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A Prospective Randomized Cross Over Study on the Effect of a Tongue Stabilising Device on Obstructive Sleep Apnea.

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A thesis submitted in partial fulfillment of the requirements for the degree of
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Dedication

For my family.

Abstract

Obstructive sleep apnea (OSA) is a complex multi-factorial condition with sufferers complaining of disturbed sleep, snoring and daytime somnolence. OSA has a significant associated morbidity and mortality and is a public health problem. Even though continuous positive airway pressure (CPAP) seems to be very effective in the management of OSA, some patients prefer oral appliances, most commonly mandibular advancement splints (MAS). Recently the tongue stabilizing device (TSD) was introduced. The aims of this study were to evaluate the effect of a new tongue stabilizing device in patients diagnosed with OSA using questionnaires, cephalometrics, polysomnography and MRI, and the efficacy of the TSD and MAS in the management of OSA. The initial sample consisted of 24 patients with proven OSA (apnea/hypopnea index (AHI) 29 ± 4). 18 of the patients completed the protocol and 15 of them completed the MRI. A randomized crossover study design was used with $p < 0.01$. After completing 4 weeks acclimatization with each device, patients underwent two polysomnographs and an MRI scan. Complete response was defined as a resolution of symptoms and a reduction in the apnea/hypopnea index (AHI) to $\leq 5/h$, and a partial response $\geq 50\%$ reduction in AHI but remaining $\geq 5/h$. Subjective improvements were reported with both the TSD and MAS, with the majority of patients (88.9%) preferring MAS. AHI was significantly improved with TSD and MAS (13 ± 3 , 12 ± 2). Arousal index decreased with TSD and MAS (22 ± 2 , 21 ± 2 compared with baseline 35 ± 4), and minimum oxygen saturation (%) improved with TSD compared to baseline (88 ± 1 versus 83 ± 2). MRI analysis indicated that TSD increased overall airway volume (mm^3) compared to baseline (19 ± 2 versus 15 ± 1). Both TSD and MAS both produced a significant volume

increase in the velopharynx (6 ± 1 , 5 ± 1 versus 4 ± 0). No difference in overall shape of the airway was detected. The TSD and MAS had similar efficacy in the management of OSA with a patient preference for MAS. Therefore TSD has a well justified indication in OSA patients who may not be suited to use other appliances.

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List of Abbreviations

AF	Atrial Fibrillation
AHI	Apnea Hypopnea Index
AI	Arousal Index
AMP	Anterior Mandibular Positioner
ap	Antero-posterior
BMI	Body Mass Index
CBCT	Cone Beam Computed Tomography
Ce	Cephalometrics
CPAP	Continuous Positive Airway Pressure
CPITN	Community Periodontal Index of Treatment Needs
CT	Computed Tomography
ECG	Electrocardiogram
EDS	Excessive Daytime Sleepiness
EEG	Electroencephalogram
EMG	Electromyogram
EOG	Electro-oculogram
ESS	Epworth Sleepiness Scale
Hz	Hertz
MAS	Mandibular Advancement Splint
MinSaO ₂	Minimum arterial oxygen saturation level
ml	Medio-lateral
MRI	Magnetic Resonance Imaging

MRS	Mandibular Repositioning Splint
NC	Neck Circumference
NREM	Non-Rapid Eye Movement
OA	Oral Appliance
OSA	Obstructive Sleep Apnea
p	level of significance
PCO ₂	Partial Pressure of Carbon Dioxide
PO ₂	Partial Pressure of Oxygen
PSG	Polysomnography
RDI	Respiratory Disturbance Index
REM	Rapid Eye Movement
sd	Standard Deviation
SSS	Stanford Sleepiness Score
TRD	Tongue Retaining Device
TSD	Tongue Stabilising Device
TST	Total Sleep Time
UPPP	Uvulopalatopharyngoplasty

1. Introduction

1.1 Background

Obstructive Sleep Apnea (OSA) is a complex multi-factorial condition produced by a combination of anatomical and physiological factors. It is characterised by repetitive complete or partial closure of the upper airway during sleep resulting in sleep fragmentation and oxygen desaturation. OSA has a significant associated morbidity and mortality. It has been linked to cardiovascular and cerebrovasacular disease, excessive daytime sleepiness, increased risk for industrial and motor vehicle accidents, psychological, endocrine and haematological problems and as such is recognised as a significant public health issue.

In recent years there has been increased interest in identifying predisposing factors and using tools such as subjective questionnaires, polysomnography (PSG), cephalometrics (Ce) and magnetic resonance imaging (MRI) to enhance diagnosis and guide patient management. While the gold standard of care combines conservative modalities such as weight loss and nasal continuous positive airway pressure (CPAP), interest in oral devices has been increasing. The mandibular advancement splint (MAS) has been extensively investigated; however little research is available regarding the tongue stabilising device (TSD) as a lower cost alternative.

The objectives of this study were to evaluate the TSD in patients diagnosed with OSA using questionnaires, cephalometrics, polysomnography and magnetic resonance imaging, and to compare the efficacy of the TSD with the MAS.

The Null hypothesis of this study was that there is no difference in the efficacy of the TSD and MAS for the management of OSA.

The literature review will elaborate on the current knowledge of OSA, focusing on prevalence, pathophysiology, clinical features and consequences, diagnosis and management strategies. The MAS and TSD devices will be discussed.

1.2 Snoring

One of the most common consequences of the changes in the properties of the upper airway that occur during sleep is snoring.

1.2.1 Definition

Snoring is an inspiratory noise caused by vibration of the elements of the airway, predominately the soft palate and posterior faucial pillars ¹.

Snoring affects people of all ages but is most common in overweight, middle- aged and elderly adults ². The prevalence of habitual snoring is extremely high and reported to be 40% in men and 20% in women ³. Others report the problem as affecting about 10% of the population ⁴. The snoring sound is the result of vibrations of the soft tissues of the pharynx, soft palate and uvula having specific acoustic characteristics with frequencies ranging from 5 to 136Hz ⁵. Primary snoring refers to snoring that is not accompanied by apnea, hypoventilation or excessive sleepiness. However, snoring in some patients without apnea has been associated with significant sleep disturbance and sleepiness ⁶.

1.2.2 Pathophysiology

Snoring is an example of a flutter valve in which elements of the airway vibrate under the force of inspiratory suction pressure ⁷. The structure most important for this fluttering is the soft palate.

Early cineradiographic recordings showed that snoring was associated with increased esophageal pressure swings during inspiration with partial pharyngeal obstruction ⁸. In studies comparing snorers and non-snorers during sleep, it has been shown that snorers have more negative inspiratory pressure, greater pulmonary resistance during snoring breaths and flow limitation ^{9,10}. These events are all thought to be normal consequences of sleep, and not necessarily pathologic; however snoring is often thought of as part of a continuum of sleep disordered breathing ¹¹.

Due to the relaxation of the muscles and soft tissues of the airway which decrease the dimensions of the airway, moveable soft tissues in the airway, such as the soft palate and uvula vibrate as a consequence of the increased air velocity ¹².

1.2.3 Clinical Consequences

Snoring has been linked to a number of conditions such as hypertension, ischaemic heart disease and stroke, however a clear role has yet to be proven. These conditions have significant morbidity and mortality in their own right, hence snoring should be regarded seriously. Snoring also presents social issues leading to embarrassment and family dysfunction.

1.3 Sleep Apnea

1.3.1 Introduction and Background

Obstructive Sleep Apnea (OSA) is a well recognized condition characterized by repetitive obstruction of the upper airway often resulting in oxygen desaturation and arousals from sleep¹³. The complete or partial obstruction of the airway leads to apneas, hypopneas and hypoxemia (decrease in blood oxygen concentration)¹⁴. These episodes disrupt normal sleep patterns such that patients awaken feeling unrefreshed and suffer from excessive daytime sleepiness. It is a common disorder with potential cardiovascular, respiratory, neuro-cognitive and occupational morbidity and mortality.¹⁵ Almost every system in the body is affected by this condition with other associated problems including altered immune function¹⁴.

Over the past thirty years, many types of abnormal breathing have been described. Consequently it has been recognized that signs and symptoms could be used to describe several syndromes.

Burwell described patients suffering from obesity combined with hypercapnia, cor pulmonale, erythrocytosis and daytime somnolence as having Pickwickian Syndrome.¹⁶ This description evolved from *The Pickwick Papers* by Charles Dickens in 1836, who wrote

And on the box sat a fat and red faced boy, in a state of somnolency....."Joe!-damn that boy, he's gone to sleep again". The fat boy rolled slowly off the box....."Joe, Joe!" said the stout gentleman. "Damn that boy, he's gone to sleep again. Be good enough to pinch him, sir-in the leg, nothing else wakes him Joe, Joe!"..... (He) taps on the head with a stick, and the fat boy, with some difficulty, roused from his lethargy.

Guilleminault *et al* introduced the term obstructive sleep apnea syndrome characterized by daytime hypersomnolence and polysomnographically proven obstructive apneas.⁴ They were the first to describe the interaction between sleep, the respiratory muscles of the chest, and the muscles of the upper airway. This partially explained why the upper airway collapses during sleep leading to OSA

Block *et al* were the first to describe hypopneas as events of shallow breathing causing oxygen desaturation¹⁷. In 1988, those patients who suffered from hypopneas, with few or no apneas were described as having sleep hypopnea syndrome¹⁸. As a result, the previous term obstructive sleep apnea syndrome was replaced by obstructive sleep apnea-hypopnea syndrome.

In 1993 Guilleminault described a series of patients that had symptoms of OSA but who did not have obstructive apneas or hypopneas on polysomnography¹⁹. The term upper airways resistance syndrome described the increasing negative oesophageal pressure during inspiration and terminating in an arousal from sleep from which these patients suffered.

The initial description of obstructive sleep apnea syndrome by Guilleminault included the criterion of a minimum duration of 10 seconds for an apnea to be scored, and that more than 30 apneas per night be considered abnormal⁴. At a later time this was standardized as the apnea index. This is the number of apneas per hour of sleep.

Since these initial descriptions were coined, terminology and definitions have changed with the advances in technology. There was lack of uniform definitions, and the overlap between the clinical signs and symptoms of Pickwickian syndrome, obstructive sleep apnea-hypopnea syndrome and central sleep apnea syndrome created confusion in clinical settings and hindered research in the field¹³.

1.3.2 Definitions

Apnea

An apnea is defined as a cessation of breathing during sleep that lasts for 10 seconds or more. The Apneic Index is the average number of episodes of apnea per hour of sleep. For sleep apnea to be diagnosed, at least 5 such episodes must occur per hour⁴. An apnea is considered obstructive if there is continued respiratory effort despite cessation of airflow. An apnea is considered to be of central origin if there is no concurrent respiratory effort¹⁴.

Hypopnea

An hypopnea, or reduction in airflow, is when a 50% or greater reduction from baseline in tidal volume occurs, simultaneously with a 4% or greater reduction in blood oxygen saturation, lasting 10 seconds or more⁶. Baseline is defined as the mean amplitude of stable breathing and oxygen saturation in the two minutes preceding onset of the event (in individuals who have a stable breathing pattern during sleep) or the mean amplitude of the three largest breaths in the two minutes preceding onset of the event (in individuals without a stable breathing pattern).¹³. The Apnea Hypopnea Index (AHI), also known as the Respiratory Disturbance Index (RDI), refers to the average number of episodes of apnea plus hypopnea per hour during sleep.

Obstructive Sleep Apnea Hypopnea Syndrome

Sleep apnea syndrome is characterized by recurrent episodes of partial or complete upper airway obstruction during sleep. This manifests as a reduction in or complete cessation of

airflow despite ongoing inspiratory efforts. The lack of alveolar ventilation leads to a decrease in oxygen saturation and gradual increase in carbon dioxide levels. The event is often terminated by an arousal. Patients may show a lack of inspiratory effort initially, followed by gradually increasing effort against an occluded upper airway.

Diagnostic criteria include excessive daytime sleepiness, choking or gasping during sleep, recurrent awakenings from sleep, unrefreshing sleep, daytime fatigue, impaired concentration and/or overnight monitoring shows 5 or more obstructed breathing events per hour of sleep.¹³.

Central Sleep Apnea

This condition is characterized by recurrent apneic episodes in the absence of upper airway obstruction during sleep, which usually results in oxygen desaturation, recurrent arousals and daytime symptoms²⁰.

Within this classification there are subtypes. Hypercapnic central sleep apnea occurs in individuals with alveolar hyperventilation, which may result from metabolic or neuromuscular disorders. Normocapnic or hypocapnic central sleep apnea can arise in a number of forms including idiopathic central sleep apnea, Cheyne-Stokes Breathing and high altitude sleep apnea.

Idiopathic central sleep apnea occurs in individuals who have an increased ventilatory response to carbon dioxide that causes them to hyperventilate and become hypocapnic.

Diagnostic criteria include; excessive daytime sleepiness, frequent nocturnal arousals, overnight monitoring showing 5 or more central apneas plus hypopneas per hour and a normocapnic status while awake.¹³.

Mixed apneas occur when initially there is no inspiratory effort but subsequently when efforts are initiated the apnea persists because the upper airway is collapsed ⁴. Mixed apnea occurs more often than central but less often than the obstructive type ⁶.

1.3.3 Prevalence

The prevalence of OSA varies significantly depending on the diagnostic criteria, the population studied and the method of study.

Young et al assessed a random sample of 602 employed men and women 30 to 60 years old³. Each individual was studied by overnight polysomnography to determine the frequency of episodes of apnea and hypopnea per hour of sleep. The estimated prevalence of sleep-disordered breathing, defined as an AHI score greater than 5 alone, was 9% for women and 24% for men. It was found that male sex and obesity were strongly correlated with sleep-disordered breathing. This study concluded that there is a wide range in severity of undiagnosed sleep-disordered breathing, and that 4% of men and 2% of women would be likely to meet the minimal diagnostic criteria for sleep apnea syndrome, defined by an AHI score greater than 5 and excessive daytime sleepiness.

The prevalence in community-dwelling elderly (older than 65 years) has been reported to be as high as 62% ²¹.

Whilst OSA is more common in middle-aged (greater than 40 years) and overweight men ⁴, it may also occur in infants, children ²² and women ²³.

1.3.4 Pathophysiology

With advances in technology, understanding of the pathophysiology of OSA has significantly improved.

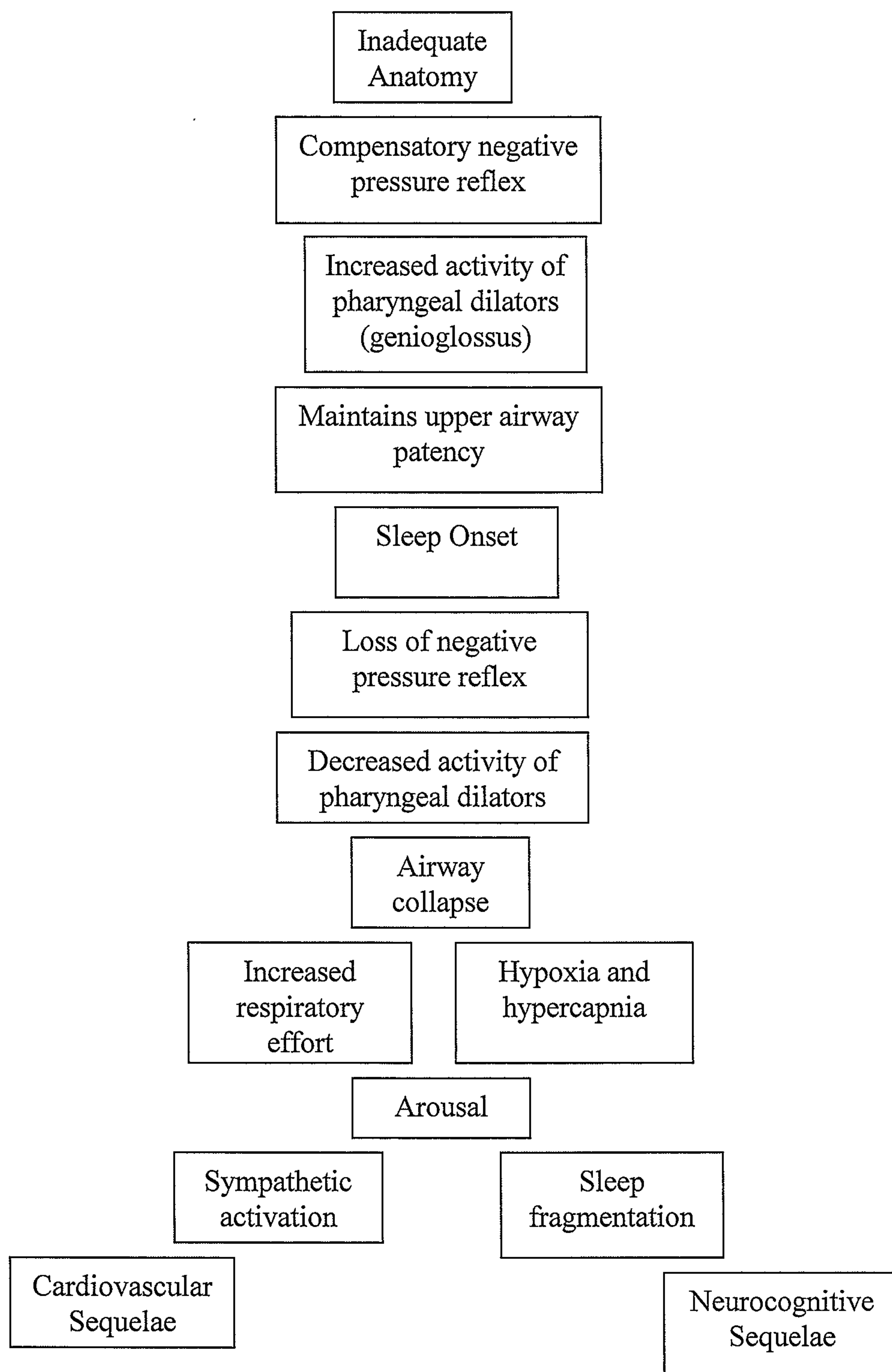
An early hypothesis to explain the hypersomnolence seen in >Pickwickian Syndrome= was carbon dioxide necrosis. Later studies reported that obstructive apneas were caused by obstruction of the upper outlet by backward movement of the tongue. This resulted in frequent awakenings and disruption of sleep, explaining the hypersomnolence.¹¹ In 1972 Walsh *et al* observed the upper airway during sleep using cineradiography in obese, hypersomnolent patients with OSA. It was found that the upper airway obstruction was produced by the 'tongue retracting into apposition with the posterior pharyngeal wall'²⁴. Remmers *et al* identified the location of the upper airway collapse during sleep as the oropharynx, and proposed that this resulted from an imbalance between negative pharyngeal pressure and the opposing force of the upper airway musculature²⁵.

In current times it is believed that the nasal cavity, nasopharynx or oropharynx may be a possible site of obstruction²⁶. The site of obstruction typically lies in the pharynx. The pharyngeal luminal area during inspiration reflects a balance between collapsing intrapharyngeal negative suction and dilating forces provided by the pharyngeal muscles. The behaviour of the relaxed pharynx is partly dependant on the transmural pressure. As the transmural pressure decreases, the pharynx becomes increasingly susceptible to collapse as its luminal area decreases. Factors which tend to narrow the airway include surface adhesive forces, neck flexion, jaw opening and gravity. Forces that tend to dilate the pharynx include tracheal tug caused by increased lung volume and neck extension.

In awake patients, pharyngeal patency is maintained by continual neuromuscular activation of the pharyngeal muscles by the central nervous system. This activation is typically reduced during sleep, compromising patency of the upper airway. The combination of reduced neural activation with anatomic abnormalities, such as excess posterior pharyngeal tissue or an enlarged tongue, increases the tendency for obstructive hypopneas and apneas in patients. Proprioceptive feedback from thoracic and upper airway receptors and chemical stimulation by hypercapnia and hypoxia increase neural output to the pharyngeal muscles, resulting in increased activation. Sleep abolishes such feedback and suppresses chemical feedback ^{14 15}.

According to Cistulli and Sullivan ⁷, the aetiology is an interplay between: predisposing factors, anatomical structures related to the upper airway muscle activity and functional processes related to upper airway muscle activity (Figures 1 and 2).

Figure 1. Pathophysiology and Sequelae of Airway Collapse. Adapted from Malhotra *et al*: processes leading to neurocognitive and cardiovascular sequelae²⁷.



These aetiological factors in combination are thought to lead to a narrowing of the airway with repetitive occlusion during sleep⁶.

Figure 2. MRI of the Airway and Adjacent Anatomy.



1.3.5 Predisposing Factors

Sleep disordered breathing is a complex, chronic disease that is expressed after a given threshold level of susceptibility is exceeded. There are multiple factors that may contribute to the severity of OSA. The strongest risk factors are obesity and male gender ²⁸.

1.3.5.1 Male Gender

Males are predisposed to sleep disordered breathing because androgenic patterns of fat distribution favour truncal deposition, including the neck area. Excess fat in both the pharyngeal and subcutaneous regions may lead to a narrowing of the oropharynx, encouraging its occlusion once the subject is supine ²⁹. In addition, sex hormones may modulate respiratory and upper airway neuromuscular activities. The extent to which this relates to the protective effects of progesterone or adverse effects of testosterone are unclear ²⁸. Sleep laboratory data suggest a five or six-fold increased risk of obstructive

sleep apnea in men compared with women. This discrepancy may arise because of an under-appreciation of this disease in women²⁷.

1.3.5.2 Obesity, particularly upper body adiposity

Obesity is defined as a body mass index (BMI) greater than 28 kg per metre squared. A BMI greater than 28 can be found in 60-90% of patients evaluated in sleep clinics¹.

Obesity, in particular truncal obesity, may precipitate or exacerbate OSA by influences related to upper airway fat deposition that may affect airway patency or compliance and abdominal mass loading²⁸. Adiposity causes displacement of the soft tissue structures within the neck which is limited by adjacent bony anatomy. As the airway is one of a few structures capable of collapse in this region, the 'pressure' generated results in reduction of the airway volume³⁰.

Neck circumference (NC) may be used as anthropometric variable reflecting the extent of upper body obesity (fat deposition around the upper airway or fat deposited in the parapharyngeal fat pads). In the Wisconsin Sleep Cohort Study, NC was the strongest predictor of sleep-disordered breathing among all the anthropometric variables studied³.

1.3.5.3 Age

Available data suggests that sleep disordered breathing, as assessed by objective monitoring, is more prevalent in elderly than in middle-aged populations. A community study from San Diego, California, demonstrated that 81% of elderly respondents had a RDI greater than 5 and that 44% had an RDI greater than 20²¹. An apparent plateau in the development of obstructive sleep apnea at age sixty five years is thought to be due to

mortality, thereby reducing the number of patients in this category in some community based studies ²⁷.

In the Cleveland Family study, the prevalence of sleep apnea was assessed in children. An RDI of greater than 10 was found in 2% of children less than 18 years of age. ³¹.

1.3.5.4 Race

Data suggests that certain races may be at risk for sleep disordered breathing. Data from the Cleveland Family Study and the San Diego study of elderly demonstrated larger levels of RDI in African Americans compared with Caucasians ^{31 21}. In the Cleveland study this effect was greater in the under 25 years of age group, and greatest in the under 13 years of age group. These racial differences were due to differences in upper airway anatomic and, possibly, physiological factors.

1.3.5.5 Craniofacial abnormalities including mandibular/maxillary hypoplasia

Hard tissue factors that reduce oral or nasal patency may increase the risk of upper airway collapse. Upper airway can be assessed by cephalometrics, magnetic resonance imaging and computerized axial tomography. Features more common in patients with OSA include facial elongation, reduced posterior facial height, reduced posterior and superior airway spaces, retrognathia and inferior displacement of the hyoid bone ^{32,33}. Nelson reports that craniofacial risk factors such as small retropositioned mandible, narrow posterior airway space, enlarged tongue and soft palate, inferiorly positioned hyoid bone and retroposition

of the maxilla, have their strongest association with sleep apnea in non-obese patients ³⁴. This would include many Asian patients where BMI is often normal.

1.3.5.6 Increased Pharyngeal or Lymphoid Tissue including Tonsillar Hypertrophy

Excess tissue reduces the dimension of the airway, having an effect on resistance to airflow and work required to maintain airflow ³⁵.

1.3.5.7 Vascular and Endocrine Abnormalities

Although hypertension is regarded as a consequence of OSA, some anti-hypertensive agents may increase apneic activity. Pre-existing heart or lung disease makes breathing more difficult, thereby favouring decreased blood oxygen tensions ⁶. Vascular diseases, through their effects on cardiac and cerebral function, may alter respiratory stability thereby increasing OSA risk. Diabetes and insulin resistance are associated with central obesity, which is linked to OSA. These conditions, through their general effects on cardiopulmonary function, metabolism, and fat distribution, may predispose OSA ²⁸.

1.3.5.8 Familial history

Many of the risk factors for OSA (obesity, body fat distribution, craniofacial morphology) have a known or suspected genetic basis. Among children related to a sibling with laboratory diagnosed sleep apnea, the prevalence was 8% ³¹. The persistence of significant estimates of familiarity following adjustment for BMI, neck size, and cephalometric

measures suggests that there may be unmeasured anatomic factors that are both inherited and predispose to OSA ²⁸.

1.3.5.9 Pharmacologic Agents (alcohol, benzodiazepines)

Central nervous system depressants such as alcohol, sedatives and sleeping pills induce relaxation of the pharyngeal musculature and, therefore, airway occlusion ³⁶.

1.3.5.10 Nasal Obstruction

Anatomical constriction of the nasal airway, or exposure to agents that promote nasal or pharyngeal inflammation or that alter neuromuscular drive to upper airway muscles are likely to increase the risk of OSA. This may include tobacco smoke and other allergens ³⁷ ²⁷.

1.3.6 Anatomical structures affecting upper airway size

Much work has been done to address the hypothesis that abnormal anatomy underlies sleep disordered breathing. Several imaging techniques have been used to study the upper airway size and changes in the airway size and soft tissue structures that surround the airway in patients with OSA. These include acoustic reflection ^{38 39}, fluoroscopy ⁴⁰, nasopharyngoscopy ⁴¹, cephalometry ⁴², CT ⁴⁰ and MRI imaging ⁴³. Results demonstrate that OSA patients have a narrower airway than control subjects.

The recent advent of cone beam computed tomography (CBCT) may allow a better understanding of the anatomical parameters in patients with Obstructive Sleep Apnea.

Despite some limitations in study techniques, such as assessing patients in the awake state and in the erect posture using cephalometric radiography, various skeletal and soft tissue structures have been implicated in narrowing of the upper airway in patients with OSA.

1.3.6.1 Cranial base

A more acute cranial base angle and a reduction in the anterior cranial base length was reported in OSA subjects by Battagel and L'Estrange²⁹.

1.3.6.2 Maxilla and Mandible

In the anterior-posterior dimension the cranial base, maxilla and mandible have been implicated as being shorter or retro-positioned²⁹. Alterations in craniofacial structure, including a posteriorly positioned maxilla and mandible have been shown⁴⁴.

However, other studies have not found such a clear link. Lowe *et al* 1996 assessed 347 patients with OSA and compared 101 control patients. The subjects were classified by gender and skeletal subtypes (Class I, Class II/1, Class II/2, Class III). They were assessed by cephalometry in both an upright and supine positions. The most atypical craniofacial and upper airway structure was found in Class I males with OSA⁴⁵.

In the vertical dimension, a steep mandibular plane angle, high upper and lower facial heights and over-erupted maxillary and mandibular teeth have been reported⁴⁴.

1.3.6.3 Head Posture and Hyoid Bone

The effect of flexion or extension of the head influencing the dimension of the oropharyngeal airway have been postulated by some authors⁴⁶.

The position of the hyoid bone, which anchors much of the tongue musculature, was often found to be abnormally low in patients with OSA³². Ferguson *et al* found that the hyoid bone was more inferiorly and anteriorly placed in patients with a large neck circumference, and that the distance between the hyoid bone and the mandibular plane increased in patients with a larger neck circumference⁴⁷. In the same study a positive correlation between OSA, neck circumference and obesity was shown.

The contemporary view regarding an inferiorly positioned hyoid bone and an extended head position suggests that, rather than predisposing factors, these are physiological adaptations to lift away the base of the tongue and the soft palate from the posterior pharyngeal wall in order to alleviate the obstructive condition⁶.

1.3.6.4 Tongue

The current literature is unclear on exactly what role the tongue plays in the aetiology of OSA. Some authors have reported a larger tongue length and area in OSA patients⁴⁸. Ferguson *et al* demonstrated that patients with a larger neck circumference had larger tongues⁴⁷. Tongue and soft palate volumes were related to BMI in a study of 80 patients with OSA⁴⁹. This explained the differences of tongue and soft palate size between OSA subjects and controls.

Other studies have found that tongue size and area is normal but the functional space of the tongue is reduced, forcing the tongue backwards into the pharynx and diminishing the airspace at this level^{29,33}. Pae *et al* assessed the tongue by cephalometry and electromyography (EMG)⁵⁰. It was found that the tongue cross-sectional area increased by 4.3%, and the oropharyngeal area decreased by 36.5% when the OSA patients changed

their body posture from upright to supine. This occurred despite a 34% increase in resting EMG activity.

It is critical to view results regarding tongue measurements with caution. Traditional cephalometric evaluations of tongue size have obvious 2-D limitations. Attempts to measure the volume of the tongue by means of fluid displacement are restricted by the distance a subject can protrude the tongue. Computed tomography (CT) measurements appear to be the most accurate assessment technique. Using CT techniques on 25 adult men with OSA, Lowe *et al* found that the more obese subjects showed larger tongue surface areas and smaller airway surface areas. It was also shown that tongue volume increased more rapidly than airway volume in subjects with OSA ⁴⁸.

1.3.6.5 Soft Palate

The soft palate in OSA patients is longer and thicker, with an area approximately 20% greater than the average individual, further reducing the effective airway ²⁹. Ferguson *et al* demonstrated that patients with a larger neck circumference had larger soft palates ⁴⁷.

1.3.6.7 Pharyngeal Dimensions

Although it has been suggested that soft tissue abnormalities are more important than skeletal factors in patients with OSA, it has not yet been established whether the soft tissue abnormalities are a consequence of vibratory trauma rather than the cause ⁶.

Three categories of OSA have been proposed based on the anatomical site of obstruction ⁵¹.

Type I (oropharynx): includes those patients with larger soft palates and related factors, such as a longer hard palate with a resultant reduction of this region of the airway.

Type II (hypopharynx): includes those patients who are retrognathic with a concurrent reduced posterior airway space due to the posterior positioning of the tongue and/or macroglossia.

Type III: is a combination of oro- and hyopharyngeal obstruction (Types I and II).

The narrowest region in OSA patients while awake has been shown to be the region posterior to the soft palate, and that this cross sectional area is smaller than in controls⁵². It has been observed that airway configuration may differ in this area in OSA patients. No abnormal collections of fat density were found to explain these differences. A recent study⁵³ has shown that the lateral pharyngeal walls are thicker in apneics: however the buccal fat pads are not closer together, and the area and width of the fat pads were not larger in apneics at the level of minimum airway⁵⁴. This has led to the conclusion that the thickness of the lateral pharyngeal walls, and not the actual size of the soft palate, tongue or fat pads, is the predominant factor causing airway narrowing in apneic patients. The reason for the thicker walls is not known. It has been suggested that an increase in muscle mass due to weight gain or the exercise of overcoming apnea might explain the increase in size of the lateral soft tissues without increase in the direct fat deposition. Another alternative explanation is that there may be folding of the lateral mucosa¹¹.

1.3.7 Functional Processes related to Upper Airway Muscle Activity

It has been postulated that the functional processes implicated in the aetiology of OSA are due to a normal physiological loss of muscle tone in the upper airway with the onset of sleep.

1.3.7.1 Awake Breathing

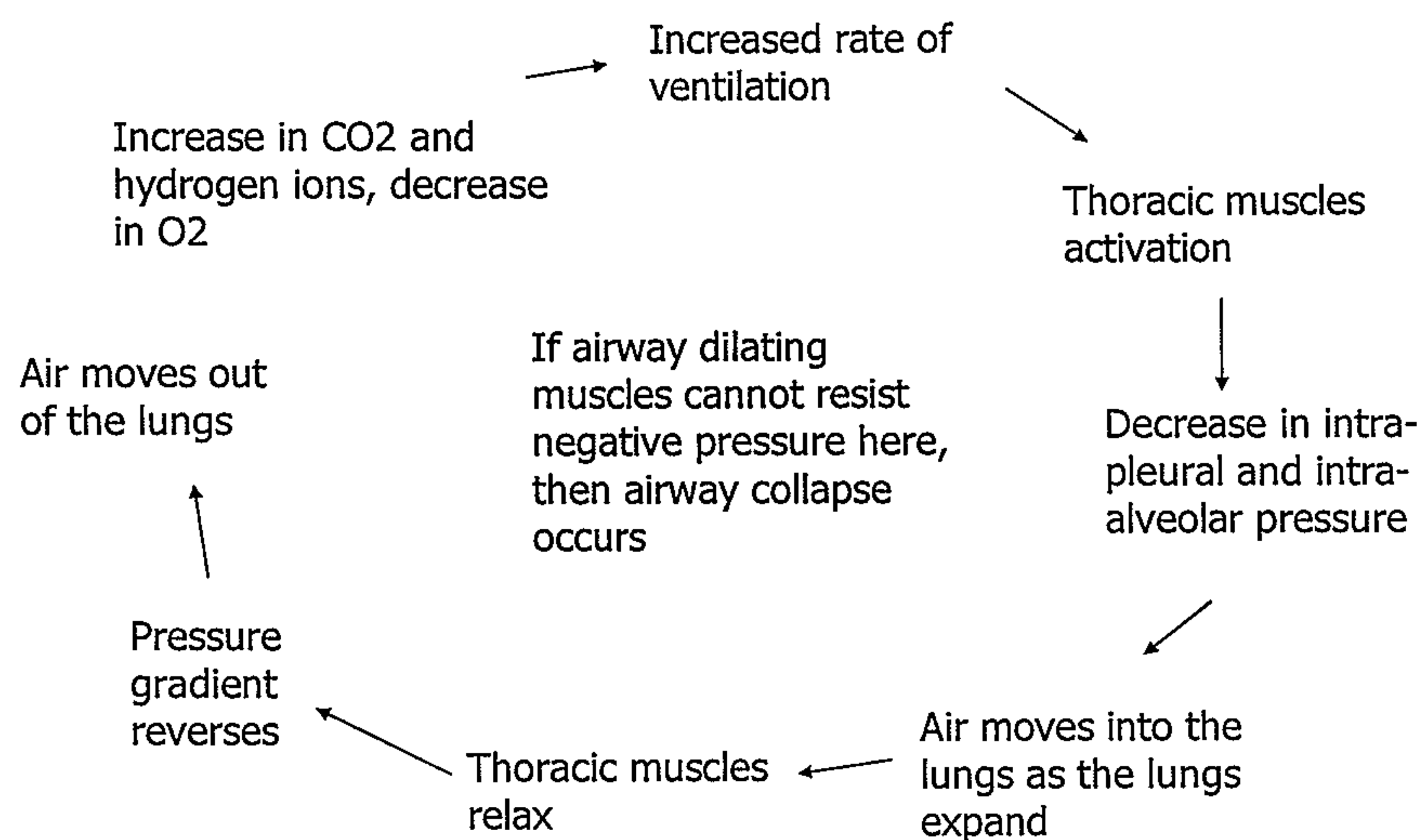
Ventilation supplies the body with oxygen, and eliminates carbon dioxide. The primary purpose is to regulate the levels of carbon dioxide, hydrogen ions and oxygen in the body. The levels of these chemicals have a profound effect on ventilation. Increases in carbon dioxide and hydrogen ions in the blood have a direct excitatory effect on the respiratory centre of the brain. This causes a marked increase in ventilation. Decreased oxygen in the blood has a less dramatic effect on ventilation ³⁵.

Inspiration is initiated by contraction of the diaphragm and external intercostal muscles, which receive electrical impulses from the brain. When the diaphragm contracts, it lowers, expanding the vertical dimension of the thoracic cavity. Contraction of the intercostal muscles expands the horizontal dimension. This causes a drop in the intrapleural pressure from 756mmHg to 754mmHg. This drop in pressure acts as a vacuum sucking the walls of the lungs outward. As the lungs expand, the intra-alveolar pressure decreases from 760mmHg to 758mmHg due to the increase in volume of the lungs. This creates a pressure gradient between intra-alveolar pressure and atmospheric pressure. Air then moves from the higher pressure to the lower pressure region, into the lungs. The negative intraluminal pressure creates a tendency for the upper airway to collapse. This is prevented by activation and contraction of the upper airway dilator muscles. Normally the upper airway

is patent during inspiration because the dilating force exerted by the upper airway muscles is greater than the subatmospheric intraluminal pressure³⁵. This balance of forces concept was illustrated by Cistulli and Sullivan⁷ is illustrated in Figure 3.

Figure 3. Physiology of Awake Breathing.

Expiration is a passive process resulting from relaxation of the inspiratory muscles, with the opposite processes occurring to inspiration



1.3.7.2 Asleep Breathing

When a person falls asleep their muscles start to relax, the degree of relaxation depending on the stage of sleep. With sleep onset, a normal physiologic loss of muscle tone can therefore lead to upper airway obstruction. This can result in snoring⁷.

When there is a 50% or greater reduction in resting tidal volume a hypopnea occurs. If the airway closes completely for 10 seconds or more, then an apnea occurs. This results in a

drop in the bloods oxygen level, an increase in the blood concentration of carbon dioxide, as well as an increase in blood pressure and heart rate.

The apnea is terminated by a brief arousal from sleep. During this arousal the partially awake brain increases stimulus to the upper airway muscles causing them to contract harder and thus open the upper airway. As this occurs the sleep apnea patient is able to take several large breaths and quickly correct the oxygen and carbon dioxide levels.

Normally, the subject will then return to sleep without recollection of arousal. The cycle of apnea and arousals repeats itself for part or all of the sleep period ⁶.

In conclusion, the underlying cause of sleep apnea is airway narrowing due to relaxation of the upper airway muscles. When awake, OSA subjects have more activation of the upper airway dilator muscles to keep the airway open ⁵⁵. Hence, the occurrence of upper airway obstruction during sleep onset is the result of a normal physiological loss of muscle tone with sleep onset and the dominant pathological element is a mechanical narrowing of the upper airway ⁶.

1.3.8 DIAGNOSIS OF OSA

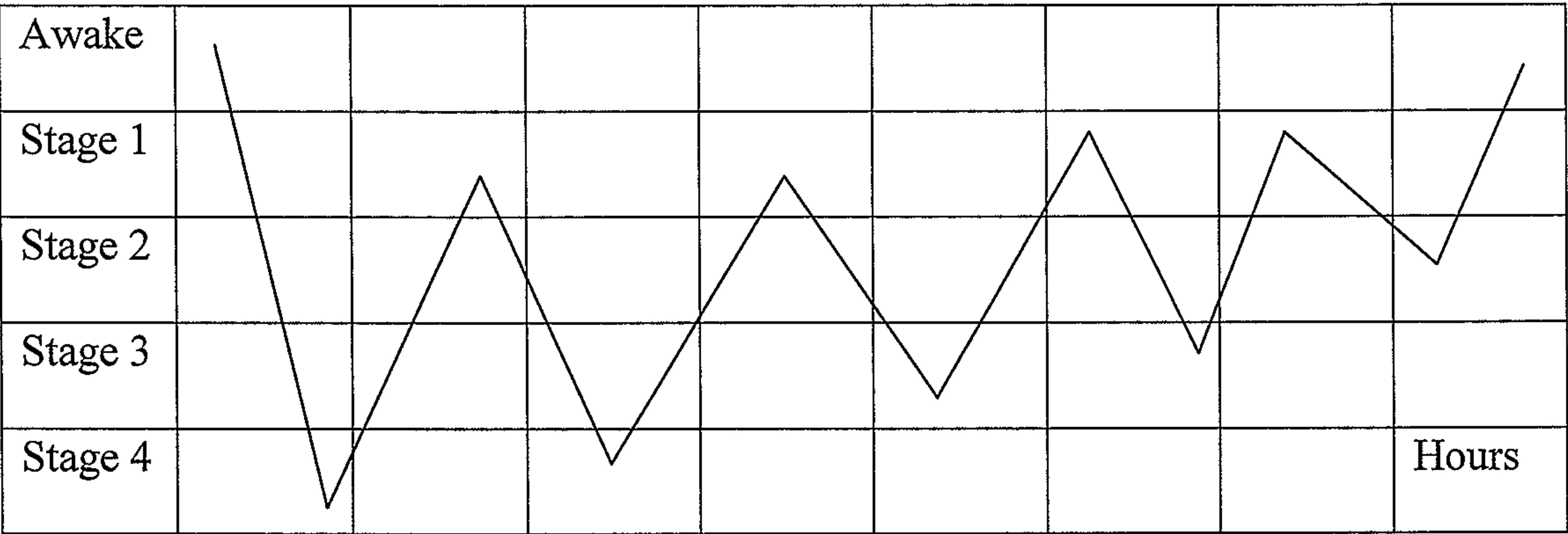
The majority of patients with sleep apnea are objectively sleepy, although daytime sleepiness is under-reported because it generally manifests itself over a long period and patients change their lifestyles gradually to compensate for it. Loud snoring, fatigue, or both are frequently the patients' only other symptoms. A thorough history and physical examination may aid in identifying persons at risk for sleep apnea ⁵⁶.

1.3.8.1 Excessive daytime sleepiness

Questionnaires may give an initial measure of the nature of the problem. Two common subjective assessments of sleepiness are the Stanford Sleepiness Score (SSS) ⁵⁷ and the Epworth Sleepiness Scale (ESS) ⁵⁸. The SSS is used to record the degree of sleepiness experienced by an individual at a given time and does not necessarily relate to his or her overall propensity to fall asleep. The ESS measures sleepiness as a reflection of a subject's tendency to fall asleep during specific, non-stimulating situations, as assessed over an interval of time. (See Appendix 1. for ESS)

1.3.8.2 Normal Sleep

Figure 4. The Normal Sleep Cycle. Each column represents one hour. Stage 1 is REM sleep. The remaining stages are non-REM sleep



The average adult requires 6-8 hours of sleep per 24 hour cycle. Sleep is a complex physiological process divided into 4 stages, each characterized by phases of rapid eye movement (REM) sleep or non-rapid eye movement (non-REM) sleep, with different types of electrical brain activity (EEG). Usually there are 4-5 cycles of REM/non-REM sleep during an 8 hour period of sleep²⁰ as demonstrated in Figure 4.

These cycles of sleep are associated with several physiologic processes. Muscle tone decreases but with short bursts of increased limb activity resulting in a change in body posture just prior to emerging from periods of REM sleep. The heart rate decreases in non-REM sleep but is also variable in REM sleep. In non-REM sleep, there are changes in atrial ventricular conduction and increased refractory periods. Blood pressure decreases by up to 20% of baseline awake levels in normotensive and hypertensive patients in non-REM sleep. These changes are demonstrated in Table 1.

In non-REM sleep, respiratory drive decreases but airway resistance increases from the decreased muscle activity in the upper airway. In the transition from wakefulness to non-REM sleep, airway resistance can increase 2-3 times. Gaseous exchange alters, with the partial pressure of carbon dioxide (PCO_2) increasing and partial pressure of oxygen (PO_2) decreasing compared to baseline awake levels.

The overall metabolic rate decreases by 10-20% in non-REM sleep compared to baseline levels. These changes allow the body to rest and repair²⁰.

Table 1. Physiology of the Stages of Sleep

Awake	EEG; Alpha waves 8-12 Hz eyes open, 14+Hz eyes closed
Stage 1	REM; Heart rate and breathing increases. Eye Movement quick and regular. Increased blood pressure and shallower breathing. Dreams.
Stage 2	Non-REM; light sleep. Brain activity increases by 50%, 5% theta waves 3-6Hz. Eye and muscle movement slows. May experience sudden muscle contraction.
Stage 3	Non-REM; small burst of brain activity begin. Waxing and waning 12-14Hz, Eye and muscle movement cease.
Stage 4	Non-REM; deep sleep. Brain activity slow delta waves. Difficult to wake sleeper.

1.3.8.3 Sleep Study

Overnight polysomnography, or sleep study, is performed to confirm the presence of upper airway closure during sleep and to assess the patient’s level of risk. A full night polysomnography conducted by a technician in a sleep laboratory is the gold standard for diagnosing sleep apnea. The polysomnogram is a comprehensive study used to record many physiologic variables in order to diagnose a wide spectrum of sleep disorders.

The patient presents in the early evening and has various monitoring devices attached and calibrated. These devices monitor the patient while they are asleep.

Common parameters measured while the subject is asleep are recorded in Table 2:

Table 2. Polysomnography Parameters

Diagnostic equipment	Code	Parameter monitored
Electro-oculogram	EOG	eye movements
Electro-encephalogram	EEG	brain wave activity
Electro-cardiogram	ECG	electrical activity of heart
Electro-myogram	EMG	activity of the submental and tibialis anterior muscles
Oronasal airflow		oral and nasal respiration
Pulse oximetry		arterial oxygen saturation
Respiratory inductive plethysmograph		chest and abdominal wall movement
Microphone		snoring and choking sounds
Video recording		Body movement

The above data allow the number of apneas and hypopneas to be quantified. This allows a definitive diagnosis to be made and also permits an evaluation of the severity of OSA ³⁶. Sleep studies can be repeated to assess whether treatment has controlled the disordered OSA.

Some patients comment that a sleep laboratory is a different environment from sleeping at home. This factor is taken into account in the interpretation of the sleep studies. Portable, unattended monitoring systems can be used outside the hospital as an alternative. Portable systems vary in the manner in which physiologic signals are recorded and scored, as well as how other variables are monitored. The main concern is that airflow, ventilatory effort

and arousal may not be measured at all. This could result in missing episodes of hypopnea or arousal due to upper airway resistance^{59 60}.

1.3.8.4 Fibreoptic nasendoscopy

Otorhinolaryngologists (ORL) may be involved in diagnosis and management of OSA. Their role is to confirm the anatomy, function and pathology of the upper airway from the nose to the larynx. A thorough history and examination should be undertaken, including imaging and direct examination of the upper airway. There are ranges of developmental, traumatic, inflammatory and neoplastic pathology which may present with upper airway obstruction⁶¹. Fibreoptic nasendoscopy is one technique to visually inspect the airway.

1.3.8.5 Sleep endoscopy

Sleep endoscopy can be undertaken in a sedated patient to induce snoring. Direct visualisation of the site of obstruction can be achieved with this technique.

1.3.8.6 Cephalometrics

It is the dental specialist's role to determine the patients' facial bone morphology both clinically and via cephalometrics. There have been numerous studies assessing the link between craniofacial morphology and OSA.

Lowe *et al* identified a link between craniofacial morphology and OSA⁴⁴. 25 adult male patients with OSA had a lateral head cephalometric film and sleep study. The sleep apnea subjects showed a posteriorly positioned maxilla and mandible, a steep occlusal plane, over-erupted maxillary and mandibular teeth, proclined incisors, a steep mandibular plane,

a large gonial angle, high upper and lower facial heights, an anterior open bite in association with long tongue and posteriorly placed pharyngeal wall.

Using both cephalometric and computed tomography in 80 patients with OSA compared to 25 controls, a high AHI was found to be associated with large tongue and soft palate volumes, a retrognathic mandible, and anteroposterior discrepancy between the maxilla and mandible and an open bite tendency between the incisors ⁴⁹.

In a meta-analysis on the influence of craniofacial structure on OSA incidence, the highest potential diagnostic parameters were found to be mandibular plane to hyoid bone distance, mandibular plane angle and mandibular body length ⁶².

In a recent trial by Sherring *et al* ⁶³, 94 patients who had been assessed by sleep study were prescribed a lateral head cephalometric radiograph. The patients were subdivided into snorers with OSA and snorers without OSA. The main findings, when comparing OSA patients with non-OSA snorers, were increased incidence of maxillary retrusion, increased incidence of maxillary and mandibular retrusion, the hyoid bone more inferiorly and anteriorly placed, a thicker soft palate, a larger tongue and a longer pharyngeal length. The most severe OSA was found in obese patients with concurrent facial retrusion.

Understanding of the link between craniofacial morphology and OSA may be further improved with the recent advancement of cone beam three dimensional computed tomography. The anatomical form and volume of the airway may be better appreciated through this technique ⁶⁴

1.3.8.7 Magnetic Resonance Imaging (MRI)

MRI can be used to assess the upper airway musculature of normal controls and patients with OSA. MRI can be useful in confirming diagnosis and better understanding the nature of the problem in a particular individual. Several studies have been undertaken with varying methodologies.

Rodenstein *et al* assessed 17 men with complaints of snoring, and 8 healthy subjects with sleep studies and MRI⁶⁵. The results indicated no difference between the groups in most MRI imaging measurements, but the pharyngeal cross-section had an elliptical shape with the long axis oriented in the coronal plane in normal subjects, whereas in the apneic and snoring patients the pharynx was circular or had an elliptical shape but with the long axis oriented in the sagittal plane. The authors suggested a change in pharyngeal cross-sectional shape, secondary to a reduction in pharyngeal transverse diameter, may be related to the risk of developing sleep-disordered breathing ⁶⁵.

Hasegawa *et al* used dynamic MRI to assess obstruction sites in 43 OSA patients. Obstruction of the soft palate type with obstruction and stenosis on the soft palate level was found in 23 subjects, and a further 17 subjects had obstruction of both the soft palate type and depression of the lingual root ⁶⁶. The authors concluded that dynamic MRI during drug-induced sleep enables observation of the morphology of the upper respiratory tract during sleep, and an accurate diagnosis of the obstruction site.

In a study using both polysomnography and MRI, it was found that the lingual muscles (genioglossus, geniohyoid, sternohyoid /sternothyroid) demonstrated altered properties in OSA patients. The changes were characteristic of overuse with resultant oedema and possibly increased fat content. As the technique is non-invasive, the authors state the

advantage that the test can be repeated in the same subject over time, providing valuable information regarding the natural course of OSA as well as an objective measure of the benefits of therapeutic intervention ⁴³.

MRI can therefore be considered an additional tool to assist in the diagnosis and management of OSA patients.

1.3.9 Clinical Features

The symptoms of OSA can be divided into daytime and night time symptoms. Loud snoring and excessive daytime sleepiness are the most common symptoms associated with OSA. Tiredness or sleepiness during the day can significantly affect normal daily activities. People with OSA have difficulty maintaining wakefulness during driving, during a meeting, watching TV, reading, or other daily activities. Work, marriage and recreational activities can all be severely affected ⁶⁷. Many of these symptoms are observed or reported by a spouse or partner.

The Calgary Sleep Apnea Quality of Life Index has been established to capture aspects of quality of life important to sleep apnea patients, such as cognitive function, performance and mood, that could be improved with appropriate treatment of sleep-disordered breathing ⁶⁸.

1.3.9.1 Nocturnal symptoms

Snoring is the most obvious night-time problem. Patients often complain that they wake up with a sore and-or dry throat ³⁶. Most patients do not remember waking up during the night as a consequence of apneic events {Flemons W Ward, 1997 #15}.

Some patients may be aware of awakenings during sleep that may include gasping or choking, and often express concern regarding fragmented and non-refreshing sleep.

1.3.9.2 Daytime symptoms

Excessive daytime Sleepiness (EDS) occurs as a result of chronic sleep disruption. The most common causes of moderate to severe excessive daytime sleepiness are sleep apnea and narcolepsy. The prevalence of EDS in Western Society is reported to be up to 5% ⁶⁹.

EDS is a significant public health issue as the subject may fall asleep at unexpected and inappropriate moments. A study of the driving abilities of 18 patients with severe sleep apnea hypopnea syndrome was undertaken to assess the benefits of treatment ⁷⁰. Using a driving simulator test, it was found that the driving performance of these patients improved within the first few days of commencing treatment, and that these improvements were sustained for up to 1 week after withdrawal of the treatment. Other studies also indicate that OSA patients have more automobile accidents ^{71 72}.

Testing of EDS may take the form of determining how easy it is for a patient to fall asleep, or, alternatively, how difficult it is for them to remain awake. This type of testing may be subjective or objective. A common assessment is the Epworth Sleepiness Scale ⁵⁸ (See Appendix 1.). This measures sleepiness as a reflection of a subjects' tendency to fall

asleep during specific, non-stimulating situations, as assessed over an interval of time. A score greater than 10 is indicative of EDS {Flemons W Ward, 1997 #15} ⁷³.

1.3.9.3 Neuropsychological symptoms

Poor memory and difficulty concentrating are further consequences for patients suffering from OSA. A study by Engleman *et al* was undertaken to assess the effect of treatment on neurocognitive function in sleep apnea patients. In this placebo-controlled, crossover study, it was found that there were no changes in verbal fluency or memory between the placebo and active-treatment periods. However, there were small but statistically significant improvements in vigilance, mental flexibility and coding speed ⁷⁴.

OSA patients may even experience depression. These symptoms are thought to be a result of the change in sleep quality and some of the symptoms of sleep apnea described above ⁷⁵.

Other complaints include irritability and personality changes, decreased sex drive and morning headaches ⁶⁷.

1.3.10 Clinical Consequences

There are numerous clinical consequences of OSA, with associated morbidity and mortality. These have been classified by Ferguson and Fleetham as follows: cardiac, neurological, psychological and psychiatric, endocrine, haematological, nephrological, neurocognitive and performance impairment and mortality.

1.3.10.1 Cardiac Consequences

Systemic hypertension

Hypertension and sleep apnea are both common disorders, and have been linked together since the first case series published by Guilleminault in 1976⁴. Approximately 40% of patients with OSA have hypertension. Approximately 30% of middle-aged men with hypertension have OSA¹⁴.

Early investigations were complicated by confounding factors associated with each of these conditions. Young *et al* demonstrated a dose-response relationship between AHI and blood pressure, which was independent of confounding factors such as age, sex, BMI, and tobacco and alcohol use⁷⁶. Three large clinical studies reported that the prevalence of OSA was associated with a 1.5 to 3-fold increase in the risk of hypertension development^{77 78 79}.

In 2004, Lavie described a mechanism by which sleep apnea could give rise to cardiovascular disease. In their laboratory studies, it was found that there was increased production of oxygen reactive species in the granulocytes and monocytes obtained from sleep apnea patients. This was associated with increased expression of adhesion molecules and pro-inflammatory cytokines, which resulted in increased avidity of monocytes and lymphocytes, and increased cytotoxicity of lymphocytes against endothelial cells in culture. In turn, this lead to an increased endothelial cell injury and dysfunction, with the possibility of atherosclerosis⁸⁰.

The most compelling epidemiological evidence that sleep apnea is causally related to systemic hypertension was generated by the Wisconsin Sleep Cohort Study. This

longitudinal study assessed apparently healthy workers. The authors found that subjects with an AHI greater or equal to 5 had significantly higher blood pressures than did subjects with snoring but without apnea or subjects with neither snoring nor apnea. Most importantly, there was an effect of sleep-disordered breathing on arterial blood pressure even when data was adjusted for weight and gender ⁸¹. These results should be viewed with caution because the study subjects' blood pressures were actually lower four years later, and the incidence of hypertension was defined on the basis of a new drug treatment and not on the actual blood pressures. It is conceivable that a positive result on the initial study influenced subsequent screening for hypertension and thus more frequent diagnosis and treatment in the subgroup with the most severe sleep apnea. As with all such studies there is also the possibility of an unrecognized confounding variable ⁸².

Systemic blood pressure normally decreases by 5-14% in non-rapid eye movement sleep (non-REM) compared to awake resistance values. Blood pressure fluctuates considerably during REM sleep and is usually 5% higher than in non-REM sleep. In patients with sleep-disordered breathing there are brief phasic changes in blood pressure superimposed on a cyclical pattern which coincides with upper airway obstruction. Systemic blood pressure may increase by up to 20% during OSA and is maximal immediately after apnea termination ⁸³.

The data indicates that OSA does contribute to the development of systemic hypertension. The management of these patients should not only address sleep apnea, but also monitor arterial blood pressure and treat as required.

Pulmonary hypertension/right heart failure

Pulmonary hypertension in patients with OSA has been reported to be between 10-20%⁸⁴.

OSA can cause mild pulmonary hypertension, but it does not usually lead to right-sided heart failure in the absence of daytime hypoxia or coexistent pulmonary disease. Some patients may display the clinical features of right-sided heart failure: oedema, hepatomegaly, jugular venous distension, and right ventricular volume overload⁸⁵. The incidence of these symptoms is indicative of the severity of the disease and requires prompt treatment.

Cardiac function

Nocturnal hypoxemia resulting from obstructive apneas-hypopneas may predispose to ischaemic heart disease in patients with OSA and coronary artery disease. The risk of having a myocardial infarction is greatest at the oxygen saturation nadir (lowest saturation), when the heart rate and blood pressure are increased. Reduced capacity for fibrinolysis has also been reported in patients with OSA, possibly further increasing the risk for coronary occlusion¹⁴.

Epstein and Weiss⁸⁵ believed that there is little evidence to conclusively support the hypothesis that untreated sleep apnea contributes to vascular morbidity. The argument revolves around a research project involving patients admitted to hospital with myocardial infarction, which is often quoted to support a causal link between sleep apnea and coronary heart disease⁸⁶. The researchers found that after adjustments for confounding factors, the odds ratio for myocardial infarction was 23. Epstein and Weiss⁸⁵ argued that as the patients with myocardial infarction are selected only after their ischaemic event, and

myocardial infarction increases the prevalence of OSA, then it is inevitable that the cases will have a higher prevalence of OSA than controls. The issue remains unresolved.

Cardiac rate normally decreases by 5-10% during non-REM sleep, with a slight increase during REM sleep. In patients with OSA the vagal stimulation caused by inspiring against upper airway resistance results in sinus bradycardia during the apnea, followed by a reflex tachycardia at apnea termination⁸³. Cardiac arrhythmias during sleep are present in up to 50% of OSA patients⁸⁷.

A link between atrial fibrillation (AF) and OSA has been suggested by Gami and co-workers⁸⁸. The prevalence of AF was found to be higher in OSA patients than the general population. The prevalence of OSA in AF patients was found to be 32-49%, depending on the population studied.

1.3.10.2 Neurological Consequences

Cerebrovascular disease

Cerebral perfusion fluctuates during apneas, which may compromise blood flow to areas of the brain with already borderline or poor circulation. An odds ratio of 3.2 for the occurrence of stroke has been reported in patients with snoring, and an odds ratio of 8 for stroke in patients with witnessed apneas, sleepiness, and obesity with snoring^{89 90}.

Excessive daytime sleepiness

Sleep fragmentation, lack of slow wave sleep, and recurrent hypoxemia have all been proposed as the cause of excessive daytime sleepiness (EDS) in subjects with OSA.

Guilleminault *et al* have shown that patients with OSA and EDS have both more sleep fragmentation and a higher AHI ⁹¹.

Patients with untreated OSA are poor drivers and have 2-3 times more automobile accidents than other drivers ⁹². Patients with sleep-disordered breathing should be warned about the risks of driving, whilst seriously impaired drivers should be kept from driving until the sleep-disordered breathing has been effectively treated ⁸³. Findley *et al* found the accident rate of patients with OSA was 0.07 crashes per driver per year as opposed to 0.01 crashes per driver per year for all drivers in the State of Colorado ⁷². With the application of CPAP therapy, the accident rate decreased to zero in compliant patients with OSA. Another study showed that 18 patients with severe sleep apnea hypopnea syndrome were subjected to a driving test in a simulator unit both prior to OSA therapy and following a 2 week period of CPAP therapy. The results showed that with treatment, the driving performance of the subjects improved and these effects were sustained for up to 1 week after withdrawal of the therapy.

1.3.10.3 Psychological and Psychiatric Consequences

Intellectual deterioration, personality and behavioural changes are well-recognised features of sleep-disordered breathing. Sleep disturbances are a common feature of psychiatric disease, usually presenting as disorders of initiating and maintaining sleep. Sleep-disordered breathing can also present with psychiatric disease such as depression, which can then improve with effective treatment ⁹³.

1.3.10.4 Endocrine Consequences

Decreased libido and/or impotence are frequently associated with OSA. This sexual dysfunction is probably related to daytime sleepiness or depression⁸³. OSA may be linked to diabetes mellitus; however, to date it is unclear whether the diabetes results in OSA, or the OSA increases the risk for development of insulin resistance.

1.3.10.5 Haematological Consequences

The degree of hypoxemia in patients with OSA may not be sufficient to stimulate erythropoietin production and cause polycythaemia unless associated with daytime hypoxemia due to coexisting lung disease.

1.3.10.6 Nephrological Consequences

Patients with sleep disordered breathing commonly complain of nocturia which then improves with effective treatment⁹⁴.

1.3.10.7 Neurocognitive Dysfunction and Performance Impairment

The ability to perform psychomotor vigilance tasks such as visual reaction tasks, divided attention tasks, and auditory learning tasks is impaired in patients with OSA. Hypersomnolence diminished the individual's capacity to maintain attention and concentration, leading to errors on vigilance tasks⁸⁵. One study demonstrated that OSA patients performed at 51% of normal levels and 63% of the level of narcoleptic patients on tests of addition and digit-symbol substitution⁹⁵. The aetiology of the cognitive

impairment is multifactorial, resulting from both EDS manifested as decreased vigilance, and hypoxemia.

1.3.10.8 Mortality

The major cause of increased mortality in sleep-disordered breathing appears to be cardiovascular in nature ⁹⁶. Partinen and Guilleminault⁹⁷ compared patients with obstructive sleep apnea who accepted advice to have a tracheotomy with those patients who rejected the surgical approach. Over 10 years there was a significant 10% difference in mortality favouring tracheotomy. Although this was not a randomized trial, it should be considered that patients who accept medical advice tend to do better than those who do not ⁹⁷.

1.3.11 Management of OSA

Therapeutic strategies for patients with OSA may be grouped into five broad categories; conservative, medical, dental, surgical and other treatments. Treatment should be based upon the effect of the sleep disorder on daytime symptoms and cardiopulmonary function rather than on the absolute number of episodes of apnea or hypopnea. The goals of treatment are to establish normal nocturnal oxygenation and ventilation, abolish snoring, and eliminate disruption of sleep due to upper airway closure ⁵⁶. A stepwise approach is recommended to guide therapy and depends on the response at each step.

1.3.11.1 Conservative Measures

All patients should undertake counselling regarding the potential benefits of treatment and the risks of going without treatment. The predisposing factors which place the patient at risk should be identified, and measures taken to either reduce or eliminate them from the equation. In particular, problems such as sleep deprivation, increased weight, and the use of alcohol, sedatives and hypnotic agents should be addressed.

In some patients, upper airway dysfunction is present only during sleep in the supine position. Training these patients to sleep in the lateral cubitus position can significantly reduce the AHI. Cartwright *et al* studied the effect of several treatment strategies for 60 male patients with OSA. The patients underwent assessment for 8 weeks. Treatment was found to reduce the AHI score to normal or near normal levels in more than half the patients. One group, who had undertaken training to sleep in a lateral position with the help of an alarm maintained this learning without the alarm, as did the group who were encouraged to learn to sleep on the side on their own. In conclusion, the authors stated that patients whose apnea showed a marked positional difference should be considered for non-invasive treatment. The patient needed to be motivated to learn to sleep in the lateral position and also needed to lose weight⁹⁸. The change in sleep position is worth trying for normal-weight snorers, although it has often been tried before the patient presents to a sleep clinic.

The cessation of respiratory depressant medications and decreasing alcohol intake are important aids in treating OSA. Alcohol reduces upper airway muscle tone and increases the frequency of abnormal breathing during sleep⁹⁹. Alcohol also prolongs apnea by delaying arousal¹⁰⁰.

Central obesity is the single most important predictor of sleep apnea. Weight loss is difficult to accomplish and maintain, but is crucial in treating OSA. The benefits of weight loss are listed by Phillips *et al*¹⁰¹ as reduced respiratory disturbance index, lower blood pressure, improve pulmonary function, improved daytime arterial blood gases, improved polycythemia, improved sleep structure, elimination of snoring, prevention of relapse after surgical treatment of OSA, improved oxygen saturation and reduced optimum CPAP pressure.

Harman *et al*¹ demonstrated that significant weight loss can cure sleep apnea in morbidly obese men. Four patients with OSA lost an average of 108 kg with the assistance of weight reduction surgery. The result was that sleep apnea was reversed with a marked improvement in daytime function¹⁰².

Weight loss does not have to be extreme as in the above study in order for the patient to derive benefit. Smith *et al* demonstrated significant improvements in sleep indices and sleep quality with moderate weight loss in 15 hypersomnolescent patients¹⁰³.

The data suggests that weight loss is an effective of treatment of OSA by whatever method it occurs¹⁰¹.

Cigarette smoking is associated with a number of sleep disturbances. In the most definitive study on the relationship of smoking and sleep-disordered breathing, Wetter *et al* found that current smokers have a greater risk of snoring (odds ratio 2.29) and of sleep apnea (odds ration 4.4) than non-smokers³⁷. Patients should be advised to cease smoking as part of their overall management.

Nasal dilators are available commercially, and have been marketed as assisting in keeping the airways open. They may be beneficial in some patients¹⁰⁴. However, reliance on these self prescribed devices should be viewed with caution. Breath Right Nasal Strips are one

such device. In a study of 35 patients with heavy snoring but no sleep apnea carried out over 14 nights, 52% of subjects showed decreased snoring and 66% reported an improvement in daytime sleepiness ¹⁰⁴.

1.3.11.2 Medical Measures (First line therapy with CPAP)

Nasal continuous positive airway pressure for OSA was first reported in 1981 ¹⁰⁵. Since then it has become the gold standard for treatment of OSA. It treats apneas and hypopneas by providing air under pressure through a nasal or facial mask, thus creating a pneumatic splint in the pharynx, which prevents collapse of the pharyngeal airway. The machines run on household current, weigh approximately 2kg and fit on a bedside table. The level of positive pressure required to sustain patency of the upper airway during sleep should be determined in a sleep laboratory through titration methods.

The major limitation of CPAP is tolerance. To be effective, CPAP should be in place for 6 hours per night, 7 days a week ³⁶. Subjective estimates of patient compliance are higher than objectively determined values. In one early covert compliance study, monitoring revealed acceptable compliance rates to be as low as 46% ¹⁰⁶. The degree to which the patient is compliant is closely related to the relief of daytime symptoms and restoration of alertness than to the severity of the AHI ¹⁰⁷.

McArdle *et al* followed the compliance and usage of CPAP in 1211 consecutive patients. 52 patients refused CPAP and 1103 took CPAP home. During the follow-up of 3 months, 20% had stopped using the device primarily due to perceived lack of benefit. 68% of the patients surveyed at 5 years were still using the device. The authors found that the best predictor for long term use was nightly use of CPAP in the first 3 months ¹⁰⁸.

Pepin *et al* recently reported a compliance rate of 80% in response to augmented support for CPAP-treated patients with OSA ¹⁰⁹.

The common side-effects of CPAP include rhinorrhea, epistaxis, nasal congestion and dryness, mask discomfort, conjunctivitis from air leak, skin abrasions, claustrophobia, irritation from noise of device, difficulty exhaling, aerophagia (swallowing air), chest discomfort and bed-partner intolerance ¹⁴.

A number of interfaces between the CPAP device and the patient are available. Sanders *et al* have found that the pressure required for maintaining upper airway patency does not vary by the type of mask. For those individuals who cannot tolerate a standard mask, a custom-made mask may provide the solution ¹¹⁰. For those patients who have difficulty getting to sleep with the CPAP due to the pressure effect, the addition of a mechanism to gradually increase the air pressure to a pre-determined level may be of assistance ¹⁴.

1.3.11.3 Dental Measures (Second line therapy with oral appliances)

Many types of oral appliances have been designed for the treatment of sleep apnea. More than eighty different oral appliances are currently available to treat snoring and obstructive sleep apnea, and the public's demand for these devices is being felt by the orthodontic profession ¹¹¹. These devices work by mechanically displacing the mandible or tongue forward to increase space in the posterior pharyngeal area. These devices should not be used for therapy in central sleep apnea, in patients with temporomandibular joint disease or those with problematic nasal obstruction. Patients need to have sufficiently healthy teeth to anchor the device. Such devices are usually not recommended in patients with severe OSA or with significant nocturnal oxygen desaturation ¹⁴.

In practice, evidence to support its use is limited. One placebo-controlled trial demonstrated an oral appliance to be more effective than the placebo ¹¹². Several studies have been undertaken to compare the efficacy of oral appliances with CPAP ^{113, 114, 115, 116}. Data suggests that CPAP therapy produced better results, with greater improvement in AHI and sleepiness than observed with oral devices. In the study by Ferguson *et al*, it was concluded that oral appliances are an effective treatment in some patients with mild-moderate OSA, and are associated with fewer side-effects and greater patient satisfaction than CPAP ¹¹³. In a subsequent study, the same group found no difference in side effects or compliance between CPAP and oral appliances ¹¹⁴. When directly compared in randomized trials, oral appliances are generally preferred by patients over CPAP, even when only partly successful in the elimination of OSA. Malhotra recommended that oral appliances be considered for patients who have failed or refused CPAP treatment ²⁷.

1.3.11.4 Surgical Measures

There are numerous surgical techniques that can aid in the treatment of OSA. These procedures are likely to be more effective for patients with discrete craniofacial abnormalities than for simply obese patients.

Tracheostomy

There remains a small group of patients who cannot tolerate CPAP and for whom other interventions are ineffective or unacceptable. A tracheostomy can provide a dramatic improvement and be lifesaving, although additional medical and psychological morbidity may be associated with the procedure. According to Guilleminault *et al*, tracheostomy is

the only procedure to be consistently effective as a sole procedure in successfully treating OSA ⁹⁴. The procedure is the gold standard surgical method for OSA. However, it does render the patient nearly voiceless and can be associated with other complications ⁶¹. Surgery is also indicated in those patients who have an anatomical abnormality that is causing the sleep apnea, such as nasal polyps, deviated nasal septa, enlarged tonsils and/or adenoids or severe craniofacial abnormalities ⁶².

Palatal Surgery

Palatal surgery is designed to modify, rather than by-pass, a specific site of upper airway closure. Although less disfiguring than tracheostomy, it has more variable results. Uvulopalatopharyngoplasty (UPPP) involves resection of the tonsils (if present), uvula and posterior palate together with reorientation of the tonsillar pillars. The procedure may have significant complications such as palatal incompetence, nasal reflux, altered voice quality, nasopharyngeal stenosis and peri-operative mortality relating to haemorrhage and airway obstruction. The criteria for success of this procedure are a reduction of AHI by 50% and a post-operative AHI of less than 10. Based on these criteria, UPPP is curative in less than 50% of patients ¹¹⁷. A study by Schwartz *et al* found a decrease in disordered breathing rate following UPPP, with some patients responding better than others. The group was unable to identify any predictors of a favourable response to this surgery ¹¹⁸. Sher supported the above data and also reported the most common complication to be velopharyngeal incompetence ¹¹⁹.

Laser-assisted uvulopalatoplasty is performed while the patient is under local anaesthesia and involves partial resection of the uvula and soft palate without resection of the tonsils

and tonsillar pillars. It is regarded as being inferior to UPPP and is limited as an outpatient treatment for snoring, and not for the management of OSA ¹¹⁹.

Palatal stiffening procedures using radiofrequency ablation of the submucosal tissues have been reported as being successful in reduction of snoring ¹²⁰.

Recent advancements have involved the use of palatal implants to cause fibrosis and submucosal scarring of the soft palate. The implants, typically made of braided polyethylene terephthalate may have lower morbidity and cost. A prospective non-randomized study of 35 habitual snoring patients was carried out at St Olav University Hospital in Trondheim. After placement of the implants (18mm long, 1.5mm diameter), the one year follow-up showed that 70% of patients' bed partners found snoring to no longer be a problem. The main problem mentioned was partial extrusion of 9 implants in 6 patients. Morbidity was therefore reported as being less than other palatal surgical procedures ¹²¹.

Tongue Surgery

Uvulopalatopharyngoglossoplasty is a modification of UPPP performed in conjunction with a limited resection of the lateral and dorsal parts of the tongue. There are no good studies on the outcome of this procedure. Some complications may occur. In a study of 22 patients, 3 patients required general anaesthesia for post-operative bleeding, and moderate odynophagia and dysphagia were common for 2-3 weeks postoperatively. One patient required prolonged intravenous hydration ¹²².

Maxillofacial Surgery

A variety of procedures have been developed to enhance upper airway patency.

Genial advancement is a difficult operation in which a hard tissue window is cut in the chin to isolate the genial tubercles. The block of bone with the tongue attached is pulled through and forward to advance the tongue. The reported success rate is 67%¹²³.

In theory, advancing the maxilla will increase airway patency at the level of the soft palate, and advancing the mandible will increase the airway at the tongue base. Advancing the mandible alone would require pre-surgical orthodontics to correct the occlusion. As a result, mandibular advancement is usually accompanied by maxillary advancement⁶¹.

The literature reports a success rate of over 90% with maxillomandibular advancement¹²⁴,¹²⁵,¹²⁶. Whenever surgical literature is assessed, limitations should always be considered. These include: no randomized studies, few control groups, sample size is generally small, often missing confidence bounds that might distinguish between statistical and clinical significance, bias caused by retrospective designs, few studies using sleep studies or quality of life indicators and baseline measures biased due to inappropriate assessment¹¹⁹.

1.3.11.5 Other Measures

The use of medication to treat OSA has been disappointing.

Fluoxetine (specific serotonin re-uptake inhibitor) and protriptyline (tricyclic antidepressant) have been used with varying degrees of success in mild cases¹²⁷.

Thyroid hormone in hypothyroid patients may significantly improve upper airway function during sleep¹²⁸.

1.4 Oral Appliances used in the Management of Obstructive Sleep Apnea

1.4.1 Background

The first reported use of any oral appliance (OA) as treatment for upper airway obstruction and mandibular deficiency was as early as 1902 by Pierre Robin ¹²⁹. No further articles were published in the English literature on the use of OA as a therapeutic method for snoring and OSA until the mid 1980's ⁶.

Cartwright and Samelson published an article describing a tongue-retaining device (TRD) ¹³⁰. This was followed 2 years later by an abstract from Meier-Ewert *et al* describing the use of a mandibular advancement device (MAD) ¹³¹.

Since then, there has been a growing interest in the use of OA in the treatment of snoring and OSA. At present there are at least 80 different OAs currently used in the treatment of snoring and OSA, with the efficacy of the individual OAs varying widely ^{111,132}.

OA are divided into 2 types:

1. Those that advance the mandible. This group makes up 93% of OA currently in use ¹³³.

These appliances have a variety of names including; mandibular advancement devices (MADs) ¹³⁴; mandibular advancement splints (MASs) ¹³⁵; and anterior mandibular positioning devices (AMP) ¹³⁶.

2. Those that hold the tongue forward during sleep are called tongue retaining devices (TRDs) ¹³⁰.

The treatment approach using OAs is simple, reversible and cost-effective.

Ferguson reviewed the status of oral appliances in the management of snoring and OSA. She concluded that the precise indications, complication rates, and reasons for treatment failure need to be determined for each oral appliance. This could be achieved by large, randomized clinical trials. Only when the mechanisms of action or OA therapy are fully understood can more effective appliances be developed ¹³⁷. In this paper the author suggest that oral appliances are indicated for patients with simple snoring or mild to moderate obstructive sleep apnea.

1.4.2 Mandibular Advancement Splint

1.4.2.1 Mechanism of Action of MASs

MASs are thought to function in the treatment of OSA in the following ways ^{138, 132, 139}:

1. Increase in the airway space
2. The provision of a stable anterior position of the mandible
3. The advancement of the tongue and soft palate
4. A possible change in the genioglossus muscle activity

The rationale for positioning the mandible forward is that the tongue is attached to the genial tubercles of the mandible and positioning the mandible forward moves the tongue forward. These devices also change the hyoid bone position and modify the lower airway space below the level of the base of the tongue ¹³⁹.

The exact mechanism of action of MAS in improving snoring and OSA during sleep is as yet undetermined. Attempts to understand the mechanism have been made by numerous researchers using various imaging techniques. The majority of these studies assess patients in the awake state resulting in limitations as these appliances are designed to be used in sleep.

Gavish *et al*¹⁴⁰ investigated the cephalometric and polysomnographic changes which occurred in 10 patients with mild-moderate OSA. They used a functional magnetic appliance to protrude the mandible. In these patients there were significant improvements in RDI, oxygen saturation, daytime sleepiness and snoring. Cephalometrically, it was found that the anterior oral cavity region increased significantly, however the pharyngeal airway passages did not change.

In contrast, other studies did find an increase in the inferior pharyngeal airway space with mandibular advancement^{141, 142, 143, 144}.

Fransson *et al*¹⁴⁵ found that following 2 years wear of a mandibular protruding device by 65 patients, cephalometric measurements showed an increase in the relative area of the pharynx by a mean of 9% in OSA patients and snorers. The authors speculate that this may be due to a reduction in oedema in the soft tissue of the pharynx related to a lessening of vibration due to weakened snoring.

In another similar study, 14 non-apneic men were fitted with a custom-made titratable mandibular advancement device¹⁴⁶. The airway was measured using MRI and cephalometrics in 7 positions (various amounts of vertical mouth opening (V) and mandibular protrusion (F)). A dose-dependant change was seen when the mandible was advanced. The cross-sectional airway was greatest at F100-V0 (that is 100% or maximal mandibular advancement and 0% or no vertical opening). The cross sectional area was less

at F50-V0 and F75-V0. The change in upper airway size varied between subjects during jaw opening (vertical). At F75-V0 the change in upper airway was significantly linked with the morphological features of the mandible, such as mandibular plane angle and lengths of the mandibular body and ramus. This is in agreement with Battagel *et al* who stated that several cephalometric variables could predict mandibular advancement, including low mandibular plane (MP) angle, normal mandibular body length, and normal antero-posterior (AP) relationship of the jaws ¹⁴⁷.

As a result, appliance design as applied to each patient may be considered important in the treatment of OSA and snoring.

1.4.2.2 MAS Appliance Designs

Various designs have been described for the treatment of snoring and OSA, but they essentially resemble a functional appliance. The majority of OAs are custom-made, thereby requiring a dental impression and protrusive bite registration, followed by fabrication in a laboratory (45%). In one survey reported in 1997, 14% of appliances were pre-fabricated, 34% adjustable and 7% were TRDs ¹³³.

Important aspects of the design of MAS ³⁶ are as follows:

1. Good retention to both the upper and lower teeth

This is important in preventing the appliance from being dislodged during sleep.

2. Sufficient protrusion to prevent pharyngeal collapse in the supine position

As shown by the previously discussed study by Gao *et al* ¹⁴⁶, the amount of protrusion has a significant effect on the change in posterior airway space. The majority of studies

suggest the desired protrusion to be 75% of maximal protrusion; however, this is subject to individual variation. As the greatest airway change was seen in patients with 100% forward mandibular protrusion, the ideal would be to protrude as far forward as the patient could tolerate. The use of titratable appliances, such as the Herbst¹⁴⁸, have the benefit of incremental advancement as tolerance increases.

3. Minimal vertical opening

According to some studies, excess vertical opening will diminish the benefits to the airway from protrusion^{36 146}. A recent study showed that the amount of bite opening induced by MAS does not have a significant effect on treatment efficacy, but does have an impact on patient acceptance¹⁴⁹. 23 adult patients were involved in a cross-over style assessment using MAS with 4mm opening and 14mm opening. Subjective improvements were reported with both appliances, a complete or partial response was seen in 74% of 4mm appliances and 61% of 14mm appliances, and patients preferred the 4mm device.

4. An anterior space between the upper and lower segments of the splint

This assists with mouth breathers.

5. Full occlusal coverage. This minimises long term dental changes from tooth eruption.

Apart from fulfilling the above criteria the ideal MAS should be:

- a. inexpensive
- b. easy to fabricate
- c. well-accepted by patients.

Many splints demonstrated in the literature do not meet these design criteria. There is no literature determining which appliance, custom-made or pre-fabricated, is more effective

at treating sleep-disordered breathing. There are very few studies comparing one appliance to another.

1.4.2.3 Evaluation of Efficacy of MASs

The clinical utility of a treatment consists of the benefit (efficacy, patient compliance) and cost (side-effects, complications, financial cost) of treatment ¹³⁴.

This can be applied to OAs:

- Benefits - effects on snoring and OSA and related problems such as hypertension, sleep disturbance, daytime sleepiness and long term sequelae
- Costs - jaw discomfort, excess salivation, dryness of mouth, grinding of teeth at night, soft tissue irritation, time to acclimatise, financial cost of appliance and so on.

The following is a review of literature regarding treatment responses.

In 1991, 68 patients with snoring and OSA were treated with a dental orthosis to advance the mandible ¹⁴¹. The appliance was made of an acrylic polymer and required dental impressions. It was fitted securely to the upper teeth, and advanced the mandible by means of a projection to engage the mandibular incisors. Much of the data was obtained by patient report using a questionnaire. After wearing this appliance for 7 months, 75% of the patients used the appliance regularly. Reported snoring was improved in all patients (except 1) and eliminated in 42% of subjects. Sleep quality and sleepiness was also reported to be improved. AHI was measured before and after in 20 of the patients, and reduced from an average of 47 to 20 events per hour. Oxygenation and sleep disturbance

were also improved. AHI was less than 20/hr in 13 patients, with a higher final AHI in those subjects who had higher initial frequencies. Side-effects were minor. The authors acknowledged that they did not perform comprehensive examinations of the temporomandibular joints but relied on patient reports of pain and malocclusion.

Eveloff *et al* investigated the effect of a Herbst mandibular advancement device on OSA. 16 male and 3 female patients with documented OSA and who had failed to tolerate CPAP were fitted with a removable Herbst appliance. 14 of the subjects showed significant improvement with AHI decreasing from 34.7 $\pm$ 5.3 to 12.9 $\pm$ 2.4 per hour. There was no change in the posterior airway space cephalometrically as a result of treatment. 14 of the 19 subjects were followed to 2 years. At the outset, no patient complained of pain or discomfort. At the follow-up, 13 of the 14 had continued to wear the appliance regularly. No patient reported pain, discomfort or temporomandibular joint problems.

In 1995, O'Sullivan *et al*¹³⁵ tested a mandibular advancement splint in 57 subjects with loud snoring, 37 of whom had an AHI greater than 10. The patients were tested with a questionnaire and polysomnography after 3.5 months. The MAS was made with 10mm opening and at 75% maximal protrusion. The results showed improvement with the appliance. Snores per sleep minute and sound intensity of snores decreased (from an average of 11.0 and 42% to 9.0 and 26.2%). The AHI dropped to under 20 for 12 out of 17 subjects (where pre-treatment AHI was 20-60), and in 2 of 9 subjects (where pre-treatment AHI was >60). 45 patients continued to wear the MAS regularly. Side-effects were described as minor, but not specified¹³⁵.

An appliance called Snore-guard was used to advance the mandible in a study by Ferguson *et al*¹¹³. 27 patients were involved in this randomized crossover study to compare the Snore-guard with CPAP. The appliance was constructed of acrylic polymer and was

designed to engage the upper teeth and advance the mandible by a projection to the lower incisors. The amount of protrusion was 3mm posterior to maximal protrusion, and with 7mm vertical opening between the incisors. The effect of the appliances was measured with home sleep-monitoring equipment. The results indicated that the AHI was lower with CPAP (3.5 +/-1.6) than with Snore-guard (9.7 +/-7.3). For the oral appliance, 48% were treatment successes, 24% were compliance failures and 28% were treatment failures. For CPAP, 62% were treatment successes, 38% were compliance failures and there were no treatment failures. Side-effects were common with the OA, especially in the first months. These included: sore teeth, a sore jaw, and excessive salivation. The authors found these problems to be mild and decreased with time. By 4 months 36% had mild, 20% had moderate, 4% had severe and 40% had no side-effects. There was no evidence of temporomandibular problems. 68% were satisfied with the treatment. Side-effects were more common and patients were less satisfied with the CPAP ¹¹³.

In a similar study, 23 male OSA subjects were treated with CPAP and a removable anterior mandibular positioning device (AMP) in a crossover design ¹³⁶. The AMP consisted of two full coverage acrylic appliances connected by Herbst attachments. Protrusion, opening and some side-to-side movement was thus allowed. The appliance was designed to advance the mandible 65% of the patient's maximal protrusion. After treatment, the CPAP reduced the AHI by 59.5% from baseline, and the AMP reduced the AHI by 38.91%. Both treatments improved oxygen saturation and decreased the amount of Stage 1 sleep while increasing the amount of REM sleep. At follow-up phone calls, intermittent usage of the appliances was found due to temporomandibular joint pains. 3 patients were not using either appliance, 3 were not using the CPAP, and 2 were not using

the AMP. The remaining 15 subjects were all using AMP nightly. Patients also expressed a preference for AMP over CPAP.

In comparing two types of OA in the treatment of OSA, Hans *et al* assessed Snore-guard with 6-8mm opening and protrusion, compared with 1mm opening and no protrusion¹³⁹. 12 patients were fitted with one appliance and 12 with the other appliance. Out of the 24 patients, 6 patients withdrew from the study for unspecified reasons and 4 patients failed to complete the trial. With the 6-8mm opening and protrusion device, AHI was reduced in most patients by 14.5, and ESS was 3.8. With the minimal opening device no protrusion device, no change or an increased AHI occurred in all patients. The authors concluded that an appliance with protrusion and vertical opening is more effective than an appliance which has no protrusion.

A short-term controlled trial of an adjustable oral appliance in OSA was completed in 1997¹¹⁴. 24 patients were fitted with an AMP with an adjustable hinge to allow progressive advancement of the mandible. The advancement was initially set at 70% of maximal mandibular advancement, and progressively advanced over the next 3 months by an average of 1.8mm or until snoring and symptoms improved, or until the patient could not tolerate further advancement. The same patients were also tested with CPAP. One patient dropped out and 3 refused to crossover, resulting in 20 subjects for analysis. The AHI was found to be lower in CPAP (4.2/hr) than with the AMP (13.6/hr). 55% of the AMP cases were treatment successes, 5% were compliance failures and 40% were treatment failures. For CPAP, 70% were treatment successes, 30% were compliance failures with no treatment failures. The patients reported greater satisfaction with the AMP due to improved comfort, lack of noise and portability, but there was no difference in reported side-effects or compliance.

Isono *et al*¹⁵⁰ studied the effect of mandibular advanced on 9 obese persons and 9 non-obese persons under general anaesthesia. The cross-sectional area of the pharynx was measured endoscopically at different static airway pressures. The authors found the mandibular advancement increased the retro-glossal area at a given pharyngeal pressure, and that mandibular advancement increased the retro-palatal area in non-obese but not in obese persons at a given pharyngeal pressure. In conclusion, forward displacement of the mandible did not improve the patency of the velopharynx in obese persons, whereas this manoeuvre improved oropharyngeal airway patency both in obese and non-obese persons. Thus mandibular advancement is shown to have a different effect on the velopharynx and the oropharynx. Applied clinically, patient weight and location of the obstruction in OSA are critical in the predicted success of an OA to protrude the mandible.

In 1998, Stradling *et al*¹⁵¹ studied 15 patients fitted with MAS over two nights with a portable sleep monitoring device, both with and without the device in place. It was found that snoring was significantly reduced from a median of 193 to 20 snores per hour. In addition there was a reduction in respiratory effort, implying enlargement of the upper airway whilst wearing the appliance. It must be noted that the authors only presented those patients who could tolerate the appliance, again reinforcing the goal of patient selection.

A 2-year study of 30 snoring and OSA patients was reported in 1999¹⁵². Patients were fitted with MAS of the monobloc design, having full tooth coverage, 70% of maximal protrusion and 5mm vertical opening. The splint was used 6-8 hours per night, 5-7 nights per week. A lateral cephalometric head film was taken at the outset and after 2 years of treatment. The appliance caused a forward and downward movement change in mandibular position. No patients reported any permanent sense of altered occlusion. No

dental movement was detected at 2 years, emphasizing the importance of full occlusal coverage in the longer-term.

Ryan *et al*¹⁵³ investigated the effect of MAS on awake calibre of the velopharynx. 15 patients participated in the study and were measured using polysomnography and videoendoscopy. The MAS caused the AHI to decrease to 8/hr. The minimal cross-sectional area of the airway increased by 18% in the hypopharynx, by 25% in the velopharynx and did not change in the oropharynx. Although the general shape of the pharynx did not change, the lateral diameter of the velopharynx increased to a greater extent than the anteroposterior diameter. The group concluded that the MAS can increase the cross-sectional area of the upper airway during wakefulness, particularly the velopharynx. If this effect is not altered by sleep, then the MAS would be useful in reducing the severity of OSA by maintaining airway patency.

Variable mandibular advancement was shown to be an effective alternative for some patients with snoring and OSA in 1999¹⁵⁴. In this study, 134 patients with a baseline AHI of 44/hr were selected. The MAS consisted of separate upper and lower components, these being shells containing a lining of thermoplastic material that becomes soft when placed in boiling water. The device is then placed over the upper and lower teeth, and the patient is then directed to close into the device, which then cools to allow custom fitting. The advancing mechanism, consisting of a bar with titrating screw in the upper component and hook in the lower component was then engaged and the mandible advanced over the following 3 weeks. Only 75 patients were available for polysomnography. These patients had a marked reduction of AHI from 44 +/-28/hr to 12 +/-15.hr. Their ESS scores fell from 11 +/-5 without treatment to 7 +/-3 with therapy. Bed-partners reported marked improvement in snoring. The most frequent side-effect was teeth discomfort in 32% of

subjects. A 1-year follow-up revealed that 86% of patients continued using the appliance, 60% were very satisfied, 27% were moderately satisfied, 11% were moderately dissatisfied and 2% were very dissatisfied. It was concluded that the appliance was effective for some patients and not others.

An OSA-monobloc and OSA-Herbst were compared in 24 OSA patients unable to use CPAP¹⁵⁵. Protrusion was set identically for both appliances. The patients were then randomized into a crossover trial, using each appliance for one week prior to clinical evaluation and questionnaire, and sleep studies. After an acclimatisation period of 159 days, the symptom scores improved, but more so with OSA-monobloc. The ESS for both appliances were similar, and less than the scores without treatment. The AHI was 8.7 +/- 1.5/hr for OSA-Herbst and 7.9 +/- 1.6/hr with OSA-monobloc. Without the therapy, the AHI was 22.6 +/- 3.1/hr. Side-effects were mild and of equal prevalence with both appliances. 15 patients preferred OSA-monobloc, 8 had no preference, and 1 preferred OSA-Herbst. Both appliances were concluded to be effective in treating OSA, with the OSA-monobloc performing better.

A mandibular repositioner constructed with 7mm incisor separation and 75% of the maximal mandibular position was given to 22 OSA patients¹⁵⁶. The trial ran over 6 months at which stage patients had a sleep study and lateral cephalometric radiographs. The RDI of the patients decreased from 40.3 to 11.7 events per hour. 59.1% of patients were considered a treatment success. The mean oxygen saturation also improved from 73.4% to 81.3%. The retropalatal airway space increased and the cross-sectional area of the soft palate decreased. Tongue posture became flatter. It was noted that the patients with a smaller reduction in AHI had certain craniofacial features such as a shorter anterior cranial base, steeper mandibular plane angle and smaller upper to lower facial height

ratios. In conclusion, the mandibular repositioner was effective in treating mild-moderate OSA, and caused an increase in the retropalatal airway space.

Henke *et al* used an oral elastic MAD to treat OSA in 28 OSA patients¹⁵⁷. The device consisted of two separate upper and lower custom-made arch forms which are then connected by elastic straps. The maxilla thus pulls the mandible forward. Different degrees of advancement are achieved by using elastic strap of different elasticity and length. The amount of advancement in this study was 88% of maximal protrusion, with bite opening of 11.5 $\pm$ 1.8mm. 68% of the patients had at least a 50% reduction in AHI with the device. Patients with obstruction at the velopharyngeal level had 80% reduction in AHI. It was suggested that this appliance was effective in all OSA patients and would be beneficial regardless of the site of obstruction.

Mehta *et al*¹¹² undertook a randomized controlled study of MAS in 28 patients with proven OSA. The appliance consisted of two pieces, and maintained a protruded mandibular position by a coupling mechanism and titrating screw on the side. The patients were advanced to the most protrusive position that could be maintained comfortably, and the amount of vertical opening was about 4mm (the thickness of the upper and lower components). Patients were blinded and were then tested by sleep study with the complete appliance in place, and also while wearing a control plate/placebo. The study found that of the 24 patients who completed the trial, 96% reported subjective improvements with the MAS. The AHI had dropped from 30 $\pm$ 2/h to 14 $\pm$ 2/h. The oxygen saturation had improved from 87% to 91%. The arousal index had also improved compared to the control. The control plate had no significant effect on these same parameters. Complete or partial resolution was achieved in 62.5% of the patients. Some minor side-effects included excessive salivation (50%), gum irritation (20%), mouth dryness (46%), jaw discomfort

(12.5%) and tooth grinding (12.5%). These problems usually did not last more than 3 weeks. 70% of patients reported substantial improvement in snoring and 87.5% reported nightly use of the device. 96% of patients stated they would like to continue using the MAS because of perceived improvement in their symptoms. This study had great strength in its design despite small sample size, and should be regarded as sound evidence for the efficacy of the MAS in treatment of OSA ¹¹².

Pitsis *et al* assessed the effect of vertical dimension on the efficacy of MAS, with either 4mm or 14mm opening¹⁴⁹. They found that a complete or partial response occurred in 74 and 61% of patients with MAS (4mm) and MAS (14mm) respectively. Subjective improvements were also reported by the majority of patients with both appliances. The study concluded that the amount of vertical opening did not have a major influence on efficacy, but did have an impact on patient compliance, with 78% preferring MSA (4mm) and 22% preferring MAS (14mm) ¹⁴⁹.

In 2002, an AMP was used in 32 patients with upper respiratory resistance syndrome, a condition very similar to OSA ¹⁵⁸. The authors found that the patient scores on the ESS, arousal index, minimal oxygen saturation level, and sleep efficiency improved significantly after insertion of the device. 3 patients experienced transitory side-effects, these being discomfort of the masticatory muscles and temporomandibular joint after first using the device. Within a few days the discomfort disappeared spontaneously. Other issues such as excessive salivation and transient tooth discomfort were minor and tolerable, and no serious complications were observed.

In a study by Walker-Engstrom *et al*, 95 male patients with mild OSA were randomized into treatment with either UPPP or MAD, and were followed over 4 years. The authors used a one-piece device that achieved a fixed mandibular advancement of 50% of each

patient's maximum protrusive capacity, a degree somewhat less than most other studies cited. The compliance at 1 year was 82%, and at 4 years was 62%. Success (as defined as a reduction in AHI >50% of baseline) was 72% at 4 years. This differed significantly from the 4 year success rate of 35% for UPPP¹⁵⁹. This study adds further weight to the growing body of evidence supporting MAD as a valid treatment for OSA. The importance of this long-term study is reinforced by Eveloff¹⁶⁰.

Engleman *et al*¹¹⁶, in a randomized crossover trial, compared two mandibular repositioning splints (with and without occlusal coverage) with CPAP. The trial period was 16 weeks with 48 patients completing the study. At the outset, the patients scores were ESS 14 and AHI 22/hr. Results favoured CPAP, with an ESS of 8 and an AHI of 8/hr. The results for MRS were an ESS of 12 and AHI of 15/hr. It was concluded that for patients with mild OSA, the results were better with CPAP, and that MRS should not be the first-line treatment.

Gotsopoulos *et al*¹⁶¹ evaluated the effect of MAS on daytime sleepiness and symptoms in OSA. Using a randomized crossover design, 73 patients received 4 weeks treatment with the MAS and 4 weeks treatment with a control device (inactive). The patients' subjective daytime sleepiness was higher with the MAS than the control device. However, the objective sleepiness results were better for the MAS than the control device. Thus it was concluded that MAS therapy can improve a range of symptoms associated with OSA¹⁶¹.

In 2003, Ng *et al* assessed the effect of a custom-made MAS incrementally adjusted during an acclimatization period for maximal advancement on upper airway collapsibility in OSA. 10 patients participated. The results demonstrated that MAS lead to a reduction in AHI from 25/h to 13/h, upper airway closing pressure in Stage 2 sleep decreased and in

slow-wave sleep also decreased compared with no therapy. This data suggested that MAS is associated with reduced upper airway collapsibility during sleep ¹⁶².

In summary the features of using MAS in the management of OSA are as follows:

- ESS - improved
- AHI - decreased
- Minimum arterial oxygen saturation - improved
- Withdrawals - variable, often reason not given
- Compliance - variable depending on length of follow-up, generally better than CPAP
- Sleep and Sleepiness - reduction in Stage 1 sleep, increase in NREM and REM sleep, reduction in sleep fragmentation, mid-sleep wake time and arousals, reduction in daytime sleepiness

1.4.2.4 Responders and Non-responders

No definitive information is available to enable the clinician to predict which patients will respond well to MAS and which will not respond. Predictive criteria would be invaluable to enable appropriate treatment to be provided to the individual and avoid the cost and chair time of an unsuccessful device. Attempts have been made demonstrating a link between success with initial AHI ^{135,141,148}. Complete success has been shown to be unlikely in patients with an AHI>60, but some improvement in these patients did occur ^{71,148}. One recent study retrospectively assessed the cephalometric variables between responders and non-responders ¹⁶³. The non-responders demonstrated a larger airway

space and oropharyngeal cross-section on lateral cephalometric films. It was hypothesised that the wider airway in non-responders might reflect an enhanced neuromuscular compensation while awake, or altered soft tissue elasticity that may affect therapeutic outcome, with the exact mechanism being difficult to define. Research is ongoing in this field.

1.4.2.5 Side-effects and Complications

Side-effects are generally reported as minor and transient, and include dry mouth, excessive salivation, tooth and jaw discomfort, tooth grinding and jaw stiffness^{112,113,164-166}. There are few studies assessing the long term sequelae of oral appliance therapy. Almeida *et al* used cephalometric and study model analysis on seventy one patients who had worn adjustable mandibular repositioners for a period of greater than 5 years. Cephalometrics revealed changes in many variables such as increased mandibular plane angle and ANB angle, decreased overbite and overjet, retroclined maxillary incisors, proclined mandibular incisors, increased lower facial height and distally tipped upper molars with mesially tipped and erupted lower molars¹⁶⁷. Using study models, the same group found that 14.3% of the patients had no occlusal changes, 41.4% had favourable changes and 44.3% had unfavourable changes¹⁶⁸. Marklund found that the design of the MAS might influence the type and magnitude of orthodontic side effects during treatment for snoring and sleep apnea¹⁶⁹. Initial deepbite and the use of a soft elastomeric device (as opposed to a hard acrylic device) were linked to a high chance of experiencing only minor reductions in overjet during wear exceeding five or more years. Overjet was found to decrease continuously during treatment, and overbite changes diminished with time. The

author recommended follow-up of bite changes every second year of appliance use to detect them at an early stage, and that patients with normal occlusion and mild OSA should use an elastomeric appliance with less than 6mm advancement and low to moderate vertical opening to minimise the risk of orthodontic side-effects.

In summary, in the last decade there has been huge interest in using OA to treat OSA. Based upon the evidence, they are generally recommended for use in patients with mild OSA or simple snoring. OA are appealing because they are easy to use, reversible, portable, and appear quite safe. Anterior mandibular positioners are the most commonly used and the best studied. The majority of published trials on OA are small, short-term, and usually retrospective in design. Other study problems include: poorly defined outcome criteria, lack of baseline polysomnography, exclusion of patients with severe OSA, lack of a control or comparison group, little detail of the appliance used, and failure to report complications and side-effects. The study by Mehta *et al* is the first prospective randomized placebo-controlled crossover trial of MAS. The patients were typical of a population of OSA patients - middle-aged, overweight and mostly male. There was also a range in severity of OSA. The results are sound and it provides “evidence (that) you can sink your teeth into”¹⁷⁰.

1.4.3 Tongue Retaining Devices

1.4.3.1 Mechanism of Action of TRDs

The mechanism of action of the Tongue Retaining Device (TRD) is to bring the tongue forward out of the airway by holding the tongue between the parted jaws in a specially

shaped compartment by applying negative pressure ¹⁷¹. The aim is to prevent backward motion of the tongue during sleep that could otherwise occlude the airway. This assumes that backward motion of the tongue plays a major role in airway occlusion ⁶.

In order to successfully use this appliance, the patient must have bilaterally patent nasal airways. According to Samelson ¹⁷¹, blocked nasal passages due to a deviated septum, deformed or obstructing turbinates or hypertrophied tonsils and adenoids require surgical correction to allow unimpeded breathing with the TRD in place. The patient becomes an obligate nasal breather, and as a result no longer suffers from dry mouth. The same author also recommended that a supine sleep posture be avoided as gravity tends to increase the tendency of the tongue to retro-lapse and block the airway. The ultimate aim is to use a simple appliance, thereby preventing the need to resort to more invasive treatments such as surgery.

1.4.3.2 TRD Appliance Designs

The literature describes several designs for the TRD. They fall into two broad categories.

1. The majority of appliances are custom-made. They consist of a one-piece mouthguard style intra-oral component which fits relatively loosely over the maxillary and mandibular dentitions. The mandible is opened slightly. A plastic bulb is located anteriorly into which the patient protrudes the tongue. A negative pressure is generated by compressing the bulb to expel air as the tongue is inserted ^{130, 172, 171, 173, 174}.

2. The tongue stabilizing device (TSD) is a non-adjustable, preformed, universal device that is available in different sizes. It consists of a narrowed isthmus which only extends intra-orally to incorporate the incisor teeth or, in edentulous patients, the alveolar ridge. This isthmus is joined anteriorly to a bulbous compartment. The tip of the tongue is inserted into the bulbous compartment, which contains vertical supports to hold the tongue in a forward position by negative pressure ¹⁷⁵.

1.4.3.3 Evaluation of Efficacy of TRDs

The first published article on TRD assessed the efficacy of the device on 14 male patients with OSA confirmed by polysomnography ¹³⁰. These patients were tested before and after treatment, and 10 went on to complete two follow-up recordings at 4 and 6 months. The authors found there was significantly improved sleep with a change toward a more normal pattern with less light sleep and more theta-wave and more REM sleep immediately after treatment commenced. There were significantly fewer and shorter apneic events on all nights when the device was worn. Patients reported waking feeling more rested and suffered from less daytime sleepiness. It was also noted that the mean AHI while wearing the device reduced from 54.4 to 22.7, which was comparable with the rate reported for UPPP. In conclusion, the authors acknowledge that the device does not replace surgery for the patient with severe OSA, but may be a viable alternative for less severe cases, or as an interim treatment to provide relief of symptoms while slower interventions are being instituted, such as weight loss.

A subsequent article ¹⁷² aimed at predicting the response to the TRD. 16 male patients were treated with TRDs, with a success rate of 69%. The strongest predictor of this

success was found to be the prevalence of an increased severity of OSA with a supine sleep posture. That is, patients with more severe OSA while in a supine sleeping position were more responsive to the TRD. The criterion for success in this study was achieving an AHI between 0-6 or a reduction in the AHI by at least 50%. It was also found that in successful patients, there was a significant reduction in Stage 1 sleep (from 32% to 14%), and a significant increase in REM sleep (from 14% to 18%). Oxygen saturation increased from 73% with the TRD out, to 82% with the TRD in place. In addition, Cartwright *et al* also observed that the patient more likely to be treated successfully with TRD would be within 25% of ideal body weight¹⁷².

The same group went on to investigate the TRD when used in combination with behaviour modification⁹⁸. In this study, 60 adult men with AHI values greater than 12.5 who had two or more times the apnea rate during supine sleep in comparison with their lateral sleep rate, were assigned to four treatment groups: TRD only, posture alarm only, TRD plus posture alarm, and health habit instruction. The results found that 73% of the TRD group and 80% of the TRD plus posture alarm group were treated successfully. The effectiveness of this treatment together with behaviour modification was thus demonstrated.

It is important to note that none of the studies by Cartwright *et al*^{98,130,172} using TRD have been able to eliminate OSA by reducing the mean AHI to below 5, the level at which sleep apnea is diagnosed. Other criticisms are that these studies have all used a small sample size, are retrospective case series, and have provided no data about relief of snoring, sleepiness or long-term patterns⁶.

In 1996, Ono *et al* investigated the effect of the TRD on awake genioglossus (GG) muscle activity in 10 patients with OSA¹⁷³. The results were compared to 6 age- and BMI-matched symptom-free control groups. Two custom-made TRDs were used for each

patient. TRD-A did not have an anterior bulb but incorporated lingual surface electrodes to record GG electromyographic (EMG) activity. TRD-B contained an anterior bulb and two similar electrodes. Patients were tested awake in both the upright and supine positions. The authors found that the GG muscle activity was greater with TRD-B than TRD-A in control subjects, but was less in TRD-B than TRD-A in OSA subjects. On the basis of these findings, it was concluded that the TRD has different effects on the awake GG muscle activity in control and OSA patients. In theory, as the TRD keeps the jaws slightly open, GG muscle activity increases which may enlarge the retroglossal space by protruding the tongue forward. In OSA patients, the GG muscle activity did not increase with the active appliance. It is speculated that the causes could be atypical neural inputs and/or outputs in OSA patients, tongue muscle in OSA patients might have different histologic and functional properties, patients with OSA may have neuro-behavioural adaptation due to chronicity of the problem, and psychological factors may alter GG muscle activity. Thus in using TRD in OSA patients, it is important to hold the tongue forward with negative pressure and not to rely on muscle activity.

The effectiveness of a TRD was examined in 8 Japanese patients with OSA¹⁷⁴ who had also received other treatments, such as CPAP or UPPP, that had been unsuccessful. The TRD was custom-made and worn for 3 months prior to sleep studies. Significant differences were found. With the TRD in place, patient's oxygen desaturation 3 index (amount of oxygen desaturation exceeding 3% per hour) dropped below baseline by more than 50% in 63% of patients, and 75% of patients had fewer than 10 events per hour. Those patients who were unsuccessful had a BMI in excess of 26 kg/m².

The most recent article assessing efficacy of a novel tongue stabilizing device (TSD) on sleep-disordered breathing was published in 2002¹⁷⁵. This pilot study used

polysomnography with and without TSD in situ to assess the benefits of the device. 6 patients were studied. The TSD was found to significantly decrease the frequency of snores per hour from 41/hour to 8/hour (in the volume range of 61-70 decibels). Trends were found for reductions in the AHI (from 26 $\pm$ 17/hour to 15 $\pm$ 13/hour). Oxygen desaturation of 4%, or more, decreased from 10 $\pm$ 10/hour to 5 $\pm$ 5/hour. Significant improvements in microarousal frequency with TSD were shown (from 34 $\pm$ 16/hour to 22 $\pm$ 14/hour). The percentage of Stage 1 sleep decreased with the TSD from 10 $\pm$ 3% to 8 $\pm$ 2%. The results of this small pilot study indicate that TSD may be effective in reducing snoring severity and microarousals, with favourable trends in sleep disordered breathing severity in selected individuals.

Limited literature is available on the TSD in compared with the MAS, and there is no research comparing these two appliances directly.

2. Research Objectives

Given the impact that obstructive sleep apnea has on an individual and those around them, and the vast number of treatment modalities with differing levels of morbidity, it would be advantageous to those suffering with this condition to be able to use a simple device to manage this problem.

The Null Hypothesis of this study is

There is no difference in the efficacy of TSD and MAS in the management of OSA.

The objectives of this study are

1. To evaluate the efficacy of TSD in patients with diagnosed OSA using questionnaires, cephalometric analysis, polysomnography and volumetric measurement of the airway using MRI.
2. To compare the efficacy of the TSD with the MAS.

Favourable results for the TSD as compared to MAS would provide patients with greater choice and a lower cost management option. In addition, the TSD could be recommended in those patients for whom the MAS would be inappropriate.

3. Patients and Methods

3.1 Sample Selection

Twenty four patients were recruited from the St George Hospital Centre for Sleep Disorders and Respiratory Failure, Sydney. This hospital is a tertiary teaching hospital attached to the University of New South Wales. The patients were referred by their sleep

physicians. Subject selection was based on agreement of the first 24 patients to participate in the study who met the eligibility criteria below.

3.2 Inclusion and Exclusion Criteria

The criteria for inclusion are; greater than twenty years of age, at least two symptoms of obstructive sleep apnea (including snoring, fragmented sleep, witnessed apneas and daytime sleepiness) and evidence of obstructive sleep apnea on polysomnography with an AHI of greater than 10 per hour. The exclusion criteria are; central sleep apnea, regular use of sedative medications, standard contra-indications for magnetic resonance imaging such as cardiac defibrillators and metallic prostheses, previous failure of a dental device for treatment of obstructive sleep apnea, exaggerated gag reflex, edentulous patients, substantial periodontal disease with a CPITN of greater than 4 in any quadrant.

3.3 Ethics Approval and Consent

The ethics approval process was initiated in April 2004. This involved two separate ethics committees and one government department. Total time to obtain all approvals was 20 months.

Ethics approval was given by Central Sydney Area Health Service Royal Prince Alfred Hospital Zone (XO-0218) on 18 February 2005, and updated in 2006.

An application was then made to the Therapeutic Goods Administration, Department of Blood, Tissues and Devices in Canberra for Clinical Trial approval. The Aveo-TSD as used in this trial has been granted FDA approval (No K993381), but to this time had not been subjected to institutional usage within Australia. A Clinical Trial Number (043/2005) was

granted on 15 June 2005 for use of the Aveo-TSD in this study, and updated in March 2006.

Ethics approval was then sought and obtained from South Eastern Sydney and Illawarra Area Health Service, Human Research Ethics Committee, Southern Section (05/73 Darendeliler) (February 2006).

An update was necessary as the sponsor company (supplying the TSD) was merged with several other medical supply companies, prompting the need for new legal paperwork.

3.4 Study Design

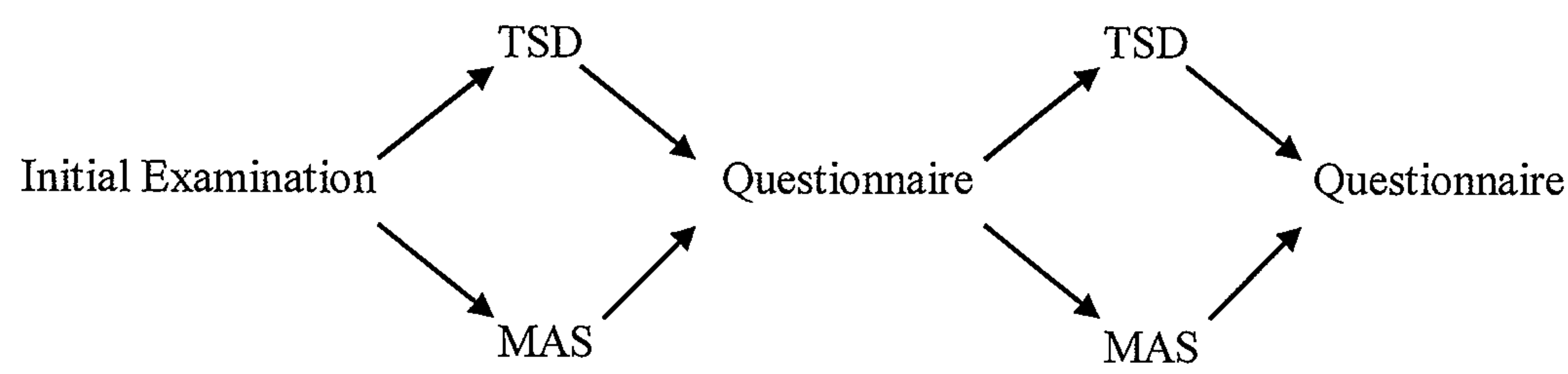
A prospective randomized crossover design was used as illustrated in Figures 5 and 6. At baseline, a routine clinical orthodontic examination including medical history, orthopantomogram and lateral cephalometric radiograph was completed for each patient. Anthropometric measurements were recorded including height and weight for body mass index (BMI), neck circumference at the level of the cricothyroid cartilage as an indication of the degree of adiposity in the upper airway region ⁴⁷ and tongue circumference. Dental impressions were also obtained. Patients were asked to complete a sleep questionnaire (See Appendix 5. Sleep questionnaire 1)

Patients were then randomized at two time points using the Minitab v 14 method. The first randomization occurred at the commencement of the acclimatisation period indicating which of the two appliances were to be provided first. The second randomization occurred at the beginning of the trial phase indicating which of the two appliances were to be used first for the sleep studies.

An eight week acclimatisation period followed during which time the patients were provided with both appliances. A questionnaire (See Appendix 6. Sleep questionnaire 2 MAS and Appendix 7. Sleep questionnaire 2 TSD) was then completed by each subject. While the author aimed for an eight week time frame, variation of the duration of this stage of the study was permitted to incorporate unforeseen patient factors.

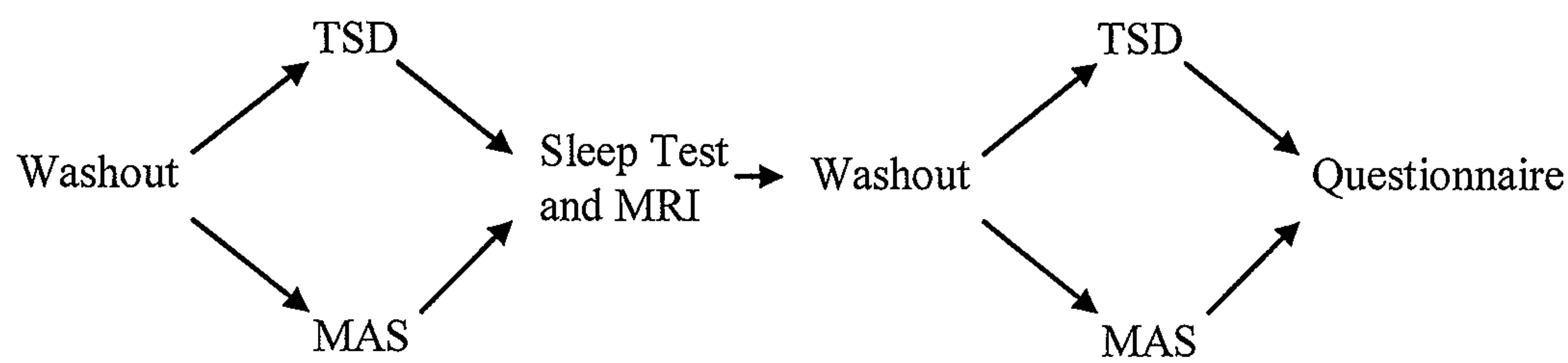
A one week washout period allowed the carry-over effect of the usage of either appliance to be reduced.

Figure 5. Study Design – Acclimatisation Phase



The second phase of the study involved two sleep studies each preceded by one week washout period and one week wearing the nominated device. A single magnetic resonance imaging scanning session was obtained on the morning after the first sleep study in the trial phase. This involved the patient being scanned in a supine position without any appliance, with the mandibular advancement splint, and with tongue-stabilising device in random order.

Figure 6. Study Design – Trial Phase



3.5 Questionnaires (See Appendices 5, 6, 7)

The aim of the questionnaires was to gain an understanding of the patient’s perception of the impact of their Obstructive Sleep Apnea on daily life. A subjective response to the two appliances used in this trial was also obtained. Several patients were asked to trial the questionnaires prior to the study to allow improvements in format and clarification of ambiguities.

The first questionnaire was completed at the initial consultation appointment, by the patient and their bed partner where possible. The second questionnaire was completed in the same manner after four weeks of using an appliance during the acclimatisation period. The second questionnaire was then repeated for the alternative appliance in the same fashion. The main focus of Sleep Questionnaire - 1 was to use the Epworth Sleepiness Scale to give a score for the patient’s perceived degree of daytime sleepiness⁵⁸. The ESS gives the patient a score between 0 and 24, with the lower score indicating minimal daytime sleepiness, and a higher score indicating greater daytime sleepiness. Patients were asked to give a score for various situations which may commonly occur during the day (0 = Never doze, 1 = Slight chance of dozing, 2 = Moderate chance of dozing, 3 = High chance of dozing).

Sleep questionnaire - 2 MAS and Sleep questionnaire - 2 TSD allowed an appreciation of the impact of the appliances on the patient's condition. Alterations in symptoms and severity and frequency of side-effects were noted.

3.6 Radiography

Orthopantomogram and lateral cephalometric head films were taken at the outset as part of the routine clinical examination. Both films were taken using the Siemens Orthophos CD (Model Number: 1538177 D 3200, Sirona Dental Australia). The exposure of the orthopantomogram was 14.1 seconds at 60kV and 16mA. The average exposure of the lateral head film was 0.32 seconds at 90kV and 12mA. The lateral head film had a magnification of 1.1, with a film focal distance of 166cm, an object to film distance of 16cm and a focal object distance of 150cm.

The lateral cephalometric films were taken in natural head position (NHP). Patients were asked to look straight ahead into the distance at eye level, and to avoid swallowing during the exposure. This was achieved by asking the patients to breathe through their nose whilst their teeth were in contact. Patients were asked to raise their hand slightly to indicate to the radiographer when they were ready for the exposure.

The concept of natural head position was introduced by Moorrees and Kean in 1958 ¹⁷⁶.

The reproducibility of this position was subsequently tested by Cooke and Wei ¹⁷⁷. 217 randomly selected 12 year old Chinese children in Hong Kong were subjected to repeat radiographs either between 4-10 minutes or 1-2 hours after their initial radiograph. The researchers found that NHP on repeated radiographs was reproducible within 2 degrees.

When patients looked at eye level into a mirror, reproducibility was 1.9 degrees, and

without the mirror was 2.7 degrees. Sandham describes the method of positioning¹⁷⁸. In particular, the patients' head is not touched, with the cephalostat height being altered such that the ear rods are aligned with the outer auditory meatus, and the patient then looks into a mirror at eye level whilst relaxed and in correct intercuspitation. In addition, Solow and Tallgren describe the method whereby the standing patient oscillates their head forward and backward until eventually settling in a self balance position¹⁷⁹. The mirror used in the majority of studies on NHP is typically placed at 200cm from the ear rods of the cephalostat. Unfortunately, no mirror could be used in this study due to the layout and small size of the room in which the radiographs were taken.

3.6.1 Cephalometric Measuring Techniques

The lateral cephalometric radiographs were hand traced by the author on acetate paper over a light box using a 0.5mm 2H lead pencil. The author was blinded to the identity of the patient. Where two bilateral structures were present as two images, an average of the two structures was drawn. Twelve radiographs were retraced one month later to test accuracy of the tracings. Due to magnification being 11%, linear measurements were adjusted accordingly, with angular measurements being unaffected.

Landmarks were identified according to the definitions listed in Table 5.

Table 5. Definitions of Anatomical Landmarks¹¹²

Point	Code	Definition
A Point	A	The deepest midline point on the maxillary alveolus between the anterior nasal spine (ANS) and the maxillary alveolar crest
Anterior nasal spine	ANS	The tip of the median sharp bony process of the palatine bone in the hard palate
B Point	B	The deepest midline point between the mandibular alveolar crest and Pogonion (Pog)
Basion	Ba	The most inferior point on the anterior margin of foramen magnum in the median plane
C2	C2	The tangent to the point on the dorsal surface of the second cervical vertebra to a line from C4
C4	C4	Postero-inferior point of the fourth cervical vertebra

Condylion	Co	The highest point on the bony outline of the mandibular condyle
Base of Epiglottis	Eb	The deepest point of the epiglottis
Gonion	Go	The most lateral external point at the junction of the horizontal and ascending rami of the mandible, found by the intersection of tangents from the posterior and inferior borders of the mandible
Gnathion	Gn	The most antero-inferior point on the bony mandibular symphysis
Hyoidale	H	The most superior-anterior point on the body of the hyoid bone
	Ht	The most superior point of the tongue in relation to the line from Eb to T
Menton	Me	The lowest point on the bony mandibular symphysis
Mandibular Plane	MP	Line joining menton and gonion

Nasion	N	The most anterior point of the fronto-nasal suture
	P	Tip of soft palate
Posterior nasal spine	PNS	Tip of the posterior spine of the palatine bone in the hard palate
	spt	The tangent point on a line parallel to pm-P on the dorsal surface of the soft palate at the maximum width
Posterior pharyngeal wall	Phw	A point on the posterior pharyngeal wall at the same horizontal level as spt
Pterygomaxillare	pm	The intersection between the nasal floor and the posterior contour of the maxilla
Sella	S	The centre of the sella turcica
Tongue tip	T	The most anterior part of the tongue which contacts the lingual surface of the mandibular incisors.

3.6.2 Cephalometric Measurements

Table 6. Lateral Cephalometric Measurements

Variable	Interpretation
Cranial Base 1. BaSN (degrees) 2. SN (mm)	Cranial base angulation in mid sagittal-plane Anterior cranial base length measured in mid-sagittal plane
Maxilla 3. ANS-pm (mm) 4. Co-A (mm)	Length of nasal cavity Distance from condylion to A point (effective midfacial length)
Mandible 5. Go-Gn (mm)	Distance from Gonion to Gnathion

Antero-posterior measurements	
6. SNA (degrees)	Angle from sella to nasion to A point
7. SNB (degrees)	Angle from sella to nasion to B point
8. ANB (degrees)	Angle from A point to nasion to B point
Vertical measurements	
9. LAFH (mm)	Lower anterior face height: from ANS to Me
10. TPFH (mm)	Total posterior face height: from S to Go
11. SN-Mp (degrees)	Angle between SN line and mandibular plane
Hyoid	
12. H-Mp (mm)	Perpendicular distance from the mandibular plane to hyoidale
Neck	
13. C2C4-SN (degrees)	Craniocervical angle formed by a line from C2 to C4 and SN line

Soft Tissues	
14. Phw-spt (mm)	Width of pharynx where soft palate is thickest
15. pm-P (mm)	Soft palate length: from pm to tip of soft palate
16. PAS (mm)	The distance from posterior pharyngeal wall and the dorsal surface of the base of the tongue. Measured on the line that intersects Go and B point
17. SPT (mm)	Soft palate thickness: maximal thickness on a line perpendicular to pm-P
18. Tl (mm)	Tongue length measured from tip to base of epiglottis
19. Tht (mm)	tongue height: perpendicular distance from Ht to the line connecting Eb and T

3.7 Mandibular Advancement Splint Construction

The Mandibular Advancement Splint used in this trial was manufactured by Somnomed Limited (Level 3, 20 Clarke Street, Crows Nest, New South Wales, Australia 2065) (Figure 7). The design was a two-piece non-titratable appliance with vertical extensions on the lower component and ramps on the upper component. The height of these vertical extensions and ramps induced a forward mandibular posture, thereby increasing posterior airways dimensions. A non-titratable version was selected as it had no metallic components and therefore could be worn during the MRI scan. Dental impressions were taken using Algident Type 1 fast setting, (Dentaform Australia Pty Ltd, PO Box 448,

Hurstville NSW 1481). Impressions were poured up within 24 hours of taking the impression, but the particular alginate used can be cast up to 100 hours later. Working models were poured in the Orthodontics Laboratory in the Sydney Dental Hospital using Orthodontic Stone (Whipmix, ADA type III, 361 Farmington Avenue, PO Box 17183, Louisville, Kentucky 40217).

A protrusion bite was taken using Investo dental modelling wax (Ainsworth Dental Company Pty Limited, Marrickville NSW 2204) and a 4 mm thick plastic bite wafer (Projet, Cat No: 150-001/150-002, Oradec Ortho Supplies, McGrath Hill NSW 2756). The method for obtaining this protrusive bite record was as follows. Overjet in centric occlusion was measured. The patient was then asked to protrude their mandible to the maximum amount at which position the overjet was again recorded. 75% of the difference was then calculated and marked on the Projet wafer. 75% was the nominated goal based on the amount of average protrusion obtained in a previous study¹¹². The protrusive bite was then registered by applying warm wax to the bite wafer and asking the patient to bite such that their lower incisors were level with the marking. The vertical opening of the bite registration was 4mm at the incisal edge as determined by the wafer itself (Figure 9).

Casts and the protrusive bite were then sent to Somnomed Limited for the manufacture of the mandibular advancement splint.

Figure 7. Somnomed Mandibular Advancement Splint

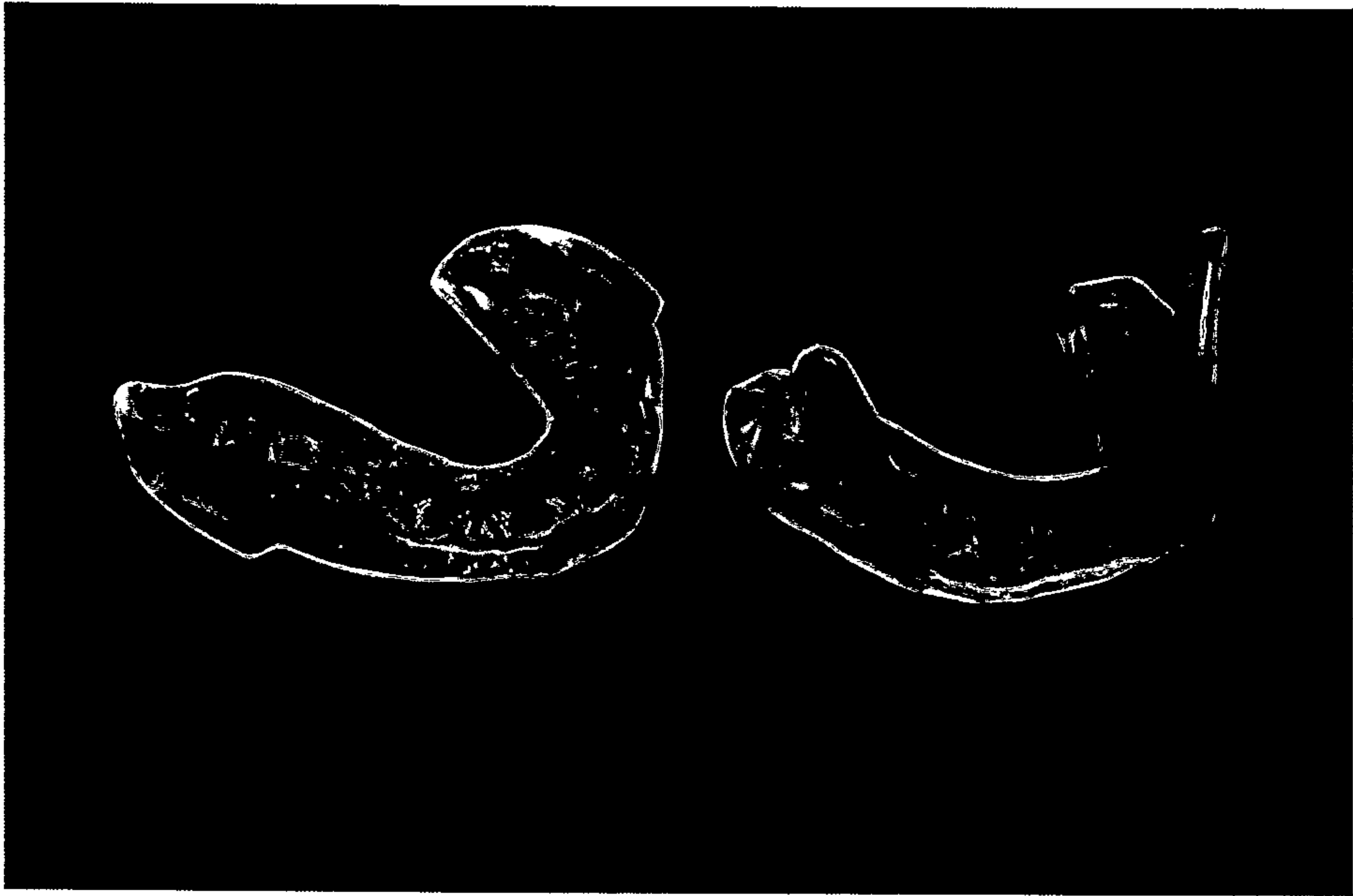
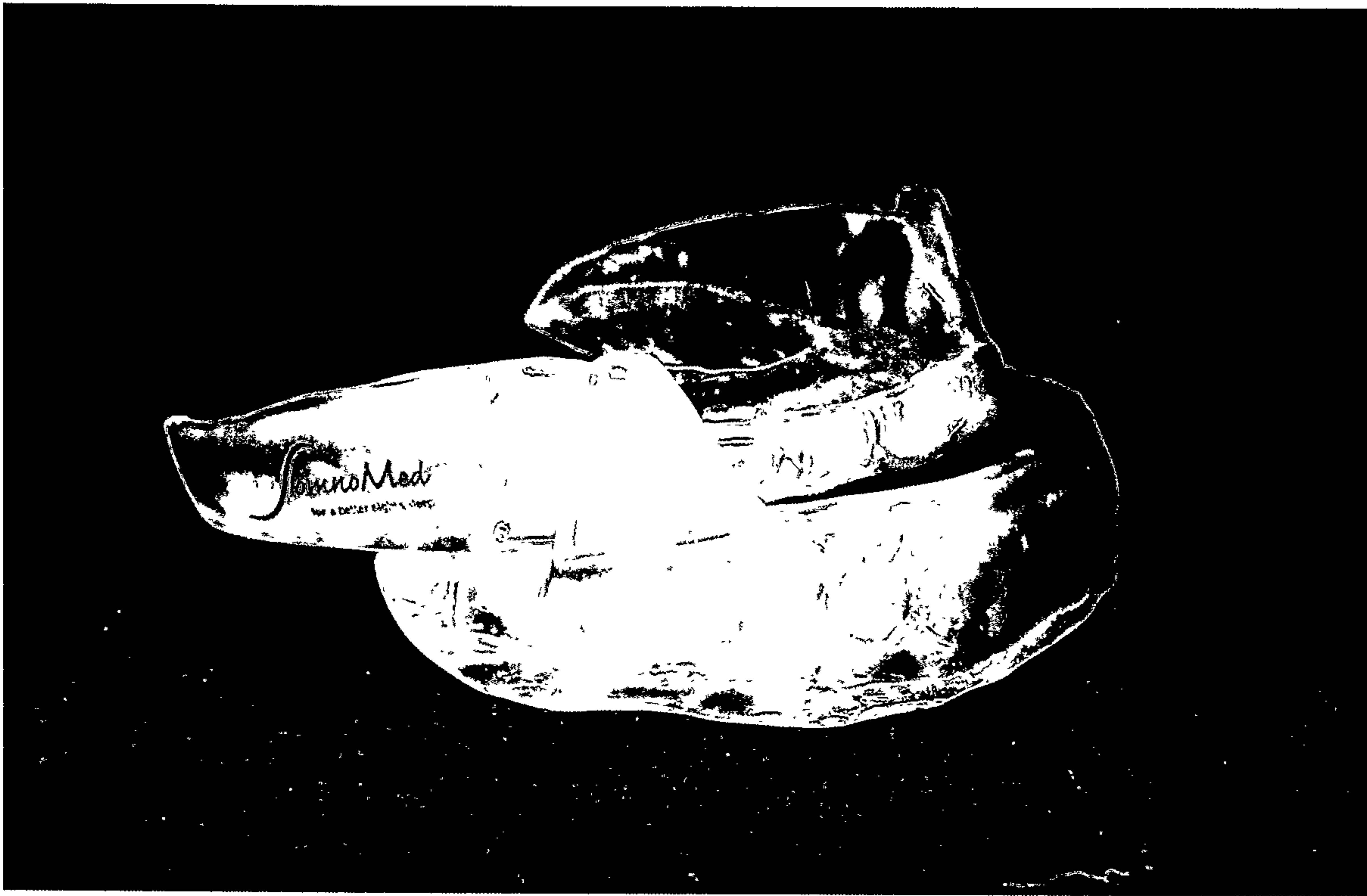
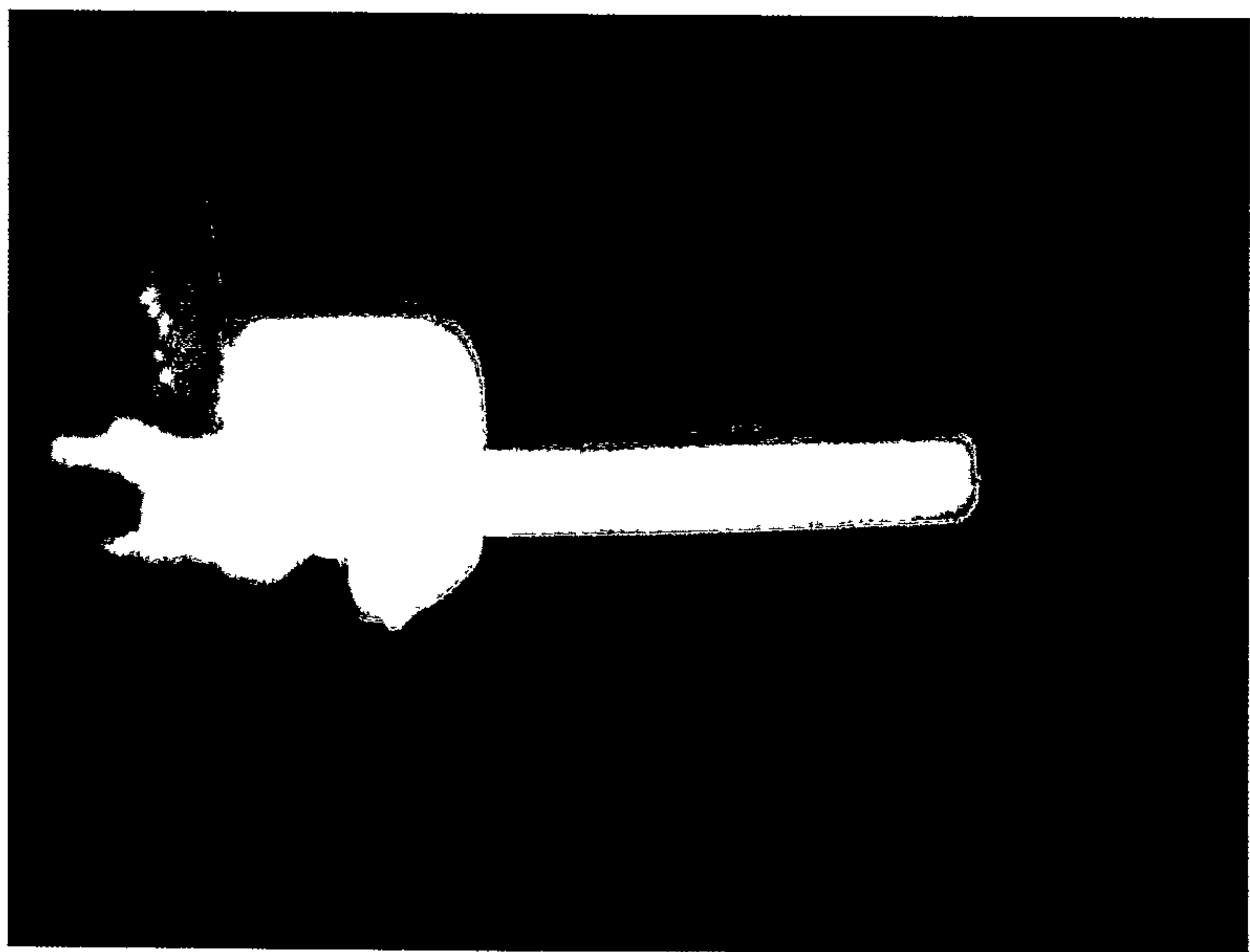


Figure 8. MAS in Situ



Figure 9. Bite Registration for MAS



3.8 TSD Construction

The tongue-stabilising device used in this trial was a preformed, non-adjustable appliance¹⁷⁵. The AveoTSD anti-snoring aid was made by Innovative Health Technologies (PO Box 17572 Christchurch, New Zealand). It is distributed by Richard Thomson Pty Ltd (PO Box 100, Kingsgrove, New South Wales, Australia 2206), an Ebos Company.

The method of construction is an injection moulded silicone. The device is available in three sizes; small, medium and large. To ascertain the appropriate size for each patient, a measurement of the tongue circumference was taken. Dental floss was wrapped around the tongue at the level of the lingual frenulum, and this value transferred to a table indicating the required size of the appliance.

Figure 10. Aveo-TSD Anti-snoring device

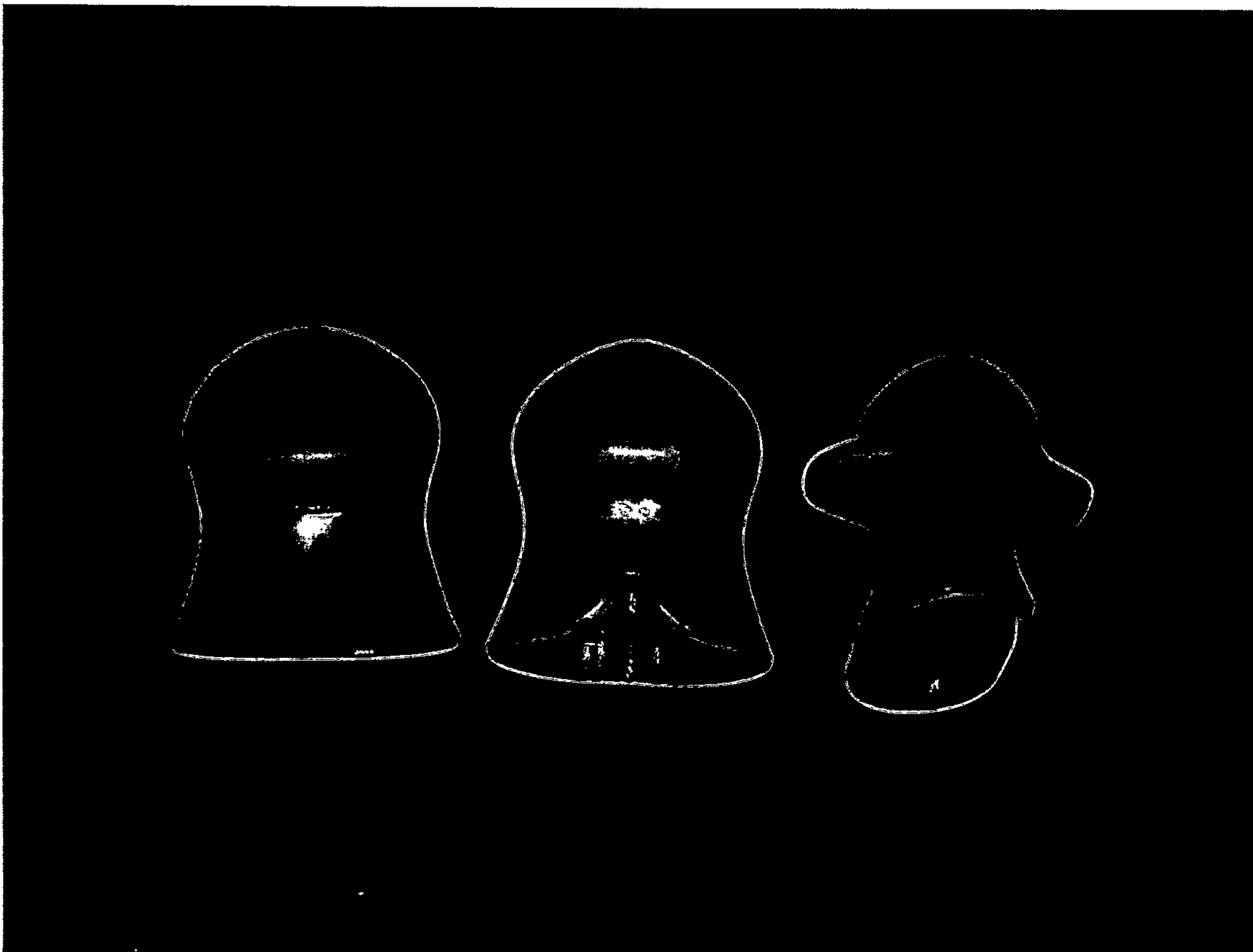
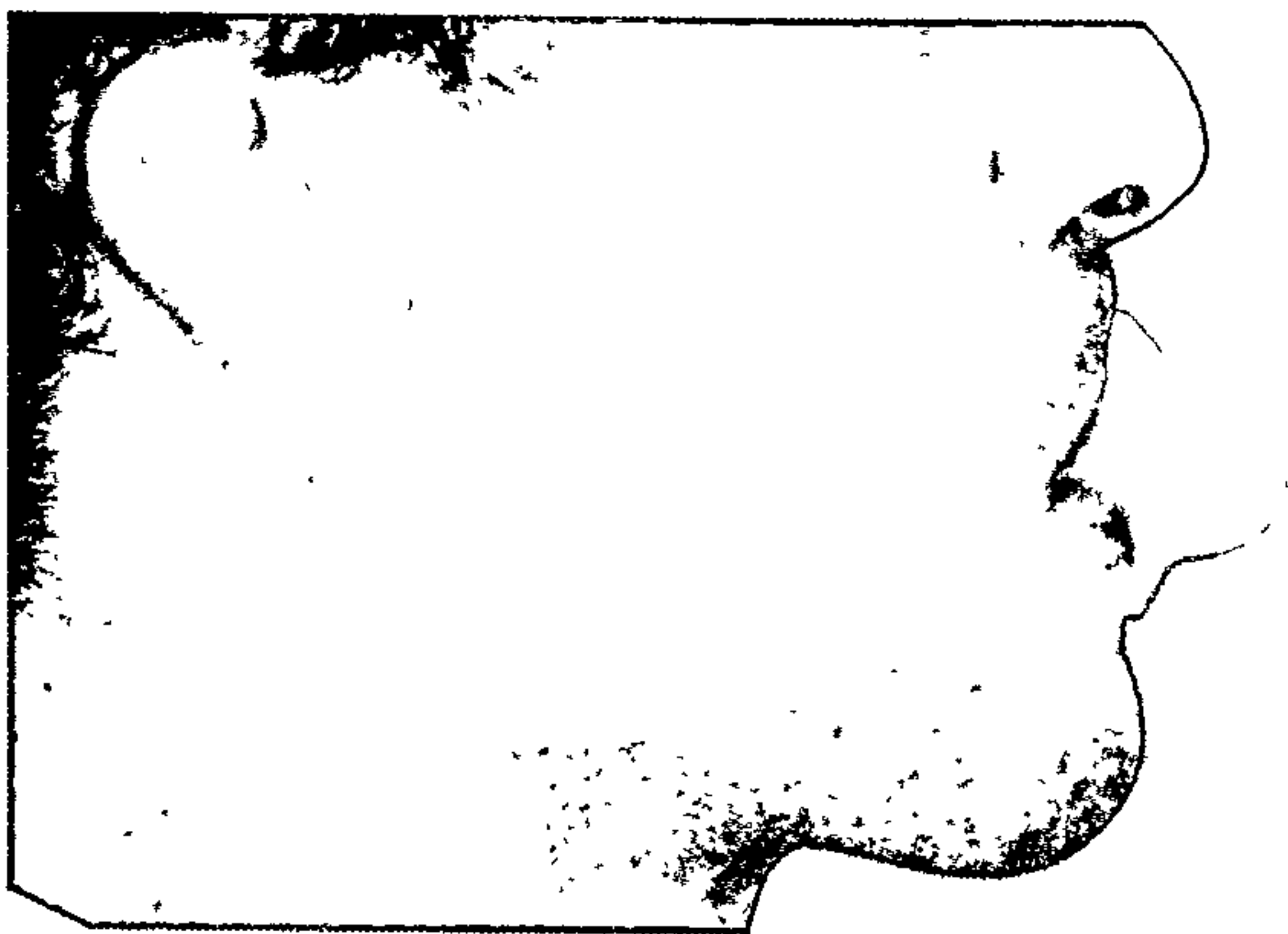


Figure 11. TSD in Situ



3.9 Acclimatisation Period

The acclimatisation period began when the appliance was first given or fitted until the patient stopped wearing the appliance for the one week washout period prior to the second sleep study phase of the study. The aim was to allow patients to adjust to these appliances for approximately four weeks each, but the times varied between the patients.

Patients were monitored by phone or email during this stage to ascertain their compliance and to detect any problems. Patients were able to contact the author at any time. Adjustments were made to the appliances as determined by patient request.

3.10 Post Acclimatisation Period

A one week washout period followed the acclimatisation period. In this time no appliance was worn by the patient to reduce any carry-over effect of the appliance last worn on the first sleep study. This protocol followed that of previous studies^{112,149}.

3.11 Sleep Studies

Each patient underwent three sleep studies: baseline (without any oral appliance), wearing MAS, and wearing TSD. The tests were completed at the Sleep Laboratory at St George Hospital. The sleep variables were recorded using the S-Series ‘Replay’ EEG/PSG (Compumedics Limited, Abbotsford, Victoria, Australia), processed by ProFusion PSG software, and monitored by sleep technicians. The variables measured were total sleep time, sleep time REM, sleep time NREM, arousal index, sleep efficiency, minimum oxygen saturation, apnea hypopnea index (overall, REM, NREM), longest apnea, longest hypopnea, and mean duration apnea plus hypopnea. These variables were then used to determine sleep architecture and respiratory function.

The severity of the patients’ obstructive sleep apnea was classified according to the baseline AHI. Mild was an AHI <20, moderate was an AHI 20-40, and severe was an AHI >40.

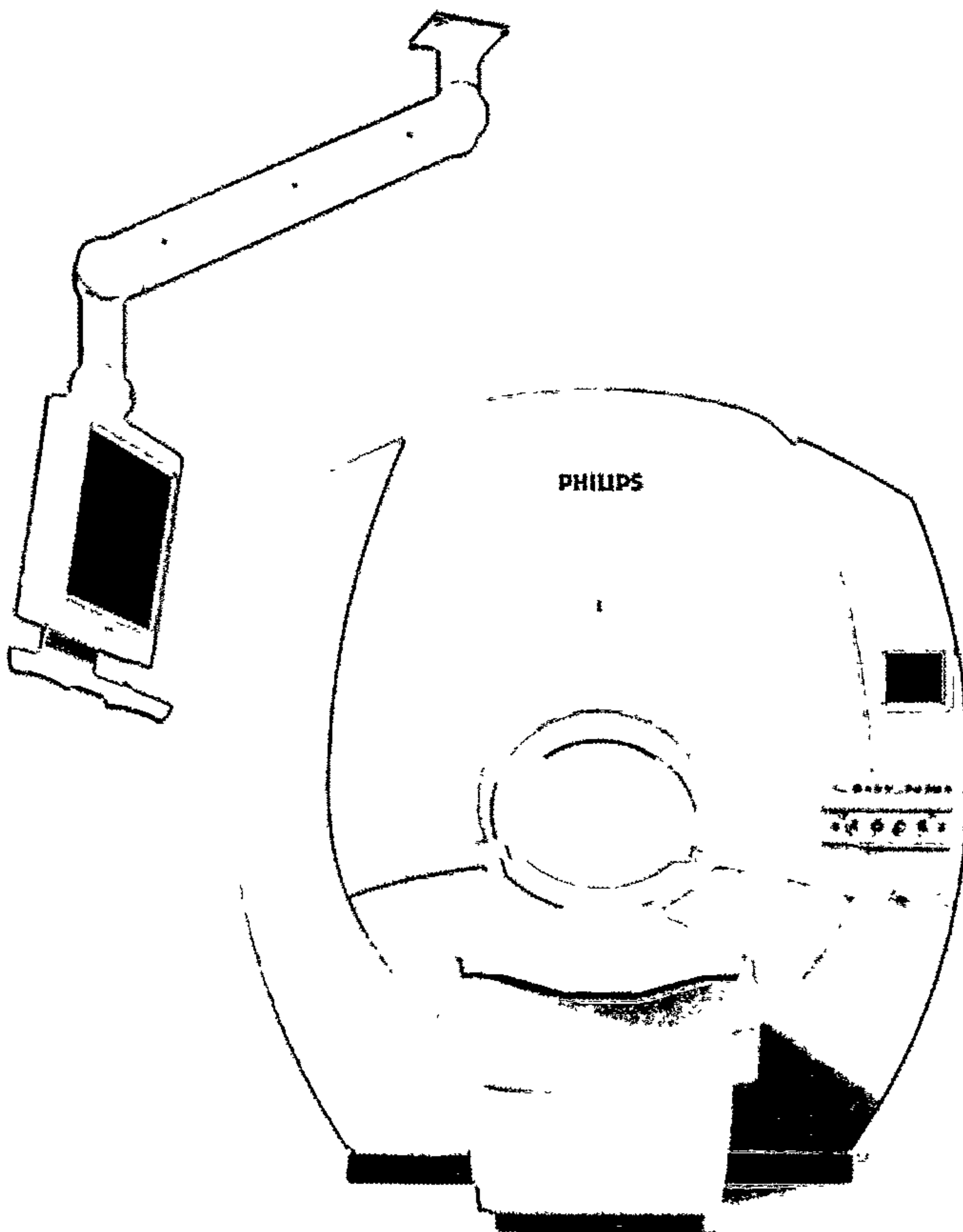
The outcome of the use of either the MAS or TSD was described in four categories:

- | | | |
|----|--------------------|---|
| a) | Treatment success | a resolution of symptoms and a reduction in AHI to ≤ 5 |
| b) | Partial success | improvement in symptoms and a $\geq 50\%$ reduction in AHI, but where AHI remains above 5 |
| c) | Treatment failure | ongoing clinical symptoms and/or reduction in AHI <50% |
| d) | Compliance failure | patient discontinued treatment |

3.12 MRI Analysis

The MRI scan was completed by Mayne Healthcare Imaging Service Pty Ltd on the morning after the first appliance sleep test in the trial period. The scan was taken using Philips INTERA 1.5 Tesla magnetic resonance imaging scanner with software version v 11.1.4.1 (Royal Philips Electronics, Netherlands), and took approximately 40minutes.

Figure 12. Philips INTERA 1.5 Tesla magnetic resonance imaging scanner



The Osiris program for personal computer by Hopital Cantonal Université de Genève, Division d'Informatique Médicale, Unite d'Imagerie Numérique (UIN/HCUG 1995-1996) was obtained through the internet¹⁸⁰. Using this program the author:

- a) reviewed the airway shape in 5mm sagittal slices and 3mm axial slices in the three regions, velopharynx (from hard palate to tip of uvula), oropharynx (from tip of uvula to tip of epiglottis) and hypopharynx (from tip of epiglottis to cricoid cartilage)
- b) identified the narrowest region of the velopharynx at baseline
- c) assessed changes in shape on the axial slice (at level b) as a result of each dental appliance at each region of the airway
- d) assessed the changes in total pharyngeal volume and volume of each region from baseline and with the two appliances. Osiris was used to measure the area of each axial slice, and the volume obtained by adding the appropriate slices together.

3.13 Statistical Analysis

3.13.1 Data Storage and Statistical Software

Data was stored and analysed on a computerised spreadsheet (Microsoft Office Excel 2003) and analysed using SPSS Version 15 (SPSS Inc 444 North Michigan Avenue, Chicago IL 60614).

3.13.2 Preparing the Data for Analysis

The raw data from the questionnaires was reviewed and coded appropriately. The sleep test and MRI data was added to the spreadsheet without coding.

3.13.3 Statistics

The demographic data describing the patient population were subjected to a Student's T-Test to compare the physical characteristics of the male and female subjects. Student's T-Tests were also used to compare the cephalometric data of the male and female subjects to each other. A paired Student's t-test was performed to identify any significant difference in the total patient data compared with the normative data. An analysis of errors of cephalometric measurements was undertaken by assessing five cephalometric variables, being both linear and angular, and accepted as being more difficult to measure. By comparing repeated tracings, the standard error of measurement was determined. The standard error was then divided by the mean to convert it into a percentage.

The results of the questionnaires were presented graphically. Paired Student's T-Tests were used to compare the Epworth Sleepiness Score at baseline, after TSD and after MAS.

The sleep study data were subjected to paired Student's T-Tests to demonstrate any difference between results for TSD and MAS. Cross Tabulation and Pearson Chi-Square Tests (using the linear by linear p-value) compared the percentage of patients within categories of success by appliance. Comparison of success and partial success against failure for the total sample between TSD and MAS was made using cross tabulation and a small sample exact test¹⁸¹.

Volumetric data obtained from the MRI were also compared between the two appliances using paired T-Tests to demonstrate the difference and calculate the significance of the differences.

The mean and standard deviation were given for all descriptive statistics. The mean and standard error of the mean were calculated for the objective test results. Due to the large

number of dependant tests carried out, an 'ad hoc' Bonferroni-type adjustment was made to the significance level and a p -value of less than 0.01 was considered significant. The significance level is the probability of rejecting the null hypothesis assuming the null hypothesis is true.

A power calculation indicated that a sample size of 19 using the AB-BA type design would have an 80% chance of showing a reduction in AHI using a significance of 0.05. The significance was nominally reduced in this study to 0.01. Given the large number of tests and the Bonferroni-type adjustment, this resulted in almost 5% overall; therefore, the original sample size calculation remained valid.

4. Results

4.1 Study Population

From the 24 patients who commenced the trial, 18 patients (75%) completed the protocol. Four patients dropped out of the study due to reasons unrelated to the study. One patient was diagnosed with a mental disorder, 1 commenced using sleeping tablet medication, 1 had increased work commitments and another had an illness in the family. Two patients are yet to complete the protocol.

The data presented is based on the 18 patients who completed the protocol. The MRI data is on a sample of 15 patients. Three patients were not able to complete the scan due to dental implant, claustrophobia attack and too large to fit within the barrel of the scanner.

4.2 Sample Characteristics

Table 5. Sample Characteristics

Sample Variables	Total	Male	Female	pValue
	Mean $\pm$ SD	Mean $\pm$ SD	Mean $\pm$ SD	
Gender	18 (100%)	14 (77.8%)	4 (22.2%)	
Age (years)	49.99 $\pm$ 9.86	48.13 $\pm$ 10.22	56.52 $\pm$ 4.98	0.14
Height (m)	1.75 $\pm$ 0.10	1.78 $\pm$ 0.08	1.63 $\pm$ 0.07	0.003*
Weight (kg)	89.6 $\pm$ 28.3	95.9 $\pm$ 26.2	67.5 $\pm$ 11.9	0.054
BMI	29.0 $\pm$ 5.8	30.0 $\pm$ 6.0	25.6 $\pm$ 3.9	0.18
Neck Circumference (m)	0.41 $\pm$ 0.05	0.42 $\pm$ 0.05	0.36 $\pm$ 0.04	0.21
Tongue Circumference (mm)	99.9 $\pm$ 8.0	100.4 $\pm$ 7.9	98.3 $\pm$ 9.5	0.65
Baseline AHI (/hr)	28.7 $\pm$ 18.6	24.1 $\pm$ 13.3	44.5 $\pm$ 27.6	0.24
Baseline Min Sa O2 (%)	83.3 $\pm$ 6.53	84.5 $\pm$ 5.93	79.3 $\pm$ 7.80	0.16
Baseline airway volume (cm3)	15.17 $\pm$ 5.74	17.30 $\pm$ 4.64	9.32 $\pm$ 4.46	0.011
MAS advancement (%)	76.0 $\pm$ 8.0	77.3 $\pm$ 7.8	71.3 $\pm$ 7.5	0.19

* Significant at $p<0.01$

Table 5 illustrates the sample characteristics classified by whole group, male and female. The patients were predominately male (77.8%), of middle age and overweight as demonstrated by a BMI of 29.0 kg/m² $\pm$ 5.8. The baseline AHI as determined by polysomnography was 28.7 $\pm$ 18.6, and was higher in the female group at 44.5 $\pm$ 27.6. The female group contained 2 patients (50%) who classified as having severe OSA, whereas the male group had 2 severe OSA patients (14.3%).

A significant difference between gender was identified for the height parameter, with females being shorter.

Table 6 indicates the proportions of the sample population with mild, moderate and severe OSA, and the BMI for each category.

Table 6. OSA Severity and Mean BMI

OSA Severity	N (%)	Mean BMI $\pm$ SD (kg/m ²)	pValue
Mild (<20/hr)	9 (50)	30.4 $\pm$ 5.1	
Moderate (20-40/hr)	5 (27.8)	26.0 $\pm$ 5.8	
Severe (>40/hr)	4 (22.2)	29.9 $\pm$ 7.4	
TOTAL	18 (100)	29.0 $\pm$ 5.8	
Between groups			0.40

*Significant at $p<0.01$

There was no significant difference in the BMI between the categories.

Table 7. Clinical Characteristics

Clinical Characteristic	Mean $\pm$ SD (mm)	Range (mm)
Overjet	2.3 $\pm$ 1.5	0.0 – 5.0
Maximum jaw protrusion (mm)	8.3 $\pm$ 2.0	5.0 – 13.0
Actual advancement (% of maximum jaw protrusion)	76.0 $\pm$ 8.0	60.0 – 95.0

Table 7 summarises the clinical characteristics for the total sample population. A goal of 75% actual advancement was used. Each patient was asked to advance their mandible as far forward as was comfortable. The MAS was constructed to this position and no further titration was made due to the requirement of a metal-free appliance. The mean advancement obtained was 76.0% $\pm$ 8.0, with a range of 60-95%, reflecting the patients' varying ability to protrude.

4.3 Cephalometric Analysis and Error

The cephalometric measurements for the total group (T), and for the male (M) and female (F) groups are presented in Table 8. The normative data is derived from the literature.

Table 8. Comparison of Cephalometric Variables and Normative Data

Ceph Variable	Group T=total M=Male F=Female	OSA Sample N=18 (M=14, F= 4)	Normative Data		<i>p</i> Value T vs Norms	<i>p</i> Value M vs F
		Mean $\pm$ SD	Mean $\pm$ SD	N		
BaSn (degrees)	T	130.1 $\pm$ 5.5	130.6 $\pm$ 4.6	58	0.731	0.886
	M	130.2 $\pm$ 6.0	129.4 $\pm$ 5.4	27		
	F	129.8 $\pm$ 3.8	131.7 $\pm$ 4.2	31		
SN (mm)	T	67.6 $\pm$ 4.5	69.1 $\pm$ 3.1	58	0.192	0.92
	M	68.5 $\pm$ 4.6	71.5 $\pm$ 3.0	27		
	F	64.3 $\pm$ 2.4	67.0 $\pm$ 1.9	31		
ANS-pm (mm)	T	53.9 $\pm$ 4.7	54.7 $\pm$ 3.8	58	0.505	0.20
	M	55.2 $\pm$ 4.4	57.2 $\pm$ 3.8	27		
	F	49.3 $\pm$ 2.5	52.6 $\pm$ 2.2	31		
Co-A (mm)	T	87.7 $\pm$ 6.0	85.8 $\pm$ 4.6	58	0.224	0.002*
	M	89.1 $\pm$ 6.1	88.7 $\pm$ 4.3	27		
	F	82.8 $\pm$ 1.3	83.3 $\pm$ 2.9	31		
Go-Gn (mm)	T	71.4 $\pm$ 6.4	75.2 $\pm$ 5.8	58	0.023	<i>p</i> <0.01*
	M	73.9 $\pm$ 4.6	79.2 $\pm$ 4.0	27		
	F	62.5 $\pm$ 1.0	71.7 $\pm$ 3.9	31		
SNA (degrees)	T	82.3 $\pm$ 3.4	81.2 $\pm$ 3.8	58	0.249	0.760
	M	82.1 $\pm$ 3.4	82.0 $\pm$ 4.6	27		
	F	82.8 $\pm$ 3.5	80.5 $\pm$ 3.4	31		
SNB (degrees)	T	79.1 $\pm$ 3.4	78.7 $\pm$ 3.8	58	0.660	0.113
	M	79.8 $\pm$ 3.3	79.7 $\pm$ 4.5	27		
	F	76.8 $\pm$ 2.5	77.9 $\pm$ 3.4	31		
ANB (degrees)	T	3.2 $\pm$ 2.7	2.3 $\pm$ 2.3	58	0.219	0.012
	M	2.4 $\pm$ 2.5	2.0 $\pm$ 2.9	27		
	F	6.0 $\pm$ 1.6	1.6 $\pm$ 2.4	31		
LAFH (mm)	T	66.5 $\pm$ 4.3	63.5 $\pm$ 2.1	58	0.005*	0.064
	M	67.5 $\pm$ 3.9	66.6 $\pm$ 6.1	27		
	F	63.0 $\pm$ 4.6	60.7 $\pm$ 4.5	31		
TPFH (mm)	T	82.7 $\pm$ 7.9	76.0 $\pm$ 6.1	58	0.001*	0.003*
	M	85.4 $\pm$ 6.7	80.5 $\pm$ 4.0	27		
	F	73.3 $\pm$ 2.1	72.0 $\pm$ 4.1	31		
SN-Mp (degrees)	T	29.7 $\pm$ 29.7	33.1 $\pm$ 6.1	58	0.071	0.213
	M	28.6 $\pm$ 7.6	31.8 $\pm$ 6.8	27		
	F	33.8 $\pm$ 3.6	34.3 $\pm$ 5.9	31		
H-Mp (mm)	T	20.8 $\pm$ 5.9	12.0 $\pm$ 3.8	30	<i>p</i> <0.01*	0.480
	M	20.3 $\pm$ 6.0	-	-		
	F	22.8 $\pm$ 6.2	-	-		
C2C4-SN (degrees)	T	109.1 $\pm$ 6.1	97.7 $\pm$ 5.7	51	<i>p</i> <0.01*	0.543
	M	108.6 $\pm$ 6.2	-	-		
	F	110.8 $\pm$ 6.1	-	-		

Phw-spt (mm)	T	11.4 ± 2.5	10.1 ± 2.8	101	0.045	0.731
	M	11.5 ± 2.2	-	-		
	F	11.0 ± 3.6	-	-		
Pm-P (mm)	T	40.8 ± 5.9	41.2 ± 4.4	36	0.787	0.845
	M	40.9 ± 6.7	-	-		
	F	40.3 ± 1.0	-	-		
PAS (mm)	T	10.7 ± 4.1	14.0 ± 2.2	30	0.001*	0.053
	M	11.6 ± 3.5	-	-		
	F	7.3 ± 4.6	-	-		
SPT (mm)	T	10.5 ± 2.7	10.0 ± 1.7	36	0.468	0.052
	M	11.1 ± 2.7	-	-		
	F	8.3 ± 0.5	-	-		
Tl (mm)	T	75.5 ± 5.7	83.3 ± 5.3	36	<i>p</i> <0.01*	0.054
	M	76.9 ± 5.5	-	-		
	F	70.8 ± 3.7	-	-		
Tht (mm)	T	36.4 ± 2.9	41.1 ± 3.6	36	<i>p</i> <0.01*	0.037
	M	37.1 ± 2.7	-	-		
		33.8 ± 2.4	-	-		

*Significant at *p*<0.01 (Normative data for most of the variables are from Bhatia and Leighton¹⁸² except Tl, Tht, pm-P and SPT¹⁸³, H-Mp and PAS³², Phw-spt adapted¹⁸⁴, and C2C4-SN¹⁸⁵.

The cephalometric variables which were statistically significant (*p*<0.01) were LAFH (distance increased), TPFH (distance increased), H-Mp (length increased), C2C4-SN (increased), Tl (length decreased) and Tht (height decreased).

When comparing the male with the female groups, the cephalometric variables found to be significantly different (*p* <0.01) were Co-A (less in females), Go-Gn (less in females) and TPFH (less in females).

Table 9 demonstrates the analysis of cephalometric errors. The five variables were chosen to examine both linear and angular measurements. These variables were also regarded as more likely to show variation due to the difficulty in landmark identification associated with them.

Table 9. Analysis of Cephalometric Error

Landmark	Mean	MSE	SE-mst	CV%
Co-A	87.7	0.6	0.77	0.88
Go-Gn	69.2	1.4	1.18	1.71
SNA	82.25	0.65	0.81	0.98
PAS	11.1	0.4	0.63	5.70
SPT	9.35	0.75	0.87	9.26

The Standard Error of Measurement (SE-mst) being the plus or minus of repeated measurement was comparable for all variables (0.6-1.2). The converted values (SE divided by the mean) ranged from less than 1% to just over 9%.

4.4 Analysis of Questionnaires

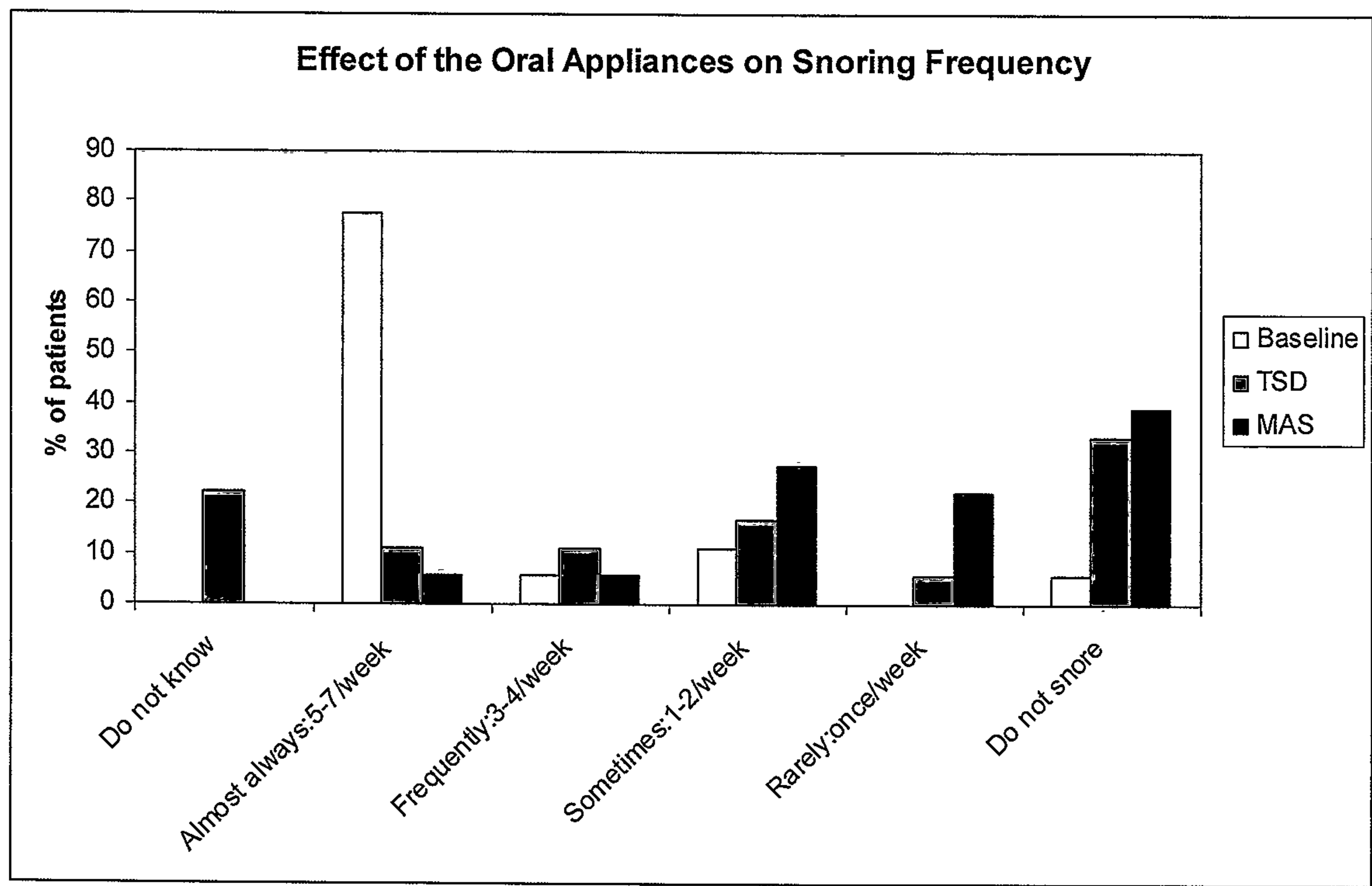
Data was collected from Sleep Questionnaire – 1 (completed at the initial examination appointment), Sleep Questionnaire – 2 TSD and Sleep Questionnaire – 2 MAS (completed after the 4 weeks acclimatisation period with the relevant appliance). 18 patients completed the questionnaires. 8 patients answered the questions related to snoring on their own having asked their bed partners at home, and 7 completed these questions with their bed partners in attendance and 3 patients who were single answered based on their experience.

4.4.1 Effect of the Oral Appliances on Snoring

(Q: On average how many days/nights during the last month have you snored or been told you snore?)

Figure 13 illustrates the improvement experienced by the patients at the end of the acclimatisation phase with the TSD and MAS. Compared to the baseline data, the TSD stopped snoring in 33.3% of patients, with a number of cases spread over the remaining categories. The MAS eliminated reported snoring in 38.9% of patients, with snoring occurring rarely in a further 22.2%. The MAS appeared to perform better than the TSD.

Figure 13

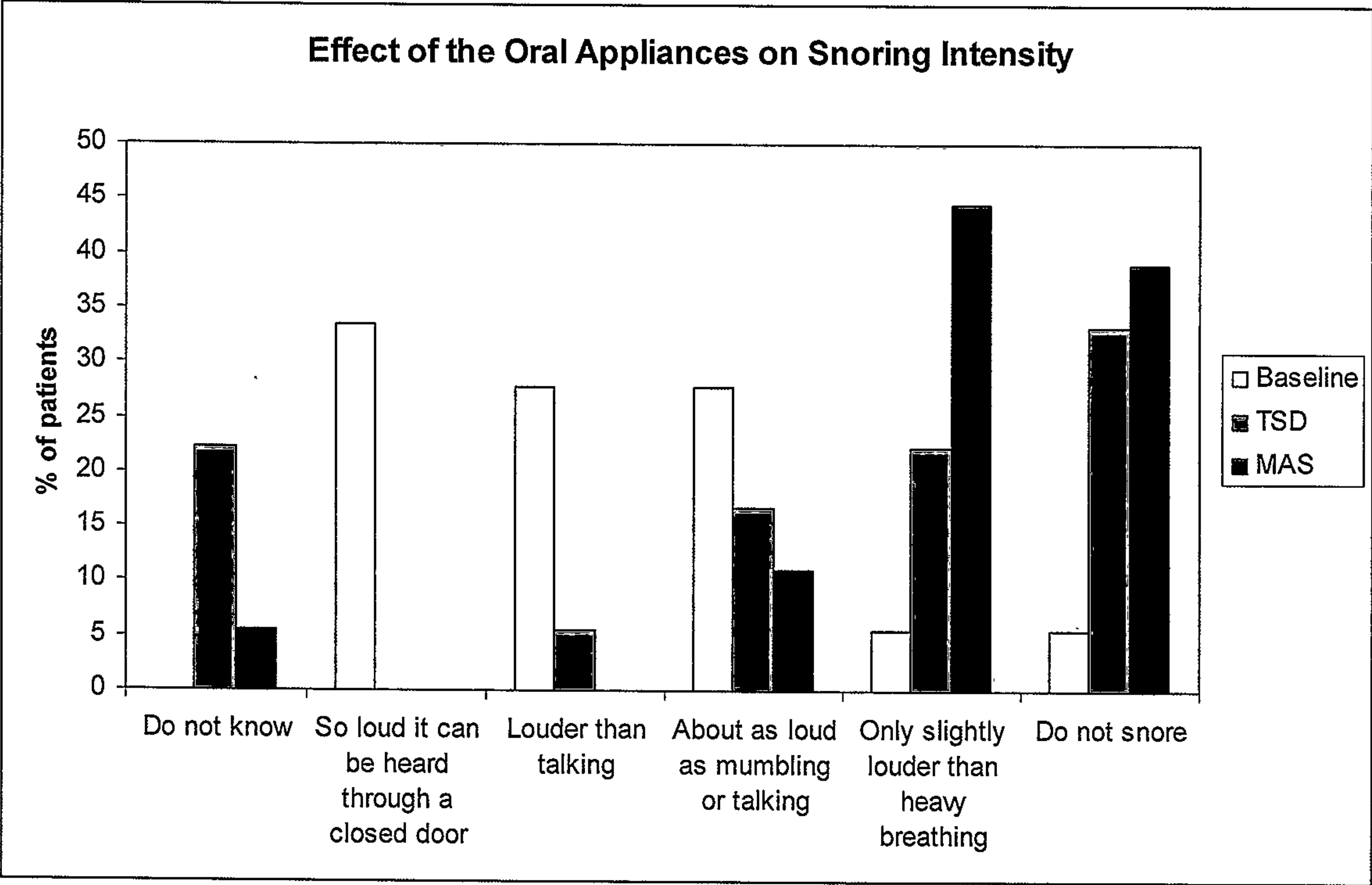


(Q: During the last month, what was your snoring volume?)

Both appliances reduced the snoring volume reported by the patients and their bed partners.

Snoring stopped or reduced it to only slightly louder than heavy breathing in 55.5% of the subjects when using TSD and 83.3% of the subjects when using MAS.

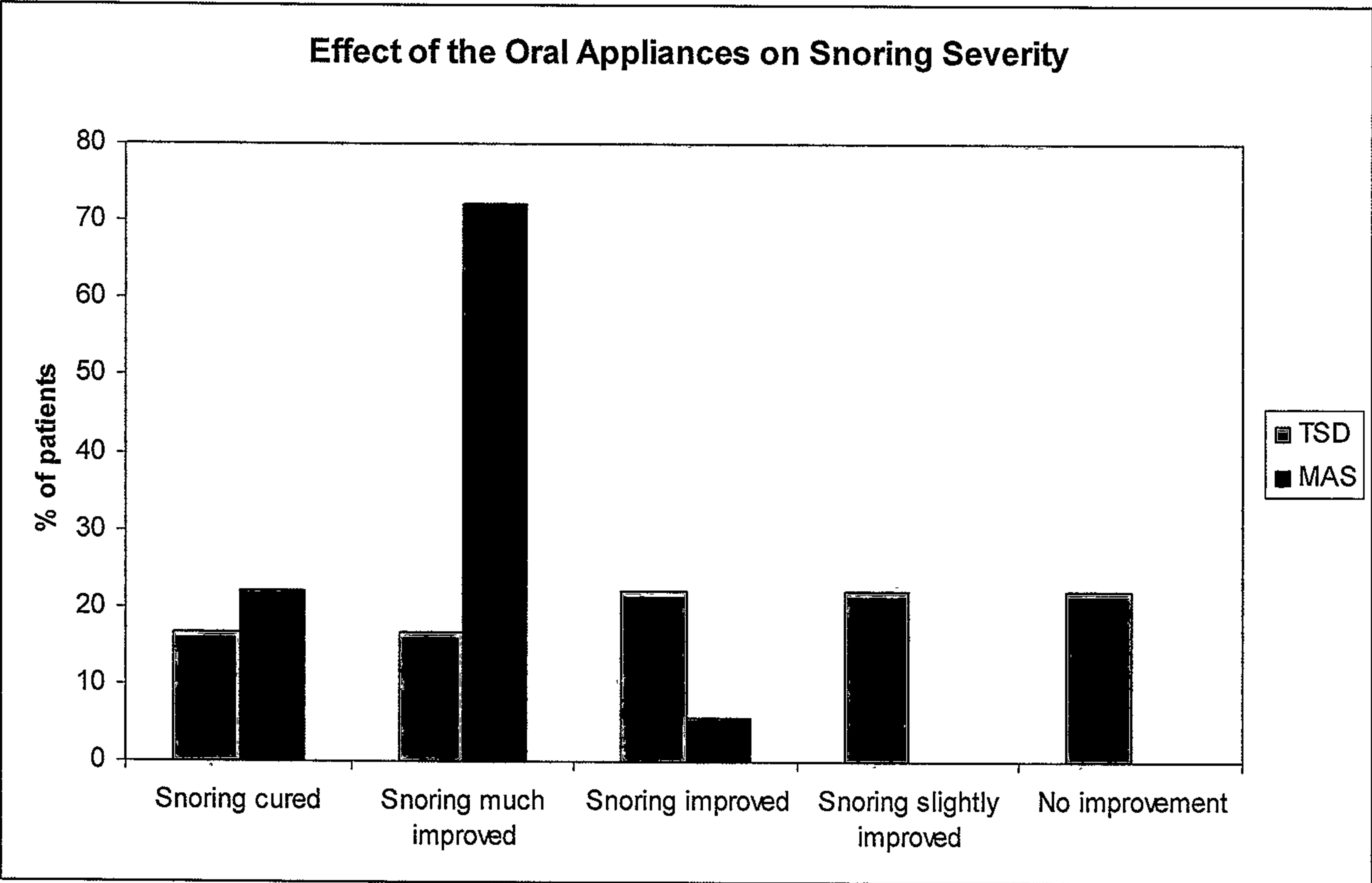
Figure 14



(Q: How would you rate the effect of the Oral Appliance on your snoring?)

Figure 15 shows a trend reported by the patients of a greater improvement in snoring severity by MAS than TSD. 94.4% of the patients reported results in the best two categories, whereas with TSD this was only 33.4%. No patient reported that snoring was only slightly improved or had no improvement with MAS.

Figure 15

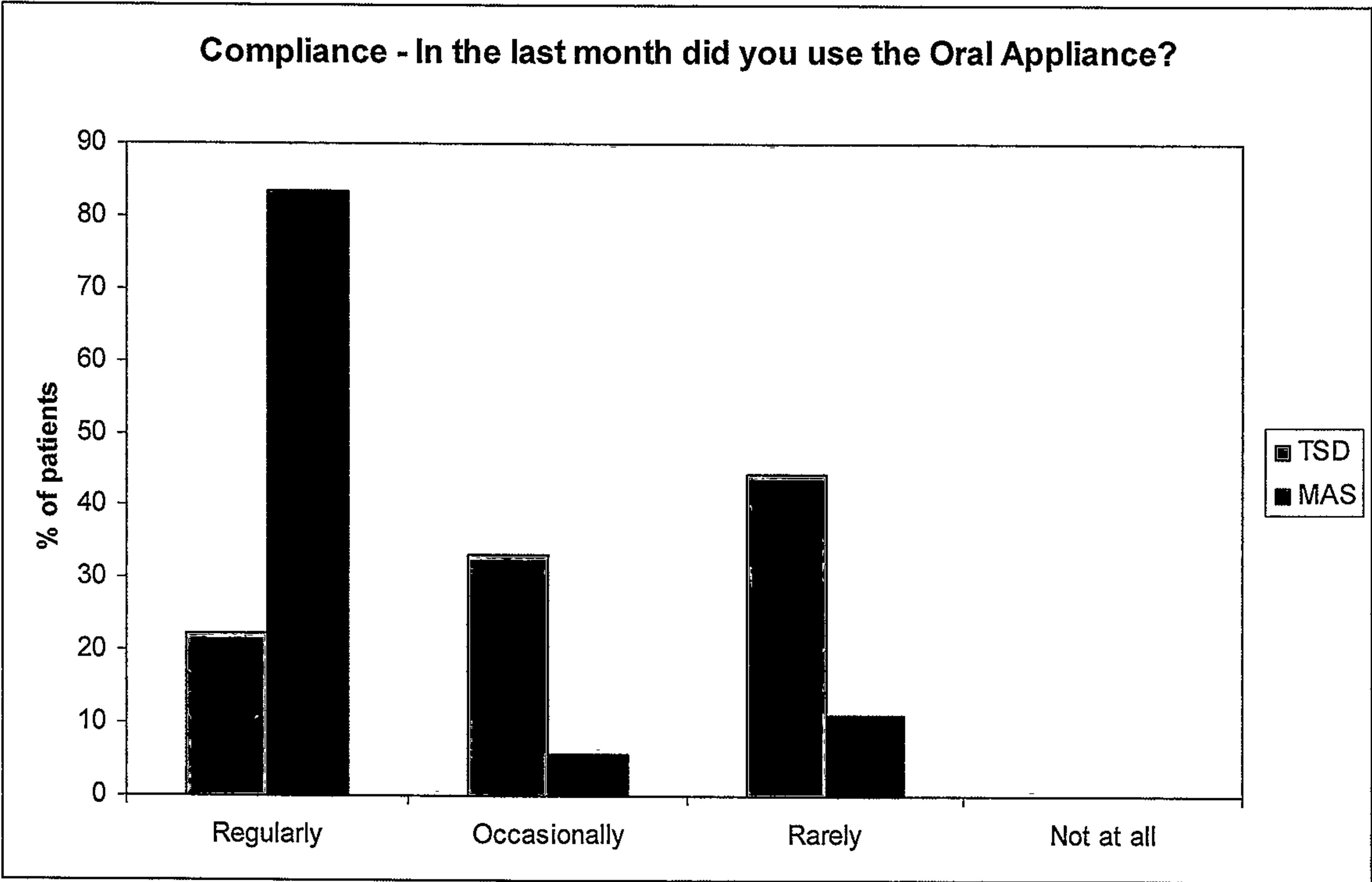


4.4.2 Patient Compliance with the Oral Appliances

(Q: In the last month did you use the Oral Appliance?)

All patients used the Oral Appliances to varying degrees in the acclimatisation phase. 83.3% of the subjects used the MAS regularly (every day of the week), with 5.6% and 11.1% using it occasionally (3-4/week) or rarely (1-2/week). Figure 16 demonstrates the reverse scenario for TSD, with the majority of patients (44.4%) using the appliance rarely.

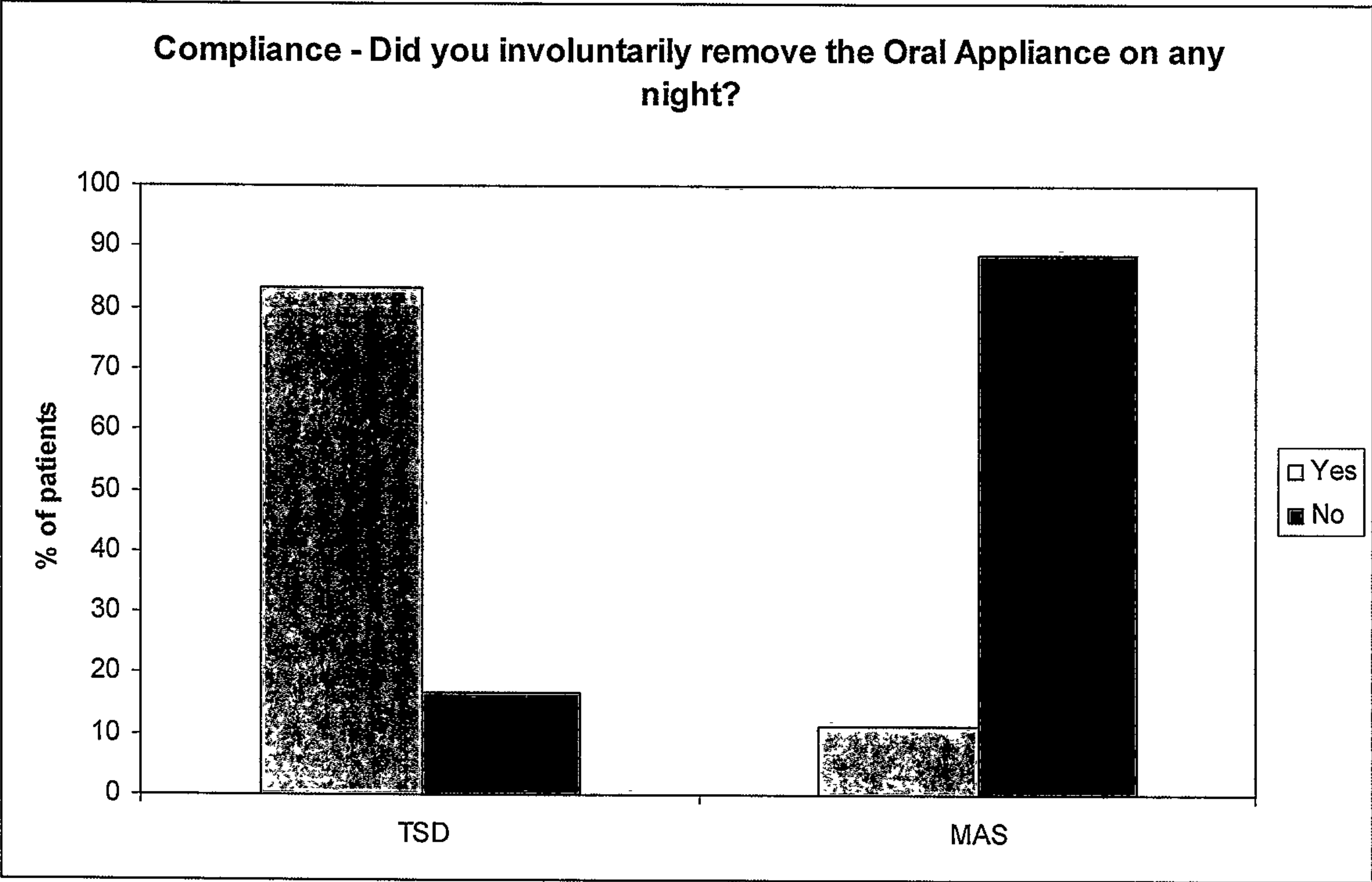
Figure 16



(Q: Did you involuntarily remove the Oral Appliance on any night?)

Patients reported loss of the TSD overnight more often than with the MAS as shown in Figure 17.

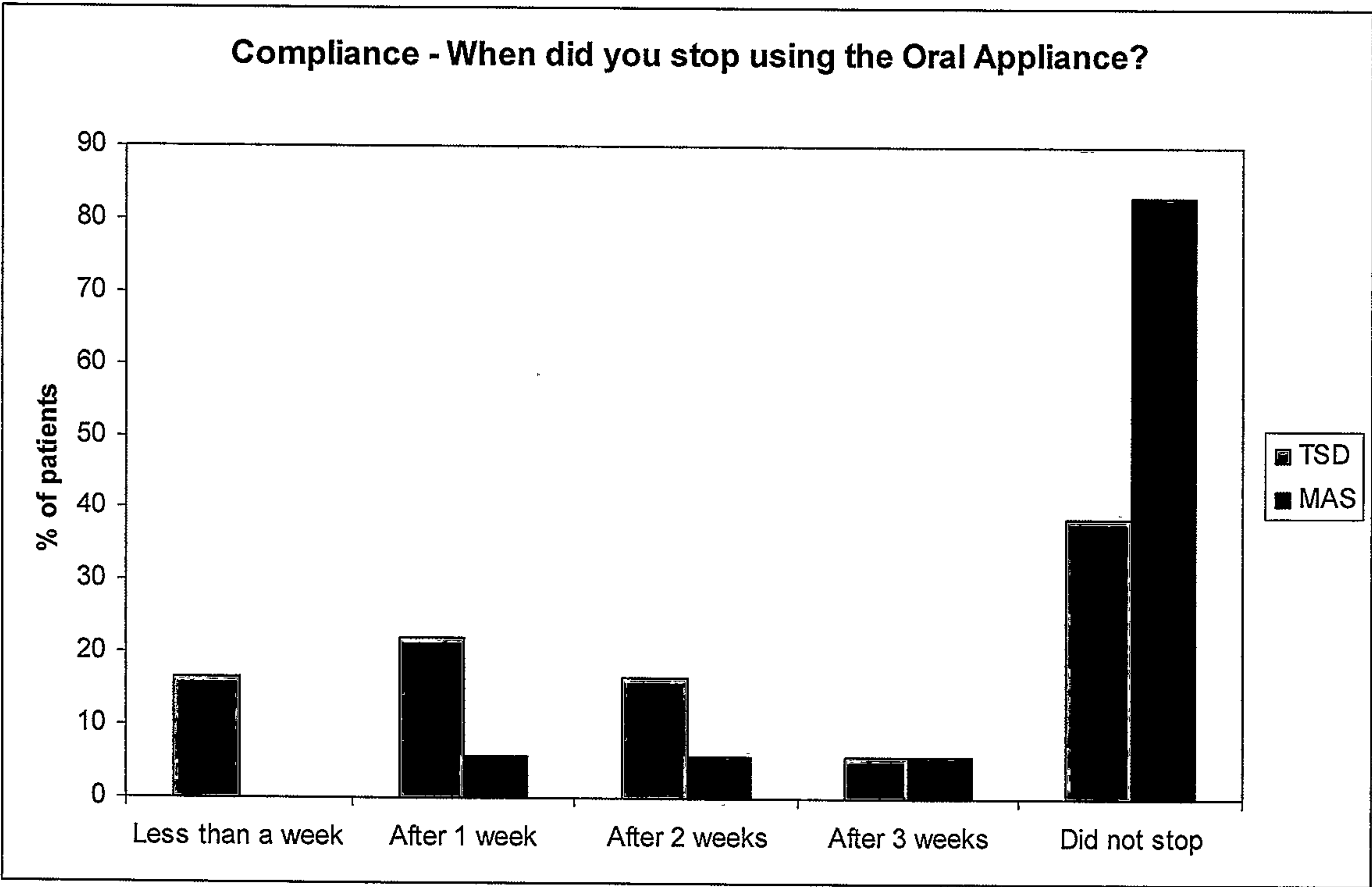
Figure 17



(Q: When did you stop using the Oral Appliance?)

83.2% of the patients did not stop using MAS whereas 38.3% did not stop using the TSD. 16.7% of the patients stopped using TSD in less than one week compared to 0% when using the MAS (Figure 18).

Figure 18



Overall compliance reported by the patients demonstrated a clear trend. The MAS permitted higher compliance than the TSD appliance.

4.4.3 Effect of the Oral Appliances on Daytime Sleepiness

(Q: How would you grade your daytime sleepiness/fatigue in the last month (whilst using the Oral Appliance at night) for the 8 situations listed in the Epworth Sleepiness Scale?)

Table 10 demonstrates the change in the Epworth Sleepiness Scale (ESS) between patient commencement in the study, with the patients’ perception of their daytime tiredness during nominated activities after using the TSD and MAS for four weeks during the acclimatisation phase. Comparison between the baseline score and the scores for TSD and MAS were significant. The score for the MAS (3.78 ± 2.53) was less than the TSD (5.94 ± 3.99) which was significant.

Table 10. Effect of TSD and MAS on ESS

	Baseline Mean $\pm$ SD	TSD Mean $\pm$ SD	MAS Mean $\pm$ SD	<i>p</i>Value B-TSD	<i>p</i>Value B- MAS	<i>p</i>Value TSD- MAS
ESS	8.72 ± 4.52	5.94 ± 3.99	3.78 ± 2.53	0.009*	$p<0.01^*$	0.009*

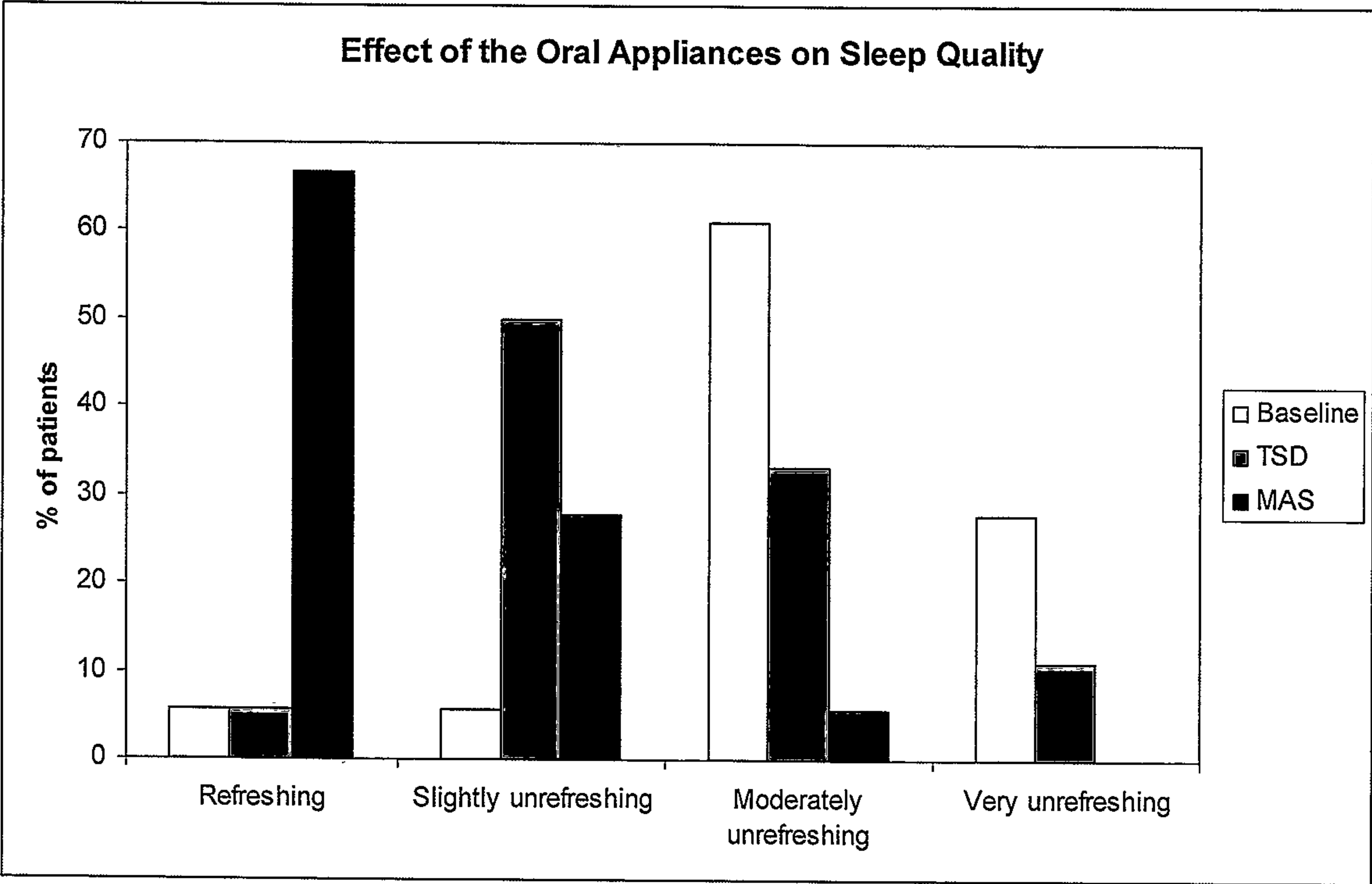
*Significant at $p<0.01$

4.4.4 Effect of the Oral Appliances on Sleep Quality

(Q: How would you rate the quality of your sleep with the Oral Appliance?)

Compared to baseline reported sleep quality, both appliances demonstrated an improvement, with 66.6% of patients reporting their sleep was refreshing with MAS, and 50% reporting their sleep as slightly unrefreshing with TSD. No patients found their sleep unrefreshing with MAS. In comparison, unrefreshing sleep was reported by 27.7% of the subjects during the acclimatisation phase with TSD (see Figure 19).

Figure 19

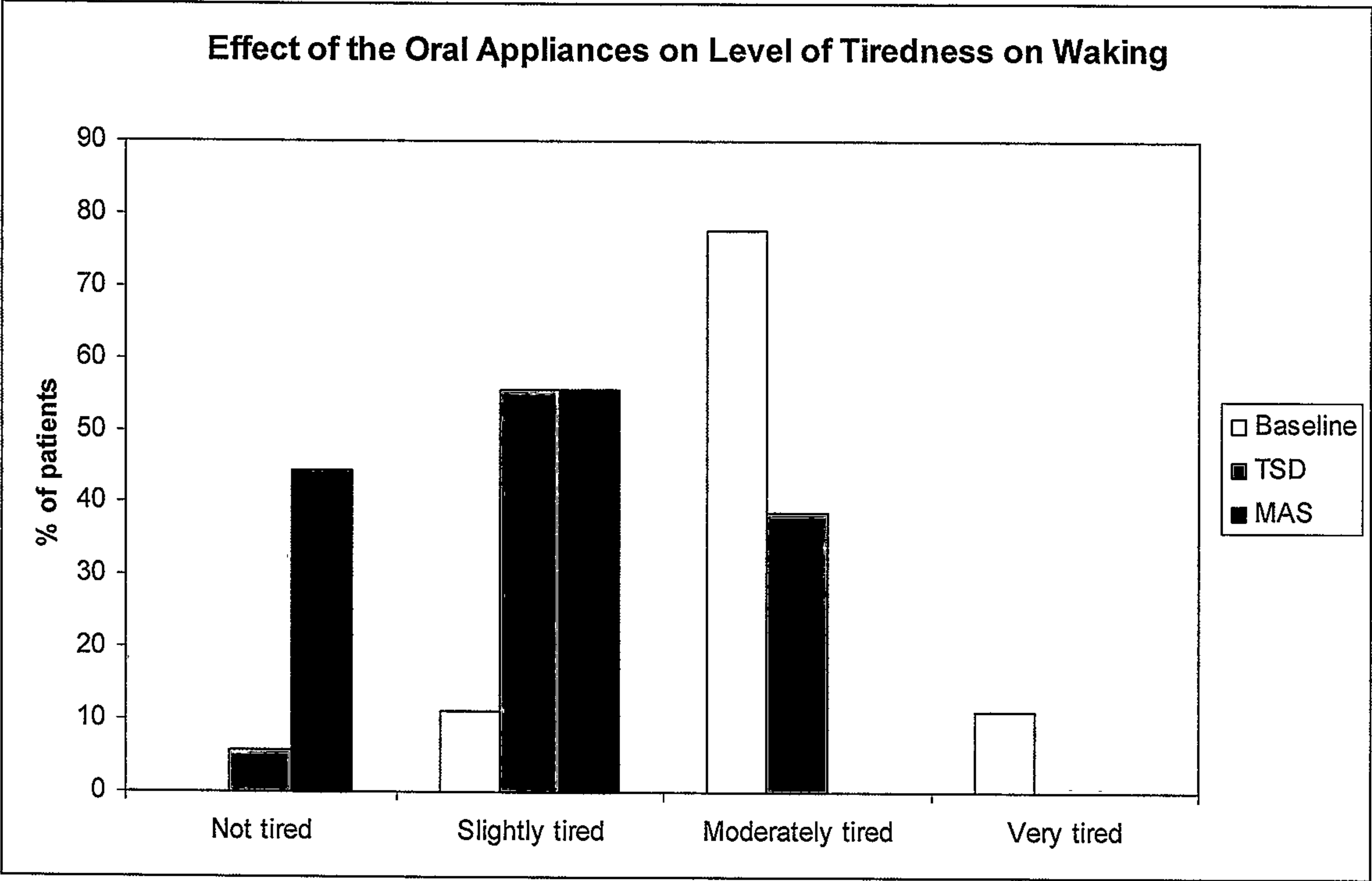


4.4.5 Effect of the Oral Appliances on Level of Tiredness on Waking

(Q: How would you grade your level of tiredness on waking while using the Oral Appliance?)

Figure 20 illustrates the reduction in levels of tiredness with TSD and MAS reported by the patients. No patients felt very tired in the acclimatization phase. Overall a greater reduction in level of tiredness on waking was demonstrated with MAS than TSD, with 38.8% of the patients still feeling tired on waking whilst using the TSD device.

Figure 20



4.4.6 Effect of the Oral Appliances on Sleeping Arrangement

(Q: Since obtaining the Oral Appliance, has your sleeping habit changed?)

Table 11 demonstrates that, of the 4 couples who slept in different rooms because of the snoring at baseline, 3 couples (TSD) and 4 couples (MAS) were now sleeping in the same room after using the oral device.

Table 11. Effect of TSD and MAS on Sleeping Arrangement

Patient’s Sleeping Arrangement	Baseline Number (% of patients)	With TSD Number (% of patients)	With MAS Number (% of patients)
Patients who were single	3 (16.7%)	3 (16.7%)	3 (16.7%)
Patients with partners	15 (83.3%)	15 (83.3%)	15 (83.3%)
Couples sleeping in same room	11 (61.1%)	15 (83.3%)	14 (77.8%)
Couples who slept in different rooms because of the snoring	4 (22.2%)	0 (0%)	1 (5.6%)

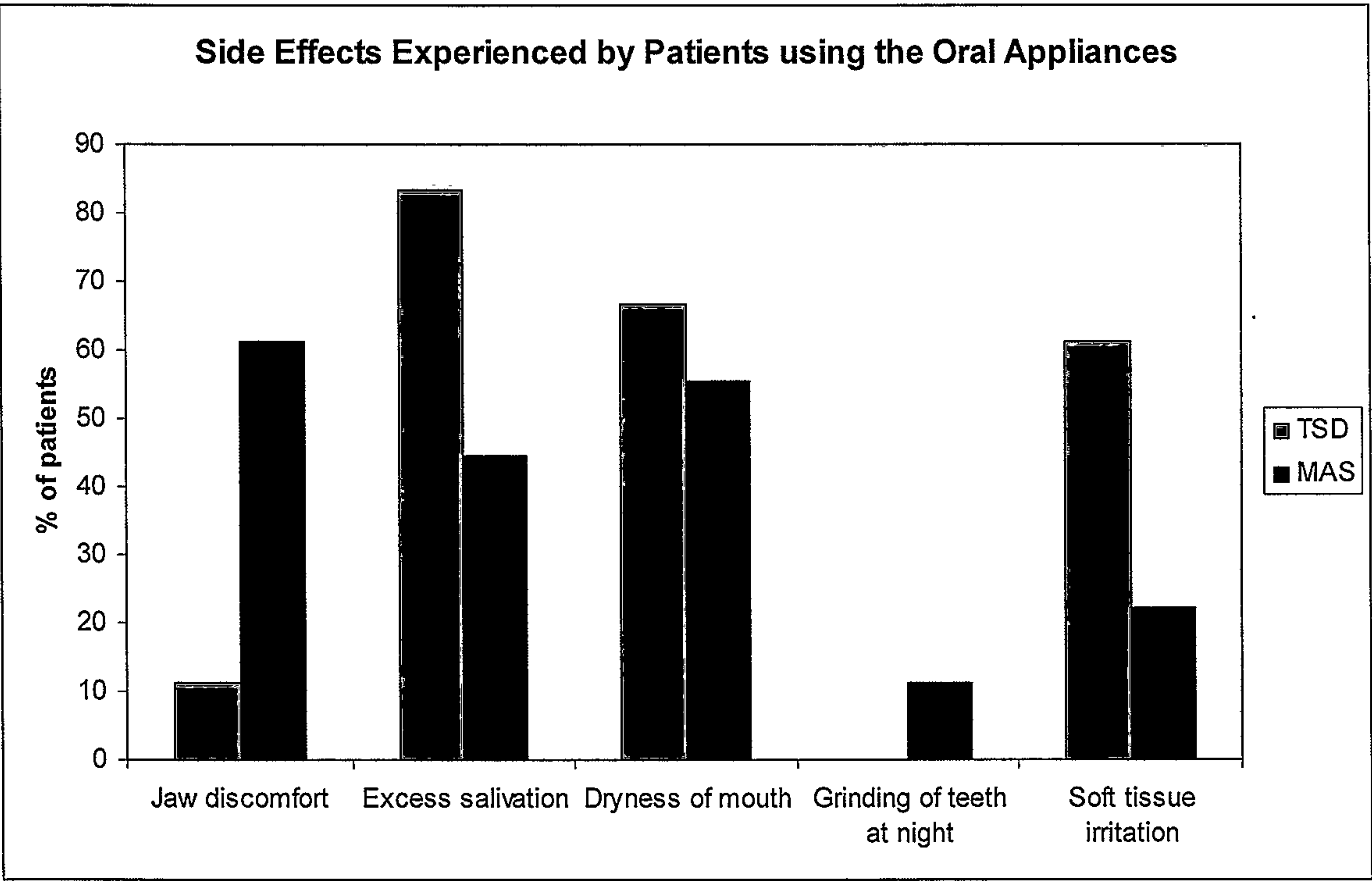
4.4.7 Side Effects Experienced with the Oral Appliances

(Q: Have you encountered any difficulties with the appliance?)

50% of the patients experienced difficulty with the oral appliances. Both the TSD and MAS were reported to cause difficulty in an equal number of patients (50%), with the type of symptom, its severity, frequency and duration varying between the TSD and MAS.

Figure 21 illustrates the percentage of patients with side-effects in the categories of jaw discomfort, excess salivation, dryness of mouth, grinding of teeth at night and soft tissue irritation. Jaw discomfort was a concern for 61.1% of the patients with MAS, and only 11.1% with TSD. Salivation and dryness of mouth was reported for TSD and MAS. Soft tissue irritation was a greater concern with the TSD (61.1%) than with MAS 22.2%).

Figure 21



Jaw discomfort was reported to be mild in 50% of the patients whilst using MAS, with a balanced distribution in frequency and duration. As shown in Figure 22, only 1 patient (5.6%) experienced jaw discomfort beyond 3 weeks. Overall the jaw discomfort reported occurred in the morning after removing the MAS and resolved within 30 minutes. Figures 23 and 24 demonstrate the severity, frequency and duration of excess salivation and dryness of the mouth, which were similar for both devices.

Figure 22

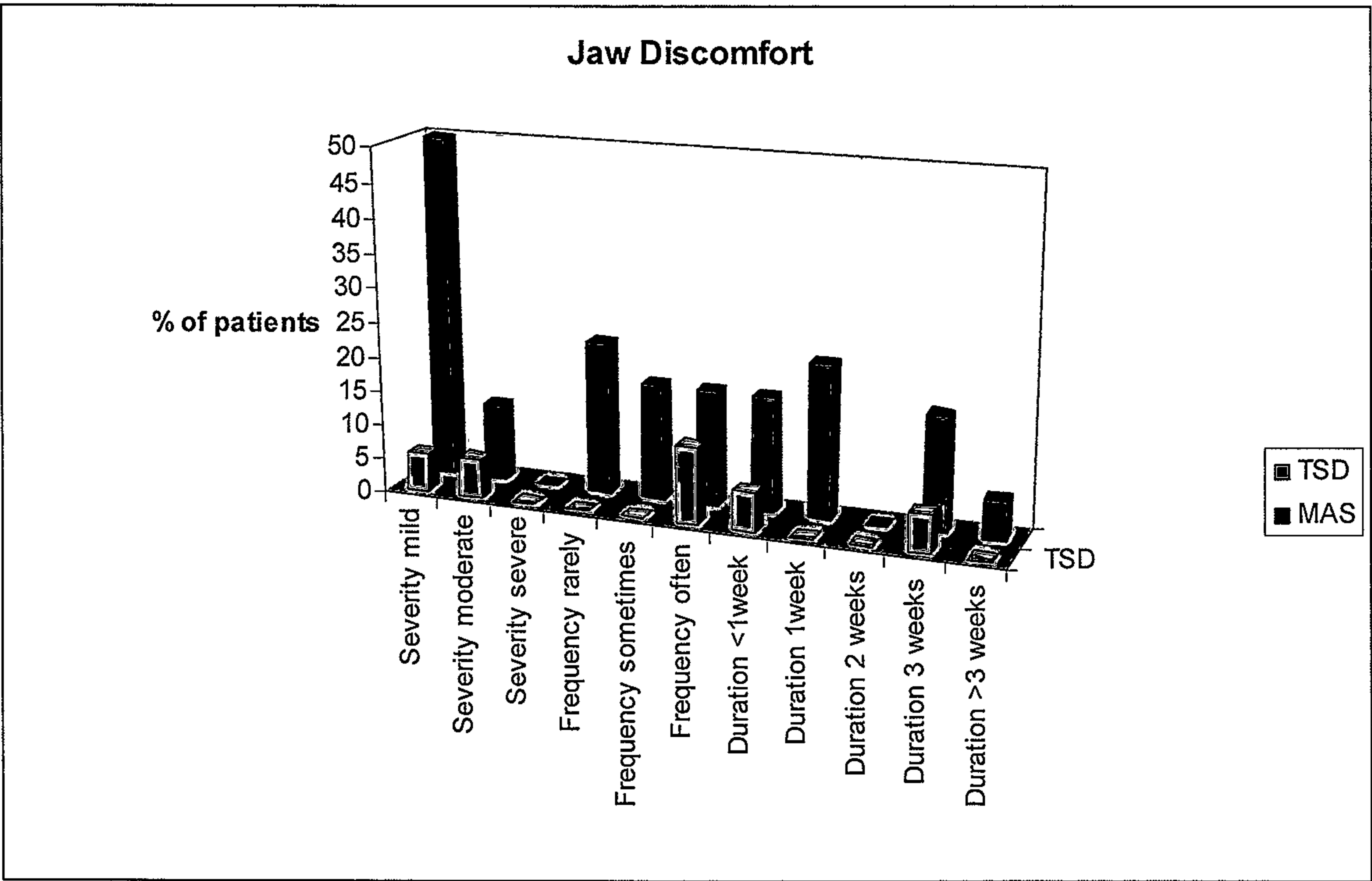


Figure 23

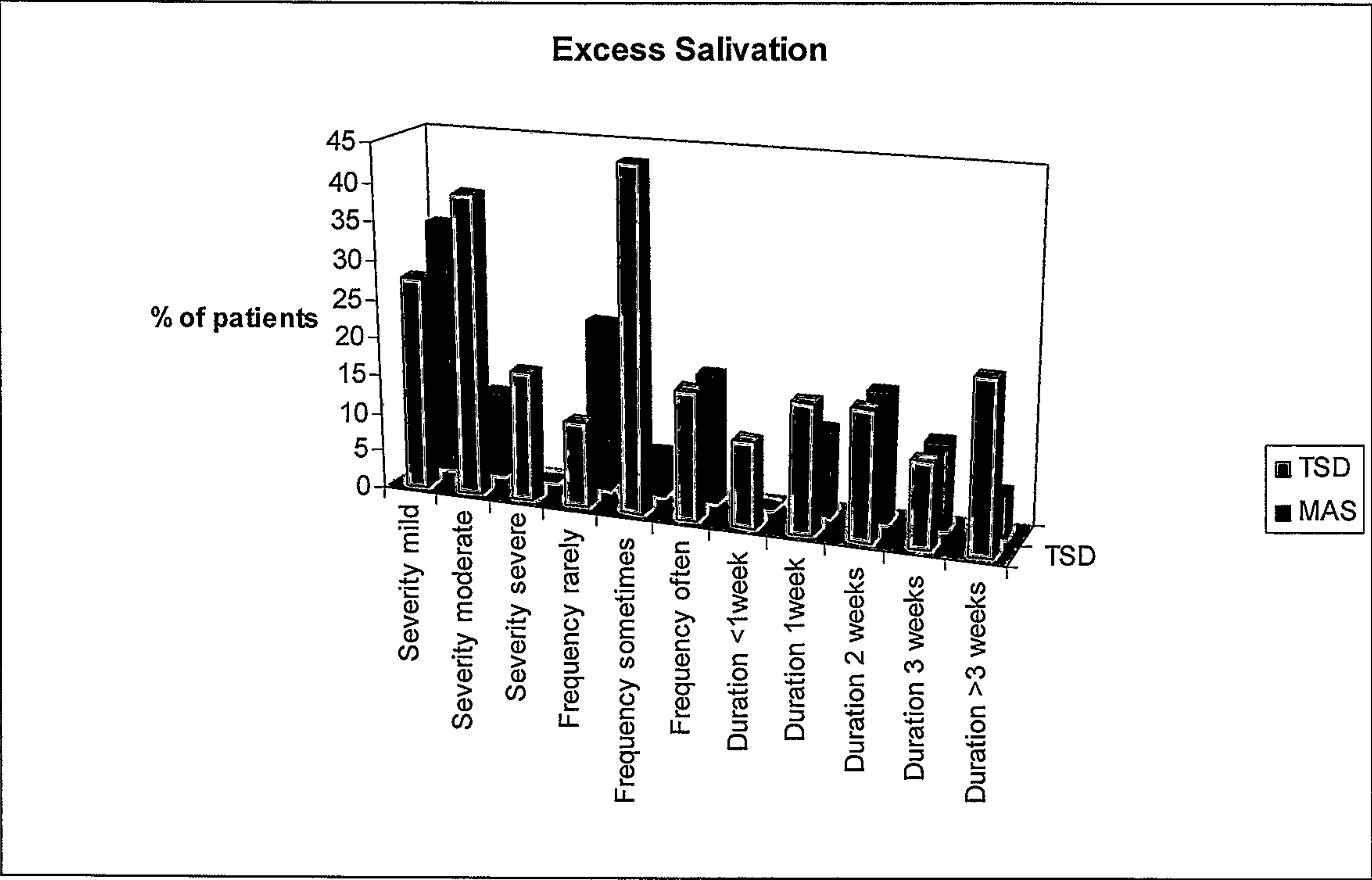
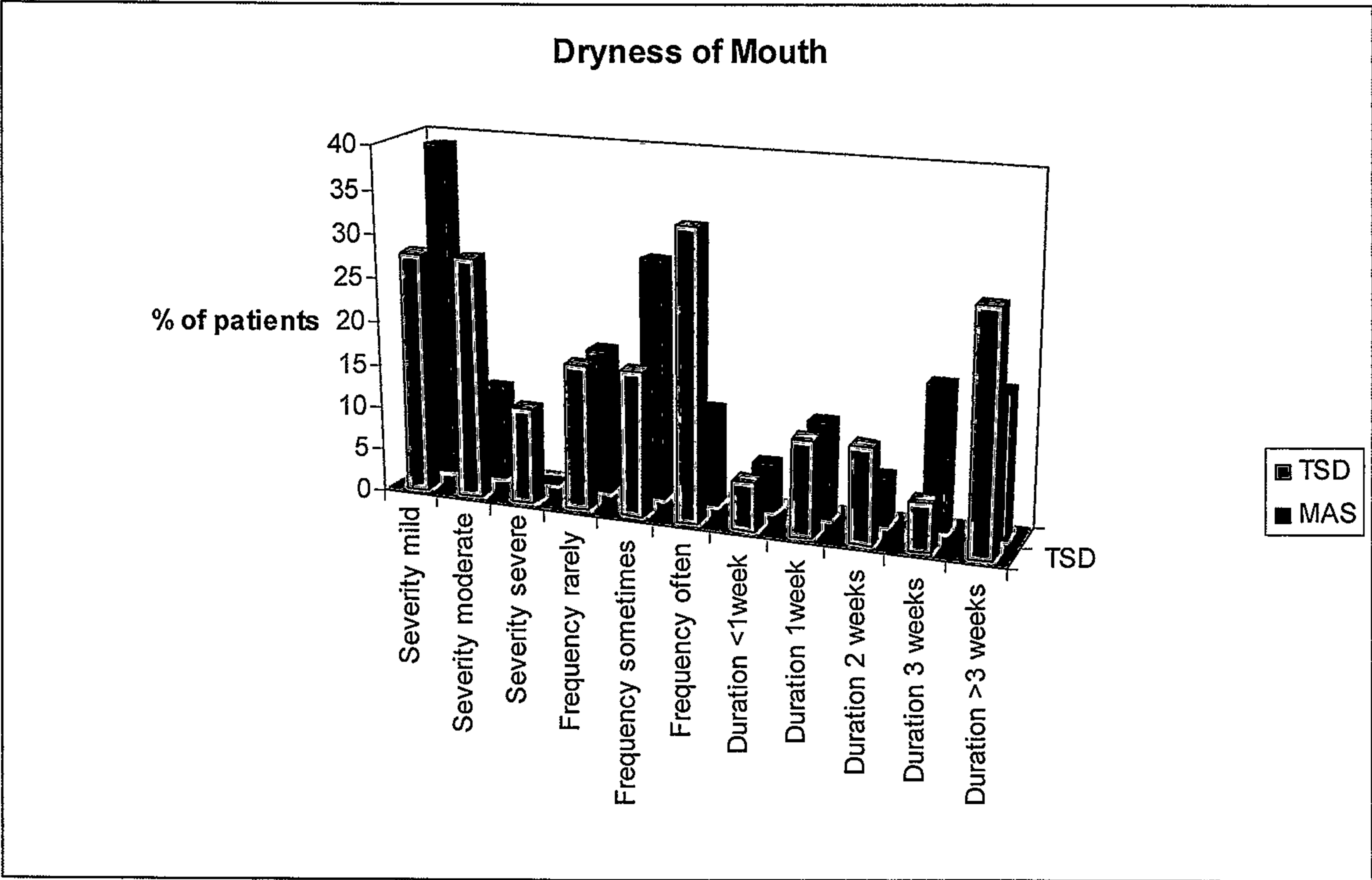
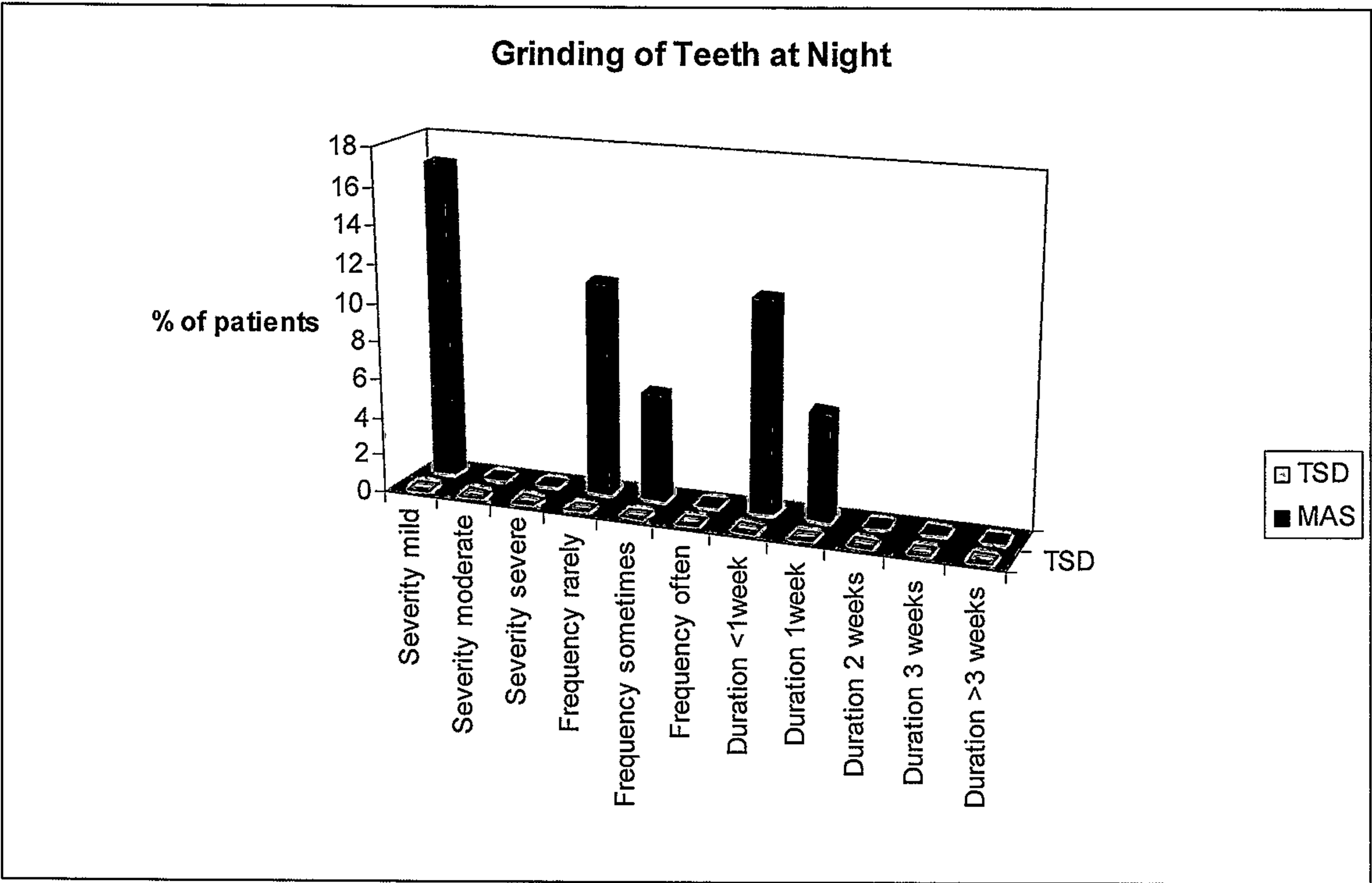


Figure 24



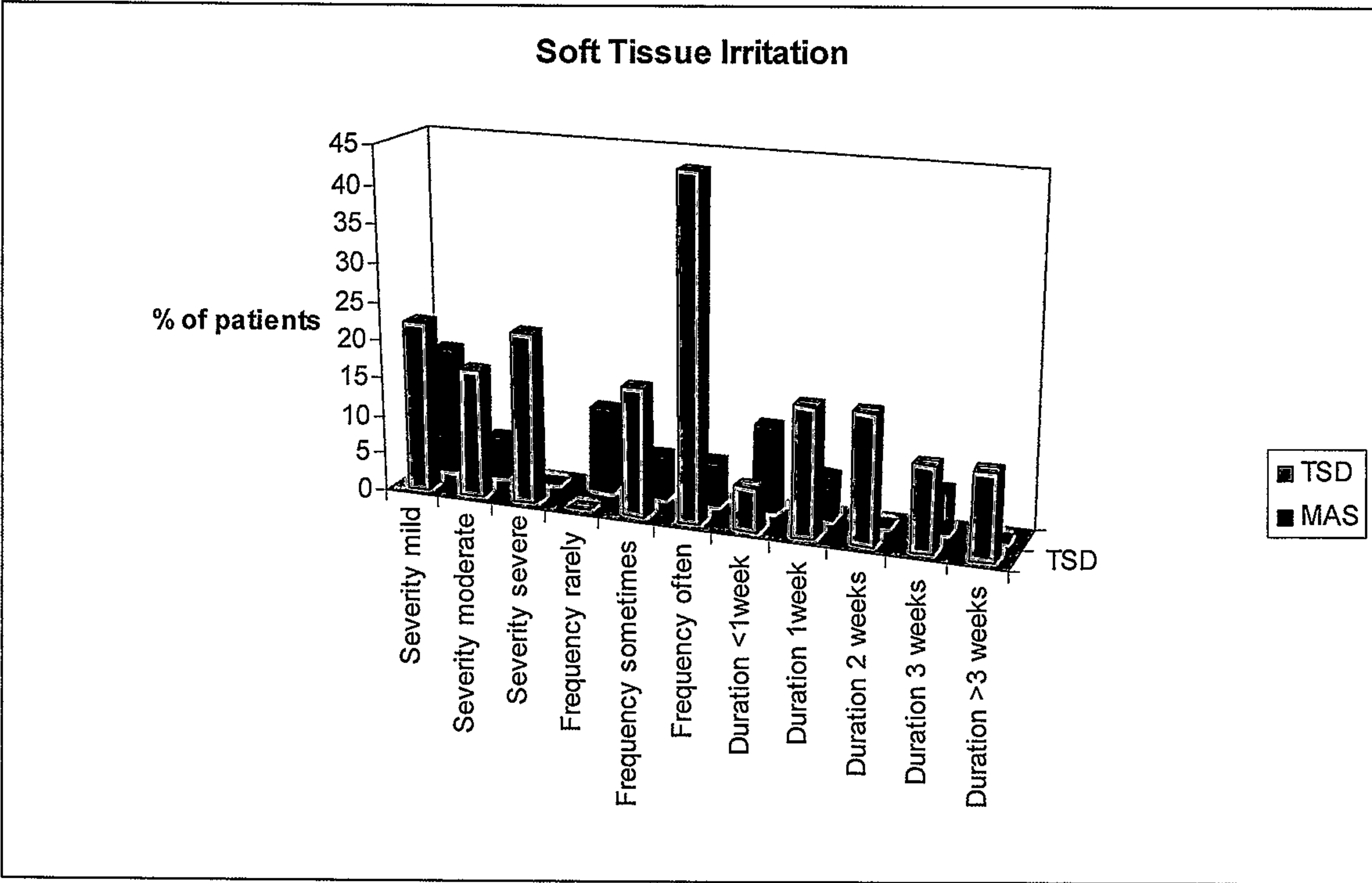
Grinding teeth at night was a minor problem reported by 3 (16.7%) of the patients whilst using MAS.

Figure 25



As demonstrated in Figure 26, soft tissue irritation affected 61.1% of the patients when using TSD, and 22.3% when using MAS. No patient using MAS reported the problem to be severe, and irritation resolved by 3 weeks. By contrast, 4 patients (22.2%) reported soft tissue irritation to be severe, with frequent occurrence in 44.4% of the subjects using TSD in the acclimatization phase. 11.1% of the patients using TSD experienced this side-effect beyond 3 weeks duration.

Figure 26



(Q: Did the side-effect prevent you from using the Oral Appliance?)

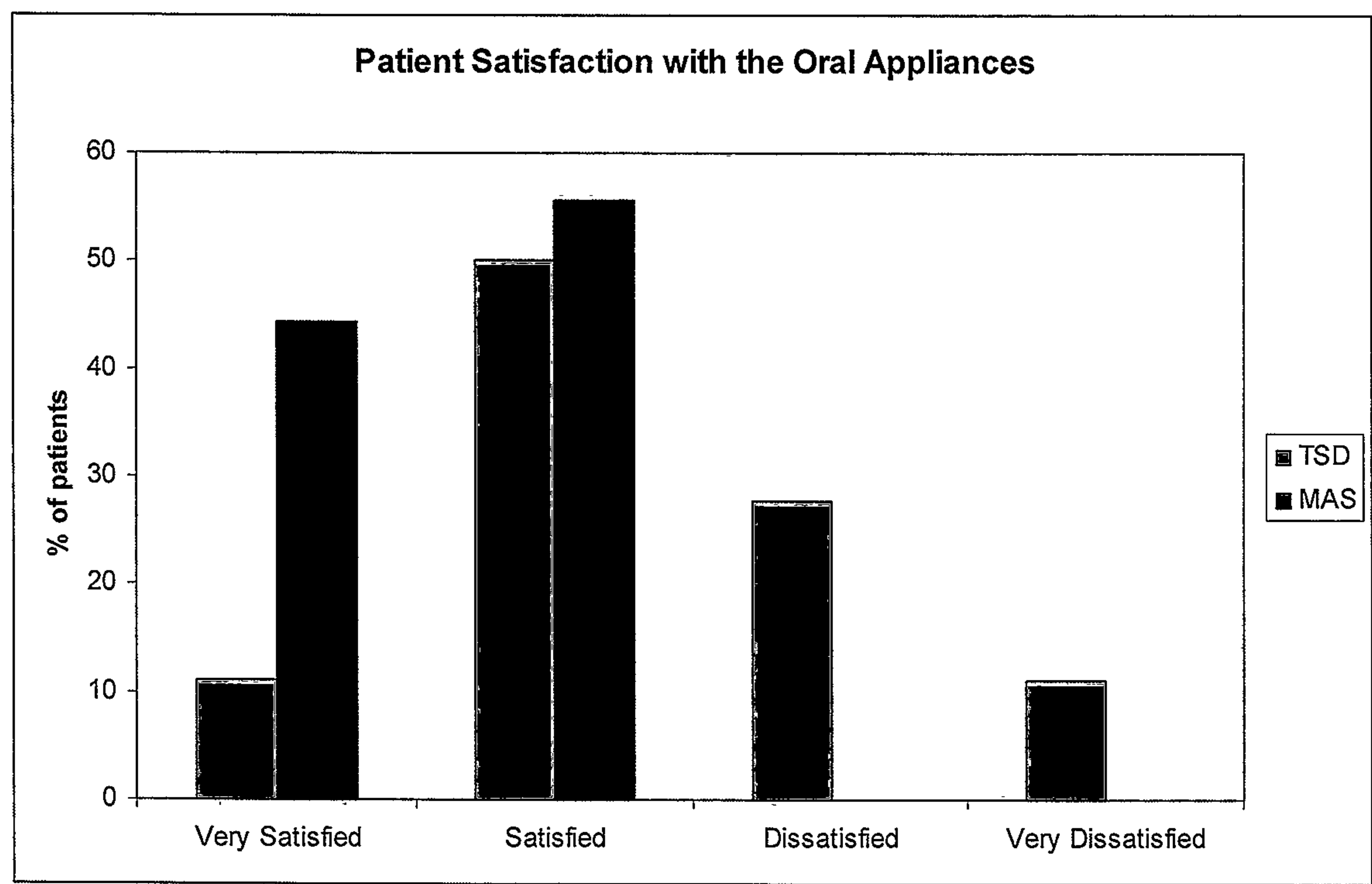
The side-effects prevented 50% of the patients from using the TSD, however 100% of the patients were able to use the MAS.

4.4.8 Patient satisfaction with the Oral Appliances

(Q: How would you rate your satisfaction with the appliance?)

Figure 27 illustrates that the patients were more satisfied with the MAS than the TSD appliance.

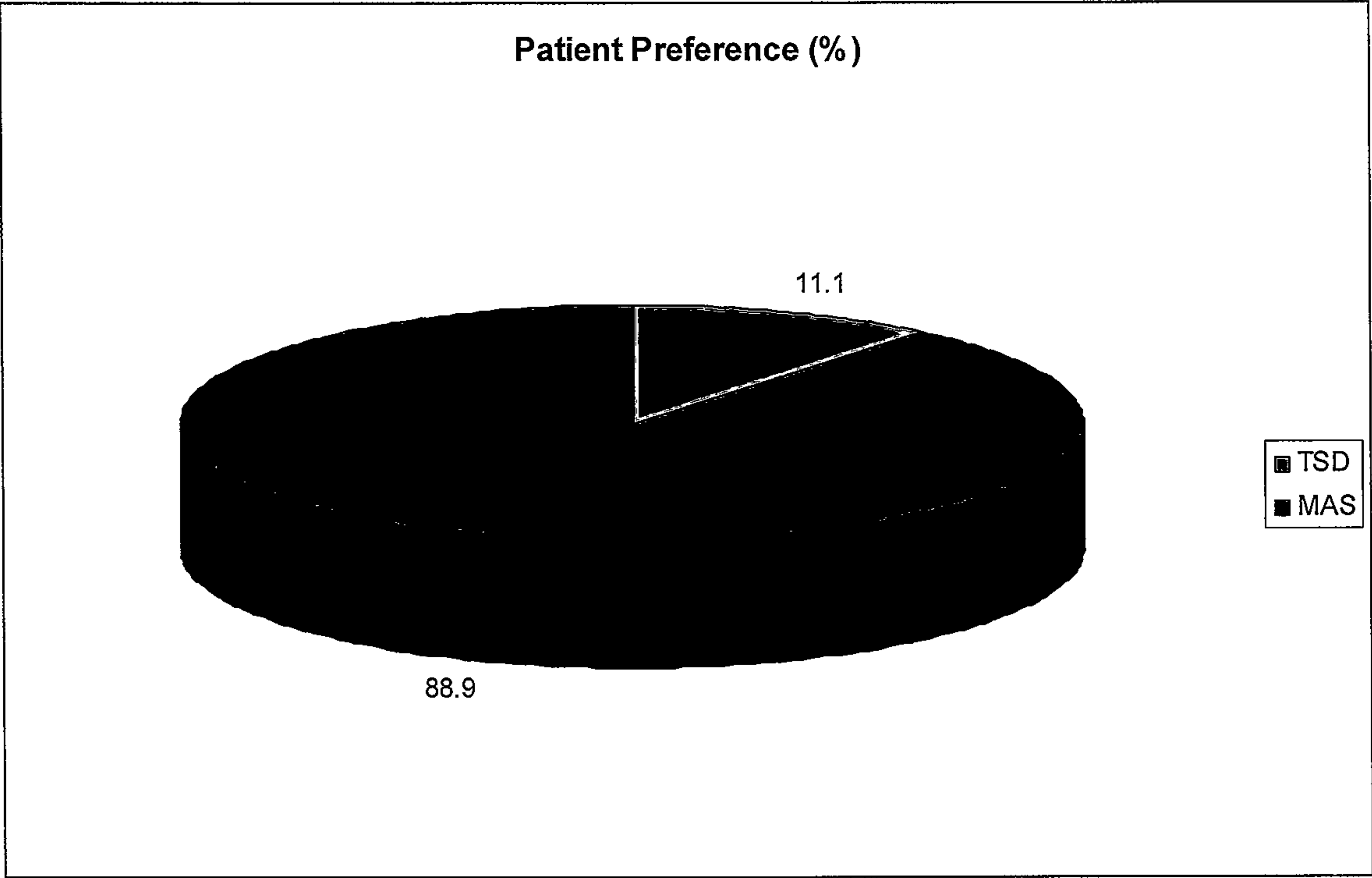
Figure 27



(Q: If you have now tried both appliances, which appliance do you prefer?)

The clear preference demonstrated in Figure 28 is in favour of MAS over TSD.

Figure 28



4.5 Sleep Study Results

Sleep studies using overnight polysomnography at St George Hospital were undertaken at baseline, and after a one week washout period, followed by one week wearing the randomly allocated oral device.

4.5.1 Sleep architecture

The duration of the sleep tests at baseline and with TSD and MAS, and the proportion of REM and NREM sleep are demonstrated in Table 12. The duration of the sleep test for TSD was slightly shorter than baseline, and for MAS was slightly longer than baseline. This was not significant. It was noted that 1 patient had a TST of 63 minutes with TSD, another patient had a TST of 91 minutes with TSD, and a third patient had a TST of 121.5 minutes with MAS. These were the shortest of the sleep studies. There was no significant difference in the proportions of REM and NREM sleep between the three studies. While sleep efficiency was not altered, the arousal index for TSD (21.93 ± 2.47) and MAS (20.51 ± 2.08) was significantly reduced from baseline (34.60 ± 4.04) $p<0.01$.

Table 12. Effect of TSD and MAS on Sleep Architecture

	Baseline Mean $\pm$ SEM	TSD Mean $\pm$ SEM	MAS Mean $\pm$ SEM	<i>p</i> Value B-TSD	<i>p</i> Value B-MAS	<i>p</i> Value TSD- MAS
Total Sleep Time (min)	336.31 $\pm$ 11.97	319.36 $\pm$ 24.85	347.75 $\pm$ 18.11	0.482	0.577	0.346
REM Sleep (min)	53.56 $\pm$ 5.06	55.97 $\pm$ 7.43	66.83 $\pm$ 5.93	0.764	0.085	0.144
NREM Sleep (min)	282.75 $\pm$ 9.53	265.06 $\pm$ 19.71	280.92 $\pm$ 14.87	0.380	0.108	0.540
TST in REM (%)	15.66 $\pm$ 1.19	15.83 $\pm$ 1.99	19.36 $\pm$ 1.25	0.941	0.042	0.108
TST in NREM (%)	84.34 $\pm$ 1.19	84.17 $\pm$ 1.99	77.86 $\pm$ 3.09	0.943	0.095	0.081
Arousal Index (/hr)	34.60 $\pm$ 4.04	21.93 $\pm$ 2.47	20.51 $\pm$ 2.08	0.003*	0.002*	0.468
Sleep Efficiency (%)	79.51 $\pm$ 2.80	80.71 $\pm$ 2.58	79.00 $\pm$ 3.87	0.537	0.904	0.661

*Significant at $p<0.01$

4.5.2 Respiratory Variables

Comparison of the means for MinSaO2, AHI, longest apnea and longest hypopnea between baseline, TSD and MAS are provided in Table 13. A significant reduction in MinSaO2 was found for TSD compared to baseline. Both TSD and MAS resulted in a significant reduction in AHI compared to baseline (0.002 and $p<0.01$ respectively). The longest apnea was also significantly reduced with the MAS device.

Table 13. Effect of TSD and MAS on Respiratory Variables

	Baseline (B) Mean $\pm$ SEM	TSD Mean $\pm$ SEM	MAS Mean $\pm$ SEM	<i>p</i> Value B-TSD	<i>p</i> Value B-MAS	<i>p</i> Value TSD- MAS
Minimum oxygen saturation (%)	83.33 $\pm$ 1.54	88.00 $\pm$ 1.24	86.61 $\pm$ 1.08	0.003*	0.028	0.238
AHI (/hr)	28.66 $\pm$ 4.39	13.01 $\pm$ 2.65	11.99 $\pm$ 1.92	0.002*	$p<0.01$ *	0.641
Longest Apnea (min)	41.51 $\pm$ 5.25	30.11 $\pm$ 5.40	17.61 $\pm$ 3.46	0.041	$p<0.01$ *	0.015
Longest Hypopnea (min)	59.34 $\pm$ 3.46	58.33 $\pm$ 6.59	64.44 $\pm$ 5.02	0.888	0.386	0.302

*Significant at $p<0.01$

4.5.3 Treatment Outcome Based on Apnea-Hypopnea Index

A reduction in AHI with the use of TSD occurred in 94% (17 patients of the sample), and with the use of MAS in 83% (15 patients of the sample). One patient showed an increase in AHI with TSD, and three patients with MAS.

The mean percentage change in AHI was 47% with TSD and 52% with MAS ($p=0.64$). The percentage change in AHI ranged from -107% to +98% (-56.8 to + 20.8 events per hour)

with TSD. With MAS the percentage change in AHI ranged from -92% to +28% (-46.3 to +5.5 events per hour).

The 18 subjects were then classified into categories (Mild OSA, Moderate OSA, Severe OSA, Failure, Partial Success and Success). Table 14 demonstrates the treatment outcome for TSD, and Table 15 for MAS. The Pearson Chi-square test, using linear by linear p-value which considers order, showed no significant difference between OSA severity and the success for each appliance.

Table 14. Outcome and OSA Severity with TSD

TSD	Failure	Partial Success	Success	Total	<i>p</i> Value
Mild OSA	6	2	1	9	
Moderate OSA	2	0	3	5	
Severe OSA	1	3	0	4	
Total	9	5	4	18	0.35

Table 15. Outcome and OSA Severity with MAS

MAS	Failure	Partial Success	Success	Total	<i>p</i> Value
Mild OSA	4	2	3	9	
Moderate OSA	2	2	1	5	
Severe OSA	0	4	0	4	
Total	6	8	4	18	0.86

Accordingly, the percentage of patients that had successes and partial treatment successes with TSD was 50%, and with MAS was 66.7%.

Table 16. Comparison of Outcome between TSD and MAS

		MAS			<i>p</i> Value
		Failure	Success/Partial Success	Total	
TSD	Failure	5	4	9	
	Success/Partial Success	1	8	9	
	Total	6	12	18	0.38

Using a small sample exact test¹⁸¹ to compare success and partial success to failure between TSD and MAS, no significant difference was found ($p=0.38$).

4.6 Magnetic Resonance Imaging Results

The MRI scan was undertaken on 15 of the 18 patients. Three patients could not participate in this test due to dental implant, claustrophobia and body size. The volumes of the velopharynx, oropharynx and hypopharynx were measured. The total volume of the airway (from hard palate to cricoid cartilage) was calculated. Anterior-posterior (ap) and medio-lateral (ml) measurements were made in each airway region (tip of the soft palate, mid-oropharyngeal slice, tip of the epiglottis) for consistency.

Table 17 illustrates the volume comparison between baseline (no device), TSD and MAS. The trend was for total and regional airway volumes to increase with both TSD and MAS, with TSD causing the greater change. A significant difference was found when comparing baseline with TSD for total airway volume ($p=0.004$). Both TSD and MAS produced a significant difference in the velopharynx ($p=0.001$ and $p=0.005$ respectively). TSD and MAS were not significantly different from each other.

Table 17. Comparison of Airway Volume between TSD and MAS

N=15 (11M,4F)	Baseline Mean $\pm$ SEM	TSD Mean $\pm$ SEM	MAS Mean $\pm$ SEM	<i>P</i> value B-TSD	<i>P</i> value B-MAS	<i>P</i> value TSD- MAS
Total airway volume cm ³	15.12 $\pm$ 1.48	18.70 $\pm$ 1.71	16.51 $\pm$ 1.55	0.004*	0.068	0.021
Airway volume velopharynx cm ³	3.96 $\pm$ 0.49	5.99 $\pm$ 0.83	4.86 $\pm$ 0.59	0.001*	0.005*	0.075
Airway volume oropharynx cm ³	3.81 $\pm$ 0.51	4.02 $\pm$ 0.49	4.02 $\pm$ 0.43	0.182	0.634	0.133
Airway volume hypopharynx cm ³	7.41 $\pm$ 0.83	8.19 $\pm$ 0.81	7.62 $\pm$ 0.75	0.080	0.501	0.042

*Significant at $p < 0.01$

When measuring the antero-posterior dimensions, the TSD and MAS did not produce any significant change compared to baseline or to each other. Table 18 does indicate a sagittal increase in size of the oropharynx and hypopharynx with TSD, although not significant.

Table 18. Comparison of Anterior-posterior Airway Measurement between TSD and

MAS

	Baseline Mean $\pm$ SEM	TSD Mean $\pm$ SEM	MAS Mean $\pm$ SEM	<i>P</i> Value B-TSD	<i>p</i> Value B-MAS	<i>p</i> Value TSD- MAS
Velopharynx	9.01 $\pm$ 1.08	9.95 $\pm$ 1.02	9.91 $\pm$ 0.93	0.267	0.375	0.965
Oropharynx	10.87 $\pm$ 1.12	13.24 $\pm$ 0.83	11.66 $\pm$ 1.00	0.032	0.323	0.106
Hypopharynx	11.28 $\pm$ 1.49	13.65 $\pm$ 1.03	12.00 $\pm$ 0.97	0.078	0.430	0.152

When measuring medio-lateral dimensions, no significant changes were found. Table 19 illustrates a trend to greater ml increase at the level of the velopharynx and oropharynx with TSD.

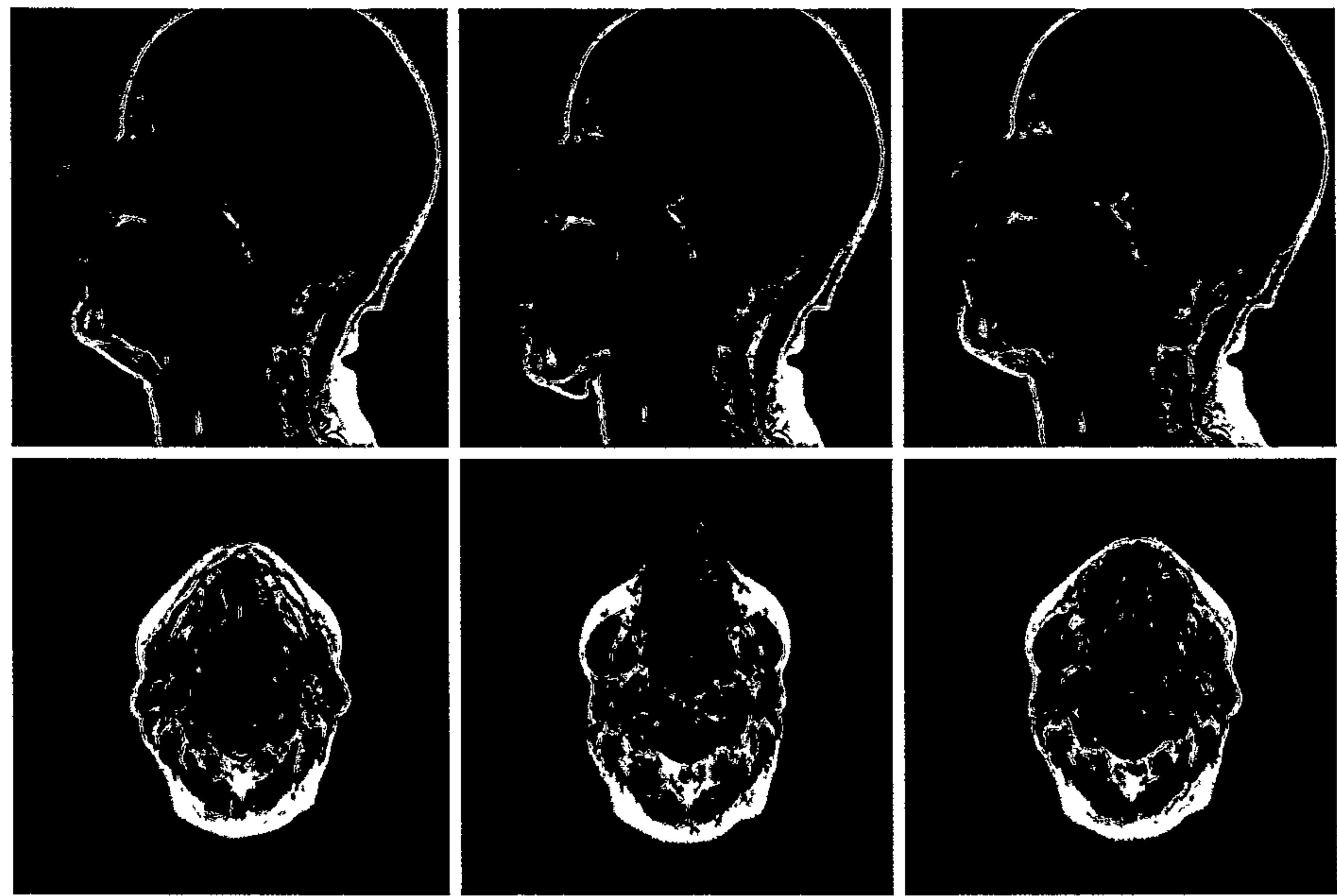
Table 19. Comparison of Medio-lateral Airway Measurement between TSD and MAS

	Baseline Mean $\pm$ SEM	TSD Mean $\pm$ SEM	MAS Mean $\pm$ SEM	<i>p</i> Value B-TSD	<i>p</i> Value B-MAS	<i>p</i> Value TSD- MAS
Velopharynx	15.43 $\pm$ 2.26	20.05 $\pm$ 2.17	16.58 $\pm$ 1.56	0.044	0.405	0.035
Oropharynx	19.85 $\pm$ 1.58	24.57 $\pm$ 1.88	21.65 $\pm$ 1.82	0.034	0.332	0.018
Hypopharynx	21.94 $\pm$ 1.79	24.63 $\pm$ 1.26	23.63 $\pm$ 1.48	0.052	0.122	0.407

Figure 29. MRI demonstrating anatomical differences between baseline, TSD and MAS.

(See Appendix 8 for additional images)

Baseline Left, TSD Centre, MAS Right



5. Discussion

Oral appliances have been used in the management of OSA for a considerable period of time. The MAS is the more widely investigated oral appliance with an abundance of literature supporting its use in the management of OSA in patients deemed appropriate^{6,112,113,149,155,156,161}. The MAS is often assessed in direct comparison with CPAP, the latter being regarded as the gold standard in OSA management, improving understanding of the effectiveness of this oral device^{113,136}. Currently, there is a good understanding of the indications for prescription of MAS and supervising this treatment modality. As yet there is an inability to predict responders and non-responders.

By contrast, the TSD has not been widely reported in the literature. A limited number of studies have been carried out with small sample populations, and with several appliance designs^{130,171,172,174,175}. No studies have been undertaken comparing the TSD with either CPAP or MAS.

Therefore, one aim of the present study was to test the clinical efficacy of the TSD device against the relatively accepted MAS in the management of OSA using a prospective, randomized cross-over study design. The outcomes were evaluated subjectively with questionnaires, and objectively using polysomnography and MRI imaging.

5.1 Study Design and Methodology

The prospective randomized cross-over study design is a strong tool and is widely used in medical research. When assessing the effectiveness of two treatment modalities it enables both devices to be used by the same patient and hence permits comparison of the treatments 'within subjects'. Although an ABB/BAA design is a higher order design because it

includes more than two treatment periods¹⁸⁶ and permits detection of carry over, period and sequence effects, the AB/BA type cross-over was chosen to comply with the requirement of the ethics committees to remain within a three month study duration. In addition, previous research within this study institution used the ABB/BAA design¹¹², enabling the power calculation for this study, and thus making a simpler study design was possible. Tests for carry-over or period effects were not undertaken as these are not regarded as being valid in an AB/BA type design. This study did use a washout (device-free) period between the acclimatisation and trial phases, and between the sleep tests, thereby remaining consistent with cross-over study protocol and previous research within the same institution^{112,149}.

Randomization was carried out at two time points: acclimatisation and trial phase. The goal was to minimise any bias in the study. Despite both appliances being similarly packaged and presented to the patients, it was observed that patients who received the TSD first were more willing to try the appliance and persist with it. Those patients receiving the MAS first displayed less enthusiasm for the TSD in general, which may have influenced their compliance. Appliances were not withheld from the patients at any time during the study to reduce the number of appointments required by the patients with associated leave from work and travel. An honour system was in place regarding adherence to the protocol.

5.2 Sample Characteristics

The sample population was recruited from a sleep disorders clinic known for its interest in dental therapy research, therefore a referral bias may have resulted. The sample size was small due to the very stringent inclusion and exclusion criteria and logistical issues. The 18 patients who completed the trial consisted of six Asians and twelve Caucasians. The Asian

patients' BMI was $23.8 \pm 2.2 \text{ kg/m}^2$. The presence of OSA in these patients was more likely to have been as a result of anatomical variables than obesity¹⁸⁷. In contrast, the BMI of the Caucasians was $31.7 \pm 5.2 \text{ kg/m}^2$, which has been shown to be one risk factor for OSA ($> 25 \text{ Kg/m}^2$)⁴. Male gender comprised 77.8% of the sample which is consistent with the general OSA population. Currently it is believed that women are under-represented due to women being more reluctant to report symptoms and the perception by physicians and patients alike that OSA is a disorder of men²⁷. Neck circumference was measured as it reflects obesity in the region of the oral airway. The sample population neck circumference was $0.41 \pm 0.05\text{m}$. This was comparable to the neck circumference of $0.43 \pm 0.03\text{m}$ reported in a sample of 161 OSA patients⁴⁷. Neck circumference for a sample of normal subjects was found to be 0.375m ³⁰. Tongue circumference was measured however there is little normative data available and high subjectivity in the measurement procedure itself. Patients in the study ranged in baseline AHI from 10.3 to 75.7 events per hour. According to the baseline AHI patients were classified into severity groups: Mild 50% of patients, Moderate 27.8% of patients, Severe 22.2% of patients. This classification remains consistent with the protocol of this institution^{112,149}. It was noted that 2 patients who were classified as severe were female and comprised 50% of the female group. The remaining severe patients comprised 14.3% of the male group. For this reason the males and females were analysed together as a total group to assess treatment outcome. There was no significant difference in BMI between severity groups. Although the sample characteristics at baseline were comparable to those of a general OSA population, the results must be reviewed with some caution.

5.3 Appliance Design

Appliance design for the MAS device was selected based on previous research within the institution¹¹². In this study the degree of mandibular protrusion with the MAS could not be increased (titrated) due to the requirement for a metal-free appliance to permit MRI scanning. The author attempted to obtain a bite registration at 75% of maximum jaw protrusion (from centric occlusion to maximum protrusion). This was not always comfortable to the patient or resulted in a mandibular deviation. The most protrusive yet comfortable position was recorded. The goal advancement of 75% was chosen based on the mean advancement at the end of the titration period in an earlier study¹¹², and by the work of Marklund and colleagues (2001) who found greater efficacy with the appliances at 75% advancement compared with 50% advancement¹⁸⁸. An actual advancement of $76 \pm 8\%$ was achieved with the patients in this study, with a wide range. The limitation of this method was that patients were not advanced further as they became used to their appliance which may have compromised their potential improvement in OSA. One patient required the amount of protrusion to be reduced. All patients were advised to regard this device as a 'trainer', and if necessary to replace it with an adjustable version in the future.

The TSD appliance was non-adjustable, with the patient controlling the amount of suction generated by the device. It was noted that patients protruded their tongue into the appliance by differing amounts and squeezed the bulb with differing force. There was no method to standardise the application of the TSD, with each individual having to establish his/her own comfort level. The use of TSD in this manner reflects the real use of the device without control of the author.

5.4 Subjective Evaluation

The subjective evaluation of the effect of the TSD and MAS on the OSA symptoms was achieved through the questionnaires. As with any questionnaire, the information must be considered with regard to the possibility of some patients giving a 'social response' that may not correspond entirely with the clinical picture. Patients were advised to answer as accurately as possible independent of social considerations. The questionnaires were completed during the acclimatisation phase after a relatively short period of time. Follow-up at one year would allow assessment of long-term symptoms and compliance rates. Eleven patients (61.1%) completed the questionnaires on their own. Hence, data concerning snoring frequency and intensity should be interpreted with this in mind.

When assessing snoring frequency, volume and severity, a clear trend was apparent. Both the TSD and MAS were regarded by the patients (and their partners) as generating an improvement. Snoring frequency was reduced from almost always in 13 patients (72.2%) at baseline, to not at all in 33.3% of patients using TSD and 38.9% patients using MAS. Although snoring parameters were not measured objectively in this study, the patients and partners perceptions correspond with polysomnographic testing. O'Sullivan and colleagues (1995) found a reduction of 18% in snoring frequency and 15.8% in snoring intensity using MAS¹³⁵. Kingshott and colleagues (2002) found the TSD significantly reduced snoring frequency in the 61-70 decibel range, but did not alter snoring in other decibel ranges¹⁷⁵. Snoring intensity was also reduced with the TSD and MAS appliances. Overall it was reported by patients when using MAS that their snoring was cured or much improved. The use of TSD did not produce as profound effects as the MAS with regard to snoring, with 4 patients (22.2%) reporting no improvement. The social aspect of this change in snoring

pattern may have contributed to 3-4 couples altering their sleeping arrangements and returning to sleep in the same room. Several patients mentioned an improved confidence and willingness to participate of group holidays with their friends.

Compliance with oral appliances in the management of OSA is difficult to ascertain. As yet there is no mechanism to verify that reported usage is the same as actual usage. Compliance (regular usage at one month) with the MAS was reported as 83.3%, whereas compliance with TSD was 22.2%. This compliance rate for MAS compares with the rates reported by other studies. Mehta *et al* reported a compliance rate of 87.5% with MAS at one month¹¹². At 9 months the compliance rate was found to be 68% in a similar study{Bates C, 2005 #210}. By four years, compliance with a monobloc-type MAS was found to be 62%¹⁵⁹. There is no literature on compliance with the TSD but it can be assumed that like MAS, compliance rates are likely to decrease relative to the length of follow up.

Although CPAP is considered the gold standard management option for OSA patients, long-term compliance rates have ranged from 50-80%¹¹³. Not only is it important to have an effective treatment modality, but to have a device which is acceptable and comfortable to the patient. The MAS although not as effective as CPAP, nevertheless appears to have a higher compliance rate. Hence it may be better to have a less effective appliance which will be used by the patient over a more effective device that will gather dust. The TSD in this study did present some challenge to the patients. It was often reported that the TSD had fallen off or been dislodged overnight, in marked contrast to the precision fitted MAS device which was retained well. Patients in this study were more likely to stop wearing the TSD (61.7%) than the MAS (16.8%) by one month.

According to the Epworth Sleepiness Scale (ESS) a score of 6 is the mean value for subjects with a history of normal sleep habits without apnea⁵⁸. In this study the mean score

for the total group was 8.72 ± 4.52 at baseline, 5.94 ± 3.99 with TSD and 3.78 ± 2.53 with MAS. These changes were statistically significant between baseline and appliance and between appliances ($p < 0.01$). 50% of the patients scored ≤ 6 with the TSD device and 88.9% with MAS. The ESS is a subjective test and the “Hawthorn effect” may have influenced the score.

Both appliances resulted in an equal percentage of patients reporting side-effects, with the problems being different in nature. Side-effects with the MAS were reported to be mild to moderate in severity, and largely resolved by three weeks. Side effects with the TSD were mild to severe, and more often persisted beyond three weeks. Jaw discomfort was more problematic with usage of the MAS due to vertical opening and protrusion of the mandible. Patients explained this phenomenon as jaw soreness on waking which resolved within 30 minutes of removing the appliance. Fewer patients complained of jaw discomfort with the TSD, where vertical opening of the mandible occurred. Excess salivation was of greater concern when using the TSD than MAS, and was a frequent phenomenon which persisted in 4 patients (22.2%) using TSD beyond three weeks. This may be attributed to the reduced ability of patients to swallow with the TSD in situ and the lip seal against the appliance. Despite concerns with excess salivation, patients also reported dryness of the mouth occurring frequently and persisting beyond three weeks with the TSD. This also occurred to a lesser degree with MAS. On further questioning, it became evident that the excess salivation was more of a problem when initially placing the appliance in the early stages of sleep, and dryness was often observed in the morning. Perhaps an increase in saliva production occurred when the appliances were first placed, and was more noticeable with TSD due to difficulty swallowing. This phenomenon was persistent and was likely to be the result of the intermittent nocturnal usage of the appliances. The dryness could be attributed

to an oral pattern of respiration. Grinding teeth at night affected 2 patients whilst using MAS, and was mild in nature lasting up to one week. Soft tissue irritation was largely problematic for patients when using TSD and occurred frequently. Specifically, the chief complaints were of ulceration and soreness of the lingual frenum requiring adjustment of the device, and a numb sensation to the tip of the tongue lasting approximately 30 minutes after removing the TSD. One patient reported this numbness lasting two hours making breakfast difficult to eat.

The side-effects with TSD were severe enough from the patients' perspective to prevent half of the sample from continuing with the device. The side-effects with MAS did not prevent any of the subjects from using the appliance.

The long-term side-effects of the MAS are not entirely understood at this time. Many studies reporting use of MAS do not follow-up the patients adequately with respect to dental, skeletal and temporomandibular joint status. De Almeida *et al* assessed the long term sequelae of MAS at five years^{165,167,168}. Cephalometric head films demonstrated increased mandibular plane and ANB angles, decreased overbite and overjet, retroclined maxillary incisors, proclined mandibular incisors, increased lower facial height, distally tipped maxillary molars and mesially tipped and erupted mandibular molars. The same group concluded that these changes were unfavourable in 44.3% of their 70 OSA patients. Ringqvist *et al* (2003) had also investigated dental and skeletal changes with MAS after 4 years¹⁸⁹. When comparing 30 OSA patients using MAS with 37 OSA patients treated with UPPP, small but statistically significant changes were found revolving around posterior rotation of the mandible with MAS use. Likewise Fransson *et al* demonstrated minor alterations in the occlusion after 2 years of MAS wear in 65 patients¹⁹⁰. By contrast, the TSD would be unlikely to generate such changes as it does not directly engage the

dentition. Forces generated by soft tissue and muscle-stretch on mandibular protrusion with MAS are transferred through the dentition to supporting structures. With TSD, the soft tissue stretch generated with vertical mandibular opening would be minimal. TSD could cause minor occlusal disturbance by contacting the incisal edges of anterior teeth only, possibly leading to passive buccal eruption. Duration of appliance usage would also contribute to the magnitude of dental change in accordance with the Equilibrium Theory¹⁹¹. In addition, there is no literature on the effect of suction of the soft tissue, and the possibility of hyperplasia, vascular or neural consequences. Further research would be required in this field.

In summary, patients were more satisfied with the MAS. 88.9% of the sample population preferred MAS to TSD.

5.5 Objective Evaluation - Cephalometric Analysis

Cephalometric head films were taken to assess the craniofacial morphology of the sample population. The small sample size precludes any conclusions aside from assessing this particular group of patients. The variables in this study found to be significantly different ($p < 0.01$) from normative data were hyoid bone position and head posture, tongue length and tongue height.

An increased hyoid bone to mandibular plane distance and extended head posture has been commonly reported in OSA patients. According to Watanabe *et al*³⁰ the hyoid bone is positioned more caudally due to excess soft tissue around the pharyngeal airway. The effect is increased when there is a concurrent reduction in the bony enclosure of the pharynx, such as retro-positioning of the maxilla and/or mandible. According to Schwab¹⁸⁷ hyoid bone

position, as one of the craniofacial risk factors, has its strongest association with non-obese patients and has been demonstrated with family aggregation in patients with sleep apnea. The mechanism by which the hyoid bone to mandibular plane distance is altered is subject to debate. In this study the distance was larger compared with the norm, and was comparable with a sample of 15 OSA patients (24.0mm) of Watanabe *et al*³⁰.

Extended head posture as indicated by an increase in craniocervical angulation (C2C4-SN) has been reported previously, often in association with reduced airway dimensions^{184,185}. It is regarded as an adaptation intended to further open the airway. In this study, the craniocervical angulation was 10 degrees greater than the norm, which was significant.

Tongue length and tongue height were found to be less compared with the norm. This would appear to be opposite to the anticipated result as the volume of the tongue is generally quoted as being larger in OSA patients^{48,49,187}. In a CT radiographic study Lowe *et al* found that patients with more severe OSA had larger tongues and smaller airway volumes⁴⁸.

Using measurements from lateral cephalometric head films to assess the airway must be regarded as an incomplete evaluation of a three-dimensional structure. Despite using a standardised radiographic technique and relying on natural head position, it would have been possible to have positioning variation between subjects, and for the subjects to posture their tongue. Altering the head position has been shown to influence the airway dimension⁴⁶ as would atypical tongue posture. Cephalometric films are typically taken in a standing position and, hence, may not reflect the clinical picture of the airway dimensions when the patient is lying down. Some attempts have been made to correlate the upright and supine airway using radiographs, with further research being required¹⁹². In addition, muscle tonicity is reduced during sleep reducing airway calibre. The normative data used in this

study was based on Caucasian subjects. Therefore some inaccuracies are inherent with this study sample which included six Asian subjects.

5.6 Objective Evaluation - Polysomnography

Objective testing of the effect of both TSD and MAS was undertaken using polysomnography.

Sleep architecture describes the pattern of an individual's sleep with particular attention to the proportion of time spent in REM and NREM states, and the manner in which REM and NREM phases alternate through the night (total sleep time) in a cyclic manner²⁰. In this study there was a minimal difference in the total sleep time (TST) with a slightly reduced the mean TST for TSD (319 ± 24.36 minutes). This was due to 2 patients recording relatively shorter sleep tests with the TSD. The TSD result was not statistically different from the baseline or MAS results. The proportion of REM to NREM sleep showed no significant difference between the three tests. When compared to normative data for young adults, which anticipates 20-25% of sleep to be REM²⁰, the sample in this study scored better, but with a lesser percentage of REM sleep at all three time points. The arousal index (AI) represents an interruption of the patient's sleep cycle, and is the mechanism by which the body attempts to deal with the obstructive event and its sequelae. In this study, the AI decreased significantly with both the TSD and MAS ($p=0.003$, $p=0.002$ respectively), representing reduced disturbance to the sleep pattern. This improvement is consistent with other studies using MAS^{112,113,149,155}, and with the limited data available on TSD¹⁷⁵.

Respiratory variables were assessed, with emphasis on AHI and oxygen saturation. This study found that the AHI decreased in 94% of the patients using TSD and 83% of the patients using MAS. The mean change in AHI with the TSD was 47% and with MAS was

52%. This result is similar to that reported with MAS by Schmidt-Nowara *et al* (AHI decreased by >50%)¹⁴¹, Clark *et al* (AHI reduced by 39%)¹³⁶, Eveloff *et al* (AHI decreased by 63%)¹⁴⁸, O'Sullivan *et al*¹³⁵, Ferguson *et al* (AHI reduced by 51%)¹¹³, Mehta *et al* (AHI reduced 51.8% with MAS)¹¹², and Pitsis *et al* (AHI decreased by 52% and 62% dependant on MAS design)¹⁴⁹. Blood oxygen saturation improved significantly with the TSD ($p=0.003$). The minimum oxygen saturation did not represent a significant change with MAS. Several studies found improvement in this parameter^{135,136,141} while others did not^{113,148}. The limitation of this parameter is that minimum oxygen saturation correlates with the most severe obstructive episode for that patient and may not reflect the overall obstruction potential with use of a dental device. The longest apnea was reduced significantly with the MAS ($p<0.001$), with hypopneas being no different.

Treatment success in this study was based on the AHI scores obtained using the TSD and MAS compared to the baseline value. A treatment success was defined as a decrease in AHI >50% and <5/hour. A partial success was a decrease in AHI >50% but >5/hour. A failure was a decrease in AHI <50%. These criteria were used in previous studies^{112,149}. Due to the small sample size, success and partial success patients were grouped. 50% of the patients had success or partial success with the TSD compared to 66.7% with MAS. When this data was further investigated by assessing OSA severity with treatment outcome, there was no significant difference between the mild, moderate and severe OSA groups for each device. Of the 4 severe OSA patients in this study, 3 subjects achieved partial success with the TSD and 4 subjects with MAS. Of the 5 moderate OSA patients, 3 achieved success with TSD, and 1 was successful and 2 partially successful with MAS. This is contrary to the previous recommendation that oral appliances should only be used to treat simple snoring or mild OSA¹³⁴. It is also important to note that there were 9 patients with mild

OSA (AHI<20), in which it would be numerically harder to achieve a reduction in AHI >50%, resulting in an increased number of failures.

The treatment outcome when comparing TSD and MAS revealed that 13 patients (72.2%) achieved the same outcome with TSD and MAS. There were more failures with TSD than MAS, although not significant.

When patients with a total sleep time of less than 180 minutes were excluded, the rate of success or partial success with TSD reduced to 38.9% and was unchanged for MAS. These patients may have had short sleep tests due to technical difficulties, including trouble become comfortable in foreign surroundings, or may not have acclimatised fully to the oral device precluding a test representative of their usual sleep disturbance. A longer acclimatisation period may have assisted. Repeat sleep tests would have been the most ideal method of validating the results but were not possible in this study.

The overall impression is a trend toward MAS being more effective than TSD in the management of OSA based primarily on the AHI. The differences between TSD and MAS using polysomnography were generally not significant.

5.7 Objective Evaluation – Magnetic Resonance Imaging

MRI was used to objectively measure the total volume of the airway (hard palate to cricoid cartilage) and to assess the change in volume and dimensions of the velopharynx (hard palate to tip of uvula), oropharynx (tip of uvula to tip of epiglottis) and hypopharynx (tip of epiglottis to cricoid cartilage) with the TSD and MAS. As muscle tonicity is different in the awake versus the sleeping patient, interpretation of the results should consider that the values are likely to be less in the clinical setting. For practical reasons MRI research in this

field is often undertaken on awake patients^{43,65,66}, however sedation has been used to be more representative of the sleep situation¹⁹³.

The total airway volume for the sample in this study was $15.12 \pm 1.48 \text{ cm}^3$ at baseline, being similar to the airway volume recorded in 25 OSA patients using CT imaging ($13.89 \pm 5.33 \text{ cm}^3$)⁴⁸. This was increased to $18.70 \pm 1.71 \text{ cm}^3$ with the TSD ($p=0.004$), with no significant difference between baseline and MAS for total volume. Assessment of the regions of the airway demonstrated improved airway volume in the velopharynx alone when compared between baseline and TSD or MAS. The retropalatal region has been quoted as the location of the greatest narrowing in OSA patients when compared to normal subjects¹⁹⁴, so improved regional volume as reported in this study is favourable. The mechanism by which this increase in airway volume occurs is unclear. The TSD holds the tongue forward directly whereas the MAS advances the mandible thereby increasing the bony enclosure of the airway and advancing the tongue by association. Perhaps the muscular and soft tissue connections between the tongue, mandible and soft palate are responsible. Observation of the way in which the patients used the TSD in this study suggested significant tongue protrusion which must be assumed is comfortable and acceptable to the patients, although not all patients could tolerate this over an extended time. A limitation of this study was that patients were informed that the TSD would be in place for ten minutes during the MRI scan, possibly resulting in some patients may have applied the TSD more firmly than they would with night time use.

Evidence indicates that the airway in OSA patients may have an altered shape, being narrower in the medio-lateral dimension when compared to control subjects¹⁹⁴. The goal with oral appliance therapy would be to increase the medio-lateral dimension thereby creating a more normal airway shape that may be less likely to collapse during sleep. In this

study the anterior-posterior and medio-lateral dimensions were measured at the tip of the soft palate, mid-oropharyngeal level and at the tip of the epiglottis. These locations were chosen based on ease of landmark identification so as to ensure the same position was measured in all subjects. These levels may not have corresponded to the narrowest region of the airway for the patients. There was no significant difference in the antero-posterior or medio-lateral dimensions between baseline (no appliance) and appliances, or between TSD and MAS. A trend to increased antero-posterior dimension in the oropharynx and hypopharynx, and medio-lateral dimension in the velopharynx and oropharynx with TSD was present. The sample size of 15 was too small to draw conclusions. Nonetheless, shape change was evident with the devices, the clinical significance of which requires further investigation.

6. Conclusions

Subjective and objective modalities have been used to assess the effectiveness of TSD and MAS in the management of OSA in a sample of 18 patients. In this study of limited duration it was demonstrated that;

1. TSD and MAS reduced snoring and improved quality of sleep.
2. TSD and MAS reduced the symptoms of daytime tiredness as measured by the Epworth Sleepiness Scale.
3. MAS appeared to have a greater improvement on OSA symptoms than TSD.
4. TSD and MAS both caused side-effects which were regarded as more severe and prolonged with the TSD.
5. TSD compliance was less than MAS.

6. Patients had a clear preference for MAS.
7. Polysomography demonstrated little difference between the TSD and MAS in the management of OSA.
8. MRI demonstrated that the TSD produces a greater overall airway volume, with both devices increasing the volume of the velopharynx. No overall change in airway shape was detected.

Based on these results the null hypothesis is accepted. The TSD is validated as a treatment alternative in the management of OSA for patients who are not eligible to use other appliances. The strong patient preference for MAS and challenges presented by TSD revealed in this study represents an obstacle for acceptance of TSD as a first line oral device. Patients with no other option may be better able to persist and acclimatise to the device.

6.1 Future Directions

The future directions in this field would be to study edentulous patients with TSD, possibly in comparison to CPAP. In the absence of teeth the TSD would have a lesser vertical effect and it is likely that the compliance rate would be higher than reported in this study.

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Appendices

- Appendix 1. Epworth Sleepiness Scale
- Appendix 2. Information for Participants
- Appendix 3. Consent Form
- Appendix 4. Revocation of Consent
- Appendix 5. Sleep questionnaire 1
- Appendix 6. Sleep questionnaire 2 TSD
- Appendix 7. Sleep questionnaire 2 MAS
- Appendix 8. MRI comparison of airway between baseline, TSD and MAS (images)

Appendix 1.

Epworth Sleepiness Scale

How would you grade your daytime sleepiness/fatigue in the last month for the following situations: Use the following scale to choose the most appropriate number for each situation and fill *ALL* boxes:

(0) **Never** doze

(1) **Slight** chance of dozing

(2) **Moderate** chance of dozing

(3) **High** chance of dozing

- | | |
|--------------------------|---|
| ☐ | Sitting and reading |
| ☐ | Watching TV |
| ☐ | Sitting, inactive in a public place (eg a theatre, meeting) |
| ☐ | As a passenger in a car for an hour without a break |
| ☐ | Lying down to rest in the afternoon when circumstances permit |
| ☐ | Sitting and talking to someone |
| ☐ | Sitting quietly after lunch without alcohol |
| ☐ | In a car, while stopped for a few minutes in the traffic |

A maximum score of 24 is possible.

A score less than 6 is considered normal.

A score greater than 10 is considered an indication of excessive daytime sleepiness.

Appendix 2.

8 August 2005

A Prospective Randomised Crossover Study of a Tongue Stabilising Device on Obstructive Sleep Apnoea

INFORMATION FOR PARTICIPANTS

Introduction

You are invited to take part in a research study into the treatment of Snoring and Obstructive Sleep Apnoea with a Tongue Stabilising Device. The objective is to investigate whether the tongue stabilising device is as effective as the mandibular advancement splint. A tongue stabilising device is an appliance which holds the tongue forward during sleep. A mandibular advancement splint is a dental device that holds the lower jaw forward during sleep.

The study is being conducted within this institution by;

- Dr Andrew Ng, Specialist Physician and Acting Director at the Centre for Sleep Disorders and Respiratory Failure, St George Hospital
- Professor M Ali Darendeliler, Head – Discipline of Orthodontics, Sydney Dental Hospital
- Associate Professor Gang Shen, Discipline of Orthodontics, Sydney Dental Hospital
- Dr Sheryn Deane, Orthodontic Registrar and MDSc student, Sydney Dental Hospital

Study Procedures

If you agree to participate in this study, you will be asked to sign the Participant Consent Form. You will then be asked to undergo the following procedures:

1. Baseline investigations

You and your partner should attend the first appointment together. Approximately 2-3 appointments will be required to complete baseline investigations. Each appointment will be of approximately 45 minutes duration.

Baseline investigations will include the following:

- Dental examination – this consists of a routine dental checkup to ascertain the health of your teeth and gums.
- Routine dental x-rays – the x-rays are part of the routine clinical assessment of patients who snore and have obstructive sleep apnoea. The x-rays involved are;

- An OPG film – which is a screening x-ray for the teeth and jaw bones. This is used to detect pathology such as dental caries, periodontal gum disease and other problems.
- A Lateral Cephalometric film – which is a side-on picture of the skull. This is used to measure and compare the size of the upper and lower jaws, and also to assess the size of the tongue and airway.
- Both x-rays will be taken at the Sydney Dental Hospital. The x-rays take approximately 10 seconds to do, and will require you to stand in the x-ray machine with your head kept stable by either biting onto a small plastic block, or with a head positioning device, similar to a hairband, gently resting on your ears.
- Impressions – upper and lower impressions of your teeth will be taken for the construction of the mandibular advancement splint. You will then be given a follow up appointment approximately two weeks later to issue you with your custom made appliance. The appliance consists of separate upper and lower plastic plates which fit over the teeth, with grooves to hold the lower jaw forward. They are similar to small upper and lower mouth guards. The appliance is worn only during sleep.
- Tongue measurement – a measurement will be taken of your tongue to allow selection of the correct size of tongue stabilizing device. You will need to protrude your tongue so that dental floss can be used to obtain the tongue circumference. The device is a soft plastic bulb, which holds the tongue forward by suction and rests on the lips.
- A sleep questionnaire – to be completed by you and your partner during the first appointment. This will take about 5 minutes.

2. Acclimatisation Period

- A period of 4 to 8 weeks will follow in which you will be asked to wear both the mandibular advancement splint and tongue stabilizing device, in random order.
- This time is to ensure that you are used to the appliances prior to proceeding to the next phase of the study.
- You will be asked to complete two questionnaires during this time, one after wearing each appliance. This will take about 10 minutes to complete on each occasion.
- You will then be randomly allocated into one of two groups, to wear either the Mandibular Advancement Splint or Tongue Stabilising Device during the first half of the study. You will wear the other device during the second half of the study.

3. Sleep studies

- **Two** sleep studies will be performed, each approximately two weeks apart. The sleep studies will be conducted overnight at the Sleep Laboratory at St George Hospital (36 Belgrave St, Kogarah 2217).
- You will be asked to spend the night at the Sleep Laboratory during both of the sleep studies.

- **Summary of steps**
- Week 1; no appliance is worn.
- Week 2; either the Mandibular Advancement Splint or Tongue Stabilising Device is worn.
- End of week 2; Sleep study is carried out.
- Week 3; no appliance is worn
- Week 4; alternate appliance is worn
- End of week 4; Sleep study is carried out.

Due to the nature of the study design, you must understand that the Mandibular Advancement Splint and Tongue Stabilising Device will only be given to you at specific times during the study. This is an important aspect of the study and requires your full co-operation.

4. Follow-up Questionnaires

- Questionnaires will need to be completed by you and your partner after using each appliance to understand in more detail the effects of the tongue stabilizing device and mandibular advancement splint on your snoring and sleep apnoea.
- Two questionnaires will be required; one after each appliance during the acclimatization period.
- Each questionnaire takes about 5 minutes to do.

5. Magnetic Resonance Imaging Scan

- At the conclusion of the study you will be asked to have an MRI scan.
- The scan will have three stages, and will be done while you are awake.
- Firstly, you will be scanned without either appliance, then while wearing the tongue stabilizing device, and finally while wearing the mandibular advancement splint.
- This scan does not involve any radiation. Some people may find the scanning machine slightly claustrophobic.
- You cannot undergo this scan if you have metal implants in any part of your body. Please ensure that you notify the clinician if you have metal implants in any part of your body at the beginning of the study.

In addition, the researchers would like to have access to your medical record to obtain information relevant to this study.

Risks

All medical procedures - whether for diagnosis or treatment, routine or experimental – involve some risk of injury. In addition, there may be risks associated with this study that are presently unknown and unforeseeable. In spite of all precautions, you might develop medical complications from participating in this study.

The risks of participating in this study are:

- Some individuals may experience discomfort with the appliances. This may include; jaw discomfort, excess salivation, dryness of the mouth, grinding of teeth at night or soft tissue irritation.
- Some individuals may find the MRI scan claustrophobic.

Attending both the Sydney Dental Hospital and the St George Hospital for study procedures may be an inconvenience.

Exposure to radiation

This research study involves exposure to a very small amount of radiation. This takes the form of routine x-rays which are part of the clinical assessment of patients who snore or have obstructive sleep apnoea.

As part of everyday living, everyone is exposed to naturally occurring background radiation and receives a dose of about 2 to 3 millisieverts (mSv) each year. The effective dose from this study is about 3.4 microsieverts (uSv). At this dose level, no harmful effects of radiation have been demonstrated and the risk is negligible. The dose from this study is comparable to that received from routine diagnostic x-ray and nuclear medicine procedures.

It is important to inform the researchers if you have participated in any other research studies using radiation in the last five years. Please keep this information sheet in a safe place for the next five years and show it to the researchers if you volunteer for any more studies using radiation.

It is important to inform the researchers if you are pregnant.

Benefits

While we intend that this research study furthers medical knowledge and may improve treatment of snoring and obstructive sleep apnoea in the future, it may not be of direct benefit to you.

Costs

Participation in this study will not cost you anything if you hold a current health care card, nor will you be paid. If you do not hold a current health care card, then the cost of the Mandibular Advancement Splint is \$400.00.

Voluntary Participation

Participation in this study is entirely voluntary. You do not have to take part in it. If you do take part, you can withdraw at any time without having to give a reason. Whatever your decision, please be assured that it will not affect your

medical treatment or your relationship with the staff who are caring for you. Of the people treating you, only those named above and the sleep technicians will be aware of your participation or non-participation.

Sometimes during the course of a study, new information becomes available about the treatment that is being studied. While you are participating in this study, you will be kept informed of any significant new findings which may affect your willingness to continue in the study.

Confidentiality

All the information collected from you for the study will be treated confidentially, and only the researchers named above will have access to it. The study results may be presented at a conference or in a scientific publication, but individual participants will not be identifiable in such a presentation.

Further Information

When you have read this information, Dr Peter Cistulli, Professor Darendeliler, Associate Professor Gang Shen or Dr Sheryn Deane will discuss it with you further and answer any questions you may have. If you would like to know more at any stage, please feel free to contact him/her at the Sydney Dental Hospital (ph; 92933388), or Sleep Disorders Clinic, St George Hospital (ph;95534425).

This information sheet is for you to keep.

Ethics Approval

This study has been approved by the Ethics Review Committee of the South East Sydney Area Health Service.

Any persons with concerns or complaints about the conduct of this study should contact the Ethics Secretariat, South East Health Human Research Ethics Committee (Southern Section), St George Hospital, Gray St, Kogarah 2217. Telephone: 02 9350 2481. Fax: 02 9350 3968. Email: finkp@sesahs.nsw.gov.au

Version No. : 4

Date: 8 August 2005

Appendix 3.

**A Prospective Randomised Crossover Study of a Tongue Stabilising
Device on Obstructive Sleep Apnoea**

PARTICIPANT CONSENT FORM

I,.....[name]

of.....[address]

have read and understood the Information for Participants (Version 4, 8th
August 2005) on the above named research study

and have discussed the study with

I have been made aware of the procedures involved in the study, including any
known or expected inconvenience, risk, discomfort or potential side effect and
of their implications as far as they are currently known by the researchers.

Before signing this consent form, I have been given the opportunity of asking
any questions relating to any possible physical or mental harm I might suffer as
a result of my participation, and I have received satisfactory answers.

I understand that if I have any questions relating to my participation in this
research, I may contact Dr Sheryn Deane on telephone 9293 3388, who will be
happy to answer them.

I understand that my participation in this study will allow the researchers to have
access to my medical record, and I agree to this. I agree that the research data
gathered from the results of the study may be published, provided that I cannot
be identified.

I freely choose to participate in this study and understand that I can withdraw at
any time without prejudice to my relationship with Sydney Dental Hospital or St
George Hospital.

I also understand that the research study is strictly confidential.

I acknowledge receipt of a copy of the Information for Participants and Consent
Form.

I hereby agree to participate in this research study.

Signature of Participant:.....
(Print Name) (Date)

Signature of Witness:.....
(Print Name) (Date)

Signature of Investigator:.....
(Print Name) (Date)

Complaints may be directed to the Ethics Secretariat, South East Health
Human Research Ethics Committee (Southern Section). St. George Hospital.
Gray St., Kogarah 2217. Telephone: 9350 2481. Fax: 9350 3968. Email:
finkp@sesahs.nsw.gov.au

Version No. : 4
Date: 8 August 2005

Appendix 4.

22 June 2005

**A Prospective Randomised Crossover Study of a Tongue Stabilising
Device on Obstructive Sleep Apnoea**

REVOCATION OF CONSENT

I was invited to take part in a research study into the treatment of Snoring and Obstructive Sleep Apnoea with a Tongue Stabilising Device. The objective is to investigate whether the tongue stabilising device is as effective as the mandibular advancement splint. A tongue stabilising device is an appliance which holds the tongue forward during sleep. A mandibular advancement splint is a dental device that holds the lower jaw forward during sleep.

I hereby wish to WITHDRAW my consent to participate in the research proposal described above, and understand that such withdrawal WILL NOT jeopardize any treatment or my relationship with the Sydney Dental Hospital, St George Hospital and my medical attendants.

Signature

Date

Please PRINT Name

Revocation of Consent should be forwarded to:

Dr Sheryn Deane
Department of Orthodontics
Sydney Dental Hospital
2 Chalmers St
Surry Hills NSW 2010

Version 1, 22nd June 2005

Appendix 5.

SLEEP QUESTIONNAIRE – 1

DATE : _____

PATIENT'S STUDY NUMBER : _____

Please consult with your spouse/sleeping partner when answering these questions.

1. Do you snore Yes No

If you answered No then proceed to Question 4

2. Snoring frequency: On average, how many days/nights during the last month have you snored or been told that you snore? **Tick** one of the following:

- ☐ Rarely: once/week
- ☐ Sometimes: 1-2/week
- ☐ Frequently: 3-4/week
- ☐ Almost always: 5-7/week
- ☐ Do not know

3. Snoring Intensity: During the past month has your snoring been:

Tick one of the following:

- ☐ Only slightly louder than heavy breathing
- ☐ About as loud as mumbling or talking
- ☐ Louder than talking
- ☐ So loud that it can be heard through a closed door
- ☐ Do not know

Information for the questions 1, 2, 3, above provided by (a) you ☐ (b) your partner ☐
or (c) both ☐ (**tick one box**)

4. How would you grade your daytime sleepiness/fatigue in the last month for the following situations: Use the following scale to choose the most appropriate number for each situation and fill **ALL** boxes:

(4) **Never** doze

(5) **Slight** chance of dozing

(6) **Moderate** chance of dozing

(7) **High** chance of dozing

- ☐ Sitting and reading
- ☐ Watching TV
- ☐ Sitting, inactive in a public place (eg a theatre, meeting)
- ☐ As a passenger in a car for an hour without a break
- ☐ Lying down to rest in the afternoon when circumstances permit
- ☐ Sitting and talking to someone
- ☐ Sitting quietly after lunch without alcohol
- ☐ In a car, while stopped for a few minutes in the traffic

5. How would you rate the quality of your sleep?

Tick one of the following:

- ☐ Refreshing
- ☐ Slightly unrefreshing
- ☐ Moderately unrefreshing
- ☐ Very unrefreshing

6. How would you grade your level tiredness on waking?

- ☐ Not tired
- ☐ Slightly tired
- ☐ Moderately tired
- ☐ Very tired

7. Do you live with a partner ☐ or as a single person ☐ ?

8. If you live with a partner do you:

☐

Share the same bedroom

☐

Sleep in different rooms because of the snoring

☐

Sleep in different rooms for a reason other than snoring

9. Age: _____years _____months

Any comments:

Thank you for your cooperation

Appendix 6.

SLEEP QUESTIONNAIRE – 2

This questionnaire pertains to the period of Appliance Use

Tongue Stabilising Device

DATE : _____

PATIENT’S STUDY NUMBER : _____

Please consult with your spouse/sleeping partner when answering these questions.

1. In the last month, did you use the Oral Appliance – **Tick** one of the following

- ☐ Regularly: Every day of the week
- ☐ Occasionally: 3-4/week
- ☐ Rarely: 1-2/week
- ☐ Not at all

2. Do you snore while using the appliance? Yes ☐ No ☐

If you answered No the proceed to Question 5

3. Snoring frequency: On average, how many days/nights during the last month have you snored or been told that you snore? **Tick** one of the following:

- ☐ Never
- ☐ Rarely: once/week
- ☐ Sometimes: 1-2/week
- ☐ Frequently: 3-4/week
- ☐ Almost always: 5-7/week
- ☐ Do not know

4. Snoring Intensity: During the past month has your snoring been:

Tick one of the following:

- ☐ Only slightly louder than heavy breathing
- ☐ About as loud as mumbling or talking
- ☐ Louder than talking
- ☐ So loud that it can be heard through a closed door
- ☐ Do not know

5. How would you rate the effect of the Oral Appliance on your snoring:

Tick one of the following:

- ☐ Snoring cured
- ☐ Snoring much improved
- ☐ Snoring improved
- ☐ Snoring slightly improved
- ☐ No improvement

6. Did you involuntarily remove the Oral Appliance on any night? Yes ☐ No ☐

If yes, why? _____

7. Did the Oral Appliance loosen with time? Yes ☐ No ☐

8. If you stopped using the Oral Appliance:

Why did you stop? _____

9. When did you stop?

- ☐ Less than a week after obtaining the appliance
- ☐ After 1 week
- ☐ After 2 weeks
- ☐ After 3 weeks

10. How would you grade your daytime sleepiness/fatigue in the last month (whilst using the Oral Appliance at night) for the following situations : Use the following scale to choose the most appropriate number for each situation (**fill in all boxes**):

(8) **Never** doze

(9) **Slight** chance of dozing

(10) **Moderate** chance of dozing

(11) **High** chance of dozing

- ☐ Sitting and reading
- ☐ Watching TV
- ☐ Sitting, inactive in a public place (eg a theatre, meeting)
- ☐ As a passenger in a car for an hour without a break
- ☐ Lying down to rest in the afternoon when circumstances permit
- ☐ Sitting and talking to someone
- ☐ Sitting quietly after lunch without alcohol
- ☐ In a car, while stopped for a few minutes in the traffic

11. How would you rate the effect of the Oral Appliance on your degree of daytime sleepiness/fatigue:

- ☐ Cured
- ☐ Improvement
- ☐ Same
- ☐ Unsure

12. How would you rate the quality of your sleep with the appliance?

Tick one of the following:

- ☐ Refreshing
- ☐ Slightly refreshing
- ☐ Moderately unrefreshing
- ☐ Very unrefreshing

13. How would rate the effect of the Oral Appliance on the quality of your sleep?

- ☐ Large improvement
- ☐ Improvement
- ☐ Same
- ☐ Unsure

14. How would you grade your level of tiredness on waking whilst using the Oral Appliance?

- ☐ Not tired
- ☐ Slightly tired
- ☐ Moderately tired
- ☐ Very tired

15. How would you rate the effect of the Oral Appliance on the level of tiredness on waking:

- ☐ Large improvement
- ☐ Improvement
- ☐ Same
- ☐ Unsure

16. Since obtaining the Oral appliance has your sleeping habit changed:

- ☐ Yes. Sleep in the same room
- ☐ No Change. Still sleep in different rooms because of snoring
- ☐ No Change. Still sleep in different rooms for a reason other than snoring.

17. Have you encountered any difficulties with the appliance? Yes ☐ No ☐

18. If yes to Question 17, then which of the following side effects did you experience with the Oral Appliance (**circle relevant options**):

SIDE EFFECT	SEVERITY	FREQUENCY	DURATION
(a) Jaw discomfort			
Yes	If yes then:	If yes then:	<1 week
No	Mild	Rarely	1 week
	Moderate	Sometimes	2 weeks
If No, then go to (b)	Severe	Often	3 weeks
			>3 weeks
(b) Excess Salivation			
Yes	If yes then:	If yes then:	<1 week
No	Mild	Rarely	1 week
	Moderate	Sometimes	2 weeks
If No, then go to (c)	Severe	Often	3 weeks
			>3 weeks
(c) Dryness of mouth			
Yes	If yes then:	If yes then:	<1 week
No	Mild	Rarely	1 week
	Moderate	Sometimes	2 weeks
If No, then go to (d)	Severe	Often	3 weeks
			>3 weeks
(d) Grinding of teeth at night			
Yes	If yes then:	If yes then:	<1 week
No	Mild	Rarely	1 week
	Moderate	Sometimes	2 weeks
If No, then got to (e)	Severe	Often	3 weeks
			>3 weeks
(e) Soft tissue irritation			
Yes	If yes then:	If yes then:	<1 week
No	Mild	Rarely	1 week
	Moderate	Sometimes	2 weeks
If No, then go to Q19	Severe	Often	3 weeks
			>3m weeks

19. Any other side effects not mentioned? _____

20. Did the side effects prevent you from using the Oral Appliance? Yes ☐ No ☐

21. How would you rate your satisfaction with the appliance?

- ☐ Very satisfied
- ☐ Satisfied
- ☐ Dissatisfied
- ☐ Very dissatisfied

22. Would you like to continue to use the Oral appliance?

Yes

☐

No

☐

23. If you have now tried both appliances in this study, which appliance do you prefer?

☐

Mandubular Advancement Splint

☐

Tongue Stabilising device

Give your reasons for your preference:

Any Comments:

Thank you for your cooperation

Appendix 7.

SLEEP QUESTIONNAIRE – 2

This questionnaire pertains to the period of Appliance Use

Mandibular Advancement Splint

DATE : _____

PATIENT'S STUDY NUMBER : _____

Please consult with your spouse/sleeping partner when answering these questions.

2. In the last month, did you use the Oral Appliance – **Tick** one of the following

- ☐ Regularly: Every day of the week
- ☐ Occasionally: 3-4/week
- ☐ Rarely: 1-2/week
- ☐ Not at all

2. Do you snore while using the appliance?

Yes ☐

No ☐

If you answered No the proceed to Question 5

3. Snoring frequency: On average, how many days/nights during the last month have you snored or been told that you snore? **Tick** one of the following:

- ☐ Never
- ☐ Rarely: once/week
- ☐ Sometimes: 1-2/week
- ☐ Frequently: 3-4/week
- ☐ Almost always: 5-7/week
- ☐ Do not know

4. Snoring Intensity: During the past month has your snoring been:

Tick one of the following:

- ☐ Only slightly louder than heavy breathing
- ☐ About as loud as mumbling or talking
- ☐ Louder than talking
- ☐ So loud that it can be heard through a closed door
- ☐ Do not know

5. How would you rate the effect of the Oral Appliance on your snoring:

Tick one of the following:

- ☐ Snoring cured
- ☐ Snoring much improved
- ☐ Snoring improved
- ☐ Snoring slightly improved
- ☐ No improvement

6. Did you involuntarily remove the Oral Appliance on any night? Yes ☐ No ☐

If yes, why? _____

7. Did the Oral Appliance loosen with time? Yes ☐ No ☐

8. If you stopped using the Oral Appliance:

Why did you stop? _____

9. When did you stop?

- ☐ Less than a week after obtaining the appliance
- ☐ After 1 week
- ☐ After 2 weeks
- ☐ After 3 weeks

10. How would you grade your daytime sleepiness/fatigue in the last month (whilst using the Oral Appliance at night) for the following situations : Use the following scale to choose the most appropriate number for each situation and fill in *ALL* boxes:

(12) **Never** doze

(13) **Slight** chance of dozing

(14) **Moderate** chance of dozing

(15) **High** chance of dozing

☐

Sitting and reading

☐

Watching TV

☐

Sitting, inactive in a public place (eg a theatre, meeting)

☐

As a passenger in a car for an hour without a break

☐

Lying down to rest in the afternoon when circumstances permit

☐

Sitting and talking to someone

☐

Sitting quietly after lunch without alcohol

☐

In a car, while stopped for a few minutes in the traffic

11. How would you rate the effect of the Oral Appliance on your degree of daytime sleepiness/fatigue:

☐

Cured

☐

Improvement

☐

Same

☐

Unsure

12. How would you rate the quality of your sleep with the appliance?

Tick one of the following:

☐

Refreshing

☐

Slightly refreshing

☐

Moderately unrefreshing

☐

Very unrefreshing

13. How would rate the effect of the Oral Appliance on the quality of your sleep?

- ☐ Large improvement
- ☐ Improvement
- ☐ Same
- ☐ Unsure

14. How would you grade your level of tiredness on waking whilst using the Oral Appliance?

- ☐ Not tired
- ☐ Slightly tired
- ☐ Moderately tired
- ☐ Very tired

15. How would you rate the effect of the Oral Appliance on the level of tiredness on waking:

- ☐ Large improvement
- ☐ Improvement
- ☐ Same
- ☐ Unsure

16. Since obtaining the Oral appliance has your sleeping habit changed:

- ☐ Yes. Sleep in the same room
- ☐ No Change. Still sleep in different rooms because of snoring
- ☐ No Change. Still sleep in different rooms for a reason other than snoring.

17. Have you encountered any difficulties with the appliance?

Yes ☐

No ☐

18. If yes to Question 17, then which of the following side effects did you experience with the Oral Appliance (circle the most appropriate answers):

SIDE EFFECT	SEVERITY	FREQUENCY	DURATION
(a) Jaw discomfort			
Yes	If yes then:	If yes then:	<1 week
No	Mild	Rarely	1 week
	Moderate	Sometimes	2 weeks
If No, then go to (b)	Severe	Often	3 weeks
			>3 weeks
(b) Excess Salivation			
Yes	If yes then:	If yes then:	<1 week
No	Mild	Rarely	1 week
	Moderate	Sometimes	2 weeks
If No, then go to (c)	Severe	Often	3 weeks
			>3 weeks
(c) Dryness of mouth			
Yes	If yes then:	If yes then:	<1 week
No	Mild	Rarely	1 week
	Moderate	Sometimes	2 weeks
If No, then go to (d)	Severe	Often	3 weeks
			>3 weeks
(d) Grinding of teeth at night			
Yes	If yes then:	If yes then:	<1 week
No	Mild	Rarely	1 week
	Moderate	Sometimes	2 weeks
If No, then got to (e)	Severe	Often	3 weeks
			>3 weeks
(e) Soft tissue irritation			
Yes	If yes then:	If yes then:	<1 week
No	Mild	Rarely	1 week
	Moderate	Sometimes	2 weeks
If No, then go to Q19	Severe	Often	3 weeks
			>3m weeks

19. Any other side effects not mentioned? _____

20. Did the side effects prevent you from using the Oral Appliance? Yes ☐ No ☐

21. How would you rate your satisfaction with the appliance?

- ☐ Very satisfied
- ☐ Satisfied
- ☐ Dissatisfied
- ☐ Very dissatisfied

22. Would you like to continue to use the Oral appliance? Yes ☐ No ☐

23. If you have now tried both appliances in this study, which appliance do you prefer?

- ☐ Mandubular Advancement Splint
- ☐ Tongue Stabilising device

Give your reasons for your preference:

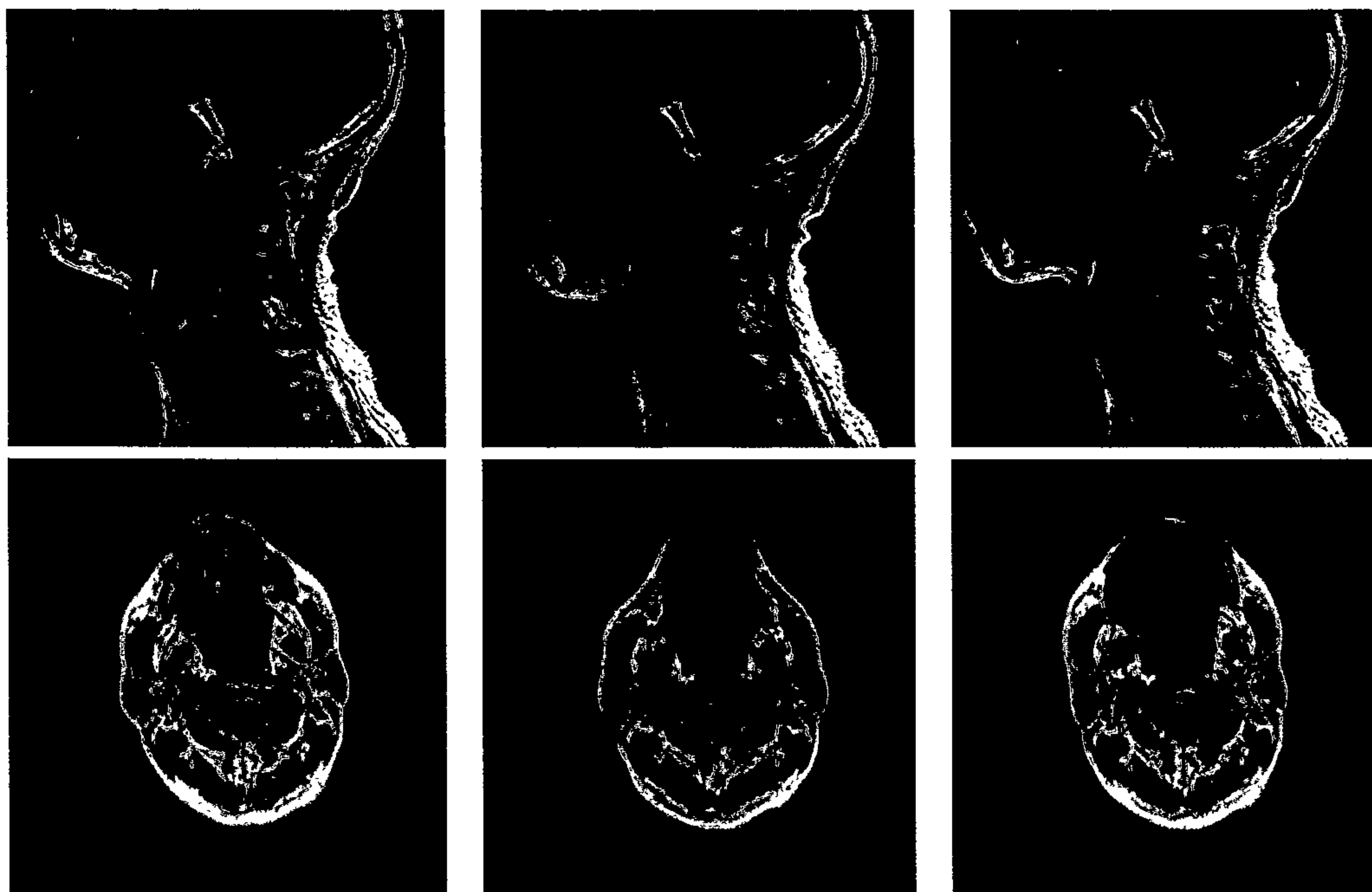
Any Comments:

Thank you for your cooperation

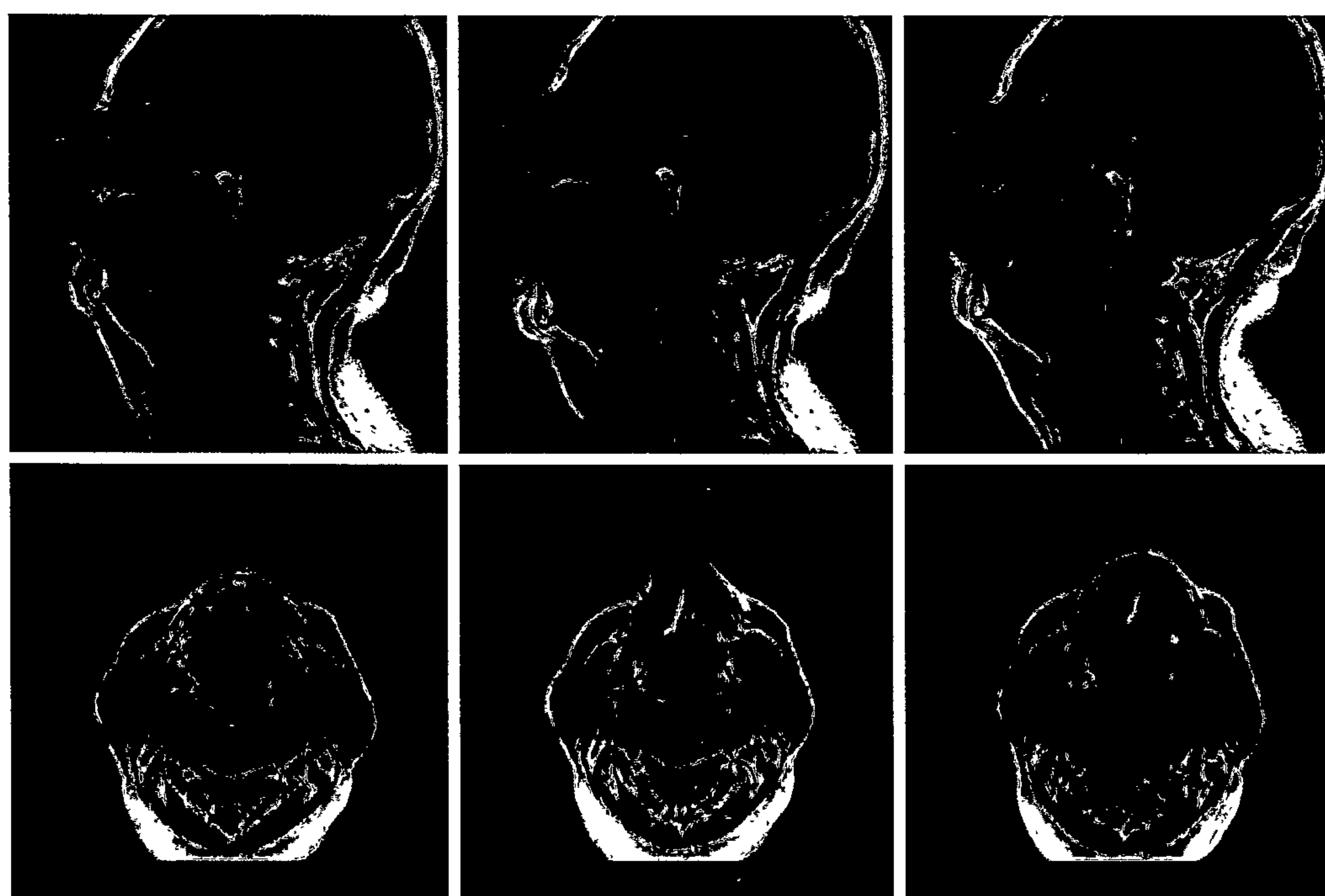
Appendix 8.

Baseline Left, TSD Centre, MAS Right

Patient 2

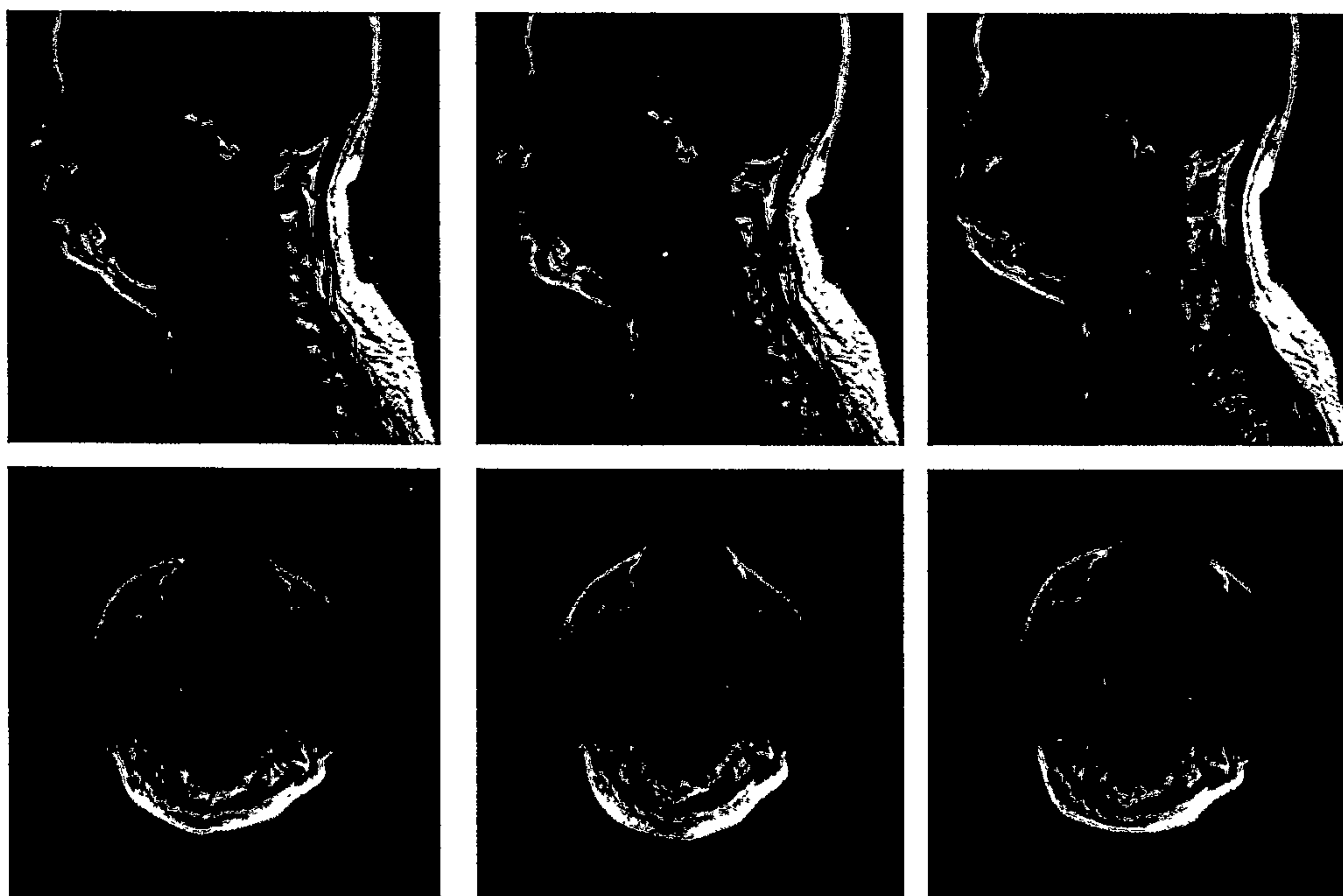


Patient 4

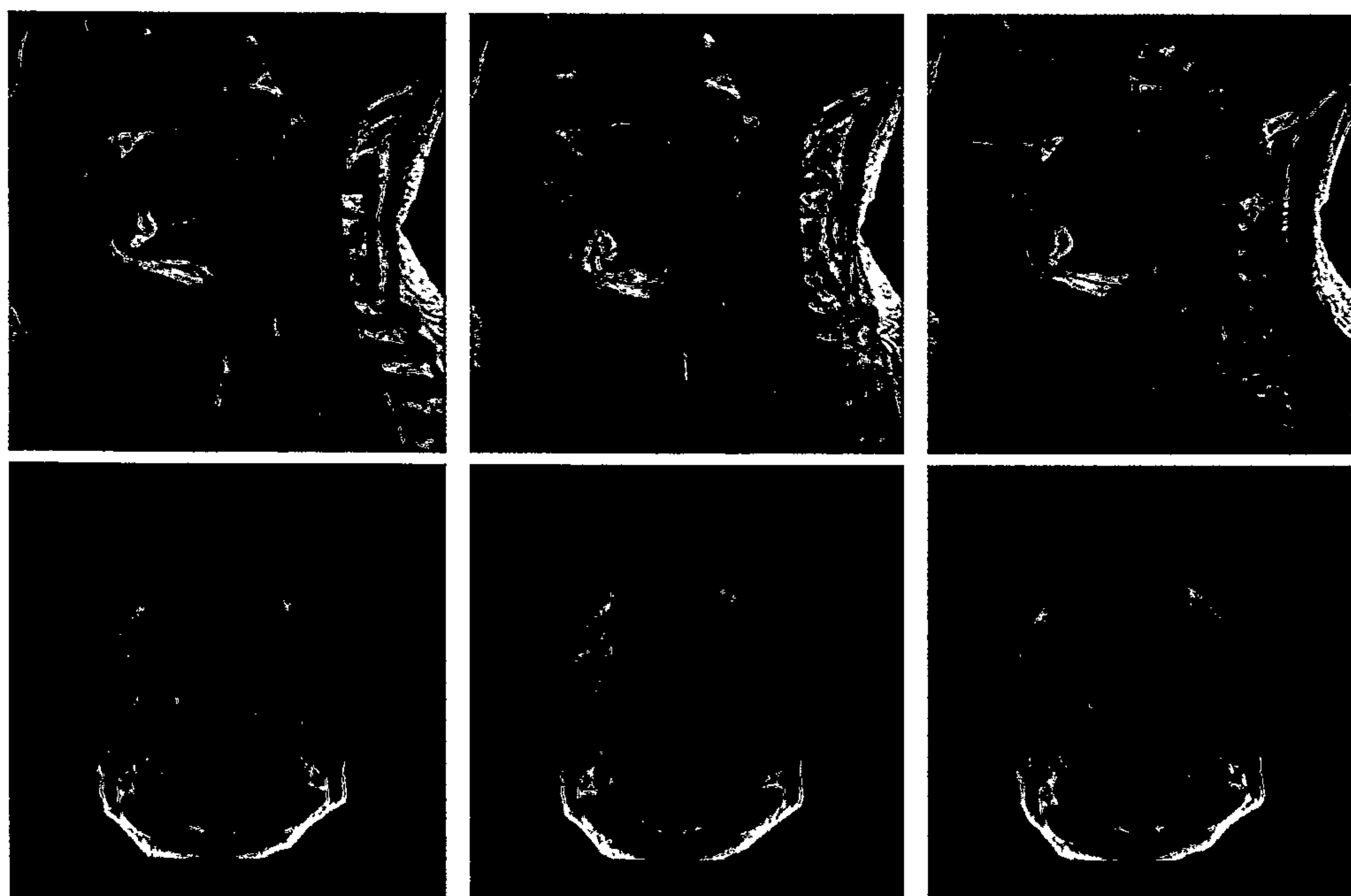


Appendices

Patient 9

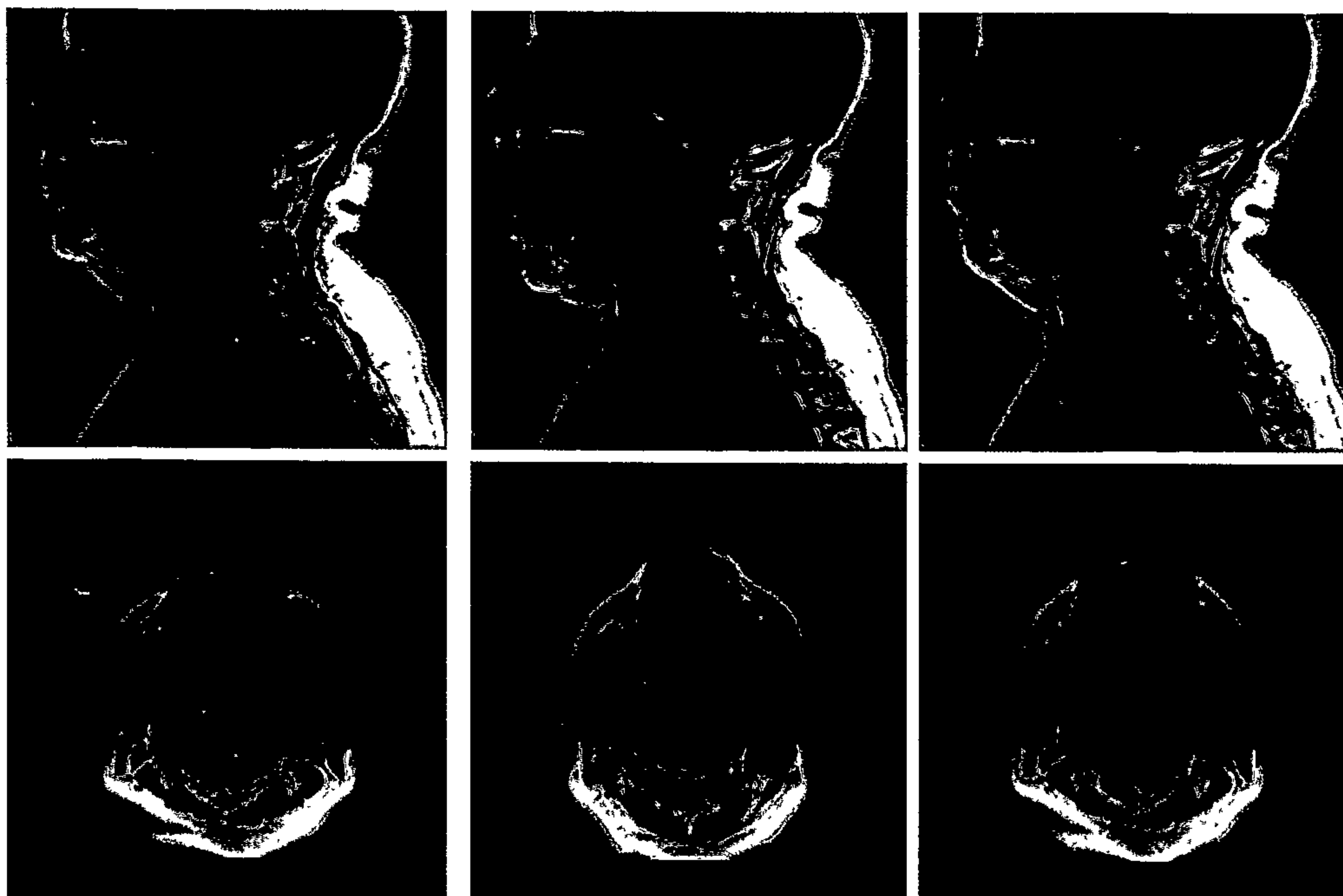


Patient 13



Appendices

Patient 14



Patient 19

