Collapsibility of The Human Upper Airway: 
The Influence of State, Posture and Instrumentation

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BSc (Hons)

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This thesis contains published work and/or work prepared for publication, some of which has been co-authored. The bibliography details of the work and where it appears in the thesis are outlined below.

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The work described in this thesis is original and my own, except where contributions of others have been acknowledged.

Student: Miss Kathleen J Maddison (BSc (Hons))
ABSTRACT

**Background.** Obstructive sleep apnoea (OSA) is a common condition characterized by recurrent partial or complete collapse of the upper airway (UA) during sleep. Individual predisposition to OSA is quantified by measurement of UA collapsibility. The pharyngeal critical pressure (the pressure at which the UA collapses, \( P_{\text{crit}} \)) is a gold standard measure of this. \( P_{\text{crit}} \) is determined by manipulating applied pressure to induce varying degrees of inspiratory flow-limitation. Ideally, inspiratory flow-limitation is identified using measurement of oesophageal pressure (Pes), which requires a transducer catheter to traverse the UA. However, it is possible that the presence of such a catheter could alter the mechanical behaviour and collapsibility of the UA. Apart from this technical issue, the \( P_{\text{crit}} \) technique is inherently difficult to perform during sleep as altering applied pressure often results in measurement-induced arousals. This is not an issue during general anaesthesia, which provides ideal conditions under which to study UA collapsibility as arousals are suppressed, muscle activation is minimised and other known modifiers, such as head posture, can be controlled while still maintaining spontaneous ventilation. Given these advantages, there is a case for using anaesthesia to characterise an individual’s UA collapsibility. However, it is important to know how such measures equate to those made during sleep. To date this relationship has been inferred by relating easily obtained indirect sleep measures of collapsibility (e.g. apnoea hypopnoea index, AHI) to anaesthesia \( P_{\text{crit}} \) measures. As yet no study has compared UA collapsibility during anaesthesia and sleep using the same metric (i.e. \( P_{\text{crit}} \)). Furthermore while the anaesthesia model has been used to demonstrate the effect of head posture on UA collapsibility, the effect during sleep has yet to be investigated.

**Aims.** The aims of the studies described in this thesis were to utilise two distinct states of human consciousness, namely sleep and general anaesthesia, to examine: (i) the effect of Pes monitoring on UA collapsibility; (ii) the mechanisms underlying the state dependent differences in UA collapsibility; and (iii) the effect of head posture on UA collapsibility.
Methods and Results. Study 1. To determine the effect of the presence of an oesophageal catheter on UA function Pcrit was assessed in 24 propofol anaesthetised subjects with and without a multi-sensor oesophageal catheter. Six subjects had polysomnography (PSG) defined OSA and 18 either did not have OSA or were at low risk of it. The presence or absence of a catheter did not change Pcrit in: (i) the group overall (-1.5±5.4cmH2O vs. -2.1±5.6cmH2O, respectively, n=24, p=0.14); (ii) those with PSG-defined OSA (3.9±2.2 cmH2O vs.2.6±1.4cmH2O,respectively,n=6); or (iii) those at low risk/without OSA (-3.3±4.5cmH2O vs. -3.7±5.6cmH2O, respectively, n=18).

Study 2. To compare the degree of UA collapsibility in anaesthesia versus sleep Pcrit was assessed in 10 subjects (8 males) under both states. Five had PSG-defined moderate-to-severe OSA and 5 did not have OSA. While Pcrit during anaesthesia was linearly related to Pcrit during non-rapid eye movement (NREM) sleep (r=0.65, n=10,p=0.04) with a similar tendency in rapid eye movement (REM) sleep (r=0.80, n=4, p=0.2), it was significantly greater during anaesthesia than NREM sleep (2.1±2.2 vs. -2.0±3.2cmH2O, respectively, n=10,p<0.001) or REM sleep (1.6±2.4 vs. -1.9±4.3cmH2O, respectively, n=4,p=0.005).

Study 3. To evaluate the effect of head posture (neutral, flexion and extension) on UA collapsibility during sleep Pcrit was assessed in 16 subjects (7 males) during NREM sleep. Eleven had PSG-defined moderate-severe OSA and 5 had no-mild OSA. Pcrit was similar in the flexed, neutral and extended head posture for: (i) the group overall (-0.6±4.0, -0.4±4.0 and -0.3±3.4cmH2O respectively, n=16, p=0.96); (ii) those with OSA (1.4±3.5, 1.2±3.5 and 0.8±3.2cmH2O respectively, n=11, p<0.001) and (iii) those without OSA (-3.4±3.0, -3.9±3.0 and -3.2±2.3cmH2O respectively, n=5, p<0.001).

Conclusions. The major findings of these studies are that: (i) the presence of a small catheter traversing the UA does not affect UA collapsibility; (ii) individual tendencies to UA obstruction during anaesthesia and sleep are directly related; and (iii) modest changes in head posture do not have significant effects on upper airway collapsibility during sleep but do so during general anaesthesia where flexion increases upper airway collapsibility and extension decreases it.
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This thesis is dedicated to the loving memory of my baby sister... Never far away from my thoughts, forever in my heart.
# LIST OF ABBREVIATIONS

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Full Form</th>
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<tbody>
<tr>
<td>AASM</td>
<td>The American Academy of Sleep Medicine</td>
</tr>
<tr>
<td>AHI</td>
<td>Apnoea hypopnoea index</td>
</tr>
<tr>
<td>AI</td>
<td>Apnoea index</td>
</tr>
<tr>
<td>ANOVA</td>
<td>Analysis of variance</td>
</tr>
<tr>
<td>BIS</td>
<td>Bispectral index score</td>
</tr>
<tr>
<td>BMI</td>
<td>Body mass index</td>
</tr>
<tr>
<td>CI</td>
<td>Confidence interval</td>
</tr>
<tr>
<td>cmH₂O</td>
<td>centimetres of water (pressure)</td>
</tr>
<tr>
<td>CPAP</td>
<td>Continuous positive airway pressure</td>
</tr>
<tr>
<td>DISE</td>
<td>Drug induced sleep endoscopy</td>
</tr>
<tr>
<td>ECG</td>
<td>Electrocardiogram</td>
</tr>
<tr>
<td>EDS</td>
<td>Excessive daytime sleepiness</td>
</tr>
<tr>
<td>EELV</td>
<td>End-expiratory lung volume</td>
</tr>
<tr>
<td>EMG</td>
<td>Electromyography</td>
</tr>
<tr>
<td>EMGgg</td>
<td>Genioglossus EMG</td>
</tr>
<tr>
<td>EOG</td>
<td>Electrooculography</td>
</tr>
<tr>
<td>events.hr⁻¹</td>
<td>events per hour of sleep</td>
</tr>
<tr>
<td>FOT</td>
<td>Forced oscillation technique</td>
</tr>
<tr>
<td>HI</td>
<td>Hypopnoea index</td>
</tr>
<tr>
<td>kg</td>
<td>kilograms</td>
</tr>
<tr>
<td>kg.m⁻²</td>
<td>kilograms per meter squared</td>
</tr>
<tr>
<td>MAS</td>
<td>Mandibular advancement splint</td>
</tr>
<tr>
<td>m</td>
<td>metres</td>
</tr>
<tr>
<td>mm</td>
<td>millimetres</td>
</tr>
<tr>
<td>mmHg</td>
<td>millimetres of mercury (pressure)</td>
</tr>
<tr>
<td>n</td>
<td>number of subjects</td>
</tr>
<tr>
<td>NEP</td>
<td>Negative expiratory pressure</td>
</tr>
<tr>
<td>NHMRC</td>
<td>National Health and Medical Research Council</td>
</tr>
<tr>
<td>NREM</td>
<td>Non rapid eye movement</td>
</tr>
<tr>
<td>O₂</td>
<td>Oxygen</td>
</tr>
<tr>
<td>OR</td>
<td>Odds ratio</td>
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<tr>
<td>Abbreviation</td>
<td>Description</td>
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<tr>
<td>--------------</td>
<td>--------------------------------------------------</td>
</tr>
<tr>
<td>OSA</td>
<td>Obstructive sleep apnoea</td>
</tr>
<tr>
<td>OSAS</td>
<td>Obstructive sleep apnoea syndrome</td>
</tr>
<tr>
<td>Pclose</td>
<td>Upper airway closing pressure</td>
</tr>
<tr>
<td>Pcrit</td>
<td>Pharyngeal critical pressure</td>
</tr>
<tr>
<td>Peff</td>
<td>Effective pressure</td>
</tr>
<tr>
<td>Pes</td>
<td>Oesophageal pressure</td>
</tr>
<tr>
<td>Pmask</td>
<td>Mask pressure</td>
</tr>
<tr>
<td>PNS</td>
<td>Phrenic nerve stimulation</td>
</tr>
<tr>
<td>PSG</td>
<td>Polysomnography</td>
</tr>
<tr>
<td>REM</td>
<td>Rapid eye movement</td>
</tr>
<tr>
<td>Rus</td>
<td>Resistance upstream to the site of collapse</td>
</tr>
<tr>
<td>SDB</td>
<td>Sleep disordered breathing</td>
</tr>
<tr>
<td>SWS</td>
<td>Slow wave sleep</td>
</tr>
<tr>
<td>UA</td>
<td>Upper airway</td>
</tr>
<tr>
<td>UPPP</td>
<td>Uvulopalatopharyngoplasty</td>
</tr>
<tr>
<td>UARS</td>
<td>Upper airway resistance syndrome</td>
</tr>
<tr>
<td>Vi\text{\textsubscript{mid}}</td>
<td>Mid-inspiratory flow</td>
</tr>
<tr>
<td>VLOP</td>
<td>Ventrolateralpreoptic nucleus</td>
</tr>
<tr>
<td>Zrs</td>
<td>Impedance</td>
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Sleep is a naturally occurring behaviour exhibited by all animals, although its purpose(s) and underlying neurophysiological pathways are still not fully elucidated. Poor sleep quality and inadequate sleep duration can have severe deleterious effects on an individual’s health and quality of life. Decrement in neurobehavioral and physiological function are associated with poor sleep. Neurobehavioral decrements include lapse in attention, decrease in cognitive speed and accuracy as reflected in working memory tasks and depressed mood. Physiological consequences of sleep deprivation include adverse endocrine function, metabolic function and increases in markers of inflammation.

Lifestyle factors (such as work commitments, shift work and social responsibilities) and medical conditions (recognised sleep disorders and non-sleep related conditions) can impact sleep quantity and quality. According to the International Classification of
Sleep Disorders-Third Edition, there are seven major categories of sleep disorders incorporating more than 100 known conditions. Of these, obstructive sleep apnoea (OSA) is one of the more common, its prevalence rising with the increase in obesity. In Australia in 2010, it was estimated that OSA cost the Australian economy more than $248 million a year in health care costs to manage the disorder itself, $409 million per year to manage other illnesses directly attributable to it, and a further $2.6 billion a year in indirect financial costs (e.g. loss of productivity, work-place accidents and motor vehicle accidents).

OSA is a common sleep-related breathing disorder characterised by repetitive episodes of partial (hypopnoeas) or complete obstruction (apnoeas) of the upper airway during sleep. The apnoea hypopnoea index (AHI), the frequency per hour of sleep of these episodes is widely used to define OSA severity. In the general adult population the prevalence of OSA (AHI ≥5 events.hr$^{-1}$) is estimated to be 26%. It may be relatively asymptomatic, particularly in milder cases. When considering those with symptoms of sleepiness in addition to OSA, the prevalence is estimated to be 14% in men and 5% in women. OSA is associated with a number of major adverse health outcomes, including an increased risk of cardiovascular disease and stroke, cognitive decline, depression and premature death. The first-line treatment for OSA is continuous positive airway pressure (CPAP). CPAP is highly efficacious in decreasing the number of apnoeas and hypopnoeas, but approximately 50% of individuals who start using CPAP therapy fail to comply adequately with it. This has encouraged a search for effective treatment alternatives. Enhancing our understanding of the pathogenesis of OSA and the underlying predisposition to collapse of the upper airway is essential to effectively develop alternate treatment options.

Individual predisposition to OSA can be quantified by measurement of upper airway collapsibility. The current ‘gold standard’ measure of upper airway collapsibility is the pharyngeal critical closing pressure technique (the applied pressure at which the upper airway collapses; $P_{crit}$). $P_{crit}$ has been used to quantify the impact of individual factors involved in the pathogenesis of OSA and the specific effects of treatment. Individuals with OSA have higher $P_{crit}$s, than those without, indicative of their more collapsible upper airways. $P_{crit}$ is determined by lowering pressure applied to the
upper airway to induce increasing degrees of inspiratory flow-limitation.\textsuperscript{20,21} The pressure at which the linear pressure-flow relationship generated during such flow limited breaths crosses zero flow is $P_{\text{crit}}$. Ideally, inspiratory flow-limitation is identified by measuring oesophageal pressure ($P_{\text{es}}$), to confirm an absence of change in inspiratory flow despite increasing inspiratory effort (i.e. a more negative $P_{\text{es}}$). The $P_{\text{es}}$ measurement requires a catheter with pressure transducers to traverse the upper airway, such that its measuring site is positioned in the mid-oesophagus. However, it is possible that the presence of such a catheter could, of itself, alter the mechanical behaviour and collapsibility of the upper airway. Chapter Three of this thesis presents a study investigating the effect of the presence of such an oesophageal catheter, longitudinally spanning the upper airway, on upper airway collapsibility.

The $P_{\text{crit}}$ technique is inherently difficult to perform during sleep as altering applied pressure often results in measurement-induced changes in sleep state (i.e. arousals). This is not an issue during general anaesthesia which provides ideal conditions under which to study upper airway collapsibility; in addition to abolishing arousal responses, it allows for careful control of muscle activity devoid of measurement-induced changes in state and the ability to control other known modifiers, such as head posture, while maintaining spontaneous ventilation. Given these advantages, complex but well-controlled measurements can be made during deep sedation and anaesthesia for the purpose of characterising and understanding the determinants of an individual’s upper airway collapsibility. It is important to understand how such measures equate to those made during sleep. To date, the relationship between upper airway collapsibility in these two states (general anaesthesia and sleep) has been inferred by relating easily obtained indirect sleep measures, such as AHI, to anaesthesia-based $P_{\text{crit}}$ measures. Thus far no study has compared upper airway collapsibility during anaesthesia and sleep using the same metric (i.e. $P_{\text{crit}}$) in the same individual. The study presented in Chapter Four of this thesis was designed to address this issue by measuring $P_{\text{crit}}$ in the same individual during both anaesthesia and sleep.

Head posture is well known to influence upper airway patency in unconscious adults.\textsuperscript{22} Head flexion (chin tucked towards the chest) obstructs the upper airway while head extension (chin lifted away from the chest), a commonly used manoeuvre to maintain
upper airway patency in resuscitation, reduces upper airway obstruction.\textsuperscript{22} The significant effects of head posture on the upper airway, with flexion markedly increasing and extension markedly decreasing collapsibility, has been demonstrated during general anaesthesia.\textsuperscript{23} Studies have also investigated the effect of head posture on AHI (an indirect measure of upper airway collapsibility). Pillows intending to promote head extension have been used during sleep to improve AHI, with improvements seen in only some OSA patients.\textsuperscript{24,25} Despite these disparate findings, the effect of head posture has on upper airway collapsibility during sleep has yet to be studied in detail. The study presented in Chapter Five of thesis examined the effect of manipulating head posture (flexion, neutral and extension) on upper airway collapsibility in individuals with and without OSA.

The overarching theme of this thesis has been to better understand upper airway behaviour, in particular the influence of readily manipulable factors that can affect its collapsibility. The studies undertaken in this thesis are presented as a series of three interrelated scientific papers, each with its own abstract, introduction, methods, results and discussion sections. The studies use two distinct states of human consciousness, namely sleep and general anaesthesia, to explore: (i) the effect of Pes monitoring on upper airway collapsibility (Chapter Three); (ii) the mechanisms underlying the state dependent differences in upper airway collapsibility (Chapter Four); and (iii) the effect of head posture on upper airway collapsibility (Chapter Five). The studies are preceded by a literature review of the most important historical and recent research studies related to OSA and the upper airway (Chapter Two). The thesis concludes with a brief general discussion of the studies, their findings, implications and future directions for research (Chapter Six).
2.1. SLEEP

Sleep is a naturally occurring state characterised by decreased awareness and loss of consciousness. Deprivation or restriction of sleep has severe deleterious consequences on neurobehavioral and physiological functioning. Hence, sleep is considered essential for human survival.

2.1.1. Sleep Architecture

The basic structural organisation of normal sleep is termed ‘sleep architecture’. Sleep is broadly classified into two categories viz. non rapid eye movement (NREM) sleep and rapid eye movement (REM) sleep. Differentiation between sleep stages is important as a number of physiologic changes occur within each sleep stage. The current recommendations from the American Academy of Sleep Medicine (AASM) separates NREM sleep into three stages viz. stage N1, N2 and N3 sleep. Prior to 2007, classification of sleep stages was based on guidelines developed in 1968, under these classification guidelines stage N3 sleep was further divided into stages III and IV sleep.
IV. Each sleep stage has unique characteristic including changes in; brain wave patterns, measured using an electroencephalogram (EEG); eye movements, measured using an electro-oculogram (EOG); and muscle tone, measured using an electromyogram (EMG). Typically NREM sleep is characterised by high voltage, low frequency EEG activity, with well-preserved skeletal muscle tone, until slow wave sleep emerges wherein muscle relaxation is more prominent, with eye movements ceasing during stages N2 and N3 sleep. REM is typically characterised by low voltage, mixed frequency EEG activity in conjunction with rapid eye movements. It has tonic (persistent) and phasic (episodic) components. During tonic REM sleep (a parasympathetically driven state) skeletal muscles become almost atonic with the exception of the extraocular muscles and the diaphragm. Phasic aspects of REM sleep (a sympathetically drive state) include irregular burst of rapid eye movements, muscle twitches and respiratory variability.

Sleep is usually entered into from wakefulness through NREM sleep. Wakefulness is defined by the presence of alpha waves (8 to 12 Hz) on the EEG traces in more than 50% of a 30 second epoch. Over the course of the sleep period NREM and REM sleep alter cyclically, approximately every 90 minutes. At the beginning of the night slow wave sleep (SWS, N3 sleep) dominates the NREM sleep cycle, however as the sleep period continues NREM sleep contains progressively greater proportions of stage N2 sleep. These NREM/REM cycles get progressively longer as the night continues (90 to 120 minutes) with more frequent and longer periods of REM sleep occurring closer to awakening. In a healthy individual NREM sleep typically accounts for 75% to 80% of total sleep time while REM sleep typically occupies 20% to 25% of total sleep time. REM sleep is associated with dreaming and contains both phasic and tonic periods.

2.1.2. Physiological Changes During Sleep

Sleep is associated with many physiological changes involving several systems of the body, including the cardiovascular system, respiratory system, nervous system and musculoskeletal system. Cardiovascular changes that occur during sleep, primarily influenced by the autonomic system, include changes in blood pressure and heart rate. The typical autonomic feature of sleep is a relative increase in parasympathetic activity and decrease in sympathetic nervous activity during NREM and tonic REM sleep.
During phasic REM there are brief bursts of parasympathetic and sympathetic nervous activity. Arousals (change in EEG activity ≥3 seconds) and morning awakening are associated with sharp increases in heart rate and blood pressure.

In general, compared to wakefulness, reflex responsiveness to circulating carbon dioxide (CO₂) is blunted during NREM sleep and is at its lowest during REM sleep. Respiratory rate and minute ventilation decrease during sleep. Skeletal muscle activity, including that of the upper airway muscles is comparable to the awake state until SWS, where relaxation is more prominent, and is further decreased during REM sleep. During REM sleep, with the exception of the extraocular muscles and diaphragm the skeletal muscles are almost completely atonic. Ventilation is decreased during sleep with the greatest reduction occurring during REM sleep when respiratory drive is reduced. This decrease in ventilation coupled with sleep-related relaxation of upper airway muscles is believed to contribute to sleep-related breathing disorders, for example obstructive sleep apnoea (OSA).

2.1.3. Obstructive Sleep Apnoea

2.1.3.1. Definition and Diagnosis

Obstructive sleep apnoea is characterised by repetitive episodes of absence of airflow due to airway collapse (apnoea) and episodes of decreased airflow due to airway narrowing (hypopnoea) during sleep. These obstructive events are often associated with cortical arousal and intermittent oxyhaemoglobin desaturation during sleep. Obstructive sleep apnoea is a common medical condition and has significant adverse medical consequences. Furthermore, individuals with OSA often suffer from excessive daytime sleepiness.

The current ‘gold standard’ evaluation technique for the diagnosis of OSA is polysomnography (PSG), also known as a sleep study. PSG refers to the monitoring and recording of a battery of physiologic variables relating to the states of sleep and wakefulness. Sleep is ‘staged’ using EEG, EOG and EMG. Other concurrent measurements include heart rate, limb movement, body posture, oxygen desaturation and respiration. The respiratory signals, oral and nasal airflow and chest and
abdominal wall movements along with oxygen saturation are used to identify and classify respiratory events as apnoea or hypopnoeas.\textsuperscript{29} Various rules have been applied to define an apnoea and hypopnoea, the most recent of which are from AASM.\textsuperscript{29} Apnoeas and hypopnoeas are classified as obstructive if they occur in the presence of respiratory effort inferred by chest and abdominal motion. The severity of OSA is classified by the apnoea hypopnoea index (AHI), the total number of respiratory events divided by the total hours of sleep (events.hr\textsuperscript{-1}). An AHI of 5 to 15 events.hr\textsuperscript{-1} is commonly used to define mild disease, an AHI of 15 to 30 events.hr\textsuperscript{-1} to define moderate disease and an AHI greater than 30 events.hr\textsuperscript{-1} to define severe OSA. Obstructive sleep apnoea syndrome (OSAS) is defined as an AHI greater than 5 events.hr\textsuperscript{-1} together with the presence of excessive daytime sleepiness.

2.1.3.2. Prevalence

Various population-based epidemiology studies report a high prevalence of OSAS and a wide spectrum of disease severity.\textsuperscript{41-49} The increasing prevalence of OSA is closely related to the increasing numbers of obese individuals although comparisons between epidemiologic studies that assess the prevalence of OSA is challenging as studies have variable methodological approaches.

The most widely quoted estimates of OSA prevalence come from the Wisconsin sleep cohort study.\textsuperscript{50} This study, performed in the early 1990's, utilised a two staged prevalence study design, specifically an initial questionnaire was used to target a large screening population from which subjects were selected at random to undergo an in-laboratory PSG. The prevalence of OSA (AHI≥5 events.hr\textsuperscript{-1}) was found to be 24\% for middle aged men and 9\% for middle aged women (aged 30 to 70 years), while the prevalence of OSAS (AHI≥5 events.hr\textsuperscript{-1} plus symptoms of daytime sleepiness) was 4\% of middle aged men and 2\% of middle aged women. More recent data from the same cohort estimates the prevalence of OSAS in 2013 to be 14\% of men and 5\% in women.\textsuperscript{9} Other similarly designed prevalence studies report similar prevalence rates.\textsuperscript{42,43,51} In a Spanish cohort study the prevalence rates of OSA in individuals aged 30 to 70 years was slightly higher than that reported by the Wisconsin sleep cohort study (26\% in
men and 28% in women), however the prevalence of OSAS (AHI≥10 events.hr⁻¹ plus symptoms of daytime sleepiness) was similar to the Wisconsin sleep cohort study.\textsuperscript{51} Similarly the prevalence of OSAS (AHI≥10 events.hr⁻¹ plus symptoms of daytime sleepiness) in the Pennsylvania cohort study was 3.9% in men and 1.2% in women.\textsuperscript{42,43} In an Australia population of men aged 40 to 65 years, using portable monitoring, the prevalence of OSAS (AHI≥5 events.hr⁻¹) plus symptoms of daytime sleepiness was estimated to be 3%.\textsuperscript{41}

The influence of obesity on OSA prevalence is highlighted in a recent study by Peppard et al.\textsuperscript{9} where the prevalence of sleep-disordered breathing was modelled as a function of age, sex and BMI. Estimates were then extrapolated to the US BMI distribution estimates to calculate current prevalence estimates. Based on these calculations, the current prevalence of moderate OSA (AHI≥15 events.hr⁻¹) is estimated to be 10% among men aged 30 to 49 years and 3% among women aged 30 to 49 years. In those aged 50 to 70 years the prevalence increased to 17% in men and 9% in women. These modelled prevalence estimates are consistent with the directly calculated previous estimated previous estimates.\textsuperscript{50,52} Given the continuing increase in occurrence of overweight and obesity in adults, and the strong association between OSA and obesity, the prevalence of OSA in the general community is expected to continue to rise.

2.1.3.3. Pathogenesis

Collapse of the upper airway is the hallmark feature of OSA. Recent evidence indicates that alterations in upper airway anatomy, mechanical disturbances and inadequate neuromuscular control play important roles in the pathophysiology of upper airway obstruction.

2.1.3.3.1. Anatomical and mechanical mechanisms of collapse

Anatomically, the upper airway can be considered as a collapsible tube surrounded by soft tissue structures. It is commonly separated into three regions of interest (Figure 2.1): the retropalatal, retroglossal and hypopharyngeal regions. Of these the most common regions of collapse are the retropalatal and retroglossal regions.\textsuperscript{23,53}
Two main factors influence upper airway collapsibility: intraluminal negative pressure generated during inspiration by the inspiratory muscles and extraluminal tissue pressure resulting from tissue and bony structures surrounding the upper airway. Anatomical factors predisposing to upper airway collapse include extraluminal tissue pressure, pharyngeal soft tissue abnormalities (e.g. large adenoids and tonsils), a small mandible and narrow pharyngeal lumen.\textsuperscript{54,55}

\textbf{Figure 2.1} A schematic diagram highlighting the anatomical regions of the upper airway. The soft tissue structures and anatomy of the upper airway are labelled on the left hand side. On the right hand side are the three regions of interest of the upper airway, namely the retropalatal region (highlighted in red; the area behind the soft palate), retroglossal region (highlighted in yellow; the area behind the tongue) and the hypopharyngeal region (highlighted in green; the area below the epiglottis).

The soft tissue structures of the upper airway are surrounded by bony structures including the mandible, maxilla, cervical vertebrae and hyoid bone which are collectively referred to as the bony box. A small bony box or over-crowding of the soft tissue structures within it can result in an increase extraluminal tissue pressure and is associated with an increase in upper airway collapsibility. Although individuals with OSA have a larger neck circumference,\textsuperscript{56} it is also well documented that they have a
smaller upper airway cross sectional area as measured by CT and MRI when compared to healthy controls. Increased fat deposition is observed in the tissues surrounding the airway. This will also tend to increase extraluminal pressure and predispose the upper airway to collapse. Other anatomical factors also thought to influence collapsibility include increased airway length, lateral pharyngeal wall thickness and tongue volume.

End-expiratory lung volume (EELV) is also thought to significantly influence upper airway patency during sleep. Airway cross sectional area is known to increase as lung volume increases from residual lung volume to total lung capacity. Upper airway collapsibility, sleep disordered breathing severity and CPAP requirements have been shown to decrease with experimentally induced increases in EELV during sleep. Animal studies have demonstrated that an increase in EELV increases caudal traction on the upper airway resulting in airway stiffening and reduced collapsibility. Increased upper airway collapsibility is observed with reduced EELV and is one of the major mechanisms proposed to explain the relationship between increase in upper airway collapsibility and obesity (particularly central obesity); obesity is likely to cause abdominal compression which has been shown to result in a decrease in EELV and in upper airway closing pressure (see section 2.2.4.5 Lung Volume).

Redistribution of fluid from the legs to the neck has recently been proposed as a potentially important factor influencing upper airway patency and OSA severity. Overnight rostral fluid shift has been shown to correlate with AHI. Furthermore, fluid displacement by lower body positive pressure has been shown to increase neck circumference and pharyngeal resistance and reduce end-expiratory pharyngeal area, in awake subjects. These studies suggest that rostral fluid shift may, at least in part, contribute to the pathogenesis of OSA through narrowing of the upper airway.

Upper airway mucosal liquid lining surface tension has also been implicated in the pathogenesis of OSA. Increased surface tension of the mucosal liquid lining is thought to impair the ability of the upper airway to reopen following collapse. This mechanism could potentially be very important in patients with OSA as their airways are exposed to repetitive obstruction that likely result in upper airway inflammation,
further worsening severity. Indeed, decreasing mucosal surface tension with exogenous surfactant has been proposed as a potential treatment for OSA.\textsuperscript{75}

While anatomical factors certainly contribute to the pathogenesis of upper airway collapse, several observations suggest that anatomical factors alone are not solely responsible for OSA. Firstly, upper airway obstruction often occurs intermittently and most OSA patients have some periods of stable breathing.\textsuperscript{76,77} Secondly, some individuals with OSA have a negative upper airway collapsing pressure, as measured by the passive pharyngeal critical pressure technique (described in detail in section\textsuperscript{2.2.2.1Pharyngeal critical pressure}) suggesting that factors other than anatomical mechanisms are also influential in the pathogenesis of OSA.

2.1.3.3.2. Neurogenic mechanisms of collapse

The pathogenesis of OSA cannot be completely explained by anatomy alone otherwise patients would obstruct during both wake and sleep, which is not the case. It is likely that upper airway patency is maintained as a result of high dilator muscle tone during wakefulness.\textsuperscript{78} In addition, negative pressure reflexes, respiratory control stability and arousal threshold have also been shown to influence airway patency.\textsuperscript{79,68,80}

There are a number of muscles within the upper airway. These include extrinsic muscles of the tongue (e.g. genioglossus), muscles controlling palatal shape (e.g. tensor palatini), muscles that influence the hyoid bone position (e.g. geniohyoid) and upper airway constrictor muscles (e.g. superior pharyngeal constrictor). Of the upper airway dilator muscles the genioglossus is the largest and most studied. This major upper airway dilator muscle is driven by locally mediated mechanoreceptor reflex mechanisms, chemoreceptor reflexes and state-dependent drive. Genioglossus tone decreases at sleep onset in both healthy controls and subjects with OSA.\textsuperscript{81-83} Hence, an individual with an upper airway anatomically predisposed to collapse is susceptible to upper airway collapse at sleep onset when muscle tone declines. Periods of collapse are typically ended with an arousal which restores muscle tone and airway patency. Unlike the transition from wake to sleep, slow wave sleep is associated with increased upper airway dilator muscle activity.\textsuperscript{82,84} This increase in genioglossus activity is not attributed to sleep itself but rather to a compensatory response to the
combined increase in pharyngeal resistance (generating larger negative pressures in the airway) and elevations in CO₂ that occur during sleep.

The ability of the upper airway to respond to a respiratory challenge is also an important factor in OSA pathogenesis. Negative pressure in the upper airway reflexively activates locally mediated mechanoreceptors to trigger dilator muscle activity.⁸⁵,⁸⁶ In healthy individuals the negative-pressure reflex is diminished during NREM sleep⁸⁷,⁸⁸ but is not completely absent, thus the muscles can still respond to negative pressure. It is thought that some individuals with OSA have a profoundly depressed negative pressure reflex which contributes to promoting upper collapse, while other individuals with OSA have a more responsive negative pressure reflex and are better able to compensate during sleep for their deficient anatomy.⁷⁷ Such variability in may explain, in part, why some individuals with ‘poor’ upper anatomy do not develop OSA while others do.

The respiratory arousal threshold is another factor influencing collapsibility. Arousal from sleep at the end of a respiratory event was traditionally considered an important protective mechanism for airway reopening.⁸ However recent work by Younes et al.⁸⁹ has challenged this theory. Younes et al.⁸⁹ studied the response to experimentally induced transient CPAP reduction in patients with OSA and noted that in 17% to 22% of individuals flow was increased and restored either before or in the absence of arousal. Such changes in flow were attributed to increased genioglossus muscle activity and changes in duty cycle. Notably, they were reported to occur in both individuals with OSA and healthy individuals.⁷⁷ Younes et al’s.⁸⁹ findings suggest that a low respiratory arousal threshold could contribute to OSA. There are several mechanisms via which this could occur: (i) by disrupting sleep thus preventing deeper stage of sleep that are often associated with stable breathing⁹⁰; (ii) as a result of an arousal related abrupt ventilatory response thus perpetuating CO₂ fluctuations leading to respiratory control instability⁹¹,⁹²; and (iii) by limiting the ability to build up sufficient respiratory stimuli to recruit upper airway muscle to open the upper airway.⁹² Thus, in some instances arousal likely serves as a last line of defence to terminate severe respiratory events, however in some individuals awakening too easily may augment breathing instability and promote subsequent respiratory events.
Respiratory control instability (often referred to as high loop gain) is also considered to be a contributing factor to OSA in some individuals.\textsuperscript{93,94} Loop gain refers to the stability of the respiratory system and how it responds to a disturbance to breathing. The two main components of loop gain are controller gain and plant gain. Controller gain reflects the body’s responsiveness to hypoxia and hypercapnia (i.e. its chemoresponsiveness), while plant gain refers to the ability of a given level of ventilation to excrete CO\textsubscript{2} (i.e. efficiency of CO\textsubscript{2} excretion and O\textsubscript{2} uptake). A high loop gain can cause fluctuations in respiratory drive with concomitant fluctuations in neural drive to the respiratory and upper airway dilator muscles. Individuals with OSA have a higher loop gain than healthy controls.\textsuperscript{95,96} Also, patients with more severe OSA have a higher loop gain that those with mild OSA.\textsuperscript{93} Indeed, decreasing loop gain with acetazolamide can result in a decrease in AHI when compared with baseline levels.\textsuperscript{97} Such findings reinforce the importance of ventilatory control and other non-anatomic factors, in OSA pathogenesis.

2.1.3.4. Independent Risk Factors for Obstructive Sleep Apnoea

Obesity, being male and increasing age are the three main risks factors for OSA, each are discussed below.

2.1.3.4.1. Obesity

Obesity is the strongest risk factor for OSA. Evidence for this is found in population based prevalence studies that show a positive association between excess weight and the occurrence of sleep-disordered breathing (SDB),\textsuperscript{41,44,45,98} with a one standard deviation increase in BMI being associated with a 4-fold increase in risk for having an AHI≥5 event.hr\textsuperscript{-1}.\textsuperscript{50,99} Conversely, weight loss decreases OSA severity.\textsuperscript{100-102}

The underlying mechanisms by which obesity and OSA interact are not clearly defined. However, it has been hypothesised that the mechanism is predominantly anatomical in nature and that the pattern of excess fat distribution might be important. The two main areas of fat deposition related to OSA are the neck and the abdomen. Fat deposition in the structures surrounding the upper airway could directly alter the geometry of the pharyngeal airway lumen, presumably altering the mechanical
function of the upper airway thus increasing upper airway collapsibility.\textsuperscript{103,104} Such an idea is supported by the observation of significantly more fat deposition at the level of the soft palate (the primary site of pharyngeal collapse in most people with OSA) in patients with OSA compared with weight-matched control subjects,\textsuperscript{103} even in non-obese OSA patients with similar BMI and neck circumferences.\textsuperscript{105} In addition, from three-dimensional volumetric soft tissue measurements, the volume of the soft tissue structures surrounding the upper airway has been shown to be larger in OSA subjects, suggesting that such soft tissue volume is an independent risk factor for OSA.\textsuperscript{54} However, such increases in soft tissue structures need to be considered in relation to the surrounding craniofacial structures/dimensions as not all soft tissue, specifically tongue volume, are always greater in patients with OSA.\textsuperscript{106-108}

Centrally distributed adiposity may also increase the risk of OSA. It is thought that this is mediated by an adiposity-induced reduction in lung volume. In normal weight individuals functional residual capacity is reduced during sleep when compared to wake.\textsuperscript{109} Lung volume is also reduced in obese individuals compared to normal weight individuals.\textsuperscript{110-112} The combination of the sleep- and obesity-related decreases in lung volume is presumed to contribute to upper airway collapse in individuals with OSA.\textsuperscript{113-115} In support of this concept, Stadler et al.\textsuperscript{69} showed that abdominal compression during sleep increased upper airway collapsibility, implicating central obesity as an important mechanism of OSA. Increasing lung volume has been demonstrated to decrease in upper airway collapsibility and increase upper airway lumen size.\textsuperscript{57,61,116-118} The ‘tethering’ effects of lung volume on the upper airway (longitudinal tracheal traction) is thought to mediate these interactions between the lower airways (i.e. the lung) and the upper airway (discussed more fully in section 2.2.4.5 Lung Volume).\textsuperscript{67,119,120} Briefly, longitudinal tracheal traction is thought influence upper airway collapsibility by: (i) stiffening the upper airway walls\textsuperscript{119}; (ii) changing pressure changes at the thoracic inlet;\textsuperscript{121} and/or (iii) displacement of the hyoid bone.\textsuperscript{122}

2.1.3.4.2. Gender
Gender is another major risk factor with males having a 1.2- to 3.7-fold\textsuperscript{51,123} greater risk of having OSA than women. The specific reason for this male predisposition remains vague, although gender related differences in anatomy (such as upper airway length and the pattern of fat distribution) and neurogenic control (such as ventilatory control and arousal threshold) have been implicated.

Modelling studies have shown pharyngeal length to also play a potentially important role in upper airway collapsibility,\textsuperscript{124-126} even when factoring for height, males have a longer pharyngeal airway than women.\textsuperscript{60} Further, men have been shown to have more central obesity than women, potentially contributing to any lung volume related increase in upper airway collapsibility via a loss of caudal traction (as discussed in section 2.1.3.4.1 Obesity). Imagining studies have shown that men also have increased fat deposition around the pharyngeal airway compared with women.\textsuperscript{127} Interestingly the gender bias diminishes with age, specifically post menopause. It is interesting to note that postmenopausal women have a longer pharyngeal airway as compared to premenopausal women\textsuperscript{128} as well as a change in the pattern of adipose tissue distribution (to more centrally) following menopause.\textsuperscript{129} Both of these mechanisms could contribute to the increased incidence of OSA post menopause.

While the majority of data available suggest that anatomical factors are the primary cause for the gender difference in the prevalence of OSA, differences in neurogenic influences may also be important. Firstly, ventilatory control varies between men and women. Compared to men, women have greater respiratory load responses\textsuperscript{130,131} and a lower ventilatory demand (i.e. minute ventilation during unobstructed breathing).\textsuperscript{130} In addition men have a greater ventilatory response to arousal from sleep (i.e. men may be more prone to cyclic breathing).\textsuperscript{91,132} Secondly, whilst there does not seem to be a systematic gender difference in loop gain in healthy subjects\textsuperscript{133} or in those with OSA, there are reported gender differences in the apnoea threshold.\textsuperscript{134,135} An imbalance in the components of ventilatory instability (i.e. loop gain and apnoea threshold) is believed to be due to differences in hormonal mechanisms, which are thought to mediate the apnoea threshold.\textsuperscript{134,136} For example, testosterone has been shown to modulate the neurochemical control of breathing\textsuperscript{137} and upper airway collapsibility,\textsuperscript{138} and the administration of testosterone in
hypogonadal men has been shown to induce OSA. However, improvements in OSA with long term hormone-based therapies have yet to be demonstrated. The precise mechanisms underlying the gender differences in upper airway collapsibility remain unclear.

2.1.3.4.3. Age

Increasing age, regardless of gender, is another important risk factor for OSA. Individuals older than 45 years have a more than 3 fold increased risk of having OSA. Beyond 65 years the risk of OSA plateaus.

A number of anatomical and neurogenic changes that affect upper airway collapsibility occur with aging. Anatomical changes include: increased fat deposition around the upper airway; modest decreases in upper airway calibre; and increased pharyngeal length. Changes in pharyngeal length have been suggested to occur during puberty in boys and post menopause in women.

Factors such as deterioration of the genioglossus negative pressure reflex; arousal threshold and lung volume changes are also believed to contribute to the increased prevalence in OSA in older individuals. Several reports suggest that there is an age-related impairment to the negative pressure reflex resulting in an upper airway that is more vulnerable to collapse. Controversy remains regarding the effect of aging on the arousal threshold and there have been no systematic studies assessing whether aging predisposes individuals to upper airway collapse due to the loss of lung elastic recoil or due to reduced lung volume. In theory there may be an age-related reduction in end-expiratory lung volume which would result in decreases caudal traction on the upper airway thus predisposing it to collapse (see section 2.2.4.5 Lung Volume).

While obesity, gender and age are the three primary risk factors for OSA there are also others, although on a population level these are not considered as important as the three previously discussed. Other predisposing factors include; genetic factors, race factors and smoking. Genetic and race risk factors affect craniofacial anatomy, obesity and pattern of fat distribution. The precise mechanisms by which smoking influences
upper airway collapsibility are unclear, however current hypotheses include; increased inflammation of the upper airway, a reduction in upper airway sensitivity to mechanical stimuli and a reduced arousal threshold.

2.1.3.5. Consequences of Obstructive Sleep Apnoea

OSA is linked to a number of serious physical and psychological health problems. Sleep deprivation (partial), excessive daytime somnolence, cognitive, metabolic and cardiovascular consequences are all features of OSAS. The effects of being untreated include an increased risk of having motor vehicle accidents and occupational injuries and a deceased quality of life. These consequences and their ramifications will be discussed in detail in the following section.

2.1.3.5.1. Sleep Deprivation

Untreated OSA causes partial sleep deprivation in three ways: (i) sleep fragmentation; (ii) selective sleep stage deprivation and (iii) sleep restriction.

Sleep fragmentation is as a result of recurrent arousals from sleep triggered by repetitive apnoeas and hypopnoeas. In untreated OSA patients these frequent repetitive arousals from sleep prevent physiological consolidation of sleep. Sleep fragmentation is associated with excessive daytime sleepiness, cognitive performance deficits and mood alterations. It is suggested that arousals occurring at a rate of 1 per minute, equating to an AHI of 60 events.hr⁻¹, lead to daytime cognitive impairments associated with one night of total sleep deprivation. The upper airway has been shown to be more collapsible following one night of sleep fragmentation (caused by auditory stimuli) than following one night of complete sleep deprivation thus potentially further predisposing OSA subjects (who suffer from chronic sleep fragmentation) to further upper airway collapse, although the mechanism for this increased collapsibility is not clear.

Selective sleep stage deprivation is a result of stage specific sleep fragmentation. Sleep disordered breathing adversely affects sleep architecture resulting in an increased percentage of stage N1 and N2 sleep and a decreased percentage of stage N3 and REM sleep. Sleep characterised by small amounts of slow wave sleep (stage
N3 sleep) is considered to be non-restorative, resulting in excessive daytime sleepiness.\textsuperscript{161,162}

Sleep restriction is defined as a reduction in total sleep duration. Subjects with OSA often have a reduced total sleep time despite spending adequate time in bed. It is well documented that cumulative sleep restriction over a number of nights has adverse neurobehavioural effects,\textsuperscript{1-4} causes an increase in sleep propensity,\textsuperscript{2,163} causes a decrease in cognitive speed as reflected in working memory tasks\textsuperscript{2,3} and increases the number of lapses of attention on psychomotor vigilance task.\textsuperscript{1-4} Several prospective studies have suggested that short sleep duration predicts future obesity.\textsuperscript{164-166} As obesity is an independent risk factor for OSA it is possible that short sleep duration may be involved in perpetuating a vicious cycle with increased OSA disease severity and further decreases in the amount of sleep attained (in untreated individuals).

Treatment of OSA with continuous positive airway pressure (CPAP) eradicates the majority of the upper airway obstructions, resulting in improvements in sleep fragmentation, selective sleep stage deprivation and sleep restriction.\textsuperscript{167-169} Immediately following commencement of treatment, both SWS and REM sleep rebound above normal baseline values.\textsuperscript{170} This rebound is thought to be a manifestation of homeostatic regulation and represents a return to normal sleep architecture following partial sleep deprivation. Restoring normal sleep results in concomitant improvements in daytime function.

### 2.1.3.5.2. Excessive Daytime Sleepiness, Impaired Health Related Quality of Life and Motor Vehicle Accidents

Excessive daytime sleepiness (EDS) is a common clinical complaint of patients with OSA whether measured objectively or subjectively. Excessive daytime sleepiness is likely a result of sleep fragmentation.\textsuperscript{171,172} Whilst a relationship between the severity of SDB and EDS has been observed, this relationship is weak.\textsuperscript{173,174} In individuals with SDB, particularly in those with OSA, health related quality of life and perceived well-being are diminished.\textsuperscript{175-177} Specifically, OSA patients report a poor quality of life in the social, emotion and physical domains.\textsuperscript{178} This emotional disturbance may escalate, resulting in family and social conflict.\textsuperscript{179,180} Further, EDS is associated with increased
morbidity, motor vehicle accidents and decreased work capacity. Compared to controls, patients with OSA are 2 to 7 times more likely to have a motor vehicle accident, they are more likely to have multiple accidents and the accident severity is greater.\textsuperscript{181-183} Treating OSA with CPAP relieves EDS, particularly in mild to moderate OSA.\textsuperscript{184-187}

2.1.3.5.3. Cognitive Consequences

Neurobehavioral decrements affected by the presence of OSA include lapses in attention\textsuperscript{1,2} and decreases in cognitive speed and accuracy as reflected in working memory tasks.\textsuperscript{2,3,188-192} Studies on the influence of OSA on cognitive function suggest that executive function (i.e. the ability to develop and sustain an organised and flexible response to problem solving)\textsuperscript{191,193-196} is impaired while others suggest a deficiency in attention (important in skills such as driving).\textsuperscript{192,196-198}

The aetiology of this OSA-related cognitive impairment is thought to result from nocturnal hypoxemia and sleep fragmentation. Neural damage caused by hypoxemia may relate to some of the deficits seen in executive function.\textsuperscript{191} Such a notion is supported by results from animal studies which have shown that both hypoxemia and sleep fragmentation\textsuperscript{199,200} lead to molecular and cellular neuronal damage (e.g. increased sensitivity to low O\textsubscript{2} conditions) in the two areas of the brain that are most closely related to memory and executive function (i.e. the hippocampus and prefrontal cortex).

Treatment of OSA with CPAP therapy is effective in improving cognitive functioning, however measurable deficits still exist in 30 to 50% of patients,\textsuperscript{201-204} perhaps due to permanent structural changes in the brain.

2.1.3.5.4. Metabolic Consequences

Obstructive sleep apnoea is associated with alterations in metabolic function compared with normal individuals. Several population based studies involving a variety of ethnic groups have reported a relationship (independent of obesity) between OSA and glucose metabolism, insulin resistance, metabolic syndrome
A link between OSA and hypertension has long been recognised. Population-based cross-sectional and prospective longitudinal studies have shown a strong and independent association between OSA and hypertension. Individuals with an AHI≥15 events.hr⁻¹ have been reported to have a 1.42 to 1.72 increased odds ratio for prevalent hypertension compared to individuals without OSA (AHI<1.5 events.hr⁻¹), even after adjusting for known confounders (e.g. BMI).²¹⁵,²¹⁶ The strongest evidence of an association between OSA and hypertension comes from a large longitudinal sleep cohort study, which after controlling for various known confounding variables (e.g. age, BMI, baseline hypertension, alcohol and smoking) found that the odds ratio for the development of hypertension at a 4 year follow-up was 2.03 (95% CI 1.29 to 3.17) for mild OSA and 2.89 (95% CI 1.46 to 5.64) for moderate or worse OSA (AHI≥15 events.hr⁻¹).²¹⁷ Several mechanism are thought to be responsible for the association between hypertension and OSA, including sympathetic nervous system overactivity, alterations in vascular function and structure due to oxidative stress and inflammation and short sleep duration.²¹⁸-²²¹ In contrast to the middle aged population, in the elderly the impact of OSA on hypertension is insignificant.²¹⁵,²¹⁶ This may be because those affected did not survive or that cardiovascular disease has already occurred and the contribution of OSA is therefore irrelevant.

Data on the effect of OSA treatment on hypertension are inconsistent.²²²-²³¹ The variable results may be due to a combination of enrolment of normotensive individuals, suboptimal CPAP adherence and methodological differences between studies. Despite these limitations a recent meta-analysis of seven randomised controlled trials assessing the impact of CPAP therapy on 24 hour ambulatory blood pressure demonstrated that CPAP was associated with a significant reduction in systolic blood pressure.²²⁶ These findings confirm the results of an earlier meta-analysis of twelve randomised controlled trials demonstrating that CPAP intervention resulted in a net decrease in mean 24 hour blood pressure of 1.69 mmHg (95% CI -2.69 to -0.69 mmHg).²³² Notably the improvements in blood pressure were greatest in those with more severe OSA, those with more sleep fragmentation at baseline and in
individuals with greater adherence to CPAP therapy. A significant reduction in blood pressure has also been reported from oral appliance therapy.

The prevalence of type 2 diabetes in OSA patients ranges from 15% to 30%. The two conditions share the same risk factors (being male, increasing obesity and age). In the sleep cohort study the prevalence of type 2 diabetes increased according to the severity of OSA. The odds ratios of having diagnosed type 2 diabetes, after adjusting for age, sex and body habitus, with an AHI≥15 events.hr⁻¹ compared to having an AHI<5 events.hr⁻¹ was 2.3 (95% CI, 1.28-4.11, p=0.005). However, in this prospective analysis, an independent causal effect of sleep disordered breathing in the development of type 2 diabetes could not be established as indicated by the non-significant odds ratio for the 4-year incidence of physician diagnosed diabetes, after adjusting for shared risk factors. Moreover, there is also a high prevalence of OSA among patients with type 2 diabetes and its precursor, impaired insulin sensitivity. Lower insulin sensitivity is associated with more severe sleep disordered breathing and nocturnal desaturations (adjusting for age, sex, ethnicity and percentage body fat) and those with OSA have a lower insulin sensitivity compared to those without OSA.

The exact mechanism for metabolic dysfunction with OSA is unknown, however it is likely that multiple interrelated factors contribute to the complex interactions between OSA, obesity and glucose control. Firstly, glucose homeostasis may be adversely affected by hypoxia. Exposure to chronic intermittent hypoxia for 12 weeks in leptin-deficient obese mice resulted in a time-dependent increase in fasting insulin level and worsening of glucose tolerance with levels normalising after discontinuation of hypoxic exposure. Secondly, there is compelling evidence that sleep loss due to sleep fragmentation may have deleterious effects on glucose metabolism. Two controlled laboratory studies have shown that in healthy young adults reductions in sleep duration result in marked decreases in glucose tolerance and an increased risk of diabetes. Lastly, the generation of reactive oxygen species (ROS) and activation of inflammatory pathways has also been proposed as an intermediate mechanism that could lead to alterations in glucose metabolism in individuals with OSA. A number of observational studies have demonstrated that OSA is independently associated with
increased markers of oxidative stress.\textsuperscript{247-251} Furthermore, obesity itself appears to also induce a low grade state of inflammation.\textsuperscript{252}

2.1.3.5.5. Cardiovascular Consequences

OSA patients have a significantly increased risk of cardiovascular complications such as hypertension (discussed in section 2.1.3.5.4 Metabolic Consequences), stroke, coronary artery disease (ischaemic heart disease) and congestive heart failure and cardiovascular disease. A number of physiological changes relating to the cardiovascular system occur in response an obstructive event. These cardiovascular changes are thought underlie the role of OSA as an independent risk factor for cardiovascular disease. Briefly, during an obstructive event systemic blood pressure increases, cardiac output and heart rate decrease, oxyhaemoglobin saturation decreases, catecholamine levels increase causing an increase in systemic vascular resistance and increase in both systemic and pulmonary artery blood flow.\textsuperscript{253-255} At the termination of an obstructive event blood pressure increases even further and heart rate and cardiac output also increase.\textsuperscript{253-255} In addition, nocturnal and diurnal sympathetic nervous system activity is irregular in patients with untreated OSA. During obstructive events sympathetic activity is elevated and peaks during arousal. During wake periods OSA patients have faster heart rate, blunted heart rate variability and increased blood pressure variability.\textsuperscript{31,256-261} The majority of evidence linking OSA to various cardiovascular consequences is from large population-based cross-sectional and prospective longitudinal studies. These cardiovascular consequences will be discussed below.

\textbf{Stroke}

The intertwined relationship between stroke and sleep disordered breathing has long been recognised with both conditions potentially causing the other. A number of large population-based studies have reported an increased risk of stroke in habitual snorers and patients with OSA with the risk increasing with disease severity.\textsuperscript{262-266} The mechanism by which OSA increases stroke risk remains debatable but various mechanisms have been proposed including elevations in the associated risk factors of hypertension and atherogenesis (as assessed by increased intima-media thickness of common carotid artery). Acute reductions in cerebral blood flow are observed during
sleep disordered breathing events with beneficial changes in blood flow being reported following CPAP therapy.\textsuperscript{267,268} The effect of long-term treatment of OSA on the prevention of stroke is yet to be established. Stroke may also potentiate OSA and sleep disordered breathing. Impaired upper airway and respiratory muscle coordination or ventilatory control due to ischemic damage to brainstem regions is thought to contribute to the development of OSA or CSA following stroke. Concomitant improvements in SDB and stroke recovery provide further evidence for the link between the two conditions.

**Coronary Artery Disease**

Coronary artery disease, defined as angina pectoris and/or myocardial infarction, is also independently associated with OSA.\textsuperscript{266,269} An adjusted odds ratio of 1.27 was observed in subjects with an AHI>11 events.hr\textsuperscript{-1}\textsuperscript{266} and in a clinic-based study OSA was a significant independent predictor of incidence of coronary artery disease.\textsuperscript{269} There are data demonstrating that effective treatment of OSA can serve as both a primary and secondary prevention of adverse cardiovascular outcomes.\textsuperscript{269,270} This increase is believed to be due to oxygen demand-supply mismatch, ischaemic electrocardiographic (ECG) changes and angina which result from cyclic apnoea induced hypoxia, negative intra-thoracic pressure and hypertension.\textsuperscript{271} Treating patients with CPAP therapy decreases the risk of cardiovascular mortality.\textsuperscript{270,272}

**Congestive Heart Failure**

Likewise, congestive heart failure is also associated with OSA. In the Sleep Heart Health Study subjects with AHI>11 events.hr\textsuperscript{-1} had an adjusted odds ratio of 2.38 for self-reported congestive heart failure compared to subjects without OSA.\textsuperscript{266} High prevalence of SDB in patients with congestive heart failure and reduced systolic function although the direction of causality has not been established. Several studies have reported increased left ventricular hypertrophy in association with OSA.\textsuperscript{273} It is speculated that OSA may also promote the development of intra-thoracic aortic aneurysms presumably due to repetitive increases in intra-thoracic pressure during obstructive inspiratory efforts.\textsuperscript{266} Randomised controlled trials have demonstrated that effective treatment of OSA with CPAP therapy in patients with systolic congestive
The mechanism by which CPAP therapy reduces cardiovascular consequences is complex and likely multifactorial in nature. Firstly, CPAP decreases sleep fragmentation, which in turn restores plasma renin levels to normal thereby reducing blood pressure.\textsuperscript{277} Secondly, CPAP reduces chronic intermittent hypoxia thereby normalising sympathetic traffic through tonic activation of chemoreflex activity, increases arterial baroreflex sensitivity and decreases vascular risk.\textsuperscript{278-281} Thirdly, CPAP reduces levels of inflammatory mediators that are increased in patients with OSA.\textsuperscript{282-285} Treating OSA positively affects morbidity and mortality as shown by a recent study demonstrating that optimal cardiovascular treatment could not be achieved until OSA was effectively treated.\textsuperscript{274}

2.1.3.6. Treatment Modalities

Although there is no cure for OSA there are a number of widely used treatment options. All are generally aimed at decreasing pharyngeal collapsibility. Treatment can be divided into five general categories, these are: (i) continuous positive airway pressure (CPAP) therapy; (ii) oral appliances; (iii) upper airway surgery; (iv) lifestyle modification (i.e. weight loss, cessation of ingestion of alcohol in the evening and sleep positional therapy) and (v) drug therapies. The most common treatments will be discussed below.

2.1.3.6.1. Continuous Positive Airway Pressure

Continuous positive airway pressure (CPAP) therapy is the current recognised ‘gold standard’ for treatment of OSA. The therapy was designed over 30 years ago, it pneumatically splints the upper airway open.\textsuperscript{286,287} Air, under positive pressure, is administered to the upper airway via a nasal or oro-nasal mask which is held in position by elastic head gear (Figure 2.2).
CPAP therapy resolves respiratory events, reduces AHI, alleviates objective and subjective symptoms of daytime sleepiness\textsuperscript{185,201,289-291} and improves sleep quality as it consolidates sleep and normalises oxygen saturation.\textsuperscript{292} CPAP has been shown to reverse a number of other complications associated with OSA, including cognitive, metabolic and cardiovascular consequences which are discussed in detail in section 2.1.3.5 Consequences of Obstructive Sleep Apnoea.

Despite CPAP being the recognised ‘gold standard’ therapy for OSA, due to its reliable therapeutic outcome, it is a cumbersome therapy and compliance is a major issue. Long term adherence to CPAP therapy is estimated to be between 32\% and 80\%.\textsuperscript{17,204,293-296} This large variability in adherence rates is in part due to numerous differences in study design and outcome variables, including differences in the definition of adherence. Factors such as disease characteristics, treatment titration, technology device factors (e.g. type of mask) and psychological and social factor all play a role in patient adherence.\textsuperscript{297-299} The Cochrane Collaboration reviewed 30 studies (n=2,047 individuals with OSA) examining: (i) education intervention; (ii) supportive intervention during follow-up and (iii) behavioural therapy, and concluded that all three interventions had an impact on CPAP usage.\textsuperscript{300} Current evidence suggests that there is a dose related response to CPAP use and that longer nightly use is associated with the most beneficial outcomes.\textsuperscript{201,301,302}
For individuals who are intolerant to CPAP other treatment modalities may be considered. These include oral appliance therapy, surgery and weight loss.

2.1.3.6.2. Oral Appliance Therapy

Oral appliance devices are designed to increase the pharyngeal space by protruding the mandible and by preventing the tongue from moving posteriorly. There are two main types of oral appliance; tongue retaining device (TRD) therapy and mandibular advancement splint (MAS) therapy. The TRDs are designed to pull the tongue into an anterior position with the application of a suction pressure. The MAS functions by anteriorly advancing the mandible which results in the tongue (and other structures in the anterior pharyngeal wall) being pulled away from the posterior pharyngeal wall (Figure 2.3). This literature review will only discuss the most commonly used oral appliance, specifically MAS therapy.

![Figure 2.3: Schematic diagram showing the upper airway with the mandible advancement splint (oral prosthesis) in situ. Anterior displacement of the mandible results in the tongue being advanced away from the posterior pharyngeal wall.](image)

Mandibular advancement, during wake and sleep, has been shown to enlarge the upper airway lumen, particularly in the lateral dimensions, and reduce pharyngeal collapsibility.\(^{304-310}\) MAS therapy is also thought to exert beneficial effects on the upper
airway dilator muscle stiffening the upper airway walls, altering peripharyngeal tissue pressure and decreasing the propensity for collapse. Mandibular advancement splints may also influence upper airway neuromuscular function, with several studies reporting an increase in EMG activity when the device is worn.

In direct comparison to CPAP therapy, oral devices are consistently found to be less efficacious in improving PSG measures of OSA severity. Treatment success (defined as an AHI<5 events.hr\(^{-1}\)) is reported in 19% to 75% of individuals, while an AHI<10 events.hr\(^{-1}\) has been reported in 30% to 90% of individuals. A meta-analysis has indicated that the reduction in the frequency of respiratory disturbances is on average 55% (ranging from 28% to 80% from all the studies). Despite being less efficacious than CPAP therapy, MAS therapy is associated with improvements in health outcomes (e.g. increases quality of life, decreases in subjective daytime sleepiness, objective daytime sleepiness and objective measures of OSA severity).

Although MAS is recommended as a first line therapy for patients with mild to moderate OSA (who fail CPAP treatment or who prefer an oral device over CPAP therapy), other patient characteristics that have been reported to be associated with great treatment success include: individuals who are younger age; females; leaner individuals; those with smaller neck circumference; in addition to individuals who have mild to moderate OSA. Thus, MAS therapy can be an effective treatment for OSA across a range of disease severities. However, patient selection is important in improving the chances of treatment success.

2.1.3.6.3. Surgery

There are a number of surgical alternatives for treatment of OSA including: tracheostomy, tonsillectomy and adnoidectomy, uvulopalatopharyngoplasty (UPPP), and genioglossal advancement and maxilla-mandibular osteotomy. The aim of these surgical procedures is to increase the upper airway size and prevent further obstruction. Surgical treatment of OSA is separated into two phases detailed below.
**Phase I Surgical Therapy**

Phase I surgery is the most conservative approach and typically address the nasal cavity, palatal region and tongue base. Nasal surgery (e.g. septoplasty, turinectomy) is conducted to treat nasal airway blockage with the aim of minimising mouth breathing. Nasal surgery may reduce snoring, and help to optimise CPAP use in individual with mild disease.

Minimally invasive surgeries, such as radiofrequency or laser-assisted UPPP and its variants, and soft palate implants, are the most commonly performed of the surgical treatments for OSA. Uvulopalatopharyngoplasty surgery has been shown to improve quality of life and daytime sleepiness, with reported success rates for improving mild to moderate OSA of 40% to 50%. However surgical efficacy appears to deteriorate over time. Soft palate implants, which aim to stiffen the soft palate, have been shown to reduce snoring, daytime sleepiness and AHI. However, it is important to note that these are not considered efficacious in adults with OSA but may be considered as a treatment for snoring.

Surgeries aimed at decreasing overall tongue volume (e.g. temperature controlled radiofrequency tissue ablation) and/or advancing the tongue (e.g. genioglossus advancement surgery) are designed to prevent upper airway obstruction at the base of the tongue during sleep. Tongue volume reduce surgery has been shown to reduce tongue volume by 20%, increase cross sectional area and decrease upper airway collapsibility. Anterior movement of the mandible and/or the hyoid bone stabilises the base of the tongue and enlarges the retroglossal and hypopharyngeal airway, with successful outcomes being achieved in 35% to 60% of individuals depending on the severity of the disorder.

**Phase II Surgical Therapy**

Phase II surgical therapy involves surgical advancement of the mandible and/or the maxilla. Maxillo-mandibular advancement is a multilevel skeletal surgery designed to enlarge the upper airway lumen without manipulating the pharyngeal tissue. It has been used to successfully treat OSA in individuals with and without craniofacial abnormalities. By advancing the mandible and/or maxilla the anterior soft tissue
(that is, the soft palate, tongue base, the suprahypoid and retropalatal muscles) structures of the upper airway are pulled forward significantly increasing the upper airway lumen size and decreases upper airway collapsibility. Furthermore, maxilla-mandibular advancement surgery is associated with postoperative decreases in OSA severity of at least 50% with an average improvement of 85%. Phase II surgeries have been demonstrated to be significantly more effective in treating OSA than phase I surgeries.

As many individuals do not respond to a single operative intervention these surgical procedures can be combined to increase treatment success. Upper airway evaluation and with drug-induce sedation (sleep) endoscopy or other imagining tools (e.g. magnetic resonance imaging) offer the ability to increase treatment success and tailor treatments to an individual.

2.1.3.6.4. Weight Loss

Obesity and OSA are related (as discussed in section 2.1.3.4.1 Obesity), particularly in individuals under the age of 60 years. It has been estimated that 50% of moderate to severe OSA in adults is attributable to obesity. The reduction in fat mass accompanying weight loss is thought to decrease OSA through a reduction in neck and abdominal fat mass. By decreasing neck fat, extraluminal pressure on the upper airway is reduced while decreasing abdominal adiposity decreases EELV and improves the potential beneficial effect of caudal traction on the upper airway (see section 2.2.4.5 Lung Volume).

Change in weight has been shown to have a significant effect on OSA severity. A 10% weight gain has been observed to be associated with a 32% increase in AHI, while a 10% weight loss has been shown to be associated with a 26% decrease in AHI (Figure 2.4). Weight loss has also been shown to decrease daytime sleepiness, increase quality of life and decrease the number of oxygen desaturations and decrease upper airway collapsibility.
Weight loss can be achieved by diet modification and lifestyle changes or as a result of bariatric surgery. Diet modification, such as very low calorie diets, in addition to exercise regimes and lifestyles counselling are techniques that are commonly used to promote weight loss. A very low calorie diet followed by lifestyle counselling (for 1 year) has been shown to significantly lower the odds of having OSA at follow-up (odds ratio 0.24, 95% CI 0.08 to 0.72). Isolated physical activity without weight loss may also have a positive effect on OSA without having a significant effect on BMI.

Weight loss achieved by bariatric surgery is also highly effective. Such surgically induced weight loss can result in a significant decrease in OSA severity. Although the remission rate of OSA following bariatric surgery is reported to be as high as 40%, initial improvements in OSA can often be maintained after a year, providing the weight loss is maintained. The mechanism by which this decrease in OSA severity occurs is believed to be a diet-induced decrease in fat deposits, resulting in a decrease in pharyngeal pressure. In the instances where weight loss is not curative it is recommended that weight loss be used as an adjunct treatment for individuals with OSA.
CHAPTER TWO: LITERATURE REVIEW

2.2. UPPER AIRWAY COLLAPSIBILITY

2.2.1. Upper Airway Collapsibility and OSA

Individual predisposition to OSA can be quantified by measurement of UA collapsibility.\textsuperscript{18,20,377-379} Upper airway collapse varies widely across the disease spectrum (viz. healthy to severe OSA) with an increasing degree of upper airway collapsibility associated with greater degrees of flow limitation and disease severity.\textsuperscript{18,380} Accurately quantifying upper airway collapsibility is important to determine disease severity and treatment efficacy. Although is not done routinely in mainstream clinical practices.

2.2.2. Measuring Upper Airway Collapsibility

Upper airway collapsibility can be directly quantified using a number of techniques including: (i) the pharyngeal critical pressure; (ii) the upper airway closing pressure and (iii) negative expiratory pressure technique. Each technique assesses either the anatomical (passive) or the neurogenic (active) properties of the upper airway or a combination of both. Typically these measurements are performed while the subject is asleep. However, some measurements are made while the subject is awake - the assumption being that wake properties of the upper airway translate to sleep. Measurements have also been made during drug-induced sleep and under general anaesthesia - again the assumption is that collapsibility of the upper airway during these states relates to upper airway behaviour during sleep. These techniques are discussed in the following section.

2.2.2.1. Pharyngeal critical pressure

Pharyngeal critical pressure (Pcrit) is a technique commonly used in a research setting to measure upper airway collapsibility. The technique is based on the premise that the upper airway can be characterised as a simple collapsible tube by applying a biological collapsible tube model or Starling resistor model.\textsuperscript{20,21} Under flow-limited conditions inspiratory flow cannot occur until the pressure upstream (at the mouth and nose) of the collapsible segment exceeds the surrounding tissue pressure. Thus under an inspiratory flow-limited state the inspiratory flow is independent of respiratory drive.
Measuring $P_{\text{crit}}$ requires the simultaneous recording of nasal pressure and flow in response to reductions in pressure from a level that is sufficient to abolish the flow limitation. Nasal pressure is intermittently decreased to different pressures, positive and negative, eliciting varying degrees of inspiratory flow limitation. Nasal pressure is plotted against the mid-inspiratory flow of the inspiratory flow-limited breaths, defined by a plateau in flow despite increasing respiratory effort, and a linear regression is fitted. The abscissa at the intercept between the regression line and zero flow is termed $P_{\text{crit}}$. That is the $P_{\text{crit}}$ is the applied nasal pressure at which inspiratory flow is zero (Figure 2.5). A more negative $P_{\text{crit}}$ value is indicative of a less collapsible upper airway while $P_{\text{crit}}$ values closer to atmospheric pressure or above represent a more collapsible upper airway. 

![Figure 2.5](image.png)

**Figure 2.5.** The relationship between nasal mask pressure ($P_{\text{mask}}$) and mid inspiratory flow (Flow) in a collapsible upper airway. For a $P_{\text{mask}}$ lower than the critical pressure of the upper airway ($P_{\text{crit}}$, represented by the red arrow), the airway is collapsed and there is no inspiratory flow (blue squares). As mask pressure increases there is an increase in inspiratory flow with persistent flow limitation (closed circles and solid line). For a $P_{\text{mask}}$ greater than the effective pressure ($P_{\text{eff}}$, represented by the green arrow),
Methods to quantify $P_{\text{crit}}$ have been adapted to assess the relative contribution of the mechanical and neuromuscular properties towards upper airway collapse. The protocol as originally described by Schwartz et al.\textsuperscript{20} involved stepwise decreases in nasal flow starting from a pressure that abolished flow limitation (see Figure 2.6A). These stepwise decreases in nasal pressure are associated with sustained flow limitation over a period of time thereby incorporated a degree of neuromuscular reflex activity. Consequently it is considered to be an ‘active’ protocol,\textsuperscript{381} it was consequently further developed to minimise these neuromuscular reflexes. It was proposed that during short reductions in mask pressure (5 breaths), from a holding pressure sufficient to eliminate flow limitation, neuromuscular activity remained low.\textsuperscript{382-384} This modified technique involving discreet drops in mask pressure is therefore considered a ‘passive’ protocol, and is believed to measure the anatomical properties of the upper airway under relative hypotonia (see Figure 2.6B). However it is notable that even in the early studies, decreases in nasal pressure were associated with increases in EMG\textsubscript{gg} suggesting a relative state of hypotonia rather than a state of atonia.\textsuperscript{385} In 2000, Boudewyns\textsuperscript{386} further investigated the passive $P_{\text{crit}}$ protocol and demonstrated that a steady state is reached at breaths 3 after the applied pressure has been decreased. Calculating $P_{\text{crit}}$ using breath 3 showed that $P_{\text{crit}}$ was significantly higher than when calculated using the previous breaths. This difference in $P_{\text{crit}}$ is most likely a result of breath-by-breath changes in lung volume associated with the reduction in applied pressure, as lung volume takes approximately 2 breaths to stabilise following a decrease in nasal pressure. Changes in lung volume have since been shown to influence $P_{\text{crit}}$ (see section 2.2.4.5 Lung Volume).\textsuperscript{114}

In addition to $P_{\text{crit}}$, resistance upstream from the site of collapse ($R_{\text{us}}$) can be calculated from the reciprocal of the slope of the regression line through nasal pressure and flow for inspiratory flow limited breaths. Resistance upstream from the site of collapse is thought to indicate how easy or difficult it is to completely open the upper airway following partial opening and provides an indication of the dynamic flow properties of the upper airway under flow-limited conditions.\textsuperscript{387,388}
A.

B.
Figure 2.6. Representative mask pressure (Pmask) and flow (Flow) recordings demonstrating (A) the active Pcrit technique and (B) the passive Pcrit technique. In both instances nasal mask pressure (Pmask) sufficient to abolish flow limitation is applied via a nasal mask. When using the abbreviated technique (B) Pmask is decreased in a stepwise fashion every 4-6 breaths (pressure drop indicated with the dashed line) eliciting varying degrees of inspiratory flow limitation (flattening of inspiratory flow profile despite increased respiratory effort - demonstrated by increasing pressure swings in the oesophageal trace (Pes)) with each pressure drop. Following a number of stepwise pressure reductions Pmask is returned to the effective pressure. When using the passive Pcrit technique (A), Pmask is abruptly decreased for 5 breaths to a level eliciting inspiratory flow limitation. Following 5 breaths Pmask is returned to effective pressure (sufficient to abolish flow limitation). This pressure drop protocol is repeated to different pressures eliciting varying degrees of flow limitation.

Pharyngeal critical pressure has been shown to vary along a disease continuum, reflecting the OSA disease severity, from healthy controls (less collapsible upper airway) to severe OSA patients (more collapsible upper airway). Specifically, Pcrit appears to quantitatively distinguish healthy subjects from snorers, obstructive hypopnoea patients and OSA patients with average Pcrits of -13.3 cmH₂O, -6.5 cmH₂O, -1.6 cmH₂O and 2.5 cmH₂O respectively. There is however significant overlap between healthy controls and patients with OSA. Consequently, Pcrit alone is unreliable in predicting OSA severity. This may be because the ‘passive’ Pcrit quantifies mechanical instability while minimising known coexisting factors such as neuromuscular reflexes and EELV. Therefore, Pcrit quantifies the contribution of anatomical factors predisposing to OSA but does not provide information relating to other factors known to contribute to OSA pathogenesis.

Alternatively, the overlap may be due, in part, to the inherent variability of the Pcrit measurement. Upper airway collapsibility is influenced by a number of factors including sleep stage, upper airway muscle activity, EELV and posture (body, jaw and head). In uncontrolled conditions the clinically significant change of
passive $P_{\text{crit}}$ ranges from $\approx 3$ cmH$_2$O to $\approx 4$ cmH$_2$O with the value decreasing to $\approx 1$ cmH$_2$O when measurement conditions are optimised.$^{393,395}$

Determination of $P_{\text{crit}}$ has many technical challenges and therefore is generally reserved for research purposes. Firstly, the technique is labour intensive and requires overnight investigators to be trained in real-time sleep staging and airflow pattern recognition. Secondly, making measurements of $P_{\text{crit}}$ can be problematic due to intrinsic or measurement-induced changes in sleep state. This is of particular concern in individuals with a low arousal threshold and/or in those individuals with more negative $P_{\text{crit}}$ values who require more negative nasal pressures. Kirkness et al.$^{395}$ reported that passive $P_{\text{crit}}$ measurements were able to be obtained in 86% of subjects while active $P_{\text{crit}}$ measurements were able to be obtained in only 48%. The subjects in whom active $P_{\text{crit}}$ measurements were unobtainable tended to be control and/or females subjects presumably requiring more negative nasal pressure than those individuals with OSA. $P_{\text{crit}}$ measurement success rates can be improved with the introduction of agents such as hypnotics or general anaesthesia. Hypnotics such as benzodiazepines have been shown not to affect upper airway collapsibility.$^{396}$ General anaesthesia induces a state of hypotonia with minimal neuromuscular influence, thereby allowing investigation of the upper airway under tightly controlled conditions.$^{397,398}$ Measurements of $P_{\text{crit}}$ made during sleep, in particular during REM sleep, have been shown to be correlated strongly with REM AHI.$^{399}$ However, this relationship between sleep and anaesthesia is based on direct measurements of upper airway collapsibility (i.e. $P_{\text{crit}}$) under anaesthesia and indirect measures of upper airway collapsibility (i.e. AHI) during sleep. To date there have been no studies using direct measures of upper airway collapsibility in the two states in the same individuals.

### 2.2.2.2. Upper airway closing pressure

Upper airway closing pressure ($P_{\text{close}}$) is an alternate method of quantifying upper airway collapsibility. The technique first described 20 years ago by Issa and Sullivan, is defined as the suction pressure at which the pharynx collapses in response to asphyxia.$^{377,378}$
In a fully patent airway nasal pressure (upstream) is synchronous with epiglottic or oesophageal pressure (downstream pressure). However, when the airway obstructs pressure up- and down-stream of the site of collapse differ. $P_{\text{close}}$ is identified as the inflection point where nasal (upstream) pressure no longer tracks epiglottic or oesophageal (downstream) pressure. Performing the measurement ideally requires the subject to be instrumented with epiglottic/oesophageal pressure catheter and a tightly sealed nasal or face mask fitted with the capacity for rapid occlusion of inspiratory and expiratory flow (typically a balloon or other valve) and a pressure transducer. Initially the airway is patent, with or without applied pressure, and the respiratory circuit is then abruptly occluded. This results in breath-by-breath increases in respiratory effort (i.e. more negative downstream pressure as measured by an oesophageal catheter) in response to asphyxia. Initially the pressure-time profile of nasal pressure and inspiratory effort parallel each other. However at a critical pressure the two profiles abruptly diverge - the inflection point of this divergence on the pressure-time profile is indicative of upper airway collapse. The nasal pressure at which the divergence occurs is termed the upper airway closing pressure ($P_{\text{close}}$, Figure 2.7.). Similar to $P_{\text{crit}}$ measurements, a more negative $P_{\text{close}}$ is indicative of a less collapsible upper airway and vice versa.
Airway collapse results from an inability of the upper airway dilator muscles to adequately stabilise the pharynx during inspiratory efforts. Accordingly, the Pclos measurement is considered to be ‘active’ i.e. measuring the net effect of the anatomical properties and the neuromuscular reflexes in response to transient external occlusion of the airway. Two different types of response to collapse have been reported.\textsuperscript{377} A Type I response is the most common and is characterised by upper airway closure only during the inspiratory phase of the respiratory cycle. A Type II response is characterised by upper airway collapse maintained throughout the entire respiratory cycle (i.e. during both inspiration and expiration). A combination of the two types can also occur, with a Type I response being followed by a Type II response. In most patients only one type of response typically occurs however there are reported instances where patients have both types.\textsuperscript{377} It is likely that upper airway surface tension forces are responsible for the two responses. Specifically, difference in surface adhesion forces within the liquid layer lining of the upper airway between occlusions could make the upper airway more or less ‘sticky’ thus influencing what phase of the respiratory cycle the upper airway collapses.\textsuperscript{400}

Pclose can quantitatively distinguish individuals with OSA from those without although there is considerable variation in the measurement across the OSA disease spectrum. Obstructive sleep apnoea subjects are reported to have a Pclose of \( \approx -4 \) cmH\(_2\)O versus snorers \( \approx -6 \) cmH\(_2\)O and healthy controls \( \approx -8 \) cmH\(_2\)O.\textsuperscript{304,377,378} The technique has been used to demonstrate variable collapsibility in different sleep stages\textsuperscript{304,377} and age groups\textsuperscript{151} as well as improvements in response to oral appliance treatment.\textsuperscript{304}
A benefit of this technique, compared to the $P_{\text{crit}}$ technique, is that it is expedient and allows for multiple measurements to be made over a short period of time. The technique critically relies on a leak-free system including between the mask and face as well as the mouth. If this is not achieved the subject is able to inspire through the leak resulting in an inaccurate inflection, this is usually seen as a plateau in pressure at 0 cmH$_2$O (i.e. atmospheric pressure). Sub-atmospheric $P_{\text{close}}$ values are commonly reported even in patients with severe OSA, most likely due to the ‘active’ nature of the measurement. It is possible that the $P_{\text{close}}$ technique tends to overestimate upper airway responses during sleep (underestimates upper airway collapsibility) as these active responses are normally decreased during sleep. An important consideration is that this technique is difficult to administer in subjects with low arousal thresholds as the abrupt nasal occlusion and resulting asphyxia frequently result in arousal before $P_{\text{close}}$ is reached.

2.2.2.3. Negative expiratory pressure

Another technique used to assess upper airway collapsibility is the negative expiratory pressure (NEP) technique. The technique was initially developed to detect flow-limitation in subjects with lung disease.$^{401}$ Subsequently it has been used to examine upper airway collapsibility.$^{402,403}$

Subjects are awake for this measurement and are either seated or supine. The technique involves applying a brief negative pressure ($\approx -5$ cmH$_2$O) at the mouth during early expiration after a control breath. The negative pressure is applied at the mouth during expiration thereby increasing the pressure differential between the alveoli and the upper airway opening. In the presence of upper or lower airway collapse the increase in pressure between alveoli and the pharyngeal airway is less. The NEP application lasts approximately 1.3 seconds or until the EELV of the previous control breath is reached. The flow-volume curve is recorded and compared to that of the previous expiration. The flow-volume curve obtained during NEP is higher than the flow-volume curve of the preceding breath.$^{402,403}$
The technique relies heavily on the quality of the preceding control breath, as upper airway collapsibility is quantified by comparing expiratory flow during NEP to the expiratory portion of the previous breath. A number of alternative analyses have been used including: (i) a quantitative index corresponding to the ratio of the area under the expiratory flow-volume curve between NEP and atmospheric pressure;\(^404\) (ii) the drop of expiratory flow under NEP expressed as percentage change of peak expiratory flow under NEP \(^405\) and more recently (iii) the expired volume at the mouth in the first 0.5 second following NEP \((V,\text{NEP}_{0.5})\).\(^406\) This last method, \(V,\text{NEP}_{0.5}\), is purported to provide an index of the ‘passive’ mechanical properties of the upper airway, as reflex activation of the upper airway dilator muscle does not occur in the first 0.5 seconds following expiration. Consequently, the volume of air expired occurs under passive conditions.\(^403\)

In both healthy controls and sleep disordered breathing subjects the flow-curve obtained during NEP is higher than the flow volume curve of the preceding breath, however the increase in expiratory flow above normal tidal volume is less in snorers and OSAS patients when compared to normal subjects.\(^391,392\) Healthy subjects have a higher \(V,\text{NEP}_{0.5}\) while OSA subjects have a lower \(V,\text{NEP}_{0.5}\).\(^406,407\) The NEP-related quantitative index and the decrease in expiratory flow under NEP are significantly different between controls and sleep disordered breathing subjects particularly when the measurement is made supine.\(^404,405\) Regardless of which measurement is used there appears to be considerable overlap across the spectrum of disease.

While NEP is a simple, quick and non-invasive technique and, as opposed to the Pcrit and Pclose techniques, can be performed while the subject is awake the timing of the application of NEP needs to be tightly controlled. If pressure is applied at end-expiration an EMGgg reflex response can be elicited.\(^86,403\) This EMGgg reflex response can unpredictably affect the area under the curve during the latter part of the expiratory flow/volume curve thus affecting the quantitative index corresponding to the ratio of the area under the expiratory flow-volume curve between NEP and atmospheric pressure. The issue can be minimised by administering the negative pressure at the onset of expiration.\(^403\)
However even if carefully applied throughout expiration, it appears that EMG activity can variably occur. For example, in one study in normal healthy adults intraoral EMG and external surface EMG were used to demonstrate that the negative pressure applied during expiration did not induce reflex upper airway activity. However another study in sixty children reported EMG activity during NEP, particularly at more negative pressures, thus indicating a degree of upper airway neuromuscular activation. It is possible that this variation in EMG response contributes to the considerable overlap in the measurement seen across the disease spectrum.

2.2.2.4. Apnoea Hypopnoea Index

The apnoea hypopnoea index (AHI) is the key metric used in research and clinical practice for defining OSA severity. The ‘gold-standard’ technique to derive AHI is from polysomnography (PSG) whereby sleep is staged and respiratory events are scored and counted. Sleep is staged using electroencephalogram (EEG), left and right electro-oculogram (EOG) and electromyogram (EMG), while respiratory signals such as airflow, nasal pressure and oxygen saturation are used to score respiratory events. The sum of complete cessations of airflow (apnoeas) and reductions of airflow (hypopnoeas) are counted per hour of sleep and define the apnoea hypopnoea index (AHI). The current American Academy of Sleep Medicine criteria for classification of respiratory events defines: an apnoea as a reduction in airflow (measured using a oronasal thermal sensor) of ≥90% lasting for ≥10 seconds; and hypopnoeas a decrease in airflow (measured using a nasal pressure sensor) of ≥30% lasting for ≥10 seconds that is associated with either an oxygen desaturation of 3% or an arousal. Thus the AHI is comprised of two key measures; firstly the apnoea index (AI) which counts the number of periods where there is no flow (inferring the presence complete of upper airway obstruction); and secondly the hypopnoea index (HI) which counts the number of periods of inspiratory flow-limitation (inferring the presence of partial upper airway obstruction).
The AHI is an indirect measure of the net effect of poor anatomy and/or poor neuromuscular control on upper airway collapsibility. A higher AHI is indicative of a more collapsible upper airway, while a lower number indicates a less collapsible upper airway. It is used to clinically stratify OSA severity into the mild (5 to 15 event.hr$^{-1}$), moderate (15 to 30 events.hr$^{-1}$) or severe (>30 events.hr$^{-1}$) category, thus enabling comment of the severity of OSA. However the AHI cannot provide information on the mechanisms underlying the changes in collapsibility or differentiate between anatomical, mechanical and neuromuscular influences.

From 1999 PSG sleep staging was based on Rechtschaffen & Kales$^{409}$ and respiratory scoring based on the “Chicago” criteria.$^{410}$ However, since 2001 there have a number of iterations of the respiratory scoring criteria with most changes relating to the scoring of hypopnoeas. These variations in scoring criteria have led to differences in the scoring criteria being employed between sleep laboratories and considerable inter-site variability in AHI.$^{411-413}$ The greatest effect is seen on classification of mild and moderate OSA, with approximately 25% of patients previously classified as having OSA not being diagnosed as such with the new rules.$^{413}$ Other factors that contribute to AHI variability include: night to night variability (20% of subjects had differences in AHI$>20$ events.hr$^{-1}$);$^{414}$ body posture,$^{415,416}$ alcohol consumption;$^{417,418}$ sleep stage;$^{415,419}$ EELV$^{65,66}$ and upper airway dilator muscle activity.$^{420}$

2.2.2.5. Other techniques

There are several other techniques available to measure upper airway collapsibility including:(i) the analysis of the relationship between upper airway pressure and pharyngeal cross-sectional area;(ii) forced oscillation and (iii) phrenic nerve stimulation (PNS) induced twitch inspiratory flow-limited breaths.

Direct measurement of the compliance of the pharyngeal wall has been used to examine the static properties of the upper airway (slope of the volume to pressure cross-sectional area pressure relationship).$^{53,382,421}$ Upper airway collapsibility can be evaluated by measuring cross-sectional area using endoscopic inspection either during drug-induced or naturally occurring sleep. Mask pressure is decreased at end-expiration for a single breath while viewing the pharynx, the cross sectional area and
pressure in the upper airway at end expiration are measured. The presence or absence of inspiratory flow limitation during the pressure drop is correlated with the slope of the pressure-area relationship i.e. static compliance. By performing these measurements in anaesthetised and paralysed individuals the mechanics of the hypotonic can be measured. These measurements have also been performed during drug-induced and naturally occurring sleep with the application of CPAP used to suppress neuromuscular influences. The genioglossus is presumed to be hypotonic for the first breath following the removal of CPAP. Using this technique, Isono et al. have shown that the relationship between pressure and cross-sectional area is exponential such that the airway becomes more compliant as it narrows and increasing pressure has little effect on cross-sectional area as it approaches maximum.

The pressure-area relationship of a static airway has been compared in those with and without OSA. In those with OSA the airway collapsed at atmospheric pressure whilst in those without OSA negative pressure was required to collapse the airway. In addition maximal airway size was smaller and the slope of the pressure-area relationship was steeper in those with OSA than without. There are however a number of limitations associated with this technique, the first being that the head and neck are typically extended to allow for insertion of the nasoendoscope and visualisation of the pharynx. As head posture is known to effect upper airway collapsibility this could potentially confound the measurement and underestimate collapsibility. Secondly, an exponential relationship describes the dependence of area on pressure such that the slope varies inversely with upper airway pressure i.e. becomes more compliant as it narrows, as lung volume varies systematically with upper airway pressure, and lung volume has been shown to influence the mechanical properties of the upper airway. Finally results of nasoendoscopy are highly dependent on the skills of the proceduralist however such variability can be minimised by using drug induced sleep with inter-rater and test-rest reliability shown to be moderate to good.

The forced oscillation technique (FOT) is an alternative technique used to quantify upper airway collapsibility. Introduced in 1956 the technique has been used for evaluation of respiratory characteristics. FOT is the application of pressure
oscillation, generated by a loud speaker, at a frequency different to that of natural breathing. Flow and pressure are continuously recorded; the relationship between the resulting pressure and flow is called impedance (Zrs) and is dependent on oscillation frequency. Thus FOT allows for a continuous measurement of airway impedance. In a patent airway FOT measures total respiratory system impedance. However during airway narrowing or collapse FOT measures the impedance of the airway segment from the mask to the point of collapse. Upper airway closure can be detected at low frequencies, at approximately 5 Hz, during sleep.\textsuperscript{428-433} Recently FOT has been used as a non-invasive method of assessing upper airway patency in patients with SDB during sleep\textsuperscript{428-432,434,435} and has been incorporated into some automatic CPAP devices to detect airway narrowing/obstruction or patency to enable upwards-or-downwards titration of nasal pressure.\textsuperscript{436,437} The FOT requires the use of a mask to measure flow and can therefore be influenced by mask leak such that impedance is underestimated.

Phrenic nerve stimulation (PNS) has also been used to assess upper airway behaviour. Brief bilateral anterior or cervical magnetic or electrical stimulation of the phrenic nerve generates negative intraluminal pressure ‘twitches’ in the upper airway thus generating a brief negative ‘collapsing’ pressure. Performed during wakefulness, this is achieved by causing diaphragm contractions at end-expiration thus disassociating pharyngeal dilating muscle activity and inspiratory muscle activation enabling assessment of the passive properties of upper airway airflow dynamics. Studies using this technique have noted that maximal inspiratory flow ($V_{\text{max}}$) in awake PNS induced flow limitation is higher in both normal and OSA subjects\textsuperscript{438,439} than that observed during sleep\textsuperscript{20}. Despite this, the technique offers the unique advantage of being able to investigate the properties of a passive upper airway during wakefulness.

### 2.2.3. Comparing measures of upper airway collapsibility

It is well documented that those with OSA have a more collapsible upper airway than those without OSA. Quantifying upper airway collapsibility has been used to elucidate the pathogenesis of OSA which includes both anatomical/mechanical and neuromuscular influences. To date, a number of techniques have been used to quantify upper airway collapsibility, each with potentially differing degrees of anatomical and neuromuscular influence (see previous section 2.2.2 Measuring Upper
Airway Collapsibility). This makes direct comparisons between techniques very challenging. To date, the majority of studies have attempted to relate upper airway collapsibility with AHI, the current clinical metric by which OSA severity is categorised.

2.2.3.1. Comparing Anatomical Measures of Upper Airway Collapsibility

When comparing measures of upper airway collapsibility the strongest relationships should exist between measures that are based on the same neurophysiological state (i.e. predominantly anatomical factors versus neuromuscular factors). The measures which best reflect the anatomical contribution to development of upper airway collapse during sleep are the passive Pcrit technique and the V.NEP technique.

Supine V.NEP\textsubscript{0.5} is significantly lower in patients with OSA as compared with normal subjects and snorers.\textsuperscript{391,392} A significant correlation has been reported between negative pressure induced expiratory flow limitation and OSA severity (measured by AHI and/or the oxygen desaturation index),\textsuperscript{402,405,406,440-443} yet the correlation between AHI and V.NEP\textsubscript{0.5} appears to be stronger in individuals with more severe OSA.\textsuperscript{406,407}

Compared to patients with OSA passive Pcrit tends to be more negative in healthy controls (range -18 cmH\textsubscript{2}O to 2 cmH\textsubscript{2}O vs. range -5 cmH\textsubscript{2}O to 6 cmH\textsubscript{2}O, respectively), although considerable overlap exists.\textsuperscript{94,96,114,146,381,386,395,397,399,444-446} Unfortunately, comparison between studies is difficult due to the large range in BMI, gender, study populations and states under which the measurements were made (e.g. anaesthesia, light sedation, sleep). The only study which has directly compared passive Pcrit and V.NEP to date reports a strong correlation between passive Pcrit and V.NEP\textsubscript{0.5} ($r^2=0.61$, Figure 2.8).\textsuperscript{407} Of interest is that these two measures were performed in different states of consciousness, that is the passive Pcrit was performed during sleep and the V.NEP\textsubscript{0.5} was performed in awake individuals suggesting that measures of passive upper airway collapsibility that influence upper airway patency during sleep may be able to be collected during periods of wake.
As with passive Pcrit, the pressure at which an individual’s airway collapses during general anaesthesia and complete paralysis also varies between individuals with (approximately -4 cmH2O) and without OSA (approximately 1 cmH2O). These values are similar to those measured when using the passive Pcrit technique and have been demonstrated to correlate with OSA severity (ODI and AHI).

2.2.3.2. Comparing Neurogenic Measures of Upper Airway Collapsibility

Other non-anatomic pathophysiologic traits are important contributors to the presence or absence of OSA and its severity. Indeed, one study has estimated that approximately 60% of differences in OSA severity relates to neurogenic factors.

Pclose is higher in those with OSA than those without. However, despite Pclose being a direct measure of upper airway collapse it has not been shown to correlate with AHI. However the lack of correlation between Pclose and AHI may be due to the small number of studies which have used this technique and the small sample sizes involved.

**Figure 2.8.** Linear regression between Pcrit and V.NEP0.5 in normal subjects (open circles), snorers (grey triangles) and patients with OSA (black circles). From Montemurro et al. 407
Data from studies which have examined the relationship between active Pcrit and AHI suggest that active Pcrit is better able to discriminate those with OSA from those without OSA than any other measure, with less overlap in the measurement between the groups. Healthy controls have an active Pcrit between -20cmH₂O to -4cmH₂O while individuals with OSA have a far more positive values ranging from -5cmH₂O to 6cmH₂O with limited overlap between the groups. An active Pcrit of -5 cmH₂O is considered a threshold to distinguish OSA patients from healthy controls.  

2.2.3.3. Phenotyping

Given the variety of factors that can influence the dynamic function of the upper airway it is not surprising that neither the anatomic measures nor neurogenic measures of upper airway collapse alone completely account for the variability in severity of OSA. In addition to the anatomical and neuromuscular traits that influence upper airway collapsibility, differences in arousal threshold and ventilatory control are also known to contribute to OSA. The impact of these factors are not reflected in most of the measurements mentioned above, hence new models and techniques are currently being developed to determine the contribution of these factors - the goal being to deliver targeted therapies on a ‘per patient’ basis according at an individual’s underlying pathophysiology.

Wellman et al. first reported a simplified method of upper airway phenotyping, which was further optimised in 2013, by which four phenotypic traits (anatomical, neurogenic, ventilatory stability and arousal threshold) could be clinically measured over the course of a single overnight study. The study showed the heterogeneous nature of OSA and a large amount of variability in the traits between individuals. Such an observation makes comparing a single trait between individuals with and without OSA problematic, as a trait need not be considered abnormal to contribute to the presence of OSA.

More recently Eckert et al. have proposed a four-point scale termed the PALM scale (an acronym for the four phenotypic traits that are measured, specifically Pcrit, Arousal threshold, Loop gain and Muscle responsiveness) which defines and weights
the relative contributions of these phenotypic traits in the development of OSA. Preliminary data suggests that non-anatomic features play an important role in greater than 50% of patients with OSA.96

These multifactorial ‘phenotyping’ methods, developed recently, require further validation and testing, but appear promising for categorising the phenotypic traits and their contribution towards the development of an individual’s OSA. Furthermore, they may make it possible to tailor therapies to a particular individual thereby potentially increasing treatment success.

2.2.4. Factors That Modify Upper Airway Collapsibility

A number of factors are known, or have the propensity, to influence measures of upper airway collapsibility. These factors include state (awake, NREM & REM sleep and anaesthesia), posture (neck & head, body and jaw), lung volume and the presence of an oesophageal catheter and will be reviewed in the following section.

2.2.4.1. State

The term ‘state’ encompasses wake, sleep (NREM and REM sleep), sedation and general anaesthesia. However for the purpose of this literature review only states in which consciousness is lost, (i.e. sleep, sedation and anaesthesia) will be discussed. The tendency for obstruction during anaesthesia and sleep is related.399 During both sleep and anaesthesia upper airway muscle tone is attenuated as a result of decreased cortical influence and chemoreceptor drive in addition to the modulation of mechanoreceptor reflexes within the upper airway. Such changes predispose the upper airway to collapse, particularly in those with poor upper airway anatomy. The effect that a change in state (loss of consciousness) has on upper airway collapsibility will be discussed in the sections below.

2.2.4.2. Sleep Stage

Sleep stage affects OSA severity, at least in some people. REM sleep is typically associated with the most severe OSA (when loss of muscle tone can be profound) while slow wave sleep associated with the least severe OSA.90,459-461 Ratnavadivel et
al.\textsuperscript{90} reported a progressive reduction in event rates from stage N1 to SWS, with REM sleep at an intermediate level. Compared to stage N2, the REM AHI was approximately 40\% higher while SWS AHI was approximate 50\% less and that this sleep-stage related dependence of respiratory events was present in individuals with and without OSA. Mador et al.\textsuperscript{462} also noted that AHI significantly increased during REM, however they also noted the changes to be more pronounced in those with mild to moderate OSA (AHI < 30 events.hr$^{-1}$).

There are several possible reasons for the sleep-stage dependence of respiratory events, with sleep-stage related changes in neurocompensatory mechanisms and changes in arousal propensity being investigated. Study of state-associated upper airway muscle activity has mainly focused on the genioglossus. Sleep onset is associated with a decrement in genioglossus (most influential upper airway dilator muscle) activity in both individuals with and without OSA, and this decrement in upper airway muscle activity is greatest in those with OSA.\textsuperscript{81,82,463-465} What drives this decrease is unclear although hypotheses included a diminished reflex input to the muscle and/or a loss of respiratory drive itself could also decease genioglossus activation.\textsuperscript{83} Genioglossus muscle activity is further reduced during REM sleep\textsuperscript{36,466,467} and remains so in both adults and children while on therapeutic levels of CPAP.\textsuperscript{383,468}

Another factor that may contribute to the difference in OSA severity between sleep stages relates to arousal characteristics. Ratnavadivel et al.\textsuperscript{469} found upper airway collapsibility to be similar in stage N2 and N3 sleep although the arousal threshold to obstructive stimuli was greater in slow wave sleep than stage N2 sleep. Indeed, increasing the arousal threshold with sedatives to reduce OSA severity has been the focus of a number of investigations.\textsuperscript{470,471} Eckert et al.\textsuperscript{472} have recently shown that eszopiclone successfully raised the arousal threshold and reduced the AHI in OSA patients with the greatest effect seen in those with a low baseline arousal threshold. Similar findings have been reported with trazadone, flurazepam, triazolam and pentobarbital although there remains some uncertainty regarding impact on dilator muscle function, particularly with benzodiazepines is likely to have raised some concerns over sedative use as a therapy for OSA.
Studies using non-AHI measures of upper airway collapsibility show a more variable response to sleep stage with some studies reporting differences in collapsibility between NREM and REM sleep while others have not. For example, Issa and Sullivan in 1984 found that, when using the Pclose technique, the upper was more collapsible during REM sleep than during SWS (-2.4 cmH₂O versus -4.2 cmH₂O respectively) however body posture, a known modifier of upper airway collapsibility, was not controlled. Of note is that a difference of <2 cmH₂O (the average difference observed between OSA subjects and snorers using the Pclose technique) would most likely not be considered clinically relevant.

Studies using the passive Pcrit technique have reported no significant of sleep stage, although most of these studies have limitations. For example, one study concluded that sleep stage had no effect on upper airway collapsibility yet presented data showing a statistically significantly lower passive Pcrit (determined from the 3rd breath during a pressure drop) during REM than NREM sleep. The magnitude of this effect while not reported seems to be in the order of approximately 1.0 cmH₂O, which would not be considered clinically significant (=4.1 cmH₂O). Another study was prone to type II statistical error in its analyses. The lack of reported difference of passive upper airway collapsibility between sleep stages in is not surprising given that it is unlikely that the anatomical properties of the upper airway would change dramatically between sleep stages when confounding factors (i.e. body posture) are controlled.

2.2.4.3. Sedation and General Anaesthesia

Collapse of the upper airway is common during anaesthesia and airway maintenance is a fundamental anaesthetic skill. General anaesthesia is associated with relaxation of the upper airway muscles and susceptibility to upper airway collapse. There is commonality between the factors that predisposed to OSA and obstruction under general anaesthesia; obesity, age, large tongue, craniocervical and mandibular hyoid abnormalities. Furthermore individuals with OSA are prone to difficulties with tracheal intubation and adverse clinical outcomes under general anaesthesia. One retrospective case control study found that OSA was not a risk factor for unplanned admissions or perioperative adverse events although another has
reported a substantial increase in post-operative adverse events in OSA patients when major surgery, specifically hip and knee arthroplasty, was involved.\textsuperscript{482} Notably, high CPAP compliance reduces the rate of serious complications.\textsuperscript{482,483}

A number of studies have quantified upper airway collapsibility during anaesthesia\textsuperscript{23,53,382,397-399,421,444,447,485,486} and two studies have reported a relationship between the propensity for the upper airway to collapse during sleep and upper airway collapsibility during anaesthesia.\textsuperscript{399,444} Anaesthesia represents a ‘worst case’ scenario for the upper airway as the main mechanisms that protect against asphyxiation during sleep (upper airway muscle activity and arousal response) are abolished during general anaesthesia.

Complete paralysis during general anaesthesia allows for the evaluation of a completely passive upper airway. Under these conditions the upper airway closing pressure is approximately -0.2 cmH\textsubscript{2}O to 2.8 cmH\textsubscript{2}O.\textsuperscript{382,449,450} Passive P\textsubscript{crit} during isoflurane anaesthesia also approximates atmospheric pressure but is reported to increase with increasing depth of anaesthesia (-0.2 cmH\textsubscript{2}O at 0.4\% end-tidal isoflurane to 1.1 cmH\textsubscript{2}O at 1.2\% end-tidal isoflurane).\textsuperscript{398} Increasing depth of propofol anaesthesia is also associated with an a linear increase in upper airway collapsibility\textsuperscript{397,477} with disproportionate increases observed near the level at which consciousness is lost. Passive P\textsubscript{crit} values vary greatly under propofol anaesthesia ranging from -20 cmH\textsubscript{2}O to 5 cmH\textsubscript{2}O.\textsuperscript{23,397,477,485} Upper airway collapsibility during midazolam-induced sedation is also dose-dependent, with reported passive P\textsubscript{crit} values between -1.0 cmH\textsubscript{2}O and -8.7 cmH\textsubscript{2}O. Measurements of passive P\textsubscript{crit} during small doses of midazolam sedation (2.4 mg) has been shown to be comparable to P\textsubscript{crit} measured during sleep.\textsuperscript{444} Further, P\textsubscript{crit} during midazolam sedation and natural occurring sleep appear to correlate with AHI in OSA subjects.\textsuperscript{444}

The mechanism considered responsible for dose-dependant increase in collapsibility during anaesthesia is neurogenic. During anaesthesia, profound relaxation of the upper airway dilator muscles occurs as a result of decreased cortical influences and sensitivity together with down regulation of mechanoreceptor input. Upper airway dilator muscle activity decreases in a dose-dependent manner\textsuperscript{397,398,477} but the relationship varies according to the agent used.\textsuperscript{474,487,488} For example, at low doses of
isoflurane EMG is near-absent but rapidly returns with the return of consciousness. In contrast, during stepwise induction of propofol anaesthesia muscle activity is sustained, even elevated in some subjects, until loss of consciousness when it abruptly decreased to minimal levels. Walsh et al. reported, under propofol anaesthesia, EMG to be less than 3% of awake maximum values, significantly less than has been reported during NREM sleep and REM sleep (where tonic and phasic activity was approximately 27% and 50% of maximum and approximately 5% and 20% of maximum, respectively). Other sedative drugs have also been reported to have variable influences on upper airway collapsibility and muscle activity. Recent studies have shown that when comparing muscle activity during sleep, before and after sedative doses of pentobarbital, dilator muscle activity is higher post drug administration. A similar recent finding has been reported for benzodiazepines where local administration induced muscle inhibition whilst systemic administration induced muscle activation. These results are consistent with a number of studies demonstrating no significant effect of benzodiazepines on OSA severity or upper airway collapsibility. However, these data are in conflict with an early case report and study in individuals without OSA which suggested that benzodiazepines are detrimental in those with OSA. Therefore, although further large-scale, systematic investigation is warranted, these data suggest that sedatives, particularly benzodiazepines, may not have the detrimental effects on upper airway muscle activity that have been traditionally believed.

Sedative use (often benzodiazepines such as diazepam and midazolam) for aiding the diagnosis of OSA is increasing with the emergence of drug induced sleep endoscopy. The premise is that patients vulnerable to upper airway collapse can be identified during brief anaesthesia/sedation. Further, by detecting the primary site of collapse patients most likely to benefit from surgical intervention (e.g. UPPP) can be predicted. Indeed such studies have shown that the most common site of upper airway collapse during anaesthesia is the retropalatal region.
Upper airway collapsibility, measured with passive Pcrit, during midazolam sedation has been shown to be similar to Pcrit measured during natural sleep and both relate closely to AHI.\(^{444}\) A similar finding has been reported from passive Pcrit measurements made during general anaesthesia \(^{399}\) although the precise relationship between Pcrit during general anaesthesia and Pcrit during sleep remains to be elucidated. Anaesthesia and sedation offer very controlled conditions in which to study the behaviour of upper airway collapse to interventions in the absence of without change in state which can often confound the measurement of upper airway collapsibility during sleep. Depending on the agent used, studies under anaesthesia can confidently produce passive conditions for measuring upper airway collapsibility.

Sedation and/or anaesthesia offer an ideal condition in which to investigate mechanisms of and influences on upper airway collapsibility. Passive Pcrit measured during sedation and during general anaesthesia have both been shown to correlate with AHI. Passive Pcrit during sedation also correlates with passive Pcrit during sleep. However the relationship between passive Pcrit and anaesthesia and sleep remains to be established.

2.2.4.4. Posture

Traditionally the study of posture and its effect on the upper airway has been limited to whole body posture. However, a number of recent studies have revealed the significant role of head and neck posture, and jaw posture (e.g. mouth opening), on upper airway function.

2.2.4.4.1. Body Posture

Body position has been shown to be an important factor in OSA. Numerous studies report that more than 50% of OSA patients have positional sleep apnoea with their supine AHI being at least twice that of their lateral AHI.\(^{377,459,499}\) Those with mild to moderate OSA are 1.24 and 1.25 times more likely to have positional sleep apnoea than those with severe OSA.\(^{462}\)

Pcrit during supine sleep is significantly increased compared to sleep in the lateral posture.\(^{386,393,473}\) Boudewyns et al.\(^{386}\) reported a 2.9 cmH\(_2\)O reduction in Pcrit in the
lateral posture versus the supine posture and Penzel et al.\textsuperscript{473} reported an effect of body posture on $P_{crit}$ regardless of sleep stage. The effect of whole body elevation has also been examined; an elevation of 30 degrees was associated with a 4.2 cmH\textsubscript{2}O improvement in $P_{crit}$ during sleep and anaesthesia.\textsuperscript{500,501}

These changes in upper airway collapsibility are believed to be primarily mechanical in nature, either due to anatomical upper airway changes or attributable to the effect of changes in lung volume. When in the lateral position the gravitational forces acting on the tongue and other soft tissue structures are alleviated and upper airway dimensions become more favourable.\textsuperscript{449,502} That is, the upper airway adopts a more circular shape in the lateral posture which is more resistant to collapse than the elliptical shape present when in the supine posture.\textsuperscript{394,503} As noted earlier, changes in lung volume relating to body position could also improve upper airway collapsibility (see section 2.2.4.5 Lung Volume).\textsuperscript{61}

While the average change in $P_{crit}$ between lateral and supine postures (irrespective of the degree of neuromuscular input) is in the order of 2.6 cmH\textsubscript{2}O, this is less than the reported difference between snorers and sleep apneic patients (4.1 cmH\textsubscript{2}O)\textsuperscript{18} and the coefficient of repeatability in the supine posture (3.2 cmH\textsubscript{2}O)\textsuperscript{393,395} and therefore would not be considered to be clinically significant. The discrepancy between the effect of body posture on AHI versus the effect of body posture on upper airway collapsibility may be explained by the fact that these studies did not control for head and neck posture thus obfuscating the full effect body posture on upper airway collapsibility.

2.2.4.4.2. Jaw and Head/Neck Posture

Studying the effect of head, neck and jaw posture on upper airway collapsibility is inherently difficult due to the multiple planes of motion each joint has. Specifically, the mandible can open and close and can be displaced anteriorly or posteriorly. While the head can flex, extend, laterally rotate, swivel and elevated around the atlanto-occipital axial joint. A number of studies have identified a significant role for jaw, neck and head position in the maintenance of upper airway patency.
Mouth breathing (typically involving jaw opening) during sleep is a common occurrence and is related to the presence of apnoeic events. In seated or sleeping subjects, mouth opening has been shown to increase upper airway collapsibility by 4 cmH\textsubscript{2}O to 5 cmH\textsubscript{2}O.\textsuperscript{391,505} During propofol sedation fixed jaw position in combination with 6cm of head elevation was associated with a decrease in collapsibility when compared to free-jaw (mouth open) and 6cm of head elevation (-7.1±3.2 cmH\textsubscript{2}O versus -3.0±2.8 cmH\textsubscript{2}O, respectively).\textsuperscript{485,506} Resolution of severe OSA has been reported in a single case study\textsuperscript{507} although a trial of chinstrap use in 26 OSA patients reported no improvement in the majority of patients.\textsuperscript{508} It is possible that those with airway collapse primarily in the retroglossal region are more likely to benefit, although this remains to be investigated.

Mandibular advancement, a common treatment for OSA increases upper airway size\textsuperscript{450,509-511} and reduces upper airway collapsibility during sedation\textsuperscript{512-514} anaesthesia\textsuperscript{515} and sleep.\textsuperscript{512-514} MAS therapy for treatment of OSA is associated with decreases in AHI of approximately 50%\textsuperscript{304,323,327} with around two thirds of OSA patients experiencing clinical benefit using an oral device.\textsuperscript{323,327,516} Despite MAS therapy being an effective treatment across a large range of disease severities, current recommendations state that individuals with severe OSA initially trial CPAP due to its superior efficacy.\textsuperscript{330}

Several mechanisms are thought to be responsible for the beneficial effects of mandibular posture therapy. In the supine posture, due to gravity mouth opening results in anatomical displacement of the mandible in a posterior and caudal direction. This movement results in a reduction of the retroglossal space,\textsuperscript{517} displacement of the hyoid bone\textsuperscript{311} and an increase in the compressive forces of the soft tissue structures surrounding the upper airway.\textsuperscript{391,505} Mandibular advancement may also provide a beneficial neurogenic influence as upper airway muscle activity has been shown to increase with MAS therapy potentially stiffening the upper airway wall protecting against collapse.\textsuperscript{313-315}

Head posture also influences upper airway patency.\textsuperscript{22} Head flexion (chin tucked towards the chest) obstructs the upper airway while head extension (chin lifted away from the chest) reduces upper airway obstruction.\textsuperscript{22} In 1980 Wilson et al.\textsuperscript{516}
demonstrated in infant cadavers that altering head posture between flexion and extension increased and decreased closing pressure respectively, although head rotation had no significant effect. This relationship has since been demonstrated under various conditions; in anaesthetised and paralysed individuals, with OSA, head extension decreases upper airway collapsibility,\textsuperscript{517} as it does in healthy subjects under midazolam sedation\textsuperscript{500} and during propofol anaesthesia.\textsuperscript{23} Head flexion increases collapsibility in anaesthetised and paralysed OSA subjects\textsuperscript{517} and in healthy subjects anaesthetised with propofol.\textsuperscript{23} The effect head extension has on upper airway collapsibility is marked, ranging from 3.5 to 7.4 cmH\textsubscript{2}O.\textsuperscript{23,500,518} The upper end of this range (i.e a change in upper airway collapsibility of 7.4 cmH\textsubscript{2}O) is substantial and would be considered clinically relevant as 7.4 cmH\textsubscript{2}O is greater than the difference reported between disease groups (non-apnoeic snorers and OSA subjects). Head rotation appears to have variable effects on upper airway collapsibility.\textsuperscript{23,500,518}

The effect of head posture on OSA severity is less clear. Two studies have investigated the effect of a pillow claiming to promote head extension and have reported improvement in AHI in those with mild OSA (n=3)\textsuperscript{24,25} compared to during sleep with their usual pillow. The degree of head movement achieved with the use of the pillow was not reported. Another study has reported that a head/jaw brace designed to induce a combination of head extension (5 degrees of extension), prevention of flexion and prevention of downward displacement of the mandible resulted in complete treatment success in 20% (AHI≤10 events.hr\textsuperscript{-1}), compared to 70% with CPAP therapy. The degree of head movement achieved whilst using the brace was not reported. Nevertheless adherence to the head position therapy (brace) was higher than adherence to CPAP therapy (89±23\% and 68±24\%, respectively). The effect of head posture on upper airway collapsibility during sleep is yet to be investigated.

The mechanisms underlying the change in upper airway collapsibility due to associated changes in head posture are thought to be predominantly anatomical in nature. The changes caused by extension and/or elevation of the head may relate to increased longitudinal tracheal traction and therefore stiffening the upper airway, while head flexion may alter extraluminal tissue pressure increasing collapsibility. Early studies on thoracic effects, airway length and neck position were conducted in animal models.
Using isolated canine airways Van De Graaf (1988) demonstrated a significant influence of thoracic caudal traction on upper airway patency. That is, due to the mechanical coupling of the thorax and trachea, increases in thoracic caudal traction in phase with respiration oppose the fluctuations in negative inspiratory pressure and promote airway patency. Subsequent studies in feline and rabbit models confirm these finding, demonstrating that a decrease in passive upper airway collapsibility can be achieved with 1cm of caudal tracheal traction. In contrast head flexion decreases upper airway space and increases extraluminal tissue pressure. 

In summary, these findings illustrate the often significant influences of body, jaw and head/neck posture on upper airway collapsibility. These factors should be considered when assessing upper airway collapsibility and OSA severity.

2.2.4.5. Lung Volume

The influence of lung volume on upper airway patency is well recognised. Higher end expiratory lung volumes (EELV) are associated with an increase in upper airway dimensions and a decrease in upper airway resistance, upper airway collapsibility, AHI, and the CPAP requirement for treatment. To determine the effect of changing lung volume on upper airway function EELV has been manipulated in a variety of ways. Series et al., used negative extrathoracic pressure (poncho) to increase EELV by 500 ml in a single patient with OSA and found AHI to reduce from 25 to 1 events.h⁻¹. Using the same techniques, a subsequent trial of 15 OSA patients reported a significant reduction in the degree of desaturation although event duration was slightly increased (25.3 to 30.5 seconds) and AHI was unchanged (64.5 to 60.7 events.h⁻¹). Using a similar negative/positive extrathoracic pressure technique (iron lung/cuirass) Heinzer et al., showed that an increase in lung volume by 421 ml was associated with a reduction in CPAP requirement by ~ 7 cmH₂O. Conversely, a 567 ml decrease in lung volume was associated in a 6 cmH₂O increased CPAP requirement. The same investigators subsequently investigated whether increases in lung volume (induced with extrathoracic negative pressure) can obviate the need for CPAP and resolve OSA. Increasing lung volume to the level similar to that achieved by effective CPAP was associated with a 40% reduction in AHI. Increasing
Using phrenic nerve stimulation to induce diaphragm contraction and increased lung volume, a recent study has demonstrated that EELV is associated with increased inspiratory flow in a dose-dependent manner such that change in lung volume with phrenic nerve stimulation correlates with change in peak flow.\textsuperscript{121} Together these findings suggest that lung volume is important in the pathogenesis of OSA and increased lung volume is one mechanism by which CPAP improves airway patency.

The potentially confounding effect of method-induced changes in Pcrit on the measurement itself was assessed by Owens et al.\textsuperscript{114} Specifically, the passive Pcrit technique which is commonly used to assess upper airway collapsibility, is associated with concomitant reductions in EELV when CPAP is reduced, thereby potentially confounding the measurement of upper airway collapsibility. Owens et al.\textsuperscript{114} quantified the reduction in EELV associated with each breath within a 5 breath Pcrit pressure drop sequence and reported that the majority of the change in EELV occurred within the first three breaths, providing that the change from holding pressure was no greater than 6 cmH\textsubscript{2}O. Furthermore an approximate increase in EELV by 500 ml was associated with a decrease in Pcrit by approximately 3.5 cmH\textsubscript{2}O with no difference between those with and without OSA. Squier et al.\textsuperscript{117} determined Pcrit under conditions where EELV was held constant during pressure drops with extrathoracic negative pressure. When performed with these isovolume conditions Pcrit was 3.5 cmH\textsubscript{2}O lower than when performed under the conventional Pcrit technique. In addition, a one litre decrease in lung volume was associated with 2 cmH\textsubscript{2}O increase in isovolume Pcrit. These findings highlight the need to considered lung volume changes during the assessment of upper airway mechanics.

A decline in lung volume is likely to contribute to the pathogenesis of OSA in a number of conditions including those involving chest wall neuromuscular deficiencies and central obesity.\textsuperscript{524} Recently, Stadler et al.\textsuperscript{69} demonstrated that a 500 ml decrease in lung volume due to abdominal compression was associated with 0.5 cmH\textsubscript{2}O decrease in upper airway closing pressure suggesting a direct link between central obesity, lung volume and airway collapsibility. The mechanism for the interaction between lung
volume and upper airway patency are believed to relate to longitudinal tracheal traction and extraluminal tissue pressure which have been describe previously (see section 2.2.4.4.2 Jaw and Head/Neck Posture). With lung inflation, the trachea is caudally displaced and stretched which in turn transmits longitudinal tension to the upper airway wall thereby reducing its collapsibility.

The influence of lung volume on upper airway collapsibility is well recognised and is a potentially important contributor to the pathogenesis of OSA. Furthermore, although isolating the effects of lung volume on upper airway collapsibility can be challenging changes in lung volume need to be considered when measuring upper airway collapsibility.

2.2.4.6. Oesophageal catheter

Catheter-based measurements of pressure changes within the pharynx and oesophagus have been widely used to define upper airway function and the magnitude of respiratory effort, respectively. Catheter mounted intraluminal pressure sensors positioned at intervals along the length of the pharynx can define the site of collapse in individuals with OSA\textsuperscript{39} and during PSG, oesophageal pressure is considered the 'gold standard' measurement of respiratory effort. It is an indispensible tool for diagnosing subtle increases in upper airway resistance (as in upper airway resistance syndrome (UARS)),\textsuperscript{29} defining arousal threshold to airway obstruction during sleep,\textsuperscript{151,525} and accurately determining Pcrit.\textsuperscript{20,21}

The catheters used to obtain these measurements are usually small, ranging from 1.9 to 2.7 mm outer diameter.\textsuperscript{23,397,526-530} However, it is possible that the presence of such a catheter in the pharynx could, of itself, influence upper airway function. This could occur in two direct mechanical ways. Firstly, by longitudinally splinting the pharyngeal walls a catheter could decrease its propensity to collapse. Secondly, a catheter could encroach on the pharyngeal lumen, decreased lumen size and increase pharyngeal resistance, with the potential to increase propensity to collapse. The latter possibility would be of particular concern in individuals with OSA who have an already reduced pharyngeal cross-sectional area.\textsuperscript{394} Other potential influences include the effects of
the catheter on mucosal function. For example, increased secretions could alter surface tension.\textsuperscript{400}

To date only two studies have examined the effect of the presence of a catheter in the pharynx on upper airway function. Skatvedt et al.\textsuperscript{526} studied 32 patients undergoing two diagnostic sleep studies for OSA, one with and one without an oesophageal catheter, and reported no difference in the number of apnoeas, hypopnoeas and snoring events between the two nights.\textsuperscript{526} This finding suggests minimal effects of a catheter on upper airway behaviour during sleep. Virkkula et al.\textsuperscript{527} studied 50 patients undergoing an overnight sleep study with an oesophageal catheter and reported increased nasal airway resistance in the ipsilateral nasal passage\textsuperscript{527} but not in overall nasal resistance.

2.3. RATIONALE FOR THE PRESENT STUDIES IN VIEW OF THE LITERATURE

At the time of data collection there were no studies examining the effect the presence of a catheter has on upper airway collapsibility despite it being the ‘gold standard’ measure of respiratory effort. It was therefore the aim of Study 1 (Chapter Three) to determine the effect, if any, of the presence an oesophageal catheter longitudinally spanning the upper airway on upper airway collapsibility.

Study 2 aimed to compare individual airway behaviour during anaesthesia and sleep, with body and head posture standardised. While \(P_{\text{crit}}\) has been used previously in sedated,\textsuperscript{444,531} anaesthetised\textsuperscript{398} and sleeping patients\textsuperscript{18,19} it has never been measured during deep anaesthesia and sleep in the same individual. Thus the aim of Study 2 (Chapter Four) was to examine the relationship between upper airway collapsibility measured using the same metric, namely the passive \(P_{\text{crit}}\), in the same individuals with head and body standardised.
While the effect of head posture on upper airway collapsibility during anaesthesia is known,\textsuperscript{23,485} the effect of head posture on upper airway collapsibility during sleep has not been fully elucidated. Therefore Study 3 (Chapter Five) aimed to determine the effect head posture had on upper airway collapsibility during sleep in individuals with and without OSA.
CHAPTER 3.

Upper Airway Collapsibility: The Effect of the Presence of an Oesophageal Catheter

3.1. FOREWARD

Catheter-based measurement of pressure changes within the pharynx and oesophagus have been widely used to define upper airway function and magnitude of respiratory effort, respectively. The catheters used to obtain these measurements are usually small, ranging from 1.9 to 2.7 mm outer diameter, however it is possible that the presence of such a catheter in the pharynx could, in and of itself, influence upper airway function.

The following study examined whether the presence of an oesophageal catheter affects measures of upper airway collapsibility.
3.2. ABSTRACT

Catheters that traverse the pharynx are often in place during clinical or research evaluations of upper airway function. The purpose of this study was to determine whether the presence of such catheters affects measures of upper airway collapsibility itself. To do so pharyngeal critical closing pressure (Pcrit) and resistance upstream of the site of collapse (Rus) were assessed in 24 propofol anaesthetised subjects (14 men) with and without a multi-sensor oesophageal catheter (external diameter 2.7 mm) in place. Anaesthetic depth and posture were maintained constant throughout each study. Six subjects had polysomnography (PSG) defined obstructive sleep apnoea (OSA) and 18 either did not have OSA or were at low risk of it. Airway patency was maintained with positive airway pressure. At intervals pressure was reduced by varying amounts to induce varying degrees of inspiratory flow limitation. The slope of the pressure flow relationship for flow limited breaths defined Rus. Pcrit was similar with the catheter in and out (-1.5±5.4 cmH2O and -2.2±5.6 cmH2O respectively, p=0.14, n=24). This remained the case both for those with PSG-defined OSA (3.9±2.2 cmH2O and 2.6±1.4 cmH2O, n=6) and those at low risk/without OSA (-3.3±4.9 cmH2O and -3.7±5.6 cmH2O, respectively, n=18). Rus was similar with the catheter in and out (20.0±12.3 cmH2O.ml⁻¹.s and 16.8±10.1 cmH2O.ml⁻¹.s, p=0.22, n=24). In conclusion, the presence of a small catheter traversing the pharynx had no significant effect on upper airway collapsibility, in these anaesthetised subjects, providing reassurance that such measures can reliably be made in their presence.
3.3. INTRODUCTION

Catheter-based measurement of pressure changes within the pharynx and oesophagus have been widely used to define upper airway function and magnitude of respiratory effort, respectively. Catheter mounted intraluminal pressure sensors positioned at intervals along the length of the pharynx can define the site of collapse in individuals with obstructive sleep apnoea (OSA).\textsuperscript{39} During polysomnography (PSG), oesophageal pressure is considered the ‘gold standard’ measurement of respiratory effort. It is an indispensable tool for diagnosing subtly increased upper airway resistance (as in upper airway resistance syndrome (UARS)),\textsuperscript{29} defining arousal threshold to airway obstruction during sleep,\textsuperscript{151,525} and accurately determining pharyngeal critical closing pressure (Pcrit).\textsuperscript{20,21}

The catheters used to obtain these measurements are usually small, ranging from 1.9 to 2.7 mm outer diameter.\textsuperscript{23,397,526-530} However it is possible that the presence of such a catheter in the pharynx could, of itself, influence upper airway function. This could occur in two direct mechanical ways. Firstly, by longitudinally splinting the pharyngeal walls a catheter could decrease its propensity to collapse. Secondly, a catheter could encroach on the pharyngeal lumen, decreased lumen size and increase pharyngeal resistance, with the potential to increase propensity to collapse. The latter possibility would be of particular concern in individuals with OSA who have an already reduced pharyngeal cross-sectional area.\textsuperscript{394} Other potential influences include the effects of the catheter on mucosal function. For example, increased secretions could alter surface tension.\textsuperscript{400}

To date only two studies have examined the effect of the presence of a catheter in the pharynx on upper airway function. Skatvedt et al\textsuperscript{526} studied 32 patients undergoing two diagnostic sleep studies for OSA, one with and one without an oesophageal catheter, and reported no difference in the number of apnoeas, hypopnoeas and snoring events between the two nights.\textsuperscript{526} This finding suggests minimal effects of a catheter on upper airway behaviour during sleep. Virkkula et al.\textsuperscript{527} studied 50 patients undergoing an overnight sleep study with an oesophageal catheter and reported
increased nasal airway resistance in the ipsilateral nasal passage but not in overall nasal resistance.

Upper airway collapsibility can be most directly measured in terms of its critical closing pressure ($P_{\text{crit}}$), the pressure at which the upper airway completely collapses. $P_{\text{crit}}$ is measured by decreasing mask pressure to levels sufficient to induce inspiratory airflow limitation, then examining the relationship between pressure and flow below this threshold to determine: (a) the mask pressure at zero flow ($P_{\text{crit}}$); and (b) the resistance of the segment upstream of the site of collapse ($R_{\text{US}}$) from the reciprocal of slope of the relationship between pressure and flow. To date, no studies have examined the effect of a catheter in the upper airway on either $P_{\text{crit}}$ or $R_{\text{US}}$.

General anaesthesia offers ideal conditions for study of the upper airway as it can be made electromyographically quiescent at clinical anaesthesia levels and abolition of the arousal response removes the problem of state changes induced by the measurement procedures. Furthermore, posture of the jaw, neck and body, which are known to affect upper airway collapsibility, can be tightly controlled under general anaesthesia. In contrast to other approaches, the use of propofol anaesthesia allows spontaneous ventilation to be preserved during these procedures, which is important as the associated fluctuations in intraluminal pressure significantly affect upper airway behaviour. The conditions afforded by study of the upper airway during propofol anaesthesia with spontaneous ventilation make it ideal to define the effect of a catheter on the mechanical function of the human upper airway.

The specific aim of this study was to evaluate the effect of a multi-sensor catheter that traversed the upper airway on its collapsibility and resistance under the strictly controlled conditions of general anaesthesia. We hypothesised that the effects, if present, were likely to be small.
3.4. METHODS

Participants
Subjects were either healthy individuals who had volunteered specifically for this study (n=18) or patient volunteers who were undergoing general anaesthesia for surgery unrelated to the head or neck and were otherwise healthy (n=6). All subjects provided written informed consent prior to participation in the study which was approved by the Human Research Ethics Committee of Sir Charles Gairdner Hospital (Nedlands, Western Australia, Australia).

Of the 24 subjects: 6 were diagnosed as having OSA (AHI>5 events.hr\(^{-1}\)), based on full laboratory-based PSG (E-series, Compumedics, Abbotsford, Victoria, Australia) scored using standard criteria;\(^2\) 6 were diagnosed as being without OSA (AHI<5 events.hr\(^{-1}\)), also based on PSG; and 12 were categorized as being at low risk of OSA, based on the absence of risk factors such as retroglossal, frequent snoring, and whether bed partners had witnessed any cessations in breathing or “choking episodes” during sleep. These latter 2 groups were pooled into a single group (n=18) considered to be “at low risk or without OSA”. Subjects were excluded from the study if they were morbidly obese (Body Mass Index (BMI) >35 kg.m\(^{-2}\)) or had a significant medical history.

Subject Preparation
No premedication was administered. Standard monitoring was applied and a vein cannulated. Anaesthesia was induced with Propofol (Diprivan) administered via a Diprifusor (Astra Zeneca) target-controlled infusion system (Alaris), which calculated effect site concentration on the basis of a three-compartment pharmaokinetic algorithm.\(^{397,533}\) The Bispectral Index Score (BIS) was derived from the frontal electroencephalogram and calculated by the A-2000 BIS® monitor using the BIS® sensor electrodes (Aspect Medical Systems, Newton, MA).

Before initiation of propofol infusion (i.e. while awake) topical lignocaine spray was applied to the nares and posterior-pharynx and a four-sensor pressure transducer catheter (Gaeltec, CTO-4; Dunvegan, Isle of Skye, Scotland) with an outside diameter of 2.7 mm was inserted via the nares into the oesophagus to measure pressures within
the pharynx and oesophagus. One transducer was visually positioned to lie 1 to 2 cm below the soft palate for measurement of oropharyngeal pressure. A transducer 4 cm above the oropharyngeal transducer measured retropalatal pressure while transducers 4 cm and 20 cm below the oropharyngeal transducer measured hypopharyngeal and oesophageal pressures, respectively.

In a subgroup of participants (n=16) two pairs of bipolar intramuscular wire electrodes were inserted percutaneously to measure genioglossus electromyogram (EMGgg) activity, as previously described. Each EMGgg signal was amplified, band-pass filtered (10-3,000 Hz, model 7P3; Grass Instruments, West Warwick, RI), full-wave rectified, and processed with leaky integrators. A time constant of 100ms was applied to yield a moving-time-averaged EMGgg to all EMGgg signals on which later analyses were performed. Maximal EMG activity was obtained by asking subjects to maximally protrude the tongue and perform a series of dry swallows.

Subjects were fitted with a chin strap and a well-sealed nasal mask was applied via which oxygen was delivered with a Bain circuit (fresh gas flow rate ≥10 L.min⁻¹). In 13 subjects, the Bain circuit was connected in series to a bilevel positive pressure source (BiPAP; Respironics, Murrysville, PA). This allowed for a continuous positive airway pressure (CPAP) to be applied using the device’s inspiratory positive airway pressure mode. Also, airway pressure could be abruptly reduced to a preset lower pressure by switching to the ventilator’s expiratory positive airway pressure mode on which this level was set. Alternatively, a preset sub-atmospheric pressure could be rapidly applied by switching to a regulated vacuum source (model VF204P; Fuji Electric Co., Tokyo, Japan). In 11 subjects a custom made device capable of delivering both positive and negative pressure was used (Resmed, Bella Vista, Australia). Airway pressure could be abruptly changed to a preset level, ranging from 20 cmH₂O to -20 cmH₂O by using custom designed software. In all subjects airflow was monitored with a pneumotachograph (either Hewlett Packard 47303A; Waltham, MA or Korr Medical Technologies, Salt Lake City, UT) that had been calibrated with a 3L syringe. A port in the nasal mask enabled measurement of mask pressure by a pressure transducer (model 143PC, Micro Switch; Honeywell, Morristown, NJ), which was calibrated with known pressures prior to subject instrumentation. Once the nasal mask had been
fitted, the mouth was occluded by adhesive tape, the head was placed in a neutral position (Frankfort plane perpendicular to the horizon) on a Shea headrest and maintenance CPAP applied that was sufficient to abolish inspiratory flow limitation. All signals were digitally recorded continuously at 1,000Hz on a PowerLab data acquisition and analysis system (model 16s; ADInstruments, Sydney, Australia).

**Protocol**

Immediately following subject preparation propofol was infused until an anaesthetic depth associated with a BIS ≤ 50 (effect site concentration variable between individuals (range 2.5 to 6.0µg·ml·kg⁻¹)) and stable ventilation was established. Nasal mask pressure was then rapidly reduced (during early expiration) from the maintenance pressure to a lower pressure for five successive breaths (Figure 3.1). Immediately following the fifth breath mask pressure was lowered, for a further five breaths. Mask pressure continued to be decreased over a range of positive and, where necessary, negative pressures to produce variable degrees of inspiratory flow limitation. Each pressure drop sequence lasted approximately between 120 to 240 seconds and included a minimum of three pressure levels in which flow limitation was observed. Immediately following the pressure drop sequence mask pressure was rapidly returned to the maintenance level. The oesophageal pressure catheter was then removed without any postural change or change in anaesthetic depth and, once stable breathing was noted, the pressure drop sequence was repeated.
Immediately after the measurements were completed EMGgg wires were removed and, in the patient volunteers, the nasal mask removed and a laryngeal mask airway (LMA-Classic™; Pacific Medical, Victoria, Australia) inserted in preparation for surgery. In the non-patient volunteers propofol infusion was ceased and the nasal mask left in place until return of consciousness, at which time it was removed.

**Data Analysis**

Upper airway pressure-flow relationships were evaluated as previously described for sleeping and anaesthetised subjects. Briefly, at each level of mask pressure, inspiratory flow and corresponding oesophageal pressure signals were examined. Flow-limited breaths were defined as those in which the inspiratory flow profile plateaued. Inspiratory flow limitation was identified by two methods with the catheter in place: (a) Inspiration was considered to be flow-limited if there was a ≥1
cmH\textsubscript{2}O decrease in oesophageal pressure without a corresponding increase in flow during inspiration\textsuperscript{23,535} and (b) only the shape of the flow profile was used to determine inspiratory flow-limitation.\textsuperscript{21} These analyses were conducted on a separate days with the investigator blinded to the results of the alternate analysis where this had been performed. For each flow-limited breath, the relationship between mid-inspiratory flow and mask pressure were examined.\textsuperscript{21,532} The mean inspiratory flow and mask pressure from the last 3 breaths at each level of mask pressure was calculated from pressure drop sequences with the catheter in and out. A least squares regression equation was calculated for the flow and pressure relationship and solved for upper airway collapsibility (P\textsubscript{crit}, the mask pressure at which flow became zero) (Figure 3.2). Airway resistance upstream (R\textsubscript{us}) to the site of pharyngeal collapse was calculated as the reciprocal of the slope of the regression equation.\textsuperscript{21}

**Figure 3.2.** Pressure-flow relationships from one OSA subject obtained with (circles) and without (squares) the oesophageal catheter in place. Least squares regression equations were calculated for each condition (solid and dashed lines). Mask pressure (P\textsubscript{mask}) at the point of zero flow was defined as the critical closing pressure (P\textsubscript{crit}), being 4.9 and 4.0 cmH\textsubscript{2}O with the catheter in and out, respectively. V\textsubscript{mid} = mid inspiratory flow.
The moving-time averaged EMG was analysed during breaths at the maintenance pressure and when mask pressure was reduced. For each breath tonic activity was defined as the difference between electrical zero and end-expiratory activity while phasic activity was defined as the difference between end-expiratory and peak activity during inspiration. Measurements were expressed as a percentage of the maximal value obtained during voluntary tongue protrusions and swallows.

**Statistical Analysis**

A paired t-test was used to compare differences between Pcrit determined from flow limitation identified from oesophageal pressure versus using the flow profile alone from measurements made while the catheter was in place. The difference in Pcrit and Rus between the catheter in and out conditions for normally distributed data was compared using repeated measures ANOVA. All comparisons between conditions were performed using flow profile to determine flow limitation. A Holm-Sidak post hoc test was used to determine significance when differences were detected. A sample size calculation was made using a change in Pcrit of 3.4cmH2O to define a significant difference \(^{393,395}\) and indicated that 16 subjects were required for an ANOVA to have a desired power of 0.9.

Values are reported as mean±SD for all data unless otherwise stated. A value of \(p<0.05\) was considered significant.
3.5. RESULTS

A total of 24 subjects, 14 males and 10 females, participated in this study. The mean age of the 24 subjects was 39.2±11.6 years and BMI was 25.8±3.8 kg.m\(^{-2}\). Subjects at low risk or without OSA (n=18) were younger (37.1±10.6 years vs. 45.8±13.0 years, \(p<0.05\)) and had lower BMI (45.8±13.0 kg.m\(^{-2}\) vs. 28.0±13.0 kg.m\(^{-2}\), \(p<0.05\)) than those with PSG-defined OSA. The AHI of individuals with PSG-defined OSA was significantly greater than those without OSA (24.0±11.5 events.hr\(^{-1}\) vs. 3.4±1.4 events.hr\(^{-1}\), \(p<0.05\)).

All measurements of upper airway collapsibility with and without the catheter were obtained at a similar level of anaesthesia and similar levels of pharyngeal muscle activity. Specifically, BIS was similar when the catheter was in and out (34.9±9.9 and 35.1±10.2 respectively, \(p=0.8, n=22\)). Tonic and phasic EMG levels were low compared to awake voluntary maximum levels and were similar when the measurements were made with the catheter in and out, being 3.8±3.3% and 4.0±3.4% for tonic EMG, respectively (\(p=0.76, n=16\)) and 10.4±13.8% and 9.7±15.3% for phasic EMG, respectively (\(p=0.64, n=16\)).

**Upper Airway Collapsibility**

From analysis of data obtained when the catheter was in place, P\(_{\text{crit}}\) using oesophageal pressure to define flow limitation was not found to be significantly different to P\(_{\text{crit}}\) using only the flow profile to define flow limitation (-1.3±5.0 cmH\(_2\)O vs. -1.5±5.4 cmH\(_2\)O, respectively, \(p=0.20\)). Results comparing catheter in and out conditions are presented using the same method to define inspiratory flow limitation (shape of flow profile) as oesophageal measurements were not available with the catheter out.

Measurements of P\(_{\text{crit}}\) obtained when the catheter was in and out are shown for each subject in Figure 3.3. For the group, P\(_{\text{crit}}\) was similar with the catheter in and out (-1.5±5.4 cmH\(_2\)O and -2.1±5.6 cmH\(_2\)O, respectively, \(p=0.14, n=24\)). Men and women behaved similarly: in the men (n=14) mean P\(_{\text{crit}}\) with the catheter in and out was -0.2±6.0 cmH\(_2\)O and -0.5±5.7 cmH\(_2\)O, respectively, in the women (n=10) P\(_{\text{crit}}\) with the catheter in and out was -3.3±4.0 cmH\(_2\)O and -4.5±4.8 cmH\(_2\)O, respectively. Similarly,
there was no difference in Pcrit when the catheter was in or out for subjects at low risk/without OSA (-3.3±4.5 cmH₂O and -3.7±5.6 cmH₂O, respectively, n=18) or in subjects with PSG-defined OSA (3.9±2.2 cmH₂O and 2.6±1.4 cmH₂O, respectively, n=6).

The airway pressure required to abolish airflow limitation, the ‘effective pressure’, was similar with the catheter in and out (10.8±3.6 cmH₂O and 10.2±3.4 cmH₂O, respectively, p=0.16, n=24).

**Upstream Resistance**

Measurements of Rus obtained when the catheter was in and out are shown for each subject in Figure 3.4. Rus was similar with the catheter in and out when the group was

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**Figure 3.3.** Effect of an oesophageal catheter on upper airway collapsibility (Pcrit) during propofol anaesthesia. Individual data are shown for n=24; males (closed symbols); females (open symbols); subjects with low risk OSA subjects (circles + solid lines, n=18); subjects with OSA (squares + dashed lines, n=6). Group mean data ± SD are represented by the red symbol and error bars.
considered as a whole (20.0±12.3 cmH₂O.ml⁻¹.s and 16.8±10.1 cmH₂O.ml⁻¹.s, respectively, p=0.22, n=24) or when the group was separated into those at low risk/without OSA (22.4±13.2 cmH₂O.ml⁻¹.s and 19.4±10.4 cmH₂O.ml⁻¹.s, respectively, n = 18) and those with PSG-defined OSA (12.8±3.9 cmH₂O.ml⁻¹.s and 9.0±1.7 cmH₂O.ml⁻¹.s, respectively, n=6). Similarly, there was no difference in Rus in the men (n=14) with the catheter in or out (19.5±12.8 cmH₂O and 15.1±10.2 cmH₂O, respectively), or within the women (n=10) with the catheter in or out (20.7±12.2 cmH₂O and 19.3±9.8 cmH₂O, respectively).

Figure 3.4. Effect of an oesophageal catheter on upper airway upstream resistance (Rau) during propofol anaesthesia. Individual data are shown for n=24; males (closed symbols); females (open symbols); subjects with low risk OSA subjects (circles + solid lines, n=18); subjects with OSA (squares + dashed lines, n=6). Group mean data ± SD are represented by the red symbol and error bars.
3.6. DISCUSSION

This study demonstrates, in subjects with or without OSA, that measurements of the mechanical behaviour of the upper airway are unaffected by the presence of a small (2.7 mm external diameter) catheter that traverses the pharynx. This finding provides reassurance that such catheters can be used to gain valuable information (e.g. respiratory effort, site of collapse) without compromising assessments of upper airway collapsibility itself.

The general anaesthesia model used in the present study provides a powerful platform on which to study human upper airway behaviour as it allows for careful control of muscle activity, state, and posture of the jaw, neck and body, all of which are known to affect upper airway collapsibility. Thus, any observed changes in upper airway collapsibility as a consequence of the presence or absence of an oesophageal catheter can confidently be attributed to the effects of the catheter alone. Of note was that the observed difference in Pcrit between the two conditions of 0.7 cmH2O was not statistically significant, is less than the reported variability of the measurement, and would not be considered clinically significant. These findings suggest that, in traversing the pharynx, the oesophageal catheter does not longitudinally splint the pharyngeal walls or otherwise influence its propensity to collapse. Such findings are consistent with a previous study by Skadvedt et al. demonstrating that OSA severity, as measured by the apnoea-hypopnoea index (AHI), was unaffected by an oesophageal catheter.

Measurement of airway resistance upstream of the site of collapse (Rus) were also unaffected by the presence of an oesophageal catheter. Derived from the inverse of the slope of the pressure-flow relationship, it would be expected that if airway size were significantly affected by the presence of the catheter protruding into the airway lumen then Rus would increase. The small, statistically insignificant difference in Rus between the two conditions when the group is considered as a whole (3.2±2.2 cmH2O.ml⁻¹.s), or when separated into low risk/without OSA (2.9±2.9 cmH2O.ml⁻¹.s) and OSA (3.8±2.3 cmH2O.ml⁻¹.s), argues against such a catheter affecting airway resistance. While this finding differs to that of Virkkula et al. who reported that the
presence of a catheter increased awake nasal airway resistance in the ipsilateral nasal passage, it was notable that total nasal resistance (inclusive of both nasal passages) was not significantly increased in their study.\textsuperscript{527}

Despite there being no change in upper airway collapsibility between the conditions for the group overall some individuals demonstrated variability with a change in Pcrit greater than that which would be considered clinically significant (3.4cmH\(_2\)O)\textsuperscript{393,395} and/or a change in Rus of greater than 10cmH\(_2\)O.ml\(^{-1}\).s. The direction of these changes was not systematically related to whether the catheter was in or out (Figures 3.3 and 3.4). These subjects were carefully examined for any characteristics that could explain their different responses: there were no systematic differences in gender, anthropometric data, AHI, anaesthetic depth (BIS) or muscle activation (all p>0.05) between them and the other subjects. Despite this it is possible, although unlikely, that small changes in jaw position and/or head posture might have occurred when the catheter was removed. Such changes have been previously noted to significantly affect Pcrit.\textsuperscript{23,513}

In the present study upper airway collapsibility was measured by progressively decreasing mask pressure in order to elicit variable degrees of flow limitation.\textsuperscript{20,23,386} If applied during sleep, such a technique would result in significant activation of pharyngeal muscles in response to progressively more flow limitation, progressively greater inspiratory efforts, and a gradual increase in PaCO\(_2\). Such compensatory neuromuscular responses would confound measurement of a ‘passive’ Pcrit during sleep. However we have previously demonstrated that these changes are minimal during propofol anaesthesia, particularly at BIS<50, thus measurements of Pcrit in the present study reflect the response of a relatively passive upper airway.\textsuperscript{23,397,477}

There are several potential limitations of this study. Firstly, it was not possible to randomise the order of measurements with and without the catheter, as insertion of the catheter required participant cooperation. Thus the catheter was always inserted prior to anaesthesia and removed during anaesthesia. Hence the possibility of order bias cannot be excluded, although we believe any such effect to be negligible. Secondly, it is possible that any local effects on airway collapsibility that the catheter
may have induced such as secretions or oedema may not have fully dissipated prior to making the catheter out measurement. We believe such effects would be unlikely due to the low-irritant medical-grade silastic surface of the catheter which can be comfortably worn for 8+hours. Thirdly, because we did not perform full laboratory PSG on all subjects it is possible that some of the 12 subjects categorised as having low risk of OSA may have had OSA. However we believe this to be unlikely as subjects in this group were excluded based on presence of the major known risk factors for OSA. Finally, the findings of the current study are limited to small catheters (external diameter of 2.7 mm or less). It remains unclear how a catheter with a larger external diameter, such as a nasoendoscope, would affect upper airway collapsibility.

In summary, we have demonstrated in a group of anaesthetised adults that the use of a small catheter that traverses the pharynx does not affect upper airway collapsibility. This provides reassurance that such catheters can be used for, or be in place during, assessments of upper airway function, at least in states associated with depressed neuromuscular activity and reflex gain such as general anaesthesia and rapid eye movement sleep without concern that their presence systematically affects the measurements themselves.
3.7. ACKNOWLEDGMENTS

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4.1. FOREWORD

Measuring upper airway collapsibility is inherently difficult to perform during sleep as altering applied pressure often results in measurement-induced arousals. This is not an issue during general anaesthesia, which provides ideal conditions under which to study upper airway collapsibility as arousals are suppressed, muscle activation is minimised and other known modifiers, such as head posture, can be controlled while still maintaining spontaneous ventilation. Given these advantages, there is a case for using anaesthesia to characterise an individual’s upper airway collapsibility. However, it is important to know how such measures equate to those made during sleep. As yet no study has compared upper airway collapsibility during anaesthesia and sleep using same metric.
The following study used the current gold standard measure of upper airway collapsibility, pharyngeal critical pressure (Pcrit), to compare individual airway behaviour in either state, with body and head posture standardised between them.

CHAPTER FOUR: SLEEP VERSUS ANAESTHESIA

4.2. ABSTRACT

Background The propensities for the upper airway to collapse during sleep and anaesthesia are related. Much of our understanding of this relationship has been inferred from indirect measures. The aim of this study was to use a direct measure - upper airway critical closing pressure (Pcrit) – to directly compare degree of upper airway collapsibility in each state. Methods Ten subjects recruited from the general community (8 males, 2 females; mean age 40.4±12.1 years; and body mass index (BMI) 28.5±4.0 kg.m⁻²) were studied. In each subject Pcrit was measured on separate days during propofol anaesthesia and during sleep. Sleep data were obtained in all subjects during non-rapid eye movement (NREM) sleep and in 4 during rapid eye movement (REM) sleep. Results While Pcrit during anaesthesia was linearly related to Pcrit during NREM sleep (r=0.64, n=10, p=0.046) with a similar tendency in REM sleep (r=0.80, n=4, p=0.200), there was an offset in values such that it was significantly greater during anaesthesia than during both NREM sleep (2.2±0.8 vs. -1.9±0.8 cmH2O respectively, p<0.001 (n=10)) and REM sleep (2.2±0.8 vs. -2.0±1.1 cmH2O respectively, p=0.002 (n=4)). Conclusion These results demonstrate that upper airway collapsibility during anaesthesia is directly related to that during sleep. However it is systematically greater during anaesthesia than sleep, suggesting greater vulnerability to upper airway obstruction in that state.
4.3. INTRODUCTION

The tendencies to upper airway obstruction during sleep and anaesthesia are related. In both states the transition to unconsciousness is associated with a decrease in upper airway dilator muscle activity and an increase in pharyngeal collapsibility.\textsuperscript{477,536} The magnitude of loss of activity and increase in collapsibility with this transition appears to be substantial relative to any further change with change in sleep state (transition from non-rapid eye movement (NREM) to rapid eye movement (REM) sleep) or with increased anaesthetic depth.\textsuperscript{393,477} This may reflect how little residual dilator muscle activity remains for further modulation following loss of consciousness.

The degree of collapsibility present when unprotected by dilator muscle activity varies between individuals, depending on anatomy, and with circumstances, such as posture.\textsuperscript{23} A range of possible consequences follow depending on this degree. In some the airway remains patent even under challenging circumstances, such as under the influence of sedating drugs. In others the airway may vibrate (snoring), airflow may be limited or there may be partial or complete obstructions.

Those vulnerable to obstructive consequences during sleep appear to also be vulnerable during anaesthesia, with a general relationship evident between degree of collapsibility in either state.\textsuperscript{399} However, while related, deep sedation and anaesthesia appear to be associated with more profound change in collapsibility than sleep as demonstrated by the high occurrence of airway obstruction in supine anaesthetised subjects (if a mechanical aid to maintain patency is not deployed), including individuals without obstructive sleep apnoea (OSA).\textsuperscript{399} Furthermore, anaesthesia abolishes the arousal responses that protect the sleeping subject from asphyxia in the case of upper airway obstruction.

To date, much of our understanding of the relationship in airway behaviour between sleep and anaesthesia has been inferred (e.g. the relationship between difficult tracheal intubation and OSA)\textsuperscript{478,537} or based on indirect measurements of upper airway collapsibility during sleep and relating them to direct measures of collapsibility during anaesthesia. (e.g. the relationship between the clinical measure of OSA (the
apnoea hypopnoea index (AHI) and upper airway critical closing pressure (Pcrit)). This reflects the difficulty of performing or standardising such direct measures during sleep as these often require lengthy periods of stable airflow. This can be particularly troublesome during REM sleep, which is characterised by unstable flow patterns.

Determining if the relationship between upper airway collapsibility during anaesthesia and sleep could provide useful insights into the forces involved in the maintenance of airway patency. If collapsibility was similar then observations made during brief sedation, such as during drug induced sedation endoscopy, could be directly related to behaviour during sleep. If, on the other hand, the upper airway was more collapsible during anaesthesia than sleep then this would imply that other factors apart from reduction in upper airway muscle activation, which is profound in both states, are involved.

The purpose of this study was to address this lack of direct comparison by using the current gold standard measure of upper airway collapsibility, Pcrit, to compare individual airway behaviour during anaesthesia and sleep, with body and head posture standardised. While Pcrit has been used previously in sedated and sleeping patients, it has never been measured during deep anaesthesia and sleep in the same individual. In addressing this issue we studied volunteers from the general community and from patients attending a sleep clinic to ensure a range of upper airway collapsibility values across the subjects. Based on our previous findings relating Pcrit measurements during anaesthesia to AHI during sleep, referred to above, we hypothesised that: (i) the degree of collapsibility in either state would be related; and (ii) its magnitude would be greater during anaesthesia than during sleep.
4.4. METHODS

Subjects
Subjects were recruited by advertisement from the community or from the hospital sleep clinic. Subjects were excluded if they were morbidly obese (body mass index (BMI) > 35 kg.m\(^{-2}\)) or had a significant medical history. All subjects provided written informed consent prior to participation in the study which was approved by the Human Research Ethics Committee at Sir Charles Gairdner Hospital (Nedlands, Western Australia). This study was registered with the Australian and New Zealand Clinical Trials Registry (ACTRN12611000100998).

Experimental Procedures

Study Design
On separate occasions (each separated by at least 48 hours) subjects underwent: (i) a standard diagnostic sleep study to establish the baseline level of sleep disordered breathing (“diagnostic sleep study”); (ii) a second overnight sleep study to measure upper airway collapsibility during NREM and REM sleep (“research sleep study”); and (iii) a brief daytime study to measure upper airway collapsibility during general anaesthesia (“anaesthesia study”).

Diagnostic Sleep Study
In-laboratory PSG was undertaken at the sleep laboratory at Sir Charles Gairdner Hospital according to American Academy of Sleep Medicine recommendations.\(^{29}\) Data were collected on a computerised data acquisition system (E-series, Compumedics, Abbotsford, Victoria, Australia). Standard criteria were used to determine AHI in each subject and thereby their degree of sleep disordered breathing.\(^{29}\)

Research Sleep Study
Subjects arrived 2 hours before their usual bedtime to be instrumented as described for baseline PSG. Topical lignocaine spray was applied to the nares and posterior-pharynx and a pressure-tipped catheter (Millar MPC-550, Millar Instruments, Houston TX, USA) was inserted via the nares to the level of the epiglottis. Subjects were instrumented for \(P_{crit}\) assessment (see below, Specific Techniques).
Approximately 30 minutes prior to lights out subjects were administered a sedative (10-20mg Temazepam) to aid with sleep-wake transition (n=9). Head and body posture, known modifiers of upper airway collapsibility, were tightly controlled during all measures of upper airway collapsibility. Specifically, subjects were positioned supine with the head in a neutral position (Frankfort plane perpendicular to the horizon) on a modified Shea headrest. An infrared camera enabled visual confirmation of neutral head posture throughout the study. Pcrit measurements were made (see below, Specific Techniques) during periods of stable NREM sleep and, where possible REM sleep.

**Anaesthesia Study**

No premedication was administered. Standard monitoring was applied and a vein cannulated. Subjects were instrumented for Pcrit assessment (see below, Specific Techniques) including application of CPAP administered via a nasal mask with the mouth occluded and head supported in a the neutral posture using a Shea headrest, according to our previously described techniques.\(^23,477\) Topical lignocaine spray was applied to the nares and posterior-pharynx and an oesophageal-pharyngeal pressure transducer catheter (Gaeltec, CTO-4; Dunvegan, Isle of Skye, Scotland) inserted via the nares as previously described.\(^23,539\) Anaesthesia was then induced with propofol (Diprivan, AstraZeneca, Alderley Park, Cheshire, UK) administered via a target-controlled infusion system (Diprifusor, Alaris PK, Cardinal Health, Switzerland).\(^397,533\) Anaesthetic depth was monitored using the bispectral index score (BIS) derived from a frontal electroencephalogram (Aspect Medical Systems, Newton, MA). The propofol infusion rate was adjusted to attain an anaesthetic depth associated with a BIS≤50 (effect site concentration varied between individuals (range 2.5 to 6.0 \(\mu\)g·ml·kg\(^{-1}\)) was established. Pcrit measurements were performed when stable breathing was observed.

**Specific techniques**

**Evaluation of Upper Airway Collapsibility – Pcrit technique**

Briefly, stable breathing was established with a CPAP (“maintenance pressure”)
sufficient to abolish inspiratory flow limitation (the presence of which was recognised by appearance of a plateau in the inspiratory flow profile). Nasal mask pressure (P\text{mask}) was controlled using a custom made device (Resmed, Bella Vista, Australia) capable of delivering both positive and negative pressures. P\text{mask} was reduced from maintenance pressure to a range of positive and, where necessary, negative pressures to induce variable degrees of inspiratory flow limitation over a 5 breath sequence before return to maintenance pressure(Figure 4.1A). A minimum of three pressure drops to levels associated with flow limitation were obtained, with care taken to get close to zero flow with at least one of the drops during this sequence. P\text{crit} was derived from the extrapolation of the linear P\text{mask} - plateau flow rate relationship obtained during these pressure drops to zero flow. P\text{mask} at this point = P\text{crit}. Where multiple pressure drop sequences were used to determine P\text{crit} under a given set of conditions, the average P\text{crit} value was used for analysis. During sleep if a brief arousal occurred when the P\text{mask} was decreased then that pressure level was excluded from the P\text{crit} analysis and the level repeated. However if the subject awoke the entire pressure drop sequence was abandoned and a new sequence initiated after return to sleep and breathing stability.

P\text{mask}, oesophageal/epiglottic pressure and flow were recorded continuously on a specific data acquisition-analysis system (model 16s; ADInstruments, Sydney, Australia) as well as on the sleep data acquisition system (E-series, Compumedics, Abbotsford, Victoria, Australia).
Figure 4.1  A. Polygraph example during anaesthesia from one subject showing a sequence of drops in mask pressure (Pmask) with accompanying decreases in respiratory flow rates. Note the decrease in peak inspiratory flow rates and flattening of the flow profile observed with the flow limitation induced by these changes. Respiratory effort persists as indicated by the negative swings in oesophageal pressure (Pes).  B. The relationship between Pmask and mid inspiratory flow (Flow) during flow limitation induced by varying decreases in Pmask is illustrated here for one subject during sleep (closed circles, Pcrit = 0cmH₂O) and anaesthesia (open circles, Pcrit = 5cmH₂O). Note the linear relationship between Pmask and Flow for these flow limited breaths. The pressure at which this relationship
Data Analysis

Upper airway pressure-flow relationships were evaluated as previously described for
the sample size of 10 subjects was required to detect a clinically significant change in
Pcrit of 3.4 cmH₂O (its coefficient of repeatability)³⁹³,³⁹⁵ (ANOVA with power of 0.8).
Values are reported as mean±SD for all data unless otherwise stated. A value of
\( p < 0.05 \) was considered significant.

Linear mixed models were used to investigate differences in Pcrit measures between
states, after adjusting for AHI. Pairwise comparisons were investigated using a 5%
significance level. Pearson product-moment correlations were performed to
determine if associations existed between upper airway collapsibility measured during
different states. Bland Altman plots were examined for evidence of systematic bias,
the presence of heteroscedasticity, and to identify the limits of agreement of the mean
difference in Pcrit (mean difference ±1.96 SD).
4.5. RESULTS

Subject Characteristics
Thirteen subjects were recruited for the study: two were excluded due to an inability to tolerate a nasal mask during sleep; one was excluded because of recurring arousal whenever the pressure was decreased from the maintenance pressure. Thus data from 10 subjects were analysed (8 males, 2 females; mean age 40.4±12.1 years; and BMI 28.5±4.0 kg.m^{-2}). Inclusion of recruits from the sleep clinic and general community ensured a range of AHI scores (1.3 to 44.0 events.hr^{-1}) with 5 subjects having an AHI >10 events.hr^{-1}. Mean (±SD) AHI for the 10 subjects was 16.6±15.3 events.hr^{-1}.

Upper airway collapsibility
Between 1 and 3 pressure drop sequences to ascertain Pcrit were obtained in each subject during NREM sleep (mean 1.5±0.7 times per subject, n=10). Pcrit was only able to be obtained during REM sleep in 4 subjects, with between 1 and 4 pressure drop sequences obtained (mean 2.0±1.4 measures per subject, n=4). A single pressure drop sequence was obtained in all subjects during general anaesthesia, which was considered adequate given the highly reproducible measurement condition in this state where arousal and posture change are not issues.

Pcrit during both NREM and REM sleep, obtained on the research sleep study, were related to baseline AHI obtained on the diagnostic study (r=0.69, p=0.026, n=10 and r=0.98, p=0.025, n=4, respectively).

Pcrit during anaesthesia and NREM sleep were linearly related (r=0.64, n=10, p=0.046, Figure 4.2A), however the airway was significantly more collapsible during anaesthesia than during NREM sleep (2.2±0.8 and -1.9±0.8 cmH2O, respectively, n=10, p<0.001). The magnitude of difference in Pcrit between anaesthesia and NREM sleep was -4.1±2.5 cmH2O with the lower and upper limits of agreements at -9.1 and 0.9 cmH2O, respectively (Figure 4.2B).
Figure 4.2  A. Linear regression of $P_{\text{crit}}$ measured during anaesthesia versus $P_{\text{crit}}$ measured during NREM sleep ($r^2=0.42$, $p=0.04$) ($n=10$). B. Bland Altman plots displaying the difference between anaesthesia and sleep $P_{\text{crit}}$ measurements. The mean difference (solid line) shows a systematic bias (-4.1±2.5 cmH$_2$O). The limits of agreement (±1.96 SD) are indicated by the dashed lines (lower limit = -9.1 cmH$_2$O; upper limit = 0.9 cmH$_2$O).

$P_{\text{crit}}$ during anaesthesia and REM sleep were linearly related, although the relationship did not reach statistical significance ($r=0.80$, $n=4$, $p=0.200$, Figure 4.3A). The airway was significantly more collapsible during anaesthesia than during REM sleep (2.2±0.8
and -2.0±1.1 cmH₂O, respectively, n=4, p=0.002). The magnitude of difference between the two states was -3.5±2.8 cmH₂O with the lower and upper limits of agreements at -9.1 and 2.1 cmH₂O (Figure 4.3B).

Figure 4.3A. Linear regression of Pcrit measured during anaesthesia versus Pcrit measured during REM sleep (\(r^2=0.64\), p=0.200) (n=4). B. Bland Altman plots displaying the difference between anaesthesia and sleep Pcrit measurements. The mean difference (solid line) shows a systematic bias (-3.5±2.8 cmH₂O). The limits of agreement (±1.96 SD) are indicated by the dashed lines (lower limit = -9.1 cmH₂O; upper limit = 2.1 cmH₂O).
Pcrit during NREM and REM sleep were linearly related ($r=0.97$, $n=4$, $p=0.03$, Figure 4.4A) and upper airway collapsibility was similar between both sleep stages (-1.9±0.8cmH$_2$O versus -2.0±1.1cmH$_2$O, respectively, $n=4$, $p=0.913$). The magnitude of difference between NREM and REM Pcrit was -0.7±1.0cmH$_2$O, with the lower and upper limits of agreement at -2.8 and 1.3cmH$_2$O (Figure 4.4B).

![Figure 4.4A. Linear regression of Pcrit measured during REM sleep versus Pcrit measured during NREM sleep ($r^2=0.94$, $p=0.03$). B. Bland Altman plots displaying the difference between REM and NREM sleep Pcrit measurements. The mean difference (solid line) shows a minimal difference](attachment:image.png)
between the states (-0.7±1.2 cmH2O). The limits of agreement (± 1.96 SD) are indicated by the dashed lines (lower limit = -2.8cmH2O; upper limit = 1.3cmH2O).
4.6. DISCUSSION

This is the first study to directly measure upper airway collapsibility, using the Pcrit technique, in the measurement of Pcrit during both general anaesthesia and sleep allows, for the first time, a direct comparison between the behaviour of the human upper airway during these two states. The study reveals that the magnitude of individual airway collapsibility is correlated between the states, but is systematically greater during anaesthesia than sleep.

Pcrit during anaesthesia and sleep were related, such that individuals with a more collapsible upper airway during anaesthesia also had a more collapsible upper airway during sleep, and vice versa. The nature of this relationship appeared to be relatively unaffected by the stage of sleep, with Pcrit being similar in NREM and REM sleep. While the small number of measurements obtained during REM sleep limits the capacity to make comparisons between these sleep stages, the lack of difference in Pcrit between REM and NREM is consistent with other studies with larger sample sizes.  

Although correlated, Pcrit was systematically greater during anaesthesia than sleep, indicative of a more collapsible airway. Specifically, during anaesthesia Pcrit was approximately 4 cmH\textsubscript{2}O greater than that observed during either NREM sleep (Pcrit values of 2.1±2.2 and -2.0±3.2cmH\textsubscript{2}O, respectively, n=10) or REM sleep (1.6±2.4 and -1.9±4.3cmH\textsubscript{2}O, respectively, n=4). There are several potential mechanisms that could account for this difference including differences in pharyngeal muscle dilator activity, head and/or body posture and lung volume.

We have previously shown that propofol anaesthesia at a level sufficient to decrease BIS<50 is accompanied by marked dilator muscle hypotonia. It is possible, that upper airway muscle activation is less during anaesthesia than sleep, particularly NREM sleep where some persisting skeletal muscle activity is evident. However, residual upper airway muscle activity following sleep onset is relatively little. Furthermore, the Pcrit technique appears, of itself, to induce a hypotonic state in the upper airway, so when applied during sleep should produce similar upper airway
muscle activation conditions to those during anaesthesia. Support for this is given by previous findings by our group and others that \( P_{\text{crit}} \) is similar during NREM and REM sleep, despite REM sleep being accompanied by profound skeletal muscle hypotonia. Thus differences in upper airway muscle activity appear unlikely to explain the difference in collapsibility observed between anaesthesia and sleep in the current study.

Both head posture and body posture can have a profound effect on upper airway collapsibility. Sleeping supine relative to the lateral posture is associated with an increased \( P_{\text{crit}} \) and more apnoeas and hypopnoeas in approximately half of all patients with OSA. During anaesthesia, head extension decreases \( P_{\text{crit}} \) and flexion increases \( P_{\text{crit}} \). It is essential therefore to standardise or account for head and body posture when interpreting and measuring \( P_{\text{crit}} \), as was done in the present study. Specifically, great care was taken to ensure that all measurements during sleep and anaesthesia were made supine and with the head maintained in a neutral position (Frankfort plane perpendicular to horizontal). For this reason it is unlikely that differences in body or head posture explain the differences in \( P_{\text{crit}} \) between anaesthesia and sleep.

Lung volume has been shown to be an important contributing factor to upper airway collapsibility. The mechanism by which lung volume affects upper airway collapsibility is thought to be by longitudinal traction exerted on the upper airway and pressure gradients developed at the thoracic inlet. Both of these are functions of functional residual capacity (FRC), which decreases during both anaesthesia and sleep. For lung volume decrease to explain the differences in \( P_{\text{crit}} \) between anaesthesia and sleep observed in the present study FRC would need to have been lower during anaesthesia than during sleep. This is possible given the dose related relaxant effect of propofol on skeletal muscles, including respiratory and chest wall muscles. While the upper airway becomes profoundly relaxed at transition to unconsciousness in both sleep and anaesthesia such a step change is not so readily apparent in rib cage and diaphragm muscle activity, evidenced, in part, by persistent ventilation beyond it. This leaves the potential for further deactivation with increasing depth of anaesthesia or sleep. This suggestion is supported by the dose-
related decrease in ventilation seen with increasing anaesthetic depth. Indeed deep anaesthesia can induce profound hypoventilation in spontaneously breathing healthy subjects of a degree that is not seen during natural sleep. This suggests anaesthesia has a substantially greater potential depressant effect on activity of respiratory/chest wall muscles than sleep. Given that, besides ventilation, activation of these muscles is responsible, at least in part, for maintenance of FRC, this more profound anaesthesia effect might be expected to be associated with a greater decreases in FRC than seen during sleep, with concordant greater increase in upper airway collapsibility.

Relevant to this possibility, our anaesthetised subjects were maintained at BIS<50 indicative of a substantial sedative effect. However, because we did not directly measure lung volume during either sleep or anaesthesia, this mechanism remains speculative.

There are potential limitations to this study. Firstly, nine of the ten subjects were administered a sedative (10-20mg of Temazepam) to assist with wake-to-sleep transition. While there is evidence to suggest that sedatives may decrease AHI by improving ventilatory stability, upper airway collapsibility does not appear to be significantly influenced by administration of modest oral doses of sedative.93 Consistent with this, the behaviour of the one subject that did not have Temazepam was comparable to those that did. Secondly, the use of topical lignocaine spray to facilitate oesophageal catheter insertion could blunt upper airway mechanoreceptor reflexes. However this effect is likely to be minimal as the spray was applied more than an hour prior to measurements of upper airway collapsibility in every case. Further, lignocaine spray was used in all subjects for both the anaesthesia and sleep studies. Thirdly, the low subject numbers in REM sleep (n=4), a result the well-recognised problem of repeated arousals and unstable breathing patterns when attempting Pcrit measurements in this stage, make it difficult to be definitive about upper airway collapsibility in REM vs. NREM sleep.

In summary, this study shows that the propensities for the upper airway collapse during general anaesthesia and sleep are related but that the upper airway is systematically more collapsible during anaesthesia than sleep. This is relevant to drug induced sedation endoscopy which is widely used to simulate upper airway behaviour.
during sleep in individuals with OSA,\textsuperscript{538} as the states do not appear to be entirely equivalent in respect to upper airway collapsibility. More generally, the findings suggest anaesthesia is a “worst case” scenario for maintenance of upper airway patency. Accordingly, while patients with OSA may be at particular risk, patients with apparently normal upper airway function during sleep are not exempt from obstruction under the influence of anaesthetic and sedative drugs.
4.7. ACKNOWLEDGMENTS

This study work was supported by a National Health and Medical Research Council of Australia Project Grant [No. 572647] and the Australia and New Zealand College of Anaesthetists [No. 11027]. DR Hillman was awarded the Mundipharma Australian and New Zealand College of Anaesthetists Research Fellowship for 2011. KJ Maddison received an Australian Postgraduate Award Scholarship from the Australian Government and Safety Net Top-up Scholarship from The University of Western Australia. PR Eastwood is funded by a National Health and Medical Research Council Senior Research Fellowship [No. 1042341].

The authors would like to thank Adam Benjafield, Jeff Armistead and Glenn Richards from the ResMed Science Center (Australia) for providing the Pcrit machine with which we made our measurements and Chrianna Bharat from the Department of Research at Sir Charles Gairdner Hospital for statistical support.
CHAPTER 5.

Upper Airway Collapsibility: The Effect of Head Posture

5.1. FOREWARD

While body position is recognised as an important factor underlying the severity of OSA and is therefore commonly monitored during diagnostic sleep studies, head posture is not routinely measured or considered during sleep, despite a general acceptance that sleep-related changes in head posture might be an important factor in the development of pharyngeal obstruction. Support for such widespread acceptance can be seen in the plethora of devices and pillows aimed at controlling head posture during sleep which are marketed to decrease snoring or prevent sleep apnoea. However, to date surprisingly few research studies have formally examined the effects of head position on upper airway behaviour during sleep, or on the role of head posture as a treatment modality for OSA.
The following study sought to examine the effect of head posture (flexion, neutral and extension) on upper airway collapsibility in individuals with and without obstructive sleep apnoea (OSA) during sleep and general anaesthesia.

This chapter is in preparation for submission to *Sleep* for consideration for publication: Maddison KJ, Hillman DR, Shepherd KL, Bharat C, Lawther BK, Platt P, Eastwood PR & Walsh JH. Upper Airway Collapsibility during Sleep and Anaesthesia: The Effect of Head Posture.
5.2. ABSTRACT

Study objective: To examine the effect head posture (flexion, neutral and extension) on upper airway collapsibility in individuals with and without obstructive sleep apnoea (OSA) during sleep and general anaesthesia.

Design: Measurements of upper airway collapsibility (Pcrit) were made during NREM sleep and under propofol anaesthesia with the head maintained in the neutral, flexed and extended postures.

Setting: Sleep laboratory and anaesthetic recovery room

Patients or Participants: During sleep: 16 subjects (11 with OSA (apnoea hypopnoea index ≥10), 10 males, aged (mean±SD) 44.1±10.9 years and (AHI) 23.6±17.7events.hr⁻¹. During Anaesthesia: 11 subjects (5 with OSA), 8 males, aged 40.2±11.5years and AHI 15.3±15.1events.hr⁻¹.

Interventions: NA

Methods and Results: During sleep: Pcrit was -0.4±4.0 cmH₂O when the head was in the neutral posture, and was similar when flexed and extended (-0.6±4.0 vs. -0.3±3.4cmH₂O, respectively, p=0.96). During anaesthesia: relative to Pcrit when the head was neutral (1.7±2.5cmH₂O), Pcrit increased with flexion (4.0±2.8cmH₂O, p=0.02) and decreased with extension (-2.3±4.1cmH₂O, p<0.001). Pcrit during sleep (n=16) was significantly less than during anaesthesia (n=11) when the head was flexed (-0.6±2.5 vs. 4.0±2.8cmH₂O, p=0.02) and neutral (-2.1±3.6 vs. 1.7±2.5cmH₂O, p=0.05) but not when extended (-2.1±2.7 vs. -2.3±4.1 cmH₂O, p=0.56). These relationships were similar between the subgroups with and without OSA.

Conclusions: Modest changes in head posture do not have significant effects on upper airway collapsibility during sleep. However, under general anaesthesia head flexion increases upper airway collapsibility and extension decreases it.
5.3. INTRODUCTION

Sleep presents a challenge for the human upper airway, as it is accompanied by a decrease in pharyngeal muscle tone and of reflexes that protect the upper airway from collapse. In patients with obstructive sleep apnoea (OSA), who have anatomically predisposed airways, these changes can result in repetitive episodes of upper airway narrowing and collapse during sleep, particularly in unfavourable circumstances such as when in the supine posture. Indeed, body position is recognised as an important factor underlying the severity of OSA and is therefore commonly monitored during diagnostic sleep studies. In contrast, head posture is not routinely measured or considered during sleep, despite a general acceptance that sleep-related changes in head posture might be an important factor in the development of pharyngeal obstruction. Support for such widespread acceptance can be seen in the plethora of devices and pillows aimed at controlling head posture during sleep which are marketed to decrease snoring or prevent sleep apnoea. However, to date surprisingly few research studies have formally examined the effects of head position on upper airway behaviour during sleep, or on the role of head posture as a treatment modality for OSA.

Kushida and colleagues\textsuperscript{24,25} showed that promotion of head extension during sleep using a specially designed cervical pillow was effective at reducing the severity of OSA in some, but not all of their subjects. It is probable that their inconsistent findings were influenced by not controlling body posture, a known modifier of OSA severity. In 2004, Skinner et al.\textsuperscript{545} studied the effect on mild-moderate OSA of a cervico-mandibular support collar designed to prevent mouth opening and neck flexion. Treatment success was achieved in only 2 of their 10 patients. A more recent study by Lee et al.\textsuperscript{546} concluded that a combination of cervical vertebral support with head extension, lateral body position and scapular support was needed in order to optimally reduce the severity of OSA. The inconsistency in results from studies to date most likely reflects the substantial challenges in measuring the effects on upper airway behaviour of changes in head posture during natural sleep.
These variable responses during sleep contrast with findings from several studies of the effects of head posture during general anaesthesia, which show a consistent, substantial effect of head posture changes on upper airway collapsibility. General anaesthesia can be considered a ‘worst case’ scenario for the upper airway due to the profound pharmacologically-induced depression of pharyngeal muscle tone, upper airway mechanoreceptor reflexes and protective arousal responses. While presenting challenges for clinical management, these properties allow study of the anatomical or mechanical properties of the ‘passive’ human upper airway i.e. in the absence of neuromuscular influences. Several published studies have taken advantage of these properties to show a significant effect of head position on upper airway behaviour. For example, in anaesthetised and paralysed individuals with sleep disordered breathing, Isono and colleagues\textsuperscript{517} showed that head extension significantly increased maximum oropharyngeal airway size and decreased the collapsibility of both the velopharynx and oropharynx (a decreased in upper airway closing pressure, Pclose), while neck flexion significantly decreased maximum oropharyngeal airway size and increased the collapsibility of both the velopharynx and oropharynx (an increase in Pclose).\textsuperscript{517} In healthy subjects sedated with midazolam, Ikeda et al.\textsuperscript{500} showed that head extension significantly decreased the pharyngeal critical closing pressure (Pcrit), indicating decreased collapsibility. Pcrit is a gold-standard measure of upper airway collapsibility that determines the applied pressure at which airflow ceases or the airway occludes.\textsuperscript{21,532} Walsh et al.\textsuperscript{394} also measured Pcrit in healthy individuals during propofol anaesthesia and reported profound increases and decreases in upper airway collapsibility with head flexion and extension, respectively.

Because of the uncertainty of head posture effects during sleep, in contrast to the consistent effects observed during anaesthesia, we undertook this study to determine Pcrit during both sleep and general anaesthesia at different head postures. Further, we sought to obtain these measurements in individuals with and without OSA. Our hope was that by using the same measure in both states, with care to standardise other conditions such as whole body posture and mouth opening we would better determine the role, if any, of neck position in the pathogenesis of OSA. Apart from the therapeutic implications of this information, it has diagnostic relevance, as changes in
head-neck posture could potentially explain considerable variability in occurrence of obstructive events during overnight sleep studies.
5.4. METHODS

Subjects
Potential participants were recruited from the sleep clinic at Sir Charles Gairdner Hospital, by radio advertisement or by advertisement circulated at the University of Western Australia. Subjects were excluded from the study if they were morbidly obese (body mass index (BMI)>35 kg.m\(^{-2}\)) or had a significant medical history. Informed written consent was obtained prior to participation in the study which was approved by the Human Research Ethics Committee of Sir Charles Gairdner Hospital and the University of Western Australia.

Experimental Procedures

Study Design
On separate occasions (each separated by a minimum of 48 hours) subjects underwent: (i) a standard diagnostic sleep study in order to establish the baseline level of sleep disordered breathing (Diagnostic sleep study); (ii) a second overnight sleep study to measure upper airway collapsibility during NREM (Research sleep study); and (iii) a brief daytime study to measure upper airway collapsibility during general anaesthesia (Daytime anaesthesia study).

Diagnostic Sleep Study
In-laboratory polysomnography (PSG) was undertaken at the West Australian Sleep Disorders Research Institute, Sir Charles Gairdner Hospital according to American Academy of Sleep Medicine recommendations\(^{29}\) and measurements collected on a computerised data acquisition system (E-series, Compumedics, Abbotsford, Victoria, Australia). Wake and sleep stages were determined using electroencephalogram, submental electromyogram and left and right electrooculograms. Respiratory events were scored using oxyhemoglobin saturation, airflow via nasal cannula, oronasal thermistor and thoracic and abdominal movements monitored via inductance plethysmography. Body posture was continuously recorded using a piezo position monitor with confirmation via infrared video camera. Presence or absence of OSA was determined using the apnoea hypopnoea index (AHI): subjects were categorised as
having OSA if they had an AHI≥10 events.hr⁻¹ and without OSA if they had an AHI<10 events.hr⁻¹, scored using standard criteria.²⁹

**Research Sleep Study**

Subjects arrived 2 hours before their usual bedtime to be instrumented for standard PSG (as described above, *Diagnostic Sleep Study*). Topical lignocaine spray was applied to the nares and oropharynx and a pressure-tipped catheter (Millar MPC-550, Millar Instruments, Houston TX, USA) inserted via the nares to a level at or distal to the epiglottis. Subjects were also fitted with a nasal mask and pneumotachograph to permit measurement of Pcrit (see below, *Specific Techniques*).

Approximately 30 minutes prior to lights out subjects were administered a sedative (10-20mg, Temazepam, Aspen, Sydney, Australia) to aid with wake-sleep transition (n=14, 2 subjects declined Temazepam). Subjects were positioned in the supine posture. While supine and awake, subjects were asked to move their head into maximal extension then slowly back to a degree of extension in which they thought they would be able to sleep. This process was repeated for flexion. The maximal degree of flexion and extension that was deemed comfortable/tolerable was noted and replicated during sleep (and the subsequent daytime anaesthesia studies).

The head was positioned on a custom-made “U-shaped” pillow, fashioned out of memory foam (Figure 5.1). The lateral sides of the pillow (the arms of the “U”) were designed to minimise lateral rotation of the head. Foam wedges of different heights were positioned under the pillow to allow the head to be maintained in predetermined degrees of extension or flexion. Care was taken to ensure that head movement was predominantly at the atlanto-occipital joint. Further care was taken to ensure that the back of the head (occiput), when resting on the base of the pillow (the cup at the bottom of the “U”), was at the same height as the back, minimising head elevation and/or depression.
Figure 5.1. A photograph of the custom-made “U-shaped” pillow, fashioned out of memory foam. The back of the head (occiput) rests on the base of the pillow (the cup at the bottom of the “U”) and the lateral sides of the pillow (the arms of the “U”) minimise lateral rotation of the head. Foam wedges of different heights were positioned under the pillow to allow the head to be maintained in predetermined degrees of extension or flexion.

Throughout the night repeated measurements of Pcrit were made (see below, Specific Techniques) during periods of stable NREM sleep in each of the three head postures (extension, neutral and flexion), the order of application was randomised. Before performing measures of upper airway collapsibility (see Specific Techniques) head angle was measured and was confirmed prior to changing the head into a different position. An infrared camera enabled visual confirmation of neutral head posture throughout the study.

Daytime Anaesthesia Study

No premedication was administered. Standard monitoring was applied and a vein cannulated. Subjects were instrumented for Pcrit assessment (see below, Specific Techniques) including application of CPAP administered via a nasal mask and pneumotachograph with the mouth occluded and head supported in the neutral posture with a Shea headrest, according to our previously described techniques.\(^\text{23,477}\) Topical lignocaine spray was applied to the nares and oropharynx prior to insertion of a pressure transducer catheter (Gaeltec, CTO-4; Dunvegan, Isle of Skye, Scotland) via the nares into the esophagus as previously described.\(^\text{23,539}\) Anaesthesia was then induced with propofol (Diprivan, AstraZeneca, Alderley Park, Cheshire, United Kingdom) administered via a target-controlled infusion system (Diprifusor, Alaris PK,
Cardinal Health, Switzerland), which calculated effect site concentration on the basis of a three-compartment pharmacokinetic model. Anesthetic depth was monitored using the bispectral index score (BIS) derived from a frontal electroencephalogram and calculated by the A-2000 BIS® monitor using the BIS® sensor electrodes (Aspect Medical Systems, Newton, MA). The propofol infusion rate was adjusted to attain a stable anaesthetic depth associated with a BIS≤50 (effect site concentration was variable between individuals, ranging from 2.5 to 6.0μg·ml·kg⁻¹).

Measurements of Pcrit were obtained with the head in the neutral (the Frankfort plane perpendicular to the horizon), the flexed and extended posture. The degree of head/neck movements achieved during sleep was replicated during anaesthesia. The head was maintained in each posture by one of the experimental team using digital pressure applied to the mentum and vertex. The teeth were held in centric occlusion and care was taken not to exert any pressure on the submental region. As previously described, head flexion and extension were largely restricted to the atlanto-occipital joint, such that occiput continued to rest on the Shea head rest and measured, with a goniometer, as the deviation from the Frankfort plane from neutral. Pcrit measurements were performed when stable breathing was observed.

**Specific techniques**

*Measuring Head Flexion and Extension (Frankfort plane)*

The Frankfort plane was defined as the plane passing through the inferior margin of the orbit (orbitale) and the upper margin of the ear canal (porion, Figure 5.2). The degree of head flexion/extension was assessed by measuring the angle between the Frankfort plane and the horizon. Neutral was defined as 90 degrees (Frankfort plane perpendicular to the horizontal). Flexion was defined as <90 degrees and extension defined as >90 degrees (i.e. 86 degrees = 4 degrees of flexion vs. 93 degrees = 7 degrees of extension). Head angle was directly measured with reference to the horizon using a custom-made protractor placed alongside the subjects’ head.
**FIGURE 5.2.** Schematic diagram indicating the Frankfort plane angle in the flexed (A), neutral (B) and extended (C) posture. The Frankfort plane angle is the angle between the Frankfort plane (plane passing through the inferior margin of the orbit and the upper margin of the ear canal) and the horizon. 

Neural = 90 degrees (B, Frankfort plane perpendicular to the horizon), flexion = <90 degrees (A) and extension = >90 degrees (C).

**Evaluation of Upper Airway Collapsibility – Pcrit technique**

A well-sealed nasal mask was fitted and attached to a custom made device capable of delivering both positive and negative pressure (Resmed, Bella Vista, Australia). Airway pressure could be abruptly changed to a preset level, ranging from 20 cmH\textsubscript{2}O to -20 cmH\textsubscript{2}O using custom designed software. Airflow was monitored with a pneumotachograph (Korr Medical Technologies, Salt Lake City, UT) that had been calibrated with a 3L syringe. A port in the nasal mask enabled measurement of mask pressure by a pressure transducer (model 143PC, Micro Switch; Honeywell, Morristown, NJ), which was calibrated with known pressures prior to subject instrumentation. For all anaesthesia studies a Bain circuit (fresh gas flow rate $\geq 10$ L.min\textsuperscript{-1}) allowed oxygen to be delivered in series with positive/negative airway pressure and the mouth was occluded with adhesive tape prior to measurements.

**Evaluation of Upper Airway Collapsibility – Pcrit technique**

Measures of upper airway collapsibility were obtained as previously described.$^{21,23,399}$ Briefly, stable breathing was established with a CPAP (“maintenance pressure”) sufficient to abolish inspiratory flow limitation (the presence of which was recognised by appearance of a plateau in the inspiratory flow profile).$^{21,384}$ Nasal mask pressure (Pmask) was controlled using a custom made device (Resmed, Bella Vista, Australia) capable of delivering both positive and negative pressures. Pmask was reduced from maintenance pressure to a range of positive and, where necessary, negative pressures to induce variable degrees of inspiratory flow limitation over a 5 breath sequence.
before return to maintenance pressure. A minimum of three pressure drops to levels associated with flow limitation were obtained, with care taken to get close to zero flow with at least one of the drops during this sequence. $P_{\text{crit}}$ was derived from the extrapolation of the linear $P_{\text{mask}}$ - plateau flow rate relationship obtained during these pressure drops to zero flow. $P_{\text{mask}}$ at this point = $P_{\text{crit}}$. Where multiple pressure drop sequences were used to determine $P_{\text{crit}}$ under a given set of conditions, the average $P_{\text{crit}}$ value was used for analysis. During sleep if a brief arousal occurred when the $P_{\text{mask}}$ was decreased then that pressure level was excluded from the $P_{\text{crit}}$ analysis and the level repeated. However if the subject awoke the entire pressure drop sequence was abandoned and a new sequence initiated after return to sleep and breathing stability.

$P_{\text{mask}}$, oesophageal/epiglottic pressure and flow were recorded continuously on a specific data acquisition-analysis system (model 16s; ADInstruments, Sydney, Australia) as well as on the sleep data acquisition system (E-series, Compumedics, Abbotsford, Victoria, Australia).

**Data Analysis**

*Sample Size and Statistical Analyses*

We have previously shown the coefficient of repeatability for measurements of $P_{\text{crit}}$ obtained in the supine posture to be 3.4cmH₂O. The estimated sample size required to detect a change of this magnitude was 10 subjects (ANOVA with power of 0.8). Values are reported as mean±SD for all data unless otherwise stated; p<0.05 was considered statistically significant.

Anthropometric variables between individuals with and without OSA were compared using t-tests. Comparisons of $P_{\text{crit}}$ between each head posture (i.e. neutral, flexion, extension) in individuals with and without OSA were obtained using one-way repeated measures ANOVA. Linear mixed models were used to investigate differences between head positions, and the effect of OSA within each head position after adjusting for BMI, with respect to $P_{\text{crit}}$. Pearson product-movement correlations were performed to assess associations between upper airway collapsibility in the neutral position and change in upper airway collapsibility that occurs with change in head posture.
5.5. RESULTS

Measurements of Pcrit were obtained in 16 subjects during sleep, 11 subjects during general anaesthesia and 8 subjects during both sleep and anaesthesia.

Sleep: Effect of Head Posture on Upper Airway Collapsibility

Twenty-two subjects participated in the sleep studies. Two were excluded from subsequent analyses due to an inability to tolerate a nasal mask during sleep and four were excluded because of recurring arousal from sleep whenever the mask pressure was decreased (such that measurements of Pcrit were unable to be obtained). Thus, data from 16 subjects were analysed (Table 5.1).

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<th>nOSA (n=5)</th>
</tr>
</thead>
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<tr>
<td>Age, years</td>
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<tr>
<td>BMI, kg.m(^{-2})</td>
<td>30.7±2.4*</td>
<td>27.0±2.4</td>
</tr>
<tr>
<td>AHI, events.hr(^{-1})</td>
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<td>3.5±1.5</td>
</tr>
<tr>
<td>NREM AHI, events.hr(^{-1})</td>
<td>32.3±12.9*</td>
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<td>REM AHI, events.hr(^{-1})</td>
<td>30.3±23.1*</td>
<td>2.5±1.7</td>
</tr>
</tbody>
</table>

Values are mean ± SD; OSA, subjects with obstructive sleep apnoea; nOSA, subjects without OSA; N, number of subjects; M, number of males; F, number of females. BMI, body mass index; AHI, apnoea-hypopnoea index; NREM AHI, Non-rapid eye movement AHI; REM AHI, rapid eye movement sleep. *p<0.05 vs. nOSA

Between 2 and 9 Pcrit measurements were obtained in each of the 16 subjects during NREM sleep (mean 4.7±2.2 times per subject). Measurements of upper airway collapsibility were obtained with the head neutral (n=16), flexed to 84.3±2.5 degrees (range 80-88 degrees, n=11) and extended to 96.6±3.0 degrees (range 93-103 degrees, n=14).
During sleep, $P_{\text{crit}}$ was $-0.4 \pm 4.0 \text{cmH}_2\text{O}$ when the head was in the neutral posture, and was similar when flexed and extended ($-0.6 \pm 4.0$, $p=0.36$, vs. $-0.3 \pm 3.4 \text{cmH}_2\text{O}$, $p=0.99$ respectively) (Figure 5.3). $P_{\text{crit}}$ was higher in subjects with (n=11) vs. those without OSA (n=5) in all head postures: neutral ($1.2 \pm 3.5$ vs. $-3.9 \pm 3.0 \text{cmH}_2\text{O}$, $p=0.005$), flexion ($1.4 \pm 3.5$ vs. $-3.4 \pm 3.0 \text{cmH}_2\text{O}$, $p=0.006$) and extension ($0.8 \pm 3.2$ vs. $-3.2 \pm 2.3 \text{cmH}_2\text{O}$, $p=0.023$).

**Figure 5.3.** NREM sleep: changes in upper airway collapsibility ($P_{\text{crit}}$) in each individual when the head was flexed, neutral and extended (n=16). The magnitude of $P_{\text{crit}}$ was not significantly different between head postures. Subjects with OSA (n=11) are represented by closed squares/solid lines and individuals without OSA (n=5) by open circles/dashed lines.

**Anaesthesia: Effect of Head Posture on Upper Airway Collapsibility**

Thirteen subjects participated in the daytime anaesthesia studies. One was excluded from subsequent analyses due to the requirement for a full face mask during the study. One was excluded because of a severe gag reflex and consequent inability to insert the pressure transducer catheter. Thus, data from 11 subjects were analysed (Table 5.2).
Table 5.2. Characteristics of subjects who participated in the daytime anaesthesia study (n=11).

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<td>NREM AHI, events.hr⁻¹</td>
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<td>REM AHI, events.hr⁻¹</td>
<td>30.3±23.0*</td>
<td>3.1±2.3</td>
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</table>

Values are mean ± SD; OSA, subjects with obstructive sleep apnoea; nOSA, subjects without OSA; N, number of subjects; M, number of males; F, number of females. BMI, body mass index; AHI, apnoea-hypopnoea index; NREM AHI, Non-rapid eye movement AHI; REM AHI, rapid eye movement sleep. *p<0.05 vs. nOSA

Measurements of Pcrit were obtained in each of the 11 subjects with the head neutral, flexed to 84.3±2.5 degrees (range 80-86 degrees) and extended to 96.6±3.0 degrees (range 93-100 degrees). The depth of anaesthesia as assessed by BIS, remained constant throughout the study, being 39.1±5.7, 37.7±6.4 and 38.8±9.6 units in the neutral, flexed and extended postures, respectively (p=0.072)

During anaesthesia, relative to Pcrit when the head was neutral (1.7±2.5cmH2O), Pcrit increased with flexion (4.0±2.8cmH2O, p=0.016) and decreased with extension (-2.3±4.1cmH2O, p<0.001) (Figure 5.4). Pcrit was similar in subjects with (n=5) and without OSA (n=6) in all head postures: neutral (2.4±2.3 vs. 0.8±2.4cmH2O, p=0.54), flexion (5.0±3.1 vs. 3.2±2.4cmH2O, p=0.38) and extension (-1.5±3.0 vs. -2.9±5.0cmH2O, p=0.75).
**Figure 5.4.** Anaesthesia: changes in upper airway collapsibility (Pcrit) in each individual when the head was flexed, neutral and extended (n=11). The magnitude of Pcrit was significantly different between head postures. Subjects with OSA (n=5) are represented by closed squares and solid lines and individuals without OSA (n=6) are represented by open circles and dashed lines. *p<0.05

**Sleep versus Anaesthesia: Effect of Head Posture on Upper Airway Collapsibility**

A subgroup of eight subjects participated in both the sleep studies and the daytime anaesthesia studies (Table 5.3). The degree of head flexion and extension was well matched between the sleep and anaesthesia conditions, being 84.4±2.1 and 82.8±2.1 degrees, respectively in head flexion and 94.6±1.0 and 95.6±2.2 degrees, respectively in head extension.
Table 5.3. Characteristics of subjects who participated in both the research sleep study and daytime anaesthesia study (n=8).

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<tr>
<td>REM AHI, events.hr(^{-1})</td>
<td>36.3±26.4*</td>
<td>2.5±1.7</td>
</tr>
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</table>

Values are mean ± SD; OSA, subjects with obstructive sleep apnoea; nOSA, subjects without OSA; N, number of subjects; M, number of males; F, number of females. BMI, body mass index; AHI, apnoea-hypopnoea index; NREM AHI, Non-rapid eye movement AHI; REM AHI, rapid eye movement sleep. *p<0.05 vs. nOSA

During sleep, Pcrit was similar between the neutral, flexed and extended postures, being -2.1±3.6, -1.7±3.8 (p=0.62) and -2.1±2.7cmH\(_2\)O (p=0.68), respectively (Figure 5.5A). During anaesthesia, relative to Pcrit when the head was neutral (1.7±2.1 cmH\(_2\)O), Pcrit increased with flexion (4.2±2.1cmH\(_2\)O, p=0.039) and decreased with extension (-2.3±4.6cmH\(_2\)O, p=0.003) (Figure 5.5B).
Figure 5.5. Changes in upper airway collapsibility (Pcrit) in a subgroup of 8 individual who had Pcrit measured during sleep (A.) and during anaesthesia (B.) when the head was in flexion, neutral and extension (n=8). Subjects with OSA (n=3) are represented by closed squares and solid lines and individuals without OSA (n=5) are represented by open circles and dashed lines. A. During sleep, the magnitude of Pcrit was not significantly different between head postures (n=8). B. During anaesthesia, the magnitude of Pcrit was significantly different between head postures. Relative to Pcrit during sleep, the magnitude of Pcrit during anaesthesia was significantly different between flexion and neutral but not extension. *p<0.05

Relative to measurements obtained during anaesthesia, Pcrit during sleep was less when the head was neutral (1.7±2.1 vs. -2.1±3.6cmH2O, respectively, n=8, p=0.004) and when flexed (5.0±1.4 vs. -0.6±2.5cmH2O, respectively, n=6, p=0.001) but not when extended (-1.0±3.0 vs. -2.1±2.7cmH2O, respectively, n=7, p=0.284) (Figure 5.5).

Similar results were obtained when performing these same analyses in the larger (unmatched) groups. Specifically, Pcrit during sleep (n=16) was significantly less than during anaesthesia (n=11) when the head was flexed (-0.6±2.5 vs. 4.0±2.8cmH2O, p=0.02) and neutral (-2.1±3.6 vs. 1.7±2.5cmH2O, p=0.05) but not when extended (-2.1±2.7 vs. -2.3±4.1cmH2O, p=0.56).
5.6. DISCUSSION

The present study has shown that during NREM sleep head flexion and extension of approximately 6 degrees either side of neutral does not alter upper airway collapsibility. In contrast, during propofol-induced anaesthesia head flexion increased and head extension decreased upper airway collapsibility. These effects were similar in individuals with and without OSA.

An important consideration in interpreting the results of this study is the magnitude of head flexion and extension under which measurements of upper airway collapsibility were obtained. The decision to measure collapsibility when the head was held between 6 and 7 degrees was based on the maximal degree of flexion and extension that subjects perceived that they would be able to sleep in. All participants indicated their reservations about attempting to sleep with the head maintained in maximal extension or flexion.

Although there have been no other studies comparing the effect of head posture during sleep on direct measures of upper airway collapsibility, such as Pcrit, several previous studies have examine the effect of controlling head posture during sleep on AHI, an indirect measure of upper airway collapsibility. Skinner et al.\textsuperscript{545} showed that a cervico-mandible support collar designed to maintain the head in a minimum of 10 degrees of extension resulted in treatment success in only 20% of patients. Notably, the study was terminated prematurely after interim analyses of data from the first 10 subjects showed that the support collar did not achieve clinically important reductions in AHI. Kushida and colleagues\textsuperscript{24,25} used a cervical pillow designed to place the head in 20 degrees of extension and reported that individuals with a less collapsible upper airway (mild OSA) had a decrease in their OSA severity, while those with more collapsible upper airway (severe OSA) did not. These findings contrast with those of the present study, which showed no effect of head posture on upper airway collapsibility, regardless of whether subjects did or did not have OSA. Potential reasons for these different findings include the greater degree of head extension used.
in Kushida’s studies and their failure to control body posture: measurements were made only in the supine posture in the present study.

While it is possible that greater changes in head posture than used in the present study could have changed upper airway collapsibility, such measurements are difficult to obtain given the difficulty in maintaining sleep under such conditions. Hence, alone, head positioning appears limited as a treatment of OSA. However it may have a role in combination with other postural modifications. Such an approach has been reported by Lee et al.\textsuperscript{546} who proposed that a combination of 40 degrees lateral body rotation, cervical support, shoulder support >30mm and head tilting >70mm (extension) to effectively treat OSA.

The lack of effect on upper airway collapsibility of head changes during sleep contrasts with the significant effects observed during general anaesthesia, despite the same Pcrit technique being applied under both conditions and the similarity in magnitudes of extension and flexion being employed. Specifically, during anaesthesia, compared to the neutral head position, 7 degrees of extension decreased upper airway collapsibility while 6 degrees of flexion increased it with an overall difference in Pcrit from extension to flexion of 5.5cm\text{H}_2\text{O}. These findings are consistent with a previous study by our group during propofol anaesthesia that showed a 12.3cm\text{H}_2\text{O} change in Pcrit when moving the head from 20 degrees of extension to 10 degrees of flexion.\textsuperscript{23} They are also consistent with a study by Isono et al.\textsuperscript{517} in anaesthetised and paralysed OSA subjects showing a change in Pcrit from maximal extension to maximal flexion of 4.5cm\text{H}_2\text{O}, and with the results from a study by Ikeda et al.\textsuperscript{500} in healthy males under midazolam sedation which reported that head extension (of unspecified magnitude) resulted in a decrease in Pcrit of 4.3cm\text{H}_2\text{O}. While the direction of change in Pcrit with head extension and flexion is the same for all anaesthesia-based studies performed to date, the variability in magnitude of response between studies is significant and most likely explained by the differences in magnitude of head extension and flexion applied.

The underlying reasons for the marked difference in response of the upper airway to changes in head posture during anaesthesia (a substantial response) and sleep (no response) require consideration. General anaesthesia can be considered a ‘worst case’
scenario for the upper airway due to the profound pharmacologically-induced depression of pharyngeal and other skeletal muscle activity, upper airway mechanoreceptor reflexes and protective arousal responses. While sleep also reduces muscle activation and depresses reflex activity it is likely that these changes are more profound during anaesthesia.

Given that the upper airway musculature is quite relaxed in NREM sleep and profoundly relaxed in REM sleep, differences in its activity are not a satisfactory explanation for the different sleep and anaesthesia behaviours. Furthermore, the Pcrit technique used to determine upper airway collapsibility in both states has been shown to render the upper airway muscles passive.\(^3^{382,384,385}\) It is possible that there is a greater difference between anaesthesia and sleep in the degree of deactivation of muscles of the chest wall, which can be profoundly depressed by anaesthesia.\(^5^{41,542}\) with resultant differences in resting lung volume and on caudal forces applied to the upper airway by virtue of these different lung volumes. Activation of the chest wall muscles are responsible, at least in part, for maintenance of functional residual capacity (FRC).\(^5^{44}\) A decrease in FRC reduces caudal traction on the upper airway, increasing its collapsibility. Several studies have shown a relationship between lung volume and upper airway collapsibility, such that a decrease in lung is associated with an increase in upper airway collapsibility, effected by a decrease in longitudinal forces applied to the upper airway via the trachea,\(^1^{119}\) or by pressure changes at the thoracic inlet,\(^1^{121}\) or by changes in the displacement of the hyoid bone.\(^1^{22}\) A greater degree of depression of chest wall muscle activity during anaesthesia than sleep with consequent greater decrease in FRC and, consequently, caudal traction on the upper airway is a feasible explanation for the overall increased collapsibility seen during anaesthesia than sleep in all head postures. It is also plausible that differences in the degree of ‘coupling’ between lung volume and the upper airway is responsible for the different responses of the upper airway to changes in head posture between the states.

This study has several potential limitations. Firstly, the degree of head flexion and extension was limited to the maximum tolerated while awake, thus it is possible that greater degrees of head movement could affect upper airway collapsibility during
sleep. Secondly, mouth opening\textsuperscript{391,513} and body posture\textsuperscript{386,393,394,473} both have significant effects on upper airway collapsibility. However all measurements during both sleep and anaesthesia were made with the subject lying supine with their mouths closed. During anaesthesia studies the mouth was taped closed and a chin-strap was worn, thus as best we could we ensured similar and stable measurement conditions for each component of the study. During sleep a closed mouth was confirmed by monitoring oral airflow, assuming mouth closure in its absence. However, it is possible that slight mouth opening and change in jaw position could have occurred, thereby affecting upper airway collapsibility. Thirdly, 14 of the 16 subjects were administered an oral sedative (10-20mg, Temazepam, Aspen, Sydney, Australia) to assist with wake-to-sleep transition. While there is evidence to suggest that sedatives may decrease AHI by improving ventilatory stability, upper airway collapsibility does not appear to be significantly influenced by administration of modest doses of oral sedatives.\textsuperscript{393}

In conclusion, modest changes in head posture do not have significant effects on upper airway collapsibility during sleep. However, under general anaesthesia head flexion makes the upper airway more collapsible and extension makes it less so. This latter finding suggests that particular care be applied to head position when performing procedures such as drug induced sedation endoscopy, which is widely used to investigate upper airway behaviour under simulated sleep conditions in individuals with OSA. Differences in resting lung volume are a potential mechanism explaining the different responses of the upper airway to changes in head posture between the two states.
5.7. ACKNOWLEDGMENTS

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This thesis consisted of a series of novel studies investigating upper airway collapsibility utilising two distinct states of human consciousness: sleep and general anaesthesia. The major findings of these studies are as follows: (i) the presence of a small catheter traversing the upper airway does not affect upper airway collapsibility; (ii) individual tendencies to upper airway obstruction during anaesthesia and sleep are directly related but systematically greater during anaesthesia; and (iii) modest changes in head posture do not have significant effects on upper airway collapsibility during sleep but do so during general anaesthesia where flexion increases upper airway collapsibility and extension decreases it. This final chapter reviews these findings, discusses their clinical implications and considers potential future studies.

Chapter Three describes an investigation of the effect of the presence an oesophageal catheter longitudinally traversing the upper airway on upper airway collapsibility itself. This is an important question as measurements of upper airway collapsibility are often undertaken in the presence of such a catheter. While it has been presumed that the
effect would be small (and at the very least consistent amongst individuals) this assumption has never previously been tested. We used the general anaesthesia model of a passive upper airway to examine for this potential confounding effect. The study demonstrated that, indeed, the presence of a small catheter longitudinally traversing the pharynx does not affect upper airway collapsibility. The study was conducted under anaesthesia which is a particularly challenging condition for the upper airway due to its increased collapsibility relative to sleep. For this reason it is highly likely that the results of this study should translate to sleep.

This finding provides reassurance that such catheters can be used for, or can be in situ, during assessments of upper airway function without concern that their presence systematically affects the measurements themselves. However, it is important to note that these findings relate to a relatively small catheter (2.7mm or less) with a relatively soft, silastic surface; the effects on upper airway behaviour of a larger diameter catheter and catheters comprised of different materials remain unknown.

The studies described in Chapters Four and Five investigate the effect of state and head posture on upper airway collapsibility. These chapters examine the factors that alter the balance of forces that maintain upper airway patency. These include upper airway neuromuscular compensatory factors (e.g. upper airway muscle activity), transmural pressure gradients developed during inspiration and changes in mechanical factors (i.e. anatomy). Isono et al. elegantly explained this concept using a schematic model (Figure 6.1) with upper airway intraluminal pressure on one side of a fulcrum and upper airway muscle dilator activity on the other. The fulcrum represents the intrinsic mechanical properties of the upper airway, that is, upper airway anatomy. In this model patency is determined by interaction of the three factors (upper airway neuromuscular activity, upper airway intraluminal pressure and upper airway anatomy). Under the condition of sleep (reduced neuromuscular compensatory factors) when the fulcrum sits to the right of centre (such as in those with anatomical predisposition to collapse (OSA)) the upper airway collapses more easily. However, when the fulcrum sits to the left of centre (as in healthy individuals without OSA) the upper airway is anatomically protected against collapse.
Figure 6.1. Schematic model explaining upper airway (UA) patency. The fulcrum represents upper airway anatomy (intrinsic mechanical properties). UA dilator muscle activity and UA pressure are on either side of the fulcrum. The fulcrum of a patient with OSA is thought to be on the right hand side of normal, that is, their UA anatomy predisposes them to UA collapse during sleep. From Isono et al.53

In Isono’s model neuromuscular compensatory influences are completely eliminated by using a neuromuscular blockade under general anaesthesia - thus the weight on the right hand side of the scale (Figure 6.1) is reduced to zero. When the model is applied to the studies in Chapter Four and Five the application of CPAP, as is required to undertake the passive Pcrit technique, attenuates neuromuscular compensatory activity thereby reducing the weight on the right hand side of the scale to near zero.

The results in Chapter Four demonstrated that the propensities for the upper airway to collapse during general anaesthesia and sleep are related but that the upper airway is
systematically more collapsible under anaesthesia than during sleep, with a $P_{\text{crit}}$ that is approximately 4 cmH$_2$O greater. The proposed mechanism for this difference is anatomical in nature; specifically, a greater state-related decrease in lung volume under anaesthesia resulting in a greater decrease in longitudinal tracheal traction on the upper airway. This decrease in lung volume and concomitant decrease in tracheal traction would have the effect of shifting the fulcrum to the right in Isono’s model (Figure 6.2). These findings are particularly relevant to drug induced sedation (‘sleep’) endoscopy which is widely used to investigate upper airway behaviour under simulated sleep in individuals with OSA, as the states do not appear to be equivalent in respect to upper airway collapsibility. More generally, the findings show that anaesthesia represents a ‘worst case’ scenario for maintenance of upper airway patency, such that individuals without OSA become especially vulnerable to the possibility of upper airway obstruction during anaesthesia.

**Figure 6.2.** Schematic model explaining the difference in upper airway (UA) patency between states (sleep vs. anaesthesia). The fulcrum represents UA anatomy (intrinsic mechanical properties). UA dilator muscle activity and UA pressure are on either side of the fulcrum. There is an imbalance during sleep (A) which is further compounded during anaesthesia (B). Specifically, during anaesthesia the fulcrum will move towards the right hand side (blue fulcrum), due to a state-related decrease in lung volume resulting in a decrease in longitudinal tracheal traction. This will result in increased UA collapsibility.
The study presented in Chapter Five examined the effects of head flexion and extension on upper airway collapsibility during sleep and anaesthesia. During anaesthesia, head posture significantly influenced upper airway collapsibility: head extension decreased collapsibility while head flexion increased it. Thus anaesthesia represents a “worst case” scenario for maintenance of upper airway patency. However, it appears from the findings in Chapter 5 that this scenario can be made ‘even worse’ under the condition of head flexion. The mechanisms underlying these changes are likely a combination of a head flexion-related decrease in both the diameter and surface area of the hypopharyngeal airways (as shown by magnetic resonance images), and an anaesthesia-related decrease in lung volume and consequent loss of longitudinal traction. These changes are represented by Isono’s model. Manipulating head posture alters the position of the anatomical fulcrum with head flexion shifting the fulcrum to the right thus making the airway more collapsible and head extension shifting the fulcrum to the left making the upper airway less collapsible (Figure 6.3). The mechanism for this shift in the anatomical fulcrum is also thought to relate to posture-related changes in anatomy/structure which may protect or predispose the upper airway to collapse, and longitudinal tracheal traction as a result of lengthening and shortening the upper airway with changes head extension and flexion.
Figure 6.3. Schematic model explaining the difference in upper airway (UA) patency between different head postures (flexion, neutral and extension) during anaesthesia. The fulcrum represents UA anatomy (intrinsic mechanical properties). UA dilator muscle activity and UA pressure are on either side of the fulcrum. During anaesthesia, relative to when the head is neutral (B; blue fulcrum), the fulcrum is thought to move towards the right hand side (A; red fulcrum) when the head is flexed and to the left hand side (C; purple fulcrum) when the head is extended due to mechanically manipulated changes in caudal tracheal traction. Therefore, relative to UA collapsibility when the head is neutral, head flexion in increases UA collapsibility and head extension decreases UA collapsibility.

It was notable that the changes in collapsibility with head posture change during anaesthesia were not seen during sleep. The most likely reasons for this relate to other factors acting on the fulcrum during sleep (e.g. changes in extraluminal tissue pressure, minor changes in jaw posture, upper airway activation of other dilator muscles, rostral fluid shift). These factors may result in a push-pull effect which negates any influences of head posture, particularly at the relatively small degrees of movement (±6 degrees of movement) that were achieved in this study.

These findings raise many mechanistic questions, which can only be answered with further experiments. For example, an obvious ‘next’ study would be to investigate the effect of altering lung volume on upper airway collapsibility under different states of consciousness. Firstly, measuring and quantifying lung volume and Pcrit in the same individual during anaesthesia and sleep could establish the relative effect of each state
on functional residual capacity and its effect on upper airway collapsibility. Secondly, manipulating lung volume using a head-out rigid shell attached to a negative pressure source to change extrathoracic pressure during anaesthesia while measuring $P_{\text{crit}}$ could allow direct evaluation of the influence of lung volume change on upper airway collapsibility. Such a study would also benefit from measures of muscle activity, including genioglossus and other upper airway dilator muscles to identify the contribution of these factors relative to lung volume on upper airway collapsibility.

Finally, while Chapter Five demonstrated that changes in head posture of ±6 degrees relative to neutral had no effect on upper airway collapsibility during sleep, an investigation of the effect of larger changes in head extension (e.g. ±15 degrees relative to neutral) on upper airway collapsibility during sleep could show therapeutic benefits in individuals with OSA. It is possible that some individuals could sleep with greater degrees of head extension, or become acclimated to such changes over time. Furthermore, the interaction between varying head postures and body posture merits further investigation, particularly as varying combinations of these postures occur during normal sleep. A focus of the studies presented in this thesis was on the behaviour of the passive upper airway. Measurement of active measures of collapsibility during sleep (i.e. upper airway collapsibility in the presence of muscle activity) could help distinguish anatomical from neuromuscular effects in this state.

The studies described in this thesis were very demanding from both a technical perspective (e.g. a large team approach was required to safely undertake the anaesthesia studies, maintaining sleep while measuring $P_{\text{crit}}$ was difficult — particularly during head flexion) and from the perspective of the participant (e.g. agreeing to participate in multiple studies on separate days, sleeping supine for a whole night while head posture and nasal mask pressure were manipulated). While the sample sizes are in general larger than most previous comparable studies, they were necessarily small given the complex physiological nature of the studies.

A patent upper airway is essential for human life. The findings presented in this thesis provide novel insights into the behaviour of the human upper airway during general anaesthesia and sleep. They highlight the complex relationships between anatomy
and neuromuscular factors that contribute to maintenance of upper airway patency. Still, we have much to learn.
Appendix A: Publications


Appendix B: Conference Abstracts and Presentations

Published conference abstracts (presentations):


Published conference abstracts (co-author):


Research Presentations:


2. Australian Society of Medical Research, Research Week. Upper Airway Collapsibility During Anaesthesia and Sleep in Patients with and without OSA. 4th June 2014.

3. Young Investigator Session. Combined Thoracic Society of Australia and New Zealand &

5. **Upper Airway Symposium.** The influence of end-expiratory lung volume on upper airway collapsibility. Pullman Resort, Bunker Bay, Dunsborough, Western Australia. 20\textsuperscript{th}-22\textsuperscript{nd} February 2013.

6. **Australian Society of Medical Research, Research Week.** The Effect of Head Posture on Upper Airway Collapsibility During Sleep. Edith Cowen University. 5\textsuperscript{th} June 2013.

7. **UWA School of Anatomy and Human Biology Annual Student Expo** Upper Airway Collapsibility during Anaesthesia and Sleep in Patients with and without OSA. University of Western Australia. 16\textsuperscript{th} July 2013.

8. **Australasian Sleep Association Annual Scientific Meeting.** Upper Airway Collapsibility During Anaesthesia and Sleep in Patients with and without OSA. Brisbane QLD, 17\textsuperscript{th} – 19\textsuperscript{th} October 2013.

9. **Upper Airway Symposium.** Upper Airway Collapsibility During Sleep and General Anaesthesia: The effect of head posture. Victor Harbor, South Australia, 8\textsuperscript{th} – 10\textsuperscript{th} February 2012.

10. **UWA School of Anatomy and Human Biology Annual Student Expo.** Upper Airway Collapsibility During Sleep and General Anaesthesia: The effect of head posture. University of Western Australia. 26\textsuperscript{th} July 2012.

11. **UWA School of Anatomy and Human Biology Annual Student Expo.** Collapsibility of the human upper airway: The effect of head posture on upper airway collapsibility in patients with and without obstructive sleep apnoea. University of Western Australia. 27\textsuperscript{th} July 2011.

12. **Department of Pulmonary Physiology & Sleep Research Meeting.** The Effect of Head Posture on Upper Airway Collapsibility During Sleep. Sir Charles Gairdner Hospital. 16\textsuperscript{th} December 2010.

13. **UWA School of Anatomy and Human Biology Annual Student Expo.** Collapsibility of the human upper airway: Relationships between sleep, sedation, anaesthesia and head posture. 20\textsuperscript{th} July 2010.

14. **Upper Airway Symposium.** The Effect of Head Posture on Upper Airway Collapsibility During Sleep. Port Stephens, NSW, 8\textsuperscript{th}-10\textsuperscript{th} Feb, 2010.
Community Presentations:

1. *Perth Modern Year 10 Science Students.* Sleep Science – Obstructive Sleep Apnoea. 12th December 2011

2. *Perth Modern Year 10 Science Students.* Sleep Science – Obstructive Sleep Apnoea. 27th November 2010
Appendix C: Awards

Young Investigator Award, Best presentation, Combined Thoracic Society of Australia and New Zealand & ANZSRS, WA Branch Annual Scientific Meeting, October 2014.

Travel Award. Comparing Upper Airway Collapsibility During Anaesthesia and NREM Sleep in Patients With and Without OSA Australasian Sleep Association Annual Scientific Meeting, Brisbane. October 2013

ASMR Medical Research Week Symposium. Industry Sponsor Award, Australian Society of Medical Research, Research Week, June 2013.

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