Objective measurement of sleep disordered breathing in mandibular advancement splint and rapid maxillary expansion therapy with the Sonomat

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Statement of Authorship

The research in this thesis was conducted in the homes of the subjects, under the supervision of Professor Colin Sullivan, Professor Karen Waters and Dr Mark Norman. All treatment procedures were carried out by Dr Joachim Ngiam at a private dental clinic in Hornsby, NSW Australia. The submission of this thesis fulfils the requirements for the Degree of Doctor of Philosophy, The University of Sydney.

Approval to carry out this research was granted by The University of Sydney Human Research Ethics Committee.

I, **Joachim Ngiam**, hereby declare that I was the principal researcher and author of all work included in this thesis, including work published with multiple authors, and this work has not been previously presented for the purpose of obtaining another degree.

Signed: _____

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Summary

This thesis presents the findings of series of investigations in adults and children using a novel diagnostic test, which has been developed at the David Read laboratory, The University of Sydney for the diagnosis of sleep disordered breathing (SDB). The Sonomat™ device is a sleep testing device that has been validated against polysomnography (PSG). It senses and records breathing sounds, respiratory and body movements. It consists of specially designed vibration sensors embedded within a thin mattress designed to overlay a standard bed. Unlike other sleep diagnostic testing devices, no wires or sensors are attached to the patient. Detection of physiologic parameters occurs via the conduction of sounds and vibrations through the patient's body and bed clothes to the sensors, similar to a stethoscope. The sensors convert body sounds, vibrations and movements into an electric signal which allows discrimination of sounds, vibration and movements relating to: breathing effort, activity (body movement), snoring, airflow and heart and lung sounds. This method of diagnosis is able to generate sleep-related indices such as the apnea hypopnea index (AHI) and also provides an objective measurement of snoring.

In both adults and children, anatomic factors have increasingly been implicated as a key contributory factor to upper airway obstruction (UAO) and obstructive sleep apnea (OSA). Craniofacial and dento-morphological abnormalities such as maxillary constriction or mandibular retrusion have also been highly associated with adults and children who snore

or have OSA. Dental treatment of these common craniofacial abnormalities often involves the use of rapid maxillary expansion (RME) and mandibular advancement splint (MAS) therapies. Today, RME therapy is a routine orthodontic procedure that has increasingly been investigated as a treatment modality for children with OSA. MAS therapy is a well-established treatment option and is widely considered to be a viable treatment alternative to positive airway pressure therapy for adults who snore or have OSA. However, current diagnostic methods of assessment for SDB in patients recruited for both therapies have been predominantly based on PSG derived indices such as the AHI. Objective measurement of snoring, a cardinal sign and symptom of OSA has proven elusive. Little data exists regarding snoring, a robust measure of UAO in adults and children referred for RME or MAS therapy. Moreover, the treatment effects of RME and MAS therapies on snoring is unclear. The Sonomat™ methodology was thus used to investigate the prevalence and characteristics of SDB, in particular snoring and OSA in adults and children in a dental sleep clinic setting. It was also employed to assess the treatment effects of RME therapy in children and MAS therapy in adults with SDB in this thesis.

Chapter 1 is a review of the literature and provides a background of snoring and OSA. An overview of the impact of SDB on adults and children is presented. This chapter outlines the current treatment modalities used to treat paediatric and adult SDB. The treatment effects of RME and MAS therapy are also discussed and compared to other treatment options.

Chapter 2 outlines the general methods used in this thesis. The majority of this chapter details the methods in which respiratory events and snoring are identified and classified. Visual examples of respiratory events and snore types that are quantified by the Sonomat™ are illustrated in detail in this section.

Chapter 3 investigates the prevalence of SDB in an unselected population of non-obese children with maxillary constriction. 59 children with minimal tonsillar hypertrophy were recruited in this study. These children exhibited the hallmarks of maxillary constriction which included maxillary transverse deficiency, a high palatal vault and dental mal-alignment that required RME therapy for orthopaedic correction. The Sonomat™ objectively quantified and characterized the nature and extent of partial UAO in these children. Few children were noted in the group to have OSA but a large proportion of children exhibited obstructed breathing (OB) as typified by snoring and stertor. Runs of snoring and stertor were noted to be linked to movement arousals resulting in sleep fragmentation. Children with OB had less apneas and hypopnea but snored more frequently, highlighting the need for objective assessment of snoring.

Chapter 4 extends the research carried out in Chapter 3 by exploring the effects of RME therapy on snoring and OSA on these children recruited. The effects of RME on OSA and OB children are discussed. RME therapy substantially improved OB in the majority of children with 60% decrease in OB duration. Full resolution of OSA occurred in all 4 OSA children studied. However, a significant proportion (26%) of OB children were observed to have worsening of snoring following RME.

Chapter 5 provides a quantitative measurement of snoring in 114 adult patients referred for MAS therapy. Many of these patients snored and presented in the clinical setting with disruptive snoring as a chief complaint. However, objective measurement of snoring was not routinely performed being often subjectively assessed with the use of questionnaires or bed-partner/spousal reports. This investigation explores SDB and snore characteristics, in particular snore duration, frequency of occurrence and snore types in primary snorers, and OSA patients referred for MAS therapy. Inspiratory snoring was noted to be the predominant snore type and this occurred more frequently in women than men.

Chapter 6 investigates the effect of progressive mandibular advancement with MAS therapy on snoring and OSA in the adult subjects recruited in Chapter 5. Key to this investigation was the exploration of the dose dependent effects of mandibular advancement on snoring and snore types. Inspiratory snoring was the predominant snore type and this was observed to decrease in a dose dependent manner with a "floor effect" noted. Assessment of the therapeutic efficacy of MAS therapy with progressive mandibular advancement, based on the AHI metric and from a snore perspective was also analyzed. Progressive mandibular advancement decreased the AHI and snoring in most patients but did not resolve the problem with a substantial proportion (17%) of patients increasing in snore duration despite progressive mandibular advancement. This finding was of important clinical relevance and the significance is reviewed from the perspective of longer-term adherence to MAS therapy and side effects with MAS use.

Chapter 7 provides a brief general discussion of the findings in adult and children studied. Overall, both RME and MAS therapies were beneficial for a good majority of adults and children with a subset of patients receiving little benefit from the respective therapies. Further studies are required to identify subjects who do not benefit from RME or MAS therapy and alternative treatment options or combination therapies may be warranted in these patients.

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ABBREVIATIONS

AASM	– American Academy of Sleep Medicine	**OAT**	– oral appliance therapy
AHI	– apnea/hypopnea index	**ODI**	– oxygen desaturation index
AI	– arousal index	**OOB**	– out of bed
AT	– adenotonsillectomy	**OSA**	– obstructive sleep apnea
BM	– body movement	**PAP**	– positive airway pressure
BMI	– body mass index	**Pcrit**	– critical closing pressure
BP	– blood pressure	**PQR**	– poor quality recording
CBCT	– cone beam computed tomography	**PSG**	– polysomnography
CPAP	– continuous positive airways pressure	**Qd**	– quiescent time
CSA	– central sleep apnea	**RCT**	– randomized controlled trial
CT	– computed tomography	**RDI**	– respiratory disturbance index
EDS	– excessive daytime somnolence	**REM**	– rapid eye movement
EEG	– electroencephalogram	**RERA**	– respiratory effort related arousal
ENT	– ear, nose and throat	**RME**	– rapid maxillary expansion
EMG	– electromyogram	**ROC**	– right electrooculogram
EOG	– electrooculogram	**SARME**	– surgically assisted rapid maxillary expansion
ESS	– Epworth sleepiness scale	**SCSB**	– static charge sensitive bed
F	– Female	**SD**	– standard deviation
FTT	– failure to thrive	**SDB**	– sleep-disordered breathing
HF	– high frequency	**SaO_2**	– oxygen saturation
Hz	– Hertz	**SO**	– sleep onset
ICC	– intraclass correlation coefficient	**SEM**	– standard error of the mean
IE	– inspiratory and expiratory	**SIDS**	– sudden infant death syndrome
IQR	– interquartile range	**SWS**	– slow wave sleep
LOC	– left electrooculogram	**$TcCO_2$**	– transcutaneous carbon dioxide
M	– Male	**TRT**	– total recording time
MAS	– mandibular advancement splint	**TS**	– total snoring
MB	– mouth breathing	**TST**	– total snore time
MMA	– maxillo-mandibular advancement	**TSR**	– total snore reduction
MP	– Maximum Protrusion	**TWT**	– total wake time

MOAHI	– mixed and obstructive apnea/hypopnea Index	**UAO**	– upper airway obstruction
NREM	– non rapid eye movement sleep	**UARS**	– upper airways resistance syndrome
O_2	– oxygen	**URTI**	– upper respiratory tract infection
OA	– oral appliance	**VAS**	– visual adaptive scoring

1 LITERATURE REVIEW

1.1 SLEEP DISORDERD BREATHING

Sleep disorder breathing (SDB) refers to a pathophysiological continuum ranging from intermittent snoring to obstructive sleep apnea syndrome during sleep. Obstructive sleep apnea (OSA) is a common SDB characterized by recurrent collapse of the pharyngeal airway during sleep, resulting in a partial reduction (hypopnea) or complete cessation (apnea) of airflow despite ongoing breathing effort [1, 2]. Snoring, is precursor to OSA and is a sound caused by the vibration of tissue in the upper airway. It is a common sleep-related complaint and is a cardinal sign and symptom of upper airway obstruction (UAO) and OSA. OSA has been linked to major adverse health outcomes especially increased cardiovascular risk [3]. These disruptions to breathing are commonly associated with intermittent blood gas disturbances (hypoxemia and hypercapnia), sleep fragmentation and surges of sympathetic activation [4, 5]. Hypertension is highly prevalent in OSA and an increased incidence of cardiovascular mortality, stroke and heart attack has been reported [6-8]. There now exists robust evidence that show conclusively that OSA is a strong and independent risk factor for cardiovascular and cerebrovascular diseases [7, 9-11]. OSA has been linked to major comorbidities including excessive daytime somnolence [12], increased rates of motor vehicle accidents [13-16], poorer quality of life [17] and neurocognitive decline [18]. Thus, OSA presents as a major public health issue with significant economic and social burden on health systems and the community [19, 20].

The disorder of OSA commonly defined as having more than five abnormal breathing episodes (hypopnea or apnea) per hour of sleep has been reported to occur in 24% of men and 9% of women [2]. The additional symptom of excessive daytime somnolence (EDS) is referred to as obstructive apnea syndrome (OSAS) and this affects 2-4 % of the adult population [2]. The prevalence of OSA has been reported to be two to three times greater in males than in females [2, 21] with its maximum prevalence in the middle age group (45 to 64 yr) [22]. The effect of increasing age has been also shown to be associated with increased pharyngeal airway collapsibility during sleep independent of gender and BMI [23].

OSA is not limited to adults only as children also suffer from SDB. Large epidemiological studies in children have observed that paediatric OSA occur in 2-3% of the paediatric population [24, 25]. What constitutes normality in relation to the identification of respiratory obstructive events and the frequency of the apnea hypopnea index (AHI) is steeped in controversy and accounts for great variability in the prevalence reported [26]. Using a stringent criteria of AHI $\geq$ 5 events per hour, 1.2-7.4% of children are reported to suffer from OSA. A more common and liberal criteria of AHI > 1 event per hour results in 25-40% of children exhibiting OSA [27, 28].

The evolution of paediatric sleep apnea dates back to 1889 when Hill described snoring and restlessness at night as a cause of "backwardness and stupidity in children" [29], but it was not until 1976 that the first case series of eight children with OSA were described [30]. In more recent years, research in children have increased significantly and it is now

recognized that paediatric OSA is not a benign condition and may have significant adverse consequences to a growing child even so in milder cases of OSA severity [31-33].

Children with paediatric OSA are not “little adults with OSA”. In contrast to adults, children with OSA are likely to occur equally in boys and girls in the prepubertal ages [34]. These children typically present with snoring, restless sleep and on occasion, periods of witnessed apneas. Due to the proliferation and growth of lymphoid tissue, it has been observed that paediatric OSA peaks in the preschool years as a result of adenotonsillar hypertrophy [35, 36]. During adolescence, male predominance has been reported [37]. However, given the recent rising levels of childhood obesity, an emerging higher risk population in the middle childhood and adolescence has been noted to occur [38]. There are several important physiological and maturational changes in sleep development that occur in children particularly during infancy and in early childhood. The pathology of sleep apnea is complex in a growing child. This occurs in a dynamically changing physiological system with different rates of growth of neural, lymphoid and bony tissues observed [39]. Not surprisingly, different pathophysiologic factors account for key differences in evaluation and the management of children with OSA in contrast to their adult counterparts.

Although normal children with adenotonsillar hypertrophy constitute the majority of children with OSA, other groups predisposed to paediatric OSA have been identified. Children with craniofacial malformations are one such phenotype that display an anatomic basis for UAO. There have been multiple studies investigating the role of maxillary constriction [40-44] and mandibular retrusion [45] as key predisposing anatomic factors for paediatric OSA. Children with neuromuscular disease and reduced muscle tone [46],

premature infants [24] and obese children are included in this group of OSA susceptibility. Other higher risk groups that exhibit elevated prevalence of OSA are have been reported particularly in syndromic children with Down syndrome [47], spina bifida [48] and Marfan syndrome [49].

The chronic comorbidities associated with untreated paediatric OSAS include cognitive deficits, behavioral problems (e.g. attention- deficit /hyperactive disorder, aggression, inattention), mood swings, excessive daytime sleepiness, poor academic performance and quality of life [50]. Untreated pediatric OSA has been highly linked to adverse cardiovascular and metabolic outcomes [51]. These markers of higher blood pressure levels, increased levels of C-reactive protein, increased insulin resistance and left ventricular hypertrophy [52] suggest that childhood OSAS may increase the risk of developing severe cardio-metabolic conditions [53].

Earlier studies of children with OSA have documented a high rate of failure to thrive [30, 54], although this observation may not be a routinely observed in the clinical setting in later studies [38, 55]. In children with significant adenotonsillar hypertrophy, an accelerated growth has been reported following adenotonsillectomy [56] but the effect of growth impairment in the milder OSA and subclinical cases remain under-investigated. There have been several reasons proposed regarding growth impairment and these have been attributed to reduced caloric intake due to adenotonsillar hypertrophy, the increased caloric expenditure required during sleep due to obstructed breathing and diminished levels of growth hormone levels during disturbed sleep [55].

1.1.1 Snoring and OSA-the Case for Early Diagnosis and Prevention

The concept of OSA as a "Heavy Snorer's disease" was first proposed by Lugaresi in the late 1900's [57-59]. He proposed that snoring and OSA were two aspects of the same basic disorder: sleep-related narrowing of the upper airways [59, 60]. Lugaresi hypothesized that patients with OSA have been heavy snorers for years and even decades [58-60]. Pioneering work by their group linked snoring to cardiocirculatory problems [61] and a high risk of myocardial infarction [62]. In fact, Norton and Dunn confirmed the findings by Lugaresi and colleagues highlighting an association between snoring, hypertension and heart disease [63]. These authors suggested that snoring presented as a risk factor for other conditions related to sleep apnoea and sleep disorders. They further implicated that the treatment of snoring had direct medical benefits in addition to the alleviation of acoustic annoyance to a bedpartner. In the light of the findings of these earlier investigations, the phenomenon of snoring has today been increasingly researched. Emerging evidence is now amassing to suggest that snoring should not be considered a "benign" entity but is instead, chronic, pathologic and progressive in nature. Snoring has now been implicated in case fatality and short term mortality of patients with first myocardial infarct [64] and ischaemic brain infarction [65-68]. Emerging evidence has now linked snoring to carotid atherosclerosis [69], excessive daytime sleepiness [70, 71], headaches [72] and impaired workplace performance[71]. In men aged between 30-69 years old, habitual snoring with coexisting obesity has been associated with an increased risk of developing diabetes [73]. Women who snore are at higher risk of hypertension [74] and are predisposed to an increased risk of cardiovascular disease independent of age, smoking and BMI [75]. Interestingly, snoring in

women has been shown to be better correlated to daytime sleepiness than the AHI metric [76]. During pregnancy, physiological changes results in the increased incidence and severity of SDB [77]. Snoring is a marker for pregnancy-induced hypertension and increases the risk of foetal growth retardation [78]. In children, snoring has been linked to hypertension with reports of increased daytime systemic blood pressure and reduced arterial distensibility [79]. These findings are clinical important and highlight snoring as a potential risk factor for cardiovascular risk in children.

Snoring causes vibrational trauma and damage due to oscillatory pressure waves. In children, local inflammatory changes induced by snoring has been proposed to contribute to the pathophysiology of adenotonsillar hypertrophy [80]. These inflammatory responses and oxidative stress, coupled with alterations of protective pharyngeal reflexes further compromise upper airway patency and have been hypothesized to cause multi-organ morbidity [80] . The effects of snoring on localised nerves, muscles and blood vessels have been the subject of numerous investigations. A study in rabbits by Amatoury and colleagues document energy transmission around the carotid artery and hypothesized the potential role of snoring in carotid atherogenesis and/or plaque rupture [81]. Another animal study on peri-carotid tissue vibration also showed endothelial dysfunction suggesting a possible direct link between heavy snoring and the development of carotid atherosclerosis [82]. In adults, snoring vibrations were thought to damage the internal carotid artery and contribute to the development of early carotid artery atherosclerosis and potentially stroke [69, 83, 84]. In a recent study, a higher prevalence of carotid atherosclerosis was noted in occur in chronic heavy snorers in comparison to mild or moderate snorers highlighting the notion that elevated levels of snoring may pose as an increased risk factor for stroke [69].

Thus, it is quite evident that based on the research described, habitual snoring and OSA are associated with a vast array of adverse health outcomes. Therefore, there exist a pressing need and rationale for timely diagnosis and treatment of SDB. As snoring is prevalent in the paediatric population, it is quite fathomable to speculate that children who snore may progress to adult SDB patient if left undiagnosed and untreated. If we subscribe to the notion of OSA as a progressive snorer's disease as proposed by Lugaresi [59], the prevention of OSA disease progression would logically embrace the need to treat snoring early. In fact, the paramount change in paradigm entails the transition from the treatment of symptoms related to SDB to the prevention of SDB before disease onset. There are speculated benefits to early diagnosis and treatment and this has been proposed to include the normalization of upper airway growth trajectory and the protection of pharyngeal reflexes, with the potential to reverse the adverse effects of SDB [85].

Some evidence to support the reversibility of SDB effects on children can be found. In fact, treatment with tonsillectomy and adenoidectomy has been extensively investigated. These improvements have been documented to improve attention deficit hyperactivity disorder [86, 87], academic performance [31], right and left ventricular ejection fractions [88] and C-reactive protein, a biomarker of inflammation [89].

In adults and children, the rationale to treat milder OSA cases particularly if asymptomatic is unclear. In children particularly, there exists some debate about the need to treat snoring [90-92]. Moreover, the decision to treat children with milder OSA symptoms is controversial. Key questions relating to the clinical outcomes of mild OSA and natural history of mild OSA if left untreated have been a subject of great consternation [93]. Some clarity into this matter can be found in a study by Li and colleagues who investigated the

natural history of mild OSA Chinese children [94]. The authors observed that 29% of the mild OSA group worsened to moderate or severe OSA severity after 2 years. However, confounding factors were observed with obesity and tonsillar hypertrophy identified as risk factors for these children aged between 6-13 years old.

1.1 Diagnosis and Management of SDB

It has been now nearly 4 decades since OSAS has been reported as a distinct and prevalent clinical entity in both adults and children. Current clinical practice relies predominantly on clinical physical examination with overnight polysomnography (PSG) constituting the definitive diagnostic tool [95]. However, despite technological advances in diagnostics and treatment approaches, routine assessment for SDB both pre-operatively and post-operatively is not routinely performed in clinical practice. One of the major reasons for such discrepancies relates to the relatively labor-intensive nature of SDB investigations. One of the pressing challenges in paediatrics is differentiating between primary snoring (PS) and OSA in a cost-effective, accurate and reliable manner before recommending invasive or costly interventions. The positional statement of the American Thoracic Society is that "Polysomnography is recommended to differentiate PS from OSA". However, as the prevalence of PS is 3-12 % of the paediatric population, the availability of sleep laboratories and the cost of performing PSG in all children is impractical and cost-prohibitive [96]. Habitual snoring has been defined per consensus as the presence of nocturnal snoring for 3 or more nights on average per week and the diagnosis of OSA on alterations in respiratory parameters observed in overnight PSG [31, 97, 98]. In 2002, the American Academy of Pediatrics (AAP) issued a set of evidence-based recommendations

whereby screening for snoring should be included in all pediatric visits. The observation of whether a child snores or not should be recorded, and if noted to be present, further process instigated to assess other symptoms of SDB should be considered [98]. However, despite AAP recommendations, adherence to the guidelines for snoring assessment and screening for OSA remains poor [99] with objective measurement of snoring not performed or routinely documented.

Supervised full-night in-laboratory PSG has been regarded as the gold standard for the diagnosis SDB in adults and particularly in children. The chief outcome measure is the apnea/hypopnea index (AHI) which is a measure of the frequency of respiratory events (apneas and hypopneas). In adults, the diagnostic threshold is ≥ 5 events per hour. In children, the threshold is much lower than adults. An AHI ≥ 2 events per hour, a mixed and obstructive apnea hypopnea index (MOAHI) ≥ 1 event per hour or an obstructive apnea index ≥ 1 have been routinely used [100]. An AHI ≥ 5 events per hour has also been proposed [100-103]. In contrast to adults, the majority of children that exhibit clinically significant SDB have long periods of partial UAO during sleep with runs of labored breathing which is not reflected in the AHI metric [104]. In this regard, the validity and utility of PSG has the gold standard has been increasingly been challenged [104]. It is now increasingly recognized that PSG-derived indices do not adequately capture partial UAO that occurs in childhood SDB [105, 106]. Contemporary PSG metrics report on apneas and hypopneas but do not adequately measure periods of obstructed breathing such as snoring and stertor which are characteristic of paediatric SDB [106].

Although many PSG diagnostic systems make use of snore sensors or microphones to record snoring, the recommendations proposed by the American Academy of Sleep Medicine (AASM) for the manual scoring of sleep only capture a small bandwidth of snore sounds which may lead to underestimation of snoring events. Concerns have been raised about the poor correlation between adverse health outcomes and abnormalities on PSG related parameters [107, 108]. The use of other lower tiered home based sleep testing methods have been reviewed but conflicting results have been reported when other comorbid conditions are present [109]. In particular, CO_2 monitoring is recommended for nocturnal hypoventilation, such as in children with obesity hypoventilation and neuromuscular disease. The use of questionnaire-based assessment like the OSA-18 survey to screen for SDB has been used increasingly. However, this has been reported to have poor validity in detecting and predicting OSA especially in moderate-to-severe OSA children [110, 111]. Clinical examination of tonsils and adenoid size may help paint a better clinical picture, but poor correlation exists between the clinical findings and the presence of OSA [112]. Thus, although clinical history taking and examination may serve as good screening tools, the predictive value of history taking and clinical examination is poor.

Although parents are concerned about their children snoring and having difficulty in breathing during sleep, assessment using subjective parental reports have proved unreliable. Moreover, despite snoring being a common sign and symptom of OSA, not all children who snore have OSA [113]. Inaccuracies in parental observations can occur especially as the child gets older and sleeps in a separate room to their parents. UAO may also occur more abundantly in rapid eye movement stage of sleep which is the time when

parents are sleeping [114]. Children with SDB have less apneas and more periods of obstructed breathing which is in stark contrast to their adult counter parts who have more obstructive apneic events culminating in pauses, choking or gasping during sleep. Thus, it is quite apparent that big deficits occur in the assessment of SDB and the reliance of subjective assessment by physician or parent is fraught with grave inconsistencies.

1.1.1 Snoring and OSA- prevalence, pathophysiology and management

Snoring has been variably defined. In one description by the AASM, snoring has been characterized as a "loud upper airway breathing sound in sleep, without episodes of apneas or hypoventilation" [115]. This phenomenon has also been characterized by high frequency vibration of the soft palate, pharyngeal walls and muscular attachments, tongue and epiglottis. Snoring is a cardinal symptom of OSA and is considered a robust sign of partial UAO [116]. Although snoring is highly prevalent in adults [2], not all adults who snore have significant OSA [2]. It has been generally thought that snoring occurs during inspiration but expiratory snoring and combined inspiratory and expiratory snoring can also occur [117]. However, the significance and implications of these observations has not been extensively researched. Expiratory snoring for example has been linked to obstructive pulmonary disease [118]. Few studies in the literature have investigated snoring particularly in oral appliance therapy [119, 120] in adults or rapid maxillary expansion therapy in children. Snoring can also occur in the absence of respiratory events and can cause sleep fragmentation [121]. It occurs less commonly in children than in adults. Assessment of snoring in children has been previously subjective, reliant on parental report

and predominantly questionnaire-based. Depending on age, 3-35% of the paediatric population have been reported to have habitual snoring [32, 35, 122-124] with large study of over 20,000 children reporting 12% of children snoring habitually. In adolescents, the estimates range between 1-10% [45, 125].

Adult men snore more than their female counterparts. A wide variability in prevalence is observed with 5-86% of men and 2-57% of women snoring in comparison [126, 127]. Socially disruptive snoring is often one of the main reason patients seek treatment and may present as a problem in the home or the bedroom setting. Problematic snoring occurs more in men at 17.9% as compared to 7.4% in women and appears to peak between the ages of 55-59 and 60-64 years of age in men and women respectively [128].

The risk factors for adult OSA are multifactorial. The epidemiological major risk factors include aging, obesity and male gender [5]. The precise underlying mechanisms remain unclear but are likely attributable to increased anatomic compromise, increased pharyngeal dilator muscle dysfunction, lowered arousal threshold, elevated ventilatory control instability and lowered arousal threshold [5]. Other factors include craniofacial morphology [44], ethnicity [129], neck circumference [130], tongue size [131] and allergic rhinitis [132]. Alcohol consumption [133], the use of sedatives [134] and sleeping in the supine position [135] have also been implicated in the pathogenesis of SDB. In addition to the risk factors described above that contribute to OSA pathogenesis, other physiological variables such as REM sleep [136], the surface tension of the liquid lining the upper airway and sensory impairment of the upper airway may impact on OSA [5].

The mechanisms underlying paediatric SDB are multi-factorial. Risk factors for paediatric SDB typically include adenotonsillar hypertrophy[30]. A two-to fourfold increase in vulnerable populations such as black Afro-American children and children born preterm has been reported [24]. Poor socio-economic status has been associated with SDB due to unhealthy diets and lack of exercise [137]. Craniofacial morphology [138, 139], septal deviation [140], the presence of respiratory allergy especially allergic rhinitis [141], asthma [142] have also been observed as risk factors.

Paediatric OSAS shares both distinct and similar characteristics to adult OSAS. From birth to adulthood, narrowing and increased collapsibility of the pharyngeal airway during sleep appears to be the final pathway to UAO [143]. Genetic factors may play a role with some evidence of intergenerational transmission within families reported [144]. In contrast to the male predominance in adult OSAS, an equal distribution between males and females is noted in pre-pubertal children with OSAS [24, 145]. The most common association in children is that of adenotonsillar hypertrophy with moderate association observed with being overweight [146, 147]. Children with OSAS have an anatomic predisposition to upper airway collapse. These reductions in upper airway calibre have been investigated with acoustic reflectometry [148] and magnetic resonance imaging (MRI) [146]. The site of maximal airway narrowing in children corresponds to the vicinity where the adenoids, tonsils and soft palate overlap [146]. Parapharyngeal fat pads and abdominal visceral fat have been reported to be larger in obese children with OSA although a direct association with severity of OSA has not observed [146]. These findings parallel the observations in the adult OSA population where obesity has been found to increase parapharyngeal fat pads or visceral neck fat as compared to healthy controls [149, 150]. However, although fat deposition in this area of the upper airway is thought to adversely impact pharyngeal size

and shape thereby increasing the propensity for upper airway collapse, MRI studies suggest that the size of the lateral pharyngeal walls contribute to increased upper airway collapsibility to a greater extent than adipose tissue [149, 151].

Given the alarming and rising rates of childhood obesity [152], the historical prototype of the paediatric OSA patient presenting with adenotonsillar hypertrophy is now being replaced by a different phenotypic presentation resembling that of an adult OSAS patient. Not surprisingly, the notion that paediatric OSA is not one but two distinct disease entities has been advocated [153]. The term Type I paediatric OSA refers to the original presentation of children with marked lymphadenoidal hypertrophy in the absence of obesity. Type II refers to obesity related OSA with milder upper airway lymphadenoidal hyperplasia in children, which mimics the typical presentation of adult OSA patient [153]. This classification delineates the different clinical manifestation and management strategies to help improve longer term treatment outcomes.

There now exist a substantial body of literature focussing on the pathophysiology and consequences of untreated OSA in adults [5]. This disorder is associated with increased mortality, morbidity [154, 155] and adverse economic implications [156] for the community. A similar picture is evolving in the paediatric arena highlighting that SDB in children can lead to significant morbidities that affect the central nervous system, the cardiovascular and metabolic systems impacting somatic growth and ultimately diminish the quality of life in children [157, 158]. In addition to the adverse effects on multi-organ systems in the developing child, The AASM states that untreated OSA children can lead to neuro-cognitive and behavioural deficits including aggressive behaviour [159], development delays leading to a failure to thrive [160], attention deficit/hyperactivity

disorder [161] and poor academic performance [31, 162]. Retrospective observations of a 11 year longitudinal study of 4 year olds with early sleep disturbances were highly associated with behavioural and emotional problems later in the adolescent years [163]. In children, snoring is no longer considered benign but a key sign and symptom of UAO that warrants early diagnosis and effective management. If left unchecked, it can alter the trajectory of normal growth and development in a child and negatively impact their future for the rest of their lives.

The management of OSA differs between adults and children. In children, the primary treatment is adenotonsillectomy (section 1.1.2). Other treatment options such as CPAP, and dental treatment options such as rapid maxillary expansion (RME) and oral appliances are also proposed. These will be reviewed in the sections below. Pharmacotherapy has also been predominantly proposed for the management of OSA [164, 165]. Recent investigations indicate that drugs with noradrenergic and antimuscarinic effects improve genioglossus muscle activity and upper airway patency during sleep [166, 167]. Leukotriene modifiers such as a montelukast in OSA children aged 2- 10 years old have shown promising results in the short term [168]. In adults, treatment can be broadly classified into surgical and non-surgical options. CPAP (section 1.1.3) remains the gold standard non-surgical option but increasingly oral appliance therapy (section 1.5) has gained popularity for the treatment of snoring and mild/moderate OSA severity. Surgical techniques by way of nasal and soft palate surgery [169], uvulopalatopharyngoplasty [170] and MMA surgery [171] are emerging as robust treatment options for OSA. Overall, currently strategies for OSA management involve the identification of key pathophysiological mechanisms that contribute to SDB. A personalized and targeted

treatment approach to the underlying causes are proposed to optimize treatment outcomes [172].

1.1.2 Adenotonsillectomy as First line Treatment for children with OSA

In 1930, Scammon first described the differential growth rates between hard and soft tissues throughout childhood development [39]. This different rate of growth has enormous ramifications for the upper airway in children with important implications for SDB. In the newborn infant, the epiglottis is located close to the soft palate [50]. Neonates are obligate or preferential nasal breathers but the mode of breathing changes as the upper airway matures. With growth, the larynx descends to the level of the fifth cervical vertebrae by age 1 and 2 years old. This vertical growth of the larynx and descent of the epiglottis facilitates the newly acquired function of speech and phonation for the child [173]. Further growth transpires with the descent of the hyoid bone and posterior third of the tongue to form the anterior wall of the oropharynx. During this period of dynamic growth, hypertrophy of the adenoid and tonsils often exceed the growth of the surrounding hard skeletal structures. This increase in soft tissue mass relative to the bony anatomic surroundings occurs during the ages of 4 and 6 years old and not surprisingly, this coincides with the peak period during which OSA is often observed in children [174-176].

In children with paediatric OSAS, adenotonsillectomy (AT) has been proposed as the first line treatment of choice. Historically, this procedure was performed in the late 1970s to treat children with enlarged tonsils or adenoids [177] and was often carried out without

objective pre-surgical measurement of OSA severity. Earlier studies with short follow up duration have previously suggested that AT was highly efficacious in children of normal weight and overweight children. However, it should be stated that in the earlier years, routine post-operative PSG assessment was not routinely performed due to practicality, economic considerations and availability to patients. Post-operative assessment has often been reliant on subjective outcomes with parental reports set as the "benchmark" for therapeutic success. However, since the earlier years, several follow-up studies have revealed that AT may not be as effective as previously thought [87, 178]. Complete resolution of OSA defined as AHI < 1 event/hour has been reported to range between 25% - 40% [178-180]. More recent studies have in fact highlighted the persistence of paediatric OSA despite AT with significant proportions of children noted to have residual OSA [87, 140, 178, 179, 181, 182].

Nonetheless, the role of AT in improving academic performance has been documented. In a large-scale study of young children (mean age 6 years old), OSA was diagnosed in 18% of the children who performed in the lowest 10% of the first grade [31]. Following AT, a significant improvement was noted in this cohort of children with OSA. Snoring and the role of AT in mitigating poorer academic performances was also investigated in middle school children aged between 13-14 years old. Gozal and colleagues found that children with lower academic performance in middle school were more likely to have snored during early childhood which required AT in comparison to better performing classmates. The authors concluded that SDB associated neurocognitive morbidity may be only partially reversible and that a "learning debt" may accrue in the earlier developing years which might impair academic performance in the later years of childhood [162].

Investigation into the natural history of snoring and paediatric OSA is critical to our understanding of the underlying pathophysiology of paediatric SDB and its management both in the short and longer term. Earlier research has unfortunately been short term in nature, predominantly focussing on younger children and often without robust objective PSG measures. Longer term follow-up studies (3-7 years) have investigated children who returned for follow-up due to relapse of SDB-related symptoms. These studies have painted a bleaker picture suggesting that post-AT intervention, paediatric OSAS and symptoms may be persistent and not expected to improve significantly in the longer term [183-186].

Thus, it is evident that AT is not a panacea for children with paediatric OSA and a complex interplay between other factors may be apparent. Several studies shed light on this matter and highlight the multi-factorial nature of this condition. Enlarged lymphoid tissue may not be solely responsible and other contributors have been implicated as risk factors with craniofacial anomalies, syndromic conditions such as Downs syndrome, obesity and OSA severity playing key factors in residual OSAS after AT intervention [178, 187-189].

Further evidence regarding anatomic factors and adenotonsillar hypertrophy contributing to residual paediatric OSAS may be found in recent data published by the Kaditis group. Their research showed minimal differences in lymphoid tissue size between OSAS and controls in younger children. However, it was noted that in older children (8-10 years old) with SDB, these tissues were similar in tonsillar size to younger children with SDB suggestive that tonsils did not shrink in children with OSA [190]. These finding sheds light onto the relative discrepancy model between tissue size and airway calibre size as proposed by Watanabe and colleagues [191] suggesting that airway compromise in this age

group may be more related to anatomic factors as caused by deficiencies in craniofacial development as opposed to excessive lymphadenoidal hypertrophy as previously thought.

Although the rationale to perform AT in severe OSA is children is warranted; in milder cases of OSA severity, as in the case for primary snorers, the decision to instigate surgical intervention may be controversial and unclear. The Childhood Adenotonsillectomy Trial (CHAT) has shed some light of this matter and has provided some evidence evaluating the efficacy of early AT versus a conservative "watchful waiting" approach in children (age range 5-9 years) with moderate OSA (AHI range 2-30 event/hr) [192]. Marcus and investigators found beneficial effects of early AT improvements in certain domains including polysomnographic outcomes and quality of life, but no significant change in attention or executive function. However, it is important to state that this landmark study was based on PSG metrics and did not vigorously explore upper airway obstruction and in particular snoring. Recent re-analysis of the CHAT study however show poor correlation with the AHI metric and treatment related outcomes following AT [193] highlighting the deficits in contemporary methods of SDB measurement.

1.1.3 Positive Airway Pressure

Positive airway pressure (PAP) applied by a nasal mask, more commonly referred to as nasal continuous positive airway pressure (CPAP) was first introduced in 1981 by Sullivan and coworkers who suggested that nasal CPAP acts as a pneumatic splint that prevents the collapse of upper airway pharyngeal space [194]. It is widely considered as the gold

standard treatment of snoring and OSA. Upper airway dilation occurs predominantly in the lateral dimension when CPAP is applied and progressive increases in pressure results in increased upper airway volume and thinning of the lateral pharyngeal walls [149].

Randomized controlled trials have demonstrated it being highly effective in improving many health outcomes including subjective sleepiness [195], blood pressure [196] and quality of life [197] in moderate to severe OSA patients [198]. Some evidence suggest that CPAP treatment may lower motor vehicle crashes [199]. In severe OSA patients, long term treatment with CPAP may also reduce the incidence of cardiovascular events [154]. However, despite its well documented efficacy in improving snoring, OSA and health related outcomes, many patients find it difficult to adhere to this mode of therapy either outright rejecting this treatment or using CPAP partially [200]. Thus, although high efficacious, these barriers to widespread adoption limits the clinical effectiveness of CPAP resulting in sub-optimal results in a high proportion of patients. Adherence to CPAP is variable and often poor and subject to individual tolerability and perception of benefit. When acceptable CPAP compliance was defined as the use of a machine for more than 4 hours a night for more than 70% of the observed nights, a rate of 46% compliance was attained [201]. More recent data from the Australian SAVE trial demonstrated low compliance with mean nightly use of 3.3 hours with CPAP in moderate-severe OSA adult patients. The authors concluded that based on the limited hours of nightly usage, CPAP did not prevent cardiovascular events but improved quality of life in OSA patients with established cardiovascular events [202]. Serious side effects with CPAP therapy in adults are rare. They generally involve nasal mask discomfort and leaks with common complaints of nasal congestion, mucosal dryness and rhinorrhea reported [203]. Dento-facial changes

as a result of CPAP use have been also highlighted [204] and these effects have been attributed to compression forces exerted on craniofacial and dental structures.

In children, nasal continuous positive airway (nCPAP) pressure generally remains secondary to AT. It serves as a non-surgical treatment option and is a highly efficacious treatment alternative for paediatric OSAS. However, limited compliance to this mode of therapy remains a realistic limitation in children [205, 206]. Moreover, the long-term implications of nCPAP therapy with mask delivered systems in growing children is poorly understood. Several studies have documented adverse dentofacial side effects including mid-facial hypoplasia following prolonged nCPAP therapy [207, 208]. However, a recent small cephalometric study in children (mean age 9.0 years) undergoing PAP for a minimum of 6 months for at least 6 hours of use showed negligible change [209]. Nonetheless there is a need for treatment alternatives that are equally effective, and preferably targeting the individual pathophysiology in each child.

1.2 Mouth breathing, Craniofacial Growth and SDB

The influence of the mode of breathing on craniofacial and dentofacial growth is widely debated and still steeped in much controversy [210, 211]. It is generally accepted that cartilage is the primary determinant of craniofacial growth at the cranial base synchondroses. According to the functional matrix theory proposed by Moss and Salentijn [212], growth in the craniofacial and dentofacial complex occurs in response to functional

needs and possibly in response to growth of the nasal cartilage [212]. This theory is based on the principle that normal nasal breathing promotes harmonious growth and exerts influence on the development of craniofacial structures by stimulating the associated structures of the head and neck region during mastication, swallowing and breathing [213, 214].

The interaction between growth of the craniofacial complex and muscle activity is complex and is believed to start in early development and continues throughout childhood to the adolescent stage. Normal upper airway patency promotes nasal respiration and normal growth and development of the naso-maxillary complex. UAO stimulated by enlargement of lymphoid tissue, asthma and respiratory infections such as allergic rhinitis can result in increased upper airway resistance that culminates in mouth breathing (MB). Chronic MB is an important clinical sign and symptom of UAO in the child. It has been proposed as a clinical marker of orofacial muscle dysfunction, which may be associated with palatal growth restriction and nasal obstruction [215].

MB is common phenomenon in the paediatric population [186] with estimates ranging from 10-25% in children reported [216]. MB has a multifactorial aetiology and may result from anatomical obstructions due to enlarged palatine and pharyngeal tonsils, enlarged turbinates, nasal septal deviation, nasal polyps or allergic rhinitis. Children who mouth breathe due to adenotonsillar hypertrophy commonly exhibit a forward head posture, a retrognathic mandible, an increased anterior facial height, a steep mandibular plane, and lowered position of the tongue and hyoid bone [217].

MB has been implicated in the re-emergence of SDB after AT in susceptibility children [215] and has been proposed as a marker of and possible precipitator of SDB in children [215]. It has been implicated in deviations in normal orofacial growth and development [218-220], respiratory infections [221], oral malodor [222] and although it has high associations with nasal obstruction and abnormal airway muscle dysfunction, its direct causal link to paediatric OSAS is unclear and warrants greater investigation. Nonetheless, the pivotal role of adequate nasal airway development and patency has been well supported in the literature underpinning its importance in normal orofacial growth and development [215, 218, 223, 224]. The next section discusses the associations of MB with nasal obstruction and abnormal airway muscle function and activity and SDB in children.

1.2.1 Craniofacial Growth and Functional Implications on Craniofacial and Dental Form

The deleterious effects of MB due to nasal obstruction on orofacial growth has been investigated over the course of the last century. As early as 1868, the term “adenoidal facies” was first observed and described by Meyer. He observed that nasal resistance caused be nasal obstruction from enlarged adenoids led to typical facial characteristics often coined as “long face syndrome”. This relationship of aberrant orofacial growth described deviations in growth of the maxilla and mandible often resulting in skeletal and dental anomalies during growth and development.

Linder-Aronson proposed the cause and effect relationship between increased airway resistance and craniofacial disharmony or malocclusion [224]. Chronic nasal obstruction leads to MB, resulting in an anterior and lowered posture of the tongue, open-mouth posture, a lowered mandibular posture and reduced orofacial muscle tonicity [224, 225]. This is thought to be a compensatory mechanism in response to the decreased nasal airflow in an attempt to maintain respiration. The imbalance results in the disharmonious growth and development of the orofacial structures and may manifest as discrepancies in craniofacial and dentofacial form [224, 226]. These may include maxillary constriction and retrusion, under-development of the mandible, altered head and neck posture and excessive proclination of maxillary teeth.

Animal studies in rhesus monkeys with induced nasal obstruction have also documented a combination of these features including an increase in facial height, reductions in maxillary length, width and anterior crossbites [227-229]. Although the findings in animal studies may not be extrapolated to humans, observations in these experimental studies attributed morphometric changes in skeletal form to the altered muscle pattern caused by nasally induced obstruction that led to chronic MB. Noteworthy in the rhesus monkey studies, attenuation of nasal obstruction at 6 months led to improvements in skeletal morphometric development and restoration of nasal breathing. However, a continuation of MB ensued when nasal obstruction persisted with no improvements in morphometric skeletal developmental changes noted. In humans, some evidence regarding the reversibility of adverse changes induced by MB due to enlarged adenoids can be found. Following adenoidectomy, the restoration of nasal breathing can appears to facilitate maxillary and

mandibular growth [217]. The flow on effects on dental structures have also been reported with normalization of incisor position noted [230].

1.2.2 Craniofacial and Dental Morphology in Obstructive Sleep Apnea

In both children and adults, an association between dentofacial morphology and SDB has been observed. Although adenotonsillar hypertrophy and obesity are the key contributors to SDB in children, dentofacial morphology has also been linked to compromised upper airway patency [231]. MB in SDB is associated with altered craniofacial growth [224]. This compensatory behaviour alters muscular recruitment in the oro-nasal region [232]; often altering habits and head posture with adverse effects on dental and craniofacial growth and development [233]. Between the ages of 6 and 8 years old, the PANIC study using questionnaires has highlighted that craniofacial morphology poses as a higher risk factor for SDB than obesity [231]. In children, cephalometric studies suggest that certain craniofacial morphological traits such as long and narrow faces, transverse insufficiencies such as maxillary constriction and mandibular retrognathia are associated with upper airway constriction and SDB [234-237].

Children who are primary snorers exhibit mandibular retrognathia [41, 139, 236]. This observation of mandibular retrognathism with a lower hyoid position and decreased mandibular volume has also been reported in 3D imaging studies [238]. Several studies have also suggested that increased lower anterior facial height and mandibular plane angle are

associated with OSA [224, 236, 239]. However, a strong association with these phenotypical traits found in vertical facial growers has not been substantiated in a meta-analysis [40]. This observation highlights the fact that OSA does and can occur in other growth patterns such as brachyfacial patients with considerable heterogeneity noted. These imaging studies suggest that anatomic factors such as retrognathia results in posterior tongue base collapse which further compromises posterior airway patency. Retrognathia has been associated with a high arched narrow palate due to lowered tongue posture. In fact, there have been multiple studies using dental models that report a link between craniofacial and dental arch morphology with snoring and OSA [41, 240, 241]. Moreover, partial UAO that occurs in asthma and perennial rhinitis has been also proposed to be highly linked to deviations in dentoalveolar morphology [242-244] with higher incidences of malocclusion noted [243]. More recently, the use of rapid maxillary expansion has been proposed as a treatment for OSA patients with maxillary constriction (Section 1.4). These preliminary studies report favourable improvement in respiratory indices. Overall, although these studies suggest an association between morphology and OSA, the causality of dentofacial morphology and the pathophysiologic pathway to SDB has not been substantiated.

In adults, dentofacial morphology has also been linked to a compromised upper airway. This has been particularly noted in the non-obese patient with OSA suggesting that other factors such as anatomic structures alone or in concert with obesity may contribute in part or whole to the pathophysiology of OSA [245, 246]. Multiple studies have identified a range of craniofacial and dental morphological characteristics associated with OSA. For example, a retrusive mandible, lowered hyoid position, retrusive maxilla are highly linked with OSA

[247] and snoring [248]. In children, the association between SDB and dental arch morphology has been well documented [138, 240]. These are summarised in Table 1 below.

Craniofacial morphological abnormalities in OSA

- Maxillo-mandibular retrusion in relation to anterior cranial base
- Increased mandibular plane angle
- Increased anterior facial heights
- Lowered hyoid bone
- Reduced mandibular length
- Reduced pharyngeal airway space
- Elongated soft palate
- Increased tongue size

Dental morphological abnormalities in OSA

- Maxillary constriction
- High and narrow palate
- Open Bite
- Anterior and Posterior Crossbite
- Maxillary/mandibular dental crowding
- Decreased intermolar width

Source: Ngiam, J., & Cistulli, P. (2015). Dental treatment for paediatric obstructive sleep apnea. Paediatric Respiratory Reviews 16; 174-181.

Table 1. Craniofacial and dento-morphological abnormalities associated with OSA. A wide spectrum of craniofacial and dento-morphological changes can be associated with OSA. Maxillary constriction in such an example that can manifest in both adults and children with OSA.

Earlier dental studies using questionnaire-based assessment and more recently PSG based investigations have linked snoring to a range of clinical symptoms and dentofacial morphological traits. Children with obstructed breathing may exhibit craniofacial abnormalities. Lofstrand et al. [38] compared 48 obstructed children with a control group of

4-year-old children with ideal occlusion. Children who snored every night or had apnoeic episodes showed a higher rate of disturbed sleep, MB and a history of throat infections. A smaller cranial base angle and a lower ratio of posterior/anterior total face height were also seen. The obstructed children had a narrower maxilla, a deeper palatal height, a shorter lower dental arch with a higher prevalence of lateral crossbite [241]. A very recent study using the Sonomat™ (see General Methods) which can provide accurate measurements of UAO supports this earlier observation of snoring with sleep disturbance [105, 106]. Norman and colleagues using the Sonomat™ identified that snoring and stertor are associated more with sleep disturbance than apneas and hypopneas in paediatric SDB [106].

In a recent study, children with chronic snoring were also documented to have a dolichofacial growth pattern with high mandibular plane angle, narrow palate, severe crowding in the maxilla and the mandible, allergies, frequent colds, and habitual MB [138]. The negative impact of respiratory obstruction is not isolated to SDB alone. Children with asthma also exhibit increased malocclusion and MB [242, 243] with significant deviations in dento-alveolar morphology such as maxillary constriction [244].

1.3 Paediatric SDB-Changing the paradigm

1.3.1 Therapeutic implications of Surgical and Dentofacial Orthopaedic Intervention

There exist now robust data that suggest that early diagnosis and treatment of SDB with tonsillectomy or adenoidectomy is associated with marked improvements and reversibility of disease-associated comorbidities [188, 249-251]. Increasingly, more studies support

improvements in dentofacial morphology following surgical intervention [251-253]. The improvements in craniofacial and dentofacial metrics have been postulated to occur from normalization of orofacial muscular patterns and tongue posture likely mediated by the restoration of nasal breathing and improved upper airway patency. In 1991, Hultcrantz and colleagues reported normalization in 77% of open bites and 50-65% of buccal and anterior crossbites in 22 children treated with tonsillectomy, with better results achieved in children operated before the age of 6 years old [252]. In 2006, Zettergren et al. in a five year study compared 17 OSA children with age and sex-matched controls [253]. At baseline, OSA children exhibited a more posteriorly inclined mandible, a more anteriorly inclined maxilla, a greater lower anterior face height, a shorter anterior cranial base, retro-clined upper and lower incisors, reduced airway space and a less pronounced nose. Five years after AT, there were no significant differences between the groups except for anterior cranial base length and a shorter nose. The results of from these surgical studies support the hypothesis that UAO in a growing child may contribute to the evolution of OSA by promoting unfavourable skeletal and dental growth, and also highlight the possibility that earlier intervention may reverse the unfavourable effects of OSA on the craniofacial and dentofacial development.

In the dental and orthodontic field, there has been a gradual evolution of a new interdisciplinary field of dental sleep medicine. The advances in dental strategies (e.g. RME and MAS therapy) have focused on the correction of anatomical imbalances thought to contribute to SDB. This has been principally based on the postulate that UAO results in MB which negatively impacts craniofacial development, and oro-musculature tone [225]. Anatomical imbalances as exemplified by skeletal insufficiencies have therefore been the key focus for orthopaedic correction. In fact, older orthodontic techniques such as cervical

headgear therapy has been reviewed in light of the possible contribution to SDB [254]. Newer orthodontic techniques are emerging for example combining RME with distraction osteogenesis in the mandible to correct transverse discrepancies in the upper and lower jaws [255]. The use of reverse pull headgear to protract the maxilla so as to ameliorate the effects of maxillary retrusion on SDB has been also proposed [256]. Progressive research into the hypothesized detrimental role of dental extractions on SDB has culminated in a retrospective questionnaire-based [257] and imaging [258] studies that evaluated upper patency from an OSA perspective.

To address anatomical discrepancies, various dental treatments have evolved over the last 2 decades to target specific areas of UAO. In children for example, the RME implemented in this study was initially used to treat dental malocclusion. Studies as early as 1975 reported medical benefits of RME [221] and it was not until several decades later, that research into RME on SDB began. In the case for MAS devices, this mode of therapy evolved from oral devices used to treat mandibular retrognathia in children with Pierre Robin sequence. The link to sagittal discrepancies as another potential source of UAO due to retroglossal tongue base collapse resulted in oral appliances for children and MAS for adults as we know it today. Surgical assisted rapid maxillary expansion (SARME) in adults [43, 259-261], maxillo-mandibular expansion [255, 262] and maxillo-mandibular advancement (MMA) surgical strategies [171, 263, 264] followed over time and enabled surgical options for orthopedic correction of transverse and bi-maxillary deficiencies.

For children with SDB, recent research has focused on emerging dental treatment options for paediatric OSAS [265], such as rapid maxillary expansion [43, 266, 267] , oral appliances

[268] and distraction osteogenesis [269, 270]. In both syndromic and non-syndromic children, the preliminary data have shown encouraging results and generally demonstrated improvements in respiratory function and some alleviation of OSAS symptoms. For adults with SDB, the use of oral appliances such as mandibular advancement splints [271] and surgical interventions (e.g. SARME and MMA) provide correction of skeletal discrepancies in the vertical, transverse and sagittal planes to improve upper airway calibre size and breathing. Weaker evidence is noted in the role of oral appliances for paediatric OSA [272]. Two Cochrane reviews have been performed by Carvalho and colleagues in 2007 and 2016 [272, 273] to examine the effectiveness of oral appliances and functional orthopaedic appliances for paediatric OSA. Noteworthy, of the hundreds of trials included for review, only one study investigating 23 children with OSA was included [272]. The review concluded that there was insufficient evidence to support or refute the effectiveness of these devices for the treatment of paediatric OSA presently.

However, robust evidence can be found in the orthodontic literature that support the role of orthodontics in the management of SDB in both adults and children [272, 274, 275]. It is important to state however that in most of these reviews and meta-analysis, assessment of therapeutic efficacy has been based on AHI metric. Nonetheless, these dental, orthodontic and surgical treatment options have been proposed to serve as viable or adjunctive treatment alternatives to AT and CPAP therapy. They play an emerging role in the management of paediatric OSAS, with the potential to normalize craniofacial and dentofacial morphology, alter tongue posture and mode of respiration, so as to restore a normal trajectory of growth and development in children.

1.4 Rapid Maxillary Expansion for Paediatric OSA

1.4.1 Rapid Maxillary Expansion (RME)- Past to Present

RME is a routine orthodontic technique first described by Angell in 1860, who used a jackscrew to widen the maxillary palatal halves [276]. When originally published in the Dental Cosmos journal for the correction of maxillary constriction [277], this novel method of maxillary expansion was met with much controversy and scepticism about its validity in attaining the described effects. It took almost a decade of clinical dormancy before it was brought back into favour by Haas in 1961 [278]. This form of therapy is essentially a form of distraction osteogenesis and was first linked to paediatric SDB when investigators observed a decrease in nocturnal enuresis in children, a common sign and symptom associated with SDB [279-281]. There now exist an expansive body of literature in the literature investigating the effects of RME on various treatment outcomes [221, 282-284]. Today, RME is still routinely used today as an orthodontic treatment to correct maxillary transverse deficiencies and posterior crossbites. The technique consists of application of orthopaedic force to the mid-palatal suture by means of a rigid device anchored to the maxillary teeth and surrounding soft tissue (Figure 1).

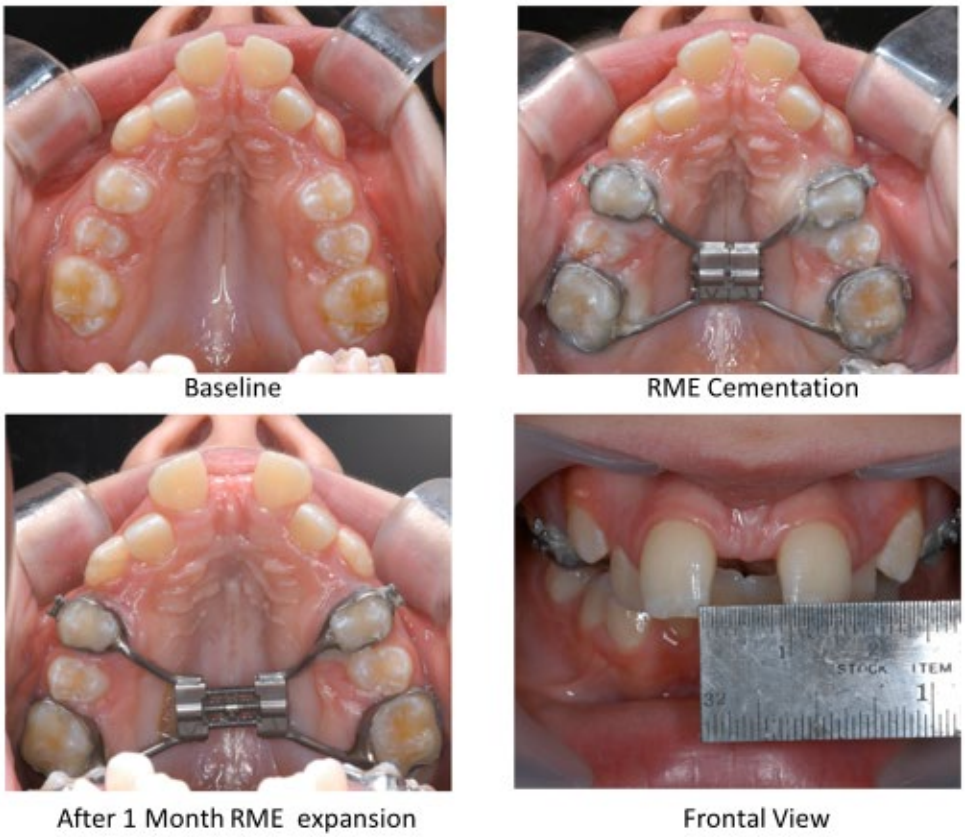


Figure 1. Maxillary Constriction and RME therapy. Maxillary constriction is depicted at baseline with dental mal-alignment and a high palatal vault noted. A fixed RME device is cemented and following screw activation, widening of the mid-palatal suture is observed. After 1 month, separation of the palatal halves can be observed with an increase in maxillary transverse width. The frontal view illustrates separating of the upper central teeth which has occurred during the 1-month period. The space between the upper central teeth will spontaneously close due to transeptal periodontal tissue attachments. The RME device is retained intra-orally for a period of up to 6 months before removal.

The maxillary and palatine bones disarticulate along the mid-palatal suture with the orthopaedic forces dissipating across cranial and circum-maxillary sutures [285, 286]. A triangular pattern of widening with a wider base in the anterior maxillary region has been noted to occur with significant increase in nasal width and decrease in maxillary sinus width seen with cone-beam computed tomography (CBCT) investigations [287].

The role of RME in promoting oral and general health in children has been canvassed by numerous authors spanning several decades. As early as 1975, the role of RME for impaired nasal respiration was proposed for medical reasons. Lindsay Gray in a study of 310 adults and children explored the effects of RME across a wide range of medical conditions including, upper respiratory infections, allergic rhinitis, septal deformity, asthma, nasal and ear infections [221]. In this study, RME was also indicated for dental crossbite, Class III malocclusion, cleft palate and maxillary constriction. Although subjectively assessed, a remarkable 87% improvement was noted over a selection of conditions reviewed.

1.4.2 Mechanism of RME on Sleep-disordered breathing

Although the exact mechanism that accounts for the beneficial effects of RME on SDB is unclear, much of these results are attributed to the way RME exerts orthopaedic forces on the maxilla and circum-maxillary sutures. Several studies have documented increases in nasal width and volume [288, 289] and decreases in airway resistance up to 90 days post RME [290]. Using computational fluid dynamics, Iwasaki et al. demonstrated significant reductions in nasal resistance and maximal negative pressure in the pharyngeal airway during inspiration [291]. These observed reductions are thought to contribute to the alleviation of paediatric OSA. Whilst the long term effects of these changes are unclear, they have been noted to persist 11 months after RME [292] but attenuate somewhat after 30 months [290, 293].

Nasal cavity and nasopharyngeal volumes have also been reported to increase significantly with CT imaging following RME [294]. In 2013, Iwasaki and co-investigators studied

twenty-eight children (mean age 9.96 ± 1.21 years) with nasal obstruction who required RME treatment with CBCT imaging. Significant enlargement in pharyngeal airway volume in the RME group was observed when compared to controls [295]. However, several CBCT studies have reported significant retropalatal and not oropharyngeal airway changes in children treated with RME [296, 297], suggesting that effects of RME were mainly attributed to changes in the nasal cavity. It has been suggested that RME can also improve oropharyngeal space as oral volume is increased through maxillary transverse expansion modifying the resting posture of the tongue [295]. In Class II patients with mandibular retrusion, forward repositioning of the mandible has also been documented to occur following RME [298, 299]. This anterior tongue repositioning associated with RME has been speculated to contribute to increased upper airway patency.

1.4.3 RME for paediatric OSA

The use of RME on OSA patients was first demonstrated in adults [43, 300] . Cistulli and colleagues demonstrated 70% improvement in their cohort of 10 adult patients, with significant reduction in AHI noted (19 ± 4 vs 7 ± 4 events/hr, $p < 0.05$) [43]. However, it is important to state that a significant proportion of the adult patients exhibited residual symptoms and required surgical assisted RME (SARME) due to ossification of the mid-palatal suture. Since then there have been a growing number of studies addressing the therapeutic effectiveness of RME in children with OSA [275]. Pirelli and colleagues prospectively studied 31 children (mean age 8.7 years) with maxillary constriction and OSA who did not exhibit adenotonsillar hypertrophy with baseline AHI of 12.2 ± 2.6 events /hour [301]. Four to six weeks after RME, the mean AHI reduced to 9.8 ± 2.7 events/hour. At the

4-month follow-up, the AHI further reduced to 0.4 ± 1.1 events/hour. A marked increase in nadir SpO_2 from 78.5 ± 8.2% to 95.3 ± 1.7% and decrease in the duration of the longest apnea time was also witnessed. A 12 year follow-up on these original 31 children to evaluate the long-term efficacy of RME was carried out by the same group of investigators [302]. Although a high dropout rate was reported, the stability of OSA resolution as measured by PSG findings was noted demonstrating the potential long-term effects of RME on OSA outcomes.

In a small prospective study, Villa and investigators studied 16 OSAS patients (mean age 6.6 ± 2.0; 9 males) with dental malocclusion treated with RME [303]. At one year follow up, 14 children completed the study with two lost to follow up. Eleven children had adenotonsillar hypertrophy but did not undergo AT during the study. The mean AHI decreased from 5.8 ± 6.8 events/hr to 2.7 ± 3.5 events/hr six months after RME with further reductions to 1.5 ± 1.6 events/hr (p=0.005), 12 months later. The authors found that significant reductions in mean AHI occurred in children with mild tonsillar hypertrophy (5.6 to 1.0 events/hr, p = 0.034) as compared to children with severe tonsillar hypertrophy (6.2 to 2.3 events/hr, p = ns).

The authors followed-up 14 patients (age range 4-11 yrs) in the above study for a period of 36 months [304]. These children with OSA had dental malocclusion (high or constricted maxillary palates with associated deep, retrusive or crossbites). A remarkable 79% of treated patients reported significant decreases in the AHI with the restoration of nasal breathing in all patients. Noteworthy, there were no objective measures of snoring reported in the above

studies. Nonetheless, the improvements were attributed by the authors to the enlargement of space made available by RME for adenoids and tonsils. To study the longer term efficacy of RME on OSA, the same authors followed 8 of the 16 children initially recruited for the study [304]. Two years after completion of RME, no significant changes were noted in the mean AHI (2.4 ± 2 events/hr vs 2.3 ± 1.7 events/hr, p = NS), highlighting the potential long-lasting effects of RME.

To date, there have been only few reviews and meta-analyses [274, 275, 305, 306] evaluating RME as a treatment modality for paediatric OSA. One meta-analysis evaluated the effect of orthodontic therapy with RME, and oral appliances in children with OSA [274]. Few studies met the inclusion criteria for analysis and although improvements were noted in PSG variables such as the AHI, the authors cited caution about coming to a definitive conclusion about treatment efficacy. In contrast, Machado-Junior and colleagues noted significant improvements in AHI in 215 children treated for OSA and concluded that RME was effective in treating OSA [305]. Camacho and colleagues in a meta-analysis on 314 children treated with RME for OSA also noted marked reductions in AHI with significant improvements in the lowest oxygen desaturation [275]. However, the effects were not curative with residual OSA noted. In studies reviewed < 3 years in duration, a sobering therapeutic success rate (based on AHI < 1/hr) was 25.6%. Children with smaller tonsil size were noted to respond better than those with larger tonsil size. Few studies were noted to be > 3 years old. In 2019, a meta-analysis on the effects of RME was performed by Sanchez-Sucar and colleagues [306]. Improvements in the AHI, mean oxygen desaturation, arousal index and REM phase sleep was observed in 9 studies included for analysis. The authors concluded that RME was efficient for children with mild/moderate

OSA severity. Collectively, these reviews highlight the paucity of data relating to the treatment effect of paediatric OSA citing lack of consistency among studies when reporting similar outcomes with a great heterogeneity in methodology, type of intervention and paediatric population studied [274, 275, 306]. Moreover, the effect of orthodontic therapy on neurocognitive and cardiovascular outcomes are unclear and require further investigation.

When presented with a paediatric OSA patient, the decision as to which treatment, RME or AT to perform first is unclear. Two randomised clinical trials, albeit with small sample size shed some light about the clinical sequencing of AT or RME treatment for OSA [307, 308]. Guilleminault and colleagues performed a clinical trial of 31 pre-pubertal children (mean age 6.5years) with OSAS [307]. The children were randomized to either AT followed by RME (group1) or RME followed by AT (group 2). No significant differences were noted in sleep parameters between the groups. However, the majority of children required both intervention (AT and RME) for complete resolution of clinical symptoms and PSG parameters. In a later RCT study in 2014, Villa et al. furthered research on AT and RME [308]. This time, the 52 children with OSAS were randomized into 3 groups. Twenty-five children underwent AT (group 1) and 22 children underwent RME (group 2). Five children underwent both treatments (group 3). RME treatment was reported to be a valid treatment for group 2 with children older than 4 years old with malocclusions and mild OSA. Of note, although group 2 had a milder OSA prior to treatment when compared to group 1, a higher post-treatment AHI was found to occur (17.25 ± 13.94 events/hr to 1.79 ± 1.82 events/hr, $p< 0.0001$ vs 5.81 ± 6.05 events/hr to 2.64 ± 3.11 events/hr, $p=0.005$). Four of these children were noted to increase in AHI at follow up. The authors reasoned that the difference and increase in AHI in group 2 could be attributed to longer duration of the disease, obesity,

allergies and potentially lower effectiveness of RME in older children. Both treatments were noted to help improve OSA, and a multidisciplinary approach with earlier RME treatment was proposed.

Overall, based on the reviews and meta-analyses discussed above, it is evident that the primary outcome measure for RME effectiveness has been typically based on PSG derived indices such as the AHI. Secondary outcome measures such as oxygen saturation level, arousal index, increase in upper airway volume or structures and sleep quality are variably included in the studies [274, 275, 306]. However, it is poignant to note that there exists a paucity of objective quantified data on snoring in the paediatric field in relation to RME and oral devices for children. Current evidence based on short term (< 3 years) evaluation suggest that orthodontic treatments that correct craniofacial skeletal imbalances may be helpful in ameliorating the risk factors of SDB in children and help reduce snoring and paediatric OSA. Huge gaps in our knowledge exist and further research of UAO particularly in relation to snoring is warranted. Future work to investigate the effects on orthodontic therapy in the longer term and to identify key phenotypes in children that will best respond to targeted treatment approaches is required.

In summary, RME is a routine orthodontic procedure that is an effective dentofacial orthopaedic technique used to treat skeletal and functional problems in the naso-maxillary complex. It has been documented to correct skeletal discrepancies particularly for the correction of maxillary constriction to improve maxillary morphology. This simple treatment may provide positive effects on oral health and general health of the patient. RME in children widens the nasal cavity width and volume. This is turn reduces nasal

resistance and improves nasal breathing with the potential to normalize orofacial muscle activity and tongue posture. The significant improvements in volumetric changes in the upper airway appears to be stable in the long term. Current evidence supports the role of RME for the treatment of maxillary transverse discrepancy such as maxillary constriction and constriction of the upper airway calibre, that is intrinsically linked to anatomical factors associated with UAO.

However, the data on the effects of RME of paediatric OSAS is limited and is predominantly short term in nature. Poor clarity exists about its longer-term impact on SDB and in particular, the effect of growth on OSA disease severity. Moreover, although other therapeutic options such as AT and PAP are currently utilized, lapses in our understanding as to which option to propose as first line therapy or in combination with RME exists particularly in the milder cases of paediatric SDB. Nonetheless, the overall sense of RME on paediatric OSA is that it may restore nasal breathing, improve respiratory events as measured by the AHI and oxygen saturation. Partial UAO as typified by snoring, a key sign and symptom of paediatric OSA has not been studied in any systematic fashion with dental interventions such as RME and oral appliance therapy at all. More research into the effects of RME on snoring is thus required. Early diagnosis is thus warranted and prompt instigation of orthopaedic correction with RME alone or other therapies such AT and PAP may be beneficial in restoring balance to a complex physiologically system in the developing child. Future research should include objective measures of snoring with key emphasis being to identify the phenotypes that will respond optimally to RME in the short and longer-terms.

1.5 Oral Appliance Therapy for Snoring and Obstructive Sleep Apnea

1.5.1 Introduction

Obstructive sleep apnea (OSA) is a common sleep disorder characterized by repetitive obstruction of the upper airway during sleep, resulting in sleep fragmentation and nocturnal desaturation. This can lead to daytime sleepiness [17], neurocognitive impairment [309] and adverse health consequences [310]. Long-term consequences of OSA include increased risk of cardiovascular morbidity and related mortality [311, 312]. It has been estimated that 24% of men and 9% of women in the middle-aged population suffer from OSA with its associated symptoms and are at risk of adverse long-term consequences [2]. Clinical symptoms such as daytime hypersomnolence, cognitive impairment and diminishment in the quality of life impact negatively in the adult population. Moreover, the association with increased risk in motor vehicle accidents, cardiovascular morbidity and all-cause mortality highlight the pressing and significant health and cost burden to the community and hence the implementation of clinically effective long-term treatment is paramount [311, 312].

The current gold standard for OSA treatment is to pneumatically splint the upper airway open with CPAP. Although CPAP is high efficacious in preventing upper airway collapse, its obtrusive nature makes adherence to this mode of therapy challenging [201]. Patient acceptance and longer term adherence may be low in a significant proportion of patients, thereby reducing effectiveness [201, 313]. Thus, the evolution of treatment alternatives to CPAP are critically warranted. In the last few decades, a great body of scientific evidence

has amassed regarding the role of oral appliance therapy (OAT) for the treatment of snoring and OSA in adults [271]. Recently in 2015, Ramar and colleagues published clinical guidelines for OAT establishing standards and guidelines for the implementation of OAs in clinical practice [314]. Today, OAs have been demonstrated to be effective in treating OSA across a range of severity [314]. Although a significant proportion of patients obtain benefit, not all patients who try OAs will receive clinical benefit. Nonetheless, a recent analysis on a large cohort (n=425) on OAT suggest that two-thirds of patients will attain clinically symptomatic improvement with OA use with at least 50% reduction in the AHI [315].

There are now a multitude of different OAs available to treat OSA of which the most commonly used and investigated are mandibular advancement splints (MAS). Other terms to describe OAs include “mandibular advancement devices (MAD)”, “mandibular repositioning devices (MRA) or “tongue retaining devices (TRD) which protrude the tongue instead of the mandible. For the investigation in Chapter 6 in this thesis, the term “MAS” will be used for our research investigations. MAS are removable devices are worn over teeth during sleep which provide support for anterior repositioning of the mandible. The precise mode of action is poorly understood but current thinking suggests that MAS protrude the mandible to alter upper airway configuration, stimulating muscle tone thereby reducing the propensity to upper airway collapse (Chapter 1.5.2).

Compared to CPAP, MAS are a portable and user-friendly alternative which does not require a power supply. In MAS therapy, patients are untethered in any form during sleep

and hence generally better accepted by patients with longer nightly use reported [316]. In the last decade, multiple randomized controlled trials (RCT) have validated the therapeutic efficacy of MAS for the treatment of OSA [317-320]. MAS are now recommended for snoring, as first line therapy for mild to moderate OSA and in more severe cases of OSA where CPAP is refused or not tolerated [314]. MAS have been noted to be preferred by patients who have experienced both CPAP and MAS suggesting greater adherence due to increased comfort and ease of use [313, 321]. Preliminary data in the short term using objective compliance monitors embedded in MAS have demonstrated increased compliance as compared to CPAP [316, 322]. Nonetheless, MAS treatment efficacy varies despite good treatment response in approximately two-thirds of patients [321]. Current deficits in MAS treatment include the inability to determine a priori which patients will receive therapeutic benefit from MAS treatment. These clinical barriers to widespread adoption of MAS are currently a key topic of research focus and highlights the pressing need for simple reliable methods for MAS treatment prediction. A range of prediction methods for MAS treatment success have been reviewed with a variability in sensitivity and specificity noted [323]. A simple clinically useful prediction method is thus urgently warranted.

The next few sections will provide a brief overview of MAS and will discuss several key topics including mechanisms of action, optimizing treatment efficacy and highlight gaps in our knowledge base in relation to the objective measurement of snoring.

1.5.2 Mechanism of Action

MAS posture the mandible in a protrusive position and this anterior movement is a key feature integral to its therapeutic effect. MAS reduces pharyngeal collapsibility as

measured during sleep [324]. Mandibular advancement increases the pharyngeal space and lumen calibre and reduces collapsibility improving pharyngeal airflow. Earlier investigation using 2 dimensional lateral cephalograms had initially documented that anterior movement of the mandible and tongue had resulted in an increase in the anteroposterior dimension of the retro-lingual airway [325]. However, physiologic and three-dimensional imaging studies have subsequently shown that MAS increases the volume of the upper airway, particularly in the velopharynx. These changes are shown to occur in the lateral dimension behind the soft palate and surrounding bony and soft tissue structures [326, 327]. The precise mode of action of MAS therapy with its predominant effect on the velopharynx and lesser degrees in the oropharynx and hypopharynx is unclear. This increase in pharyngeal patency is likely mediated by the stretching of soft tissue structures within the lateral pharyngeal walls. In severe OSA and obese patients, MAS has been shown to improve pharyngeal collapsibility primarily improving passive pharyngeal anatomy with minimal effect on genioglossus muscular activity [328]. The palatoglossal and palatopharyngeal arches which connect the mandible, tongue and soft palate are proposed to stretch due to mandibular advancement [329]. OSA patients with primary site of pharyngeal collapse noted in the oropharyngeal region have been shown to receive the most benefit from MAS therapy [330]. Key OSA endotypic traits such as pharyngeal collapsibility [331] and low loop gain [331, 332] have been identified as determinants of greater oral appliance efficacy. In older obese OSA patients, palatal collapse as demonstrated by “pinching” in expiratory flow shape modeling identify non-responders to oral appliance therapy [333].

Three-dimensional magnetic resonance imaging (MRI) imaging studies have also documented other anatomical changes in response to mandibular advancement. Anterior

"en-bloc" movement of the tongue and soft palate and lateral movement of the parapharyngeal walls and parapharyngeal fat pads have been also observed [334]. In addition to the anatomical effects of MAS, mandibular advancement may have a direct impact on pharyngeal muscle activity. Studies on the effect of MAS on pharyngeal dilator muscle activity are limited and although the precise mechanism is unclear, it is believed that MAS increases dilator muscle activity thereby producing a stabilization effect on pharyngeal airway patency. Nonetheless, a decrease in dilator muscle activity has also been reported and this is likely attributed to the decreased need for compensatory neuromuscular activity to maintain upper airway patency [335]. A study by Yoshida and colleagues demonstrated an increase in electromyographic activity of oro-facial musculature in the genioglossus, geniohyoid and masseter muscles during wakefulness and with MAS in situ during sleep [336]. With increasing mandibular advancement, a dose dependent decrease in genioglossus activity has also been reported during sleep [337]. Overall, these studies underscore the complex interplay between MAS effect on upper airway dilator muscle activity with considerable variation noted between individuals. It is speculated that device specific factors and localized anatomic factors may also influence soft tissue response to MAS therapy and in this regard, further research is clearly warranted.

1.5.3 Therapeutic Efficacy of Oral Appliances and Definitions of Treatment Success

There exist of great variation in the definitions of MAS treatment "success" reported in the literature. Treatment success historically and currently has been defined by the reduction in the AHI with or without consideration of symptomatic improvement. The AHI defined as

the number of apnea events (complete cessation of airflow) and hypopneas (partial reduction in airflow) per hour of total sleep time, is currently the primary measure of OSA severity.

MAS have been shown to improve the AHI in both non-REM and REM stages of sleep [318]. Improvements in other sleep related indices have also been reported. The reduction of arousal index, improved sleep quality with increased REM sleep time, and increased oxygen saturation levels have been well documented [119, 318, 338-340]. A stringent criterion of AHI < 5 events per hour is often used as a marker for resolution of OSA. A less stringent criteria of AHI < 10 events per hour has been proposed as a more clinically relevant benchmark for therapeutic success reflecting a milder category of OSA severity. A more liberal category of percentage reduction in AHI from baseline (typically 50% AHI reduction) has also been used in the literature. Thus, a wide variability in treatment success definitions exist in the literature but reduction in AHI to below a threshold of less than 5 (no OSA), less than 15 (mild OSA), and less than 30 (moderate OSA) have been widely adopted. These definitions of therapeutic success may or may not include a requirement for symptomatic improvement. This is particularly relevant from the perspective of snoring as objective measurement in MAS treatment has not been routinely performed and there currently exist no definitions of therapeutic success for snoring noted in the literature.

Using the most stringent definition of AHI to normative levels with resolution of OSA (AHI < 5 events/hr), a mean response of 48% was reported by Sutherland and colleagues [321]. Nonetheless a wide variability was noted in this analysis of 7 randomized controlled trials with a range of 29-71% reported [321]. It is important to state that a wide selection of MAS was noted to be used with varying degrees of mandibular advancement employed.

Overall, in a large study of 425 patients by the same group of researchers, two-thirds of patients were found to have at least 50% reduction of AHI which can be considered to be clinically relevant and positive in most patients [315]. A 2019 study reviewing therapeutic success based on the AHI in 82 patients however showed sobering results. 49% of patients were noted to have no clinically significant change with 18% of patients worsening in OSA severity following MAS therapy [341]. Thus, although OAs have been documented to improve objective measures of OSA severity, the degree of effects can vary from patient to patient, with some patients receiving minimal or no therapeutic benefit and all from OA therapy [315].

Therapeutic benefit has predominantly been based on the primary outcome measure of the reduction in obstructive respiratory events based on the AHI. However, other therapeutic benefits have been vigorously reported and today, there exists currently a great body of evidence which document improvements in snoring and other health outcomes. There have been many studies that evaluated the effects of OAs on snoring. However, the great majority of studies that evaluated snoring have been subjectively based [342]. A detailed review of these findings is presented in section 1.5.5. In relation to the effects of MAS on secondary outcomes measures, other beneficial effects on health-related outcomes such as quality of life [339, 340], mood [318, 339] , blood pressure [338, 343-346] and daytime sleepiness [119, 339, 340] have been reported.

However, despite recent systematic reviews that document modest reduction in blood pressure [345, 346], the effects of MAS therapy on a broad spectrum of cardiovascular

outcomes is unclear [346]. Some earlier MAS studies have shown positive effects on reducing blood pressure [344, 347, 348]. These improvements have been found at 3 months and 3 year follow up [343] and the effects have been noted to be more significant in subjects with OSA and hypertension [338]. Although one study showed no improvement in blood pressure [349], some reviews showed modest improvements in blood pressure and highlighted the need for more randomized controlled trials [345, 350]. A recent meta-analysis by De Vries and colleagues found however inconclusive evidence of significant effect on other cardiovascular outcomes such as heart rate variability, endothelial dysfunction, arterial stiffness and circulating cardiovascular biomarkers [346]. Nonetheless, it has been speculated that MAS therapy may lead to a reduction in longer-term cardiovascular morbidity and mortality in OSA patients. Some evidence of this may be found in an observational study by Anandam and colleagues who found comparable effects in the reduction of cardiovascular death between severe OSA patients treated with CPAP or MAS [351]. However, it should be stated that this study was not an RCT and selection bias could have occurred with the need for longer term review required.

In summary, MAS has been shown to provide benefit across multiple sleep and breathing related domains. In the majority of studies, the AHI has been used as the key metric for the assessment of clinical efficacy and success. However, increasingly there exist great contention on whether AHI is the best respiratory parameter to be used instead of other measures, for example, the oxygen desaturation index (ODI). The AHI has been criticized for not being well correlated to clinical symptoms such as daytime somnolence, and equal weighting between obstructive apneas and hypopneas in the calculation of the AHI metric; has been thought to trivialize the subtleties between full obstructive (apneas) and partial

obstructive (hypopneas) events. In the context of cardiovascular outcomes, the duration of apneas and hypopneas or the amount of time spent under a defined oxygen saturation threshold has been proposed as a better outcome measure than the AHI [346]. Intermittent hypoxia is thought to evoke of chain of events including sympathetic nerve activation, systemic inflammation [352], endothelial dysfunction [353], oxidative stress [310] and atherosclerosis [354]. Cardiovascular consequences of OSA include systemic hypertension [355, 356] and cardiovascular disease such as myocardial infarction, cardia arrhythmias and stroke [3, 154, 357]. Recent data have demonstrated that the ODI, and not the AHI is an independent predictor of prevalent hypertension [358]. Moreover, studies showed hypopneas and ODI based on a threshold of oxyhaemoglobin desaturation of at least 4% were better associated with cardiovascular disease [11, 358].

1.5.4 Clinical Effectiveness and Compliance

In the literature, there have been several randomized controlled trials comparing the efficacy of MAS with CPAP. The outcome measures have generally been limited to OSA alleviation as measured by the AHI [320, 349, 351]. Collectively, robust evidence suggest that superior efficacy can be found with CPAP based on the AHI metric. However, a key feature for clinical effectiveness in OSA intervention is compliance. Although it is generally considered that CPAP is superior in treatment efficacy as compared to MAS, it is now widely accepted nowadays that MAS are better tolerated than CPAP with clearer patient preference and higher compliance rates noted [271, 313]. The concept of "mean disease alleviation (MDA)" was first introduced by Grote et al. which incorporated the

effect of compliance on therapeutic efficacy [359]. This proposed measure of therapeutic effectiveness is defined as a combined function of efficacy and compliance. The MDA calculation allows direct comparison of other non-CPAP therapeutic options including MAS therapy in terms of actual clinical effectiveness and its impact on health outcomes and mortality.

The effect of CPAP on cardiovascular events and mortality has been well documented with two meta-analyses showing positive effects of CPAP therapy [360, 361]. However, cardiovascular effects of MAS therapy have been less well investigated and understood [346]. However, clinical effectiveness of any treatment modality can be hampered by poor compliance. Objective compliance monitoring with CPAP has been well established. Recently, the SAVE study by McEvoy and colleagues reported that CPAP therapy did not prevent cardiovascular events [202]. Poor compliance in their study with a mean of 3.3 hours of nightly CPAP use has been reasoned to negate the potential positive effects of CPAP. Beneficial cardiovascular health outcomes with CPAP are reliant on clinical effectiveness mediated by superior compliance to therapy. Post hoc analysis suggested that at least a minimum of 4 hours of CPAP use was required before a translation to lower incidences of cardiovascular events can be noted. The results in this study underscores the importance of patient adherence to a prescribed therapy with adequate usage time.

Recent advances in technology now enable objective monitoring of MAS. Preliminary data in short term studies using objective compliance monitoring employing microchips embedded in MAS have demonstrated increased compliance as compared to CPAP [316, 322]. In a 3-month, prospective clinical trial involving 51 patients, the rate of regular MAS use was 82% among patients with an average of 6.7 hrs per night highlighting higher

compliance rates with MAS compared to CPAP treatment [316]. A 1-year follow-up study on MAS use noted a 9.8% discontinuation rate with the remaining patients averaging 6.1 hrs per night for 83% of nights per week [322].

Thus, despite its inferior efficacy compared to CPAP, comparative clinical effectiveness of health outcomes with MAS may be attributable to the higher adherence rates reported. Some evidence suggests that comparative improvements in health outcomes may occur in severe OSA patients who exhibit higher compliance with MAS as compared to CPAP [349]. However, the current MAS compliance studies described above are noted to be short term and longer-term compliance studies are clearly warranted. Future prospective OA studies should also include long-term objective compliance monitoring to investigate OA effects on cardiometabolic, cardiovascular, and neurocognitive function.

1.5.5 Measurement of Snoring

Although snoring is easily recognizable and frequently complained about, objective measurement of this phenomenon has proven elusive. The sound properties of snoring can be characterized by its frequency spectrum (e.g. 30-250 Hertz), intensity (e.g. decibels) and its relationship to the breathing cycle (e.g. inspiratory or expiratory snoring). The duration (e.g. minutes) and frequency of snoring (e.g. percentage, snores per hour) can be also quantified during sleep. A great variability and the lack of consistency in the methodology of measuring snoring can be observed in the literature. Based on current methods recommended by the American Academy of Sleep Medicine (AASM) [115], a

piezoelectric sensor, acoustic sensor and nasal pressure transducer (cannula) are the general methods. Arnardottir and colleagues conducted a comparison of the 3 methods to measure snoring and found a lack of consistency between techniques [362]. These deficiencies were related to the varying sensitivities of each method to volume and fundamental frequency of snore events. It is important to state that the AASM scoring guidelines stipulate recording snoring using a high frequency filter of 100 Hz [363, 364]. However, the sound frequency of snoring has been documented to occur at much higher frequencies by Arnardottir et al. showing fundamental frequencies of over 100 Hz [362]. Other studies evaluating the sound frequency of snoring have also noted a high prevalence of snoring occurring in frequency range of 100-500 Hz [365]. Perez-Padilla and colleagues noted elevated frequency up to 2000 Hz with differences in snoring frequencies between nasal and oronasal snorers [366]. The authors highlighted the potential role of analyzing snore characteristics to differentiate between apneic and non-apneic snorers. Thus, it is likely that even in PSG based reported outcomes on snoring, a significant degree of underestimation may occur due to the applied 100 Hz filters if AASM guidelines are adhered to. Furthermore, there are many other factors that can account for variability in snore characteristics with respect to snoring intensity and sound frequency. Gender, age, upper airway morphology and BMI are contributory factors [367, 368]. Body habitus, sleep staging and levels of oxygen saturation can cause variability within the same subject [369].

Measuring Snoring with Oral Appliances

In a review of MAS for the treatment of SDB, Victor Hoffstein found 47 investigations that commented on snoring with few commenting on the efficacy of MAS treatment on

snoring. Only 18 studies in the review were noted to provide a measure of snoring with MAS with an explanation of snoring measurement [342]. Varying methods of snoring measurement were noted with poor standardization of snoring outcome measures observed. Poorly and frequently absent descriptions in the method of sound recording and definitions in snoring were noted overall. These snoring measurements included VAS [370, 371], number of snores per minute [120], number of snores per hour [119, 317, 372-374], percent of sleep time spent in loud snoring [375], nights per week with disturbing snoring [319, 376], minutes of snoring per hour [377, 378], snoring epochs per hour [379], noise level [380], total snoring time [381] and number of snores per hour of sleep [382]. Of the 529 patients in these 18 studies reviewed by Hoffstein, all were given a "number" to quantify snoring based on the metric used to measure snoring. Comparison between baseline and MAS therapy was analyzed based on the percentage change. Despite the diversity in the measurement of snoring, type of MAS used and the degree of mandibular advancement employed, the studies collectively found reductions in snoring with pooled data suggesting a 45% reduction in snoring [342].

Thus, although measurement of snoring with MAS have been performed in the past, the lack of consistency in objective measurement of snoring is clearly evident. This is reflected in the literature showing varying methods to measure snoring. The use of sound meter recordings [119, 317], surface throat microphones [383] and home sleep test device using a microphone attached to a strap worn on the upper lip [384] are examples. The study by Stouder and colleagues investigating the role of an MAS in reducing palatal flutter or tongue base snoring for example objectively measured snoring (snoring index and intensity), but noteworthy in this study, the endpoint of this titration based only on the

subjective symptom (snoring, daytime somnolence, witnessed apneas) assessment of the patient and/or bed partner [384]. Studies that objectively measure snoring use different definitions of snore events [69, 385] and often do not report specifics on snoring data and assessment [119, 317]. Moreover, studies that do measure snoring objectively are often questionnaire-based [76, 386]. A gold standard method of objective measurement is clearly warranted and the focus to standardize measurement and scoring of snore events has been vigorously proposed [362].

In the literature, a wide variety of questionnaires can be found to assess the effects of snoring and OSA [387]. As exemplified by the review by Hoffstein [342], in MAS studies that use self-reported measurement, an informal question such as “Is your snoring improved?” was often asked of the patient. The use of VAS scale (analogue or digital) was also frequently reported as a method to quantify snoring. However, it is prudent to highlight that in most investigations, the answers to the subjective questions were predominantly provided by the snorer. This scenario exemplifies a frequent occurrence in the dental setting as although snoring may be noted in the clinical history to be the chief complaint of the patient, the complainant is essentially the bedpartner. In this regard, a truer reflection of subjective snoring assessment would have been better obtained if the questionnaires or VAS was completed by the bedpartner instead of the patient. Some concordance between patient and bedpartner reports on snoring assessed by questionnaire however has been noted in patients after 3 months of OA use [388]. Nonetheless, another study highlighted the need for objective measurement of snoring finding significant discrepancies between self-reported perception and objective measurement of snoring [385].

The chief concern of snoring is often the primary reason patients seek treatment. When snoring disturbs a bed-partner, this often compromises social harmony in the bedroom and it is not uncommon for bedpartners or household to comment about the disruptive nature of snoring to their personal sleep quality. Not surprisingly, the motivation to seek intervention to resolve this complaint is often instigated by a spouse/bedpartner or household member. A common scenario in the clinical setting is when a patient presents to a clinician for the chief complaints of snoring and/or daytime sleepiness. PSG is carried out and diagnosis is focused around the metric of the AHI. When AHI < 5 events per hour are identified, the patient is immediately classified as a non-apneic snorer and reassured about the lower risk factors of snoring as compared to OSA and counselled about weight loss, positional therapy and minimizing alcohol intake before bed. Snoring may often be trivialized and not addressed adequately. In depth clinical assessment of the upper airway or intra-oral examination may frequently be not performed. The reasons for this gap in clinical practice is multi-faceted and often include an overlap between the lack of clinician training and expertise, affordability and varying models of patient care. In some instances, bedpartners are encouraged to wear earplugs or sleep in separate rooms. In instances where comic relief is deemed appropriate, a cheeky suggestion to “change” bedpartner may provide light humour. Treatment options in the way of referral to an otolaryngologist or sleep dentist for clinical opinion and management may not be routinely provided. As often is the case, the patient leaves without resolution to the chief complaint of snoring and is dissatisfied having incurred substantial clinical costs for investigations. Quite frequently, the patient’s impression is that diagnostic process has been overwhelmingly convoluted for a “simple” snoring complaint that has not been resolved. For apneic snorers, the likely management pathway has been CPAP which effectively manages snoring.

1.5.6 Degree of Mandibular Advancement

The degree of mandibular advancement required to obtain therapeutic success is unclear. There have been a multitude of studies investigating mandibular advancement as anterior positioning of the mandible has been thought to be the key mechanism enabling the improvements in upper airway calibre size. Four systematic reviews are noted to describe controlled trials which utilize mandibular advancement as compared to control devices which do not advance the mandible [342, 389-391]. These reviews collectively highlight improved treatment efficacies with mandibular advancement. However, these studies have predominantly been based on PSG derived indices such as the AHI and no objectively measured data on snoring exist to date regarding the dose dependent effects with mandibular advancement.

Crossover OA studies investigating the role of mandibular advancement against inactive plate with no mandibular advancement support the integral mechanism of mandibular advancement in obtaining improvements in OSA indices [119, 317] with improvements in NREM and REM AHI also reported [318]. In support of these findings, MAS set at 75% maximum mandibular protrusion were also noted to be more efficacious as compared to no advancement in control devices in the reduction of the AHI [338-340], arousal index [339] and oxygen desaturation [340]. However, therapeutic efficacy of MAS therapy can vary from patient to patient and not all patients experience therapeutic benefit [271, 315, 321]. Hence, prediction methods to clearly define treatment responders from non-responders is

of paramount importance. Currently, patients who are diagnosed with PSG with severe OSA are generally prescribed CPAP whilst mild/moderate OSA patients may be offered MAS as a treatment option. Many factors account for this decision making process but OSA severity based on the AHI metric and sleep position [392] are frequently used. However, using the AHI has low predictive accuracy as severe OSA patients have been reported to respond well to MAS therapy [119, 393]. A systematic review of the methods for predicting MAS treatment success has been performed by Okuno and colleagues [323]. Several techniques were noted to be employed but overall, a wide variability in results in sensitivity, specificity, positive and negative prediction values were found. Of note, several techniques such as remote controlled mandibular positioners [394, 395], multisensory catheter[330] and nasopharyngeal fiberscope[396] observed showed promising results but these techniques were found to be costly, invasive and not routinely applicable to clinical practice.

The optimization of MAS treatment outcomes is in stark contrast to CPAP which can be titrated during PSG or with an automatic PAP machine. Although the use of remote controlled mandibular positioners demonstrated the ability to estimate the degree of mandibular advancement required for optimal results [394, 395], most MAS to date require manual activation of the protrusive components specific to the MAS for mandibular advancement. The protrusive range of movement can vary from patient to patient. One study document a range of 6-14mm with a mean of 11mm [397]. However, the exact position required for peak therapeutic success may vary from patient to patient.
With recent increasing concerns about the progressive bite alteration effects of long term MAS use reported [398-400], the required level of mandibular advancement for optimal

treatment outcomes has been a topic of increasing research focus. The titration approach with incremental titration over time to determine the optimal level of protrusion has previously been proposed as a protocol to achieve better treatment outcomes [401]. Using a combination of symptomatic improvements including subjective assessment of snoring and objective assessment with nocturnal oximetry, Fleury and colleagues also optimized treatment success rates [401].

Current research suggests that the adjustable MAS achieve better outcomes as compared to a fixed non-adjustable version based on the AHI [402]. The general consensus of opinion is that better treatment effect is achieved with a titratable MAS [314, 403]. However, the dogma of mandibular advancement to a patient's comfortable limit as opposed to maximum protrusion must be weight against treatment success and side effects which invariably impact longer term MAS adherence. Tegelberg and colleagues challenged the need for aggressive levels of mandibular protrusion in their investigations on mild/moderate OSA patients randomized to 50% or 75% maximum protrusion with MAS use. No significant differences were noted in treatment AHI or treatment success (79% vs 73%) between these two mandible positions [404]. Lower degrees of mandibular advancement have also been investigated by Aarab and colleagues [405]. Their investigations demonstrated a dose dependent effect on AHI with 4 randomized levels of advancement (0%, 25%, 75% and 100%). Advancement from 0% to 25% mandibular protrusion resulted in a significant reduction of the AHI. At the 50% and 75% positions, even lower AHI values were found. However, side effects were reported to be larger starting at the 50% protrusion position. These results suggest that lower degrees of mandibular advancement can still improve clinical outcomes but as mandibular

advancement increases, side effects also increase. Hence, the process of mandibular advancement and position required for therapeutic success may vary from one individual to the next requiring several months of progressive mandibular advancement to the final desired mandibular position. The degree of mandibular advancement however, should be balanced against a patient's level of tolerance and longer-term side effects.

1.5.6.1 Dose dependent effects

There have been several studies that demonstrate dose dependents effects on PSG variables, muscle responsiveness and upper airway calibre. However, to date there exist no objective data on the dose dependent effects of mandibular advancement on snoring. Multiple studies have noted a dose dependent decrease in AHI with progressive mandibular advancement [405-407]. Kato and colleagues investigated 3 levels of mandibular advancement (2, 4 and 6mm) and found a dose dependent relationship in improvement in overnight oximetry showing greater improvements in oxygen desaturation with increasing mandibular advancement during anaesthesia [408]. In this study, each 2-mm mandibular advancement coincided with approximately 20% improvement in number and severity of nocturnal desaturations. Advancement of mandibular position was found to produce dose-dependent in improvement of closing pressure reduction of all pharyngeal segments. Normalization of nocturnal oxygenation was associated with negative closing pressure, especially at the velopharynx [408]. Muscle activity, specifically the genioglossus muscle activity was also demonstrated to decreases in a dose dependent manner [409]. Bamagoos and colleagues however observed that in severe and obese OSA patients, pharyngeal collapsibility as measured by critical closing pressure decreased in dose

dependent fashion. However, significant changes in genioglossus muscle responsiveness was not observed [328]. Similar dose dependent effects of mandibular advancement on optimal CPAP pressure requirements were also reported by the same group of investigators to support the beneficial role of MAS therapy on pharyngeal collapsibility [410]. MRI imaging on the effect of progressive mandibular advancement have documented a dose dependent increase in the cross-sectional diameter of velopharyngeal airway space. These changes were noted in the transverse dimension [411]. These dose dependent improvements were supported by another MRI study but variability changes were noted when vertical opening occurred in conjunction with mandibular advancement [412]. Overall, although imaging, physiologic and investigative studies based on PSG metrics have demonstrated improvement with progressive mandibular advancement, a knowledge gap exists with regard to the effects of mandibular advancement on snoring and its characteristics.

1.6 Conclusion

SDB is a common condition that affects both adults and children. Early diagnosis and management is paramount and may reverse the adverse effects of SDB. Current methods of diagnosis are reliant on PSG based investigations. Although formal PSG in an attended sleep laboratory setting has played an essential role in the advancing the field of sleep medicine, this method of diagnosis has not been routinely performed in the dental setting due to cost, availability and its laborious nature. Given the high prevalence of SDB, a simpler, self-administered method of diagnosis is clearly warranted.

Over the last few decades, anatomical factors have been increasingly associated with SDB. Various treatment modalities both surgical and non-surgical have been proposed for the treatment of snoring and OSA. In children with OSA, RME a routine orthodontic treatment has been proposed to alleviate OSA. In adults, MAS therapy has also been increasingly adopted as a viable treatment option to CPAP and surgical intervention. Current research on both treatments show beneficial effects in the good majority of patients. However, not all patients benefit from RME or MAS therapy with partial or residual OSA observed.

Contemporary methods for diagnosis and assessment of RME and MAS treatment effects are reliant on PSG derived indices such as the AHI metric. However, emerging evidence show poor correlation between the AHI metric and treatment outcomes in both adult and paediatric populations. Although PSG metrics report on apneas and hypopneas, they do not adequately measure periods of partial UAO such as snoring which are characteristic of paediatric SDB. Children with SDB often present with less apneas but more obstructed breathing which is a more relevant measure of UAO.

Snoring can disrupt sleep and is associated with a wide array of adverse medical conditions. Although the complaint of snoring is often the chief reason why patients are motivated to seek treatment, snoring may often be trivialized during the diagnostic process. Moreover, objective measurement of snoring may not be routinely performed before or after treatment. In children with maxillary constriction and adults who snore, gaps in our knowledge exists with respect to the prevalence and characteristics of snoring before and after RME or MAS treatment. In adults, objective measurement of residual snoring with

MAS therapy is lacking but is of importance clinical relevance as residual snoring can affect longer term MAS adherence and present as a significant health risk. Moreover, the effects of progressive mandibular advancement on snoring with MAS therapy is unknown.

To date, assessment of the treatment effects of RME and MAS therapy has been PSG based. However, in PSG based reported outcomes on snoring, a significant degree of underestimation may occur due to the applied 100 Hz filters if AASM guidelines are adhered to. A great variability and the lack of consistency in the methodology of measuring snoring can be observed in the literature. Thus, a standardized method of objective measurement of snoring is clearly warranted to further our understanding of SDB in adults and children.

AIM OF THESIS

The overall aim of the thesis was to investigate sleep disordered breathing (SDB) in adults referred for mandibular advancement splint (MAS) and children referred for rapid maxillary expansion (RME) therapy using the Sonomat™. The Sonomat™ is a portable recording device that has been validated against polysomnography for the quantification of SDB. It records breathing sounds, heart sounds, breathing effort and body movement and provides a very accurate measure of snoring. It is easily utilized in the home environment and requires minimal technical training on the part of the patient, parent or carer in attendance. A key feature of this recording system is that the patient is untethered by any

attachment or sensor which makes it comfortable and unobtrusive especially in paediatric patients.

The first aim of our paediatric study investigates the prevalence of SDB in children that exhibited maxillary constriction who required RME therapy. Our key focus in this respect was to identify the characteristics of obstructed breathing in these children and to objectively quantify snoring. Our secondary aim in the paediatric study was to investigate the effect of RME on snoring and OSA.

The final part of this work investigates a large cohort of adult patients referred for MAS therapy. The first aim was to evaluate SDB and to objectively quantify snoring in these patients who presented with snoring as a chief complaint. Key to this investigation was the quantitative measurement of snore duration and snore types (inspiratory, expiratory and combined inspiratory and expiratory (IE) snoring). Our secondary aim was to evaluate the effects of MAS therapy, in particular the dose dependent effects of progressive mandibular advancement on snoring and OSA.

2 GENERAL MATERIALS AND METHODS

This chapter outlines methods common to most chapters with the predominant content related to the identification and quantitative objective measurement of respiratory events and snoring used with the Sonomat™ recording device. Methodology pertaining to specific protocols for MAS therapy in adults or RME therapy in children are described in detail in the relevant chapters in the later sections of this thesis. The PhD candidate JN declares no conflicts of interest with the Sonomat™ (Sonomedical, Balmain NSW Australia) and Somnomed (Crows Nest, NSW Australia). The sleep studies in this thesis recorded with the Sonomat™ was provided free of charge to all participants.

2.1 Outcome Measures: Sonomat Sleep Study

2.1 The Sonomat

The Sonomat™ device is a diagnostic device that senses and records breathing sounds in addition to respiratory and body movements. It consists of specially designed vibration sensors embedded within a thin mattress designed to overlay a standard bed (Figure 2.1). Unlike other sleep diagnostic testing devices, no wires or sensors are attached to the patient. Detection of physiologic parameters occurs via the conduction of sounds and vibrations through the patient's body and bed clothes to the sensors, similar to a stethoscope. Four identical sensors provide redundancy, and are strategically positioned to ensure at least one remains in contact with the patient's thorax as the patient changes position during sleep (Figure 2.2). Each of the four sensors converts body sounds, vibrations and movements into an electric signal. Each signal is then processed and split

into two channels, one low frequency (movements) and one high frequency (sounds). This allows discrimination of sounds, vibration and movements relating to: breathing effort, activity (body movement), snoring, airflow (in and out of lungs) and heart, lung and other body sounds. Signal data is recorded onto a SD memory card housed within the Sonomat™ device.

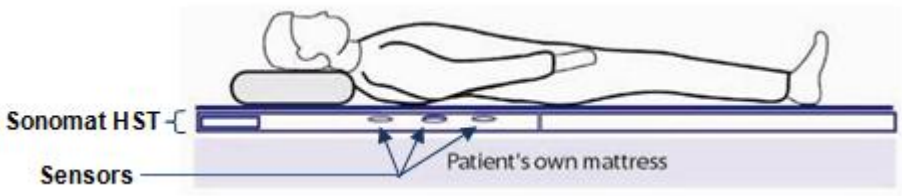


Figure 2.1 A schematic representation of the Sonomat™ HST showing patient and sensor positions. The Sonomat™ mattress is placed on top of the patient's own mattress. Unlike other sleep diagnostic testing devices, no wires or sensors are attached to the patient. Detection of physiologic parameters occurs via the conduction of sounds and vibrations through the patient's body and bed clothes to the sensors, similar to a stethoscope.

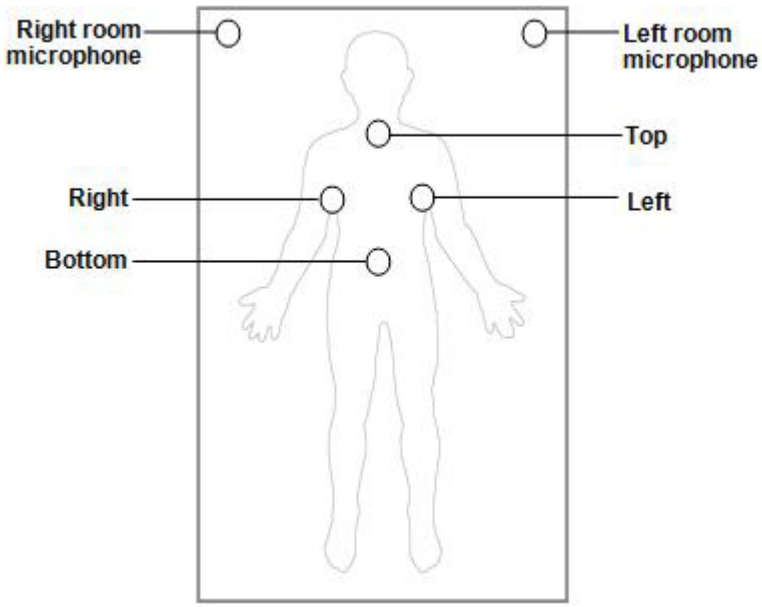


Figure 2.2 A schematic representation of the sensor positions on the Sonomat™ HST (bird's eye view). Four identical sensors are strategically positioned to ensure at least one remains in contact with the patient's thorax as the patient changes position during sleep. Each of the four sensors converts body sounds, vibrations and movements into an electric signal. This allows discrimination of sounds, vibration and movements relating to: breathing effort, activity (body movement), snoring, airflow (in and out of lungs) and heart, lung and other body sounds.

2.2 Recording a Sonomat™ Study

Adults participants, or parents of the children recruited for the studies were instructed with a brief and simple educational session on how to implement the Sonomat™ recording device. A brief test recording to assess functionality was performed and a written instruction sheet provided. In both adult and paediatric studies, a baseline study was performed prior to any treatment being initiated. For multiple studies in adults involving progressive mandibular advancement with the MAS, a brief review of the recording instructions was routinely performed prior to each study with MAS in situ. In the adult participants, multiple recordings were performed in numerous subjects who had recordings

made over consecutive nights. It was not necessary to download a study prior to the next study as the capacity of the SD card could accommodate multiple nights of consecutive recordings.

In the paediatric studies, formal instructions in the use of the Sonomat™ were given to the parent for the baseline, RME1 and RME2 studies. A brief review of the recording instructions was routinely performed with the parent prior to each sequential Sonomat™ recordings with RME in situ at the later intervals (Chapters 3 and 4).

2.3 Sonomat™ Analysis software

After the sleep study, data from the card is uploaded to a computer where, using Sonomat™ Replay software (Sonomedical, Balmain, NSW Australia), each channel can be viewed in the form of a visual trace similar to that of polysomnography (PSG). With some channels, the processing of the signals is such that they can be replayed audibly, similar to a digital stethoscope recording.

The Sonomat™ device also includes two embedded microphones that detect ambient room sounds. These sounds are recorded synchronously with the signals from the four sensors. The signal from each microphone is split into two channels: one which processed (rectified and integrated) and one which is unprocessed. Using Replay software, the unprocessed signal can be played back to allow identification of extraneous sounds (e.g. snoring from bed partner). A trace for the processed signal allows for easy visualization of overall ambient noise levels during the sleep study, and for measuring of snoring sound level.

All studies were manually scored in random order by a scorer blinded to the identity of the subject and the nature of the study, baseline or treatment. The Sonomat™ studies were scored both visually and aurally using Sonomat™ Replay software following accepted respiratory scoring guidelines [363] with slight modifications: no oximetry was used to aid in identifying respiratory events, body movements were taken to be equivalent to arousals as detected by EEG, and breathing sounds were used to detect the absence of or a reduction in airflow.

2.4 Validation of the Sonomat™

The Sonomat™ has undergone extensive validation against polysomnographic recordings with both in-laboratory and at home portable sleep studies. The results show an 89% sensitivity and 93% specificity for detecting SDB. These results have been published in abstract form [413, 414] and have been validated against PSG [105, 414, 415] and in various other publications [106, 413].

The comparison of the detection of OSA using cardio-respiratory monitoring and modified sonographic technology embedded in the Sonomat™ mattress overlay has been previously reported [413]. Validation with polysomnographic evaluation of the ability of the Sonomat™ to diagnose sleep-disordered breathing (SDB) has also been demonstrated [414].

However, the Sonomat™ also records snoring very accurately. Very few of the current standard methods for performing sleep studies (PSG or polysomnogram studies) routinely record snoring accurately; exceptions are the Nox and Medibyte.

Definitions

Sonomat™ scoring criteria [415] were developed similarly to PSG scoring guidelines [363]. The key difference is that the breath sound signal is used as a surrogate for airflow rather than a thermistor or nasal pressure measures. To identify a sound that is graphically represented in the breathing sound signal, a section of the trace is selected with the Sonomat™ replay software and replayed back through either speakers or headphones. Normal breath sounds are acoustically soft and incorporate many different frequencies over a wide frequency spectrum and are easily identified by trained personnel [416]. An example of normal breathing is illustrated in Figure 2.3.

Normal Breathing Sounds

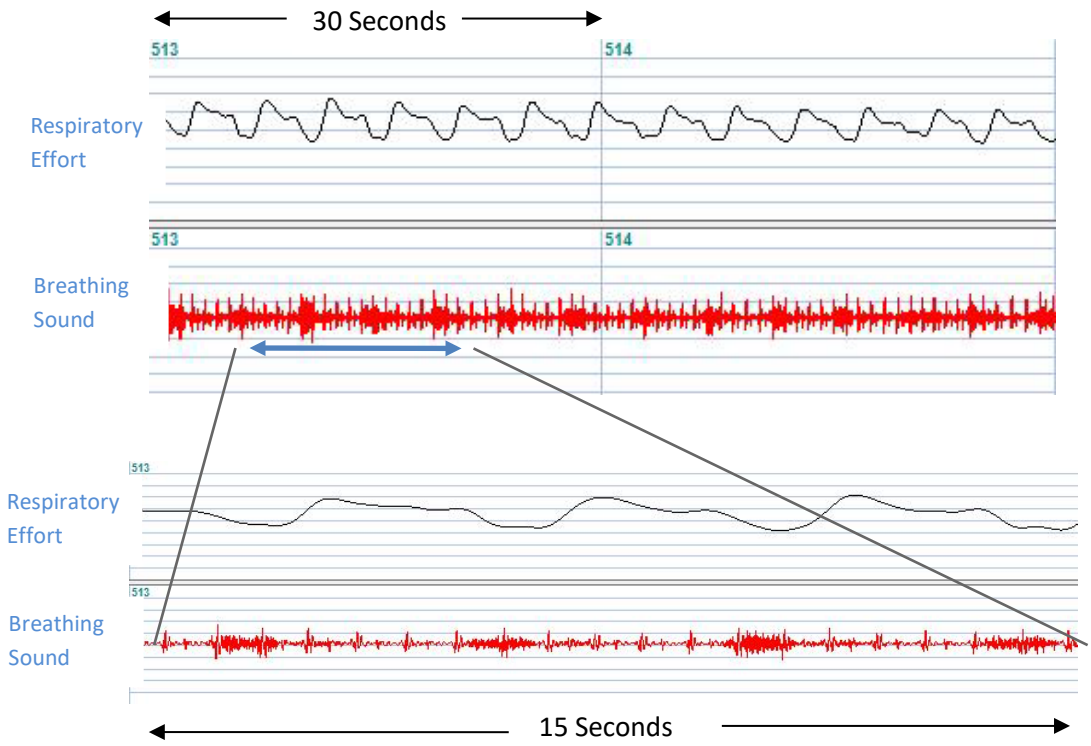


Figure 2.3 A period of normal breathing is identified by the breathing sound signal. An example of four normal breaths is marked with the blue double arrows. Normal breaths as seen in the four normal breaths often display a characteristic "bead-like" pattern. The identification of normal breathing is performed by replaying and listening to the sound.

2.2 Snore Classification

In contrast to normal breathing sounds, snoring is a loud sound and displays a fundamental frequency from 30- 250 Hz [416]. Snoring was scored when breath sounds contained periodic components with fundamental frequency peaks from 20-30 Hz up to

approximately 250-300 Hz. Snoring was identified aurally and distinctive characteristics to differentiate between inspiratory snores (IS), expiratory snores (ES) and the combined inspiratory and expiratory (IE) snore types can be seen in the breathing signal. Examples of these are illustrated below.

2.2.1 Inspiratory Snore

If the snoring sounds occurred during the inspiratory phase of the respiratory cycle the sound was labeled “Inspiratory snoring”. An example of inspiratory snoring is illustrated in Figure 2.4.

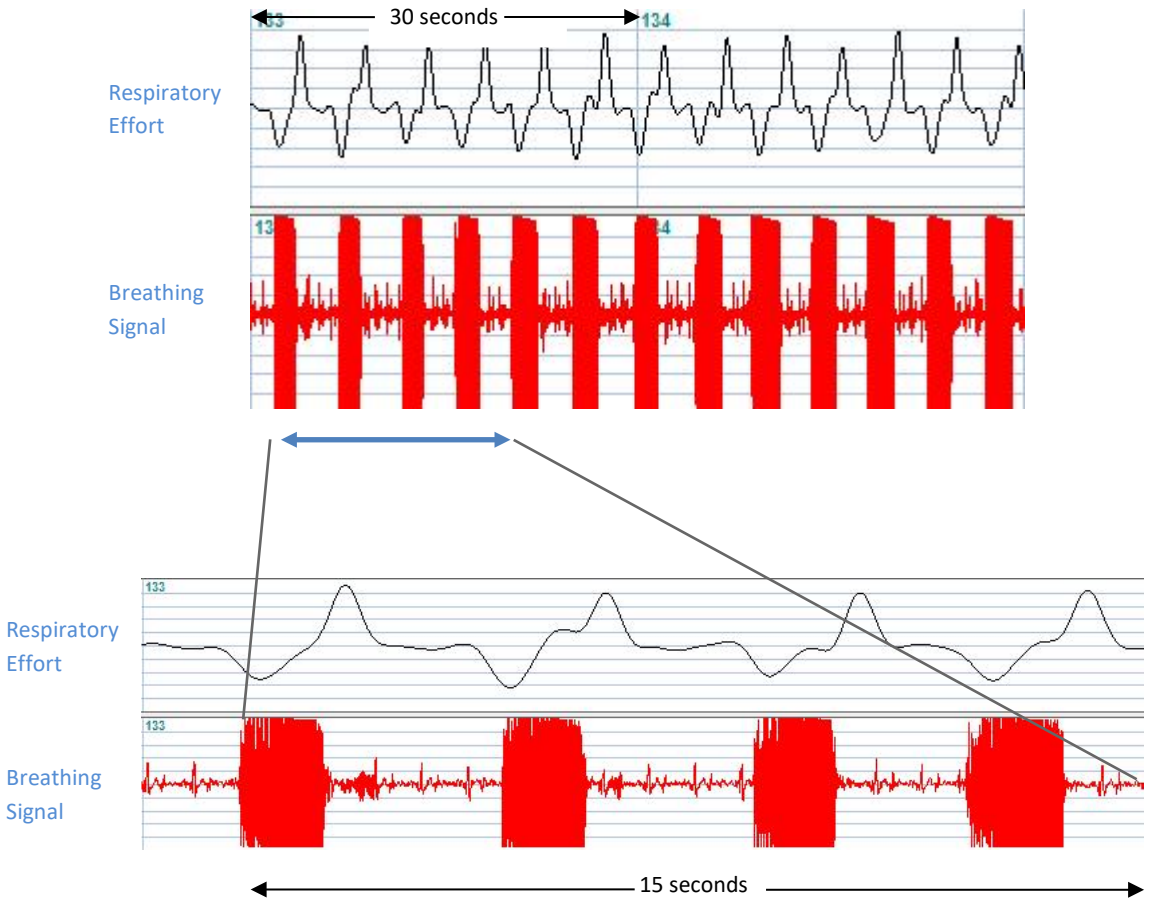


Figure 2.4 A period of inspiratory snoring is identified by the breathing sound signal. An example of four inspiratory snores is marked with the blue double arrows. The identification of inspiratory snoring is performed by replaying and listening to the sound.

2.2.2 Expiratory Snore

If the sounds occurred during the expiratory phase of the respiratory cycle the sound was labeled as “Expiratory snoring”. An example of expiratory snoring is illustrated in Figure 2.5.

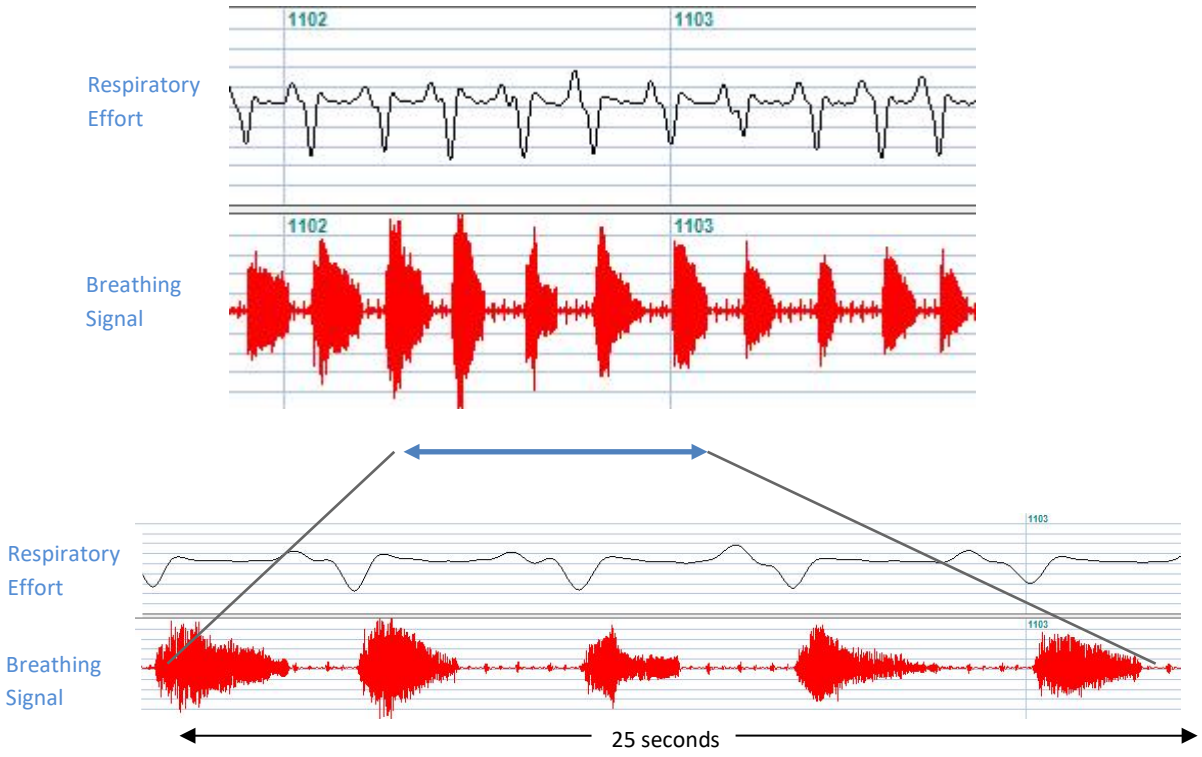


Figure 2.5 A period of expiratory snoring is identified by the breathing sound signal. An example of five expiratory snores is marked with the blue double arrows. The identification of expiratory snoring is performed by replaying and listening to the sound. Expiratory snores often display a characteristic tapered pattern and may have a duration lasting from 2 to as long as 6 seconds.

2.2.3 Inspiratory and Expiratory (IE) Snore

When an inspiratory snore was followed immediately by an expiratory snore, within the same respiratory cycle, the event was labeled “Inspiratory/expiratory snoring” (IE Snoring). An example of inspiratory and expiratory snoring is illustrated in Figure 2.6

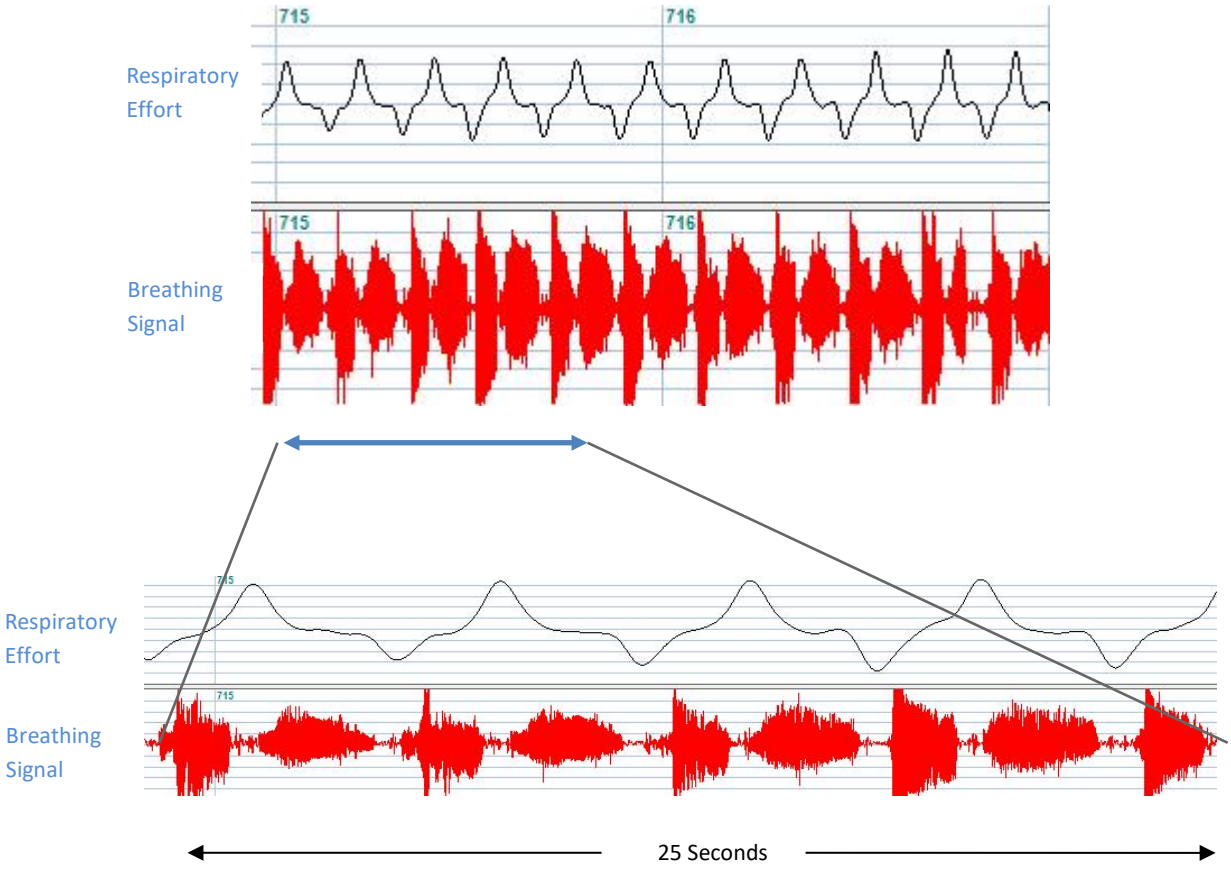


Figure 2.6 A period of inspiratory and expiratory (IE) snoring is identified by the breathing sound signal. An example of five IE snores is marked with the blue double arrows. The identification of IE snoring is performed by replaying and listening to the sound. IE snores often visually display a combined characteristic of an inspiratory snore followed by the tapered pattern of an expiratory snore. They may occur in quick succession or may have a longer duration from 4 to 8 seconds.

All percentage values and indices reporting events per hour were calculated using the quiescent time (Qd) as the index time. This is the time in which the subject was lying immobile on the Sonomat™ and is calculated as the recording time minus the sum of all gross body movements. One exception to this is the respiratory movement index (RMI) which is calculated using the recording time as the index.

2.3 Respiratory Events

2.3.1 Hypopnea events

Hypopneas were identified by a decrease in the amplitude of breathing effort, or a steady increase in amplitude in a crescendo type pattern, or a combination of the two (as detected on the low frequency channel). The classification of the hypopnea type was made by listening to the breathing sounds from the breathing sound signal during the time in which the hypopnea has been visually identified. If the presence of snoring or other sounds that indicate an obstructed airway was heard, the event was classified as an obstructive hypopnea (Figure 2.7). If the breath sounds exhibited a reduction in intensity with no evidence of obstructive sounds (normal breath sounds), the event was classified as a central hypopnea.

2.3.1.1 Obstructive Hypopnea

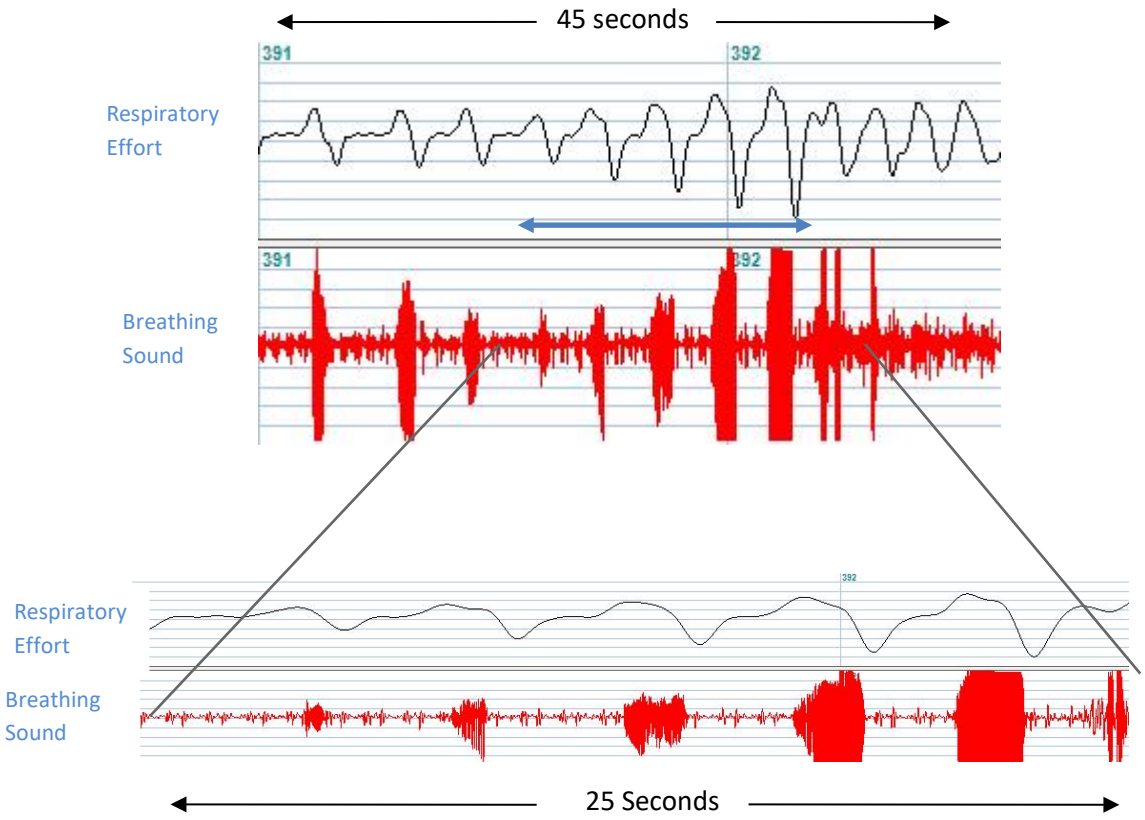


Figure 2.7 An obstructive hypopnea is identified by the blue double arrow. A steady increase in amplitude in a crescendo type pattern in the respiratory effort signal is clearly seen and is accompanied by a change in the breathing sound signal. The frequency components of the breathing sound signal determine if the event is obstructive or central in nature. In this example, the presence of snoring indicates an obstructed airway and the event was classified as an obstructive hypopnea.

2.3.2 Apneic events

Apneas were identified by a marked decrease in or the complete absence of any breath sounds in the breathing sound signal with the continued presence of heart sounds (as

detected on the high frequency channel) for a period ≥ 10 seconds. The presence of heart sounds confirms that the subject is still lying on the sensors. Apneas were classified according to the presence or absence of breathing movements (as detected on the low frequency channel) occurring during the period of apnea identified on the high frequency channel. If respiratory movements were detected throughout the period of apnea, the event is classified as an obstructive apnea (Figure 2.8). If there are no respiratory movements during the period of apnea, the event is classified as a central apnea (Figure 2.9). When the absence of respiratory movements was combined with the presence of respiratory movements during the single apneic period, the event was classified as a mixed apnea (Figure 2.10).

2.3.2.1 Obstructive apneas

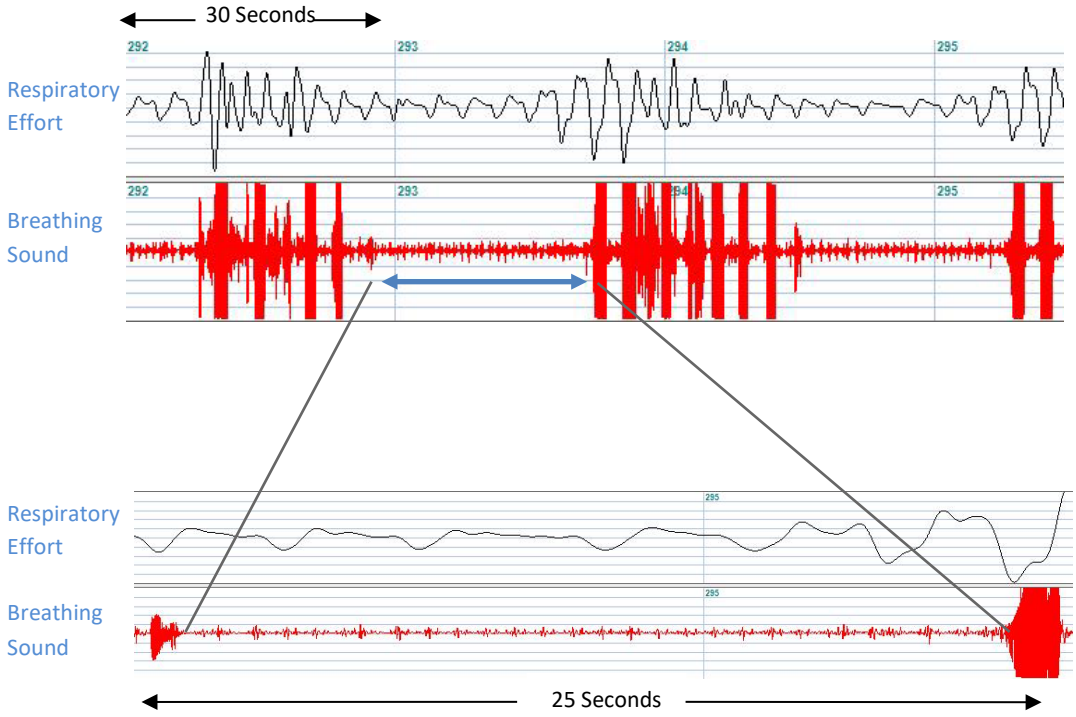


Figure 2.8 An obstructive apnea is identified by the blue double arrow. The absence of breathing sounds in the continued presence of heart sounds indicates an apnea. Continued breathing effort in the respiratory effort signal confirms the event is obstructive in nature.

2.3.2.2 *Central apneas*

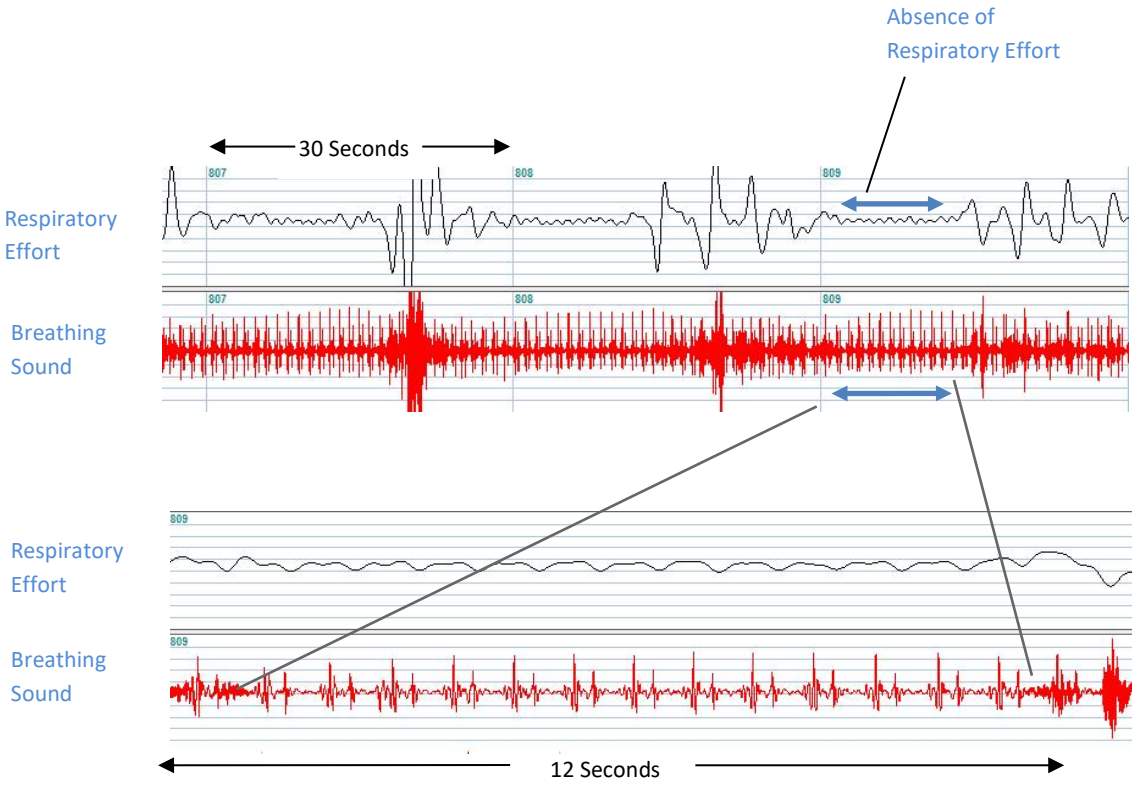


Figure 2.9 A central apnea is identified by the blue double arrow. The absence of breathing sounds in the continued presence of heart sounds indicates an apnea. The absence of breathing effort in the respiratory effort signal confirms the event is central in nature.

2.3.2.3 Mixed apneas

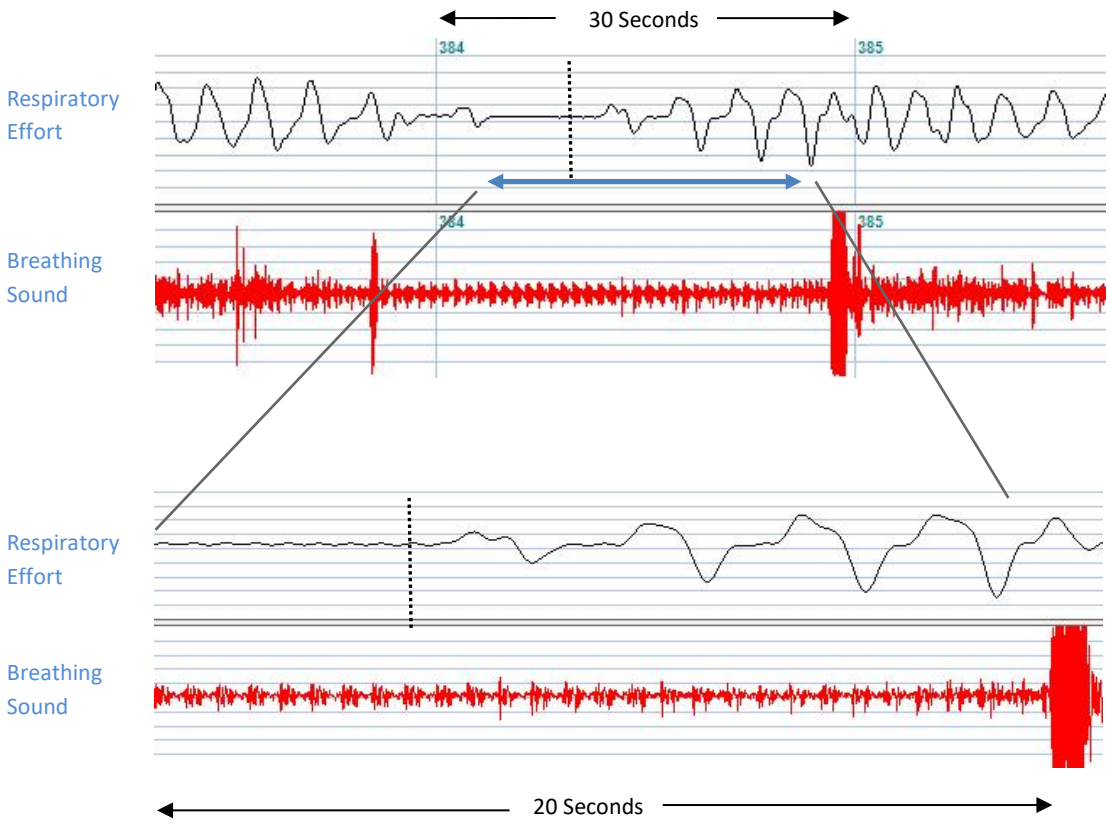


Figure 2.10 A mixed apnea is identified by the blue double arrow. The absence of breathing sounds in the continued presence of heart sounds indicates an apnea. The initial absence of breathing movements followed by a resumption of breathing movement on the respiratory effort signal confirms the event is a mixed apnea. The vertical broken line indicates where the obstructive component begins with respiratory movements increasing as the apneic event progresses.

Once scored, the Sonomat™ events were exported as a delimited text file containing the following event information: event name, start time, end time and duration of event. This file was opened in Microsoft Excel™ which was used to calculate the respiratory event related numbers and indices for comparison of baseline and treatment studies.

2.3.3 Body Movements: Spontaneous and Respiratory movements

All gross body movements ≥ 3 seconds were scored. A movement arousal (MAr) was identified as a period in which the respiratory effort signal exhibited an abrupt change in frequency as compared to a baseline regular pattern of breathing movement. MAr was classified as spontaneous or respiratory-induced based on the breath sounds occurring in the 5 seconds prior to their occurrence. Any body movement preceded by normal breathing was labeled a "Spontaneous Movement" and those preceded by an apnea, hypopnea or snoring was labeled a "Respiratory Movement". In this study, the number of respiratory movements that occurred each hour were quantified by the Respiratory Movement Index (RMI).

2.5 Sonomat™ Time Values

Data from the Sonomat™ recordings can generate 4 different time values for the analysis. They are the recording time, analysis time, quiescent time (Qd) and total sleep time (TST). In both adult and paediatric research studies, we present data for the analysis time and Qd time. Overall, it should be stated that the recording time > analysis time > Qd time> total sleep time. Information relating to how each time value has been calculated follows.

2.5.1. Recording Time

The recording time is defined as the time interval between which the Sonomat™ recording starts and stops. This period may include periods where the subject is out of bed (OOB) and/or periods of poor-quality recording (PQR).

Recording Time = (Total duration of recording) min

2.5.2 Analysis Time

The analysis time is the period of time within the recording time in which the data collected can be analyzed.

Quiescent time (Qd)

The periods of time between all movements, were the patient was quiescent was quantified as quiescent time (Qd). This is the time in which the subject was lying immobile on the Sonomat™ and is calculated as the recording time minus the sum of all gross body movements. The Qd were considered analogous to sleep and used as a denominator for calculating respiratory event indices.

2.2 Ethics Approval and Informed Consent

Ethical approval for the research studies within this thesis were provided by the Human Research Ethics Committees (HREC) at the University of Sydney. The adult studies were covered under approval HREC protocol No: 11476-2012/023 and all adult participants provided written informed consent. The paediatric studies involving rapid maxillary expansion were covered under approval HREC protocol. No: 2014/571 by the institutional Ethics Committee and written consent was obtained from all parents with children providing assent if able. All appropriate undertakings were performed to maintain patient confidentiality.

2.9 Statistical Analyses

Statistical and graphical analysis was performed using GraphPad Prism 7 (GraphPad Software Inc., La Jolla, CA, USA).

Data was tested for normality using the Kolmogorov-Smirnov statistic with a Lilliefors significance correction. Normally distributed data are presented as mean ± standard deviation (SD). Data that was non-normally distributed are presented as the median and interquartile range (IQR) with the significance of any measures compared using a Wilcoxon signed-rank test.

Continuous variables were compared using the Student's t test or Mann Whitney U test as appropriate. Categorical variables were compared using the chi-square test or the Fisher's exact test. In multiple measures, repeated measures ANOVA was performed for normally distributed data or Kruskal-Wallace test for non-normally distributed data. Correlation was performed using Spearman's rank-order method. All tests of significance were two tailed and a p value of <0.05 was considered to be significant.

3 PREVALENCE OF SLEEP-DISORDERED BREATHING IN CHILDREN WITH MAXILLARY CONSTRICTION-OBJECTIVE ASSESSMENT WITH THE SONOMAT™

3.1 Introduction

Paediatric obstructed sleep-disordered breathing (SDB) is a common disorder caused by upper airway obstruction associated with a broad spectrum of severity ranging from primary snoring (PS) to obstructive sleep apnea (OSA). Large epidemiological studies show that OSA occurs in 2-3% of the paediatric population [24, 25]. Snoring is a cardinal sign and symptom of SDB and OSA. Depending on age, 3-35% of the paediatric population have been reported to have habitual snoring with large study of over 20,000 children reporting 12% of children snoring habitually [32, 35, 122-124]. Most authors report the prevalence of 10% for snoring and <3% for OSA but this estimation may vary depending on the method used to diagnose SDB. Although snoring has been trivialized in the past and thought to be benign, it is increasingly being shown to contribute to sleep disruption [106], adverse quality of life [417], poor behavioral and neurocognition [418], and cardiovascular and metabolic dysregulation in children [53, 419, 420].

Supervised polysomnography (PSG) is the recommended diagnostic test for paediatric SDB. However, PSG is intrusive, expensive, labor intensive and associated with long waiting lists. Thus, it is not surprising that paediatric SDB is largely under-diagnosed in clinical practice with a high incidence of under-reporting of paediatric SDB symptoms by parents to their medical practitioners found [421]. As a result, children with a high clinical

suspicion of paediatric SDB, are often not formally or routinely screened and diagnosed for SDB.

The primary cause of obstructed SDB in children is adenotonsillar hypertrophy with obesity increasingly being implicated as a major contributory factor [153]. Another important group with a strong link to obstructed SDB are children with craniofacial deficiencies. Craniofacial characteristics such as maxillary constriction, a high palatal vault and mandibular retrognathia are associated with SDB in non-syndromic children [139, 236, 240, 241]. Imaging studies using lateral cephalogram [41, 422] and visual clinical screening [138] have produced conflicting results with low predictability in diagnosing paediatric SDB. PSG based studies have investigated dentofacial orthopedics, in particular the use of rapid maxillary expansion (RME) [275], but these have been in preselected children with OSA. There are multiple studies that quantify surrogate measures of upper airway size and/or respiratory events but none objectively measure snoring, the cardinal, most robust and most frequently occurring sign of upper airway obstruction in children.

Diagnosis of paediatric OSA is reliant on laboratory-based PSG which generates indices such as the apnea hypopneas index (AHI), the number of apneas and hypopneas that occur per hour of sleep. It is now widely recognized that PSG-derived indices do not adequately capture partial upper airway obstruction (snoring and stertor) that are characteristic of paediatric SDB [105]. To date, there are no data objectively measuring all relevant signs of upper airway obstruction and the prevalence of SDB in an unselected population of children with maxillary constriction.

The Sonomat™ is a portable mat system with non-contact sensors, validated against PSG [105, 415], that identifies quiescent (sleep) time, apneas, hypopneas and accurately quantifies snoring and stertor in children. This chapter explores paediatric SDB recorded in the home using the Sonomat™ in a population of children with maxillary constriction.

3.2 AIM

The aim of this study was to assess paediatric SDB in children with maxillary constriction requiring RME therapy.

3.3 METHODS

3.3.1 Study Participants

We prospectively recruited 59 consecutive children referred for orthodontic assessment requiring RME expansion therapy. Mal-alignment of the dentition, dental crowding and maxillary constriction were the primary reasons for referral; suspected SDB was not a cause of referral. The OSA-18 questionnaire (see Appendix 9.1) was completed at baseline and at the conclusion of RME therapy. The OSA-18 is an 18-item questionnaire that utilizes a Likert-type scoring system to gather information about a patient across 5 sub-scales that are deemed to be relevant to elements in quality of life: sleep disturbance, physical symptoms, emotional symptoms, daytime function and caregiver concerns [423]. A summary score is generated that ranges from 18 (no impact on quality of life) to 126 (major negative impact). A value of 60 or more is considered abnormal [423]. A single overnight Sonomat™

(Sonomedical, Balmain, Australia) recording was performed in the subject's own home. A detailed description of the Sonomat™ and the data acquisition for snoring and sleep indices are described in Chapter 2.

The inclusion criteria were (1) children with maxillary constriction requiring RME therapy (2) age between 3 -16 years; and (3) the presence of at least 6 teeth in the posterior maxillary dental arch. Exclusion criteria were (1) previous orthodontic treatment or RME therapy (2) uncontrolled dental caries; (3) cranio-facial syndromes; (4) cleft palate; (5) periodontal disease; (6) temporomandibular joint dysfunction; (7) an exaggerated gag reflex; (8) current treatment with positive airway pressure (PAP).

Obstructive sleep apnea (OSA) was defined as MOAHI ≥ 1 event/hr and primary snoring (PS) was defined as MOAHI < 1 event/hr with ≥ 10 minutes of snoring.

Ethical approval (HREC Ref. No: 2014/571) was granted by the institutional Ethics Committee and written consent was obtained from all parents with children providing assent if able.

3.4 Sonomat™ Scoring Criteria

An overnight sleep study was performed with the Sonomat™ (refer to General Materials and Methods). Apneas, hypopneas, snoring, stertor, body movements and quiescent time (Qd) were scored manually by an experienced scorer (MN) [105]. See General Materials and Methods section for the scoring criteria. Partially obstructed upper airway sounds were classified as snoring or stertor. Although both sounds, referred to collectively herein as

"obstructed breathing," are associated with partial upper airway obstruction, snoring has relatively low frequency peaks with harmonics whereas stertor contains much higher frequencies with no clear frequency peaks or harmonics. Snoring was scored when breath sounds contained periodic components with fundamental frequency peaks from 20–30 Hz up to approximately 250–300 Hz. In this study, inspiratory, expiratory and combined inspiratory and expiratory snoring were not differentiated but collectively scored as "snoring". Stertor was scored when breath sounds contained no clear frequency peaks but instead white noise containing frequencies from approximately 300-2000 Hz. The minimum duration of snore/stertor event was one breath and all consecutive snoring/stertorous breaths were scored as one event (i.e., as runs). These runs were terminated by a return to normal breathing or the occurrence of a respiratory event. Wheeze was defined as an adventitious, continuous sound having a musical character. Acoustically, it is characterized by periodic waveforms with a dominant frequency usually over 100 Hz. The quiescent time was used to generate the MOAHI, AHI and obstructed breathing indices with the analysis time used to generate movement indices.

3.5 Statistical analysis

Statistical analysis was performed using methods outlined in the General Methods section in Chapter 2.

3.6 RESULTS

All 59 children were sleep test naïve, as none had previously undergone testing for assessment of SDB, however, some patients had previously consulted an otolaryngologist for clinical assessment for possible SDB. Few of these children had previous surgical intervention (adenoidectomy or adenotonsillectomy) with the majority being conservatively managed with nasal sprays and pharmacological agents (e.g. Nasonex). Successful baseline Sonomat™ recordings were obtained in 56 children (95%) with 3 excluded having < 4 hours of interpretable data. The study population consisted of 26 (46%) boys and 30 (54%) girls, age = 8.9 ± 2.4 years (range 3-15 years) with BMI z-score = 0.22 (-0.8, 1.0). Baseline characteristics of the 56 children are summarized in Table 3.1.

TABLE 3.1. BASELINE CHARACTERISTICS of CHILDREN STUDIED (n=56)

Variable	All Patients
Sex	26M, 30F
Age, yr	8.9 ± 2.4 (range 3-15)
Height, cm	137.0 (130.1, 148.0) (range 108-173)
Weight, kg	31.6(26.6,43.0) (range 16.8-78.0)
BMI, kg/m^2	16.8(14.9,19.0) (range 12.0-29.4)
BMI Z score	0.22(-0.8,1.0) (range -4.1-2.0)
OSA-18 Score	44.0 (29.5, 54.8)
Tonsil grade	0.0(0.0,0.8) (range 0-3)
Bedwetting	10Y (17.9%), 46N
Asthma	13Y (23.2%), 43N
Repeat Otitis	5Y (8.9%), 51N
Repeat Upper Airway Infection	13Y (23.2%), 43N

Definition of abbreviations; BMI = body mass index; Y=Yes, N=No; Continuous data are presented Mean ± Standard deviation or Median (25^{th},75^{th} interquartile range) or proportion of group.

Table 3.1. Baseline characteristics of children studied (n=56). The children were aged 8.9 ± 2.4 years, non-obese with the majority exhibiting normal tonsillar size. Low OSA-18 scores were recorded suggesting a low impact on quality of life. A previous history of bedwetting, asthma and upper respiratory tract infections were noted in a small proportion of children.

The frequency distribution of the age of the study group is illustrated in Figure 3.1. The mean age was 8.8 ± 2.4 with the youngest 3 and oldest 15 years old. The majority of children were noted to be 8 or 9 years old with 13 and 10 subjects noted in each group respectively. There were 10 children older than 12 years; three were 12, four were 13, two were 14, and one was 15 years old. The 56 children were non-obese with BMI z score of 0.22 (-0.8, 1.0) with four children noted to be underweight, (Figure 3.2).

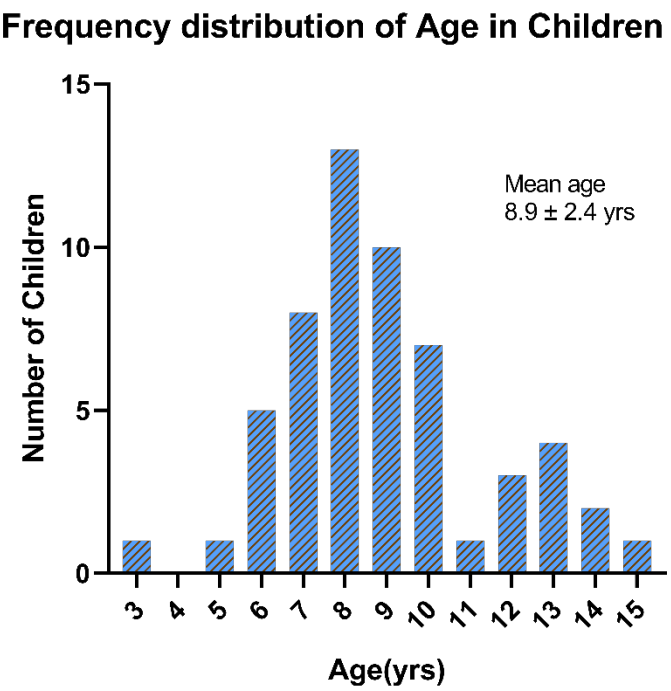


Figure 3.1 Distribution of the ages of the children studied (n=56). The youngest child was 3 years old with the oldest at 15 years old. The mean age of the group was 8.9 ± 2.4 years. Overall, the majority of children were noted to be 8 or 9 years old.

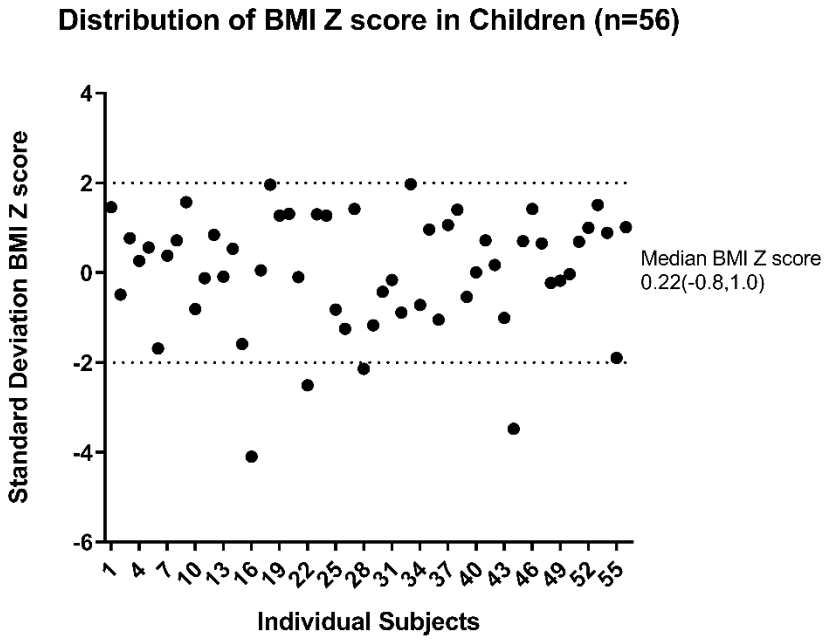


Figure 3.2 Distribution of the BMI z score of the children. The mean BMI z score was 0.22 (-0.8, 1.0) with a range (-4.1-2.0). There were no overweight children and 4 underweight children.

Clinical history indicated that 10 children (17.9%) exhibited nocturnal enuresis with 13 (23.2%) having a history of asthma. Five children (8.9%) had repeat otitis with repeat upper respiratory tract infections (URTI) noted in 13 children (23.2%).

Intra-oral examination revealed minimal tonsillar hypertrophy in the entire group with median tonsillar grade of 0.0 (0.0, 0.8). Forty-two children (75%) were normal grade 0, 7 (12.5%) grade 1, 5 (8.9%) grade 2 with 2 (3.6%) children noted to have grade 3 tonsillar size (Figure 3.3).

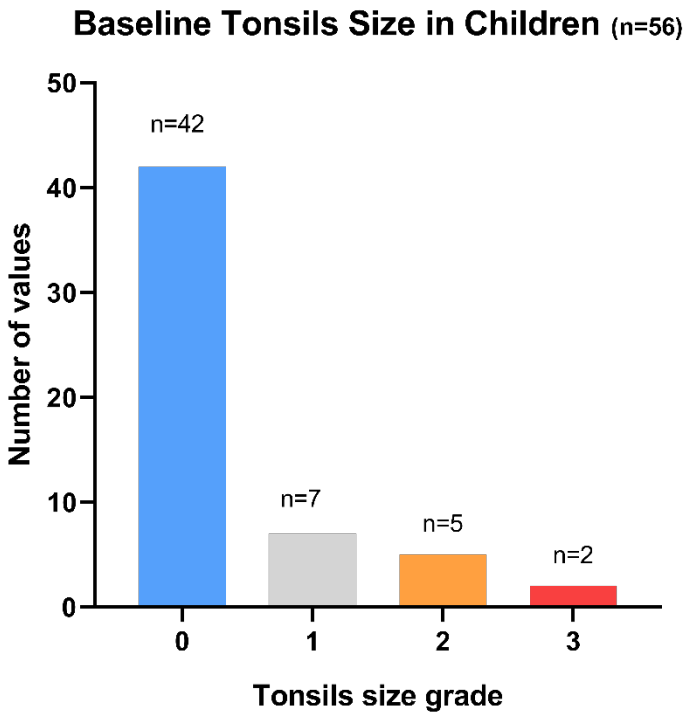


Figure 3.3. Distribution of tonsil size grading of the children studied. Most children had normal tonsil size. Only 2 children had grade 3 tonsillar size observed with 5 children with grade 2 tonsils noted. Individual characteristics of children with grade 2 and 3 tonsil are explored further in the sections below.

Closer investigation of the 2 children with grade 3 tonsils and 5 children with grade 2 tonsils was performed and is presented in Table 3.2 below. All children with tonsillar hypertrophy, with the exception of patient 7, did not have OSA (MOAHI <1/hr). Patient 7 (grade 2 tonsils) had moderate OSA (MOAHI = 6.3/hr) and significant OB runs (25.1 runs/hr) and duration (178.2 mins). This child also had frequent URTI but their OSA-18 total score was 27 suggestive of a minimal impact on quality of life. In contrast, patient 5 did not have OSA but had significant OB duration (126.7 mins) and frequent runs of OB (16.8 runs/hr) with minimal OSA-18 total score of 43. Patient 1 and 2 had grade 3 tonsils but exhibited significantly different levels of OB with patients 2 exhibiting frequent URTI

with greater duration in OB duration (52.5mins vs 0.9 mins) and OB runs/hr (4.7 vs 1.6) as compared to patient 1. Although patient 6 presented with a history of asthma and OSA-18 score of 83 suggestive of severe impact on quality of life, obstructed breathing was 9.8 minutes in duration with no OSA detected. A broad spectrum of clinical presentations was thus noted in these 7 children with grade 2/3 tonsils with nocturnal enuresis (patient 3,4); asthma (patient 6), URTI (patients 2,5,7) recorded. Overall, tonsillar size, clinical history and OSA-18 questionnaire was variable and of limited utility in predicting the severity of obstructed breathing and OSA.

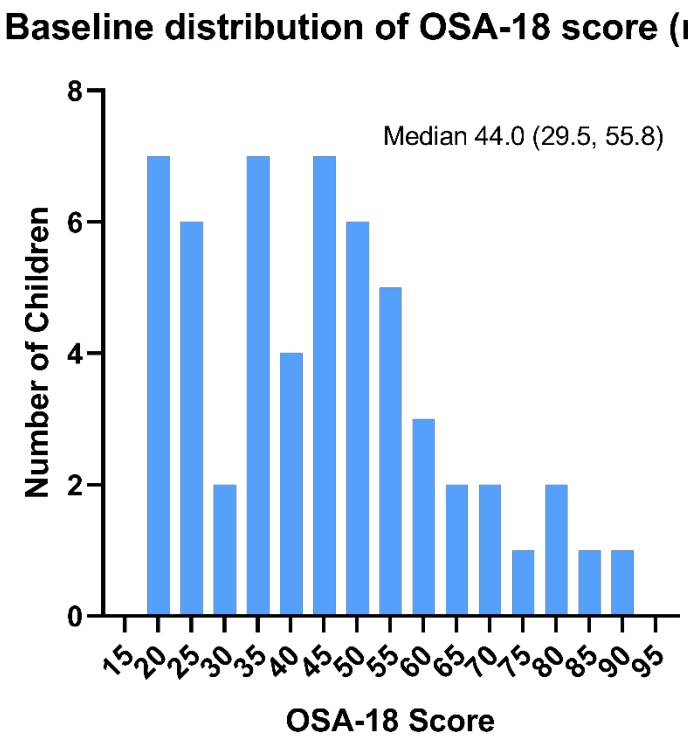
TABLE 3.2 Characteristics of Children with Tonsillar Hypertrophy (grade 2 and 3)

Patient	Tonsil grade	*Age (yrs)*	BMI z score	*Nocturnal enuresis*	Asthma	URTI	OSA-18 total score	MOAHI (/hr)	OB (mins)	OB (runs/*hr*)
Patient 1	3	8	0.77	N	N	N	33	0.0	0.9	1.6
Patient 2	3	7	1.27	N	N	Y	19	0.9	52.5	4.7
Patient 3	2	8	0.26	Y	N	N	37	0.0	11.9	4.5
Patient 4	2	8	-1.69	Y	N	N	20	0.6	2.0	1.1
Patient 5	2	9	1.96	N	N	Y	43	0.0	126.7	16.8
Patient 6	2	10	1.3	N	Y	N	83	0.0	9.8	3.4
Patient 7	2	7	-0.43	N	N	Y	27	6.3	178.2	25.1

Definition of abbreviations: URTI = upper respiratory tract infection; MOAHI = Mixed obstructive apnea and hypopnea index; OB = obstructed breathing.

Table 3.2 Characteristics of children with grade 2 and 3 tonsils. All children with the exception of patient 7 had a MOAHI <1/hr. A broad spectrum of clinical presentations was noted in these 7 children with grade 2/3 tonsils with nocturnal enuresis (patient 3,4); asthma (patient 6), URTI (patients 2,5,7) recorded. Overall, tonsillar size, clinical history and OSA-18 questionnaire was variable and of limited utility in predicting the severity of obstructed breathing and OSA.

As a group, an OSA-18 score of 44.0 (29.5, 55.8), range 18-91 was noted representing a small impact on health-related quality of life (QOL) outcomes at baseline. Forty-five (80.4%) children had scores < 60 indicating minimal impact on health-related outcomes. Eight (14.2%) children had scores between 60-80 and three (5.4%) children had scores above 80 indicating more severe QOL health related outcomes. The distribution of OSA-18 QOL total score is shown in Figure 3.4 with OSA-18 values across 5 domains detailed in Table 3.3.



Quality of Life Survey (OSA-18) Score
0-60 small impact on health-related quality of life
60-80 moderate impact
80+ Severe impact

Figure 3.4 Distribution of Quality of Life Survey (OSA-18) score in the 56 children studied. A median OSA-18 score of 44.0 (29.5, 55.8), (range 18-91) was recorded for the group. The majority (80.4%) of children had scores < 60 (minimal impact on QOL), eight (14.2%) scored between 60-80 (moderate impact on QOL) and three (5.4%) scored > 80 (severe impact on QOL).

Table 3.3 Baseline OSA-18 Quality of Life scores

		OSA-18 Median Domain Score				
	OSA-18 Total Score	**Sleep Disturbance**	**Physical Suffering**	**Emotional Distress**	**Daytime Problems**	**Caregiver Concern**
Baseline	44.0 (29.5-54.8)	8.0 (5.0-12.0)	10.0 (6.3-14.8)	7.0 (3.0-12.0)	7.0 (4.3-9.8)	8.0 (5.0-11.0)
CI of median	(37.0-50.0)	(6.0-11.0)	(8.0-13.0)	(4.0-10.0)	(6.0-8.0)	(7.0-9.0)

Abbreviation" OSA-18, 18-item quality-of life survey for obstructive sleep apnea.
Baseline data are median score (25^{th},75^{th} interquartile range).
CI of median- 95% confidence interval of median

Table 3.3 Baseline OSA-18 Quality of life scores across five different domains. All domain scores were low indicating minimal impact on QOL.

Sub-analysis of the 5 children with the highest OSA-18 total scores is presented in Table 3.4 below. Patients A and B both exhibited high OSA-18 total scores (>80) and presented with a history of asthma and were older (12 and 10 years old) than the mean age (8.8 ± 2.4 years) for the entire group. Both children exhibited significant obstructed breathing although Patient A was tending to be underweight (BMI z score -1.9), whereas Patient B recorded a BMI z score of 1.3. Despite higher OSA-18 scores, no OSA (MOAHI ≤ 1/hr) was noted in these 5 children with only 2 children exhibiting marked levels of obstructed breathing (Patient A and B). In these 2 children, the significant duration of obstructed breathing correlated to their respective high OSA-18 scores (91 and 83). Overall, the findings in tonsillar size and clinical examination and history was variable in these 5 children.

TABLE 3.4 Characteristics of Children with higher OSA-18 total scores (n=5)

Patient	Tonsil grade	*Age (yrs)*	BMI z score	*Nocturnal enuresis*	Asthma	URTI	OSA-18 total score	MOAHI (/hr)	OB (mins)	OB (runs)
Patient A	0	12	-1.9	N	Y	N	91	0.0	33.1	112
Patient B	2	10	1.3	N	Y	N	83	0.9	21.3	29
Patient C	1	9	-0.54	Y	N	Y	81	0.0	0.0	0.0
Patient D	0	8	0.7	N	N	N	79	0.6	0.8	8
Patient E	0	6	1.51	Y	Y	N	76	0.0	0.8	14

Definition of abbreviations: URTI = upper respiratory tract infection; MOAHI = Mixed obstructive apnea and hypopnea index; OB = obstructed breathing.

Table 3.4 Characteristics of the 5 children with highest OSA-18 total scores. Only 2 children (Patients A and B) exhibited significant duration of obstructed breathing (33.1 and 21.3 mins respectively). High OSA-18 scores were noted in these 2 children (91 and 83 respectively). The remaining children did not exhibit elevated levels of obstructed breathing.

Total recording time was 589.4 (514.4, 635.7) mins of which time available for analysis was 519.4 (446.0, 588.0) mins. The quiescent time was 492.7 (424.6, 546.7) mins which represented 94.8% (93.1, 95.4) of analysis time (analogous to sleep efficiency). There were 25.8 (19.0, 36.0) mins of spontaneous movement arousals at a rate of 14.2 (10.6, 17.7) movements per hour. Respiratory induced movement arousals occurred less frequently, at a rate of 0.8 (0.4, 2.4) events per hour, with a total duration of 1.0 (0.4, 2.6) mins. Table 3.5 details the recording time, body movement and quiescent time for the group at baseline.

TABLE 3.5 BASELINE RECORDING TIME, BODY MOVEMENT AND QUIESCENT TIME (n=56)

Variable	Duration (min)	Percentage	Number (/h)
TRT	589.4 (514.4, 635.7)	-	-
Analysis time	519.4 (446.0, 588.0)	87.1 (78.0, 94.9)	-
Quiescent time (Qd)	492.7 (424.6, 546.7)	94.8 (93.1, 95.4)	-
Spont. MAr	25.8 (19.0, 36.0)	5.0 (4.0, 6.5)	14.2 (10.6, 17.7)
Resp. MAr	1.0 (0.4, 2.6)	0.2 (0.2, 0.5)	0.8 (0.4, 2.4)

Definition of abbreviations: TRT = total recording time; Qd = quiescent time; Spont. = spontaneous, MAr = movement arousal, Resp.= respiratory induced; Continuous data are presented as Median (25^{th},75^{th} interquartile range).

Table 3.5 Baseline recording time, body movement and quiescent time. Total recording time was 589.4 (514.4, 635.7) mins of which time available for analysis was 519.4 (446.0, 588.0) mins. The quiescent time was 492.7 (424.6, 546.7) mins which represented 94.8% (93.1, 95.4) of analysis time. Respiratory induced movement arousals occurred less frequently than spontaneously induced movement arousals. These occurred at a rate of 0.8 (0.4, 2.4) events per hour with a total duration of 1.0 (0.4, 2.6) mins.

3.6.1 Prevalence of SDB in children with Maxillary constriction

Apnea and hypopnea events

No child had repetitive obstructive apneas or hypopneas (any obstructive events were isolated events) with most events being central. Obstructive apneas were present in 10 (18%), central apneas in 43 (77%), and mixed apneas in 9 (16%) children. Obstructive hypopneas were noted in 10 (18%) and central hypopneas in 32 (57%) children. Five children out of 56 (9%) had no apneas or hypopneas.

Obstructive apneas were negligible at 0 (0, 0) events (maximum number = 13) occurring at a rate of 0 (0, 0) events per hour (maximum = 1.5/hr). There were 2 (1, 4) central apneas occurring at a rate of 0.3 (0.1, 0.5) events per hour. Overall, a total of 2 (1, 5) apneas (central, obstructive and mixed) occurred at a rate of 0.3 (0.1, 0.7) events per hour. There was a median of 1 (0, 2) central hypopnea recorded occurring at a rate of 0.1 (0.0, 0.2) events per hour. Obstructive hypopneas were negligible at 0 (0, 0) events (maximum number = 47) occurring at 0 (0, 0) events per hour (maximum = 5.8/hr). There was a total of 1 (0, 3) hypopneas (central and obstructive) occurring at a rate of 0.1 (0.0, 0.4) events per hour. The AHI, MOAI and CAHI were 0.2 (0.0, 0.4), 0.0 (0.0, 0.2) and 0.3 (0.2, 0.8) events per hour, respectively. Apnea and hypopnea events are shown in Table 3.6.

TABLE 3.6 APNEAS and HYPOPNEAS IN CHILDREN (n=56)

Variable	No.
OA, events	0 (0, 0)
CA, events	2 (1, 4)
MA, events	0 (0, 0)
All apneas, events	2 (1, 5)
OH, events	0 (0, 0)
CH, events	1 (0, 2)
All hypopneas, events	1 (0, 3)
All Resp. events[a]	3 (2, 9)
Obstructive events[b]	0 (0, 1)
Central events[c]	3 (1, 6)
OAI, events/hr	0.0 (0.0, 0.0)
CAI, events/hr	0.3 (0.1, 0.5)
MAI, events/hr	0.0 (0.0, 0.0)
AI, events/hr	0.3 (0.1, 0.7)
OHI, events/hr	0.0 (0.0, 0.0)
CHI, events/hr	0.1 (0.0, 0.2)
HI, events /hr	0.1 (0.0, 0.4)
AHI, events/hr	0.2 (0.0, 0.4)
MOAHI, events/hr	0.0 (0.0, 0.2)
CAHI, events/hr	0.3 (0.2, 0.8)

Definition of abbreviations: No.= number; OA =Obstructive apnea; CA = Central apnea; MA= Mixed apnea; OH = Obstructive Hypopnea; CH = Central Hypopnea; [a] = Apneas + Hypopneas; [b] = OA + MA + OH; [c] = CA + CH; OAI =Obstructive apnea index; CAI = Central apnea index; MAI= Mixed apnea index; OHI = Obstructive Hypopnea index; CHI = Central Hypopnea index; HI= hypopnea index; AHI = Apnea hypopnea index; MOAHI = Mixed obstructive apnea hypopnea index; CAHI = Central apnea hypopnea index; Continuous data are presented as Median (25^{th},75^{th} interquartile range).

Table 3.6 Apnea and hypopneas in the entire group (n=56). No child had repetitive obstructive apneas or hypopneas with the majority of events being central. Few obstructive apneas and hypopneas were noted. The AHI, MOAI and CAHI were 0.2 (0.0, 0.4), 0.0 (0.0, 0.2) and 0.3 (0.2, 0.8) events per hour, respectively.

Snoring, stertor and obstructed breathing events

Snore runs occurred in 49 (87.5%), runs of stertor in 10 (17.9%) and obstructed breathing (snoring + stertor) was present in 49 (87.5%) children. A total of 7 (12.5%) children did not have any obstructed breathing. Ten snoring children (17.9%) also had stertor and, in stark contrast, all (100%) stertorous children snored. The predominant component in obstructed breathing (OB) was snoring as compared to stertor. The children spent 8.6 (0.6, 31.4) mins (maximum 290.7) snoring at a rate of 4.6 (0.8, 7.9) snoring runs/hr. Stertor was negligible in the entire group at 0.0 (0.0, 0.0) mins (maximum 53) at a rate of 0.0 (0.0, 0.0) stertorous runs/hr. Table 3.7 details snoring, stertor and obstructed breathing in all children. Stertor in the ten stertorous children was minimal at 0.4 (0.1, 7.9) mins of stertor at a rate of 0.1 (0.1, 0.4) runs/hr. Notably 2 children had stertor for 22.7 and 53 mins. Stertorous children are presented in detail in Figure 3.5 and Table 3.8.

Snore runs occurred in 49 (87.5%), runs of stertor in 10 (17.9%) and obstructed breathing (snoring + stertor) was present in 49 (87.5%) children. A total of 7 (12.5%) children did not have any obstructed breathing. Ten snoring children (17.9%) also had stertor and, in stark contrast, all (100%) stertorous children snored. The predominant component of obstructed breathing was snoring as compared to stertor. The children spent 8.6 (0.6, 31.4) mins (maximum 290.7) snoring at a rate of 4.6 (0.8, 7.9) snoring runs/hr. Stertor was negligible in the entire group at 0.0 (0.0, 0.0) mins (maximum 53) at a rate of 0.0 (0.0, 0.0) stertorous runs/hr (maximum 7.5 runs/hr). Table 3.7 details snoring, stertor and obstructed breathing in all children. Although classified as “stertorous children” due to the presence of stertor, when grouped the amount of stertor was minimal at 0.4 (0.1, 7.9) mins at a rate of

0.1 (0.1, 0.4) runs/hr. However, 2 children had long periods of stertor, one for 22.7 and the other for 53 mins. Stertorous children are presented in detail in Figure 3.5 and Table 3.8.

TABLE 3.7 SNORING, STERTOR AND OBSTRUCTED BREATHING AT BASELINE (n=56)

Variable	% of children	No. of runs	Number (/hr)	Total duration (mins)	Max. (mins)
Snore	87.5%	39 (7, 65)	4.6 (0.8, 7.9)	8.6 (0.6, 31.4)	290.7
Stertor	17.9%	0 (0, 0)	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)	53.0
Obstructed breathing [a]	87.5%	40(7,65)	4.6 (0.8, 7.9)	8.6 (0.6, 31.5)	290.7

Definition of abbreviations; No.= number; Qd = Quiescent time; Max = maximum; Obstructed breathing [a] = Snore + Stertor; Continuous data are presented as Median (25^{th},75^{th} interquartile range).

Table 3.7 Snoring, Stertor and Obstructed breathing at baseline. The duration of Obstructed Breathing (OB) in the entire group (n=56) is shown. Note that the majority of OB comprised snoring with only minimal stertor noted in 10 children (17.9%). Although the data shows negligible stertor, one child exhibited 53 mins of stertor.

Stertor duration in the 10 stertorous children is presented in Figure 3.5.

Figure 3.5 Duration of stertor for 10 stertorous children. The majority had minimal stertor at baseline with only 2 having long durations of stertor (53 mins and 22.7 mins). The remainder had ≤ 2.9 mins of stertor.

Detailed analysis of the 10 stertorous children are presented in Table 3.8 below. The 2 children (patients 4 and 8) with significant stertor (22.7 and 53.0 mins) presented with grade 2 tonsils and had a clinical history of frequent upper respiratory tract infections. These two children differed in their BMI z scores (1.96 vs -0.43) but both recorded low OSA-18 total scores (43 vs 27). Patient 8 was one of two children in the stertorous group that had significant OSA (MOAHI = 6.3/hr). The other stertorous child (patient 3) with OSA (MOAHI = 2.2/hr) had, surprisingly, normal sized tonsils (grade 0). A key observation was that both stertorous children with OSA snored significantly (238.6 mins vs 125.2mins). Both stertorous OSA children (patients 3 and 8) rated low on the OSA-18 total

score; (53 vs 27). Overall, all stertorous children snored with 2 children presenting with OSA (patients 3 and 8). Notably, the remaining two (50%) children with OSA did not exhibit stertor. All stertorous children were noted to snore (range 1.3 - 238.6 mins) with a great variability in tonsil size noted. Additionally, a wide spectrum of clinical findings of nocturnal enuresis (20%), asthma (10%), frequent respiratory infections (50%) in stertorous children was observed.

Detailed analysis of the 10 stertorous children are presented in Table 3.8 below. The 2 children (patients 4 and 8) with significant stertor (22.7 and 53.0 mins) had grade 2 tonsils and had a clinical history of frequent upper respiratory tract infections. They differed in their BMI z scores (1.96 vs -0.43) and both recorded low OSA-18 total scores (43 vs 27). Patient 8 was one of two children in the stertorous group that had significant OSA (MOAHI = 6.3/hr). The other stertorous child (patient 3) with OSA (MOAHI = 2.2/hr) had, surprisingly, normal sized tonsils (grade 0). A key observation was that both stertorous children with OSA snored significantly (238.6 mins and 125.2mins). The two stertorous children with OSA (patient 3 and patient 8) rated low on the OSA-18 total score;(53 vs 27).

Overall, all stertorous children snored with 2 children presenting with OSA (Table 3.8). Notably, the remaining two (50%) children with OSA did not have any stertor. All stertorous children were noted to snore (range 1.3 - 238.6 mins) with a great variability in tonsil size noted. Additionally, a wide spectrum of clinical findings of nocturnal enuresis (20%), asthma (10%), frequent respiratory infections (50%) in stertorous children was observed.

TABLE 3.8 Baseline Characteristics of Children with Stertor (n=10)

Patient	Tonsil grade	Age *(yrs)*	BMI z score	NE	Asthma	URTI	OSA-18 total score	MOAHI (/hr)	Stertor (mins)	Stertor (runs)	Snoring (mins)	Snoring (runs)
Patient 1	1	10	1.46	N	N	N	29	0.6	0.3	2.0	10.8	89.0
Patient 2	0	7	-3.48	N	N	N	67	0.0	0.9	1.0	23.5	64.0
Patient 3	0	8	-1.01	N	N	N	53	2.2	2.9	5.0	238.6	249.0
Patient 4	2	9	1.96	N	N	Y	43	0.0	22.7	2.0	104.1	120.0
Patient 5	3	7	1.27	N	N	Y	19	0.9	0.1	1.0	52.4	40.0
Patient 6	0	8	1.57	Y	N	Y	64	0.2	0.1	1.0	12.7	52.0
Patient 7	2	8	-1.69	Y	N	N	20	0.6	0.1	1.0	1.9	10.0
Patient 8	2	7	-0.43	N	N	Y	27	6.3	53.0	61.0	125.2	142.0
Patient 9	0	9	-1.25	N	Y	N	49	0.1	0.4	1.0	1.3	21.0
Patient 10	1	7	0.65	N	N	Y	40	0.0	0.4	1.0	30.6	45.0

Definition of abbreviations: NE = nocturnal enuresis; URTI = upper respiratory tract infection; MOAHI = Mixed obstructive apnea and hypopnea index; OB = obstructed breathing.

Table 3.8 Baseline characteristics of 10 stertorous children. All stertorous children snored and 2 had OSA (patients 3 and 8). Significant differences in stertor (2.9 mins vs 53.0 mins) were noted in these OSA children but both snored significantly (238.6 mins and 125.2mins). As a group, snore duration was variable (range 1.3-238.6 mins) with also a great variability in tonsil size noted.

Wheeze events

Two boys (3.6%) were found to wheeze during the night at baseline with data shown in Tables 3.9 and 3.10. They were aged 9 and 12 years old, had normal tonsillar size, were slightly under-weight (BMI z score -1.25 and -1.9) and, not surprisingly, both presented with a clinical history of asthma. These children are referred to as W1 and W2 respectively.

OSA-18 total scores were higher in patient W2 (91 vs 49) although both did not have OSA (MOAHI<1/hr). In addition to wheezing both children snored (1.3 vs 33.1mins) with only one having a very small amount of stertor (patient W1 = 0.4 mins). However, it is interesting to note that patient W2 was more underweight (BMI z score -1.9) and had a high OSA-18 higher score of 91 indicating a severe impact of quality of life. This is reflected in the increased snoring duration (33.1 mins vs 1.3 mins) and snore runs (112 runs vs 21 runs) as compared to patient W1 but a larger amount of wheezing (62.4 mins vs 8.4 mins) may have also contributed to the higher OSA-18 score.

TABLE 3.9 Baseline Characteristics of 2 Children with Nocturnal Wheezing

Patient	Tonsil grade	*Age (yrs)*	BMI z score	Nocturnal enuresis	Asthma	URTI	OSA-18 total score
Patient W1	0	9	-1.25	N	Y	N	49
Patient W2	0	12	-1.9	N	Y	N	91

Definition of abbreviations: URTI = upper respiratory tract infection;
Continuous data are presented as absolute values.

Table 3.9 Baseline characteristics of 2 children with nocturnal wheezing. The children were aged 9 and 12 years old, had normal tonsillar size and were slightly under-weight. Both presented with a clinical history of asthma with a higher OSA-18 score in patient W2.

TABLE 3.10 Baseline Sleep Disordered Breathing Characteristics of 2 children with Nocturnal Wheeze.

Patient	MOAHI (/hr)	Wheeze (runs)	Wheeze (runs/hr)	Wheeze (mins)	Wheeze duration (% of Qd)	Stertor (mins)	Stertor (runs)	Snoring (mins)	Snoring (runs)
Patient W1	0.1	73	7.2	8.4	1.4	0.4	1	1.3	21
Patient W2	0.0	51	5.1	62.4	11.1	0.0	0	33.1	112

Definition of abbreviations: NE = nocturnal enuresis; URTI = upper respiratory tract infection; MOAHI = Mixed obstructive apnea and hypopnea index; Qd = quiescent time; Continuous data are presented as absolute values.

Table 3.10 Baseline SDB characteristics of 2 children with nocturnal wheeze. Patients W2 exhibited greater wheeze duration (62.4 vs 8.4 mins) and snored longer than patient W1. Both children did not have OSA (MOAHI < 1/hr) with negligible stertor noted.

Prevalence of OSA and Obstructed Breathing

Using widely used criteria for defining and classifying the severity of OSA, 52 (93%) children did not have OSA (MOAHI < 1 event/h) and 4 (7%) had OSA. Three (5%) had mild OSA (1 ≤ MOAHI < 5 events/h), 1 child (2%) had moderate OSA (5 ≤ MOAHI <10 events/h) and no child had severe OSA (MOAHI ≥ 10 events /h).

The duration and frequency of OB of the entire group is presented in Figure 3.6. Of significance, OSA and non-OSA children were often indistinguishable with regard to the frequency and duration of OB. Several non-OSA children were noted to have a longer duration and more frequent runs of OB than did children with OSA.

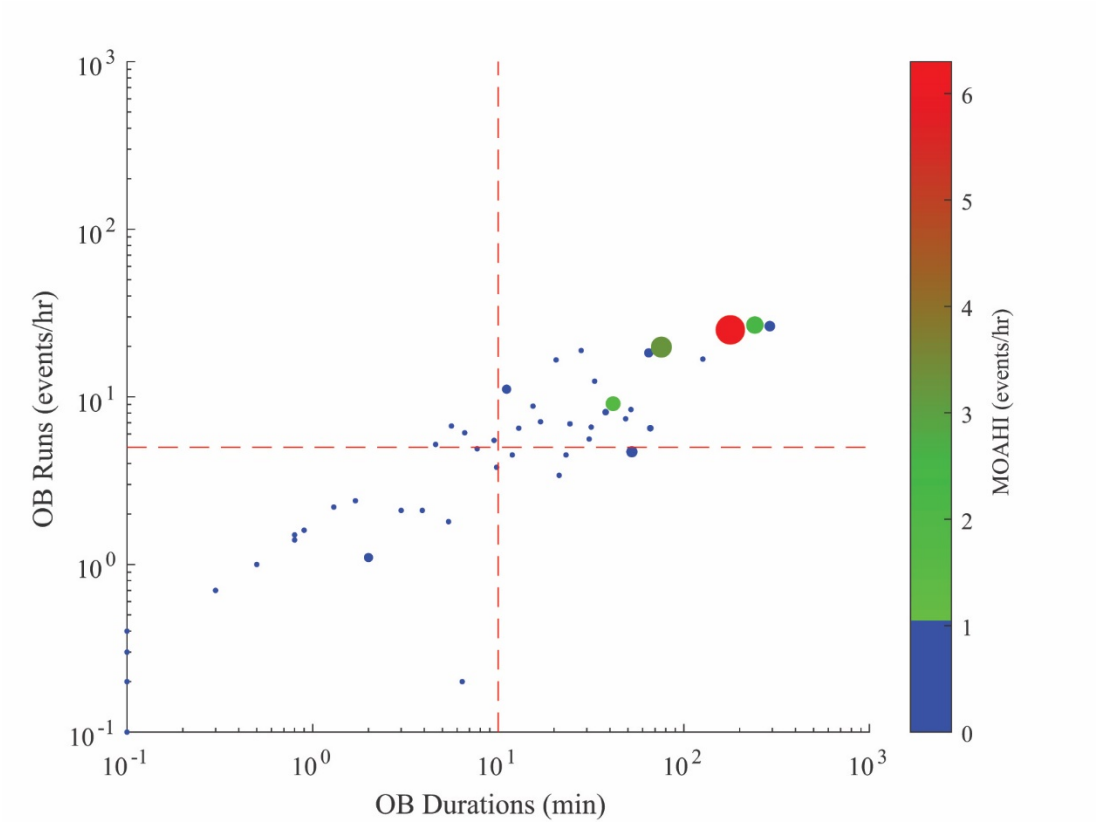


Figure 3.6 Bubble plot showing total duration ($log_{10,}$ x-axis) plotted against number of runs ($log_{10,}$ y-axis) of OB for each child. MOAHI values are on the z-axis; blue circles are non-OSA children with hotter colors and larger circles indicating increasing severity of OSA. Only 4 children had OSA (MOAHI ≥ 1). Red dashed lines indicate OB thresholds of 10 mins (x-axis) and 5 runs/h (y axis) with all OSA children located above both thresholds. Importantly, many non-OSA children were also above both thresholds with several having longer durations and more frequent runs of OB than children with OSA.

Children with OSA (n=4)

Of the 4 OSA children all snored for ≥ 10 min; snore = 100.5 (50.1, 210.3) mins (range 41.6-238.6) at a rate of 18.7 (11.2, 24.6) snoring runs/h (range 9.1-26.2). Two OSA children (50%) had no stertor, 1 child (25%) had 1.0-4.9 min of stertor present and 1 (25%) had ≥ 10 min stertor. The stertorous OSA children had 1.5 min (0.0, 40.5) of stertor (range 0.1-53.0) occurring at a rate of 0.3 (0.0, 5.8) stertor runs/h (range 0.0-7.5). Baseline

characteristics and sleep-disordered breathing and movement metrics of the OSA children are shown in Tables 3.11 and 3.12.

TABLE 3.11 Baseline Characteristics of OSA Children (n=4)

Patient	*Gender (M/F)*	Tonsil grade	*Age (yrs)*	BMI z score	Nocturnal enuresis	Asthma	URTI	OSA-18 total score
Patient 1	F	0	8	-1.01	N	N	N	53
Patient 2	M	0	12	-1.42	N	N	N	43
Patient 3	F	2	7	-0.43	N	N	Y	27
Patient	F	0	8	1.06	N	Y	N	36

Definition of abbreviations: M= male; F= Female; URTI = upper respiratory tract infection; Continuous data are presented as absolute values.

Table 3.11 Baseline characteristics of the 4 OSA children. Three (75%) were female and only 1 had tonsillar hypertrophy (grade 2). Clinical history of asthma (25%) and frequent URTI (25%) was noted. Interestingly, all children scored <60 in OSA-18 total score despite having OSA (MOAHI >1).

TABLE 3.12 Baseline Sleep-Disordered breathing and Movement Variables of OSA Children in entire group (n=4)

Patient	MOAHI (/hr)	Spont. MAr (mins)	Spont MAr (/hr)	Resp. MAr (mins)	Resp. MAr (/hr)	Stertor (mins)	Stertor (runs)	Snoring (mins)	Snoring (runs)
Patient 1	2.2	25.1	12.3	13.1	11.5	2.9	5	238.6	249
Patient 2	1.6	21.6	10.4	2.5	3.0	0.0	0	41.6	80
Patient 3	6.3	17.6	12.0	7.8	8.7	53.0	61	125.2	142
Patient 4	3.2	56.8	14.6	3.6	3.7	0.0	0	75.7	110

Definition of abbreviations: NE = nocturnal enuresis; Spont. = spontaneous; Resp. = respiratory; MAr = movement arousals; MOAHI = Mixed obstructive apnea and hypopnea index; Qd = quiescent time; Continuous data are presented as absolute values.

Table 3.12 Baseline SDB and movement variables of 4 OSA children. All OSA children snored significantly with 2 exhibiting stertor (patients 1 and 3). All 4 children exhibited significant levels of respiratory induced movement arousals.

Non-OSA children

In the non-OSA group (n=52, 25 male), 7 (13.4%) had no evidence of snoring, 10 (19.2%) snored for < 1.0 min, 6 (11.5%) snored ≥ 1.0-4.9 min, 7 (13.4%) snored ≥ 5.0-9.9 min, and 22 (42.3%) snored for ≥10 min.

Non-OSA snoring children (n=22)

The 22 non-OSA group who snored ≥ 10 mins spent 29.3 (19.6, 52.0) mins (range 10.8-290.7) snoring. This occurred at a rate of 7.3 (6.2, 13.5) snoring runs/h, (range 3.4-26.4). There were 16 (30.7%) with no stertor, 5 (9.6%) with minimal stertor present (< 1min) and only 1 with stertor present for ≥ 10 min. These non-OSA stertorous children had 0.4 min (0.1, 6.4) of stertor (range 0.1-22.7) occurring at a rate of 0.1 (0.1, 0.2) runs/h (range 0.1-0.3).

All snoring children

Sub-analysis of all 26 snoring children (22 non-OSA and 4 OSA) was undertaken and the baseline characteristics of both groups are summarized in Table 3.13. Overall, there were no significant differences in baseline characteristics between these two groups of children.

TABLE 3.13 BASELINE CHARACTERISTICS of Non-OSA Snorers (n=22) AND OSA children(n=4)

Variable	Non-OSA snorers (n=22)	OSA Children (n=4)	p value
Sex	13M, 9F	1M, 3F	0.21
Age, yr	8.0 (7.0, 10.0)	8.0 (7.3, 11.0)	0.97
Height, cm	136.5 (128.3, 145.0)	130.3 (125.5, 146.6)	0.50
Weight, kg	30.1 (25.5, 43.8)	28.3 (23.2, 48.5)	0.62
BMI, kg/m^2	16.9 (11.1, 23.4)	16.9 (14.5, 22.3)	0.96
BMI Z score	0.7 (-0.3, 1.3)	0.3 (-0.9, 1,3)	0.96
OSA-18 Score	79.5 (63.8, 95.5)	78.6 (56.5, 99.0)	0.91
Mouth breathing score	4.5 (2.8, 6.0)	3.5 (3.0, 4.0)	0.26
Tonsil grade	0.0(0.0,1.0) (range 0-3)	0.0(0.0, 1.5) (range 0-2)	0.91
Bedwetting	5/22 (22.7%)	0/4 (0%)	0.29
Asthma	6/22 (27.3%)	1/4 (25%)	0.93
Repeat Otitis	2/22 (9.1%)	0/4 (0%)	0.53
Repeat Upper Airway	9/22 (40.9%)	1/4 (25%)	0.55

Definition of abbreviations; BMI = body mass index; Y=Yes, N=No; Continuous data are presented as Median (25th,75th interquartile range).

Table 3.13 Baseline Characteristics of non-OSA snorers and OSA children. There were no significant differences noted between the groups with respect to gender, age, BMI and OSA-18 scores and clinical history.

3.6.2 Baseline comparison between Snorers and Non-Snorers

A comparison of sleep and respiratory variables in snoring and non-snoring children is shown in Table 3.14. Significant differences were noted in the MOAHI (p=0.005), OAI (p=0.02) and OHI (p=0.001) with snoring children having higher values.

Not surprisingly, snorers (snore >10 mins) exhibited longer periods of snoring (32.4 (21.1, 65.0) mins vs 0.8 (0.1, 4.8) mins, snoring for a greater proportion (7.5 (4.2, 12.0) % vs 0.2

(0.0, 1.0) %); at a greater rate of 8.3 (6.5, 16.8) runs vs 1.0 (0.1, 2.2) runs per hour in comparison to non-snorers (snore <10 mins). Significant differences were also noted between the groups with respect to stertor duration, stertor % and stertor runs per hour (all p=0.02); although they were of smaller magnitude and frequency (Table 3.14). Overall, obstructed breathing, which was predominantly snoring in nature, occurred significantly more in duration, percentage and rate (all $p < 0.0001$) as compared to non-snorers (Figure 3.7). Non-snorers had significantly more spontaneously induced movement arousals (119.0 (94.3, 175.8) events vs 100.5 (79.0, 134.8), events, $p = 0.04$) occurring more frequently (15.3, (12.8, 18.7) events/hr vs 13.0 (9.9, 15.4), $p = 0.007$).

A key observation in this analysis was the presence of a significantly greater number of respiratory induced movement arousals in the snoring children (Table 3.14). The number (19 (10, 28) events vs 3 (1, 5 events, $p < 0.0001$) (Table 3.8), frequency (2.5 (1.1, 3.3) events/hr vs 0.3 (0.1, 0.7) events/hr, $p < 0.0001$) and total duration (Fig 3.7) of respiratory induced movement arousals was greater in the snoring children.

TABLE 3.14 BASELINE SLEEP AND BREATHING CHARACTERISTICS OF NON-SNORING AND SNORING CHILDREN

Variable	Non-Snorers (n=30)	Snorers (n=26)	p value
Analysis Time, mins	512.8 (445.5, 590.3)	544.3 (444.6, 584.3)	0.81
Qd, mins	487.3 (420.5, 547.3)	502.9 (423.7, 547.3)	0.71
MOAHI, events/hr	0.0 (0.0, 0.0)	0.1 (0.0, 0.7)	0.005
AHI, events/hr	0.3 (0.2, 1.1)	0.6 (0.3, 1.3)	0.26
OAI, events/hr	0.0 (0.0, 0.0)	0.0 (0.0, 0.1)	0.02
OHI, events/hr	0.0 (0.0, 0.0)	0.0 (0.0, 0.4)	0.001
CAI, events/hr	0.3 (0.1, 0.7)	0.2 (0.0, 0.4)	0.32
CHI, events/hr	0.1 (0.0, 0.2)	0.1 (0.0, 0.2)	0.70
Spont. MAr mins	27.9 (19.4, 37.5)	23.5 (17.6, 33.3)	0.15
Spont. MAr events	119.0 (94.3, 175.8)	100.5 (79.0, 134.8)	0.04
Spont. MAr events/hr	15.3 (12.8, 18.7)	13.0 (9.9, 15.4)	0.007
Resp. MAr mins	0.5 (0.1, 0.6)	2.6 (1.6, 6.3)	<0.0001
Resp. MAr events	3.0 (1.0, 5.0)	19.0 (9.5, 28.3)	<0.0001
Resp. MAr events /hr	0.3 (0.1, 0.7)	2.5 (1.1, 3.3)	<0.0001
Snoring, mins	0.8 (0.1, 4.8)	32.4 (21.1, 65.0)	<0.0001
Snoring, %	0.2 (0.0, 1.0)	7.5 (4.2, 12.0)	<0.0001
Snore runs, /hr	1.0 (0.1, 2.2)	8.3 (6.5, 16.8)	<0.0001
Stertor, mins	0.0 (0.0, 0.0)	0.0 (0.0, 0.2)	0.02
Stertor, %	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)	0.02
Stertor, runs, /hr	0.0 (0.0, 0.0)	0.0 (0.0, 0.1)	0.02
Obstructed breathing, mins	0.8 (0.1, 4.8)	32.4 (21.1, 65.0)	<0.0001
Obstructed breathing, %	0.2 (0.0, 1.0)	7.5 (4.2, 12.0)	<0.0001
Obstructed breathing runs, /hr	1.1 (0.1, 2.3)	8.3 (6.5, 17.2)	<0.0001

Definition of abbreviations; Qd = Quiescent time; Resp. =respiratory; MOAHI = Mixed + Obstructive apnea hypopnea index; AHI = apnea+hypopnea index; OAI = Obstructive apnea Index; OHI = Obstructive Hypopnea Index; CAI = Central apnea index; Spont = spontaneous, MAr =movement arousal, Resp.= respiratory induced; Continuous data are presented as Median (25^{th},75^{th} interquartile range).

Table 3.14 Baseline Sleep and Breathing characteristics of non-snoring and snoring children. Significant differences were noted in the MOAHI (p=0.005), OAI (p=0.02) and OHI (p=0.001) with snoring children tending to higher values. Significantly more respiratory induced movement arousals were noted in snorers with respect to duration, number of events and events/hr, (all $p < 0.0001$).

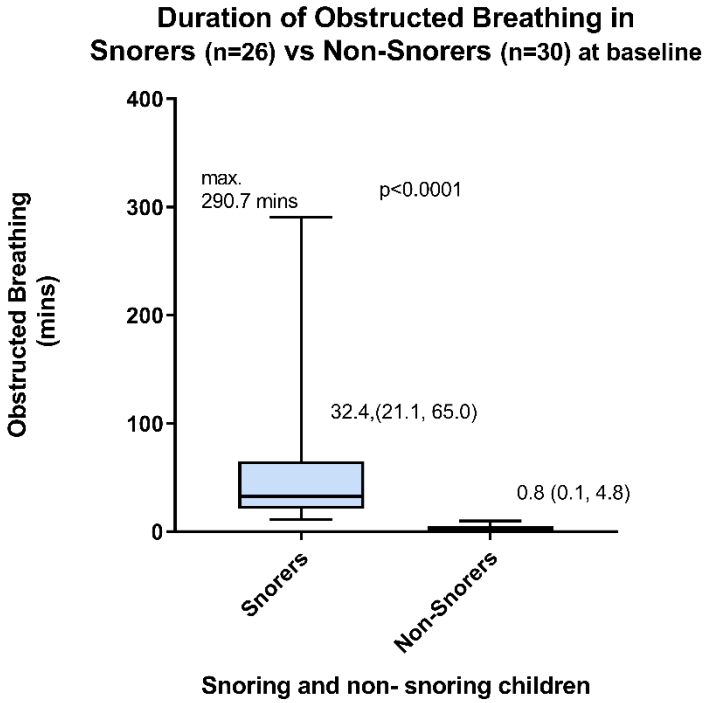


Figure 3.7 Comparison of the duration of obstructed breathing snoring and non-snoring children. Snorers had significantly more obstructed breathing (snoring and stertor) than non-snoring children (32.4 [21.1, 65.0] min vs 0.8 [0.1,4.8] min, p<0.0001). Notably, a 3-year old girl exhibited 290.7 mins of obstructed breathing. Of note, this child had a MOAHI of 0.8 events/hr but exhibited a significant duration of snoring (290.7 mins) with no stertor observed. Surprisingly, no tonsillar hypertrophy was noted (grade 0) with OSA-18 total score of 34 suggestive of a low impact of quality of life. However, relevant findings were found in her clinical history in relation to asthma and nocturnal enuresis.

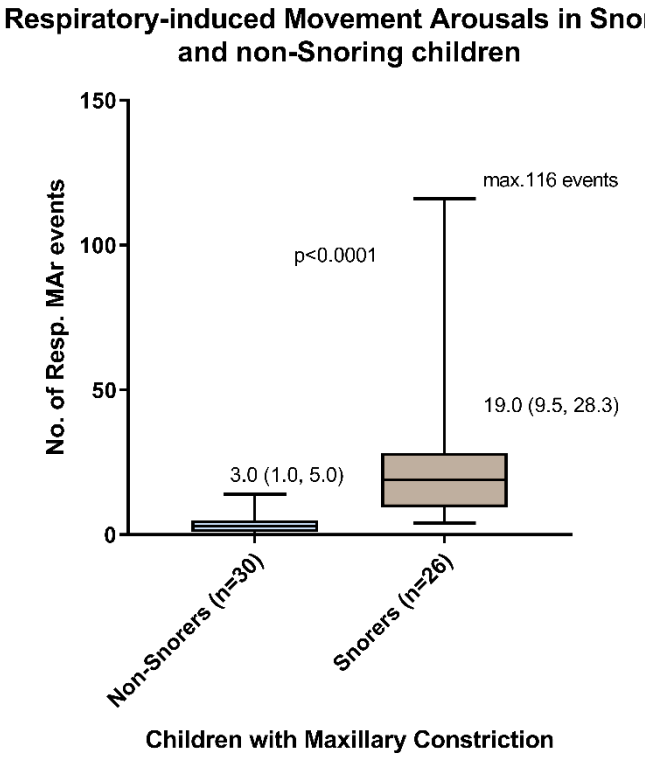


Figure 3.8 Comparison of respiratory induced movement arousals (Resp. MAr) in snoring and non- snoring children. Snorers had significantly more Resp. MAr than non- snoring children (19.0 [9.5, 28.3] events vs 3.0 [1.0,5.0] events, p<0.0001). Notably, one girl (8-year old) had 116 events of Resp. MAr during the night (total duration 13.1 mins, 11.5 events/hr). Not surprisingly, this child also had OSA (MOAHI 2.2 events/hr) with significant obstructed breathing (241.5 mins) comprised of snoring (238.6 mins) and stertor (2.9 mins). Surprisingly, there was no tonsillar hypertrophy (tonsil grade 0) and the OSA-18 total score was 53 which suggests minimal impact on quality of life. No significant findings were found in her clinical history in relation to asthma, nocturnal enuresis or respiratory infections.

3.7 DISCUSSION

Although childhood SDB is a common disorder characterized by prolonged periods of partial upper airway obstruction (UAO) presenting as snoring and stertor, objective measurement of snoring has proven elusive. Snoring and stertor are cardinal signs and symptoms of partial UAO and OSA with approximately 3-35% of the paediatric population thought to snore [32, 35, 122-124].

Previous studies have specifically recruited children with OSA and investigated the role of rapid maxillary expansion therapy on OSA [275]. Other studies have investigated patients with craniofacial syndromes [47, 424] with several studies linking childhood SDB to maxillary constriction and specific cranio-facial and dento-morphological features [41, 241]. Most of these studies have used polysomnography (PSG) with PSG derived indices such as the apnea hypopnea index (AHI). However, PSG is invasive, complex, labor intensive and the costly nature has precluded widespread adoption in clinical practice. Moreover, periods of partial UAO during sleep with runs of labored breathing is not reflected in the AHI metric [104]. In this regard, the utility of PSG as the gold standard has increasingly been challenged [104] with a recent study questioning the validity of changes in severity of OSA, as measured by the AHI, to treatment related outcomes [193]. To date, there exist no studies objectively measuring obstructed breathing, particularly snoring, a robust and cardinal sign of UAO in children with maxillary constriction.

This study utilized the Sonomat™ home sleep test system, previously validated against PSG [105, 415], that provides an accurate and objective measure of obstructive breathing (snoring and stertor) [106]. Noteworthy about this ambulatory system of diagnosis is its portability and ease of use without a child being tethered in any form or manner. This is the first study to evaluate the prevalence of SDB in an unselected population of non-obese maxillary constricted children with minimal tonsillar hypertrophy. Children recruited in this study presented with the hallmarks of maxillary constriction including maxillary transverse deficiency, a high palatal vault and dental mal-alignment that required rapid maxillary expansion (RME) therapy for orthopaedic correction.

The key findings in this study are as follows: 1) few children with maxillary constriction (7%) had complete obstruction (i.e. had OSA), 2) obstructed breathing (OB) predominates with snoring occurring in the majority (87.5%) of children with maxillary constriction, 3) 42% of children with maxillary constriction snored for ≥ 10 min, 4) stertor and wheezing were infrequent, 4) runs of snoring and/or stertor are linked to movement arousals resulting in sleep fragmentation that is in the order of magnitude greater than that associated with apneas/hypopneas.

Our results in this study extends previous work in which the method was validated against PSG [105] and presents the novel finding that OB predominates as an indicator of paediatric SDB in children with maxillary constriction. In our study, using standard AASM criteria for OSA severity, 7% of children with maxillary constriction were diagnosed as having OSA. This prevalence rate is higher than epidemiological studies showing a

prevalence of 2-3% of the general paediatric population [24, 25] and can be explained by the known relationship between maxillary constriction and UAO. Multiple studies have previously suggested an association between cranio-facial abnormalities, dental morphological changes with OSA [41]. The relatively low incidence of OSA observed in this group, although higher than in the general population, may suggest that there is no clear indication to routinely perform sleep studies in all children with maxillary constriction. By all accounts, based on the contemporary cutoff of MOAHI <1/hr, 93% of these children would have been considered as "normal" as there was no OSA. However, objective quantification of OB with the Sonomat™ confirmed that many of these "normal" children snored extensively indicating that, although they may not have OSA, they do have significant SDB.

In total, 87.5% of the entire group snored of which 46% of children had OB for ≥ 10 mins during the night; these included all of those with OSA. Thus, the absence of OB could be used to discount the presence of OSA. More importantly, the significant levels of OB in children with maxillary constriction is of clinical significance as prolonged partial obstruction is a key mechanism of elevated carbon dioxide levels and in turn, a driver of cerebrospinal fluid pressures and sympathetic output [106]. Of significance, OSA and non-OSA children were often indistinguishable with regard to the frequency and duration of OB. Additionally, many asymptomatic children had significant amounts of OB.

A key finding is that runs of snoring and stertor are linked to movement arousals resulting in sleep fragmentation that is in the order of magnitude greater than that associated with

apneas/hypopneas per se. Current PSG derived indices focus almost entirely on apneas and hypopneas but underestimates the nature and magnitude of partial UAO in children and its deleterious role in sleep disruption. We show that children with maxillary constriction have few apneas and hypopneas but the majority have OB.

Although no significant differences were noted in all forms of apnea and hypopnea between snorers and non-snorers, significant differences were noted in respiratory induced movement arousals with respect to duration, the number of events and rate of occurrence (all $p<0.0001$). This finding suggests that many children previously classified as "simple snorers" without OSA may have significant partial UAO with runs of OB that may play a greater contributory role in sleep fragmentation than classical thinking may lead us to believe. This extends previous work by Norman and colleagues and supports their observation that snoring and stertor are associated with more sleep disruption than are obstructive apneas and hypopneas [106]. Increasingly, mounting evidence is accumulating to suggest that robust measures of SDB outcomes do not have a linear relationship to the PSG derived indices and that all levels of SDB severity including "simple" snoring may contribute to SDB morbidity, in the case of blood pressure for example [425].

A recent study re-analyzing treatment outcomes of the CHAT study highlight the discrepancy between improvements in OSA, as measured by the AHI, to treatment related outcomes [193]. Our data, showing a high incidence of OB in children with maxillary constriction, support the notion that OB is a major pathophysiological pathway in childhood SDB. Although not causative, our study supports previous studies linking SDB

and in particular OB to craniofacial abnormalities such as maxillary constriction [41, 241, 426] and advocate for objective assessment of OB in children who present with parentally reported snoring. We support previous recommendations of the need to provide an accurate measurement of OB [106], complimentary to AHI metrics to investigate downstream effects of cardiovascular risks and craniofacial growth and development.

In addition to snoring, our analyses identified 10 (18%) stertorous children in the group. All stertorous children snored and they exhibited a wide variability in tonsillar size, clinical history and included both non-OSA and OSA children. The significance of these incidental findings is unclear. Although previous studies have linked greater tonsillar hypertrophy to increased OSA severity, the precise mechanism that results in stertor in maxillary constricted children with minimal tonsillar enlargement warrants further investigation. Further analysis of snore and stertor characteristics may play a pivotal role in identifying potential sites of upper airway collapse in children.

A chance finding in our investigation was that 2 children (3.6%) exhibited nocturnal wheeze. Both parents of the wheezing children reported a previous history of asthma with the impression that asthma had been comprehensively managed. However, our data suggest that both wheezing children with normal tonsil size also snored with significantly more snoring noted in one child. This child had considerably more snoring (33.1 vs 1.3 mins) and wheezing (62.4 vs 8.4 mins) than the other asthmatic child. Not surprisingly, this child recorded a higher OSA-18 score (91 vs 49) signifying a severe impact on quality of life as compared to the other less symptomatic wheezing child. This observation confirms

previous observations that parental reports are unreliable in determining the severity of OSA [427] and in identification of wheeze [428] and has significant clinical implications.

Although only 2 children with maxillary constriction were noted to have asthma our study, it is evident that a complex relationship exists in airway physiology that contributes to varying degrees of lower and UAO. Previous studies have associated asthma with maxillary constriction [242-244], with snoring and OSA proposed as triggering mechanism for asthmatic attacks [429]. To date, no studies have documented wheezing and OB in an objective fashion in children with maxillary constriction. Further research into upper airway physiology in asthmatic children with OB is thus warranted.

This study integrated in its protocol, clinical assessment of tonsillar size, dental examination, clinical history taking and employed the use of the OSA-18 quality of life questionnaire. Used alone or in combination, these techniques used to evaluate the prevalence of SDB in an unselected population of children with maxillary constriction are imprecise, subjective and of limited utility in the screening of SDB in the clinical setting. Our finding of the limited utility and reliability of clinical history and assessment for OSA screening is supported by previous systematic review highlighting the poor reliability of clinical assessment and history taking for OSA prediction [112]. Poor correlation between tonsil size and OSA severity was observed in our study and this finding is supported by a previous study highlighting a weak association [430] between tonsillar grade and SDB.

Our study recruited children that were predominantly non-obese, presenting with minimal tonsillar hypertrophy in the majority; with a broad spectrum of clinical findings in relation to nocturnal enuresis, previous history of asthma, ear infections or upper respiratory infections. We found poor correlation between OSA-18 scores and clinical symptoms as several children who recorded lower OSA-18 scores exhibited severe episodes of OB or OSA. This suggests that parental reports may often be inaccurate and unreliable. Studies assessing the validity in the use of the OSA-18 questionnaire as screening tool for SDB has been previously challenged [110, 111].

Limitations of this study include the lack of EEG to stage and identify neurophysiologic sleep and arousal. However, previous work by Norman and colleagues have confirmed a close relationship between quiescent time and EEG-defined sleep as well as the use of quiescent time providing an accurate MOAHI value [105]. Body movement has been demonstrated to be a robust indicator of sleep disturbance [431]. The utilization of oximetry would undoubtedly have provided a fuller picture of SDB but this requires attachment to the body and can be problematic, particularly so in a child in the home setting. Transcutaneous carbon dioxide measurement may provide a better indicator of the flow on effects of obstructed breathing but also requires physical attachment to a child [432].

3.8 CONCLUSION

The Sonomat™ is a reliable method for quantifying and characterizing the nature and extent of partial UAO in children with maxillary constriction. Few children with maxillary constriction had OSA with obstructive apneas and hypopneas rare events; central events occurred more frequently. However, a large proportion of non-obese, maxillary constricted children had marked OB with snoring the predominant feature. All had minimal tonsillar hypertrophy and SDB symptoms. Runs of snoring and stertor are linked to movement arousals resulting in sleep fragmentation that is in the order of magnitude greater than that associated with apneas/hypopneas. Despite presenting with minimal symptoms of SDB, an objective assessment of UAO is warranted in children with maxillary constriction. Further research is warranted to investigate snore characteristics in obstructed breathers with cranio-facial deficiencies.

4 THE EFFECT OF RAPID MAXILLARY EXPANSION ON PAEDIATRIC SLEEP DISORDERED BREATHING IN CHILDREN WITH MAXILLARY CONSTRICTION.

4.1 Introduction

Obstructive Sleep Apnea (OSA) in children is a common disorder characterized by partial or complete obstruction of the upper airway during sleep. This disorder poses a significant health problem for children and is associated with significant morbidity [155]. Multiple medical therapies and surgical interventions (e.g. soft tissue surgery, adeno-tonsillectomy, maxillo-mandibular advancement surgery for children with dentofacial/congenital anomalies, hypoglossal nerve stimulation and tracheostomy) are available for the management of paediatric sleep disordered breathing (SDB). The primary treatment is adenotonsillectomy [87, 433] although continuous positive airway pressure (CPAP) is a non-surgical treatment option proposed for children that are contraindicated for or do not respond to surgical intervention [206, 434].

There has recently been increasing interest in the role of dental and orthodontic intervention [265, 274]. Several different treatments have been proposed and, collectively, a broad spectrum of response to therapy has been reported in rapid maxillary expansion (RME) [275, 306], oral appliances [268, 272] and myofunctional therapy [435]. Children with craniofacial abnormalities such as maxillary constriction are predisposed to SDB. RME is well described in the orthodontic literature and has been classically used to correct

maxillary transverse deficiency and dental crowding. In the paediatric population, it is generally performed without the need for invasive surgical intervention. A customized orthodontic appliance with an expansion screw attached to multiple arms is fabricated. This appliance is fixed to the posterior dentition which applies forces directly to the median palatal and circum-maxillary sutures through the anchored teeth.

Over the last few decades a multitude of studies have emerged that document the positive effects of RME on upper airway size and volume [292, 297], nasal respiration [282, 291], a range of medical conditions [221], hearing [436], nocturnal enuresis [281, 437], school performance [284], tongue position [295] and mandibular repositioning [299]. It has increasingly been proposed as a treatment option for children with paediatric SDB [265, 266, 274, 303, 306].

However, all relevant literature investigating the effects of RME on SDB have been reliant on polysomnography (PSG) using indices such as the apnea hypopnea index (AHI), oxygenation and sleep disruption to assess the severity of SDB and the effects of RME. These PSG based studies have recruited children with OSA and reported treatment efficacy based on reductions in the AHI [266, 275, 303, 306] and improvements in oxygen saturation indices. However, periods of partial upper airway obstruction (UAO) during sleep with runs of labored breathing is not reflected in the AHI metric [104]; no PSG metric adequately reflects periods of partial UAO such as snoring which are characteristic of paediatric SDB [105].

Although PSG based studies may use snore sensors, the recommended recording parameters only capture a small bandwidth of snore sounds [105]. Increasingly, the validity of PSG as the benchmark for clinical diagnosis has come under closer scrutiny [104] with a recent reanalysis of the data in the CHAT study by Isaiah and colleagues showing poor correlation between the improvements in OSA severity, classically measured by the AHI, to OSA treatment outcomes [193].

To date, there are no studies objectively measuring obstructed breathing (OB), particularly snoring, a robust and cardinal sign of UAO, in an unselected population of children with maxillary constriction requiring RME therapy. The Sonomat™ is a portable mat system with non-contact sensors, validated against PSG [105], that identifies quiescent (sleep) time, apneas, hypopneas and accurately quantifies snoring in children. This chapter investigates the effects of RME therapy in an unselected population of children with maxillary constriction using the Sonomat™.

4.2 AIM

The aim of this study was to investigate the effect of RME on snoring and OSA in children with maxillary constriction undergoing RME therapy.

4.3 METHODS

4.3.1 Study Participants

A detailed description of the children with maxillary constriction recruited for this chapter is presented in the previous chapter (Chapter 3). In summary, 59 consecutive children

referred for orthodontic assessment requiring RME expansion therapy were recruited. All participants paid full fee for RME treatment and subsequent orthodontic therapy. Suspected SDB was not the reason for referral with chief parental concerns predominantly related to mal-alignment of the dentition with dental crowding and maxillary constriction (Fig 4.1). A clinical examination of the dentition was performed to assess the oral structures for RME therapy suitability. Clinical history of previous episodes of asthma, nocturnal enuresis, repeat otitis or upper respiratory tract infection (URTI) was obtained at baseline prior to RME cementation. Visual grading of tonsillar hypertrophy was performed according to a standardized scale ranging from 0 to 4 [250]. A Quality of Life OSA-18 questionnaire (see Appendix 9.1) was applied for all children at baseline and at the conclusion of RME therapy. Overnight Sonomat™ recordings were performed in the home at baseline, a few months during RME therapy (RME1) and at the end of RME therapy (RME2). Successful baseline recordings were obtained in 56 children (95%); 3 children with unsuccessful baseline studies were excluded from the study.

A total of 56 children (26 male, 30 female; mean age of 8.9 ± 2.4 years (range 3-15 years); BMI z score = 0.22 (-0.8,1.0)) with no history of previous orthodontic treatment with maxillary constriction were recruited for the study. Minimal tonsillar hypertrophy (median size 0.0 (0.0, 0.8), (range 0-3)) was noted. The majority (75%) had normal tonsil size (grade 0) with 7 (12.5%) children noted to have grade 1 tonsils. A further 5 (9%) had grade 2 tonsils with 2 (3.5%) children having grade 3 tonsil size. Only one child with grade 3 tonsils was found to have OSA (MOAHI = 6.3 events/hr). No child had either an a priori diagnosis of SDB or a history of previous orthodontic treatment.

Of the 56 children studied, only 4 children (7%) had OSA (MOAHI ≥1) with 52 (93%) children classified as non-OSA (MOAHI<1). In the non-OSA children, 22 children (42%) were primary snorers (MOAHI <1, snore ≥ 10 mins) with the remaining 30 children (58%) classified as normal (MOAHI < 1, snore < 9.9 mins). Overall, 26 children (46%) were determined to have significant obstructed breathing (snoring and stertor) and/or OSA.

Inclusion criteria for this part of the investigation were as follows: (1) children with maxillary constriction requiring RME therapy (2) age between 3 -16 years; and (3) the presence of at least 6 teeth in the posterior maxillary dental arch.

Exclusion criteria were (1) Previous orthodontic treatment or RME therapy (2) uncontrolled dental caries; (3) cranio-facial syndromes; (4) cleft palate; (5) periodontal disease; (6) temporomandibular joint dysfunction; (7) an exaggerated gag reflex; (8) current treatment with positive airway pressure (PAP).

The research protocol was approved the University of Sydney Human Research Ethics Committee (HREC Ref. No: 2014/571). Parents of children requiring RME expansion treatment were invited to participate and provided written informed consent if agreeable. Children provided assent when able.

4.3.2 Rapid Maxillary Expansion (RME) therapy

A custom-made Rapid Maxillary Expander, (Hyrax screw, Dentaurum, Germany) was fabricated for each patient from dental impressions and stone models. The key feature of

the bonded RME device is that it consists of an expansion screw located above the mid-palatal suture site in the maxilla. The Hyrax screw is welded to stainless steel supports which form a rigid framework circum-navigating the buccal and lingual surfaces of the maxillary posterior teeth (Fig 4.2). Although there are several variants of the RME device and dental tipping effect is generally observed with all types of expanders, the bonded RME used in this study incorporates acrylic flanges that encapsulate the surface area of the posterior dentition. The bonded RME version in one study allows more favorable distribution of orthopaedic forces through the centre of resistance to maxillary expansion at the aperture piriform, so as to minimize tipping of the maxillary posterior teeth [438]. This promotes efficient separation of the median palatal suture. RME therapy widens the palate, resulting in inferior displacement of the maxilla and increases nasal cavity width.

Each child was fitted individually with the RME by the research clinician (JN). The bonded RME is temporarily fixated to the maxillary posterior teeth with light activated resin cement (3M Multi-cure). Following fixation of the RME, the child's parent is instructed to incrementally activate the Hyrax expansion screw twice a day (morning and night) for a period of 12 days. The parent and child return for a follow up intra-oral assessment. The Hyrax screw is expanded in a maxillary transverse manner such that on visual expansion the palatal cusps of the upper molars overlap the buccal surface of the lower molars. At this point, maxillary expansion ceases and the Hyrax screw is fixed in the expanded position with a copper wire by the research clinician. Following separation of the median palatal suture, a separation of the upper anterior central incisor teeth is routinely observed. Figures 4.2 and 4.3 illustrates this phenomenon following successful orthopaedic separation of the sutures. This space between the anterior central teeth closes

spontaneously due to periodontal trans-septal fiber attachments between the teeth such that the space generally diminishes within 4-8 weeks. At the 2 treatment intervals (RME1 and RME2) a Sonomat™ sleep study was performed. Of note, RME1 study was performed with RME in situ whereas RME2 study following RME removal.

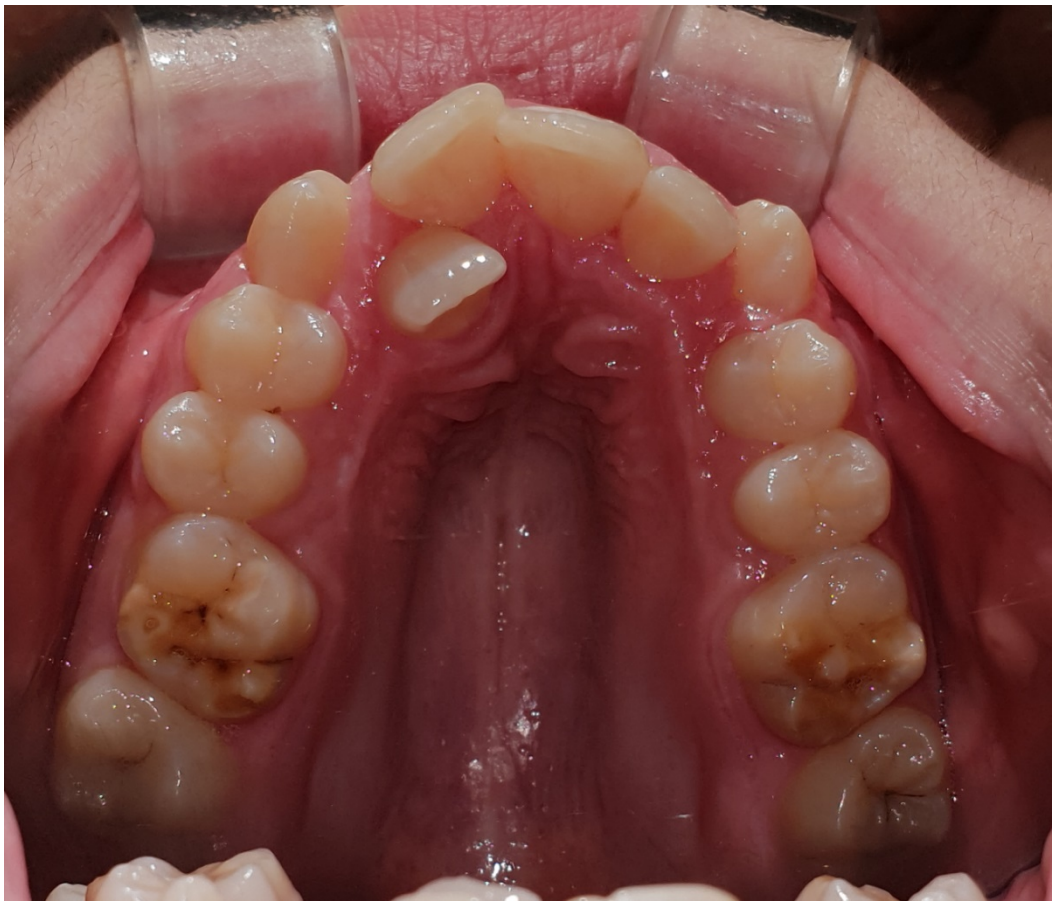


Figure 4.1 Occlusal view of a child with maxillary transverse deficiency. Upper anterior dental crowding is observed with palatal displacement of an upper lateral tooth. Maxillary constriction with a high palatal vault and narrow inter-molar width can be observed.

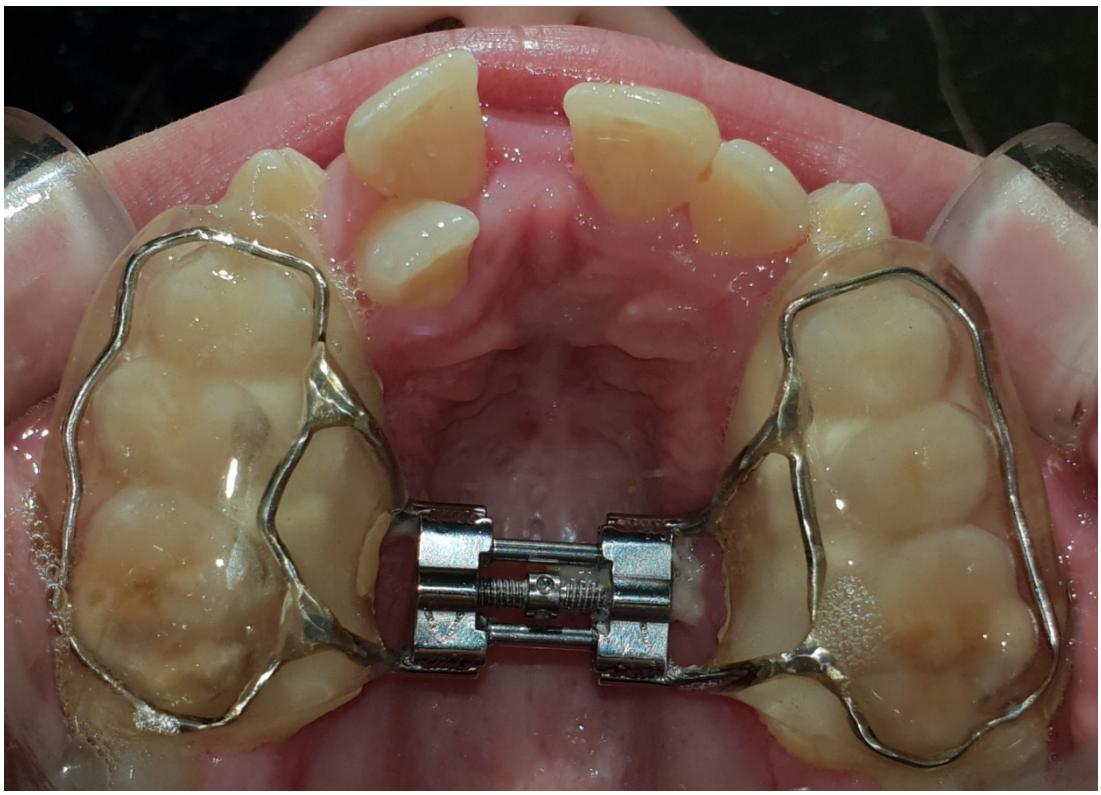


Figure 4.2 Intra-oral occlusal view of a bonded RME is displayed post-RME therapy. The Hyrax screw is welded to stainless steel supports which form a rigid framework circum-navigating the buccal and lingual surfaces of the maxillary posterior teeth. The bonded RME used in this study incorporates acrylic flanges that encapsulate the surface area of the posterior dentition. Note the increase in maxillary transverse width and widening of the Hyrax screw. The separation of the upper anterior teeth is clearly noted signifying orthopaedic expansion of the mid-palatal suture.

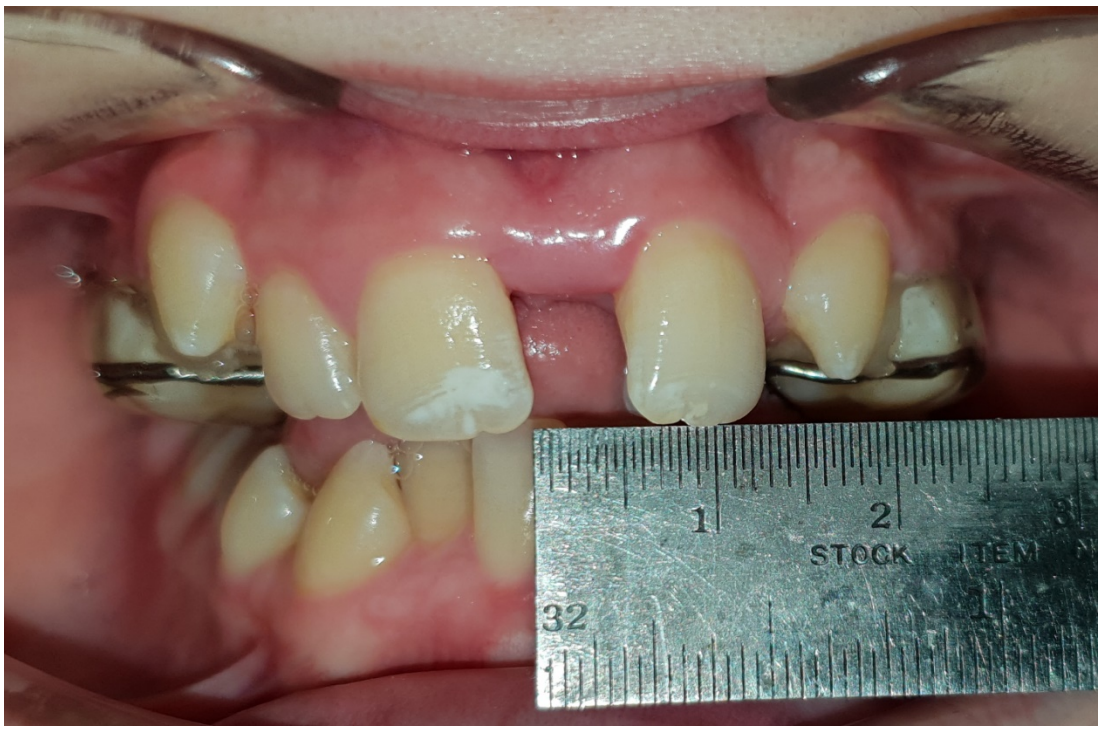


Figure 4.3 Frontal view of the bonded RME expander in situ post-RME expansion. Note the separation of the upper anterior central teeth with approximately 5mm of space created. The Hyrax screw is expanded in a maxillary transverse manner such that on visual expansion the palatal cusps of the upper molars overlap the buccal surface of the lower molars as depicted in this image.

4.3.3 Sonomat™ Sleep study

A Sonomat™ sleep test, as described in the General Methods section was performed at baseline and to assess treatment outcomes at RME1 and RME2. Scoring was performed by an expert scorer (MN) blinded to the stage of therapy. Apneas, hypopneas and obstructed breathing (comprising of snoring and stertor) were objectively quantified as in the previous chapter (section 3.4). Obstructive sleep apnea (OSA) was defined as an MOAHI ≥ 1 event/hr and primary snoring (PS) was defined as MOAHI < 1 event/hr with ≥ 10 minutes of snoring.

Secondary outcomes measures included the OSA-18 questionnaire were measured at RME2 stage and compared with baseline values.

4.3.4 Data analysis

All studies were manually scored in random order. In this investigation, inspiratory, expiratory and combined inspiratory and expiratory snoring were not classified but collectively scored as "snoring". As no EEG signals were recorded, the quiescent time (Qd) was used to calculate the MOAHI and AHI. Statistical analysis was performed using methods outlined in the General Methods section (Section 3.5).

4.4 RESULTS

At baseline, 56 children recorded successful sleep studies. 41/56 (73%) children completed RME1 sleep studies with RME in situ with a further 50/56 (89%) children completing RME 2 sleep studies with RME removed. There were 38 children who had recordings performed at all three timepoints (baseline, RME1 (mean (SD) 95.5 ± 76.9 days) and RME2 (mean (SD) 280.9 ± 172.1 days).

4.4.1 Baseline Characteristics of Children with Maxillary Constriction

A detailed description of the baseline characteristics of the study group is presented in Methods 1.3.1 section of this chapter. In brief, the 56 children consisted of 26 (46%) boys and 30 (54%) girls, mean (SD) age of 8.9 ± 2.4 years (range 3-15 years), non-obese with

BMI z-score = 0.22 (-0.8, 1.0). The majority (75%) of children had normal tonsil size with grade 1 tonsillar hypertrophy noted in 7 children. Only 2 children had grade 3 tonsillar size observed with 5 children with grade 2 tonsils noted. The majority (80.4%) of children had OSA-18 total scores < 60 with minimal impact on health-related outcomes. Only 8 (14.2%) of the children had scores between 60-80 suggesting a moderate impact on quality of life (QOL) health related outcomes. Three children (5.4%) had OSA-18 scores > 80 exhibiting more severe QOL health related outcomes. Clinical history showed that 10 children (17.9%) had nocturnal enuresis with 13 (23.2%) presenting with a history of asthma. Five children (8.9%) had repeat otitis. Repeat upper respiratory tract infections (URTI) were also noted in 13 children (23.2%). Table 4.1 summarizes baseline characteristics of children in the entire group.

TABLE 4.1 BASELINE CHARACTERISTICS OF CHILDREN STUDIED (n=56)

Variable	All Patients
Gender	26M, 30F
Age, yr	8.9 ± 2.4 (range 3-15)
Height, cm	137.0 (130.1, 148.0) (range 108-173)
Weight, kg	31.6(26.6,43.0) (range 16.8-78.0)
BMI, kg/m^2	16.8(14.9,19.0) (range 12.0-29.4)
BMI Z score	0.22(-0.8,1.0) (range -4.1-2.0)
OSA-18 Score	44.0 (29.5, 54.8)
Tonsil grade	0.0(0.0,0.8) (range 0-3)
Bedwetting	10Y (17.9%), 46N
Asthma	13Y (23.2%), 43N
Repeat Otitis	5Y (8.9%), 51N
Repeat Upper Airway Infection	13Y (23.2%), 43N

Definition of abbreviations: M= male; F = female; BMI = body mass index; Y=Yes, N=No; Continuous data are presented Mean ± Standard deviation or Median (25^{th},75^{th} interquartile range) or proportion of group.

Table 4.1 Baseline characteristics of children studied (n=56). The children were aged 8.9 ± 2.4 years, non-obese with the majority (75%) having normal tonsillar size. Low OSA-18 scores were recorded suggesting a low impact on quality of life. A previous history of bedwetting, asthma and upper respiratory tract infections were noted in a small proportion of children. (previously shown in Chapter 3)

4.4.2 Comparison between Snoring and Non-Snoring children at Baseline.

A comparison between snorers (snore ≥ 10 mins) and non-snorers (MOAHI < 1, snore < 9.9 mins) was performed (Table 4.2). There were no statistically significant differences in baseline characteristics, clinical findings or history between the groups. No significant

differences were noted in the OSA-18 scores (42.9 ± 19.5 vs 47.3 ± 16.6, p=0.38), mouth-breathing score (2.5 (1.0, 5.0) vs 4.0 (3.0, 6.0), p=0.11) or tonsillar grade (0.0 (0.0, 0.0) vs 0.0 (0.0, 0.0), p=0.31).

TABLE 4.2 COMPARISON OF BASELINE CHARACTERISTICS OF NON-SNORERS AND SNORERS

Variable	Non-Snorers (n=30)	Snorers (n=26)	p value
Gender	12M, 18F	14M, 12F	0.30
Age, yr	9.0 (8.0, 10.3)	8.0 (7.0, 10.0)	0.31
Height, cm	141.8 ± 12.4	138.0 ± 15.2	0.30
Weight, kg	35.0 ± 11.3	35.5 ± 13.9	0.88
BMI, kg/m^2	16.5 (15.1, 18.2)	16.9 (14.8, 21.4)	0.55
BMI Z score	-0.1 (-0.8, 0.8)	0.7 (-0.5, 1.3)	0.14
OSA-18 Score	42.9 ± 19.5	47.3 ± 16.6	0.38
Mouth breathing score	2.5 (1.0, 5.0)	4.0 (3.0, 6.0)	0.11
Tonsil grade	0.0 (0.0,0.0) (range 0-3)	0.0 (0.0, 1.0) (range 0-3)	0.31
Bedwetting	5/30 (16.7%)	5/26 (19.2%)	0.80
Asthma	6/30 (20.0%)	7/26 (26.9%)	0.54
Repeat Otitis	3/30 (10.0%)	2/26 (7.7%)	0.76
Repeat Upper Airway Infection	3/30 (10.0%)	0/26 (0%)	0.10

Definition of abbreviations: M= male; F = female; BMI = body mass index; Y=Yes, N=No; Continuous data are presented Mean ± Standard deviation or Median (25^{th},75^{th} interquartile range) or proportion/percentage of group.

Table 4.2 Baseline characteristics of non-snorers and snorers. No significant differences in baseline characteristics, clinical findings or history were found between the groups. Additionally, no significant differences were noted in the OSA-18 scores (p=0.38), mouth-breathing score (p=0.11) or tonsillar grade (p=0.31).

Baseline sleep/breathing characteristics between snorers and non-snorers are summarized in Table 4.3 below. Although there were few respiratory events significant differences were noted in MOAHI (0.0 (0.0, 0.0) vs 0.1 (0.0, 0.7) events/hr, p=0.005), OAI (0.0 (0.0,

0.0) vs 0.0 (0.0, 0.1) events/hr, p=0.02), OHI (0.0 (0.0, 0.0) vs 0.0 (0.0, 0.4) events/hr ,p=0.001).

Spontaneous movement arousals occurred more frequently in non-snorers (15.3 (12.8, 18.7) events/hr vs 13.0 (9.9, 15.4) events/hr, p=0.007). Snorers exhibited significantly more respiratory induced movement arousals in duration, number of events and frequency (all $p<0.0001$) as compared to non-snorers.

Stertor duration, percentage and frequency were all greater in snorers (all p=0.02), although stertor occurred infrequently in all groups. Overall, obstructed breathing in snorers was significantly more in duration (32.4 (21.1, 65.0) mins vs 0.8 (0.1, 4.8) mins, $p<0.0001$), percentage (7.5 (4.2, 12.0) % vs 0.2 (0.0, 1.0) %, $p<0.0001$) and frequency (8.3 (6.5, 17.2) runs/hr vs 1.1 (0.1, 2.3) runs/hr, $p<0.0001$) as compared to non-snorers.

TABLE 4.3 BASELINE SLEEP AND BREATHING CHARACTERISTICS OF NON-SNORING AND SNORING CHILDREN.

Variable	Non-Snorers (n=30)	Snorers (n=26)	p value
Analysis Time, mins	512.8 (445.5, 590.3)	544.3 (444.6, 584.3)	0.81
Qd, mins	487.3 (420.5, 547.3)	502.9 (423.7, 547.3)	0.71
MOAHI, events/hr	0.0 (0.0, 0.0)	0.1 (0.0, 0.7)	0.005
AHI, events/hr	0.3 (0.2, 1.1)	0.6 (0.3, 1.3)	0.26
OAI, events/hr	0.0 (0.0, 0.0)	0.0 (0.0, 0.1)	0.02
OHI, events/hr	0.0 (0.0, 0.0)	0.0 (0.0, 0.4)	0.001
CAI, events/hr	0.3 (0.1, 0.7)	0.2 (0.0, 0.4)	0.32
CHI, events/hr	0.1 (0.0, 0.2)	0.1 (0.0, 0.2)	0.70
Spont. MAr mins	27.9 (19.4, 37.5)	23.5 (17.6, 33.3)	0.15
Spont. MAr events/hr	15.3 (12.8, 18.7)	13.0 (9.9, 15.4)	0.007
Resp. MAr mins	0.5 (0.1, 0.6)	2.6 (1.6, 6.3)	<0.0001
Resp. MAr events	3.0 (1.0, 5.0)	19.0 (9.5, 28.3)	<0.0001
Resp. MAr events /hr	0.3 (0.1, 0.7)	2.5 (1.1, 3.3)	<0.0001
Snoring, mins	0.8 (0.1, 4.8)	32.4 (21.1, 65.0)	<0.0001
Snoring, %	0.2 (0.0, 1.0)	7.5 (4.2, 12.0)	<0.0001
Snore runs, /hr	1.0 (0.1, 2.2)	8.3 (6.5, 16.8)	<0.0001
Stertor, mins	0.0 (0.0, 0.0)	0.0 (0.0, 0.2)	0.02
Stertor, %	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)	0.02
Stertor, runs, /hr	0.0 (0.0, 0.0)	0.0 (0.0, 0.1)	0.02
Obstructed breathing, mins	0.8 (0.1, 4.8)	32.4 (21.1, 65.0)	<0.0001
Obstructed breathing, %	0.2 (0.0, 1.0)	7.5 (4.2, 12.0)	<0.0001
Obstructed breathing runs, /hr	1.1 (0.1, 2.3)	8.3 (6.5, 17.2)	<0.0001

Definition of abbreviations; Qd = Quiescent time; MOAHI = Mixed + Obstructive apnea hypopnea index; AHI = apnea+hypopnea index; OAI = Obstructive apnea Index; OHI = Obstructive Hypopnea Index; CAI = Central apnea index; CHI= Central hypopnea index; Spont. = spontaneous, MAr =movement arousal, Resp.= respiratory induced; Continuous data are presented as Median (25^{th},75^{th} interquartile range).

Table 4.3 Baseline sleep and breathing characteristics of non-snoring and snoring children. Snorers exhibited significantly more respiratory induced movement arousals in duration, number of events and frequency (all p<0.0001) as compared to non-snorers. Obstructed breathing in snorers was significantly more in duration, percentage and frequency (all p<0.0001) as compared to non-snorers.

4.4.3 Baseline characteristics of Children with Obstructed Breathing (n=26)

Table 4.4 summarizes baseline characteristics of children with obstructed breathing (OB). The 26 OB children consisted of 14 (54%) boys and 12 (46%) girls, with a mean (SD) age of 8.5 ± 2.4 years (range 3-14 years); BMI z-score = 0.7 (-0.5, 1.3). Minimal tonsillar hypertrophy was noted overall with 4 (15.4%) grade 2 and 1 (3.8%) grade 3 tonsil size noted in the OB group. As a group, OB children recorded OSA-18 total score of 47.3 ± 16.6 with the OSA 18 mouth-breathing score being 4.0 (3.0, 6.0). Of note, a significant proportion of children (19.2%, 26.2%, 38.5%) reported nocturnal enuresis, a history of asthma and repeat upper respiratory tract infections respectively.

TABLE 4.4 BASELINE CHARACTERISTICS OF CHILDREN WITH OBSTRUCTED BREATHING

Variable	Snorers (n=26)
Sex	14M, 12F
Age, yr	8.5 ± 2.4 (range 3-14)
Height, cm	138.0 ± 15.2
Weight, kg	35.5 ± 13.9
BMI, kg/m^2	17.9 ± 3.5
BMI Z score	0.7 (-0.5, 1.3)
OSA-18 Score	47.3 ± 16.6
Mouth breathing score	4.0 (3.0, 6.0)
Tonsil grade	0.0(0.0,1.0) (range 0-3)
Bedwetting	5/26 (19.2%)
Asthma	7/26 (26.9%)
Repeat Otitis	2/26 (7.7%)
Repeat Upper Airway Infection	10/26 (38.5%)

Definition of abbreviations: BMI = body mass index; Y=Yes, N=No; Continuous data are presented Mean ± Standard deviation or Median (25th,75th interquartile range) or proportion/percentage of group.

Table 4.4 Baseline characteristics of children with obstructed breathing. These children were non-obese and recorded low OSA-18 scores. The majority of children had normal tonsil size with 4 (15.4%) children grade 2, and 1(3.8%) child grade 3 tonsil size noted. Bedwetting, asthma and repeat upper airway infections were notably prevalent.

4.4.4 The Effect of RME therapy on Sleep Characteristics in the Entire Group of Children with Maxillary Constriction

Fifty of 56 (89.3%) children completed a Sonomat™ study at RME 2. This consisted of 23 children with OB and 27 children normal children with no evidence of SDB (MOAHI <1/hr, snoring < 10 mins) at baseline. Table 4.5 presents the effect of RME therapy on

these 50 children. Significant changes were noted in analysis time (529.2 vs 500.7 mins) and Qd time (493.9 vs 471.3 mins), both p=0.03.

Statistically significant changes were also noted in MOAHI (0.0 (0.0, 0.2) vs 0.0 (0.0, 0.0) events/hr, p=0.004) and AHI (0.4 (0.2, 1.3) vs 0.4 (0.2, 1.3) events/hr, p=0.04). Statistically significant decreases in OAI (0.0 (0.0, 0.0), (range 0-1.5) events/hr vs 0.0 (0.0, 0.0), (range 0-0.2) events/hr, p=0.002) and OHI (0.0 (0.0, 0.0), (range 0-5.8) events/hr vs 0.0 (0.0, 0.0), (range 0-0.6) events/hr, p=0.05) were noted although the absolute values were small and of a lower order of magnitude. No other significant differences were noted in other sleep parameters including OB and movement arousals following RME.

TABLE 4.5 THE EFFECT OF RME THERAPY ON SLEEP AND BREATHING IN SNORING AND NON-SNORING CHILDREN

Variable	Baseline (n=50)	RME 2 (n=50)	p value
Analysis Time, mins	529.2 (447.5, 591.1)	500.7 (390.0, 550.8)	0.03
Qd, mins	493.9 (425.3, 549.2)	471.3 (372.1, 520.5)	0.03
MOAHI, events/hr	0.0 (0.0, 0.2)	0.0 (0.0, 0.0)	0.004
AHI, events/hr	0.4 (0.2, 1.3)	0.4 (0.2, 1.3)	0.04
OAI, events/hr	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)	0.002
OHI, events/hr	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)	0.05
CAI, events/hr	0.3 (0.1, 0.5)	0.1 (0.0, 0.4)	0.09
CHI, events/hr	0.1 (0.0, 0.3)	0.1 (0.0, 0.2)	0.50
Spont. MAr mins	25.3 (18.8, 35.1)	24.8 (19.3, 30.7)	0.11
Spont. MAr events/hr	14.3 ± 4.9	14.1 ± 4.0	0.78
Resp. MAr mins	1.0 (0.4, 2.7)	0.8 (0.2, 2.2)	0.23
Resp. MAr events	6.0 (2.0,19.0)	5.0 (2.0, 12.5)	0.26
Resp. MAr events /hr	0.8 (0.2, 2.5)	0.7 (0.2, 2.0)	0.48
Snoring, mins	8.6 (0.7, 31.2)	4.7 (0.2, 22.5)	0.31
Snoring, %	1.9 (0.1, 6.8)	1.0 (0.0, 5.6)	0.39
Snore runs, /hr	4.8 (0.9, 8.3)	2.2 (0.3, 5.9)	0.21
Stertor, mins	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)	0.22
Stertor, %	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)	0.24
Stertor, runs, /hr	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)	0.16
Obstructed breathing, mins	8.6 (0.7, 31.5)	4.7 (0.2, 22.5)	0.27
Obstructed breathing, %	1.9 (0.1, 6.8)	1.0 (0.0, 5.7)	0.35
Obstructed breathing runs, /hr	4.8 (0.9, 8.3)	2.2 (0.3, 5.9)	0.17

Definition of abbreviations; Qd = Quiescent time; MOAHI = Mixed + Obstructive apnea hypopnea index; AHI = apnea+hypopnea index; OAI = Obstructive apnea Index; OHI = Obstructive Hypopnea Index; CAI = Central apnea index; CHI= Central hypopnea index; Spont. = spontaneous, MAr =movement arousal, Resp.= respiratory induced; Continuous data are presented as Median (25^{th},75^{th} interquartile range).

Table 4.5 The effect of RME on Sleep and Breathing in Snoring and Non-Snoring children. There were 23 children with OB and 27 non-snoring children. Statistically significant changes were noted in MOAHI (p=0.004), AHI (p=0.04), OAI (p=0.002) and OHI (p=0.05). Non-significant changes in OB duration (p=0.27) and frequency of OB runs (0.17) were noted. This observation is likely due to the inclusion of 27 normal (non-snoring) children in the group.

4.4.5 The Effect of RME therapy on Non-Snoring Children with Maxillary Constriction at RME 2

Table 4.6 below shows the effect of RME therapy on normal children (non-snoring and without OSA) following RME therapy. Twenty-seven of these 30 children completed a Sonomat™ study at the RME2 time-point. Small but significant changes were noted in the rate of spontaneous movement arousals, (Baseline = 16.1 ± 4.6, RME2 = 14.2 ± 3.7 moves/hr; p=0.02). No significant differences were noted in any variable related to respiratory events or obstructed breathing.

TABLE 4.6 THE EFFECT OF RME THERAPY ON SLEEP AND BREATHING CHARACTERISTICS IN NON-SNORING CHILDREN (n=27)

Variable	Baseline (n=27)	Post-RME (n=27)	p value
Analysis Time, mins	512.1 ± 94.8	503.0 ± 88.7	0.65
Qd, mins	480.3 ± 89.8	475.4 ± 83.8	0.79
MOAHI, events/hr	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)	0.83
AHI, events/hr	0.3 (0.2, 1.3)	0.4 (0.2, 1.0)	0.69
OAI, events/hr	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)	0.50
OHI, events/hr	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)	>0.99
CAI, events/hr	0.3 (0.1, 0.8)	0.2 (0.0, 0.5)	0.49
CHI, events/hr	0.1 (0.0, 0.3)	0.1 (0.2, 0.2)	0.80
Spont. MAr mins	31.2 ± 13.0	26.4 ± 9.6	0.06
Spont. MAr events	138.0 ± 49.0	120.6 ± 41.8	0.07
Spont. MAr events/hr	16.1 ± 4.6	14.2 ± 3.7	0.02
Resp. MAr mins	0.4 (0.1, 0.6)	0.3 (0.1, 1.3)	0.42
Resp. MAr events	3.0 (1.0, 5.0)	3.0 (1.0, 8.0)	0.24
Resp. MAr events /hr	0.3 (0.1, 0.7)	0.3 (0.1, 0.8)	0.16
Snoring, mins	0.8 (0.0, 5.4)	1.4 (0.0, 6.2)	0.18
Snoring, %	0.2 (0.0, 1.1)	0.3 (0.0, 1.3)	0.16
Snore runs, /hr	1.0 (0.0, 2.2)	1.5 (0.0, 3.6)	0.17
Stertor, mins	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)	>0.99
Stertor, %	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)	>0.99
Stertor, runs, /hr	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)	>0.99
Obstructed breathing, mins	0.8 (0.0, 5.4)	1.4 (0.0, 6.2)	0.73
Obstructed breathing, %	0.2 (0.0, 1.1)	0.3 (0.0, 1.3)	0.17
Obstructed breathing runs, /hr	1.1 (0.0, 2.4)	1.5 (0.0, 3.6)	0.17

Definition of abbreviations; Qd = Quiescent time; MOAHI = Mixed + Obstructive apnea hypopnea index; AHI = apnea+hypopnea index; OAI = Obstructive apnea Index; OHI = Obstructive Hypopnea Index; CAI = Central apnea index; CHI= Central hypopnea index; Spont. = spontaneous, MAr =movement arousal, Resp.= respiratory induced; Continuous data are presented as Median (25^{th},75^{th} interquartile range).

Table 4.6 The effect of RME on Sleep and Breathing characteristics in Non-Snoring children. There were no significant differences in any variable related to respiratory events or obstructed breathing. Small but statistically significant decrease in the rate of spontaneous movement arousals (16.1 ± 4.6 vs 14.2 ± 3.7 moves/hr, p=0.02) were noted post-RME.

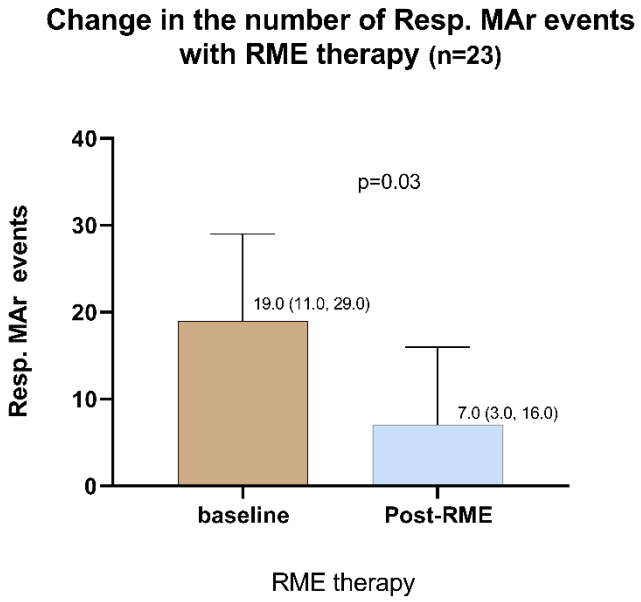
4.4.6 The Effect of RME therapy on Obstructed Breathing Children with Maxillary Constriction

A total of 26 children with OB were observed in this study of which 4 were also noted to have OSA. Twenty-three of 26 (88.5%) children in this group completed RME 2 sleep studies. Table 4.7 shows the effect of RME therapy on OB children with maxillary constriction.

Significant changes were noted in analysis time (538.0 (445.2, 591.0) mins vs 495.6 (324.9, 530.3) mins) and Qd time (493.9 (424.2, 548.1) mins vs 457.4 (300.7, 505.3) mins, both p=0.02). Although the absolute values tended to be small there were statistically significant decreases in MOAHI (0.1 (0.0, 0.8) vs 0.0 (0.0, 0.0), p=0.003), AHI (0.6 (0.3, 1.8) vs 0.4 (0.0, 0.6), p=0.03), OAI (0.0 (0.0, 0.1) vs 0.0 (0.0, 0.1), p=0.008), OHI (0.0 (0.0, 0.5) vs 0.0 (0.0, 0.0), p=0.02) and CAI (0.2 (0.0, 0.4) vs 0.1 (0.0, 0.3), p=0.05).

Significant reductions in the duration of respiratory induced movement arousals, ((2.6 (1.5, 6.9) mins vs 0.9 (0.4, 3.6) mins, p=0.05) and number of arousals (19.0 (11.0, 29.0) vs 7.0 (3.0, 16.0), p=0.03) were noted following RME therapy (Fig 4.4). The frequency of respiratory induced movement arousals decreased but were not statistically significant (2.5 (1.3, 3.7) events/hr vs 1.0 (0.4, 2.0) events/hr, p=0.06).

There were no significant differences noted in the duration (22.5 (17.5, 28.7) mins vs 23.2 (19.2, 29.9) mins, p=0.81), number (99.0 (76.0, 132.0) events vs 97.0 (84.0, 124.0) events, p=0.70) or frequency (12.3 (9.7, 14.6) event/hr vs 13.2(11.1, 16.6) events/hr, p=0.21) of spontaneous movement induced arousals.



Definition of abbreviations: Resp. MAr = respiratory induced movement arousal; RME = rapid maxillary expansion.

Figure 4.4 Comparison between the number of Respiratory induced movement arousals at baseline and post-RME therapy. A significant reduction in the total number of respiratory induced movement arousals (19.0 (11.0, 29.0) events vs 7.0 (3.0, 16.0) events, p=0.03) was noted. This indicates that sleep is less disrupted post-RME.

The duration, percentage and frequency of runs of OB were noted to decrease significantly following RME [duration ((33.1 (20.5, 66.0)mins vs 13.1 (0.3, 30.3)mins, p=0.03); OB percentage ((7.2 (4.1, 12.5)% vs 2.8 (0.1, 7.7), p=0.05); and OB runs per hour [(8.8 (6.5, 18.3) runs/h vs 4.0 (0.7, 10.1) runs /h, p=0.03), Figure 4.5]. These values comprise predominantly snoring data. No significant change was noted in stertor variables.

TABLE 4.7 THE EFFECTS OF RME THERAPY ON OBSTRUCTED BREATHING CHILDREN (n=23)

Variable	Baseline (n=23)	Post-RME (n=23)	p value
Analysis Time, mins	538.0 (445.2, 591.0)	495.6 (324.9, 530.3)	0.02
Qd, mins	493.9 (424.2, 548.1)	457.4 (300.7, 505.3)	0.02
MOAHI, events/hr	0.1 (0.0, 0.8)	0.0 (0.0, 0.0)	0.003
AHI, events/hr	0.6 (0.3, 1.8)	0.4 (0.0, 0.6)	0.03
OAI, events/hr	0.0 (0.0, 0.1)	0.0 (0.0, 0.1)	0.008
OHI, events/hr	0.0 (0.0, 0.5)	0.0 (0.0, 0.0)	0.02
CAI, events/hr	0.2 (0.0, 0.4)	0.1 (0.0, 0.3)	0.05
CHI, events/hr	0.1 (0.0, 0.3)	0.0 (0.0, 0.2)	0.51
Spont. MAr mins	22.5 (17.5, 28.7)	23.2 (19.2, 29.9)	0.81
Spont. MAr events	99.0 (76.0, 132.0)	97.0 (84.0, 124.0)	0.70
Spont. MAr events/hr	12.3 (9.7, 14.6)	13.2 (11.1, 16.6)	0.21
Resp. MAr mins	2.6 (1.5, 6.9)	0.9 (0.4, 3.6)	0.05
Resp. MAr events	19.0 (11.0, 29.0)	7.0 (3.0, 16.0)	0.03
Resp. MAr events /hr	2.5 (1.3, 3.7)	1.0 (0.4, 2.0)	0.06
Snoring, mins	33.1 (20.5, 66.0)	13.1 (0.3, 28.2)	0.04
Snoring, %	7.2 (4.1, 12.5)	2.8 (0.1, 7.1)	0.06
Snore runs, /hr	8.8 (6.5, 17.5)	3.9 (0.7, 9.9)	0.03
Stertor, mins	0.0 (0.0, 0.3)	0.0 (0.0, 0.0)	0.23
Stertor, %	0.0 (0.0, 0.1)	0.0 (0.0, 0.0)	0.23
Stertor, runs, /hr	0.0 (0.0, 0.1)	0.0 (0.0, 0.0)	0.20
Obstructed breathing, mins	33.1 (20.5, 66.0)	13.1 (0.3, 30.3)	0.03
Obstructed breathing, %	7.2 (4.1, 12.5)	2.8 (0.1, 7.7)	0.05
Obstructed breathing runs, /hr	8.8 (6.5, 18.3)	4.0 (0.7, 10.1)	0.03

Definition of abbreviations; Qd = Quiescent time; MOAHI = Mixed + Obstructive apnea hypopnea index; AHI = apnea+hypopnea index; OAI = Obstructive apnea Index; OHI = Obstructive Hypopnea Index; CAI = Central apnea index; CHI= Central hypopnea index; Spont. = spontaneous, MAr = movement arousal, Resp.= respiratory induced; Continuous data are presented as Median (25^{th},75^{th} interquartile range).

Table 4.7 The effects of RME on Obstructed Breathing children. Although the absolute values tended to be small there were statistically significant decreases in MOAHI (p=0.003), AHI (p=0.03), OAI (p=0.008), OHI (p=0.02) and CAI (p=0.05). The duration, percentage and frequency of runs in OB were noted to decrease significantly (p=0.03, p=0.05, p=0.03 respectively) following RME. Significant reductions in the duration of respiratory induced movement arousals, ((2.6 (1.5, 6.9) mins vs 0.9 (0.4, 3.6) mins, p=0.05) and number of arousals (19.0 (11.0, 29.0) vs 7.0 (3.0, 16.0), p=0.03) were noted.

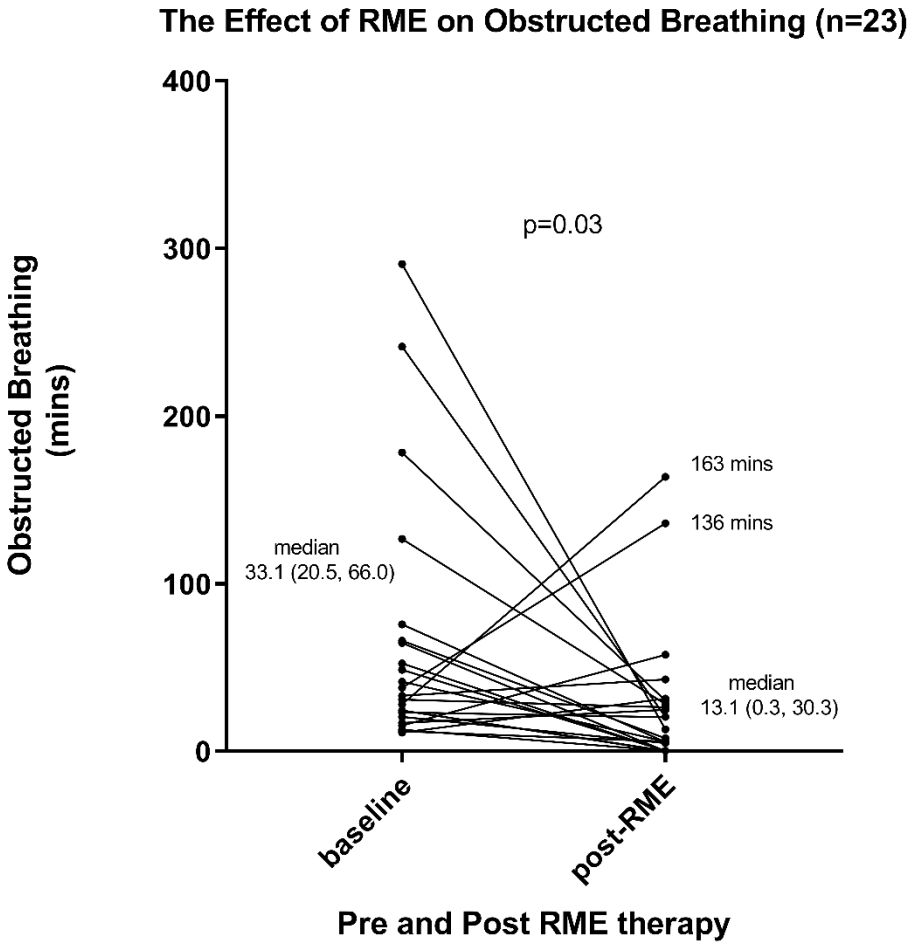


Figure 4.5 Individual changes in the duration of Obstructed Breathing (OB) in maxillary constricted children at baseline and post-RME therapy. A significant reduction in the duration of obstructed breathing (33.1 (20.5, 66.0) mins vs 13.1 (0.3, 30.3) mins, p=0.03) occurred. Remarkable reductions were noted in 4 children who snored > 100 mins at baseline. However, 6 children (26.1%) were found to have more OB (range 24.7-163.7 mins at RME2 timepoint) after RME therapy. These will be discussed in the section 4.4.7 below.

4.4.7 Children who worsened in Obstructed Breathing with RME therapy

The children whose OB durations increased following RME therapy were classified as non-responders. They are examined separately in Tables 4.8 and 4.9 below. There were 6 non-responding OB children who worsened in OB duration (range of residual OB 24.7-163.7 mins) following RME. None of these 6 non-responders had OSA at baseline, recorded low baseline OSA-18 scores (<60, range 21-50) signifying minimal impact on quality of life and all were normal in weight for their respective ages.

Most children, except for patient LC (age 7), were past the peak age of lymphoidal hypertrophy. All patients had normal tonsil grade with the exception of patient TA (grade 1). In this patient, no significant clinical history in relation to nocturnal enuresis, previous asthma or URTI was noted. A previous history of asthma was noted in 2 patients (patients AS and JSE) with 2 children (patients AS and LC) reporting frequent URTI at baseline.

Overall, the findings of minimal tonsillar size and variable observations in clinical history/examination at baseline did not correlate strongly to the likelihood of poor OB response with RME. This was further exemplified by the post-RME OSA-18 score. 5/6 (83%) of the children who worsened in snoring had a decrease in OSA-18 scores despite worsening in snoring.

Post-RME, no non-responder had OSA. OB duration worsened markedly (37.9 vs 136.1 mins, 28.0 vs 163.7 mins) in 2 children (patients MG and AS) respectively. In these 2 patients, the frequency of snore run increased substantially (8.1 vs 41.3 runs/hr and 18.9 vs

33.6 runs/hr). The remaining 4 patients also worsened in snoring duration as compared to baseline. Overall, snoring was the predominant feature with negligible stertor noted (range 0-3mins) post-RME.

TABLE 4.8 Baseline Characteristics of Non-Responding Obstructed Breathing Children

Patient	Tonsil grade	Age (yrs)	BMI z score baseline	*Nocturnal enuresis* baseline	Asthma baseline	URTI baseline	OSA-18 total score baseline	OSA-18 score post RME
Patient MG (Female)	0	9	-0.03	N	N	N	50	35
Patient AS (Female)	0	10	1.4	N	Y	Y	54	69
Patient JS (Male)	0	14	-1.31	N	N	N	36	21
Patient JSE (Male)	0	12	-1.9	N	Y	N	91	34
Patient TA (Male)	1	10	1.46	N	N	N	29	23
Patient LC (Female)	0	7	0.72	N	N	Y	50	24

Definition of abbreviations: URTI = upper respiratory tract infection; OSA = obstructive sleep apnea.

Table 4.8 Characteristics of Non-responding Obstructed Breathing children (n=6). With the exception of patient LC, all patients were >10 years old. No child was bedwetting with 2 noted to have asthma and URTI respectively. 83% of non-responding children had lower OSA-18 scores post-RME which was surprising considering the increase in snoring.

TABLE 4.9 Sleep and Breathing Characteristics of Non-Responding Obstructed Breathing Children (n=6)

Patient	MOAHI (/hr) baseline	MOAHI(/hr) post RME	OB (mins) baseline	OB (mins) post RME	Snoring (mins) baseline	Snoring (mins) post RME	Snore (runs/hr) baseline	Snore (runs/hr) post RME	Stertor (mins) baseline	Stertor (mins) post RME
Patient MG (Female)	0.3	0.4	37.9	136.1	37.9	136.0	8.1	41.3	0.0	0.1
Patient AS (Female)	0.0	0.0	28.0	163.7	28.0	163.5	18.9	33.6	0.0	0.2
Patient JS (Male)	0.1	0.0	15.4	57.5	15.4	57.5	8.8	3.9	0.0	0.0
Patient JSE (Male)	0.0	0.0	33.1	42.8	33.1	42.8	12.4	10.1	0.0	0.0
Patient TA (Male)	0.6	0.2	11.1	31.5	10.8	28.5	10.8	9.9	0.3	3.0
Patient LC (Female)	0.0	0.3	16.9	24.7	16.9	24.5	7.1	15.9	0.0	0.2

Definition of abbreviations: MOAHI = Mixed obstructive apnea and hypopnea index; OB = obstructed breathing; RME = rapid maxillary expansion.

Table 4.9 Sleep and Breathing characteristics of Non-responding Obstructed Breathing children. None had OSA post-RME. OB duration worsened markedly (37.9 vs 136.1 mins, 28.0 vs 163.7 mins) in 2 children (patients MG and AS) respectively. In these 2 patients, the frequency of snore run increased substantially (8.1 vs 41.3 runs/hr and 18.9 vs 33.6 runs/hr). The remaining 4 patients also worsened in snoring duration as compared to baseline. Snoring occurred predominantly with negligible stertor noted (< 3mins) post-RME.

4.4.8 The Effects of RME therapy on OSA children (n=4)

The effects of RME therapy on sleep and breathing characteristic are presented in Table 4.10 and Figures 4.6 and 4.7. Only 4 children in the entire study were found to have OSA at baseline. Baseline characteristics of all four OSA children can be found in Table 3.11 in Chapter 3. In brief, only one child had tonsillar hypertrophy (grade 2) with all four children registering low OSA-18 scores (all <53). Post-RME therapy, all 4 children experienced full

OSA resolution with significant decreases in MOAHI (2.7 events/hr vs 0.1/ events/hr, p=0.04); and AHI (3.7 events/hr vs 0.4 event/hr, p=0.01).

Significant decreases in OB percentage (29.7 % vs 4.1%, p=0.04) and frequency of OB runs (22.5 runs/hr vs 4.4 runs/hr, p=0.05) were noted. A marked decrease in OB duration was observed (127.0 mins vs 13.2 mins) but the values were not statistically significant (p=0.06). Two (50%) children still had OB >20 mins post-RME. Large but statistically insignificant reductions in snore duration (100.5 (50.1, 210.3) vs 13.2 (5.6, 26.3) mins, p=0.08) occurred with the same 2 children snoring >20mins post-RME. However, significant decreases in snoring percentage (24.3 (11.5, 37.9) vs 4.1 (1.2, 6.9), p=0.04) and the frequency of snoring runs (18.7 (11.2, 24.6) runs/hr vs 3.7 (1.7, 5.9) runs/hr, p=0.05) were found.

There were no significant changes in stertor duration, percentage and frequency (all p=0.50). Respiratory induced movement arousals decreased markedly with respect to the number of events (51 vs 5 events, p=0.09) and frequency (6.2 vs 0.7 events/hr, p=0.07), but these were, again, not statistically significant.

TABLE 4.10 SLEEP AND BREATHING CHARACTERISTICS OF OSA CHILDREN WITH RME THERAPY

Variable	Baseline (n=4)	Post-RME (n=4)	p value
Analysis Time, mins	532.6 (423.0, 594.3)	385.7 (332.1, 522.7)	0.38
Qd, mins	507.9 (371.3, 559.6)	361.9 (307.7, 498.2)	0.38
MOAHI, events/hr	2.7 (1.8, 5.5)	0.1 (0.0, 0.7)	0.04
AHI, events/hr	3.7 (2.8, 5.8)	0.4 (0.1, 0.8)	0.01
OAI, events/hr	0.8 (0.1, 1.4)	0.0 (0.0, 0.2)	0.25
OHI, events/hr	2.0 (0.3, 5.2)	0.1 (0.0, 0.5)	0.15
CAI, events/hr	0.2 (0.1, 0.3)	0.0 (0.0, 0.1)	0.25
CHI, events/hr	0.3 (0.0, 1.5)	0.2 (0.1, 0.2)	0.50
Spont. MAr mins	23.4 (18.6, 48.9)	24.0 (20.4, 24.7)	0.45
Spont. MAr events	99.0 (96.0, 119.3)	94.0 (81.3, 97.8)	0.13
Spont. MAr events/hr	12.2 (10.8, 14.0)	14.2 (10.8, 16.1)	0.57
Resp. MAr mins	5.7 (2.8, 11.8)	0.7 (0.3, 2.9)	0.12
Resp. MAr events	51.0 (25.0, 105.5)	5.0 (1.5, 12.3)	0.09
Resp. MAr events /hr	6.2 (3.2, 10.8)	0.7 (0.3, 1.7)	0.07
Snoring, mins	100.5 (50.1, 210.3)	13.2 (5.6, 26.3)	0.08
Snoring, %	24.3 (11.5, 37.9)	4.1 (1.2, 6.9)	0.04
Snore runs, /hr	18.7 (11.2, 24.6)	3.7 (1.7, 5.9)	0.05
Stertor, mins	1.5 (0.0, 45.5)	0.0 (0.0, 1.6)	0.50
Stertor, %	0.3 (0.0, 8.3)	0.0 (0.0, 0.4)	0.50
Stertor, runs, /hr	0.3 (0.0, 5.8)	0.0 (0.0, 1.1)	0.50
Obstructed breathing, mins	127.0 (50.1, 225.7)	13.2 (5.6, 27.9)	0.06
Obstructed breathing, %	29.7 (11.5, 41.0)	4.1 (1.2, 7.3)	0.04
Obstructed breathing runs, /hr	22.5 (11.8, 26.4)	4.4 (1.8, 6.2)	0.05

Definition of abbreviations; Qd = Quiescent time; MOAHI = Mixed + Obstructive apnea hypopnea index; AHI = apnea+hypopnea index; OAI = Obstructive apnea Index; OHI = Obstructive Hypopnea Index; CAI = Central apnea index; CHI= Central hypopnea index; Spont. = spontaneous, MAr =movement arousal, Resp.= respiratory induced; RME = rapid maxillary expansion; Continuous data are presented as Median (25^{th},75^{th} interquartile range).

Table 4.10 Sleep and Breathing characteristics of OSA children with RME therapy. All 4 children experienced full OSA resolution (MOAHI<1 event/hr). Significant decreases in OB percentage (p=0.04) and frequency of OB runs (p=0.05) was noted. Significant decreases in snoring percentage (p=0.04) and snoring rate (p=0.05) were found. There were no significant changes in stertor duration, percentage and frequency (all p=0.50).

Table 4.11 below details the individual response of each OSA child. Although remarkable reductions in OB duration was noted in all 4 children, residual snoring (20.5 mins and 28.2 mins) remained in 2 children (patients 1 and 3) respectively. The other 2 children had minimal snoring (5.5 and 5.8) mins. Patient 3 had enlarged tonsils (grade 2) with the remaining 3 children normal. This patient was aged 7 years old and had a remarkable resolution of OSA (MOAHI 6.3 events/hr vs 0.8 events/hr) post-RME. The frequency of snore runs was noted to decrease remarkably (26.2 vs 1.1 runs/hr, 17.5 vs 3.6 runs/hr, 19.8 vs 3.7 runs/hr) in 3 patients (patients 1, 3 and 4) respectively. Patient 3 recorded significant stertor at baseline (53 mins) but this reduced markedly in 2.1 mins post-RME. No stertor was noted in the remaining 3 OSA children.

TABLE 4.11 Change in Sleep and Breathing Characteristics in OSA Children with RME therapy (n=4)

Patient (gender, age-yrs)	MOAHI (/hr) baseline	MOAHI (/hr) post RME	OB (mins) baseline	OB (mins) post RME	Snoring (mins) baseline	Snoring (mins) post RME	Snore (runs/hr) baseline	Snore (runs/hr) post RME	Stertor (mins) baseline	Stertor (mins) post RME
Patient 1 (F, 8)	2.2	0.0	241.5	20.5	238.6	20.5	26.2	1.1	2.9	0.0
Patient 2 (M, 12)	1.6	0.2	41.6	5.8	41.6	5.8	9.1	6.6	0.0	0.0
Patient 3 (F, 7)	6.3	0.8	178.2	30.3	125.2	28.2	17.5	3.6	53.0	2.1
Patient 4 (F, 8)	3.2	0.0	75.7	5.5	75.7	5.5	19.8	3.7	0.0	0.0

Definition of abbreviations: MOAHI = Mixed obstructive apnea and hypopnea index; OB = obstructed breathing; RME = rapid maxillary expansion; F=female; M=male.

Table 4.11 Change in Sleep and Breathing characteristics in OSA children with RME therapy. Post-RME, all 4 children did not have OSA. The duration of OB reduced in all patients. Residual snoring was noted in all OSA patients with 2 (patients 1 and 3) having 20.5 and 28.2 mins of snoring post-RME. Of note, patient 3 had a significant reduction (53.0 vs 2.1 mins) in stertor post-RME.

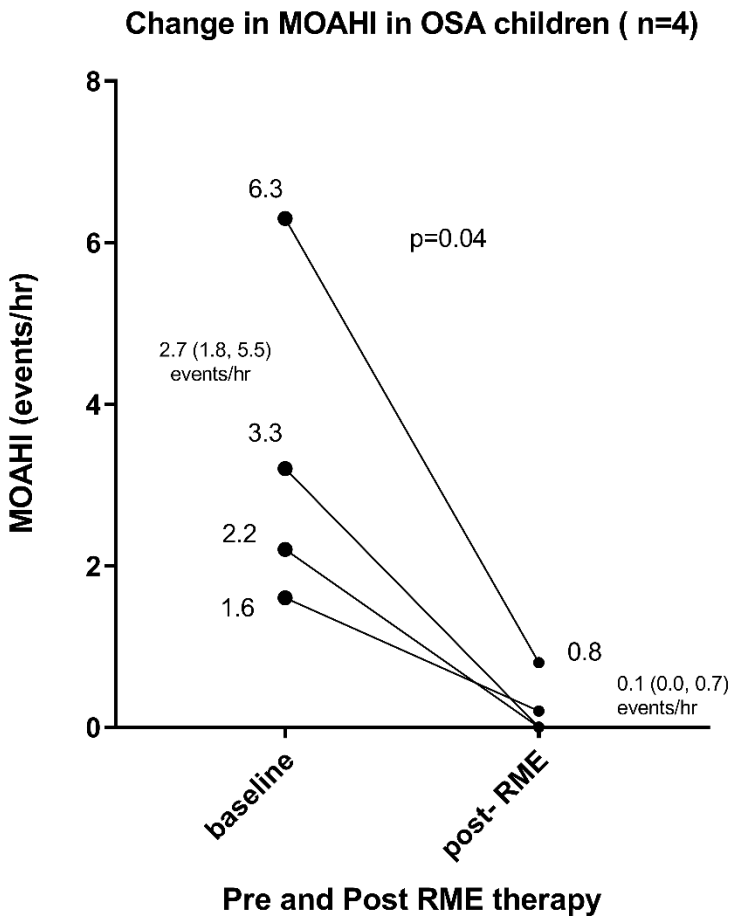


Figure 4.6 Change in MOAHI in OSA children with RME therapy. All 4 OSA children responded favorably with resolution of OSA (MOAHI <1 event/hr).

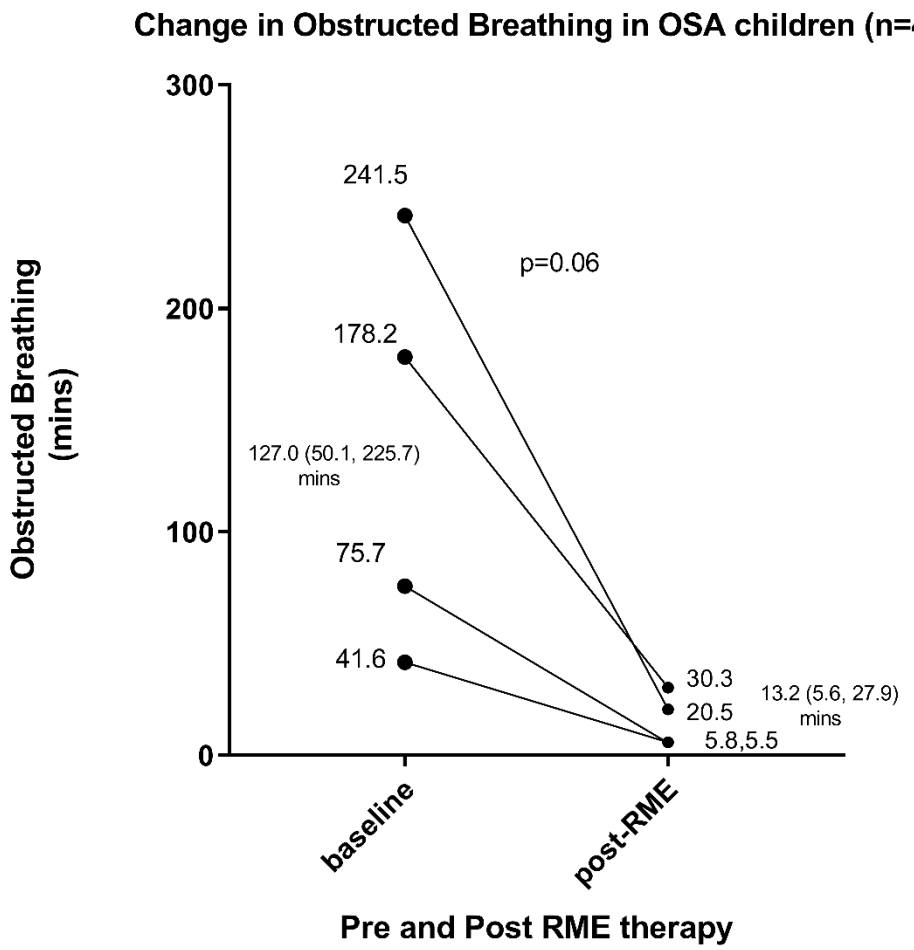


Figure 4.7 Change in the duration of Obstructed Breathing in OSA children with RME therapy. All children with OSA children had large amounts of obstructed breathing at baseline. Although not statistically significant (p=0.06), there were remarkable reductions in the duration of OB, ((127.0 (50.1, 225.7) mins vs 13.2 (5.6, 27.9) mins, p=0.06) at the RME2 point. The lack of significance may have been due to the small numbers in this group.

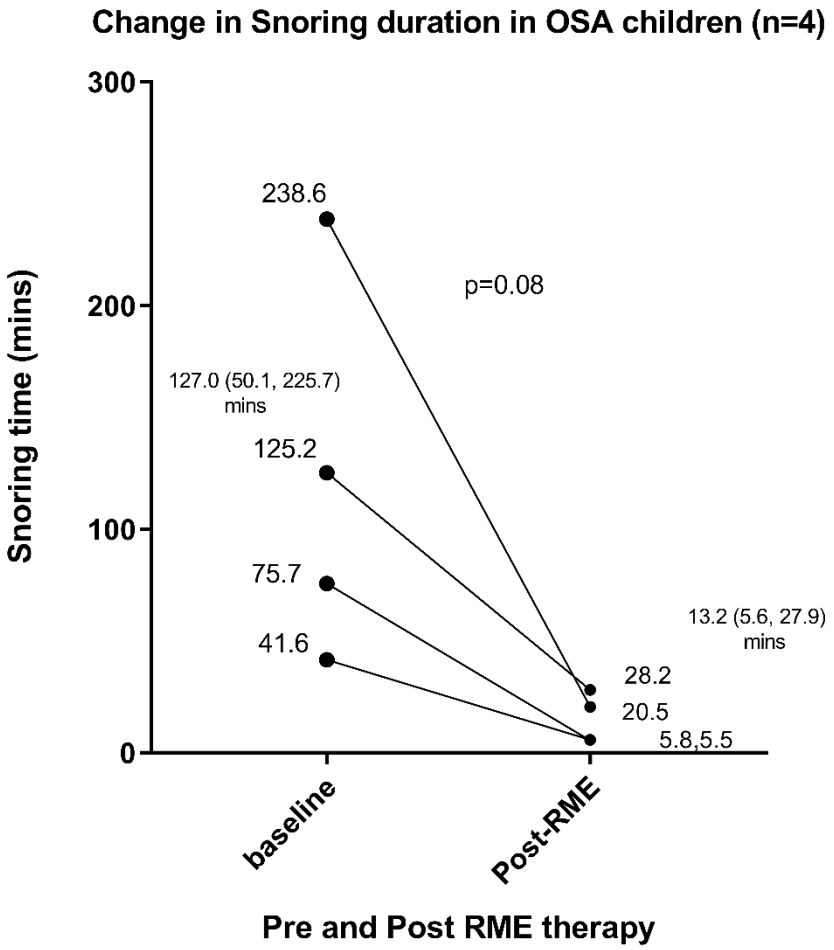


Figure 4.8 Change in the duration of Snoring in OSA children at baseline and post-RME therapy. All 4 OSA children responded favorably with marked reductions in snoring duration. All OSA children had significant levels of snoring at baseline. Remarkable reductions in snoring duration ((127.0 (50.1, 225.7) mins vs 13.2 (5.6, 27.9) mins) was noted but this was not statistically significant (p=0.06). Two of the 4 OSA children (50%) still had > 10 mins (28.2 and 20.5 mins) of snoring despite RME therapy. The remaining 2 OSA children with minimal snoring (< 10 mins) post-RME did start at a lower baseline.

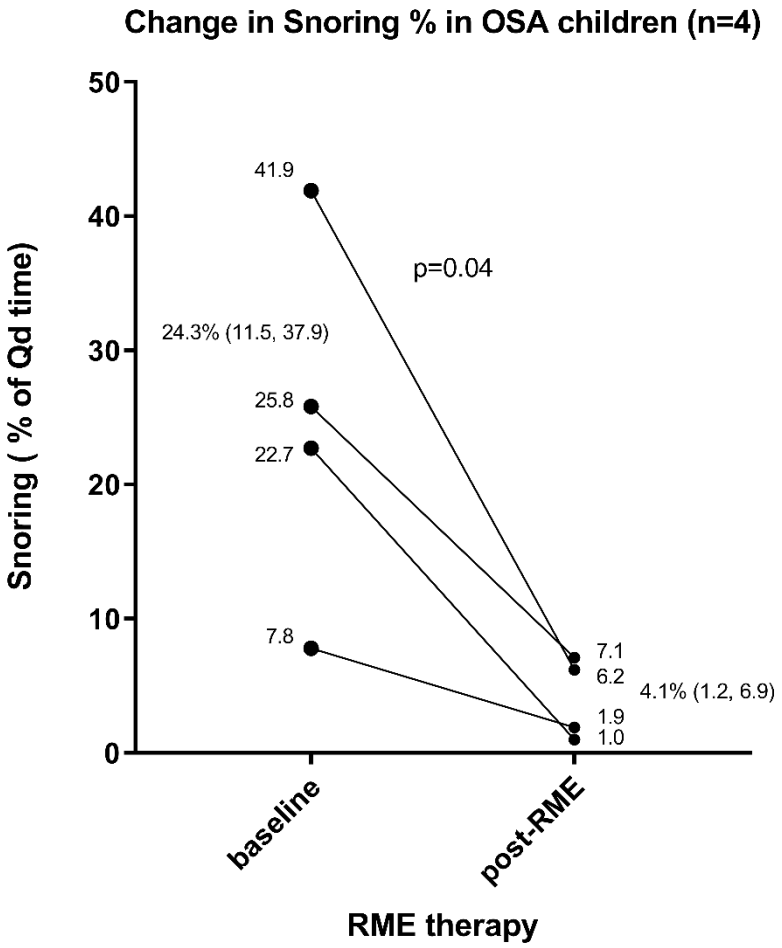


Figure 4.9 Change in the Snoring Percentage of Quiescent (Qd) time in OSA children at baseline and post-RME therapy. All OSA children had significant levels of snoring percentage at baseline. These children responded favorably with marked reductions in snoring percentage post-RME. Statistically significant reduction in snoring percentage was noted (24.3 (11.5, 37.9) % vs 4.1 (1.2, 6.9) %, p=0.04).

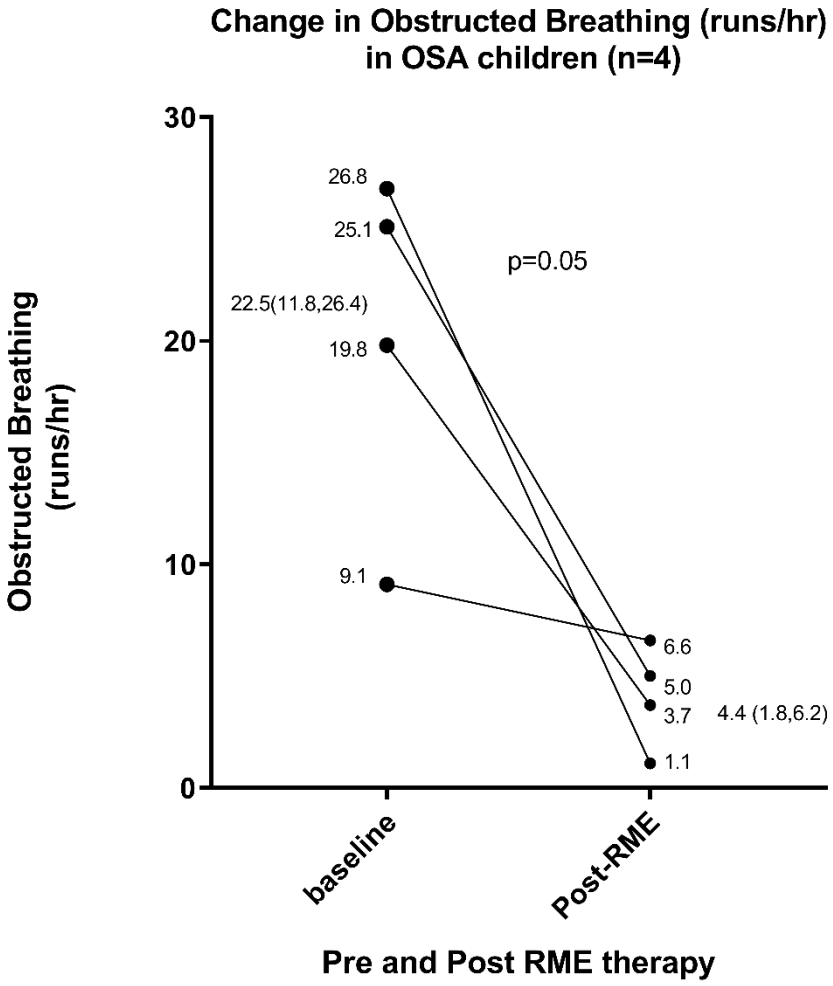


Figure 4.10 Change in the frequency of OB runs in OSA children with RME therapy. All OSA children had frequent runs of OB at baseline. A statistically significant reduction in the frequency of OB runs was noted (22.5 (11.8, 26.4) runs/hr vs 4.4 (1.8, 6.2) runs/hr, p=0.05). The child that reduced in the frequency of OB run from 9.1 to 6.6 runs/hr had a remarkable reduction in snoring (41.6 vs 5.8 mins) with no stertor noted.

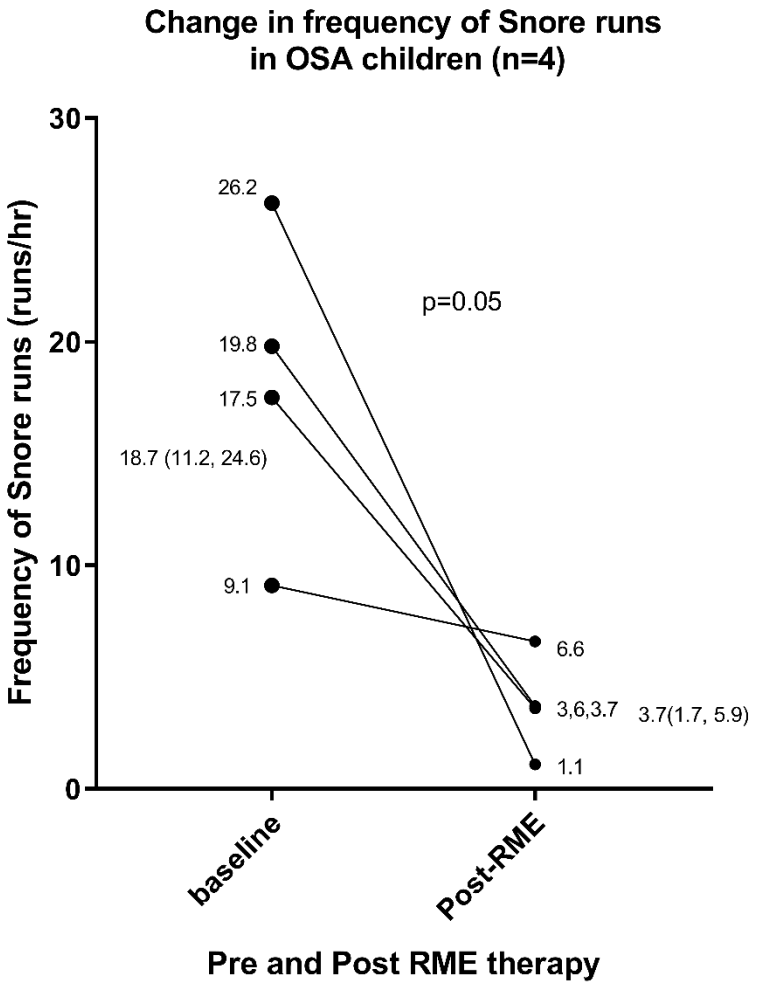


Figure 4.11 Change in the frequency of Snore runs in OSA children with RME therapy. All OSA children had frequent snore runs at baseline. A statistically significant reduction in the frequency of snore runs was noted (18.7 (11.2, 24.6) runs/hr vs 3.7 (1.7, 5.9) runs/hr, p=0.05).

4.4.9 The Effect of RME therapy on Sleep Variables at RME1 and RME2

There were 38 children who had recordings performed at all three timepoints (baseline, RME1 and RME2). Table 4.12 shows the change caused by RME therapy at these timepoints.

Significant changes were noted in analysis time (540 (454, 592) (baseline) vs 555 (460, 602) (RME1) vs 501 (383, 543) mins (RME2), p=0.01) and Qd time (494 (433, 555) (baseline) vs 529 (428, 559) (RME1) vs 471 (366, 513) mins (RME2), p=0.02).

Statistically significant decreases were also noted in OAI (0.0(0.0,0.0), (range 0.0-1.5) baseline vs 0.0(0.0,0.0), (range 0.0-1.2) (RME1) vs 0.0(0.0,0.0) (range 0.0-0.1) (RME2), p=0.02). The absolute values noted were small and of a lower order of magnitude. CAI decreased significantly, (0.3 (0.1, 0.6) (baseline) vs 0.2 (0.0, 0.5) (RME1) vs 0.1 (0.0, 0.3) events/hr (RME2), p=0.05).

Significant changes in the duration of respiratory induced movement arousals (Resp. MAr) (1.3 (0.5, 3,3) (baseline) vs 1.4 (0.3, 3.4) (RME1) vs 0.9 (0.2, 3.1) mins (RME2), p=0.04); Resp. MAr events (8.5 (3.0, 20.0) (baseline) vs 12.0 (3.0, 21.3) (RME1) vs 5.0 (1.0, 15.3) (RME2) events, p=0.02), and frequency of Resp. MAr runs (0.9 (0.4, 2.6) (baseline) vs 1.3 (0.3, 3.0) (RME1) vs 0.7 (0.2, 2.3) runs/hr (RME2), p=0.03) were found. Increases from baseline were noted at RME1 but values improved at RME2 as compared to baseline.

Overall, no significant changes were noted for obstructed breathing, snoring and stertor. However, it is prudent to state that at RME1, 2 children with no OSA at baseline worsened at RME1 stage. These 2 children subsequently improved to normalized levels at RME2 stage.

TABLE 4.12 THE EFFFECT OF RME THERAPY ON SLEEP VARIABLES IN CHILDREN WITH MAXILLARY CONSTRICTION AT RME1 AND RME2.

Variable	Baseline (n=38)	RME 1 (n=38)	RME 2 (n=38)	p value
Analysis Time, mins	540 (454, 592)	555 (460, 602)	501 (383, 543)	0.01
Qd, mins	494 (433, 555)	529 (428, 559)	471 (366, 513)	0.02
MOAHI, events/hr	0.0 (0.0, 0.2)	0.0 (0.0, 0.1)	0.0 (0.0, 0.0)	0.14
AHI, events/hr	0.7 (0.3, 1.4)	0.4 (0.1, 0.8)	0.3 (0.1, 0.5)	0.10
OAI, events/hr	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)	0.02
OHI, events/hr	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)	0.81
CAI, events/hr	0.3 (0.1, 0.6)	0.2 (0.0, 0.5)	0.1 (0.0, 0.3)	0.05
CHI, events/hr	0.1 (0.0, 0.3)	0.0 (0.0, 0.2)	0.1 (0.0, 0.2)	0.22
Spont. MAr mins	24.7 (19.2, 33.9)	27.3 (16.3, 37.5)	24.5 (20.0, 30.0)	0.35
Spont. MAr events/hr	13.5 ± 4.4	12.9 ± 4.6	13.7 ± 3.7	0.50
Resp. MAr mins	1.3 (0.5, 3,3)	1.4 (0.3, 3.4)	0.9 (0.2, 3.1)	0.04
Resp. MAr events	8.5 (3.0, 20.0)	12.0 (3.0, 21.3)	5.0 (1.0, 15.3)	0.02
Resp. MAr events/hr	0.9 (0.4, 2.6)	1.3 (0.3, 3.0)	0.7 (0.2, 2.3)	0.03
Snoring, mins	11.4 (0.9, 34.3)	14.3 (0.5, 45.9)	5.2 (0.2, 25.0)	0.36
Snoring, %	2.4 (0.2, 7.4)	2.8 (0.1, 10.0)	1.3 (0.0, 6.0)	0.52
Snoring runs/hr	5.4 (1.6, 9.5)	5.3 (0.6, 15.0)	2.9 (0.3, 7.4)	0.08
Stertor, mins	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)	0.94
Stertor, %	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)	0.82
Stertor runs/hr	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)	0.63
OB mins	11.5 (0.9, 34.3)	14.3 (0.5, 46.9)	5.2 (0.2, 25.1)	0.36
OB, %	2.4 (0.2, 7.4)	2.8 (0.1, 10.2)	1.3 (0.0, 6.3)	0.52
OB, runs/hr	5.4 (1.6, 9.6)	5.6 (0.6, 15.0)	2.9 (0.3, 7.5)	0.08

Definition of abbreviations; Qd = Quiescent time; MOAHI = Mixed + Obstructive apnea hypopnea index; AHI = apnea+hypopnea index; OAI = Obstructive apnea Index; OHI = Obstructive Hypopnea Index; CAI = Central apnea index; CHI= Central hypopnea index; Spont. = spontaneous, MAr = movement arousal, Resp.= respiratory induced; OB = Obstructed Breathing; Continuous data are presented ± Mean Standard deviation or Median (25^{th},75^{th} interquartile range).

Table 4.12. The effect of RME on Sleep variables at timepoints baseline, RME1 and RME2. There were significant differences noted in analysis time (p=0.01) and Qd time (p=0.02). OAI and CAI decreased significantly (p=0.02, p=0.05 respectively), but the absolute values were small. Significant changes were also noted in the duration (p=0.04), number (p=0.02) and frequency (p=0.03) of respiratory induced movement arousals.

4.4.10 Therapeutic Success of RME therapy on Sleep disordered breathing

In this study, therapeutic success was analyzed based on OSA and snore response. Full OSA resolution was defined as MOAHI < 1 event/hr. Snore response has been categorized based on tiers of residual snoring expressed as a percentage. The snore response categories were defined as follows: Resolution of snoring = snore < 1%, residual snoring = snore 1-4.9%, persisting snoring = snoring 5-9.9%, continuing snoring = snore ≥ 10%.

Of the 26 children noted to have OB at baseline, 23 children had final post-RME studies for analysis. These 23 children consisted of 19 non-OSA and 4 OSA children who all snored >10 mins at baseline.

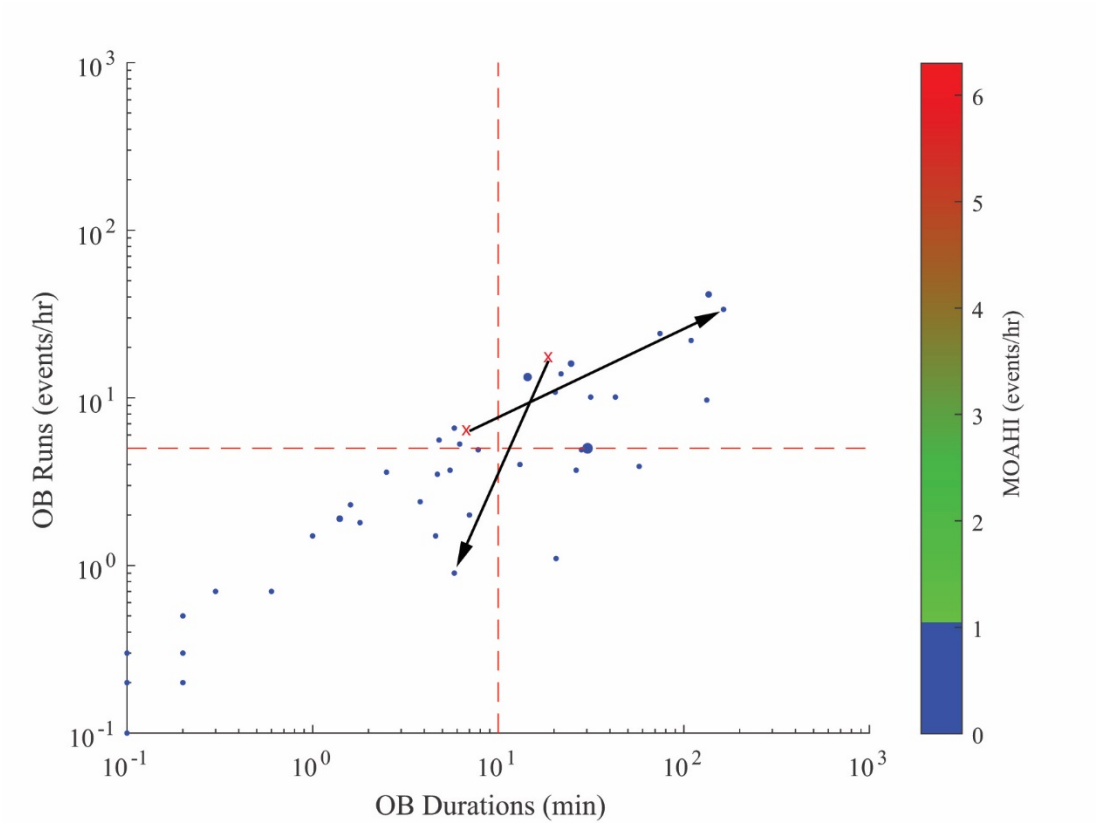
Post-RME, all 23 (100 %) children had full resolution of OSA. When both OSA and snore response was taken into consideration, 26.1 % of children met the "full OSA and snoring resolution (snore <1%)" criteria. Partial response of 30.4% was noted when "full OSA resolution with residual snoring (snore 1-4.9%)" criteria was used. 26.1% of the group had "full OSA resolution with persisting snoring (snore 5-9.9%)" with a further 17.4 % with "full OSA resolution with continuing snoring (snore ≥ 10%)" of the night. There were no complete failures (MOAHI ≥ 5, snore ≥ 10%) observed in the group. The therapeutic success of RME on SDB is shown in Table 4.13. Bubble plot showing total duration ($\log_{10,}$ x-axis) plotted against number of runs ($\log_{10,}$ y-axis) of obstructed breathing for each child at RME2 is presented in Figure 4.12.

TABLE 4.13 THERAPEUTIC SUCCESS OF RME THERAPY ON SDB (n=23)

Degree of Therapeutic Success	Number
MOAHI ONLY	
Full Response of OSA (MOAHI <1)	23/23 (100%)
Partial response of OSA (MOAH1 1-4.9)	0/23 (0%)
Total Failure (MOAHI ≥ 5)	0/23 (0%)
MOAHI and Obstructed Breathing	
Full Response of OSA and snoring (MOAHI <1, snore < 1%)	6/23 (26.1%)
Partial Response -OSA resolved, residual snore (MOAHI <1, snore 1-4.9%)	7/23 (30.4%)
Partial Response -OSA resolved, persisting snore (MOAHI <1, snore 5-9.9%)	6/23 (26.1%)
Partial Response -OSA resolved, continuing snore (MOAHI <1, snore ≥ 10%)	4/23 (17.4%)
Complete Failure (MOAHI ≥ 5, snore ≥ 10%)	0/23 (0%)

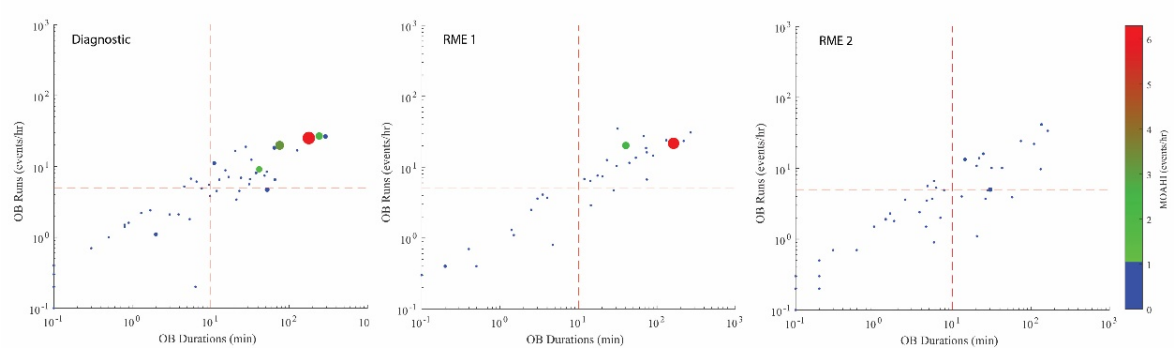
Definition of abbreviations; SDB= Sleep disordered breathing; MOAHI = Mixed apnea and hypopnea index; RME = rapid maxillary expansion; Continuous data are presented fraction and percentage of group

Table 4.13 Therapeutic success of RME therapy on SDB. Using the classical definition of MOAHI< 1 event/hr, RME therapy resolved OSA in all the 4 OSA children with all OB children defined as “normal”. However, when snore response when taken into consideration, children with OB were noted to have a heterogenous response with several children having significant duration of residual snoring than others in the group.



Definition of abbreviations: MOAHI = Mixed obstructive apnea and hypopnea index; OB = obstructed breathing.

Figure 4.12 Bubble plot showing total duration ($log_{10,}$ x-axis) plotted against number of runs ($log_{10,}$ y-axis) of obstructed breathing for each child at RME2. MOAHI values are on the z-axis; blue circles are non-OSA children with hotter colors and larger circles indicating increasing severity of OSA. Red dashed lines indicate thresholds of 10 mins (x-axis) and 5 events/h (y axis). At RME2, there were no children with OSA. The OB trajectory of 2 children from baseline to RME2 is presented (in the figure the red "x" is where there started on at baseline and the end of the arrow represents their result at RME2). Note that 1 child improved significantly to the bottom left quadrant with significant improvement in obstructed breathing (frequency of OB runs and duration). In contrast, the other child worsened in the frequency of OB runs and duration moving to the top right quadrant. These 2 children exemplify the importance of objective measurement of snoring as both children did not have OSA (MOAHI > 1/hr) at baseline or post-RME therapy but have a stark contrast with respect to OB.



Definition of abbreviations: MOAHI = Mixed obstructive apnea and hypopnea index; OB = obstructed breathing; RME = rapid maxillary expansion.

Figure 4.13 Bubble plot showing total duration ($log_{10,}$ x-axis) plotted against number of runs ($log_{10,}$ y-axis) of obstructed breathing for children at baseline, RME1 and RME2 stages of treatment. MOAHI values are on the z-axis; blue circles are non-OSA children with hotter colors and larger circles indicating increasing severity of OSA. Red dashed lines indicate thresholds of 10 mins (x-axis) and 5 events/h (y axis). At RME1, two children worsened in OSA severity (Child1-MOAHI 0.9/hr vs 5.3 hr; and Child2-MOAHI 1.6/hr vs 2.2/ hr). At RME2, these 2 children had resolution of OSA (MOAHI = 0.0 /hr and 0.2/hr respectively). At RME2, there were no children with OSA. A significant proportion of children without OSA at baseline improved in OB duration and frequency of runs transposing to the lower left quadrant. However, despite RME therapy, residual OB was noted in a significant proportion of children who did not exhibit OSA at baseline.

4.4.11 RME therapy in children with Tonsillar Hypertrophy

There were 7 children with tonsillar hypertrophy; two with grade 3 and five with grade 2 tonsillar size. Table 4.14 shows the baseline characteristics of these 7 children. All children with the exception of patient 7 recorded MOAHI <1/hr. Patient 7 had a remarkable MOAHI 6.3/hr and significant OB runs (203) and duration (178.2 mins) with grade 2 tonsil size. This child also had frequent URTI but OSA-18 score was surprisingly low (score 27) suggestive of a minimal impact on quality of life. By way of contrast, patient 5 did not have OSA but had significant OB duration (126.7 mins) and runs (122 runs) with OSA-18

score of 43. Patient 1 and 2 had grade 3 tonsils but had significantly different levels of OB with patient 2 having frequent URTI with greater duration in OB duration (52.5mins vs 0.9 mins) and OB runs (41 vs 15) as compared to patient 1. Although patient 6 presented with a history of asthma and high OSA-18 score (score 83), suggestive of severe impact on quality of life, OB duration was 9.8 minutes with no OSA detected. Thus, a broad spectrum of clinical presentations was observed in these 7 children with grade 2/3 tonsils with nocturnal enuresis (patient 3,4); asthma (patient 6), URTI (patients 2,5,7) recorded.

Overall, tonsillar size, clinical history and OSA-18 questionnaire was variable and of limited utility in predicting the severity of obstructed breathing and OSA.

TABLE 4.14 Baseline Characteristics of Children with Tonsillar Hypertrophy

Patient	Tonsil grade	*Age (yrs)*	BMI z score	*Nocturnal enuresis*	Asthma	URTI	OSA-18 total score	MOAHI (/hr)	OB (mins)	OB (runs)
Patient 1	3	8	0.77	N	N	N	33	0.0	0.9	15
Patient 2	3	7	1.27	N	N	Y	19	0.9	52.5	41
Patient 3	2	8	0.26	Y	N	N	37	0.0	11.9	32
Patient 4	2	8	-1.69	Y	N	N	20	0.6	2	11
Patient 5	2	9	1.96	N	N	Y	43	0.0	126.7	122
Patient 6	2	10	1.3	N	Y	N	83	0.0	9.8	29
Patient 7	2	7	-0.43	N	N	Y	27	6.3	178.2	203

Definition of abbreviations: BMI = body mass index; URTI = upper respiratory tract infection; MOAHI = Mixed obstructive apnea and hypopnea index; OB = obstructed breathing.

Table 4.14 Baseline characteristics of children with tonsillar hypertrophy. Despite tonsillar hypertrophy, only one child (patient 7) had OSA (MOAHI 6.3 events). This child was 7 years old and also had significant OB (178.2 mins). Only one child reported a high OSA-18 score (score 83, patient 6). Overall, clinical history and snoring was variable.

Table 4.15 below presents the effect of RME on the 7 children with tonsillar hypertrophy. Patient 6 was lost to follow up. In the remaining patients, all exhibited a MOAHI <1 /hr post-RME. Of note, patient 7 demonstrated resolution of OSA with MOAHI decreasing from 6.3/hr to 0.8/hr. OB duration reduced from 178.2mins to 30.3 mins. Patient 5 had similar improvements reducing OB duration from 126.7 mins to 28.1 mins post-RME. Despite the remarkable reductions in these 2 patients (patient 5 and 7), it is important to state that residual OB still persisted in 4/7 (57%) of children with tonsillar hypertrophy. Overall, it is noteworthy to state that all 6 children with tonsillar hypertrophy demonstrated significant improvements in OB with full resolution of OSA in patient 7.

TABLE 4.15 The Effect of RME on Children with Tonsillar Hypertrophy (grade 2 and 3)

Patient	OSA-18 total score baseline	OSA-18 *total score Post-RME*	MOAHI (/hr) baseline	MOAHI (/hr) post RME	OB (mins) baseline	OB (mins) Post-RME	OB (runs) baseline	OB (runs) Post-RME	OB (runs/hr) baseline	OB (runs/hr) Post-RME
Patient 1	33	24	0.0	0.0	0.9	0.0	15	0	1.6	0.0
Patient 2	19	19	0.9	0.0	52.5	0.0	41	0	4.7	0.0
Patient 3	37	53	0.0	0.0	11.9	5.8	32	9	4.5	0.9
Patient 4	20	20	0.6	0.0	2	1.8	11	16	1.1	1.8
Patient 5	43	22	0.0	0.0	126.7	28.1	122	17	16.8	4.9
Patient 6	83	LFU	0.0	LFU	9.8	LFU	29	LFU	3.4	LFU
Patient 7	27	33	6.3	0.8	178.2	30.3	203	33	25.1	5.0

Definition of abbreviations: URTI = upper respiratory tract infection; MOAHI = Mixed obstructive apnea and hypopnea index; OB = obstructed breathing; LFU = Lost to Follow-up.

Table 4.15 The effect of RME on children with tonsillar hypertrophy. Although patient 6 was lost to follow up, the remaining 6 patients did not have OSA post-RME. OB duration was reduced substantially in these patients but 2 patients (patient 5 and 7) had residual OB (28.1 mins and 30.3 mins).

4.4.12 Change in Wheezing with RME therapy (n=2)

Two boys (aged 9 and 12 years old, BMI z score -1.25 and -1.9) without OSA had nocturnal wheeze. Normal tonsil size (grade 0) was noted in both children with a high OSA-18 score (91) in patient W2. This child had increased duration of wheezing (62.4 mins vs 8.0mins) and obstructed breathing duration (33.1 mins vs 1.7 mins) as compared to patient W1 at baseline. A detailed description of these baseline characteristics in these 2 children can be found in Tables 3.9 and 3.10 in the previous chapter.

Post-RME therapy, both children did not have OSA. Significant increases in the wheezing duration (8.4 vs 98.1 mins, 62.4 vs 199.7 mins), frequency of wheezing runs per hour (7.2 vs 64.0 runs/hr, 5.1vs 20.1 runs/hr) and percent of Qd time wheezing (1.4 vs 19.9 %, 11.1 vs 40.1 %) was noted in both boys respectively. Interestingly, small increases in obstructed breathing duration (1.7 vs 2.5 mins, 33.1 vs 42.8 mins) in both children was found post-RME. Table 4.16 presents the changes noted in the 2 wheezing children.

TABLE 4.16 Change in Sleep and Breathing Characteristics of 2 Children with Wheezing following RME therapy.

Patient	MOAHI (/hr) baseline	MOAHI (/hr) Post-RME	Wheeze (/hr) baseline	Wheeze (/hr) Post-RME	Wheeze (mins) baseline	Wheeze (mins) Post-RME	Wheeze duration (% of Qd) baseline	Wheeze duration (% of Qd) Post RME	OB (mins) baseline	OB (mins) Post-RME
Patient W1	0.1	0.0	7.2	64.0	8.4	98.1	1.4	19.9	1.7	2.5
Patient W2	0.0	0.0	5.1	20.1	62.4	199.7	11.1	40.1	33.1	42.8

Definition of abbreviations: NE = nocturnal enuresis; MOAHI = Mixed obstructive apnea and hypopnea index; Qd = quiescent time; Continuous data are presented as absolute values.

Table 4.16 Change in Sleep and Breathing characteristics of 2 children with Wheezing following RME therapy. Both boys (aged 9 and 12 yrs old) recorded an increase in wheezing and obstructed breathing following RME therapy. Significant changes in the duration, percentage and frequency of wheezing runs/hr were observed. Noteworthy, the MOAHI remained unchanged.

4.4.13 The Effect of RME therapy on Stertorous Children

At baseline, stertor was noted in 10/56 (17.9%) children with 2 children noted to have OSA. The majority of children with stertor had small amounts present, with only 2 having long durations of stertor (53 mins and 22.7 mins). The remainder had ≤ 2.9 mins of stertor. A detailed description of these baseline characteristics in these ten children with stertor can be found in Table 3.8 in Chapter 3.

Post-RME, all 10 children had no OSA. Remarkable resolution of OSA was observed in the two OSA patients (patient 3 and 8) with significant reductions in MOAHI noted, (2.2

/hr vs 0.0 /hr and 6.3/hr vs 0.8/hr, respectively). In these 2 patients, snoring decreased significantly (238.6 mins vs 20.5 mins and 125.2 mins vs 28.2 mins respectively). With the exception of patient 1, all patients improved in the duration and frequency of stertor. Notable stertor reductions were noted in patients 4 and 8 where stertor duration reduced remarkably, (22.0 mins vs 0.0 mins and 53.0 mins vs 2.1 mins, respectively). Patient 1 exhibited minimal increase in stertor duration (0.3mins vs 3.0 mins) but snoring increased from 10.8 mins to 28.5 mins. Snoring duration improved in 80% of stertorous children with only 2 patients (patient 1 and 9) showing increases in snoring (10.8 mins vs 28.5 mins and 1.3 mins vs 2.5 mins respectively). However, snoring persisted (>10 mins) in 50% of stertorous children. Table 4.17 shows the effect of RME therapy on stertorous children.

TABLE 4.17 Change in Sleep Characteristics of Stertorous Children with RME therapy

Patient	OSA-18 total score baseline	OSA-18 total score Post-RME	MOAHI (/hr) baseline	MOAHI (/hr) Post-RME	Stertor (mins) baseline	Stertor (mins) Post-RME	Stertor (runs/*hr*) *baseline*	Stertor (runs/hr) Post-RME	Snoring (mins) baseline	Snoring (mins) Post-RME
Patient 1	29	23	0.6	0.2	0.3	3.0	0.2	0.2	10.8	28.5
Patient 2	67	19	0.0	0.0	0.9	0.0	0.1	0.0	23.5	0.2
Patient 3	53	48	2.2	0.0	2.9	0.0	0.5	0.0	238.6	20.5
Patient 4	43	22	0.0	0.0	22.7	0.0	0.3	0.0	104.1	28.1
Patient 5	19	19	0.9	0.0	0.1	0.0	0.1	0.0	52.4	0.0
Patient 6	64	33	0.2	0.0	0.1	0.0	0.1	0.0	12.7	0.3
Patient 7	20	20	0.6	0.0	0.1	0.0	0.1	0.0	1.9	1.8
Patient 8	27	27	6.3	0.8	53	2.1	7.5	1.4	125.2	28.2
Patient 9	49	61	0.1	0.0	0.4	0.0	0.1	0.0	1.3	2.5
Patient 10	40	35	0.0	0.0	0.4	0.0	0.0	0.0	30.6	26.3

Definition of abbreviations: OSA = Obstructive sleep apnea; MOAHI = Mixed obstructive apnea and hypopnea index; RME = rapid maxillary expansion.

Table 4.17 Change in Sleep characteristics of Stertorous children with RME therapy. Post-RME, no child had OSA with normalization in the 2 OSA children (patients 3 and 8). In these 2 patients, snoring decreased significantly (238.6 mins vs 20.5 mins and 125.2 mins vs 28.2 mins respectively). With the exception of patient 1, stertor improved in all patients. 8/10 (80%) patients improved in snoring duration, however 50% of stertorous children still snored >20 mins post-RME.

4.4.14 Change in OSA-18 Total Scores

Change in OSA-18 score in the entire group

Figure 4.14 illustrates the change in OSA-18 scores with RME therapy in the entire group. At baseline, this group had a median OSA-18 total score of 44 (30, 55) suggestive of a low impact on quality of life (QOL). Significant reductions were noted post-RME to 30 (24, 44), p<0.0001. Notably, 5 children obtained OSA-18 scores >76 indicating moderate to severe impact on QOL at baseline. One child was lost to follow up. The remaining four of these children scored reductions in total scores post-RME as compared to baseline, (91 vs 34, 81 vs 49, 79 vs 66, 76 vs 41).

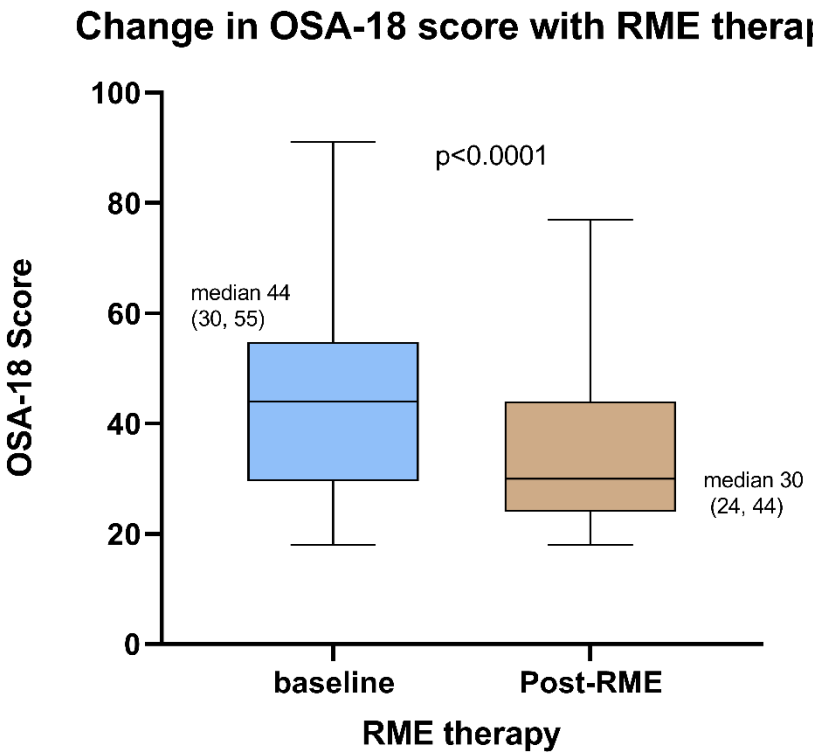


Figure 4.14 The change in OSA-18 total scores with RME therapy in the entire group (n=56). A significant reduction was noted in total scores following RME (44 (30, 54) vs 30 (24, 44), p<0.0001).

Table 4.18 shows the change in OSA-18 total scores in 5 domains (sleep disturbance, physical suffering, emotional distress, daytime problems, caregiver concerns) in the entire group. Overall, small but significant improvements were noted in the questions assessed across the 5 domains. There were only 2 questions that did not register significant improvements ("difficulty getting out of bed in the morning", p=0.11, "mood swings and temper tantrums", p=0.29). Notably, small but significant improvements in ".. loud snoring" (3 (1, 4) vs 2 (1, 3), p=0.007), "mouth breathing…" (4 (2, 6) vs 2 (1, 3), p<0.0001), "breath holding spells…" (1 (1, 3) vs 1 (1, 2), p=0.0014), "choking and gasping while sleeping" (1 (1, 1) vs 1 (1, 1), p=0.0035) were noted. A detailed account of the questions included in the OSA-18 questionnaire is presented in Appendix 9.1.

TABLE 4.18 TOTAL AND DOMAIN OSA-18 SCORES PRE AND POST-RME IN THE ENTIRE GROUP.

Domain	Baseline	Post-RME	p value
Sleep disturbances			
…loud snoring?	3 (1, 4)	2 (1, 3)	0.0007
…breath holdings spells or pauses in breathing at night?	1 (1, 3)	1 (1, 2)	0.0014
…choking or gasping while sleeping?	1 (1, 2)	1 (1, 1)	0.0035
…restless sleep or frequent awakenings from sleep?	3 (1, 4)	2 (1, 3)	0.071
Physical suffering			
…mouth breathing due to nasal obstruction?	4 (2, 6)	2 (1, 3)	<0.0001
…frequent common colds or upper airway infection?	2 (1, 4)	2 (1, 2)	0.0059
…nasal discharge or runny nose?	3 (1, 4)	2 (1, 3)	0.0039
…difficulty swallowing foods?	1 (1, 2)	1 (1, 1)	0.035
Emotional distress			
…mood swings, temper tantrums?	3 (1, 4)	2 (1, 4)	0.29
…aggressive or hyperactive behavior?	3 (1, 4)	1 (1, 3)	0.0013
…discipline problems?	2 (1, 4)	1 (1, 3)	0.0122
Daytime problems			
…excessive daytime drowsiness or sleepiness?	1 (1, 3)	1 (1, 2)	0.09
…poor attention span or concentration?	2 (1, 4)	2 (1, 3)	0.026
…difficulty getting out of bed in the morning?	3 (1, 4)	2 (1, 4)	0.11
Caretaker concern			
…worried about the general health of your child?	2 (1, 3)	1 (1, 2)	0.0009
…created a concern that your child is not getting enough air?	2 (1, 3)	1 (1, 2)	0.0002
…interfered in your ability to perform daily activities?	1 (1, 3)	1 (1, 1)	0.015
…made you frustrated?	2 (1, 4)	1 (1, 3)	0.07
OSA-18 Total Score	44 (30, 55)	30 (24, 44)	0.0001

Definition of abbreviations: OSA = Obstructive sleep apnea; RME = rapid maxillary expansion.

Table 4.18 Total and domain OSA-18 scores following RME therapy in the entire group. Significant improvements were noted the majority of questions across the 5 domains (sleep disturbance, physical suffering, emotional distress, daytime problems, caregiver concerns). Small but significant improvements were observed in loud snoring (p=0.0007), breath holding (p=0.0014), choking and gasping (p=0.0035).

Change in OSA-18 score in the OB group

Figure 4.15 illustrates the change in OSA-18 scores with RME therapy in the OB group. At baseline, this group had a median OSA-18 total score of 43 (36, 54) suggestive of a low impact on quality of life (QOL). Significant reductions were noted post-RME to 28 (23, 35), p=0.004.

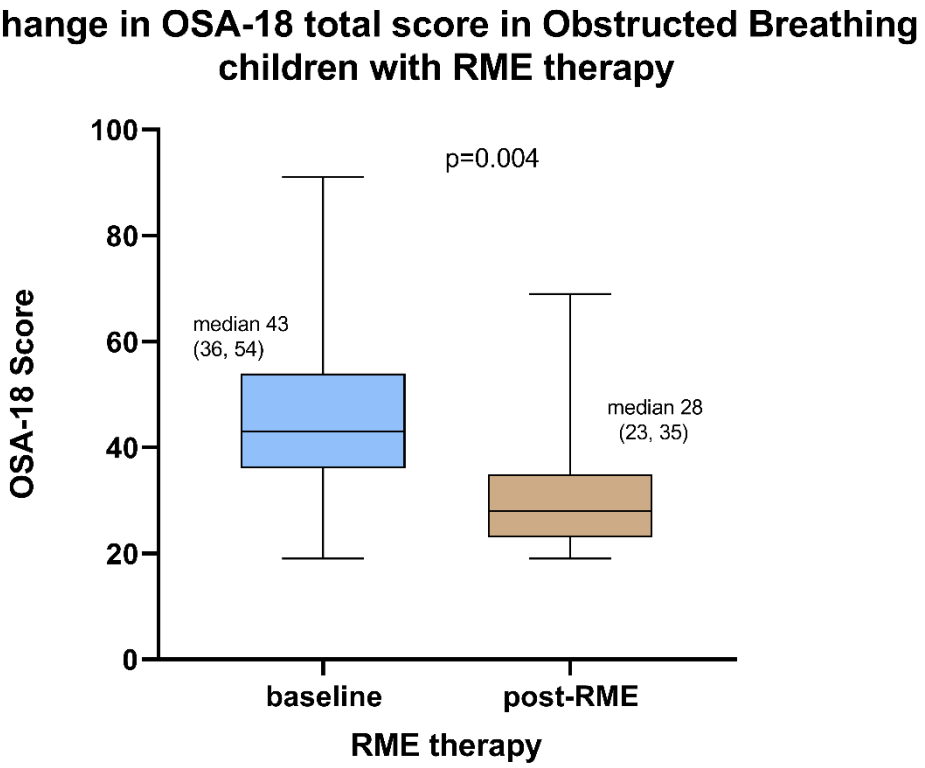


Figure 4.15 The change in OSA-18 Total scores with RME therapy in Obstructed Breathing children (n=23). A significant reduction was noted in total scores following RME (43 (36, 54) vs 28 (23, 35), p=0.004).

Table 4.19 shows the change in OSA-18 total scores in the OB group over 5 domains (sleep disturbance, physical suffering, emotional distress, daytime problems, caregiver concerns). Overall, small but significant improvements were noted in the questions assessed across the 5 domains. Notable changes were seen in the domain of sleep disturbance with significant improvements noted in the questions improvements in ".. loud snoring" (4 (2, 5) vs 2 (1, 3), p=0.0005), "breath holding spells…" (1 (1, 3) vs 1 (1, 2), p=0.014), "choking and gasping while sleeping" (1 (1, 3) vs 1 (1, 1), p=0.002) were noted. In the domain of physical suffering, "mouth breathing…" significantly improved (4 (3, 6) vs 2 (1, 4), p<0.0001). Of note, "aggressive and hyperactive behaviour" reduced (2 (1, 4) vs 1 (1, 2) but this was not significant (p=0.09). However, "poor attention span and concentration" domain improved significantly (2 (1, 3) vs 1 (1, 3), p=0.03).

TABLE 4.19 TOTAL AND DOMAIN OSA-18 SCORES PRE AND POST-RME IN OBSTRUCTED BREATHING CHILDREN.

Domain	Baseline	Post RME	p value
Sleep disturbances			
…loud snoring?	4 (2, 5)	2 (1, 3)	0.0005
…breath holdings spells or pauses in breathing at night?	1 (1, 3)	1 (1, 2)	0.014
…choking or gasping while sleeping?	1 (1, 3)	1 (1, 1)	0.002
…restless sleep or frequent awakenings from sleep?	2 (1, 4)	2 (1, 3)	0.43
Physical suffering			
…mouth breathing due to nasal obstruction?	4 (3, 6)	2 (1, 4)	<0.0001
…frequent common colds or upper airway infection?	3 (1, 4)	2 (1, 3)	0.11
…nasal discharge or runny nose?	3 (2, 4)	2 (1, 4)	0.11
…difficulty swallowing foods?	1 (1, 2)	1 (1, 1)	0.42
Emotional distress			
…mood swings, temper tantrums?	3 (1, 4)	1 (1, 4)	0.31
…aggressive or hyperactive behavior?	2 (1, 4)	1 (1, 2)	0.09
…discipline problems?	1 (1, 3)	1 (1, 2)	0.39
Daytime problems			
…excessive daytime drowsiness or sleepiness?	1 (1, 3)	1 (1, 2)	0.19
…poor attention span or concentration?	2 (1, 3)	1 (1, 3)	0.03
…difficulty getting out of bed in the morning?	2 (1, 5)	1 (1, 4)	0.18
Caretaker concern			
…worried about the general health of your child?	2 (1, 4)	1 (1, 2)	0.03
…created a concern that your child is not getting enough air?	2 (1, 3)	1 (1, 1)	0.005
…interfered in your ability to perform daily activities?	1 (1, 2)	1 (1, 1)	0.12
…made you frustrated?	2 (1, 4)	1 (1, 3)	0.13
OSA-18 Total Score	43 (36, 54)	28 (23, 35)	0.004

Definition of abbreviations: OSA = Obstructive sleep apnea; RME = rapid maxillary expansion.

Table 4.19 Total and domain OSA-18 scores following RME therapy in the OB group. Significant improvements were noted in several domains (sleep disturbance, physical suffering, daytime problems, caregiver concerns). Small but significant improvements were observed in loud snoring (p=0.0005), breath holding (p=0.014), choking and gasping (p=0.002), mouthbreathing (p<0.0001). Notably, attention span and concentration improved (p=0.03). Overall, parents were less worried about their child's health (p=0.03) with perceived improvements in breathing noted (p=0.0005).

4.5 DISCUSSION

While it has been long postulated that a bi-directional association exist between craniofacial abnormalities and paediatric SDB (characterized by prolonged partial UAO) objective measurement of UAO in children pre and post-orthodontic intervention has not been routinely performed. This is the first prospective study to objectively quantify the effects of RME therapy on snoring, a robust indicator of partial UAO in children with maxillary constriction.

Our study recruited an unselected population of children referred by otolaryngologist/ primary care physician for orthodontic assessment of dental mal-occlusion. The children were non-obese with minimal tonsillar hypertrophy. A range of mild SDB symptoms were noted with the children requiring RME for orthopaedic correction of maxillary constriction. In our study, children with no significant SDB at baseline did not worsen post-RME as no increase in obstructive apnea/hypopneas variables or OB was noted. A small but significant decrease (16 vs 14 events/hr, p=0.02) in the frequency of spontaneous movement arousals was noted. The relevance of this finding on sleep quality is unclear and warrants further investigation.

All OSA children (n=4) had full resolution of OSA with RME. Although this is a very small sample size, this finding aligns with previous investigations on the efficacy of RME on paediatric OSA [275, 301, 303, 306]. These studies demonstrate therapeutic benefit with RME based on the AHI, but objective measurement of OB was not performed. Our observations of significant decrease in OB percentage and frequency of OB runs (p=0.04, p=0.05 respectively) in OSA children extends previous studies that have subjectively assessed snoring [275]. Children whose OSA resolved post-RME also snored significantly less during the night (24% vs 4%) with snoring frequency also significantly reduced (19 runs/hr vs 4 runs/hr, p=0.05) post-RME. In one OSA child with grade 3 tonsils, OSA resolved (MOAHI 6.3 vs 0.8 events/hr) with marked reduction of snoring (125 vs 28 mins). This is of clinical significance and highlights the potential role of RME for the treatment of snoring despite tonsillar enlargement. Although the duration of snoring decreased (101 vs 13 mins) in the OSA group, this was not statistically significant (p=0.06) and can be explained by the lower sample size. A larger study is thus warranted to further elucidate the effects of RME on snoring in OSA children.

In this study, OB runs were brief and were noted to occur in clusters. In OB children, RME resulted in significant reductions in the duration (33 mins vs 13 mins, p=0.03), percentage (7% vs 3%, p=0.05) and frequency of OB runs (9 runs/hr vs 4 runs/hr, p=0.03). Post-RME therapy, OB children exhibited approximately 60% reduction in OB duration, 61% in OB percentage and 55% reduction in the frequency of OB runs. These remarkable changes were predominantly attributable to snoring with no significant change in stertor observed.

Despite remarkable results in the majority, six OB children (26%) worsened in OB duration with residual snoring noted (range 25-164 mins at RME2) post-RME. The majority (83%) of these children (aged 9-14 years old) were past the peak age of lymphoidal hypertrophy with normal tonsillar size. This observation of significant residual snoring in OB children without tonsillar hypertrophy, obesity or maxillary constriction following RME is a key novel finding.

Although tonsillar hypertrophy [138], obesity [153] and maxillary constriction [41, 231] have been classically linked to paediatric OSA, our children did not exhibit these factors post-RME. This suggests that the correction of maxillary constriction with RME may not resolve snoring in a subset of children implying that other contributory factors may be at play and typifies the complex and multi-factorial nature of childhood SDB and its management.

There are several possible reasons for the residual snoring. One possible explanation could be that OB children recruited may represent a distinct phenotype with a non-anatomical pathophysiological mechanism. The contributory factors include high loop gain, low arousal threshold and diminished pharyngeal muscle function [439]. These factors could account in part to the residual OB noted. Another reason may be found in the way RME exerts its effect on craniofacial structures. Maxillary constriction is a key feature of chronic nasal obstruction and orthopaedic widening of the median palatal sutures have documented beneficial effects on OSA in adults [43] and children [275, 306]. These positive changes

are thought to be mediated by increase in nasal cavity width and volume [289, 440]. Rhinomanometric [441] and rhinometric studies show a decrease in nasal resistance following RME [442, 443].

Computational fluid dynamic imaging also show improvements in nasal airway ventilation [444] with decreases in pharyngeal pressures noted during inspiration [291]. CT imaging suggest that RME achieves its effect by increasing nasal volume [445]. However, although robust evidence suggests that the predominant effect of RME is in the nasal cavity, the influence on velo and oropharyngeal regions is unclear. Minimal changes have been reported in the retroglossal region [297, 445] but conflicting data exists in the retropalatal regions [297]. Thus, although RME corrects maxillary transverse discrepancy producing positive effects in the nasal cavity, these effects may not positively impact other potential sites of UAO in OB children that cause snoring.

In addition to maxillary constriction, our OB patients exhibited additional skeletal deficiencies in the sagittal and vertical dimension which were to be treated by supplementary orthodontic procedures post-RME. Sagittal and vertical growth differences have been documented to affect upper airway volumes [296]. This rationale is supported by CT studies that show significant decrease in the nasopharynx volume in Class II malocclusion as compared to normal controls [446] and patients with Class III malocclusion [447]. Retroglossal tongue base collapse which is characteristic of skeletal Class II patients with mandibular retrusion is common established factor [448, 449]. However, the downstream effects of RME in the nasopharynx [450] and oropharyngeal

region [296, 297] has not been demonstrated. Thus, although treatment of maxillary constriction can improve snoring in a large proportion of OB children, it can be speculated that other potential sites of UAO induced by craniofacial abnormalities such as maxillary or mandibular retrusion may account for residual snoring. This clearly has important orthodontic treatment implications. Further research of snore characteristics in subgroups of dental malocclusion is clearly warranted and may elucidate sites of skeletal imbalances that contribute to UAO.

A chance finding in this study was that two children identified with asthma at baseline worsened with RME therapy. Despite no OSA observed, wheezing duration worsened substantially (8 mins to 98 mins, 62 vs 200 mins) with small increases (1 and 10 mins) in snoring also observed. The reason for the increase in wheezing and snoring is unclear and may be co-incidental. Even though RME is not used for the treatment of asthma the correction of maxillary transverse discrepancies may improve SDB which may, indirectly, improve asthma. Previous studies have associated asthma with maxillary constriction [242-244] with snoring and OSA proposed as triggering mechanisms for asthmatic attacks [429]. Further RME research in a larger cohort of asthmatic children is clearly warranted. Of the two wheezing children, a high OSA-18 score (91) signifying a severe impact on quality of life was reported by one parent. However, both parents of these children were not aware that their children were experiencing nocturnal wheeze, despite having been diagnosed as having asthma. This finding highlights the unreliability of subjective parental reports in identifying wheeze [428] and OSA severity [427] and is of significant clinical relevance.

OB has previously been proposed to contribute to sleep fragmentation and interrupt sleep processes [106]. The improvements in OB metrics post-RME were associated with concomitant decreases in the duration (2.6 vs 0.9 mins, p=0.05), and number (19.0 vs 7.0 events, p=0.03) of respiratory induced movement arousals (Resp.MAr). Our findings that OB duration and runs are associated with sleep disruption at baseline and the Resp.MAr improvements noted post-RME are significant positive findings. These reductions in Resp.MAr observed suggest that children who snore less experience less sleep fragmentation and better sleep quality following RME. This is supported by the significant improvements observed in OSA-18 total score (46 vs 28, p=0.004) in OB children.

These results, an improvement in SDB (objectively measured snoring) and quality of life, differ to the findings in the CHAT study which showed poor correlation between SDB (measured by the AHI) and treatment outcomes. In this study, snoring was not quantified at all [433, 451]. Our study shows significant improvements in some domains of sleep disturbance, physical suffering and daytime concerns. Subjective parental assessment showed significant decrease in loud snoring (p=0.0005), choking and gasping (p=0.002), mouth-breathing (p<0.0001) post-RME. Notably, small but significant improvements (p=0.03) in the domain of attention and concentration was observed. However, improvements in aggressive and hyperactivity behavior was not significant (2 (1, 4) vs 1 (1, 2), p=0.09) and may be explained by sample size. These results highlight the recent work by Hunter and colleagues who found greater association between behavioral changes in children with mild SDB (habitual snoring with no OSA) [452]. Further research is thus needed to clarify these preliminary observations as although sleep fragmentation induced

by OB reduced with RME, the impact on the domains of behavior and cognitive function will require further investigation.

Overall, our findings of full therapeutic success in all OSA children confirms previous investigations that show significant improvement using the AHI and that RME may play an adjunctive role in OSA management in children [275, 303, 306]. However, when snoring was assessed objectively, a significant proportion of OB children had residual snoring despite RME. Using the criteria of full response of OSA and snoring resolution (MOAHI <1/hr, snore < 1%), therapeutic success was 26%. Partial response (MOAHI <1/hr, snore 1-9.9%) was noted in 56% of OB children. 17% of the children had no OSA but continued snoring ≥ 10% of sleep time. No complete failures (MOAHI ≥ 5, snore ≥ 10%) were noted in the group.

While standard PSG metrics report apnea and hypopneas, they do not capture periods of partial UAO such as snoring that are characteristic of paediatric SDB. This study proposes that the objective quantification of OB is warranted and should be implemented for diagnosis and treatment planning to improve clinical outcomes. Our observations of residual snoring post-RME has clinical implications as snoring has been linked to blood pressure at all levels of SDB severity [425]. Our data support the notion that the objective measurement of OB, not just AHI-linked events should be performed, as a complimentary measurement to AHI metrics to further clarify links to cardiovascular and treatment related outcomes.

Our study presents novel data on 10 stertorous children who snored. Although occurring rarely, two children presented with significant duration of stertor which improved dramatically (23 vs 0 mins, 53 vs 2 mins) following RME. In most stertorous children, despite improvement in snoring, 50% had residual snoring (>20 mins). This finding of unresolved snoring with RME in stertorous children has significant clinical implications and further research is warranted into the clinical outcome of stertor.

Limitations include the inability to monitor sleep position and the lack of EEG to stage and identify sleep and arousal. However, previous work by Norman and colleagues have confirmed a close relationship between quiescent time and EEG-defined sleep as well as the accurate calculation of the MOAHI [105], and the use of body movement has demonstrated to be a robust indicator of sleep disturbance [431]. The utilization of oximetry would undoubtedly have provided a fuller picture of SDB but this requires attachment to the body and can be problematic, particularly so in a child in the home setting. Transcutaneous carbon dioxide measurement may provide a better indicator of the flow on effects of obstructed breathing but also requires physical attachment to a child [432].

Although only 4 OSA children were recruited in this study, our primary aims were to investigate paediatric SDB by measuring OB, not specifically OSA, in children with maxillary constriction. Thus, our cohort of children included wide age variability with 10 children above the age of 12 years old. This is however representative of clinical orthodontic practice whereby parents often only seek orthodontic treatment when dental

mal-alignment becomes more visible. Future work involving a larger sample will undoubtedly shed more light on the effects of RME on OB in OSA children. In our study, it is important to highlight the RME1 studies were performed with RME in situ whereas RME2 occurred after RME removal. Thus, the results at RME1 should be interpreted with caution due to the potential reduction of oral tongue volume caused be the RME. Moreover, the confounding effect of posterior rotation of the mandible due to the thickness of the bonded RME warrants consideration. Collectively, these RME device specific factors may be speculated to increase UAO due to adverse effects on tongue posture and tone. Finally, a limitation and strength of our study is the wide interval between RME1 and RME2 studies. Our results at RME2 (mean 281 days) is a strong contrast to the literature whereby most RME studies conducted are of a shorter term. The extended time taken to perform sleep studies in our children is reflective of the clinical barriers encountered in coordinating sleep studies in children. Parents of children studied were noted to be chiefly motivated by orthodontic concerns and to a lesser extent by sleep-related issues. These may be as a result of the subclinical symptoms noted in our children studied. Nonetheless, the results at RME2 add to the field in relation to the effects of RME in the longer term.

4.6 CONCLUSION

Although few children in this cohort had OSA, a significant proportion exhibited OB with snoring the predominant feature. Many runs of OB terminated in body movements, thus, many children that may be classified as habitual snorers without OSA may have significantly fragmented sleep. RME therapy substantially improved obstructed breathing in the majority of children with resolution of OSA in all children with OSA. However, a significant proportion of children had a worsening of snoring following RME. Thus, objective measurement of OB may help in determining effectiveness of RME in treating SDB and further clarify the downstream effects of paediatric SDB.

5 QUANTITATIVE MEASUREMENT OF SNORING IN PATIENTS REFERRED FOR MANDIBULAR ADVANCEMENT SPLINT THERAPY

5.1 Introduction

In the last decade, mandibular advancement splint (MAS) therapy has been increasingly popular and has emerged as a viable treatment alternative to continuous positive airway pressure (CPAP) for the treatment of snoring and obstructive sleep apnea (OSA) [271, 314, 321]. Although a strong evidence based exists demonstrating its therapeutic efficacy across a wide range of OSA severity, MAS may not be efficacious for all patients with approximately one-third of patients experiencing no therapeutic benefit at all [315].

Assessment of MAS treatment success has historically been reliant on polysomnography (PSG), the presumed "gold standard" for diagnosis and has been predominantly defined by one metric, the apnea hypopnea index (AHI). The definitions of MAS treatment success reported in the literature are based on the reduction of the AHI, rather than a normalization, with or without other measures of symptomatic improvement. Snoring, a cardinal sign and symptom of OSA has not been investigated in a systematic method for patients undergoing MAS therapy. Moreover, the therapeutic effects of MAS on snoring and OSA patients are poorly understood.

Most patients that snore, or those diagnosed with OSA, frequently present in the clinical setting with disruptive snoring as a chief complaint. However, the consequences of snoring have often been trivialized with objective measurement of snoring not routinely performed. The assessment of snoring prior to treatment and with MAS has been predominantly subjectively based, often with the use of questionnaires or bed-partner/spousal reports [342]. There are few studies that objectively measure snoring at all in patients referred for MAS [119]. Pooled data from a review of multiple MAS devices, involving varying methodologies in snore measurement document a reduction of 45% in snoring [342]. To date, there exist minimal data that objectively measure snore duration and snore types in MAS patients.

5.2 Aim

The aim of this study was to objectively measure baseline snore duration and snore characteristics in primary snorers (PS) and OSA patients prior to MAS treatment.

5.3 MATERIALS AND METHODS

5.3.1 MAS Study Participants

One hundred and fourteen consecutive MAS naive patients referred from sleep physicians/otolaryngologist for MAS therapy were recruited into this study. All participants in the study paid full fees for their MAS and treatment reviews independent of any financial support from industry. The study population consisted of 81(71%) male and 33(29%) female, age = 51.0 ± 12.9 years (range 22-77 years) with BMI = 28.5 ± 4.4 kg/m^2,

(range 19.3-40.3). All patients in this chapter progressed to the next stage of investigations involving progressive mandibular advancement with MAS therapy (Chapter 6).

Baseline characteristics of these 114 patients are summarized in Table 5.1. Most patients had previously undergone a full PSG study after consulting a sleep physician or otolaryngologist. These patients were diagnosed with OSA or as being snorers (negative PSG result with a history of snoring). Some patients, however, presented without a formal PSG diagnosis despite having been clinically and naso-endoscopically assessed by the referring otolaryngologist. Importantly, snoring was noted in the majority of patients and was also the chief reason patients sought intervention with MAS. Some patients had undergone a trial of CPAP but found this mode of therapy intolerable and several had refused CPAP in the first instance. Overall, most patients were noted in the clinical history as "socially disruptive snorers" by the referring clinician with or without mild to moderate OSA.

The inclusion criteria for the participants were: (1) evidence of OSA on PSG or at least two of the following symptoms: daytime sleepiness, witnessed apneas, snoring or fragmented sleep; (2) aged 20 years or older; and (3) the presence of at least 5 teeth remaining in either dental arch.

Exclusion criteria were (1) inability to protrude the mandible by at least 5 mm; (2) pre-existing lung disease; (3) psychiatric disease; (4) regular use of narcotics or sedatives; (5) periodontal disease; (6) shift work; (7) major medical illness; (8) temporomandibular joint dysfunction; (9) exaggerated gag reflex; (10) previous MAS treatment or a need for immediate treatment based on clinical judgement.

All study procedures were approved by with the Institutional Human Research Ethics Committee (Approval protocol No: 11476-2012/023) and written consent was obtained from all participants.

5.3.2 Study Design

All participants (n=114) were clinically assessed by PhD research clinician (JN) to evaluate suitability of MAS therapy. At the initial visit, patients were informed about MAS treatment and the treatment protocol involved (Chapter 6). Dental impressions were performed for all patients who met the eligibility criteria. Measurement of the range of mandibular protrusion was also performed. Using a George Gauge™ instrument [453], measurements were recorded for the most retrusive and protrusive position of the mandible. The protrusive range of mandibular advancement was thus established for each individual patient. To assess excessive daytime sleepiness, the Epworth Sleepiness Scale (ESS) [454] was completed by all subjects at baseline.

5.3.3 Sonomat™ Sleep Study

A diagnostic home sleep test with the Sonomat™ (see General Methods) was performed at baseline prior to MAS therapy. Patients slept in their own bed at home and the Sonomat™ was returned the following day. Patients were instructed on the use of the Sonomat™ and informed to avoid the use of alcohol or stimulants (e.g. caffeine) on the night of the study.

The Sonomat™ is a portable recording system, validated against polysomnography; containing sensors embedded in a mattress overlay with no requirement for sensor attachment. It detects breathing and body movements, breath sounds, snoring, apneas and hypopneas allowing generation of snoring indices and the apnea hypopnea index (AHI). Respiratory events, total snoring and the characterization of snore types (inspiratory, expiratory and combined inspiratory + expiratory (IE) snoring, (General Materials and Methods, section 2.2), were objectively quantified and are presented in this chapter.

Primary Snorers (PS) and OSA patients in this study were classified as follows: PS (AHI < 5 events/hr with snoring), mild OSA (AHI 5-14.9 events/hr), moderate OSA (AHI 15-29.9 events/hr), severe OSA (AHI > 30 events/hr).

5.4 RESULTS

5.4.1 Baseline characteristics of all patients (n=114)

Baseline characteristics of the 114 adult patients are presented in Table 5.1 There were 81(71%) male and 33(29%) females, age = 51.0 ± 12.9 years (range 22-77 years), BMI = 28.5 ± 4.4 kg/m^2, (range 19.3-40.3) in the study population. The AHI was 9.3 (6.3, 14.4) events/hr with fewer obstructive apneas (OAI = 0.2 [0.0,1.0] events/hr) than obstructive hypopneas (OHI = 8.3 [5.5, 12.9] events/hr). The respiratory movement index (RMI) was 10.9 (2.9, 21.3) events/hr.

TABLE 5.1 BASELINE CHARACTERISTICS of ALL PATIENTS (n=114)

Variable	All Patients
Gender	81M, 33F
Age, yr	51.0 ± 12.9 (range 21-77)
BMI, kg/m^2	28.5 ± 4.4 (range 19.3-40.3)
Neck circumference, cm	39.6 ± 4.2 (range 30-55)
Epworth sleepiness scale	6.0 (3.0,10.0) (range 0-18)
Maximum Protrusion, mm	10.0 (9.0, 12.0) (range 5-14)
AHI, events/hr	9.3 (6.3, 14.4)
OAI, events/hr	0.2 (0.0, 1.0)
OHI, events/hr	8.3 (5.5, 12.9)
RMI, events/hr	10.9 (2.9, 21.3)
Total Snore, mins	95.5 (55.9, 183.4)
Total Snore %	24.7 (13.0, 44.8)
Inspiratory Snore, mins	84.8 (44.8, 155.3)
Inspiratory Snore %	19.8 (11.4, 38.4)
Expiratory Snore, mins	1.9 (0.4, 7.0)
Expiratory Snore, %	0.4 (0.1, 1.7)
IE Snore, mins	2.3 (0.5, 9.9)
IE Snore %	0.6 (0.1, 2.7)

Definition of abbreviations: M = male; F = female; BMI = body mass index; AHI = apnea+hypopnea index; OAI = Obstructive Apnea Index; OHI = Obstructive Hypopnea Index; RMI = respiratory movement index; Total Snore % = Total Snore Percentage; IE = Inspiratory and Expiratory; Continuous data are presented Mean ± Standard deviation or Median (25th,75th interquartile range).

Table 5.1 Baseline characteristics of MAS patients (n=114). Patients were 51.0 ± 12.9 years old and overweight (BMI 28.5 ± 4.4 kg/m^2). Mild OSA (AHI 9.3 (6.3, 14.4) events/hr) was observed. Snoring occurring for 95.5 (55.9, 183.4) minutes accounting for 24.7% (13.0, 44.8) of quiescent time. Inspiratory snoring was the predominant type with expiratory and IE snoring minimal.

5.4.2 Duration of Snoring and Snoring Types

Snoring data for the entire group is presented in Table 5.1 above. Total snoring occurring for 95.5 (55.9, 183.4) minutes accounting for 24.7% (13.0, 44.8) of quiescent time (Qd).

Of interest, inspiratory snoring was the predominant type (84.8 [44.8, 155.3] minutes) noted, representing 19.8% (11.4, 38.4) of Qd. In contrast to inspiratory snoring, both expiratory snoring and IE snoring occurred less frequently (Exp. snoring = 1.9 (0.4, 7.0) minutes at 0.4% (0.1,1.7) of Qd; IE snoring = 2.3 (0.5, 9.9) minutes at 0.6% (0.1, 2.7) of Qd).

5.4.3 Baseline characteristics of Primary Snorers (n=19) vs OSA patients (n=95)

Primary snorers (PS) and OSA patients were classified based on AHI metric (section 5.3.3). Of these 114 patients there were 19 (16.7%) PS and 95 (83.3%) OSA patients (PS and OSA groups shown in Table 5.2). The obstructive hypopnea index (OHI) was significantly greater in OSA patients (OSA = 9.2 (6.8, 14.1) events/hr vs PS = 1.8 (0.5, 3.0) events/hr, $p<0.0001$). In contrast, the obstructive apnea index (OAI) was not significantly different between PS and OSA patients (0.1 (0.0, 0.3) event/hr vs 0.2 (0.0, 1.2) events/hr, $p=0.08$) highlighting that the predominant respiratory events were not complete obstructive events. Not surprisingly, significant differences in the AHI were found between OSA and PS groups (OSA = 10.9 (8.0, 15.7) events/hr vs PS = 1.9 (1.3, 3.2) events/hr; $p<0.0001$).

There were no significant differences between the PS and OSA groups with respect to the duration and percentage of total snoring, anthropomorphic measurements or other sleep variables. Additionally, no significant statistical differences were noted in the duration of

inspiratory (79.8 (52.7, 111.5) mins vs 84.8 (44.2, 155.5) mins, p=0.74), expiratory (0.8 (0.3, 12.3) mins vs 1.9 (0.6, 7.0) mins, p=0.51) and combination IE snoring (3.1 (0.4, 15.1) mins vs 1.9 (0.5, 9.7) mins, p=0.66).

Although OSA patients tended to snore for longer in duration as compared to PS (OSA = 95.7 (53.3, 184.7) mins vs PS = 86.3 (57.7, 166.8) mins), the duration was not statistically significant (p=0.86).

TABLE 5.2 BASELINE CHARACTERISTICS OF PRIMARY SNORERS AND OSA PATIENTS (n=114)

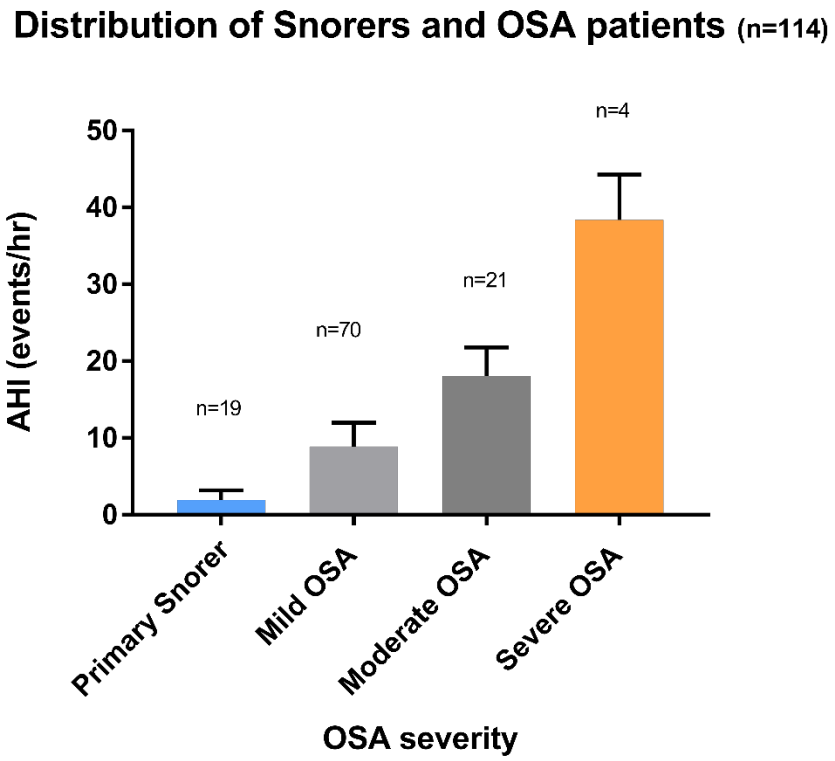
Variable	Primary Snorers (AHI < 5) (n=19)	OSA group (AHI ≥ 5) (n=95)	p value
Gender	12M,7F	69M, 26F	0.41
Age, yr	48.5 ± 15.3 (range 21-70)	51.5 ± 12.4 (range 21-77)	0.36
BMI, kg/m^2	27.2 (25.9, 30.7) (range 20.3-40.3)	28.9 (25.0, 31.3) (range 19.7- 38.6)	0.53
Neck circumference, cm	38.5 ± 3.7 (range 31-44)	39.9 ± 4.3 (range 30.55)	0.20
Epworth sleepiness scale	6 (3, 12) (range 2-15)	6 (3, 10) (range0-18)	0.54
Maximum Protrusion, mm	10.0 (9.0, 11) (range 8-15)	10.0 (9.0, 12.0) (range 5-14)	0.13
Analysis Time, mins	450.9 (377.9, 514.0)	452.1 (408.0, 497.5)	0.62
Qd Time, mins	432.5 (363.3, 464.6)	428.9 (386.5, 470.4)	0.79
AHI, events/hr	1.9 (1.3, 3.2)	10.9 (8.0, 15.7)	<0.0001
OAI, events/hr	0.1 (0.0, 0.3)	0.2 (0.0, 1.2)	0.08
OHI, events/hr	1.8 (0.5, 3.0)	9.2 (6.8, 14.1)	<0.0001
RMI, events/hr	6.2 (1.8, 16.0)	11.1 (3.0, 21.4)	0.49
Total Snore, mins	86.3 (57.7, 166.8)	95.7 (53.3, 184.7)	0.86
Total Snore %	21.2 (13.1, 44.3)	25.0 (12.8, 44.9)	0.94
Inspiratory Snore, mins	79.8 (52.7, 111.5)	84.8 (44.2, 155.5)	0.74
Inspiratory Snore %	19.1 (12.2, 31.4)	22.0 (10.8, 40.3)	0.85
Expiratory Snore, mins	0.8 (0.3, 12.3)	1.9 (0.6, 7.0)	0.51
Expiratory Snore, %	0.2 (0.1, 2.8)	0.4 (0.1, 1.6)	0.61
IE Snore, mins	3.1 (0.4, 15.1)	1.9 (0.5, 9.7)	0.66
IE Snore %	0.7 (0.1, 3.8)	0.5 (0.1, 2.7)	0.56

Definition of abbreviations; BMI = body mass index; Qd= quiescent; AHI = apnea + hypopnea index; OAI = Obstructive Apnea Index; OHI = Obstructive Hypopnea Index; RMI = respiratory movement index; Total Snore % = Total Snore Percentage; IE Snore = Inspiratory and Expiratory snore. Continuous data are presented Mean ± Standard deviation or Median (25^{th},75^{th} interquartile range).

Table 5.2 Baseline characteristics of Primary Snorers and OSA patients (n=114). The OHI was significantly greater in OSA patients (9.2 (6.8, 14.1) vs 1.8 (0.5, 3.0) events/hr, p<0.0001). In contrast, the OAI was not significantly different between PS and OSA patients (0.1 (0.0, 0.3) vs 0.2 (0.0, 1.2) events/hr, p=0.08). Snoring duration, percentage and types did not differ significantly between the groups.

5.4.4 Distribution of Snorers and OSA patients

Figure 5.1 shows the distribution of PS and OSA patients in the study. Of the 95 with OSA 70/114 (74%) had mild OSA, 21 (22%) had moderate OSA and 4 (4%) had severe OSA.



Data presented as median and maximum range.

Figure 5.1 The distribution of Primary snorers (PS) and OSA patients at baseline (n=114). The majority of patients were in the mild/moderate OSA category (n=91, 80%) and the 4 severe OSA patients were CPAP intolerant. The 19 PS were also recruited with the chief complaint of disruptive snoring noted by the bed partner.

5.4.5 Apnea Hypopnea Index (AHI) in Primary Snorers and OSA patients

The AHI in primary snorers (PS) and OSA patients are presented in Table 5.3 below.

TABLE 5.3 AHI OF PRIMARY SNORERS AND OSA PATIENTS AT BASELINE

	Primary Snorers (n=19)	Mild OSA (n=70)	Moderate OSA (n=21)	Severe OSA (n=4)
AHI (events/ hour)				
Median	1.9	8.0	18.0	38.4
Interquartile range	(1.3, 3.2)	(5.1, 12.0)	(15.5, 22.0)	(33.4, 44.3)

Definition of abbreviations: AHI = Apnea Hypopnea Index; Continuous data are presented as Median (25^{th},75^{th} interquartile range).

Table 5.3 Baseline AHI of Primary Snorers and OSA patients. The participants were predominantly mild to moderate OSA patients (n=91). Only 4 severe OSA patients were recruited, this group had a median AHI of 38.4 (33.4, 44.3) events/hr.

5.4.6 Snore duration in Primary Snorers and OSA subgroups at baseline

Table 5.4 summarizes and Figure 5.2 illustrates the snoring characteristics of PS and OSA patients. Snoring was noted to occur in all groups of patients spanning the spectrum of primary snorers, mild/moderate and severe OSA.

5.4.6.1 Total Snoring

Our results show similar levels of total snoring in PS, mild and severe OSA subgroups, (86.3 (57.7, 166.8) mins vs 85.8 (53.1, 179.0) mins vs 88.8 (20.1, 251.6) mins respectively. Of key interest, a notable increase in total snoring was observed in the group with moderate OSA, (160.2 (77.3, 212.8) mins). The duration was approximately 1.9 times more as compared to the other subgroups. Nonetheless, despite the increase in snoring noted, the differences across all groups were not statistically significant, (p=0.36).

5.4.7 Snore types in Primary Snorers and OSA subgroups at baseline

A novel aspect in this study was that snoring was sub-categorized into 3 snore types: inspiratory, expiratory and IE snoring. Of interest, inspiratory snoring was noted to be the predominant snore type in both PS and all OSA subgroups (mild/moderate/severe). Expiratory and IE snore types were less prevalent and of shorter duration in all groups. (Table 5.4 and Fig 5.2).

5.4.7.1 Inspiratory Snoring

In PS and all OSA subgroups, inspiratory snoring was the predominant snore type observed. Inspiratory snoring was similar in duration in PS, mild and severe OSA

subgroups, (79.8 (52.7, 111.5) mins vs 76.7 (44.1, 145.9) mins vs 76.3 (4.1, 245.8) mins respectively. However, notably more inspiratory snoring was observed in the moderate OSA group, (122.6 (59.2, 202.6) mins), approximately 1.6 times more as compared to the other subgroups. However, the differences between subgroups were not statistically significant, (p=0.51).

5.4.7.2 Expiratory Snoring and combined Inspiratory + Expiratory (IE) Snoring

By way of contrast, in primary snorers and all OSA subgroups, there was significantly less expiratory and IE snoring noted. The median absolute values (range 0.8-7.3 mins) were remarkably smaller as compared to median inspiratory snoring values (range 76.3-122.6 mins). Moderate OSA patients had more IE snore duration at 6.5 (0.6, 17.6) minutes as compared to PS, mild and severe OSA groups, (3.1 (0.6, 15.1) mins vs 1.8 (0.5, 6.1) mins vs 2.3 (0.6, 8.2) mins, respectively). However, this was not statistically significant, (p=0.72).

Severe OSA patients had slightly more expiratory snore times of 7.3 (0.5, 15.8) minutes as compared to PS, mild and moderate OSA groups, (0.8 (0.3, 12.3) mins vs 2.0 (0.3, 7.0) mins vs 1.7 (1.1, 5.4) mins, respectively). These differences were again not statistically significant, (p=0.86). (Table 5.4 and Fig 5.2).

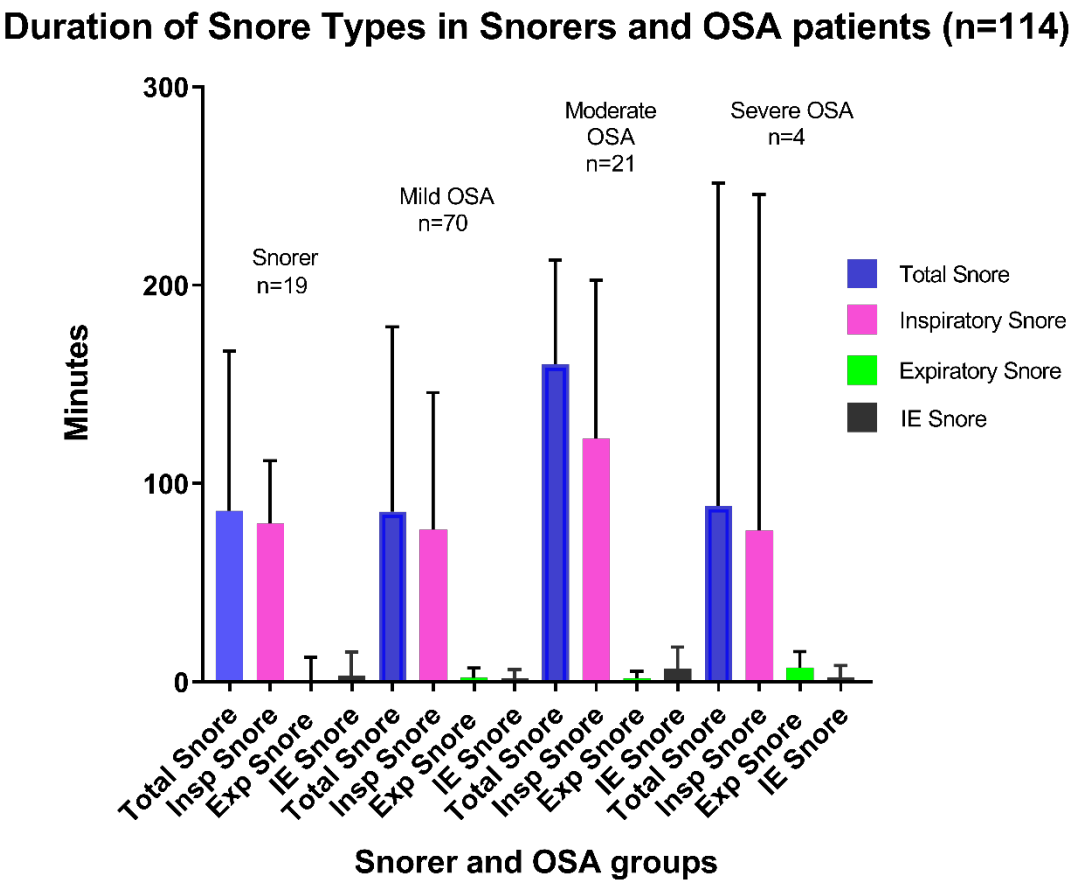
The duration of snoring and all snore types (inspiratory, expiratory, and IE snoring) for PS and OSA subgroups are presented in stratified fashion based on OSA severity (Table 5.4 and Fig 5.2).

TABLE 5.4 DURATION OF SNORING AND SNORE TYPES FOR PRIMARY SNORERS AND OSA GROUPS AT BASELINE

Snoring (mins)	Primary Snorers (n=19)	Mild OSA (n=70)	Moderate OSA (n=21)	Severe OSA (n=4)	p value
Total Snoring (mins)					
Median	86.3	85.8	160.2	88.8	0.36
Interquartile range	(57.7, 166.8)	(53.1, 179.0)	(77.3, 212.8)	(20.1, 251.6)	
(min, max)	(19.2, 300.0)	(0.1, 362.0)	(8.4, 306.0)	(19.7, 283.2)	
Inspiratory Snoring (mins)					
Median	79.8	76.7	122.6	76.3	0.51
Interquartile range	(52.7, 111.5)	(44.1, 145.9)	(59.2, 202.6)	(4.1, 245.8)	
(min, max)	(0.0, 264.8)	(0.1, 333.2)	(0.0, 296.7)	(3.4, 278.9)	
Expiratory Snoring (mins)					
Median	0.8	2.0	1.7	7.3	0.86
Interquartile range	(0.3, 12.3)	(0.3, 7.0)	(1.1, 5.4)	(0.5, 15.8)	
(min, max)	(0.0, 58.5)	(0.0, 78.4)	(8.4, 306.0)	(0.5, 15.8)	
IE Snoring (mins)					
Median	3.1	1.8	6.5	2.3	0.72
Interquartile range	(0.6, 15.1)	(0.5, 6.1)	(0.6, 17.6)	(0.6, 8.2)	
(min, max)	(0.0, 36.2)	(0.0, 86.5)	(0.0, 64.6)	(0.5, 9.7)	

Definition of abbreviations: Total Snoring = Total of Inspiratory, expiratory & IE Snoring; IE = Inspiratory and Expiratory; mins= minutes; min, max= minimum and maximum; data presented as median and interquartile range. Continuous data are presented as Median (25^{th},75^{th} interquartile range).

Table 5.4 Duration of Snoring and Snore types in PS and OSA groups at baseline. In PS and all OSA subgroups, inspiratory snoring was the predominant snore type noted. Although total snoring, inspiratory and IE snoring was observed to occur more in the moderate OSA group, this was not statistically significant (p=0.36, p=0.51, p=0.72 respectively). The severe OSA group demonstrated small but longer duration in expiratory snoring as compared to other subgroups but this was also not statistically significant (p=0.86).



Definition of abbreviations: Total Snore = Total of Inspiratory, Expiratory & IE Snore; Insp Snore = Inspiratory Snoring; Exp Snore = Expiratory Snoring; IE Snore = Inspiratory and Expiratory Snoring; data presented as median and 75th interquartile range

Figure 5.2 The duration of snore types in PS and OSA patients at baseline (n=114). Moderate OSA patients tended to have more total snoring (primarily inspiratory snoring) as compared to PS, mild OSA and severe OSA patients. The duration of expiratory and IE snoring was significantly lower than inspiratory snoring in all groups. Moderate and severe OSA patients tended to have more of an expiratory component to their snoring than those with PS and mild OSA.

5.4.8 Correlation between Snoring duration, BMI and AHI

Figures 5.3 and 5.4 illustrate the relationships between total snoring duration with the body mass index (BMI) and the AHI. A moderately strong positive relationship was observed between snoring duration and BMI (r=0.30, p=0.0013), however, there was no relationship between snoring duration and the AHI (r=0.07, p=0.43).

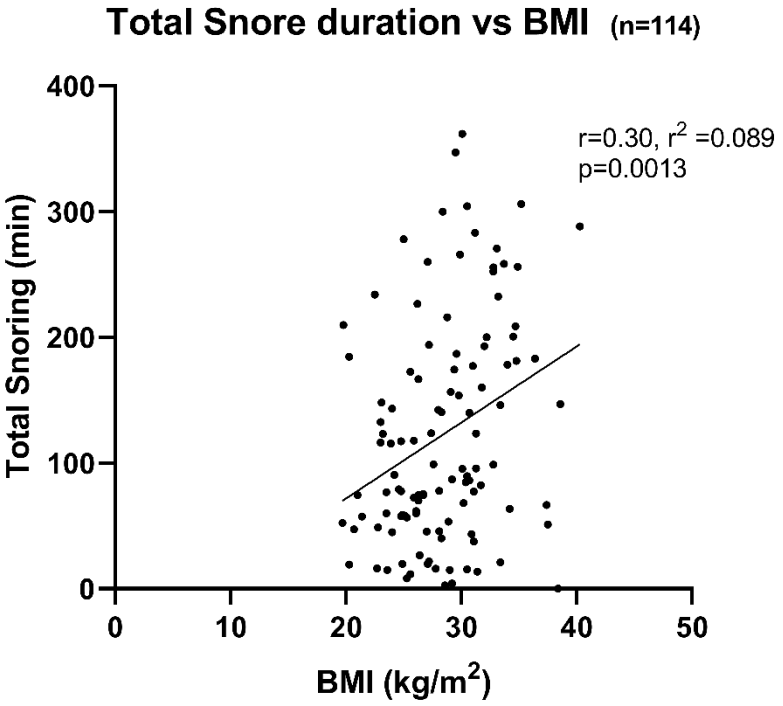


Figure 5.3 The relationships between total snoring duration and the body mass index (BMI). A statistically significant relationship was observed with increasing BMI associated with a longer snore duration (r=0.30, p=0.0013).

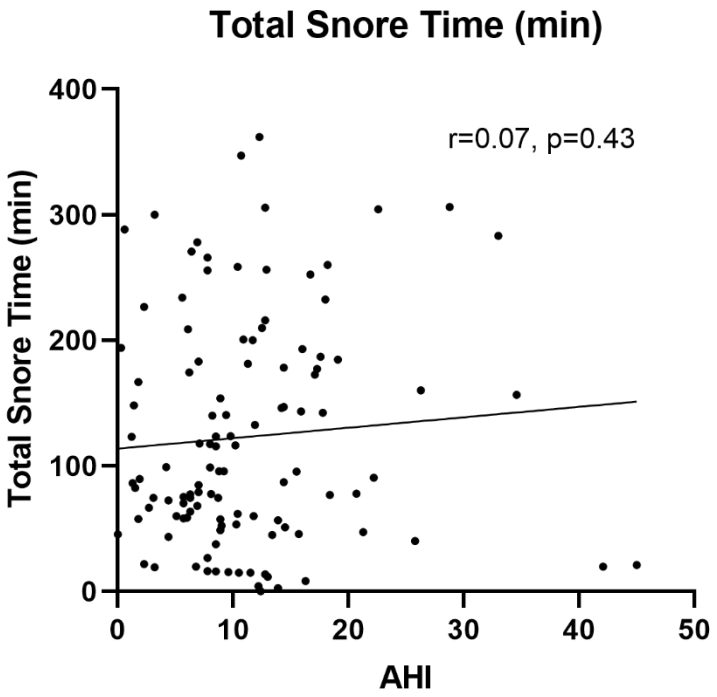


Figure 5.4 The relationships between total snoring duration and the apnea hypopnea index (AHI). No significant correlation was observed (r=0.07, p=0.43).

5.4.9 Baseline characteristics of Male and Female Patients

The baseline characteristics for male and female patients are summarized in Table 5.5 Females were significantly older (female = 55.4 ± 10.9 yrs vs. male = 42.2 ± 13.2 yrs, p=0.02), but males had a significantly larger neck circumference (male = 42.0 (40.0,43.0) cm vs female = 35.0 (32.3,36.7) cm, p<0.0001). Male patients were also noted to have a greater capacity for mandibular protrusion as compared to females, (male = 11.0 (10.0, 12.0) mm vs female = 10.0 (9.0, 10.0) mm, p<0.0001).

There were no significant differences in TST, Qd time, AHI, OAI, OHI and RMI across genders.

Total snoring duration was observed to be on average 62 minutes or 1.7 times more in female than male patients. However, the difference was not statistically significant, (female = 148.2 (58.3, 197.1) mins vs male = 86.3 (48.0, 158.4) mins, p=0.08). When total snoring was expressed as a percentage of Qd time, the trend towards statistical significance was also noted (female = 34.5 (13.5, 50.7) % vs male = 22.8 (12.8, 36.9) %). However, this difference was not statistically significant, (p=0.08).

Notably, sub-analysis of snore types revealed statistical differences in inspiratory snoring duration with females snoring 1.5 x longer during inspiration than males, (111.5 mins (57.4, 192.6) vs 75.3 mins (36.8, 138.7), p=0.02). Inspiratory snore percentage was also significantly more in female than males, (female = 22.2 (13.1, 46.5) % vs male = 17.2 (10.1, 33.1) %, p=0.04).

No significant differences were noted in expiratory snoring and IE snoring variables.

TABLE 5.5 BASELINE CHARACTERISTICS OF MALE AND FEMALE PATIENTS (n=114)

Variable	Male (n=81)	Female (n=33)	p value
Gender	81M (71.1%)	33F (28.9%)	-
Age, yr	42.2 ± 13.2 (range 21-77)	55.4 ± 10.9 (range 31-73)	0.02
BMI, kg/m^2	28.6 ± 4.0 (range 20.3-40.3)	28.2 ± 5.4 (range 20.3- 40.3)	0.65
Neck circumference, cm	42.0 (40.0, 43.0)	35.0 (32.3, 36.7)	<0.0001
Epworth sleepiness scale	6 (3, 10) (range 0-18)	6 (3, 12) (range 1-16)	0.65
Maximum Protrusion, mm	11.0 (10.0, 12.0) (range 7-15)	10.0 (9.0, 10.0) (range 4-12)	<0.0001
Study Time, mins	451.0 (397.1, 498.3)	457.1 (415.8, 499.0)	0.69
Qd Time, mins	425.9 (374.3, 472.3)	440.5 (389.7, 468.7)	0.54
PS/OSA group %	15% / 85%	21% / 79%	0.41
AHI, events/hr	9.4 (6.4, 15.0)	8.9 (5.8, 13.8)	0.27
OAI, events/hr	0.3 (0.0, 1.1)	0.1 (0.0, 0.9)	0.22
OHI, events/hr	5.0 (1.0, 12.0)	8.2 (4.3, 12.5)	0.34
RMI, events/hr	11.2 (3.6, 21.9)	8.1 (2.3, 17.2)	0.33
Total Snore, mins	86.3 (48.0, 158.4)	148.2 (58.3, 197.1)	0.08
Total Snore %	22.8 (12.8, 36.9)	34.5 (13.5, 50.7)	0.08
Inspiratory Snore, mins	75.3 (36.8, 138.7)	111.5 (57.4, 192.6)	0.02
Inspiratory Snore %	17.2 (10.1, 33.1)	22.2 (13.1, 46.5)	0.04
Expiratory Snore, mins	1.9 (0.6, 7.1)	1.9 (0.1, 7.0)	0.60
Expiratory Snore, %	0.4 (0.1, 1.9)	0.4 (0.0, 1.6)	0.57
IE Snore, mins	2.7 (0.4, 9.9)	2.1 (0.6, 12.8)	0.90
IE Snore %	0.6 (0.1, 2.8)	0.5 (0.1, 3.1)	0.87

Definition of abbreviations: M = male; F = female; PS = primary snorer; OSA= obstructive sleep apnea; BMI = body mass index; Qd = quiescent; AHI = apnea + hypopnea index; OAI = Obstructive Apnea Index; OHI = Obstructive Hypopnea Index; RMI = respiratory movement index; Total Snore % = Total Snore Percentage; IE Snore = Inspiratory and Expiratory snore. Continuous data are presented Mean ± Standard deviation or Median (25th,75th interquartile range).

Table 5.5 Baseline characteristics of Male and Female patients. Females were older (55.4 ± 10.9 yrs vs 42.2 ± 13.2 yrs, p=0.02), but males had a significantly larger neck circumference (42.0 (40.0, 43.0) cm vs 35.0 (32.3, 36.7) cm, p<0.0001). Male patients could also protrude their mandible more than female subjects (11.0 (10.0, 12.0) mm vs 10.0 (9.0, 10.0) mm, p<0.0001). Females had significantly more inspiratory snoring duration (111.5 (57.4, 192.6) mins vs 75.3 (36.8, 138.7) mins, p=0.02) and inspiratory snore percentage (22.2 (13.1, 46.5) % vs 17.2 (10.1, 33.1) %, p=0.04) than males.

5.1 DISCUSSION

This prospective study aimed to objectively measure and classify snoring in patients referred for MAS therapy. We used a non-contact diagnostic tool, the Sonomat™ (which has been validated against PSG) [105, 415] that provides objective measurement of snoring on a breath by breath basis in addition to the typical indices used to assess SDB. Of key interest in our investigation was the ability to objectively quantify snoring and sub-classify snoring into 3 snore types; namely inspiratory snoring, expiratory snoring and combined inspiratory and expiratory (IE) snoring.

We observed several novel findings in our investigation: 1) snoring was predominantly inspiratory with a median duration of 85 mins; 2) expiratory and IE snoring was found to be less prevalent and of shorter duration, (2 mins respectively); 3) moderate OSA patients snore twice as much as PS, mild and severe OSA patients; 4) females tended to snore more than males.

There are few studies in the literature that objectively measure snoring in MAS patients with the majority subjectively assessed by bed-partner/spouse or questionnaires [342]. Our results extend previous work that have investigated snoring in MAS patients [119, 120, 384]. Some of these studies utilized microphones with calibrated sound meters suspended about the beds and assessed snoring frequency (snores per hour) and snoring intensity in an in-lab setting [119, 120]. Others assessed snoring with home sleep testing but definitions of snoring were poorly defined [384]. These studies present limited baseline snoring data and

have recruited OSA patients. In contrast, our cohort of 114 consecutive patients referred for MAS therapy included PS and a broad spectrum of OSA patients. The majority were mild/moderate OSA with only four severe OSA patients who were CPAP intolerant. Our cohort of patients are thus representative of typical patients referred from an allied sleep specialist to a dental sleep clinic for MAS therapy.

A complaint of snoring from the bed-partner or spouse was often the main motivating factor for these patients seeking treatment. Although it has been widely accepted that snoring may be trivialized by a patient, particularly if he/she sleeps alone; snoring can cause sleep disruption to a bed-partner. Evidence support the significant disruptive effects snoring can play on the sleep quality of bed partners [455]. Thus, it came as no surprise that the instigation for MAS therapy in our group stemmed from a snoring complaint from a bed-partner. In fact, we noted that our study group were generally quite unperturbed by daytime somnolence only registering low ESS scores (median score 6/24). Moreover, few patients presented with concerns about frequent episodes of cessation of breathing and this was borne out with relatively few obstructive events observed; most had mild/moderate OSA severity. As expected, patients with more severe OSA reported gasping or choking during sleep or bedpartners reported witnessed apneas more frequently. Notable in our group, the median AHI was 9.3 events/hr with few complete apneic events found when compared to obstructive hypopneic events. This observation suggests that obstructive hypopneas were the predominant form of airway compromise and supports previous observations that patients with milder OSA severity have less upper airway collapsibility as typified by obstructive hypopneas as compared to obstructive apneas [456].

As a group, patients referred for MAS therapy snored for over 1.5 hours in duration accounting for approximately 25% of total sleep time. This observation of significant levels of snoring has important clinical implications. OSA has historically been proposed as a progressive snorers disease [59, 60], however, snoring in its own right has been linked to cerebro-vascular disease including hypertension [457, 458], cerebral infarction [66, 68] and increased incidence of diabetes [73]. Snoring is characterized by oscillations/vibrations of the soft palate, pharyngeal walls, tongue and epiglottis. Howitt and investigators hypothesized that vibrations from snoring result in oscillatory pressure waves that may be transmitted from the upper airway lumen to the peri-pharyngeal tissues and across to the carotid artery wall [83]. Both animal [81] and human studies have highlighted that exposure to vibrational stimuli can lead to pathological damage to endothelial cells in the arterial walls [459, 460]. These findings may have implications for carotid atherogenesis and/or plaque rupture and has been hypothesized to lead to an inflammatory cascade leading to changes associated with early atherosclerosis.

Recent evidence has associated heavy snoring to the formation of carotid artery atherosclerosis. Lee and colleagues hypothesized that snoring could constitute a risk factor for the presence of carotid atherosclerotic plaques [69]. Categorization of 110 subjects into 3 snoring groups was performed: mild (0%-25% night snoring), moderate (> 25%-50% night snoring), and heavy (>50% night snoring). The prevalence of carotid atherosclerosis was 20% with mild snoring, 32% with moderate snoring, and 64% with heavy snoring. The authors concluded that heavy snoring significantly increases the risk of carotid atherosclerosis, and the increase is independent of other risk factors, including measures of nocturnal hypoxia and OSA severity. Although oximetry was not performed in our study,

elevated percentages of snoring in our patients during the night (PS group 21%, OSA group 25% of TST) was observed with several subjects snoring in excess of 40% of the night. Thus, based on the snoring criteria proposed by Lee et al., the potential for a 20%-32% prevalence of carotid atherosclerosis in our study group can be speculated and warrants closer investigation.

Of novel interest in our study, snoring was classified based on when it occurred within the respiratory cycle. Inspiratory snoring was the predominant snore type observed with expiratory and IE snoring occurring much less frequently in the entire group. The finding is of clinical interest. Craniofacial morphology has been associated with breathing patterns [41] and variations in growth patterns have been linked to airway size and breathing mode [296]. Mouth-breathing can increase upper airway collapsibility [461] and in fact the degree of obstruction may differ between inspiration and expiration [462]. A cineradiographic study shows different patterns of snoring during inspiration through the nose and mouth. During inspiratory snoring through the nose, the soft palate was noted to be in close contact to the back of the tongue with only the uvula observed to oscillate. In contrast, snoring through the mouth resulted in the whole soft palate oscillating [463]. Thus, breathing mode may contribute to variations in airflow limitation and result in the differences in snore types noted. In our study, a small increase in expiratory snoring in severe OSA patients was observed. This may be explained by the changes in pharyngeal calibre in the breathing cycle. A CT study showing decreased cross-sectional diameter at the level of the uvula (oropharyngeal) in severe OSA patients during expiration [464] provides a plausible explanation. Further analysis of snore types and craniofacial

characteristics may potentially screen patients susceptible to SDB and identify sites of UAO. This is a clinical imperative and warrants further investigation.

In our study, we noted that despite the different AHI values across the OSA severity range, there was no significant difference in snoring duration and snore types between PS and OSA severity. However, a study by Liistro and colleagues reported different patterns of snoring between OSA subjects and heavy snorers [465]. These differences noted in supraglottic pressures and flow rates between non-apneic and OSA patients may explain the increases in obstructive hypopneas observed. We observed no significant differences between groups with respect to gender, age, BMI and neck circumference.

The similarities in these variables may suggest that PS and OSA patients recruited in our study population were essentially similar and that a complex interplay between other contributory factors may preside to influence individual variations in UAO and AHI noted. Craniofacial abnormalities such as maxillary constriction[44], body position [135], mandibular and hyoid position [248, 466] and ethnicity [467] have been implicated in SDB in adults. Other non-anatomical pathophysiological traits such as respiratory dilator muscle insufficiency, low arousal threshold and high loop gain, may also play a part in these findings [172].

Notable in subgroup analysis, moderate OSA patients snored 1.8 times more than PS and mild/severe OSA groups. This was principally attributable to inspiratory snoring which occurred 1.5 times more, and to a smaller extent, IE snoring which was more than double

in duration than the other groups. These observations in moderate OSA patients is not surprising when we consider that as upper airway collapsibility increases, the decrease in pharyngeal lumen size may account for increases in snoring. Histological evidence showing plasma cell infiltration and interstitial oedema in the uvula mucosa of moderate OSA patients lend support to this theory of increased snoring mediated by inflammatory response [468]. Additionally, as OSA severity worsens from moderate to severe category, the increased frequency of respiratory events could potentially decrease the time available for snoring resulting in decrease in snoring as observed. However, despite the trends to increased duration, the differences were not significant.

Soft tissue neurogenic injury [469] and peripheral afferent nerve damage [470] may also account for the differences in snore characteristics noted and cause increased upper airway collapsibility. Snoring causes vibrational trauma and can result in soft tissue oedema in the soft palate and surrounding tissue structures. These inflammatory changes induced by chronic snoring may account for the changes in snoring noted. Some evidence to support this hypothesis can be found in imaging studies that show significant differences in soft tissue structures between PS and OSA patients. A longer [471] and thicker soft palate [464] in OSA patients as compared to non-apneic snorers has been reported. These localized soft tissue changes may further compromise upper airway patency, impair upper airway dilator muscle response and lead to changes in snore characteristics discussed.

Thus, while it is widely accepted that a complex interplay exists between hard and soft tissue structures that influence upper airway patency and OSA severity, the precise

mechanism that influences snoring characteristics is not clearly understood and requires further investigation. Already, investigation into the MAS effect on snoring caused by palatal flutter and tongue based obstruction has been explored [384] to prospectively identify key sites of UAO. Objective quantification of snoring and snore characteristics may shed more light on our understanding of the multi-level sites of potential collapse in the upper airway. More detailed analysis of sound characteristics will undoubtedly provide clarity about the phenotypic features in snoring patients.

Notable in our study, females snored more during inspiration, 1.5 times longer than males. Although no significant differences were noted in obstructive respiratory events, this finding of increased inspiratory snoring in females is noteworthy. The exact reason for this is unclear but there may be several plausible explanations. Females were older than men (55.4 years vs 42.2 years) with smaller neck circumferences (35.0 cm vs 42.0 cm). These may account for the differences noted as the role of neck circumference, fat deposition and hormonal changes in post-menopausal females have been implicated in SDB [21]. We found a moderate correlation between BMI and snoring duration but not with AHI. However, it has been suggested that females may be protected from developing OSA due to a less collapsible upper airway for any degree of obesity [472], with females having similar BMI and AHI to males in this cohort. This suggests that other factors may account for the snoring related gender differences. Lower facial heights and hyoid bone position differences between the sexes may be a possible reason for increased upper airway collapsibility [473]. Gender differences in pharyngeal length have also been reported to influence airway collapsibility [474]. Body position may impact tongue position and pharyngeal soft tissue attachment [475] and account for the differences in inspiratory

snoring observed. Tonsillar size, tongue posture, width of the soft palate and mandibular retrognathia have also been reported to contribute to differences between the sexes [476]. Thus, there are several gender differences in upper airway anatomy and tissue characteristics that are inter-related in a complex manner and these may contribute to the differences observed [472, 477].

As our study recruited more males than females, one might initially confirm a higher prevalence of SDB in men as previously reported [21, 472, 478]. However, another explanation for the older age in females seeking treatment could be that females were not significantly sleepier than men as observed in the similar ESS scores, but may complain about tiredness at a later age than men. Moreover, the social stigma and embarrassment of admitting to "socially disruptive" snoring may also delay women seeking treatment and translate to under-reporting and diagnosis. This is clinically relevant as snoring in females has been independently associated with hypertension and cardiovascular risk [74, 75]. Although it has been reported that females respond more favorably with MAS therapy [479], gender may not be robust predictor for treatment response [315]. Thus, gender specific investigations are warranted particularly from the snore perspective.

Our study has several potential limitations. Patients were referred by allied sleep specialist groups that had an interest in dental treatment for SDB. Hence, there may be a referral bias. In addition, many patients had a priori elected to use MAS as a treatment option instead of CPAP, leading to further potential sample bias. However, the chief aim of our study was to objectively investigate snoring in patients referred for MAS in a dental sleep clinic and we believe our participants are representative of this population. In our study only 4 severe OSA patients were recruited, thus, any conclusions regarding severe OSA

should be treated with caution. Nonetheless, a key strength of this study was the robust sample size (n=114) which recruited a broad spectrum of patients with PS and mild/moderate OSA severity patients. Another limitation was as the inability to monitor sleep and the lack of EEG to stage and identify sleep and arousal. However, previous work by Norman and colleagues have confirmed a close relationship between quiescent time and EEG-defined sleep as well as the accurate calculation of the AHI [105] and the use of body movement has demonstrated to be a robust indicator of sleep disturbance [431]. The utilization of oximetry would undoubtedly have provided a fuller picture of SDB. Also, assessment of sleep position may have clarified the effect of body habitus on snore type.

5.2 CONCLUSION

Objective measurement of snoring in patients referred for MAS therapy is not routinely performed. The duration of the three snore types and total snoring in patients referred for MAS therapy did not differ significantly between PS and OSA patients with inspiratory snoring predominant in all groups. No increase in snoring was found between PS and mild OSA, a trend to increase in snoring occurred from mild to moderate OSA (as upper airway obstruction worsens) and a decrease in snoring occurred from moderate to severe OSA (possibly as there is less time available to snore due to an increased frequency of apneic events). Women snored more during inspiration than did men although the total amount of snoring did not differ significantly. We aim to further assess changes in snoring characteristics during MAS therapy in consideration with other characteristics of upper airway structure and function.

6 THE EFFECT OF PROGRESSIVE MANDIBULAR ADVANCEMENT WITH MAS THERAPY ON SNORING AND OBSTRUCTIVE SLEEP APNEA

6.1 Introduction

Obstructive sleep apnea (OSA) is characterized by repetitive obstruction in the upper airway and is associated with serious adverse health outcomes including cardiovascular morbidity and mortality [11, 357]. Multi-factorial factors including anatomic and non-factors are thought to contribute to increased pharyngeal collapsibility. Increasingly, mandibular advancement splints (MAS) have been proposed as a viable treatment alternative to continuous positive airway pressure (CPAP) for OSA [314]. The therapeutic effect of MAS is thought to be mediated by improvements or stabilization of upper pharyngeal anatomy with mandibular advancement (MA) [327, 330]. These changes are thought to promote pharyngeal muscle activity and tonicity and induce improvements in upper airway mechanics [334, 335, 480, 481]. Despite lower treatment efficacy reported as compared to CPAP, the comparable health benefits observed [349, 482] are thought be attained due to increased patient compliance and nightly usage [316, 322].

The precise degree of MA required for therapeutic success is unclear. Some authors propose only minimal MA [405], whereas others advocate greater MA that show improvement in upper airway calibre [483] and treatment success [407, 484]. Given the

wide variability in treatment response, recent research with remote controlled mandibular positioners have been used to estimate the target level of MA required for optimal outcomes [394, 395]. Physiological studies have also shown a dose-dependent decrease in pharyngeal collapsibility [328] and decrease in optimal CPAP pressure requirements with progressive MA [410].

Previous investigations of MAS treatment efficacy have predominantly focused on sleep and breathing variables such as the AHI [271, 321] and levels of oxygen saturation [408]. However, there are limited studies that report snoring in an objective manner [119, 120]. To date, there exist no study on the dose dependent effects of progressive MA on snoring and snore type.

6.2 Aim

The aim of this study was to: 1) investigate the effects of progressive MA on snoring and respiratory events, 2) objectively quantify the dose dependent effects of MA on snoring and snore types, 3) assess the therapeutic efficacy of MA on snoring in primary snorers (PS) and OSA patients treated with MAS therapy.

6.3 Methods

6.3.1 Study Participants

One hundred and fourteen consecutive MAS naive patients (81 Male, 33 Female) were recruited for this study. Baseline characteristics of these patients are described in in Chapter 5.3.1. In summary, the patients had a mean age of 51.0 ± 12.9 years (range 21-77

years), BMI of 28.5 ± 4.4 kg/m^2 (range 20.6-40.3 kg/m^2) and neck circumference of 39.6 ± 4.2cm (range 30-55 cm). Epworth Sleepiness Score (ESS) was 6.0 (3.0, 10.0) and with maximum protrusive range (MP) of the mandible at 10.0 (9.0, 12.0) mm at baseline. AHI was 9.3 (6.3, 14.4) events/hr with the majority of patients in the mild/moderate OSA category. Overall, the group consisted of 19 PS, 70 mild, 21 moderate and 4 severe OSA patients.

The inclusion and exclusion criteria have been previously described in Chapter 5.3.1. Dental eligibility was assessed by the PhD candidate (JN). All study procedures were approved with the Institutional Human Research Ethics Committee (Approval protocol No: 11476-2012/023) and written consent was obtained from all participants.

6.3.2 MAS Treatment Protocol

This study was undertaken at a private dental sleep clinic under the care of the PhD research clinician (JN). All participants in the study paid full fees for their MAS and treatment reviews independent of any financial support from industry. Following a thorough dental evaluation for assessment of eligibility for recruitment to the study, dental impressions were taken on the upper and lower dental arches of each participant. Using a George Gauge^{TM} instrument [453], measurements were recorded for the most retrusive and protrusive position of the mandible. The protrusive range of MA was thus established for each patient. An inter-occlusal bite record set at 70% of the patient's maximum protrusive capability (70%MP) was performed with a poly-vinyl silicone material. With the dental

impressions and inter-occlusal bite record provided, a customized adjustable mandibular advancement splint (MAS), (SomnoDent MAS Classic; SomnoMed Ltd, Crows Nest, New South Wales, Australia) was fabricated for each patient from dental impressions set at 70%MP. The key features of the MAS are described in section 6.3.3 below.

At a subsequent dental visit, each patient was fitted with the MAS by the research clinician (JN) with the mandible positioned at 70%MP. Following an acclimatization phase of 4-6 weeks, the patient returned for a follow up assessment. The MAS device was further titrated by a further 1mm (70%MP1) and 2mm (70%MP2) anteriorly such that the mandible was incrementally positioned a further 1 and 2mm from the initial 70%MP position respectively. Mandibular advancement (MA) was performed by the clinician (JN) by activating the screw mechanism located bilaterally in the posterior region of the upper oral device at each review visit prior to the next Sonomat™ sleep test. At each of the review visits, an assessment of the fit, retention and comfort of the MAS was undertaken. At each of the mandibular positions (70%MP, 70%MP1 and 70%MP2), a Sonomat™ Sleep study was performed with MAS in situ in the patient's home.

6.3.3 Mandibular Advancement Splint

The key features of the custom-made adjustable mandibular advancement splint (MAS), (SomnoDent MAS Classic; SomnoMed Ltd, Crows Nest, New South Wales, Australia) are described below. As previously published [119, 317, 344], the MAS consisted of several key features including : 1) separate upper and lower acrylic appliances anchored onto the

dental arches and covering the occlusal surfaces of teeth. 2) bilateral acrylic flanges located on the lower appliance enabled the mandible to be guided anteriorly while allowing free opening of the mouth. 3) unique flange coupling mechanisms that prevent posterior repositioning of the mandible. 4) Two screws located bilaterally on the upper appliance that permitted incremental protrusion of the mandible to the desired anterior position. The average occlusal thickness of acrylic in each custom-made appliance was between 1.5 and 2.0 mm providing full occlusal coverage with range of interincisal opening of 5-8 mm. Lateral and occlusal views of the MAS demonstrating the unique design features is shown in Figure 6.1 and 6.2 below.

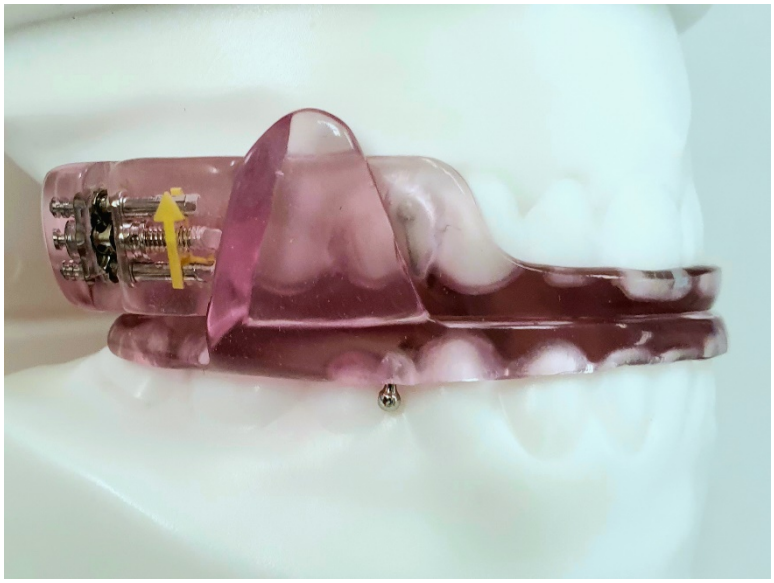


Figure 6.1 SomnoDent Classic MAS: lateral view. The two-piece MAS (SomnoDent Classic MAS; SomnoMed Ltd, Crows Nest, New South Wales, Australia) has unique upper and lower features that attach to the patient's upper and lower dentition. The adjustable coupling mechanism located bilateral of each side of the MAS allow incremental advancement of the mandible.

Figure 6.2 SomnoDent Classic MAS: occlusal view showing the upper and lower halves of the MAS device.

6.3.4 Sonomat™ Sleep study

A Sonomat™ sleep test is described in detail in the General Methods section. Prior to MAS treatment, baseline recordings were performed without the MAS in the patient's own home (Chapter 5). Three additional single overnight sleep recordings were performed on consecutive nights with MAS in situ with the Sonomat™ at 70%MP, 70%MP1 and 70%MP2 mandibular jaw positions respectively. Patient instructions on the use of the Sonomat™ are detailed in Chapter 5.3.3. Respiratory events and snoring were identified as defined in the General Methods. Of novel interest, we objectively quantified duration of total snoring; which comprised 3 snore types (inspiratory snoring, expiratory snoring and

combined inspiratory and expiratory (IE) snoring). Each of these snore types were quantified both in duration and as a percentage of quiescent time (Qd) in our sub-analysis.

The Epworth sleepiness scale was measured post-MAS treatment.

Primary Snorers (PS) and OSA patients in this study were defined as follows: PS (AHI < 5 events/hr with snoring > 10mins), mild OSA (AHI 5-14.9 events/hr), moderate OSA (AHI 15-29.9 events/hr), severe OSA (AHI > 30 events/hr).

6.3.5 Data analysis

All studies were manually scored blinded in random order. Statistical analysis was performed using methods outlined in the General Methods section.

6.3.6 Treatment Outcome Definitions

6.3.6.1 AHI response

Complete AHI treatment response was defined as either a stringent cutoff of AHI < 5 events/hr or a more liberal cutoff of AHI < 10 events/hr. AHI treatment failure or non-response was defined as AHI > 10 events/hr with ongoing clinical symptoms.

6.3.6.2 Snore response

The study participants were stratified according to increasing total snoring (TS) duration ranging from zero to 360 minutes. Total snoring reduction percentage (TSR %) was defined as the reduction in total snoring time (mins) expressed as a percentage of baseline

snoring time. Snore non-responders (TS failure) were defined as TSR < 0%; these subjects increased in snoring when expressed as a percentage of baseline snoring.

Secondary outcomes measures included the Epworth Sleepiness scale (ESS). The ESS is a validated short questionnaire developed to measure subjective levels of daytime sleepiness [454]. All subjects completed the ESS at baseline and post-MAS treatment.

6.4 RESULTS

Of the 114 patients recruited, all completed Sonomat™ studies at 70%MP and 70%MP1 mandibular positions. A further 84 patients (74%) proceeded to the additional 1mm mandibular advancement to 70%MP2 position; 30 patients (26%) did not proceed to the 70%MP2 position. This latter group consisted of a combination of patients who were lost to follow up or who elected not to have their MAS device advanced a further 1mm to the 70%MP2 position as they had attained their maximum comfortable protrusive limit at 70%MP1 position. Additionally, some patients had perceived adequate, albeit a subjective reduction of snoring and other clinical symptoms such as witnessed apneas and were reluctant to be titrated to the 70%MP2 position. General concerns about side effects such as temporo-mandibular disorder (TMD) pain, teeth pain and minor bite alteration effects were noted.

6.4.1 Comparison of Baseline characteristics between MAS (70% MP2) treatment group (n=84) vs excluded MAS group (n=30)

As there were only 84/114 patients who completed final titration to the 70%MP2 mandibular position, the baseline characteristics between the excluded group (n=30) and MAS treatment group (n=84) at 70%MP2 were analyzed and summarized in Table 6.1. No significant differences were noted between the two groups with respect to gender, age, BMI, neck circumference and mandibular protrusive range. There were no significant differences in analysis time, Qd time, AHI, OAI, OHI and RMI. Total snoring and snore types with respect to duration, percentage were not observed to be significantly different between the groups. Thus, the effects of MA on snoring and respiratory indices in 84 patients at 70%MP, 70%MP1 and 70%MP2 mandibular positions were analyzed and presented in later sections of this investigation.

TABLE 6.1 BASELINE CHARACTERISTICS OF EXCLUDED PATIENTS (n=30) and MAS TREATMENT GROUP (n=84)

Variable	Excluded patients (n=30)	Treatment group (n=84)	p value
Gender	21M,9F	60M, 24F	0.88
Age, yr	49.5 (42.0, 55.5) (range 21-77)	50.5 (41.0, 63.0) (range 25-76)	0.29
BMI, kg/m^2	29.3 ± 4.4 (range 21.4-38.4)	28.2 ± 4.4 (range 19.7 - 40.3)	0.23
Neck circumference, cm	40.0 (36.8, 43.0)	40.0 (37.0, 42.4)	0.61
Epworth sleepiness scale	6.0 (4.5, 11.3) (range 0-15)	6.0 (3.0, 10.0) (range 0-18)	0.86
Max. Pro, mm	10.0 (9.0, 12.0) (range 7-15)	10.0 (9.0, 12.0) (range 5-14)	0.79
Analysis Time, mins	465.4 (428.1, 517.6)	442.4 (389.1, 479.3)	0.16
Qd Time, mins	439.3 (408.2, 479.6)	425.4 (371.6, 469.2)	0.18
AHI, events/hr	8.8 (5.9, 12.8)	10.3 (6.9, 15.7)	0.18
OAI, events/hr	0.2 (0.0, 1.3)	0.2 (0.0, 1.0)	0.33
OHI, events/hr	6.9 (5.1, 9.9)	8.8 (5.8, 13.9)	0.06
RMI, events/hr	13.6 (3.6, 23.9)	8.1 (2.4, 19.7)	0.53
Total Snore, mins	91.0 (58.0, 220.2)	97.1 (48.5, 182.6)	0.35
Total Snore %	22.3 (13.2, 48.2)	24.7 (12.8, 43.5)	0.61
Inspiratory Snore, mins	82.3 (56.9, 181.3)	87.4 (36.4, 150.1)	0.26
Inspiratory Snore %	18.7 (13.0, 40.0)	20.9 (10.3, 39.2)	0.50
Expiratory Snore, mins	1.4 (0.4, 5.0)	2.1 (0.4, 8.3)	0.98
Expiratory Snore, %	0.3 (0.1, 1.3)	0.5 (0.1, 1.9)	0.92
IE Snore, mins	2.0 (0.5, 10.5)	2.6 (0.5, 9.9)	0.50
IE Snore %	0.5 (0.1, 2.5)	0.6 (0.1, 2.8)	0.43

Definition of abbreviations: 70% MP2= 70% of Maximum Protrusion +2mm; BMI = body mass index; Qd = quiescent; Max. Pro = maximum protrusion; AHI = apnea+hypopnea index; OAI = Obstructive Apnea Index; OHI = Obstructive Hypopnea Index; RMI = respiratory movement index; Total Snore % = Total Snore Percentage; IE Snore = Inspiratory and Expiratory snore. Continuous data are presented Mean Standard deviation or Median and interquartile range.

Table 6.1 Baseline characteristics between the excluded group (those that did not progress to 70%MP2) and MAS 70%MP2 treatment group. 84/114 patients (74%) were advanced to 70%MP2 mandibular position. The remaining 30 patients were advanced to 70%MP1 only. No statistically significant differences were noted between the excluded group and MAS treatment group in any variables.

6.5 MAS Treatment Outcomes

6.5.1 MAS therapy on Sleep and Breathing Variables

Table 6.2 summarizes the results of MAS therapy on sleep and breathing variables at 70%MP, 70%MP1 and 70%MP2 positions (n=84). At 70%MP2 position, significant mandibular advancement of 9.0 (8.3, 10.4) mm, representing 89.6% of maximum protrusive capability was noted, (both $p<0.0001$). Significant decreases in AHI, OAI, OHI were observed. AHI decreased in a dose dependent fashion from 10.3 (6.9, 15.7) at baseline to 6.3 (4.1, 10.0), 5.3 (2.9, 7.6) and 4.8 (2.5, 6.8) events/hour at 70%MP, 70%MP1 and 70%MP2 mandibular positions respectively; ($p<0.0001$), (Figure 6.3).

Small but significant decreases were noted in OAI, (baseline = 0.2 (0.0, 1.0), range (0.0-9.6) events/hr, vs 70% MP2 = 0.0 (0.0, 0.0), range (0.0-1.0) events/hr, $p<0.0001$. The OHI decreased in a dose dependent fashion from 8.8 (5.8, 13.9) at baseline to 5.7 (3.4, 9.2), 5.2 (2.3, 7.0) and 4.2 (2.1, 6.3) events/hour at 70%MP, 70%MP1 and 70%MP2 mandibular positions respectively, ($p<0.0001$).

Significant decreases were also noted in RMI and ESS, (both $p<0.0001$). The duration and percentage of total snoring was noted to decrease significantly (both $p<0.0001$). These significant improvements were attributed to the significant decreases in inspiratory snoring duration and percentage (both $p<0.0001$). There were no significant changes observed in

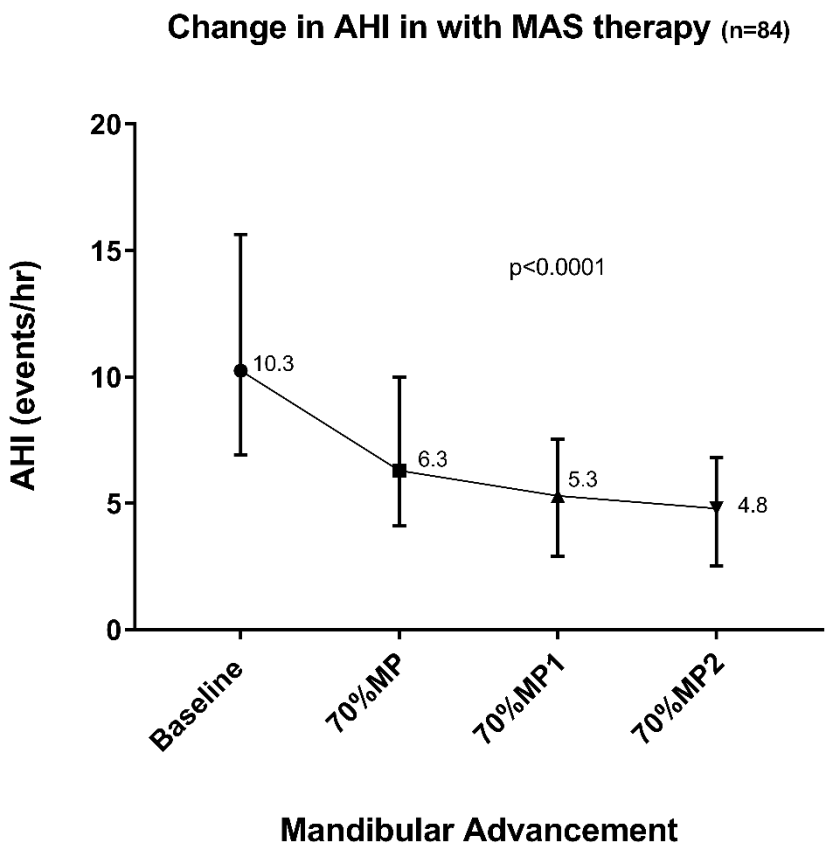
expiratory snoring. However, small but significant changes were noted in IE snoring duration ($p=0.03$). The corresponding changes observed in RMI, ESS, total snoring, snore types (inspiratory, expiratory and IE snoring) are explored in detail in the sections below.

TABLE 6.2 SUMMARY OF CHANGES IN SLEEP AND BREATHING VARIABLES WITH MANDIBULAR ADVANCEMENT IN ALL PATIENTS (n= 84)

Variable	Baseline (n=84)	70%MP (n=84)	70%MP1 (n=84)	70%MP2 (n=84)	p value
Max. Pro, mm	0.0	7.0 (6.3, 8.4)	8.0 (7.4, 9.4)	9.0 (8.3, 10.4)	<0.0001
Max. Pro, %	0.0	70.0%	79.9%	89.6%	<0.0001
Analysis Time, mins	450.0 ± 70.5	447.0 ± 69.4	427.9 ± 75.5	437.6 ± 86.3	0.06
Qd Time, mins	424.7 ± 65.3	424.0 ± 65.1	405.6 ± 70.2	411.9 ± 74.1	0.06
AHI, events/hr	10.3 (6.9, 15.7)	6.3 (4.1, 10.0)	5.3 (2.9, 7.6)	4.8 (2.5, 6.8)	<0.0001
OAI, events/hr	0.2 (0.0, 1.0)	0.0 (0.0, 0.2)	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)	<0.0001
OHI, events/hr	8.8 (5.8, 13.9)	5.7 (3.4, 9.2)	5.2 (2.3, 7.0)	4.2 (2.1, 6.3)	<0.0001
RMI, events/hr	8.1 (2.4, 19.7)	3.1 (1.4, 13.6)	2.5 (0.8, 9.8)	2.0 (0.9, 6.8)	<0.0001
ESS	6.0 (3.0, 10.0)	n/a	n/a	3.0 (1.3, 7.0)	<0.0001
Total Snore, mins	97.1 (48.5, 182.6)	44.0 (10.5, 109.9)	37.8 (10.6, 109.7)	32.6 (10.6, 80.8)	<0.0001
Total Snore %	24.7 (12.8, 43.5)	11.0 (2.5, 24.7)	8.7 (2.8, 26.6)	8.4 (2.6, 20.6)	<0.0001
Inspiratory Snore, mins	87.4 (36.4, 150.1)	23.3 (3.3, 63.7)	18.2 (2.2, 64.8)	11.8 (1.9, 44.6)	<0.0001
Inspiratory Snore %	20.9 (10.3, 39.2)	5.8 (0.7, 14.2)	3.6 (0.5, 17.3)	3.1 (0.5, 11.1)	<0.0001
Expiratory Snore, mins	2.1 (0.4, 8.3)	2.7 (0.4, 15.8)	3.3 (0.2, 12.7)	2.2 (0.6, 16.3)	0.13
Expiratory Snore, %	0.5 (0.1, 1.9)	0.6 (0.1, 3.7)	0.9 (0.0, 2.6)	0.6 (0.1, 4.1)	0.11
IE Snore, mins	2.6 (0.5, 9.9)	1.3 (0.2, 9.2)	0.8 (0.1, 5.1)	1.9 (0.1, 9.2)	0.005
IE Snore %	0.6 (0.1, 2.8)	0.3 (0.1, 2.2)	0.2 (0.0, 1.4)	0.5 (0.0, 2.1)	0.03

Definition of abbreviations: Max. Pro =maximum protrusion; Max. Pro % = percentage of maximum mandibular protrusive capability; Qd = quiescent; BMI = body mass index; AHI = apnea+hypopnea index; OAI = Obstructive Apnea Index; OHI = Obstructive Hypopnea Index; RMI = respiratory movement index; ESS = Epworth Sleepiness Scale; Total Snore % = Total Snore Percentage; IE = Inspiratory and Expiratory. Continuous data are presented Mean ± Standard deviation or Median (25^{th},75^{th} interquartile range).

Table 6.2 Summary of changes in sleep and breathing variables with mandibular advancement (n=84). At 70%MP2, mandibular advancement of 9.0 (8.3, 10.4) mm representing 89.6% of maximum protrusive capability was noted, (both p<0.0001). AHI, OAI, OHI, RMI, ESS decreased significantly (all p<0.0001). Total snoring time and percentage decreased significantly with decreases predominantly linked to inspiratory snoring (all p<0.0001). Small but significant differences were in IE snoring but not expiratory snoring.



Definition of abbreviations: AHI = apnea hypopnea index. 70%MP =70% Maximum Protrusion, 70%MP1 = 70% Maximum Protrusion +1mm, 70%MP2 = 70% Maximum Protrusion +2mm. Data presented as median (25^{th},75^{th} interquartile range).

Figure 6.3 The effect of MAS therapy on AHI (n=84). MAS treatment reduced AHI in a dose dependent fashion from 10.3 (6.9, 15.7) at baseline to 6.3(4.1,10.0), 5.3(2.9,7.6), 4.8(2.5,6.8) events/hr at 70%MP, 70%MP1 and 70%MP2 positions respectively; p<0.0001.

6.5.2 MAS Treatment Success- an AHI perspective

All 95 OSA patients were titrated to 70%MP1 position with 69 patients (73%) titrated to the 70%MP2 position. The overall AHI treatment success at 70%MP, 70%MP1 and 70%MP2 positions in the OSA group (n=95) are summarized in Table 6.3 and figure 6.4 below. Based on our predefined stringent cutoff of AHI < 5 events/hr to define treatment success, complete MAS treatment response rate was 33.7 % (32/95 patients) at 70%MP position. Therapeutic success increased in a dose dependent manner with increasing mandibular advancement (MA) to 46.3% (44/95 patients) and 53.6% (37/69 patients) at 70%MP1 and 70%MP2 positions respectively. When using a more liberal cutoff of AHI <10/hr, therapeutic success rate increased to 77.9%, 86.3% and 85.5% at 70%MP, 70%MP1 and 70%MP2 positions respectively.

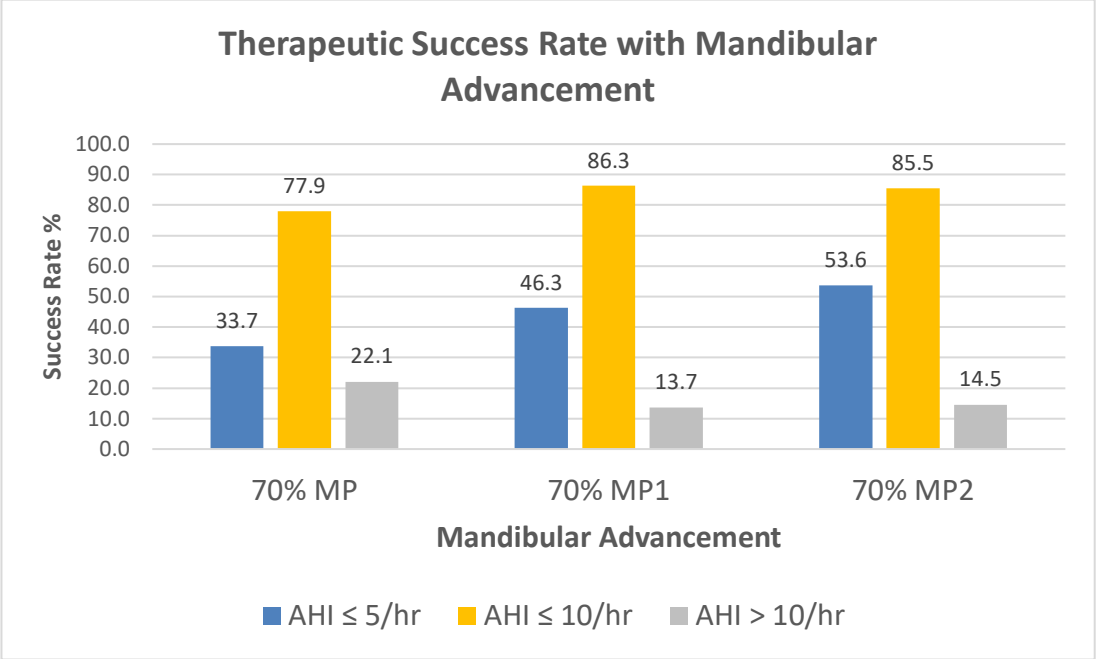
In this study, patients with AHI > 10/hr were classified as AHI treatment non-responders. At the 70%MP position, there were 21 patients (22.1%) classified as treatment failure with an AHI>10/hr. This decreased with increasing MA to 13.7% at 70%MP1 position. A minimal increase to 14.5% at 70%MP2 position was noted but the values were of similar magnitude to the values observed at 70%MP1 (13.7% failure rate at 70%MP1 vs 14.5% failure rate at 70%MP2). Thus, despite an additional 1mm MA from 70%MP1 to 70%MP2, there was negligible improvement in failure rates at the more pronounced level of mandibular protrusion.

TABLE 6.3 MAS TREATMENT SUCCESS BASED ON AHI IN THE OSA GROUP (n=95) WITH PROGRESSIVE MANDIBULAR ADVANCEMENT.

Treatment Response	70% MP (n=95)	70% MP1 (n=95)	70% MP2 (n=69)
AHI responders			
AHI < 5/hr	32/95 (33.7%)	44/95 (46.3%)	37/69 (53.6%)
AHI < 10/hr	74/95 (77.9%)	82/95 (86.3%)	59/69 (85.5%)
Treatment failure			
AHI > 10/hr	21/95 (22.1%)	13/95 (13.7%)	10/69 (14.5%)

Definition of abbreviations: AHI = apnea hypopnea index. 70% MP =70% Maximum Protrusion, 70% MP1 = 70% Maximum Protrusion +1mm, 70% MP2 = 70% Maximum Protrusion +2mm; data presented as fraction and percentage of the group.

Table 6.3 MAS treatment success based on the AHI in OSA group with progressive mandibular advancement. Using an AHI < 5 events/hr to define complete treatment success, success rate increased in a dose dependent manner. However, a significant proportion of patients (22%) were classified as treatment failure based on AHI > 10 events/hr at 70%MP. Mandibular advancement to 70% MP1 and 70%MP2 reduced failure rates to 13.7% and 14.5% respectively.



Definition of abbreviations: Success rate % = Percentage of patients attaining defined AHI success criteria, AHI = apnea hypopnea index. 70% MP =70% Maximum Protrusion, 70% MP1 = 70% Maximum Protrusion +1mm, 70% MP2 = 70% Maximum Protrusion +2mm; data presented as fraction and percentage of the group.

Figure 6.4 The effect of progressive mandibular advancement on therapeutic success rate based on the AHI. Using an AHI < 5 events/hr, therapeutic success rates increased in a dose dependent manner with progressive mandibular protrusion from 33.7%, 46.3% to 53.6% at 70%MP, 70%MP1 and 70%MP2 positions respectively. Treatment failure rates decreased with mandibular protrusion from 22.1% to 13.7% to 14.5% at 70% MP, 70%MP1 and 70%MP2 positions respectively.

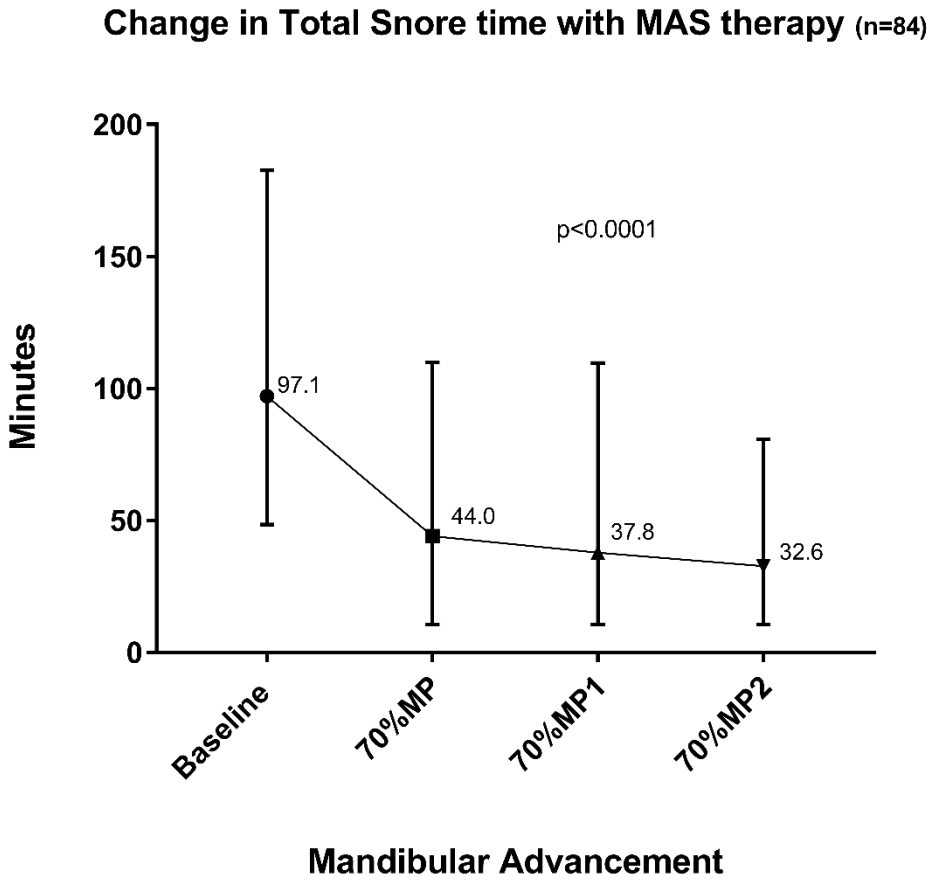
6.5.3 MAS therapy on Snoring duration and frequency- Dose dependent effects of mandibular advancement

6.5.3.1 Dose dependent effect of mandibular advancement on the duration of total snoring

The changes in snoring variables for the MAS treated group (n=84) to the 70%MP2 mandibular position are summarized in Table 6.2 and Figure 6.5 Significant reductions in the total snoring duration and percentage of quiescent time (Qd) was found. Total snoring time decreased in a dose dependent fashion exhibiting a "floor effect" at the final 70%MP2 position. Significant decreases ($p<0.0001$) from the baseline of 97.1 (48.5, 182.6) to 44.0 (10.5, 109.9), 37.8(10.6, 109.7) and 32.6(10.6, 80.8) minutes of snoring at 70%MP, 70%MP1 and 70%MP2 mandibular positions respectively were observed.

As illustrated in Figure 6.5, a greater reduction in total snoring occurred from baseline to 70%MP position as depicted by the steepness of the gradient in the slope. This gradient diminished considerably from 70%MP to 70%MP1 and 70%MP2 positions respectively highlighting decreasing but diminishing reductions in the duration of total snoring. Overall, at 70%MP2 (89.6% maximum mandibular protrusive capability), total snoring duration reduced by approximately two-thirds (66.4%) from baseline. However, it should be highlighted that despite incremental mandibular advancement, total snoring was not totally abolished even at the final 70%MP2 position with 32.6 (10.6, 80.8) minutes of residual snoring still noted to be present. As the snoring response was noted to be non-linear, the

individual snoring response in snore responders and non-responders are explored in later sections of this thesis, (section 6.3.3).

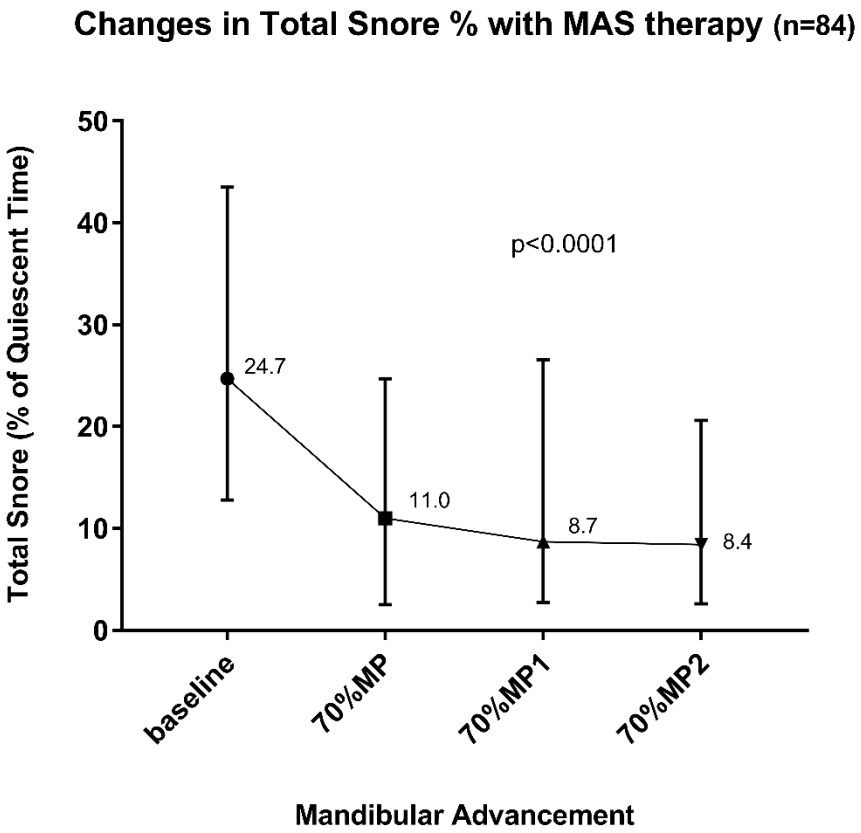


Definition of abbreviations: AHI = apnea hypopnea index. 70%MP =70% Maximum Protrusion, 70%MP1 = 70% Maximum Protrusion +1mm, 70%MP2 = 70% Maximum Protrusion +2mm. Data presented as median (25^{th},75^{th} interquartile range).

Figure 6.5 The effect of progressive mandibular advancement on the duration of total snoring (n=84). MAS treatment reduced total snoring in a dose dependent fashion from 97.1 (48.5, 182.6) minutes at baseline to 44.0(10.5, 109.9), 37.8(10.6,109.7), 32.6(10.6, 80.8) minutes at 70%MP,70%MP1 and 70%MP2 positions respectively; p<0.0001.

6.5.3.2 Dose dependent effect on the percentage of Total Snoring of Quiescent time (Qd)

When total snoring was expressed as a percentage of Qd time, a dose dependent response with a "floor effect" was also noted with diminishing reductions following progressive mandibular advancement. Significant reductions from the baseline of 24.7 (12.8, 43.5) to 11.0 (2.5, 24.7), 8.7 (2.8,26.6) and 8.4 (2.6, 20.6) percent of Qd at 70%MP, 70%MP1 and 70%MP2 mandibular positions respectively, ($p<0.0001$) were found. Figure 6.6 illustrates the changes in total snoring percentage with progressive mandibular advancement.



Definition of abbreviations: 70% MP =70% Maximum Protrusion, 70% MP1 = 70% Maximum Protrusion +1mm, 70% MP2 = 70% Maximum Protrusion +2mm. Data presented as median (25^{th},75^{th} interquartile range).

Figure 6.6 The effect of MAS therapy on total snoring percentage (TS %) (n=84). MAS treatment reduced TS % in a dose dependent fashion from 24.7% (12.8, 43.5) at baseline to 8.4% (2.6, 20.6) at 70%MP2 mandibular position. Overall, significant reductions in TS % occurred with mandibular advancement from baseline to 70%MP, 70%MP1 and 70%MP2 positions respectively; p<0.0001. At 70%MP2, the frequency of snoring was reduced by approximately 66%.

Pooled data from this study showed that the patients snored almost a quarter of Qd time (24.7% (12.8, 43.5) mins) at baseline. Overall, as a group, the objectively quantified data suggest that approximately 66% of total snoring was abolished with a substantial reduction

to 8.4% (2.6, 20.6) of Qd time at 70%MP2 position. Nonetheless, individual variations in snoring response were noted and the non-responders at the 70%MP2 position are presented in a later section of this thesis (Section 6.6.3).

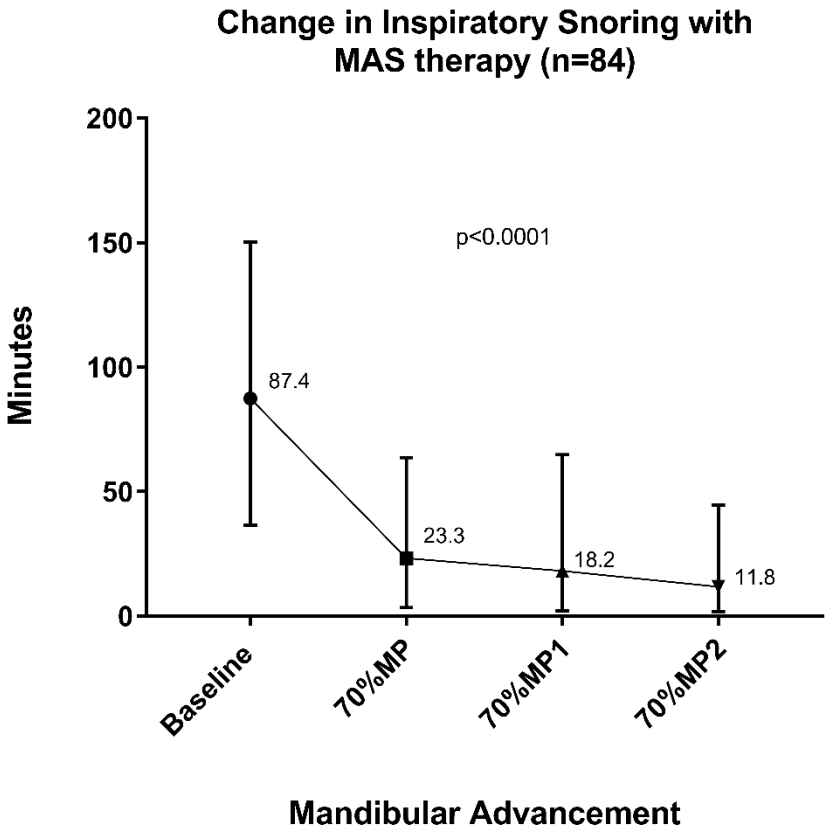
6.5.4 The effect of Mandibular advancement on Snore Types (Inspiratory, Expiratory and combined Inspiratory + Expiratory (IE) snoring)

Of novel interest, the predominant type of snoring noted was inspiratory snoring with 87.4 (36.4, 150.1) minutes recorded. This represented 20.9% (10.3, 39.2) of Qd time. At baseline, the duration of inspiratory snoring was in stark contrast to both expiratory and IE snoring both of which occurred significantly less often (inspiratory snoring 87.4 (36.4, 150.1) mins vs expiratory snoring 2.1 (0.4, 8.3) mins vs IE snoring 2.6 (0.5, 9.9) mins respectively.

6.5.4.1 Inspiratory Snoring

Figure 6.7 illustrates the changes in inspiratory snoring with MAS therapy with significant reductions observed. Inspiratory snoring decreased in a dose dependent fashion exhibiting a "floor effect" at the final 70%MP2 position. Significant decreases from 87.4 (36.4, 150.1) to 23.3 (3.3, 63.7), 18.2(2.2, 64.8) and 11.8 (1.9, 44.6) minutes of inspiratory snoring at 70%MP, 70%MP1 and 70%MP2 mandibular positions respectively, ($p<0.0001$) was recorded. However, a diminishing ability of MAS to reduce levels of inspiratory snore

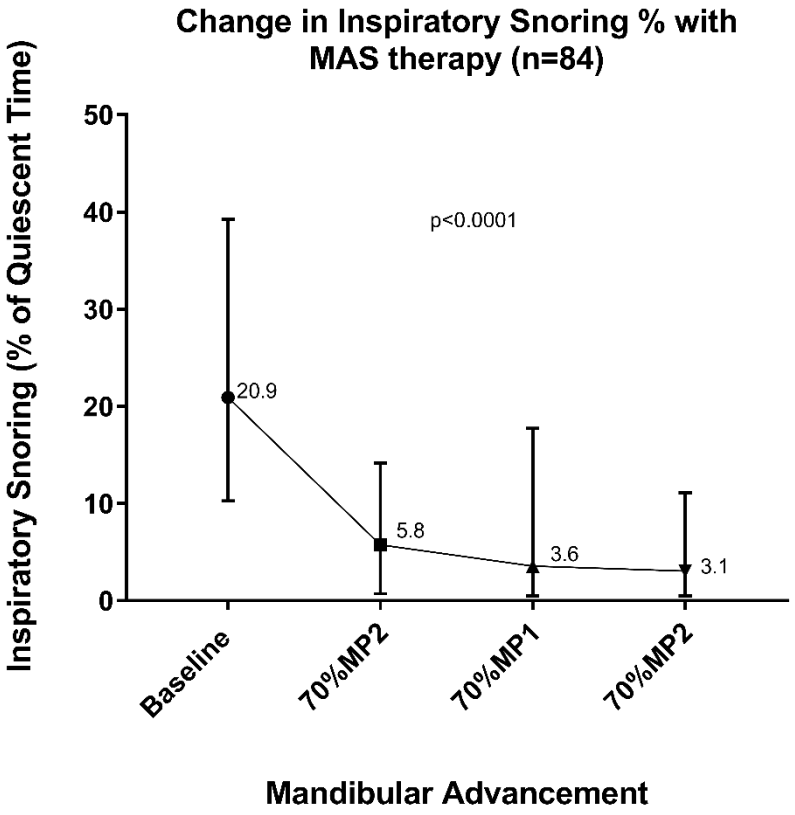
with progressive mandibular advancement was noted. Overall, at 70%MP2 (89.6% maximum mandibular protrusive capability), an average reduction of 86.5% of inspiratory snoring was noted.



Definition of abbreviations: 70% MP =70% Maximum Protrusion, 70% MP1 = 70% Maximum Protrusion +1mm, 70% MP2 = 70% Maximum Protrusion +2mm. Data presented as median (25^{th},75^{th} interquartile range).

Figure 6.7 The effect of MAS therapy on the duration of inspiratory snoring (n=84). MAS treatment reduced inspiratory snoring in a dose dependent fashion from 87.4 (36.4, 150.1) min baseline to 11.8 (1.9, 44.6) min at 70%MP2 mandibular position. Overall, significant reductions in total snoring occurred with mandibular advancement from baseline to 70%MP, 70%MP1 and 70%MP2 positions respectively; p<0.0001.

Similarly, when the duration of inspiratory snoring was expressed as a percentage of Qd time (inspiratory snoring %), a dose dependent effect with diminishing reductions with each stage of mandibular advancement was also found. Significant reductions from the baseline 20.9% (10.3, 39.2) to 5.8% (0.7, 14.2), 3.6% (0.5, 17.3) and 3.1% (0.5, 11.1) of Qd time at 70%MP, 70%MP1 and 70%MP2 mandibular positions respectively, ($p<0.0001$) were observed, (Figure 6.8).



Definition of abbreviations: 70% MP =70% Maximum Protrusion, 70% MP1 = 70% Maximum Protrusion +1mm, 70% MP2 = 70% Maximum Protrusion +2mm. Data presented as median (25^{th},75^{th} interquartile range).

Figure 6.8 The effect of MAS therapy on inspiratory snoring (% of Qd time) (n=84). MAS treatment reduced inspiratory snoring % in a dose dependent fashion from 20.9 (10.3, 39.2) at baseline to 3.1 (0.5, 11.1) % at 70%MP2 mandibular position. Overall, significant

reductions in total snoring % occurred with mandibular advancement from baseline to 70%MP,70%MP1 and 70%MP2 positions respectively; p<0.0001.

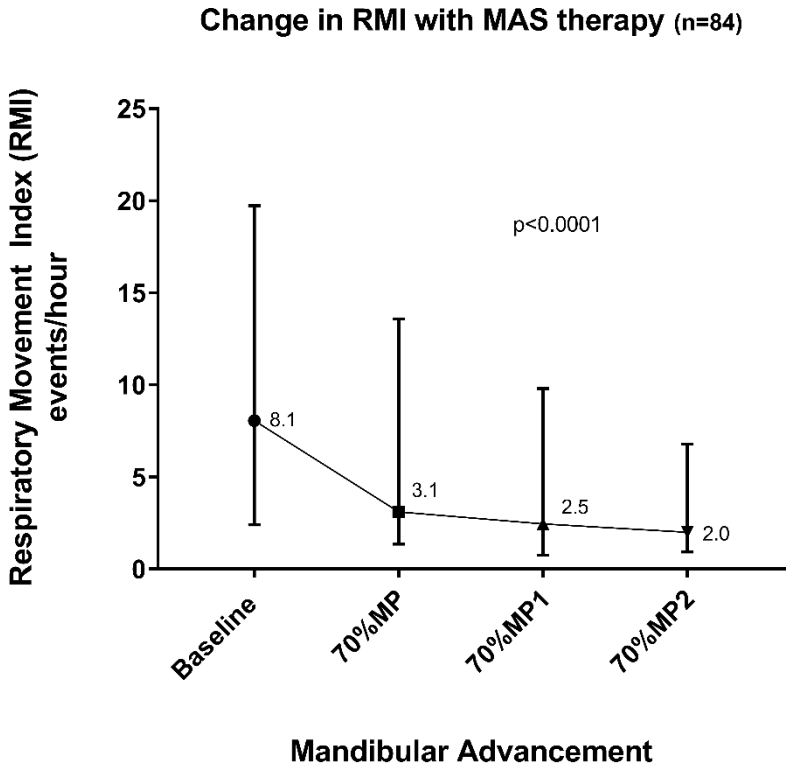
6.5.4.2 Expiratory Snoring and combined Inspiratory and Expiratory (IE) Snoring

Table 6.2 summarizes the changes in expiratory and IE snoring with MAS therapy. No significant changes in expiratory snoring variables were observed with progressive mandibular advancement. IE duration decreased from 2.6 (0.5, 9.9) mins at baseline to 1.3 (0.2, 9.2), 0.8 (0.1, 5.1) and 1.9 (0.1, 9.2) mins at 70%MP, 70%MP1 and 70%MP2 mandibular positions respectively, (p=0.005). IE snoring % also changed significantly although the absolute values were small. This decreased from 0.6 (0.1, 2.8) % at baseline to 0.3 (0.1, 2.2) %, 0.2 (0.0, 1.4) % and 0.5 (0.0, 2.1) % at 70%MP, 70%MP1 and 70%MP2 mandibular positions respectively, (p=0.03).

6.5.5 MAS therapy on Respiratory Movement Index (RMI)

In this study, any body movement preceded by an apnea, hypopnea or snoring was labeled a "Respiratory Movement". The number of respiratory movements that occurred each hour were quantified by the Respiratory Movement Index (RMI), (previously defined in General Methods, section 2.3.3).

MAS treatment resulted in significant reductions in the RMI. A dose dependent reduction from 8.1 (2.4, 19.7) to 3.1(1.4,13.6), 2.5(0.8,9.8) and 2.0 (0.9, 6.8) events/hour, at 70%MP, 70%MP1 and 70%MP2 mandibular positions respectively, ($p<0.0001$) was noted. (Table 6.2 and Figure 6.9).



Definition of abbreviations: RMI = Respiratory Movement index. 70% MP =70% Maximum Protrusion, 70% MP1 = 70% Maximum Protrusion +1mm, 70% MP2 = 70% Maximum Protrusion +2mm. Data presented as median (25^{th},75^{th} interquartile range).

Figure 6.9 The effect of MAS therapy on Respiratory Movement Index (RMI) (n=84). MAS treatment reduced RMI significantly in a dose dependent fashion from 8.1 (2.4, 19.7) events/hr at baseline to 3.1(1.4, 13.6), 2.5(0.8, 9.8) events/hr and 2.0 (0.9, 6.8) events/hour at 70%MP, 70%MP1 and 70%MP2 positions respectively; $p<0.0001$.

6.5.6 Subjective Outcomes- Epworth Sleepiness Scale

Significant reductions in daytime sleepiness (measured by the ESS) was noted with MAS therapy; (6.0 (3.0, 10.0) vs 3.0 (1.3, 7.0), p<0.0001). Individual ESS responses are illustrated in Figure 6.10 showing decreases in ESS score in the majority of patients. However, it was noted that some patients did not perceive subjective improvement in levels of daytime sleepiness with several individuals reporting higher levels of daytime sleepiness.

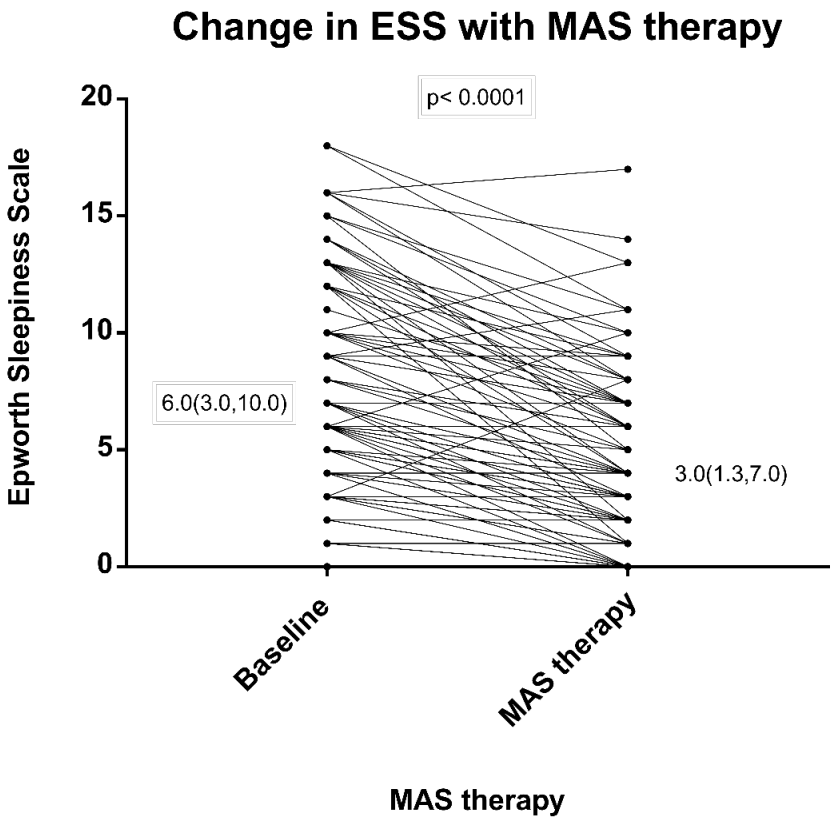
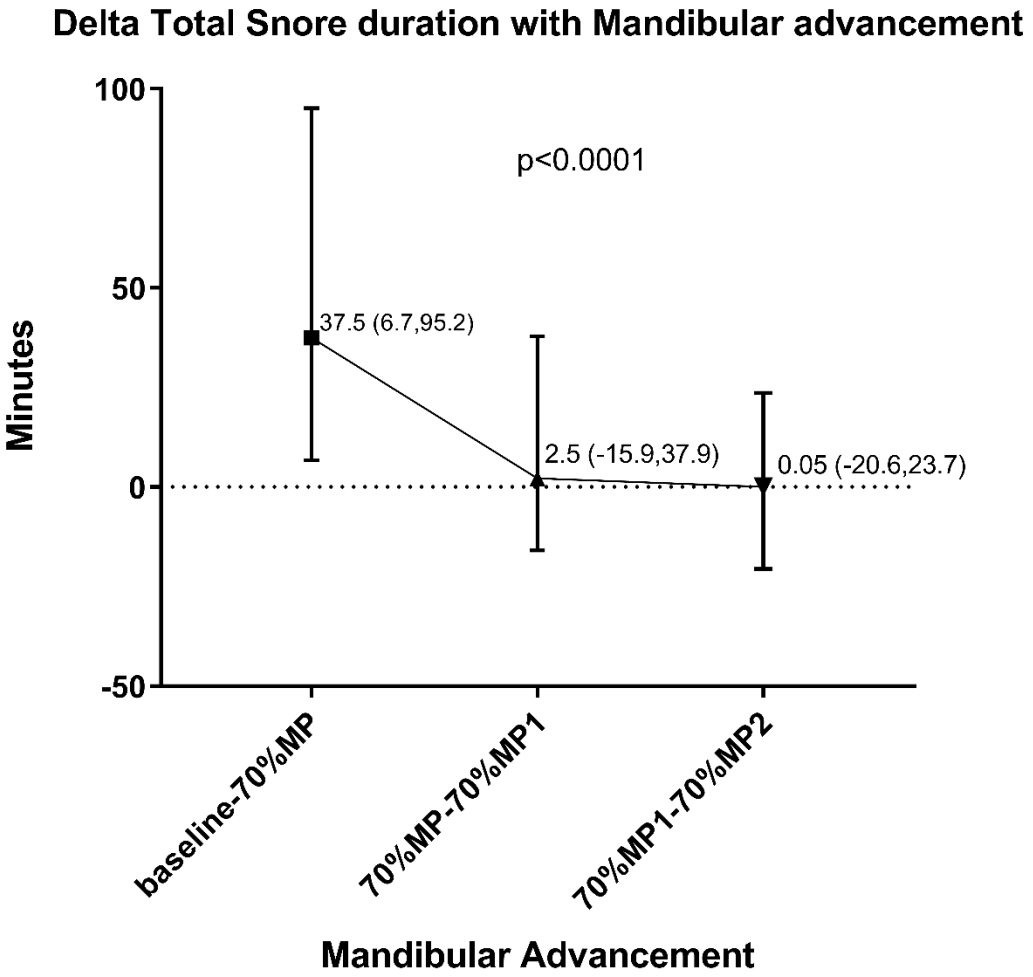


Figure 6.10 Change in Epworth Sleepiness Scale (ESS) scores in the entire group (n=114) with MAS therapy. Overall, significant decreases in ESS were noted in the entire group. Scores decreased from 6.0 (3.0, 10.0) to 3.0 (1.3, 7.0); p<0.0001 with the majority of patients showing decreased levels of daytime sleepiness. However, it should be noted that the response was not homogenous with several patients exhibiting minimal changes with several patients exhibiting higher levels of daytime somnolence.

6.5.7 Delta Total Snoring duration and percentage with Mandibular Advancement

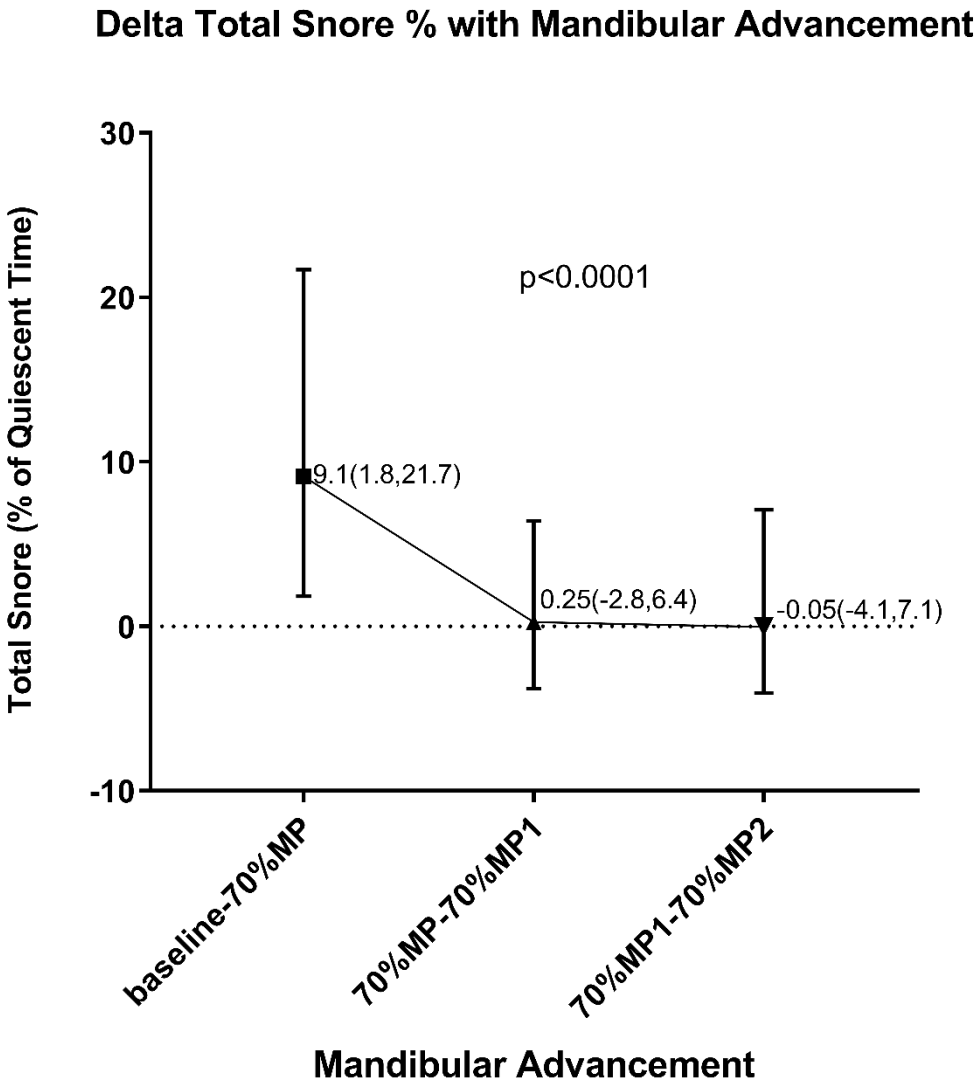
Delta total snore duration and percentage of Qd time was noted to significantly improve between each stage of mandibular advancement (both $p<0.0001$). The greatest reduction in total snoring occurred at 70%MP with snoring reduced by 37.5(6.7, 95.72) minutes. This represents, approximately, a 61% reduction from a baseline snore duration of 97.1 (48.5, 182.6) minutes. With increasing mandibular advancement to 70%MP2, snoring reduced to approximately 66%, however it was observed that only minimal improvement (2.5 (-15.9, 37.9) mins) in snoring duration occurred with the additional 1mm advancement from 70%MP to 70%MP1 position (Figure 6.11). An additional 1mm advancement from 70%MP1 to 70%MP2 position yielded only 0.05 (-20.6, 23.7) mins of snore reduction.



Data presented as median and interquartile range.
Definition of abbreviations: 70%MP =70% Maximum Protrusion, 70%MP1 = 70% Maximum Protrusion +1mm, 70%MP2 = 70% Maximum Protrusion +2mm.

Figure 6.11 Delta Total Snore duration with MAS therapy (n=84). Overall, a significant difference was noted in the delta change in total snore duration between baseline-70%MP, 70%MP-70%MP1 and 70%MP1-70%MP2 positions, p<0.0001. The group had a baseline of 97.1 (48.5, 182.6) minutes total snoring which reduced to 37.5(6.7, 95.72) mins at 70%MP. Thus, an average of 61% reduction in total snoring duration was noted at 70%MP. However, progressive mandibular advancement to 70%MP1 and 70%MP2 position yielded only minimal improvement in total snore duration with 2.5(-15.9,37.9) and 0.05 (-20.6, 23.7) minutes of further change noted at 70%MP-70%MP1 and 70%MP1-70%MP2 position respectively. In some instances, patients worsened in total snore duration with further mandibular advancement.

When delta total snore percentage was analyzed as a percentage (of Qd time), there was a significant difference delta total snore % between baseline-70%MP, 70%MP-70%MP1 and 70%MP1-70%MP2 positions, $p<0.0001$. The group had 24.7 (12.8, 43.5) % of Qd time in total snoring at baseline. At 70%MP, a median 9.1(1.8, 21.7) % of snoring was present. Thus, an average of 63% reduction in total snoring % was noted at 70%MP. However, it was observed that only minimal improvement (0.25 (-2.8, 6.4) %) in total snore % duration occurred with the additional 1mm advancement from 70%MP to 70%MP1 position. An additional 1mm advancement from 70%MP1 to 70%MP2 position yielded only -0.05(4.1, 7.1) % of snore reduction, (Figure 6.12).



Definition of abbreviations: Total Snore %= Total Snore percentage of quiescent time; 70%MP =70% Maximum Protrusion, 70%MP1 = 70% Maximum Protrusion +1mm, 70%MP2 = 70% Maximum Protrusion +2mm.

Figure 6.12 Delta total snore % (of Qd time) with MAS therapy (n=84). A significant difference was noted in the delta change in total snore % of Qd time between baseline-70%MP, 70%MP-70%MP1 and 70%MP1-70%MP2 positions, p<0.0001. The group had a baseline of 24.7 (12.8,43.5) percent of Qd time in total snoring which reduced to 9.1(1.8,21.7) at 70%MP. Thus, an average of 63% reduction in total snoring % was noted at 70%MP. However, progressive mandibular advancement to 70%MP1 and 70%MP2 position yielded only minimal improvement in total snore %.

6.5.8 Delta AHI and Total Snoring at 70% MP2 mandibular position

One of the key questions in the study was to explore the dynamic changes in AHI and snoring. The focus of this analysis addresses the question of whether or not the change in AHI correlated to the change in total snoring. The results of the change in AHI (Delta AHI) and change in total snoring (Delta Total Snoring) between baseline and MAS therapy at 70%MP2 mandibular position is illustrated in Figure 6.13 below. A weak but positive and significant correlation was observed for changes in AHI and total snoring at 70%MP2 mandibular position with MAS therapy with correlation coefficient of r=0.22, p=0.047 noted. This suggest that the decreases in both AHI and total snoring was weakly correlated and statistically significant. Linear regression analysis showed non-significance; r^2 =0.035, p=0.09.

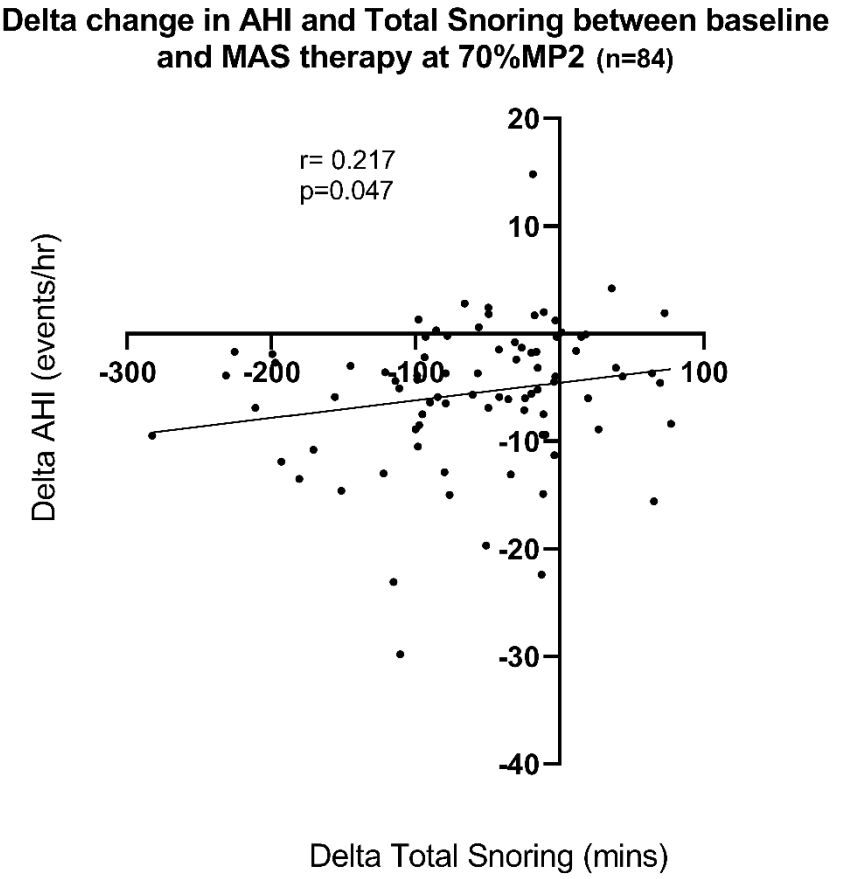


Figure 6.13 The relationship between the change in AHI (Delta AHI) and change in total snoring (Delta Total Snoring) duration between baseline and MAS therapy at 70%MP2 mandibular position. Weak correlation between Delta AHI and Delta total snoring was noted (r=0.217, p=0.047). Linear regression was not significant (r^2=0.035, p=0.09).

6.5.9 MAS therapy for Severe OSA

6.5.9.1 AHI perspective

This study recruited only 4 patients diagnosed with severe OSA. The individual responses are summarized in Table 6.4. Figures 6.14 and 6.15 illustrate the treatment response with progressive mandibular advancement for each patient in AHI and snoring duration respectively. At 70%MP2 position, it was noted that 50% of subjects (patients 1 and 2) of the patients recorded AHI < 10 events/hr. It should be highlighted that the remarkable reductions were attained at 70%MP with only minimal reductions in AHI with the additional 1 and 2 mm of incremental protrusion. The remaining 2 patients (patient 3 and 4) had varied AHI responses with increasing mandibular protrusion with both patients remaining in the severe OSA category at the 70%MP2 position. Patient 4 worsened from 45.0 to 59.8 events/hr, whereas patient 3 reduced, marginally, from 42.1 at baseline to 36.5 events/hr at 70%MP2.

Overall, when using the AHI metric as a basis for MAS therapeutic success, half of the patients achieved resolution of OSA (using a threshold of AHI < 10 events/hr) at the 70%MP2 position (patient 1 and 2). When using a more stringent criteria (AHI < 5 events/hr), 1 patient (25%) in the severe OSA category (patient 2) achieved full resolution of OSA (improvement from 34.6 events/hr at baseline to 4.8 events/hr at 70%MP2).

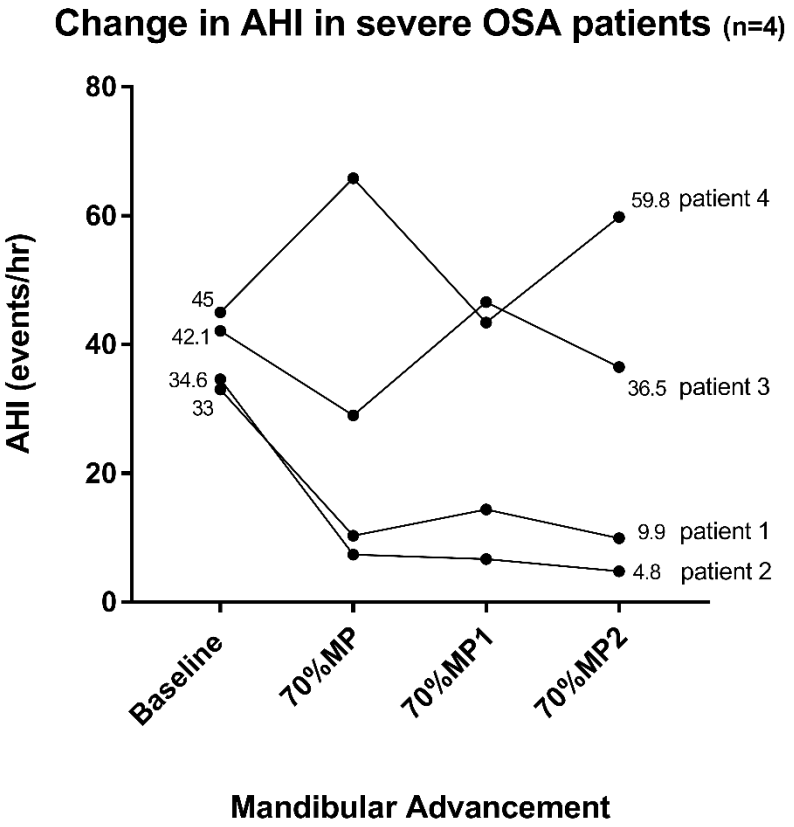
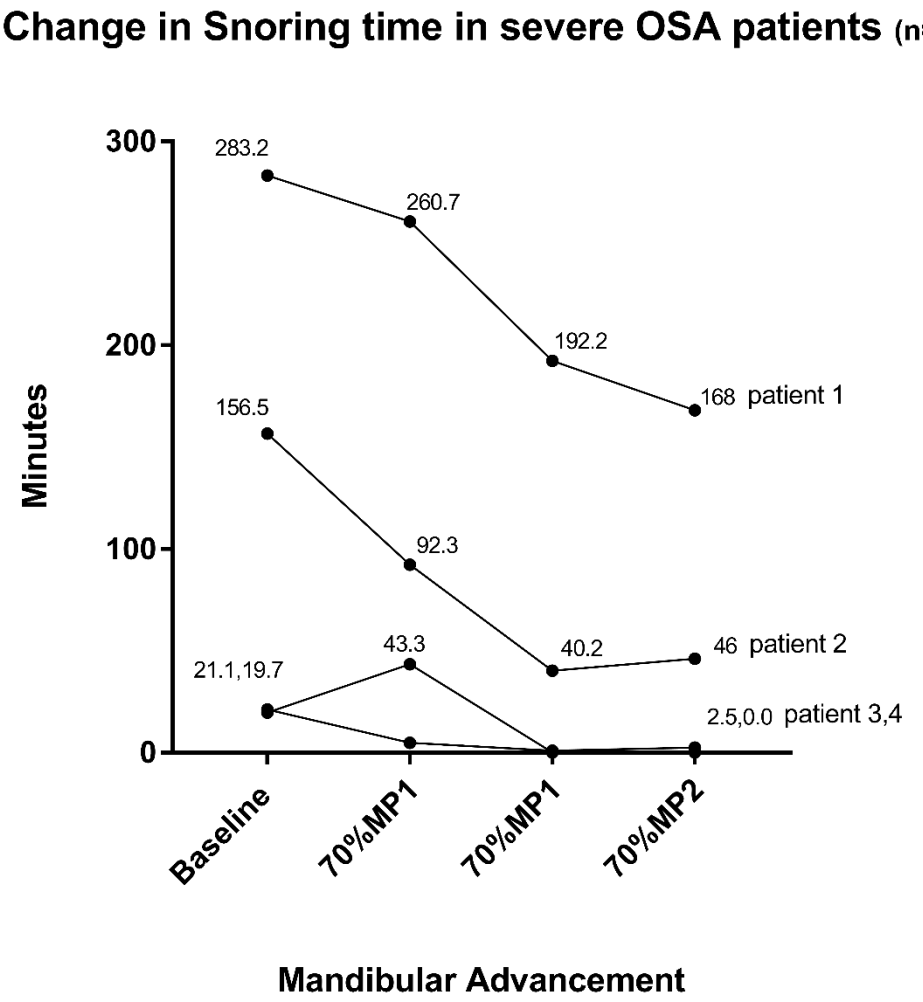


Figure 6.14 The effect of mandibular protrusion with MAS therapy on AHI in severe OSA patients. Immediate improvement was noted in 3 patients at 70%MP2 (patients 1, 2 and 3) with only 2 maintaining reduced AHI values at further levels of protrusion. In contrast, 50% of patient (patient 3 and 4) did not respond despite additional protrusion to 70%MP2 with one patient (patient 4) increasing their AHI from baseline at 70%MP2.

6.5.9.2 Snoring perspective

From the snoring perspective, a great variability was noted in response with resolution of snoring in 2/4 patients (50%). Figure 6.15 illustrates the individual snore responses with MAS therapy at increased levels of mandibular position. Overall, remarkable reductions in

total snoring were noted in all patients studied. Patient 1 demonstrated a dose dependent response with marked reduction in total snoring from 283.2 minutes at baseline to 260.7, 192.2 and 168 minutes at 70%MP, 70%MP1 and 70%MP2 mandibular positions respectively. Patient 2 had marked improvements overall, reducing from 156.5 minutes at baseline to 92.3, 40.2 and 46.0 minutes at 70%MP, 70%MP1 and 70%MP2 mandibular positions respectively. A small increase of 5.8 minutes was noted between the 70%MP1 and 70%MP2 positions in this patient. Patients 3 and 4 had significantly less snoring initially, compared to patients 1 and 2, but in both snoring was abolished with mandibular advancement. Patient 3 experienced a greater than twofold increase in snoring (19.1 vs 43.3 minutes) at 70%MP but this was completely abolished to 0 minutes at 70%MP1 position. At 70%MP1 position, patient 4 reduced snoring from 21.1 to 1.0 minutes with only a negligible increase to 2.5 minutes at 70%MP2 position.



Definition of abbreviations: AHI = apnea hypopnea index. 70%MP =70% Maximum Protrusion, 70%MP1 = 70% Maximum Protrusion +1mm, 70%MP2 = 70% Maximum Protrusion +2mm.

Figure 6.15 The effect of Mandibular protrusion with MAS therapy on snoring duration in severe OSA patients. Remarkable resolution was noted in 50% of the patients (patient 3 and 4) at 70%MP2 with negligible snoring recorded. Patients 1 and 2 also exhibited significant improvement in snoring as compared to baseline but residual snoring was observed.

As a whole, a great variability was noted in both AHI and snoring duration at different levels of mandibular protrusion. In 2 patients that demonstrated remarkable AHI reductions to AHI <10 events/hr at 70%MP2 (patients 1 and 2), a substantial reduction of snoring was observed (283.2 mins vs 168 mins (48.3% reduction), 156.6 mins vs 46.0 mins (70.6% reduction); respectively. However, despite the significant improvements in snoring, significant residual snoring remained at 70%MP2 position (patients 1 and 2). In contrast, patients 3 and 4 demonstrated residual severe OSA at 70%MP2 (AHI 36.5 and 59.8 events/hr respectively), with negligible snoring noted (0.0 and 2.5 mins respectively).

TABLE 6.4 CHANGE IN AHI AND SNORING IN SEVERE OSA PATIENTS (n=4).

	Baseline		70%MP		70%MP1		70%MP2	
	AHI	Snoring (mins)	AHI	Snoring (mins)	AHI	Snoring (mins)	AHI	Snoring (mins)
Patient 1	33	283.2	10.3	260.7	14.4	192.2	9.9	168.0
Patient 2	34.6	156.5	7.4	92.3	6.7	40.2	4.8	46.0
Patient 3	42.1	19.1	29.0	43.3	46.6	0.0	36.5	0.0
Patient 4	45.0	21.1	65.8	4.8	59.8	1.0	59.8	2.5

Definition of abbreviations: AHI = apnea hypopnea index. 70%MP =70% Maximum Protrusion, 70%MP1 = 70% Maximum Protrusion +1mm, 70%MP2 = 70% Maximum Protrusion +2mm.

Table 6.4 The effect of Mandibular protrusion on AHI and snoring in severe OSA patients (n=4). At 70%MP2, patients 1 and 2 exhibited remarkable reductions in AHI. (patient 1- 70%MP2 AHI = 9.9 events/hr, patient 2- 70%MP2 AHI = 4.8 events/hr). Snoring was noted to reduce in both patients but residual snoring remained. Poorer AHI responses were noted in patients 3 and 4 with minimal reduction in patient 3 (42.1 events/hr vs 36.5 events)/hr). Patient 4 worsened in AHI at 70%MP2 (45.0 events/hr vs 59.8 events/hr) and snoring was noted to decrease (21.1 mins vs 2.5 mins) as obstructive events increased.

6.6 Snoring Treatment Success- Total Snoring duration (TS) and percentage reduction (TSR%)

This section reports the effect of progressive mandibular advancement on the duration of total snoring (TS) and the percentage of total snoring reduction (TSR%) as compared to baseline. Snore responses for the entire group are summarized in Table 6.5 and illustrated in Figure 6.16. Sub-analysis of snore responders and non-responders are presented.

6.6.1 Duration of Total Snoring (TS)

The study participants were stratified according to increasing tiers of TS duration ranging from zero to 360 minutes, (range = TS 0-59.9 mins, TS 60-119.9 mins, TS 120-179.9 mins, TS 180=239.9 mins, TS 240-299.9 mins and TS 300-360 mins). Baseline TS data without MAS and with MAS in situ at 70%MP, 70%MP1 and 70%MP2 positions are presented in Table 6.5 and Fig 6.16. At baseline, 33/114 patients (28.9%) had up to 59.9 minutes (TS 0-59.9 tier) of snoring. 32/114 patients (28.1%) snored in excess of one hour to under two hours (TS 60-119.9 tier) of snoring during the night. 33/114 patients (28.1%) snored more in the range of 2 to 4 hours of snoring. Overall, a total of 98/114 patients (86%) snored up to 4 hours of Qd time. Surprisingly, 10/114 patients (8.8%) snored in excess of 4 hours to under 300 minutes of snoring (TS 240-299.9 tier). Noteworthy, 6/114 patients (5.3%) snored more than 5 hours of the nights (TS 300-360 tier).

6.6.1.1 Snore Responders

Snoring decreased using MAS with the majority of patients transitioning to lower tiers of snore duration as compared to baseline. At 70%MP position, 62/114 patients (54.5%) were categorized into TS 0-59.9 tier when compared to baseline (28.9%). The proportion of patients in this lower snoring tier (TS 0-59.9 minutes) increased in a dose dependent manner from baseline to 70%MP, 70% MP1 and 70%MP2 position (54.5% vs 56.1% vs 65.5%) respectively with increasing mandibular protrusion. At 70%MP position, fewer patients were categorized in higher tiers of snoring (TS 240-299.9 and TS 300-360). 3/114 patients (2.6%) were classified in the TS 240-299.9 minutes of snoring tier at 70%MP; this value remaining relatively similar at 70%MP2 with 2/84 patients (2.4%) in this tier of snoring severity. In the highest tier of snoring severity (TS 300-360 minutes), 6/114 (5.3%) were noted at baseline and the number reduced significantly at all levels of mandibular protrusion with no patients noted to be in this severe snoring category at 70%MP2. Overall, in snore responders, it was noted that patients transposed into lower tiers of snoring with incremental mandibular advancement to 70%MP2 position. More patients were noted in tier TS 0-59.9 minutes at 70%MP2 position as compared to baseline (63.1% vs 28.9%) respectively.

6.6.1.2 Snore non-responders

In this study, snore non-response (TS failure) was defined by an increase in snoring duration as compared to baseline. Of interest was that fact that the proportion of patients who worsened in snoring remained relatively constant despite progressive mandibular

advancement to the final 70%MP2 position. The proportion of TS failure patients were 22.8%, 21.1% and 16.7% at 70%MP, 70%MP1 and 70%MP2 positions respectively (Table 6.5 and Fig 6.16). At the 70%MP position, 22.8% (26/114) of patients worsened in snoring duration compared to baseline. With an incremental 1mm of anterior mandibular advancement to the 70%MP1 position, 21.1% (24/114) of patients worsened in snoring duration. Despite an additional 1mm titration to 70%MP2 position, 16.7% (14/84) of patients had an increase in snoring as compared to baseline.

TABLE 6.5 STRATIFICATION OF TOTAL SNORING DURATION WITH MANDIBULAR ADVANCEMENT.

Total Snoring (minutes)	Baseline (n=114)	70%MP (n=114)	70%MP1 (n=114)	70%MP2 (n=84)
TS 0-59.9	33/114 (28.9%)	62/114 (54.4%)	64/114 (56.1%)	53/84 (63.1%)
TS 60-119.9	32/114 (28.1%)	12/114 (10.5%)	14/114 (12.3%)	9/84 (10.7%)
TS 120-179.9	19/114 (16.7%)	8/114 (7.0%)	7/114 (6.1%)	6/84 (7.1%)
TS 180-239.9	14/114 (12.3%)	3/114 (2.6%)	4/114 (3.5%)	0/84 (0.0%)
TS 240-299.9	10/114 (8.8%)	3/114 (2.6%)	0/114 (0.0%)	2/84 (2.4%)
TS 300-360	6/114 (5.3%)	0/114 (0.0%)	1/114 (0.9%)	0/84 (0.0%)
TS Failure (Increase in Snoring)	0/114 (0.0%)	26/114 (22.8%)	24/114 (21.1%)	14/84 (16.7%)

Definition of abbreviations: TS = Total Snoring (minutes); 70%MP =70% Maximum Protrusion, 70%MP1 = 70% Maximum Protrusion +1mm, 70%MP2 = 70% Maximum Protrusion +2mm; data presented as number of subjects in group (percentage of group).

Table 6.5 Stratification of Total Snoring duration with Mandibular Advancement. Snoring decreased with most patients transitioning to lower tiers of snore duration relative to baseline. At 70%MP position, 54.4% of the group were categorized into TS 0-59.9 tier when compared to baseline (28.9%). At 70%MP2, an increase to 63.1% was noted. However, a significant proportion of patients had an increase in snoring. TS failure was observed in 22.8%, 21.1% and 16.7% at 70%MP, 70%MP1 and 70%MP2 positions respectively.

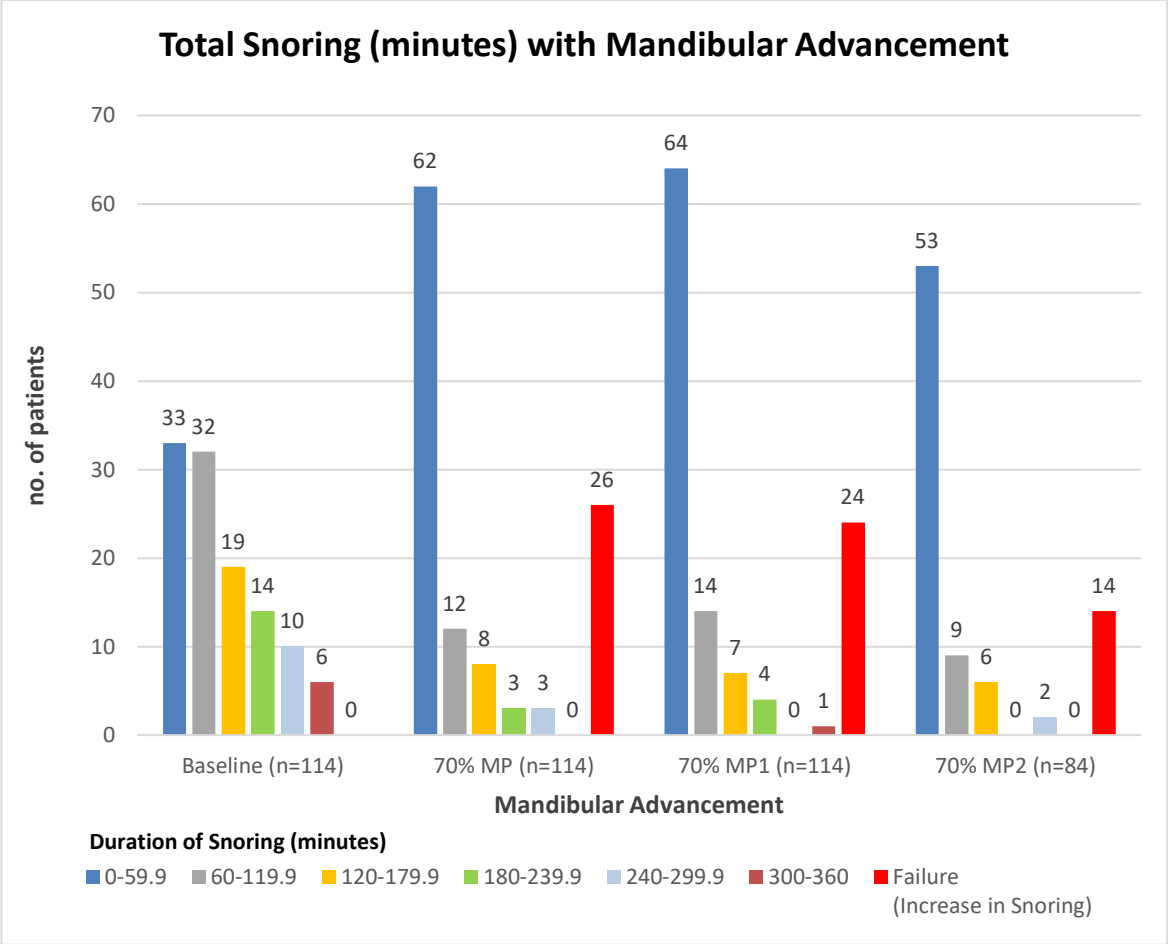


Figure 6.16 Stratification of total snoring duration with mandibular advancement. Snore responders transposed into lower tiers of snoring with incremental mandibular advancement to 70%MP2 position. More patients were noted in tier 0-59.9 minutes at 70%MP2 position as compared to baseline (53 patients (63.1%) vs 33 patients (28.9%) respectively. In snore non-responders, snore treatment failure was observed in 26 patients (22.8%) at 70%MP, 24 patients (21.1%) at 70%MP1 and 14 patients (16.7%) at 70%MP2 positions respectively. Despite titration to 70%MP2 position, 14 patients (16.7%) increased in snoring as compared to baseline.

6.6.2 Total Snore Reduction (TSR%)

In our analysis, we defined total snore reduction as the reduction in total snoring time expressed as a percentage of baseline snoring time (TSR %).

Table 6.6 summarizes TSR% treatment response in snore responders and non-responders stratified in incremental tiers of snoring reduction in patients at 70%MP, 70%MP1 and 70%MP2 positions. Snore non-responders were defined as TSR < 0%. These patients were observed to have more snoring with MAS therapy compared with baseline.

6.6.2.1 SNORE RESPONDERS

In snore responders, we observed a distinct improvement in the TSR 75-100% tier with progressive mandibular advancement from the 70%MP to 70%MP1 and 70%MP2 positions. Patients in this tier reduced their snoring by 75% to 100% as compared to baseline. In other words, ¾ or more of snoring duration was abolished with MAS therapy at the defined mandibular position. At 70%MP position, 35.9% (41/114) of patients were noted in the TSR 75-100% tier. This increased to 38.6% (44/114) and 38.1% (32/84) at 70%MP1 and 70%MP2 positions respectively, (Table 6.6).

At the final 70%MP2 position, 38.1% (32/84) of patients attained marked reduction of 75-100% in snoring. Other patients were noted to have lesser degrees of snoring reduction with 21.4% (18/84) experiencing 50-74.9% snoring reduction. 13.1% (11/84) of patients shown to have a 25-49.9% reduction in snoring. Minimal reduction in snoring was noted in 10.7% (9/84) of patients who improved only up to 25% of baseline snoring duration.

Overall, it was noted that more than 75% of MAS patients improved in snoring at each defined position of mandibular advancement. The percentage of patients exhibiting snoring

improvement was 77.1%, 78.9% and 83.3% at positions 70%MP, 70%MP1 and 70%MP2 respectively. It is noteworthy to observe that a consistent proportion of patients received the highest tier of snore reduction (TSR 75-100%) and this remained at comparable levels between the 3 mandibular positions (35.9% vs 38.6% vs 38.1%). In fact, pooled data from the 2 highest tiers of snore reduction (TSR 50-74.9% and TSR 75-100%) show that 59.5% of patients attained > 50% reduction in snoring at 70%MP2 position. Pooled data from the 2 lower tiers of snoring improvement (TSR <24.9% and TSR 25-49.9%) suggest that 23.8% of patients obtained lesser benefit with < 50% decrease in snoring reduction observed. Nonetheless, it is important to note that a significant proportion of patients did not response favorably to MAS therapy despite mandibular advancement. This is explored in section 6.6.3 below.

6.6.2.2 SNORE NON- RESPONDERS

In this analysis of snore non-responders, we defined total snoring failure (TSR <0%) as patients who increased in snoring when expressed as a percentage of baseline snoring. Like the observations noted for the duration of snoring in non-responders, the proportion of patients who worsened with MAS therapy remained relatively constant despite progressive mandibular advancement to the final 70%MP2 position. The proportion of TSR <0% patients where noted to be 22.8%, 21.1% and 16.7% in the 70%MP, 70%MP1 and 70%MP2 positions respectively (Table 6.6 and Fig 6.17). At the 70%MP position, 22.8% (26/114) of patients worsened in snoring duration compared to baseline. With an incremental 1mm of mandibular advancement to the 70%MP1 position, 21.0% (24/114) of patients still reported poor outcomes with worsening in snoring percentage. Despite an

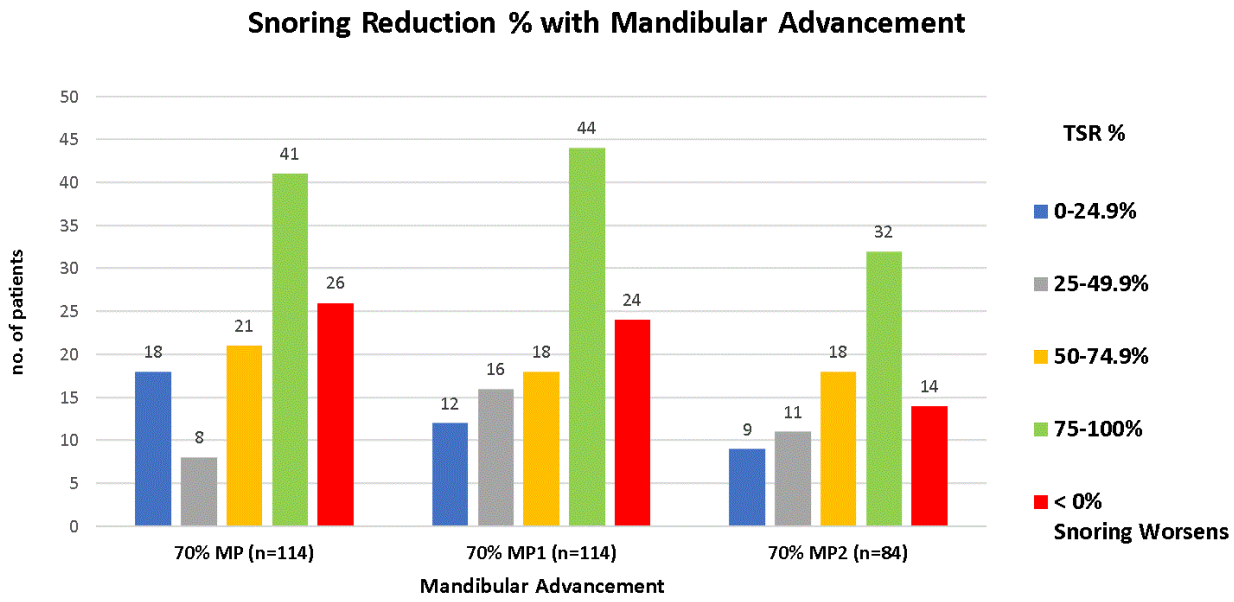
additional 1mm titration to 70%MP2 position, 16.7% (14/84) of patients exhibited poorer snoring outcomes with worsening in snoring compared to baseline.

TABLE 6.6 TOTAL SNORE REDUCTION RESPONSE IN ALL PATIENTS.

Treatment Response	70%MP (n=114)	70%MP1 (n=114)	70%MP2 (n=84)
TSR < 25%	18/114 (15.8%)	12/114 (10.5%)	9/84 (10.7%)
TSR 25 - 49.9%	8/114 (7.0%)	16/114 (14.0%)	11/84 (13.1%)
TSR 50 - 74.9%	21/114 (18.4%)	18/114 (15.8%)	18/84 (21.4%)
TSR 75 - 100%	41/114 (35.9%)	44/114 (38.6%)	32/84 (38.1%)
TSR < 0%	26/114 (22.8%)	24/114 (21.0%)	14/84 (16.7%)

Definition of abbreviations: TSR = Total Snoring Reduction expressed as a percentage of baseline; data presented as number of subjects in group (percentage of group). 70%MP = 70% Maximum Protrusion, 70%MP1 = 70% Maximum Protrusion +1mm, 70%MP2 = 70% Maximum Protrusion +2mm.

Table 6.6 Total Snore Reduction (TSR) response in all patients (n=114). Patients who experienced the greatest reduction in snoring are noted in the TSR 75-100% tier. In this tier, 75-100% of snoring was abolished. Note that comparable proportions of patients (35.9% vs 38.6% vs 38.1%) were found at the 3 mandibular positions. At 70%MP2, 59.5% of patients obtained >50% reduction in snoring. The remaining 23.8% of patients achieved smaller improvements (<50% snore reduction). However, at 70%MP2, 16.7% of the group worsened in snoring.



Definition of abbreviations: TSR% = Total Snoring Reduction expressed as a percentage of baseline snoring; data presented as number of subjects in group (percentage of group). 70% MP =70% Maximum Protrusion, 70%MP1 = 70% Maximum Protrusion +1mm, 70%MP2 = 70% Maximum Protrusion +2mm.

Figure 6.17 Stratification of Total Snoring Reduction (TSR%) with mandibular advancement. In the highest tier of snore reduction (TSR 75-100%), a comparable proportion of patients (41 (35.9%) vs 44 (38.6%) vs 32 (38.1%) patients) obtained marked reduction, at 70%MP, 70%MP1 and 70%MP2 positions respectively. In snore non-responders, snore treatment failure was observed in 26 patients (22.8%) at 70%MP, 24 patients (21.1%) at 70%MP1 and 14 patients (16.7%) at 70%MP2 positions respectively. Despite titration to 70%MP2 position, 14 patients (16.7%) worsened in snoring compared to baseline.

6.6.3 Comparison between Snore responders and non-responders

Individual snore responses from the 14 failure and top 16 snore responders at 70%MP2 position are shown in Figures 6.18 and 6.19. In snore non-responders, there was a heterogeneity in response to MAS therapy despite progressive mandibular advancement

(Figure 6.18). Several patients improved in snoring with incremental mandibular advancement at 70%MP and 70%MP1 positions but increased in snoring substantially at 70%MP2 position. Others worsened immediately at 70%MP with no improvements noted as 70%MP1 or 70%MP2 positions and yet other subjects improved at 70%MP position but worsened with more advanced stages of mandibular protrusion.

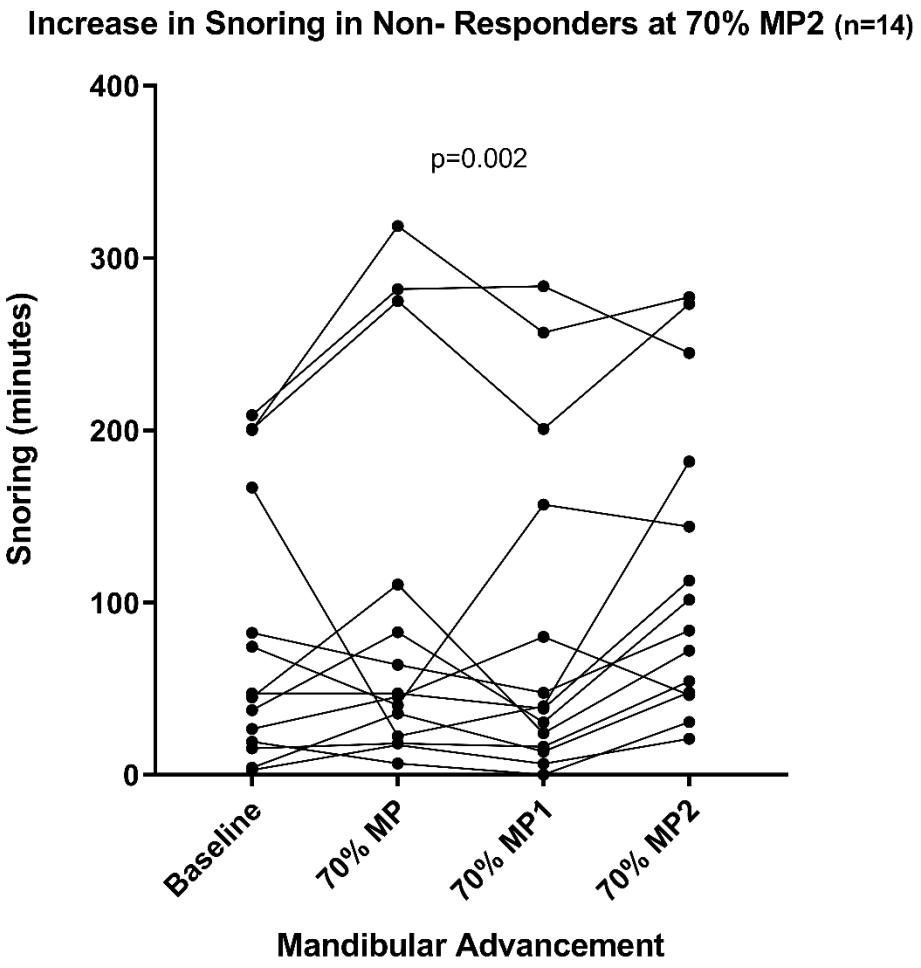


Figure 6.18 The effect of MAS therapy on total snoring (minutes) in the 14 non-responders at all advancement levels. Several patients improved in snoring with incremental mandibular advancement at 70%MP and 70%MP1 positions but increased in snoring substantially at 70%MP2 position. A heterogeneity in snore response was noted but overall, at 70%MP2 position, all subjects worsened in snoring as compared to baseline.

The individual response in the best 16 snore responders are shown in Figure 6.19 below. In contrast to snore non-responders (Fig 18), all patients improved in snoring with mandibular advancement from the outset at 70%MP position. Further decreases, in the majority of subjects, were noted at 70%MP1 position. With further titration to the 70% MP2 position, all experienced marked decreases in snoring as compared to baseline with several patients having minimal or no snoring.

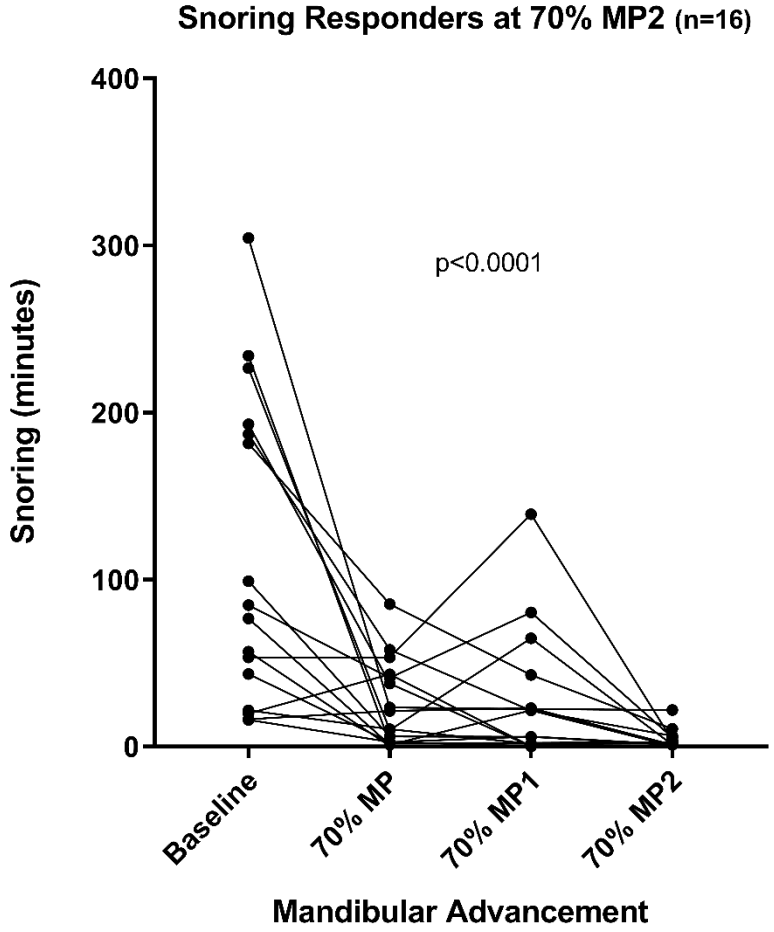


Figure 6.19 The effect of MAS therapy on total snoring duration in the 16 snore responders at all advancement levels. All patients improved in snoring with incremental mandibular advancement at 70%MP position. Further decreases in snoring were noted at 70%MP1 position in most patients with several patients increasing slightly at 70%MP1. However, with further titration to the 70% MP2 position, all patients experienced a marked decrease in snoring with several noted to have negligible snoring recorded.

The baseline characteristics between the top snore responders (n=16) and snore non-responders (n=14) at 70%MP2 are summarized in Table 6.7. No significant differences were found between the two groups with respect to gender, age, BMI, neck circumference, ESS and mandibular protrusive range. There were no significant differences in AHI, OAI, OHI and RMI. Total snoring and snore types with respect to duration, percentage were not observed to be significantly different between the groups.

TABLE 6.7 BASELINE CHARACTERISTICS OF TOP SNORE RESPONDERS (n=16) vs NON-RESPONDERS (n=14)

Variable	Responders (n=16)	Non-responders (n=14)	p Value
Gender	11M,5F	8M,6F	0.80
Age, yr	49.1 ± 12.9	56.1 ± 8.4	0.09
BMI, kg/m^2	27.8 ± 3.5	27.9 ± 5.0	0.93
Neck circumference, cm	38.8 ± 4.1	39.1 ± 5.2	0.85
Epworth sleepiness scale	7.6 ± 4.0	5.9 ± 4.3	0.29
Max. Pro, mm	10.3 ± 1.3	10.5 ± 1.7	0.73
AHI, events/hr	12.1 ± 10.1	9.3 ± 5.3	0.36
OAI, events/hr	0.3 (0.0, 1.3)	0.1 (0.0,0.5)	0.59
OHI, events/hr	10.1 ± 6.6	8.3 ± 5.1	0.40
RMI, events/hr	6.2 (2.3, 14.4)	5.6 (0.9, 15.1)	0.52
Total Snore, mins	113.4 ± 93.2	80.8 ± 78.3	0.31
Total Snore %	16.9 (5.9, 50.3)	14.1 (4.1,37.7)	0.24
Inspiratory Snore, mins	102.9 ± 98.5	56.2 ± 56.2	0.13
Inspiratory Snore %	15.9 (3.6, 49.2)	10.3 (3.1,18.8)	0.39
Expiratory Snore, mins	1.4 (0.3, 13.8)	4.7 (1.4, 20.2)	0.20
Expiratory Snore, %	0.4 (0.1, 2.9)	1.1 (0.3, 4.9)	0.17
IE Snore, mins	0.8 (0.1, 5.0)	2.6 (0.7, 23.3)	0.16
IE Snore %	0.2 (0.0, 1.1)	0.7 (0.2, 6.8)	0.16

Definition of abbreviations: BMI = body mass index; AHI = apnea+hypopnea index; OAI = Obstructive Apnea Index; OHI = Obstructive Hypopnea Index; RMI = respiratory movement index; % = Percentage; IE = Inspiratory and Expiratory; Continuous data are presented Mean ± Standard deviation or Median and interquartile range.

Table 6.7 Baseline characteristics of top 16 snore responders vs non-responders. No significant differences were noted in gender, age, BMI, neck circumference, ESS and mandibular protrusive range. Sleep variables (AHI, OAI, OHI, RMI) were not significantly different. Total snoring and snore types with respect to duration, percentage were not observed to be significantly different between the groups.

6.7 DISCUSSION

While it has been long recognized that adult SDB is characterized by repetitive episodes of complete or partial upper airway obstruction (UAO) snoring, the cardinal sign and symptom of OSA, has not been objectively measured comprehensively. Quantitative measurement of snoring with the Sonomat™ in this study provided a simple, practical way to assess SDB as well as identifying apneic and hypnoeic events to generate the AHI. This is the first and largest study to objectively determine the dose-response effects of mandibular advancement (MA) on snoring and snore types in primary snorers and OSA patients referred for MAS therapy. We made a number of novel findings: 1) Progressive MA decreases snoring by two-thirds in most patients but does not resolve the problem with a proportion of patients increasing in snore duration despite progressive MA; 2) Snoring reduces in a dose dependent manner from 70%MP to 70%MP2 with a "floor effect" noted at the maximum level of protrusion; (3) Inspiratory snoring is the predominant snore type and it decreases significantly with MAS but minimal changes are present in expiratory and IE snoring; 4) the greatest improvements in snore reduction occurred at 70%MP with lesser improvement with progressive MA.

In this study, patients undergoing MAS therapy were provided with a customized MAS fitted at 70%MP and progressively advanced by 1mm increments to the 70%MP1 and 70%MP2 positions. Our results of complete AHI response (AHI <5/hr) in 54% in our subjects is in concordance with previous studies [407, 485]. The dose dependent reduction in AHI with progressive MA also aligns with previous reports [328, 404, 410, 484, 486].

At 70%MP2, 60% of patients obtained >50% reduction in snoring with the remaining 23% of snore responders receiving lesser improvements of <50% snore reduction. However, 17% of patients worsened in snoring compared to baseline. MAS treatment reduced total snoring significantly in a dose dependent fashion (baseline = 97 to 44 vs 38 vs 33 minutes) at 70%MP, 70%MP1 and 70%MP2 respectively. At 70%MP2, approximately 66% of total snore duration and percentage was abolished. Our results are comparable to that observed by Gindre and colleagues who noted a 60% reduction in snores per hour (snore index) in which patients commenced MAS at the 80%MP position [407]. In the literature, a great variability in snore response rates can be observed. A previous review by Victor Hoffstein reported a 45% reduction in snoring [342]. However, snoring was predominantly subjectively assessed with varying degrees of MA performed.

Subjectively assessed snore reduction of 76% was reported by Johnston et al. using a questionnaire [376]. A 47% reduction in snore frequency by Mehta and co-workers [119], 36 and 58% reductions in Herbst and monobloc devices respectively used by Bloch and colleagues have been reported [373]. A low reduction rate of 15.8% has also been described by O'Sullivan et al. [120]. These authors quantified snoring frequency (snores per hour) and snoring intensity (dB). In contrast we objectively quantified snoring using total duration and percentage of Qd time. The variability in results can be attributed to different MAS devices used with varying degrees of MA. More importantly, it highlights the poor uniformity in methods of snore measurement.

Although the duration and percentage of total snoring reduced significantly, a "floor effect" was observed in our study. Additional increments of 1mm advancement to 70%MP1 and 70%MP2 resulted only in minimal decreases in snoring duration (2.5 and 0.1 mins respectively) and total snore % (2.5 and -0.05 %) respectively from the initial position.

Although our findings document a dose-dependent response with reductions in snoring duration from baseline to 70%MP2, the greatest decrease in snoring occurred at 70%MP with diminishing reductions noted with further 1mm increments to 70%MP2. This diminishing improvements in snore duration has clinical implications. Adherence to MAS therapy has been shown to be linked to a patient's perception of snore improvement [487]. However, adverse side effects and progressive bite alteration changes are an ongoing concern [398, 399]. Hence, although effective resolution of snoring is paramount, a delicate balance between optimal therapeutic outcomes and the degree of MA employed is critical. The degree of MA required for optimal treatment outcomes has been a topical issue and still much controversy exists today. Importantly, treatment outcomes have been based on the AHI metric and no study has objectively reported changes in snoring with progressive MA. Some propose only minimal MA [405, 488] whilst others advocate greater levels of MA. These studies have shown that increasing levels of MA improves upper airway calibre [483], treatment efficacy and success rates [407, 484]. Our observation of a "floor effect" in snore reduction and that the greatest reduction occurred at 70%MP is a key finding and has important clinical implications. Furthermore, as variability in snore response was noted to occur in snore-responders, non-responders and even severe OSA patients at different degrees of MA, this may imply that device specific,

and patient specific factors can influence individual response. Thus, our findings challenge the concept of using predefined "threshold" of MA (e.g. percentage of maximum protrusion) for clinical success but advocate objective quantification during treatment that are clinically correlated to patient symptoms.

In our study, an arbitrary MA of 70%MP was used as a previous investigation of this device type has demonstrated greater therapeutic efficacies at higher degrees of MA [119]. An advancement of 70%MP2 represents 90% maximum protrusive capability. Thirty patients did not elect to increase MA past 70%MP1 due to increased side effects (jaw pain, teeth pain, bite alteration effects); these are consistent with those found in the literature [342, 487]. Thus, although there was variability in the absolute value (mm) of mandibular advancement, our approach to begin MA at 70%MP and titrating by additional 1mm increments was thought to be applicable to clinical practice.

At 70%MP2, all patients were titrated to their maximal comfortable protrusive capability. Vertical opening of MAS device has been shown to worsen upper airway collapsibility due to retro-positioning of the mandible and restricting the degree of MA [489-491]. Previous studies have also shown a clear patient preference of limited jaw opening which improves patient comfort and compliance [490]. Hence, we limited vertical opening with < 8 mm interincisal opening noted. Aarab and colleagues noted increased AHI improvement at higher degrees (50%MP and 75%MP) of MA at a constant vertical dimension [405]. However, the impact of vertical opening with progressive MA on snore characteristics is unclear and warrants further investigation.

In our study, 66% of total snoring (duration and percentage) was abolished with inspiratory snoring noted to be the predominant snore type. Inspiratory snoring % decreased in a dose dependent manner by 85% at 70%MP2 position. In contrast, small but significant changes in IE snoring was noted with no significant change in expiratory snoring observed. The reason for these findings is unclear and warrants further investigation.

Several plausible reasons may account for the differences noted in snore characteristics. Our study recruited predominantly milder SDB patients and "en-bloc" anterior movement of the tongue has been reported in milder OSA patients [334]. A dose-dependent effect of MA on genioglossus muscle activity has been reported [337] but a recent study show minimal effect on genioglossus muscle responsiveness in severe OSA patients suggestive that the primary mode of MAS action is improvement in passive pharyngeal anatomy [328]. A thicker soft palate in OSA patients as compared to non-apneic snorers has been reported [464]. Moreover, severe OSA patients have significantly narrower cross-sectional area at the level of uvula in expiration and experience greater expiratory snoring [464]. However, we noted only small significant changes in IE snoring with MA and not in expiratory snoring. This could be rationalized due to the milder SDB severity in our group or the fact that the inspiratory component of the IE snoring may have improved resulting in "conversion" of IE to expiratory snoring, also explaining why there was no significant change in expiratory snoring.

Overall, localized soft tissue factors may further compromise upper airway patency, impair upper airway dilator muscle response and lead to changes in snore characteristics observed.

Thus although MRI imaging show lateral widening predominantly in the velopharynx [327], recent physiologic studies with MAS suggest different patterns of anatomic capacity and dynamics in pharyngeal dilatation between responders and non-responding groups [328].

A significant proportion of patients did not improve in snoring despite varying degrees of MA. Snore non-responders had a heterogeneous response with progressive MA. At 70%MP2, 17% of subjects worsened in snoring compared to baseline. In our best snore responders, the majority of snore improvement occurred at 70%MP with minimal but additional improvements occurring at 70%MP2. The reasons for this occurrence are unclear. Snore non-responders were noted to be older than responders, (56.1 ± 8.4 vs 49.1 ± 12.9 years), but this was not significant, p=0.09. We observed no differences in BMI, neck circumference, ESS, AHI and baseline snore characteristics. Anatomic and non-anatomical factors could be reasoned to contribute to the results noted. However, 61% of our study group was noted to have mild OSA. Previous phenotyping studies have highlighted that mild OSA may represent a distinct phenotype with non-anatomical pathophysiological mechanisms. The contributory factors include high loop gain, low arousal threshold and diminished pharyngeal muscle function [172, 492, 493]. Nonetheless, anatomic factors such maxillary constriction [44] have been also implicated and the effects of MA on the displacement of internal upper airway structures have been proposed. Physiologic investigation of MA in rabbits show non-uniform changes in peri-pharyngeal tissue structures. These changes in tissue deformation and hyoid bone position are speculated to promote upper airway dilation [494].

In humans, physiologic investigation show that different levels of mandibular advancement may displace internal upper airway structures to varying degrees which results in differences in Pcrit improvement between responding and non-responding groups [328]. Differences in tongue and lateral pharyngeal wall deformation [334] and a lower position of the hyoid bone has been linked to increased upper airway collapsibility [466]. MAS has also been thought to promote upper airway patency by maintaining the new or existing relationship of the hyoid and its surrounding structures [495]. Nasal resistance has also been proposed as a key contributor to the development of OSA and impacts MAS response [496, 497]. Our study design was clinically focused on snore investigation and hence did not measure maxillary morphology, non-anatomical mechanisms or nasal resistance due to clinical constraints. It is feasible that closer scrutiny of snoring characteristics including snore frequency and concurrent analysis of anatomic and non-anatomic and clinical factors will clarify our understanding and help elucidate the potential sites of increased UAO related to snoring.

As a group, improvements in daytime somnolence occurred with significant decreases in ESS scores. This observation aligns with previous studies [342, 407, 498] and can be explained in part by the improvements in respiratory events and snoring. The role of cortical arousals has been proposed as a key factor in the pathogenesis of OSA [499, 500]. Our results of significant decreases in RMI suggest that our patients experience less sleep fragmentation which may translate to less daytime somnolence. Our study recruited only 4 severe OSA patients. In 2, AHI reduced markedly to <10 events/hr with residual snoring noted. However, in the remaining 2 patients, OSA remained unresolved (AHI >30 events/hr) despite negligible snoring (0 and 2.5 mins) noted. This observation typifies the

deficiencies of using AHI as a metric to propose MAS therapy and challenges the dogma that severe OSA patients should not be treated with MAS. However, the observations of negligible snoring in patients with marked residual OSA has serious implications if patients correlate minimal snoring with OSA resolution. Thus, our results advocate for the need for an accurate and objective measurement of snoring, complimentary to AHI metrics to improve personalized treatment approaches for optimal outcomes.

Although the Sonomat™ enabled us to objectively quantify snoring and provide novel insights into the progressive effects of MA on snoring characteristics, the study has several limitations. The reported results were obtained by using one particular type of MAS design. Given the multitude varying MAS designs available, it is conceivable that different outcomes may be achieved. Moreover, the results were obtained from mandibular position ranging from 70%MP to 70%MP2. At 70%MP2, this represented 90% of MP with 26% of patients electing not to pursue additional MA. This was generally related to adequate control of clinical symptoms or reluctance due to the fear of increasing MAS side effects. Thus, the results obtained are reflective of clinical practice and represents a key strength of our study. The generalizability of our results to other mandibular positions however should be interpreted with caution. Future work investigating the dose dependent effects of MAS at lower degrees of mandibular advancement is needed. Although a key strength in our study was a large sample size, we acknowledge that our study consisted of primary snorers, mild/moderate OSA patients with few severe OSA subjects. Thus, our findings may not necessarily extend to severe OSA patients. Another limitation was as the inability to monitor sleep and the lack of EEG to stage and identify sleep and arousal. However, the Sonomat™ has been validated against PSG [414, 415] and previous work by Norman and

colleagues have confirmed a close relationship between Qd time and EEG-defined sleep as well as the accurate calculation of the AHI [105]. In addition, the use of body movement has demonstrated to be a robust indicator of sleep disturbance [431]. The utilization of oximetry would undoubtedly have provided a fuller picture of SDB. Also, assessment of sleep position may have clarified the effect of body habitus on snore characteristics.

6.8 CONCLUSION

Progressive MA decreases the AHI and snoring in most patients but does not resolve the problem in all with a proportion of patients increasing in snore duration despite progressive MA. Inspiratory snoring was the predominant snore type, this decreased in a dose dependent manner with a "floor effect" noted. Future studies are warranted to investigate factors identifying snore responders and non-responders to define who may be contraindicated for MA. This may clarify the variability in snore responses noted with MAS therapy, with the view to improving personalized approaches to patient selection.

7 GENERAL DISCUSSION AND CONCLUSION

Obstructive sleep apnea (OSA) is a common form of sleep disordered breathing (SDB) that affects both adult and children. The diagnosis of OSA has been classically reliant on polysomnography (PSG), however, in the dental setting, assessment by PSG is not routinely performed. Formal supervised PSG requires the attachment of multiple sensors to the face, head and body with recordings performed in a laboratory/hospital setting. Sleeping in a supervised and foreign environment can be disruptive with many patients finding this method of diagnosis not representative of a typical night sleep. PSG is invasive, complex, labor intensive and its costly nature has precluded widespread adoption in clinical practice. Moreover, paediatric SDB is characterized by prolonged periods of partial upper airway obstruction (UAO) with runs of labored breathing that is not reflected in PSG-derived indices such as the most used metric, the apnea/hypopnea index (AHI).

In adults, conducting multiple studies, as in the case of MAS titration studies to determine the required level of mandibular advancement (MA) for optimal therapeutic outcomes is cost-prohibitive and often unrealistic. This process can be convoluted resulting in many patients not having an a priori diagnosis before commencing mandibular advancement splint (MAS) therapy or experiencing poorer treatment outcomes due to a failure to titrate the MAS at follow-up. In children, although intra-oral examination, dental and cephalometric assessment may be performed, objective measurement of SDB is rarely conducted. Furthermore, although portable monitoring diagnostics systems are widely available, and are increasingly used in adults, these are generally not indicated in children.

It is for these reasons, and others, that routine assessment of SDB in adults and children is not conducted in a dental setting, before or after treatment performed. Thus, a simple, effective and self-administered method of diagnosis is required. In this regard, the Sonomat™ used in our investigations allowed accurate measures of SDB for prompt diagnosis and dynamic treatment planning.

It is now widely recognized that SDB can negatively impact cardiovascular and metabolic outcomes in both adults and children. The association of OSA with hypertension in adults, children and pregnant women are now well documented in the literature. Adults with significant cardiovascular morbidity such as atrial fibrillation and stroke require immediate diagnosis and treatment. In children, chronic comorbidities associated with untreated OSA include cognitive deficits, behavioral problems, poor academic performance and poor quality of life. Robust evidence now exists suggesting that paediatric OSA may increase the risk of developing severe cardio-vascular and metabolic conditions, with ongoing "learning debt" issues. Snoring more recently has also been linked to stroke, increased prevalence of carotid atherosclerosis in adults, and behavioral problems and blood pressure at all levels of SDB severity in children.

Adenotonsillar hypertrophy and, increasingly, obesity are implicated in paediatric OSA. In adults, obesity, nasal and tongue-based obstruction are key contributory factors. However, over the last two decades, anatomical factors have been increasingly implicated to play a contributory role in SDB. Craniofacial abnormalities such as maxillary constriction and mandibular retrognathia are typical traits proposed to contribute to SDB. A complex

relationship exists between UAO that influences the mode of breathing and craniofacial growth and development. Although still steeped in much controversy, it has been proposed that UAO induces mouth breathing which results in neuromuscular imbalances. These factors are thought to alter tongue posture which results in maxillary constriction, a craniofacial modification associated with SDB. Partial UAO as exemplified by snoring is a common sign and symptom of SDB and although commonly recognized and subjectively appraised, objective measurement of snoring is not performed adequately. Thus, a core focus of this thesis evaluated the prevalence of snoring and snore characteristics in adults and children with varying anatomical imbalances. As previous data has predominantly been AHI based, with little snoring data reported, the Sonomat™ was utilized to provide accurate measure of SDB and snoring to quantify treatment effects of rapid maxillary expansion (RME) and MAS therapy.

In our study, we observed that many parents often presented with the chief concern of mal-alignment of teeth in their children. Some of these children exhibited clinical features commonly coined as “long face syndrome” or “adenoid facies”; with accompanying symptoms of snoring and clinical history of asthma, allergic rhinitis, bedwetting, or frequent respiratory infections. Parents of these children did suspect some degree of SDB in their children but few were aware about the associations between UAO and craniofacial growth and that this condition was not benign but required management. Thus, a significant knowledge gap existed and it fell upon the clinician to educate and better inform the parents about the influence of UAO on growth and development. Evidence exists to support the reversibility of the adverse effects of SDB on dento-facial structures if

normal breathing is restored. Thus, there exists an imperative for early diagnosis and timely management of SDB.

In children with OSA, adenotonsillectomy (AT) has classically been proposed as first line therapy. However, recent evidence suggests that not all children benefit from AT with a significant proportion of children having residual OSA. In children and adults with increased levels of OSA severity, CPAP has been proposed as a treatment option. However, adherence to CPAP is poor and many patients, especially children, find CPAP intolerable. As anatomical factors were hypothesized to play a contributory role in SDB, dental treatments have evolved over the last two decades to target specific anatomical areas that contribute to UAO. In children for example, the RME procedure implemented in this study was initially used to treat dental malocclusion. Studies as early as the 1970's reported medical benefits of RME but it was not until several decades later that research into the effects of RME on SDB for maxillary constriction began. In the case of MAS devices, this mode of therapy evolved from oral devices used to treat children with Pierre Robin sequence. This link to sagittal discrepancies highlighted another potential source of UAO due to retroglossal tongue base collapse. As a result, oral appliances for children and MAS for adults have gradually evolved over the last 2 decades for SDB.

Our study showed that few non-obese children with maxillary constriction (7%) had OSA and that obstructive apneas and hypopneas were rare evets, occurring less than once per hour. However, despite presenting with minimal symptoms of SDB, 46% of children were noted to snore significantly and the frequency of snoring was found to be a better measure,

with a much larger gain, than the mixed and obstructive apnea/hypopnea index (MOAHI). Thus, many children previously classified as “simple snorers” without OSA may have significant obstructed breathing (OB) with runs of snoring and/or stertor which may play a greater contributory role in sleep fragmentation as compared to obstructive apneas or hypopneas as classically hypothesized.

A preliminary conclusion from our results of few children with maxillary constriction having MOAHI > 1event/hr would suggest no clear indication to routinely screen children with maxillary constriction. However, our observations that a significant proportion of children had snoring despite mild SDB symptoms, normal or minimal tonsillar size with low OSA-18 scores is noteworthy as clinical assessment may be inaccurate. Furthermore, parental reports of witnessed apneas, snoring and wheezing were found to be unreliable when compared to the objective Sonomat™ recordings. This observation suggests that although clinical assessment and subjectively based questionnaire may provide some insight to the clinical picture, it may be unreliable. The results underscore the need to objectively measure breathing during sleep. The observation of wheezing and stertor in children with maxillary constriction is of novel interest. The chance finding of wheezing in two children highlights the unique ability of the Sonomat™ to identify respiratory pathology as well as SDB variables. Wheezing is characteristic of asthma and the ability to diagnose this pathological sounds adds a new dimension of potential research linking asthma to SDB disease states.

With RME therapy, all four OSA children resolved with MOAHI < 1event/hr. In these children, marked reductions in snoring duration and frequency were also noted. Our research extends previous work highlighting the potential role of RME for the treatment of snoring in OSA children. In OB children, RME reduced snore duration by 60%. However, 26% of OB children worsened in snoring despite RME. This key finding is of great clinical importance and underscores the limitation of being solely reliant on PSG metrics such as the AHI and highlights the need to objectively measure snoring.

In adults, we noted that our patients referred for MAS were generally primary snorers (PS) or had OSA of a mild/moderate severity. Inspiratory snoring was the predominant snore type and this was noted to occur more in women than men. This gender differences is interesting and paves the way for future research. With MAS therapy, 60% of patients experienced a > 50% reduction in snore duration and overall, 66% of snoring was abolished. However, one-third of subjects still had residual snoring following treatment. This finding, of a marked reduction in snoring with MAS, is encouraging from the perspective that a patient's MAS adherence is linked to their perception of a reduction in their snoring. This is a pertinent finding as patients sought treatment primarily due to snoring complaints from bed-partners and the significant improvements noted would likely translate to increased MAS compliance. Additionally, as snoring decreased, respiratory movement arousals decreased which resulted in less sleep fragmentation, hence improvements in daytime somnolence.

A dose dependent reduction in snoring with a “floor effect” was noted with minimal reductions in snoring past the initial 70%MP position. This finding suggests that consideration should be given to a weighted compromise between the level of mandibular advancement employed and snore reduction obtained; bearing in mind recent evidence highlighting progressive bite alteration effects with MAS use. Notably, a subset of patients had a worsening of snoring at all levels of MA with 17% of patients having more snoring at maximum protrusion (70%MP2). This level of protrusion is significant and represents approximately 90% of the maximum protrusive capability in patients recruited. It was thus evident that despite extensive mandibular advancement, a subset of patients did not improve in snoring and may have benefited from adjunctive input such as surgical treatment or alternative treatment options. Future research into the causes of increased snoring in MAS non-responders are required and detailed analysis of snore characteristics may help identify keys sites of UAO.

Overall, it is evident from the research in this thesis that a significant proportion of patients benefit from RME and MAS therapy. However, mono-therapies such as RME in children and MAS therapy in adults when proposed as stand-alone treatment options are not curative and do not abolish snoring in all patients. A subset of children with RME and adults with MAS worsened in snoring despite the instigated treatment option proposed to target localized sites of anatomical imbalances. Thus, it is likely that a combination of strategies will be required and may need to be coordinated and implemented at diagnosis and during the course of treatment. For example, children who snore post-RME may require MAS type devices which address tongue base obstruction. On the other hand, adults who fail MAS may require ENT intervention and possibly surgical input such as

surgically assisted RME and/or maxillo-mandibular advancement surgery. This hypothesis requires further work and future research will undoubtedly tease out specific treatment combinations that optimize treatment outcomes.

The unique ability of the Sonomat™ to characterize and objectively quantify snoring adds immense value to treatment planning and outcomes and future research into snore characteristics may help identify potential sites of UAO that could be targeted with conservative or surgical intervention. In instances where a distinct phenotype with a non-anatomical pathophysiological mechanism is thought to occur, the consideration of other non-anatomical contributory factors such as high loop gain, low arousal threshold and diminished pharyngeal muscle function is warranted. Already, current research on myo-functional therapy in both adults and children shows promising results. A personalized targeted treatment approach based on the identification of individual pathophysiological mechanisms of SDB is hence supported by our research findings.

In conclusion, the Sonomat™ used in this thesis is a validated diagnostic system that can contribute to our understanding of SDB to help identify and treat both adults and children in the dental setting. In diagnosis and during RME and MAS therapy, the unique ability to objectively measure sleep and breathing variables; and in particular snoring in the patient's own home over multiple nights was of immense value. The identification that a significant proportion of children with maxillary constriction have OB underscores the need to objectively measure snoring. The ability to assess therapeutic response in both RME and MAS in a timely manner allows a prompt and personalized response to individual patient

needs. Objective measurement of snoring with the Sonomat™ compliments the PSG based metric of the AHI and presents a paradigm shift by providing accurate measures of SDB that promotes dynamic treatment strategies to be implemented in the dental setting.

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9 APPENDICES

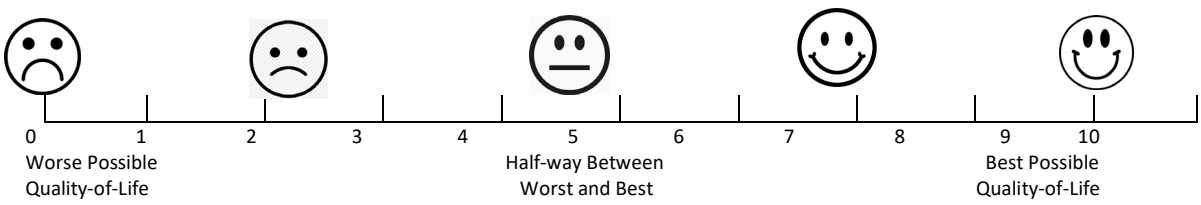
9.1 Quality of life OSA 18 Questionnaire

OSA-18 Quality of Life Survey
Evaluation of Sleep-Disordered Breathing

Instructions. For each question below, please circle the number that best describes how often each symptom or problem has occurred during the past *4 weeks* (or since the last survey if sooner). Thank you.

	None of the time	Hardly any of the time	A little of the time	Some of the time	A good bit of the time	Most of the time	All of the time
SLEEP DISTURBANCE							
During the past *4 weeks*, how often has your child had…							
…loud snoring?	1	2	3	4	5	6	7
…breath holding spells or pauses in breathing at night?	1	2	3	4	5	6	7
…choking or gasping sounds while asleep?	1	2	3	4	5	6	7
…restless sleep or frequent awakenings from sleep?	1	2	3	4	5	6	7
PHYSICAL SUFFERING							
During the past *4 weeks*, how often has your child had…							
…mouth breathing because of nasal obstruction?	1	2	3	4	5	6	7
…frequent colds or upper respiratory infections?	1	2	3	4	5	6	7
…nasal discharge or runny nose?	1	2	3	4	5	6	7
…difficulty in swallowing foods?	1	2	3	4	5	6	7
EMOTIONAL DISTRESS							
During past *4 weeks*, how often has your child had…							
…mood swings or temper tantrums?	1	2	3	4	5	6	7
…aggressive of hyperactive behaviour?	1	2	3	4	5	6	7
…discipline problems?	1	2	3	4	5	6	7
DAYTIME PROBLEMS							
During the past *4 weeks*, how often has your child had…							
…excessive daytime drowsiness or sleepiness?	1	2	3	4	5	6	7
…poor attention span or concentration?	1	2	3	4	5	6	7
…difficulty getting out of bed in the morning?	1	2	3	4	5	6	7
CAREGIVER CONCERNS							
During the past *4 weeks*, how often have the above problems…							
…caused you to worry about your child's general health?	1	2	3	4	5	6	7
…created concern that your child is not getting enough air?	1	2	3	4	5	6	7
…interfered with your ability to perform daily activities?	1	2	3	4	5	6	7
…made you frustrated?	1	2	3	4	5	6	7

OVERALL, HOW WOULD YOU RATE YOUR CHILD'S QUALITY OF LIFE AS A RESULT OF THE ABOVE PROBLEMS?
(Circle one number)



9.2 Epworth Sleepiness Scale

Name: _____

Date: / /

Epworth Sleepiness Scale

How likely are you to fall asleep in the following situations:

0 = Would never doze

1 = Slight chance of dozing

2 = Moderate chance of dozing

3 = High chance of dozing

Activity	Score
Sitting and reading	
Watching television	
Sitting, inactive in a public place (meeting, cinema)	
As a passenger in a car for an hour with no break	
Lying down for an afternoon nap, if time permits	
Sitting and talking to someone	
Sitting quietly after lunch without alcohol	
In a car while stopped for a few minutes in traffic	
TOTAL	

A score of 10 or above indicates you may be having a problem with daytime sleepiness. However, below 10 does not necessarily mean you do not have a problem.

9.3 Publications and Abstracts

Publications

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Abstracts

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