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The Role of Phenotyping in the Personalised Management of OSA

Matthew Eugene Lam

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Matthew Eugene Lam

Supervisors:

Professor Stuart MacKay

Associate Professor Bruce Ashford

Doctor Theresa Larkin

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Abstract

Background: Obstructive sleep apnoea (OSA) is estimated to affect up to 1 billion people in the world. Those who fail first-line continuous positive airway pressure (CPAP) therapy have salvage treatment options available. Patient assessment can incorporate multidisciplinary teams to better select therapy. Traditional parameters that define OSA severity do not always correlate with symptoms of the disease. Newly identified pathophysiological "phenotypes" of airway vulnerability, low arousal threshold, loop gain and muscle responsiveness may explain the heterogeneity of OSA for up to two-thirds of patients. Little data exists on the effectiveness of phenotyping in a real-world clinical setting for patients undergoing contemporary management paradigms.

Aims and Hypothesis: To evaluate the prevalence of the four OSA phenotypic traits and explore the clinical validity of endotyping in predicting future treatment outcomes. It is expected that non-responders to treatment will have unfavourable non-anatomical phenotypes.

Design: An observational prospective cohort study of 49 patients referred after failure of CPAP for consideration of salvage therapy was conducted. Treatments included upper airway surgery (n = 17), mandibular advancement splint (n = 7), positional therapy (n = 7), weight loss (n = 4), nerve stimulation (n = 5) and combination therapy (n = 9). Treatment "success" was defined using polysomnographic parameters and patient-reported outcome measures of sleepiness and function. Phenotypic traits were analysed according to these outcomes.

Results: Nearly all surgical patients had unfavourable loop gain ($LG_1 > 0.72$), which improved after surgical treatment ($p < .05$). Patients who had decreased sleepiness (Epworth Sleepiness Scale reduction ≥ 3, total score < 10, $p = .01$) after any treatment had favourable traits of low loop gain, lower arousal threshold and lower muscle compensation. There may be a potential role for phenotyping in predicting expected outcomes from salvage treatment for OSA, although more prospective clinical data is required to further investigate its utility and relevance.

Acknowledgements

Firstly, thanks must go to my supervisors, Professor Stuart MacKay, Associate Professor Bruce Ashford and Dr Theresa Larkin. They have provided invaluable support and assistance behind the scenes in navigating the last two years. My heartfelt thanks go to Prof MacKay, for providing his relentless encouragement both in the clinical and research setting, all whilst never failing to ensure that I (and the rest of the ENT team) was always well fed with some variation of fried chicken, Samaras, meat pies or Chomps.

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I am indebted to Alana and the rest of the team at Illawarra ENT, who have been absolute gems in tracking patients down and ensuring that all the appropriate paperwork was always scanned and documented in their medical records.

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I cannot express enough gratitude to our phenotyping collaborators at Monash University (Associate Professor Bradley Edwards, Dr Dwayne Mann, Dr Simon Joosten, Associate Professor Garun Hamilton), who have been very generous in providing invaluable advice and expertise within this rapidly growing field of OSA.

Finally, my love and thanks to Charini, for her tireless support in allowing me to spend two years of our life down in this little corner of the world, even though we were not together for a lot of it (thanks COVID19).

Certification

I, Matthew Eugene Lam, declare that this thesis submitted in fulfilment of the requirements for the conferral of the degree Masters of Philosophy, from the University of Wollongong, is wholly my own work unless otherwise referenced or acknowledged. This document has not been submitted for qualifications at any other academic institution.

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Matthew Eugene Lam

3rd January 2021

List of Abbreviations

- AASM – American Academy of Sleep Medicine
- AHI – apnoea/hypopnoea index
- ANOVA – analysis of variance
- AP – antero-posterior
- APAP – auto-titrating positive airway pressure
- ASA – Australian Sleep Association
- BiPAP – bilevel positive airway pressure
- BMI – body mass index
- COPD – chronic obstructive pulmonary disease
- CPAP – continuous positive airway pressure
- CTx – combination therapy
- CT – computed tomography
- dBP – diastolic blood pressure
- DISE – drug induced sleep endoscopy
- ECG - electrocardiogram
- EEG – electroencephalogram
- EMG – electromyogram
- EOG – electrooculogram
- ESS – Epworth Sleepiness Scale
- FOSQ – Functional Outcomes of Sleep Questionnaire
- FTG – Friedman tongue grade
- GP – general practitioner
- LG_1 – loop gain as calculated in response to a 1 cycle/min ventilatory disturbance
- LG_n – loop gain as calculated in response to the actual cycle/min ventilatory disturbance
- Lsat – nadir oxygen saturation (on polysomnography)
- MAS – mandibular advancement splint
- MPH – mandibular-plane hyoid distance
- MRI – magnetic resonance imaging
- N1, N2, N3 – stage 1, 2, 3 (in NREM sleep)
- NREM – non-rapid eye movement
- NS – hypoglossal nerve stimulation
- O_2 – oxygen
- ODI – oxygen desaturation index
- OSA – obstructive sleep apnoea
- OSA50 – Obesity, Snoring, Apnoeas, aged >50 years
- PALM – P_{CRIT}, arousal threshold, loop gain, muscle responsiveness
- pCO_2 – carbon dioxide concentration
- P_{CRIT} – critical closing pressure
- P_{DS}, R_{DS} – downstream pressure, resistance
- PLM – periodic limb movement

- PROM – patient reported outcome measure
- PSG – polysomnography
- PTx – positional therapy
- P_{US}, R_{US} – upstream pressure, resistance
- RDI – respiratory disturbance index
- REM – rapid eye movement
- RERA – respiratory effort related arousal
- SAGIC – Sleep Apnoea Global Interdisciplinary Consortium
- sBP – systolic blood pressure
- SNA – sella-nasion distance to subspinale
- SNB – sella-nasion distance to supramentale
- SSS – Snoring Severity Scale
- STOP-Bang – Snoring, Tiredness, Observed apnoeas, blood Pressure, BMI, Age, Neck circumference, Gender
- Sx – upper airway surgery
- UPPP – uvulopalatopharyngoplasty
- V_{active} – ventilation at the arousal threshold
- V_{comp} – difference between Vactive and Vpassive
- V_{eupnea} – ventilation during resting (eupneic) ventilatory drive
- V_{max} – ventilation as a measure of maximum theoretical airflow in an airway
- V_{min} – minimum per breath calculated ventilation during 7 minute epoch
- $V_{passive}$ – median level ventilation during resting phase of ventilatory drive
- VOTE – Volume, Oropharynx, Tongue, Epiglottis

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Chapter 1
Introduction

1. Background

Adult obstructive sleep apnoea (OSA) is a prevalent condition affecting up to 1 billion people in the world[1] and is characterised by repeated episodes of partial or complete upper airway obstruction during sleep. This results in oxygen desaturation and carbon dioxide retention, leading to arousal from sleep in an effort to maintain airway patency[2]. Repeated oxygen desaturations and arousals throughout the night lead to primary sleep deprivation, neurocognitive dysfunction and secondary adverse cardiometabolic effects[2, 3]. Common nighttime symptoms experienced in adults include snoring, choking or gasping, while daytime symptoms include somnolence, poor concentration and morning headaches[4, 5].

Diagnosis is made with polysomnography (PSG), ideally performed overnight in a sleep laboratory or alternatively as a home-based study[6]. A battery of physiological measurements are recorded, including the number of complete and partial obstructive events per hour as the apnoea/hypopnoea index (AHI), oxygen desaturations per hour as the oxygen desaturation index (ODI) and the lowest oxygen saturation (Lsat). A diagnosis of OSA in adults is conventionally made based on an AHI of 5 (events per hour), with further severity stratification into mild OSA defined by an AHI of 5-14, moderate 15-30 and severe over 30[7].

The existing treatment options for OSA can be summarised into lifestyle modifications (such as weight loss), positional therapy, positive airway pressure, airway mandibular advancement splint (MAS) devices and surgical therapy[8]. Continuous positive airway pressure (CPAP) is first-line therapy in adult OSA treatment; failure of treatment is commonly due to problems with adherence or tolerance, with varying rates reported in the literature[9]. For these patients, other airway devices such as MAS or tongue retaining devices can be explored[10]. Salvage surgery is an option in those who fail first-line treatment with techniques such as “pre-phase” nasal surgery[11, 12], contemporary variants of uvulopalatopharyngoplasty (UPPP) with or without palatal advancement[13-15] and tongue reduction or suspension[16-20].

Research demonstrates that the traditional polysomnographic diagnostic definition based on AHI is imperfect[21], particularly regarding cardiovascular risk stratification in OSA. Equally there is a growing acceptance that CPAP cannot be used as a “one-size fits all” treatment in

clinical practice. This has led to a new model of OSA, characterised by pathophysiological "phenotypes" expressed to differing degrees in each individual. These accepted phenotypic traits, or more accurately, "endotypes", are: (1) airway vulnerability, (2) low arousal threshold, (3) loop gain and (4) muscular excitability[22, 23]. It is proposed that established and emerging treatments for OSA have roles to play in modifying the disease burden based on these phenotypes, and it is therefore possible to personalise therapy based on the individual profile of OSA for each patient[23, 24].

This chapter identifies the gap in the literature surrounding the role of personalised management of OSA and how established treatment pathways can be utilised as a part of this new paradigm.

2. Anatomy and Physiology of Obstructive Sleep Apnoea

2.1 Upper Airway Anatomy[25]

The upper airway is comprised of the nasal airway, oral cavity, pharynx (divided into three levels, the nasopharynx, oropharynx and laryngopharynx) and larynx. Contiguous with this is the lower airway, comprised of the trachea, bronchi, bronchioles and subsequent divisions thereof.

The nasal airway is relatively fixed in terms of its anatomical structure and does not fluctuate significantly during sleep. Its key boundaries are the external and internal nasal valves, nasal septum and inferior turbinates. The nasopharynx sits immediately posterior to the nasal cavity and continues as the oropharynx.

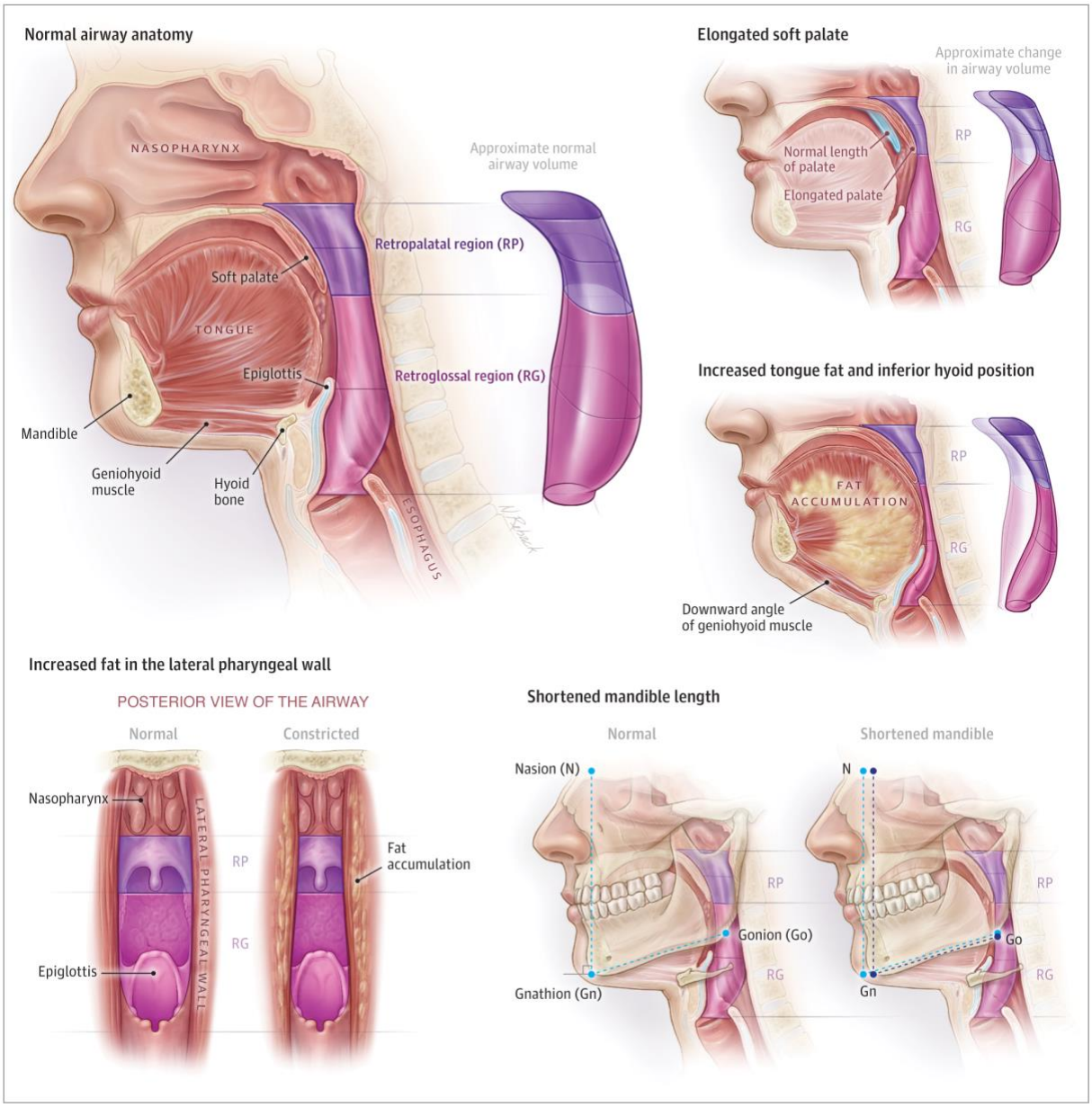
The oral cavity and oropharynx are formed from fixed and dynamic structures. Fixed ("hard") structures include the facial skeleton (maxilla, mandible), teeth and the hard palate. Dynamic ("soft") structures include the tongue, adenoid (if present), palatine and lingual tonsils and soft palate including the uvula. The oropharynx sits at the junction of the nasopharynx and oral cavity.

The tongue is composed of four paired intrinsic muscles and four paired extrinsic muscles. Intrinsic muscles (superior longitudinal, inferior longitudinal, vertical and transverse) are responsible for altering the shape of the tongue while retaining a constant volume. Extrinsic muscles (genioglossus, hyoglossus, styloglossus, palatoglossus) protrude, retract and draw the sides of the tongue down and up respectively. The tongue is tethered to the mandible and hyoid bone, the latter of which also suspends the floor of mouth, suprahyoid and infrahyoid musculature.

The soft palate and uvula is a complex unit that incorporates multiple muscle insertions into a singular fibrous sheet known as the palatal aponeurosis[26]. The soft palate can be divided into a proximal and distal segment, which is separated by the palatal genu. It can be thought of as being comprised of several muscular slings. The tensor palati is responsible for tensing

the palate to enable it to retain its shape when being elevated or depressed by other muscles. The levator palati pulls the palate upwards and backwards. The palatoglossus (as discussed above) raises the sides of the tongue and is sphincteric at the oropharyngeal entrance. The palatopharyngeus has an anterior head that elevates the pharynx and arches the relaxed palate, and a posterior head that depresses the tensed palate.

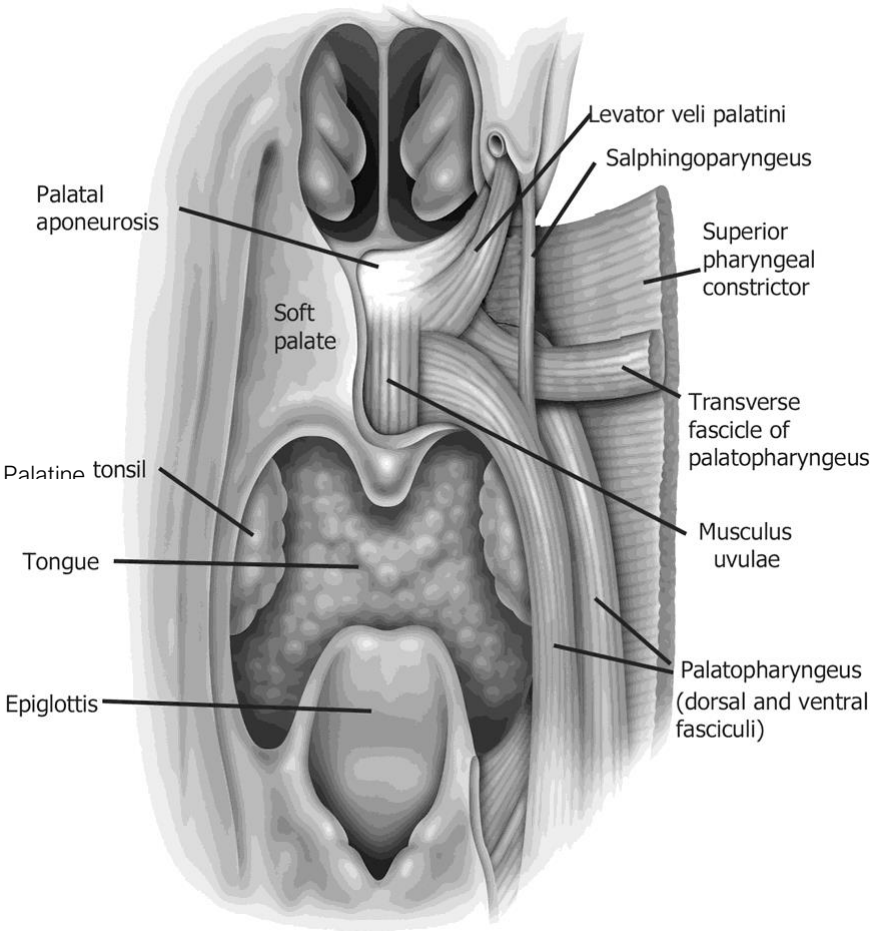
Figure 1. Anatomic features contributing to OSA with impacts on the retropalatal (RP) and retroglossal (RG) spaces. Adapted from Gottlieb DJ, Punjabi NM. Diagnosis and Management of Obstructive Sleep Apnea: A Review. Jama. 2020 Apr 14;323(14):1389-400[27].



The pharynx can be considered a muscular tube attached to the above structures. The space within this tube can be divided according to adjacent relations from superior to inferior as the nasopharynx, oropharynx and laryngopharynx. The muscular wall comprises three sheets of muscle that are the superior, middle and inferior constrictors overlapping posteriorly like three stacked cups. These are supported by three smaller muscles, the palatopharyngeus (discussed above), salpingopharyngeus and stylopharyngeus. Around the level of the superior constrictor and palatopharyngeus, there is also a palatopharyngeal sphincter (also known as Passavant's ridge) that moves the posterior pharyngeal wall forward to assist in closing the nasopharynx from the oropharynx (although closure is predominantly achieved by the soft palate). In sleep medicine, the part of the pharynx posterior to the palate is referred to as the retropalatal airway and that posterior to the tongue is known as the retroglossal (or retrolingual) airway.

The adenoid, palatine and lingual tonsils make up Waldeyer's ring, which is a nexus of lymphoid tissue that is most prominent in childhood and recedes into adulthood. In certain adult patients these tissues remain prominent and can also contribute to airway collapse in sleep. The adenoids sit in the posterior nasopharynx and superior to Passavant's ridge and are rarely identified in adults. The palatine tonsils sit nestled between the palatoglossus and palatopharyngeus muscles (known as the anterior and posterior tonsillar pillars). The lingual tonsils are located at the base of the tongue in the vallecula and at the same level of the epiglottis. The epiglottis is draped in mucosa that extends across the sides of the laryngeal inlet as the aryepiglottic folds and border the pyriform recesses along the side of the posterior laryngopharynx.

Figure 2. Posterior pharyngeal anatomy with key structures. Adapted from Olszewska E, Woodson BT. Palatal anatomy for sleep apnea surgery. Laryngoscope Investigative Otolaryngology. 2019.[26]



2.2 Anatomical Sites of Collapse and Risk Factors for OSA

The upper airway does not collapse homogenously but is dependent on surrounding tissue pressure exceeding the intraluminal pressure. Airway evaluation during wakefulness and sleep has been achieved with direct endoscopy[28] and dynamic radiological imaging techniques (including computed tomography (CT)[29] and magnetic resonance imaging (MRI)[30]) to identify key points of vulnerability at the retropalatal and retroglossal levels, as well as the lateral pharyngeal walls.

Larger volumes in the soft palate, tongue and parapharyngeal tissue have been identified in patients with OSA[31]. In particular, the lateral pharyngeal walls contribute to the largest fluxes in lateral airway diameter between inspiration and end-expiration as compared to the antero-posterior dimension[32].

One of the most frequent comorbidities identified in adults with OSA is obesity. An increase of body mass index (BMI) by one standard deviation triples the prevalence of OSA (Wisconsin Sleep Cohort Study)[3]. An increase in regional adiposity has been linked to fat deposition in critical upper airway soft tissue structures[33, 34]. Studies have demonstrated obese apnoeics have greater adiposity in tongue tissue compared to normal controls[35]. Recent evidence reveals the complex interaction between OSA and obesity, with data demonstrating a large reduction in BMI does not correlate with a comparable improvement in AHI. To add complexity, not all obese patients have OSA[36, 37].

Body position during sleep has an impact on OSA, with the oropharynx and tongue being particularly vulnerable to collapse in a supine position due to the effects of gravity compared with a lateral or upright position[38]. The palate can also be directly observed to collapse during a Müller manoeuvre[28], explained in more detail below.

Craniofacial features have been linked to patients with OSA, with smaller mandibles[39], caudally positioned hyoid bones[40] and retroposed maxillae[41] all significantly more prevalent in apnoeics. Cephalometric measurements that have been used to identify patients at risk include sella-nasion to subspinale (SNA), sella-nasion to supramentale (SNB) and mandibular

plane-hyoid (MPH) distances[42]. Patients with smaller SNA/SNB and longer MPH are more likely to have OSA[43, 44].

There is a difference in gender in OSA, with more men affected overall and women having lower AHIs compared to men of equivalent BMI[45]. Women more likely have a history of depression and hypothyroidism at the time of diagnosis of OSA[46]. Men generally have longer airways, larger neck and soft tissue structures that all increase collapsability[47]. Data supporting the conclusion that hormonal levels may also play a part is mixed, with some studies suggesting there is a link between post-menopausal women and OSA[48], and others finding no association[49].

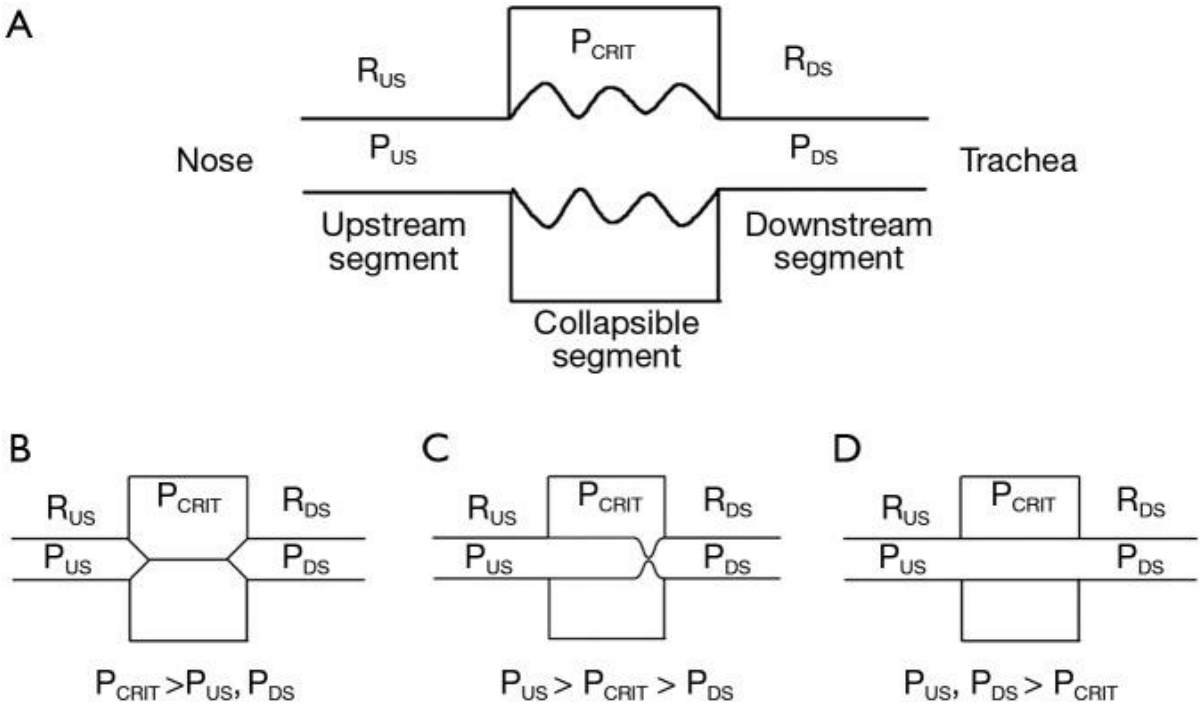
Ethnic differences have been observed in OSA, with likely links to rates of obesity, craniofacial morphology, dietary habits and lifestyle[50]. As an example, Asian men have lower BMI for any degree of OSA compared with Caucasians, a finding attributable to craniofacial features[51]. However, the ratio of obesity to craniofacial bony size is comparable between these populations for a given severity of OSA, suggesting that patients with skeletal restriction are likely more sensitive to an increase in BMI[52]. In Polynesians, nasal aperture and retrognathia were correlated with OSA severity compared to Caucasians[50].

Age also impacts OSA, with older patients tending to have more severe disease compared to younger counterparts. In addition, genioglossus muscle responsivity decreases, parapharyngeal fat pad size increases and jaws are relatively more retrognathic in older men. In older women, pharyngeal length is relatively greater than younger women[53].

2.3 Biomechanics of the Upper Airway

The subdivisions of the upper and lower airway has been expressed in the form of a Starling resistor model[54], even though this over-simplifies the airway, with a collapsible segment (soft/dynamic tissues) bounded by two rigid segments upstream (nasal cavity) and downstream (larynx/trachea)[55]. The rigid segments have a fixed diameter and resistance, with varying intraluminal pressure according to the phase of respiration in sleep (expressed as P_{US} and P_{DS}).

Figure 3. Schematic representation of the Starling resistor model of the upper airway. The collapsible segment is bordered by rigid upstream and downstream segments (A). The airway is completely occluded when P_{CRIT} exceeds P_{US} and P_{DS} (B). The airway is flow limited when P_{CRIT} exceeds P_{DS} but is less than P_{US}, so can still equilibrate and open and close (C). The airway is patent when both P_{US} and P_{DS} exceed P_{CRIT} (D). Adapted from Pham LV, Schwartz AR. The pathogenesis of obstructive sleep apnea. Journal of thoracic disease. 2015;7(8):1358.[54]



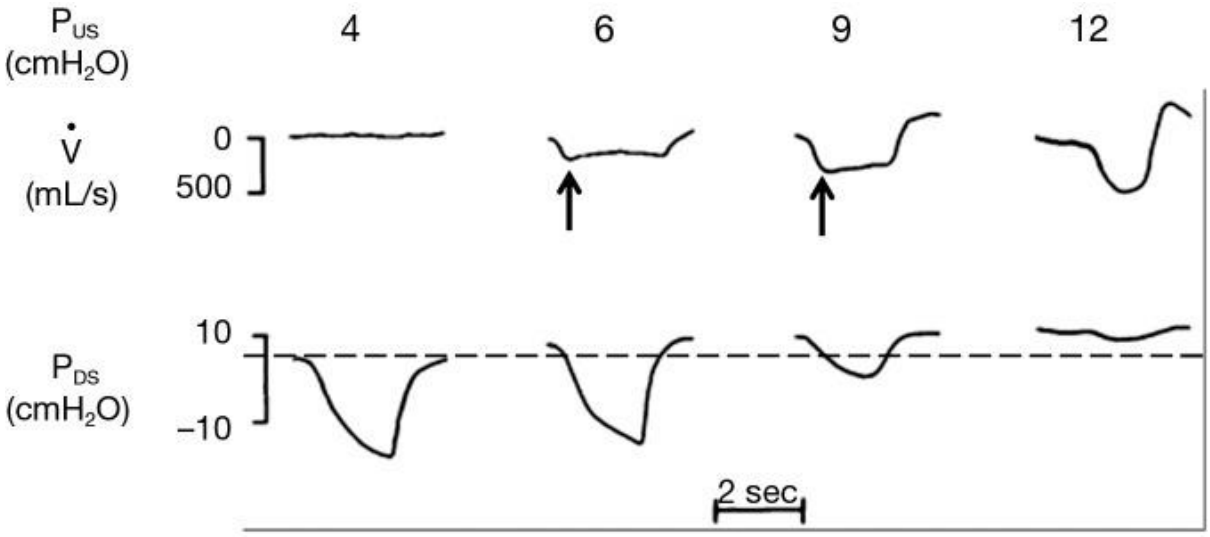
In this model, there is a critical closing pressure (P_{CRIT}) at which the collapsible segment will become completely occluded, thereby ceasing all airflow. If P_{CRIT} is less than P_{US} but greater than P_{DS}, this creates a flow-limited system whereby some occlusion would occur within the collapsible segment, but as the segment adjacent to the occlusion equilibrates to P_{US}, this rises above P_{CRIT} and subsequently re-opens the segment downstream to the occlusion. This causes the airway to cycle between an open and closed state at a pressure equivalent to P_{CRIT}.

While pressure remains constant, airflow will do so as well and thus plateaus at a maximal level (V_{max}), calculated as shown below using Ohm's law[56, 57].

$$V_{max} = \frac{P_{US} - P_{CRIT}}{R_{US}}$$

Airflow limitation is important in the pathogenesis of OSA as it is responsible for two differing strains on the respiratory system. One, resistance in the airways is increased significantly in the flow-limited state (up to 20-40 $cmH_2O/L/s$) when compared with the non-flow-limited state (1-2 $cmH_2O/L/s$). Two, further load is imposed during any period of flow limitation due to exertion of increasing effort of inspiration without ever increasing inflow, hence wasting pressure generated by the muscles of respiration[54].

Figure 4. Effects of varying upstream pressure on inspiratory flow. P_{CRIT} is represented by the dashed line. At P_{US} 4cmH2O, this is less than P_{CRIT} and so the airway is closed. At P_{US} 6 and 9cmH2O, the P_{US} is greater and so there is flow, but this is limited as P_{DS} falls below P_{CRIT} during inspiration. This results in flow limitation in the form of a plateau at V_{max} (arrows). At P_{US} 12cmH2O, P_{US} and P_{DS} remain above P_{CRIT} and so there is no further flow limitation. Adapted from Pham LV, Schwartz AR. The pathogenesis of obstructive sleep apnea. Journal of thoracic disease. 2015;7(8):1358.[54]



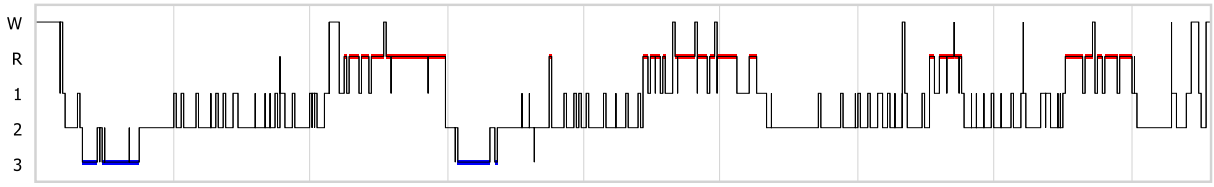
Multiple studies demonstrate that P_{CRIT} is a sensitive and specific marker to distinguish patients with OSA[56-64]. The diagnosis of OSA is strongly linked with patients who have a P_{CRIT} of -5cmH_2O or above while higher P_{CRIT} correlates with disease severity. Likewise, treatment to decrease P_{CRIT} below -5cmH_2O is effective in improving OSA severity or even resolving

disease[56, 65]. This has implications for management, and P_{CRIT}'s usefulness as a phenotypic marker will be explored in chapter 2.

2.4 Sleep Patterns in Normal Humans

The architecture of normal sleep can be divided into two states based on electroencephalography (EEG), electrooculography (EOG), electromyography (EMG) and behavioural features: non-rapid eye movement (NREM) and rapid eye movement (REM) sleep. During an episode of sleep, these two states alternate cyclically approximately every 90-120 minutes[66].

Figure 5. Sleep hypnogram of a normal adult for a complete night of sleep. W = wakefulness, R = REM sleep, 1/2/3 = NREM sleep stages 1/2/3.



NREM sleep can be divided into three sleep stages (N1, N2, N3). The arousal threshold (to wake someone from sleep) is lowest in N1, and highest in N3, representing deeper sleep. NREM is characterised by synchronous cortical EEG traces (sleep spindles, K complexes and slow waves are features) along with reduced muscle tone[67].

During REM sleep there are two main forms; tonic and phasic REM sleep. Tonic REM sleep is characterised by muscle atonia and desynchronisation of the EEG. Phasic REM sleep is characterised by bursts of rapid eye movements accompanied by phasic twitches of peripheral muscles. Dreaming is common during REM sleep[68] - in essence, the brain is activated while the body remains paralysed[66].

Autonomic nervous system function fluctuates depending on the state of sleep. During NREM, parasympathetic activity is increased while sympathetic activity remains similar to the awake state. During tonic REM, parasympathetic activity is also increased while sympathetic activity

is decreased. Finally, during phasic REM sympathetic activity is significantly increased and predominates despite increased parasympathetic activity[69].

Patterns of respiration during sleep are noticeably different to wakefulness. There are two main forms of control of breathing during wakefulness, being the metabolic (or automatic) and voluntary (or behavioural). During sleep the voluntary system is removed and breathing is driven entirely by the metabolic system, which is dependent on the respiratory control mechanism located in the medulla of the brainstem[69]. Consequently, during sleep, respiratory rate is reduced due to a combination of loss of voluntary control and increased airway resistance from muscle hypotonia. The latter is particularly significant in REM during the tonic phase, while muscle atonia further increases airway resistance.

In terms of metabolic control of sleep, hypoxic ventilatory drive is reduced during NREM and even more so during REM sleep. Hypercapnic ventilatory response is likewise reduced during NREM and essentially absent in REM sleep, meaning a larger carbon dioxide concentration (pCO_2) is required to trigger breathing during sleep[70]. When the ventilatory drive reaches a certain threshold, arousal from sleep is triggered as a protective mechanism to bring the individual back to wakefulness which is the primary reason for fragmented sleep in patients with OSA[71]. This definition is further expanded upon in the following chapter.

2.5 Airway Muscle Physiology During Sleep

Muscle collapsibility is increased during sleep due to various sleep states and muscle tonic activity[72], affecting the rigidity of and patency of the upper airway.

Remmers initially described the genioglossus as a driver to maintain oropharyngeal patency[73]. It acts as an oropharyngeal dilator and has been noted to have phasic and tonic activity during REM sleep[74], with significant impact on pharyngeal pressures[75]. Likewise there is phasic activity noted in other associated airway dilating muscles in the upper airway, including the geniohyoid[76], pharyngeal constrictors[77, 78], alae nasi and posterior cricoarytenoid muscles[79].

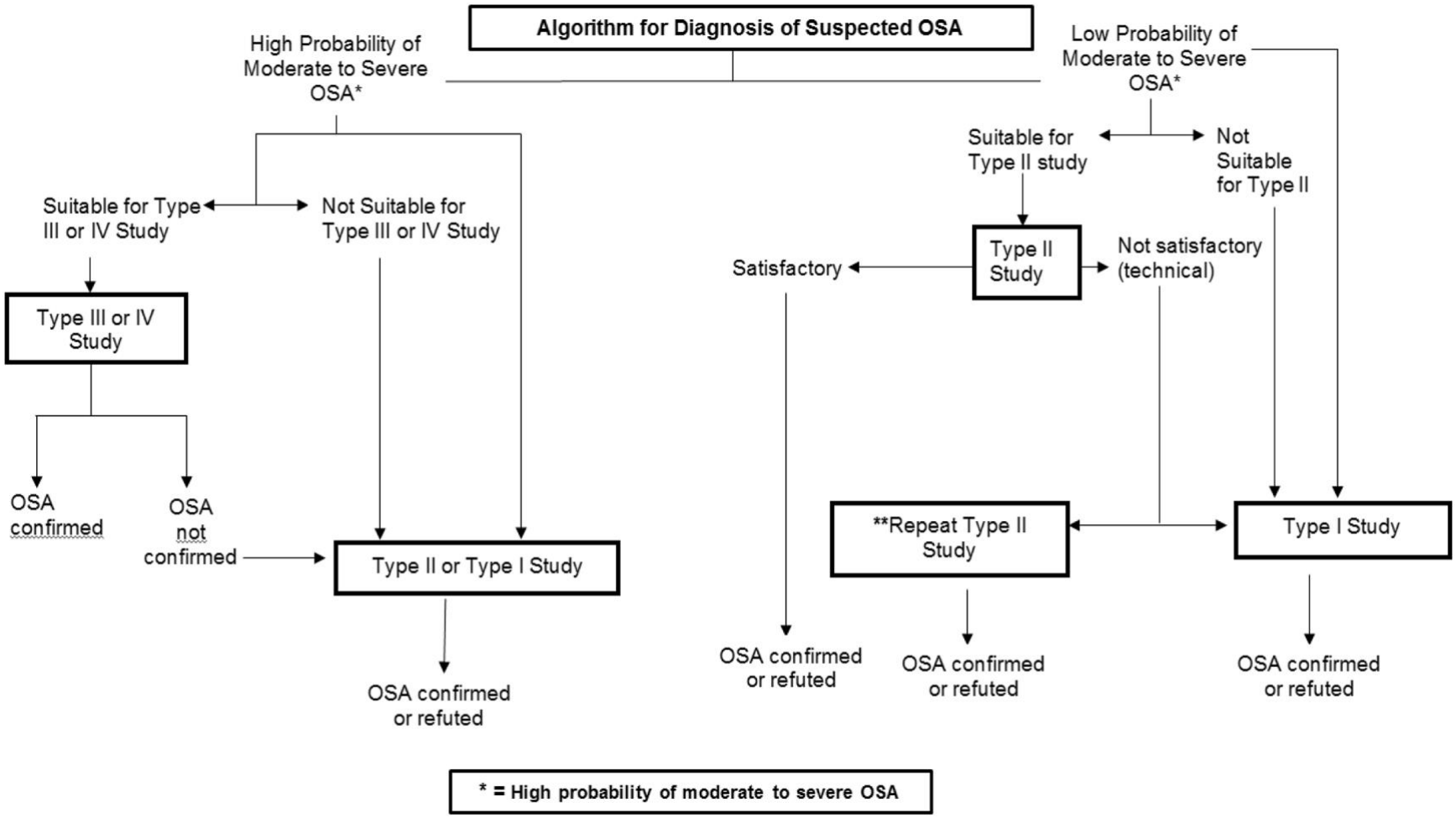
Muscle hypotonia is most pronounced at the transition from wake to sleep, with several studies demonstrating decreased tone in the genioglossus, geniohyoid, tensor palati, levator palati and palatoglossus at sleep onset. There is a similar trend seen in the main muscles of respiration, the diaphragm and intercostal muscles. When subjected to occlusion, the upper airway dilators have been demonstrated to be preferentially activated during the process of arousal compared with the diaphragm[80, 81]. The strength of this dilating effect is weaker in sleep than in wakefulness, and it has been suggested patients with OSA may have an even weaker muscular response in sleep compared to normal patients and thus be predisposed to airway collapse[82]. This has been illustrated with increased compensatory genioglossus activity in patients with OSA while awake compared with normal controls[83].

3. Clinical Evaluation and Diagnosis of Obstructive Sleep Apnoea

Patients who have OSA may present with upper airway symptoms (snoring, choking, gasping), sweating during sleep, generalised fatigue, daytime somnolence, headaches, dry mouth and sleep disturbance. A proportion may have coincident hypertension, diabetes, arrhythmia or other cardiovascular comorbidities. Medical history may reveal motor vehicle accidents, obesity or issues with general anaesthesia and a family history of OSA or snoring.

Despite these well-known symptoms a significant proportion of patients can present with non-specific symptoms, and even more will never present, with an estimated 5% of the world population living with undiagnosed OSA[3, 84]. The Australian Sleep Association (ASA) has generated an algorithm based on the combination of screening questionnaires to stratify patients into high or low risk of OSA and PSG testing to confirm or refute the diagnosis[85].

Figure 6. Algorithm for diagnosing suspected OSA. Adapted from Douglas JA, Chai-Coetzer CL, McEvoy D, Naughton MT, Neill AM, Rochford P, et al. Guidelines for sleep studies in adults – a position statement of the Australasian Sleep Association. Sleep Medicine. 2017;36:S2-S22.[85]



3.1 Questionnaires

There are multiple validated OSA symptom-focused questionnaires published in the literature. The Epworth Sleepiness Scale[86] (ESS) is an 8-item scale that patients answer on a 4-point basis (0-3), the sum of which quantifies a patient's daytime sleepiness. A score of 0-8 is considered normal, 9-10 is borderline, and >10 is excessive daytime sleepiness. The Snoring Severity Scale[87] (SSS) is a 3-item questionnaire that the bed partners of patients answer on a 4 point scale (0-3), quantifying loudness, length and frequency of snoring. The Functional Outcomes of Sleep Questionnaire[88] (FOSQ) is a 30-item questionnaire on a 4-5 point scale that quantifies the impact of sleepiness on a patient's life from a functional perspective. Others are directed at different measures such as insomnia, sleep patterns and sleep quality[89].

A number of questionnaires have been specifically evaluated for their feasibility, generalisability and accuracy as screening tools for OSA. An ideal screening test should have high sensitivity and negative predictive value[90] in order to "rule-out" disease. The Berlin questionnaire is an 11-item form that is less frequently used and has a sensitivity of 86% in primary care patients and 57-68% in sleep laboratory patients[91, 92]. STOP-BANG (**S**noring, **T**iredness, **O**bserved apnoeas, blood **P**ressure, **B**MI, **A**ge, **N**eck circumference, **G**ender) is an 8-item questionnaire developed as an anaesthetic screening tool. It utilises a 2 point scale (0-1) that has a sensitivity of 87% in identifying patients at risk of having moderate-severe OSA with a score ≥ 3[93, 94]. Finally, the OSA50 (**O**besity, **S**noring, **A**pnoeas, aged >**50** years) is a 4-item questionnaire scored out of 10 (O, S worth 3 points and A, 50 worth 2 points each) developed as a primary care tool in Australia. A score of ≥ 5 and a 3% ODI ≥ 16 had sensitivity and specificity >80% in identifying OSA[95].

The use of each questionnaire is at the discretion of the treating clinician in order to answer specific clinical questions relevant to their practice. In Australia, prerequisite scores must be met prior to ordering of investigations such as PSG according to the Medicare Benefits Schedule[96]. All described questionnaires can be used at initial and follow-up appointments to risk-stratify patients or track response to treatment.

3.2 Polysomnography

If the diagnosis of OSA is suspected, medical practitioners can refer patients to undergo PSG testing. PSG is the primary tool used to diagnose OSA. It can be applied as an initial diagnostic study, an interventional study (e.g. to assist in titration of CPAP or nerve stimulator devices) or a follow-up study after treatment. Depending on the type of the study multiple parameters can be measured, including EEG, EOG, oronasal pressures (or CPAP pressures during a titration study), cardiac (using electrocardiography – ECG), jaw movements, respiratory and limb movement activity (using EMG)[67]. Body position monitors also allow documentation of patient position (lateral, supine or prone) throughout the course of the night.

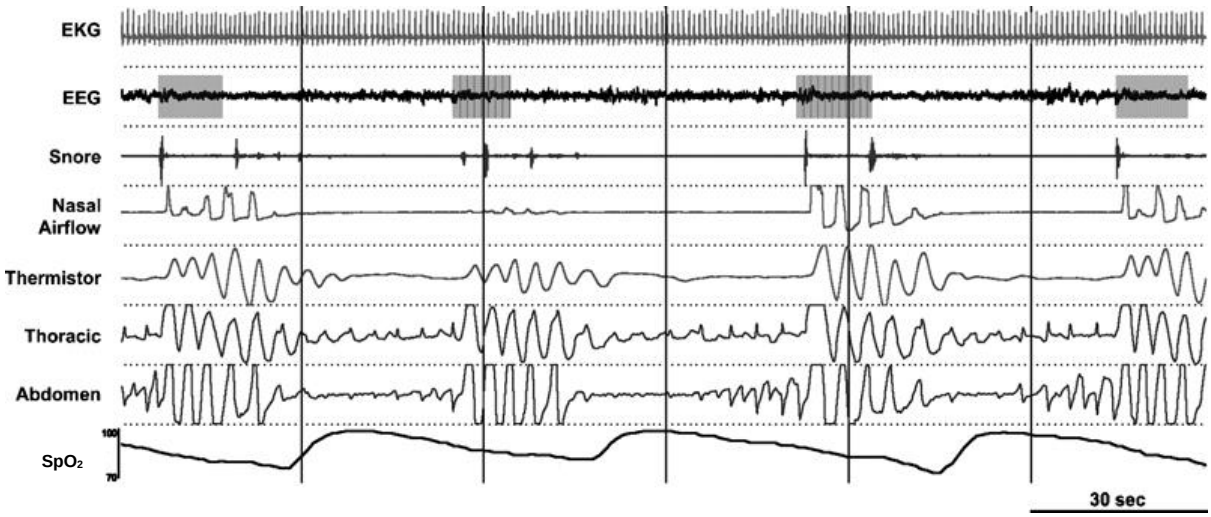
The ASA guidelines outline 4 main types of sleep study[85]:

1. Type 1 tests are in-laboratory PSG studies, routinely attended by a sleep technician and allow for recording of the greatest amount of physiologic signals[85].
2. Type 2 tests are home-based portable PSG studies that are not attended by trained technical staff. However they may be set-up by a sleep technician either in-lab or at home prior to the study. There is a higher chance of underestimating the severity of OSA (<10%), typically due to signal loss, but this may not significantly alter treatment advice[85].
3. Type 3 tests are limited channel studies that record only a few variables and do not usually allow for sleep staging. These have at least 4 variables, typically including oximetry, respiratory effort (thoracoabdominal movements), airflow, head and body position, jaw movements, ECG, tonometry (marker of autonomic control), actigraphy and sound[85].
4. Type 4 tests only measure 1 or 2 variables, using oximetry, heart rate or airflow. Of these, oximetry is the most informative, reliable and accurate, providing key correlates of hypoxaemia[85].

Type 3 and 4 studies are most suitable to use in populations that have no significant cardio-respiratory comorbidities. Patients should have a high pre-test probability of the diagnosis of OSA as determined by screening tools that have high sensitivity and negative predictive values

(rule-out tests as discussed above). Health services which have limited access to type 1 and 2 studies may use these.

Figure 7. Example of data traces used in a patient with OSA. Note the drops in SpO_2 associated with snoring, interruptions in airflow and thoracoabdominal movements. Adapted from Edwards BA, O'Driscoll DM, Ali A, Jordan AS, Trinder J, Malhotra A, editors. Aging and sleep: physiology and pathophysiology. Seminars in respiratory and critical care medicine; 2010: © Thieme Medical Publishers.[53]



3.3 Respiratory Events

While EEG, EOG and EMG traces are primarily used for staging sleep, events that occur throughout the night need to be noted. These include apnoeas, hypopnoeas, oxygen (O_2) desaturations, arousals and body movements. Respiratory events are often divided according to the stage of sleep in which they occurred, usually either NREM or REM.

The most crucial for the diagnosis of OSA are apnoeas and hypopnoeas, which are complete and partial cessations of airflow respectively. An apnoea is defined when both[97]:

1. There is a drop of ≥90% drop in the peak signal flow as detected by pressure monitors (oronasal thermal sensors, CPAP device flow), and
2. This drop is sustained for ≥10 seconds.

A hypopnoea is defined when the following criteria are all met[97]:

1. There is a drop of ≥30% in the peak signal flow, and
2. This drop is sustained for ≥10 seconds, and
3. There is a ≥3% O_2 desaturation from baseline OR there is an associated arousal.

The AHI is the average number of apnoeas and hypopnoeas per hour over the course of the night. An AHI of 5-14 constitutes mild OSA, 15-30 is moderate and ≥30 is severe[7]. Events can be defined as obstructive (due to increased upper airway resistance) or central (due to reduction in ventilatory effort) depending on their antecedent cause. An obstructive event is associated with a flattening of the pressure waveform during inspiration, often accompanied by snoring and paradoxical thoracoabdominal wall movements, while a central event will not have any of the above[97].

An additional event that is sometimes incorporated in sleep studies is Respiratory Effort-Related Arousal (RERA), which refers to arousals from sleep that are caused by increasing respiratory effort that do not fall into either apnoea or hypopnoea criteria. The RERA is defined when there is a sequence of breaths ≥10 seconds associated with increasing respiratory effort (measured on EMG) or flattening of the inspiratory pressure curve. The respiratory disturbance index (RDI) is measured as the sum of AHI and RERA index[97].

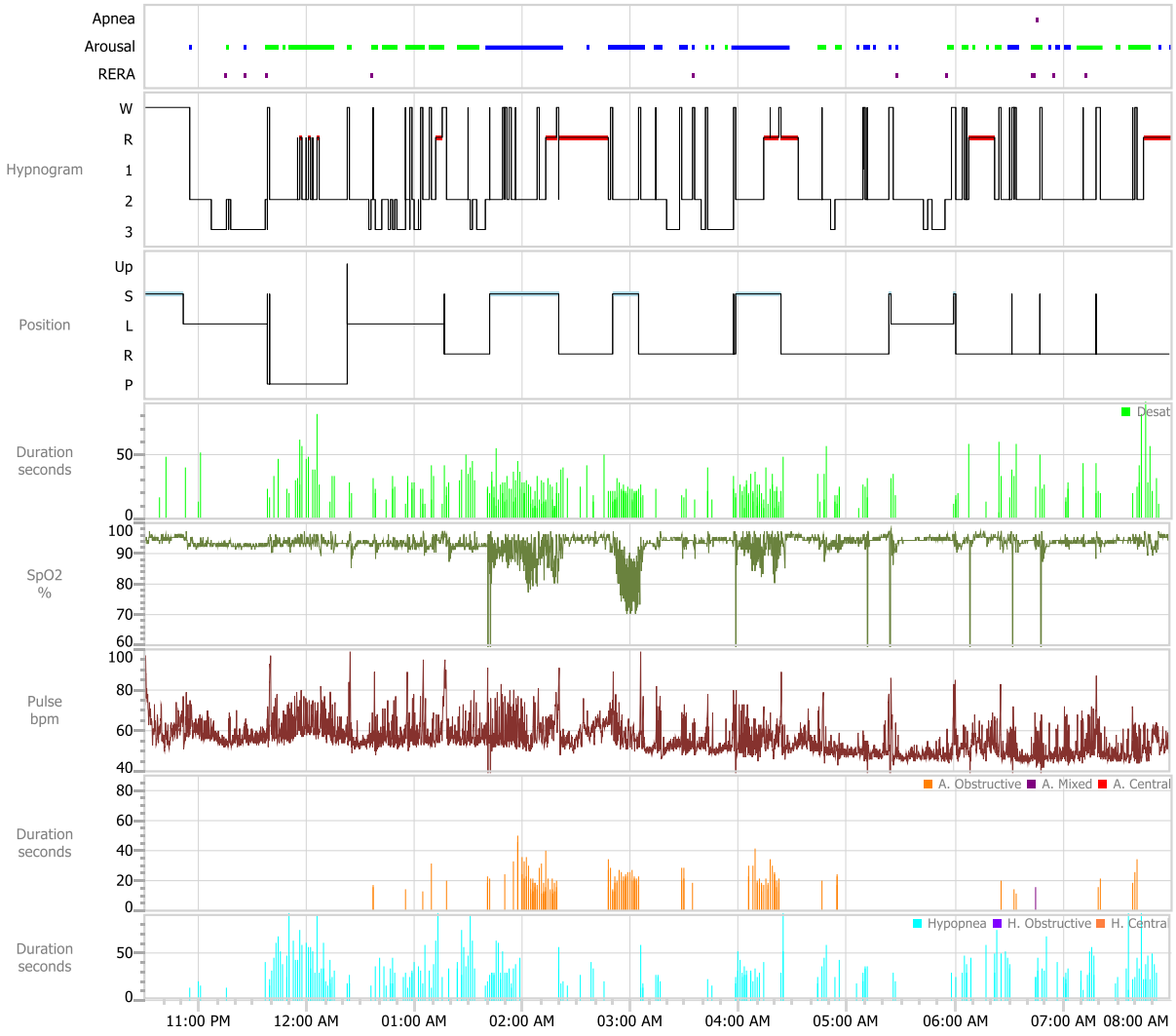
In the past there has been some disagreement between the use of a threshold of ≥2%, ≥3% or ≥4% O_2 desaturation as an event[98]. This has been investigated and 3% has found to be the best performing marker across BMIs >25kg/m^2 when detecting moderate to severe OSA[99], while 4% is a better predictor of cardiovascular risk[100]. The American Academy of Sleep Medicine (AASM) 2018 guidelines utilise the standardised threshold as ≥3% based on this evidence[101]. The ODI is an index of number of desaturations per hour over the course of a night.

Limb movements are recorded using an EMG electrode on the tibialis anterior muscle on the leg or extensor digitorum on the hand. These must not be associated with a respiratory disturbance to be considered an event. They can also be measured in terms of events per hour as the periodic limb movement (PLM) index[97].

The output of a sleep study can be summarised in terms of the indices described above and graphically as a hypnogram. This displays the stages of sleep across the course of the night

along with the timestamps of any respiratory events that may have occurred. It allows easy interpretation for clinicians to correlate between sleep stage-specific events and associated desaturations or limb movements.

Figure 8. Sample patient PSG summary for clinical interpretation including hypnogram, body position, events and oxygen saturation.

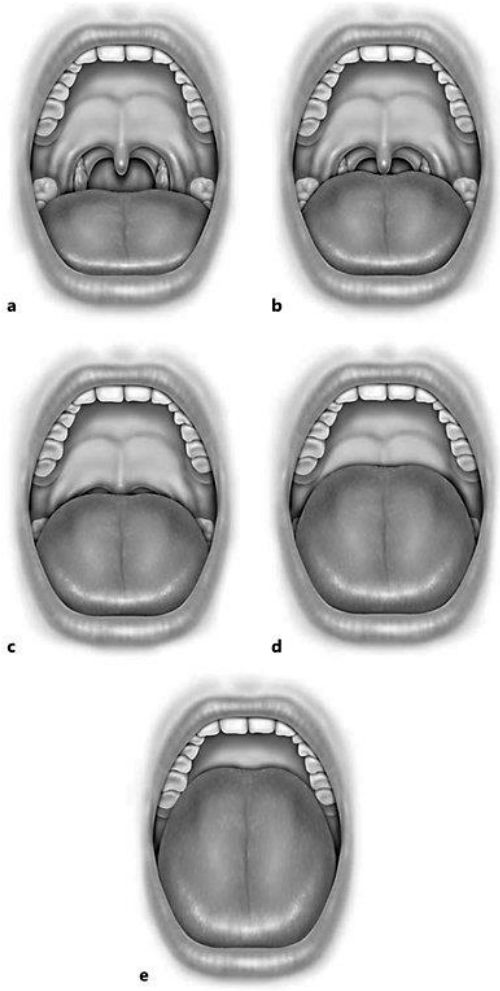


While the PSG has been conventionally used for the measurements described above, there is a wealth of information contained within the raw data that can be used for novel and clinically relevant analysis of OSA, particularly in the burgeoning field of precision (or personalised) medicine in OSA[102], including phenotyping/endotyping.

3.4 Comprehensive Upper Airway Evaluation

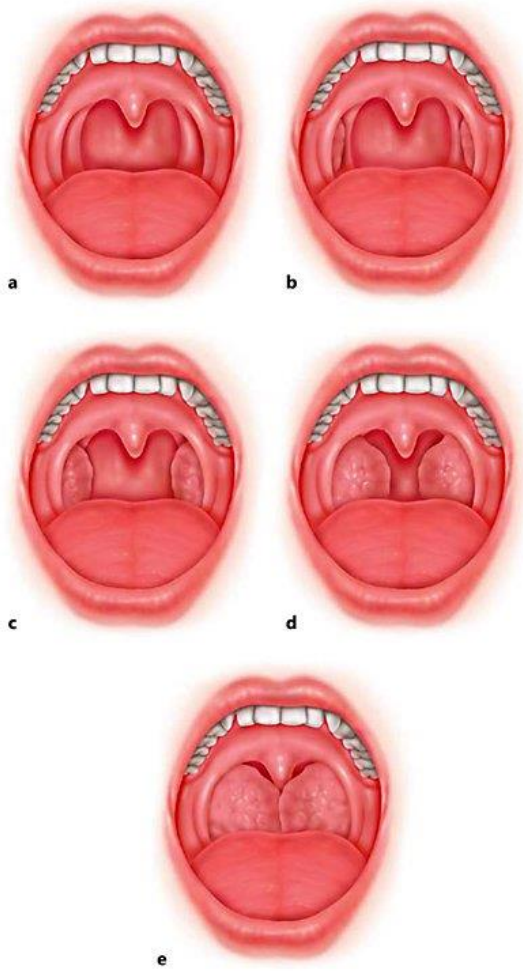
An increasing part of the practice of sleep medicine is incorporating a comprehensive upper airway evaluation in conjunction with an otolaryngologist. This involves a thorough oral examination for malocclusion, palatal phenotype[26, 103], Friedman tongue grade and tonsillar hypertrophy[104] followed by nasendoscopy either conducted awake in the office or with a sedative in what is known as drug induced sleep endoscopy (DISE)[28, 105]. This enables the evaluation of possible anatomical planes of collapse *in vivo*, which can help identify patients who would benefit from certain anatomical treatments such as MAS or upper airway surgery.

Figure 9. Friedman tongue grade (FTG). (a) FTG I, with uvula and tonsils/pillar visible. (b) FTG IIa, with most of uvula but not tonsils/pillar. (c) FTG IIb, entire soft palate to base of uvula. (d) FTG III, some of soft palate, distal end absent. (e) FTG IV, hard palate only. Adapted from Friedman M, Salapatas AM, Bonzelaar LB. Updated friedman staging system for obstructive sleep apnea. Sleep-Related Breathing Disorders. 80: Karger Publishers; 2017. p. 41-8.[104]



Transoral examination can reveal the presence of malocclusion or craniofacial abnormalities, which are associated with OSA[106]. Hard palate features such as a narrow or high arch can be indicative of maxillary constriction (which may increase nasal resistance[107, 108]). The soft palate phenotype is more easily evaluated with nasendoscopy (described below). Friedman tongue grade is used to approximate obstruction at the oropharyngeal level and is determined by the tongue's position relative to the tonsils/tonsillar pillars, uvula, soft palate and hard palate. It is similar to the Mallampati system but evaluates the tongue while it is in a neutral position within the mouth[104]. Tonsil grade is also noted, given its propensity to generate oropharyngeal collapse and its significance in compromising airway space[109].

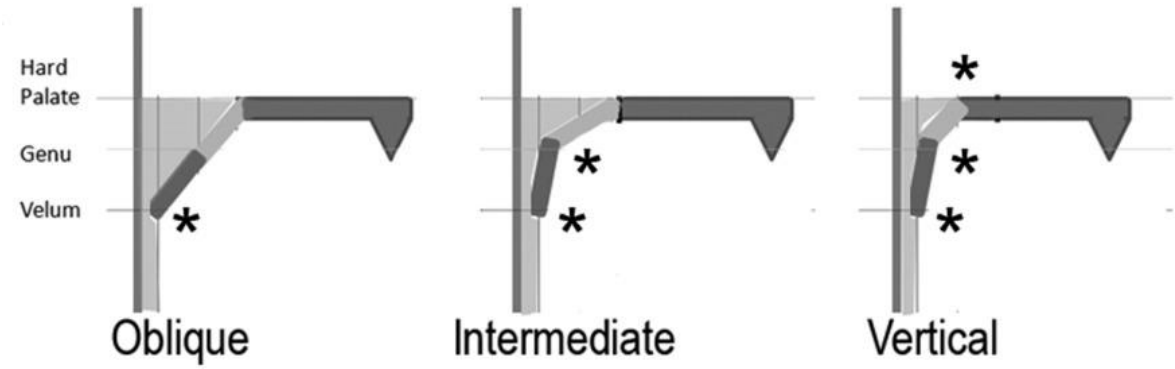
Figure 10. Tonsil grade. (a) Grade 0, no tonsillar tissue. (b) Grade 1, within the pillars. (c) Grade 2, extended to the pillars. (d) Grade 3, extended beyond the pillars. (e) Grade 4, extended to the midline. Adapted from Friedman M, Salapatas AM, Bonzelaar LB. Updated friedman staging system for obstructive sleep apnea. Sleep-Related Breathing Disorders. 80: Karger Publishers; 2017. p. 41-8.[104]



Nasal examination is conducted externally with anterior rhinoscopy and internally through nasendoscopy. Key features contributing to nasal resistance include internal and external nasal valve patency, inferior turbinate hypertrophy and septal deviation[110]. The presence of allergic rhinitis is also a treatable factor in facilitating other therapies in OSA[111].

Nasendoscopy is then continued to evaluate the soft palate, which has been divided into 3 main subtypes by Woodson et al, based on the gradient of the genu relative to the posterior pharyngeal wall, with a more vertically oriented palate more amenable to a surgical procedure such as transpalatal advancement[103].

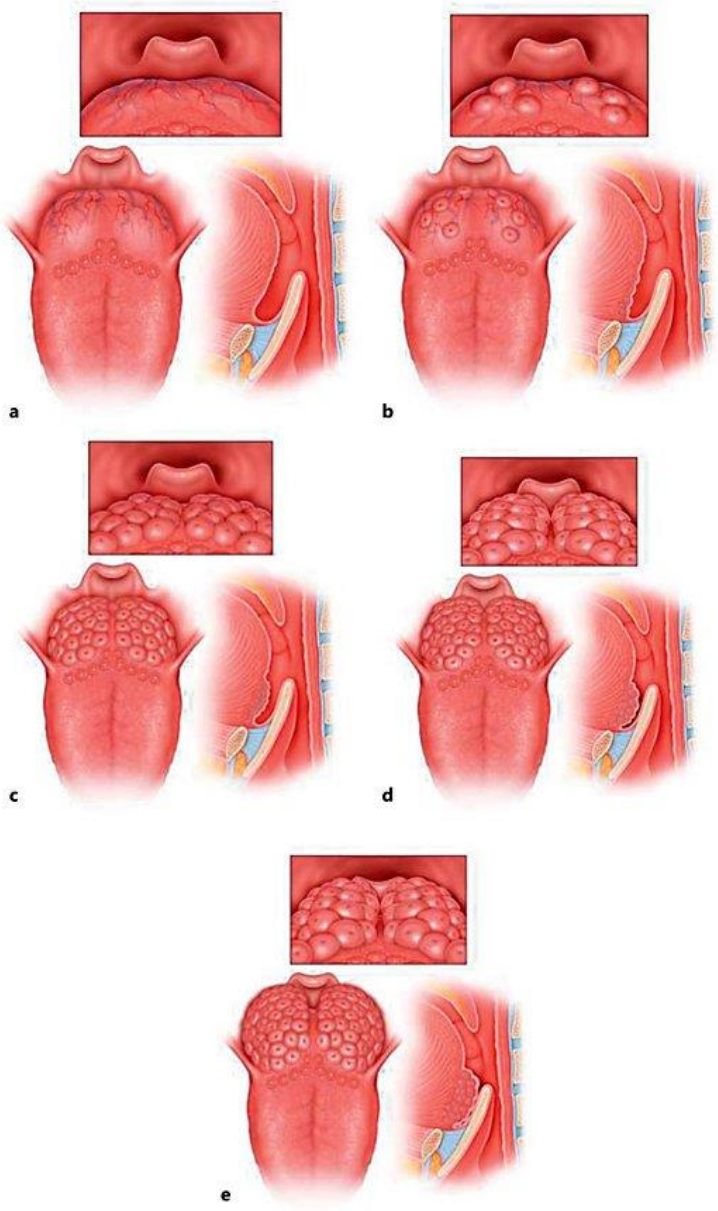
Figure 11. Palate grade. Patients with a vertical palate are amenable to procedures such as transpalatal advancement. Adapted from Woodson BT. A method to describe the pharyngeal airway. The Laryngoscope. 2015;125(5):1233-8[103].



Lingual tonsil grade is most easily evaluated next as a possible cause of retroglossal obstruction, with the tongue relaxed, then protruded[104].

Figure 12. Lingual tonsil grade. (a) Grade 0, no lymphoid tissue. (b) Grade 1, scattered lymphoid tissue. (c) Grade 2, lymphoid tissue covering tongue base, limited vertical thickness. (d) Grade 3, lymphoid tissue covering entire tongue base, vertical thickness 5-10mm. (e) Grade 4, lymphoid tissue covering entire tongue base, rising to or above tip of epiglottis, approximately 1cm in height. Adapted from Friedman M, Salapatas AM, Bonzelaar LB.

Updated friedman staging system for obstructive sleep apnea. Sleep-Related Breathing Disorders. 80: Karger Publishers; 2017. p. 41-8.[104]



Dynamic manoeuvres are employed to visualise collapse in various anatomical planes under direct vision. A simple full jaw thrust can be employed to mimic the effect of a 70% (maximally titrated) MAS. The Müller manouevre was initially described by Borowiecki and Sassin[112] and involves forced inspiration against a closed mouth and nares, thereby inducing negative upper airway pressures. Woodson's hypotonic method[113] involves maximal expiration to induce a state akin to a completely flaccid and atonic airway. These manoeuvres are often conducted at the retropalatal and retroglossal levels, and are further augmented when conducted in a

supine position and possibly during sedation, more accurately mimicking the appearance of the airway in sleep[28].

Figure 13. Woodson's Hypotonic Method. Airway structure is better defined by controlling for physiologic variables. Adapted from Fairbanks DN, Mickelson SA, Woodson BT. Snoring and obstructive sleep apnea: Lippincott Williams & Wilkins; 2003[114].

$$Size_x = f(Structure_x + MuscleTone_x + Airflow_x)$$

$$x = moment\ in\ time$$

$$when\ MuscleTone\ and\ Airflow = 0$$

$$Size_x = f(Structure_x)$$

Given the relative complexity of upper airway anatomy and the possible areas of collapse, there has been a need to standardise the examination. One simple classification system that has been proposed to summarise the findings from airway endoscopy is the Velum, Oropharynx, Tongue, Epiglottis (VOTE) classification, allowing assessors to document the degree of collapse in each anatomical area of interest[115].

Table 1. The VOTE Classification. Adapted from Kezirian EJ, Hohenhorst W, de Vries N. Drug-induced sleep endoscopy: the VOTE classification. European Archives of Oto-Rhino-Laryngology. 2011;268(8):1233-6.[115]

Structure	Configuration		
	A-P	Lateral	Concentric
Velum			
Oropharynx			
Tongue base			
Epiglottis			

4. Current Treatment Paradigms for Obstructive Sleep Apnoea

OSA should be treated as chronic disease with the treatment goal being mitigation of long-term cardiovascular effects and reduction of daytime symptoms such as sleepiness. Other reasons that patients request treatment are for social and quality of life reasons such as snoring and partner disturbance[116].

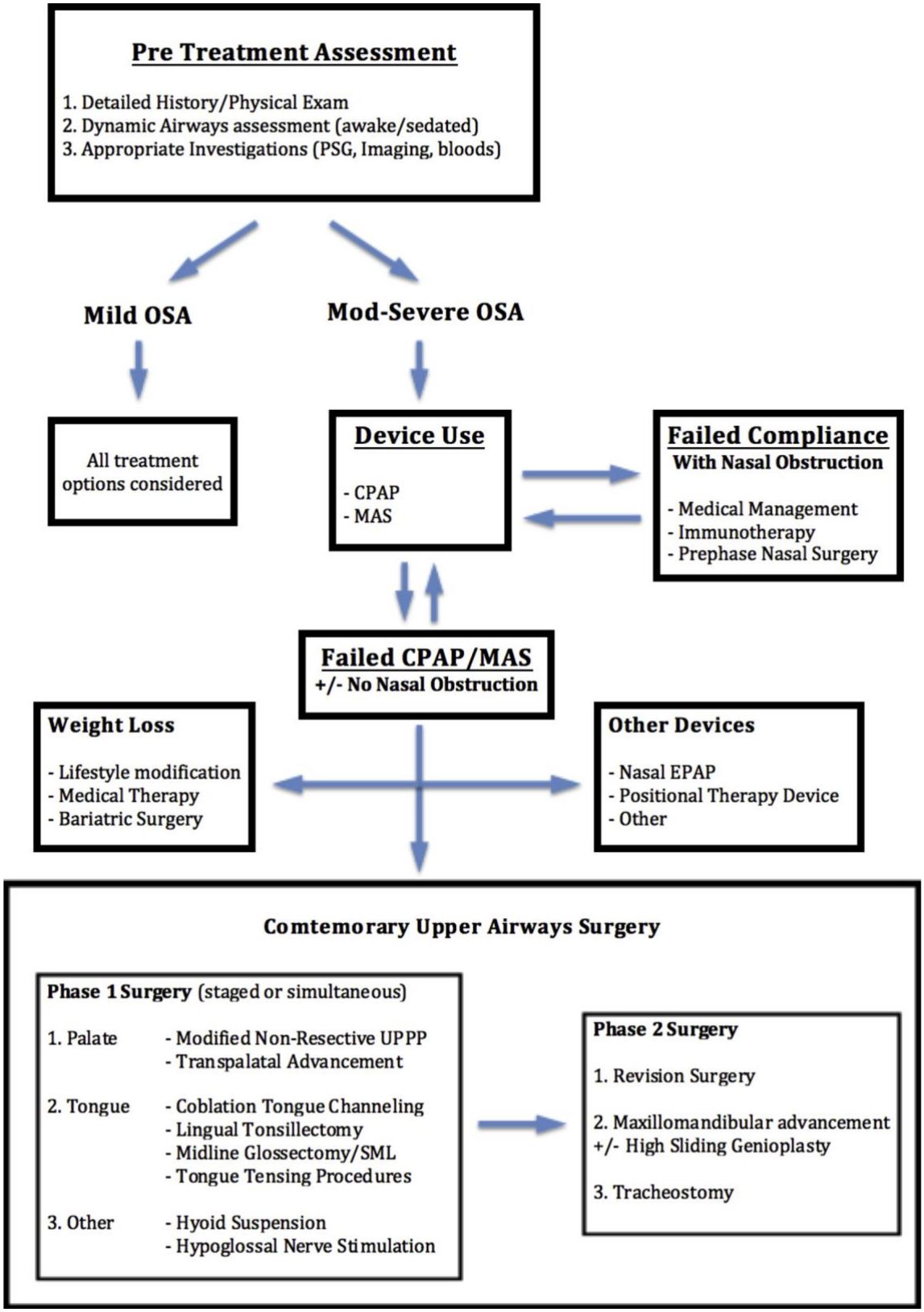
OSA is a heterogenous disease and there is a need to consider a range of treatments due to patient anatomical, physiological and social factors. There is a benefit in a multidisciplinary approach to managing OSA, as quite frequently there are treatment options that patients and even clinicians will not always consider in isolation[117].

4.1 CPAP

The accepted first-line treatment for adults with moderate or severe OSA is CPAP[116]. This comes in various forms, including nasally delivered CPAP, oral and full-face masks (depending on pressure requirements, patient anatomy, finances and preference). At the initial prescription of CPAP patients should attend the sleep laboratory for a titration study to determine the optimum pressure required to control their OSA. The forms of ventilation pressure delivery can be fixed (conventional CPAP) or variable including autotitrating (APAP) and bilevel (BiPAP) modes that can be considered in select patients.

Treatment failure occurs commonly due to non-adherence to CPAP, often defined as less than 5 hours of usage per night, less than 5 nights per week or outright cessation of therapy, which is a universal problem irrespective of ethnicity[118], care setting[119] and socioeconomic status[120, 121]. Cited reasons for failure include misconceptions about the treatment[122], dry mouth[123], nasal stuffiness/rhinorrhea[124], claustrophobia[125], bloating/discomfort[126] and concurrent comorbidities like depression[127] or cardiovascular disease[128, 129]. There may be an impact of pressure interference that influences adherence, and there is a significant role that prescribers and nursing staff play in facilitating adherence long-term.

Figure 14. Typical algorithm of how OSA patients come to surgical treatment. Adapted from MacKay SG, Chan L. Surgical approaches to obstructive sleep apnea. Sleep medicine clinics. 2016;11(3):331-41.[130]



4.2 Non-Surgical Treatment

4.2.1 Weight Loss

Lifestyle changes include options such as weight loss. Weight loss in obese patients with OSA has been shown to improve AHI and in some cases cure their disease. Weight loss is typically achieved via caloric restriction and exercise[37], with the option of weight loss (bariatric) surgery in those who fail conservative measures[129, 131].

4.2.2 Positional Therapy

A subset of patients with OSA have the majority of apnoeic events in a supine position. Such patients are suitable for positional therapy to prevent them from rolling onto their back. The "tennis-ball technique" is a rudimentary option where a tennis ball can be sewn onto a patient's pyjamas, causing discomfort and encouraging repositioning into the lateral or prone position[132]. Long-term compliance is poor[133], which has led to the development of novel devices including the Sleep Position Trainer[134], BuzzPod[135] and NightShift[136]. These are vibrotactile devices worn either on the chest or neck that can detect supine positioning and vibrate to notify the wearer to reposition themselves. Compliance for these is better than the tennis-ball technique[137, 138]. These devices can additionally monitor sleep time, body position and snoring.

4.2.3 Mandibular Advancement Splints

MAS is a therapy for patients who fail with or decline CPAP, or perhaps with less significant OSA. These are fitted by accredited dentists using custom made impressions. They are comprised of two plates that fit both upper and lower dental arches, with a coupling mechanism to prevent posterior movement of the mandible while allowing mouth opening. There is also a screw to enable titration of the splint to achieve the largest tolerable treatment effect. Studies have shown improvements in AHI and acceptable tolerance[10]. MAS can be combined with other devices including CPAP and positional therapy.

Typical side effects include jaw discomfort, tooth tenderness and excessive salivation as a result of MAS wear[139, 140]. Patients will often require an adaptation period to the device that can sometimes last for months[10, 140]. Side effects are comparable in severity to those experienced by CPAP users[123, 129].

4.3 Surgery for OSA

There is a plethora of published surgical techniques that have been utilised in patients with OSA. Surgery is mainly a salvage treatment when other options have failed[20], and should be used in patients who have favourable anatomy or specific deformity. Any surgery carries with it perioperative risk, and the presence of OSA is itself an independent risk factor for increased complications and may mandate a higher level of perioperative care[141, 142]. Surgery is often considered in "levels" and in "phases". Levels refer to the anatomical location where the surgery is directed, such as the retropalatal, retroglossal airway or multilevel. Phases refer to separate operations, such as in the instance when operating on multiple levels can pose too great a cumulative risk on post-operative complications, so procedures are staged into different operations to facilitate recovery in-between[130, 143]. Definitive treatment is complete upper airway bypass with tracheostomy, which is utilised rarely[144].

This section is divided into nasal surgery (and medical treatment), upper airway surgery (soft tissue), maxillofacial surgery (hard tissue – maxilla and mandible) and weight loss surgery.

4.3.1 Nasal Treatment

While treatment of the nose is not intended to cure OSA, it can often provide improvements to PSG parameters and patient-perceived quality of life as a supplement to primary treatment, often by reducing the pressures required via CPAP[145] or providing improvements in sleep parameters including ESS and RDI[146]. The most frequently employed operations are nasal valve surgery, turbinoplasty and septoplasty which are often used as "pre-phase" surgery to facilitate delivery of CPAP[11, 130]. Other operations include functional endoscopic sinus surgery, polypectomy and adenoidectomy. In patients with concomitant allergic rhinitis,

intranasal steroids and leukotriene receptor agonists have also been demonstrated to improve some PSG parameters[111].

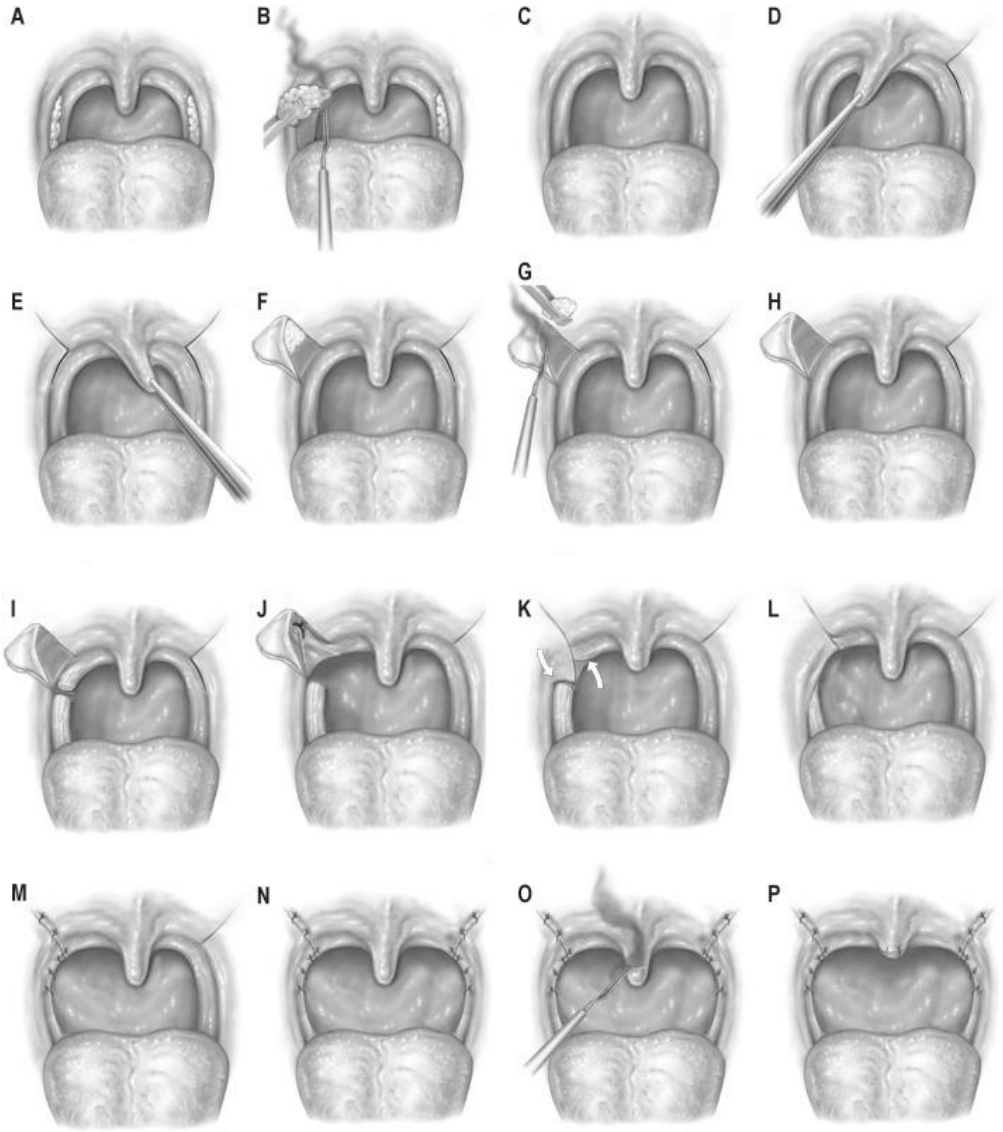
4.3.2 Upper Airway Surgery

The first line treatment for OSA in children is adenotonsillectomy, due to the relative size of tonsillar tissue in the paediatric airway[109]. In adults tonsillar tissue constitutes a target for upper airway surgery, particularly in patients with tonsillar hypertrophy. Tonsillectomy is often incorporated as part of uvulopalatopharyngoplasty (UPPP), which is used to reposition the soft palate. There are various iterations and variations of UPPP, although contemporary modifications focus on repositioning the palate without resecting functional tissues[13, 20, 147-150]. Transpalatal advancement in patients who require anterior re-positioning of the palate in conjunction with a UPPP might be performed[15, 151].

Table 2. Sample of procedures used in upper airway surgery. Adapted from MacKay SG, Chan L. Surgical approaches to obstructive sleep apnea. Sleep medicine clinics. 2016;11(3):331-41.[130]

Traditional Procedures	Contemporary Procedures
• Tonsillectomy • Adenoidectomy • UPPP • Geniotubercle advancement • Hyoid suspension • Epiglottopexy	• Modified or variant UPPP • Expansion sphincteroplasty • Uvulopalatal flap • Lateral palatoplexy • Transpalatal advancement • Radiofrequency systems • Coblation channelling • Midline glossectomy • Submucosal linguoplasty • Lingual tonsillar reduction

Figure 15. Surgical technique for the Australian variant of contemporary UPPP. Adapted from MacKay SG, Carney AS, Woods C, Antic N, McEvoy RD, Chia M, et al. Modified uvulopalatopharyngoplasty and coblation channeling of the tongue for obstructive sleep apnea: a multi-centre Australian trial. Journal of Clinical Sleep Medicine. 2013;9(02):117-24.[13]



Surgery to achieve tongue reduction in patients with macroglossia can be accomplished with various techniques. Radiofrequency tongue "channelling" is used to achieve submucosal reduction in the intrinsic tissue of the tongue[13, 20]. Lingual tonsillectomy or tonsil reduction is used in patients with bulky lingual tonsil. This can be achieved with suction diathermy or coblation. There are also other mucosal sparing surgeries[18, 19] and new robotic techniques[152] that have been developed. Recently, multilevel upper airway surgery incorporating a

combination of modified UPPP and radiofrequency to the tongue has been shown effective in improving PSG measures and patient-reported sleepiness[20].

4.3.3 Maxillofacial Surgery

Whilst upper airway surgery reduces or repositions soft tissue in order to achieve a larger airway, maxillofacial surgery can be used to expand the entire facial unit to create a larger airway[153]. It is generally reserved for those patients who either are refractory to phase 1 surgical procedures or have significant craniofacial features such as retrognathia, micrognathia or maxillary hypoplasia[154]. Various forms exist, including maxillomandibular advancement (also known as bimaxillary) surgery[155].

4.3.4 Weight Loss Surgery

Bariatric surgery can be utilised in the morbidly obese for OSA and reliably reduces AHI[131]. While particularly effective at reducing BMI and mitigating risk associated with obesity such as diabetes mellitus, it will not always produce complete obliteration of the disease and may not be superior to non-surgical weight loss[37, 156]. It is mostly recommended in patients with concomitant OSA and obesity. Interventions include gastric bypass[131, 157].

Chapter 2
Phenotyping in OSA

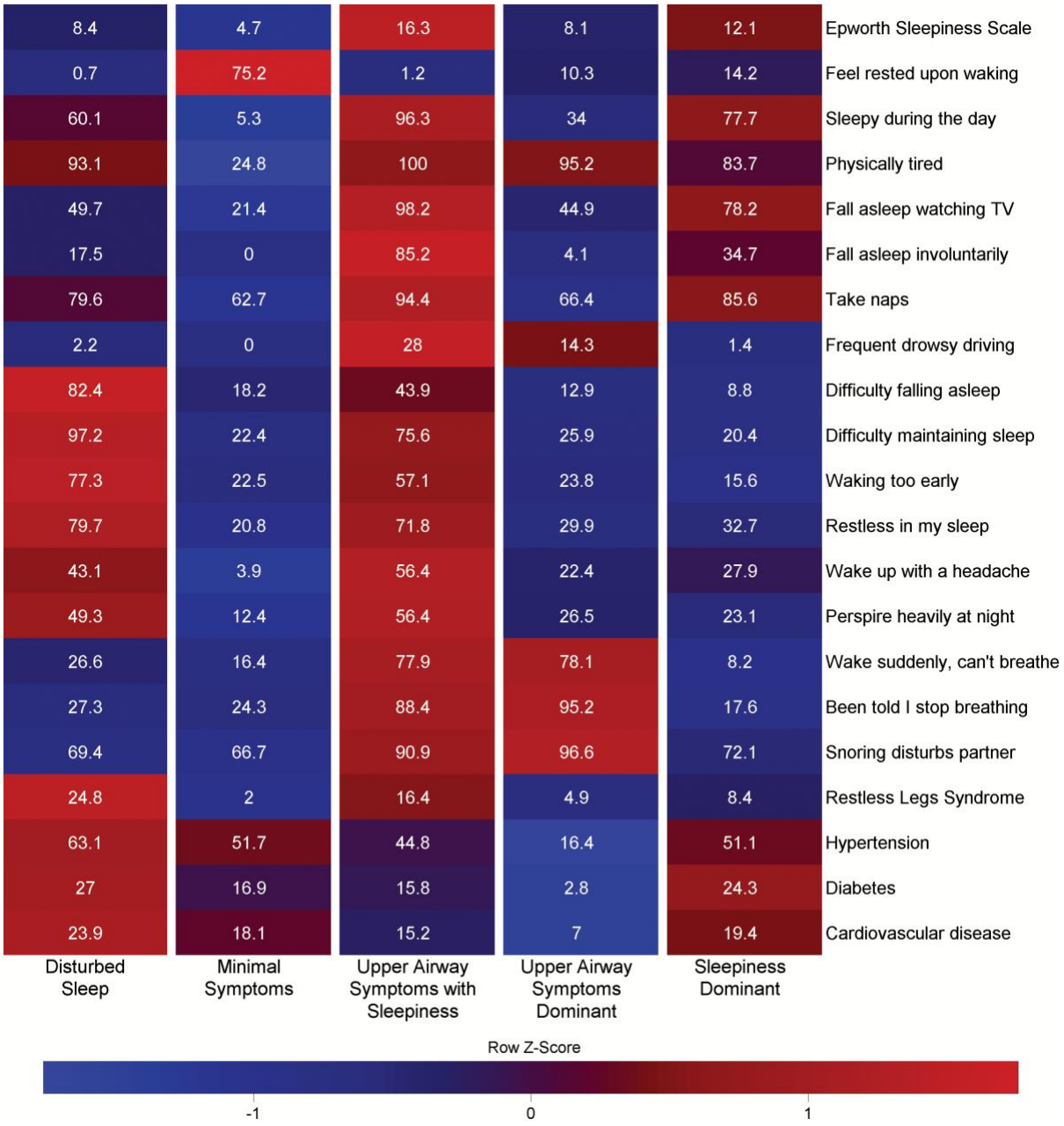
1. AHI – A Poor Surrogate Marker of OSA Disease Severity

A recent study[158] and further validation papers in international cohorts[159, 160] have proposed a new method of clustering patients according to their symptomatology, and found that the defined clusters responded very differently to treatment with CPAP. One cluster breakdown from the Sleep Apnoea Global Interdisciplinary Consortium (SAGIC) proposes five main groups; (1) those who exhibit *disturbed sleep*, (2) those who are *minimally symptomatic*, (3) patients with *both upper airway symptoms and sleepiness*, (4) patients with *dominant upper airway symptoms* and (5) patients with *dominant sleepiness symptoms*[159]. Each of these symptom clusters were associated with different secondary outcomes, summarised in figure 14.

All clusters of patients had equivalent AHIs on conventional PSG, yet displayed a large variation in symptomatic burden and secondary outcomes. This large population study highlights the weakness of AHI as the surrogate metric in OSA and further supports the need for a more personalised approach to the disease.

Figure 16. Profiles of the five optimal OSA clusters in the International SAGIC Sample. The relative symptom burden is shown as a heatmap, ranging from low burden (blue) to high burden (red). Adapted from Keenan BT,

Kim J, Singh B, Bittencourt L, Chen N-H, Cistulli PA, et al. Recognizable clinical subtypes of obstructive sleep apnea across international sleep centers: a cluster analysis. Sleep. 2018;41(3):zsx214.[159]



2. The New Phenotype Paradigm

The push for personalised medicine in OSA is encapsulated in the P4 medicine model (personalised, predictive, preventative and participatory)[161]. It is apparent that the measurements of AHI, ODI and Lsat are not sufficient to identify how patients respond to treatment nor the long-term implications of untreated disease. Sleep researchers are turning to the model of phenotyping OSA in order to better understand and treat traits that are expressed differently in each patient.

In respiratory medicine, the terms "endotyping" and "phenotyping" have been used in varied ways when describing the mechanisms of disease in asthma[162], bronchiolitis[163], chronic obstructive pulmonary disease (COPD) and bronchiectasis[164]. In OSA, **endotyping** refers to the process of polysomnographic measurement to derive pathophysiological processes[165] while **phenotyping** refers to the manifestation of these processes as an observable attribute of the airway as it relates to OSA[23]. In essence, endotyping is used to identify phenotypes.

The main contributing factors that have been identified in the pathogenesis of OSA thus far can be summarised into at least 4 unfavourable phenotypes: 1 anatomical and 3 non-anatomical[23, 166-168].

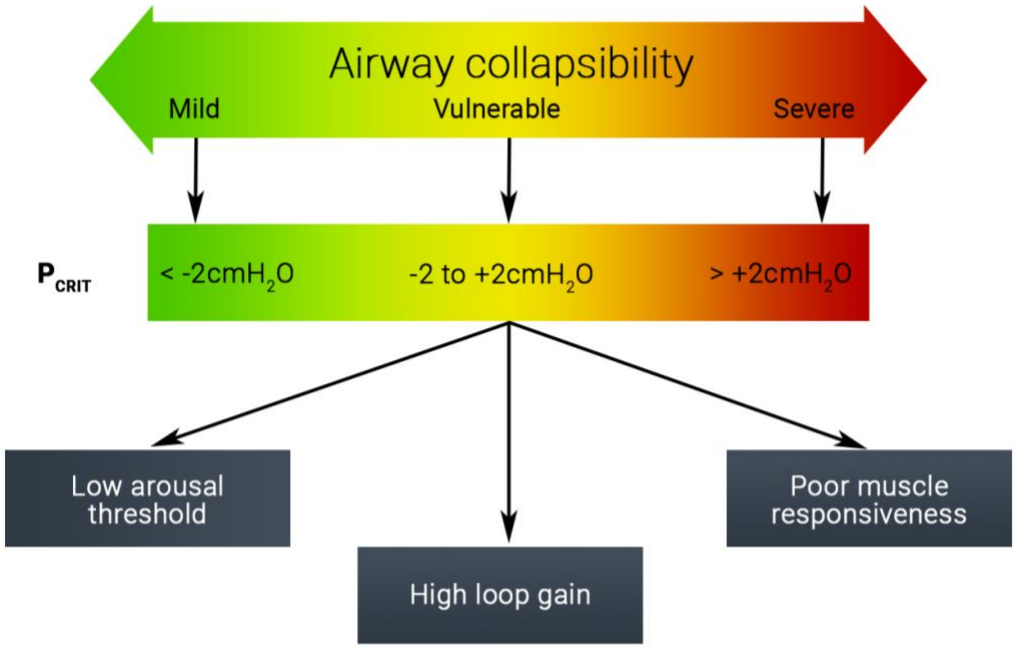
1. A small, vulnerable or collapsible airway (measured by P_{CRIT}),
2. Low respiratory arousal threshold,
3. High loop gain (a large compensatory ventilatory response to airflow disturbance), and
4. Poor muscle responsiveness during sleep (measured by genioglossus activity).

Eckert et al found the prevalence of patients with non-anatomical, unfavourable phenotypes contributing to OSA was 69%, suggesting that large proportion of patients were not being optimally treated[168].

Airway collapsibility is the most significant of the phenotypes by the definition of the disease – patients with a non-collapsible airway will never have OSA, while patients with a highly collapsible airway will have severe OSA and will invariably require treatment. In the group of

patients who have a moderately collapsible airway ("vulnerable") there is some variation on the burden of disease and this is where the significance of the other 3 phenotypes becomes apparent.

Figure 17. Relationship of anatomical (airway collapsibility) to non-anatomical, unfavourable phenotypes (low arousal threshold, high loop gain, poor muscle responsiveness).



Cortical arousal during sleep may be vital in restoration of normal airflow and correcting blood-gas instability at the conclusion of an obstructive apnoea. However, there are some deleterious after-effects of arousals that contribute to destabilisation of sleep. This includes prevention of progression to deeper and more stable stages of sleep, excessive reductions in pCO_2 and subsequent reduction in respiratory drive[169]. Patients who have low arousal thresholds are more frequently woken from sleep and experience more sleep fragmentation. Conversely, a patient with a high arousal threshold may not be woken during a time of need, such as during hypoxaemia. There may be a benefit in achieving balance between the positive and negative effects of arousal from sleep.

Loop gain is a phrase borrowed from engineering which refers to the stability of a system that is controlled by negative feedback[170]. In OSA, a high loop gain system has a large corrective ventilatory response to an airflow disturbance. Over time, repeated stimulation will lead to

larger and larger responses, excessive respiratory effort and greater swings in intrathoracic pressure. A low loop gain system will have minimal fluctuations in ventilatory drive and likely result in stable breathing. However, an excessively low loop gain may result in sustained hypoventilation and subsequent blood-gas disturbances (such as in obesity hypoventilation syndrome)[171].

Muscle activity has been shown to have differing effects during sleep. Muscle responsiveness is mediated by upper airway mechanoreceptors that detect abnormal intraluminal pressure[172], and peripheral and central chemoreceptors that detect hypercapnia[173]. In patients with OSA, muscle hypotonia is more likely to produce obstruction particularly during REM sleep. Those who belong to the subset of patients with poor muscle responsiveness are at higher risk of apnoeic events, particularly those with vulnerable anatomy (e.g. macroglossia).

3. Measuring Phenotypic Traits

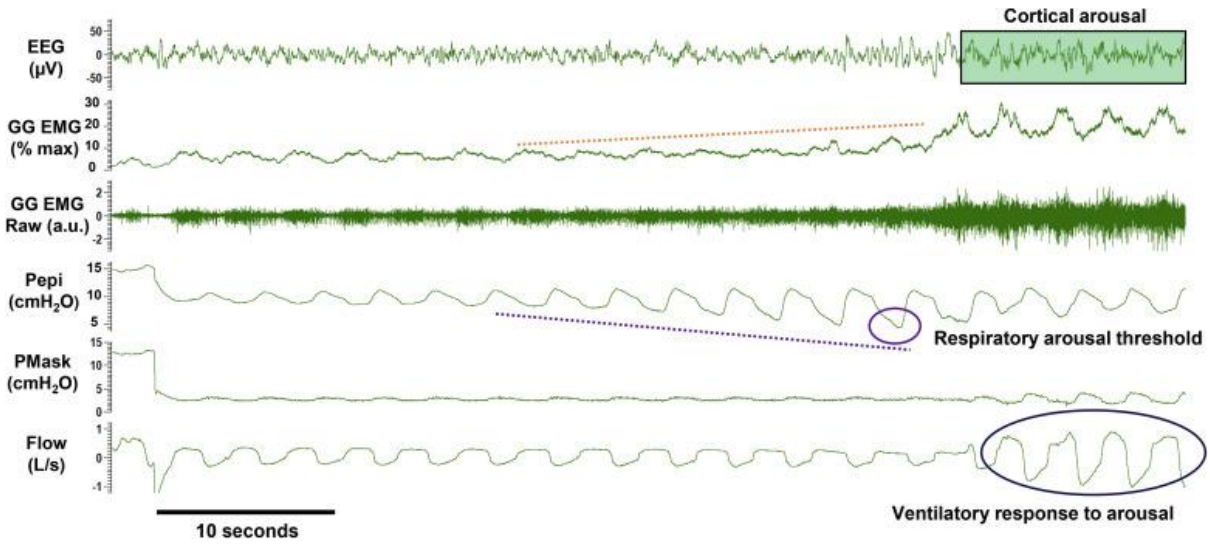
Phenotypic traits can be measured using the PSG with application of CPAP titration techniques and mathematical modelling[166, 167]. A number of important values and cut-offs have been defined based on comparisons to the traditional metric of AHI.

The collapsibility of the airway can simply be defined with the P_{CRIT}. This can be obtained experimentally using "gold standard" CPAP titration studies with a mask capable of administering positive or negative pressure. Patients are initially treated overnight at the minimum positive pressure required to prevent inspiratory airflow limitation (therapeutic level of CPAP in patients with OSA, or 4-5cmH_2O in people without OSA). This is then followed by a transient lowering of pressure for up to 5 breaths (potentially to negative pressures), until the upper airway collapses. The P_{CRIT} is the pressure difference at which the collapse occurs, after a linear regression analysis is performed on breaths 3-5 (breaths 1-2 are not included as lung volume changes after CPAP require 1-2 breaths to stabilise[174] and can affect upper airway collapsibility[175]). Eckert et al found that patients with OSA generally had a P_{CRIT} between -5 to +5cmH_2O. A mildly collapsible airway would have a P_{CRIT} <-2cmH_2O, moderate -2cm to +2cmH_2O and severely collapsible airway >+2cmH_2O[168]. While overall there is a positive correlation between P_{CRIT} and AHI, even between these P_{CRIT} cut-offs there is a large variation in AHI that is better explained by the presence of non-anatomical phenotypes.

Arousal threshold with CPAP titration is defined by the ventilatory pressure change at which a cortical arousal is stimulated and observable on EEG. This pressure change is calculated as the difference between the nadir epiglottic pressure during inspiration and end-expiration. It is taken from the last breath just prior to the cortical arousal. In a normal person without OSA the arousal threshold requires a minimum of -15cmH_2O[71]. A low arousal threshold is defined when pressures require minimal fluctuation to stimulate an arousal with a pressure difference >-15cmH_2O[168, 176].

Figure 18. Respiratory arousal threshold. Note the progressive increasing swings in epiglottic pressure (Pepi) followed by a cortical arousal, increase in genioglossus (GG) muscle activity and a ventilatory response. Adapted

from Eckert DJ. Phenotypic approaches to obstructive sleep apnoea–new pathways for targeted therapy. Sleep medicine reviews. 2018;37:45-59.[22]



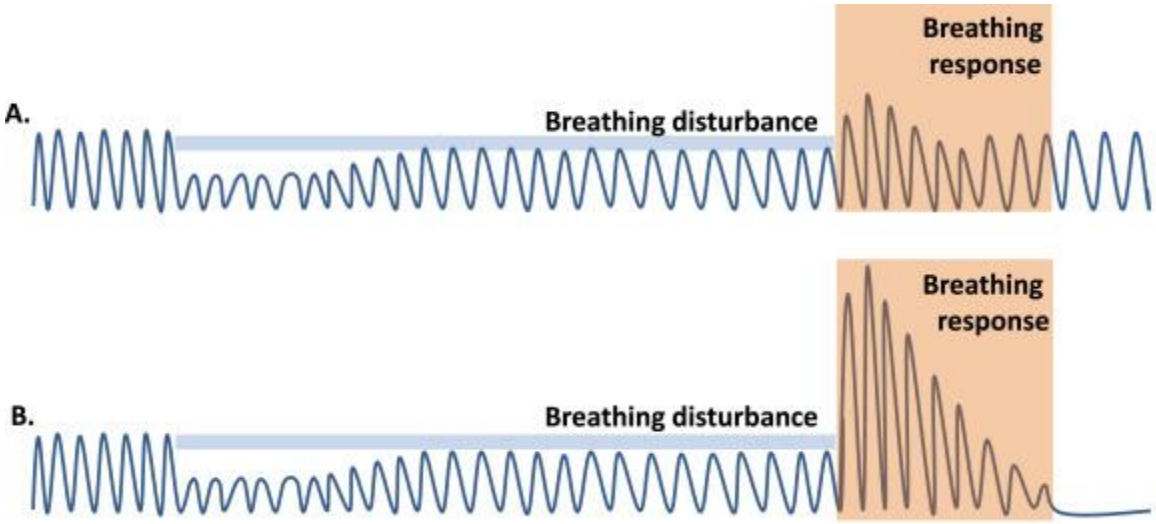
Loop gain is defined using a dimensionless integer that is calculated from the minute ventilation (L/min) of the maximum compensatory breath after a series of breaths at a minimally tolerable CPAP pressure. The method for obtaining this requires titration of a patient to a therapeutic level to establish their baseline **optimum** pressure. Minute ventilation is measured at this level and recorded. CPAP pressure can then be reduced to the **minimum** tolerable CPAP pressure when flow-limited breathing occurs (i.e. snoring) for at least 3 minutes[168]. Minute ventilation is again recorded. CPAP can then be returned to optimum pressure and the minute ventilation is recorded from the subsequent **compensatory** breaths. The loop gain is represented by the following equation (where V refers to the minute ventilation in L/min):

$$LG = \frac{V_{compensatory} - V_{optimum}}{V_{optimum} - V_{minimum}}$$

A high loop gain is defined as a gain greater than 5L/min in the compensatory breaths per 1L/min reduction during flow-limited breathing[167].

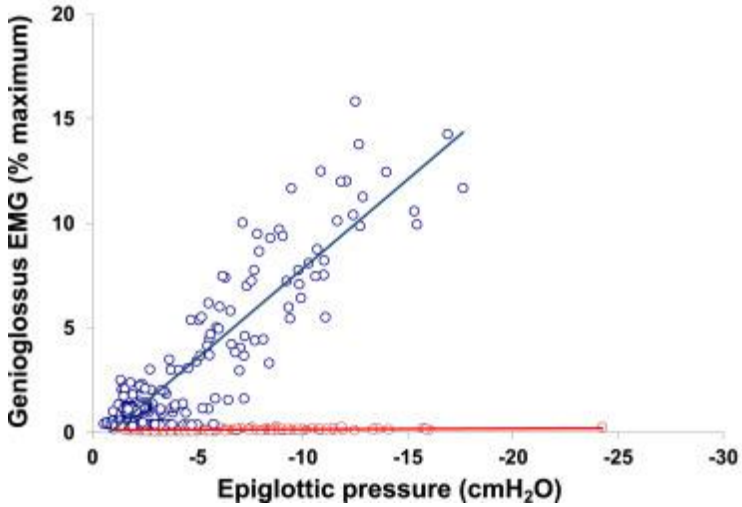
Figure 19. Schematic representation of low (A) versus high (B) loop gain. The patient is stabilised initially for 7 breaths, then a temporary breathing disturbance occurs for approximately 3 minutes. The breathing response in B peaks approximately 9-fold before decreasing until an apnoea occurs due to reduced respiratory drive from the

excessive response. Adapted from Eckert DJ. Phenotypic approaches to obstructive sleep apnoea–new pathways for targeted therapy. Sleep medicine reviews. 2018;37:45-59.[22]



Muscle responsiveness is measured as the function of the percentage of maximum genioglossus activity on EMG per unit of nadir epiglottic pressure during a breath (%GG_{max}/cmH_2O). Both artefact-free breaths and arousals can be used to plot several points, with the gradient of the regression fit defining muscle responsiveness. A patient with a flatter gradient (<0.1%GG_{max}/cmH_2O) is defined as having poor muscle responsiveness[168].

Figure 20. The calculation of genioglossus (GG) muscle response. Excellent responsiveness is shown in the blue line (0.86% GG_{max}/cmH_2O), compared to poor and virtually no responsiveness in the red line (0.004% GG_{max}/cmH_2O). Adapted from Eckert DJ. Phenotypic approaches to obstructive sleep apnoea–new pathways for targeted therapy. Sleep medicine reviews. 2018;37:45-59.[22]



The PALM scale (**P**$_{CRIT}$, **A**rousal threshold, **L**oop gain, **M**uscle responsiveness) was proposed to assist in categorising patients according to their phenotypic traits[22, 168]. Approximately one quarter of patients with OSA will be PALM category 1, with features of a highly collapsible airway that is inevitably going to require CPAP or a major anatomical intervention even if they do have non-anatomic phenotypic traits. Almost two thirds of patients with OSA have PALM category 2, with one third of these in category 2a not requiring non-anatomical treatment and two thirds in 2b that may benefit from a combination of anatomic and non-anatomic treatments. One fifth of all patients are in PALM category 3[168].

Table 3. The PALM scale. Adapted from Eckert DJ, White DP, Jordan AS, Malhotra A, Wellman A. Defining phenotypic causes of obstructive sleep apnea. Identification of novel therapeutic targets. American journal of respiratory and critical care medicine. 2013;188(8):996-1004.[168]

PALM Category	Category Cut-Offs	Patient Features	Possible Treatment Targets
1	P_{CRIT} > +2cm H_2O	Highly collapsible upper airway Severe OSA	Major anatomic or mechanical intervention likely required (e.g. CPAP)
2	P_{CRIT} -2 to +2cm H_2O	Moderately collapsible upper airway Mostly severe OSA	Candidate for one or a combination of targeted therapies
2a	P_{CRIT} -2 to +2cm H_2O without nonanatomic vulnerability	Moderately collapsible upper airway, primarily anatomically driven	Anatomic intervention (e.g. CPAP, MAS, upper airway surgery, positional therapy, weight loss)
2b	P_{CRIT} -2 to +2cm H_2O with nonanatomic vulnerability	Moderately collapsible upper airway and one or more vulnerable nonanatomic traits	Combination of anatomic and nonanatomic interventions (e.g. MAS + weight loss + oxygen or sleep consolidation aid)
3	P_{CRIT} < -2cm H_2O	Some vulnerability to upper airway collapse Mild-moderate OSA	One or a combination of targeted therapies, with nonanatomic interventions likely to be beneficial (e.g. oxygen, sleep consolidation aid)

4. Treatment Effects for the Anatomical Phenotype and Emerging Treatments for Non-Anatomical Phenotypes

Multiple studies have been performed evaluating the effects of anatomical treatment on P_{CRIT}. The use of a MAS has been shown to reduce P_{CRIT} by an order of 2.2-2.3cmH_2O[63]. Traditional UPPP has been shown to reduce P_{CRIT} by 3.3cmH_2O[177], while transpalatal advancement reduces P_{CRIT} by 8.4cmH_2O[178]. Positional therapy with supine avoidance has shown a 2.2cmH_2O reduction in P_{CRIT}[179]. Weight loss with a 17% reduction in BMI also reduced P_{CRIT} by 7.5cmH_2O[65].

It follows that these non-anatomical traits require a different approach to treatment than the conventional anatomical interventions outlined above. Studies investigating novel agents will be summarised below.

The aim of treating low arousal threshold is to reduce cortical responsivity, therefore requiring a larger pressure stimulus to induce arousal. This has been achieved with hypnotic agents that do not induce muscle relaxation (so as not to impair muscle responsiveness). Agents that have been trialled include eszopiclone[176], zopiclone[180] and trazodone[181]. These have been shown to achieve a 4-5cmH_2O increase in arousal threshold. As discussed earlier, it is crucial to ensure that arousal threshold is not reduced to the point of hypoventilation.

High loop gain is treated by stabilising the compensatory response to hypoventilation. Given that the ventilatory control system is modulated primarily by CO_2 concentration, treatments that alter and stabilise pCO_2 are preferred here[182]. Supplemental O_2 has been observed to be effective in achieving a 50% reduction in loop gain[171]. Alternatively, acetazolamide has been employed to create a 40% reduction in loop gain[183].

Muscle responsiveness requires an improvement in dilator muscle function during sleep. Upper airway muscle training is a conservative option that can achieve a 50% reduction in AHI, but the exact mechanism and the effects on muscle are unknown[184, 185]. Despiramine is a tricyclic antidepressant that mitigates the reduction of sleep-state tonic genioglossus activity by an order of 25% and has demonstrated a reduction in P_{CRIT} by -2-3cmH_2O[186, 187].

Finally, direct hypoglossal nerve stimulation has been explored and achieves up to 50-70% reduction in AHI[188, 189]. Two forms of stimulators have been published in the literature which involve surgical implantation and application of stimulator electrodes to selective branches of the hypoglossal nerve that only innervate dilator muscles (such as the genioglossus)[188-191].

5. Non-Invasive Endotyping

More recently, a validated method to quantify the four phenotypes using non-invasive routine PSG[192-194] has been developed without need for CPAP titration[166, 167]. This endotyping model utilises EEG monitoring to assess sleep/wake staging and cortical arousals in addition to nasal pressure (square-root transformed), providing a semi-quantitative measure of airflow, and is comparable to the "gold-standard" method described previously.

Loop gain is quantified by the observed size of the increase in "ventilatory drive" (overshoot) in response to an apnoea or hypopnoea. "Ventilation" refers to the uncalibrated breath-by-breath ventilation time series (tidal volume x respiratory rate) and is derived from the nasal pressure airflow signal (square-root transformed), integrated and normalised by dividing the mean nasal pressure in a window. This allows approximation of the eupneic (or resting/baseline) ventilation level[194]. Ventilatory drive, which is essentially the intended ventilation if the upper airway had no resistance, is calculated for each respiration by fitting a physiologically constrained statistical model calculated from four ventilatory control parameters (chemoreflex gain, response-time, circulatory delay, non-chemical response to arousal – see supplementary material[194]). This data is fit so that the ventilatory drive signal matches the measured ventilation signal outlined above during periods of recovery hypoventilation after each apnoea/hypopnoea. This is done so because the ventilatory drive and ventilation are known to be equal during these periods of recovery. A separate ventilation model is applied to each 7 minute window of data from the PSG and the average loop gain in this window can thus be obtained (the 7 minute duration is chosen to allow time for approximately 10 cyclic obstructive events to occur)[194].

There are two measures of loop gain that can be obtained (LG_1 and LG_n). LG_1 is calculated as the response to a cyclical ventilatory disturbance that occurs once each minute. LG_n is

calculated as the response to the individual's actual baseline cycling period, where n is the frequency of disturbances per minute.

After calculation of the ventilatory drive the remaining phenotypes can be identified. The arousal threshold (ArThres) is the median ventilatory drive occurring in the breaths immediately prior to scored EEG arousals or awakening from sleep[193]. Upper airway collapsibility is measured as the median level of ventilation ($V_{passive}$) during normal (eupneic) ventilatory drive[192]. Further unpublished data suggests that the minimum level of ventilation during this period (V_{min}) may also provide an alternative metric of airway collapsibility and P_{CRIT}. The median level of ventilation during the arousal threshold is taken as active airway collapsibility (V_{active}). The difference between V_{active} and $V_{passive}$ is used to determine muscle responsiveness (V_{comp}). These phenotypes are then averaged from each 7 minute epoch throughout the PSG to provide a single representative trait estimate for each individual.

This method of endotyping produces different units for phenotypic traits: Loop gain is expressed as a dimensionless integer. ArThres, V_{comp}, $V_{passive}$ and V_{min} are expressed as a percentage of the eupneic ventilation (V_{eupnea}).

Table 4. Literature cut-offs for "unfavourable" and "favourable" phenotypic traits as measured using non-invasive endotyping[192-194].

Phenotypic Trait	Unfavourable	Favourable
Airway collapsibility *$V_{passive}$ (%V_{eupnea})*	< 95.5%	> 95.5%
Loop gain *LG_1 (dimensionless)*	> 0.72	< 0.72
Arousal threshold *ArThres (%V_{eupnea})*	< 120%	> 120%
Muscle responsiveness *V_{comp} (%V_{eupnea})*	< 0%	> 0%

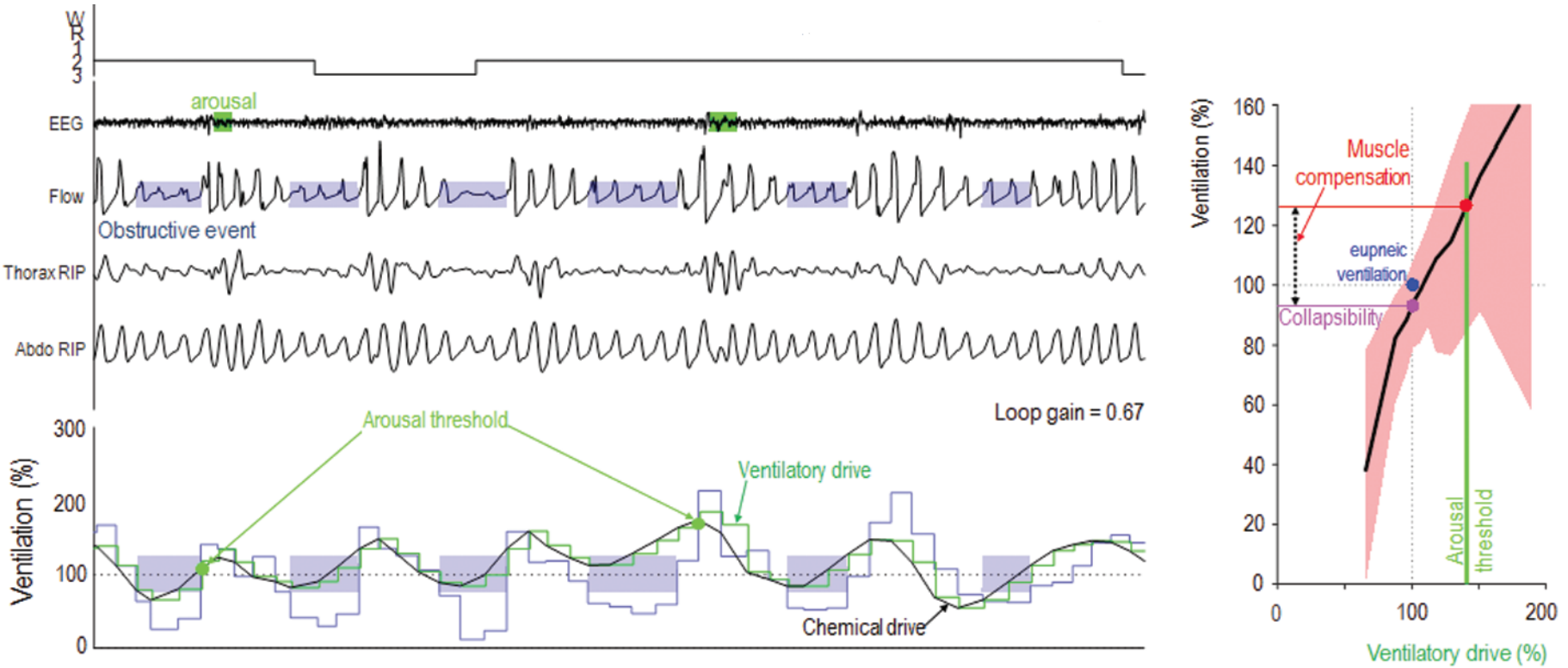


Figure 21. Non-invasive method of measuring OSA phenotypes. EEG and nasal pressure traces from a PSG can be used to generate the four main phenotypes. Respiratory disturbances and subsequent ventilatory responses are used to estimate the breath-by-breath ventilatory drive. Loop gain (LG_1) is the overshoot in ventilatory drive (dark green) in response to an apnoea/hypopnoea (shaded blue). Arousal threshold (ArThres) is the median level of ventilatory drive immediately prior to an arousal, measured as a percentage of eupneic ventilatory drive (light green). Upper airway collapsibility ($V_{passive}$) is the median level of ventilation during periods of resting ventilatory drive (purple). This is displayed as a percentage of the eupneic ventilation calculated from a physiologically constrained model (chemical drive). Muscle compensation (V_{comp}) is taken as the difference between ventilation at the arousal threshold (V_{active}) and $V_{passive}$ (red). V_{min} is the minimum level of ventilation as represented on the graph on the right (not marked). Reproduced with permission.

6. Directions for Research

Understanding phenotypic traits may allow clinicians to predict patient response to, and perhaps understand the reasons for failure of conventional treatments for OSA. There is therefore a need for further prospective data that evaluates the relevance of phenotypic traits in a clinical setting. To that end, we utilised the resources available within the Illawarra, with the study based out of a multidisciplinary sleep team directing complex OSA management. We conducted a clinically based prospective study in collaboration with sleep physiology researchers from Monash University using the described non-invasive method of determining phenotypic traits[192-194]. This allowed us to evaluate the prevalence of phenotypic traits in our referral cohort and whether certain traits would predict treatment success.

Chapter 3
Research

1. Aims and Hypothesis

Aim: The goal of this study was to determine the diagnostic value of endotyping in patients who undergo salvage treatment for their OSA.

Hypothesis: It would be anticipated that anatomical phenotypes (P_{CRIT} and its surrogate markers) will be key in predicting responders to salvage treatment pathways. Non-anatomical phenotypes (arousal threshold, loop gain and muscle responsiveness) may account for non-responders to treatment.

To determine this, our primary aim was to evaluate the prevalence of the four phenotypic traits and explore the clinical effectiveness of endotyping as a means of predicting future treatment outcomes. Treatment "success" was defined based on criteria described in the sleep literature:

1. PSG: 50% reduction in AHI, with overall AHI <20[195]
2. ESS: ≥3 point reduction in ESS, with overall ESS <10[196]
3. FOSQ: ≥1 reduction in FOSQ[88]

Given that there is limited data that exists in the literature about the phenotypic effects of non-CPAP therapy, the secondary aim of this study was to perform an exploratory analysis to identify the impact of salvage treatment on phenotypes in a prospective clinical cohort.

2. Methods

2.1 Study Design and Recruitment

An observational prospective consecutive study was conducted evaluating contemporary multidisciplinary clinical pathways that are used to decide upon treatment for patients. All participants were recruited via the Sleep Multidisciplinary Team Meeting based at the Illawarra Sleep Medicine Centre and One Airway Clinic (Illawarra ENT Head and Neck Clinic), which takes referrals from within the region, Sydney and interstate. Ethics approval was obtained from the Joint University of Wollongong and Illawarra Shoalhaven Local Health District Health and Medical Human Research Ethics Committee (2019/ETH09854).

As discussed in the aims there was no published literature at the time of this study on the prevalence of phenotypes or the diagnostic power of endotyping in a real-world clinical population. We aimed to achieve a power of 0.8 for sensitivity and specificity. Based on the literature estimate of 60% success in the salvage treatment of OSA[195], a minimum overall sample size of 32 for sensitivity and 48 for specificity was required to achieve a power of 0.885[197]. Due to interruption by the SARS-CoV-2 pandemic throughout 2020, recruitment occurred over a duration of one and a half years between May 2019 and October 2020. 49 participants were recruited overall.

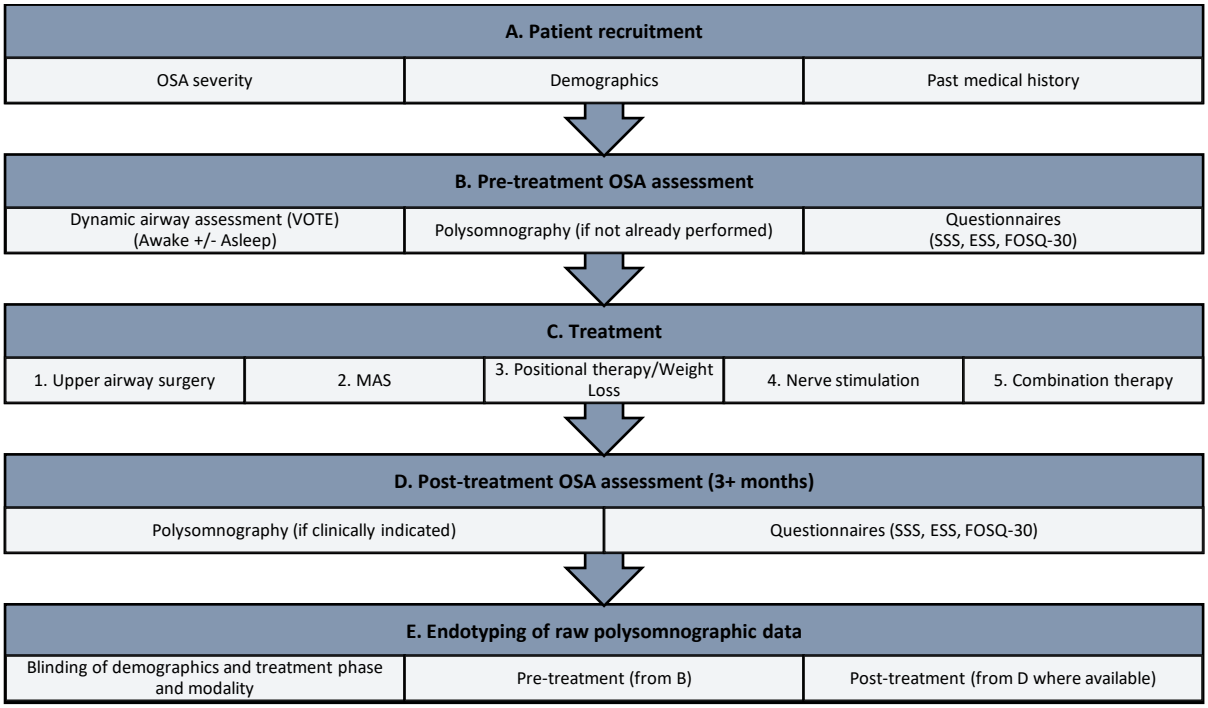
Table 5. Inclusion and exclusion criteria.

Inclusion criteria	Exclusion criteria
1. Age ≥18 years 2. AHI ≥5 events/h 3. BMI <45	1. Severe psychiatric disease 2. Severe medical co-morbidities restricting treatment pathways 3. Significant sleep co-morbidities affecting phenotyping assessment (e.g. untreated severe insomnia or circadian rhythm disorders) 4. Significant impairment to accurate phenotyping of sleep disorder determined by treating clinicians 5. Commercial drivers

Inclusion and exclusion criteria are outlined in table 5. Patient recruitment included new referrals, or patients previously seen in the clinic but re-referred for failure of initial

management. Patients were allowed to leave the study prematurely for their own reasons but had their data collected up to that point retained for analysis. This included patients who failed to attend subsequent follow-up appointments. Patients who experienced any complications related to their treatment including failure of treatment and surgical complications were also included in this study.

Figure 22. Patient clinical pathway.



At the initial clinic appointment patient data was collected including history, examination and PSG findings (if already obtained). Basic demographic information was collected including height, weight, age and sex. Medical comorbidities, past medical history and baseline blood pressure were documented. Standardised examination of the airway was performed and documented according to the VOTE classification. This included:

- Friedman stage (tongue, palatine and lingual tonsil)
- Palatal position
- Assessment of dental malocclusion
- Awake (erect and supine) with or without sleep (under general anaesthesia) endoscopy

Formal in-laboratory PSG was performed at the Illawarra Sleep Medicine Centre if not already performed or if the existing PSG was not deemed of sufficient quality for clinical correlation. In cases where this did not occur, a type 2 ambulatory study that was reviewed by a sleep physician was also acceptable. Scoring was undertaken by a qualified sleep technician according to the most recent iterations of the AASM scoring manual at the time of the study (versions 2.5 and 2.6)[97, 198].

Patients were then allocated to a treatment group per existing clinical protocols. The main categories of treatment included: mandibular advancement splint (MAS), non-nasal upper airway reconstruction surgery (Sx), positional therapy (PTx), weight loss (WL), nerve stimulation (NS) and combination therapy (CTx) of any of the above options. Note that pre-phase nasal surgery was not considered a surgical treatment category due to its adjunct role in facilitating the use of CPAP or MAS but was included in CTx. Any discussion regarding the patient's preferred route of management and the recommendation of the clinic team was also documented. Those who deviated from their original treatment pathway for reasons including second-line treatments, patient preference, non-tolerance to treatment or for other reasons at the discretion of the treating clinicians were evaluated according to their final pathway. This included patients who reverted to CPAP at the conclusion of their treatment. Generalised patient characteristics and a brief outline of these treatment pathways is in table 6.

Table 6. Main treatment groups and pathways.

Treatment group	Brief description	Patient characteristics
Mandibular advancement splint (MAS)	Referral to dentist to fit MAS (SomnoMed™ twin block titratable devices fitted by Gold and Platinum dental providers)	Patients with anatomy favourable to advancement of mandible
Upper airway surgery (Sx)	Various non-nasal options available including mUPPP, radiofrequency tongue reduction and transpalatal advancement	Patients who fail/have failed conservative management previously or have vulnerable anatomical features (e.g. tonsillar hypertrophy, macroglossia, vertical retroposed palate)
Positional therapy (PTx)	Usage of worn positional therapy device at night (NightShift™)	Patients who demonstrate significantly worse supine compared with lateral AHI
Weight loss (WL)	Referral to dietician or exercise physiologist for formal weight loss programme (also includes bariatric surgery)	Patients with significantly elevated BMI and minimal favourable anatomical features for surgery, MAS or PT
Nerve stimulation (NS)	Implantation of hypoglossal nerve stimulator (open loop, bilateral stimulation with implantable component and external stimulator)	Patients who have failed or unwilling to trial other salvage treatment options and meet minimal enrolment criteria for NS clinical trial
Combination therapy (CTx)	Any use of the above options in combination, including pre-phase nasal surgery	Patients who require multiple approaches to management Patients with nasal pathology and require surgery to facilitate use of airway appliance

Outcomes defined prior to and following treatment included OSA severity using PSG and patient reported outcome measures (PROMs). Key PSG parameters included:

- Apnoea-hypopnoea index (AHI)
    - Supine AHI
    - Non-supine AHI
- Apnoea index (AI)
- Hypopnoea index (HI)
- Oxygen desaturation index (ODI)
- Lowest oxygen saturation (Lsat)

PROMs included SSS[87], ESS[86] and FOSQ[88]. Blood pressure recordings were obtained at the index and subsequent PSG appointments, with the main metric of blood pressure comparison used being the systolic (sBP) and diastolic (dBP) taken the morning after sleep.

2.2 Data and Statistical Analysis

Patient demographic data (name, date of birth) were de-identified for analysis. Data entry for demographics, clinical examination and PSG scores was performed with Microsoft Excel (Microsoft Corporation, WA, USA 2019). Raw PSG data obtained locally was scored using three software options: Noxturnal™ Sleep Study Software (Nox Medical USA, GA, USA 2020), Embla RemLogic™ PSG Software (Natus Neuro, WI, USA 2020) and Profusion™ Sleep Software (Compumedics Limited, VIC, Australia 2020). De-identified traces from all studies were standardised into European Data Format and securely sent for endotyping by an off-site sleep technician based in Monash University (VIC, Australia) blinded to treatment phase and modality.

Endotyping was automated using MATLAB (MathWorks, MA, USA 2020). Unfavourable phenotypic traits were defined according to published data: high loop gain as LG_1 >0.72, low arousal threshold as ArThres <120%, low muscle compensation as V_{comp} <0% and high airway collapsibility was defined as $V_{passive}$ <95.5%[192-194]. There are no standardised values for V_{min} or

LG_n but these were analysed as surrogate markers for airway collapsibility and loop gain respectively as well.

Statistical analysis was conducted using Prism 9.0.0 (GraphPad Software, CA, USA 2020). A *p*-value of < .05 was considered statistically significant. Variables with normal distributions as measured by Shapiro-Wilk test were compared with independent samples t-test, and those without were compared with Wilcoxon signed rank or Mann Whitney U test. Multiple groups comparisons were performed with one-way analysis of variance (ANOVA) or Kruskal-Wallis test. Linear bivariate regression analysis was performed to evaluate relationships between phenotypic traits and individual variables such as AHI, BMI, Lsat and treatment categories. Logistic regression was utilised to determine phenotypic traits present in individuals who had successful treatment as defined in our aims. Fisher's exact tests were used to determine proportions of patients who demonstrated abnormal and favourable phenotyping traits. Correlation between traits and different variables was performed with Pearson correlation for normally distributed data and Spearman's rank correlation for non-normally distributed data.

3. Results

3.1 Baseline Characteristics

Data from 49 patients (73.5% male) were analysed. On average, the age of patients was 44 years (range 18–72) and patients were obese with BMI 31.1 kg/m^2 (range 20.8–42.3). The average patient had moderate OSA with AHI 26.2 (range 6.0–113.8), 10 had mild OSA, 17 had moderate OSA and 22 had severe OSA.

A proportion of patients (8/49 (16.3%)) had not attended follow-up appointments at the time of conclusion of this study (due to significant delays caused by the SARS-CoV-2 pandemic) or were uncontactable and so were unable to attend PSG or provide PROMs. Repeat PSG after treatment was clinically indicated and ultimately performed in 31/41 (75.6%) patients, leaving a total of 80 potential raw PSGs available for phenotypic analysis.

3.2 History and Examination Findings

Apart from obesity, the most common reported comorbidity on history was hypercholesterolaemia (n = 5). Four patients were on antihypertensive medication, and 4 had a form of cardiac arrhythmia (2 atrial fibrillation, 1 supraventricular tachycardia, 1 bundle branch block). Two patients had asthma, and 4 were current smokers. Four had depression or anxiety.

In 10 patients the proforma for VOTE classification was not utilised as the clinical decision for management was selected without need for dynamic manoeuvres. Airway assessment was conducted with awake fibreoptic nasendoscopy for all other patients. Dimensions of collapse according to the VOTE classification, palatine tonsil, lingual tonsil and palate relative to tongue findings are summarised in table 7. Of note, 4/49 (8.2%) patients demonstrated complete concentric retropalatal collapse and were therefore considered unfavourable for surgery. Nearly all patients (13/14 (92.9%)) who had a significant degree of tonsillar generated collapse (either retropalatal or oropharyngeal) had upper airway surgery. All epiglottic

collapse was secondary to collapse either laterally from the hypopharyngeal wall, AP from lingual tonsil or tonsillar from lower poles of the palatine tonsils.

Table 7. Prevalence of anatomical features and planes of collapse.

Anatomical features, n/49 (%)		Dominant planes of collapse, n/49 (%)	
Palatine tonsil grade		Retropalatal/velum (direction)	
0	9 (18.4)	Anteroposterior (AP)	7 (14.3)
1	11 (22.4)	Lateral	5 (10.2)
2	7 (14.3)	AP/lateral	14 (28.6)
3	13 (26.5)	Tonsillar	9 (18.4)
4	2 (4.1)	Concentric	4 (8.2)
Lingual tonsil grade		Oropharyngeal (direction)	
0	2 (4.1)	No collapse	21 (42.9)
1	13 (26.5)	Lateral	4 (8.2)
2	9 (18.4)	Tonsillar	12 (24.5)
3	17 (34.7)		
4	1 (2.0)		
Friedman tongue grade		Retroglossal/tongue (AP% of airway)	
1	3 (6.1)	No collapse	3 (6.1)
2a	3 (6.1)	33%	16 (67.3)
2b	9 (18.4)	66%	17 (34.7)
3	20 (40.8)	100%	1 (2.0)
4	1 (2.0)		
Palate position		Epiglottis (AP% of airway)	
Oblique	3 (6.1)	No collapse	29 (59.2)
Intermediate	14 (28.6)	33%	3 (6.1)
Vertical	11 (22.4)	66%	5 (10.2)

Nasal pathology as defined by any features consistent with deviated nasal septum, septal spurs or hypertrophic turbinates was present in 20/49 (40.8%) patients. Malocclusion secondary to distortion of the maxillary/mandibular interface such as overbite (class II), underbite (class III), maxillary hypoplasia or micrognathia was present in 7/49 (14.3%) patients.

3.3 Treatment Groups

Groups were separated according to prescribed treatment modalities. The 9 patients who had combination therapy (CTx) were also analysed according to the separate modalities of treatment they had undergone. There were 60 total treatments, of which:

- 22 were patients who had upper airway surgery (Sx),
- 14 patients who were prescribed positional therapy (PTx),
- 10 patients who were referred for a mandibular advancement splint (MAS),
- 9 patients who were referred for a formal weight loss programme or bariatric surgery (WL), and
- 5 patients who underwent implantation of a hypoglossal nerve stimulator (NS).

One patient who had Sx presented to hospital with a post-operative day 7 bleed. He was admitted and observed for 24 hours with no further intervention required. Three patients (1 combination MAS/PTx, 1 PTx, 1 WL) reverted to CPAP therapy at the conclusion of the study due to ineffective symptom control with prescribed treatment. The patient treated under the WL pathway also obtained nasal surgery to facilitate CPAP therapy. Two patients (1 MAS, 1 PTx) remained untreated at the conclusion of the study as they had changed their mind and did not wish to pursue the prescribed sleep appliance. These 5 (untreated and CPAP) were included and considered as treatment “failures” for statistical analysis.

Of the 8 patients that were lost to follow-up or had their final scheduled follow-up outside the reporting period; 2 were CTx patients (1 combination MAS/PTx/WL, 1 Sx/PT), 3 were MAS only patients and 3 were WL only patients. As per study protocol, all data collected for these patients until the conclusion of the study was analysed.

Figure 23. Patient treatment groups and final clinical pathways. Red numbers have been considered treatment "failures" for statistical analysis.

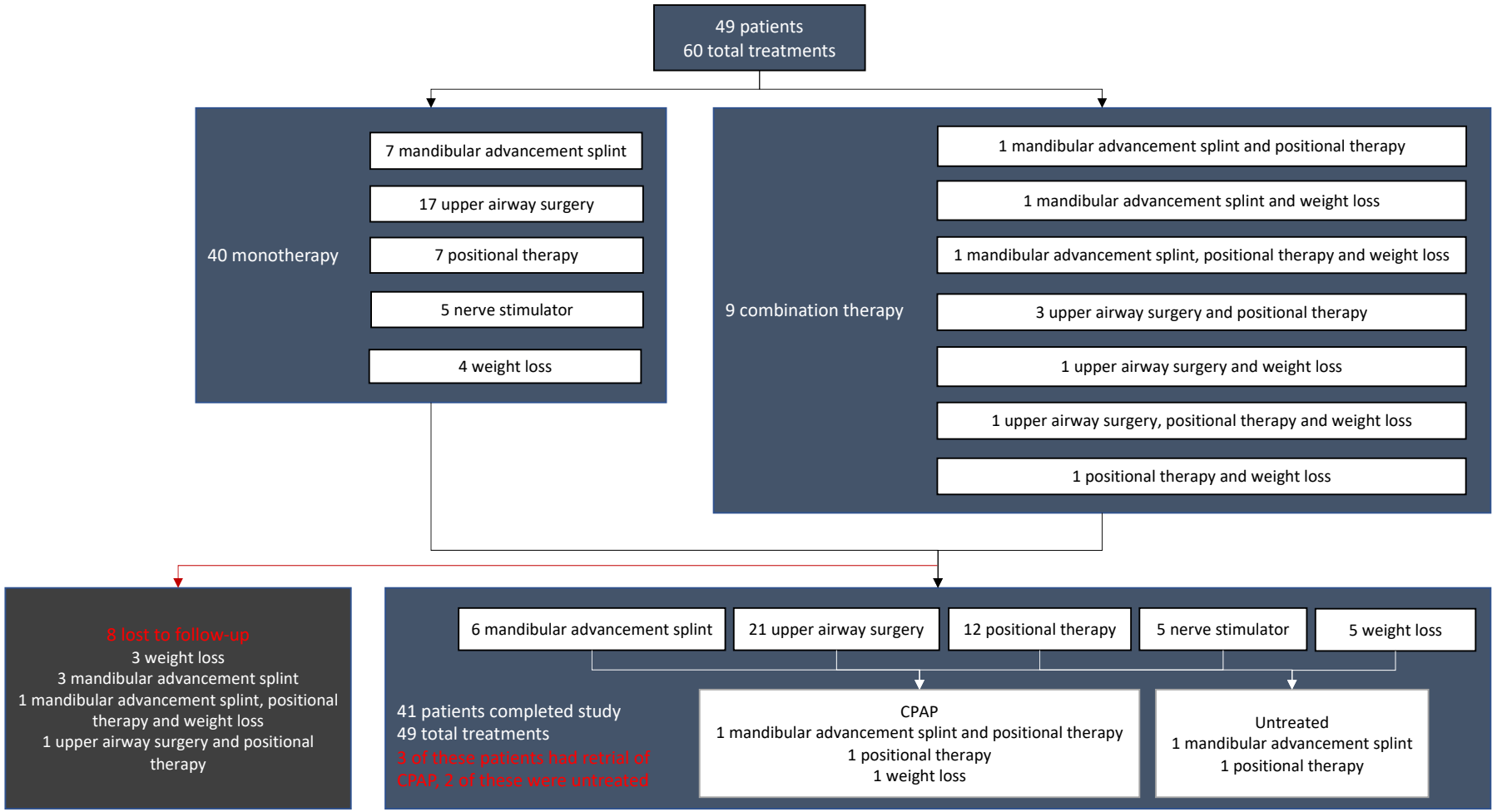


*Table 8. Baseline characteristics, PSG and PROM data for all patients per treatment modality. Values are displayed as mean ± SEM for normally distributed or median (interquartile range) for non-normally distributed data as per Shapiro-Wilk test. p-values are calculated from **unpaired t-tests** or **Mann Whitney U test** for patients within all groups.*

Treatment	All		*p*	MAS		*p*	Sx		*p*
Phase (PSG n)	Pre (49)	Post (31)		Pre (10)	Post (4)		Pre (22)	Post (19)	
Characteristic									
Gender, M:F	36:13			5:5			18:4		
Age, yr	44±2.3			54.3±4.3			33.2±3.0		
BMI, kg/m^2	31.1±0.7	29.9±0.8	.28	31.5±1.6	27.6±1.3	.16	31±1.1	31.4±1.0	.81
sBP, mmHg	120.9±2.7	121.1±2.7	.97	113.8±11.7	120±12.8	.43	123.9±4.0	122.5±3.8	.81
dBP, mmHg	74.4±2.3	75.7±1.7	.66	67±4.7	71.3±6.9	.36	75.6±3.8	76.6±2.4	.82
AHI, events/h	26.2(15.1-41.5)	8(2.0-24.3)	<.0001	14.2(6.4-18)	2.9(0.2-32)	.19	32.8(25.2-49.2)	8(2.4-24.2)	.0003
Supine AHI, events/h	54.7(30-75.3)	14.5(0.8-41.8)	.0001	46(7.6-62.4)	0(0-54)	.19	54.4(32.3-77.3)	15.5(9.3-53.3)	.01
Non-supine AHI, events/h	16.2(7.2-30.5)	5.7(1.0-17.8)	.003	8(6.4-21)	2.9(0.2-31.3)	.31	22(12.7-32.9)	6.6(1.3-23.3)	.02
AI, events/h	7(2.2-19.4)	1.5(0.2-7.0)	.004	2.7(1.6-5.8)	0.6(0.1-1.0)	.008	10(5.5-24.1)	2.4(0.4-7.3)	.002
HI, events/h	14.8(7.9-20.4)	3(1.2-13.5)	<.0001	10(4.6-12.2)	1.9(0-31.0)	.20	16.7(10-25.4)	3.4(1.8-12.9)	.005
ODI, events/h	22.8(11.7-39.0)	7.2(1.1-22.9)	.0002	10.9(4.9-16.9)	0.6(0-38.1)	.50	30(16.4-55.7)	7.3(1.7-27.4)	.004
Lsat, SpO2%	80.5±1.3	85.7±1.2	.004	84.6±1.2	88±3.4	.26	78.3±2.3	84.1±1.6	.06
SSS, /9	7.7±0.2	2.5±0.5	<.0001	7.4±0.4	4.0±4.0	.08	7.6±0.3	2.2±0.5	<.0001
ESS, /24	10±0.7	5±0.7	.0001	8.0±1.6	4.7±2.7	.32	9.7±0.9	5.3±0.7	.0004
FOSQ, /20	15.5±0.6	18.3±0.5	.01	17.5±1.1	19.9	.45	14.4±1.0	17.9±0.6	.02

Treatment	PTx		*p*	NS		*p*	WL		*p*	CPAP
Phase (PSG *n*)	Pre (14)	Post (7)		Pre (5)	Post (5)		Pre (9)	Post (3)		Pre (3)
Characteristic										
Gender, M:F	12:2			4:1			4:5			3:0
Age, yr	46.9±3.5			54.2±4.4			50.3±4.3			55.7±1.8
BMI, kg/m^2	30.4±1.0	29.7±1.1	.69	27.5±2.0	26.6±1.8	.77	36.6±1.7	31.9±2.6	.18	33.3±3.3
sBP, mmHg	119.2±4.4	117.4±4.6	.79	134.5±6.6	121.2±5.1	.15	125±6.5	117±11	.52	109.5±2.5
dBP, mmHg	71.8±3.5	74±2.1	.63	86.8±6.9	77.8±3.2	.25	69.7±2.7	71.7±2.3	.66	65.5±9.5
AHI, events/h	23.8(11.1-32.7)	14.2(2-41)	.36	21(17.5-41.5)	22.5(5.5-27.5)	.55	41(15.3-55.9)	15(0-21)	.1	16(8.4-60.6)
Supine AHI, events/h	48.1(27.5-61.8)	14(0-54)	<.05	50(40.3-59.8)	22(3.8-44.8)	.11	70(30-79.1)	14(0-39)	.12	60(58-70)
Non-supine AHI, events/h	10(3.6-16.2)	2.8(2-40)	.71	13.5(5-43.8)	11.3(4.3-25.4)	.74	22(16-49.1)	8(0-40)	.38	27.5(5-50)
AI, events/h	4.6(0.6-8.6)	1(0-2.8)	.25	14(4.9-30.5)	7(3.3-19)	.55	2.6(0.9-13.2)	4(0-7)	.81	6.3(6-14.5)
HI, events/h	14.1(5-24.6)	11.8(2-39.7)	.65	8.3(5-17.5)	3(1.5-15.6)	.52	26.6(9.6-39.7)	11(0-14)	.13	9(2.1-46.1)
ODI, events/h	16.4(11.0-29.4)	5.4(1.6-38.5)	.24	20(14.8-37.7)	9.2(4.4-24.7)	.22	34.3(21.4-48.8)	7.1(0.4-13.7)	.07	11(5.5-59.4)
Lsat, SpO2%	83.4±1.1	86±2.3	.26	83.2±1.5	87.4±1.5	.08	77.9±2.9	88±3.1	.09	80.3±5.0
SSS, /9	7.3±0.3	3±0.8	<.0001	7.8±0.8	-		7.9±0.5	1.3±0.8	<.0001	7±1.2
ESS, /24	8.4±1.1	6.5±1.6	.29	13.8±1.9	-		11.6±1.8	4.8±1.1	.03	13±4.6
FOSQ, /20	15.7±1.1	18.4±0.4	.14	15.7±2.0	-		15.0±1.2	17.0±0.7	.43	12.4±1.1

Abbreviations: PSG polysomnography, M:F male:female, BMI body mass index, sBP systolic blood pressure, dBP diastolic blood pressure, AHI apnoea-hypopnoea index, AI apnoea index, HI hypopnoea index, ODI oxygen desaturation index, Lsat oxygen saturation nadir, SSS Snoring Severity Scale, ESS Epworth Sleepiness Scale, FOSQ Functional Outcomes of Sleep Questionnaire, MAS mandibular advancement splint, Sx surgery, PTx positional therapy, NS nerve stimulation, WL weight loss, CPAP continuous positive airway pressure.

3.4 Demographic, Polysomnographic and Questionnaire Outcomes

The mean age of patients who underwent Sx (33.2±3.0) was significantly lower than all other groups as determined by one-way ANOVA and Tukey post-hoc analysis ($F(5,57) = 5.8$, $p < .05$). There were no other significant differences in age between patients who had MAS, PTx, NS or WL.

Pre-treatment BMI was significantly greater in patients who were recommended for WL (36.6±1.7) when compared to Sx, PTx and NS ($F(5,57) = 2.9$, $p < .05$), but not MAS ($p = .17$) as measured by one-way ANOVA and Tukey post-hoc analysis.

Paired comparisons between pre-treatment and post-treatment sBP across all groups suggested a significant improvement of 6.9±3.3mmHg as measured by paired t-test ($t(18) = 2.1$, $p < .05$). Comparisons between dBP demonstrated a mean improvement of 4.8±2.5mmHg but this was not statistically significant ($t(18) = 2.0$, $p = .07$). There were no significant differences in sBP or dBP in subgroup analysis for each of MAS, Sx, PTx, WL or NS.

Pre-treatment AHI was significantly different between modalities, with median AHI highest in Sx patients and lowest in MAS patients as measured by Kruskal-Wallis test ($H(6) = 16.1$, $p = .007$). Overall AHI improved by a median 17 (13.2-27, $W = -394$, $p < .0001$) events/h and supine AHI by 31 (13-45, $W = 275$, $p < .0001$) events/h for all treatment groups when measured with Wilcoxon matched pairs signed rank test. Non-supine AHI improved by 13.6 (1-18.2) events/h ($W = -230$, $p = .0005$). Patients who had Sx had a median improvement of 26.6 (13.2-42.2) events/h in their overall AHI ($W = -166$, $p < .0003$), 33.6 (8.9-53) events/h in supine AHI ($W = -104$, $p = .005$) and 13.7 (0-28) events/h in non-supine AHI ($W = -81$, $p = .02$). Patients who had PTx had a significant improvement of 23.5 (4.1-99.1) in supine AHI only ($W = -24$, $p < .05$). No other treatment group reached a statistically significant improvement in overall, supine or non-supine AHI on subgroup analysis with Wilcoxon matched pairs signed rank test.

All treatment groups had a median improvement of 15.9 (8-29.3) events/h in ODI when measured with Wilcoxon matched pairs signed rank test ($W = -243$, $p = .001$). This was significantly improved in the Sx group by 27.5 (4.6-47.5) events/h ($W = -104$, $p = .005$). No

other subgroups demonstrated significant improvement. Lsat demonstrated a mean improvement of 5.8±1.5% for all treatments with paired t-test ($t(29)=3.9$, $p = .0005$). Lsat in the Sx group improved by 7.2±2.3% ($t(17) = 3.1$, $p = .006$), but no other subgroup analyses with paired t-test were statistically significant.

SSS significantly improved in all groups by 4.8±0.5 points as measured by paired t-test ($t(27) = 10.1$, $p < .0001$). This was consistent with improvements in subgroup analysis for Sx (5.4±0.4, $t(18) = 12.6$, $p < .0001$), PTx (4.1±0.7, $t(8) = 6.3$, $p = .0002$) and WL (5.8±1.2, $t(3) = 4.9$, $p = .02$) with paired t-test. MAS and NS were not analysed as there were 2 and 0 pairs of SSS data respectively.

ESS was also significantly improved for all groups by 3.8±1.0 points when measured with paired t-test ($t(31) = 3.9$, $p = .0005$). Paired subgroup analysis demonstrated significant improvements in Sx (4.6±1.4, $t(19) = 3.4$, $p = .003$) only. There was an improvement in mean scores in WL (6±2.2, $t(4) = 2.8$, $p = 0.05$), PT (2.3±1.2, $t(10) = 1.9$, $p = .09$) and MAS (5.3±2.3, $t(2) = 2.3$, $p = .15$) but these were not statistically significant with paired t-test. NS was not analysed as there was no paired data.

FOSQ was analysed for all groups with a mean improvement of 3.3±0.8 points by paired t-test ($t(9) = 4.0$, $p = .003$). Given this was not consistently completed post-treatment in all groups further subgroup analysis was not performed.

Criteria for successful treatment as defined in the aims were applied to pre- and post-treatment results for each of AHI, ESS and FOSQ scores and summarised in table 8.

Table 9. "Successful" treatment as defined by: (1) AHI reduction >50% AND overall AHI <20, (2) ESS reduction ≥3 and (3) FOSQ reduction ≥1. Denominators depict the available pairs of pre- and post-treatment datasets analysed.

Criteria	All	MAS	Sx	PTx	NS	WL
AHI	20/31 (64.5%)	3/4 (75%)	12/19 (63.2%)	4/7 (57.1%)	2/5 (40%)	2/3 (66.7%)
ESS	19/32 (59.4%)	1/3 (33.3%)	13/20 (65%)	6/11 (54.5%)	-	4/5 (80%)
FOSQ	7/10 (70%)	0/1 (0%)	6/7 (85.7%)	3/4 (75%)	-	2/2 (100%)

Abbreviations: AHI apnoea-hypopnoea index, ESS Epworth Sleepiness Scale, FOSQ Functional Outcomes of Sleep Questionnaire, MAS mandibular advancement splint, Sx surgery, PTx positional therapy, NS nerve stimulation, WL weight loss.

Patients who reverted to CPAP at the end of their prescribed treatment were not significantly different in terms of age ($F(5,57) = 5.8$) or BMI ($F(5,57) = 2.9$) compared to other treatment groups as measured by one-way ANOVA and Tukey post-hoc comparison ($p > .05$), nor were they different in terms of pre-treatment AHI with Kruskal-Wallis test and Dunn post hoc comparison ($H(5) = 16.1$, $p > .05$).

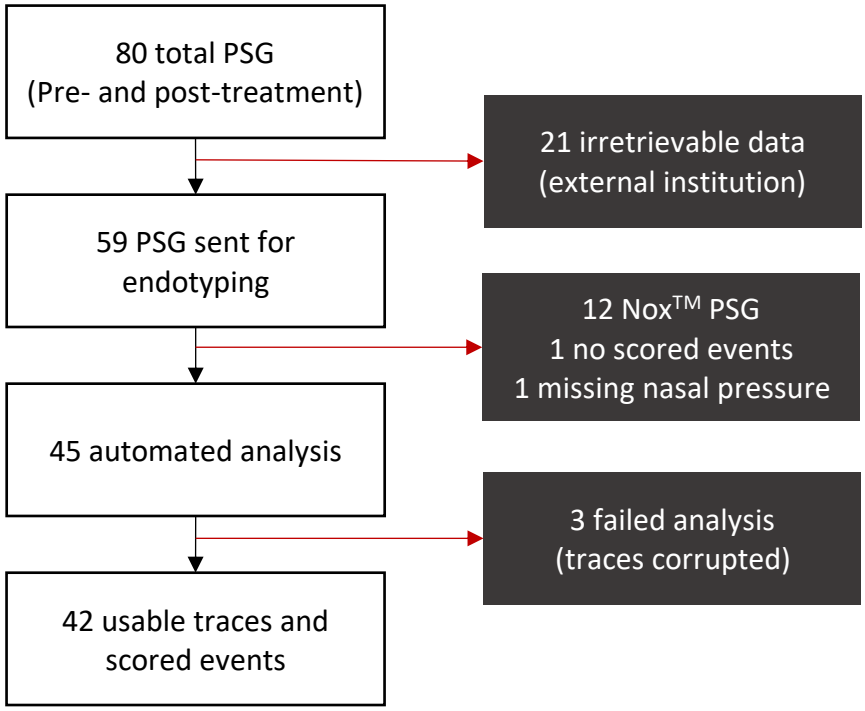
3.5 Phenotypic Traits and Baseline Characteristics

Raw data was acquired for 59/80 (73.8%) of the performed PSGs and sent for phenotyping analysis. The remaining 21 studies were irretrievable as they had been performed outside our institution and had either been archived or the original laboratory failed to respond to request for transfer of data. 45/59 (76.3%) of traces were usable for endotyping, with the remaining excluded due to missing nasal pressure traces, missing events or being a Noxturnal™ study. With the latter, current iterations of software did not allow for export of files that were compatible with phenotyping at the time of this study.

Endotyping was performed on the remaining 45 studies with computation of values for loop gain (LG_1 and LG_n), arousal threshold (ArThres), muscle compensation (V_{comp}) and airway collapsibility ($V_{passive}$ and V_{min}). Three values of each were generated according to sleep stage and position: (1) supine only NREM sleep, (2) all supine sleep and (3) all NREM sleep. In some studies endotyping analysis was attempted but failed due to inadequate obstructive events

in certain positions or embedded filters within signal traces. For purposes of determining whether each phenotype was favourable or not, these values were averaged and compared to the definitions as outlined above.

Figure 24. Raw PSG data breakdown for phenotypic analysis.



Age was compared with the four phenotypes with a significant proportional correlation between age and muscle compensation in all NREM sleep (r^2 = .21, p = .03) when measured with Pearson correlation. There were no other significant correlations found across loop gain, arousal threshold or airway collapsibility.

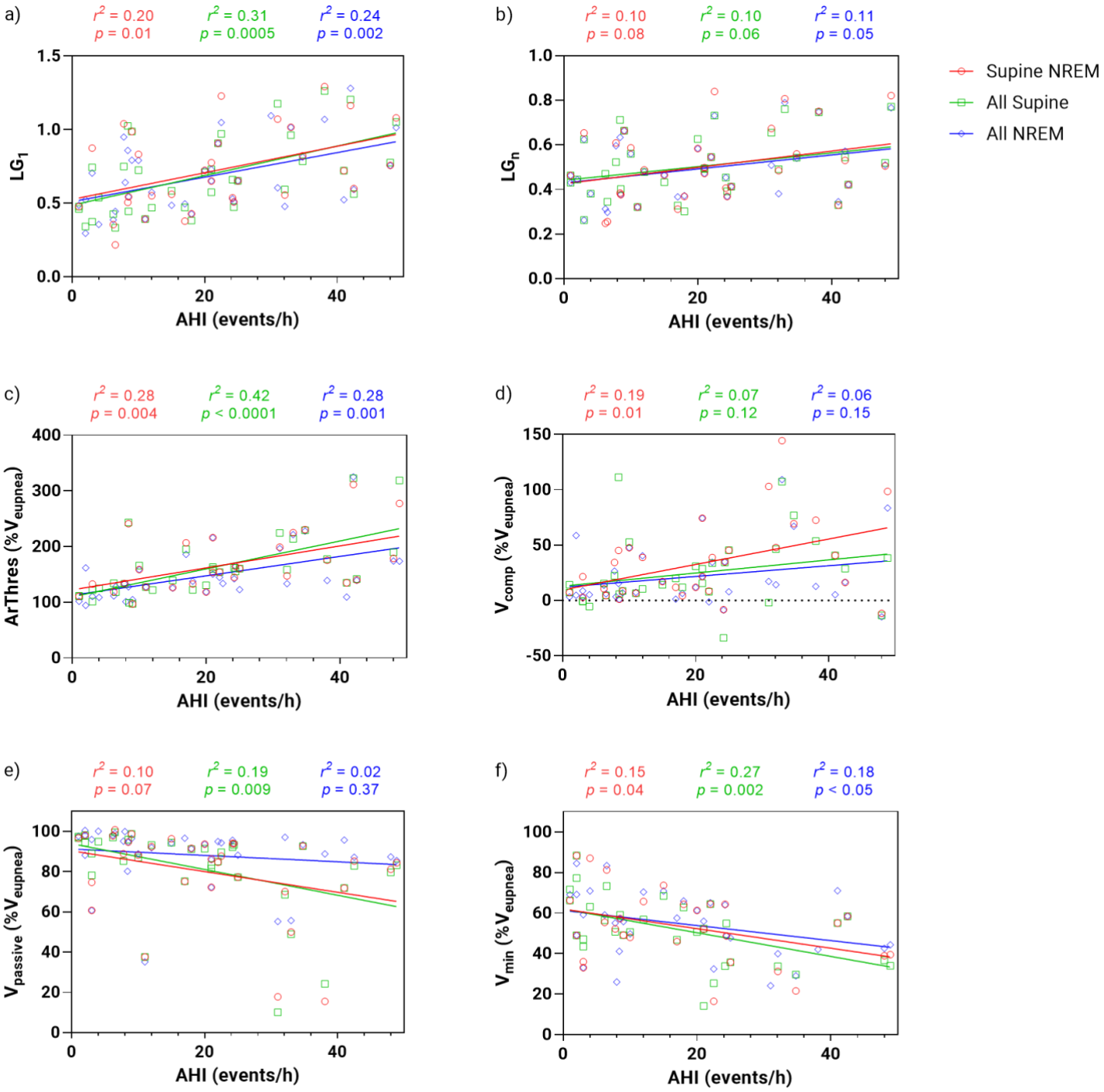
The relationship between BMI and the four phenotypes was also analysed with Pearson correlation, with no significant correlation found across all of loop gain, arousal threshold, muscle compensation and airway collapsibility.

Phenotypes were compared with their corresponding AHI with linear regression and graphed (figure 22), with relationship analysed by Pearson correlation. AHI and loop gain were proportionally related, with Pearson correlation significant for LG_1 and approaching significance for LG_n (supine NREM r^2 = .10, p = .08, all supine r^2 = .10, p = .06, all NREM r^2 = .11, p = .05). There was a proportional relationship between AHI and arousal threshold that

was significant. AHI and muscle compensation were significantly proportionally correlated during supine NREM, and approached significance during other analysed sleep periods (all supine sleep r^2 = .07, p = .12, all NREM sleep r^2 = .06, p = .15). Airway collapsibility was significantly inversely proportional with AHI when measured with V_{min}. When measured with $V_{passive}$, this was significant during all supine sleep and approached significance during supine NREM sleep (r^2 = .11, p = .07) but was not significant during all NREM sleep (r^2 = .02, p = .37).

The presence of tonsillar collapse on examination was found to be associated with pre-treatment V_{min} <42.7 $\%V_{eupnea}$ with logistic regression ($\beta 0$ = 3.6, $\beta 1$ = -0.08, p <.05). When analysed for $V_{passive}$, this was not significant ($\beta 0$ = -0.8, $\beta 1$ = -0.003, p = .93). Likewise, presence of nasal pathology had no significant relationship to $V_{passive}$ ($\beta 0$ = 1.2, $\beta 1$ = -0.01, p =.6) or V_{min} ($\beta 0$ = 1.3, $\beta 1$ =-0.02, p = .6).

Figure 25. Linear comparisons between AHI (all PSG) and phenotypic traits. Loop gain is represented in a) and b), arousal threshold in c), muscle compensation in d) and airway collapsibility in e) and f). Supine NREM data points are represented in red, all supine data points are in green and all NREM data points are in blue.



3.6 Phenotypic Traits and Treatment

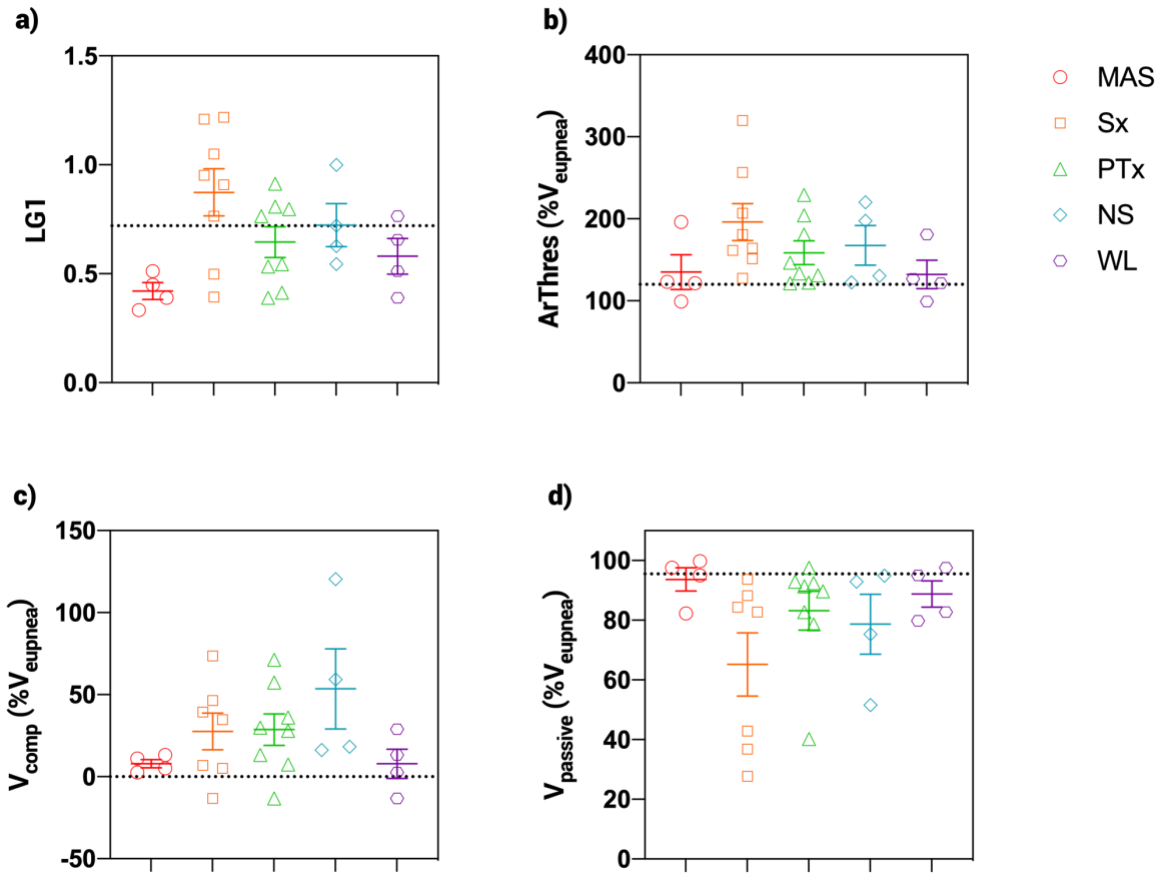
Overall values for each phenotypic measurement are summarised in table 9. Patients generally had **unfavourable** loop gain and airway collapsibility, but **protective** arousal threshold and muscle compensation. Median and mean arousal threshold was significantly lower in treated patients as measured with unpaired t-test (supine NREM, $t(26) = 2.1$, $p = .04$) and Mann Whitney U test (all supine, $U = 75$, $p = .01$, all NREM, $U = 92$, $p = .02$). Loop gain was variable in its relation to treatment phase, muscle compensation was reduced in treated patients compared to non-treated patients and mean airway collapsibility was higher in treated patients compared to non-treated patients but these were not significant differences.

Table 10. Phenotypes compared between pre-and post-treatment cohorts. Values are expressed as mean±SEM for normally distributed or median (interquartile range) for non-normally distributed data as measured by Shapiro-Wilk test. p values are calculated from unpaired t tests or Mann-Whitney U tests.

Phenotype, unit	Pre-treatment (23)	Post-treatment (19)	*p*
LG_1			
Supine NREM	0.71±0.06	0.77±0.08	.54
All supine	0.72±0.06	0.63±0.06	.36
All NREM	0.69±0.05	0.57±0.07	.16
LG_n			
Supine NREM	0.49±0.03	0.55±0.05	.35
All supine	0.51±0.03	0.49±0.04	.65
All NREM	0.49±0.03	0.47±0.04	.63
ArThres, $\%V_{eupnea}$			
Supine NREM	181.1±12.5	137.3±8.1	.04*
All supine	155.4(130.5-213.7)	122(99.1-161.1)	.01*
All NREM	139.2(127.7-191.3)	116.7(101.3-148.4)	.02*
V_{comp}, $\%V_{eupnea}$			
Supine NREM	39.5±8.5	20.2±5.9	.16
All supine	21.2(7.6-42.2)	8.0(-0.7-30.0)	.08
All NREM	14.0(5.9-36.2)	5.2(3.1-19.1)	.14
$V_{passive}$, $\%V_{eupnea}$			
Supine NREM	84.5 (65.1-93.7)	87.7(77.2-96.7)	.28
All supine	84.1(63.7-93.2)	90.9(83.2-96.8)	.07
All NREM	93.5(84.2-95.2)	95.8(87.9-99.9)	.13
V_{min}, $\%V_{eupnea}$			
Supine NREM	50.4±4.8	52.6±5.7	.77
All supine	49.9±3.8	54.1±4.4	.47
All NREM	54.1±3.6	55.7±5.4	.81

Pre-treatment phenotypes were compared to each other with one-way ANOVA between loop gain, arousal threshold, muscle compensation and airway collapsibility subgroups. There were significant differences in loop gain (LG_1, $F(4,23) = 3.1$, $p = .03$, LG_n, $F(4,23) = 3.3$, $p = .03$) between treatment subgroups identified (figure 23, supplementary material table A). In pre-treatment patients who had PTx, V_{min} was significantly lower in all supine by 5.0±1.7 $\%V_{eupnea}$ ($t(7) = 3.0$, $p = .02$) and supine NREM sleep by 4.6±1.0 $\%V_{eupnea}$ ($t(6) = 4.8$, $p = .003$) when compared to all NREM sleep with paired t-test, consistent with improved airway collapsibility during non-supine sleep. There were no other significant differences between sleep stage or position identified within $V_{passive}$, ArThres or loop gain phenotyping for patients treated with PTx.

Figure 26. Pre-treatment phenotypic traits (averaged from supine NREM, all supine and all NREM sleep) per treatment group. Dotted line represents cut-off value for favourable traits (LG1 <0.72, ArThres >120%, Vcomp >0%, Vpassive >95.5%). Lines and error bars are mean±SEM.



Post-treatment phenotypes were also compared to each other with one-way ANOVA and Tukey post-hoc analysis, although these were not significantly different for any of loop gain,

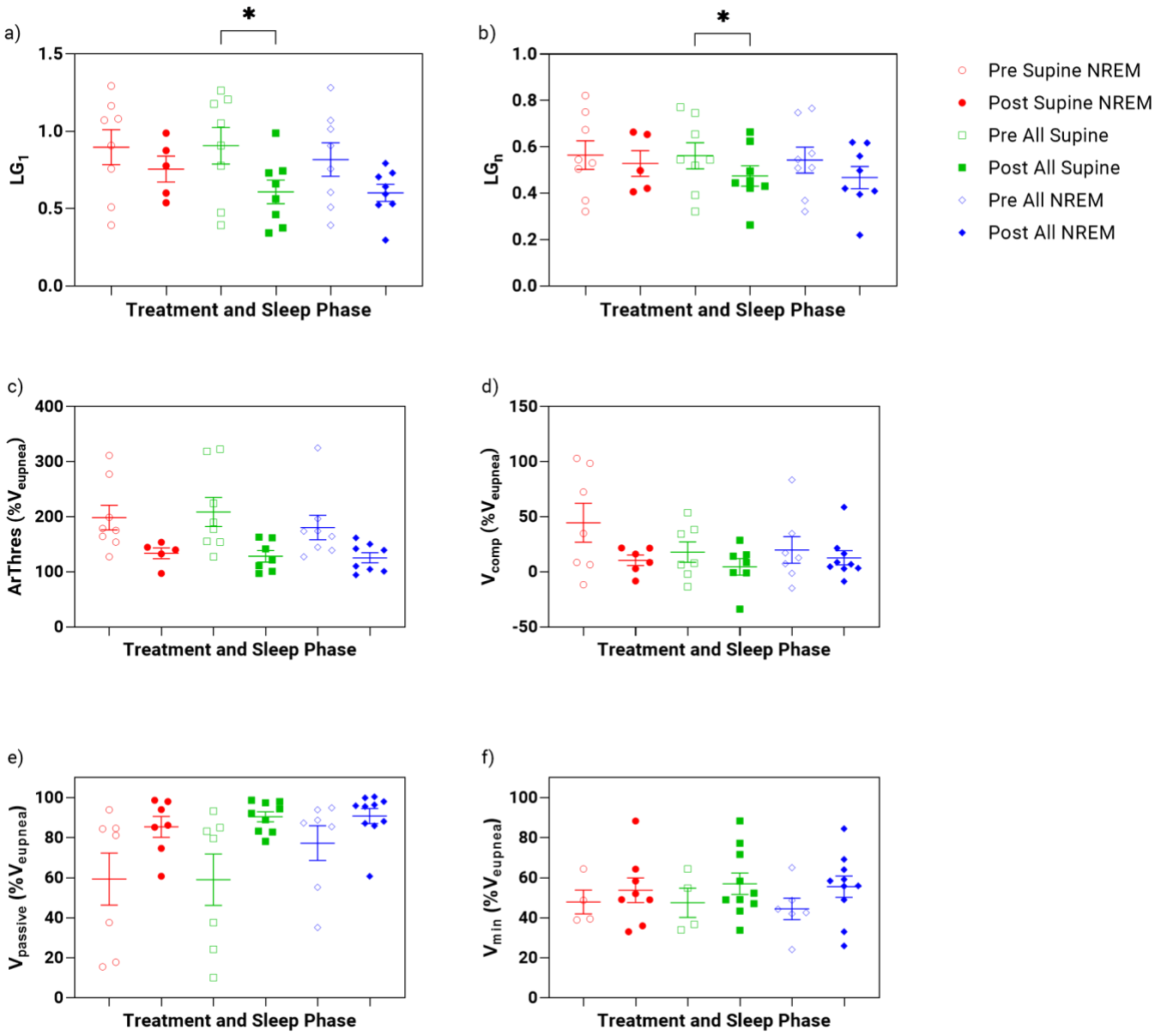
arousal threshold, muscle compensation and airway collapsibility (supplementary material figure A).

Paired pre- and post-treatment analysis was also performed. As a result of loss of usable traces as outlined in the previous section, there were only 9 complete pairs of PSGs that had undergone phenotypic analysis (5 Sx, 4 NS).

Paired subgroup analysis of Sx (figure 24) revealed significant improvements in loop gain during all supine sleep, manifest in both LG_1 with -0.46±0.13 ($t(4) = 3.5$, $p = .03$) as well as LG_n with -0.19±0.05 ($t(4) = 3.9$, $p = .02$) when measured with paired t-tests. This was not significant when treatment phases were compared during all NREM or supine NREM sleep. Muscle compensation and arousal threshold were not significantly impacted by surgery with paired analysis, although post-operative patients as a cohort had significantly lower ArThres than pre-operative patients by 80.5±30.0 $\%V_{eupnea}$ when measured with unpaired t-test ($t(13) = 2.7$, $p = .02$). Interestingly, $V_{passive}$ and V_{min} did not significantly improve with paired t-tests, although post-operative patients had a significantly higher $V_{passive}$ on average by 31.4±11.6 $\%V_{eupnea}$ compared with pre-operative patients as measured by unpaired t-test ($t(14) = 2.7$, $p = .02$).

Paired subgroup analysis of NS (supplementary material figure B) did not reveal any significant improvements in any of loop gain, muscle compensation, arousal threshold or airway collapsibility when measured with paired t-tests. It should be noted that post-treatment PSG sent for nerve stimulator patients were taken at the 3-month mark post-recruitment, and further titration of all nerve stimulator devices was required as per the manufacturer's clinical trial protocol before treatment was considered complete.

Figure 27. Group comparisons between pre- and post-treatment phenotypes in Sx patients. Loop gain is represented in a) and b), arousal threshold in c), muscle compensation in d), airway collapsibility in e) and f). Supine NREM data points are represented in red, all supine data points are in green and all NREM data points are in blue.



Contingency analysis was performed comparing pre-treatment loop gain with treatment success as measured by ESS. Patients with low loop gain pre-treatment had a higher chance of treatment success than those with high loop gain but this was not significant as measured by Fisher's exact test (7/8 vs 4/9, p = .13). Contingency analysis could not be performed for any other phenotypic traits for ESS or AHI, particularly because of the skewed population of phenotypes in the Sx and NS groups (high arousal threshold, high airway collapsibility, high

muscle compensation). Only 3 paired FOSQ responses were available and precluded contingency analysis.

To further elucidate the relationship between pre-treatment phenotypes and treatment success, bivariate logistic regression was performed for each phenotypic measurement. Success as defined by an AHI reduction of >50% and overall AHI <20 was not significantly associated with any of LG_1 (p = .98), LG_n (p = .069), ArThres (p =.47), V_{comp} (p = .94) $V_{passive}$ (p = .68) or V_{min} (p = .97).

Success as defined by ESS reduction ≥3 and total ESS <10 was analysed in a similar fashion. Low LG_n <0.64 was significantly associated with successful improvement in ESS ($\beta 0$ = 5.7, $\beta 1$ = -8.9, p = .03). LG_1 <1.05 tended to improve ESS, although this did not reach significance ($\beta 0$ = 4.0, $\beta 1$ = -3.8, p = .06). Patients with lower ArThres <222.2 $\%V_{eupnea}$ also had success in reducing ESS ($\beta 0$ = 7.1, $\beta 1$ = -.03, p = .004). Lower V_{comp} <55.0% V_{eupnea} (including negative V_{comp}) was also associated with improved ESS ($\beta 0$ = 3.3, $\beta 1$ = 0.06, p = .01). Pre-treatment $V_{passive}$ did not significantly impact ESS (p = .85), but V_{min} > 35.7 $\%V_{eupnea}$ approached significance with ESS success ($\beta 0$ = -4.3, $\beta 1$ = 0.12, p = .06).

4. Discussion

4.1 Key Findings

The correlation between clinical severity of OSA and phenotypic traits was consistent with published and expected trends – with higher loop gain, high arousal threshold and increased airway collapsibility directly proportional to increasing severity of OSA as measured by AHI[24]. When utilising published cut-offs for the four phenotypic traits, this cohort tended to have the protective traits of high arousal threshold and normal muscle compensation. Loop gain was evenly distributed, while nearly all patients had highly collapsible airways.

Patients who underwent Sx and NS had high loop gain compared with patients who had MAS, PTx or WL. Loop gain in supine sleep was also improved after surgical treatment, which is in contrast to previous data in the literature that suggests high loop gain patients may not benefit from anatomical intervention and specifically upper airway surgery[199]. Patients who were treated with PTx had higher airway collapsibility during supine sleep. Trends toward lower loop gain, lower muscle compensation and less collapsible airways were observed in patients who had MAS/WL.

Decreased sleepiness after treatment was linked to patients who had non-anatomical phenotypical traits of lower loop gain, lower arousal threshold and lower muscle compensation. Airway collapse did not have a significant influence on sleepiness.

4.2 Clinical Trends and Comparison to Literature

Patient demographics were comparable to the published literature, with similarities to international and Australian data on the prevalence of OSA in gender ratio (73.5% males), age (mean 44) and BMI (mean 31.1)[1]. The rate of treatment success within our study across all modalities was similar to published literature values (59.4% for ESS, 64.5% for AHI)[195, 196] although improvements were seen across a wide range of clinical criteria including snoring (as measured by SSS), supine AHI, AI, HI, ODI and Lsat that did not neatly fit into the literature definition of “success”.

As expected, a large proportion of patients had highly collapsible airways. Similar to published literature, more severe AHI was associated with higher arousal threshold[193] which reduced after treatment. Loop gain was normally distributed (with both measures of LG_1 and LG_n) for both pre- and post-treatment patients. There was a trend towards reduced muscle compensation with treatment, which should be expected with an increase in $V_{passive}$ and improvement in airway collapsibility. Our figures for muscle compensation seemed to be higher on average to published literature[200], but phenotypic analysis did not specifically isolate REM sleep which would be expected to demonstrate lower V_{comp} values.

In comparison to Eckert et al[168] figures on phenotypic trait prevalence in a general population of patients with OSA, there were few individual patients with "pathological" low arousal threshold (5.8% vs 37%) and muscle compensation (5.8% vs 37%), and a large amount of patients with "pathological" high loop gain (52.9% vs. 36%). Based on the above similarities and differences, our subset of patients may reflect the phenotypic traits expected in a community cohort of patients who present for salvage treatment of OSA.

Collapsibility of the airway was assessed with both $V_{passive}$ and V_{min}, despite there being no pre-defined cut-offs for what a high or a low V_{min} may be. These were chosen because V_{min} theoretically should serve as a marker of complete airway collapse and may be a more accurate representation of P_{CRIT} than $V_{passive}$. This theory is supported by the increased sensitivity V_{min} had to change in AHI than $V_{passive}$ in each of the analysed stages of sleep. Notably, patients with tonsillar-generated collapse on Modified Müller manoeuvre and Woodson hypotonic method tended to have lower V_{min} than those without, which suggests that tonsillar tissue may play a significant role in contributing to the point of critical airway collapse. The impact of tonsillar tissue and collapse is a significant factor in the pathophysiology of paediatric OSA where adenotonsillectomy is considered first-line management[109]. As expected, presence of nasal pathology did not have a significant impact on V_{min} or $V_{passive}$. This is consistent with accepted dogma that nasal treatment is an adjunct/facilitatory pathway only.

The largest treatment group within this cohort were patients who underwent Sx. Surgical patients tended to be younger in comparison to the rest of the cohort, which would suggest that loop gain would play a greater role in the pathogenesis of their OSA compared to older patients who are more susceptible to airway collapsibility[201]. This seemed to correspond with our findings, in that a large proportion of patients had high loop gain pre-operatively. Importantly, our data contrasts with published literature that asserts patients with high loop gain (>0.50)[199] have a higher chance of "surgical failure" using an identical definition of treatment "success". Only 1 patient had a loop gain <0.5, with nearly all remaining patients above the cut-off of 0.72, which was defined as per the literature to be **unfavourable loop gain**. This data is more consistent with a recent study by Li et al[202], although the cohort they analysed was of a different ethnicity to those in our study and may not be directly comparable to a Caucasian population[200]. While loop gain is classically understood to be a non-anatomical phenotype, upper airway surgery may play an underappreciated yet significant role in stabilising the anatomical contributions to fluctuations in ventilatory stability.

Although the breakdown of phenotypic data was not provided for patients in non-supine sleep, patients who had supine dominant OSA and were treated with PTx had lower V_{min} during supine sleep compared to a combination of all sleep positions. This supports the notion that these patients primarily have anatomic vulnerability depending on their sleep position, with the other non-anatomical phenotypes seemingly having little relation to AHI in these patients.

Patients selected for treatment with MAS tended to have lower loop gain, muscle compensation, arousal threshold and more stable airway collapsibility as measured by $V_{passive}$. Although this was not significantly different to other treatments due to the small sample size of MAS patients, it is consistent with literature that describes improved efficacy of MAS with the above four phenotypic traits[165].

BMI was demonstrated in our data to have no significant association with AHI or with any of the phenotypic traits. Notably all patients who were recommended WL had similar phenotypic traits to those who were treated with MAS, including lower muscle compensation,

which is postulated to be a key factor in the pathogenesis of OSA for obese patients[203]. However it is unknown whether treatment with WL would mitigate that trait.

Finally, patients who had favourable non-anatomic phenotypic traits (lower loop gain, arousal threshold and muscle compensation) tended to have a higher chance of success in treating sleepiness symptoms regardless of treatment modality, as measured by ESS score, while airway collapsibility was not correlatable. In addition, there was no clear link to any phenotypic trait in treating AHI "successfully". This complements the SAGIC consortium findings[159]; treatment of sleepiness may not be as simple as reducing AHI, and yet again demonstrates the complex pathophysiology of OSA. This highlights a potential role for phenotyping in pre-treatment workup of patients: it may be useful for clinicians to adequately inform patients about expected outcomes from a symptom perspective (in addition to the known cardiovascular and neurocognitive benefits associated with ODI or AHI reduction).

4.3 Strengths

This is the first study to prospectively analyse the prevalence of phenotypic traits in a routine clinical cohort of patients undergoing all salvage treatments for OSA. As a result of a prospective study design, selection bias was minimised. All patient management was undertaken under the combined supervision of a respiratory physician and ENT surgeon, each with subspeciality fellowship training in sleep medicine. Both were blinded to patient phenotypic traits, thereby reducing performance bias. Endotyping was performed by an assessor who was blinded to phase of patient treatment and modality, serving to reduce detection bias.

4.4 Limitations

Conclusions drawn from these results must be guarded given the limited data from phenotypic analysis available. A reasonable proportion of patients (16.3%) who failed to attend routine clinical follow-up were treated non-surgically, and therefore a degree of attrition bias is notable. Our study was also impacted by the unprecedented advent of the SARS-CoV-2 pandemic, which caused repercussions with delays to routine clinical care and

limiting clinicians to preferentially follow-up patients with more urgent conditions. This may have reduced recruitment of patients with mild-moderate OSA, who tender to be better candidates for non-surgical management. The pandemic also caused complete cessation of patient recruitment, restricted the sleep laboratory from performing PSG and delayed phenotypic analysis with our collaborators in Melbourne for a period of at least 6 months. Unfortunately, extension of recruitment during a pandemic with an uncertain endpoint was not deemed to be appropriate.

A large proportion of patients referred from out of the area resulted in PSG data that was external to our sleep laboratory, and thus caused difficulties with data acquisition and software compatibility issues. Turnover and a lack of handover in local sleep technicians at our own laboratory impeded timely re-scoring of PSG data to the stricter standards required by the endotyping team. The lack of compatibility of Nox^{TM} PSG software with data sent for endotyping was not anticipated and also precluded analysis of a proportion of patients, however work is currently being undertaken to generate an algorithm to allow endotyping compatibility with Nox^{TM} PSG. In future, a dedicated local sleep research laboratory with staff specifically trained in endotyping would greatly contribute to consistent and usable PSG data in this increasingly important field of sleep medicine.

As expected, the majority of patients who were enrolled in this study were treated with upper airway surgery by virtue of the Illawarra ENT Head and Neck clinic being a quaternary referral centre for sleep surgery. As such, the majority of "polysomnographic success" was driven by surgical outcomes. Regardless, the impact of this on selection bias is likely limited, given the multidisciplinary nature of patient recruitment and its effectiveness in highlighting unsuitable candidates for surgery[117].

There were several patients who were prescribed MAS who had incomplete datasets due to failure to attend follow-up or proceed with treatment. In addition, post-treatment PSGs were not indicated for most of these patients, given the majority only had mild-moderate OSA. Likewise, compliance with WL treatment was variable, with several patients not opting to follow-up with dietician or exercise physiologist referrals.

Specific mention must be made about patients who had NS treatment, as they were simultaneously enrolled in a concurrent clinical trial with permission from the trial investigators. As such, their outcomes are considered exploratory and are not for publication outside of this thesis.

4.5 Future Directions

These results demonstrate that current clinical paradigms in selecting patients for salvage OSA treatment appear to be effective at distinguishing those with favourable phenotypes. The relationship between loop gain and surgery warrants further exploration in a larger cohort given our data contrasts with published literature.

This study highlights a need for more prospective clinical data on the prevalence of phenotypic traits in patients who undergo salvage OSA treatment after CPAP failure. While our institution had a referral bias of patients who opt for surgical management, a multicentre study with collaboration of multidisciplinary sleep clinics would be the next logical step in providing a thorough overview of the prevalence and associations of phenotypic traits with patient treatment success.

Our data demonstrates that phenotypic traits can be determined outside of major sleep research centres and have clinical relevance. As the process of endotyping is increasingly automated and can now be performed non-invasively, it is possible that it will become easier for sleep laboratories to incorporate phenotypic trait analysis as part of their diagnostic algorithm.

With recently published randomised controlled trial data demonstrating the effectiveness of upper airway surgery in treating OSA using a reproducible combined palatal and tongue procedure (modified UPPP and coblation channelling tongue)[20], there is a renewed interest in surgical management of OSA. It is therefore increasingly important for ENT surgeons interested in practicing in the field of sleep to understand the impact of phenotypic traits in OSA to optimally select suitable candidates for sleep surgery.

5. Conclusion

As the complex pathophysiology of OSA is unravelled, it is evident that a multifaceted approach is required to manage the disease. While some centres are already incorporating a multidisciplinary team approach and directing management according to individual patient anatomy and PSG characteristics[117], it is not the current standard of practice. This is going to become increasingly relevant as the focus shifts to a P4 medicine approach to managing OSA and phenotyping becomes widely available.

This study has provided some clinical context and has complemented the paucity of literature around these newly defined phenotypes of airway collapsibility, arousal threshold, loop gain and muscle responsiveness in a laboratory setting. There remains a gap in our knowledge in the real-world application of phenotyping to current treatment paradigms, and thus more research needs to be performed in community cohorts undergoing best standard of care to further investigate the clinical utility and relevance of phenotyping.

References

1. Benjafield AV, Ayas NT, Eastwood PR, Heinzer R, Ip MSM, Morrell MJ, et al. Estimation of the global prevalence and burden of obstructive sleep apnoea: a literature-based analysis. The Lancet Respiratory Medicine. 2019;7(8):687-98.
2. Kainulainen S, Töyräs J, Oksenberg A, Korkalainen H, Sefa S, Kulkas A, et al. Severity of desaturations reflects OSA-related daytime sleepiness better than AHI. Journal of Clinical Sleep Medicine. 2019;15(8):1135-42.
3. Young T, Palta M, Dempsey J, Peppard PE, Nieto FJ, Hla KM. Burden of sleep apnea: rationale, design, and major findings of the Wisconsin Sleep Cohort study. WMJ: official publication of the State Medical Society of Wisconsin. 2009;108(5):246.
4. Rangel ÂJdA, Barros VdM, Seraidarian PI. Snoring and obstructive sleep apnea syndrome: a reflection on the role of dentistry in the current scientific scenario. Dental Press Journal of Orthodontics. 2012;17:58-63.
5. Quintana-Gallego E, Carmona-Bernal C, Capote F, Sánchez-Armengol Á, Botebol-Benhamou G, Polo-Padillo J, et al. Gender differences in obstructive sleep apnea syndrome: a clinical study of 1166 patients. Respiratory medicine. 2004;98(10):984-9.
6. Kushida CA, Littner MR, Morgenthaler T, Alessi CA, Bailey D, Coleman Jr J, et al. Practice parameters for the indications for polysomnography and related procedures: an update for 2005. Sleep. 2005;28(4):499-523.
7. Sleep-related breathing disorders in adults: recommendations for syndrome definition and measurement techniques in clinical research. Sleep. 1999;22:667-89.
8. Qaseem A, Wilt TJ, Weinberger SE, Hanania NA, Criner G, van der Molen T, et al. Diagnosis and management of stable chronic obstructive pulmonary disease: a clinical practice guideline update from the American College of Physicians, American College of Chest Physicians, American Thoracic Society, and European Respiratory Society. Annals of internal medicine. 2011;155(3):179-91.
9. Weaver TE, Grunstein RR. Adherence to continuous positive airway pressure therapy: the challenge to effective treatment. Proceedings of the American Thoracic Society. 2008;5(2):173-8.
10. Mehta A, Qian J, Petocz P, Darendeliler MA, Cistulli PA. A randomized, controlled study of a mandibular advancement splint for obstructive sleep apnea. American journal of respiratory and critical care medicine. 2001;163(6):1457-61.
11. MacKay SG. Nasal Obstruction and Surgical Effects on OSA in Adults. Advanced Surgical Techniques in Snoring and Obstructive Sleep Apnea. 2013:97.
12. Camacho M, Riaz M, Capasso R, Ruoff CM, Guilleminault C, Kushida CA, et al. The effect of nasal surgery on continuous positive airway pressure device use and therapeutic treatment pressures: a systematic review and meta-analysis. Sleep. 2015;38(2):279-86.
13. MacKay SG, Carney AS, Woods C, Antic N, McEvoy RD, Chia M, et al. Modified uvulopalatopharyngoplasty and coblation channeling of the tongue for obstructive sleep apnea: a multi-centre Australian trial. Journal of Clinical Sleep Medicine. 2013;9(02):117-24.
14. Rosvall BR, Chin CJ. Is uvulopalatopharyngoplasty effective in obstructive sleep apnea? The Laryngoscope. 2017;127(10):2201-2.

15. Woodson BT, Robinson S, Lim HJ. Transpalatal advancement pharyngoplasty outcomes compared with uvulopalatopharygoplasty. Otolaryngology—Head and Neck Surgery. 2005;133(2):211-7.
16. Omur M, Ozturan D, Elez F, Unver C, Derman S. Tongue base suspension combined with UPPP in severe OSA patients. Otolaryngology—Head and Neck Surgery. 2005;133(2):218-23.
17. Woodson BT. A tongue suspension suture for obstructive sleep apnea and snorers. Otolaryngology-Head and Neck Surgery. 2001;124(3):297-303.
18. Gunawardena I, Robinson S, MacKay S, Woods CM, Choo J, Esterman A, et al. Submucosal lingualplasty for adult obstructive sleep apnea. Otolaryngology--Head and Neck Surgery. 2013;148(1):157-65.
19. MacKay S, Jefferson N, Grundy L, Lewis R. Coblation-assisted Lewis and MacKay operation (CobLAMO): new technique for tongue reduction in sleep apnoea surgery. The Journal of Laryngology & Otology. 2013;127(12):1222-5.
20. MacKay S, Carney AS, Catcheside PG, Chai-Coetzer CL, Chia M, Cistulli PA, et al. Effect of multilevel upper airway surgery vs medical management on the apnea-hypopnea index and patient-reported daytime sleepiness among patients with moderate or severe obstructive sleep apnea: the SAMS randomized clinical trial. JAMA. 2020;324(12):1168-79.
21. Edwards BA, Redline S, Sands SA, Owens RL. More than the Sum of the Respiratory Events: Personalized Medicine Approaches for Obstructive Sleep Apnea. American journal of respiratory and critical care medicine. 2019(ja).
22. Eckert DJ. Phenotypic approaches to obstructive sleep apnoea–new pathways for targeted therapy. Sleep medicine reviews. 2018;37:45-59.
23. Kitipornchai L, Jones A, MacKay SG. Patient Phenotyping in OSA. Current Otorhinolaryngology Reports. 2019:1-8.
24. Carberry JC, Amatoury J, Eckert DJ. Personalized management approach for OSA. Chest. 2018;153(3):744-55.
25. McMinn RM. Last's anatomy-regional and applied: London: Churchill Livingstone, 1994; 1994.
26. Olszewska E, Woodson BT. Palatal anatomy for sleep apnea surgery. Laryngoscope Investigative Otolaryngology. 2019.
27. Gottlieb DJ, Punjabi NM. Diagnosis and Management of Obstructive Sleep Apnea: A Review. Jama. 2020;323(14):1389-400.
28. Soares D, Folbe AJ, Yoo G, Badr MS, Rowley JA, Lin H-S. Drug-induced sleep endoscopy vs awake Müller's maneuver in the diagnosis of severe upper airway obstruction. Otolaryngology--Head and Neck Surgery. 2013;148(1):151-6.
29. Schwab RJ, Gefter WB, Pack AI, Hoffman EA. Dynamic imaging of the upper airway during respiration in normal subjects. Journal of Applied Physiology. 1993;74(4):1504-14.
30. Ciscar M, Juan G, Martinez V, Ramon M, Lloret T, Minguez J, et al. Magnetic resonance imaging of the pharynx in OSA patients and healthy subjects. European Respiratory Journal. 2001;17(1):79-86.
31. Li Y, Lin N, Ye J, Chang Q, Han D, Sperry A. Upper airway fat tissue distribution in subjects with obstructive sleep apnea and its effect on retropalatal mechanical loads. Respiratory care. 2012;57(7):1098-105.
32. Abramson Z, Susarla S, August M, Troulis M, Kaban L. Three-dimensional computed tomographic analysis of airway anatomy in patients with obstructive sleep apnea. Journal of Oral and Maxillofacial Surgery. 2010;68(2):354-62.

33. Vgontzas AN. Does obesity play a major role in the pathogenesis of sleep apnoea and its associated manifestations via inflammation, visceral adiposity, and insulin resistance? Archives of physiology and biochemistry. 2008;114(4):211-23.
34. Sutherland K, Lee RW, Phillips CL, Dungan G, Yee BJ, Magnussen JS, et al. Effect of weight loss on upper airway size and facial fat in men with obstructive sleep apnoea. Thorax. 2011;66(9):797-803.
35. Kim AM, Keenan BT, Jackson N, Chan EL, Staley B, Poptani H, et al. Tongue fat and its relationship to obstructive sleep apnea. Sleep. 2014;37(10):1639-48.
36. Joosten SA, Hamilton GS, Naughton MT. Impact of Weight Loss Management in OSA. Chest. 2017;152(1):194-203.
37. Dixon JB, Schachter LM, O'Brien PE, Jones K, Grima M, Lambert G, et al. Surgical vs Conventional Therapy for Weight Loss Treatment of Obstructive Sleep Apnea: A Randomized Controlled Trial. JAMA. 2012;308(11):1142-9.
38. Joosten SA, O'Driscoll DM, Berger PJ, Hamilton GS. Supine position related obstructive sleep apnea in adults: pathogenesis and treatment. Sleep medicine reviews. 2014;18(1):7-17.
39. Battagel J, L'estrange P. The cephalometric morphology of patients with obstructive sleep apnoea (OSA). European journal of orthodontics. 1996;18(6):557-69.
40. Yucel A, Unlu M, Haktanir A, Acar M, Fidan F. Evaluation of the upper airway cross-sectional area changes in different degrees of severity of obstructive sleep apnea syndrome: cephalometric and dynamic CT study. American journal of neuroradiology. 2005;26(10):2624-9.
41. Guilleminault C, Partinen M, Hollman K, Powell N, Stoohs R. Familial aggregates in obstructive sleep apnea syndrome. Chest. 1995;107(6):1545-51.
42. Riley R, Guilleminault C, Herran J, Powell N. Cephalometric analyses and flow-volume loops in obstructive sleep apnea patients. Sleep. 1983;6(4):303-11.
43. Lee RW, Sutherland K, Chan AS, Zeng B, Grunstein RR, Darendeliler MA, et al. Relationship between surface facial dimensions and upper airway structures in obstructive sleep apnea. Sleep. 2010;33(9):1249-54.
44. Genta PR, Schorr F, Eckert DJ, Gebrim E, Kayamori F, Moriya HT, et al. Upper airway collapsibility is associated with obesity and hyoid position. Sleep. 2014;37(10):1673-8.
45. Bixler EO, Vgontzas AN, Lin H-M, Ten Have T, Rein J, Vela-Bueno A, et al. Prevalence of sleep-disordered breathing in women: effects of gender. American journal of respiratory and critical care medicine. 2001;163(3):608-13.
46. Shepertycky MR, Banno K, Kryger MH. Differences between men and women in the clinical presentation of patients diagnosed with obstructive sleep apnea syndrome. Sleep. 2005;28(3):309-14.
47. Malhotra A, Huang Y, Fogel RB, Pillar G, Edwards JK, Kikinis R, et al. The male predisposition to pharyngeal collapse: importance of airway length. American journal of respiratory and critical care medicine. 2002;166(10):1388-95.
48. Block A, Wynne JW, Boysen PG. Sleep-disordered breathing and nocturnal oxygen desaturation in postmenopausal women. The American journal of medicine. 1980;69(1):75-9.
49. Kripke D, Ancoli-Israel S, Klauber M, Wingard D, Mason W, Mullaney D. Prevalence of sleep-disordered breathing in ages 40–64 years: a population-based survey. Sleep. 1997;20(1):65-76.

50. Villaneuva ATC, Buchanan PR, Yee BJ, Grunstein RR. Ethnicity and obstructive sleep apnoea. Sleep medicine reviews. 2005;9(6):419-36.
51. Lee RW, Vasudavan S, Hui DS, Prvan T, Petocz P, Darendeliler MA, et al. Differences in craniofacial structures and obesity in Caucasian and Chinese patients with obstructive sleep apnea. Sleep. 2010;33(8):1075-80.
52. Sutherland K, Lee RW, Cistulli PA. Obesity and craniofacial structure as risk factors for obstructive sleep apnoea: impact of ethnicity. Respirology. 2012;17(2):213-22.
53. Edwards BA, O'Driscoll DM, Ali A, Jordan AS, Trinder J, Malhotra A, editors. Aging and sleep: physiology and pathophysiology. Seminars in respiratory and critical care medicine; 2010: © Thieme Medical Publishers.
54. Pham LV, Schwartz AR. The pathogenesis of obstructive sleep apnea. Journal of thoracic disease. 2015;7(8):1358.
55. Gleadhill IC, Schwartz AR, Schubert N, Wise RA, Permutt S, Smith PL. Upper airway collapsibility in snorers and in patients with obstructive hypopnea and apnea. American Review of Respiratory Disease. 1991;143(6):1300-3.
56. Schwartz AR, Smith PL, Wise RA, Gold AR, Permutt S. Induction of upper airway occlusion in sleeping individuals with subatmospheric nasal pressure. Journal of Applied Physiology. 1988;64(2):535-42.
57. Smith PL, Wise RA, Gold AR, Schwartz AR, Permutt S. Upper airway pressure-flow relationships in obstructive sleep apnea. Journal of Applied Physiology. 1988;64(2):789-95.
58. Meurice J-C, Marc I, Series F. Effects of naloxone on upper airway collapsibility in normal sleeping subjects. Thorax. 1996;51(8):851-2.
59. Meurice J-C, Marc I, Carrier G, Sériès F. Effects of mouth opening on upper airway collapsibility in normal sleeping subjects. American journal of respiratory and critical care medicine. 1996;153(1):255-9.
60. Issa FG, Sullivan CE. Upper airway closing pressures in obstructive sleep apnea. Journal of Applied Physiology. 1984;57(2):520-7.
61. Gold AR, Marcus CL, Dipalo F, Gold MS. Upper airway collapsibility during sleep in upper airway resistance syndrome. Chest. 2002;121(5):1531-40.
62. Philip-Joet F, Marc I, Series F. Effects of genioglossal response to negative airway pressure on upper airway collapsibility during sleep. Journal of Applied Physiology. 1996;80(5):1466-74.
63. Ng AT, Gotsopoulos H, Qian J, Cistulli PA. Effect of oral appliance therapy on upper airway collapsibility in obstructive sleep apnea. American journal of respiratory and critical care medicine. 2003;168(2):238-41.
64. Kirkness JP, Eastwood PR, Szollosi I, Platt PR, Wheatley JR, Amis TC, et al. Effect of surface tension of mucosal lining liquid on upper airway mechanics in anesthetized humans. Journal of applied physiology. 2003;95(1):357-63.
65. Schwartz AR, Gold AR, Schubert N, Stryzak A. Effect of weight loss on upper airway collapsibility in obstructive sleep apnea1-3. Am Rev Respir Dis. 1991;144(3 pt 1):494-8.
66. Carskadon MA, Dement WC. Normal human sleep: an overview. Principles and practice of sleep medicine. 2005;4:13-23.
67. Carskadon MA, Rechtschaffen A. Monitoring and staging human sleep. Principles and practice of sleep medicine. 2011;5:16-26.
68. Levitan L, LaBerge S, DeGracia DJ, Zimbardo PG. Out-of-body experiences, dreams, and REM sleep. Sleep and Hypnosis. 1999;1(3):186-96.

69. Chokroverty S. Sleep Disorders Medicine E-Book: Basic Science, Technical Considerations, and Clinical Aspects, Expert Consult-Online and Print: Elsevier Health Sciences; 2009.
70. Roehrs T. Sleep physiology and pathophysiology. Clinical cornerstone. 2000;2(5):1-12.
71. Gleeson K, ZWILLlCH CW, White DP. The Influence of Increasing Ventilatory Effort on Arousal from Sleep1-3. Am Rev Respir Dis. 1990;142:295-300.
72. Ayappa I, Rapoport DM. The upper airway in sleep: physiology of the pharynx. Sleep medicine reviews. 2003;7(1):9-33.
73. Remmers J, DeGroot W, Sauerland E, Anch A. Pathogenesis of upper airway occlusion during sleep. Journal of Applied Physiology. 1978;44(6):931-8.
74. Sauerland E, Mitchell S. Electromyographic activity of intrinsic and extrinsic muscles of the human tongue. Texas reports on biology and medicine. 1975;33(3):444-55.
75. Malhotra A, Pillar G, Fogel RB, Beauregard J, Edwards JK, Slamowitz DI, et al. Genioglossal but not palatal muscle activity relates closely to pharyngeal pressure. American journal of respiratory and critical care medicine. 2000;162(3):1058-62.
76. Van de Graaff WB, Gottfried SB, Mitra J, van Lunteren E, Cherniack NS, Strohl KP. Respiratory function of hyoid muscles and hyoid arch. Journal of Applied Physiology. 1984;57(1):197-204.
77. Kuna ST. Effects of pharyngeal muscle activation on airway size and configuration. American journal of respiratory and critical care medicine. 2001;164(7):1236-41.
78. Kuna ST, Vanoye CR. Mechanical effects of pharyngeal constrictor activation on pharyngeal airway function. Journal of Applied Physiology. 1999;86(1):411-7.
79. van Lunteren E, Van de Graaff WB, Parker DM, Mitra J, Haxhiu MA, Strohl KP, et al. Nasal and laryngeal reflex responses to negative upper airway pressure. Journal of Applied Physiology. 1984;56(3):746-52.
80. Aronson RM, Onal E, Carley DW, Lopata M. Upper airway and respiratory muscle responses to continuous negative airway pressure. Journal of Applied Physiology. 1989;66(3):1373-82.
81. Wiegand L, Zwillich CW, Wiegand D, White DP. Changes in upper airway muscle activation and ventilation during phasic REM sleep in normal men. Journal of Applied Physiology. 1991;71(2):488-97.
82. Mezzanotte WS, Tangel DJ, White DP. Waking genioglossal electromyogram in sleep apnea patients versus normal controls (a neuromuscular compensatory mechanism). The Journal of clinical investigation. 1992;89(5):1571-9.
83. Fogel RB, Malhotra A, Pillar G, Edwards JK, Beauregard JE, Shea SA, et al. Genioglossal activation in patients with obstructive sleep apnea versus control subjects: mechanisms of muscle control. American journal of respiratory and critical care medicine. 2001;164(11):2025-30.
84. Young T, Peppard PE, Gottlieb DJ. Epidemiology of obstructive sleep apnea: a population health perspective. American journal of respiratory and critical care medicine. 2002;165(9):1217-39.
85. Douglas JA, Chai-Coetzer CL, McEvoy D, Naughton MT, Neill AM, Rochford P, et al. Guidelines for sleep studies in adults – a position statement of the Australasian Sleep Association. Sleep Medicine. 2017;36:S2-S22.
86. Johns MW. A new method for measuring daytime sleepiness: the Epworth sleepiness scale. sleep. 1991;14(6):540-5.

87. Lim PV, Curry AR. A new method for evaluating and reporting the severity of snoring. The Journal of Laryngology & Otology. 1999;113(4):336-40.
88. Weaver TE, Laizner AM, Evans LK, Maislin G, Chugh DK, Lyon K, et al. An instrument to measure functional status outcomes for disorders of excessive sleepiness. Sleep. 1997;20(10):835-43.
89. Ibáñez V, Silva J, Cauli O. A survey on sleep assessment methods. PeerJ. 2018;6:e4849.
90. Chung F, Yegneswaran B, Liao P, Chung SA, Vairavanathan S, Islam S, et al. Stop questionnairea tool to screen patients for obstructive sleep apnea. Anesthesiology: The Journal of the American Society of Anesthesiologists. 2008;108(5):812-21.
91. Netzer NC, Stoohs RA, Netzer CM, Clark K, Strohl KP. Using the Berlin Questionnaire to identify patients at risk for the sleep apnea syndrome. Annals of internal medicine. 1999;131(7):485-91.
92. Ahmadi N, Chung SA, Gibbs A, Shapiro CM. The Berlin questionnaire for sleep apnea in a sleep clinic population: relationship to polysomnographic measurement of respiratory disturbance. Sleep and Breathing. 2008;12(1):39-45.
93. Chung F, Subramanyam R, Liao P, Sasaki E, Shapiro C, Sun Y. High STOP-Bang score indicates a high probability of obstructive sleep apnoea. British journal of anaesthesia. 2012;108(5):768-75.
94. Silva GE, Vana KD, Goodwin JL, Sherrill DL, Quan SF. Identification of patients with sleep disordered breathing: comparing the four-variable screening tool, STOP, STOP-Bang, and Epworth Sleepiness Scales. Journal of Clinical Sleep Medicine. 2011;7(05):467-72.
95. Chai-Coetzer CL, Antic NA, Rowland LS, Catcheside PG, Esterman A, Reed RL, et al. A simplified model of screening questionnaire and home monitoring for obstructive sleep apnoea in primary care. Thorax. 2011;66(3):213-9.
96. MBS. Fact Sheet: Changes to diagnostic services for sleep disorders. In: MBS Online DoH, editor. Australia: Australian Government; 2019.
97. Berry RB. The AASM manual for the scoring of sleep and associated events: rules, terminology and technical specifications: American Academy of Sleep Medicine; 2018.
98. Ruehland WR, Rochford PD, O'Donoghue FJ, Pierce RJ, Singh P, Thornton AT. The new AASM criteria for scoring hypopneas: impact on the apnea hypopnea index. Sleep. 2009;32(2):150-7.
99. Ling IT, James AL, Hillman DR. Interrelationships between body mass, oxygen desaturation, and apnea-hypopnea indices in a sleep clinic population. Sleep. 2012;35(1):89-96.
100. Marin JM, Carrizo SJ, Vicente E, Agusti AG. Long-term cardiovascular outcomes in men with obstructive sleep apnoea-hypopnoea with or without treatment with continuous positive airway pressure: an observational study. The Lancet. 2005;365(9464):1046-53.
101. Berry RB, Brooks R, Gamaldo CE, Harding SM, Marcus C, Vaughn BV. The AASM manual for the scoring of sleep and associated events. Rules, Terminology and Technical Specifications, Darien, Illinois, American Academy of Sleep Medicine. 2012;176.
102. de Chazal P, Sutherland K, Cistulli PA. Advanced polysomnographic analysis for OSA: A pathway to personalized management? Respirology. 2019.
103. Woodson BT. A method to describe the pharyngeal airway. The Laryngoscope. 2015;125(5):1233-8.

104. Friedman M, Salapatas AM, Bonzelaar LB. Updated friedman staging system for obstructive sleep apnea. Sleep-Related Breathing Disorders. 80: Karger Publishers; 2017. p. 41-8.
105. Rodriguez-Bruno K, Goldberg AN, McCulloch CE, Kezirian EJ. Test-retest reliability of drug-induced sleep endoscopy. Otolaryngology—Head and Neck Surgery. 2009;140(5):646-51.
106. Lyberg T, Krogstad O, Djupesland G. Cephalometric analysis in patients with obstructive sleep apnoea syndrome.: I. Skeletal Morphology. The Journal of Laryngology & Otology. 1989;103(3):287-92.
107. Cistulli PA, Palmisano RG, Poole MD. Treatment of obstructive sleep apnea syndrome by rapid maxillary expansion. Sleep. 1998;21(8):831-5.
108. Seto BH, Gotsopoulos H, Sims MR, Cistulli PA. Maxillary morphology in obstructive sleep apnoea syndrome. The European Journal of Orthodontics. 2001;23(6):703-14.
109. Redline S, Amin R, Beebe D, Chervin RD, Garetz SL, Giordani B, et al. The Childhood Adenotonsillectomy Trial (CHAT): rationale, design, and challenges of a randomized controlled trial evaluating a standard surgical procedure in a pediatric population. Sleep. 2011;34(11):1509-17.
110. Lai VW, Corey JP. The objective assessment of nasal patency. Ear, nose & throat journal. 1993;72(6):395-400.
111. Chirakalwasan N, Ruxrungtham K. The linkage of allergic rhinitis and obstructive sleep apnea. Asian Pacific journal of allergy and immunology. 2014;32(4):276.
112. Borowiecki Bd, Sassin JF. Surgical treatment of sleep apnea. Archives of Otolaryngology. 1983;109(8):508-12.
113. Woodson BT, Feroah T, Connolly LA, Toohill RJ. A method to evaluate upper airway mechanics following intervention in snorers. American journal of otolaryngology. 1997;18(5):306-14.
114. Fairbanks DN, Mickelson SA, Woodson BT. Snoring and obstructive sleep apnea: Lippincott Williams & Wilkins; 2003.
115. Kezirian EJ, Hohenhorst W, de Vries N. Drug-induced sleep endoscopy: the VOTE classification. European Archives of Oto-Rhino-Laryngology. 2011;268(8):1233-6.
116. Epstein LJ, Kristo D, Strollo PJ, Friedman N, Malhotra A, Patil SP, et al. Clinical guideline for the evaluation, management and long-term care of obstructive sleep apnea in adults. Journal of clinical sleep medicine. 2009;5(03):263-76.
117. Mackay S, Jefferson N, Jones A, Sands T, Woods C, Raftopulous M. Benefit of a contemporary sleep multidisciplinary team (MDT): Patient and clinician evaluation. 2014.
118. Wang Y, Gao W, Sun M, Chen B. Adherence to CPAP in patients with obstructive sleep apnea in a Chinese population. Respiratory care. 2012;57(2):238-43.
119. Nadal N, de Batlle J, Barbé F, Marsal JR, Sánchez-de-la-Torre A, Tarraubella N, et al. Predictors of CPAP compliance in different clinical settings: primary care versus sleep unit. Sleep and Breathing. 2018;22(1):157-63.
120. Queiroz DL, Yui MS, Braga AA, Coelho ML, Küpper DS, Sander HH, et al. Adherence of obstructive sleep apnea syndrome patients to continuous positive airway pressure in a public service. Brazilian journal of otorhinolaryngology. 2014;80(2):126-30.
121. Hussain SF, Irfan M, Waheed Z, Alam N, Mansoor S, Islam M. Compliance with continuous positive airway pressure (CPAP) therapy for obstructive sleep apnea among privately paying patients-a cross sectional study. BMC pulmonary medicine. 2014;14(1):188.

122. Balachandran JS, Yu X, Wroblewski K, Mokhlesi B. A brief survey of patients' first impression after CPAP titration predicts future CPAP adherence: a pilot study. Journal of Clinical Sleep Medicine. 2013;9(03):199-205.
123. Engleman HM, Martin SE, Douglas NJ. Compliance with CPAP therapy in patients with the sleep apnoea/hypopnoea syndrome. Thorax. 1994;49(3):263-6.
124. Kreivi H-R, Maasilta P, Bachour A. Persistence of upper-airway symptoms during CPAP compromises adherence at 1 year. Respiratory care. 2016;61(5):652-7.
125. Edmonds JC, Yang H, King TS, Sawyer DA, Rizzo A, Sawyer AM. Claustrophobic tendencies and continuous positive airway pressure therapy non-adherence in adults with obstructive sleep apnea. Heart & Lung. 2015;44(2):100-6.
126. Boyacı H, Gacar K, Barış S, Başyiğit I, Yıldız F. Positive airway pressure device compliance of the patients with obstructive sleep apnea syndrome. Advances in clinical and experimental medicine: official organ Wroclaw Medical University. 2013;22(6):809-15.
127. Law M, Naughton M, Ho S, Roebuck T, Dabscheck E. Depression may reduce adherence during CPAP titration trial. Journal of Clinical Sleep Medicine. 2014;10(02):163-9.
128. Chai-Coetzer CL, Luo Y-M, Antic NA, Zhang X-L, Chen B-Y, He Q-Y, et al. Predictors of long-term adherence to continuous positive airway pressure therapy in patients with obstructive sleep apnea and cardiovascular disease in the SAVE study. Sleep. 2013;36(12):1929-37.
129. Love RL, Naughton MT, Cistulli P, McArdle N, MacKay SG. Complications and safe prescription of interventions for adult sleep disordered breathing in Australia. Australian Journal of Otolaryngology. 2019;2.
130. MacKay SG, Chan L. Surgical approaches to obstructive sleep apnea. Sleep medicine clinics. 2016;11(3):331-41.
131. Greenburg DL, Lettieri CJ, Eliasson AH. Effects of surgical weight loss on measures of obstructive sleep apnea: a meta-analysis. The American journal of medicine. 2009;122(6):535-42.
132. Kavey N, Gidro-Frank S, Sewitch D. The importance of sleeping position in sleep apnea and a simple treatment technique. Sleep Res. 1982;11:152.
133. Bignold JJ, Deans-Costi G, Goldsworthy MR, Robertson CA, McEvoy D, Catcheside PG, et al. Poor long-term patient compliance with the tennis ball technique for treating positional obstructive sleep apnea. Journal of Clinical Sleep Medicine. 2009;5(05):428-30.
134. van Maanen JP, Meester KA, Dun LN, Koutsourelakis I, Witte BI, Laman DM, et al. The sleep position trainer: a new treatment for positional obstructive sleep apnoea. Sleep and breathing. 2013;17(2):771-9.
135. Bignold JJ, Mercer JD, Antic NA, McEvoy RD, Catcheside PG. Accurate position monitoring and improved supine-dependent obstructive sleep apnea with a new position recording and supine avoidance device. Journal of clinical sleep medicine. 2011;7(04):376-83.
136. Levendowski DJ, Seagraves S, Popovic D, Westbrook PR. Assessment of a neck-based treatment and monitoring device for positional obstructive sleep apnea. Journal of Clinical Sleep Medicine. 2014;10(08):863-71.
137. van Maanen JP, de Vries N. Long-term effectiveness and compliance of positional therapy with the sleep position trainer in the treatment of positional obstructive sleep apnea syndrome. Sleep. 2014;37(7):1209-15.

138. Scarlata S, Bartoli IR, Santangelo S, Giannunzio G, Pedone C, Incalzi RA. Short-term effects of a vibrotactile neck-based treatment device for positional obstructive sleep apnea: preliminary data on tolerability and efficacy. Journal of thoracic disease. 2016;8(7):1820.
139. Aarab G, Lobbezoo F, Hamburger HL, Naeije M. Oral appliance therapy versus nasal continuous positive airway pressure in obstructive sleep apnea: a randomized, placebo-controlled trial. Respiration. 2011;81(5):411-9.
140. Gotsopoulos H, Chen C, Qian J, Cistulli PA. Oral appliance therapy improves symptoms in obstructive sleep apnea: a randomized, controlled trial. American journal of respiratory and critical care medicine. 2002;166(5):743-8.
141. Vasu TS, Grewal R, Doghramji K. Obstructive sleep apnea syndrome and perioperative complications: a systematic review of the literature. Journal of clinical sleep medicine. 2012;8(02):199-207.
142. Adesanya AO, Lee W, Greilich NB, Joshi GP. Perioperative management of obstructive sleep apnea. Chest. 2010;138(6):1489-98.
143. MacKay SG, Weaver EM. Surgery for adult obstructive sleep apnoea. The Medical Journal of Australia. 2013;199(7):450-1.
144. Camacho M, Certal V, Brietzke SE, Holty JEC, Guilleminault C, Capasso R. Tracheostomy as treatment for adult obstructive sleep apnea: a systematic review and meta-analysis. The Laryngoscope. 2014;124(3):803-11.
145. McLean H, Urton A, Driver H, Tan A, Day A, Munt P, et al. Effect of treating severe nasal obstruction on the severity of obstructive sleep apnoea. European Respiratory Journal. 2005;25(3):521-7.
146. Ishii L, Roxbury C, Godoy A, Ishman S, Ishii M. Does nasal surgery improve OSA in patients with nasal obstruction and OSA? A meta-analysis. Otolaryngology–Head and Neck Surgery. 2015;153(3):326-33.
147. Rotenberg BW, Theriault J, Gottesman S. Redefining the timing of surgery for obstructive sleep apnea in anatomically favorable patients. The Laryngoscope. 2014;124(S4):S1-S9.
148. Pang KP, Woodson BT. Expansion sphincter pharyngoplasty: a new technique for the treatment of obstructive sleep apnea. Otolaryngology—Head and Neck Surgery. 2007;137(1):110-4.
149. Cahali MB, Formigoni GG, Gebrim EM, Miziara ID. Lateral pharyngoplasty versus uvulopalatopharyngoplasty: a clinical, polysomnographic and computed tomography measurement comparison. Sleep. 2004;27(5):942-50.
150. Browaldh N, Nerfeldt P, Lysdahl M, Bring J, Friberg D. SKUP3 randomised controlled trial: polysomnographic results after uvulopalatopharyngoplasty in selected patients with obstructive sleep apnoea. Thorax. 2013;68(9):846-53.
151. Volner K, Dunn B, Chang ET, Song SA, Liu SY-C, Brietzke SE, et al. Transpalatal advancement pharyngoplasty for obstructive sleep apnea: a systematic review and meta-analysis. European Archives of Oto-Rhino-Laryngology. 2017;274(3):1197-203.
152. Crawford JA, Montevechi F, Vicini C, Magnuson JS. Transoral robotic sleep surgery: the obstructive sleep apnea–hypopnea syndrome. Otolaryngologic Clinics of North America. 2014;47(3):397-406.
153. Faria AC, da Silva-Junior SN, Garcia LV, Dos Santos AC, Fernandes MRF, de Mello-Filho FV. Volumetric analysis of the pharynx in patients with obstructive sleep apnea (OSA) treated with maxillomandibular advancement (MMA). Sleep and Breathing. 2013;17(1):395-401.

154. Holty J-EC, Guilleminault C. Maxillomandibular advancement for the treatment of obstructive sleep apnea: a systematic review and meta-analysis. Sleep medicine reviews. 2010;14(5):287-97.
155. Hochban W, Brandenburg U, Peter JH. Surgical Treatment of Obstructive Sleep Apnea by Maxillomandibular Advancement. Sleep. 1994;17(7):624-9.
156. Lettieri CJ, Eliasson AH, Greenburg DL. Persistence of obstructive sleep apnea after surgical weight loss. J Clin Sleep Med. 2008;4(4):333-8.
157. Peromaa-Haavisto P, Tuomilehto H, Kössi J, Virtanen J, Luostarinen M, Pihlajamäki J, et al. Obstructive sleep apnea: the effect of bariatric surgery after 12 months. A prospective multicenter trial. Sleep Medicine. 2017;35:85-90.
158. Ye L, Pien GW, Ratcliffe SJ, Björnsdottir E, Arnardottir ES, Pack AI, et al. The different clinical faces of obstructive sleep apnoea: a cluster analysis. European Respiratory Journal. 2014;44(6):1600-7.
159. Keenan BT, Kim J, Singh B, Bittencourt L, Chen N-H, Cistulli PA, et al. Recognizable clinical subtypes of obstructive sleep apnea across international sleep centers: a cluster analysis. Sleep. 2018;41(3):zsx214.
160. Gagnadoux F, Le Vaillant M, Paris A, Pigeanne T, Leclair-Visonneau L, Bizieux-Thaminy A, et al. Relationship between OSA clinical phenotypes and CPAP treatment outcomes. Chest. 2016;149(1):288-90.
161. Pack AI. Application of Personalized, Predictive, Preventative, and Participatory (P4) Medicine to Obstructive Sleep Apnea. A Roadmap for Improving Care? Annals of the American Thoracic Society. 2016;13(9):1456-67.
162. Chung KF. Defining Phenotypes in Asthma: A Step Towards Personalized Medicine. Drugs. 2014;74(7):719-28.
163. Hasegawa K, Dumas O, Hartert TV, Camargo CA. Advancing our understanding of infant bronchiolitis through phenotyping and endotyping: clinical and molecular approaches. Expert Review of Respiratory Medicine. 2016;10(8):891-9.
164. Blasi F, Chalmers JD, Aliberti S. COPD and Bronchiectasis: Phenotype, Endotype or Co-morbidity? COPD: Journal of Chronic Obstructive Pulmonary Disease. 2014;11(6):603-4.
165. Bamagoos AA, Cistulli PA, Sutherland K, Madronio M, Eckert DJ, Hess L, et al. Polysomnographic endotyping to select obstructive sleep apnea patients for oral appliances. Annals of the American Thoracic Society. 2019(ja).
166. Wellman A, Eckert DJ, Jordan AS, Edwards BA, Passaglia CL, Jackson AC, et al. A method for measuring and modeling the physiological traits causing obstructive sleep apnea. Journal of applied physiology. 2011;110(6):1627-37.
167. Wellman A, Edwards BA, Sands SA, Owens RL, Nemati S, Butler J, et al. A simplified method for determining phenotypic traits in patients with obstructive sleep apnea. Journal of applied physiology. 2013;114(7):911-22.
168. Eckert DJ, White DP, Jordan AS, Malhotra A, Wellman A. Defining phenotypic causes of obstructive sleep apnea. Identification of novel therapeutic targets. American journal of respiratory and critical care medicine. 2013;188(8):996-1004.
169. Eckert DJ, Younes MK. Arousal from sleep: implications for obstructive sleep apnea pathogenesis and treatment. Journal of Applied Physiology. 2014;116(3):302-13.
170. Wellman A, Jordan AS, Malhotra A, Fogel RB, Katz ES, Schory K, et al. Ventilatory control and airway anatomy in obstructive sleep apnea. American journal of respiratory and critical care medicine. 2004;170(11):1225-32.

171. Wellman A, Malhotra A, Jordan AS, Stevenson KE, Gautam S, White DP. Effect of oxygen in obstructive sleep apnea: role of loop gain. Respiratory physiology & neurobiology. 2008;162(2):144-51.
172. Horner RL, Innes JA, Morrell MJ, Shea SA, Guz A. The effect of sleep on reflex genioglossus muscle activation by stimuli of negative airway pressure in humans. The Journal of Physiology. 1994;476(1):141-51.
173. Schwartz AR, Thut DC, Brower RG, Gauda EB, Roach D, Permutt S, et al. Modulation of maximal inspiratory airflow by neuromuscular activity: effect of CO2. Journal of Applied Physiology. 1993;74(4):1597-605.
174. Owens RL, Malhotra A, Eckert DJ, White DP, Jordan AS. The influence of end-expiratory lung volume on measurements of pharyngeal collapsibility. Journal of Applied Physiology. 2009;108(2):445-51.
175. Stadler DL, McEvoy RD, Sprecher KE, Thomson KJ, Ryan MK, Thompson CC, et al. Abdominal compression increases upper airway collapsibility during sleep in obese male obstructive sleep apnea patients. Sleep. 2009;32(12):1579-87.
176. Eckert DJ, Owens RL, Kehlmann GB, Wellman A, Rahangdale S, Yim-Yeh S, et al. Eszopiclone increases the respiratory arousal threshold and lowers the apnoea/hypopnoea index in obstructive sleep apnoea patients with a low arousal threshold. Clinical science. 2011;120(12):505-14.
177. Schwartz AR, Schubert N, Rothman W, Godley F, Marsh B, Eisele D, et al. Effect of uvulopalatopharyngoplasty on upper airway collapsibility in obstructive sleep apnea. Am Rev Respir Dis. 1992;145(3):527-32.
178. Woodson BT. Retropalatal airway characteristics in uvulopalatopharyngoplasty compared with transpalatal advancement pharyngoplasty. The Laryngoscope. 1997;107(6):735-40.
179. Ong JS, Touyz G, Tanner S, Hillman DR, Eastwood PR, Walsh JH. Variability of human upper airway collapsibility during sleep and the influence of body posture and sleep stage. Journal of sleep research. 2011;20(4):533-7.
180. Carter SG, Berger MS, Carberry JC, Bilston LE, Butler JE, Tong BK, et al. Zopiclone increases the arousal threshold without impairing genioglossus activity in obstructive sleep apnea. Sleep. 2016;39(4):757-66.
181. Eckert DJ, Malhotra A, Wellman A, White DP. Trazodone increases the respiratory arousal threshold in patients with obstructive sleep apnea and a low arousal threshold. Sleep. 2014;37(4):811-9.
182. Xie A, Teodorescu M, Pegelow DF, Teodorescu MC, Gong Y, Fedie JE, et al. Effects of stabilizing or increasing respiratory motor outputs on obstructive sleep apnea. Journal of Applied Physiology. 2013;115(1):22-33.
183. Edwards BA, Sands SA, Eckert DJ, White DP, Butler JP, Owens RL, et al. Acetazolamide improves loop gain but not the other physiological traits causing obstructive sleep apnoea. The Journal of physiology. 2012;590(5):1199-211.
184. Guimarães KC, Drager LF, Genta PR, Marcondes BF, Lorenzi-Filho G. Effects of oropharyngeal exercises on patients with moderate obstructive sleep apnea syndrome. American journal of respiratory and critical care medicine. 2009;179(10):962-6.
185. Camacho M, Certal V, Abdullatif J, Zaghi S, Ruoff CM, Capasso R, et al. Myofunctional therapy to treat obstructive sleep apnea: a systematic review and meta-analysis. Sleep. 2015;38(5):669-75.

186. Taranto-Montemurro L, Edwards BA, Sands SA, Marques M, Eckert DJ, White DP, et al. Desipramine increases genioglossus activity and reduces upper airway collapsibility during non-REM sleep in healthy subjects. American journal of respiratory and critical care medicine. 2016;194(7):878-85.
187. Taranto-Montemurro L, Sands SA, Edwards BA, Azarbarzin A, Marques M, De Melo C, et al. Desipramine improves upper airway collapsibility and reduces OSA severity in patients with minimal muscle compensation. European Respiratory Journal. 2016;48(5):1340-50.
188. Eastwood PR, Barnes M, Walsh JH, Maddison KJ, Hee G, Schwartz AR, et al. Treating obstructive sleep apnea with hypoglossal nerve stimulation. Sleep. 2011;34(11):1479-86.
189. Schwartz AR, Bennett ML, Smith PL, De Backer W, Hedner J, Boudewyns A, et al. Therapeutic electrical stimulation of the hypoglossal nerve in obstructive sleep apnea. Archives of Otolaryngology–Head & Neck Surgery. 2001;127(10):1216-23.
190. Eastwood PR, Barnes M, MacKay SG, Wheatley JR, Hillman DR, Nguyên X-L, et al. Bilateral Hypoglossal Nerve Stimulation for Treatment of Adult Obstructive Sleep Apnea. European Respiratory Journal. 2019.
191. Woodson BT, Soose RJ, Gillespie MB, Strohl KP, Maurer JT, de Vries N, et al. Three-year outcomes of cranial nerve stimulation for obstructive sleep apnea: the STAR trial. Otolaryngology--head and neck surgery. 2016;154(1):181-8.
192. Sands SA, Edwards BA, Terrill PI, Taranto-Montemurro L, Azarbarzin A, Marques M, et al. Phenotyping pharyngeal pathophysiology using polysomnography in patients with obstructive sleep apnea. American journal of respiratory and critical care medicine. 2018;197(9):1187-97.
193. Sands SA, Terrill PI, Edwards BA, Taranto Montemurro L, Azarbarzin A, Marques M, et al. Quantifying the arousal threshold using polysomnography in obstructive sleep apnea. Sleep. 2018;41(1):zsx183.
194. Terrill PI, Edwards BA, Nemati S, Butler JP, Owens RL, Eckert DJ, et al. Quantifying the ventilatory control contribution to sleep apnoea using polysomnography. European Respiratory Journal. 2015;45(2):408-18.
195. Lin HC, Friedman M, Chang HW, Gurpinar B. The efficacy of multilevel surgery of the upper airway in adults with obstructive sleep apnea/hypopnea syndrome. The Laryngoscope. 2008;118(5):902-8.
196. Patel S, Kon SS, Nolan CM, Barker RE, Simonds AK, Morrell MJ, et al. The Epworth Sleepiness Scale: minimum clinically important difference in obstructive sleep apnea. American journal of respiratory and critical care medicine. 2018;197(7):961-3.
197. Bujang MA, Adnan TH. Requirements for minimum sample size for sensitivity and specificity analysis. Journal of clinical and diagnostic research: JCDR. 2016;10(10):YE01.
198. Iber C, Ancoli-Israel S, Chesson AL, Quan SF. The AASM manual for the scoring of sleep and associated events: rules, terminology and technical specifications: American academy of sleep medicine Westchester, IL; 2007.
199. Joosten SA, Leong P, Landry SA, Sands SA, Terrill PI, Mann D, et al. Loop gain predicts the response to upper airway surgery in patients with obstructive sleep apnea. Sleep. 2017;40(7):zsx094.
200. O'Driscoll DM, Landry SA, Pham J, Young A, Sands SA, Hamilton GS, et al. The physiological phenotype of obstructive sleep apnea differs between Caucasian and Chinese patients. Sleep. 2019;42(11):zsz186.

201. Edwards BA, Wellman A, Sands SA, Owens RL, Eckert DJ, White DP, et al. Obstructive sleep apnea in older adults is a distinctly different physiological phenotype. Sleep. 2014;37(7):1227-36A.
202. Li Y, Ye J, Han D, Zhao D, Cao X, Orr J, et al. The effect of upper airway surgery on loop gain in obstructive sleep apnea. Journal of Clinical Sleep Medicine. 2019;15(6):907-13.
203. Sands SA, Eckert DJ, Jordan AS, Edwards BA, Owens RL, Butler JP, et al. Enhanced upper-airway muscle responsiveness is a distinct feature of overweight/obese individuals without sleep apnea. American journal of respiratory and critical care medicine. 2014;190(8):930-7.

Appendix

1. Supplementary Tables and Figures

Table S1. Pre-treatment phenotypes according to treatment modality. Categories are expressed with (number of phenotyped PSGs). Values are expressed as mean±SEM for normally distributed or median (interquartile range) for non-normally distributed data as measured by Shapiro-Wilk test. p values are determined from one-way ANOVA.

Phenotype, unit	MAS (4)	Sx (8)	PTx (8)	NS (4)	WL (4)	p
LG_1						
Supine NREM	0.38±0.07	0.90±0.11	0.63±0.08	0.74±0.10	0.59±0.09	.03
All supine	0.42±0.03	0.91±0.12	0.65±0.08	0.71±0.09	0.59±0.09	
All NREM	0.47±0.03	0.82±0.11	0.66±0.08	0.72±0.11	0.55±0.08	
LG_n						
Supine NREM	0.30±0.03	0.56±0.06	0.46±0.04	0.58±0.08	0.37±0.05	.03
All supine	0.39±0.03	0.56±0.06	0.50±0.04	0.58±0.07	0.43±0.04	
All NREM	0.34±0.02	0.54±0.06	0.48±0.04	0.58±0.08	0.39±0.04	
ArThres, $\%V_{eupnea}$						
Supine NREM	162.8	198.6±22.4	169±18.7	171.6±28.4	144.3±17.9	.20
All supine	136.7±20.7	208.9±26.4	166.7±17.2	160.9±18.6	139.6±18.7	
All NREM	142±22.6	180.7±22.1	149.4±14.9	170.4±28.1	131.7±21.2	
V_{comp}, $\%V_{eupnea}$						
Supine NREM	7.0±2.6	44.7±17.7	29.9±9.4	62.0±30.9	10.2±11.2	.19
All supine	11.4±3.7	18.0±9.2	35.2±14.5	45.4±21.0	12.1±11.3	
All NREM	5.5±3.0	20.0±12.1	21.1±8.6	53.2±23.5	1.3±6.0	
$V_{passive}$, $\%V_{eupnea}$						
Supine NREM	92.1±5.8	59.3±13.0	87.8±3.5	78.0±10.8	86.4±6.0	.19
All supine	91.9±5.6	59±12.8	88.2(71.3-93.1)	79.1±10.4	86.1±6.2	
All NREM	97.1±1.0	77.3±8.7	91.2±2.1	78.9±9.3	93.9±2.3	
V_{min}, $\%V_{eupnea}$						
Supine NREM	60.0±7.5	47.9±6.0	47.1±6.4	67.5±6.2	51.7±4.3	.48
All supine	58.9±5.5	47.5±7.3	46.7±5.0	44.4±16.0	51.8±5.1	
All NREM	64.3±6.4	44.5±5.4	50.4±5.1	66.0±4.8	57.5±5.8	

Figure S1. Post-treatment phenotypic traits (averaged from supine NREM, all supine and all NREM sleep) per treatment group. Dotted line represents cut-off value for favourable traits (LG1 <0.72, ArThres >120%, Vcomp >0%, Vpassive >95.5%). Lines and error bars are mean±SEM.

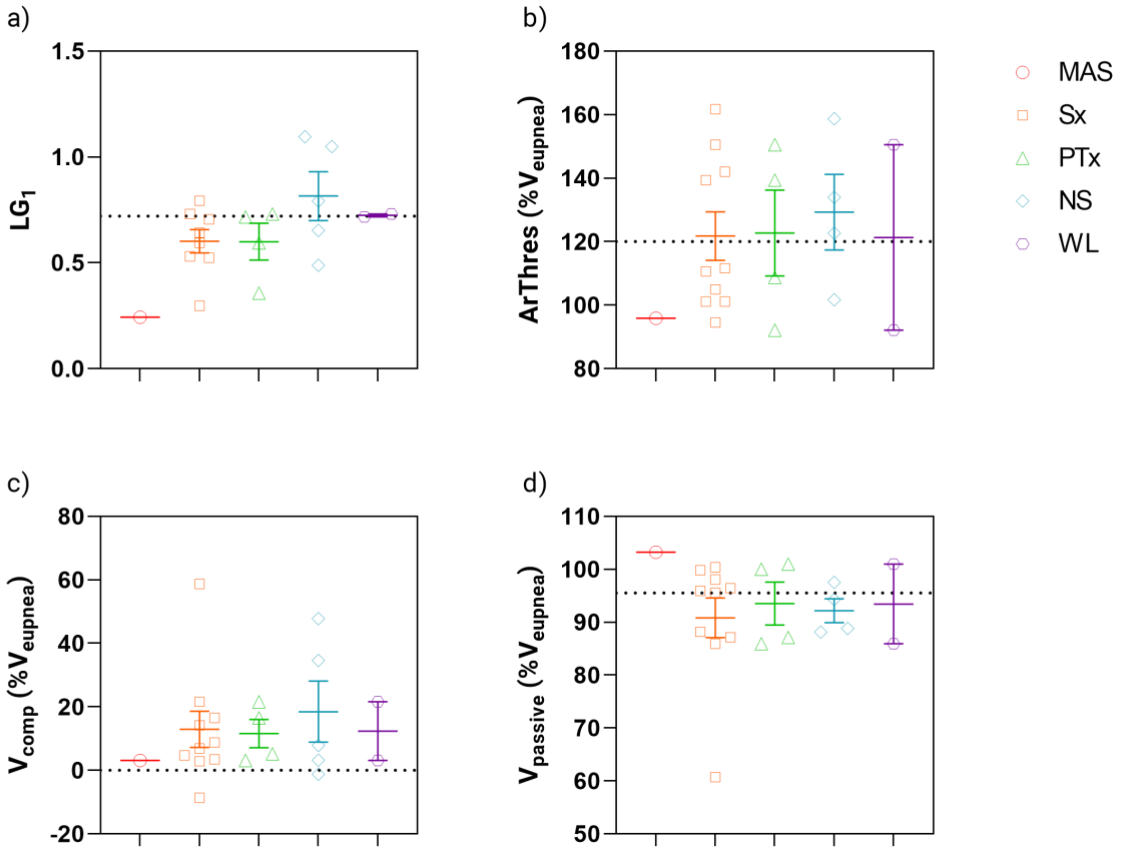
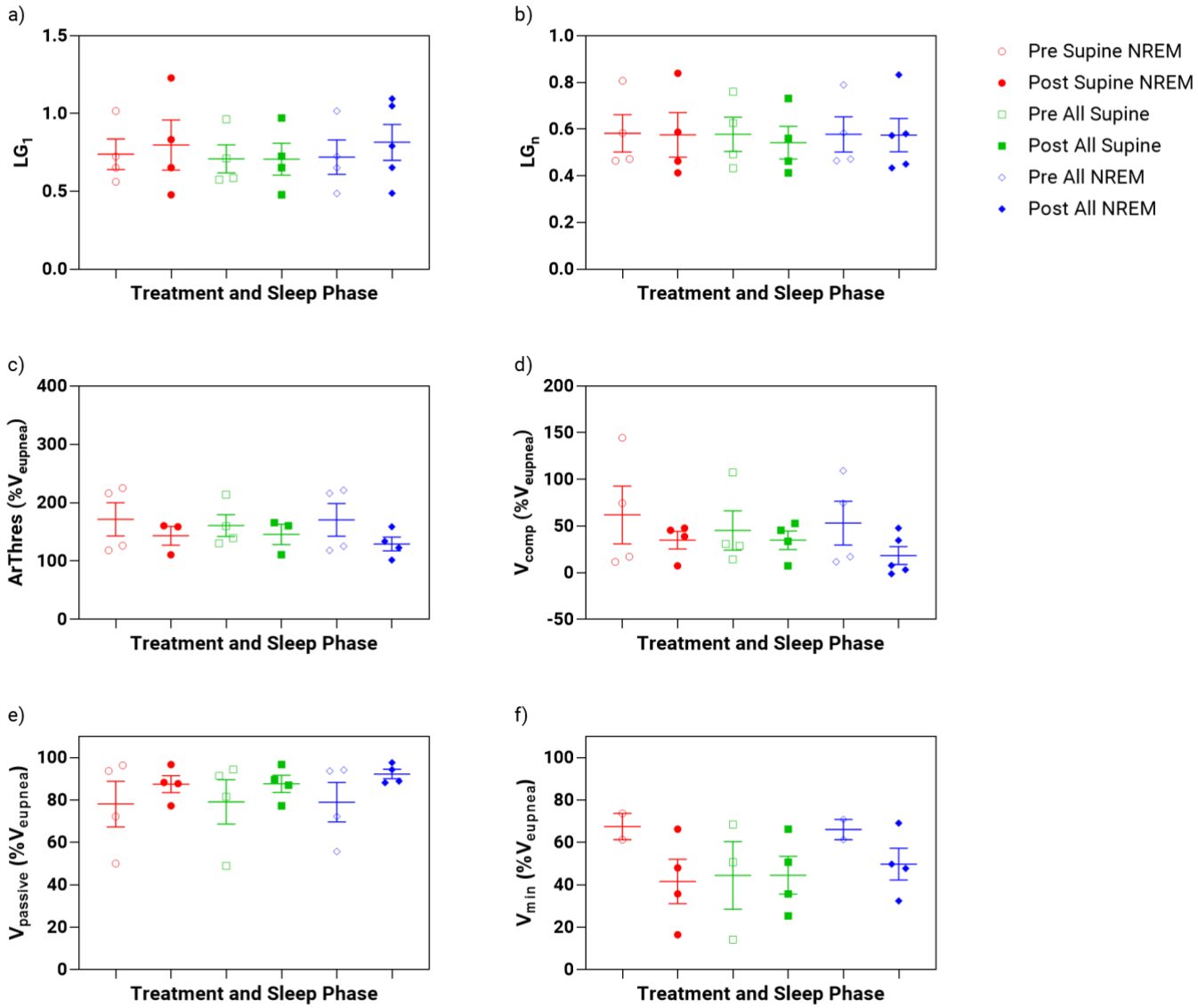


Figure S2. Group comparisons between pre- and post-treatment phenotypes in NS patients. Loop gain is represented in a) and b), arousal threshold in c), muscle compensation in d), airway collapsibility in e) and f). Supine NREM data points are represented in red, all supine data points are in green and all NREM data points are in blue.



2. Documents for Questionnaires, Dynamic Airway Assessment

Snoring Severity Scale (SSS)	
Name:	Date:
Age (years):	Sex: M / F
Please pick the answer in each of the three questions below that best describes your partner's/spouse's snoring.	
	Score
1. How often does your partner/spouse snore? a. Every night b. Snores on most nights (i.e. more than 50% of nights) c. Snores on some nights (i.e. less than 50% of nights) d. Snores on very rare occasions or never snores	 3 2 1 0
2. How much does your partner/spouse snore? a. Snores all the time throughout the night b. Snores most of the time throughout the night (i.e. more than 50% of the time) c. Snores some of the time during the night (i.e. less than 50% of the time) d. Hardly snores or no snoring	 3 2 1 0
3. How loud is the snore a. Snoring can be heard throughout the floor/flat or louder with the bedroom door closed b. Snoring can be heard in the next room with the bedroom door closed c. Snoring can only be heard in the bedroom d. There is no snoring noise	 3 2 1 0

Adapted from Lim PV, Curry AR. A new method for evaluating and reporting the severity of snoring. The Journal of Laryngology & Otology. 1999 Apr;113(4):336-40.

Epworth Sleepiness Scale (ESS)				
Name:		Date:		
Age (years):		Sex: M / F		
How likely are you to doze off or fall asleep in the following situations, in contrast to feeling just tired? This refers to your usual way of life in recent times. Even if you have not done some of these things recently try to work out how they would have affected you. Use the following scale to choose the most appropriate number for each situation. DIRECTIONS: Please put an X in the box for your answer to each question. Select only <u>one</u> answer for each question. Please try to be as accurate as possible. All information will be kept confidential.				
Situation	(0) Would never doze	(1) Slight chance of dozing	(2) Moderate chance of dozing	(3) High chance of dozing
Sitting and reading	□	□	□	□
Watching TV	□	□	□	□
Sitting, inactive in a public place (e.g. a theatre or a meeting)	□	□	□	□
As a passenger in a car for an hour without a break	□	□	□	□
Lying down to rest in the afternoon when circumstances permit	□	□	□	□
Sitting and talking to someone	□	□	□	□
Sitting quietly after a lunch without alcohol	□	□	□	□
In a car, while stopped for a few minutes in the traffic	□	□	□	□

Adapted from Johns MW. A new method for measuring daytime sleepiness: the Epworth sleepiness scale. sleep. 1991 Nov 1;14(6):540-5.

Functional Outcomes of Sleep Questionnaire (FOSQ-30)					
Name:		Date:			
Age (years):		Sex: M / F			
Some people have difficulty performing everyday activities when they feel tired or sleepy. The purpose of this questionnaire is to find out if you generally have difficulty carrying out certain activities because you are too sleepy or tired. In this questionnaire, when the words "sleepy" or "tired" are used, it means the feeling that you can't keep your eyes open, your head is droopy, that you want to "nod off", or that you feel the urge to take a nap. These words do not refer to the tired or fatigued feeling you may have after you have exercised. DIRECTIONS: Please put an X in the box for your answer to each question. Select only one answer for each question. Please try to be as accurate as possible. All information will be kept confidential.					
	(0) I don't do this activity for other reasons	(4) No difficulty	(3) Yes, a little difficulty	(2) Yes, moderate difficulty	(1) Yes, extreme difficulty
1. Do you have difficulty concentrating on the things you do because you are sleepy or tired? (P)		□	□	□	□
2. Do you generally have difficulty remembering things, because you are sleepy or tired? (P)		□	□	□	□
3. Do you have difficulty finishing a meal because you become sleepy or tired? (P)		□	□	□	□
4. Do you have difficulty working on a hobby (e.g. sewing, collecting, gardening) because you are sleepy or tired? (P)	□	□	□	□	□
5. Do you have difficulty doing work around the house (e.g. cleaning house, doing laundry, taking out the trash, repair work) because you are sleepy or tired? (A)	□	□	□	□	□
6. Do you have difficulty operating a motor vehicle for short distances (less than 100km) because you become sleepy or tired? (V)	□	□	□	□	□
	(0) I don't do this activity for other reasons	(4) No difficulty	(3) Yes, a little difficulty	(2) Yes, moderate difficulty	(1) Yes, extreme difficulty
7. Do you have difficulty operating a motor vehicle for long distances (greater than	□	□	□	□	□

100km) because you become sleepy or tired? (V)					
8. Do you have difficulty getting things done because you are too sleepy or tired to drive or take public transportation? (P)	□	□	□	□	□
9. Do you have difficulty taking care of financial affairs and doing paperwork (e.g. writing checks, paying bills, keeping financial records, filling out tax forms, etc) because you are sleepy or tired? (P)	□	□	□	□	□
10. Do you have difficulty performing employed or volunteer work because you are sleepy or tired? (P)	□	□	□	□	□
11. Do you have difficulty maintaining a telephone conversation, because you become sleepy or tired? (P)	□	□	□	□	□
12. Do you have difficulty visiting with your family or friends in <u>your</u> home because you become sleepy or tired? (S)	□	□	□	□	□
13. Do you have difficulty visiting with your family or friends in <u>their</u> home because you become sleepy or tired? (S)	□	□	□	□	□
14. Do you have difficulty doing things for your family or friends because you are too sleepy or tired? (A)	□	□	□	□	□
		(4) No	(3) Yes, a little	(2) Yes, moderately	(1) Yes, extremely
15. Has your relationship with family, friends or work colleagues been affected because you are sleepy or tired? (A)		□	□	□	□
	(0) I don't do this activity for other reasons	(4) No difficulty	(3) Yes, a little difficulty	(2) Yes, moderate difficulty	(1) Yes, extreme difficulty
16. Do you have difficulty exercising or participating in	□	□	□	□	□

a sporting activity because you are too sleepy or tired? (A)					
17. Do you have difficulty watching a movie or videotape because you become sleepy or tired? (V)	□	□	□	□	□
18. Do you have difficulty enjoying the theatre or a lecture because you become sleepy or tired? (V)	□	□	□	□	□
19. Do you have difficulty enjoying a concert because you become sleepy or tired? (V)	□	□	□	□	□
20. Do you have difficulty watching TV because you are sleepy or tired? (V)	□	□	□	□	□
21. Do you have difficulty participating in religious services, meetings or a group or club, because you are sleepy or tired? (V)	□	□	□	□	□
22. Do you have difficulty being as active as you want to be in the <u>evening</u> because you are sleepy or tired? (A)		□	□	□	□
23. Do you have difficulty being as active as you want to be in the <u>morning</u> because you are sleepy or tired? (A)		□	□	□	□
	(0) I don't do this activity for other reasons	(4) No difficulty	(3) Yes, a little difficulty	(2) Yes, moderate difficulty	(1) Yes, extreme difficulty
24. Do you have difficulty being as active as you want to be in the <u>afternoon</u> because you are sleepy or tired? (A)		□	□	□	□
25. Do you have difficulty keeping pace with others your own age because you are sleepy or tired? (A)		□	□	□	□
		(4) High	(3) Medium	(2) Low	(1) Very low
26. How would you rate your general level of activity? (A)		□	□	□	□
	(0) I don't do this for other reasons	(4) No	(3) Yes, a little	(2) Yes, moderate	(1) Yes, extreme

27. Has your intimate or sexual relationship been affected because you are sleepy or tired? (I)	□	□	□	□	□
28. Has your desire for intimacy or sex been affected because you are sleepy or tired? (I)	□	□	□	□	□
29. Has your ability to become sexually aroused been affected because you are sleepy or tired? (I)	□	□	□	□	□
30. Has your ability to have an orgasm been affected because you are sleepy or tired? (I)	□	□	□	□	□

Adapted from Weaver TE, Laizner AM, Evans LK, Maislin G, Chugh DK, Lyon K, Smith PL, Schwartz AR, Redline S, Pack AI, Dinges DE. An instrument to measure functional status outcomes for disorders of excessive sleepiness. Sleep. 1997 Oct 1;20(10):835-43.

DYNAMIC AIRWAY ASSESSMENT

RESEARCH PROJECT:
The role of phenotyping in the personalised management of OSA

Name:	Date:
Age (years):	Sex: M / F
Clinician (initials):	

Awake or asleep dynamic assessment (please circle one):

AWAKE	ASLEEP

VOTE classification (0% / 33% / 66% / 100%):

Structure	Configuration		
	A-P	Lateral	Concentric
Velum			
Oropharynx			
Tongue base			
Epiglottis			

Lingual tonsil grade (please circle one):

I	II	III	IV

Palate classification (please circle one):

I (horizontal)	II (intermediate)	III (vertical)

Palatine tonsil grade (please circle one):

0	I	II	III	IV

Friedman tongue grade (please circle one):

I	IIa	IIb	III	IV

Nasal pathology:

Other comments on anatomy:

3. List of Presentations and Publications during Candidature

Presentations

Lam ME, Kitipornchai L, Ball N, Sarkissian L, Sands T, Grundy L, MacKay SG. *Incidence of Allergen Specific and Total IgE Positivity in Children Undergoing Adenotonsillectomy.* Sleep DownUnder, October 2019. Australasian Sleep Association. (Oral and poster)

Lam ME, Roberts ST, Hayward NJ, Thompson M, Kitipornchai L, Clanfield M, Jones AC, MacKay SG. *Long-Term Adherence with New Generation Positional Therapy in Treatment of Obstructive Sleep Apnoea.* ASOHNS ASM, March 2020. Australian Society of Otolaryngology Head and Neck Surgery. (Oral)

Lam ME, Kitipornchai L, MacKay SG. *PANtonsillectomy for Obstructive Sleep Apnoea.* ASOHNS ASM, March 2020. Australian Society of Otolaryngology Head and Neck Surgery. (Poster)

Lam ME, Kirstensen H, Kitipornchai L, MacKay SG. *Subglottic Plasma Cell Mucositis – An Interesting Case of Management.* ASOHNS ASM, March 2020. Australian Society of Otolaryngology Head and Neck Surgery. (Poster)

Lam ME, Jones AC, Edwards BA, Mann D, Sands T, MacKay SG. *The Role of Phenotyping in Salvage Therapy for OSA*. ASOHNS ASM, August 2021. Australian Society of Otolaryngology Head and Neck Surgeyr. (Oral)

Publications

Kristensen H, **Lam ME**, MacKay SG. *Subglottic plasma cell mucositis: a case study highlighting challenge in management.* May 2020. ANZ Journal of Surgery.

Lam ME, Kitipornchai L, Chan L, Creber NJ, Hayward NJ, Jones AC, Petersen AJ, Sarkissian L, MacKay SG. *Assessment of macroglossia as a cause of failed continuous positive pressure adherence.* July 2020. Australian Journal of Otolaryngology.

Sideris AW, Ghosh N, **Lam ME**, MacKay SG. *Peritonsillar abscess and concomitant COVID-19 in a 21-year-old male.* September 2020. BMJ Case Reports.

Sideris AW, Wallace G, **Lam ME**, Kitipornchai L, Lewis R, Jones AC, Jeiranikhameneh A, Beirne S, Hingley L, MacKay SG. *Smart polymer implants as an emerging technology for treating airway collapse in obstructive sleep apnoea: a pilot (proof of concept) study.* October 2020. Journal of Clinical Sleep Medicine.