Upper airway physiology and respiratory phenotyping to understand and improve mandibular advancement treatment outcomes in people with obstructive sleep apnoea

Author:
Tong, Kwei Yuan

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Upper airway physiology and respiratory phenotyping to understand and improve mandibular advancement treatment outcomes in people with obstructive sleep apnoea

Kwei Yuan Tong

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Thesis Title and Abstract | Declarations | Inclusion of Publications Statement | Corrected Thesis and Responses

Thesis Title

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Thesis Abstract

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Study 1 examines the role of body posture and mandibular advancement on nasal resistance in people with OSA. Efficacy of a novel titanium-based oral appliance with an in-built oral airway was also quantified. Awake nasal resistance increased systematically from seated, to supine, to lateral but was not altered by acute mandibular advancement. Unlike conventional devices, the novel oral appliance had similar therapeutic efficacy in people with high and low nasal resistance.

Study 2 used a detailed physiological approach to carefully quantify therapeutic CPAP requirements during combination therapy with CPAP and an oral appliance in the clinically relevant group of non-responders to oral appliance therapy alone. CPAP requirements reduced by ~40% with combination therapy.

Study 3 prospectively explored potential differences in the 4 pathophysiological traits that contribute to OSA between responders and non-responders to oral appliance therapy using gold standard respiratory phenotyping methodology and validated algorithm-based estimates. Efficacy of a next generation nylon-based novel oral appliance with a built-in oral airway was also assessed as was awake nasal resistance. Oral appliance therapy reduced OSA severity by ~40%. OSA severity reduced by >50% in half of the participants in both people with and without high nasal resistance. Responders to therapy tended to have a less collapsible upper airway and better pharyngeal muscle compensation at baseline when these traits were estimated via polysomnography but not when measured directly in this prospectively recruited cohort, none of whom had major anatomical compromise at baseline (Pcrit all <2cmH_2O).

These findings provide new insight into the effects of a novel oral appliance on upper airway physiology and therapeutic efficacy and the potential for combination therapy for those with an incomplete therapeutic response to monotherapy with an oral appliance and the potential for estimates of OSA pathophysiological traits to help predict a favourable treatment response.

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Publication Details #1

Full Title:	Efficacy of a novel oral appliance and the role of posture on nasal resistance in obstructive sleep apnea
Authors:	Benjamin K. Tong, Carolin Tran, Andrea Ricciardiello, Alan Chiang, Michelle Donegan, Nick Murray, Irene Szollosi, Jason Amatoury, Jayne C. Carberry, Danny J. Eckert
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The Candidate's Contribution to the Work:	Benjamin K. Tong conceived and designed the study, performed experiments, analysed data, interpreted results of experiments, prepared figures, drafted, edited, revised and approved final version of manuscript.
Location of the work in the thesis and/or how the work is incorporated in the thesis:	This work is included in lieu of Chapter 2

Publication Details #2

Full Title:	CPAP combined with oral appliance therapy reduces CPAP requirements and pharyngeal pressure swings in obstructive sleep apnea
Authors:	Benjamin K. Tong, Carolin Tran, Andrea Ricciardiello, Michelle Donegan, Alan K.I. Chiang, Irene Szollosi, Jason Amatoury, Jayne C. Carberry, Danny J. Eckert
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Candidate's Declaration

I confirm that where I have used a publication in lieu of a chapter, the listed publication(s) above meet(s) the requirements to be included in the thesis. I also declare that I have complied with the Thesis Examination Procedure.

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Abstract

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appliance, and the potential for estimates of OSA pathophysiological traits to help predict a favourable treatment response.

Publications

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

1. **Tong BK**, Tran C, Ricciardiello A, Chiang A, Donegan M, Murray N, Szollosi I, Amatoury J, Carberry JC, Eckert DJ. Efficacy of a novel oral appliance and the role of posture on nasal resistance in obstructive sleep apnea. J Clin Sleep Med. 2020 Apr 15;16(4):483-492. doi: 10.5664/jcsm.8244.

2. **Tong BK**, Tran C, Ricciardiello A, Donegan M, Chiang AKI, Szollosi I, Amatoury J, Carberry JC, Eckert DJ. CPAP combined with oral appliance therapy reduces CPAP requirements and pharyngeal pressure swings in obstructive sleep apnea. J Appl Physiol (1985). 2020 Nov 1;129(5):1085-1091. doi: 10.1152/japplphysiol.00393.2020. Epub 2020 Sep 10.

The following are published abstracts and conference proceedings resulting from work towards this thesis:

1. **Tong B**., Tran C., Ricciardiello A., Donegan M., Murray N., Chiang A., Amatoury J. Eckert D., Postural effects on nasal resistance in obstructive sleep apnoea (OSA) and efficacy of a novel oral appliance, European Respiratory Journal Sep 2018, 52 (suppl 62) PA4339; DOI: 10.1183/13993003.congress-2018.PA4339

2. **Tong B.**, Amatoury J., Carberry J., Eckert D., Role of posture on nasal resistance and OSA severity with a novel mandibular advancement device., J Sleep Res 2017, 26: 70-70. https://doi.org/10.1111/jsr.99_12619

3. **Tong B.**, Amatoury J., Carberry J., Eckert D., The effects of posture and mandibular advancement on nasal resistance and obstructive sleep apnea treatment outcome with novel oral appliance therapy device., Sleep Medicine, Volume 40, Supplement 1, 2017, page e87, https://doi.org/10.1016/j.sleep.2017.11.249

4. **Tong B.**, Tran C., Ricciardiello A., Donegan M., Murray N., Chiang A., Amatoury J., Eckert D., Combined CPAP and oral appliance (OA) therapy reduces PAP requirements and pharyngeal pressure (Pepi) swings in OSA.,

European Respiratory Journal Sep 2018, 52 (Suppl 62) PA 4346; DOI: 10.1183/13993003.congress-2018.PA4339

5. **Tong B.**, Tran C., Ricciardiello A., Donegan M., Murray N., Chiang A., Szollosi I., Amatoury J., Eckert D., Combination therapy with CPAP plus MAS reduces CPAP therapeutic requirements in incomplete MAS responders. J Sleep Res (2018), 27: e179_12766. https://doi.org/10.1111/jsr.179_12766

6. **Tong B.**, Bull C., Chiang A., Donegan M., Brown E., Kwan B., Eckert D., Efficacy of a novel oral appliance and the influence of OSA pathophysiological traits on treatment response. SLEEP2021 (Submitted)

Other related publications that have arisen during candidature:

1. Lai V, **Tong BK**, Tran C, Ricciardiello A, Donegan M, Murray NP, Carberry JC, Eckert DJ. Combination therapy with mandibular advancement and expiratory positive airway pressure valves reduces obstructive sleep apnea severity. Sleep. 2019 Aug 1;42(8):zsz119. doi: 10.1093/sleep/zsz119. PMID: 31180512

2. Osman AM, **Tong BK**, Landry SA, Edwards BA, Joosten SA, Hamilton GS, Cori JM, Jordan AS, Stevens D, Grunstein RR, McEvoy RD, Catcheside PG, Eckert DJ. An assessment of a simple clinical technique to estimate pharyngeal collapsibility in people with obstructive sleep apnea. Sleep. 2020 Oct 13;43(10):zsaa067. doi: 10.1093/sleep/zsaa067. PMID: 32267509

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Glossary of abbreviations

AASM	American Academy of Sleep Medicine
AHI	Apnoea/hyponoea index
BMI	Body mass index
CPAP	Continuous positive airway pressure
CPAP+OA	Combination therapy with CPAP and oral appliance
CSA	Central sleep apnoea
EEG	Electroencephalogram
EMG	Electromyogram
EPAP	Expiratory positive airway pressure
ESS	Epworth sleepiness scale
IQR	Interquartile range
LG1	Loop gain determined at 1cycle/min
LGn	Loop gain determined at the natural cycling frequency
MAS	Mandibular advancement splint
MRI	Magnetic resonance imaging
N1	NREM stage 1
N2	NREM stage 2
N3	NREM stage 3
NARES	Non-allergic rhinitis with eosinophilia syndrome
NOSE	Nasal Obstruction Symptom Evaluation scale
NREM	Non-rapid eye movement
O_2	Oxygen
OA	Oral appliance
ODI	Oxygen desaturation index
OSA	Obstructive sleep apnoea
P_{CO2}	Carbon dioxide partial pressure
Pcho	Choanal pressure
Pcrit	Critical closing pressure
Pepi	Epiglottic pressure
Pmask	Mask pressure
PSG	Polysomnography
REM	Rapid eye movement

SARAH index	Sleep Adjusted Residual AHI
SD	Standard deviation
T90	Time spent with blood oxygen saturation below 90%
TST	Total sleep time
WASO	Wake after sleep onset

1. Literature review

1.1. Obstructive sleep apnoea

1.1.1. Description

Obstructive sleep apnoea (OSA) is a common sleep-related breathing disorder characterised by repetitive episodes of upper airway collapse during sleep. OSA is associated with a partial reduction or complete cessation in airflow, a decrease in oxygen saturation, progressive increases in respiratory effort throughout each breathing disturbance (108) and microarousals or cortical arousals from sleep (202).

1.1.2. Prevalence

Prevalence estimates of moderate to severe OSA (apnoea/hypopnoea index [AHI]≥15 events/h sleep) among Australian adults is approximately 10% (287). OSA is more common in men than women (27, 246, 287, 316, 347). US population data from the Wisconsin cohort estimates that 13% of men and 6% of women aged between 30 to 70 years old have moderate to severe OSA (AHI≥ 15 events/h sleep) (246). A recent Swiss community-based study found that approximately 50% of men and 25% in women aged 35-75 years had an AHI≥15 events/h based on current polysomnography standards (116).

OSA is more prevalent with increasing age. It is estimated that OSA prevalence in older men is double of that compared to younger men of similar body habitus (246). A Spanish population based study of people aged between 30 to 70 years of age found that for each decade increase in age the odds ratio in OSA prevalence doubles (69). Obesity is also a major risk factor for OSA (246, 348). Data from the Wisconsin cohort indicates that people are six times more likely to develop OSA from just a 10% increase in body weight (348).

OSA prevalence differs among different ethnic groups. Far east Asian men tend to have more severe OSA compared to their Caucasian counterparts despite having significantly lower BMI (175). African Americans are more likely to have OSA compared to Caucasians. For example, Redline and colleagues found that OSA prevalence among young African Americans is higher compared to Caucasians of similar age (<25 years) (257). Similarly, older African Americans are twice more likely to develop severe OSA compared to older Caucasians (>65 years) (4). Differences

in OSA between ethnic groups suggest potential differences in upper airway structures (195). For example, Li and colleagues demonstrated that east Asian men have a more crowded upper airway compared to Caucasians which explains, at least in part, the increased OSA severity seen in east Asian men (175).

1.1.3. Consequences

Excessive daytime sleepiness is a key symptom of OSA. This can result in major adverse health and quality of life consequences. Untreated OSA increases the risk of cardiovascular disease (198), hypertension (247), stroke (258, 340) and metabolic disorders (242, 261). Links between OSA and cancer in patients younger than 65 years old have also been reported (37).

OSA is associated with neurocognitive deterioration in attention, vigilance, learning and memory (35, 166) which affects general safety and quality of life. Sleepy individuals with untreated OSA are seven times more likely to be involved in a motor vehicle crash (273). The odds of workplace accidents among individuals with OSA is twice that of those without OSA (98).

1.2. Pathophysiology of OSA

OSA pathogenesis is heterogeneous. Recent studies have defined at least four primary pathophysiological traits that contribute to OSA (79). These traits can be further categorised as anatomical and non-anatomical factors.

Anatomical causes of OSA are related to a narrow or impaired upper airway anatomy that contributes to increased pharyngeal collapsibility. Non-anatomical causes of OSA includes increased propensity to awakening from respiratory disturbances (low respiratory arousal threshold), unstable ventilatory control (high loop gain) and poor upper airway muscle responsiveness (79). Considering that upper airway collapse only occurs during sleep, a combination of both anatomical and non-anatomical factors is necessary to contribute to upper airway obstruction (Figure 1.1). However, the relative contributions of the various traits to OSA pathogenesis varies substantially between patients (79).

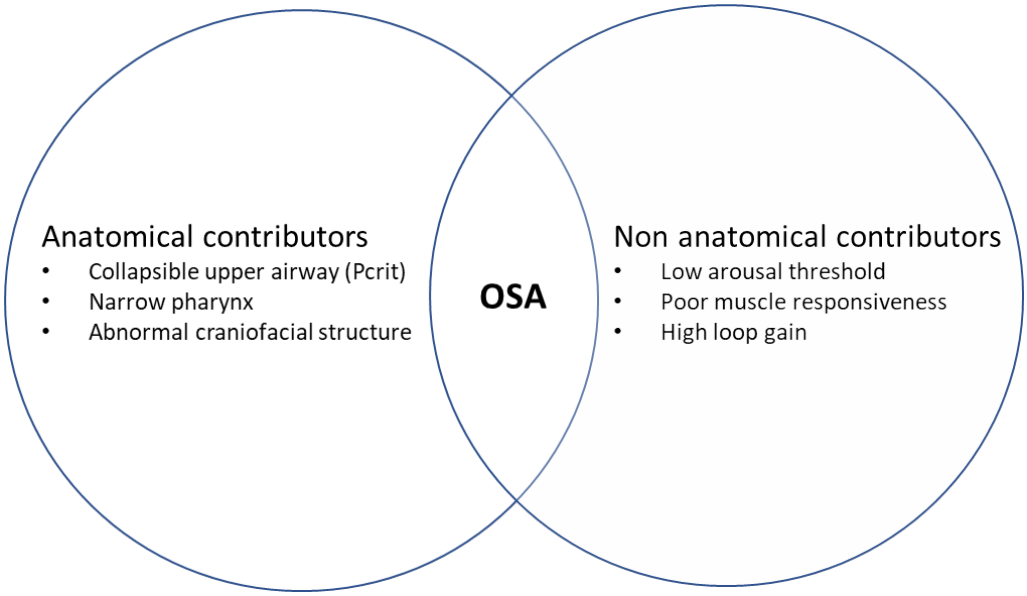

Figure 1.1: Obstructive sleep apnoea is caused by a combination of anatomical and non-anatomical factors.

1.2.1. Pcrit

OSA requires some degree of anatomical compromise within the upper airway. Modern imaging techniques have revealed key differences in the pharyngeal anatomy between people with OSA and without OSA (32, 113, 277, 278). Individuals with OSA tend to have a narrower pharyngeal cross sectional area compared to those without OSA (113, 277). This narrowing is often a result of excess fat or enlarged soft tissues surrounding the pharynx (123, 153, 278). Abnormal craniofacial structures surrounding the airway also contribute to a reduced airway calibre (11, 101, 132, 225). Additionally, increased length of the pharyngeal airway is associated with the severity and presence of OSA in humans (194, 281). Mechanical properties of the soft tissues within the upper airway can contribute to the pathogenesis of OSA. A recent study by Brown and colleagues found that the tongue in people with OSA is softer versus those without OSA (34).

The gold standard technique to quantify the degree of anatomical compromise within the upper airway during sleep is the critical closing pressure (Pcrit). Pcrit is defined as the pressure at which the pharyngeal airway collapses. Pcrit is based the assumption that the upper airway behaves according to a Starling resistor model (105, 128, 289) which dictates that the upper airway will collapse when the pressure difference within the airway is less than pressure acting externally on the airway.

Pcrit is quantified during stable sleep through transient continuous positive airway pressure (CPAP) reductions from therapeutic levels until the airway closes (79, 105, 280). Each CPAP reduction is conducted for five breaths before returning CPAP to therapeutic levels. Peak inspiratory flow measurements are taken for flow limited breaths 3-5 (to avoid initial lung-volume related effects on airway collapsibility during breaths 1-2) (241) and plotted against the corresponding CPAP level. Pcrit is then calculated via a linear regression of the peak inspiratory flow versus CPAP level where the fitted curve intersects at zero flow (Figure 1.2).

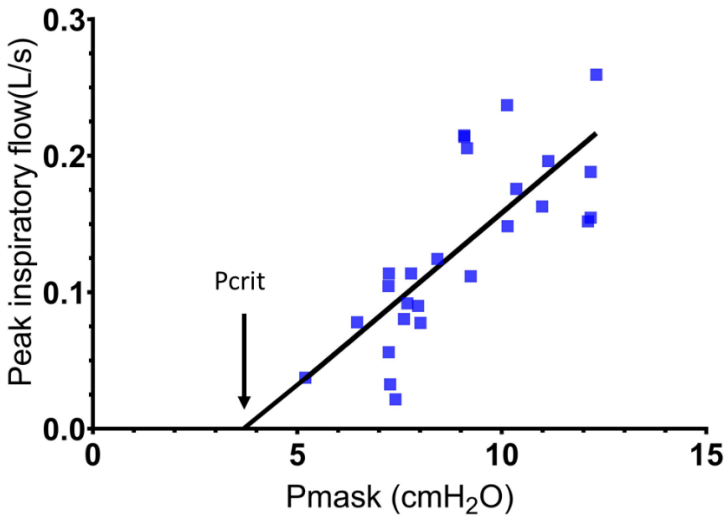

Figure 1.2: Calculation of Pcrit

Pcrit is calculated by extrapolating the linear regression line of peak inspiratory flow versus mask pressure (Pmask) plot to 0 flow.

Measurement of Pcrit via this method is known as the “passive Pcrit” which assumes minimal pharyngeal dilator muscle activity due to CPAP (39, 279). Accordingly, passive Pcrit provides an estimate of upper airway collapsibility based on the properties of the pharynx.

Pcrit is positively correlated with OSA severity. Individuals with OSA typically have a Pcrit above atmospheric pressure (> 0cmH_2O) consistent with a highly collapsible airway (79, 105). However, approximately 20% of individuals with OSA (who have varying OSA severity as measured by the AHI) only have a mildly collapsible pharyngeal airway similar to many people without OSA (Pcrit = 0 cmH_2O to -5 cmH_2O) (79). This indicates that non-anatomical factors are also important contributors to OSA pathogenesis for many patients. In contrast, most people without

OSA do not have pharyngeal anatomical impairment and have negative Pcrit values (<-5cmH_2O) (79, 105, 280).

Upper airway collapsibility is gender, age and BMI dependent. On average, passive Pcrit is at least 2 cmH_2O higher in males compared to females (156). Anatomical differences between males and females contribute to the gender difference in Pcrit (194). Upper airway collapsibility also increases with obesity with a 1.4cmH_2O increase in Pcrit per 10kg/m^2 increase in BMI (156). Higher fat composition around the upper airway in obese individuals can result in increased external pressure on the upper airway resulting in increased airway resistance (159) and a more collapsible airway (55, 159). Obese individuals tend to have fat deposits around the torso and abdomen which can decrease lung volumes (285, 350) and create caudal traction on the upper airway resulting in increased airway collapsibility (117) and increased OSA severity. Pcrit increases by 0.5cmH_2O per decade of age (156). However, this effect is more prominent in perimenopausal women due to redistribution of fat from the periphery to central regions (156).

Pcrit also varies with head (325) and body position (237), surface tension of the pharyngeal mucosa (155), nocturnal rostral fluid redistribution (335), degree of mouth opening (7), sleep states (39) and ethnicity (232).

1.2.2. Arousal threshold

Arousals (rapid transitions from sleep to wake) are a common feature of polysomnographic sleep studies. The American Academy of Sleep Medicine (AASM) defines an arousal as a sudden change in EEG frequency (including alpha, theta and/or frequencies greater than 16Hz (but not spindles)) which lasts for 3 seconds or more with at least 10 seconds of stable sleep prior (23).

Arousals resulting from respiratory disturbances are common in people with OSA (260). Originally, arousals were thought to be necessary to allow upper airway opening at the termination of an OSA episode (250). However, up to a third of obstructive events do not end with an arousal (65, 140, 259). In the late 1990s, Berry and Gleeson comprehensively reviewed the role of arousals in OSA and begun to challenge traditional views on the relationship between arousal and OSA (24). Subsequently, a milestone study by Younes and colleagues, discovered that

arousals were not necessary at the end of a respiratory event to restore respiratory airflow in OSA (342). In fact, arousals can have detrimental or beneficial roles in different individuals with OSA depending on their underlying pathophysiology (342).

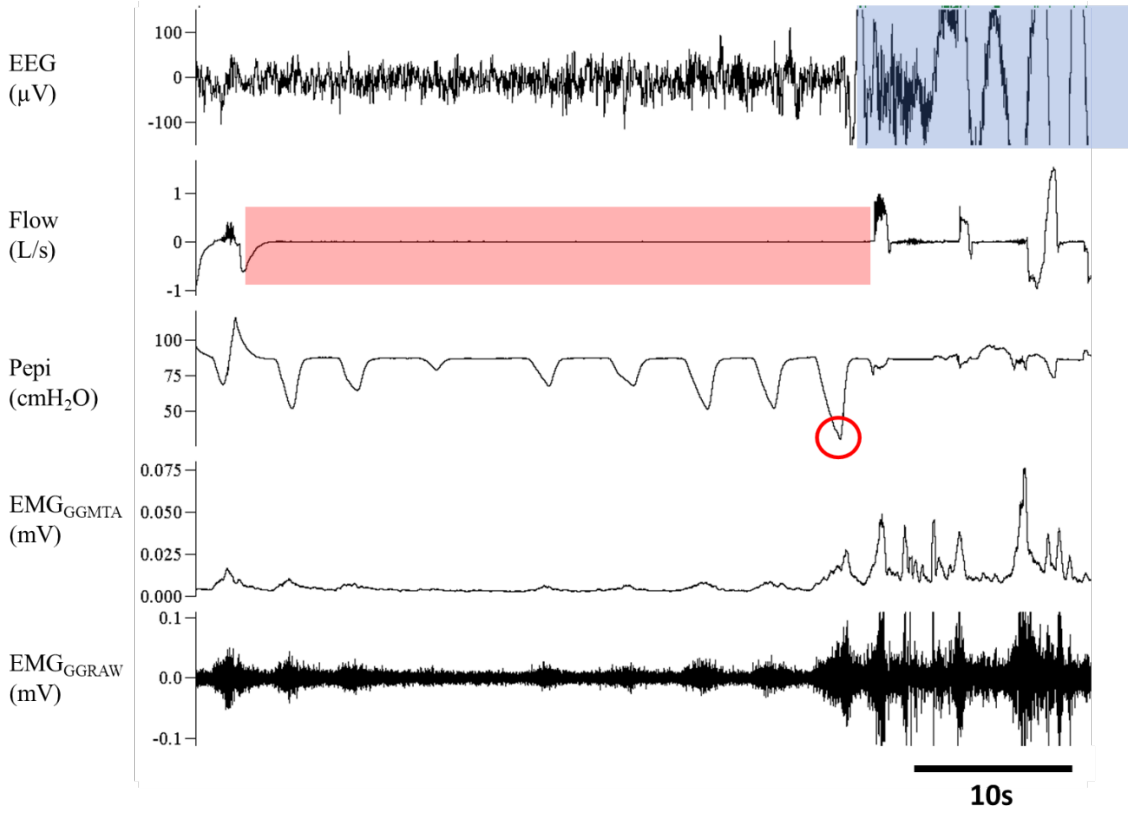

Figure 1.3: Quantification of the respiratory arousal threshold

Arousal threshold is described to be the nadir epiglottic pressure (Pepi) immediately prior to an arousal (highlighted blue) resulting from a respiratory disturbance (highlighted red) as indicated by the red circle. EMG_{GGRAW}=Raw signal of genioglossus electromyogram, EMG_{GGMTA}=0.1s moving time average of rectified raw genioglossus electromyogram, Pepi= epiglottic pressure, EEG=Electroencephalogram.

Respiratory arousals are mediated by respiratory chemoreceptors and mechanoreceptors in response to changes in blood gases and mechanical loading(106). Changes in blood gases (↑ P_{CO2}) and increases in respiratory drive during an obstructive episode result in increasing ventilatory effort to breathe. Effectively, when a threshold is reached an arousal occurs which is associated with the level of ventilatory effort(106). Interestingly, it was discovered that arousal from sleep occurred at similar peak negative oesophageal pressures regardless of ventilatory disturbance stimulus(106). This value which varies substantially between individuals is known as the respiratory arousal threshold. Specifically, the arousal

threshold is defined as the nadir epiglottic or oesophageal pressure immediately prior to an arousal from a respiratory disturbance (79) (Figure 1.3).

Recent studies that have investigated the arousal threshold have classified people with OSA as having a low (0 to -15cmH_2O) or high arousal threshold (larger negative pressure swings) (78, 79). A low arousal threshold (waking up too easily) can contribute to the pathogenesis of OSA (24, 80, 342) through several pathways. First, frequent arousals to respiratory disturbances can cause sleep fragmentation and reduced sleep continuity (80) preventing the progression to deeper stages of sleep where OSA rarely occurs (256). Next, an arousal threshold which is lower than the upper airway dilator muscle recruitment threshold which is also triggered by the respiratory drive limits activation of this protective mechanism to open the airway without arousal (343). Finally, ventilatory overshoot from end of respiratory event arousals causes breathing instability which can perpetuate further respiratory events (342). Moreover, the severity of the following obstructive events is a function of the intensity of the arousal (2). Delaying arousal can provide sufficient opportunity for the upper airway muscles to reopen the airway while maintaining sleep in these individuals (342, 343). However, people who have poor upper airway muscles are not able to restore airway patency (67).

Individuals with a high arousal threshold however, are also susceptible to OSA from other means. Reduced propensity to awakening can be detrimental for these individuals especially when coupled with blunted respiratory drive which can result in prolonged apnoeas (e.g. obesity hypoventilation phenotype) (80). In this case, arousals which are associated with wakefulness levels of upper airway muscle activation, act to reopen the airway (80, 250).

1.2.3. Loop gain

Periodic breathing is a common feature of OSA (236). The occurrence of periodic breathing is a result of an unstable ventilatory control system (152). The ventilatory control system consists of a negative feedback loop system in which a change in ventilation causes variations in blood gas tensions. Chemoreceptors within the control system sense these changes and produce a ventilatory response to counterbalance the initial change (152).

Loop gain refers to the quantification of the ventilatory response to the initial disturbance (73, 152). The measurement of loop gain is a ratio between the ventilatory response to a disturbance (328, 344). It is characterised by the plant gain (lungs, blood), controller gain (chemosensitivity) and mixing delay (mixing of blood gases). Any disruptions, to either of these components will alter the balance of the control system and affect loop gain (74).

Approximately a third of people with OSA have a high loop gain (79). Individuals with a high loop gain are more sensitive to blood gas changes and have large ventilatory responses to minor ventilatory disturbances resulting in further periodic breathing (74). Conversely, those with a low loop gain have a more stable ventilatory control system (73). Loop gain is associated with OSA severity. Younes demonstrated that loop gain is higher in people with severe OSA compared to those with a mild or moderate severity (344). More recent studies indicate that loop gain is higher in people with mild-moderately collapsible upper airways as measured by Pcrit (79, 329).

Loop gain is conventionally measured from CPAP manipulations or by using a proportional assist ventilation device as described previously (79, 328, 329, 344). Due to the complexity in measuring loop gain via these labour intensive and technically challenging methods, new techniques have been explored to estimate loop gain in people with OSA. For example, breath holding for up to 20 seconds and maximal breath hold manoeuvres can be used to estimate loop gain (212). Other methods such as estimating loop gain from standard clinical polysomnography studies have also shown promise (311).

Several studies have explored the role of loop gain in the pathophysiology of OSA. Loop gain is reduced in REM sleep compared to NREM sleep (167, 211). Messineo and colleagues demonstrated that loop gain in REM sleep is reduced by 25% compared to NREM sleep (211). Loop gain is also similar between genders regardless of OSA diagnosis (141, 330).

Long term CPAP use is associated with reduced loop gain in people with OSA (183). Oxygen therapy lowers loop gain and improves OSA severity in those with a high loop gain phenotype (331). Acetazolamide reduces loop gain and reduces OSA severity (82).

1.2.4. Muscle responsiveness

The pharyngeal airway is a flexible structure. It is crucial for breathing, speech and swallowing. It lacks rigidity with the absence of cartilage or bones for support, making it prone to collapse. The patency of the pharyngeal airway is largely regulated by the surrounding dilator muscles. The largest dilator muscle within the pharyngeal airway is the genioglossus muscle. The genioglossus is an extrinsic muscle which facilitates tongue movement and pharyngeal patency (158).

Given that the genioglossus is the largest upper airway dilator muscle, it is widely studied for its role in breathing and the pathogenesis of OSA (142). Neural drive to the genioglossus originates from pattern generator neurons located in the brain stem and reflex drives from mechanoreceptors and chemoreceptors. Summation of activation patterns of the genioglossus during quiet breathing is increased during inspiration (phasic activity) compared to expiration (tonic activity) (266). During sleep onset, upper airway muscle activity is reduced due to the loss of wakefulness drive (182, 338). Additionally, genioglossus muscle activity is sleep stage dependent and increases from N2 to N3 sleep with major reductions in REM (39).

In people with OSA, dilator muscle activity is higher compared to age and BMI matched controls during quiet breathing (215). This suggests that people with OSA are highly reliant on the pharyngeal dilator muscles to maintain airway patency even during wakefulness (215). The combined reduction in wakefulness and reflex drive and the inability to recruit the pharyngeal dilator muscles during sleep are suggested to be contributors to OSA pathogenesis (76, 77, 141). Roughly a third of people with OSA are unable to activate the genioglossus during flow limitation or obstructive events during sleep (79). Although obesity is a risk factor for OSA, some obese individuals do not have OSA due to robust upper airway muscles (270).

Uncoordinated activation of the upper airway muscles during sleep in some individuals with OSA can result in failure to reopen a collapsed airway (67). A recent MRI imaging study identified four distinct movement patterns of the tongue during inspiration in people with OSA (32). Individuals with very severe OSA exhibited minimal tongue movement whereas those with mild-moderate severity exhibited bidirectional tongue movement which was counterproductive in terms of airway dilation (32). These variation in tongue movement within people with OSA has suggested possible neuromuscular abnormalities within the tongue. For instance,

Saboisky and colleagues demonstrated evidence of neural remodelling within the genioglossus in people with OSA (267). This finding is further supported by an earlier study which suggested inflammatory cell infiltrates and denervation within the upper airway muscle which explains the poor performance of the upper airway muscles in establishing or maintaining airway patency (30). Histology analysis of the genioglossus between people with and without OSA revealed structural changes within the fibres of the genioglossus muscle in OSA (40) resulting in an increased propensity of fatiguability despite being stronger (40, 75). Similar abnormalities have also been detected in the tissues of the soft palate (177). These abnormalities however, were largely corrected with CPAP therapy (40, 222). In addition to neuropathy, Kim and colleagues reported higher fat content in the tongue of OSA patients compared to controls (153). Increased fat within the tongue may also affect the performance of the genioglossus to maintain airway patency (153).

Muscle activity in OSA human studies have been conventionally measured using bipolar recordings of fine wire electrodes inserted perorally or percutaneously into the genioglossus muscle (275). Muscle activity measurements are scaled relative to maximal genioglossus activity to produce a percentage of maximum genioglossus activity (215). This allows for patient-to-patient comparisons. Muscle responsiveness is calculated from the slope of the relationship between peak muscle activity and peak negative epiglottic pressure (79) (Figure 1.4).

Understanding the role of the upper airway muscles in the pathogenesis of OSA is fundamentally important to tailor treatment solutions for those with a poor muscle responsiveness phenotype. Recent studies have demonstrated electrical stimulation of the hypoglossal nerve leads to stiffening of the upper airway from tongue protrusion (70). In addition, OSA severity was found to be reduced by at least half in people with OSA (70, 296). Pharmacotherapies to stimulate the upper airway muscles have also been explored recently. For instance, desipramine has been found to increase genioglossus muscle activity while reducing pharyngeal collapsibility resulting in lower OSA severity in OSA patients with poor muscle responsiveness (308, 310). Additionally, a combination of atomoxetine and oxybutynin was found to increase genioglossus muscle responsiveness by three folds and reduce OSA severity by more than half (309). Upper airway muscle training has also been proposed as a potential therapeutic option to target this OSA phenotype with promising outcomes (36, 109, 125).

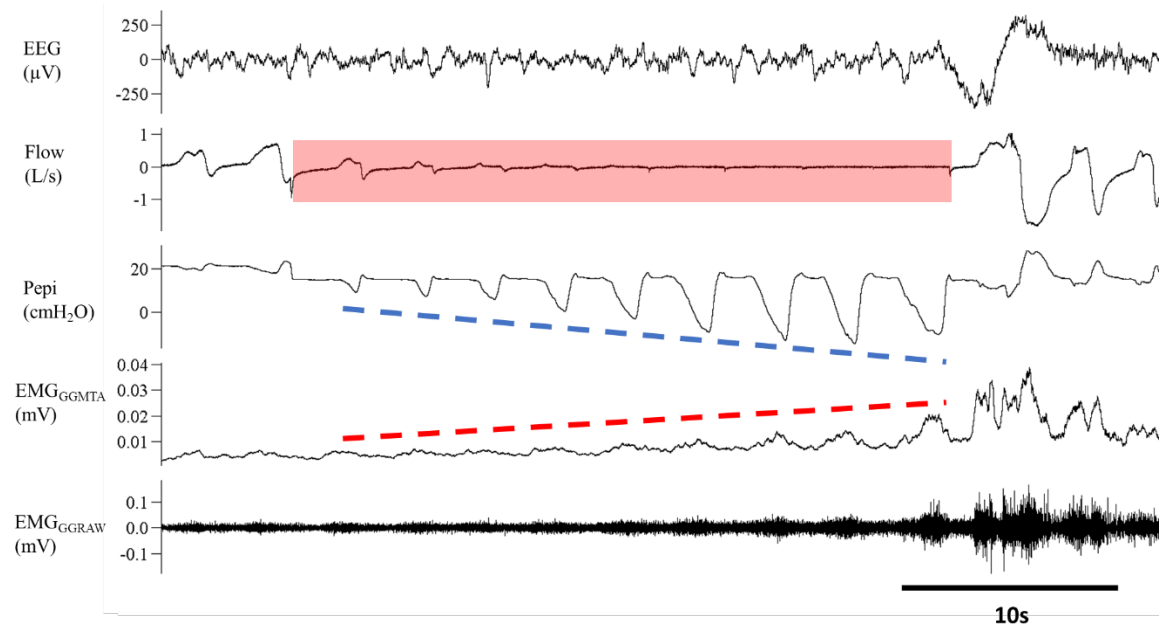

Figure 1.4: Quantification of muscle responsiveness

Genioglossus muscle responsiveness is determined by quantifying the slope of the relationship between peak muscle activity (red dotted line) and nadir epiglottic pressure (blue dotted line) on a breath by breath basis during respiratory events (highlighted red). EMG_{GGRAW}=Raw signal of genioglossus electromyogram, EMG_{GGMTA}=0.1s moving time average of rectified raw genioglossus electromyogram, Pepi=epiglottic pressure, EEG=Electroencephalogram

1.3. The PALM scale approach

The **P**crit, **A**rousal threshold, **L**oop gain, **M**uscle responsiveness (PALM) scale categorises OSA patients based on their anatomical and non-anatomical traits to help advance OSA pathogenesis and identify suitable targeted OSA therapies (79). Briefly, the PALM scale categorises OSA patients in to three categories based on their upper airway collapsibility. A PALM scale of 1 describes a patient with very collapsible upper airway as the primary cause of OSA and will most likely do well with a major anatomical intervention (e.g. CPAP). A patient with mild to moderate anatomical collapsibility is categorised as PALM scale 2. OSA patients within this PALM scale category can be further classified without (2a) or with (2b) vulnerable non-anatomical traits. Those who are classified as 2a would tend to be more suitable to anatomical interventions (e.g. mandibular advancement splint or upper airway surgery) as their OSA is primarily caused by anatomical deficiencies. Those classified as 2b would benefit from combination therapies that target both the anatomical and relevant non-anatomical trait or traits. The final category within the

PALM scale is 3. OSA patients in this group tend to have non-anatomical deficiencies as the main cause of OSA while having only mild anatomical impairment. These patients may benefit from therapies that target the non-anatomical trait or traits.

Favourable outcomes to OSA therapy can be predicted based on the PALM scale by targeting these anatomical and non-anatomical deficiencies. This could help streamline the current trial and error approach in clinical settings resulting in better patient outcomes (38). A predictive model has estimated that by knowing the effect sizes of non-CPAP therapies which target these vulnerable pathophysiological traits, approximately 50% of patients with OSA can be treated from either one or a combination of these therapies (240). However, translating the application of the PALM scale approach to a clinical setting remains a challenge. Accurately identifying and quantifying these pathophysiological traits using gold standard approaches requires specialised equipment which are not readily available in clinics. Moreover, the PALM scale was developed based on data in NREM sleep and obese patients (79). The effect of the pathophysiological traits in REM sleep and non-obese patients remain unclear. Nonetheless, the PALM scale approach provides a new perspective in tailoring OSA therapies to improve treatment effectiveness and compliance for patients with OSA.

1.4. Treatment for OSA

1.4.1. Continuous positive airway pressure

Continuous positive airway pressure (CPAP) is the gold standard therapy for OSA (1). CPAP acts as a pneumatic splint to maintain upper airway patency (295, 298). CPAP also increases lung volume and indirectly stiffens the airway through caudal traction (117).

CPAP is highly efficacious in abolishing OSA and can improve daytime sleepiness (85, 87), cognitive function (85, 87) and blood pressure (19, 90, 185, 203, 341). CPAP use may also reduce the risk of comorbidities such as diabetes (10), hypertension (219) and cardiovascular disease (198). However, a recent large randomised clinical trial did not find that CPAP prevent further cardiovascular events in people with pre-existing cardiovascular conditions despite improvements in other OSA symptoms (206).

The effectiveness of CPAP treatment however is largely limited by patient adherence to treatment. Based on the common definition for adequate CPAP compliance of greater than 4 hours per night, at least half of all patients prescribed CPAP therapy are non-compliant (161, 327). In addition, roughly a third of patients with OSA on CPAP therapy are non-adherent to treatment after a month on therapy with an additional 15% abandoning treatment within 10 months of commencing therapy (339). Common reasons for non-compliance to CPAP therapy include mask related discomfort (100, 231, 339), pressure intolerance (100) and preference for alternative OSA therapies (339).

1.4.2. Mandibular advancement devices

Mandibular advancement devices are popular alternatives to CPAP therapy. The American Academy of Sleep Medicine recommends that mandibular advancement devices should be prescribed to patients with OSA who fail CPAP therapy and those with less severe OSA (254). Mandibular advancement devices are a type of dental oral appliance which aim to pull the mandible forward to assist with upper airway dilation and alleviate OSA. Mandibular advancement devices can improve symptoms of OSA including subjective sleepiness and quality of life comparatively to CPAP (16, 66, 88, 97, 249). CPAP however, is superior at reducing OSA severity (16, 66, 88, 97, 249) and improving arterial oxygen saturation (97, 249).

The mechanisms of action of mandibular advancement devices in dilating the upper airway have been studied in recent years. One study showed that mandibular advancement devices increase the lateral upper airway dimensions primarily within the velopharyngeal area (43). Expansion of the lateral upper airway dimensions is the result of stretching of the lateral soft tissues (33). Additionally, anterior movement of the tongue with mandibular advancement contributes to increased airway calibre (33). A recent study also showed that mandibular advancement improves upper airway collapsibility without affecting genioglossus muscle function (13). An earlier study showed that upper airway collapsibility improves by approximately 2cmH_2O with mandibular advancement device therapy as measured using the Pclose technique (similar to Pcrit) (226). This is further supported by Bamagoos and colleagues recent findings that indicate that mandibular advancement reduces therapeutic CPAP requirements in a dose dependent manner (14).

Patients with OSA are generally more adherent and prefer mandibular advancement therapy compared to CPAP (83, 91, 307). Comparison of objective compliance data show roughly 80% of patients on mandibular advancement therapy are compliant (62, 319) compared to 50% to 70% of CPAP users who are compliant (96, 339) at 1 year follow up. Despite the high adherence rate among patients, only half of oral appliance users achieve complete resolution of OSA (AHI < 5events/hour) (304). The precise reasons for variability in the efficacy of mandibular advancement device therapy remain unclear. However, multiple studies have attempted to predict favourable mandibular advancement therapy outcomes in people with OSA.

Studies have shown that predictors of favourable outcomes with mandibular advancement therapy include patients who are leaner (120, 303, 305), younger (228, 303), female (199, 228), have a lower Mallampati score (315) and mild severity of OSA (120, 199, 303). Cephalometric studies have identified that craniofacial features such as retrognathism (120, 204, 286), shorter soft palate (89, 204, 228), larger cranial base angle (228), shorter distance between the hyoid and mandibular plane (89), shorter anterior face height (286) and narrow oropharynx (204, 286) are associated with favourable mandibular advancement therapy outcomes. Sutherland and colleagues demonstrated that incomplete responders to therapy have a higher soft tissue to intra-mandible area ratio (300), suggesting that upper airway crowding from enlarged surrounding soft tissues contributes to poor mandibular advancement therapy outcome. A previous study however, showed that responders have a larger tongue for a given cavity size (223). However, this study was restricted only to a two-dimensional analyses and did not account for other pharyngeal tissues. Responders to therapy were also associated with an ‘en bloc’ anterior tongue movement with mandibular advancement whereas non-responders were found to have minimal to no movement of the tongue with mandibular advancement during quiet breathing during a recent dynamic MRI study (33). Despite these potential predictors, prospectively identifying which patients will respond to mandibular advancement therapy remains a major clinical challenge. Indeed, most of these metrics when applied prospectively fail to predict treatment response better than chance.

1.4.3. Combination therapy

Increased knowledge of the different pathophysiological causes of OSA and available OSA therapies, has enabled development of a predictive model. Using this model, it is estimated that combination therapy can effectively treat more than 50% of people with OSA (240). Thus, combination therapy may be a viable approach to personalised OSA therapy whereby one or more abnormal traits can be targeted with specific OSA therapies to yield additive or potentially even synergic benefit.

A recent study demonstrated that concurrent use of CPAP and mandibular advancement splint (MAS) therapy eliminates OSA in patients intolerant to CPAP therapy (84). One study explored the use of MAS as a mandibular stabiliser for patients who require oronasal masks (145). Another study assessed patient comfort and compliance to combination therapy with CPAP and MAS (180). These studies all shared the common finding that the CPAP levels required to abolish OSA were significantly lower when MAS is used in combination with CPAP (84, 145, 180). Compliance and patient comfort to combination therapy was similar to using CPAP alone (180).

Dieltjens and colleagues explored combining positional therapy with MAS and demonstrated that OSA severity reduced by half in patients with supine dependent OSA (64). Another study investigated the use of expiratory positive airway pressure (EPAP) valves with MAS therapy as a potential combination therapy option for incomplete responders to MAS therapy alone (164). This combined anatomical approach reduced OSA severity for a substantial proportion of the participants including resolution of OSA in several cases (164). Compliance for these combination therapies however, remain unknown. Although combination therapy has been minimally studied, treatment efficacy is favourable supporting the need for long term compliance studies in this area.

1.5. The nose

1.5.1. Anatomy and function

The nose serves multiple important functions pertaining to smell, sensation and air conditioning during breathing (103, 137). The anatomy of the nose can be divided into two sections, an external structure and the nasal passage.

Figure 1.5 has been removed due to copyright restrictions.

Figure 1.5: Anatomical diagram of the external nose
Figure adapted from Poirrier et al. (2013) (252).

The external structure of the nose comprises the nasal pyramid which protrudes anteriorly from the face. The nasal pyramid consists of bony, cartilage and epithelial tissues. The nasal bones sit at the upper third of the nasal pyramid and provide support for the nasal septum. It is laterally attached to the maxilla by a syndesmosis. The bottom two thirds of the nose are cartilage tissues. The septum which divides the nasal cavity is made up of the quadrilateral cartilage, vertical plate of ethmoid and the vomer. Continuing laterally from the septum is the upper lateral cartilage which makes up the middle third of the nose and part of the nasal valve. At the lower third of the nose the lesser alar cartilage and the greater alar cartilage forms the nares. The external structure of the nose also contains several muscle groups which alter the shape of the nose such as dilating the nares (92).

The internal nasal passages consist of multiple different structures which contribute to the various physiological functions of the nose. The vestibule is the first point at which air from the external environment enters the respiratory tract. Stratified squamous epithelium cells line the vestibule. The vestibule also acts as an initial air filter, filtering out large particles via the vibrissae (268). Additionally, the vestibule is lined with thermoreceptors which makes it highly sensitive to changes in temperature (136) and airflow (45, 46). Stimulation of receptors within the vestibule can influence subjective nasal resistance (135).

Figure 1.6 has been removed due to copyright restrictions.

Figure 1.6: Anatomical image highlighting the skeletal structures surrounding the nose. Figure adapted from Mete et al. (2018) (213).

Posterior to the nasal vestibule is the nasal valve. The nasal valve is enclosed by the caudal end of upper lateral cartilage, medially by the septum and inferiorly by the base of the pyriform aperture (332). The nasal valve is bounded by the ostium internum at the anterior and the isthmus nasi at the posterior (230). The area of the nasal valve is described to be the narrowest region within the nasal passage with an estimated cross sectional area of 20-60mm^2 at the valve to 100-300mm^2 in the nasal cavum (332). The narrow structure of the nasal valve creates a change from laminar to turbulent airflow during inspiration to enhance heat, humidification and filtering between air and the nasal mucosa (50).

Within the nasal cavity are scroll like bony projections from the medial lateral wall known as turbinates or conchae. It consists of the superior turbinate, middle turbinate and inferior turbinate. Turbinates also contain erectile tissues and are highly vascular which play a role in nasal congestion (137) as well as the nasal cycle (54). The inferior turbinate plays a key function in temperature regulation, humidification and filtration of inspired air (21). The middle turbinate has a similar function to the inferior turbinate with the additional role of directing inspired air towards the olfactory epithelium (22). Both the inferior and middle turbinate are lined with psuedostratifed ciliated columnar epithelium. Mucosal glands are also found on both turbinates, but a higher proportion are located on the middle turbinate (21, 22). Venous sinusoids which act as erectile tissue regulates nasal airflow through sympathetic and parasympathetic neurons and thermal stimuli are predominantly found on the inferior turbinate (22). The superior turbinate contains olfactory neuroepithelium (168). The turbinates end at the level of the choanae, where both sides of the nasal cavity converge into the nasopharynx.

Figure 1.7 has been removed due to copyright restrictions.

Figure 1.7: Nasal turbinates

A) Coronal CT image of the nose. i) Middle turbinate ii) Inferior turbinate. Figure adapted from Mlynski (2013) (218).
B) Nasal anatomical figure showing a sagittal view of the nasal turbinates. Figure adapted from Mete et al. (2018) (213).

The olfactory region of the nose is located at the ceiling of the nasal cavity between the septum, middle and superior turbinate (268). The olfactory region of the nose is approximately 2cm^2 covered with olfactory neuroepithelium (220). The olfactory

neuroepithelium also extends to the anterior insertion of the middle turbinate (174). The olfactory neuroepithelium is a multicellular structure made up of olfactory receptor neurons, microvillar cells, basal cells and supporting cells (220). This epithelium is covered by a layer of olfactory mucus which facilitates odorant-receptor interactions and acts as a protective barrier from foreign pathogens (210, 251). Within the epithelium are odour sensing receptors known as olfactory neurons. These bipolar neurons have a dendrite extended to the olfactory epithelium and an axon to the glomeruli of the olfactory bulb through the cribriform plate (220, 243). In addition, the olfactory system has a close interaction with the trigeminal system which innervates the nasal cavity via the ophthalmic and maxillary branch of the trigeminal nerve (31). The trigeminal or somatosensory system is involved in sensing touch, temperature, and pain. Our sense of smell is mediated by both the olfactory and trigeminal systems. A few sensations activate either the olfactory or trigeminal system but most activate both systems. For example, vanillin and decanoic acid do not activate trigeminal senses and carbon dioxide triggers trigeminal sensations with no olfactory stimulus (68, 124). Several mechanisms of interaction between the trigeminal and olfactory systems have been described (124). There are suppression and enhancing effects between both systems depending on the concentration of the stimulus. Activity of the olfactory bulb is modulated by the trigeminal system. Neuropeptide compounds from trigeminal nerve fibres regulate olfactory receptor sensitivity. Olfactory perception is altered by trigeminal activation via a trigeminal reflex response. This mechanism acts as a protective mechanism to prevent inhalation of harmful substances (282).

Surrounding the nasal cavity are hollow spaces within the skull known as the paranasal sinuses. They consist of the maxillary, sphenoid, frontal, and ethmoid sinuses. These hollow spaces drain into the osteomeatal complex which is situated under the middle turbinate. The paranasal sinuses are thought to play a role in pulmonary function and immunity through the production of nitric oxide (187). Nitric oxide is a known for its role in vasodilation (126), neurotransmission (99) and immune response (28). Nitric oxide within the nasal cavity is continuously produced by epithelial cells which line the paranasal sinuses (189). Lundberg and colleagues (187) proposed that nitric oxide production reduces the risks of bacterial infection within the nasal cavity given the bacteriostatic effects of nitric oxide (197). A case study demonstrated that when nitric oxide production is inhibited within the sinuses,

the individual succumbed to sinusitis within 3 days (186). Nasal nitric oxide is also involved in regulating mucociliary clearance (131). Furthermore, individuals diagnosed with primary ciliary dyskinesia have markedly reduced nasal nitric oxide (188) and are highly prone to recurrent infections (336). In addition, nasal nitric oxide enhances oxygen uptake (190) and reduces pulmonary vascular resistance (191). Nasal nitric oxide is also involved in the thermoregulation of nasal air conditioning by modulating nasal vascular tone within the nasal mucosa (122).

1.5.2. Nasal cycle

The nasal cycle refers to the cyclic congestion and decongestion of the right and left nasal passages. This physiological feature was first described in 1895 by Kayser and colleagues (148) and again in 1927 by Heetderks and colleagues (115) where the venous cavernous tissue dilates and constricts reciprocally. In addition, the ethmoid sinuses have been found to contribute to the nasal cycle via similar mechanics (149). It is estimated that at least 70% of individuals exhibit a regular nasal cycle (244) with a cycle length ranging between 25 minutes to 6 hours (104, 115, 294).

Four patterns of the nasal cycle have been described to date (93). First is the classic nasal cycle which is the common definition used and is defined as a regular congestion and decongestion which alternates between the left and right nasal passages. As described previously the classic nasal cycle is seen in at least 70% of individuals (244). However, Flanagan and colleagues demonstrated that only 21% of individuals exhibited a nasal cycle based on a modified definition (95). Gilbert and colleagues similarly demonstrated based on cycle periodicity and rhythmicity parameters only 13% of participants met the original definition of a nasal cycle (104). Second, is an in-concert pattern whereby both nasal passages congest and decongest in parallel. It is estimated that the occurrence of an in-concert pattern occurs in 30-50% of individuals (93, 245). Third, is an irregular pattern defined as a combination of both classical and in concert patterns or simply no discernible pattern at all. Last, no cycle where there are no flow fluctuations in either nasal passages. Three no cycle patterns were described by Kern and colleagues based on rhinomanometry measurements (150). Short measuring times has been suggested as a possible contributor to the apparent absence of a nasal cycle in some individuals who have actually had a prolonged nasal cycle (107). This demonstrates the variation

in the types of nasal cycle patterns among individuals with some exhibiting more prominent cyclic patterns than others.

The nasal cycle is described to have two phases, a working phase referring to the decongested side of the nasal passage and a resting phase referring to the congested side of the nasal passage (169). The cyclic congestion and decongestion of the nasal passages tend to cause fluctuations in flow, cross sectional area and airway resistance of individual nasal passages (93, 104, 151). Despite these fluctuations, overall nasal resistance remains constant throughout the nasal cycle (151). In addition, flow characteristics change between laminar and turbulent flow when the nasal passages transition between resting and working phases (169).

Regulation of the nasal cycle is controlled by the autonomic nervous system (71, 284, 293). Stoksted et al. proposed that the nasal cycle is specifically regulated by a central sympathetic centre located in the hypothalamus (293). Other studies have also explored the role of the autonomic nervous system in regulating the nasal cycle in animal models. Electrical stimulation on the cat hypothalamus demonstrated nasal vasoconstriction (193). Studies on a dog model demonstrated nasal oscillations ceased after cervical sympathectomy (5). Similar findings are found in humans with high spinal cord injury (>T1) but the absence of a nasal cycle appears to be reversible over time (274).

The nasal cycle has been described to have several physiological roles. Nasal cycle has been described to play a role in the air conditioning function of the nose (333). White and colleagues (333) suggested that the nose maintains a hydration of the airway surface liquid by regulating inter nasal air flow via the nasal cycle. This is in line with previous theories that the nasal mucosa undergoes a working and resting phase during the nasal cycle (169).

Mucociliary clearance has been reported to be affected by the nasal cycle, with rapid clearance in the obstructed nostril (179). In contrast, a recent study found rapid mucociliary clearance in the patent nostril (290). The differences in findings were attributed to different methodologies in each study. The nasal cycle may also be described to play a role in nasal defence through the excretion of plasma exudate resulting from congestion and decongestion of the nasal venous sinusoids (72).

Positional effects have been found to influence nasal cycle. Hasegawa et. al. demonstrated a change in unilateral nasal resistance in the more congested nostril between seated and supine positions (114). In addition, the amplitude of the nasal cycle was found to increase in the order of upright, lateral and supine (53). Lateral position changes during sleep have been shown to cause phase reversals in the nasal cycle where the resting phase or congestion moves to the lower nostril (262).

The nasal cycle period during sleep is notably longer in duration compared to wakefulness (143, 154, 262). The reversal of the cyclic phase was found to occur only in REM sleep and tended to coincide with postural changes (154). Furthermore, the reversal of nasal cyclic phases during REM sleep is associated with the synchronisation with the sleep cycle (312).

1.5.3. Nasal resistance

The nasal passages account for approximately 70% of upper airway resistance during inspiration (8). The nasal valve is the narrowest region of the nasal passages with the smallest cross-sectional area and a region of greatest airflow resistance. Approximately 30% of total nasal airflow resistance originates from the nasal valve (111).

The cause of nasal obstruction is categorised into anatomical contributors and physiological contributors. Anatomical causes of nasal obstruction include septal deviation, inferior turbinate hypertrophy and nasal valve collapse (44). Approximately 70% of individuals experience nasal obstruction from an anatomical cause which generally requires surgical interventions (44). Physiological causes of nasal obstruction are mucosal inflammation and secretions which generally present as rhinitis or rhinosinusitis (291). The prevalence of rhinitis and rhinosinusitis range from 10-20% (18, 291). At least two thirds of people with rhinitis and rhinosinusitis experience nasal obstruction (18, 291). Typical nasal airway resistance in healthy individuals is within the range of 2-3 $cmH_2O/L/s$ (52) and symptoms of nasal obstruction are present when nasal resistance is well above this range (205).

The following section focuses on the effects of nasal resistance on body posture, mandibular advancement and obstructive sleep apnoea and the quantification of nasal resistance by rhinomanometry.

1.5.3.1. Nasal resistance measurement by rhinomanometry

Rhinomanometry is the concurrent measure of nasal airflow and pressure. It provides a functional assessment of the nasal airway (276). This technique is commonly used clinically and in research. Rhinomanometry quantifies the pressure drop across the nasal cavity at a specific point on the breathing cycle. It assumes a constant flow rate across the nasal passage, although physiologically this is not the case (217). Nasal resistance is expressed in terms of resistance according to the International Committee on Standardisation of Rhinomanometry (47). Nasal resistance is calculated based on Ohm's law $R = \Delta P/\Delta V$, where ΔP is the pressure drop across the nasal cavity and ΔV is the change in airflow across the nasal cavity. Rhinomanometry is performed using either the anterior method, posterior method or postnasal method.

Anterior rhinomanometry is performed by measuring nasal pressure on one side of a sealed nasal cavity and flow on the other open nasal cavity. An airtight mask connected to a pneumotachograph is used for flow measurement and a tube to measure pressure is placed at the nasal vestibule sealed with tape. Anterior rhinomanometry is the recommended form of measuring nasal resistance clinically (47). Limitations of anterior rhinomanometry include breathing is artificially augmented (165), distortion of the nasal vestibule during measurements (49) and nasal resistance can only be measured unilaterally. Patients with septal deviations are contraindicated for anterior rhinomanometry and posterior rhinomanometry will be required (60). Total nasal resistance is derived mathematically by Ohm's law of parallel resistors.

Posterior rhinomanometry (Figure 1.8ii) is the gold standard approach to quantify nasal resistance. It involves measuring nasal pressure with a pressure catheter inserted perorally to the level of the oropharynx. Posterior rhinomanometry overcomes several limitations of anterior rhinomanometry such as total nasal resistance can be measured without distortion to the nasal vestibule and breathing is not artificially augmented (165). However, coordination is required to prevent the soft palate from isolating the oropharynx (49, 60) and results may be affected by gag reflexes (48). Technical expertise is also required to position the pressure catheter correctly with a variation of 8% between personnel (165). Postnasal rhinomanometry (Figure 1.8i) is a similar method but involves placing the pressure catheter

intranasally to the level of the nasopharynx. The effect of the catheter on nasal resistance measurements postnasal has been deemed negligible (51). Moreover, nasal resistance values measured are 10% less than posterior rhinomanometry as it excludes oropharyngeal pressure (51) thus, providing an accurate measure of nasal resistance.

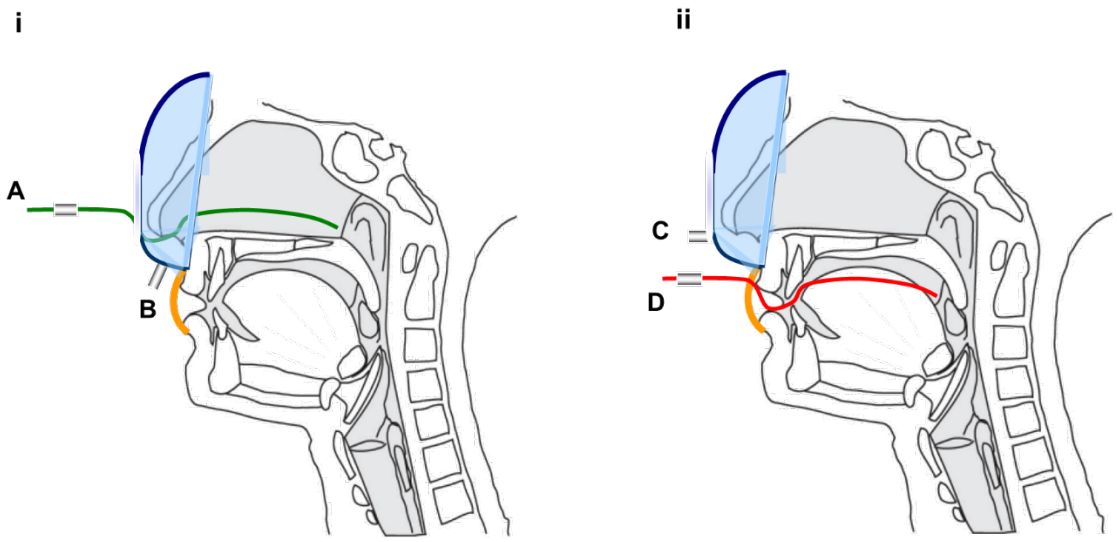

Figure 1.8: Position of pressure catheter in postnasal rhinomanometry and posterior rhinomanometry

i) Postnasal rhinomanometry. A=Pressure tipped catheter positioned intranasally along the nasal floor to the level of the choanae or nasopharynx. B=Mask pressure measured from the sealed nasal mask. ii) Posterior rhinomanometry. C=Mask pressure measured from the sealed nasal mask. D=Pressure tipped catheter positioned perorally to the oropharynx.

1.5.3.2. Body posture and nasal resistance

Like the nasal cycle, nasal resistance is influenced by body posture. Early studies conducted by Rundcrantz and colleagues demonstrated that nasal resistance increases in individuals with allergic rhinitis in the supine position (265). In a subsequent study, Rundcrantz demonstrated that nasal resistance increases in a stepwise manner at various degrees of dorsal recumbency in healthy individuals, individuals with allergic rhinitis and individuals with the common cold (264). This increase in nasal resistance is attributed to the increase in venous pressure in the head and neck resulting in the filling of the nasal cavernous tissues upon assuming a supine position. In healthy individuals nasal resistance changes by approximately 8% when body posture changes from seated to supine (326). Venous pressure increases by at least 6 mmHg when transitioning from an upright to supine position (138). Kase and colleagues further supported this hypothesis by demonstrating a

16% reduction in cross-sectional area of the nasal passages when transitioning from seated to supine (146). Other subsequent studies also demonstrated reductions in nasal cross-sectional area with positional changes in healthy individuals (233) and patients with rhinitis (263). Alternatively, Hasegawa proposed that alterations in the sympathetic tone to the nasal mucosa may explain the postural effects on unilateral nasal resistance which dictates total nasal resistance and is modulated by the nasal cycle (114).

Upon assuming lateral recumbency, nasal resistance increases significantly in the ipsilateral nostril (52). Rao and colleagues further demonstrated that pressure applied to the axillary and shoulder increases nasal ventilation in the ipsilateral nostril similar to assuming a lateral recumbent position (255). A similar finding was also reported in another study which quantified nasal resistance and found increased nasal patency in the contralateral nostril (9, 56). Rao proposed that activation of nerve fibres within the brachial and axillary artery produces a reflex response which changes nasal resistance via the sympathetic pathway (255). However, Davies suggested that the reflex response is likely triggered by pressure receptors in the skin which causes the change in nasal sympathetic tone (56). This reflex response is known as the coporo-nasal reflex (248).

1.5.3.3. OSA and nasal resistance

Nasal obstruction is an associated risk factor for sleep disordered breathing (345). It is estimated that a third of people with untreated OSA experience nocturnal nasal obstruction (320).

Several studies have demonstrated associations between nasal obstruction and OSA using various methodologies. Artificially induced nasal obstruction via nasal packing induces OSA in normal healthy participants (299, 352) and worsens OSA severity in those who already have OSA (306). Similarly, partial nasal obstruction (unilateral obstruction) increases OSA associated microarousals (171). Other nasal packing studies in septoplasty, rhinoplasty and epistaxis patients demonstrate significant decreases in arterial blood oxygen partial pressures (42, 234, 288) and an increases in the frequency and duration nocturnal oxygen desaturation episodes (133). Nasal anaesthesia during sleep to simulate reduced airflow stimulation to nasal receptors during nasal obstruction also increases the number of sleep

disordered breathing events (334). Virkkula and colleagues investigated relationships between nasal resistance and nasal volumes with the AHI and oxygen desaturation index (324). Nasal volumes were inversely correlated to both AHI and oxygen desaturation index in the study group. Notably, both AHI and oxygen desaturation index were positively correlated to supine total nasal resistance in non-obese patients. A similar finding was also demonstrated in a recent study with a non-obese cohort in additional oximetry variables such as nadir oxygen saturation and the total time with oxygen saturation below 90% (T90) (216). Another study by Virkkula further suggested that combined nasal resistance and the position of the mandible while supine are independent contributors to OSA severity in non-obese patients (323). Findings from these studies suggest that nasal obstruction may play a significant role in OSA pathophysiology of non-obese patients.

Approximately 60% of OSA patients experience some degree of rhinitis as a cause of nasal obstruction (283). A study from the 1980s found that patients with allergic rhinitis had longer and more frequent OSA during symptomatic periods of nasal obstruction (209). Lavie and colleagues (172) compared sleep disordered breathing in patients with and without allergic rhinitis. Patients with allergic rhinitis had a significantly higher number of microarousals associated with sleep disordered breathing compared to those without allergic rhinitis (171). Unfortunately, this study did not report the OSA severity of the patients and nasal resistance was not measured. Kramer and colleagues (160), compared patients with non-allergic rhinitis with eosinophilia syndrome (NARES) and healthy individuals and demonstrated that patients with NARES tend to be diagnosed with severe OSA with a higher hypopnoea index. The hypopnoea index, arousal index and the AHI correlated inversely with nasal flow in patients with NARES (160). A more recent study (144), further explored the differences in allergic rhinitis and non-allergic rhinitis patients and found that non-allergic rhinitis patients had frequent apnoeas and were sleepier based on the Epworth Sleepiness Scale (ESS).

Postural effects on nasal resistance in patients with OSA have also been investigated. De Vito and colleagues demonstrated an increase in supine nasal resistance from seated in 16 out of 36 patients with OSA (57). In contrast, Hellgren and colleagues showed no significant change in nasal resistance from seated to supine position (118). There are currently no studies that have investigated the effects of lateral posture on nasal resistance in patients with OSA.

Population based studies such as the Wisconsin Sleep Cohort study found nasal obstruction is not directly associated with severity of sleep disordered breathing but is a risk factor for sleep disordered breathing (345). A follow up on the same cohort 5 years later maintained that nasal obstruction is a strong independent risk factor for habitual snoring but not associated with habitual snoring and complete apnoeas (346). This finding is also in line with a recent study, which demonstrates that individuals with high nasal resistance are three times more likely to have more frequent hypopnoeas based on the hypopnoea apnoea ratio (121). Furthermore, a Japanese study, demonstrated that people with chronic nasal obstruction are 5 times more likely to have habitual observed apnoea (317). In addition, there were no associations between high nasal resistance and habitual snoring. However, high nasal resistance was associated with smoking (322). Similarly, De Vito and colleagues demonstrated no differences between OSA and degree of nasal resistance (57). A study by Atkins and colleagues also demonstrated nasal resistance was not a risk factor for OSA (6). In contrast, Lofaso and colleagues, showed a weak relationship between daytime nasal resistance and the AHI (184). The variations in findings in the relationship between nasal resistance and OSA is unknown but may relate to differences in patient population, demographics, experimental methodology and design.

Several theories have been proposed to explain the association between nasal obstruction and OSA. The Starling resistor model which describes the upper airway as a tube with a collapsible section suggests that negative intraluminal pressure could be generated from a narrowed opening resulting in upper airway occlusion (289). However, this model does not account for the transition from nasal to oral breathing to compensate for insufficient nasal airflow. Oral breathing during sleep is not ideal as upper airway resistance is significantly increased compared to nasal breathing (94). This increase in upper airway resistance from oral breathing is due to decreases in the calibre at the velopharynx and retroglossal region resulting from jaw opening (94, 173). Furthermore, oral breathing during sleep compromises the ability of the upper airway dilator muscles to maintain upper airway patency (214). Nasal breathing may be beneficial physiologically versus oral breathing because upper airway dilator muscles activity is higher (17), nasal receptors are stimulated resulting in increased minute ventilation and inspiratory flow rate (208) and ventilatory responses to hypercapnia are lower (130). In addition, nitric oxide produced in the

paranasal sinuses act as an aerocrine regulating respiratory muscle activity and pulmonary ventilation perfusion ratio (112). Oral breathing which bypasses the nasal cavity may create an inhibitory effect on nasal ventilatory reflex and reduce nitric oxide delivered down the respiratory tract thereby contributing to OSA (102, 334).

High nasal resistance has also been associated with OSA treatment outcome in patients with OSA. Initial acceptance of CPAP therapy is higher in patients with OSA with lower nasal resistance (127, 297). In addition, nasal disease causing obstruction is a key factor in early discontinuation of CPAP therapy (127). Zeng and colleagues, also described that increased nasal resistance negatively impacts oral appliance treatment outcome in patients with OSA (349).

1.5.3.4. Mandibular advancement and nasal resistance

There are two studies that have evaluated the relationship between mandibular advancement and nasal resistance in healthy individuals. Hiyama and colleagues (119) compared nasal resistance at three mandibular positions. Nasal resistance was reduced as the mandible was advanced (119). Nasal resistance in this study however was measured only in the upright seated position. A couple of years later, Okawara and colleagues demonstrated a similar finding where nasal resistance decreased as the mandible was advanced in the seated and supine positions in healthy individuals (235). The effect of mandibular advancement on nasal resistance has not been explored in people with obstructive sleep apnoea.

1.6. Aims and outline of subsequent chapters

The overall aim of this thesis is to use respiratory phenotyping techniques to evaluate the effect of oral appliance therapy on upper airway physiology and to identify potential phenotypic differences between responders and incomplete responders to therapy.

In Chapter 2 the aim is to understand the effect of body posture and mandibular advancement on nasal resistance measured using gold standard methodology in people with OSA. In addition, the efficacy of a novel oral appliance with a built-in oral airway is investigated including in people with OSA with high nasal resistance who typically do not do well with oral appliance therapy.

In Chapter 3, I aimed to recruit the clinically relevant group of incomplete responders to oral appliance therapy to compare therapeutic CPAP requirements and negative pressure swings within the pharyngeal airway between combination therapy (CPAP plus oral appliance therapy) versus CPAP alone using gold standard physiology methodology.

In Chapter 4, I prospectively investigate the effect of baseline OSA pathophysiological traits and nasal resistance on oral appliance therapy using gold standard respiratory phenotyping methodology and validated computational methodology. In addition, I assess the efficacy of a next generation nylon-based novel oral appliance with built-in oral airway.

Chapter 5 briefly summarises the study findings and highlights areas for future research investigation.

2. Efficacy of a novel oral appliance and the role of posture on nasal resistance in obstructive sleep apnea

I have published the work conducted in this chapter (313):

Tong, B. K., et al. (2020). "Efficacy of a novel oral appliance and the role of posture on nasal resistance in obstructive sleep apnea." J Clin Sleep Med 16(4): 483-492.

2.1. Abstract

Study Objectives: High nasal resistance is associated with oral appliance (OA) treatment failure in OSA. A novel OA with an in-built oral airway has been shown to reduce pharyngeal pressure swings during sleep and may be efficacious in those with high nasal resistance. The role of posture and mandibular advancement on nasal resistance in OSA remains unclear. This study aimed to determine the: 1) effects of posture and mandibular advancement on nasal resistance in OSA and 2) efficacy of a new OA device including in patients with high nasal resistance.

Methods: A total of 39 people with OSA (7 females, AHI (mean±SD)= 29±21events/h) completed split-night polysomnography with and without OA (order randomized). Prior to sleep, participants were instrumented with a nasal mask, pneumotachograph, and a choanal pressure catheter for gold standard nasal resistance quantification seated, supine and lateral (with and without OA, order randomized).

Results: Awake nasal resistance increased from seated, to supine, to lateral posture (median [IQR]= 1.8 [1.4,2.7], 2.7 [1.7,3.5], 3.4 [1.9,4.6]cmH_2O/L/s, $p<0.001$). Corresponding measures of nasal resistance did not change with mandibular advancement (2.3 [1.4,3.5], 2.5 [1.8,3.6], 3.5 [1.9,4.8]cmH_2O/L/s, $p=0.388$). The median AHI reduced by 47% with OA therapy (29±21 vs. 18±15events/h, $p=0.002$). Participants with high nasal resistance (>3cmH_2O/L/s) had similar reductions in AHI versus those with normal nasal resistance (61 [-8,82] vs. 40 [-5,62]%, $p=0.244$).

Conclusions: Nasal resistance changes with posture in people with OSA. A novel oral appliance with an in-built oral airway reduces OSA severity in people with OSA, including in those with high nasal resistance.

Keywords: sleep-disordered breathing, upper airway physiology, mandibular advancement therapy, lung.

2.2. Introduction

Obstructive sleep apnea (OSA) is a common disorder characterized by recurrent pauses in breathing during sleep. This results in sleep disruption and blood oxygen desaturations. Common symptoms of untreated OSA include excessive daytime sleepiness and impaired cognitive function. Other co-morbidities include cardiovascular disease, hypertension (247) and stroke (340).

Continuous positive airway pressure (CPAP) is the gold standard treatment for OSA (1, 162). It is highly efficacious in reducing breathing disturbances during sleep and can improve daytime sleepiness, cognitive function, blood pressure and quality of life outcomes (10, 25, 85, 87, 185). Despite the health benefits of CPAP, only about half of all patients with OSA are compliant with CPAP therapy (339). Many people complain that CPAP is cumbersome, have difficulty tolerating high pressures, and experience issues with mask leak (86, 339) which may have an adverse impact on adherence and compliance.

Oral appliance devices are used as an alternative therapy to CPAP. Oral appliances work via protrusion of the mandible, which can increase pharyngeal airway caliber through an increase in the lateral dimensions (33, 43). Oral appliance devices are typically well-tolerated with one study reporting compliance of 83% after a year of treatment (62). However, efficacy varies, with only approximately 50% of patients achieving complete resolution of OSA (AHI <5 events/h) (304). Successful treatment outcomes with oral appliance therapy for OSA are challenging to predict. Gender, OSA severity, subtypes of OSA (position dependent OSA, REM or NREM predominant OSA), age, BMI, craniofacial structure and nasal resistance are factors that have been identified as contributors to treatment success (120, 181, 199, 303, 349).

High nasal resistance is recognized as a risk factor for OSA (345). Several studies have shown that high nasal resistance contributes to increased OSA severity (299, 306, 352). Additionally, patients with OSA and high nasal resistance tend to be intolerant of CPAP and oral appliance therapy (297, 349). Nasal resistance is body

position dependent with increases from seated to the supine position in healthy individuals and those with rhinitis (264). A similar effect has also been observed in people with OSA (57, 349). However, one study did not find a positional effect of nasal resistance in OSA (118). The effects of lateral body position on nasal resistance in OSA is unknown. In addition, the role of mandibular advancement on nasal resistance in OSA has been minimally studied. Two studies demonstrated a reduction in nasal resistance in healthy individuals at different levels of mandibular advancement while seated (119, 235). In contrast, Zeng and colleagues found no change in seated nasal resistance with mandibular advancement at therapeutic levels in people with OSA in both responders and non-responders to mandibular advancement therapy (349). The same study showed an increase in nasal resistance with mandibular advancement in the supine position in non-responders (349).

A novel oral appliance with an in-built oral airway, which can allow for oral breathing without mouth opening and consequent mandible retraction, may be a suitable therapeutic option for patients with OSA and nasal obstruction. An initial mono-block prototype device was shown to reduce OSA severity by an average of 60% with compliance of 80% in patients with and without nasal obstruction assessed subjectively (170). A more recent pilot study investigated a two-piece titratable oral appliance with an in built oral airway and found that pharyngeal pressure swings were reduced when the device oral airway was open (3). However, efficacy data for this newer two-piece oral appliance device are not yet available.

Accordingly, the goals of this study were to determine the: 1) effect of body posture and mandibular advancement on nasal resistance in OSA and 2) efficacy of a novel oral appliance with an in-built oral airway in patients with OSA including those with high nasal resistance. We hypothesized that nasal resistance would vary with posture and mandibular advancement in people with OSA and that the oral appliance would reduce OSA severity including in people with high nasal resistance.

2.3. Materials and methods

2.3.1. Participants

39 participants with OSA were recruited from the Prince of Wales Hospital sleep clinic and local private sleep clinics. Participants were documented to have OSA (AHI >10 events/h). Untreated and CPAP intolerant participants were included in the study. All participants were recommended for oral appliance therapy by their treating sleep

physician. Participants were excluded if they were contraindicated for oral appliance therapy by the study dentist (periodontal disease, insufficient teeth for device retention or a strong gag reflex), were diagnosed with central sleep apnea (>5 events/h), had intellectual or mental impairment which rendered them unable to provide informed consent, were pregnant or nursing mothers or taking medications known to affect sleep or breathing. All participants provided written informed consent prior to enrolment. The study was approved by the South Eastern Sydney Local Health District Human Research Ethics Committee and the protocol was pre-registered on the Australian New Zealand Clinical Trials Registry (ANZCTRN 12617000492358, Part A).

2.3.2. Protocol

2.3.2.1. Dental visits

Initially, participants with a referral for oral appliance therapy from their treating sleep physician were scheduled for a dental assessment with a dentist experienced in fitting oral appliance devices. During the visit, dental impressions were taken and the maximum tolerable level of mandibular advancement was determined. Participants were then scheduled for a follow-up dental visit for fitting and initial titration of the oral appliance. A novel custom-made oral appliance device (O_2Vent™ T, Oventus Medical, Indooroopilly, QLD, Australia) was used (Figure 2.1). The device is a two-piece titratable oral appliance that fits on the lower and upper teeth. An in-built hollow core on the maxillary piece enables oral breathing through the device whilst maintaining mandibular advancement as well as lip seal around the device opening. This allows air to be delivered directly to the oropharynx through the device without mouth opening, which tends to cause mandibular retraction and airway narrowing.

Figure 2.1: An image of the novel oral appliance used in this study

The oral appliance is a two piece titratable device with a hollow core in the maxillary arch to allow oral breathing directly to the oropharynx without mouth opening and mandibular retraction.

Oral appliance therapy commenced at approximately 50-60% of each participant's maximal mandibular advancement range, followed by an 8-12 week acclimatization period. During this time, the oral appliance was incrementally advanced to at least 75% of maximum mandibular advancement. The majority of participants were contacted every two weeks by phone during the acclimatization period to assess subjective compliance and perceived changes in their sleep. Specifically, participants were asked: "Are you wearing the device every night? If no, how long per night and how many times per week?" and "Did you notice any differences in your sleep?". Following acclimatization, participants were reassessed by the dentist immediately prior to their treatment efficacy sleep study where any necessary device adjustments were made to ensure comfort and maximum tolerable advancement.

2.3.2.2. Awake nasal resistance assessments

Awake nasal resistance was objectively quantified (see below) in the evening prior to the sleep study. At least 5 minutes of quiet nasal breathing in 3 body positions (supine, seated upright, and left lateral recumbent) with and without mandibular advancement were assessed. Both body positions and order of mandibular advancement were randomized. The in-built oral airway of the oral appliance device was blocked to ensure nasal breathing during the nasal resistance protocol.

2.3.2.3. Overnight polysomnography

Standard in-laboratory split night polysomnography was conducted to assess oral appliance treatment outcome. The study allocation order (oral appliance vs. no oral appliance) was randomized to either oral appliance followed by no oral appliance or no oral appliance followed by oral appliance (Figure 2.2). Where possible, at least one period of REM sleep was obtained during the first intervention period before switching to the other intervention arm (either oral appliance or no oral appliance).

2.3.3. Participant set-up and equipment

2.3.3.1. Nasal resistance set up

Nasal resistance was measured using gold standard methodology (337). Briefly, participants were instrumented with a modified non-vented nasal mask (ComfortGel, Phillips Respironics, Murrysville, PA, USA) with a pneumotachograph (Series 3700A, Hans-Rudolph, Shawnee, KS, USA) connected to a differential pressure transducer (DP-45, Validyne, Northridge, CA, USA) to measure flow, in addition to another pressure transducer (DP45, Validyne) for mask pressure. Choanal pressure was measured using a pressure transducer tipped catheter (MPR-500, Millar, Houston, TX, USA) inserted via the most patent nostril to the level of the choanae. Data acquisition was performed using a 16-bit analogue to digital converter (Power 1401, Cambridge Electronic Design, Cambridge, UK) and data acquisition software (Spike 2, version 7.2, Cambridge Electronic Design, Cambridge, UK).

2.3.3.2. Overnight polysomnography

Electroencephalograms (F3, F4, C3, C4, O1, O2, referenced to A1-A2), electrooculograms, surface submental and leg electromyograms, pulse oximetry, body position, nasal pressure flow, oronasal thermistor flow, thoracic and abdominal respiratory bands, and snore sound were measured. Data acquisition was conducted using a Level 1 diagnostic sleep system (Alice 6 LDxN, Phillips Respironics, Murrysville, PA, USA) and data acquisition software (Sleepware G3, version 3.7.4, Phillips Respironics, Murrysville, PA, USA).

2.3.3.3. Data analysis

Nasal resistance measurements were analyzed on a breath-by-breath basis using in-house semi-automated software (229). Quantification of nasal resistance commenced 2 minutes after each change in body position. Nasal resistance was calculated as the difference between choanal pressure and mask pressure at a flow rate of 0.2L/s (337). In cases where the participant did not achieve a nasal airflow of 0.2L/s or higher, nasal resistance was calculated at either 0.1L/s or 0.05L/s as necessary. Values for nasal resistance of >3cmH_2O/L/s were deemed high , as defined previously (205).

Polysomnography data were scored for sleep and respiratory events according to AASM criteria (23). Scoring was performed by a single board-registered sleep technologist (RPSGT) who was blinded to the order of treatment. Responders to oral appliance therapy were defined according to several commonly used definitions: 1) treatment AHI <5 events/h, 2) treatment AHI <10 events/h, 3) ≥50% reduction in baseline AHI, and 4) proportion of participants who had a reduction in OSA severity category (e.g. from severe to moderate or moderate to mild; where mild >5 and <15 events/h, moderate ≥15 and <30 events/h and severe ≥30 events/h).

2.3.4. Statistical analysis

A mixed model analysis was used to determine the effects of body position (seated, supine and lateral recumbent) and the effect of mandibular advancement (with and without oral appliance therapy) on nasal resistance (SPSS version 24, IBM). In the absence of an interaction, Friedman repeated measures ANOVA on ranks (SigmaPlot version 12.5, IBM) were performed to examine the effects of body position on nasal resistance (with and without oral appliance). Pairwise comparisons were performed according to the Student-Newman-Keuls method (SigmaPlot version 12.5, IBM). Sleep and breathing parameters were compared between conditions (no oral appliance vs. oral appliance) using two-tailed, paired Student's t-tests for normally distributed data or Wilcoxon Signed Rank Tests (SigmaPlot version 12.5, IBM) for non-normally distributed data (Shapiro-Wilk). Data are reported as mean±SD or median (inter-quartile range [IQR]) for non-normally distributed variables.

2.4. Results

2.4.1. Participant characteristics

41 participants fitted with an oral appliance for the study returned for an overnight polysomnography to assess treatment response. Data for 3 participants were excluded from analysis (2 individuals were found not to have OSA without the oral appliance and 1 had insufficient sleep). Thus, data from 39 participants with OSA were analyzed for awake nasal resistance measurements and 38 for oral appliance efficacy (see Figure 2.2 for CONSORT diagram). Participant characteristics are detailed in Table 2.1.

Sex	7♀, 32♂
Age (years)	49 ± 11
Body mass index (kg/m^{-2})	29 ± 4
% Maximum mandibular advancement	80 ± 14
Epworth sleepiness scale	8 ± 4

Table 2.1: Participant characteristics

Epworth sleepiness scale scores was obtained during oral appliance therapy. Data are mean±SD unless otherwise stated. n=39.

2.4.2. Effect of posture and mandibular advancement on awake nasal resistance

Awake nasal resistance increased from seated, to supine, to lateral posture with and without mandibular advancement ($p<0.001$, Figure 2.3). However, mandibular advancement had no overall effect on nasal resistance ($p=0.338$, Figure 2.3) and there was no interaction effect with posture ($p=0.12$). When separated according to responders (n=18) vs. non-responders (n=21), defined as >50% reduction in AHI with oral appliance therapy, non-responders had an increase in nasal resistance with mandibular advancement when seated (1.8 [1.3, 2.4] vs. 2.4 [1.2, 3.3]cmH_2O/L/s, $p=0.007$). This increase in nasal resistance with mandibular advancement did not occur in responders (2.0 [1.5, 3.2] vs. 2.3 [1.5, 4.2]cmH_2O/L/s, $p=0.347$). There was no difference in nasal resistance with mandibular advancement in responders or non-responders compared to no advancement in the supine or lateral postures (data not shown).

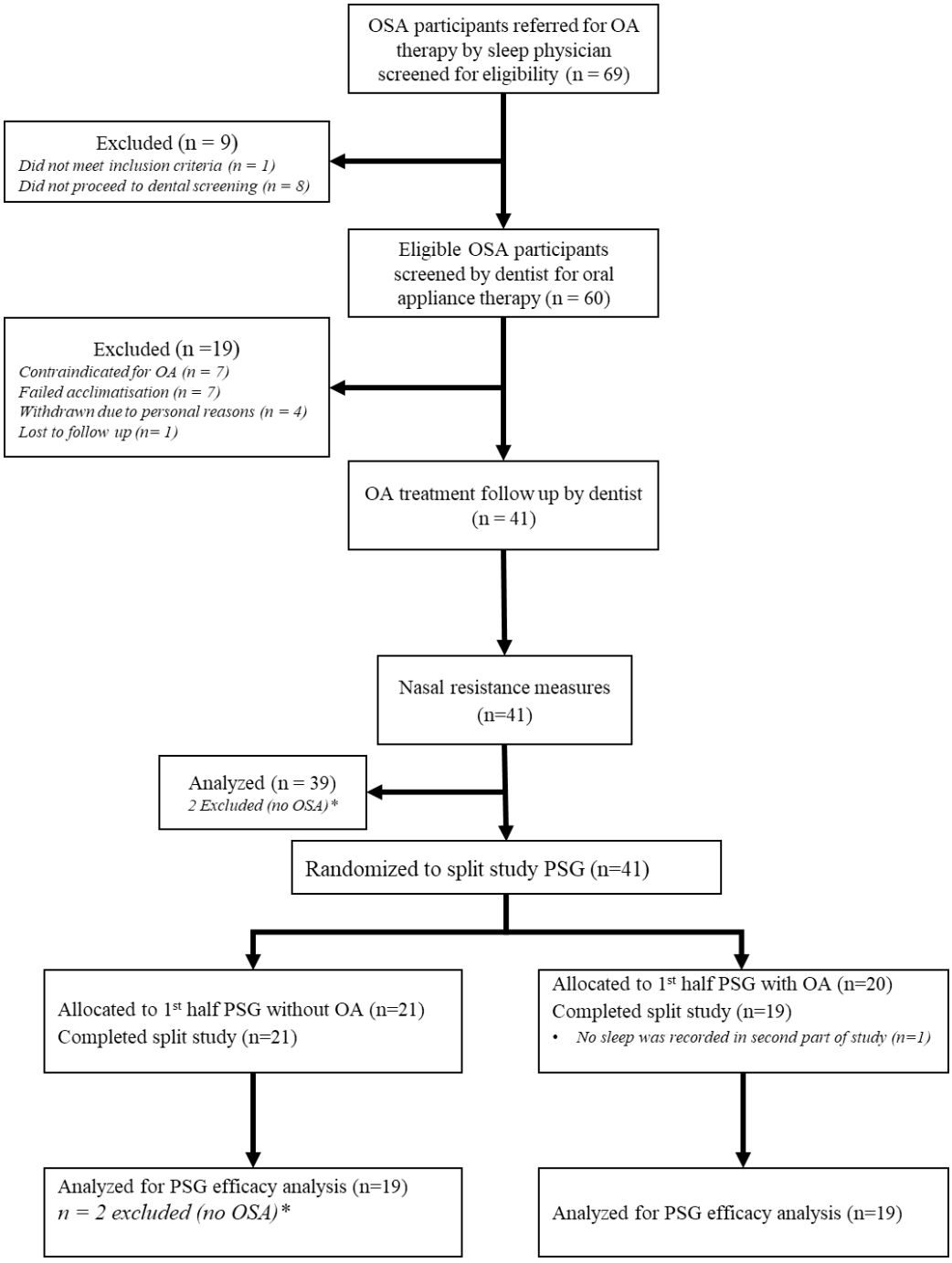

Figure 2.2: CONSORT diagram detailing participant recruitment and flow through the study procedures.

n=69 participants recommended for oral appliance therapy were screened for eligibility. n=60 eligible participants were screened by a qualified sleep dentist for oral appliance therapy. Following 8-12 weeks of acclimatization to oral appliance therapy, n=41 participants were studied for awake nasal resistance measurements and oral appliance efficacy (split night in-laboratory PSG). N=2 participants were excluded from analysis as they were found not to have OSA during the split night PSG. n=1 participant was excluded from analysis as there was no sleep recorded in the second portion of the sleep study. Data from a total of n=39 participants were analyzed for awake nasal resistance and n=38 for the efficacy split night PSG. * indicates the same participants without OSA were excluded from analysis. OA: oral appliance, OSA: obstructive sleep apnea, PSG: polysomnography.

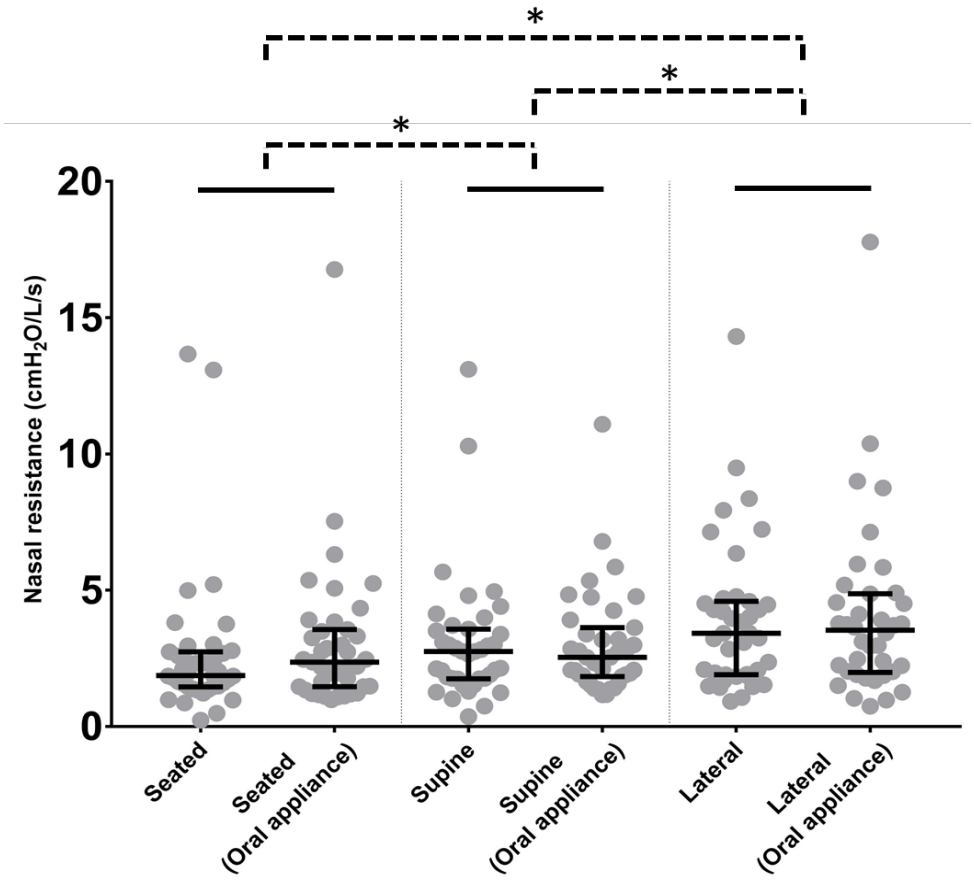

Figure 2.3: Awake nasal resistance scatter plots at different postures with and without an oral appliance (n=39)

Each data point denotes an individual participant. Lines and error bars indicate the median and interquartile ranges. * indicates a significant difference (P<0.05) in nasal resistance between each posture. Refer to the Results section for further detail.

2.4.3. Effect of mandibular advancement on OSA severity and sleep parameters

Oral appliance therapy significantly reduced OSA severity, as measured by the total AHI, by 47 [-6.1, 70]% (Figure 2.4a). Table 2.2 summarizes the effects of oral appliance therapy on other key polysomnographic variables. Similar to the total AHI, supine AHI (48 [2.2, 69.0]%) and NREM supine AHI (58 [6.0, 88.8]%) were significantly reduced with oral appliance therapy. However, oral appliance therapy did not change the total REM AHI in those who had REM sleep during both conditions (31±22 vs. 24±17, p=0.113, N=28) but did reduce the supine REM AHI (Table 2). When present, hypopneas were of shorter duration during oral appliance therapy.

14 participants were classified to have high nasal resistance in the supine position. Oral appliance therapy reduced OSA severity (total AHI) in these individuals by 61 [-8, 82]%. There was no difference between the percentage reduction in OSA severity between participants with high versus low nasal resistance (Figure 2.4b).

	No therapy	Oral appliance	P-value
Sleep efficiency (% sleep)	88 (78, 91)	89 (81, 94)	0.567
Total sleep time (mins)	181 ± 56	190 ± 53	0.545
Stage 1 sleep (% total sleep time)	11 (7, 17)	7 (4, 11)	<0.001
Stage 2 sleep (% total sleep time)	57 ± 10	53 ± 12	0.062
Stage 3 sleep (% total sleep time)	11 ± 13	17 ± 12	0.092
REM sleep (% total sleep time)	18 (11, 29)	23 (13, 30)	0.31
Wake after sleep onset (minutes)	20 (11, 35)	12 (8, 25)	0.026
Arousal index (#arousals/h sleep)	21 (16, 30)	14 (10, 20)	<0.001
Percent supine (% total sleep time)	67 ± 31	78 ± 27	0.01
NREM supine AHI (#events/h)	33 ± 25	17 ± 18	<0.001
REM supine AHI (#events/h)	41 ± 21	26 ± 17	0.003
Total supine AHI (#events/h)	36 ± 2	21 ± 18	<0.001
Hypopnea event duration (s)	23 ± 4	21 ± 7	0.049
Nadir SpO_2 (%)	87 (81, 91)	89 (83, 90)	0.51
Total ODI (3%)	14 (8, 34)	8 (3, 23)	0.004
T90 (mins)	0.6 (0.1, 4.8)	0.25 (0, 4.1)	0.01
T90 (%TST)	0.3 (.01, 2.8)	0.1 (0, 2)	0.023

Table 2.2: Polysomnography data on versus off oral appliance therapy

Data are mean ± SD or medians with interquartile ranges in parentheses. AHI: Apnea hypopnea index; REM: Rapid eye movement; NREM: Non-rapid eye movement sleep; ODI: Oxygen desaturation index; TST: Total sleep time; SpO_2: Estimated blood oxygen saturation via pulse oximetry; T90: time spent with a blood oxygen saturation level below 90%. Note: supine REM AHI data during both conditions were available in n=21. All other values n=38.

The proportion of treatment responders on oral appliance therapy according to commonly used definitions are summarized in Table 2.3. Oral appliance therapy reduced the total AHI by 50% or more in half of the participants. Approximately 50% of participants had a reduction in OSA severity on oral appliance therapy. Table 2.4 further illustrates treatment response rates of participants categorized according to the presence of high versus low nasal resistance.

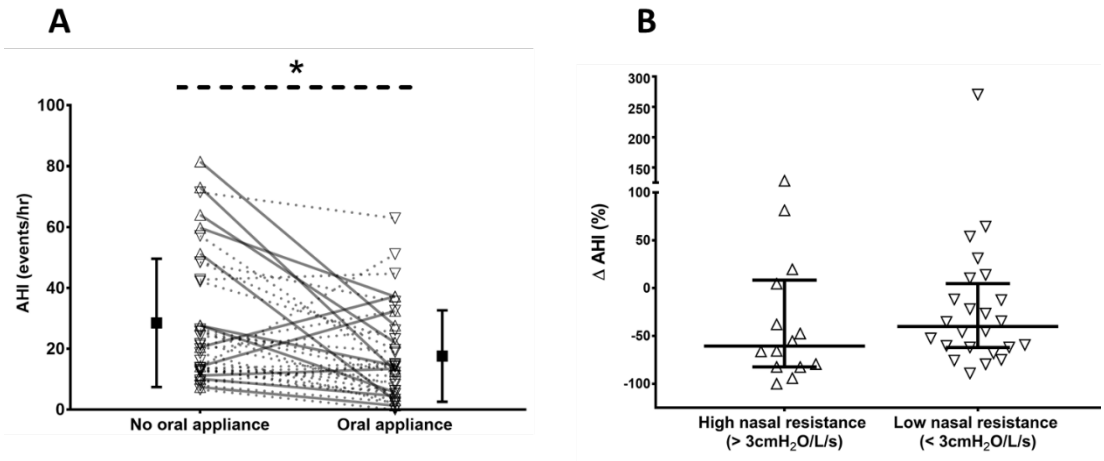

Figure 2.4: Effect of the novel oral appliance on OSA severity

a) Effect of oral appliance therapy on obstructive sleep apnea severity (total apnea hypopnea index: AHI). Black squares with error bars=group mean±SD. b) Percentage reduction in total AHI with oral appliance therapy between people with high and low nasal resistance. Each data point denotes an individual participant. Horizontal lines indicate the medians and interquartile ranges. Triangles indicate people with high nasal resistance, inverted triangles indicate individuals with low nasal resistance. * indicates a significant difference (P<0.05) between no oral appliance and oral appliance conditions. Refer to the Results section for further detail.

	% responders		
	Total AHI	**NREM Supine AHI***	**Supine AHI***
Treatment AHI < 5 events/h	18 (7)	38 (14)	16 (6)
Treatment AHI < 10 events/h	38 (14)+	51 (19)+	35 (13)+
≥ 50% reduction in baseline AHI	47 (18)	59 (22)	46 (17)
Reduction in OSA severity category	54 (20)	59 (22)	46 (17)

Table 2.3: Oral appliance response rates according to different treatment outcome definitions

Number of participants in each category are listed in parenthesis. *Data calculated from n=37 participants with obstructive sleep apnea (OSA), 1 participant did not have any NREM sleep in the supine position. + Count includes participants with AHI < 5 events/h. AHI: apnea-hypopnea index; NREM: non-rapid eye movement; Reduction in OSA severity category: proportion of participants who had a reduction in OSA severity category (e.g. from severe to moderate or moderate to mild etc. where mild=5< and <15, moderate=≥15 but <30 and severe=≥30 events/h).

Total sleep time was similar between conditions. Sleep efficiency was high in both arms during these split night studies. Sleep quality improved on oral appliance therapy as reflected by reduced wake after sleep onset (WASO) events, less N1 sleep and a reduction in the arousal index. There was no statistical significance between N2, N3 and REM sleep duration with oral appliance therapy. This is despite significantly more time spent supine on oral appliance therapy.

The oxygen desaturation index (ODI) was lower and the amount of sleep time spent below an O_2 saturation of 90% was less with oral appliance therapy. On the other hand, nadir O_2 saturation was similar between the split night conditions.

	% responders	
	High nasal resistance n= 14	**Low nasal resistance n= 24**
Treatment AHI <5 events/h	29 (4)	13 (3)
Treatment AHI <10 events/h	36 (5)$^{+}$	38 (9)$^{+}$
≥50% reduction in baseline AHI	57 (8)	42 (10)
Reduction in OSA severity category	57 (8)	50 (12)

Table 2.4: Treatment response rates with oral appliance therapy separated according to high versus low nasal resistance

Treatment response rates based on total apnea-hypopnea index (AHI) in participants with high and low nasal resistance. Number of participants in each category are listed in parenthesis. $^{+}$Count includes participants with AHI<5 events/h. OSA: obstructive sleep apnea, Reduction in OSA severity category: proportion of participants who had a reduction in OSA severity category (e.g. from severe to moderate or moderate to mild etc. where mild=5< and <15, moderate=≥15 but <30 and severe=≥30 events/h).

2.4.4. Subjective compliance and perceived changes in sleep with oral appliance therapy

Subjective compliance and perceived changes in sleep were collected in 34 participants during the acclimatization period. Just prior to the efficacy study, participants reported using the oral appliance device for an average of 6.7 h/night (range 3-7 h/night) for 6.4 nights/week (range: 3-7 nights/week). 30 of these 34 participants (88%) were deemed compliant with therapy based on the definition of at least 4 h/night for at least 5 days/week (63). Of these 34 participants, 11 did not notice any difference in their sleep with oral appliance therapy, 1 reported waking up feeling tired whereas 22 participants reported improvements in their sleep and/or reduced snoring or apneas.

2.5. Discussion

The main finding of this study is that nasal resistance increased from seated to supine, with even higher values in the lateral position. Mandibular advancement however, did not alter nasal resistance within each corresponding posture. The exception was non-responders to oral appliance therapy in whom nasal resistance increased with mandibular advancement while seated. The novel oral appliance was efficacious in reducing OSA severity by approximately 50% in people with and without high nasal resistance. Other key sleep parameters also improved with oral appliance therapy including WASO and the arousal index.

2.5.1. Postural effects on awake nasal resistance

Similar to the current findings, previous studies in healthy individuals have demonstrated increases in nasal resistance from the seated to supine posture (114, 264, 326). Another study in healthy individuals also detected higher total nasal resistance in the lateral position compared to supine (9). Our OSA cohort had an increase in nasal resistance of approximately 10% from seated to supine and approximately 20% from supine to lateral. In comparison, the data in healthy individuals from previous nasal resistance studies tends to show greater positional changes of up to 50% from seated to supine (264, 326) and, similarly, almost 50% from supine to lateral (9). Smaller postural changes in nasal resistance in the current study may be due to several factors including differences in methodology. First, quantification of nasal resistance in previous studies was measured using anterior rhinomanometry (9, 264, 326) rather than the gold standard posterior nasal resistance methodology used in the current study. In addition, two of the previous studies quantified nasal resistance unilaterally and estimated total nasal resistance as the mean values of each nostril measured (9, 326). This approach is highly dependent on the patency of each nostril and anterior measurements may not necessarily mirror posterior nasal resistance values (114).

Mechanically, positional changes in nasal resistance have been attributed to hydrostatic effects in response to changes in venous blood flow through the nasal mucosa (264) and positional reflex responses under autonomic sympathetic control (157). Reduced positional changes in nasal resistance between healthy individuals and people with OSA suggest attenuated positional reflex responses in OSA. Consistent with attenuated postural changes in nasal resistance in OSA but in contrast to our findings, Hellgren and colleagues found no change in nasal patency from seated to supine in people with OSA (118). This may be due, at least in part, to increased OSA severity (AHI: 46 vs. 29 events/h) and the treatment status of the participants. For example, in the previous study all patients were treatment naïve whereas participants in the current study were all on oral appliance therapy for 2-3 months prior to testing. Intermittent hypoxia and reoxygenation in OSA contributes to elevated levels of pro-inflammatory cytokines (207). Pro-inflammatory cytokines can contribute to nasal obstruction and, thus, may mask any positional effects (224). Impaired neurovascular control in OSA may also diminish positional changes in nasal resistance (118), an effect which may be more pronounced in severe OSA. The

current findings of reduced positional changes in nasal resistance compared to healthy controls, but not an absence of an effect like the earlier findings in people with untreated OSA, suggests that impaired neurovascular control may be reversible, at least in part, after OSA therapy. These possibilities require further investigation.

2.5.2. Effects of mandibular advancement on nasal resistance

Consistent with our findings, a previous study (349) in patients with OSA showed no overall effect of mandibular advancement on nasal resistance while seated. Additionally, similar to the current findings during the seated position, nasal resistance increased with an oral appliance in the supine posture in non-responders but not in responders (349). The patient characteristics in our study were similar to the previous report with the exception of higher baseline (seated) nasal resistance in the earlier study (349). In addition, measurement techniques and the oral appliance used were different, both of which could have influenced the findings. Nonetheless, both studies showed increased nasal resistance with mandibular advancement in non-responders to therapy albeit during different postures. The mechanisms mediating increased nasal resistance with mandibular advancement in non-responders are unclear. Regardless, these findings highlight the complex interactions that can occur when one section of the upper airway is altered resulting in changes in adjacent structures. This may be especially true in those with highly crowded upper airways given the confines of the upper airway.

In contrast, two studies in healthy individuals have shown reductions rather than increases in nasal resistance with mandibular advancement in both the seated (119, 235) and supine (235) positions. The increase in nasal patency with mandibular protrusion was postulated to occur due to passive displacement of the soft palate and changes that affect the nasal valve (119). Absence of a similar effect in OSA may be explained by an impaired functional response within the nasopharynx due to airway crowding. Mandibular advancement is known to change structural dimensions in the upper airway including within the velopharynx (43). This is further supported by findings in which the soft palate stretches following anterior tongue movement via the palatoglossal arch (129). The pattern of anterior tongue motion from mandibular advancement in severe OSA is variable and smaller compared to healthy individuals

(33). Thus, this may explain, at least in part, the lack of overall change in nasal resistance with mandibular advancement in the current study.

2.5.3. Efficacy of the novel oral appliance including in people with high nasal resistance

Previous data shows that on average, oral appliance therapy reduces OSA severity by approximately 55% (200). A recent study in which an earlier version of the current novel oral appliance was used reported a similar overall reduction in the AHI of about 60% (170), which is comparable to our findings of approximately 50%. The subjective compliance rate was also similar (88% vs. 83%) (170).

However, the overall treatment success rate was on the lower range compared to the reported literature (200). This may be due to the fact that our participants spent more time supine on the oral appliance therapy arm of the study, which tends to worsen OSA severity and oral appliance efficacy (303). Despite this, there were major improvements in several polysomnographic indices with oral appliance therapy including reduced stage 1 sleep, WASO, arousal frequency and overnight oxygenation. Most participants also reported they felt that their sleep improved and/or their snoring or apneas decreased.

OSA severity worsens and oral appliance therapy efficacy tends to reduce during REM sleep (303). Indeed, in one study oral appliance therapy resolved REM predominant OSA in just 12% of patients (303), which is comparable to 11% in the current study. Oral appliance therapy decreases upper airway collapsibility (13, 226) without systematically altering upper airway muscle function (13). The upper airway is also more collapsible and dilator muscle activity is lower during REM sleep (39). Thus, decreased oral appliance efficacy during REM sleep may be explained by REM-related decrements in airway collapsibility which cannot always be overcome with an anatomical intervention that yields variable absolute and relative levels of improvement in airway collapsibility between individuals (13). Additionally, physiological variability increases during REM sleep and there is relatively less time available in which to get an accurate estimate of REM AHI, particularly during a split study design and in people with severe OSA in whom REM duration may be limited. This may have also contributed to a lack of a significant difference in the overall REM AHI with oral appliance therapy in the current study. However, when a major source

of variability in AHI was controlled, (i.e. body position), the supine REM AHI was significantly reduced with therapy albeit to a lesser absolute extent compared to NREM.

In addition, high nasal resistance is associated with increased OSA severity (345) and oral appliance treatment failure (349). Consistent with our findings, Lavery and colleagues found comparable treatment response rates between those with self-reported high and low nasal resistance with a similar oral appliance (170). Thus, unlike traditional mandibular advancement devices, these findings suggest that the addition of an oral breathing route within the oral appliance device provides an alternate route of breathing without requiring mouth opening, which may cause mandibular retraction for those with nasal obstruction resulting in similar efficacy rates to those without nasal obstruction.

2.5.4. Methodological considerations

A major strength of this study was that nasal resistance was objectively measured using gold standard methodology whereby total nasal resistance is measured at the choanae. This is likely to be more relevant for upper airway collapsibility and OSA compared to anterior rhinomanometry. The sleep physician referral pathway with clinical follow up, titration and acclimatization with a qualified dentist prior to the treatment efficacy study also reflects best standards of care.

Despite its strengths, this study is not without limitations. Efficacy studies were conducted via a split night polysomnography. This limits the amount of sleep available in each portion of the night. Additionally, REM sleep duration is longer as the night progresses (59). OSA is also more severe during REM sleep (110). This may result in the AHI being higher in the second portion of the split night. However, to minimize the effects of these potential confounders, we attempted to obtain at least one period of REM sleep in each portion of the polysomnography and the order of intervention was randomized. Interruptions to sleep due to the changeover of interventions was also minimal and was carried out during lighter stages of sleep where possible.

OSA severity is known to be dependent on body position, with more apneic episodes occurring in the supine position (41). Body position was not controlled in this study.

As highlighted, participants slept predominantly in the supine position in both portions of the night. However, there was less supine sleep during the baseline portion of the night. Hence, OSA severity may have been underestimated in some cases and treatment effect may have been underestimated. To address this potential limitation, we analyzed our data during NREM and REM supine sleep to minimize the variability from positional and sleep stage effects.

Finally, as we did not have a traditional mandibular advancement device control arm in the current protocol, we cannot be certain that people with high nasal resistance would have been poor responders with a traditional device. Rather, these statements rely on historical data in which high nasal resistance was a predictor of mandibular advancement treatment failure (349). Thus, to address this question definitively, an appropriately designed prospective and powered cross-over study is required to directly compare the current novel oral appliance with a traditional mandibular advancement in those with high nasal resistance.

2.6. Summary

We found that nasal resistance is dependent on body posture in people with OSA following approximately three months of oral appliance therapy. Mandibular advancement did not alter awake nasal resistance except in the seated posture where nasal resistance increased in non-responders to therapy. The novel oral appliance with an in-built oral airway had similar efficacy in reducing the total AHI in people with objectively quantified high versus low nasal resistance. These findings suggest that this novel oral appliance may be a treatment alternative for people with high nasal resistance in whom traditional mandibular advancement devices may be less efficacious.

3. CPAP combined with oral appliance therapy reduces CPAP requirements and pharyngeal pressure swings in obstructive sleep apnea

I have published the work conducted in this chapter (314):

Tong, B. K., et al. (2020). "CPAP combined with oral appliance therapy reduces CPAP requirements and pharyngeal pressure swings in obstructive sleep apnea." Journal of Applied Physiology 129(5): 1085-1091.

3.1. Abstract

Study objectives: Oral appliance (OA) therapy is the leading alternative to continuous positive airway pressure (CPAP) for obstructive sleep apnea (OSA). It is well tolerated compared to CPAP. However, ≥50% of patients using OA therapy have incomplete resolution of their OSA. Combination therapy with CPAP and oral appliance (CPAP+OA) is a potential alternative for incomplete responders to OA therapy. This study aimed to determine the extent to which combination therapy reduces therapeutic CPAP requirements using gold standard physiological methodology in those who have an incomplete response to OA therapy alone.

Methods: 16 incomplete responders (residual AHI> 10events/h) to a novel OA with a built-in oral airway were recruited (3F:13M, aged 31-65 years, BMI: 22-38kg/m^2, residual AHI range 13-63events/h). Participants were fitted with a nasal mask, pneumotachograph, epiglottic pressure catheter and standard polysomnography equipment. CPAP titrations were performed during NREM supine sleep in each participant during 3 conditions (order randomized): 1) CPAP only, 2) CPAP+OA(oral airway open), and 3) CPAP+OA(oral airway closed).

Results: OSA was resolved at pressures of 4±2 and 5±2cmH_2O during CPAP+OA (oral airway open) and CPAP+OA (oral airway closed) conditions versus 8±2cmH_2O during CPAP only ($P<0.01$). Negative epiglottic pressure swings in oral airway open and closed conditions were normalized to CPAP only levels (-2.5[-3.7,-2.6] vs. -2.3[-3.2,-2.4]vs. -2.1[-2.7,-2.3]cmH_2O).

Conclusions: Combined CPAP and OA therapy reduces therapeutic CPAP requirements by 35-45% and minimizes epiglottic pressure swings. This combination may be a therapeutic alternative for patients with incomplete responses to OA therapy alone and those who cannot tolerate high CPAP levels.

Keywords: sleep-disordered breathing, upper airway, non-CPAP therapies.

3.2. Introduction

CPAP is the recommended first line therapy for obstructive sleep apnea (OSA) (162). It is highly efficacious in reducing OSA severity in most people with OSA (298). Additional benefits of CPAP may include reductions in blood pressure (19), subjective daytime sleepiness (25) and improved cognitive function (86, 87). However, these health benefits are often limited by poor adherence to CPAP therapy. Approximately 30% of patients prescribed CPAP are not adherent to treatment after one month of therapy (253). A further 15% abandon treatment within 10 months (339). Common reasons for poor CPAP adherence include physical complaints (i.e. mouth dryness, nasal obstruction) (100, 231), mask related discomfort (100, 231, 339), pressure intolerance (100), dislike of equipment (100, 339) and preference for other treatment options (339). Indeed, individuals who use their CPAP less than 4 hours/ night are effectively undertreated and have some degree of residual OSA as estimated by the Sleep Adjusted Residual AHI (SARAH index) (302). Given the substantial portion of patients who fail CPAP therapy, strategies to improve treatment effectiveness and development of alternative therapeutic approaches are required.

Oral appliance therapy is recommended for mild-moderate OSA and as second-line therapy for those who are intolerant to CPAP (254). Oral appliances are well tolerated with adherence rates of approximately 80% at 3 months (319) and after 1 year of treatment (62). OSA severity reduces by approximately 50% on average with oral appliance therapy (199). However, successful treatment outcome (AHI <5 events/hour) varies between patients ultimately influencing treatment effectiveness. Indeed, at least 50% have some degree of residual OSA on therapy (304). Prediction of treatment success with oral appliance therapy is difficult and current prediction methods are inadequate (303).

Alternative treatment options are urgently needed for OSA patients who are CPAP intolerant and incomplete responders to oral appliance therapy. Combination therapy with CPAP plus an oral appliance (CPAP+OA) has been suggested as a viable alternative for these patients (61, 192, 318). Recent studies have demonstrated that CPAP requirements needed to resolve OSA is lower with CPAP+OA therapy compared to CPAP alone (84, 180). Additionally, compliance and comfort with CPAP+OA therapy may also be superior compared to CPAP therapy alone (58).

However, previous studies that have assessed CPAP+OA therapy on these outcomes have used standard polysomnographic measures. This includes surrogate measures of airflow via a pressure transducer which is typically highly filtered and respiratory effort via abdominal and thoracic bands from commercially available diagnostic software. Standard CPAP titration methods to identify the therapeutic CPAP level rely on visual identification of respiratory events or auto-titration from these signals. However, subjective assessments that rely on imprecise and often over filtered signals can easily lead to under titration (i.e. missing mild-moderate airflow limitation) or over titration (i.e. difficult to precisely identify the point where airflow limitation first subsides). Thus, gold standard physiological techniques such as pneumotachograph derived airflow and respiratory effort from an airway catheter downstream from the site of pharyngeal narrowing/collapse combined with an objective quantification approach are required to accurately determine the mechanistic effect of CPAP+OA therapy on the upper airway and the precise reductions in CPAP requirements that combination therapy can yield.

A recent pilot study found that a novel oral appliance with a built-in oral airway (Figure 3.1A) was able to reduce pharyngeal pressure swings during sleep and CPAP requirements when used in combination with CPAP (3). However, the patient population in this preliminary investigation was small (n=4) and the efficacy of the oral appliance therapy alone in these participants was not known. Therefore, this study aimed to compare pharyngeal pressure swings and therapeutic CPAP requirements in CPAP+OA therapy versus CPAP only via objective physiologically derived measures in the clinically relevant group of incomplete responders to oral appliance therapy.

3.3. Materials and methods

3.3.1. Participant

16 incomplete responders to oral appliance therapy alone (residual AHI >10 events/h) were recruited for this sub-study from a larger clinical study (Figure 3.2) that investigated the efficacy of a novel oral appliance device (O_2Vent™ T, Oventus Medical, Indooroopilly, Australia, Figure 3.1A) on OSA. Findings from the larger clinical study (ANZCTRN12617000492358, Part A) were recently reported (313). The current protocol was pre-registered on the Australian New Zealand Clinical Trials Registry (ANZCTRN12617000492358, Part B). Some of the study participants also completed an oral appliance plus expiratory positive airway pressure valve combination therapy study on a separate occasion (ANZCTRN12617000492358, Part C) (164).

Participants were otherwise healthy with documented OSA, were untreated or CPAP intolerant and were recommended oral appliance therapy by their treating sleep physician. Exclusion criteria included contraindications for oral appliance therapy by the study dentist (e.g. periodontal disease, insufficient teeth for device retention or a strong gag reflex), central sleep apnea (>5 events/h), intellectual or mental impairment, pregnant or nursing mothers or medications known to affect sleep or breathing. Written informed consent was obtained from participants prior to enrolment. The study was approved by the Prince of Wales Human Research Ethics Committee (HREC No. 16/356).

3.3.2. Participant set up and equipment

3.3.2.1. Overnight polysomnography

Participants were fitted with electroencephalograms (F3, F4, C3, C4, O1 and O2 referenced to A1-A2), electrooculograms, surface submental electromyograms, and finger pulse oximetry for overnight polysomnography.

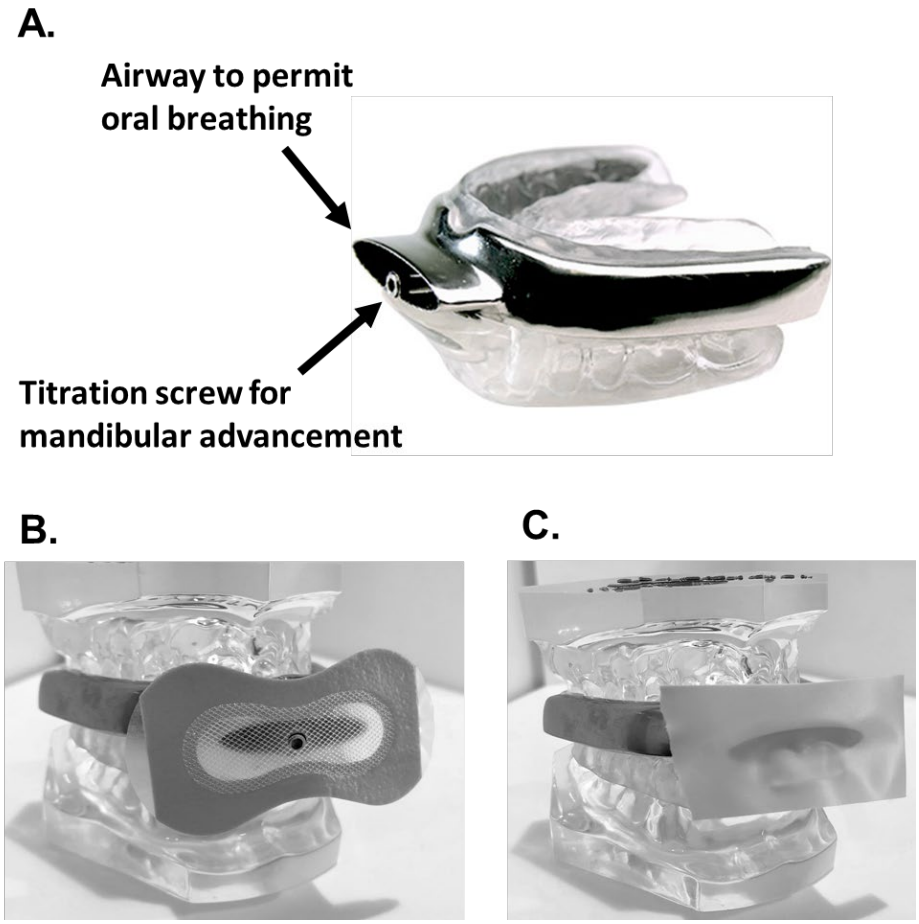

Figure 3.1: Oral appliance device set up

A. Picture of the 2-piece titratable oral appliance (OA) that was used in the study. It incorporates a hollow enclosure which enables air to flow directly from the mouth to the pharyngeal airway. B. Picture of the one-way valve that was used to seal the oral airway to allow oral breathing but minimize continuous positive airway pressure (CPAP) leak via the oral airway during the CPAP+OA (Open) condition. C. Picture of the non-porous adhesive tape that was used to completely seal the oral airway for the CPAP+OA (Closed) condition.

3.3.2.2. Physiological measurements

A modified non-vented nasal mask (ComfortGel, Phillips Respironics, Murrysville, PA, USA) was attached to a pneumotachograph (Series 3700A, Hans-Rudolph, Kansas, USA) and differential pressure transducers (DP-45, Validyne, Northridge CA, USA) for measurement of airflow and mask pressure. A pressure transducer tipped catheter (MPR-500, Millar, Houston, TX, USA) was inserted via the most patent anesthetized nostril (Co-phenylcaine™ Forte spray, ENT Technologies Pty. Ltd. Hawthorn, Victoria, Australia) 1-2cm below the base of the tongue for epiglottic pressure (Pepi) measurement.

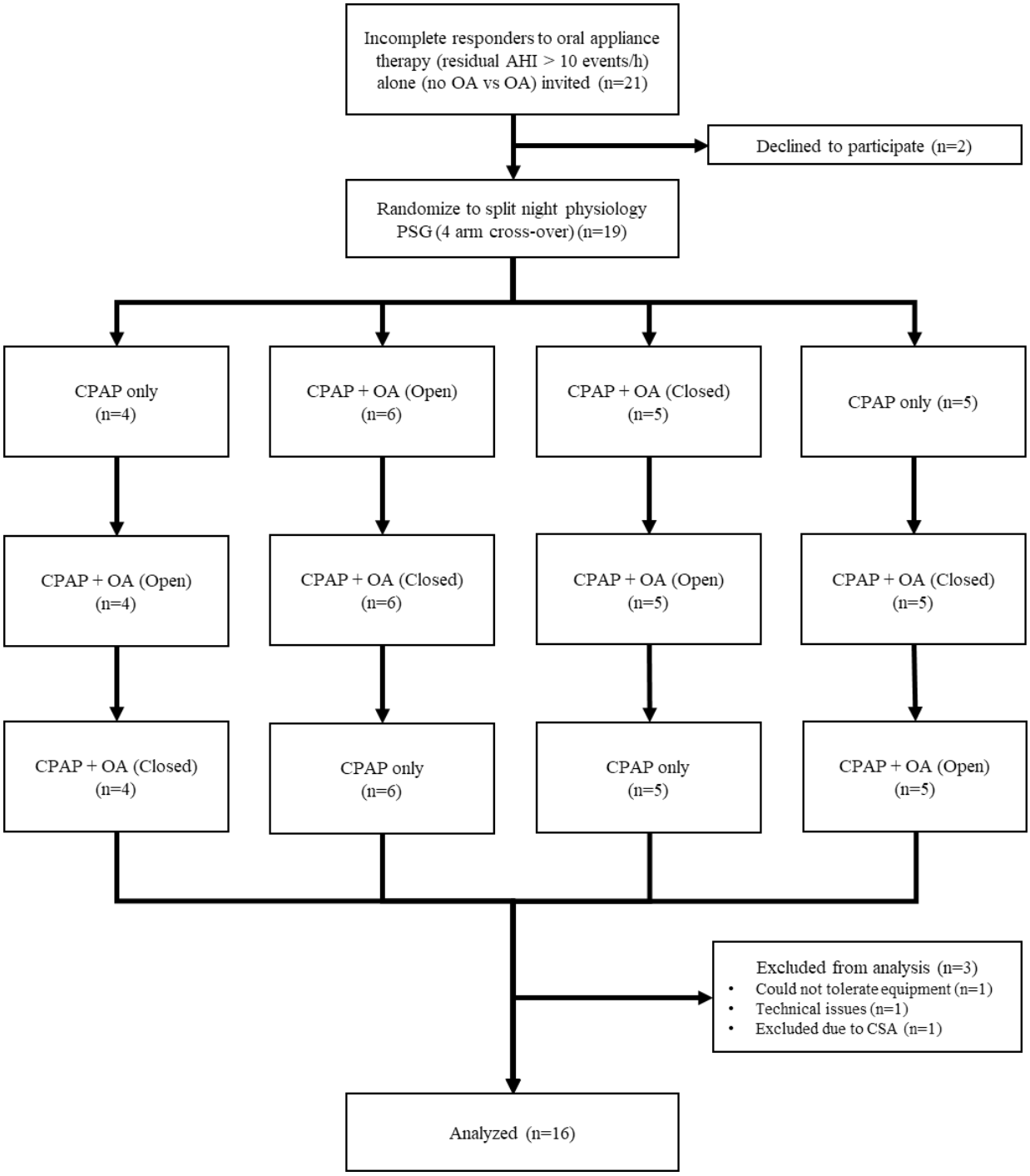

Figure 3.2: CONSORT diagram detailing participant recruitment and flow through the study

N=21 incomplete responders to oral appliance therapy were invited to participate. N=2 participants declined to participate. N=19 participants were recruited and randomized to split night physiology PSG (4 arm cross-over). N=3 participants were excluded from the final analysis due to technical issues, equipment discomfort and intolerance, and presence of central sleep apnea during the study. N=16 participants were included in the final analysis. OA: Oral appliance, PSG: Polysomnography, AHI: Apnea hypopnea index, CPAP: Continuous positive airway pressure, CSA: Central sleep apnea.

3.3.2.3. Oral appliance

Participants were fitted with an O2Vent™ T oral appliance (Oventus Medical, Indooroopilly, QLD, Australia, Figure 3.1A), followed by an 8 to 12-week acclimatization period. The magnitude of mandibular advancement was kept consistent with at least 75% of maximum mandibular advancement similar to our previous study (313).

3.3.2.4. CPAP titrations

CPAP from a positive pressure device (Pcrit 3000, Phillips Respironics, Murrysville, PA, USA) was delivered through standard CPAP tubing to the modified non-vented nasal mask with a whisper swivel expiratory valve (Phillips Respironics, Murrysville, PA, USA) in series.

CPAP titrations during the CPAP+OA combination conditions were conducted with the oral appliance in place. In the CPAP+OA (Open) condition, the oral airway in the device was sealed with a one way valve (Theravent®, Foundation Consumer Healthcare LLC, Pittsburgh, PA, USA) in the CPAP+OA (Open) condition to facilitate oral inspiration if required and prevent CPAP leakage (Figure 3.1B). Non-porous adhesive tape (Hy-Tape®, Hy-Tape International, Patterson, NY, USA) was applied over the device oral airway in the CPAP+OA (Closed) condition to promote nasal breathing only (Figure 3.1C).

3.3.3. Protocol

Initially, at least 5 minutes of quiet nasal breathing data were collected while awake in the supine position without OA or CPAP. Pepi swings and CPAP requirements were then measured throughout an overnight sleep study during the following three study conditions in all participants in random order: 1) CPAP only, 2) CPAP plus oral appliance with the oral airway open (CPAP+OA (Open), Figure 3.1B), and 3) CPAP plus oral appliance with the oral airway closed (CPAP+OA (Closed), Figure 3.1C). Randomization order of the study conditions was conducted by an external study clinical trials monitor. Set up of each study condition was conducted by a research assistant to blind the investigator to the intervention assignment during data

collection. A summary of the patient flow through the study protocol is detailed in Figure 3.2.

During the split night polysomnography, participants were instructed to sleep supine. CPAP titrations were conducted throughout the night during NREM sleep (N2 and N3) in each condition. CPAP was initiated at 1 cmH_2O and incrementally increased at 0.5 to 1cmH_2O increments as required. Each pressure level was assessed for at least 2 minutes prior to the next CPAP increase. Increments in CPAP were delivered until at least 3cmH_2O above the level in which sleep disordered breathing/snoring/airflow limitation was abolished based on the airflow/Pepi relationship where airflow limitation= no increase in inspiratory flow despite ≥-1cmH_2O increase in Pepi (Figure 3.3). Sleep and breathing data at the established therapeutic CPAP level were then recorded for at least 15 minutes prior changing over to the next condition.

3.3.4. Data acquisition and analysis

Data were collected using a 16-bit analogue to digital converter (Power 1401, Cambridge Electronic Design Limited, Cambridge, UK) and data acquisition software (Spike 2, version 7.20, Cambridge Electronic Design Limited, Cambridge, UK).

Data analysis was performed on a breath by breath basis using validated, custom-designed, semi-automated software (229). Minimal therapeutic CPAP requirements for each participant were objectively quantified based on a plot of the mean Pepi swings vs. CPAP level within each condition (at least 20 stable breaths analyzed per condition). Specifically, minimal therapeutic CPAP requirements were defined as the CPAP level at which Pepi first stabilized (Figure 3.3) where the Pepi swings were within one standard deviation or less than the average wakefulness levels. Data analysis was performed blinded to the intervention conditions.

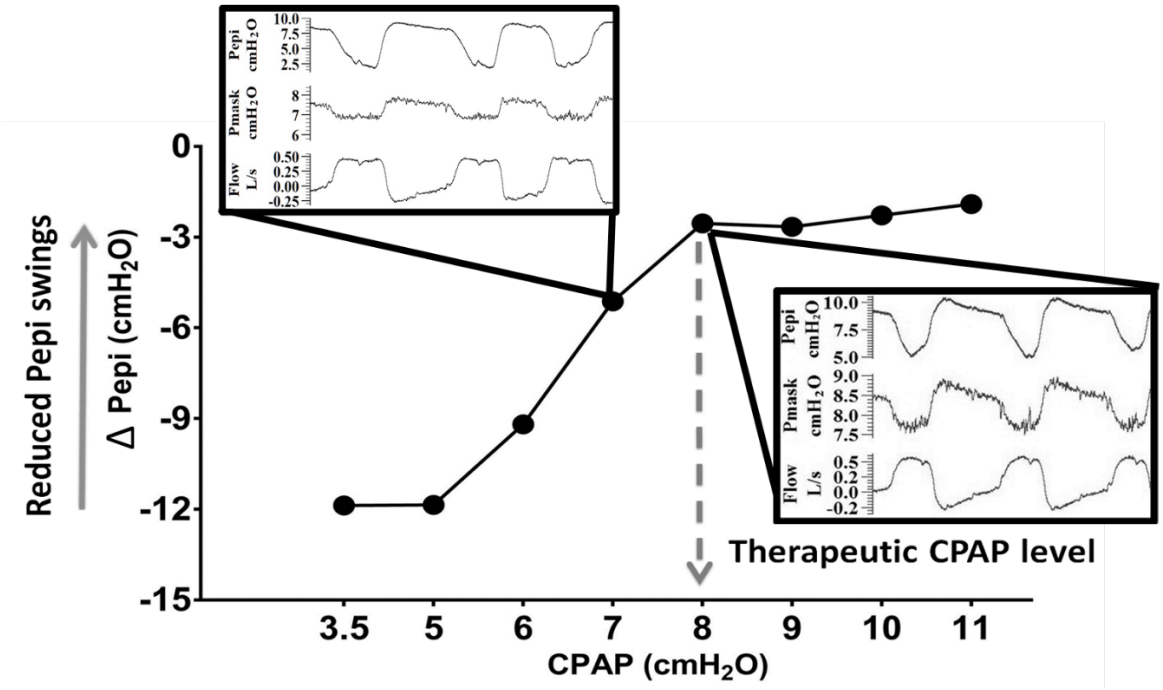

Figure 3.3: Determining therapeutic CPAP requirements

Therapeutic CPAP requirements were determined by plotting pharyngeal pressure swings vs. CPAP as shown in this individual example. The therapeutic CPAP level was defined as the first point where pharyngeal pressure swings stabilized. In this example, flow limitation and large pharyngeal pressure swings are present at 7 cmH_2O. At 8cmH_2O, airflow is restored, and pharyngeal pressure swings are minimized. Hence, this point is defined as the therapeutic CPAP level. Pepi: Epiglottic pressure, CPAP: Continuous positive airway pressure, Pmask: Mask pressure. Black circles represent mean delta (Δ) epiglottic pressure (difference between end expiration and nadir during inspiration) at each CPAP level.

3.3.5. Statistical analysis

Data normality was assessed using a Shapiro-Wilk test. Therapeutic CPAP requirements, Pepi swings and proportion of N2 and N3 sleep between conditions were compared using a one-way repeated measures ANOVA (Sigma Plot, version 11). Pairwise comparisons were conducted using the Student-Newman-Keuls method. Friedman repeated measures ANOVA on ranks were conducted for non-normally distributed data. Data are reported as mean±SD or median with interquartile ranges for non-normally distributed data.

3.4. Results

3.4.1. Participant characteristics

21 incomplete responders to oral appliance therapy alone were invited to participate in the current combination therapy study. 19 consented and were randomized. 3 were

excluded from analysis (1 could not tolerate the equipment set up, 1 had central sleep apnea (> 5 events/h) and 1 due to technical issues in data collection). Thus, data were analyzed in 16 across all conditions (Figure 3.2). The characteristics of these participants are detailed in Table 3.1.

Sex	3♀, 13♂
Age (years)	48 ± 11
Body mass index (kg/m^2)	29 ± 5
No. of participants who were CPAP intolerant	3
Maximum mandibular advancement (%)	83 ± 14
Epworth sleepiness scale	7 ± 4
Residual AHI on OA therapy alone (events/h)	26 ± 13

Table 3.1: Participant characteristics

AHI=apnea/hypopnea index, OA=oral appliance. Data are mean±SD unless otherwise stated. N=16.

3.4.2. Effect of combination therapy (CPAP+OA) on therapeutic CPAP requirements

The effect of combination therapy (CPAP+OA) on minimal therapeutic CPAP requirements is summarized in Figure 3.4. Therapeutic CPAP levels were reduced with CPAP+OA compared to CPAP only. CPAP requirements were reduced by 43±27% in the CPAP+OA (Open) condition ($p<0.001$) and 33±31% in the CPAP+OA (Closed) condition ($p<0.001$). There was no difference in the CPAP requirements between the CPAP+OA (Open) and CPAP+OA (Closed) conditions ($p=0.386$).

The average total sleep time for data collection in each condition (CPAP only, CPAP+OA (Open) and CPAP+OA(Closed)) was 102±75 vs. 70±30 vs. 67±20 minutes. CPAP requirements were measured during supine NREM sleep predominantly in N2 sleep. There was no difference in the proportion of N2 sleep (53±17 vs. 60±19 vs. 59±18 %TST, $p=0.445$) and N3 sleep (26±25 vs. 25±24 vs. 17±16 %TST, $p=0.508$) between the three study conditions (CPAP only, CPAP+OA (Open) and CPAP+OA (Closed)).

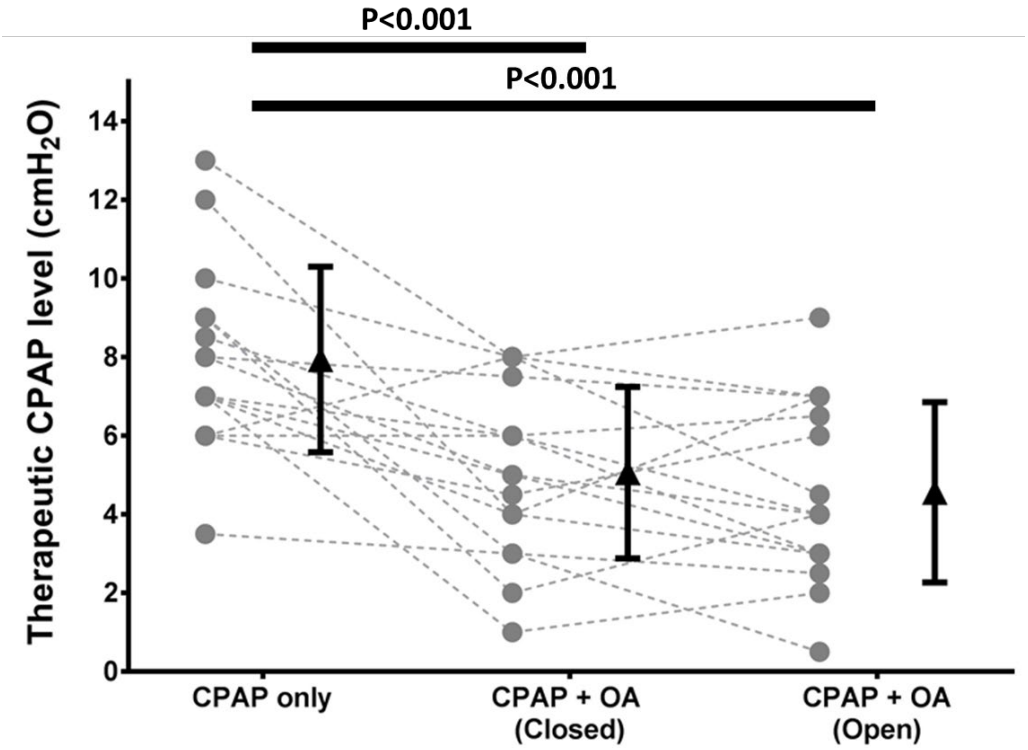

Figure 3.4: Therapeutic CPAP requirements for each of the three conditions: CPAP only, CPAP+OA (closed) and CPAP+OA (open).

Grey circles represent individual data. Black triangles with error bars represent the group mean±SD. CPAP: Continuous positive airway pressure, OA: Oral appliance.

3.4.3. Pharyngeal pressure swings with combination therapy (CPAP+OA)

Figure 3.5 summarizes the Pepi swings at therapeutic CPAP requirement levels during combination therapy conditions compared to CPAP only. Pepi swings were successfully normalized to CPAP levels and were not different between conditions (p=0.144).

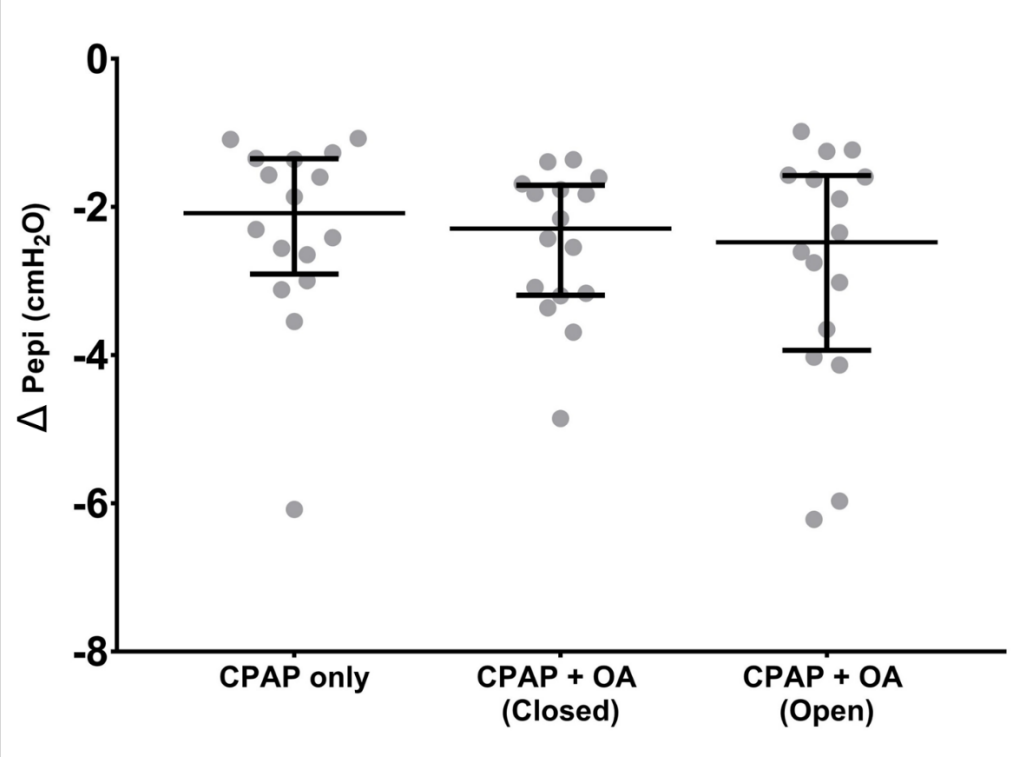

Figure 3.5: Pharyngeal pressure swings at therapeutic CPAP requirements for each of the three conditions: CPAP only, CPAP+OA (closed) and CPAP+OA (open).

Grey circles represent individual data. Black lines and error bars represent the median and interquartile range. CPAP: Continuous positive airway pressure, OA: Oral appliance, ΔPepi: difference in epiglottic pressure swings between end expiration and nadir during inspiration.

3.5. Discussion

The main findings of this study are that combination therapy with CPAP and a novel oral appliance can normalize pharyngeal pressure swings and lower CPAP requirements by ~40% compared to CPAP alone. These findings, conducted in the clinically relevant group of incomplete responders to oral appliance therapy alone and derived using gold-standard physiological assessments to objectively quantify CPAP requirements, provide novel insight into the role of combination therapy on upper airway physiology and breathing during sleep. This information is important to inform combination therapy strategies for OSA.

The magnitude of the reduction in CPAP requirements with combination therapy in the current study is comparable with previous studies that used standard polysomnography approaches in which therapeutic CPAP requirements were reduced by 29 to 48% (58, 84, 180). Thus, despite the use of different oral

appliances, methodology and patient characteristics, combination therapy appears to reduce CPAP requirements by 30-50%.

The reduction in CPAP requirements in the current study of 3-4cmH_2O are also comparable to previous physiology studies that have investigated the mechanisms of oral appliance therapy. For example, Bamagoos and colleagues demonstrated a dose dependent reduction in the critical closing pressure of the upper airway (Pcrit) of 3-6cmH_2O with oral appliance therapy (13) and a 4cmH_2O reduction in therapeutic CPAP requirements with combination therapy (14). A similar reduction in the closing pressure of the upper airway (Pclose) of 5.5cmH_2O was observed in patients under anaesthesia with 6mm of mandibular advancement (147) whereby anterior movement of the mandible widens the retropalatal airway and tongue base in the passive pharynx (129). Our findings therefore suggest that the reduction in therapeutic CPAP requirements with combination therapy is related to reduced upper airway collapsibility from oral appliance therapy.

Two participants did not have a reduction in therapeutic CPAP requirement with combination therapy. Both were obese and had high nasal resistance while supine (>3cmH_2O/L/s) (313). One had upper airway crowding based on the Mallampati score of 3. Previous studies have indicated that obesity, upper airway crowding (128, 315) and increased nasal resistance (349) are predictors of unsuccessful oral appliance therapy outcome. Thus, this combination of factors likely yielded minimal anatomical benefit with oral appliance therapy in these individuals and therefore, no change in therapeutic CPAP requirements.

Lower CPAP levels have been assumed to help improve CPAP compliance. Patient preference between the different conditions in the current acute physiology studies was not assessed. Nonetheless, previous studies have demonstrated high compliance with combination therapy with an average usage time of 6 hours per night (58, 84, 180). Indeed, in one study, long-term compliance with combination therapy was reported to be ~75 % with an average nightly usage of 6 hours per night over 3 years (180). De Vries and colleagues also reported that patients who require high therapeutic CPAP levels, prefer combination therapy (CPAP+OA) (58). The current findings indicate that the addition of an oral appliance can reduce CPAP requirements by ~40% while normalizing pharyngeal pressure swings. Thus, this approach may be a viable alternative for people with high CPAP requirements who

have difficulty tolerating the high pressures and for people who have an incomplete response to oral appliance therapy alone. However, the role of combination therapy on adherence and compliance was not assessed in the current physiological study. This remains an important clinical question to pursue in the clinically relevant patient groups including those who have incomplete responses to oral appliance therapy alone and those who are unable to tolerate CPAP alone due to high pressure requirements.

In the current study, epiglottic pressure swings and CPAP requirements were comparable when the oral airway within the novel oral appliance device was open versus closed. This finding suggests that CPAP can be delivered effectively while providing an oral breathing option which may offer an alternative to oronasal masks in those who have difficulty breathing exclusively through their nose. Borel and colleagues also demonstrated that velopharyngeal resistance is reduced when CPAP and an oral appliance are used together compared to other mask interfaces (29).

3.5.1. Methodological considerations

While the current study has several methodological strengths including the rigorous objective assessment of CPAP requirements across the conditions using epiglottic pressures and pneumotach-derived airflow and a clinically relevant patient population, there are certain limitations that need to be acknowledged. For example, this study was designed as a single night study in which three different conditions were assessed throughout the night. This limits the amount of sleep time available for each condition. However, on average over 1 hour of sleep data were obtained in each condition which was sufficient to address the study aims. Sleep architecture also changes across the night with a greater proportion of REM sleep later in the night (59). Additionally, upper airway collapsibility and pharyngeal muscle activity are sleep stage dependent (39). This likely results in different therapeutic CPAP requirements between sleep stages especially during REM and NREM sleep. Therefore, the current study focused on the effects on supine NREM sleep comprised of comparable amounts of N2 and N3 between conditions. Thus, while this design was appropriate to address our primary study aims, we cannot be certain that the magnitude of the reductions detected are comparable in REM sleep and in different

body positions. However, study conditions were randomized to prevent potential time of night biases on the study outcomes. In addition, we did not measure airflow through the oral airway of the oral appliance during the airway open condition. Thus, we may have underestimated airflow and therefore over-titrated CPAP during this condition. However, this is unlikely as we were able to take advantage of the epiglottic pressure sensor to assess upper airway function accurately and objectively across the study conditions. Finally, an EPAP valve was used in the current study to prevent CPAP leakage which as recently demonstrated (164), may have in of itself led to some improvement in airway stability.

3.5.2. Summary

In conclusion, combination therapy using CPAP and oral appliance therapy can normalize pharyngeal pressure swings and lower CPAP requirements by 35-45% compared to CPAP alone. Combination therapy may be a therapeutic option for OSA patients who are incomplete responders to oral appliance therapy alone and those who struggle with CPAP due to high pressure requirements. This requires further investigation.

4. Efficacy of a novel oral appliance and the influence of nasal resistance and OSA pathophysiological traits on treatment response

4.1. Abstract

Background: Approximately 50% of patients have a major reduction in OSA severity with oral appliance therapy but successful treatment outcome remains difficult to predict. Previous prediction methods have largely focused on clinical variables which have poor predictive value. High nasal resistance has also been reported as a predictor of treatment failure with traditional oral appliance therapy. However, this was not the case with a new oral appliance prototype with a built-in oral airway that had similar treatment efficacy in those with versus without high nasal resistance. OSA is a heterogenous disorder caused by at least 4 pathophysiological traits. The influence of OSA pathophysiological traits on oral appliance treatment outcome has been explored in recent retrospective physiological studies using simplified but not gold standard detailed phenotyping methods.

Objectives: This study aimed to determine 1) the efficacy of a next generation oral appliance with a built-in oral airway and 2) the potential influence of nasal resistance and baseline phenotypic traits on treatment responses.

Methods: 24 healthy people with OSA (AHI>10 events/h confirmed via overnight in-laboratory PSG) were studied. A detailed physiology PSG was then performed to quantify nasal resistance, upper airway collapsibility (Pcrit) and estimate the other key pathophysiological traits prior to commencement of oral appliance therapy. In addition to standard PSG equipment, participants were fitted with a nasal mask, pneumotachograph, epiglottic and choanal pressure catheters and intramuscular electrodes inserted perorally into the genioglossus to quantify baseline OSA phenotypic traits and nasal resistance. Pcrit was quantified via CPAP dial downs and the non-anatomical traits were quantified from naturally occurring apnoeas and hypopnoeas off-CPAP. OSA phenotypic traits were also estimated via polysomnography referenced to eupneic ventilation using validated algorithms. Participants were then fitted with a novel, nylon-based oral appliance with a built-in

oral airway (Oventus O_2Vent Optima™) and titrated to at least 75% of maximum mandibular advancement. After acclimatisation to therapy (>4 weeks), participants were invited to undergo a treatment efficacy study (standard in-laboratory PSG).

Results: Oral appliance therapy with the new nylon-based O_2Vent Optima™ device reduced the AHI by 41% (22[15,36] vs. 11[7,17] events/h, P<0.001). 42% of participants were classified as "responders" defined as an AHI <10 events/h on oral appliance therapy. There was no significant difference in nasal resistance (1.9[1.2,4.4] vs. 2.5[2.0,4.8] $cmH_2O/L/s$, p=0.164) or the directly measured phenotypic traits between responders and incomplete responders Pcrit (-1.5±2.2 vs. -1.6±2.1 cmH_2O, p=0.936), Arousal threshold (-21±6.9 vs. -25±9.1 cmH_2O, p=0.342), Loop gain (0.7±0.2 vs. 0.6±0.2, p=0.713) and Muscle responsiveness (-0.1[-1.0,-0.1] vs. -0.1[-0.2,-0.1], p=0.832) in this prospectively recruited patient cohort. However, estimates of upper airway collapsibility under passive (93[84,97] vs. 79[37,91] $\%V_{eupnea}$, p=0.025) and active (102[92,112] vs 72[0,100] $\%V_{eupnea}$, p=0.041) conditions indicated a less collapsible airway at baseline in responders to therapy and baseline pharyngeal muscle compensation also tended to be better in responders versus non-responders (5[3,27] vs. -7[-26,2] $\%V_{eupnea}$, p=0.051).

Conclusions: The next generation, nylon-based novel oral appliance with a built-in oral airway reduced OSA severity by ~40% in people with and without high nasal resistance. Responders to therapy tended to have less upper airway collapsibility and better pharyngeal muscle compensation at baseline when these traits were estimated via polysomnography but not when measured directly in the current prospectively recruited cohort, none of whom had major anatomical compromise at baseline (Pcrit all <2cmH_2O).

4.2. Introduction

Oral appliance therapy is frequently recommended for patients who are CPAP intolerant and for those with mild to moderately severe OSA (254). Oral appliances such as mandibular advancement devices work by protruding the mandible anteriorly to increase velopharyngeal volume and reduce upper airway collapsibility (33, 43, 129). Oral appliances are associated with higher compliance rates but lower treatment efficacy when compared to CPAP (15). Indeed, approximately 50% of patients achieve therapeutic resolution of their OSA with oral appliance therapy

(304). Prediction of favourable treatment outcome remains challenging and has heavily relied on clinical measures such as age, gender, BMI, OSA severity, cephalometric measures (120, 181, 199) and polysomnographic measures (303). However, the prospective predictive value of these measures is often poor and non-standard measures are challenging to implement into routine clinical practice (15, 301).

Nasal resistance varies with body posture in people with (313) and without OSA (263, 264). These posture dependent effects have been attributed to hydrostatic pressure changes in venous blood flow within the nasal cavernous tissues (138) and potentially changes in pressure reflex responses (52, 255). Increased nasal resistance negatively impacts OSA treatment outcomes (297, 349) and may worsen OSA (299, 306). In Chapter 2, the effects of changes in body posture on nasal resistance in people with OSA was carefully quantified (313). Unlike traditional oral appliance therapy where high nasal resistance is associated with treatment failure (349), people with high and low nasal resistance had similar treatment responses to a new, titanium based oral appliance prototype with built-in oral airway (313). However, this finding requires replication including with the next generation nylon-based device (O_2Vent Optima™) for which efficacy is currently unknown.

OSA is a heterogenous disorder (351). Recent work has identified four anatomical and non-anatomical pathophysiological contributors: 1) a collapsible upper airway (high Pcrit/anatomical impairment), 2) low respiratory arousal threshold (waking up too easily to minor airway narrowing), 3) unstable respiratory control (high loop gain), and 4) poor pharyngeal dilator muscle responsiveness during sleep (79, 280, 331, 342). These pathophysiological traits have been proposed as important contributors to the observed between-patient variability in oral appliance efficacy and may hold the key to accurately predicting oral appliance therapy outcomes (12, 81). Indeed, recent studies that have estimated key OSA traits have shown that a severely collapsible upper airway is a negative predictor for oral appliance therapy (12, 201). In addition, the site of airway collapse is also associated with oral appliance treatment outcome (201, 227). Furthermore, high loop gain at baseline is predictive of oral appliance treatment failure (81, 238). However, these initial studies have used simplified estimates rather than direct methods to quantify the key OSA pathophysiological traits and in most cases trait estimates were performed after patients had been treated which may later alter the predictive profile.

Accordingly, the aims of this study were to determine: 1) the efficacy of a next generation oral appliance with a built-in oral airway and 2) the potential influence of nasal resistance and baseline phenotypic traits on treatment responses.

4.3. Methods

4.3.1. Participants

24 untreated (including those who were intolerant to CPAP) people with OSA (AHI > 10events/h) were recruited from the Prince of Wales Hospital sleep clinic and local sleep clinics. All participants were recommended for oral appliance therapy by their treating sleep physician. Reasons for exclusion included: 1) any oral appliance therapy contraindication identified by the study dentist (periodontal disease, insufficient teeth for device retention or a strong gag reflex), central sleep apnoea (>5 central events/h), intellectual or mental impairment, pregnant or nursing mothers, or any medication use known to affect sleep or breathing. All participants provided written informed consent prior to enrolling in the study. The study was approved by the South Eastern Sydney Local Health District Human Research Ethics Committee (HREC18/047) and was preregistered on the Australian New Zealand Clinical Trial Registry (ACTRN12618001995268).

4.3.2. Protocol

4.3.2.1. Overnight diagnostic polysomnography

Initially, standard overnight polysomnography was conducted to confirm OSA diagnosis (>10 events/h). Participants were encouraged to sleep supine for as much of the night as possible.

4.3.2.2. Dental visits

Participants referred for oral appliance therapy by their treating sleep physician were scheduled for a dental assessment with a dentist experienced in fitting oral appliance devices. During the visit, dental scans were made using a dental scanner (TRIOS3, 3Shape, Copenhagen, Denmark) and the maximum tolerable mandibular advancement was determined. A follow-up dental visit within 4 weeks of the initial visit was scheduled for fitting and initial titration of the oral appliance (O_2Vent Optima™, Oventus Medical, Indooroopilly, QLD, Australia, Figure 4.1). Mandibular

advancement was titrated to at least 75% of maximum mandibular advancement over an 8 to 12 week acclimatisation period.

Every 2 weeks participants were contacted by phone or email during the acclimatisation period to assess self-reported adherence and perceived changes in their sleep. Participants were asked “Are you wearing the device every night? If no, how long per night and how many times per week?” and “Did you notice any differences in your sleep?”.

Figure 4.1: A photo of the Oventus O_2Vent Optima™ nylon-based next generation oral appliance device that was used in this study.

4.3.2.3. Detailed physiology overnight sleep study

Approximately two weeks after the initial diagnostic study and prior to commencement of oral appliance therapy, participants returned to the laboratory for detailed upper airway physiology and overnight respiratory phenotyping assessment. Subjective daytime sleepiness was assessed using the Epworth Sleepiness Scale (ESS) questionnaire (134). Subjective nasal obstruction was assessed using the NOSE questionnaire where scores of 5-25 indicates mild, 30-50 indicates moderate, 55-75 indicates severe and 80-100 indicates extreme nasal obstruction (178, 292). Visual assessment of the pharyngeal structures was conducted according to the modified Mallampati scale (196, 269). The insomnia severity index was also assessed as part of routine clinical assessment (221). These questionnaires were administered prior to sleep. Once all the monitoring equipment was in place (see participant set up and equipment section below), awake nasal resistance during quiet nasal breathing was performed supine using gold standard methodology as described previously (313). Several large swallows and tongue protrusions were then

performed to measure the maximum EMG activity of the genioglossus as described previously (79).

Participants were encouraged to sleep supine. During sleep, CPAP was titrated from 4cmH_2O until the therapeutic CPAP level confirmed by elimination of respiratory events and inspiratory flow limitation (defined as >1cmH_2O increase in epiglottic pressure with no increase in inspiratory flow). During NREM supine sleep, CPAP dial downs (transient pressure reductions) were conducted for up to 1 minute using a modified CPAP machine (Pcrit 3000, Phillips Respironics, Murrysville, PA, USA) to induce inspiratory flow limitation to quantify upper airway collapsibility (Pcrit) (79).

Following at least 1 sleep cycle and quantification of Pcrit (typically ~2 hours after sleep onset), CPAP was removed, and participants slept with the detailed recording equipment but without CPAP for the remainder of the night. This allowed for direct measurement of the respiratory arousal threshold and muscle responsiveness during NREM respiratory events and estimation of loop gain.

4.3.2.4. Oral appliance efficacy sleep study

Following acclimatisation and adequate titration to at least 75% of maximum mandibular advancement, participants were invited to return for a sleep study to determine oral appliance efficacy. Participants were once again encouraged to sleep supine. The Epworth Sleepiness Scale questionnaire was administered prior to sleep to assess subjective daytime sleepiness on therapy.

4.3.3. Participant set up and equipment

4.3.3.1. Overnight polysomnography

Electroencephalogram (F3, F4, C3, C4, O1 and O2, referenced to A1-A2), electrooculograms, surface submental and leg electromyograms, finger pulse oximetry, body position, nasal pressure flow, oronasal thermistor flow, thoracic and abdominal respiratory bands and snore sound was measured for both the initial diagnostic and follow-up efficacy sleep studies. Data were acquired using a Level 1 diagnostic sleep system (Alice 6 LDxN, Phillips Respironics) and data acquisition software (Sleepware G3, version 3.7.4, Phillips Respironics).

4.3.3.2. Detailed physiology overnight polysomnography

In addition to the standard polysomnography measurements, airflow and mask pressure were measured via a modified non-vented nasal mask (ComfortGel, Phillips Respironics, Murrysville, PA, USA) attached to a pneumotachograph (Series 3700A, Hans Rudolph, KS, USA) and differential pressure transducers (DP45, Validyne, Northridge, CA, USA). Epiglottic pressure (Pepi) was measured using a pressure tipped catheter (MPR-500, Millar, Houston, TX, USA) inserted through the most patent anaesthetised nostril (Co-Phenylcaine Forte spray, ENT, Technologies Pty. Ltd. Hawthorn, Vic, Australia) and positioned at 1-2cm below the base of the tongue (79). Choanal pressure (Pcho) was measured using a second pressure tipped catheter inserted through the same nostril and positioned to the level of the choanae. Genioglossus electromyography was measured via two intramuscular electrodes to create a bipolar recording. After 5 minutes of topical anaesthesia (1% Lignocaine HCl, Pfizer, West Ryde, NSW, Australia), two Teflon coated fine wire electrodes (A-M Systems, WA, USA) were inserted approximately 3-4mm on each side of the frenulum and up to 1.5cm deep perorally into the genioglossus muscle via 25G needles (BD PrecisionGlide™, Temse, Belgium) according to previously described methodology (79). Data were acquired using a 16-bit analog to digital converter (Power 1401, Cambridge Electronic Design Limited, Cambridge, UK) and data acquisition software (Spike 2, version 7.20, Cambridge Electronic Design Limited, Cambridge, UK).

4.3.4. Data analysis

Overnight sleep study data were staged and respiratory events scored according to recommended AASM criteria (23). The scorer was blinded to the study condition. Validated, semi-automated, custom designed software was used to quantify key respiratory measures of interest including nasal resistance on a breath by breath basis (229). Data were manually reviewed and artifact breaths removed (e.g. due to swallows or poor signal quality such as electrical noise for EMG signals or leak for respiratory variables).

Awake nasal resistance was calculated as the magnitude of the pressure difference between choanal pressure and mask pressure at a flow rate of 0.2L/s (337). High nasal resistance was defined as >3cmH_2O/L/s (205).

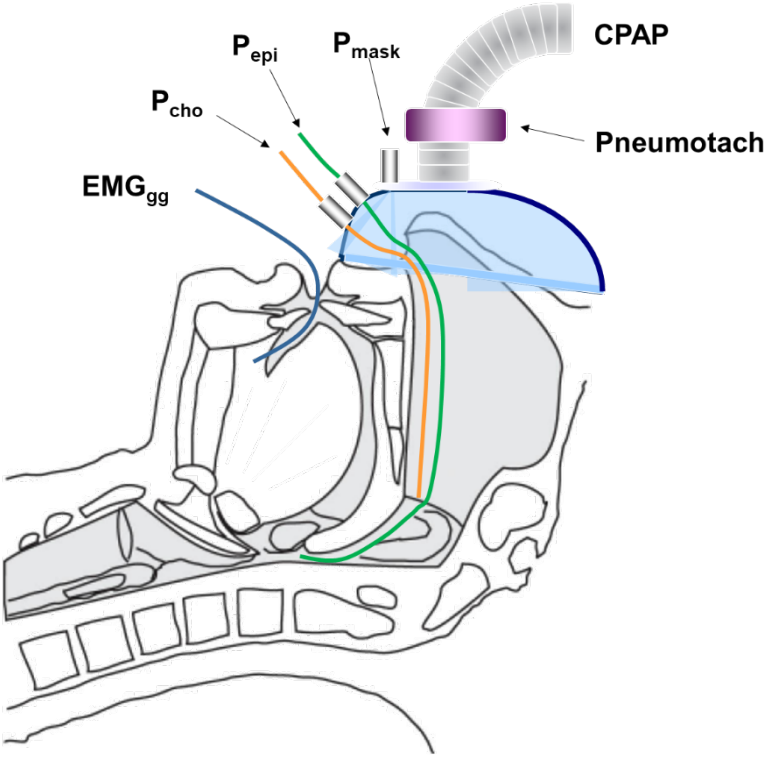

Figure 4.2: Schematic diagram of the detailed upper airway physiology set up.
CPAP=continuous positive airway pressure, Pmask=mask pressure, Pepi=epiglottic pressure, Pcho=choanal pressure, EMGgg=Genioglossus electromyography

Upper airway collapsibility (Pcrit), respiratory arousal threshold, and genioglossus muscle responsiveness were quantified according to previously described gold standard methodology (79). Briefly, upper airway collapsibility (Pcrit) was quantified using linear regression of the flow versus mask pressure relationship for all flow-limited breaths (breaths three to five following each CPAP dial down). Pcrit was quantified as the x-intercept (Flow = 0L/s) of the linear regression fit (39, 241, 279). Arousal threshold was quantified as the average nadir epiglottic pressure of the breath preceding a cortical arousal during hypopnoea and obstructive apnoeas (78). Genioglossus muscle responsiveness was quantified as the slope of the relationship between peak genioglossus muscle activity and nadir epiglottic pressure for each breath during hypopnoea and obstructive apnoeas (79). Loop gain was quantified using a validated computational methodology (311). In addition, estimates of upper airway collapsibility ($V_{passive}$), respiratory arousal threshold ($V_{arousal}$) and upper airway muscle compensation (V_{active} and V_{comp}) as a % of eupnoea were also calculated from the airflow signals and corresponding arousals and events scoring data from the detailed physiology PSG using semiautomated, validated, custom software (271, 272).

4.3.5. Statistical analysis

Two tailed, unpaired Students t-tests were used for normally distributed data to compare 1) OSA pathophysiological traits between responders and non-responders to oral appliance therapy, 2) key variables in those who did versus not return for the efficacy study and 3) sleep and breathing parameters between no therapy versus oral appliance therapy conditions. Mann-Whitney rank sum tests were used to compare non-normally distributed data. Normality was assessed using the Shapiro-Wilk test. All statistical analyses were performed using SigmaPlot version 12.5, (Systat Software, San Jose, CA, USA). Data are reported as mean ± standard deviation for normally distributed data or median (interquartile range [IQR]) for non-normally distributed data.

4.4. Results

4.4.1. Participant characteristics

41 participants with OSA were screened by our in-house study dentist for oral appliance therapy. 9 were contraindicated for therapy and 32 were fitted with an oral appliance and progressed through the trial. 24 participants completed the trial, 6 were lost to follow-up, 1 withdrew from the study due to personal reasons and 1 failed to acclimatise to therapy (Figure 4.3). Anthropometric data for the 24 participants who completed the study are detailed in Table 4.1.

Sex	22 Males: 2 Females
Age (yr)	47 [34,60]
Body mass index (kg/m^2)	27.6 ± 3.8
Mandibular advancement (mm)	10.5 ± 2.0
Mandibular advancement (% max)	85.5 ± 9.0
Epworth sleepiness score	7.8 ± 3.7
Baseline AHI (events/h)	21.5 [15.2,36.3]
NOSE questionnaire	19.5 ± 17.1
Mallampati score	3 [2,4]
Insomnia severity index	8.5 ± 5.9

Table 4.1: Participant anthropometric data

Data are mean ± standard deviation or median (interquartile range). N=24. AHI=apnoea/hypopnoea index.

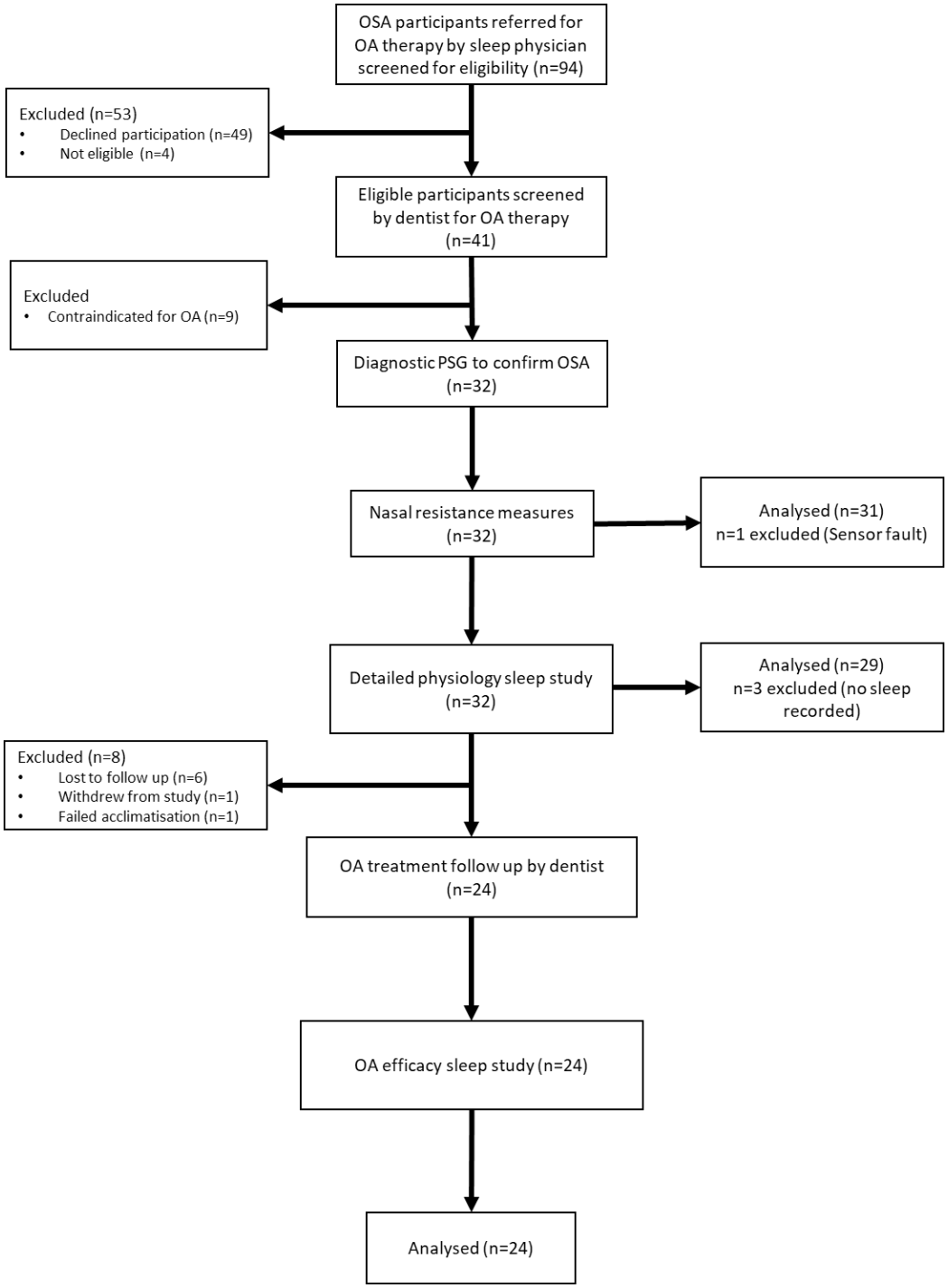

Figure 4.3: CONSORT diagram detailing participant recruitment and flow through the study protocol.

94 patients with OSA referred for oral appliance therapy were screened for eligibility. 41 eligible patients were then screened by a qualified sleep dentist for oral appliance therapy. 9 patients were contraindicated for therapy and excluded. The remaining 32 participants were invited to undergo a diagnostic in lab PSG to confirm OSA. Following confirmation of OSA, 32 participants were studied for nasal resistance measures and detailed physiology overnight sleep study. These 32 participants were then fitted with an oral appliance and went on to acclimatise to therapy for 8-12 weeks. 6 were lost to follow up, 1 withdrew from the study due to personal reasons and 1 failed acclimatisation. 24 participants returned following acclimatisation for an overnight oral appliance efficacy in-lab PSG. OSA=obstructive sleep apnoea, OA=oral appliance.

4.4.2. Efficacy of the next generation novel oral appliance

Key polysomnographic variables are summarised in Table 4.2. The next generation novel oral appliance reduced OSA severity by 41±32% (Figure 4.4A). 7 participants had high nasal resistance in the supine position. OSA severity in this group was reduced by 40±24% with oral appliance therapy. The reduction in OSA severity was similar between participants of high and low nasal resistance (Figure 4.4B, p=0.917).

NREM supine AHI was reduced by 62[35,82]% and NREM AHI was reduced by 49[27,82]% with oral appliance therapy. Similarly, oral appliance therapy reduced both supine REM AHI and REM AHI by 39[-8,70]% and 25±49% , respectively. Oral appliance therapy did not reduce the duration of hypopnoeas. However, the frequency of hypopnoeas were reduced with oral appliance therapy. In contrast, oral appliance therapy reduced both apnoea duration and frequency.

The oxygen desaturation index decreased with oral appliance therapy. However, nadir O_2 saturation and sleep time spent below 90% O_2 saturation were not systematically different between baseline and therapy nights. Total sleep time and sleep efficiency were similar between baseline and therapy nights. Sleep architecture on therapy improved with oral appliance therapy as evidenced by reduced time in stage N1 sleep, increased REM sleep, and a tendency towards a lower arousal index and increased time spent supine. Half of the study participants has a greater than 50% reduction in OSA severity. Table 4.3 and 4.4 summarises the participant response rate to the next generation oral appliance according to standard clinical treatment outcome definitions. Subjective sleepiness as measured by the ESS score were similar between baseline and therapy nights (8±4 versus 6±3).

	No therapy	Oral appliance	P-value
Sleep efficiency (%)	86 [80,91]	90 [80,92]	0.734
Total sleep time (minutes)	407 ± 50	415 ± 55	0.592
Stage N1 sleep (%TST)	15 [11,21]	12 [6,16]	0.068
Stage N2 sleep (%TST)	45 ± 9	43 ± 9	0.484
Stage N3 sleep (%TST)	18 ± 7	18 ± 6	0.732
REM sleep (%TST)	20 ± 8	25 ± 7	0.016
Wake after sleep onset (minutes)	49 [26,79]	42 [32,91]	0.975
Arousal index (events/h)	25 [17,30]	19 [12,24]	0.081
Time spent supine (%TST)	59 ± 36	71 ± 27	0.191
NREM supine AHI (events/h)	31 [17,53]	10 [6,15]	<0.001
REM supine AHI (events/h)	50 [35,58]	28 [17,40]	0.003
Total supine AHI (events/h)	37 [22,55]	14 [9,21]	<0.001
Total AHI (events/h)	22 [15,36]	11 [7,17]	<0.001
Total NREM AHI (events/h)	19 [11,32]	8 [4,11]	<0.001
Total REM AHI (events/h)	34 ± 13	22 ± 12	0.002
Hypopnoea event duration (seconds)	25 ± 5	24 ± 6	0.36
No. of hypopnoeas (events)	103 [86,186]	67 [43,110]	0.004
Apnoea event duration (seconds)	18 [15,25]	13 [3,20]	0.01
No. of apnoeas (events)	18 [9,46]	1.5 [0,7]	<0.001
Nadir SpO_2 (%)	84 [79,87]	84 [80,88]	0.782
Total ODI (3%)	16 [10,34]	9 [5,14]	0.001
T90 (minutes)	4 [1,18]	4 [0,14]	0.655
T90 (%TST)	1 [0,4]	1 [0,3]	0.876

Table 4.2: Polysomnography data no therapy vs. oral appliance therapy

Data are mean ± standard deviation or median (interquartile range). N=24. AHI=apnoea/hypopnoea index, NREM=non-rapid eye movement sleep, ODI=oxygen desaturation index, REM=rapid eye movement, SpO_2=estimated blood oxygen via pulse oximetry, T90=time spent with a blood oxygen saturation level below 90%, TST=total sleep time.

	Responders % (n)		
	Total AHI	NREM supine AHI	Supine AHI
Treatment AHI<5 events/h	0 (0)	16 (4)	0 (0)
Treatment AHI<10 events/h	42 (10)	50 (12)[a]	29 (7)
Treatment AHI<10 events/h & >50% reduction in baseline AHI	33 (8)	42 (10)	25 (6)
>50% reduction in baseline AHI	46 (11)	67 (16)	50 (12)
Reduction in OSA severity category	50 (12)	79 (19)	75 (18)

Table 4.3: Participant response rate to oral appliance therapy according to different treatment outcome definitions.

Number of participants in each category are listed in parentheses. Data calculated from n=24 participants. [a] Count includes participants with AHI<5events/h. AHI=apnoea/hypopnoea index, NREM=non-rapid eye movement, OSA=obstructive sleep apnoea, Reduction in OSA severity category=proportion of participants who had a reduction in OSA severity category (e.g., from severe to moderate or moderate to mild etc. where mild=AHI 5 to <15, moderate=AHI 15 to <30 and severe=AHI ≥ 30events/h).

	Responders, % (n)	
	High nasal resistance	*Low nasal resistance*
Treatment AHI<5 events/h	0	0
Treatment AHI <10 events/h	29 (2)	47 (8)
Treatment AHI<10 events/h & >50% reduction in baseline AHI	14 (1)	41 (7)
>50% reduction in baseline AHI	29 (2)	53 (9)
Reduction in OSA severity category	43 (3)	53 (9)

Table 4.4: Treatment response rates according to high versus low nasal resistance

Number of participants listed in each category are listed in parentheses. Data for high nasal resistance group calculated from n=7 participants. Data for low nasal resistance group calculated from n=17 participants. High nasal resistance is defined as >3cmH_2O/L/s. AHI=apnoea/hypopnoea index, OSA=obstructive sleep apnoea, Reduction in OSA severity category=proportion of participants who had a reduction in OSA severity category (e.g., from severe to moderate or moderate to mild etc. where mild=AHI 5 to <15, moderate=AHI 15 to <30 and severe=AHI ≥ 30events/h).

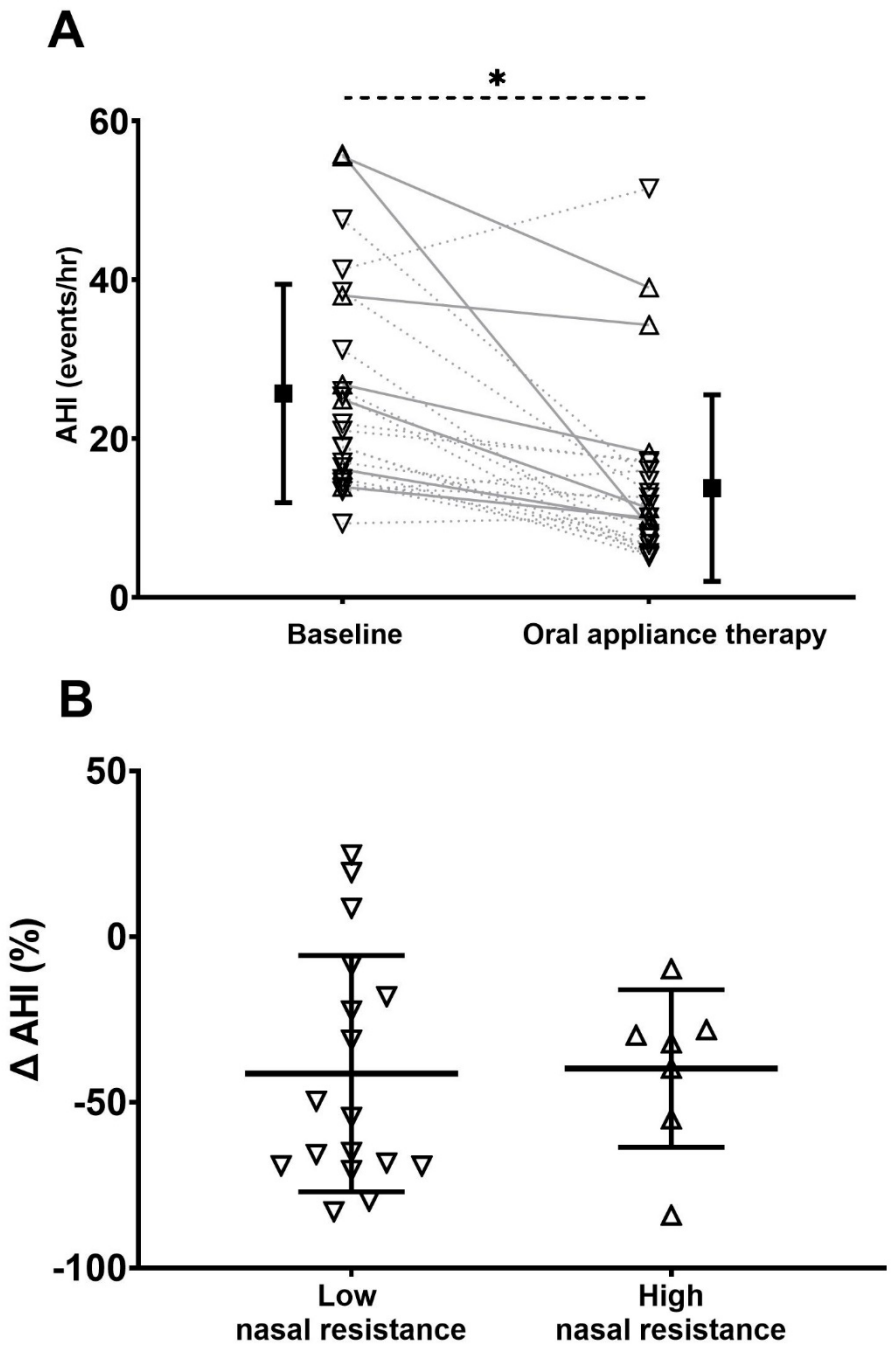

Figure 4.4: Efficacy of next generation novel oral appliance

(A) Effect of oral appliance on obstructive sleep apnoea severity (total apnoea/hypopnoea index [AHI]). Black squares with error bars=group mean ± standard deviation. (B) Percentage reduction in obstructive sleep apnoea severity with oral appliance between people with high and low nasal resistance. High nasal resistance is defined as >3cmH_2O/L/s. Black error bars=group mean ± standard deviation.

Each data point denotes an individual participant. Clear triangles indicate people with high nasal resistance. Inverted triangles indicate people with low nasal resistance. Nasal resistance measured in the supine position. Asterisk indicates a significant difference ($P<0.05$) between baseline and oral appliance therapy.

4.4.3. Self-reported compliance to oral appliance therapy

Participants reported using the oral appliance for an average of 7±1 hours/night (range: 4-8 nights) for 6±1 nights/week (range: 2-7 nights). All participants used their oral appliance for at least 4h/night. 7 participants reported subjective improvements in sleep quality, 8 reported that their partners noticed a reduction in snore intensity and 9 reported no improvements in sleep quality.

4.4.4. Effects of nasal resistance and OSA pathophysiological traits on treatment response

While values varied between participants, consistent with subjective perception of low nasal resistance (NOSE questionnaire, Table 4.1), median objective awake nasal resistance while supine for the group was 2.5[1.8,3.7] $cmH_2O/L/s$. Nasal resistance was not different between responders and incomplete responders to oral appliance therapy (1.9[1.2,4.4] vs. 2.5[2.0,4.8] $cmH_2O/L/s$, p=0.164).

There were no significant differences in any of the OSA pathophysiological traits as measured by gold standard methodology between responders and incomplete responders to oral appliance therapy (Residual AHI >10 events/h) (Table 4.5). Additionally, OSA pathophysiological traits were similar between responders and non-responders according to the definition of greater than 50% reduction in AHI (data not shown).

	Responder	Non-responder	P-value
Pcrit (cmH_2O)	-1.5 ± 2.2	-1.6 ± 2.1	0.936
Arousal threshold (cmH_2O)	-21.0 ± 6.9	-25.2 ± 9.1	0.342
Muscle responsiveness (%max/cmH_2O)	-0.1 [-1.0,-0.1]	-0.1 [-0.2,-0.1]	0.832
LG1	0.7 ± 0.2	0.6 ± 0.2	0.713
LGn	0.5 ± 0.1	0.5 ± 0.1	0.736

Table 4.5: Comparison of OSA pathophysiological traits measured by gold standard methodology between responders and non-responders to oral appliance therapy.

Data are mean ± standard deviation or median (interquartile range). N=9 in the responders group. N=12 in the non-responders group. Pcrit=critical closing pressure (upper airway collapsibility), LG1=loop gain determined at 1cycle/min, LGn=loop gain at the natural cycling frequency.

OSA pathophysiological traits calculated using a custom semi-automated script (271, 272) was compared between responders and non-responders (Residual AHI>10events/h) and is summarised in Table 4.6. Passive upper airway collapsibility ($V_{passive}$) and active upper airway collapsibility (V_{active}) were higher (less collapsible airways) in those who responded to oral appliance therapy versus those who did not. Pharyngeal muscle compensation (V_{comp}) also tended to be worse in non-responders versus responders to oral appliance therapy. The estimated arousal threshold was similar between groups.

	Responder	**Non responder**	**P-value**
Arousal threshold (%V_{eupnea})	124 [109,140]	147 [126,180]	0.166
$V_{passive}$ (%V_{eupnea})	93 [84,97]	79 [37,91]	0.025
V_{active} (%V_{eupnea})	102 [92,112]	72 [0,100]	0.041
V_{comp} (%V_{eupnea})	5 [3,27]	-7 [-26,2]	0.051

Table 4.6: Comparison of OSA pathophysiological traits as calculated using a custom semi-automated script (271, 272) between responders and non-responders to oral appliance therapy.

Data are median (interquartile range). N=10 participants who were responders. N=12 participants who were non-responder (residual AHI>10 events/h). $V_{passive}$=passive upper airway collapsibility, V_{active}=active upper airway collapsibility, V_{comp}=pharyngeal muscle compensation.

4.4.5. Participant characteristics in those who did versus did not return for the final efficacy study

6 participants did not return for the efficacy study as they were lost to follow up. Table 4.7 summarises the anthropometric data between participants who returned and did not return for the efficacy study.

Table 4.8 summarises the OSA pathophysiological traits between participants who returned for their treatment efficacy study and those who did not. Pcrit, arousal threshold and muscle responsiveness and loop gain were similar between both groups.

	Returned for efficacy study	Did not return for efficacy study	P-value
Age (yr)	47 [34,60]	42 [31,49]	0.287
Body mass index (kg/m^2)	28 ± 4	28 ± 5	0.884
Epworth sleepiness score	8 [6,11]	7 [3,16]	0.938
Baseline AHI (events/h)	21 [15,36]	25 [15,34]	0.979
NOSE questionaire	20 ± 17	19 ± 17	0.958
Mallampati score	3 [2,4]	4 [3,4]	0.510
Insomnia severity index	9 ± 6	12 ± 7	0.315

Table 4.7: Comparison of anthropometric data between participants who returned and did not return for their final efficacy study.

Data are means ± standard deviation or median (interquartile range). N=6 did not return for the efficacy study. N=24 in the group who returned for the efficacy study. AHI=apnoea/hypopnoea index

	Returned for efficacy study	Did not return for efficacy study	P-value
Pcrit (cmH_2O)	-1.5 ± 2.1	-1.2 ± 2.6	0.849
Arousal threshold (cmH_2O)	-23.5 ± 8.2	-20.2 ± 6.0	0.417
Muscle responsiveness (%max/cmH_2O)	-0.1 [-0.2,-0.1]	0.0 [-0.2,0.0]	0.063
LG1	0.6 ± 0.2	0.6 ± 0.1	0.847
LGn	0.5 ± 0.1	0.4 ± 0.1	0.139

Table 4.8: Comparison of OSA pathophysiological traits between participants who returned for their efficacy night and those who did not return for their efficacy study.

Data are mean ± standard deviation or median (interquartile range). N=6 in the group who did not return for the efficacy study. N=23 in the group who returned for the efficacy study. Pcrit= critical closing pressure (upper airway collapsibility), LG1=loop gain determined at 1cycle/min, LGn=loop gain at the natural cycling frequency.

4.5. Discussion

The main findings of this study are that the next generation novel oral appliance reduced OSA severity by approximately 40% in participants with high and low nasal resistance. In addition, OSA pathophysiological traits measured using gold standard methodology did not differ between responders and non-responders to oral appliance therapy. However, when the traits were calculated using a custom semi-

automated script (271, 272), baseline upper airway collapsibility (higher $V_{passive}$ and V_{active}) was less severe in responders to oral appliance therapy versus non-responders. In addition, responders to oral appliance therapy tended to have better pharyngeal muscle compensation at baseline (V_{comp}) compared to non-responders.

4.5.1. Efficacy of the next generation novel oral appliance

The approximately 40% overall reduction in OSA severity with the next generation nylon-based novel oral appliance with built-in oral airway was similar to the titanium-based oral appliance studied in Chapter 2. The magnitude of the reduction in OSA severity is also comparable to traditional oral appliances (200). However, an earlier study that used a mono-style prototype titanium-based oral appliance with built-in oral airway reported more pronounced overall reductions in OSA severity of approximately 60% (170). This apparent discrepancy between studies is likely explained by differences in participant characteristics such as OSA severity.

On average, it is reported that at least 30-90% of patients on oral appliance therapy achieve an AHI<10 events/h (200, 304). This is comparable to the current study findings where 40% of participants had an AHI of <10 events/h on therapy. This is also similar to the first generation mono-style oral appliance (170) and the findings reported in Chapter 2 (313). However, none of the participants in the current study had an AHI of <5 events/h on therapy. Four participants however, did have AHI values of 5-6 events/h on therapy. Lack of complete resolution of OSA according to the AHI <5 events/ definition in the current study may be explained, at least in part, by the instructions given to participants to sleep supine as much as possible during their sleep study. Indeed, on average, participants spent 70% of total sleep time supine. Supine position results in more severe OSA due to increased gravitational effects on airway collapsibility and has been reported to negatively impact oral appliance therapy outcome (303).

Unlike traditional oral appliance therapy where high nasal resistance is associated with poor treatment outcome (349), similar to the findings outlined in Chapter 2 (313), and subjective assessment of nasal resistance in an earlier study with the mono-type device (170), reductions in OSA severity in the current study using the oral appliance with built-in oral airway were comparable in people with and without objectively measured high nasal resistance.

Self-reported short term compliance to oral appliance therapy has been reported to vary between approximately 75-95% (200). This is comparable with the current study findings of 80% compliance according to the standard OSA treatment compliance definition of at least 4 hours/night for a minimum of 5 nights/week (63).

4.5.2. Differences in OSA pathophysiological traits between responders and incomplete responders to oral appliance therapy

Contrary to our hypothesis and previous studies where OSA pathophysiological traits such as a less collapsible airway and lower loop gain were associated with favourable responses to oral appliance therapy (12, 81, 201, 238, 321), this was not the case in the current study when the traits were quantified using gold standard methodology. However, this finding is similar to the recently reported detailed upper airway physiology findings from Bamagoos and colleagues (13) where genioglossus muscle responsiveness and upper airway collapsibility measured using gold standard methodology were also not systematically different between responders and incomplete responders. This outcome was largely attributed to the relatively small sample size (n=12).

However, in accordance with previous studies that used the same custom-design, validated algorithms to estimate the OSA traits (12, 81, 201, 238, 321), important differences in baseline OSA traits including estimates of pharyngeal collapsibility in responders versus non-responders to oral appliance therapy were found in the current study. Thus, the methodology used to quantify OSA pathophysiological traits appears to be of crucial importance for oral appliance treatment prediction.

The algorithm-based estimates of OSA pathophysiological traits when quantified using nasal pressure to determine ventilatory drive and airflow from a standard sleep study (271, 272, 311) have a reported accuracy of between 70-90% (271) compared with direct gold standard methodology. However, the semi-automated calculations of pathophysiological traits are derived on whole night estimates, or in the current study most of the night, from the detailed overnight sleep study. In contrast, gold standard measurement methods used in the current study to quantify Pcrit were conducted during the first sleep cycle where sleep drive tends to be strongest and slow wave sleep predominates. Indeed, there are large differences in upper airway collapsibility as measured via the Pcrit technique between N2 and slow wave sleep whereby the

upper airway is less collapsible during slow wave sleep (39). This may explain, at least in part, why none of the participants in the current study had a severely collapsible pharyngeal airway (>+2cmH_2O) as measured via Pcrit and the lack of treatment prediction performance. Thus, while gold standard physiological methodology provides precise calculation of Pcrit at the time of measurement, like all physiology measures, it is prone to both measurement and physiological variation. Indeed, direct quantification of Pcrit and the pathophysiological traits using gold standard methodology is technically challenging and requires subjective interpretation of airflow and muscle data (74). This may inadvertently introduce measurement noise and variability (328) and hence, a larger sample size may be required to detect changes between groups and predict treatment outcomes. Accordingly, the current findings indicate whole night estimates of upper airway collapsibility have superior oral appliance treatment predictive performance compared to direct Pcrit measurement calculated from just the early portion of the night. This is encouraging from a translation perspective.

In addition to the consistent findings of baseline estimates of pharyngeal collapsibility as an important predictor of oral appliance therapy (12, 81, 201, 238, 321), the current findings also suggest that poor pharyngeal muscle compensation may be a predictor of poor treatment outcome. This is consistent with phenotyping concepts (163) whereby improving one trait (i.e. upper airway anatomy with an oral appliance) may be insufficient for major reductions in OSA severity if one or more of the other traits remains impaired. Indeed, while conceptually mandibular advancement may improve the ability of the pharyngeal dilators to restore airflow (26), the only study to measure this directly did not find that this was the case (13). These individuals may require combination therapy with an agent that also improves pharyngeal muscle responsiveness (309, 310) or an additional anatomical intervention (164) for complete resolution of their OSA.

In contrast to previous studies (81, 238) however, high loop gain was not a negative predictor of treatment outcome in the current study. This may be due to differences in participant characteristics between studies and potentially the different types of oral appliances used.

4.5.3. Methodological considerations

A key strength of this study was that OSA pathophysiological traits were prospectively and directly quantified using established gold standard methodology (79). In addition, nasal resistance was objectively measured. Moreover, participants in this study were well titrated and acclimatised to oral appliance therapy prior to their efficacy study.

Nevertheless, this study had limitations. First, while double the sample size of the largest published direct detailed physiology study conducted to date (13), the current sample size may still have been insufficient to detect differences in directly measured OSA pathophysiological traits between responders and incomplete responders. Second, there was also quite a high proportion of participants who discontinued participation during the acclimatisation period or did not attend the follow-up efficacy study (8/32 - in part due to COVID-19 pandemic challenges) which could have biased the study sample. However, this is unlikely as comparison of OSA pathophysiological traits between those who completed the study and those who did not return were not different. In addition, participants in the current study were recruited via referral from experienced sleep specialists familiar with OSA phenotyping concepts. This may have inadvertently introduced patient selection bias based on clinical variables which favour oral appliance treatment response (303). However, this is unlikely as treatment response rates were similar to the published literature. Finally, use of the gold standard methodology to quantify OSA pathophysiological traits is invasive and procedurally intensive. This can limit total sleep time and therefore the amount of data collected. However, only three participants in the current study were not able to tolerate the recording equipment.

4.6. Summary and conclusions

The next generation novel oral appliance therapy with an in-built oral airway reduced OSA severity by 40% including those with high nasal resistance. Half of the participants had a greater than 50% reduction in OSA severity. OSA pathophysiological traits as measured by gold standard methodology did not differ between responders and incomplete responders to oral appliance therapy. However, computational estimates of upper airway collapsibility and pharyngeal muscle compensation were different in responders versus non-responders. These findings

have important implications for OSA phenotyping. Similar to other recently published findings that highlight the potential to predict treatment responses to upper airway surgery including hypoglossal nerve stimulation (139, 176, 239), the current findings provide further encouraging support for the potential to translate these concepts into the clinic to predict oral appliance treatment outcome using estimates of OSA traits.

5. Thesis summary and conclusions

OSA is a common and underdiagnosed condition with an estimated global prevalence of nearly 1 billion people (20). Untreated OSA compromises quality of life and is associated with other major health consequences and co-morbidities. Oral appliances have emerged as a leading alternative to CPAP therapy. Yet efficacy of oral appliances varies and is difficult to predict using standard clinical variables. Several studies have investigated the mechanisms by which oral appliances reduce OSA severity. Other studies have also sought to identify the favourable physiological characteristics associated with improved efficacy of oral appliance therapy in people with OSA.

In this thesis, I assessed the effects of changes in body position on nasal obstruction and the influence of high nasal resistance on the efficacy of two iterations of a novel oral appliance with built-in oral airway, studied the mechanisms and magnitude by which combining oral appliance therapy with CPAP improves pharyngeal stability in incomplete responders to oral appliance therapy alone and investigated potential differences in OSA pathophysiological traits between responders and incomplete responders to oral appliance therapy using direct gold standard methodology and validated computational estimates.

Increased nasal resistance is recognised as a risk factor for OSA and a negative predictor for oral appliance therapy outcome (349). Nasal resistance varies with body posture in healthy individuals but previous investigations into the effects of changes in body posture on nasal resistance in people with OSA have yielded variable results (57, 118, 349). Furthermore, the effect of mandibular advancement on nasal resistance in people with OSA remains unclear. Accordingly, in Chapter 2, the role of mandibular advancement and body posture on nasal resistance was explored in people with OSA using gold standard methodology (337). Nasal resistance increased by up to 20% from seated, to supine, to lateral recumbent postures in people with OSA. Comparing to previous studies in healthy individuals, the magnitude of the increase in nasal resistance was markedly lower in people with OSA compared to previous studies in healthy individuals. This suggests a diminished positional reflex response and neurovascular control within the OSA cohort. However, this requires further investigation including simultaneous measurements in people with and without OSA.

The second finding from Chapter 2 was that nasal resistance did not change with mandibular advancement regardless of body position in people with OSA. Notably however, nasal resistance increased with mandibular advancement in incomplete responders to oral appliance therapy in the seated position. In contrast to healthy individuals in previous studies (119, 235), these findings indicate an absence of an effect in nasal resistance with mandibular advancement. This may be due to an impaired functional response within the upper airway in patients with OSA. Indeed, advancement of the mandible is known to alter upper airway structures and differences in the degree of change have been reported between healthy individuals and people with OSA (33, 43).

The novel titanium-based oral appliance with a built in oral airway decreased the severity of OSA by approximately 50% in patients with and without nasal obstruction. This indicates that with the addition of an alternate breathing route, OSA patients with nasal obstruction can yield a similar benefit from oral appliance therapy.

Approximately 50% of people with OSA have incomplete resolution of their OSA with oral appliance therapy (304). Thus, a substantial proportion of people prescribed oral appliance therapy remain inadequately treated. In addition, despite the high efficacy of CPAP therapy, it is often poorly tolerated (86). Discomfort due to high CPAP levels may be an important contributor to poor adherence for certain patients. Alternative approaches such as combining CPAP and oral appliance therapy has been proposed as a strategy to accommodate incomplete responders to oral appliance therapy and CPAP intolerant patients (84). Chapter 3 describes the findings from a detailed physiological study which aimed to understand the mechanisms and magnitude by which combination therapy using CPAP and oral appliance reduces the therapeutic CPAP requirements in people with OSA. Incomplete responders to oral appliance therapy from the study detailed in Chapter 2 were recruited. A pressure tipped catheter was used to objectively measure pharyngeal pressure swings during CPAP titrations. This approach is superior to the standard measure of airflow via a pressure transducer and CPAP titrations conducted via visual inspection of respiratory events during routine polysomnography. I found that therapeutic CPAP requirements were reduced by at least 35% when CPAP was combined with oral appliance therapy in the clinically relevant group of incomplete responders to oral appliance therapy alone. These findings provide novel physiological insight into the mechanisms of oral appliance therapy and combination therapy with CPAP.

Prediction of successful treatment outcomes with oral appliance therapy remains challenging. Clinical and standard anatomical parameters have proved insufficient to consistently predict successful treatment outcomes of oral appliance therapy. More recent estimates of OSA pathophysiological phenotypes such as upper airway collapsibility and loop gain (12, 81, 201, 238, 321) have shown considerable promise for accurate predication of oral appliance therapy outcome. To date, baseline pathophysiological OSA phenotypes have primarily been compared using simplified phenotyping methods between responders and incomplete responders to oral appliance therapy. In Chapter 4, I prospectively assessed the effect of baseline pathophysiological OSA phenotypes and nasal resistance on oral appliance treatment responses using gold standard and validated computational methodology. In addition, efficacy of a next generation nylon-based novel oral appliance with a built-in oral airway was investigated.

The next generation nylon-based novel oral appliance reduced OSA severity by 40% in those with high and low nasal resistance. At least half of participants achieved a greater than 50% reduction in OSA severity and a reduction in OSA severity category. This finding was comparable to the previous generation titanium-based oral appliance studied in Chapter 2 (313). Baseline OSA pathophysiological traits measured using gold standard phenotyping methodology were similar between responders and incomplete responders to oral appliance therapy. However, responders to oral appliance therapy tended to have less collapsible upper airways and better pharyngeal dilator responses when the pathophysiological traits were estimated using validated computational algorithms. Potential reasons for the apparent disparities between methodologies are highlighted in the Discussion section of Chapter 4. However, the important translational finding is that computational estimates of OSA phenotypes may be more appropriate and relevant for oral appliance treatment prediction. An important next step will be to incorporate these tools clinically to determine if their use improves oral appliance treatment outcomes prospectively.

Collectively, the detailed upper airway physiology and respiratory phenotyping studies outlined in this thesis provide important new insights into the role of posture and high nasal resistance on the efficacy of two iterations of a novel oral appliance with built-in oral airway, the potential benefit of combination therapy with CPAP for incomplete responders to oral appliance therapy alone, and the potential for OSA

pathophysiological trait estimates to be used clinically to improve oral appliance treatment prediction.

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