the propensity for airway obstruction. Further studies are needed to elucidate the relative contribution of relatively small changes in lung volume versus changes in respiratory and UA muscle activity *per se* on UA patency in OSA patients.

PUBLICATIONS

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

Journal article:

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DL Stadler, PG Catcheside, D Paul, J Bradley, RD McEvoy. Changes in Lung Volume and Upper Airway Dilator Muscle Activity at Sleep Onset in Obese Male Obstructive Sleep Apnea Patients. *Am J Resp Crit Care Med* **179** A5405, 2009

D Stadler, P Catcheside, D Paul, J Bradley, R McEvoy. Changes in Lung Volume and Upper Airway Dilator Muscle Activity at Sleep Onset in Obese Male Obstructive Sleep Apnoea Patients. *Sleep Biol Rhythms* **6** (Suppl 1) A10, 2008

Stadler DL, Catcheside PG, George KE, Thomson K, Thompson CC, Ryan M, McEvoy RD. Abdominal compression increases upper airway collapsibility during sleep in obese male obstructive sleep apnea patients. *Proceedings of the American Thoracic Society* A51, 2007

Stadler DL, Catcheside PG, George K, Thompson C, Ryan M, McEvoy RD. The effect of abdominal compression on upper airway function during sleep in obese male obstructive sleep apnoea patients. *Sleep Biol Rhythms*, **4** (Supp 1) A23, 2006

Unpublished conference proceedings:

D Stadler, P Catcheside, J Bradley, D Paul and R Doug McEvoy. The Effect Of Sleep Onset On Lung Volume In Obese Male Obstructive Sleep Apnoea Patients. *Australian Society for Medical Research Annual Scientific Meeting, South Australian Branch, Adelaide, Australia*. 2008

DECLARATION

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

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GLOSSARY OF ABBREVIATIONS

ΔAP_{ABDO}	Change in abdominal anterior-posterior dimension
ΔAP_{CHEST}	Change in chest anterior-posterior dimension
AHI	Apnoea hypopnoea index (events·hr^{-1})
BMI	Body mass index (kg·m^{-2})
CPAP	Continuous positive airway pressure
ECG	Electrocardiography
EEG	Electroencephalography
EELV	End-expiratory lung volume
$eEMG_{DI}$	Average minimum tonic diaphragm activity
$eEMG_{GG}$	Average minimum tonic genioglossus activity
EMG	Electromyography
EMG_{DI}	Diaphragm muscle activity
EMG_{GG}	Genioglossus muscle activity
F_B	Breathing frequency (breaths·min^{-1})
FEV_1	Forced expiratory volume in 1 sec (% predicted)
FVC	Forced vital capacity (% predicted)
HC	Hip circumference (cm)
IAP	Intra-abdominal pressure
$iEMG_{DI}$	Average inspiratory diaphragm activity
$iEMG_{GG}$	Average inspiratory genioglossus activity
NREM sleep	Non rapid eye movement sleep
OSA	Obstructive sleep apnoea
OSAS	Obstructive sleep apnoea syndrome
P_{ACO_2}	Arterial CO_2
P_{CRIT}	Upper airway critical closing pressure

P_{CUFF}	Cuff pressure (cmH_2O)
P_{DI}	Transdiaphragmatic pressure (cmH_2O)
P_{EPI}	Epiglottic pressure (cmH_2O)
P_{ETCO_2}	End-tidal partial pressure of carbon dioxide (mmHg)
P_{GA}	Gastric pressure (cmH_2O)
PIF	Peak inspiratory flow ($L \cdot min^{-1}$)
P_{MASK}	Mask pressure (cmH_2O)
P_{OES}	Oesophageal pressure (cmH_2O)
REM sleep	Rapid eye movement sleep
R_{UA}	Upper airway resistance ($cmH_2O \cdot L^{-1} \cdot s$)
SDB	Sleep-disordered breathing
SEM	Standard error of the mean
SWS	Slow-wave sleep
T_E	Duration of expiration (secs)
T_I	Duration of inspiration (secs)
T_{TOT}	Total duration of inspiration and expiration (secs)
UA	Upper airway
UACP	Upper airway closing pressure (cmH_2O)
V_I	Inspiration minute ventilation ($L \cdot min^{-1}$)
V_T	Inspiration tidal volume (L)
WC	Waist circumference (cm)
WHR	Waist-to-hip ratio

CHAPTER 1. GENERAL INTRODUCTION

1.1 General background

Obstructive sleep apnoea (OSA) is a common sleep disorder characterised by repetitive periods of upper airway (UA) narrowing and hypoventilation (hypopnoea) or complete obstruction (apnoea)[1]. During these respiratory events, the chemoreflex drive to breathe increases along with hypercapnia and hypoxia, culminating in airway re-opening generally near coincident with brief arousal from sleep[2]. The increased frequency of arousals and sleep fragmentation result in daytime hypersomolence[3, 4] and associated increased risk of motor vehicle[5, 6] and workplace accidents[7]. Long term untreated OSA is believed to contribute to impaired cognition[8] and depression[9, 10] as well as cardiovascular disease risk such as hypertension[11, 12], nocturnal cardiac arrhythmias[13], atherosclerosis[14] and stroke[15].

There are several key risk factors for OSA in adults including male gender[16-18], middle-age[19, 20] and obesity[16, 18, 21]. Further evidence suggests that fat distribution may be a more important risk factor than obesity *per se*[21-24]. The pathogenic mechanisms of OSA in any given individual are likely to be complex and multifactorial in nature. While the presence of a smaller UA is likely to be a major factor contributing to OSA[25-27], other more dynamic factors including the degree of axial tension exerted on the UA by the trachea and other intrathoracic structures

(caudal tracheal traction), intra-abdominal pressure (IAP), lung volume, impaired UA neurocompensatory reflexes following sleep onset, central drive to the UA dilator muscles versus respiratory pump muscles and exaggerated ventilatory responses to arousal, are also likely to be important. The aim of this doctoral study was to examine key physiological mechanisms likely contributing to the pathogenesis of OSA in obese males. This chapter provides a review of the literature, primarily focusing on the current understanding of the potential physiological mechanisms underpinning the development of OSA in the obese population.

1.2 Prevalence of OSA

1.2.1 Gender

Estimates of the prevalence of sleep-disordered breathing (SDB) in the community range between 1 and 5% of the adult population[18, 28-32], with differences in estimates likely attributable to variable sample sizes and populations studied (e.g. ethnicity) and the definition of OSA. The prevalence of OSA has been shown to be consistently higher in males, with male to female ratio of between 1.3:1 and 4.75:1[18, 29, 30, 32-34]. In one of the earliest and largest community based reports (n=602)[18], the prevalence of OSA defined on the basis of respiratory event frequency alone (apnoea-hypopnoea index [AHI] ≥5 events·hr^{-1}), was found to be 24% and 9% of middle-aged males and females respectively. When daytime hypersomnolence was included to define symptomatic OSA syndrome (OSAS), an estimated 4% of males and 2% of females exhibited OSAS.

The prevalence of SDB has been shown to increase in post-menopausal women[29, 35, 36]. For example, Bixler et al[29] found the prevalence of OSAS (defined as AHI ≥10 events·hr^{-1} plus daytime symptoms) to be 2.7% in post-menopausal women compared to 0.6% in pre-menopausal women. In another study[17], despite a similar definition of OSA, the prevalence of OSA in pre-menopausal women was found to be much higher (~32%) and even more so in post-menopausal women (~68%). The difference between the two studies may reflect a higher body mass index (BMI) in pre- and post-menopausal groups in the study by Resta et al[17]. The authors found increased neck circumference and waist-to-hip ratio in the post-menopausal group and attributed the increased prevalence of OSAS in post-menopausal women to the accumulation of adipose tissue in the upper body. Given that age and obesity are two important risk factors for OSA, the higher prevalence of OSA in post-menopausal women is likely confounded by these variables. When adjusting for age and BMI, Young et al[36] showed that the odds ratio for demonstrating an AHI ≥5 events·hr^{-1} was 2.6 in post-menopausal women, increasing to 3.5 for an AHI ≥15 events·hr^{-1} when compared to an AHI <5 events·hr^{-1}. These data suggest that female hormones potentially play a protective role against OSA and may help explain the male gender bias in OSA prevalence. However, while the beneficial effects of hormone replacement therapy in post-menopausal women have been reported in some studies[29, 37], others have failed to demonstrate improvements in OSA severity[38, 39], suggesting that hormonal influences may not be the primary factor explaining the gender bias in OSA.

1.2.2 Obesity

The World Health Organisation estimated that approximately 1.6 billion adults (aged >15 years) globally were overweight (BMI ≥25 kg·m^{-2}) in 2005, including >400 million defined as obese (BMI ≥30 kg·m^{-2})[40]. In a 2008 report by the National Centre for Health Statistics reporting data from 2003-2006, 72.6% and 61.2% of American males and females respectively aged 20-74 years were overweight, with 35.2% of females and 33.1% males classified as obese[41]. In Australia, the 2004–05 National Health Survey reported that 62% of adult males and 45% of adult females were overweight, with 19% of males and 17% of females defined as obese[42]. Future projections by the World Health Organisation estimate that the number of overweight and obese adults world-wide will increase to approximately 2.3 billion and 700 million respectively by the year 2015[40].

Given obesity is a major risk factor for OSA[16, 18, 22, 23, 43, 44], combined with more recent trends towards increased obesity, the current OSA prevalence is likely higher than previous estimates. In morbidly obese patients (BMI ≥40 kg·m^{-2}), the prevalence of OSA has been reported to be as high as 98% (AHI ≥5 events·hr^{-1}), with 33% of these patients demonstrating severe OSA (AHI ≥65 events·hr^{-1})[24]. Young et al[18] showed that an increase in 1 standard deviation of body habitus measurements, such as weight, BMI, neck and waist circumference and waist-to-hip ratio, was associated with a 2-5 fold increase in the risk of exhibiting an AHI ≥5 events·hr^{-1}. Consequently, the higher prevalence of OSA in males is potentially attributed to by different patterns of obesity compared to females.

Women show a higher BMI for a given severity of OSA compared to males[17, 34, 45], supporting that differences in weight distribution likely contribute to gender differences in OSA severity and potentially the male prevalence bias. Obese males tend to store their fat centrally around the neck, chest and abdomen (android distribution) compared to a more peripheral (gynoid) distribution in obese females. Measurements of central obesity such as increased neck and/or waist circumference consistently appear as independent predictors of OSA[16, 20-22, 24, 46, 47]. Intra-abdominal (visceral) fat is also strongly predictive of OSA severity[48, 49]. In the Wisconsin Sleep Cohort Study[50], men were approximately three times more likely to have OSA than women, increasing to approximately six times when adjusting for BMI in the model. However, male gender was no longer predictive of OSA after adjusting for either neck circumference or waist-to-hip ratio. In combination, these data suggest that fat distribution and not overall obesity *per se* is important in OSA, and may help explain gender differences in the expression of SDB and point towards potential underlying pathogenic mechanisms.

1.3 Craniofacial abnormalities and fat distribution surrounding the upper airway

On average, UA size is reduced in OSA patients[25-27, 51-53], likely as a result of several factors. The UA is surrounded by extraluminal tissue, which is partially enclosed within a bony box composed of the mandible, maxilla, skull and cervical spine. It has been proposed that UA size and shape is influenced by the size of the bony box and the amount of soft tissue surrounding the UA[54]. Several craniofacial abnormalities in OSA patients have been reported. Retrusion of the mandible[55, 56]

and maxilla[57, 58] are commonly present in OSA patients, particularly in the Asian OSA population[59]. Dempsey et al[60] demonstrated that BMI and four cephalometric measurements accounted for an impressive ~57% of the variance in AHI in a group of 51 OSA patients. Furthermore, craniofacial abnormalities such as a lengthened soft palate, distance from the hyoid bone to the posterior pharyngeal wall and the distance from the hyoid bone to posterior nasal space, are significantly correlated with UA collapsibility[61].

Evidence from UA imaging studies clearly shows that OSA patients exhibit enlarged soft tissues and increased fat deposition surrounding the UA. In a study by Shelton et al[62], OSA patients demonstrated significantly greater adipose tissue volumes surrounding the UA compared to controls, with the volume of tissue predictive of AHI (r=0.59). Using MRI, obese OSA patients were found to have increased neck fat volumes compared to non-obese OSA patients and non-OSA controls[63]. Furthermore, neck fat volume was greater in the non-obese OSA group compared to controls, despite matching for age and neck circumference. Compared to weight-matched non-OSA subjects, Horner et al[64] found that obese OSA patients had larger fat deposits postero-lateral to the oropharyngeal airspace at the level of the soft palate. Similar findings were identified by Schwab and colleagues[26], with OSA patients demonstrating a significantly smaller retropalatal airway and greater narrowing in the lateral dimensions, due to increased pharyngeal wall thickness in OSA patients compared to non-apnoeic controls. However, the parapharyngeal fat pads were not closer together, nor greater in size at the level of the minimum airway volume, suggesting that increased thickness of the lateral pharyngeal wall and not compression by parapharyngeal fat pads, primarily contributes to narrowing

of the UA in OSA patients. In a follow up study by the same group[25], UA size was found to be significantly smaller in obese OSA patients compared to marginally overweight controls, particularly retropalatally. In addition, volumes of several tissues surrounding the UA including the pharyngeal fat pads, lateral pharyngeal walls, soft palate, genioglossus and total tongue, were significantly larger in obese OSA patients compared to control subjects. Except for soft palate volumes, these group differences remained even when adjusting for visceral neck fat volume, suggesting that apparent disparate findings between the two groups were not accounted for by fat. In multiple linear regression analyses, total tongue volume and total lateral wall volume remained the only significant independent predictors of OSA.

Genetic influences presumably play a fundamental role in UA anatomical influences on OSA propensity and prevalence as several tissue volume abnormalities are evident in non-OSA siblings of OSA patients[65]. Increased fat surrounding the airway lumen likely contributes to a smaller UA common in OSA patients. However, UA anatomical factors such as neck circumference, fat surrounding the UA and other UA abnormalities, typically explain <35% of the variance in AHI[21, 22, 46, 62, 66, 67], suggesting that factors other than airway anatomy alone must be important in the pathogenesis of OSA.

1.4 Assessment of upper airway collapsibility

The UA is usefully and commonly modelled as collapsible conduit surrounded by extraluminal tissue with rigid segments both proximal and distal to the collapsible

segment. A schematic of the passive (i.e. hypotonic) UA behaviour is shown in Figure 1.1A.

In a normal open airway and in the absence of flow limitation (Figure 1.1B), downstream pressure is above critical closing pressure (P_{CRIT}) and flow through the airway is governed by a general resistance equation analogous to Ohm's law of electrical circuits:

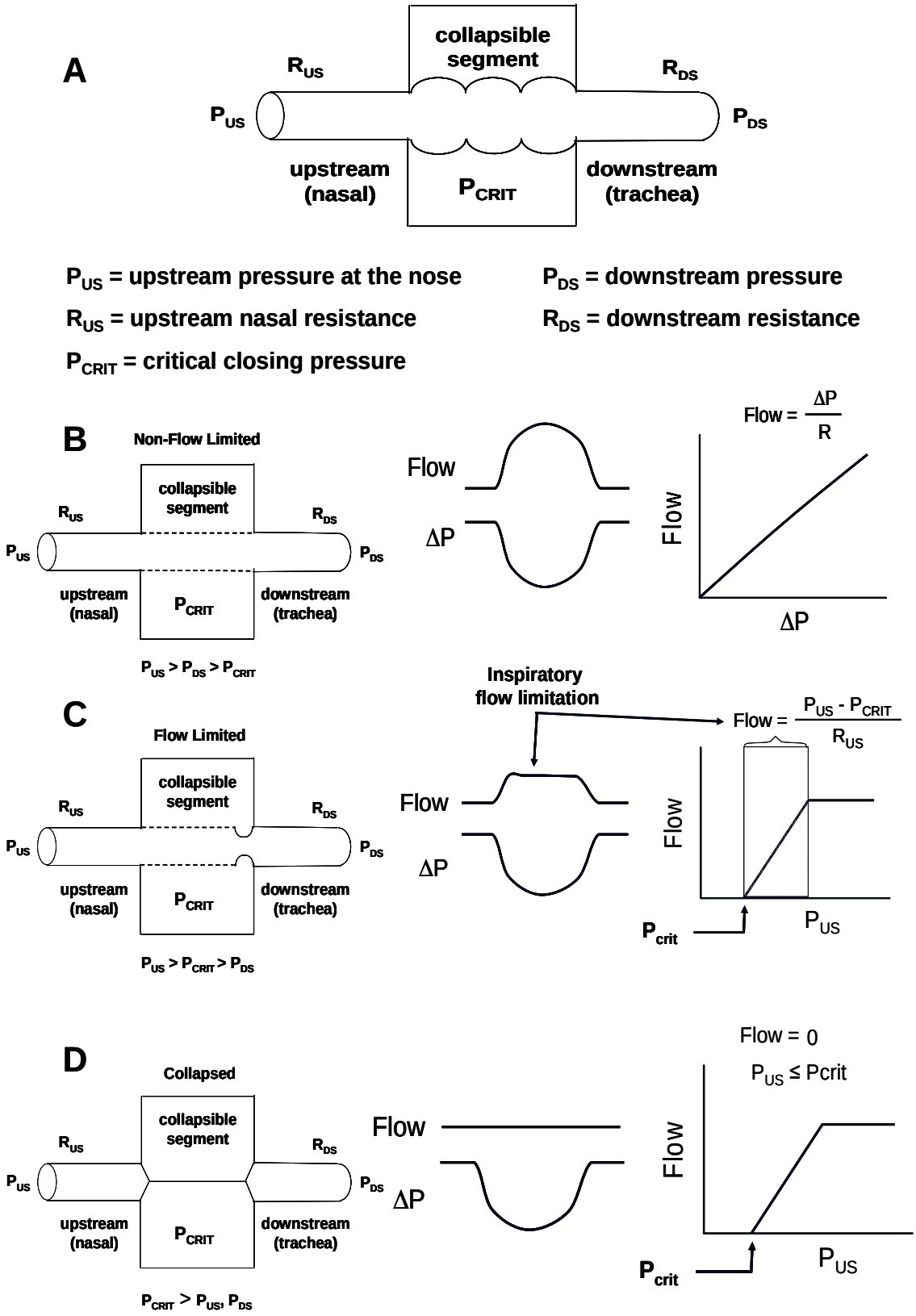
$$\text{Flow} = \frac{P_{US} - P_{DS}}{R_{US} + R_{DS}}$$

However, when downstream pressure falls below P_{CRIT} (Figure 1.1C), a choke point develops and flow becomes independent of downstream pressure (i.e. Starling Resistor) with flow governed by:

$$\text{Flow} = \frac{P_{US} - P_{CRIT}}{R_{US}}$$

Peak flow continues to fall if P_{US} decreases, and becomes zero when $P_{US} \leq P_{CRIT}$ (Figure 1.1D).

Figure 1.1: Schematic representation of the passive UA



Starling resistor model of the UA. See text for more details.

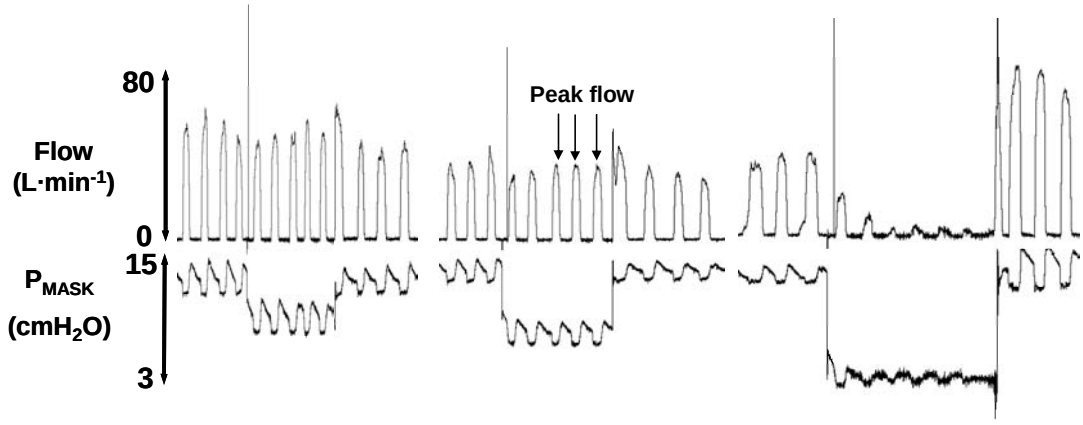
UA collapsibility can be assessed under passive (muscle hypotonia) or active (dynamic neuromuscular response) conditions. For passive P_{CRIT} measurements, continuous positive airway pressure (CPAP) is rapidly dropped from therapeutic CPAP (holding pressure, Figure 1.2 and Figure 1.3) for approximately five breaths and then returned back to holding pressure. Least squares regression of peak flow versus varying levels of CPAP is then used to estimate P_{CRIT} as the pressure at which flow equals zero, generally requiring extrapolation (Figure 1.4). Peak flow is typically measured from the 3rd-5th breaths following pressure dial-down before any substantial chemoreflex augmentation of ventilatory drive. Given therapeutic CPAP prior to dial-down leads to low UA muscle tone[68], P_{CRIT} measured in this manner is generally considered to reflect the mechanical properties of the "passive" UA. However, Schwartz and colleagues[69] noted that phasic genioglossus muscle activity progressively increased over the first three breaths following rapid dial-down, suggesting that augmentation of the genioglossus via the negative-pressure reflex does occur even during these brief pressure drops. Nevertheless, despite increased genioglossal activity, P_{CRIT} became significantly more positive, indicating an increase in airway collapsibility. This rise in UA collapsibility over the first three breaths directly following a rapid dial-down, may be the result of falling end-expiratory lung volume (EELV)[69, 70] and decreasing caudal traction on the UA (see section 1.5.3), or some other hysteresis in P_{CRIT}[69].

Similar to "passive" P_{CRIT} measurements, assessment of "active" P_{CRIT} also involves rapid dial-downs. However, pressure drops are sustained for longer periods (~10 mins[68]) to allow sufficient time for UA dilator muscle recruitment as a consequence of increased mechanical (negative pressure) and chemical (CO_2) stimuli (Figure 1.3). An alternative approach to measure "active" P_{CRIT} is to rapidly drop mask

pressure from therapeutic CPAP in a step-wise fashion every 3-5 min by ~2 cmH_2O until inspiratory airflow decreases to zero or until a sustained arousal occurs[71].

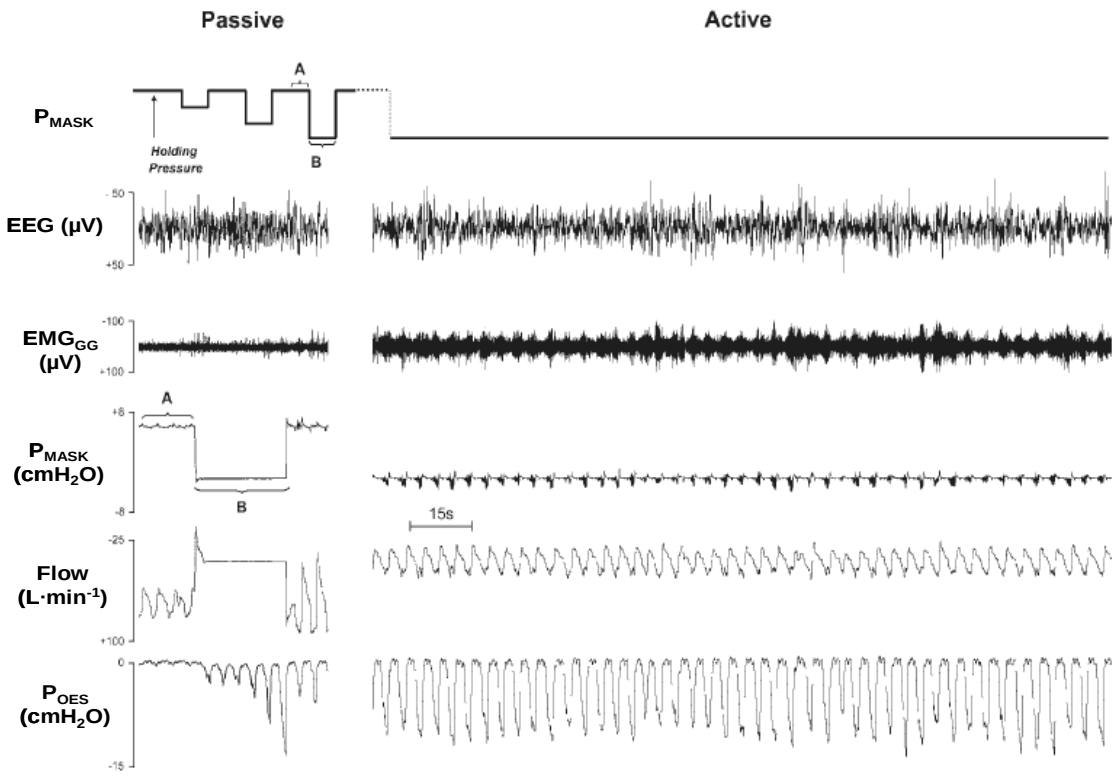
While the ranges of P_{CRIT} measurements will likely vary depending on the methods used and the experimental conditions, differences between groups with varying degrees of UA obstructon from health (normal breathing) to disease (OSA patients) are nevertheless distinguishable. "Passive" P_{CRIT} was found to be -4.5 ± 0.7 cmH_2O in non-OSA individuals and -0.05 ± 0.6 cmH_2O in a group of age- and BMI-matched OSA patients[68]. With UA muscle recruitment, "active" P_{CRIT} significantly increased to -11.1 ± 1.2 cmH_2O and -1.6 ± 0.9 cmH_2O in the non-OSA and OSA groups respectively[68]. Also using an "active" P_{CRIT} technique during sleep, P_{CRIT} was found to be -15 ± 6.1, -1.6 ± 2.6 and 2.4 ± 2.8 cmH_2O in non-OSA individuals, mild-to-moderate OSA (AHI ≥10 and <40 events·hr^{-1}) and moderate-to-severe OSA (AHI ≥40 events·hr^{-1}) patients respectively[72]. While there was overlap between groups, P_{CRIT} differences between any two groups were all statistically significant. Gleadhill et al[73] also found significant differences in "active" P_{CRIT} between snorers, obstructive hypopnoea and obstructive apnoea patients matched for gender, age and BMI. Comparable P_{CRIT} data utilising the "passive" and "active" P_{CRIT} techniques have been reported elsewhere[61, 73-75].

Figure 1.2: Example measurement of P_{CRIT}



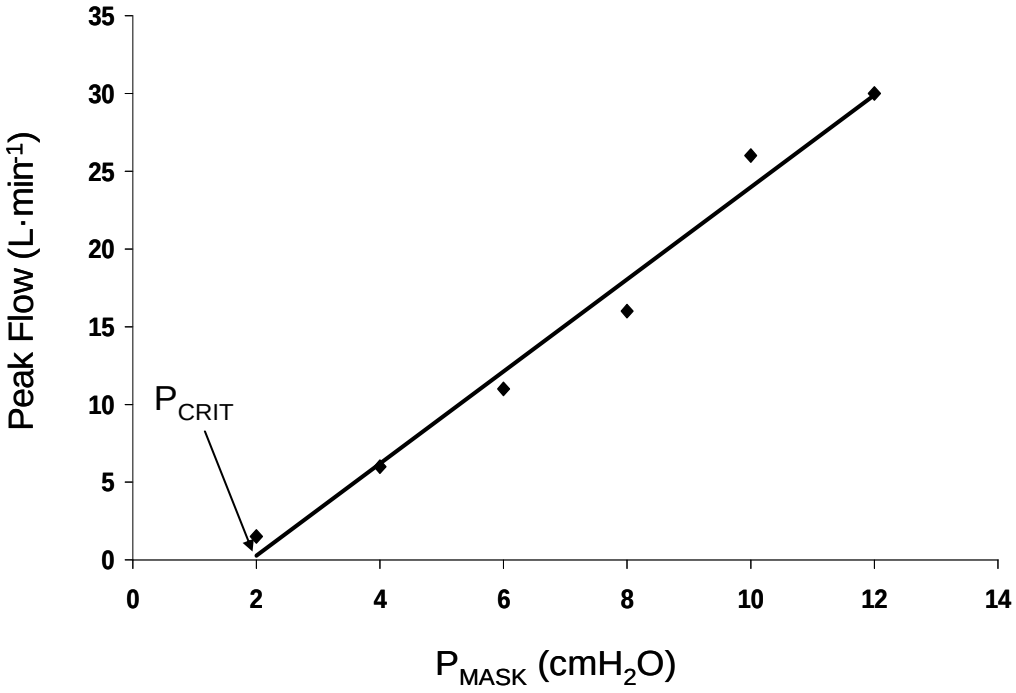
Raw data from one OSA patient showing changes in mask pressure (P_{MASK}) and inspiratory flow during progressively larger CPAP dial-downs over five breaths from therapeutic levels (holding pressure). A greater drop in CPAP leads to inspiratory flow limitation.

Figure 1.3: Comparison between passive and active P_{CRIT} measurements



Left: Mask pressure (P_{MASK}) is abruptly reduced from holding pressure (A), to a reduced pressure (B) leading to an obstructive apnoea without any clear genioglossus (EMG_{GG}) augmentation (passive conditions). *Right*: Raw data from the final three minutes of a ten minute period during which P_{MASK} was dropped to the same level in the same subject. Under these conditions, obstruction was partially overcome, but with flow limitation, large oesophageal pressure (P_{OES}) swings and increased genioglossus drive. (Modified from Patil et al[68]. http://jap.physiology.org/cgi/reprint/102/2/547. Used with permission).

Figure 1.4: Pressure-flow relationship to determine P_{CRIT}



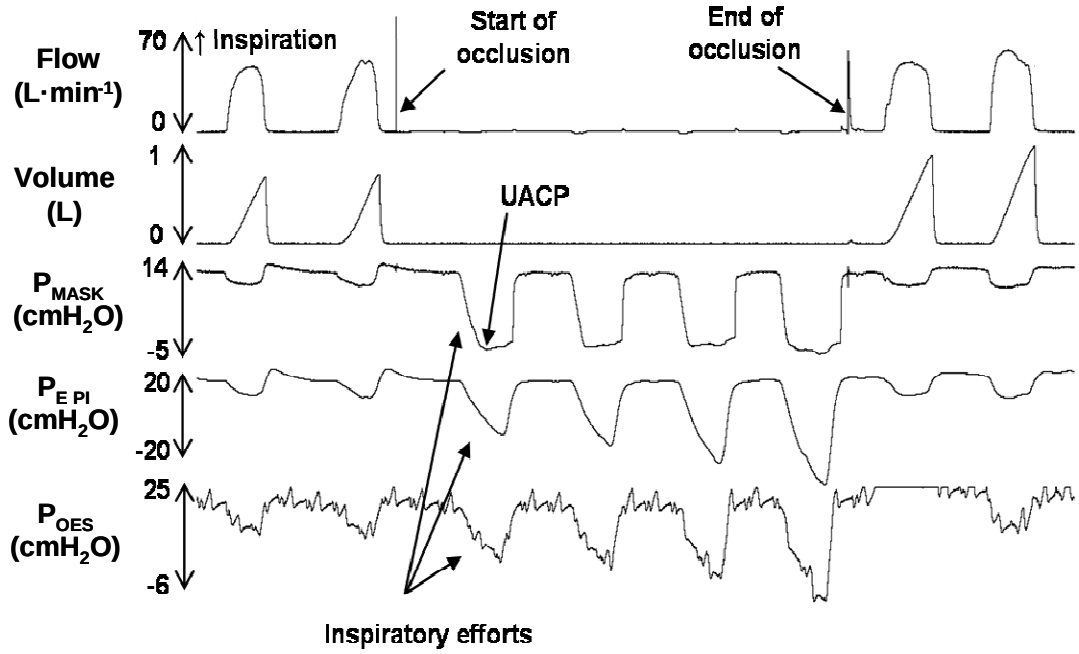
Plot of mask pressure (P_{MASK}) versus peak inspiratory flow during CPAP dial-downs in one OSA patient. P_{CRIT} is determined from the pressure intercept at zero flow from the line of best fit.

UA collapsibility has also been assessed by brief inspiratory mask occlusions[76-79]. Participants breathe through a specially designed circuit allowing delivery of CPAP as well as complete airway occlusion external to the nose, achieved via rapid inflation of a balloon upstream to the mask at end-expiration. With an open airway, inspiratory efforts against the occlusion (Figure 1.5) generate parallel decreases in mask (P_{MASK}) and oesophageal (P_{OES}) pressure throughout each inspiratory effort, with suction pressures augmenting along with chemoreceptor drive. With sufficiently negative airway pressures, the UA collapses and P_{OES} changes fail to be transmitted to P_{MASK} despite continuing inspiratory effort, as evidenced by ongoing decreases in P_{OES} and P_{MASK} flattening. This critical P_{MASK} is generally referred to as the UA closing pressure (UACP). Issa and Sullivan[76, 77] reported UACP measurements of approximately -8.2 cmH_2O in non-snorers[76], -5.7 cmH_2O in heavy snorers[76], -3.7 cmH_2O in heavy snores with the occasional obstructive event[76] and approximately -3.1 cmH_2O in OSA patients[77]. Unlike previous studies employing the P_{CRIT} technique, Issa and Sullivan[76, 77] failed to demonstrate significant differences in UACP between patients with severe OSA and heavy snorers. In addition, despite severe OSA, UACP was subatmospheric.[77] The reasons for negative UACP, in contrast to near atmospheric to positive values noted in OSA patients using P_{CRIT}[68, 72, 73] is unclear, but likely reflects important methological differences between these techniques. Firstly, P_{CRIT} measurements are governed by Starling resistor properties of dynamic airflow in a collapsible tube, which clearly does not apply in the absence of flow during mask occlusions. Secondly, unlike P_{CRIT} measurements, EELV is clamped above normal resting volume during mask occlusion, and elevated EELV is likely to improve UA patency via caudal tracheal traction (see section 1.5.3). Finally, augmentation of drive to the

genioglossus is likely more substantial due to more negative intraluminal airway pressures in occlusions than in CPAP dial-downs. Direct comparisons of P_{CRIT} versus UACP measurements do not appear to have been examined. It therefore remains unclear how comparable these techniques are, and what differential impacts of the main potential confounders are likely to be in the assessment of UA collapsibility.

The mask occlusion technique has several advantages over P_{CRIT} assessed following CPAP dial-downs. Determination of P_{CRIT} involves several CPAP dial-downs to enable construction of a pressure-flow relationship. In contrast, the mask occlusion technique allows for more rapid and repeated measurements of UACP over a shorter time. Secondly, as mentioned above, pressure drops during P_{CRIT} determination inevitably produce systematic reductions in EELV which very likely impacts upon UA function (see section 1.5.1) via modulation of the degree of caudal tracheal traction exerted on the UA (see section 1.5.3) that may further impact on UA collapsibility that the technique is designed to measure. Transient changes in the pressure-flow relationship within the first few breaths following dial-down may well be partly indicative of such effects. Thirdly, extrapolation of the least squares regression fit to the pressure-flow relationship below a lower practical limit of measurement due to increased arousals at reducing pressures, may lead to greater errors and variability in P_{CRIT} estimates.

Figure 1.5: Measurement of UACP



Raw data from one OSA patient showing changes in mask pressure (P_{MASK}), epiglottic (P_{EPI}) and oesophageal pressure (P_{OES}) during a brief mask occlusion. Following occlusion onset (start of occlusion), P_{MASK} initially tracks P_{EPI} and P_{OES} until a point at which P_{MASK} no-longer reflects changes in P_{EPI} and P_{OES}. This deflection point is indicative of UA collapse and is classified as the UACP. Occlusion offset is shown (end of occlusion).

1.5 Factors influencing upper airway size and function

1.5.1 Lung volume

1.5.1.1 Effect on upper airway size

Several studies have reported lung volume dependent effects on UA size[27, 52, 80]. For example, using fast-CT scanning, Burger et al[80] clearly showed that UA size is greatest at total lung capacity and smallest at residual lung volume, with maximum changes occurring at the level of velopharynx. Brown and colleagues[81] found similar lung volume dependent effects on UA size using acoustic reflection in healthy-weight individuals, with the greatest changes in UA size occurring between EELV and residual lung volume. In addition, males demonstrated a greater lung volume dependence of UA size, even after correcting for body surface area. Hoffstein et al[52] found that the change in UA size per unit change in lung volume from total lung capacity to residual volume was significantly greater in OSA patients compared to age- and weight- (% ideal body weight) matched non-OSA individuals, such that absolute differences in UA size were greatest at residual lung volume compared to total lung capacity. These data suggest that UA size in OSA patients is more sensitive to changes in lung volume, particularly at lower lung volumes.

1.5.1.2 Effect on upper airway function

The effect of lung volume on pharyngeal resistance and UA collapsibility during wakefulness and sleep has already been well established. In a study by Series and colleagues[82], changes in pharyngeal resistance in awake healthy-weight individuals

were investigated following lung volume inflation and deflation via negative and positive extrathoracic pressure in an iron lung. Lung volume inflation in the order of ~1.2 L led to a ~30% reduction in pharyngeal resistance, whereas resistance increased by ~120% with a ~400 ml fall in lung volume, further supporting that lung volume effects on the UA are more sensitive at reduced lung volumes. The same group[83] demonstrated similar results when lung volume was manipulated via continuous negative and positive airway pressure.

In a study by Stanchina and colleagues[84], UA collapsibility increased by ~1.2 cmH_2O during sleep in healthy-weight individuals following a ~600 ml decrease in EELV induced via positive extrathoracic pressure in an iron lung. A similar increase in EELV (~700 ml) in anaesthetised and paralysed overweight OSA patients led to improved UA collapsibility, with P_{CRIT} decreasing by ~1.2 cmH_2O[85]. In the absence of neuromuscular influences, these findings strongly support the presence of mechanical effects of lung volume change on passive UA properties. Furthermore, the degree of improvement in P_{CRIT} correlated with BMI suggesting that UA patency is more sensitive to changes in lung volume in heavier individuals. Using an iron lung to manipulate EELV, Heinzer and colleagues[86] recently showed the level of CPAP required to abolish flow limitation in obese OSA patients during sleep, increased from ~12 to ~17 cmH_2O following a ~0.6 L reduction in lung volume and was reduced from ~12 to ~4 cmH_2O with ~0.4 L lung inflation. A subsequent study by the same group[87], showed significant lung volume effects on OSA severity, with total AHI decreasing from ~62 $events \cdot hr^{-1}$ to ~31 $events \cdot hr^{-1}$ following a ~770 ml increase in EELV. However, a further ~530 ml increase in EELV had no additional effect on OSA severity. The lack of change in AHI despite a further increase in lung

volume may indicate a ceiling effect of lung volume influences on OSA severity. While an earlier case report by Series and colleagues[88] supported beneficial lung volume effects on OSA severity, with AHI decreasing from 53 to 38 events·hr^{-1} with a ~0.5 L increase in EELV in one patient, a follow up study by the same group[89] showed no improvements with a similar increase in EELV in nine overweight OSA patients. These contrasting results with those of Heinzer et al[87] may reflect several factors. Heinzer et al[87] achieved greater lung volume increases (~770 ml vs. ~500 ml) that may have had a greater effect on AHI. Series et al[89] first determined the negative extrathoracic pressure required to induce a 0.5 L increase in lung volume during wakefulness and then applied the same pressure during sleep such that it is unclear if the change in lung volume during sleep was similar to that achieved during wakefulness. While there are some conflicting data, the majority of studies appear to support that lung volume has potent effects on UA function and apnoea severity. If present, these effects are likely to be more pronounced in obese individuals given that EELV is substantially reduced in this group[90-92].

1.5.2 Posture

1.5.2.1 Effect on upper airway size

UA size, particularly at the level of the pharynx, significantly decreases when healthy-weight individuals move from a seated position to the supine posture[93, 94], an effect potentially explained by the fall in lung volume when moving to the supine position[91, 92]. In addition, males experienced a greater change in pharyngeal cross-sectional area when moving to the supine position[95]. Further studies illustrate that UA size in OSA patients also declines following a similar change in posture[96] and in

anaesthetised and paralysed healthy-weight OSA patients when moving from the lateral to supine posture[97]. A recently developed novel technique, known as optical coherence tomography, has been undertaken to quantitatively measure UA dimensions. Walsh et al[98] showed that velopharyngeal cross-sectional area was smaller in overweight OSA patients in the supine position compared to age- and BMI-matched controls. However, in contrast to an earlier report[74], moving to the lateral position had little effect on cross-sectional area of the UA in both groups. This apparent discrepancy may be due to different techniques used to assess UA dimensions and/or differences in awake[98] versus anaesthetised[74] states. Walsh and colleagues[98] noted that the shape of the airway was elliptical with a greater lateral orientation when both groups were supine, compared to a more circular shape when individuals were in the lateral posture. The authors suggested that UA shape changes may be important in the pathogenesis of UA collapse, given that a laterally oriented ellipsoid shaped airway may have a greater propensity for collapse compared to a more circular shaped airway.

1.5.2.2 Effect on OSA severity and upper airway function

The supine position is commonly associated with increased AHI[78]. In one study[99], ~56% of OSA patients showed posture dependent OSA, defined by at least two times higher AHI in the supine position compared to the average AHI in the remaining sleep positions. In a separate report[100], posture dependent OSA, defined as >50% reduction in AHI and AHI <5 events·hr^{-1} in non-supine postures, was found to be inversely related to OSA severity with ~50% of the mild sleep apnoea (AHI 5-15 events·hr^{-1}) patients showing posture dependent OSA, decreasing to

19.4% and 6.5% in moderate (AHI, 15-30 events·hr^{-1}) and severe OSA (AHI >30 events·hr^{-1}) patients respectively. Sleep posture has significant effects on several other OSA variables including apnoea duration, minimum O_2 desaturation, ΔO_2 saturation, arousal duration and snoring intensity, which all significantly increase in the supine posture compared to the lateral position in severe OSA patients[101]. An earlier report by the same group[102], demonstrated a ~2.4 cmH_2O higher therapeutic CPAP in the supine versus lateral posture, further supporting the negative effects of supine sleep on UA function.

These changes appear to be primarily modulated by effects of body posture on UA collapsibility during sleep. Using brief inspiratory negative pressure pulses, UA collapsibility has been shown to decrease by ~1.6 cmH_2O in the lateral versus supine postures in a group of healthy-weight individuals[103]. OSA patients also show improvements in UA function when sleeping in the lateral position, with P_{CRIT} decreasing by ~2.8 cmH_2O in light sleep, ~2 cmH_2O in slow-wave sleep (SWS) and ~3.2 cmH_2O in rapid-eye movement (REM) sleep versus the supine posture. During midazolam sedation, P_{CRIT} has also been found to decrease with upper body elevation[104], consistent with positional effects during sleep[78].

1.5.3 Caudal tracheal traction

Patency of the UA is influenced directly and indirectly by the movement of several intrathoracic structures including the trachea, oesophagus and the diaphragm. These structures are pulled caudally during inspiration by the descending diaphragm, increasing tension on the UA in a process termed caudal tracheal

traction[105, 106]. A further component contributing to caudal tracheal traction is the pressure gradient between the intra- and extrathoracic structures[105, 106]. Several studies in anaesthetised animals have demonstrated the important modulating effects that caudal tracheal traction has on UA resistance (R_{UA}) and UA collapsibility[105, 107-109]. A study by Van de Graaff[105] demonstrated that R_{UA} decreased synchronously with caudal tracheal movement during inspiration in tracheotomised and anaesthetised dogs. Similar reductions in R_{UA} were noted during paced diaphragmatic breathing undertaken to eliminate the influence of UA dilator muscle activity, and also following denervation of UA muscles. However, cutting structures connected to the UA, including ventrolateral cervical structures, the trachea and the oesophagus, prevented these inspiratory related decrements in R_{UA} and frequently led to complete UA collapse. These data firmly establish that caudal traction alone has significant dilating effects on the UA, independent of UA dilator muscle influences.

Further animal studies support the importance of caudal traction for UA patency. Increasing tension on the isolated trachea in anaesthetised and paralysed cats and pigs led to significant rises in peak airflow and a reduction in P_{CRIT}[108, 109]. While the precise mechanism(s) by which caudal tracheal traction improves UA patency is unclear, it is speculated that traction may either lead to decreased pharyngeal folding or reduced UA wall compliance[105].

Increased compliance of the UA in awake[110], sleeping[51] and anaesthetised OSA patients[74] versus healthy controls may indicate changes in the degree of traction exerted on the UA[74], either via direct effects on the UA wall or via modulation of

extraluminal tissue pressure. In support of this latter view, Kairaitis et al[111] demonstrated that tissue pressure surrounding the pharyngeal lumen in anaesthetised rabbits decreased when tension on the trachea was increased mechanically. As with previous reports, UA collapsibility also decreased following increased tracheal tension, an effect potentially attributable to the fall in extraluminal tissue pressure. While clearly important in animals, the role of caudal tracheal traction remains unclear and inevitably difficult to investigate in humans. However, well known lung volume dependence of UA function is potentially predominantly mediated via caudal tracheal traction effects.

1.5.3.1 Intra-abdominal pressure and diaphragm position

Increased IAP may importantly influence lung volume, diaphragm position, the degree of caudal tracheal traction exerted on the UA and consequently, the propensity for UA collapse. Such effects are likely to be most evident in the obese population, particularly in the supine posture when hydrostatic forces on the diaphragm are at their greatest and also following muscle relaxation during sleep.

While direct measurements of IAP require insertion of a catheter into the peritoneal cavity[112], less invasive intrabladder[113-116] or intragastric[117-120] pressure measurements have both been validated as suitable alternative indirect measures. Obesity has a significant effect on IAP, with values ranging from ~11.5-18.0 cmH_2O in morbidly obese individuals (BMI >40 $kg \cdot m^{-2}$)[114, 115, 121] compared to ~6.5-9.0 cmH_2O in healthy-weight individuals (BMI <25 $kg \cdot m^{-2}$) [114, 115, 122]. In addition, IAP is highly correlated with sagittal abdominal diameter (distance from table to apex of

abdominal girth)[115]. Morbidly obese males show a larger sagittal abdominal diameter and a significantly higher IAP compared to BMI-matched females[115], indicative of substantial gender differences in fat distribution.

The higher IAP in obese males is likely to have a greater influence on lung volume and diaphragm position and hence tracheal traction, compared to equally obese females, and may help explain the increased prevalence of OSA in males. External abdominal compression and water immersion up to the xiphoid process and the neck results in diaphragm ascent by ~1.2-3.5 cm[123, 124]. In addition, cephalad movement of the diaphragm in the order of 1.9 cm has been demonstrated following a rise in IAP induced by CO_2 insufflation into the abdominal cavity[125]. Migration of the carina towards the tip of an endotracheal tube by between 0.8-1.4 cm is evident following similar procedures[126, 127]. The direct impact this displacement in end-expiratory diaphragm and carinal position has on UA tension in humans remains unclear. Some evidence supporting the potential importance of these effects includes increased snoring and respiratory events during pregnancy, particularly during the third trimester[128-131]. These changes may be a direct consequence of elevation of the diaphragm by ~2 cm[132] and reduced EELV in the order of 20%[133-135] following development of the fetus. In addition, preliminary data suggest that UA compliance is increased when pregnant women move from the seated position to the supine posture compared to non-pregnant women[136].

1.5.4 Neck position

Neck position has been shown to have important effects on UA function[104, 137]. Neck flexion significantly reduces maximal airflow and increases P_{CRIT} in anaesthetised and paralysed decerebrate cats[108]. In a recent study in anaesthetised healthy-weight individuals[138], neck extension (~20^{o}) led to a ~7.5 cmH_2O reduction in P_{CRIT} while and neck flexion (~10^{o}) resulted in a ~5 cmH_2O increase in P_{CRIT}. The precise mechanisms via which neck posture influences UA function are not completely understood, but likely reflect changes in airway wall compliance given airway length has been shown to decrease following neck flexion and increase following neck extension in decerebrate cats[108].

1.5.5 Fluid shifts

Increased oedema surrounding the UA may also contribute to increased R_{UA} and UA collapsibility. Chui and colleagues[139] showed that lower body positive pressure (~55 cmH_2O), decreased total leg fluid volume by ~340 ml, increased neck circumference and caused a 102% rise in pharyngeal resistance during wakefulness in a group of healthy-weight individuals. There was no change in EELV following lower body compression, indicating the increase in R_{UA} was not explained by changes in lung volume. Two subsequent studies by the same group showed similar levels of lower body positive pressure during wakefulness, produced a decrease in UA area by ~10%[140] , while UA collapsibility increased by ~20%[141]. Similarly, lung volume remained unaffected by lower body positive pressure, suggesting that fluid displacement into the neck was the primary cause of these effects. While these data indicate that lower body positive pressure leads to

significant changes in UA size and UA function during wakefulness in healthy-weight individuals, it is unclear if fluid shifts contribute to SDB in OSA patients. However, a strong correlation between overnight leg fluid volume shifts and AHI[142] supports that these effects may well be important.

1.6 Upper airway dilator muscles

There are at least twenty UA muscles which actively dilate or constrict the UA[143], thereby modulating UA patency. The largest of the UA dilator muscles, the genioglossus, is the major protrusion muscle of the tongue. Therefore, the genioglossus is thought to play a pivotal role in maintaining UA patency and has attracted the most attention in studies of pathogenic mechanisms underlying SDB. The genioglossus is one of several muscles which make up the tongue. Intrinsic tongue muscles act mainly to alter the shape of the tongue[144], whereas the extrinsic muscles of the tongue, namely the genioglossus, hypoglossus, styloglossus and palatoglossus, help to protrude and/or suspend the tongue[144]. The position of the soft palate, including the uvula, is controlled by the tensor palatini, levator veli palatini, musculus uvulae, palatoglossus and the palatopharyngeus[144]. Several UA dilator muscles show increased (phasic) activity during inspiration[1, 145-152], which helps to oppose the collapsing negative pressure generated by contraction of the diaphragm and other inspiratory pump muscles. There is also residual background (tonic) activity during expiration[1, 145-152], which is likely to help stiffen the airway. In contrast, activity of the tensor palatini and other “tonic” muscles is generally stable throughout the respiratory cycle[146, 148, 149, 151, 152].

1.6.1 Neural inputs to the genioglossus

Genioglossus muscle activity is modulated by three main neural inputs:

(1) a local negative-pressure reflex

(2) respiratory pattern generator neurons from the medulla (central drive)

(3) wakefulness tone

1.6.1.1 Negative pressure reflex

Negative changes in airway pressure are thought to be sensed by mechanoreceptors located mainly in the larynx, leading to increased firing of superior laryngeal nerve afferents[153] and increased hypoglossal output to the genioglossus[154]. Inhibiting this pathway via local anaesthesia applied to the UA mucosa, leads to significant decrements in respiratory related changes in genioglossus muscle activity in rabbits[154] and humans[155], reduces the sensitively of the genioglossus to respond to changes in airway pressure[156] and peak activity during brief inspiratory negative pressure pulses[155, 157] in OSA patients and controls during wakefulness. Similar inhibition is evident with selective blockade of trigeminal nerves (nasal anaesthesia), superior laryngeal nerves (laryngeal mucosa anaesthesia) or glossopharyngeal and lingual nerves (oropharyngeal mucosa anaesthesia)[158].

Activation of the genioglossus muscle during wakefulness is tightly regulated by changes in airway pressure during inspiration. Robust relationships (r=0.69-0.97) between peak negative epiglottic pressure and peak genioglossus muscle activity under varying conditions of ventilation and inspiratory resistive loads, have been

demonstrated in OSA patients and control subjects during wakefulness[156, 159-161]. Furthermore, correlations between epiglottic pressure and genioglossus activity and the slope of the relationships were not different between OSA patients and controls during wakefulness in one study[160]. In a study by Malhotra et al[162], a substantial decrease in both peak and tonic genioglossus muscle activity was identified in tracheostomised individuals breathing through a tracheal stoma compared to nasal breathing. Switching breathing route from nasal to tracheostomy breathing in anaesthetised and vagotomised rabbits also resulted in a reduction in phasic genioglossus activity[163]. These findings further support the sensory role of airway mechanoreceptors to negative airway pressure mediated effects on genioglossus activity.

In addition to activation via respiratory-related changes in airway pressure, the genioglossus is also capable of responding quickly to abrupt negative changes in airway pressure during wakefulness[103, 155, 164-166]. The onset of activity in response to brief negative pressure pulses typically occurs within ~30 msec[165], with peak activity appearing ~10 msec later[165]. This negative pressure reflex does not appear to be significantly impaired in OSA patients, at least during wakefulness[164], since muscle activation has been found to be significantly higher in OSA patients compared to controls during modest intensity (~-10 cmH_2O) brief negative pressure pulses, but with no group differences in reflex activation with larger stimulus intensity (~-20 cmH_2O)[164].

Studies of the effect of state on the genioglossus negative pressure have shown inconsistent results. While genioglossus muscle responsiveness to negative airway

pressure remained unchanged immediately following sleep onset (2-5 breaths following the wake-sleep [α-θ EEG] transition) in healthy-weight individuals[167], it was significantly attenuated during non-rapid eye movement (NREM) sleep. Previous work also identified a significant reduction in peak activity during NREM[166, 168] and REM[167] sleep compared to wakefulness, while onset latency and onset to peak activity was shown to be delayed during sleep[166, 168]. In contrast, recent work by Eckert and colleagues[165] demonstrated that peak amplitude, onset latency and onset to peak were unaffected by sleep stage. Furthermore, a previously unidentified period of suppression shortly after the initial peak response was evident, with the magnitude of this suppression found to be greater during NREM and REM sleep compared to wakefulness. While the precise reasons for discrepant peak amplitude and onset latency findings are not clear, this may relate to postural and other methodological differences. For instance, posture was either not controlled[168] or participants were asked to sleep in the lateral position[166, 167]. In healthy-weight individuals, the genioglossus reflex appears to be augmented during sleep compared to wakefulness in the supine posture, and during supine versus lateral NREM sleep[103]. The authors speculated that the augmented reflex evident in the supine position may act to help maintain UA patency. However, despite increased responsiveness to negative airway pressure, UA collapsibility was higher in the supine compared to the lateral position, indicating that heightened reflex responsiveness is not sufficient to prevent posture related increases in UA collapsibility during sleep.

In summary, activation of the genioglossus is tightly regulated by changes in negative airway pressure. This response is clearly of reflex origin given its short

onset latency following a rapid drop in airway pressure. In addition, the response does not appear to be impaired in OSA patients, at least during wakefulness, although this does not rule out impaired reflex responses via abnormal electromechanical coupling from anatomical influences. The reflex is speculated to involve primarily laryngeal afferents, given topical anaesthesia results in an attenuated response. Sleep appears to have a variable effect on the response, with some studies demonstrating a reduction, and others increased or no change in the response, potentially reflecting differences in posture between studies.

1.6.1.2 Central drive

The genioglossus muscle is innervated by the hypoglossal nerve which projects from the hypoglossal nucleus and has inputs from inspiratory neurons, such as raphe neurons, located in the medulla. The neurotransmitter serotonin (5-hydroxytryptamine [5-HT]) is released from raphe neurons of the medial medulla[169] and has potent excitatory effects in *in vitro* preparations of hypoglossal motoneurons from rats[170] and the genioglossal branch of the hypoglossal motor nucleus in decerebrate, paralysed, vagotomised and artificially ventilated cats[171]. Similarly, administration of 5-HT to the hypoglossal motor nucleus *in vivo* results in genioglossus recruitment in anaesthetised and tracheostomised rats, while delivery of a 5-HT antagonist reduces genioglossus activation[172]. Central drive from these respiratory pattern generating neurons are thought to pre-activate UA dilator muscles, such as the genioglossus and alae nasi, ~50-100 ms before onset of flow to protect the airway against the impending negative airway pressure generated by the inspiratory pump muscles[173, 174].

Chemical stimuli have also been shown to have powerful effects on genioglossus output. Onal and colleagues[175] demonstrated strong correlations between genioglossus and diaphragm muscle activity with increasing alveolar partial pressure of CO_2 (P_{ACO_2}, r=0.93 and r=0.87 respectively) in awake healthy-weight humans. The slope of diaphragm response to CO_2 versus the slope of the genioglossus response to CO_2 was also highly correlated (r=0.96, $P < 0.001$). Similar augmentation in muscle activity was also evident under hyperoxia with varying levels of hypercapnia[176]. These data support that increased drive to the genioglossus during hypercapnia is likely predominantly mediated via activation of raphe neurons in the medulla by the central chemoreceptor, as peripheral chemoreceptor output is substantially depressed with hyperoxia[177]. In support of this view, several groups have demonstrated that increased CO_2/H^+ concentrations results in stimulation of raphe neurons *in vitro*[178] and *in vivo*[179], leading to increased hypoglossal outflow[180].

Given that airway pressure becomes more negative with increased ventilation to a hypercapnic stimulus[161, 181], changes in genioglossus muscle activity could at least in part reflect activation of the negative pressure reflex (see section 1.6.1.1) and not necessarily central drive *per se*. To investigate this mechanism, Shea et al[181] examined changes in genioglossus muscle activity and airway pressure during wakefulness in 18 healthy-weight subjects under several conditions; (1) baseline (end-tidal CO_2 [P_{ETCO_2}] = 40.1 ± 2.8 mmHg), (2) hypercapnia (P_{ETCO_2} = 45.3 ± 2.7 mmHg) and (3) hypocapnia (P_{ETCO_2} = 34.6 ± 3.4 mmHg) induced by mechanical hyperventilation. While peak genioglossus muscle activity was shown to increase and decrease compared to baseline during hypercapnia and hypocapnia

respectively, muscle activity was strongly correlated with airway pressure (r=0.87), suggesting that genioglossus muscle activation is importantly modulated by airway pressure in lieu of chemical stimulation.

Nevertheless, several reports show that hypercapnia has stimulatory effects on genioglossus muscle activity independent of airway pressure. Hypercapnia led to increased genioglossus activation in laryngectomised patients breathing through a tracheal stoma, thereby eliminating any influence of airflow and changes in airway pressure[182]. In addition, the relationship between peak muscle activity with varying levels of hypercapnia, was found to be similar in tracheostomised patients and controls. In a study by Lo et al[183], the effects of two levels of hypercapnia (~5 and 10 mmHg above eucapnic levels) on muscle activity was investigated in healthy-weight individuals during wakefulness, with and without application of CPAP to reduce the influence of UA negative pressure. CPAP significantly reduced genioglossus muscle activity whereas hypercapnia increased peak activity despite similar airway pressure compared to baseline conditions. The slope of the muscle activity versus pressure relationship during hypercapnic stimuli was not different between CPAP on and off conditions, supporting that augmentation of genioglossus activity can be driven by chemical stimuli independently of negative airway pressure.

The effect of state and sleep stage on muscle responsiveness to chemical stimuli has been investigated in animals and humans. In rats, diaphragm activity increases linearly with CO_2 during wake, NREM and REM sleep[184]. However, a greater CO_2 concentration was required to stimulate the genioglossus during sleep, particularly

in REM. In a similar study in goats, while not significant, the change in genioglossus muscle activity as a function of P_{ETCO_2} tended to be lower in NREM and REM[185]. The influence of state on the genioglossus response to hypercapnia appears to be quite variable in humans. In some studies, the hypercapnic ventilatory response appears to decrease during sleep; by ~20% in one study[186] and by greater than 50% during NREM versus wake and even further during REM in another study[187]. On the other hand, Pillar et al[188] demonstrated that activation of the genioglossus and tensor palatini remained unchanged between stage 2 and SWS despite a stage-dependent increase in P_{ETCO_2} of ~0.8 Torr. In addition, both muscles failed to respond following CO_2 administration (6 Torr above eupnoiec levels) during stage 2 and SWS. The slope of the relationship between peak genioglossus muscle activity and P_{ETCO_2} was also not different between wake and NREM sleep[183] and did not change when sleep related increments in R_{UA} were normalised with application of CPAP. While these findings suggest that central drive to the genioglossus is unaffected by sleep stage, a combination of both resistive loads (5, 10 and 15 $cmH_2O \cdot L^{-1} \cdot s$) and hypercapnia (5-10 mmHg above baseline) has been shown to elicit increased genioglossus activity during NREM sleep in healthy-weight individuals, where no change in muscle activity was observed during hypercapnia or at each level of resistive load when given individually[161].

In summary, activation of the genioglossus muscle is modulated by the central pattern generator neurons within the medulla. Administration of CO_2 has potent stimulatory effects on the genioglossus at least during wakefulness, with activation tightly correlated with P_{ETCO_2}. While the rise in genioglossus muscle activity during

hypercapnia may partly reflect the genioglossus' response to increased negative airway pressure, studies in laryngectomised individuals and individuals on CPAP, support that hypercapnia stimulates genioglossus muscle activity independently of airway pressure. In humans, the genioglossus response to hypercapnia during sleep appears to be inconsistent. A decrease in CO_2 activation of the genioglossus during sleep could be a primary factor contributing to UA instability in OSA patients.

1.6.1.3 Wakefulness tone

The wake-sleep transition, characterised by α-θ changes in the EEG, is associated with an abrupt but transient fall in respiratory drive to UA dilator muscles (genioglossus and tensor palatini) and the diaphragm, leading to a decrease in ventilation and a rise in R_{UA}[146, 148, 149]. The decline in genioglossus activation appears most likely due to a transient reduction in chemical (CO_2) drive to breathe since the UA negative pressure reflex does not appear to be impaired across the wake-sleep transition, at least in healthy-weight individuals[167]. In addition, genioglossus and tensor palatini activity continues to fall at sleep onset even when CPAP is applied to match R_{UA} between wakefulness and sleep[146]. Lo and colleagues[189] also showed that genioglossus and tensor palatini muscle activity significantly decreased at sleep onset, despite minimising pressure fluctuations and R_{UA} as well as chemical influences via non-invasive positive pressure ventilation. In contrast to transient changes in genioglossus activity at sleep onset, tonically active UA muscles, such as tensor palatine, show a persistent reduction in activity following sleep onset[146, 148, 149]. These and several other lines of evidence support the presence of a tonic 'wakefulness' drive acting on the respiratory system which

is lost during sleep[190-193]. Animal studies clearly show that serotonergic neurons of the dorsal raphe nucleus, which fire at a steady rate during wakefulness, show a decreased firing rate during sleep[190, 192, 193], particularly in REM[190, 192]. These data strongly suggest that wakefulness *per se* has independent tonic effects on UA dilator muscle activity.

1.6.2 Effects of upper airway dilator muscle activity on upper airway collapsibility and size

Contraction of UA dilator muscles, particularly the genioglossus, is thought to play an important role in improving UA patency by dilating the oropharyngeal airway. In a recent study by Cheng et al[194], movement of the genioglossus muscle was tracked in awake healthy-weight individuals using a technique known as MRI tagging, where timed application of an interference grid applied to the magnetic field, allows temporospatial tracking of multiple image elements within the MRI field of view. The genioglossus was shown to move anteriorally during inspiration and posteriorally during expiration, with the greatest movement in the order of ~1 mm, supporting an important UA dilating role of genioglossus activity during inspiration.

In isolated UA preparations in anaesthetised animals, direct electrical stimulation of UA dilator muscles or via hypoglossal nerve stimulation, led to a significant improvement in maximal airflow, R_{UA} and UA collapsibility[195-198], with P_{CRIT} decreasing by ~8 cmH_2O in cats[196] and dogs[197]. Consequently, UA electrical stimulation may have beneficial therapeutic effects in OSA patients. Early work by Miki et al[199], showed that several measurements of OSA severity such as AHI,

apnoea time and the number of times O_2 saturations dropped below 85%, significantly decreased with submental surface electrical stimulation. While the authors attributed these findings to genioglossus stimulation, a significant or perhaps dominant contribution from other muscles such as the digastric, stylohyoid, mylohyoid and geniohyoid cannot be ruled out. In a small trial of 7 healthy-weight males and 5 male OSA patients, the effect of intra-oral surface stimulation of the genioglossus on UA mechanics was investigated during sleep[200]. In both groups, stimulation resulted in a substantial increase in peak airflow and a reduction in R_{UA}, particularly in the OSA group. However, genioglossus stimulation was generally unable to re-open the UA during complete UA obstruction unless accompanied by an arousal. Similar results were reported in a recent study employing intramuscular electrical stimulation in 14 OSA patients[201], where P_{CRIT} was found to decrease from ~2.9 to 0.9 cmH_2O with genioglossus stimulation, and decreased even further (~-4.2 cmH_2O) when used in combination with a mandibular advancement splint. While electrical stimulation increased the cross-sectional area of the pharynx, it had little effect on pharyngeal compliance. In another study, AHI was shown to decrease from ~52 to 23 events·hr^{-1} following hypoglossal nerve stimulation in a group of 8 OSA patients[202]. In combination, these data clearly support that genioglossus activation plays an important role in promoting UA patency and that genioglossus stimulation could provide a viable treatment option for some OSA patients. However, given genioglossus stimulation alone does not appear to decrease P_{CRIT} below atmospheric pressure[201], favourably alter pharyngeal compliance[201] or normalise respiratory event frequency[202], it appears that other factors, such as lung volume mediated effects on caudal tracheal traction and

potentially respiratory control and arousal factors may importantly interact in the pathogenesis of OSA.

1.7 Neurocompensatory reflexes during wakefulness in OSA patients

Unlike during sleep, the UA is quite resistant to collapse during wakefulness in OSA patients[203]. This indicates that wakefulness dependent neurcompensatory reflexes are able to maintain UA patency in the presence of abnormal underlying UA anatomy and/or collapsibility. This is supported by several studies that have identified augmented levels of tonic and phasic genioglossus and tensor palatini muscle activity during wakefulness in OSA patients compared to non-OSA individuals[145, 146, 160, 204], even when groups were matched for age and BMI[145].

Increased UA dilator muscle activity in OSA patients is perhaps one of several reflexes activated during wakefulness to compensate for mass loading effects of obesity. EELV decreases in healthy-weight individuals when moving from the upright posture to the supine position[91, 92], an effect likely dominated by diaphragm ascent. Despite increased mass loading, there is little to no change in EELV when obese individuals move to the supine condition[91, 92]. While it is perhaps surprising and unclear why obesity has little influence upon lung volume when changing positions, this could indicate a ceiling effect of lung volume decrements in obesity. Alternatively, obese individuals may actively defend against postural-related decrements in lung volume via compensatory increases in diaphragm muscle activity. Muller[205] demonstrated that abdominal compression leads to a significant

increase in expiratory diaphragm muscle activity and speculated this may be due to stretch reflex activation of the diaphragm. In healthy-weight individuals in the supine position, external mass loading to the chest and abdomen failed to reduce lung volume, supporting the presence of such compensatory mechanisms[92]. However, there are currently no data available to evaluate if obese OSA patients experience augmented levels of diaphragm muscle activity during wakefulness compared to healthy-weight individuals.

1.8 Changes in ventilation and upper airway function at sleep onset

There are several physiological changes at the wake-sleep transition including an abrupt decrease in ventilation, a fall in UA dilator (genioglossus and tensor palatini) and ventilatory pump muscle activity, and an increase in R_{UA}[146, 148, 149, 204, 206]. The magnitude of these changes appears to be greater in OSA patients compared to both older and younger control subjects[146]. In addition, the change in activity across sleep onset appears to vary between muscles. For example, despite the abrupt decrease in genioglossus muscle activity over the initial few breaths, the genioglossus is recruited over subsequent breaths and eventually returns to pre-sleep onset levels[146, 148, 149]. In contrast, tensor palatini and diaphragm muscle activity continues to remain below wakefulness levels[146, 148, 149]. While the eventual rise in genioglossus activity suggests that the negative pressure reflex is at least partially maintained during sleep in OSA patients, it appears to be ineffective in re-opening the UA, as R_{UA} continues to rise[148, 149]. Thus, the reduced ventilation and increased R_{UA} evident following sleep onset may be explained by the decline in other UA dilator and inspiratory pump muscles. However, other factors, such as

reduced lung volume, may also contribute to increased UA instability via caudal traction effects.

EELV decreases by ~15-20% during sleep in healthy-weight individuals[207, 208], which would likely contribute to UA instability (see section 1.5.1). However, there are currently limited data concerning the changes in lung volume at sleep onset in either healthy-weight individuals or obese OSA patients. Acute lung volume decrements at sleep onset could importantly contribute to respiratory events shortly after sleep onset in OSA patients[146], particularly if augmented levels of diaphragm muscle activity defend against obesity related decreases in lung volume during wakefulness. A reduction in this activity immediately following sleep onset, similar to that already established in the genioglossus, would very likely result in a decline in lung volume via diaphragm ascent, reducing tracheal traction on the UA and potentially increasing UA collapsibility. Lung volume is profoundly reduced during decreased muscle tone with general anaesthesia in obese individuals[209], with cranial displacement of the diaphragm identified as a key contributor to this decrease[210, 211]. Similar changes are potentially experienced at sleep onset, with the magnitude likely to be greater in obese OSA patients due the compressive effects of obesity in combination with decreased muscle tone at sleep onset. Such effects could help explain the increased prevalence of SDB events in this group.

The fall in ventilation at sleep onset is at least partially explained by the increase in R_{UA}, secondary to the decline in respiratory drive to the UA muscles such as the genioglossus. However, ventilation and genioglossus muscle activity was still shown to decrease at the wake-sleep transition in OSA patients[146] and controls[146,

[206], even when sleep-related increments in R_{UA} were prevented by the application of CPAP, likely reflecting a loss in a 'wakefulness' ventilatory stimulus. While CPAP significantly decreased phasic genioglossus muscle tone in OSA patients during wakefulness, the level of activity was still above that of older and younger controls and decreased by a greater magnitude at sleep onset, so that ventilation still fell by a greater magnitude in the patient group[206]. These data further support that there is potentially a greater ventilatory 'wakefulness' compensatory drive present in OSA patients such that loss of this drive component at sleep onset likely contributes to the development of SDB.

1.9 Arousals: consequences on ventilatory stability

Termination of partial or complete UA obstruction is generally accompanied by arousals and/or bursts of UA dilator muscle EMG activity[1, 2, 212, 213]. These events are generally considered part of a protective response helping to resolve airway collapse and rapidly dissipate increased respiratory drive developed during airway obstruction. Arousals are associated with a brief period of hyperventilation which is likely the result of reflex ventilatory activation with arousal and homeostatic processes activated to reduce P_{ACO_2} to waking levels, increased wakefulness chemoresponsiveness, the sudden removal of sleep-related increments in R_{UA} and the return of the 'wakefulness' stimulus[189, 214-217]. However, it has been proposed that an exaggerated ventilatory response following arousals from sleep and those coincident with the termination of SDB events may be deleterious, and potentially contribute to the development of subsequent respiratory events and periods of unstable breathing[2, 218, 219].

The increased ventilatory response with brief arousals promotes hypocapnia and subsequent low ventilatory drive in the post arousal period coincident with sleep restoration[219]. Experimental work by Younes[2] showed that the magnitude of the initial hyperventilatory response and the subsequent hypoventilatory period following the termination of CPAP dial-down induced UA obstruction, was greater when airflow restoration was accompanied by an arousal compared to events without arousal. Arousals in healthy-weight individuals are also followed by a period of increased ventilation[216, 220, 221] and a subsequent period of hypoventilation[221], with the response appearing to be larger in males[221]. In a follow up study in male and female OSA patients on therapeutic CPAP (minimum pressure required to abolish flow limitation) and suboptimal CPAP (lowest level tolerated without apnoea, hypopnoea or repetitive arousals from sleep), the hyperventilatory response to arousals was again found to be elevated in males[222]. The reasons for the greater ventilatory response in healthy-weight males and obese males with OSA are unclear, but the authors speculated the gender disparities may be due to different waking reflexes or ventilatory chemoresponsiveness to CO_2. The ventilatory response in OSA patients was also found to be significantly larger when studied on suboptimal CPAP compared to therapeutic CPAP. In healthy-weight individuals, Khoo et al[223] also showed that the ventilatory response to arousal was prolonged off compared to on CPAP. This difference in the ventilatory response between CPAP conditions is likely the result of sudden removal of sleep-related increments in R_{UA} during the suboptimal treatment[222] and no CPAP condition[223].

The ventilatory response to arousal is likely to be exaggerated in untreated OSA patients due to increased R_{UA} and also at the termination of respiratory events due

to heightened respiratory drive. A period of very low ventilatory drive is therefore a more likely consequence around the resumption of sleep, potentially establishing conditions ideal for the development of further SDB events. Ventilatory responses are also likely further exaggerated in obese OSA patients since a lower lung volume is less effective in damping out fluctuations in alveolar gas tensions[218, 224]. The response is potentially even greater in centrally obese male OSA patients, given the significant inverse correlations between waist-to-hip ratio and static lung volumes, including forced vital capacity and EELV[225, 226]. Therefore, the exaggerated ventilatory response in suboptimally treated OSA patients is potentially not only contributed to by increased R_{UA}, but also via a lower lung volume compared to patients when on therapeutic CPAP. Despite this exaggerated ventilatory response on suboptimal CPAP, only ~2% of arousals were followed by obstructive or central respiratory events[222]. While R_{UA} was certainly elevated under these conditions, it was lower than that experienced by untreated OSA patients. In addition, suboptimal CPAP would result in a rise in lung volume above untreated conditions, potentially helping to dampen fluctuations in alveolar gas tensions and prevent cyclical breathing. Increased R_{UA}, reduced lung volume and elevated respiratory drive at the termination of UA obstruction in untreated obese OSA patients, are all likely to exaggerate the ventilatory response to arousal, potentially helping to perpetuate further respiratory events. However, temporal relationships between respiratory events and arousals and changes in R_{UA}, lung volume and respiratory drive to support such potentially important interactive events have yet to be examined in detail.

1.10 Summary and aims of thesis

In summary, OSA is more common in males and particularly in the obese population. However, the precise mechanisms by which these factors contribute to OSA risk remain unclear. While abnormalities in UA anatomy clearly play a pivotal role in OSA, other obesity factors such as body fat distribution appear to importantly contribute to OSA and its severity. Abdominal obesity, particularly common in males, leads to increased IAP, inevitably tending to displace the diaphragm and other intrathoracic structures towards the head. This movement potentially reduces the degree of tension exerted on the UA by the diaphragm and other intrathoracic structures effecting UA patency. There are currently limited data concerning the effects of raised IAP on UA collapsibility. Therefore, the study detailed in the first experimental chapter was designed to investigate the effect of external abdominal compression on UA collapsibility and R_{UA} during sleep in obese male OSA patients.

The augmented activity of the genioglossus in OSA patients during wakefulness may represent one of several neurocompensatory reflexes operating to counteract compressive effects of obesity. However, it remains unclear if obese OSA patients actively defend against postural-related decrements in lung volume during wakefulness. If evident, a reduction in this compensatory reflex at sleep onset in obese individuals is very likely to produce substantial falls in lung volume, potentially negatively impacting upon caudal tracheal traction mechanics and UA function. The study described in the second experimental chapter explored whether obese OSA patients show augmented levels of diaphragm muscle activity during wakefulness compared to healthy-weight controls, and whether the changes in

diaphragm muscle activity and lung volume at sleep onset differ between the two groups. Relationships between the degree of SDB following sleep onset and the associated decline in diaphragm muscle activity and lung volume were also examined.

To date, there have been no studies that have simultaneously measured changes in ventilatory, muscle activity, lung volume and transdiaphragmatic pressure changes leading into and out of UA obstruction to help elucidate potentially important antecedent events contributing to obstruction onset and subsequent changes potentially facilitating their cyclical nature. The final experimental study examined in detail the time-course of changes in a comprehensive range of potentially key relevant variables including ventilation, R_{UA}, UA dilator and ventilatory pump muscle activity, lung volume and end-expiratory gastric, oesophageal and transdiaphragmatic pressures before during and after obstructive events. In addition, the temporal relationship between arousal and respiratory event onsets and offsets were explored to further examine potential associations between arousals and subsequent obstructive events. While observational in nature where causal relationships cannot be established, the magnitude and time-course of systematic changes in the key candidate variables leading into obstruction, are likely to provide important insight into which factors and factor combinations most importantly contribute to UA collapse. This study was therefore designed to more strategically inform future interventional studies designed to examine key mechanisms promoting the development of UA obstruction in OSA.

CHAPTER 2. ABDOMINAL COMPRESSION INCREASES UPPER AIRWAY COLLAPSIBILITY DURING SLEEP IN OBESE MALE OBSTRUCTIVE SLEEP APNOEA PATIENTS

2.1 Introduction

Obstructive sleep apnoea (OSA) is a common sleep disorder characterised by repetitive periods of upper airway (UA) collapse during sleep. Male gender and obesity are two key predictors of OSA[18, 43], but the mechanisms via which these factors contribute to OSA remain unclear. Central obesity, particularly common in male OSA patients, leads to increased intra-abdominal pressure (IAP). This pressure may have an important influence on diaphragm position, which may affect the degree of axial tension (caudal traction) exerted on the UA, and therefore the propensity for UA collapse. Such effects are likely to be most evident in the supine posture and during sleep, when other compensatory mechanisms are diminished and may at least partly explain gender and obesity influences in OSA.

While airway patency is importantly modulated by respiratory drive and negative airway pressure reflex activation of UA dilator muscles during inspiration, caudal traction is also likely to influence UA patency throughout the respiratory cycle. Studies in anaesthetised animals[105, 107] show that decreased UA tension via cranial tracheal movement promotes UA collapse, emphasising the potential importance of tracheal traction for maintaining airway patency.

Investigating the influence of tracheal traction on UA function in humans is inevitably difficult. Changes in lung volume are well known to affect UA function and may reflect predominantly tracheal traction effects. Several studies have shown UA patency to decrease with compression of the abdominal and thoracic compartments via positive extrathoracic pressure[82, 83, 86]. While data concerning the magnitude of lung volume changes during sleep with obesity are currently lacking, end-expiratory lung volume (EELV), which normally falls ~15% during sleep in healthy weight individuals[207, 208], is profoundly reduced in obese patients during general anaesthesia[209] and likely during sleep. EELV reductions, at least in anaesthesia, appear to be largely explained by cranial movement of the diaphragm[227]. Consequently, changes in lung volume with obesity alone may substantially underpin the increased propensity for UA collapse in OSA.

Extrathoracic pressure induced changes in lung volume may have different effects on transdiaphragmatic forces, lung volume and tracheal traction than the thoracoabdominal compressive effects of obesity. While closely related to lung volume changes, intra-abdominal and transdiaphragmatic pressure changes are potentially stronger determinants of UA function than lung volume change *per se*. IAP, a key determinant of transdiaphragmatic force, is approximately doubled in obese compared to healthy-weight individuals[114]. Consequently, abdominal mass loading effects of obesity appear likely to influence UA function during sleep via influences on tracheal traction. However, direct evidence that abdominal compression has any impact on UA function during sleep is currently lacking.

The aim of this study was to examine the effect of experimental abdominal compression on UA function during sleep in obese male OSA patients, to test the hypothesis that acute abdominal compression would increase UA collapsibility and UA resistance (R_{UA}) during sleep.

2.2 Methods

2.2.1 Patient selection

Twenty-five obese (body mass index [BMI] 30-40 $kg \cdot m^2$) male OSA patients with moderate-to-severe OSA (apnoea-hypopnoea index [AHI] >30 $events \cdot h^{-1}$) and between the ages of 18-65 years participated. Apart from OSA, patients were void of any other respiratory diseases and all demonstrated normal lung function (forced expiratory volume in 1 sec [FEV_1] and forced vital capacity [FVC] >80% predicted, JLab software version 4.53; Compactlab, Jaeger, Wuerzburg, Germany). Patients were asked to refrain from consuming caffeine and alcohol for 12 and 24 hours prior to the experiment respectively. The study was approved by the Daw Park Repatriation General Hospital and Adelaide University Human Research and Ethics Committees. Each patient gave informed written consent to participate in the study.

2.2.2 Measurements and equipment

Sleep was monitored by two channels of EEG (C_4/A_1, C_3/A_2), left and right electro-oculograms, submental EMG, and ECG. Sleep recordings were classified according to standard sleep staging[228] and arousal scoring criteria[229] by a single experienced polysomnographer who was blinded to the experimental conditions.

The nostrils were decongested with xylometazoline hydrochloride nasal spray (Otrivin, Novartis Australasia, Rowville, Victoria, Australia) and anaesthetised (2% lignocaine spray). Oesophageal (P_{OES}) and gastric (P_{GA}) pressures were recorded via two separate latex balloon catheters consisting of a 5 cm balloon (Viasys Healthcare, Hoechberg, Germany) attached to the distal end of polyethylene tubing (2.08 mm OD, 1.57 mm ID; Microtube Extrusions, North Rocks, NSW, Australia). P_{GA} and P_{OES} catheters were advanced approximately 60 cm and 45 cm respectively through the most patent nostril. The balloons were then filled with ~0.5 ml air, and each catheter connected to solid-state pressure transducers (Spectramed DTX, Oxnard, USA). Catheter positions were adjusted until positive P_{GA} and negative P_{OES} swings were detected during and in phase with inspiration. Epiglottic (P_{EPI}) pressure was assessed by a thin air-perfused nasal catheter (see Hilditch et al[230] for further detail). This catheter was advanced 1–2 cm below the base of the tongue under direct visualisation and connected to another pressure transducer (MP45; Validyne Engineering, Northridge, CA). All catheters were taped at the nose. Patients were fitted with a nasal mask (Series 2600, Hans Rudolph, Kansas City, MO, USA). Nasal flow and volume were measured by a pneumotachograph (PT16, Jaeger, Germany). Arterial oxyhaemoglobin saturation was recorded by finger pulse oximetry (POET II model 602-3; Criticare Systems, Waukesha, WI) while end-tidal CO_2 was measured at the mask (Capstar-100, CWE Inc, PA). Mask pressure (P_{MASK}) was measured by a differential pressure transducer (MP45; Validyne Engineering, Northridge, CA) referenced to atmospheric pressure. Transdiaphragmatic pressure (P_{DI}) was determined as P_{GA}-P_{OES} at end-expiration. Abdominal and thoracic excursions were measured continuously using two pairs of magnetometer coils (Polhemus Liberty, Colchester,

USA) placed in the anterior-posterior axis of the chest and abdomen. Abdominal compression was achieved by two large inflatable pneumatic cuffs (5082-88-1, Welch Allyn Inc, Arden, USA) with a width of 21 cm connected in series and placed externally around the abdomen. Care was taken to ensure abdominal compression did not directly restrict lower rib cage movement. This was achieved by positioning the cranial edge of the pressure cuff below the anterior lower ribs. The cuff was inflated and rapidly deflated remotely via delivery of compressed air, and via suction respectively. Cuff pressure (P_{CUFF}) was recorded throughout each study using a solid-state pressure transducer (Spectramed DTX, Oxnard, USA) connected via a T-piece at the cuff inlet.

A custom designed breathing circuit (Figure 2.1) similar to that described by Issa and Sullivan[77] was constructed to allow delivery of nasal continuous positive airway pressure (CPAP) as well as rapid external occlusion of the airway. External mask occlusion was achieved via a computer-controlled solenoid valve that delivered compressed air to rapidly inflate a balloon occlusion valve near the inspiratory port of the mask (Figure 2.1). Occlusions were commenced near end-expiration and were sustained until UA closure had developed or until there was clear evidence of EEG arousal. During occlusions (Figure 2.2), inspiratory efforts produce parallel increases in P_{MASK}, P_{EPI}, and P_{OES} throughout inspiration when the airway is patent. Subsequent inspiratory efforts produce progressively larger pressure deflections with increasing respiratory drive until a critical pressure is reached where P_{MASK} ceases to change despite progressively more negative P_{EPI} and P_{OES}. This critical pressure is indicative of UA collapse and was defined as UA closing pressure (UACP)[77, 231].

2.2.3 Data acquisition

All conventional sleep-related signals were recorded on a Compumedics data acquisition system (E-series, Compumedics Inc., Melbourne, Australia). X, Y, and Z coordinates for each of the four magnetometer sensors were acquired on a second computer at a sample rate of 120 Hz. The remaining signals were recorded on a 32-channel Windaq (DI-720 DATAQ Instruments Inc, OH, USA) data acquisition system at 200 Hz. To allow accurate time-matching among the three recording systems, a computer activated event mark signal was simultaneously placed on all three acquisition systems coincident with the onset of each mask occlusion.

2.2.4 Protocol

Following equipment setup and with patients supine, a trial of abdominal compression was performed during wakefulness to find a cuff inflation pressure that the patient believed was likely tolerable during sleep. This pressure was designated as the “inflated” cuff pressure for the remainder of the study. Patients were asked to relax and breathe nasally during five minutes of quite wakefulness for baseline ventilatory recordings prior to lights out. The patient’s mouth was then taped (Sleek; Smith and Nephew, London, UK) to ensure nasal breathing and prevent mouth leaks. CPAP was commenced at the therapeutic level and the patient was allowed to fall asleep while remaining in the supine position. All subsequent experimental manipulations conducted by the researchers were undertaken from an adjacent room. Patients were monitored continuously by a video camera and polysomnograph recordings. Once asleep, the minimum level of CPAP required to abolish flow limitation was determined and then maintained throughout the

remainder of the night unless adjustments became necessary (see below). Cuff state (deflated or inflated), chosen at random prior to the study, was then initiated. Following at least one full 30 sec epoch of stable stage 2 sleep, a brief external mask occlusion was performed to assess UA collapsibility. An occlusion was terminated if the patient aroused during the occlusion or following 2-3 inspiratory efforts showing UA closure (Figure 2.2). At least 30 sec of stable stage 2 sleep without arousal was subsequently required before the next occlusion. Approximately 3-5 occlusions were conducted under the initial cuff condition before cuff state was alternated. This process continued throughout the remainder of the night to record as many replicate measures of UACP as was possible under both cuff conditions during stage 2 sleep. In 4 patients, flow limitation recurred later in the night requiring a 1-2 cmH_2O increase in CPAP. In addition, 6 patients moved briefly from the supine posture due to discomfort and were allowed to return to sleep in another posture. Following ~10 min of sleep, patients were awoken and asked to shift back to the supine position. CPAP was monitored and adjusted if required before mask occlusions were again undertaken once stage 2 sleep was re-established. To control for minor CPAP adjustments, postural and other potential sleep stage effects, all cuff deflated vs. inflated comparisons were restricted to supine stage 2 sleep where CPAP was at the same level between cuff conditions.

2.2.5 Data analysis

Chest and abdominal anterior-posterior excursions (ΔAP_{CHEST} and ΔAP_{ABDO}) and pneumotachograph derived tidal volume (V_T) during the baseline wake period were calculated breath-by-breath via custom software[232]. A statistical calibration

method[233] was employed to solve the regression constants achieving the best fit of V_T (change in lung volume from EELV to end-inspiration, ΔEELV) versus magnetometer excursion in the following equation;

$$V_T \text{ (ml)} = \Delta\text{EELV (ml)} = M*[(K*\Delta AP_{CHEST} \text{ (cm)})+\Delta AP_{ABDO} \text{ (cm)}]$$

Where: *K* = the relative contribution of chest versus abdominal excursions and

M = a scaling factor

Changes in EELV induced by external abdominal compression were calculated using the best fit regression constants *K* and *M* and the appropriate measurements of chest and abdominal displacements. ΔAP_{CHEST} and ΔAP_{ABDO} were defined as the difference between the minimum AP_{CHEST} and AP_{ABDO} dimensions (in cm) at end-expiration, for each breath in the preceding 30 sec prior to occlusions between periods with and without abdominal compression.

Respiratory data including V_T, inspiratory, expiratory and total breath time (T_I, T_E, T_{TOT}), breathing frequency (F_B), minute ventilation (V_I), peak inspiratory flow (PIF), end-expiratory P_{GA}, P_{OES} and P_{DI}, and R_{UA} were calculated on a breath-by-breath basis using custom analysis software used previously[221, 232]. Baseline ventilatory parameters were determined by averaging breath-by-breath measures in the 30 sec prior to each occlusion. A single observer, blinded to cuff condition and P_{CUFF}, as well as patient and occlusion number, determined UACP. The first breath clearly exhibiting P_{MASK} flattening was identified for each trial. The pressure at which P_{MASK} flattening began was defined as the UACP (Figure 2.2). Trials were excluded from

data analysis if UACP was not reached (e.g. due to arousal), if the occlusion occurred other than in stage 2 sleep or if the patient was not in the supine position (confirmed by video camera) during the mask occlusion.

2.2.6 Statistical analysis

Data from replicate trials were averaged within each condition in each subject and the effect of cuff state (deflated vs. inflated) on UACP, lung volume change and respiratory parameters analysed using Student's paired *t*-tests. Univariate relationships were examined using Pearson correlation. Backwards step-wise multiple linear regression with P values > 0.1 for removal were undertaken to explore independent predictors of UACP. Variables entered were end-expiratory P_{GA} and P_{DI}, BMI, waist circumference, hip circumference, waist-to-hip ratio, and AHI. All data are expressed as means ± SEM. Statistical significance was inferred when $P < 0.05$. Statistical analyses were performed using SPSS for Windows software version 16.0 (SPSS, Inc., Chicago, IL.).

2.3 Results

2.3.1 Anthropometric data

Twenty-five patients were recruited, with fifteen successfully completing the study. Data from the remaining ten patients were excluded due to inability to sleep (five patients) or mask leak and/or oral breathing despite all efforts to prevent leaks (five patients). Of the fifteen successful studies, one patient was unable to tolerate the gastric and oesophageal catheters and R_{UA} data from two patients were

unavailable because of catheter blockage. Anthropometric measurements of the fifteen OSA patients are displayed in Table 2.1. Patients were middle-aged, obese with severe OSA. Lung function was in the normal range for this group.

2.3.2 Effect of abdominal compression

Parameters recorded in the 30 sec period preceding each cuff deflation and inflation occlusion trial are presented in Table 2.2. CPAP was not different between cuff conditions and there were no instances in which CPAP needed to be adjusted directly as a result of abdominal compression. Abdominal cuff inflation produced a significant increase in F_B via T_E shortening. However, a concomitant V_T reduction was evident such that V_I remained unchanged with abdominal compression. There was a non-significant trend for a decrease in PIF with abdominal compression (P = 0.07).

An average of 16.2 ± 3.8 (range 4–62) and 15.7 ± 4.0 (range 2–64) occlusion trials with and without cuff inflation respectively, were successfully completed during stage 2 sleep. Abdominal compression significantly increased end-expiratory P_{GA} and end-expiratory P_{DI} in the order of 50% (Figure 2.3A, P < 0.001 for both), while there was a trend for increased end-expiratory P_{OES} (4.6 ± 0.8 vs. 3.2 ± 0.8 cmH_2O, P = 0.07). UACP also increased following abdominal compression (Figure 2.3B, 1.4 ± 0.8 vs. 0.9 ± 0.9 cmH_2O, P = 0.04). While UACP varied between subjects, UACP measurements in both the cuff deflated and inflated states were highly reproducible within subjects (cuff deflated; intraclass correlation 0.83 [95% confidence interval 0.56-0.94, P = 0.006]; cuff inflated intraclass correlation 0.87 [95% confidence

interval 0.66-0.95, P = 0.002]). Abdominal compression had no significant effect on R_{UA} (Table 2.2, P = 0.59). Abdominal compression was accompanied by an abdominal volume shift of 1.1 ± 0.2 L (P < 0.001) and an increase in thoracic volume of 0.5 ± 0.1 L (P = 0.001), leading to an overall decrease in EELV of 0.5 ± 0.2 L (P = 0.045). Within subject changes in EELV following abdominal compression were variable (intraclass correlation 0.53 (95% confidence intervals 0.04-0.81, P = 0.09).

2.3.3 Regression analyses

Baseline (cuff deflated) end-expiratory P_{GA} was significantly correlated with waist circumference (r^2 = 0.30, P = 0.049). No variables correlated with AHI. However, baseline UACP was strongly correlated with baseline end-expiratory P_{DI} (Figure 2.4A) and baseline end-expiratory P_{GA} (Figure 2.4B), r^2 = 0.645 and r^2 = 0.572 respectively (both P < 0.001) and there was a trend for a correlation between end-expiratory P_{GA} and UACP following abdominal compression (r^2 = 0.24, P = 0.08). There was no correlation between the ΔUACP with either the Δend-expiratory P_{DI} or Δend-expiratory P_{GA}. In multivariate analyses, baseline end-expiratory P_{DI} was the only independent predictor of baseline UACP (P < 0.001), accounting for 73% (r^2 = 0.731) of the variance in UACP.

Table 2.1: OSA patient anthropometric data

	Mean ± SEM	Range
Age (years)	50.0 ± 2.6	33-65
BMI ($kg \cdot m^{-2}$)	34.5 ± 1.1	29.7-41.6
AHI ($events \cdot h^{-1}$)	58.1 ± 6.8	30-114
WC (cm)	119.3 ± 3.3	104-136
HC (cm)	119.0 ± 2.8	103-130
WHR	1.0 ± 0.1	0.89-1.06
FEV_1 (% predicted)	98.3 ± 3.1	82-122
FVC (% predicted)	93.7 ± 3.0	79-110

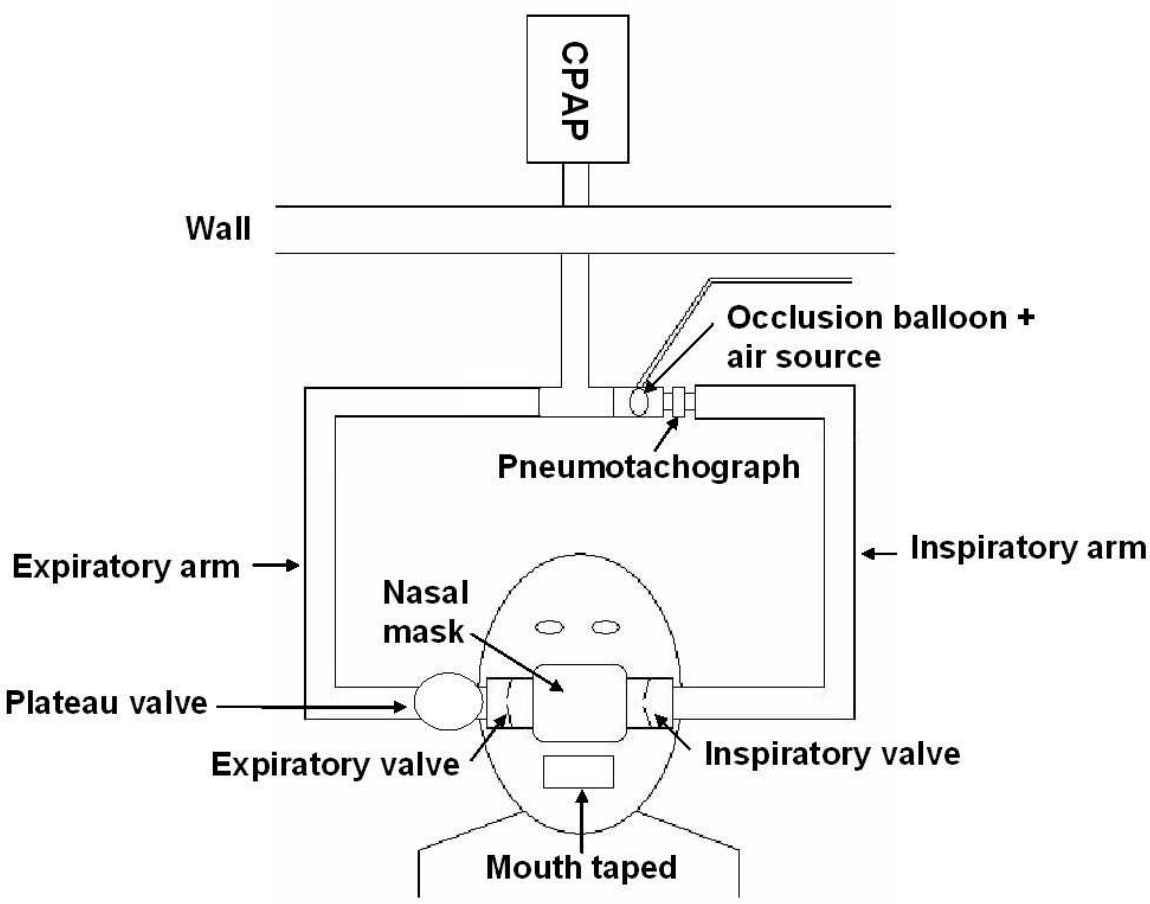
BMI = body mass index, AHI = apnoea-hypopnoea index, WC = waist circumference, HC = hip circumference, WHR = waist-to-hip ratio, FEV_1 = forced expiratory volume in 1 second, FVC = forced vital capacity. N=15.

Table 2.2: Parameters recorded in the 30 sec baseline period preceding airway occlusion trials with and without abdominal compression

	Cuff Deflated	Cuff Inflated	P value
P_{CUFF} (cmH_2O)	0	26.5 ± 1.3	<0.001
CPAP (cmH_2O)	13.2 ± 1.1	13.3 ± 1.1	0.304
T_I (sec)	1.9 ± 0.1	2.0 ± 0.1	0.233
T_E (sec)	2.4 ± 0.2	2.2 ± 0.2	0.023
T_{TOT} (sec)	4.3 ± 0.2	4.2 ± 0.2	0.318
F_B ($breaths \cdot min^{-1}$)	14.5 ± 0.6	14.8 ± 0.6	0.039
V_T (L)	0.54 ± 0.02	0.52 ± 0.02	0.011
V_I ($L \cdot min^{-1}$)	7.7 ± 0.3	7.6 ± 0.2	0.343
PIF ($L \cdot min^{-1}$)	43.4 ± 1.7	41.7 ± 1.7	0.070
R_{UA} ($cmH_2O \cdot L^{-1} \cdot s$)$^{\#}$	6.8 ± 1.4	6.5 ± 1.4	0.585

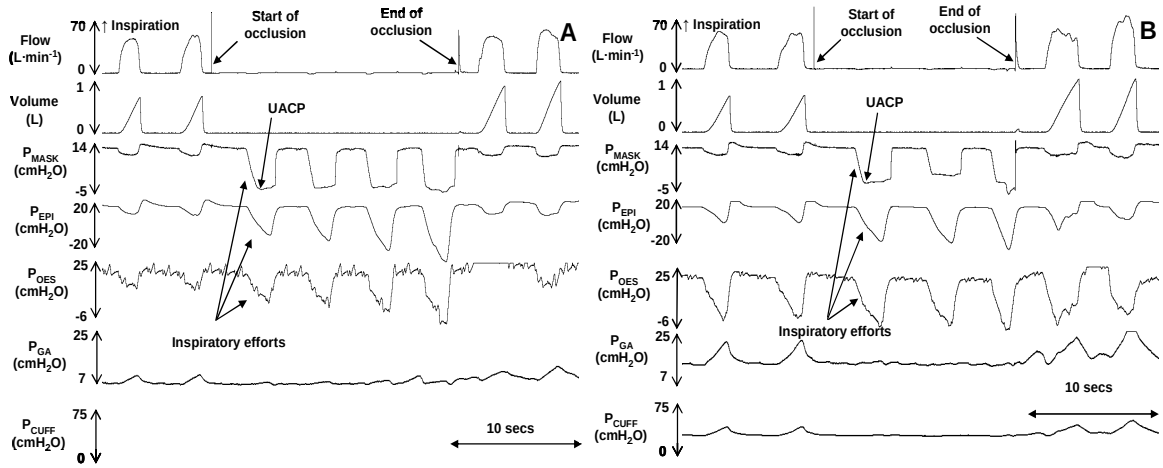
P_{CUFF} = cuff pressure, CPAP = continuous positive airway pressure, T_I, T_E, T_{TOT} = inspiratory, expiratory and total breath time respectively; F_B = breathing frequency; V_T = tidal volume; V_I, = minute ventilation; PIF = peak inspiratory flow; R_{UA} = upper airway airflow resistance. Values are mean ± SEM. N = 15, $^{\#}$N = 13.

Figure 2.1: Breathing circuit used to deliver CPAP and external mask occlusions



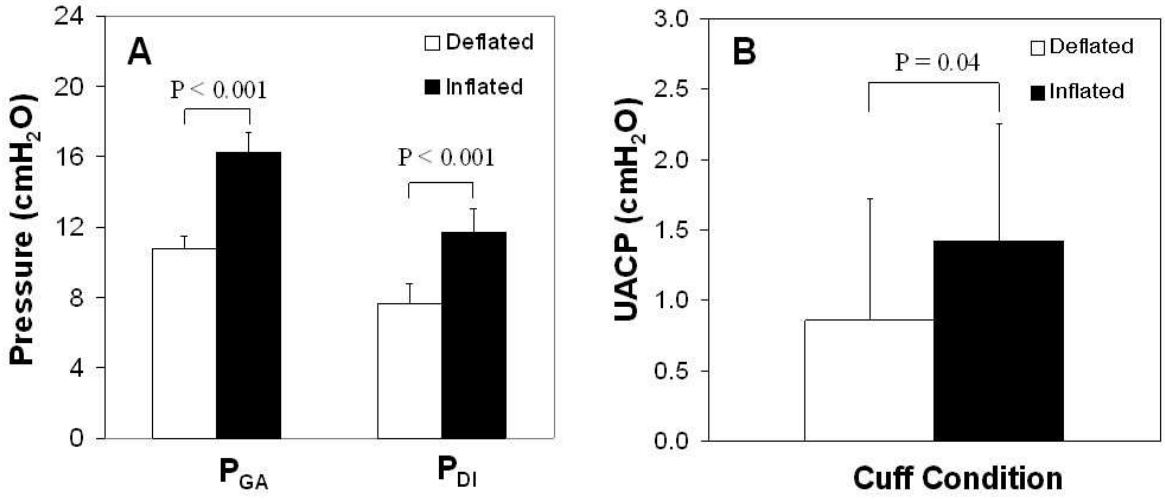
CPAP was delivered to the patient via the inspiratory limb with expirate exiting via a plateau valve. During an external mask occlusion, a balloon located upstream of the mask was rapidly inflated near end-expiration. Occlusion was terminated by rapid balloon deflation.

Figure 2.2: Example traces from brief external mask occlusions



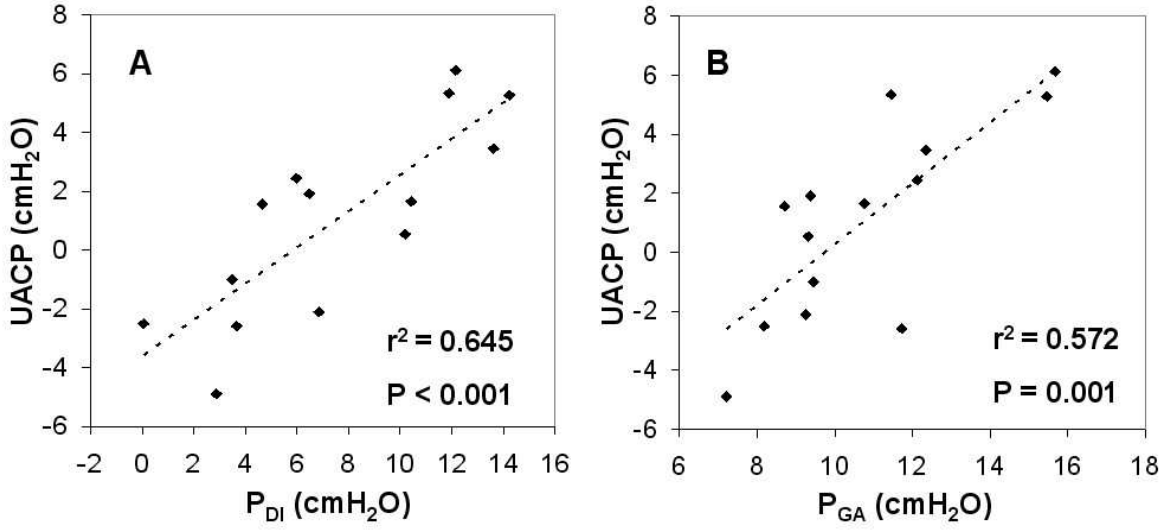
Two 30 sec traces showing events during a brief external mask occlusion in an OSA patient without abdominal compression (A) and with abdominal compression (B). Note the increase in P_{GA} following cuff (P_{CUFF}) inflation. Following the initiation of a mask occlusion, there is a parallel increase in mask (P_{MASK}), epiglottic (P_{EPI}) and oesophageal (P_{OES}) pressures until a point at which it deflects away from P_{EPI} and P_{OES}. This deflection point is indicative of UA collapse and was classified as the upper airway closing pressure (UACP).

Figure 2.3: End-expiratory P_{GA} and end-expiratory P_{DI} and UACP with and without abdominal compression



The effect of external abdominal compression on (A) end-expiratory gastric pressure (P_{GA}) and end-expiratory transdiaphragmatic pressure (P_{DI}) and (B) upper airway closing pressure (UACP) Values are mean ± SEM. N = 14 for P_{GA} and P_{DI} and N = 15 for UACP.

Figure 2.4: Relationships between UACP and end-expiratory P_{DI} and end-expiratory P_{GA} without abdominal compression



The relationship between upper airway closing pressure (UACP) and (A) end-expiratory transdiaphragmatic pressure (P_{DI}) and (B) end-expiratory gastric pressure (P_{GA}) without abdominal compression. N=14.

2.4 Discussion

The major finding of this study was that abdominal compression significantly increased UA collapsibility during sleep in obese OSA patients. This is the first study to demonstrate a direct effect of abdominal loading on UA collapsibility in sleep and implicates mechanical effects of abdominal obesity as a potentially important mechanism causing increased UA collapsibility in OSA.

2.4.1 Effect of abdominal compression on upper airway function and respiratory variables

It is not possible to determine the precise mechanisms underpinning changes in UACP with abdominal compression in this study. Potential mechanisms include (a) direct mechanical effects of increased IAP and/or lung volume mediated influences on UA compliance, and/or (b) haemodynamic effects or increased oedema surrounding the UA.

There are likely to be complex interactions between variables potentially mediating increased UA collapsibility following abdominal compression, because of the nature of anatomical connections between the UA and surrounding/distal tissues, the geometry of diaphragm insertion to the rib cage and variable effects of obesity and abdominal compressive forces on chest and abdominal compartment volumes and compliances. A smaller EELV seen in obese individuals in the supine position compared to healthy-weight controls[91] is likely dominated by cranial ascent of the diaphragm as a consequence of increased IAP, with further rises in IAP promoting additional cranial displacement limited by diaphragm stretch and opposing

inspiratory effects of rib cage expansion[234]. In the current study, abdominal compression increased end-expiratory P_{GA} and end-expiratory P_{DI} in the order of ~50%, produced a marginal increase in P_{OES} and decreased the abdominal anterior-posterior dimension by ~1.8 cm, with slight anterior-posterior chest expansion. Given that the abdominal compartment is relatively incompressible, the reduced abdominal anterior-posterior dimension with abdominal compression indicates abdominal volume redistribution, equating to a volume shift of ~1 L, of which ~0.5 L was exhaled and ~0.5 L translated to an increase in rib cage anterior-posterior dimensions and volume, resulting in a net fall in EELV of ~0.5 L. Increased IAP, via external loading or CO_2 insufflation into the peritoneal cavity, leads to a rightward shift and a decrease in the slope of the pressure-volume curve of the total respiratory system, primarily via a fall in chest wall compliance[235-237]. The expansion of the rib cage following abdominal compression has been documented by others[123] and likely reflects lateral lower rib displacement at the zone of apposition of the diaphragm and rib cage (appositional effect) while passive tension generated by the diaphragm elevates the rib cage by its insertions at the costal margin (insertional effects)[123, 234] leading to an inspiratory effect on the rib cage.

A change in EELV is known to have profound effects on UA function. Lung inflation above resting EELV increases UA cross-sectional area[52, 80], reduces airway collapsibility[84] and airflow resistance[82]. Conversely, lung deflation below EELV reduces UA size[52, 80] and produces marked increases in pharyngeal resistance[82]. A study by Stanchina and colleagues[84] showed greater airway collapsibility (~1.1 cmH_2O increase in UA critical closing pressure, [P_{CRIT}]) in healthy-weight

individuals following a decrease in lung volume of ~0.6 L via positive extrathoracic pressure. Using an iron lung to manipulate lung volume in a group of obese OSA patients, the level of CPAP required to abolish flow limitation increased from ~12 to ~17 cmH_2O following a ~0.6 L reduction in lung volume, and was reduced from ~12 to ~4 cmH_2O with ~0.4 L lung inflation[86]. With similar lung inflation via negative extrathoracic pressure (~0.7 L), Tagaito and colleagues[85] found a reduced P_{CRIT} in the order of ~1.2 cmH_2O in anaesthetised and paralysed obese OSA patients. In the absence of neuromuscular influences, these latter findings strongly support mechanical effects of lung volume change on passive UA properties.

Lung volume effects on UA function may be mediated primarily by changes in caudal tracheal traction. This “tracheal tug” is an axial force pulling on the airway via negative intrathoracic pressure and movements of the trachea and interconnected mediastinal structures that move along with the diaphragm[106]. While end-expiratory diaphragm position was not directly assessed in the present study, the observed changes in chest/abdominal anterior-posterior dimensions and volumes, end-expiratory P_{DI} and end-expiratory P_{OES} are consistent with cranial diaphragm displacement and would be expected to reduce axial tension transmitted to the UA via intrathoracic structures. Classic studies in anaesthetised dogs[105], clearly show tracheal tug is a major factor promoting UA patency. Severing the oesophagus and trachea caused marked pharyngeal airway narrowing or collapse. Axial tension exerted on the caudal end of the severed trachea was very strongly related to negative intrathoracic pressure and diaphragm descent. Similar findings have subsequently been reported in cats[107] and in pigs[238]. Caudal tracheal traction has also been shown to decrease UA collapsibility and extraluminal tissue pressure

in anaesthetised and tracheostomised rabbits[111]. These animal studies suggest mechanical interdependence between the diaphragm and intrathoracic and UA structures is critically important for maintaining pharyngeal patency.

While the mechanisms of lung volume influence on UA size and function remain unclear, thoracoabdominal distortion, through interventions specifically designed to alter lung volume or through abdominal compression performed in this study, appear likely to operate via similar mechanisms; predominantly via mechanical coupling between the upper and lower airway structures. Nevertheless, abdominal compression/mass loading and extrathoracic pressure induced changes in lung volume may have somewhat different effects on diaphragm position and UA function. Since the abdominal compartment is less compressible than the chest, extrathoracic pressure changes in an iron lung will tend to influence thoracic more than abdominal compartment volume and may have variable effects on diaphragm position, pleural pressure and tracheal traction. In contrast, raised IAP with abdominal compression or mass loading will likely produce predominantly diaphragm ascent, either with or without (i.e., counterbalanced by mass loading of the chest) concomitant chest expansion. While cranial displacement of the diaphragm potentially reduced the degree of tracheal traction on the UA, chest inflation seen following abdominal compression may have attenuated the effects of abdominal compression on UA collapsibility. For example, thoracic inflation may elongate cervical strap muscles which are known to improve UA patency by pulling the larynx and other UA structures toward the thorax[105, 239].

The failure to find a relationship between changes in UACP and the changes in transdiaphragmatic pressure or gastric pressure is perhaps surprising in light of the strong correlation between baseline UACP and baseline gastric and transdiaphragmatic pressures. One possibility is that gastric/transdiaphragmatic pressure is an important determinant of UACP and potentially OSA severity, but that more substantial within subject variability, perhaps in resting lung volume and thoraco-abdominal mechanics, combined with possible non-linear relationships with caudal traction effects may explain these findings. For example, additional abdominal compression in a patient with an already elevated P_{GA} and collapsible airway may have relatively little further impact on UACP. Further studies examing within-subject dose-response relationships between abdominal compression and UA collapsibility and function appear to be warranted.

While abdominal compression led to a significant increase in UACP, there was no change in R_{UA}. Diaphragm ascent and UA shortening, while potentially reducing UA wall tension and increasing UA collapsibility, may have relatively little net impact on overall UA size and consequently R_{UA}. In support of this view, Rowley and colleagues[240] found no change in R_{UA} despite a ~2 cmH_2O decrease in UA collapsibility with 1 cm tracheal stretch in anaesthetised cats.

Increased central venous volume and/or oedema surrounding the airway may also contribute to increased UA collapsibility. Chui and colleagues[139] found an increase in neck circumference and a 102% rise in pharyngeal resistance following expulsion of leg fluid volume via lower body positive pressure (~55 cm H_2O). Two subsequent studies by the same group showed similar levels of lower body positive

pressure produced a decrease in UA area by ~10%[140], while UA collapsibility increased by ~20% during wakefulness[141]. Reduced lung volume did not appear to explain these findings suggesting that fluid displacement into the neck was the primary cause of these effects. In addition, a recent study[142] found that AHI was strongly correlated with changes in overnight leg fluid volume. Increased IAP (maximum of ~27 cmH_2O) via CO_2 insufflation into the peritoneal cavity has also been shown to displace blood from the abdominal compartment into the chest[241] and to result in enlargement of left end-diastolic ventricular volumes[242], indicative of venous congestion. Consequently, while the IAP achieved in this study was lower than in these previous studies, displacement of blood into the chest and neck cannot be discounted as a potential mechanism contributing to increased UA collapsibility with abdominal compression.

Abdominal compression significantly altered breathing patterns in these patients, indicating respiratory compensatory mechanisms with abdominal loading. Both V_T and T_E significantly decreased whilst F_B increased. On the other hand, T_I and V_I were unchanged, while PIF tended to be lower following cuff inflation. Similar changes in breathing pattern have been observed in obese compared to healthy weight individuals[243], and with externally applied elastic loads during wakefulness[244, 245]. Given abdominal compression impairs diaphragm descent, it may have similar effects to externally applied inspiratory elastic loads. While there are limited data available in sleep, ventilation has been shown to fall acutely with an elastic load, followed by partial ventilatory recovery in NREM sleep in three healthy-weight individuals[246]. The changes in breathing pattern following prolonged

abdominal compression during sleep in this study likely reflect similar compensatory responses.

2.4.2 Methodological considerations

There are several methodological limitations that warrant brief discussion. Firstly, diaphragm/trachea displacement following abdominal compression could not be directly measured and inferences regarding diaphragm and tracheal ascent are somewhat speculative, based on changes in other interrelated measures. Imaging methods such as radiography, CT scanning and ultrasonography, potentially useful for more direct measurements of intrathoracic changes with abdominal compression, are difficult during sleep. Based on a ~3 cm decrease in abdominal anterior-posterior dimension and an increase in P_{GA} of ~23 cmH_2O, Reid et al[123] inferred a 3.5 cm rise in end-expiratory diaphragm position following upright water immersion to the neck. Tokics and colleagues[124] observed ~1.2 cm cranial diaphragm displacement following thoracoabdominal restriction. Following CO_2 insufflation of the abdomen, 1.9 cm cephalad movements of the diaphragm[125] and 1.4 cm migration of the carina towards the tip of an endotracheal tube[127] have been observed. Consequently, abdominal compression almost certainly produced ascent of the diaphragm and intrathoracic structures.

The current study utilised a mask occlusion protocol[77, 79] rather than the more widely used P_{CRIT} technique to assess UA collapsibility. This was chosen for two reasons: (1) it allows for more rapid and repeated measurements over a shorter time, and (2) pressure drops during P_{CRIT} determination inevitably produce

systematic reductions in lung volume that may further impact on UA collapsibility that the technique is designed to measure. With inspiratory mask occlusion, lung volume is effectively maintained at the same initial pressure. Our circuit did not occlude expiration such that some expiratory lung volume loss was possible if UA patency returned with increasing expiratory drive. However, UA closure tended to occur within 1-3 breaths following mask occlusions, before any substantial increase in ventilatory drive necessary to overcome the majority of obstructive events and therefore produce expiratory volume loss.

Magnetometer coils allow measurement of lung volume change such that further studies using body plethysmography or helium dilution measurements would be useful to assess absolute lung volume with and without abdominal loading in obese and non-obese individuals. In addition, the calibration constant *K* used to estimate lung volume change is likely influenced by posture[247]. However, all measurements were restricted to the supine position and cuff inflated versus deflated conditions continued throughout the study such that overnight changes in *K* are unlikely to have importantly influenced lung volume comparisons between conditions.

The effects of acute abdominal compression may well differ from chronic mechanical effects of abdominal obesity on UA function. Increasing IAP with abdominal obesity occurs over a long time frame, potentially has different mechanical effects depending on visceral versus subcutaneous fat deposition and may be associated with other effects that may independently influence UA function, such as UA and thoracic adiposity, hormonal, metabolic and haemodynamic effects and potentially progressive respiratory compensatory changes. Nevertheless, our

findings of increased airway collapsibility following acute abdominal compression demonstrate the existence of compressive effects that may well still operate with chronic natural abdominal compression with obesity.

2.4.3 Clinical significance

The effect of a ~0.5 cmH_2O increase in UACP on OSA severity remains unclear. However, studies investigating the relationship between P_{CRIT} and AHI[248, 249] suggest that changes of this order may well be important. Sforza et al[248] found a weak (r = 0.23) but significant correlation, with small differences in P_{CRIT} associated with substantial increases in AHI in 106 patients. In 25 OSA patients, Wellman and colleagues[249] demonstrated a tighter relationship (r = 0.66), with an increase in AHI of ~10 events·h^{-1} with a ~0.5 cmH_2O increase in P_{CRIT}. In a study by Gold et al[72], the average P_{CRIT} in mild/moderate OSA patients (AHI ≥10 and <40 events·h^{-1}) and moderate/severe OSA patients (AHI ≥40 events·h^{-1}) was approximately −1.6 and 2.4 cmH_2O respectively, although there was considerable overlap in P_{CRIT} between the two groups. Given the importance of UA collapsibility in OSA and relatively steep relationships between P_{CRIT} and AHI across patients, a ~0.5 cmH_2O within-patient increase in UACP appears likely to significantly impact OSA severity. Further studies are needed to establish if this is the case and the magnitude of the effect.

Obesity and male gender are well known major risk factors for OSA[18, 43]. However, the mechanisms via which obesity and male gender influence UA in sleep remain poorly defined. While experimental abdominal compression in the current study

may not directly simulate the effects of obesity *per se*, increased IAP appears the most likely dominant factor underpinning increased UA collapsibility in this study. Of all available variables influenced by obesity, including BMI, waist-hip ratio, and waist and hip circumference, only end-expiratory P_{DI} emerged as a significant independent predictor of UA collapsibility, accounting for an impressive ~73% of the variance in UACP. Consequently, compressive effects of obesity and the male propensity to an abdominal pattern of fat distribution could therefore largely underpin strong associations between obesity/male gender and OSA.

While increased neck circumference/fat deposition are known predictors of OSA severity[21, 26] and could directly affect UA function, they may also co-vary with other potentially more important measures of central obesity. In the Wisconsin Sleep Cohort[18], men were three times more likely than women to have OSA and six times more likely after adjusting for BMI. However, male gender was no longer predictive of OSA following adjustment for waist-hip ratio. These data are consistent with a primary underlying role of central adiposity as a cause of OSA in most patients and the gender difference in OSA prevalence. In smaller samples, observations that measures of central adiposity including waist circumference and visceral fat consistently emerge as stronger predictors of OSA severity than BMI are consistent with this view[22, 48]. Reports of increased snoring and OSA in the third trimester of pregnancy, despite increased ventilatory drive from hyperprogesteronaemia, are also consistent with abdominal compressive forces importantly influencing UA function in sleep[250].

2.4.4 Summary and conclusions

This is the first study to show a direct effect of abdominal compression on UA collapsibility during sleep. The results support and extend previous work showing detrimental effects of reduced lung volume on UA patency and suggest that increased IAP with obesity may negatively impact on UA function. While IAP appears the most likely dominant factor underpinning these effects, further studies are needed to better elucidate the mechanisms behind these findings.

CHAPTER 3. CHANGES IN LUNG VOLUME AND DIAPHRAGM MUSCLE ACTIVITY AT SLEEP ONSET IN OBESE MALE OBSTRUCTIVE SLEEP APNOEA PATIENTS VERSUS HEALTHY-WEIGHT CONTROLS

3.1 Introduction

Obstructive sleep apnoea (OSA) is a common sleep disorder characterised by repetitive periods of upper airway (UA) collapse during sleep. Male gender and obesity are two key predictors of OSA[18, 43], but the mechanisms via which these factors contribute to OSA pathophysiology remain unclear. OSA is likely attributable to a combination of an anatomically smaller airway and an abrupt fall in UA dilator muscle activity following sleep onset[25, 146, 204]. In addition, reduced lung volume has also been shown to negatively impact UA function[84, 87], with a fall in lung volume potentially reducing the degree of axial tension (caudal traction) exerted on the UA, and therefore the propensity for UA collapse. We recently demonstrated increased UA collapsibility with experimental abdominal compression during sleep in OSA patients (Chapter 2)[251], strongly supporting mechanical effects of abdominal obesity on UA function. These effects are likely to be most evident in the supine posture and during sleep, particularly at the wake-sleep transition when other compensatory mechanisms become diminished, and may at least partly explain gender and obesity influences in OSA.

Several groups have demonstrated important effects of changes in lung volume on UA patency, with a decrease in lung volume during sleep resulting in marked increases in UA collapsibility, pharyngeal resistance and the airway pressure required to abolish flow limitation[84, 86]. Data from animal studies suggest that changing lung volume may impact upon UA stiffness by modulating traction generated on the trachea and the UA[105, 107]. End-expiratory lung volume (EELV) decreases when healthy-weight individuals move from an upright position to the supine posture[91, 92], largely due to cranial displacement of the diaphragm[252]. Despite increased thoracoabdominal mass loading and intra-abdominal pressure[114], there is little change in EELV following a similar postural transition in obese individuals[91, 92]. One possible explanation is that obese individuals may actively defend against a fall in lung volume via neurocompensatory reflexes. While previous studies have shown minimal expiratory tonic diaphragm muscle activity in healthy-weight individuals[253-255], obese OSA patients may have augmented expiratory (tonic) diaphragm activity to help maintain the diaphragm in a more favourable neuro-mechanical position, and to help preserve lung volume and UA tension. In healthy-weight individuals, Muller[205] found augmented tonic diaphragmatic activity with external abdominal compression, consistent with defence of lung volume during wakefulness. However, few data are available to evaluate the potential effects of obesity on diaphragm muscle tone.

Reduced tonic diaphragm muscle activity at sleep onset potentially allows for further diaphragm ascent with decreased end-expiratory gastric pressure (P_{GA}) and transdiaphragmatic pressure (P_{DI}). These changes are likely to contribute to a decrease in EELV, facilitating UA instability via tracheal traction effects. However,

data concerning the magnitude of lung volume and transdiaphragmatic pressure changes at sleep onset in obese OSA patients are currently lacking. In healthy weight individuals, EELV has been shown to fall by ~15% during sleep[207, 208] and is profoundly reduced following induction of general anaesthesia in the obese[209], again largely via cranial displacement of the diaphragm[227]. Consequently, a fall in EELV at sleep onset, particularly in obese individuals, could importantly contribute to an acute increase in the propensity for UA collapse at sleep onset in OSA patients. Whilst it is difficult to separate effects of obesity *per se* from other potential pathogenic factors operating in OSA patients, lung volume and tracheal traction effects are likely dominated by thoracoabdominal mass loading effects of obesity itself. Consequently, we elected to first establish if diaphragm muscle activity and lung volume changes occurring in the immediate sleep onset period are any different in obese OSA patients versus healthy weight controls before further separate studies designed to separate obesity from other potential contributory effects in OSA.

The aims of this study were to compare minimum expiratory (tonic) diaphragm activity ($eEMG_{DI}$) during wakefulness and to compare changes in inspiratory diaphragm muscle activity ($iEMG_{DI}$), $eEMG_{DI}$, end-expiratory P_{GA}, and P_{DI}, and EELV following sleep onset between OSA patients and age-matched, healthy-weight controls. Given sleep onset is frequently associated with respiratory events in OSA patients, we also aimed to investigate if the magnitude of lung volume, $iEMG_{DI}$, $eEMG_{DI}$ and end-expiratory P_{GA}, and P_{DI} changes differ according to the degree of UA collapse following sleep onset. We hypothesised that $eEMG_{DI}$ would be higher during wakefulness in obese OSA patients and that there would be a

greater fall in lung volume, $iEMG_{DI}$, $eEMG_{DI}$ and end-expiratory P_{GA}, and P_{DI} following sleep onset in OSA patients compared to healthy-weight controls, with a greater reduction at sleep onset shortly followed by respiratory events.

3.2 Methods

3.2.1 Participant selection

Obese (body mass index [BMI] 30-40 $kg \cdot m^{-2}$) male OSA patients with moderate-to-severe OSA (apnoea-hypopnoea index, [AHI] >30 $events \cdot hr^{-1}$), aged between 18-65 years and healthy-weight (BMI <25 $kg \cdot m^{-2}$) age-matched male subjects without sleep-disordered breathing (AHI <15 $events \cdot hr^{-1}$) participated. Apart from OSA, patients had no other respiratory disorders and all participants demonstrated normal lung function (forced expiratory volume in 1 sec [FEV_1] and forced vital capacity [FVC] >80% predicted, JLab software version 4.53; Compactlab, Jaeger, Wuerzburg, Germany). Participants were asked to refrain from consuming caffeine and alcohol for 12 and 24 hours respectively prior to the experiment. The study was approved by the Daw Park Repatriation General Hospital and Adelaide University Human Research and Ethics Committees. Each patient gave informed written consent to participate in the study.

3.2.2 Measurements and equipment

Sleep was monitored by two channels of EEG (C_4/A_1, C_3/A_2), left and right electro-oculograms, submental EMG and ECG. Arterial oxyhaemoglobin saturation was

recorded by finger pulse oximetry (POET II model 602-3; Criticare Systems, Waukesha, WI).

Both nostrils were decongested with xylometazoline hydrochloride nasal spray (Otrivin, Novartis Australasia, Rowville, Victoria, Australia) and anaesthetised (2% lignocaine spray). A custom made, multilumen, intraoesophageal catheter (MuiScientific, Ontario, Canada) was used to assess gastric (P_{GA}) and oesophageal (P_{OES}) pressure and intraoesophageal diaphragmatic EMG (EMG_{DI}). For P_{GA} measurements, a latex balloon 5 cm in length (Viasys Healthcare, Hoechberg, Germany) was attached to the distal end of catheter. P_{OES} was measured by a separate latex balloon (10 cm in length) attached 10 cm above the P_{GA} balloon. The catheter was inserted into the most patent nostril and advanced approximately 60 cm. The balloons were filled with ~1.5-2 ml of air (within the flat portion of each balloon pressure-volume curve) and the position of the catheter adjusted until positive P_{GA} and negative P_{OES} pressure swings were detected during and in phase with inspiration. Both pressure channels were connected to solid state pressure transducers (Spectramed DTX, Oxnard, USA). Epiglottic (P_{EPI}) pressure was assessed using a thin air-perfused nasal catheter (see Hilditch et al[230] for further detail). This catheter was advanced 1–2 cm below the base of the tongue under direct visualisation, taped at the nose, and connected to another pressure transducer (MP45; Validyne Engineering, Northridge, CA).

Participants were fitted with a nasal mask (ComfortGel Nasal Mask, Philips Respironics, Murrysville, PA) attached to a non-rebreathing valve (Series 2600, Hans Rudolph, Kansas City, MO, USA) equipped with sealable luer ports to

accommodate each catheter. Inspiratory nasal flow and volume were measured by a pneumotachograph (PT16, Jaeger, Germany) attached to the inspiratory port of the mask. End-tidal CO_2 (P_{ETCO_2}, Capstar-100, CWE Inc, PA) and mask pressure (MP45; Validyne Engineering, Northridge, CA) were also measured. Transdiaphragmatic pressure (P_{DI}) was determined as P_{GA}-P_{OES} at end-expiration.

EMG_{DI} was recorded via a series of nine equally spaced (1 cm inter-electrode distance) stainless steel rings situated between the P_{GA} and P_{OES} balloons of the multilumen catheter. Electrodes were connected in sequentially adjacent pairs (electrodes 1 (most proximal) and 2, 2 and 3 etc) to an amplifier (Model15LT, Grass Instruments, Quincy, MA, USA) and band-pass filtered (0.3-1 kHz) to provide eight bipolar EMG channels with an inter-pair distance of 1 cm. Once connected, catheter position was further adjusted to achieve maximal inspiratory EMG_{DI} activity near the centre of the electrode array, and then secured at the mask using a tight-sealing stainless steel luer (SSA1380, S4J Manufacturing Services, Cape Coral, FL, USA).

Abdominal and thoracic excursions were measured continuously using two pairs of magnetometer coils (Polhemus Liberty, Colchester, USA) placed in the anterior-posterior axis of the chest and abdomen (Chapter 2)[251].

3.2.3 Data acquisition

All conventional sleep-related signals were recorded on a Compumedics data acquisition system (E-series, Compumedics Inc., Melb., Australia). X, Y and Z co-

ordinates for each of the four magnetometer sensors were acquired on a second computer at a sample rate of 120 Hz (Polhemus Liberty, Colchester, USA). The remaining signals were recorded on a 32 channel data acquisition system at 200 Hz, except EMG_{DI} channels which were sampled at 1 kHz (DI-720 DATAQ Instruments Inc, OH, USA). To facilitate accurate time-matching (within ~100 msec) between the three recording system, a computer actuated event mark signal was simultaneously placed on all three acquisition systems approximately every hour.

3.2.4 Protocol

Following instrumentation and whilst supine, participants undertook a five minute baseline period in which they were instructed to remain relaxed, with their eyes open, breathing solely through their nose. For recording maximal $iEMG_{DI}$ activity, participants then performed a minimum of three maximal Muller manoeuvres by maximally inspiring against a closed glottis at end expiration until plateaus in both $iEMG_{DI}$ and P_{OES} activity were reached. The mouth was then taped to ensure nasal breathing, the lights switched off and the participant allowed to fall asleep in the supine position (confirmed by a position sensor and video camera monitoring). Following approximately five sleep-disordered breathing events in the obese OSA patients or a similar time period (approximately five minutes) in control subjects, participants were fully awoken by a researcher and asked to keep their eyes open for at least one minute before a subsequent sleep onset opportunity. This cycle was continued throughout the remainder of the night. If the participant was unable to sleep due to discomfort, they were allowed to briefly change postures for a short period of time (<15 min), then woken if necessary and asked to return to the supine

posture to continue the experiment. Non-supine periods were excluded from analysis.

3.2.5 Data analysis

Sleep recordings were analysed by an accredited sleep technologist using 30 sec epochs and Rechshaffen and Kales criteria for staging sleep[228]. Arousals and respiratory events were scored according to standard criteria[229, 256]. Sleep onset was defined as α EEG activity followed by ≥10 secs of θ EEG activity. Each sleep onset was then categorised according to the absence or presence of scored respiratory events within the 30 sec period immediately following sleep onset as either 1) stable breathing 2) hypopnoea (a ≥10 sec event defined by either a) >50% decrease in flow compared to the previous 2 mins of breathing or b) a discernable decrease in effort followed by an arousal or a ≥3% desaturation) or 3) apnoea sleep onsets (a ≥10 sec event defined by complete cessation of inspiratory airflow followed by an arousal or ≥3% desaturation). Wake-sleep transitions were only included for data analysis if there was at least 30 sec of wakefulness prior to sleep onset and at least three breaths of sleep following sleep onset. Transitions were also excluded from analysis if any one of the following occurred: 1) a hypopnoea, apnoea or ≥3% oxygen desaturation was scored within 30 sec prior to sleep onset 2) if a swallow was present within the 30 sec prior to sleep onset 3) mask leaks or mouth breathing was evident prior to or following the wake-sleep transition.

For each wake-sleep transition meeting the inclusion criteria for analysis, breaths either side of the transition were numbered relative to the transition from -5 to +3.

Inspiratory minute ventilation (V_I), $iEMG_{DI}$ and $eEMG_{DI}$ were calculated for each breath (see below), and expressed as a percentage of the mean of breaths -5 to -2, excluding breath -1 to avoid potential confounding by α-θ EEG changes within this breath. Several control subjects showed near zero end-expiratory P_{DI} and end-expiratory P_{GA} at baseline. Consequently changes in end-expiratory P_{DI} and end-expiratory P_{GA} across the wake sleep transition were evaluated as absolute changes from the mean of breaths -5 to -2 rather than percentage change from baseline pressures.

For each electrode pair, ECG artefact in the raw EMG_{DI} signals was removed using a software implementation of conventional electronic ECG blanking. The QRS complex of the ECG was used to trigger substitution of brief periods (~150-200 msec) of EMG contaminated with ECG artefact with an equivalent duration of adjacent EMG from the same channel. $iEMG_{DI}$ was calculated by integrating rectified EMG_{DI} electrical activity over each inspiratory period and dividing by inspiratory time. Given EMG activity is dependent on muscle-to-electrode distance[257], $iEMG_{DI}$ was averaged across all electrode pairs within each breath to minimise potential confounding by crural diaphragm movement with respiration and sleep onset. $eEMG_{DI}$ was calculated using methods similar to those described by Fogel et al[146]. Expiration was divided into ten equal segments and raw data for each segment for all electrode pairs were rectified and integrated, divided by the time interval, then averaged across all electrode pairs. $eEMG_{DI}$ was considered that of the expiratory time segment showing the minimum activity. For pre-sleep onset EMG_{DI} comparisons between groups, $iEMG_{DI}$ and $eEMG_{DI}$ were quantified as a percent of maximal activity elicited during Muller manoeuvres as well as in

calibrated values (μV). For each Muller manoeuvre, EMG data across all pairs were divided into 100 msec segments. Activity for each pair was rectified, integrated and divided by the time interval and averaged across all pairs. The segment with the highest activity of all Muller manoeuvres was identified with this activity being defined as maximal inspiratory activity. $iEMG_{DI}$ and $eEMG_{DI}$ were subsequently expressed as a percentage of this maximal activity for each breath during the pre-sleep onset period, and averaged across breaths to provide average pre-sleep onset $iEMG_{DI}$ and $eEMG_{DI}$ (% max) for each subject.

EELV changes were assessed as previously described (Chapter 2)[251]. Changes in EELV across the wake-sleep transition were calculated as the difference between each breath and the mean of anterior-posterior chest and abdomen values at end-expiration for breaths -5 to -2.

Respiratory data including V_I, tidal volume (V_T), breathing frequency (F_B), P_{ETCO_2}, UA airflow resistance (R_{UA}), $iEMG_{DI}$, $eEMG_{DI}$ (% maximum), $iEMG_{DI}$, $eEMG_{DI}$ (μV), and end-expiratory P_{GA} and P_{DI} were calculated on a breath-by-breath basis and averaged across breaths -5 to -2 prior to sleep onset.

For hypopnoea and apnoea transitions, breath-by-breath changes in V_I, EELV, $iEMG_{DI}$ and $eEMG_{DI}$ were also examined in the last two breaths leading into respiratory events and the first two breaths/inspiratory efforts during events.

3.2.6 Statistical analysis

All group data are presented as means ± SEM of averaged replicate measurements within each individual. Anthropometric data were compared between groups with two sample Student's *t*-tests. Pre-sleep onset group differences were examined using linear mixed model analysis (SPSS 16.0, SPSS Corp., Chicago). For these analyses, individual sleep onset data within each participant were retained without averaging across replicated observations, using sleep onset number as a factor. In addition, for V_I, end-expiratory P_{GA} and P_{DI}, EELV and EMG variables, effects of group, breath number and post sleep onset respiratory event severity (stable breathing, hypopnoea and apnoea) were examined using linear mixed model analysis with breath number, sleep onset number and respiratory event severity as repeated factors with an autoregressive covariance structure and subject as a random effect each with a separate intercept. Subgroup analyses were conducted to further examine breath and respiratory event severity effects within each group separately. Linear mixed models were also used to examine differences in V_I, EELV and EMG variables for the period leading into hypopnoeas and apnoeas. Custom contrasts within each mixed model were also undertaken to calculate V_I, EELV and muscle activity differences between average wakefulness (breaths -5 to -2) and post-sleep onset breaths, and the first breath/inspiratory effort in hypopnoeas and apnoeas. $P < 0.05$ was considered significant.

3.3 Results

3.3.1 Anthropometric and pre-sleep onset data

A total of nine obese OSA patients and eight control subjects were recruited for this study. Data from one obese OSA patient were excluded due to significant mask leaks. Complete pre-sleep measurements of breath-by-breath ventilatory data were obtained in eight patients and eight control subjects. One control subject could not tolerate the multilumen catheter and R_{UA} measurements could not be assessed in one obese OSA patient and one control subject due to catheter blockage. Thus, end-expiratory P_{GA} and P_{DI} measurements were obtained in eight obese OSA patients and seven control subjects, while R_{UA} measurements were obtained in seven obese OSA patients and seven control subjects. Two obese OSA patients and one control subject could not reliably perform Muller manoeuvres. Consequently, between group comparisons in $iEMG_{DI}$ and $eEMG_{DI}$ (%maximum) data are represented by six obese OSA and six control individuals.

Anthropometric variables in each group are presented in Table 3.1. Both groups were matched for age and had healthy lung function, while OSA patients were significantly heavier than controls and had severe OSA by design. Maximal EMG_{DI} was not significantly different between groups (OSA vs. controls, 29.7 ± 4.0 μV vs. 23.6 ± 4.3 μV, P = 0.27).

Average pre-sleep onset (sleep onset categories combined) data are shown in Table 3.2. V_I, $R_{UA,}$ end-expiratory P_{GA}, $P_{DI,}$ $iEMG_{DI}$ (%max) and iEMG (μV) were all significantly higher in the obese OSA group prior to sleep onset (V_I, P = 0.007; R_{UA},

$P < 0.001$; P_{GA}, $P = 0.001$, P_{DI}, $P = 0.008$; $iEMG_{DI}$ (%max), $P = 0.019$ and iEMG (μV), $P = 0.006$). There was a trend for increased $eEMG_{DI}$ (μV) in the OSA group ($P = 0.063$).

3.3.2 Changes at sleep onset

An example of raw data for a stable breathing, hypopnoea and apnoea wake-sleep transition in one OSA patient are shown in Figure 3.1. There were 20.9 ± 2.9 (range 13-33) sleep onsets in the obese OSA group and 22.9 ± 2.6 (range 14-35) in control participants that met the inclusion criteria for analysis. Overall, 78/167 (46.7%), 48/167 (28.7%) and 41/167 (24.6%) of sleep onsets were classified as stable, hypopnoea and apnoea wake-sleep transitions in the obese OSA patients, and 149/179 (83.2%) and 30/179 (16.8%) of sleep onsets classified as stable and hypopnoea wake-sleep transitions in the control participants. There were no apnoeas following sleep onsets in control subjects that met the inclusion criteria. There was a greater number of wake-sleep transitions followed by respiratory events (hypopnoea and apnoeas) in the obese OSA group compared to the controls ($P = 0.02$).

Figure 3.2 shows changes in V_I across the wake-sleep transition in the obese OSA patients and control subjects for all sleep onsets combined (Figure 3.2A) and with stable sleep, hypopnoea and apnoea transitions shown separately for the obese OSA patients (Figure 3.2C) and stable sleep and hypopnoea transitions in the control subjects (Figure 3.2E). There was a significantly greater and more rapid reduction in V_I in obese OSA patients (Figure 3.2A, group, $P = 0.009$; group x

breath, $P < 0.001$). By analytical design, the fall in V_I following sleep onset was dependent upon the degree of subsequent airway obstruction (Figure 3.2C and E, category, $P < 0.001$).

EELV significantly decreased by 61.4 ± 8.0 ml and 34.0 ± 4.2 ml by the third sleep onset breath from wakefulness in obese OSA patients and control subjects respectively (Figure 3.2B, $P < 0.001$). While there were no between group differences in the overall reduction in EELV following sleep onset ($P = 0.528$), there was a greater decline in EELV over time following sleep onset in the obese OSA patients (Figure 3.2B, group x breath, $P = 0.007$), with this group experiencing greater decrements in EELV over time in apnoea and hypopnoea transitions (Figure 3.2D, category x breath, $P < 0.001$). While there was no category x breath interaction effect in the control group, the overall decrease in EELV was significantly greater in hypopnoea compared to stable breathing transitions (Figure 3.2F, category, $P = 0.01$). By the third breath following sleep onset in the obese OSA group, EELV had statistically significantly fallen in each transition category (stable, 25.9 ± 10.8 ml, $P = 0.017$; hypopnoea, 84.7 ± 16.3 ml, $P < 0.001$ and apnoea, 118.9 ± 16.4 ml, $P < 0.001$, Figure 3.2D). Similar decrements in lung volume by the third post sleep onset breath were evident for each transition type in the controls (stable, 34.2 ± 4.3 ml, $P < 0.001$; hypopnoea, 41.0 ± 13.1 ml, $P = 0.002$, Figure 3.2F). Although there were consistent and significant post-sleep onset changes in EELV, sleep onset responses in OSA patients and control participants were highly variable, both between and within individuals. For OSA patients, between versus within subject standard deviations for each transition type were; stable breathing 63 vs. 107 ml; hypopnoea onsets 86 vs. 151 ml; apnoea

onsets 28 vs. 90 ml. In control participants, between versus within subject standard deviations were; stable breathing 40 vs. 65 ml; hypopnoea onsets 65 vs. 53 ml.

Changes in $iEMG_{DI}$ and $eEMG_{DI}$ activity following sleep onset are shown in Figure 3.3. $iEMG_{DI}$ and $eEMG_{DI}$ showed significantly greater (Figure 3.3A, $P = 0.02$, and Figure 3.3B, $P = 0.017$ respectively) and more rapid (Figure 3.3A, group x breath, $P < 0.001$, and Figure 3.3B, group x breath, $P < 0.001$ respectively) reductions following sleep onset in the obese OSA group, with activity significantly decreasing by a maximum of 14.5 ± 1.6% of baseline ($P < 0.001$) and 8.3 ± 1.2% of baseline ($P < 0.001$) from wakefulness respectively. In the obese OSA group, decreases in $iEMG_{DI}$ and $eEMG_{DI}$ were significantly greater and more rapid in sleep onset categories accompanied by respiratory events (Figure 3.3C and D, category, $P < 0.001$, category x breath $P < 0.001$). $iEMG_{DI}$ and $eEMG_{DI}$ decreased by a maximum of 28.3 ± 2.7% of baseline ($P < 0.001$) and by 13.2 ± 2.6% of baseline ($P < 0.001$) respectively for apnea transitions. In contrast, the control group showed no significant sleep onset category or sleep onset category x breath dependent effects. $eEMG_{DI}$ changes at sleep onset in OSA patients and control participants were also highly variable, both between and within individuals. For OSA patients, between versus within subject standard deviations for each transition type were; stable breathing 4 vs. 8%; hypopnoea onsets 6 vs. 15%; apnoea onsets 9 vs. 13%. In control participants, these were; stable breathing 2 vs. 39%; hypopnoea onsets 7 vs. 13%.

Changes in end-expiratory P_{GA} and end-expiratory P_{DI} following sleep onset are shown in Figure 3.4. There were no group or interaction effects in changes in P_{GA} following sleep onset (Figure 3.4A). Similarly, there were no sleep onset category or sleep onset category x breath dependent effects in changes in P_{GA} in either the obese OSA group or the control group (Figure 3.4C and E). However, there was a greater increase in end-expiratory P_{DI} over time following the wake-sleep transition in the control group (Figure 3.4B, group x breath, P = 0.003) and more rapid decreases in end-expiratory P_{DI} over time following sleep onsets accompanied by respiratory events in the OSA group (Figure 3.4D, category x breath, P = 0.003). In contrast, the control group showed no significant sleep onset category or sleep onset category x breath dependent effects.

3.3.3 Changes preceding respiratory events

Figure 3.5 shows changes in V_I leading into hypopnoeas and apnoeas in obese OSA patients (Figure 3.5A) and leading into hypopnoeas in the control group (Figure 3.5B). V_I significantly decreased preceding respiratory events in both groups (breath effect, all $P < 0.001$), with V_I decreasing by 51.0 ± 4.2% and 35.7 ± 8.1% below wakefulness levels by the first hypopnoeic breath (both $P < 0.001$) in the obese OSA patients and control subjects respectively. EELV significantly decreased by 29.4 ± 12.3 ml (P = 0.018) and 89.6 ± 14.2 ml ($P < 0.001$) below wake levels by the first hypopnoeic breath and apnoeic inspiratory effort respectively in the obese OSA group (Figure 3.5C). However, there were no sleep onset category or sleep onset category x breath differences between the decrease in EELV leading into hypopnoeas and the decline leading into apnoeas in this

group. EELV also significantly decreased by 51.1 ± 14.8 ml below baseline levels ($P = 0.001$) by the first hypopnoeic breath in the controls (Figure 3.5D). $iEMG_{DI}$ significantly decreased leading in hypopnoeas and apnoeas in the obese OSA group (Figure 3.5E, breath effect, $P < 0.001$), with activity decreasing by 20.9 ± 2.7% ($P < 0.001$) and 30.7 ± 2.8% ($P < 0.001$) by the first hypopnoeic and apnoeic breath respectively. $iEMG_{DI}$ was also significantly lower during the period leading into apnoeas compared to the level preceding the onset of hypopnoeas ($P = 0.002$). Similar results were evident in $eEMG_{DI}$ in the obese group (Figure 3.5G). $eEMG_{DI}$ was significantly below wakefulness levels at the beginning of hypopnoeas and apnoeas (hypopnoeas, 11.0 ± 3.0% below awake levels, $P < 0.001$; apnoeas, 11.1 ± 2.9% below awake levels, $P < 0.001$). In respect to the control group, $iEMG_{DI}$ was 7.7 ± 3.7% below awake levels at the onset of hypopnoeas (Figure 3.5F, $P = 0.038$), whereas $eEMG_{DI}$ was not significantly different compared to baseline at the onset of hypopnoeas (Figure 3.5H).

Table 3.1: OSA patient and control anthropometric data

	OSA	Controls	P value
Age (years)	47.4 ± 3.4	48.3 ± 3.9	0.867
BMI ($kg \cdot m^{-2}$)	35.0 ± 1.4	23.8 ± 0.5	<0.001
FEV_1 (% predicted)	94.9 ± 5.6	104.8 ± 3.6	0.886
FVC (% predicted)	90.9 ± 6.7	102.0 ± 5.1	0.977
AHI ($events \cdot hr^{-1}$)	73.5 ± 9.2	10.0 ± 1.6	<0.001

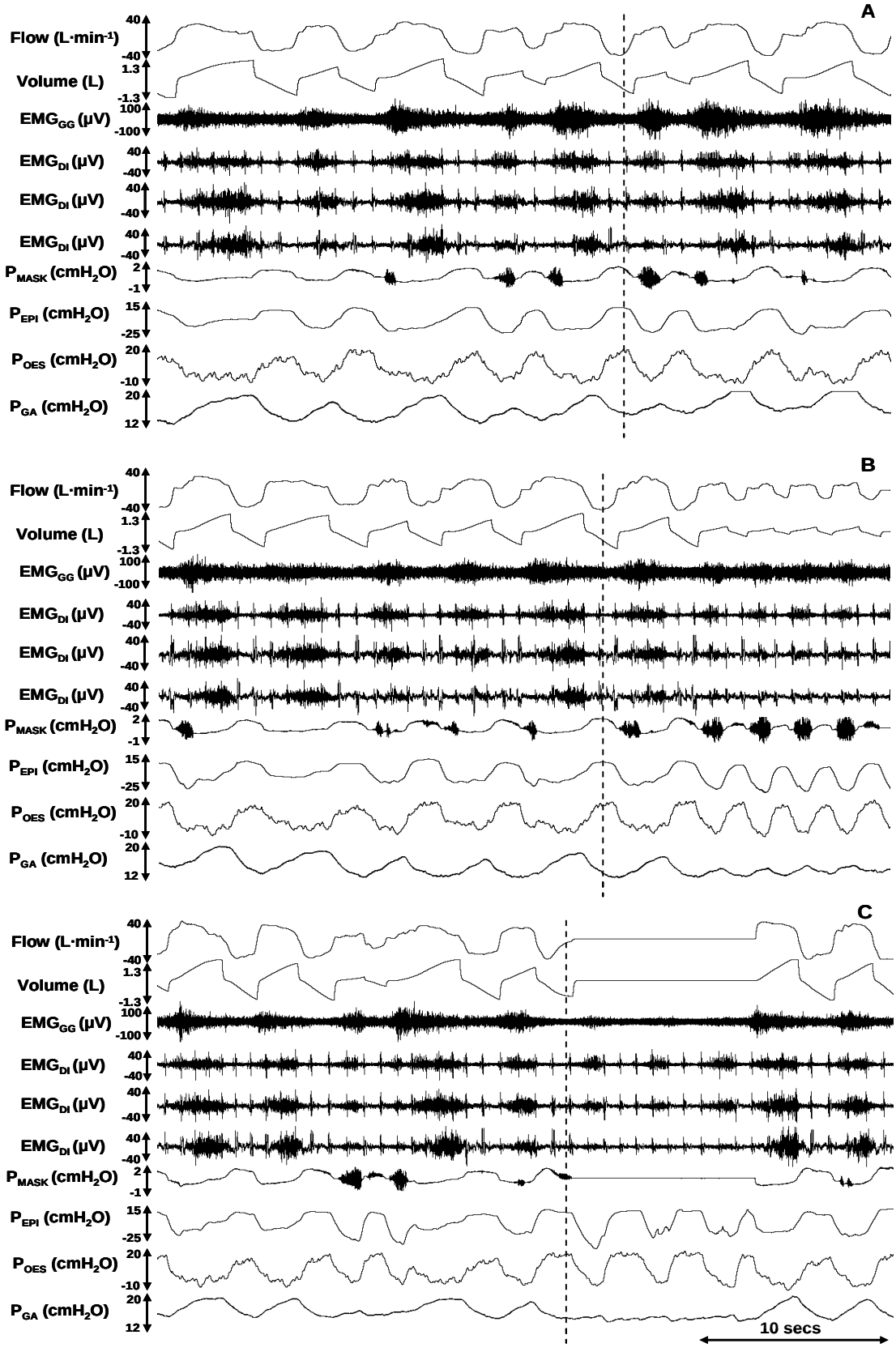
Age, body mass index (BMI), forces expiratory volume in 1 sec (FEV_1), forced vital capacity (FVC) and apnoea-hypopnoea index (AHI). Data are means ± SEM. N=8 obese OSA patients N=8 controls.

Table 3.2: Average pre-sleep onset (breaths -5 to -2) data in obese OSA patients and controls

	OSA	Controls
V_I (L·min^{-1})	8.1 ± 0.5*	6.4 ± 0.2
V_T (L)	0.53 ± 0.04	0.46 ± 0.03
F_B (breaths·min^{-1})	16.0 ± 1.0	14.4 ± 0.3
P_{ETCO_2} (mmHg)	41.9 ± 0.6	44.1 ± 1.3
R_{UA} ($cmH_2O \cdot L^{-1} \cdot s$)$^{+}$	15.3 ± 1.0*	9.0 ± 0.6
P_{GA} (cmH_2O)†	12.3 ± 0.8*	6.6 ± 1.5
P_{DI} (cmH_2O)†	5.3 ± 0.5*	0.2 ± 1.8
$iEMG_{DI}$ (% max) ††	20.6 ± 1.6*	14.6 ± 1.7
$eEMG_{DI}$ (% max) ††	10.1 ± 0.6	9.2 ± 0.8
$iEMG_{DI}$ (μV) ††	5.9 ± 0.5*	3.3 ± 0.5
$eEMG_{DI}$ (μV) ††	2.9 ± 0.3	2.0 ± 0.3

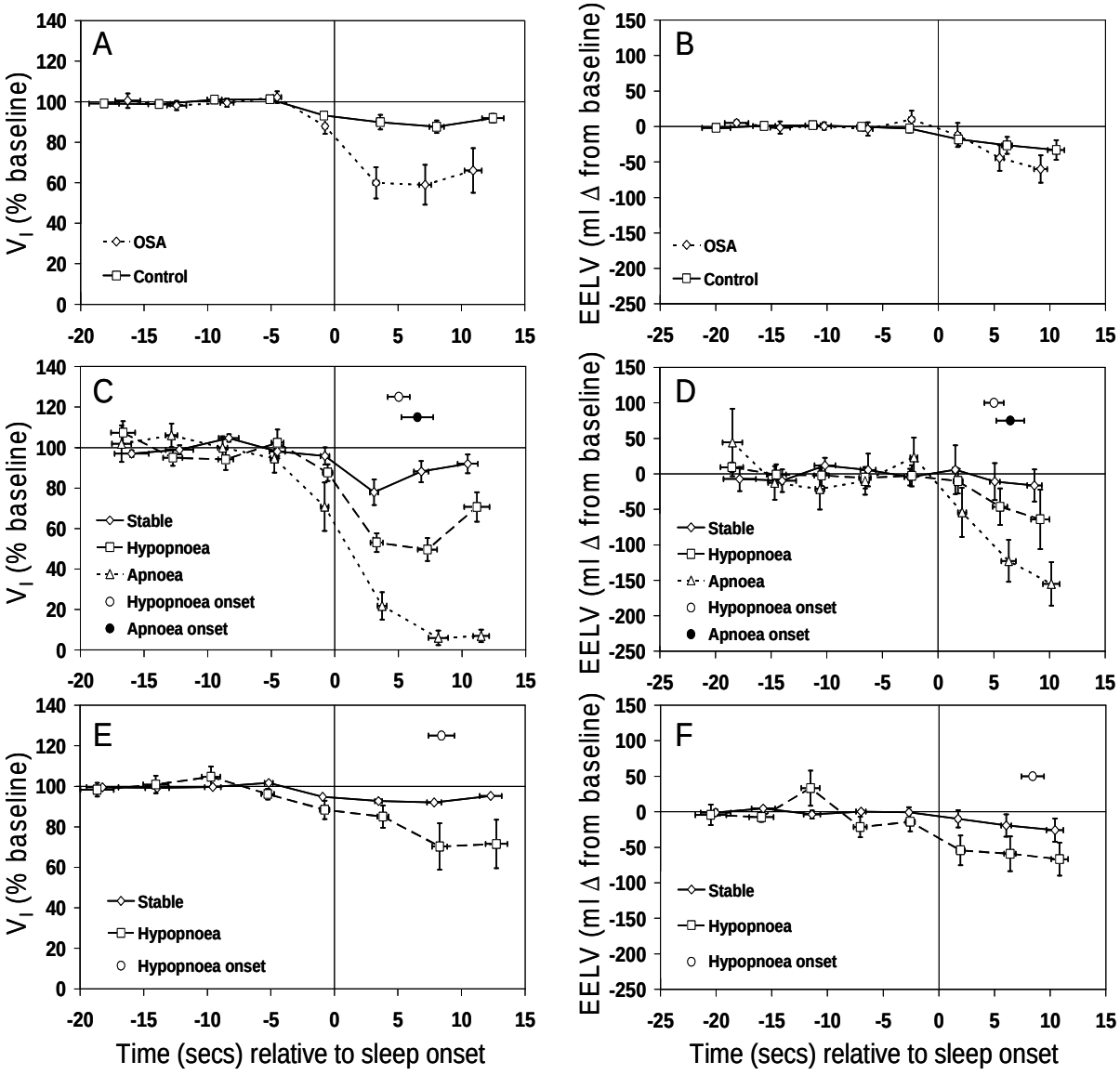
Minute ventilation (V_I), tidal volume (V_T), breathing frequency (F_B), end-tidal CO_2 (P_{ETCO_2}), upper airway resistance (R_{UA}), end-expiratory gastric (P_{GA}) and transdiaphragmatic (P_{DI}) pressures, and average inspiratory ($iEMG_{DI}$) and tonic expiratory ($eEMG_{DI}$) diaphragm activity. Data are means ± SEM. N=8 obese OSA patients and N=8 controls, $^{+}$N=7 obese OSA patients and N=7 controls, †N=8 obese OSA patients and N=7 controls, ††N=6 obese OSA patients and N=6 controls. *P < 0.05 obese OSA patients vs. controls.

Figure 3.1: Raw data across wake-sleep transitions in one OSA patient



Changes in flow, volume, genioglossus EMG (EMG_{GG}), diaphragm EMG (EMG_{DI}), mask pressure (P_{MASK}), epiglottic pressure (P_{EPI}), oesophageal pressure (P_{OES}) and gastric pressure (P_{GA}) across a (A) stable breathing transition, (B) hypopnoea transition and (C) apnoea transition. Sleep onset defined by dashed vertical line.

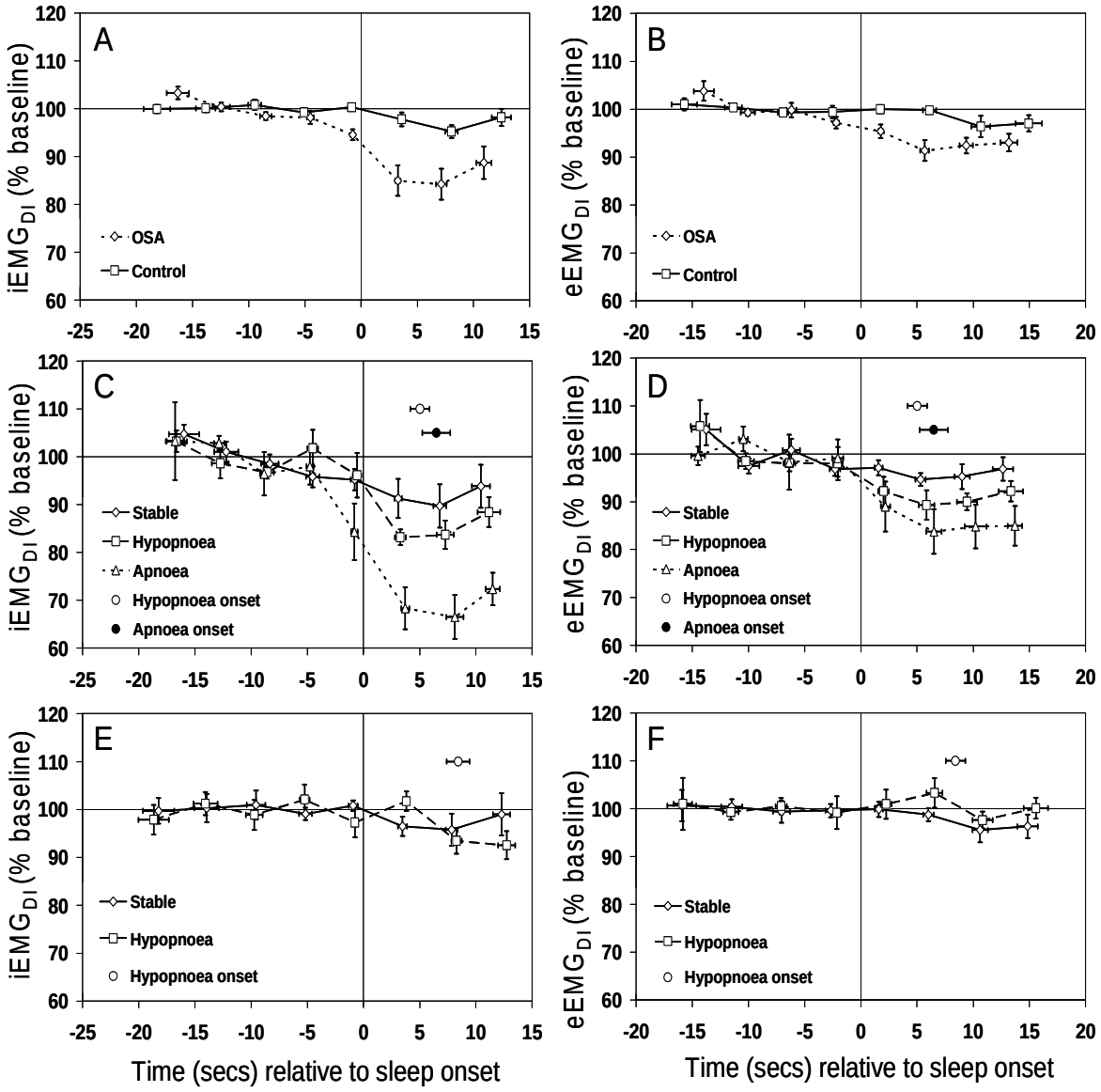
Figure 3.2: Changes in V_I and EELV following sleep onset in obese OSA patients and controls



Breath-by-breath changes in minute ventilation (V_I, left panel) and end-expiratory lung volume (EELV, right panel) across the wake sleep transition (vertical line). Changes in V_I are expressed as a percentage of the stable pre-sleep onset baseline period while EELV changes are expressed as ml difference from baseline. (A) and (B) obese OSA patients and controls (categories combined), (C) and (D) obese OSA patients (stable sleep, hypopnoea and apnoea categories separated),

(E) and (F) control subjects (stable sleep and hypopnoea categories separated). Average apnoea (OSA patients) and hypopnoea (OSA and control participants) onset times relative to sleep onset are shown as isolated points above baseline. Values are mean ± SEM, N=8 OSA and N=8 controls.

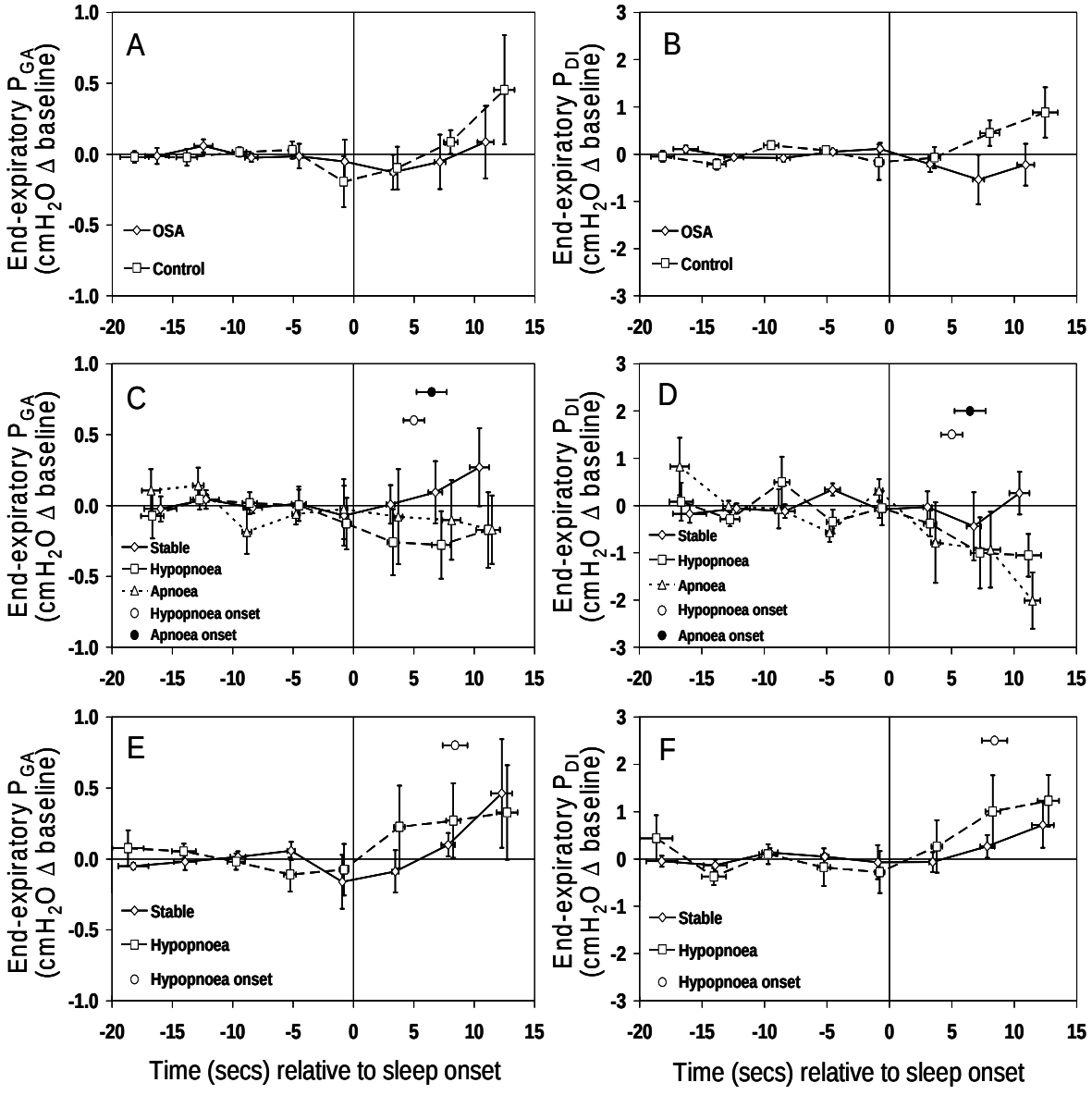
Figure 3.3: Changes in $iEMG_{DI}$ and $eEMG_{DI}$ following sleep onset in obese OSA patients and controls



Breath-by-breath changes in inspiratory (left panel) and tonic (right panel) diaphragm EMG activity ($iEMG_{DI}$ and $eEMG_{DI}$ respectively) across the wake sleep transition (vertical line) as a percentage of the stable pre-sleep onset baseline. (A) and (B) obese OSA patients and controls (categories combined), (C) and (D) obese OSA patients (stable sleep, hypopnoea and apnoea categories separated), (E) and (F) control subjects (stable sleep and hypopnoea categories separated). Average

apnoea (OSA patients) and hypopnoea (OSA and control participants) onset times relative to sleep onset are shown as isolated points above baseline. While inspiration of breath -1 began before sleep onset, tonic activity for this breath occurred following sleep onset. Values are mean ± SEM, N=8 OSA and N=7 controls.

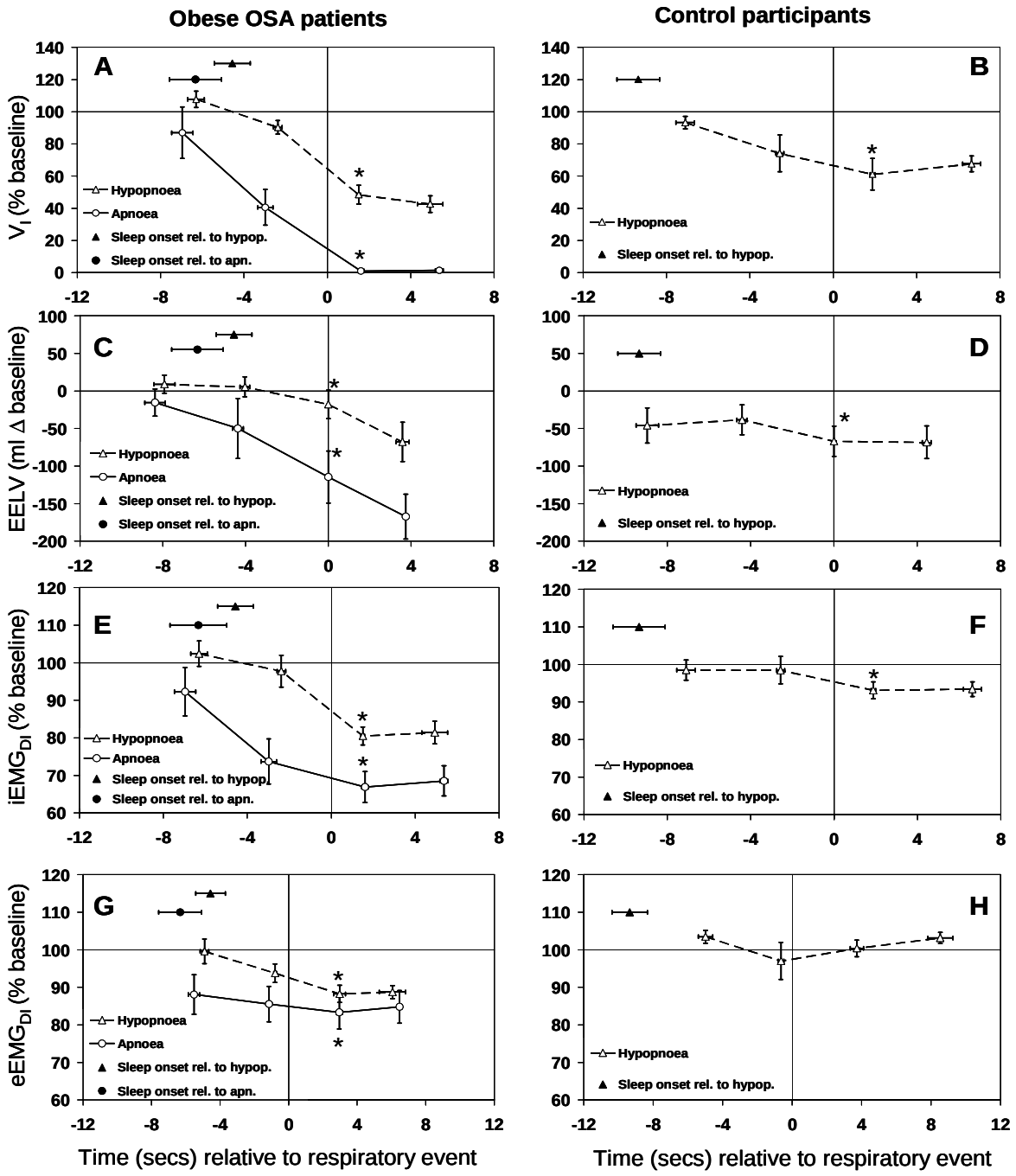
Figure 3.4: Changes in end-expiratory P_{GA} and end-expiratory P_{DI} following sleep onset in obese OSA patients and controls



Breath-by-breath changes in end-expiratory P_{GA} (left panel) and end-expiratory P_{DI} (right panel) across the wake sleep transition (vertical line) as the difference between each absolute breath value minus the average pre-sleep onset baseline (breaths -5 to -2), such that a negative value indicates a decrease in pressure relative to baseline. (A) and (B) obese OSA patients and controls (categories combined), (C) and (D) obese OSA patients (stable sleep, hypopnoea and apnoea

categories separated), (E) and (F) control subjects (stable sleep and hypopnoea categories separated). Average apnoea (OSA patients) and hypopnoea (OSA and control participants) onset times relative to sleep onset are shown as isolated points above baseline. Values are mean ± SEM, N=8 OSA and N=7 controls.

Figure 3.5: Changes in V_I, EELV, $iEMG_{DI}$ and $eEMG_{DI}$ leading into hypopnoeas and apnoeas in obese OSA patients and controls



Breath-by-breath changes in minute ventilation (V_I, A and B), end-expiratory lung volume (EELV, C and D), inspiratory and tonic diaphragm muscle activity ($iEMG_{DI}$ and $eEMG_{DI}$, E-H) for the last two breaths prior to and the first two

breaths/inspiratory efforts during hypopnoeas and apnoeas in obese OSA patients, and hypopnoeas in control participants. Average sleep onset time relative to the onset of hypopnoeas and apnoeas are shown as isolated points above baseline. Values are mean ± SEM. *P < 0.05 first respiratory event breath/inspiratory effort vs. awake levels.

3.4 Discussion

The key findings of this study were that acute decrements in EELV accompany sleep onset in both obese OSA patients and healthy weight controls, and that greater decrements in EELV and end-expiratory P_{DI} occur during wake-sleep transitions immediately followed by respiratory events. However, despite obesity and substantially raised intra-abdominal pressure, consistent with previous reports[114, 115], there was no evidence for a greater overall sleep onset related reduction in lung volume, end-expiratory P_{GA} or end-expiratory P_{DI} in obese OSA patients compared to controls. While some caution is warranted given the small sample size, we estimate that lung volume changes in the order of ~145 ml could have been detected between groups with 80% power and a two-tailed significance level of 0.05. Given that significant lung volume changes of this magnitude were detected accompanying apnoea events following sleep onset, it appears unlikely that similar magnitude or larger systematic effects of obesity on average lung volume responses at sleep onset in OSA patients would have been missed due to type II error. However, given more frequent hypopnoea and apnoea events and greater lung volume decrements over time in OSA patients compared to controls, more substantial lung volume changes were nevertheless a more common outcome following sleep onset in OSA patients compared to healthy weight controls.

EELV significantly decreased in the order of ~100 ml at the onset of complete UA obstruction in the obese OSA group. The contribution of this decrement to the development of obstruction in the immediate post sleep onset period is not clear

and cannot be separated from other potential effects of reduced respiratory drive on UA function. Previous reports have demonstrated significant modulating effects of modest changes in EELV (~500 ml) above normal EELV on UA collapsibility[85-87]. While the effects of lung volume changes below EELV are unknown, longitudinal traction effects on UA compliance could be alinear at the lower range of tension rendering UA function more sensitive to lung volume changes below EELV, particularly in obese patients with already reduced lung volume[91, 92] and UA size during wakefulness[26]. OSA patients demonstrate larger changes in UA size over the normal tidal breathing range[52], consistent with an exaggerated sensitivity to volume related effects on UA function. Consequently, modest lung volume changes at sleep onset, at least equivalent to those seen in normal weight controls, may therefore reflect larger relative effects on lung volume and lung volume mediated effects on UA function. Further studies are needed to elucidate the impact of experimentally induced lung volume decrements in the order of 100-150 ml below EELV on UA function in obese versus non-obese controls.

A similar pattern and time-course of changes in V_I, $iEMG_{DI}$ and $eEMG_{DI}$ activity at sleep onset support that ventilatory and lung volume decrements reflect an acute and wide-spread reduction in phasic and tonic respiratory muscle tone at the wake-sleep transition, with periods of greater reduction associated with more severe respiratory events. The greater decline in end-expiratory P_{DI} over time following sleep onset followed shortly by respiratory events in obese OSA patients, is consistent with diaphragm relaxation and ascent. Different changes in end-expiratory P_{DI} over time in the control versus OSA group likely indicate different chest wall vs. abdominal conformational changes associated with acute diaphragm

relaxation at sleep onset in obese versus non-obese individuals. Consistent with a previous study[258], inspiratory EMG_{DI} was found to be significantly higher in the obese group, likely reflecting increased inspiratory work required to offset mass loading effects on the respiratory system. In contrast, we found little evidence of increased tonic EMG_{DI} to support active defence of lung volume during wakefulness, although post sleep onset falls in activity did appear to be greater and more rapid in obese OSA patients. While these findings do not support a diaphragm neurocompensatory reflex, caution is warranted given the small sample size. We estimate that wakefulness tonic EMG_{DI} in the order of ~3% of maximal activity could have been detected between groups with 80% power and a two-tailed significance level of 0.05. Therefore, it appears unlikely that larger systematic effects of obesity on tonic diaphragm activity in OSA patients would have been missed due to type II error. Also, between group comparisons of EMG were made by referencing individual supine resting pre-sleep onset EMG values to EMG values observed during maximum voluntary contractions. A higher maximum level of activity in OSA patients than controls, e.g. due to diaphragm hypertrophy/diaphragm fibre remodelling[259], secondary to years/months of increased respiratory work due to mass loading, could lead to an underestimation of absolute tonic diaphragm activity in patients. While maximum activity was not found to be statistically significantly different between groups in this study, $eEMG_{DI}$ (expressed in μV) tended to be increased in OSA patients compared to control subjects, suggesting that this group may have higher absolute muscle activity compared to healthy-weight individuals.

The larger decline in ventilation and inspiratory diaphragm muscle activity following sleep onset in OSA patients supports previous findings[146]. In addition to decrements in diaphragm muscle activity and EELV observed in this study, reduced ventilation in OSA patients is known to be importantly influenced by reduced UA dilator muscle activity at sleep onset[146, 204]. In a follow up protocol, Fogel et al[146] found that the decline in diaphragm muscle activity at sleep onset was not significantly different between OSA patients and controls when R_{UA} was matched between groups via application of continuous positive airway pressure (CPAP), but that overall ventilation and genioglossus muscle activity continued to fall to a lower level in OSA patients. In addition, while CPAP led to a significant reduction in phasic activation of the genioglossus during wakefulness in obese OSA patients, activity remained substantially higher than in control individuals. These findings support the presence of a heightened centrally mediated respiratory drive output beyond the negative neurocompensatory reflex component of UA dilator muscle activation. Combined with the present findings, these data support that OSA patients exhibit an increased and widespread wakefulness dependent drive to the respiratory system that is not limited to the UA. This may be an adaptation necessary to compensate for respiratory system mass loading effects. A widespread reduction of drive to respiratory muscles other than UA dilator muscles, such as tonic drive to the diaphragm and thoracic muscles, may also contribute to the development of UA obstruction, potentially via lung volume mediated effects on tracheal traction.

3.4.1 Methodological considerations

There are several methodological issues to consider in this study. Greater decreases in lung volume and diaphragm muscle activity with more severe respiratory events at sleep onset clearly do not establish that causal relationships with UA collapse necessarily exist. Nevertheless, these observations are consistent with, and do not discount the presence of causal relationships, and are in contrast to ruling out lung volume influences had we found no changes at sleep onset. That lung volume/caudal traction changes with obesity *per se* contribute to increased UA collapse and the strength of such effects remain to be established.

We did not attempt to recruit an obese non-OSA comparator group for several reasons. The primary intent of the study was to investigate the impact of obesity, a known major factor in OSA risk, on ventilatory parameters potentially contributing to UA collapse in the context of OSA. Obese non-OSA individuals are difficult to recruit, may be skewed towards abnormally robust UA function despite obesity effects, and/or exhibit a different pattern of obesity than captured by conventional BMI measurements. Consequently, we elected to first establish the nature and magnitude of lung volume changes at sleep onset before further studies designed to examine these mechanisms in more detail. Nevertheless, it is conceivable that sleep onset differences between groups are potentially confounded by differences in baseline awake measurements such as weight (BMI), R_{UA}, disease status, EELV and diaphragm EMG activity.

We used conventional criteria using manual scoring of sleep recordings (blinded to group allocation and independent from the respiratory analysis) to identify sleep onset as α EEG activity followed by ≥3 breaths of θ EEG activity. We did not employ a breath-by-breath α-θ criterion ratio as has been performed by others[146, 149]. While it is not clear what impact this may have on the measured outcomes, we speculate that manually scored sleep onset periods would include fewer and more prolonged transitions into sleep, and potentially underestimate transitory effects identified from shorter episodes of sleep in closer proximity to prior respiratory and arousal events.

In contrast to previous studies in which diaphragm activity was assessed by surface electrodes[146, 149], the current study measured diaphragm activity via intra-oesophageal recordings over a larger area of the crural diaphragm[260]. Surface recordings are likely to be highly influenced by changes in lung volume/diaphragm position[261] and must be interpreted with considerable caution as apparent decreases in activity may reflect diaphragm movement away from the recording electrodes. Although intra-oesophageal recordings must also be interpreted with caution, by averaging across all electrode pairs over a wide distance, these measures are more robust to confounding by diaphragm movement with respiration and lung volume changes. Consequently, the apparent loss in diaphragm activity at sleep onset is unlikely a recording artefact and was consistent with simultaneous decrements in lung volume and ventilatory output.

Our method of quantifying diaphragm EMG activity is somewhat of a departure from more conventional methods[146, 148] and was chosen on the basis of superior

signal:noise characteristics via integration over the full period of inspiration. In six subjects from a previous study undertaken in our laboratory, the coefficient of variation in $iEMG_{DI}$ and $eEMG_{DI}$ was 7.8 ± 0.5% and 6.2 ± 0.9% compared to 12.9 ± 2.4% and 6.4 ± 1.1% derived from conventional peak and tonic activity measurements.

3.4.2 Summary and conclusions

Despite increased intragastric pressure, we found no significant difference in tonic diaphragm muscle activity during wakefulness between obese OSA patients versus healthy-weight controls. Sleep onset was accompanied by significant decrements in ventilation and both inspiratory and tonic diaphragm muscle activity, with the overall decreases greater in OSA patients. Muscle activity and EELV significantly decreased below wakefulness levels at the onset of respiratory events, particularly in the obese OSA patients. This is consistent with a widespread acute decline in phasic and tonic respiratory muscle activity, with greater decrements potentially promoting more severe respiratory events. In the presence of an already more collapsible airway, both UA muscle activity and EELV changes potentially contribute to the increased propensity for UA collapse in OSA patients at sleep onset.

CHAPTER 4. LUNG VOLUME, TRANSDIAPHRAGMATIC PRESSURE AND EMG CHANGES LEADING INTO AND OUT OF OBSTRUCTIVE RESPIRATORY EVENTS IN OBSTRUCTIVE SLEEP APNOEA PATIENTS

4.1 Introduction

Obstructive sleep apnoea (OSA) is a common sleep disorder characterised by repetitive periods of upper airway (UA) collapse during sleep, and is particularly prevalent in obese males[18, 43]. An anatomically smaller and more collapsible UA is likely to be a primary pathogenic factor in many OSA patients[26, 72]. However, acute reductions in respiratory drive to UA dilator and inspiratory pump muscles, interactions with mass loading effects of obesity on lung volume that may influence UA function, and exaggerated arousal responses, potentially all interact to promote conditions favouring cyclical UA collapse in OSA. We recently found that experimentally increased intragastric pressure with abdominal compression in obese OSA patients, already with raised intragastric pressure, led to increased UA collapsibility during sleep[251]. This finding suggests that mass loading effects of obesity on the degree of caudal tracheal traction on the UA exerted via intrathoracic structures and/or lung volume effects, could play a significant role in promoting UA collapse. Furthermore, these effects might importantly depend on drive to UA and respiratory pump muscles that change over the course of the obstructive apnoea cycle. However, to date there have been no studies to evaluate the time-course of

changes in respiratory and UA muscle drive as well as transdiaphragmatic pressure and lung volume changes preceding and following UA collapse in OSA to explore these potential effects.

Low drive to UA dilator muscles is considered to be a major contributor to UA collapse during sleep, with several groups identifying a decline in genioglossus muscle activity preceding UA obstruction[1, 150, 213]. In addition, absent phasic respiratory drive can give rise to UA obstruction (i.e. mixed apnoeas)[262]. Consequently, in addition to more direct effects of reduced UA muscle tone *per se*, a widespread reduction in drive to other respiratory muscles may allow chest and abdominal relaxation to promote UA obstruction via tracheal traction and lung volume effects[105, 108]. Several groups have shown that reducing end-expiratory lung volume (EELV), via positive extrathoracic pressure, leads to increased UA resistance (R_{UA}) and UA collapsibility[84, 85]. While there is some evidence that EELV decreases prior to and increases following respiratory events[263-265], these changes have not been measured simultaneously with other potentially important interrelated physiological variables. Furthermore, given different chest versus abdominal compliance[266], cranial displacement of the diaphragm from mass loading effects of obesity may have different caudal traction mediated effects on UA function than lung volume changes induced by extrathoracic pressure. Increased gastric pressure (P_{GA}) and transdiaphragmatic pressure (P_{DI}), presumably importantly underlie cranial displacement of the diaphragm and lower EELV in obese compared to healthy-weight individuals[91]. Reduced diaphragm muscle activity leading into UA obstruction potentially allows for further diaphragm ascent with decreased end-expiratory P_{GA} and P_{DI}. However, there are no systematic data

available to evaluate if end-expiratory P_{GA} and P_{DI} change leading into and out of UA collapse in OSA.

Brief arousals from sleep, likely arising from increased inspiratory effort[267], are a key component of OSA and may predispose OSA patients to subsequent cyclical respiratory events[2, 222]. Several groups have demonstrated that brief tone-induced arousals during stable sleep are followed shortly by a period of hyperventilation and subsequently hypocapnia/low ventilatory drive around the resumption of sleep[2, 221, 222]. Therefore, the ventilatory response following the termination of apnoeas, particularly when accompanied by arousal, establishes conditions potentially ideal for the development of further respiratory events in patients vulnerable to UA collapse. Consequently, there may be important reciprocal relationships between obstructive and arousal events with each promoting the other, thereby helping to support the characteristic cyclical pattern of events in OSA.

The primary aim of this study was to examine the magnitude and temporal relationships of changes in UA dilator and diaphragm muscle drive, end-expiratory P_{GA}, P_{DI} and lung volume leading into, during and post obstructive events during sleep in obese male OSA patients. We hypothesised that the onset of UA obstruction would be preceded by systematic decreases in respiratory drive to UA and pump muscles as well as end-expiratory P_{GA} and P_{DI} and lung volume, over a similar time-course. We also postulated there would be close temporal relationships, not only between the offset of obstructive events and the onset of arousal, as has been shown previously[2], but between arousal events and subsequent respiratory event onsets, with close temporal proximity to respiratory

changes that exacerbate low ventilatory drive, potentially placing the UA at greater risk of further collapse.

4.2 Methods

4.2.1 Patient selection

All patients who were recruited in the study presented in Chapter 2, also participated in this study. As this study was undertaken to evaluate events leading into and out of complete UA obstruction, an additional inclusion criteria of diagnostic study NREM supine obstructive apnoea index of >10 events·hr^{-1} was employed. Patients were excluded if their NREM supine, mixed or central apnoea index was >5 events·hr^{-1}. Patients were required to have normal lung function (forced expiratory volume in 1 sec [FEV_1] and forced vital capacity [FVC] >80% predicted, JLab software version 4.53; Compactlab, Jaeger, Wuerzburg, Germany) and were instructed to refrain from consuming caffeine and alcohol for 12 and 24 hours prior to the experiment respectively. The study was approved by the Daw Park Repatriation General Hospital and Adelaide University Human Research and Ethics Committees. Each participant gave informed written consent to participate in the study.

4.2.2 Measurements and equipment

Sleep was monitored by two channels of EEG (C_4/A_1, C_3/A_2), left and right electro-oculograms, submental EMG and ECG. Arterial oxyhaemoglobin saturation was

recorded by finger pulse oximetry (POET II model 602-3; Criticare Systems, Waukesha, WI).

Both nostrils were decongested with xylometazoline hydrochloride nasal spray (Otrivin, Novartis Australasia, Rowville, Victoria, Australia) and anaesthetised (2% lignocaine spray). A custom made, multilumen, intraoesophageal catheter (MuiScientific, Ontario, Canada) was used to assess P_{GA} and oesophageal (P_{OES}) pressure and intraoesophageal diaphragmatic EMG (EMG_{DI}). For measurement of P_{GA}, a latex balloon, 5 cm in length (Viasys Healthcare, Hoechberg, Germany) was attached to the distal end of the catheter. P_{OES} was measured by a separate latex balloon (10 cm in length) attached approximately 10 cm above the P_{GA} balloon. The catheter was inserted into the most patent nostril and advanced approximately 60 cm. The balloons were filled with ~1.5-2 ml of air and the position of the catheter was initially adjusted until positive P_{GA} and negative P_{OES} pressure swings were detected during and in phase with inspiration. Both pressure channels were connected to solid state pressure transducers (Spectramed DTX, Oxnard, USA). Epiglottic (P_{EPI}) pressure was assessed by a thin air-perfused nasal catheter (see Hilditch et al[230] for further detail). This catheter was advanced 1–2 cm below the base of the tongue under direct visualisation, taped at the nose and connected to another pressure transducer (MP45; Validyne Engineering, Northridge, CA). Patients were fitted with a nasal mask (ComfortGel Nasal Mask, Philips Respironics, Murrysville, PA) attached to a non-rebreathing valve (Series 2600, Hans Rudolph, Kansas City, MO, USA) equipped with sealable luer ports to accommodate each catheter. Inspiratory nasal flow and volume were measured by a pneumotachograph (PT16, Jaeger, Germany) attached to the inspiratory port.

End-tidal CO_2 (P_{ETCO_2}, Capstar-100, CWE Inc, PA) and mask pressure (MP45; Validyne Engineering, Northridge, CA) were measured from separate mask ports. Transdiaphragmatic pressure (P_{DI}) was determined as P_{GA}-P_{OES} at end-expiration.

Genioglossus muscle activity (EMG_{GG}) was recorded as previously described.[165] Following surface anaesthesia (4% lignocaine), two fine-wire Teflon-coated stainless steel intramuscular wires (316SS3T wire, Medwire, Mt. Vernon, NY, USA) were inserted ~4 mm either side of the frenulum to a depth of approximately 1-1.5 cm using 27G needles (PrecisionGlide, Becton Dickinson and Company, Franklin Lakes, NJ, USA).

EMG_{DI} was recorded via a series of nine equally spaced (1 cm inter-electrode distance) stainless steel rings situated between the P_{GA} and P_{OES} sensing balloons of the multi-lumen catheter. Electrodes were connected in sequentially adjacent pairs (electrodes 1 (most proximal) and 2, 2 and 3 etc) to an amplifier (Model15LT, Grass Instruments, Quincy, MA, USA) and band-pass filtered (0.3-1 kHz) to provide eight bipolar EMG channels with an inter-pair distance of 1 cm. Once connected, the catheter position was further adjusted to achieve maximal inspiratory EMG_{DI} activity within the centre of the electrode array, and then secured at the mask using a tight-sealing stainless steel luer (SSA1380, S4J Manufacturing Services, Cape Coral, FL, USA).

Abdominal and thoracic excursions were measured continuously using two pairs of magnetometer coils (Polhemus Liberty, Colchester, USA) placed in the anterior-posterior axis of the chest and abdomen (Chapter 2)[251].

4.2.3 Data acquisition

All conventional sleep-related signals were recorded on a Compumedics data acquisition system (E-series, Compumedics Inc., Melb., Australia). X, Y and Z co-ordinates of each of the four magnetometer sensors were acquired on a second computer at a sample rate of 120 Hz (Polhemus Liberty, Colchester, USA). The remaining signals were recorded on a 32 channel Windaq (DI-720 DATAQ Instruments Inc, OH, USA) data acquisition system at 200 Hz, except genioglossus and diaphragm EMG channels which were sampled at 1 kHz. To facilitate accurate time-matching between the three recording system (within ~100 msec), a computer actuated event mark signal was simultaneously placed on all three acquisition systems approximately every hour.

4.2.4 Protocol

Following instrumentation and whilst supine, patients undertook a five minute baseline period in which they were instructed to remain relaxed, with their eyes open, breathing solely through their nose. The mouth was then taped to ensure nasal breathing, lights were switched off and the patient was allowed to fall asleep in the supine position. Patients were asked to remain on their back for the duration of the study, confirmed by a position sensor and video camera monitoring. If the patient was unable to sleep due to discomfort, they were allowed to briefly change postures for a short period of time (<15 min), then were woken if necessary and asked to return to the supine posture to continue the experiment. Non-supine sleep data were excluded from analysis.

4.2.5 Data analysis

Sleep recordings were analysed by an accredited sleep technologist using 30 sec epochs and Rechshaffen and Kales criteria for staging sleep[228]. Arousals and respiratory events were scored according to standard criteria[229, 256].

Only obstructive apnoeas scored in stage 2 sleep preceded by at least one epoch of stage 2 sleep were analysed. For each obstruction, apnoea onset time was defined as the start of the first inspiratory effort (drop in P_{OES} or P_{EPI}) in which there was an absence of inspiratory flow, while apnoea offset was defined as the time point at which flow (inspiratory or expiratory) was restored. Breath-by-breath analyses were restricted to the four last (-4 to -1) and first four (1 to 4) breaths prior to and following the termination of apnoeas respectively, and the first and final two inspiratory efforts during occlusions (obstructed breaths 1 and 2, -2 and -1 respectively).

For each pre- and post-apnoeic ventilatory breath, minute ventilation (V_I), inspiratory tidal volume (V_T), peak inspiratory flow (PIF), P_{ETCO_2} and R_{UA} were calculated on a breath-by-breath basis using custom analysis software used previously[221]. End-expiratory pressures (P_{DI}, P_{GA} and P_{OES}) and inspiratory ΔP_{OES} and expiratory ΔP_{GA} were calculated across all periods (pre-apnoeic, apnoeic and post-apnoeic breaths).

Several values were calculated on a breath-by-breath basis for both EMG_{GG} and EMG_{DI}. Custom written software was used to rectify and integrate raw inspiratory EMG_{GG} activity, which was then divided by inspiratory time to produce average

activity across inspiration ($iEMG_{GG}$). Minimum (tonic) expiratory activity ($eEMG_{GG}$) was calculated using methods similar to those described by Fogel et al[146]. Expiration was first divided into ten equal segments and raw data for each segment were rectified, integrated and then divided by the time interval. $eEMG_{GG}$ was considered to be that of the expiratory time segment showing minimum activity. Average inspiratory ($iEMG_{DI}$) and minimum tonic ($eEMG_{DI}$) diaphragm activity for each electrode pair were calculated in a similar fashion. However, given EMG activity is dependent on muscle-to-electrode distance[257], $iEMG_{DI}$ and $eEMG_{DI}$ were then averaged across all electrode pairs for each breath to minimise potential confounding by crural diaphragm movement with respiration and changes in lung volume. For each muscle, all EMG parameters were expressed as a percent of average wakefulness tonic activity calculated during each patient's wakefulness baseline period.

EELV changes were assessed as previously described (Chapter 2)[251]. Changes in EELV leading into, during and post apnoeas were referenced to the last pre-apnoeic breath.

For each apnoea, cessation of airflow was defined as either inspiratory or expiratory in nature based on the initial time point within the respiratory cycle where there was zero flow despite respiratory swings in either P_{EPI} or P_{OES}. The timing of this cessation was also expressed as a precent of total inspiratory or expiratory time according to the phase of respiration at the initiation of UA collapse.

To examine the effect of EEG arousal on ventilatory and muscle response for the first four breaths following termination of apnoeas, arousal events were classified using the following criteria:

1) ***Arousal (type 1):*** arousals in close proximity to airflow restoration; defined if an arousal occurred between the onset of the last apnoeic inspiratory effort and the start of the third post apnoeic breath.
2) ***No arousal (type 2):*** where arousal was absent during obstruction and before the onset of the third post apnoeic breath.
3) ***Excluded events (type 3):*** if an arousal occurred after the onset of the third post apnoeic breath or if an arousal occurred during the occlusion prior to the last apnoeic inspiratory effort.

Histograms were constructed to determine the temporal relationship between several potential key related events (Figure 4.5 top panel). These included the time difference between the:

(1) offset of the previous respiratory event (hypopnoea, apnoea, central or mixed apnoea in any stage of sleep) and onset of obstruction
(2) offset of the previous arousal and the onset of obstruction
(3) start of flow at the offset of obstruction and the onset of the closest (preceding or following) arousal to the termination of the obstruction
(4) offset of obstruction and the onset of the nearest subsequent respiratory event (hypopnoea, apnoea, central or mixed apnoea in any stage of sleep)

(5) offset of the closest arousal to obstruction and the onset of the nearest subsequent respiratory event (hypopnoea, apnoea, central or mixed apnoea in any stage of sleep)

4.2.6 Statistical analysis

All group data are presented as means ± SEM of averaged replicate measurements within each patient. For ventilatory, EELV and EMG variables, effects of breath number within the pre-apnoeic, apnoeic and post-apnoeic periods were examined using linear mixed model analysis with breath number and apnoea number as repeated factors, using an autoregressive covariance structure and subject as a random effect, each with a separate intercept (SPSS 16.0, SPSS Corp., Chicago). For these analyses, individual data within each patient were retained without averaging across replicated observations, using obstruction number as a factor. Linear mixed models were also undertaken to determine interaction effects (type x breath number) between arousal and non-arousal events across the four post-apnoeic breaths. Selected custom contrasts within each mixed model were also undertaken to examine differences between breaths and average wakefulness levels. $P < 0.05$ was considered significant.

4.3 Results

A total of eight OSA patients participated in this study. Data from two patients were excluded due to significant mask leaks and/or mouth breathing. Anthropomorphic data for the remaining six patients are shown in Table 4.1. Patients were middle-

aged, obese and had severe OSA. A total of 170 obstructive apnoeas among the six patients (mean 28.3 ± 6.6 per subject) met the inclusion criteria for breath-by-breath analysis. A representative trace of raw data showing cyclical respiratory events from one OSA patient is shown in Figure 4.1 (top panel).

4.3.1 Ventilatory period prior to upper airway obstruction

Respiratory variables such as V_I, V_T and PIF were initially above wakefulness levels (Figure 4.2A, B and C, $P < 0.003$) before significantly decreasing ($P < 0.001$) leading into UA obstruction. P_{ETCO_2} began below awake values (Figure 4.2D, $P < 0.001$) before rising to wakefulness levels by the last pre-obstruction breath ($P < 0.001$). R_{UA} quickly rose above wakefulness levels, roughly doubling from 14.1 ± 1.6 to 26.9 ± 6.1 $cmH_2O \cdot L^{-1} \cdot s$ during the pre-apnoeic period (Figure 4.2E, $P < 0.001$). Lung volume decreased by 183 ± 26 ml (Figure 4.3A, $P < 0.001$) from breath -4 to the first obstructed breath. Although there were consistent and significant reductions in EELV leading into obstruction, they were highly variable, both between and within individuals. The between vs. within subject standard deviation of mean lung volume difference between breaths 1-3 vs. breath 4 was 46 ml vs. 162 ml. The contribution of changes in overall EELV by the thoracic and abdominal compartments is shown in Figure 4.3B. There was a greater change in abdominal compartmental volume with time between breath -4 and the first obstructed breath (compartment x breath, $P < 0.001$). Initially at wakefulness levels, end-expiratory P_{GA} fell below awake values leading into UA collapse (Figure 4.3C, $P < 0.001$). End-expiratory P_{DI} began above awake values (Figure 4.3C, $P < 0.001$) before significantly decreasing prior to UA obstruction ($P < 0.001$). In contrast, end-

expiratory P_{OES} started below wakefulness levels (Figure 4.3C, P < 0.001) before significantly increasing (P = 0.009) during the pre-apnoeic period, reaching awake levels by breath -2. $iEMG_{GG}$ and $eEMG_{GG}$ were 38.4 ± 12.0% (P = 0.001) and 18.2 ± 4.9% (P < 0.001) above wakefulness levels respectively before falling to levels equivalent to that seen during wakefulness (Figure 4.3D, both P < 0.001). Overall, $iEMG_{GG}$ and $eEMG_{GG}$ activity decreased by 43.7 ± 7.9% and 24.0 ± 3.9% respectively between breaths -4 to -1 (Figure 4.3D, both P < 0.001). Similar changes were seen in $iEMG_{DI}$ and $eEMG_{DI}$ (Figure 4.3E). While $eEMG_{DI}$ was initially at awake levels at breath -4, $iEMG_{DI}$ began 48.7 ± 9.1% (P < 0.001) above wakefulness values. $iEMG_{DI}$ and $eEMG_{DI}$ significantly decreased by 59.8 ± 7.1% and 18.8 ± 2.8% during the pre-apnoeic period respectively (Figure 4.3E, both P < 0.001). Average $iEMG_{GG}$ and $iEMG_{DI}$ leading into obstructions were less variable than EELV data (between vs. within subject standard variation; $iEMG_{GG}$ 66 vs. 42%; $iEMG_{DI}$ 115 vs. 51%). While ΔP_{OES} was higher compared to wakefulness throughout the pre-apnoeic period (P < 0.001), there were no changes over time prior to UA obstruction (P = 0.117).

4.3.2 Apnoeic period

The average apnoea length was 13.9 ± 1.5 secs. Cessation of airflow occurred in the expiratory phase of respiration in 96.5 ± 1.8% of apnoeas with the remaining 3.5 ± 1.8% occurring during the inspiratory phase. Of those events beginning during expiration, the average onset time at which airflow ceased as a percentage of total expiratory time was 93.6 ± 3.7%. For inspiratory related events, the average onset time at which airflow ceased as a percentage of inspiratory time was 15.4 ±

8.8%. EELV fell by a further 126 ± 24 ml during apnoeas (Figure 4.3A, $P < 0.001$). Figure 4.1 (bottom panel) shows brief episodes of expiratory flow achieved in one OSA patient despite the absence of inspiratory flow during inspiratory efforts throughout UA obstruction. End-expiratory P_{DI} and P_{GA} remained below wakefulness levels during obstructed breaths (Figure 4.3C, $P < 0.01$), while P_{OES} remained above awake levels (Figure 4.3C, $P < 0.03$). Nadir muscle activity typically occurred on the second or second to last obstructed breath ($iEMG_{GG}$, 53.7 ± 11.2%; $eEMG_{GG}$, 21.0 ± 4.5%; $iEMG_{DI}$, 73.5 ± 8.2% and $eEMG_{DI}$, 21.1 ± 2.6% below awake levels, all $P < 0.001$). While $iEMG_{GG}$ did not change during apnoeas ($P = 0.173$), $eEMG_{GG}$, $iEMG_{DI}$ and $eEMG_{DI}$ significantly increased by 10.6 ± 3.9% ($P = 0.007$), 29.8 ± 4.5% ($P < 0.001$) and 3.8 ± 1.3% ($P = 0.04$) above nadir levels respectively. Despite this increased drive, activity for all EMG variables continued to remain below wakefulness levels (Figure 4.3D and Figure 4.3E, $P < 0.02$). ΔP_{OES} for the first 2 obstructed breaths were similar to that seen prior to obstruction, but increased by 8.2 ± 0.4 cmH_2O by the end of the apnoeas ($P < 0.001$). Figure 4.1 (bottom panel) demonstrates expiratory ΔP_{GA} during UA obstruction in one OSA patient. In the overall group, expiratory ΔP_{GA} significantly increased from 1.4 ± 0.6 to 3.2 ± 1.1 cmH_2O ($P < 0.001$) during apnoeas.

4.3.3 Ventilatory period following termination of upper airway obstruction

Restoration of airflow occurred early during an inspiratory effort in all analysed events (Figure 4.1, top panel). After airway re-opening, V_I, V_T and PIF increased substantially above wakefulness levels on the first post-apnoeic breath (Figure

4.2A, B and C, $P > 0.001$) before declining with time ($P < 0.001$). The post-apnoeic ventilatory response produced transient hypocapnia, with P_{ETCO_2} significantly reduced below wakefulness levels (Figure 4.2D, $P < 0.001$), before rising over the remaining post-apnoeic period ($P < 0.001$). R_{UA} decrease below wakefulness levels in the first two post-apnoea breaths ($P < 0.03$) before increasing to awake values by the second-to-last post-apnoea breath. Apnoea termination was associated with a significant and large (348 ± 17 ml) rise in EELV (Figure 4.3A, $P < 0.001$), before decreasing by 61 ± 21 ($P = 0.003$) from the peak level to the fourth post-apnoeic breath. The overall increase in EELV was contributed to more by abdominal than rib cage compartmental volume changes (Figure 4.3B, $P = 0.01$). End-expiratory P_{GA} and P_{DI} significantly increased above wakefulness levels (Figure 4.3C, $P < 0.001$), with P_{GA} returning to wakefulness levels by the fourth post-apnoeic breath, whereas P_{DI} remained above awake values ($P = 0.006$). These changes were mirrored by a significant decrease in end-expiratory P_{OES} below wakefulness levels (Figure 4.3C, $P < 0.001$). While P_{OES} decreased following this peak ($P < 0.001$), it remained below wake values by the fourth post-apnoeic breath ($P = 0.005$). In addition, all EMG variables reached maximal activity on either the first (Figure 4.3D, $iEMG_{GG}$ and $eEMG_{GG}$; Figure 4.3E, $eEMG_{DI}$) or second post-apnoeic breath in the case of $iEMG_{DI}$ (Figure 4.3E). This activity was significantly higher than wakefulness levels ($iEMG_{GG,}$ 86.7 ± 11.2%, $P < 0.001$; $eEMG_{GG,}$ 47.5 ± 4.5%, $P < 0.001$; $iEMG_{DI}$, 115 ± 8.2%; $eEMG_{DI,}$ 31.4 ± 2.6%, $P < 0.001$, above awake values). All parameters decreased with time ($P < 0.001$), with only $eEMG_{GG}$ reaching wakefulness levels by the fourth post-apnoeic breath. ΔP_{OES} was highest on the first post-apnoeic breath, with this value greater than that seen during wakefulness ($P < 0.001$), before subsequently falling over time ($P < 0.001$).

4.3.4 Arousal versus non-arousal events

Of the 170 apnoea events analysed, 139 events (82%) terminated with an EEG arousal (type 1), 21 events (12%) terminated without an EEG arousal (type 2), with the remaining 10 events (6%) demonstrating a type 3 response. There were significant post-apnoea breath by arousal type (arousal vs. no-arousal) interaction effects in V_I, PIF, $iEMG_{GG}$ and $iEMG_{DI}$, with larger early post-arousal responses following arousal vs. no arousal events (Figure 4.4A, B, C and D respectively, $P < 0.05$).

4.3.5 Temporal relationships

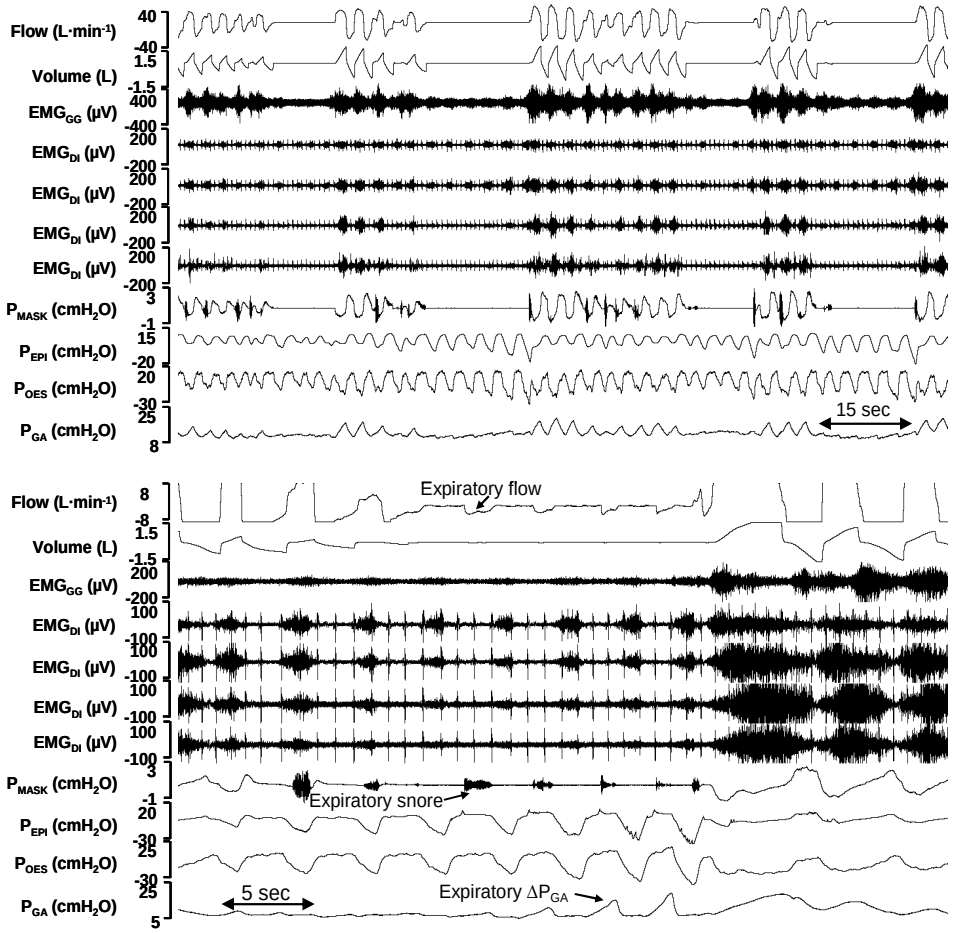
Figure 4.5A shows the temporal relationship between 1) the offset of the previous respiratory event and 2) offset of the previous arousal relative to the onset of obstruction. Approximately 80% of obstructions occurred with a respiratory event terminating within 30 secs before obstruction onset, and ~65% of obstructions began within 20 secs of the offset of the previous arousal. There was a strong temporal relationship between the termination of apnoeas (airflow restoration) and the onset of the closest arousal to the offset of obstruction (Figure 4.5B), with arousal commencing within ±2 secs of airflow restoration in ~76% of obstruction events. Approximately 66% of apnoeas were followed by another respiratory event (apnoea, hypopnoea, central or mixed) within 30 secs of apnoea termination (Figure 4.5C). The distribution of the time interval between the next respiratory event (apnoea, hypopnoea, central or mixed) and the offset of the closet arousal to apnoea termination was quite wide (Figure 4.5C), although the onset of the next respiratory event occurred within 20 secs following the offset of arousal in ~59% of events.

Table 4.1: OSA patient anthropometric data

	Mean (± SEM)	Range
Age (years)	44.2 ± 3.7	34-56
BMI ($kg \cdot m^{-2}$)	35.0 ± 1.9	30-41
AHI ($events \cdot hr^{-1}$)	77.2 ± 11.7	31-114
$NREM_{SUPINE}$ OI ($events \cdot hr^{-1}$)	41.7 ± 9.0	17-72
$NREM_{SUPINE}$ CI ($events \cdot hr^{-1}$)	0.4 ± 0.2	0-1
FEV_1 (% predicted)	98.6 ± 7.4	79-117
FVC (% predicted)	93.6 ± 9.3	79-119

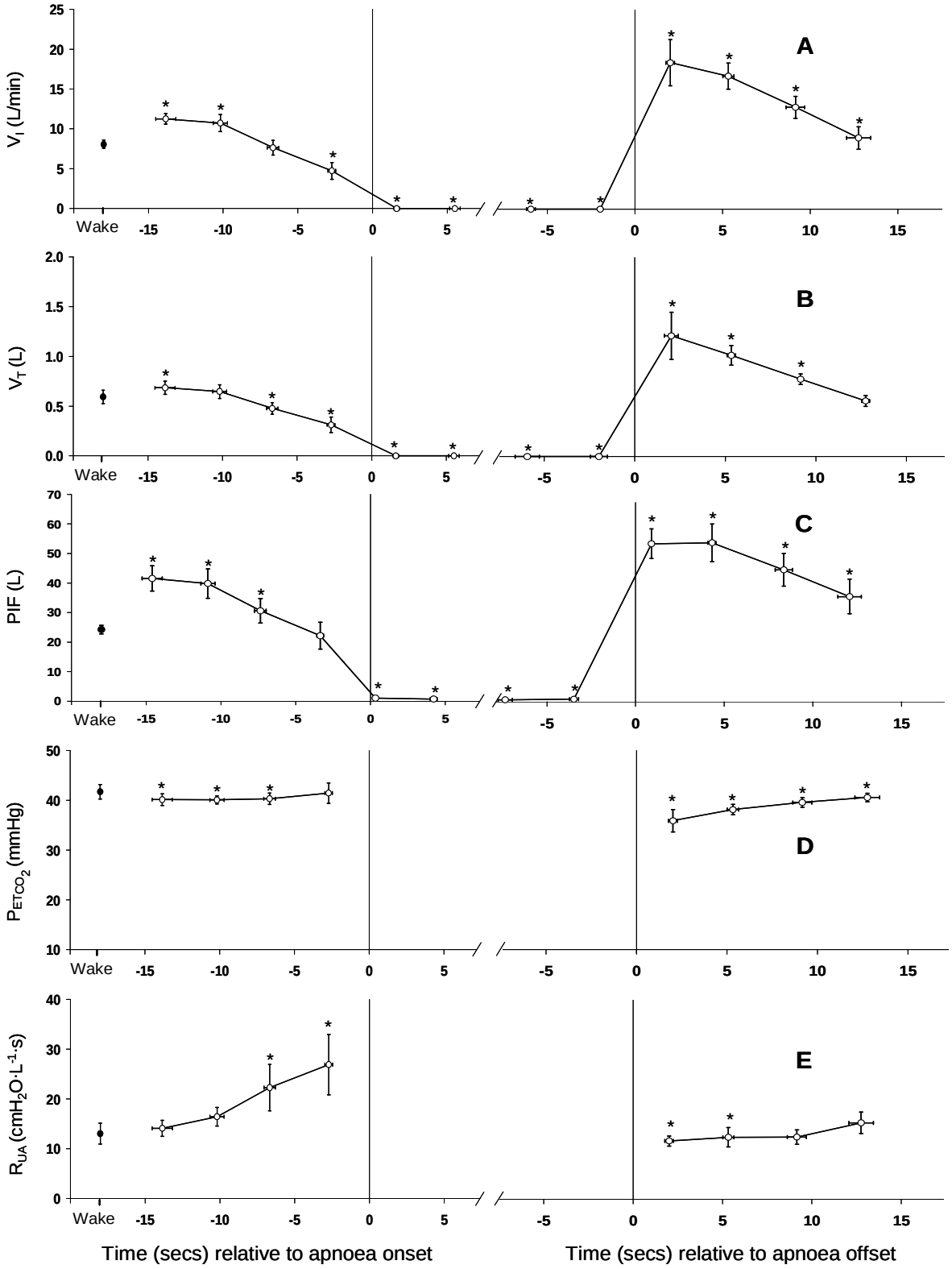
Age, body mass index (BMI), apnoea-hypopnoea index (AHI), non-rapid eye movement obstructive apnoea index in the supine posture ($NREM_{SUPINE}$ OI), non-rapid eye movement central apnoea index in the supine posture ($NREM_{SUPINE}$ CI), forced expiratory volume in 1 sec (FEV_1) and forced vital capacity (FVC). N=6.

Figure 4.1: Example recordings in one OSA patient showing multiple UA obstruction events and expiratory flow and expiratory ΔP_{GA} changes during obstruction



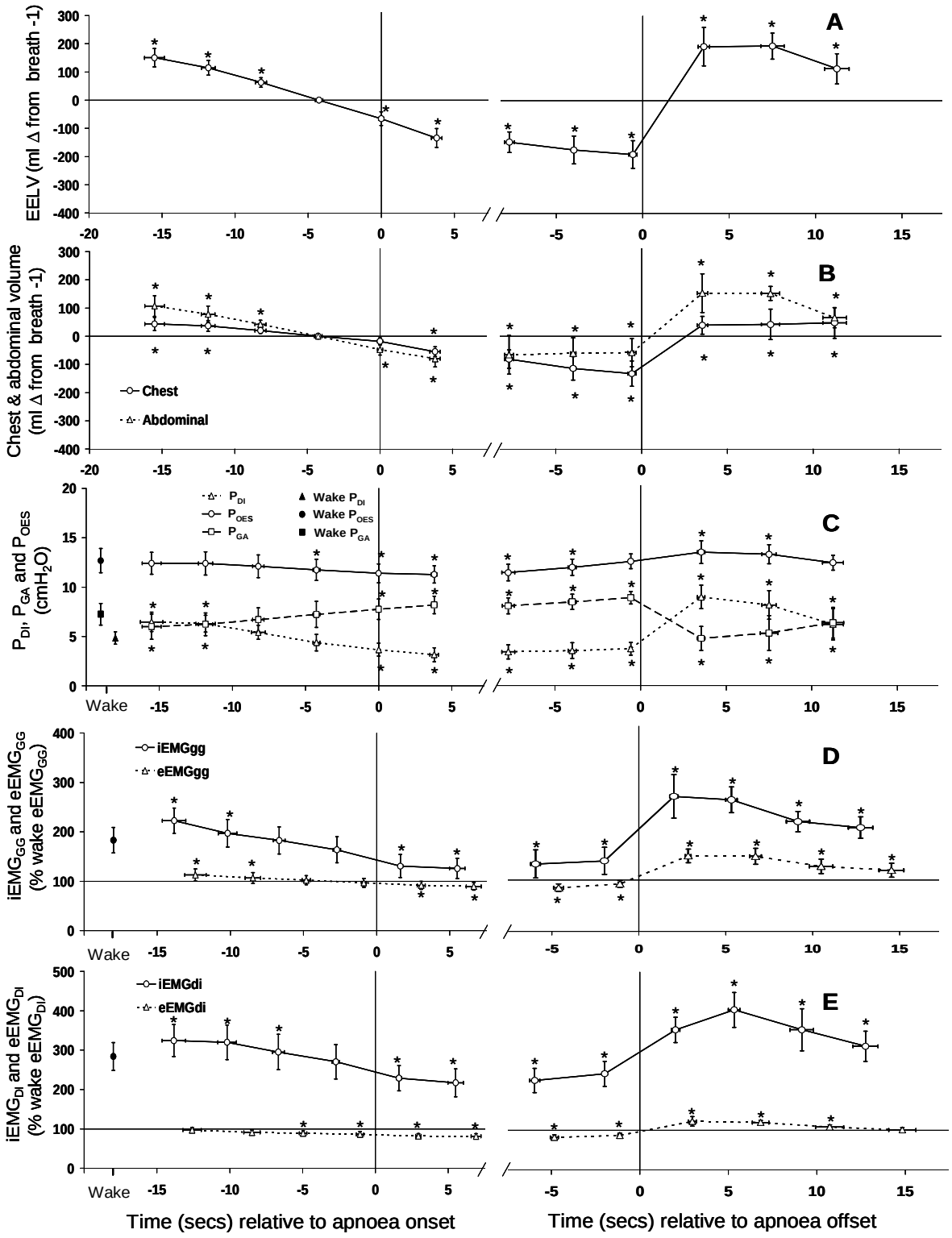
Top panel: Example recording showing four upper airway obstruction events in an OSA patient. Tracings are of airflow (inspiration up), volume, raw genioglossus muscle activity (EMG_{GG}), four pairs of raw diaphragm muscle activity (EMG_{DI}), mask pressure (P_{MASK}), epiglottic pressure (P_{EPI}), oesophageal pressure (P_{OES}) and gastric pressure (P_{GA}). EMG_{GG} and EMG_{DI} were lowest during obstruction followed by augmentation following apnoea termination. *Bottom panel:* Evidence of small bursts of expiratory flow in the absence of inspiratory flow in association with augmented expiratory $\Delta P_{GA.}$ Note expiratory snores in P_{MASK}.

Figure 4.2: Changes in V_I, V_T, PIF, P_{ETCO_2} and R_{UA} leading into, during and following the termination of complete UA obstruction



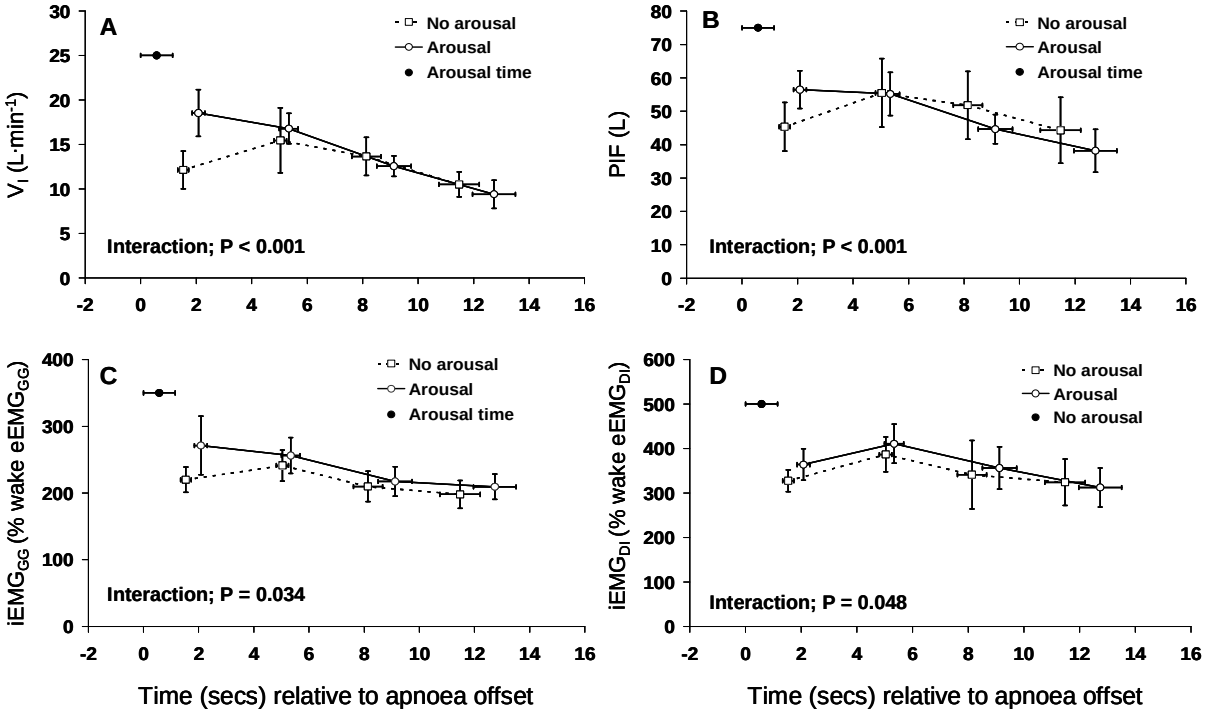
Breath-by-breath changes in (A) minute ventilation (V_I), (B) tidal volume (V_T), (C) peak inspiratory flow (PIF), (D) end-tidal CO_2 (P_{ETCO_2}) and (E) upper airway resistance (R_{UA}) for the last four breaths leading into airway obstruction, the first two and last two apnoeic inspiratory efforts and the first four post apnoeic breaths. Onset and offset of obstruction are shown by vertical lines. Average wake data are shown by isolated filled symbols. Data are means ± SEM. N=6. *P < 0.05 vs. wake.

Figure 4.3: Changes in EELV, chest and abdominal volume, end-expiratory P_{GA}, P_{OES} and P_{DI}, $iEMG_{GG}$, $iEMG_{DI}$, $eEMG_{GG}$ and $eEMG_{DI}$ leading into, during and following the termination of complete UA obstruction



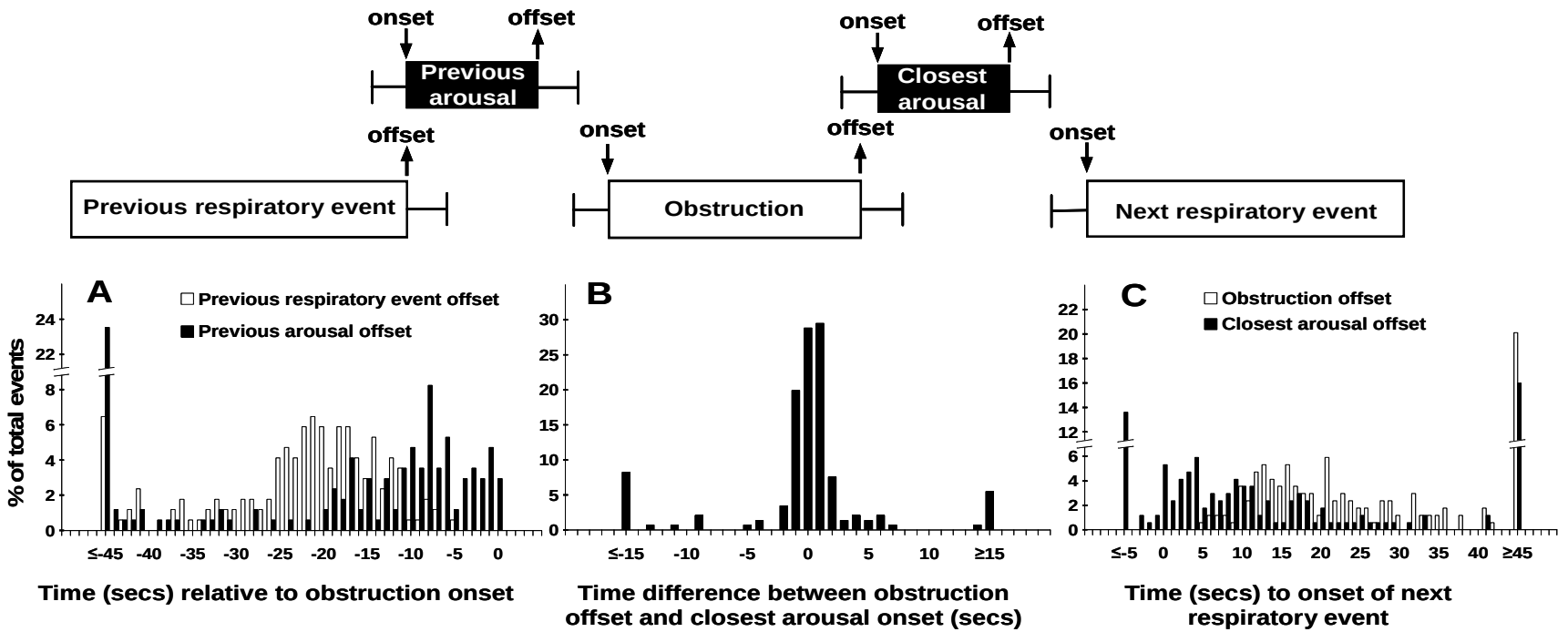
Breath-by-breath changes in (A) end-expiratory lung volume (EELV), (B) changes in abdominal and thoracic compartmental volumes, (C) end-expiratory transdiaphragmatic (P_{DI}), gastric (P_{GA}) and oesophageal (P_{OES}) pressures, (D) inspiratory and tonic expiratory genioglossus muscle activity ($iEMG_{GG}$ and $eEMG_{GG}$) and (E) inspiratory and tonic expiratory diaphragm muscle activity ($iEMG_{DI}$ and $eEMG_{DI}$) for the last four breaths leading into airway obstruction, the first two and last two apnoeic inspiratory efforts and the first four post apnoeic breaths. Onset and offset of obstruction are shown by vertical lines. Average wake data are shown by isolated filled symbols. Data are means ± SEM. N=6. *P < 0.05 vs. wake.

Figure 4.4: Changes in V_I, PIF, $iEMG_{GG}$ and $iEMG_{DI}$ following apnoea termination with and without an EEG arousal



Breath-by-breath changes in (A) minute ventilation (V_I), (B) peak inspiratory flow (PIF), (C) inspiratory genioglossus muscle activity ($iEMG_{GG}$) and (D) inspiratory diaphragm muscle activity ($iEMG_{DI}$) for the first four post-apnoeic breaths separated on the basis of an arousal or no arousal between the last occluded inspiratory effort and the onset of the third post occlusion breath. Time zero represents offset of obstruction. Average arousal onset time is shown by isolated filled symbols. Data are means ± SEM. N=6.

Figure 4.5: Temporal relationships between respiratory events and arousals, and between flow onset and arousal onset



Histograms showing temporal relationship between (A) offset of previous respiratory event (hypopnoea, apnoea, central or mixed in any sleep stage) and offset of previous arousal with onset of obstruction, (B) time difference between offset of obstruction (flow onset) and onset of closest arousal, (C) offset of obstruction and offset of closest arousal to obstruction with the onset of the next respiratory event (hypopnoea, apnoea, central or mixed in any sleep stage).

4.4 Discussion

While several findings largely confirm and support previous studies, the overall response patterns of several of the key physiological variables have not previously been examined together, such their relationships and time course over respiratory events has not previously been clear. The major new findings from this study are: (1) there were acute decrements in lung volume leading into UA obstruction that were associated with a decline in diaphragm EMG activity, end-expiratory P_{GA} and P_{DI}, increased end-expiratory P_{OES} and a greater abdominal than rib cage contribution. Given simultaneous decrements in genioglossus EMG, these changes are consistent with a widespread reduction of respiratory EMG activity including diaphragm relaxation and ascent. These changes were rapidly reversed following apnoea termination; (2) R_{UA} significantly increased leading into UA collapse despite genioglossus muscle activity at or above wakefulness levels; (3) The ventilatory and muscle activity (genioglossus and diaphragm) response varied according to the presence or absence of an arousal close to the termination of UA obstruction; (4) Previous and subsequent respiratory events and arousals occurred in close temporal proximity to UA obstructions, consistent with a degree of reciprocal co-dependence between arousals and respiratory events.

Several groups have identified a decline in genioglossus and diaphragm muscle activity preceding UA obstruction, and recruitment following the termination of respiratory events[1, 150, 213, 268]. These changes in activity are potentially part of widespread fluctuations in respiratory drive to phasic and tonic muscles likely contributing to the rise and fall in lung volume seen prior to and following the

termination of UA obstruction. The fall in EELV prior to the onset of UA obstruction in the present study was relatively small, but of a similar magnitude to that reported by others[264, 265]. The contribution of ~100-200 ml decrements in EELV on the development of UA obstruction is not clear and cannot be separated from other potential effects of reduced respiratory drive on UA function. Similarly, the role of the ~380 ml rise in EELV in helping to restore normal UA function at apnoea termination is not clear. However, in the context of obese patients with low resting EELV this magnitude of change appears quite large. Previous reports have demonstrated significant modulating effects of modest changes in EELV (~500 ml) above normal EELV on UA collapsibility in obese OSA patients[85-87]. While the effects of lung volume changes below EELV are largely unknown, longitudinal traction effects on UA compliance could be alinear at the lower range of tension rendering UA function more sensitive to lung volume changes below EELV, particularly in obese patients with already reduced lung volume[91, 92] and UA size during wakefulness[26]. OSA patients demonstrate larger changes in UA size over the normal tidal breathing range[52], consistent with an exaggerated sensitivity to volume related effects on UA function. Consequently, lung volume changes prior to UA collapse and at the termination of obstruction may play a pivotal role in OSA pathogenesis via caudal traction effects. Alternatively, the modest decrease in EELV leading into obstruction may indicate that changes in lung volume potentially play a modulating rather than pivotal role. Further studies are needed to elucidate the impact 100-200 ml lung volume changes below resting EELV on UA function in obese OSA patients during sleep.

While overall decrements in EELV clearly have negative effects on UA function, a fall in EELV occurring predominantly by cranial displacement of the diaphragm may have greater tracheal traction effects on UA instability than lung volume changes *per se*. While inferences regarding diaphragm position and tracheal ascent in the present study are inevitably speculative based on changes in other interrelated measures, the decrease in the abdominal anterior-posterior dimension, fall in end-expiratory P_{GA} and P_{DI} and the loss of respiratory drive to the diaphragm, are all consistent with diaphragm ascent. Conversely, caudal displacement of the diaphragm leads to a rise in end-expiratory P_{GA} and P_{DI} following apnoea termination. In turn, lung volume changes and diaphragm displacement would be expected to modulate tension exerted on the UA by the trachea and other intrathoracic structures, and via changes in intrathoracic pressure[105, 106], thereby influencing UA compliance. We recently demonstrated increased UA collapsibility with experimental abdominal compression during sleep in OSA patients[251], strongly supporting that mechanical effects of abdominal obesity may be an important factor promoting UA collapse. The current study extends these findings by showing that systematic changes in lung volume, transdiaphragmatic pressure and deteriorating UA function all appear to be part of the normal obstruction cycle.

Similarly to findings reported by Aronson and colleagues[263], EELV also continued to decrease following the onset of UA obstruction. In the present study, expiratory flow, with no evidence of inspiratory flow, was common in individuals displaying increased expiratory $\Delta P_{GA.}$ Imaging work by Morrell et al[265] identified partial re-opening of the UA during expiratory efforts with minimal airflow in some patients. Increased expiratory drive to muscles, such as rectus abdominis[269], has been

identified during obstructive events. With sufficient intraluminal pressure, this could transiently re-open the airway and allow further decrements in lung volume below resting EELV. The precise role of expiratory drive in sleep is not known but may be similar to the orderly pattern of ventilatory muscle recruitment during exercise which likely contributes to a reduced EELV[270, 271]. Expiratory abdominal muscle contraction could place the diaphragm on a more favourable part of its length-tension curve[272] and increase the contractile efficiency during subsequent inspiratory efforts. However, any increase in efficiency is only likely to be beneficial following inspiratory airflow restoration and may not be present if the diaphragm is over-stretched as is likely below resting EELV in obese patients already with an elevated diaphragm[273]. In addition, in the context of UA obstruction, such a response likely exacerbates airway collapse, not only via further diaphragm ascent and reduced airway traction, but by establishing lung elastic recoil induced negative airway pressure at end-expiration that would render airway re-opening progressively more difficult.

The maintenance of ΔP_{OES} despite falling EMG_{DI} is perhaps unexpected but is consistent with previous reports[1, 212]. While ΔP_{OES} has been shown to decrease slightly leading into obstruction[268], the changes in ΔP_{OES} were found to be less than and disproportionate to the changes in EMG_{DI}. This presumably indicates the generation of more negative inspiratory pressure for a given level of inspiratory muscle activity, likely due to a concurrent increase in R_{UA} leading into obstruction. Furthermore, cranial displacement of the diaphragm leading into airway obstruction would result in diaphragmatic fibre lengthening potentially enhancing diaphragmatic contraction efficiency[261]. Consequently, ΔP_{OES} is confounded by airway resistance

and changes in lung volume and caution is warranted when interpreting these measures.

R_{UA} was higher than wakefulness levels during the pre-apnoeic period despite EMG_{GG} also being equal or above awake values. While it is unclear why augmented muscle activity was unable to prevent UA collapse, activation of other UA dilators such as the tensor palatini, levator veli palatini and palatoglossus[150, 151], are also likely to be involved in promoting UA patency, with at least some showing abrupt and sustained reductions in activity at sleep onset[146, 148, 149]. Greater genioglossus activity may therefore be required to sustain airway patency in sleep compared to wakefulness. In addition, the increased UA compliance with decreased EELV leading into obstruction may impair the effectiveness of genioglossus activity to dilate the UA.

As reported by Martin et al[212], UA obstruction, inferred from abrupt mask pressure flattening despite downstream pressure changes (e.g. Figure 4.1 bottom panel), began predominantly near end expiration. Badr et al[262] demonstrated that mechanically induced central apnoeas led to passive collapse of the airway, indicating that subatmospheric pressure is not necessarily required to induce UA obstruction. Via UA imaging, Morrell et al[265] found significant decrements in UA cross-sectional area at end-expiration in the last four breaths preceding obstruction. Similar to that seen in the present study, cessation of airflow tended to occur at end-expiration. However, UA airway imaging revealed that the airway remained partially open at this time point and did not typically completely collapse until early inspiration on the subsequent breath, with end-expiratory collapse identified in only

~5% of events. Progressive airway narrowing during expiration is potentially explained by several mechanisms. The decrease in genioglossus muscle activity, particularly tonic activity, would likely reduce UA dilation and contribute to increased airway wall compliance. Furthermore, pharyngeal compliance increases as cross-sectional area of the UA decreases[274] and is greater in OSA patients compared to non-obese normal subjects[74], particularly at lower lung volumes. Therefore, the smaller EELV seen in obese compared to healthy weight individuals[91] and the significant decline in EELV may amplify these effects, further contributing to UA narrowing leading into obstruction.

Historically, arousals from sleep were widely considered necessary to terminate UA obstruction. Remmers and colleagues[1] first noted that arousals generally occurred coincident with, or as much as one second before the termination of apnoeas, supporting that increased respiratory muscle activity with arousal plays a key role in resolving UA obstruction. However, data from this study, demonstrating that not all apnoeas are associated with arousal, are consistent with other reports[2, 275]. Nevertheless, arousals were very common with ~76% of obstructive apnoea events exhibiting an arousal within ±2 sec of flow restoration. While perhaps important for restoration of airflow, the exaggerated ventilatory response following arousal at the termination of respiratory events may facilitate further periods of unstable breathing[2, 216, 276]. Tone-induced arousals from stable sleep clearly lead to a brief period of hyperventilation, resulting in hypocapnia[221, 222] and subsequent low ventilatory drive[277]. The magnitude of the response appears to be greater in males compared to females[221], in OSA patients versus controls[222] and greater in OSA patients on suboptimal versus therapeutic CPAP[222], supporting effects of increased

pre-arousal R_{UA} on post-arousal ventilatory responses. However, despite increased R_{UA} during the suboptimal CPAP condition, only ~2% of arousals were followed shortly by further respiratory events, arguing against arousal effects promoting subsequent respiratory events. On the other hand, UA pressure support and lung volume influences with suboptimal CPAP may be sufficient to substantially counteract post-arousal influences, and may not be indicative of arousal effects in untreated OSA patients. Consequently, we and others[222] speculate there would likely be a greater incidence of respiratory events following arousals in the presence of higher levels of R_{UA} in untreated OSA patients. In support, the present study showed that the V_I and P_{ETCO_2} changes on obstructive apnoea resolution appeared considerably greater than those observed by Jordan et al[222]. In addition, different responses in ventilation and muscle activity over time between arousal and non-arousal events were evident following apnoea termination. Furthermore, respiratory events tended to occur in close temporal proximity, with the onset of subsequent respiratory events frequently occurring within 10-30 sec after obstructive event offset and within ~20 sec of arousal offset in ~60% of subsequent respiratory events. This time frame is consistent with the period of perhaps expected greatest risk of re-collapse with reduced ventilatory drive. While the most pronounced period of hypocapnia occurred immediately after apnoea termination, given lung to peripheral and central chemoreceptors circulatory delays in the order of ~10-30 secs[278, 279], the effect of hypocapnia on subsequent respiratory drive would be expected to be delayed accordingly. While arousals at the termination of respiratory events may have deleterious effects on UA function, other reports have shown that ventilation and muscle activity were not significantly higher when associated with an arousal compared to non-arousal events[150, 280]. Therefore,

ventilatory overshoot appears to be a typical outcome following apnoea resolution irrespective of the presence or absence or arousal. Further studies are needed to examine the contribution of the ventilatory response to arousal in promoting subsequent respiratory events in OSA patients.

4.4.1 Methodological considerations

There are several methodological considerations that warrant some discussion. Given the observational nature of the study it is not possible to gauge causal relationships between physiological variables potentially contributing to airway collapse. Nevertheless, we considered systematic observations of changes in largely unexplored variables, such as lung volume and transdiaphragmatic pressure, relative to the time-course of changes in more established variables leading into obstructive events were needed to inform future studies to examine underlying mechanisms. In this manner, we aimed to explore if temporal changes in key variables over the course of the obstructive apnoea cycle were consistent with a potentially important contribution to airway collapse. For example, had there been minimal or no consistent changes in transdiaphragmatic pressure and/or lung volume over the time course of obstructive apnoeas, this would argue against a potential contributory role to obstruction onset. Given the findings of systematic changes in most variables, further experimental studies are needed to determine the contribution of specific mechanisms to cyclical obstructive apnoea.

We restricted patients to supine sleep to maximise the hypothesised compressive effects of obesity on UA function. While it appears likely that postural effects on

lung volume/diaphragm position influences on UA function may help explain the increased frequency[78] and severity[101] of apnoea events in this posture, this and potential sleep stage interactions remain to be examined.

Given that end-expiratory P_{GA}, P_{OES} and P_{DI} vary with lung volume, changes in EELV were referenced to the last pre-apnoeic breath as end-expiratory P_{GA}, P_{OES} and P_{DI} for this breath was similar to wakefulness levels. Nevertheless, further studies using either body plethysmography or helium dilution measurements, would be useful to assess changes in absolute lung volume.

Finally, our method of quantifying diaphragm EMG activity is somewhat of a departure from more conventional methods[146, 148] and was chosen on the basis of superior signal:noise characteristics via integration over the full period of inspiration. In 6 subjects from a previous study undertaken in our laboratory, the coefficient of variation in $iEMG_{DI}$ and $eEMG_{DI}$ was 7.8 ± 0.5% and 6.2 ± 0.9% compared to 12.9 ± 2.4% and 6.4 ± 1.1% derived from conventional peak and tonic activity measurements.

4.4.2 Summary and conclusions

This study adds new insight into physiological changes leading into and out of UA obstruction during sleep in obese male OSA patients. Decreases in genioglossus and diaphragm muscle activity, as well as transdiaphragmatic pressure and lung volume leading into UA obstruction, are consistent with a widespread reduction in respiratory drive precipitating airway collapse. While the decline in genioglossus

muscle activity would be expected to contribute to the rise in R_{UA}, decreases in lung volume may also negatively impact UA patency via tracheal traction effects. Apnoea termination was frequently associated with arousal and a period of hyperventilation, with temporal relationships quite consistent with reciprocal co-dependence between obstruction-induced events promoting arousal, and ventilatory-overshoot induced low ventilatory drive promoting subsequent airway obstruction. The relative contribution of lung volume and caudal traction versus reduced UA muscle tone mediated effects on UA function in OSA remain to be established.

CHAPTER 5. SUMMARY AND CONCLUSIONS

The prevalence of OSA is significantly higher in males and the obese population[16, 18-20]. The precise mechanisms by which these factors contribute to impaired UA function are not entirely clear. While an anatomically smaller UA, potentially resulting from increased fat deposition surrounding the UA lumen may underpin poor UA function in many and perhaps most obese OSA patients[25, 26], other factors must also be important in the pathogenesis of OSA. While increased neck circumference, neck fat deposition and UA abnormalities have consistently been shown to be independent predictors of OSA severity[20, 21, 24, 25, 46, 62, 67], these factors explain <35% of the variance in OSA[21, 22, 46, 62, 66, 67], indicating that other variables operating independently or interactively, must also contribute. Sleep-related decrements in UA dilator muscle activity are thought to be a major contributor to UA instability during sleep[1, 146, 148-150]. However, lung volume mediated effects on UA function, IAP influences on diaphragm position, and exaggerated ventilatory responses following the termination of UA obstruction are also very likely to contribute to UA instability. The studies presented in this thesis were designed to evaluate the potential contribution of factors other than simple UA anatomical deficits to UA instability in obese male OSA patients.

A central pattern of obesity appears to be a key factor underlying OSA risk and may be indicative of mass loading effects of obesity on UA function. Given the propensity towards abdominal obesity in males such effects may also help explain the male predominance of OSA. Waist circumference appears to be a stronger

independent predictor of OSA severity than BMI or neck circumference[16, 22] and obese males show higher levels of IAP than BMI-matched females[115]. Abdominal visceral fat also appears to more strongly correlate with OSA severity[48, 49]. In addition, several groups have previously shown that reduced lung volume leads to increased pharyngeal resistance and UA collapsibility[82-84, 86]. While the precise mechanism by which abdominal obesity affects UA function is not entirely clear, increased IAP, an underlying feature in the obese population[114, 115, 121], inevitably promotes reduced lung volume and diaphragmatic elevation, potentially reducing tension exerted on the UA via mediastinal structures and negative intrathoracic pressure. Animal studies clearly demonstrate that experimentally decreased tension on the trachea leads to increased UA collapsibility, via both mechanical interdependence and intrathoracic pressure effects[105, 107, 108, 111]. In humans, the impact of abdominal compression on UA function during sleep was previously unknown. In the first study presented in this thesis (Chapter 3), the effect of acute experimental increases in IAP on UA function were investigated in a group of obese male OSA patients who slept with a large pneumatic cuff wrapped around the abdomen. Abdominal compression to increase P_{GA} and P_{DI} in the order of 50% resulted in an increase in UACP of ~0.6 cmH_2O. Abdominal compression also led to a ~1.8 cm decrease in the anterior-posterior dimension of the abdomen, equating to a re-distribution of ~1 L of abdominal volume, of which ~0.5 L was exhaled, ~0.5 L converted into chest expansion, resulting in an overall decrease in EELV of ~0.5 L. Baseline (cuff deflated) P_{GA} and P_{DI} were both strongly correlated with UACP, explaining up to 64% of the variance in UACP. While direct assessment of underlying mechanisms in humans is very difficult, increased UA collapsibility with abdominal compression is consistent with and appears most likely to be explained

by increased UA compliance secondary to elevation of the diaphragm. These findings support that increased IAP has detrimental effects on UA function during sleep in humans. Given the greater propensity to abdominal obesity in men compared to women, this may help explain why obesity and male gender are the two main risk factors for OSA.

While abdominal compressive effects of obesity on lung volume and UA function appear to promote UA collapse during sleep in OSA, neurocompensatory reflexes, including but not necessarily limited to augmented genioglossus muscle activity[145, 146], are clearly sufficient to maintain airway patency during wakefulness. A further mechanism potentially protecting UA function in obese OSA patients awake might therefore be active defense against mass loading facilitated decrements in EELV during wakefulness. Such a mechanism would likely be mediated primarily via increased tonic diaphragmatic muscle activity. If present, a partial or complete loss of such a reflex at sleep onset, similar to that seen in genioglossus EMG, would be expected to appear as an acute reduction in expiratory diaphragmatic activity accompanied by decrements in lung volume. To seek evidence for such an effect, the second study reported in Chapter 3 was undertaken to establish if tonic diaphragmatic muscle activity is higher in obese male OSA patients compared to age-matched, healthy-weight controls during wakefulness, and to assess changes in diaphragm muscle activity and EELV across the wake-sleep transition. Despite significantly increased IAP, tonic diaphragm muscle activity was not significantly elevated in obese OSA patients compared to healthy controls during wakefulness. While sleep onset was followed by a relatively minor but significant fall in EELV (<70 ml) in both groups, the magnitude of the decline in tonic diaphragm activity

and EELV was related to the severity of respiratory events beginning shortly after sleep onset, with greater decrements at transitions followed shortly by hypopnoeas in both groups, and particularly obstructive apnoea transitions in the OSA group. While these data do not support the presence of any substantial diaphragm neurocompensatory reflex protecting lung volume during wakefulness in obese OSA patients, this does not discount that the relatively small decrements in lung volume at sleep onset may nevertheless importantly contribute to impaired UA function in the immediate post sleep onset period in obese OSA patients. Further studies are needed to elucidate the impact of 100-200 ml decrements in lung volume on UA function during sleep in obese OSA patients.

A decrease in UA dilator muscle activity is thought to be a major contributor to UA collapse during sleep[1, 146, 150]. However, reductions in UA dilator muscle activity may be part of a global decline in muscle activity serving to promote UA instability via a number of mechanisms. A widespread decline in tonic muscle activity is likely to result in a fall in lung volume and elevation of the diaphragm, both potentially contributing to increased UA compliance and collapsibility[105, 107, 108]. Following airway collapse at low lung volume, increased respiratory drive at the termination of obstructive apnoeas, either alone or when combined with arousal-induced hyperventilation, may exaggerate reduced ventilatory drive coincident with the return to sleep and exacerbate the propensity for subsequent cyclical respiratory events[2, 216, 221-223]. Lung volume effects with obesity would likely contribute further to exaggerated responses since a lower lung volume is less effective in buffering fluctuations in alveolar gas tensions[218, 224]. To explore the magnitude and time-course of change in the major variables potentially contributing to the propensity for

airway collapse, physiological responses in 6 obese OSA patients were investigated immediately before, during and following the termination of obstructive apnoeas in the third study reported in Chapter 4. Prior to UA obstruction, there was a decline in both phasic and tonic genioglossus and diaphragm muscle activity while R_{UA} increased. Significant decreases in end-expiratory P_{GA}, P_{DI} and EELV, primarily from abdominal volume redistribution evident during the same period were all consistent with diaphragm ascent. Although changes were relatively small, lung volume continued to decrease during UA obstruction in association with increasing expiratory drive (expiratory ΔP_{GA}). There was a marked increase in ventilation, muscle activity and EELV immediately following the termination of obstructive events, recovering to pre-apnoea levels within approximately four breaths. In addition, ventilatory and muscles responses immediately following apnoea termination were further augmented by arousals occurring in close proximity to apnoea resolution. Respiratory events and arousals occurred in close temporal proximity prior to and following obstructive apnoeas, perhaps supporting co-dependence between respiratory events and arousals that may help perpetuate further events. Alternatively, these observations might also be consistent with a more incidental and inevitably sequential temporal relationship in patients with highly collapsible airways in sleep, and in whom arousal is a likely consequence of augmented ventilatory drive during obstructive events. Nevertheless, the results from this study support that a systematic 'global' loss in respiratory drive to UA dilator and inspiratory pump muscles contributes to impaired UA function not only via direct neuromuscular effects on the airway itself, but potentially via simultaneous lung volume effects associated with diaphragmatic relaxation. Consequently, the associated decreases in UA dilator muscle activity and lung

volume, in addition to hyperventilatory responses following apnoeas and arousals, may all interact to promote conditions favoring UA re-obstruction.

Several unanswered questions arise from these studies. While the study reported in Chapter 2 clearly demonstrates a negative influence of abdominal compression on UA collapsibility, the effects on diaphragm and mediastinal structure displacement, and the degree of similarity to mechanisms potentially operating in central obesity remain unknown. Nevertheless, given previous reports showing that increased IAP leads to both diaphragm ascent and cranial displacement of the carina[123, 124, 126, 127], and that carinal movement is considered to be a good marker of caudal tracheal traction[106], these results support that increased UA collapsibility was most likely mediated via caudal traction effects. However, a potential influence from abdominal compression induced venous redistribution and oedma surrounding the UA cannot be discounted. In addition, although the findings reported in Chapters 3 and 4 demonstrate associations and temporal relationships between potentially key physiological variables contributing to respiratory events following sleep onset and cyclical airway obstruction, these clearly do not establish causal relationships. Further studies designed to manipulate factors independently and in combination are needed to elucidate the most important factors contributing to UA obstruction in OSA. The relative contribution of relatively small changes in lung volume versus changes in UA muscle activity on UA patency, and the influence of exaggerated ventilatory responses and the subsequent low respiratory drive state following the termination of UA obstruction in particular appear to warrant further investigation as mechanisms promoting cyclical airway obstruction.

In summary, the studies presented in this thesis provide important new insights into factors potentially contributing to UA collapse in OSA. Increased IAP led to increased UA collapsibility, consistent with previous reports identifying waist circumference and abdominal visceral fat as strong independent predictors of OSA. Lung volume compressive effects of obesity may also help explain the increased prevalence of OSA in obese males given that abdominal obesity is particularly common in this group. Decrements in lung volume preceding obstructive events further support that lung volume mediated effects occurring simultaneously with a decline in overall respiratory drive may contribute to the propensity for airway obstruction in OSA patients. Consequently, obese OSA patients may rely on both increased UA dilator and diaphragm muscle activity to counteract adverse effects of airway narrowing and lung compression on UA function in sleep.

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