COMPLIANCE, TITRATION AND SIDE EFFECTS OF ORAL APPLIANCES IN SNORING AND OBSTRUCTIVE SLEEP APNEA PATIENTS

by

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ABSTRACT

Long-term compliance, titration modalities and side effects of oral appliances (OAs), used for the management of snoring and obstructive sleep apnea (OSA), have been investigated in a large sample of subjects. The majority of patients were compliant with OA treatment (64.1%) after a mean period of 5.7 years. The most frequent reasons why patients discontinued wear were uncomfortable (44.4%), had little or no effect (33.6%), or switched to nasal Continuous Positive Airway Pressure (23.3%). Side effects, such as dry mouth and tooth and/or jaw discomfort, were more frequent and more severe in non-compliant subjects ($p<0.05$). Subjects who were compliant with OA therapy reported long periods of use, a lower perception of side effects and a greater decrease in snoring as compared to the non-compliant. In order to improve efficacy, an apnea monitor revealed a good correlation of 0.805 with polysomnography. In the calculation of a receiver operating characteristic curve at a threshold value of apnea and hypopnea index (AHI) of 10/hour, the area under the curve was 0.915. The tested snoring monitor (based on a nasal cannula pressure transducer), when compared to a noise level meter, presented a significant correlation of 0.77 and its correlation with the AHI was $r = 0.47$ for patients with an AHI smaller than 30/h. These instruments are probably useful tools to improve the titration of OAs and consequently increase OA effectiveness. Over a mean period of 7.3 years, OAs induce changes in the dental structures that appear to be progressive over time when measured by cephalometric and study model analyses. These changes were expressed as a decrease in overbite and overjet of 2.8 and 2.6 mm respectively, retroclination of the maxillary incisors and proclination of the mandibular incisors. Interestingly, for half of those patients, the changes were considered favorable for their occlusion. Favorable changes were also correlated with a greater initial overjet. Since OSA is a life-threatening disease, OA therapy should be maximized in terms of compliance and efficacy and override the concept that only maintenance of a baseline occlusion is important. Long-term follow-up should be encouraged in all OA clinical protocols.

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LIST OF ABREVIATIONS

AASM	American Academy of Sleep Medicine
AHI	apnea and hypopnea index
BMI	body mass index
CPAP	continuous positive airway pressure
CT	computed tomography
dBA	audible decibels
ECG	electrocardiography
EEG	electroencephalography
EMG	electromyography
EOG	electrooculography
Hz	hertz
MR	mandibular repositioners
MRI	magnetic resonance imaging
nCPAP	nasal continuous positive airway pressure
OA	oral appliance
OB	overbite
OJ	overjet
OSA	obstructive sleep apnea
OSAS	obstructive sleep apnea syndrome
PSG	polysomnography
RDI	respiratory disturbance index
RERA	respiratory effort related to arousal
ROC	receiver operating characteristic
SaO_2	oxygen saturation
SC	SleepCheck
TMD	temporomandibular disorder
TMJ	temporomandibular joint
TRD	tongue retaining device
UA	upper airway
UPPP	uvulopalatopharyngoplasty

LIST OF CEPHALOMETRIC ABREVIATIONS

A	point A
ANS	anterior nasal spine
B	point B
C3	third vertebra point
Cd	condylion
Eb	base of epiglottis
Et	tip of epiglottis
Go	gonion
H1	hyoid point
H1	hyoid point
HH1	vertical position of hyoid
HYPOXA	hypopharynx cross-sectional area
IIA°	interincisor angle
L1	lower incisor
L1i	lower incisor edge
L1toMP°	mandibular incisor angle
L6	lower molar
L6c	lower molar mesial cusp tip
L6toMP°	mandibular molar angle
LFH	lower facial height
MDMH	mandibular molar height
MDUL	mandibular length
Me	menton
MP	mandibular plane
MXMH	maxillary molar height
N	nasion
NASOXA	nasopharynx cross-sectional area
OB	overbite
OJ	overjet
OP	occlusal plane
OROXA	oropharynx cross-sectional area
P	tip of soft palate
Pg	pogonio
PNS	posterior nasal spine
PP	palatal plane
PPMP°	mandibular plane angle to the palatal plane
R	roof of the pharynx
RGN	retrognation
S	sella
SN	anterior cranial base

SNA°	anteroposterior position of the maxilla
SNB°	anteroposterior position of the mandible
SNMP°	mandibular plane angle to the base of the cranium
SNPg°	chin position relative to cranium
SNPP°	palatal plane angle
SPXA	soft palate cross-sectional area
TFH	total facial height
TGH	tongue height
TH	superior tongue curve point
TNGXA	tongue cross-sectional area
TT	tongue tip
U1	upper incisor
U1i	upper incisor edge
U1toPP°	maxillary incisor angle
U1toSN°	maxillary incisor angle
U6	upper molar
U6c	upper molar mesial cusp tip
U6L6SN	maxillary molar distance to mandibular molar
U6toPP°	maxillary molar angle
U6toSN°	maxillary molar angle
VAL	vertical airway length

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CO-AUTHORSHIP STATEMENT

Dr. Fernanda Almeida had developed all five projects design, submitted the projects for ethical review, elaborated the analyses tools, collected the data, analyzed and interpreted the results and wrote the manuscripts included in this thesis.

Dr. Alan Lowe, as supervisor throughout this PhD, contributed the original design for each project, discussed data collection, analysis and interpretation, and also reviewed each of the manuscripts in depth.

Dr. C. Frank Ryan, as a sleep physician and member of my thesis committee, discussed the overall protocols and particularly interpretation of the results in Chapters 3, 4 and 5.

Dr. Najib Ayas advised me with his expertise in the development of new portable home monitors for sleep apnea, and in the interpretation of the results in Chapters 4 and 5.

Mrs. Mary Wong assisted in the development of a template for the input of the questionnaire data (Chapter 3) and aided in the development of the software for the methodology, which I required for the project in Chapter 5.

Mr. Peter Hamilton was responsible for the blinded analysis of the respiratory variables included in Chapter 4.

As part of our research group, Drs. Ryo Otsuka, Satoru Tsuiki and Sandra Fastlicht added their opinions on the establishment of the protocol and in the interpretation of the results.

To decrease the analysis error and bias in the interpretation of these variables, cephalometric and model analyses were done in conjunction with orthodontists in the Division of Orthodontics. Dr. Jung Ok Sung was responsible for the cephalometric tracings in the project cited in Chapter 6 and Drs. Sandra Fastlicht and Maryam Farbood were responsible for the model analyses in Chapter 7.

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CHAPTER 1

INTRODUCTION

1.1. Obstructive Sleep Apnea Syndrome

Obstructive Sleep Apnea Syndrome (OSAS) is a disease seen in humans and animals,[1] that is characterized by a repetitive upper airway narrowing or closure during sleep. Sleep-related upper airway (UA) narrowing is a combination of anatomical and neuromuscular factors, which results in an imbalance of the UA dilating muscle activity versus the collapsing intraluminal pressure generated during inspiration.[2] The consequences of OSAS are related to the recurrent arousals and to asphyxia.[3] The recurrent arousals and consequent sleep deprivation consequences include daytime sleepiness and an increase in motor vehicle and occupational accidents[4] as well as neurocognitive[5] and quality of life impairment.[6] The recurrent arousals lead to an autonomic nervous system activation which, together with the decrease in oxygen saturation (asphyxia), another important characteristic of OSAS, can induce systemic hypertension, pulmonary hypertension, myocardial infarction, cerebrovascular accidents, reduced libido and congestive heart failure[7-11]. Because of these health-related problems, sleep clinicians are searching for the most appropriate, effective and well-tolerated therapy approaches. The prevalence of this syndrome is estimated to affect the middle-aged population in about 4% of men and 2% of women.[12]

Respiratory Effort Related to Arousal (RERA) is considered a less severe or more subtle form of obstructive hypopnea. RERAs are characterized by a flow limitation of ten seconds or more which does not achieve a 50% reduction in flow, as hypopneas do, but promotes an arousal.[13] It has been recommended that RERA be included in the AHI analysis, but since a careful examination of the nasal cannula flow or the esophageal pressure is required, sometimes the RERA evaluation is underestimated in regular clinical polysomnography (PSG).[11] Following the decrease of the severity of the above-mentioned respiratory events,

snoring appears to be the milder and initial form of upper airway dysfunction leading to OSA.[14] As the upper airway diameter decreases, in order for the airway flow to be maintained, the velocity of the flow increases and vibrates the pharyngeal tissues, producing the snore.[15] Primary snoring, which is characterized by loud upper airway breathing sounds in sleep, without episodes of apnea, hypoventilation or arousal, has been reported to affect 40-60% of the middle-aged population.[16] There is some controversy as to whether snoring, in the absence of hypoxemia and arousal, predisposes to certain health problems previously referred only to OSAS such as hypertension and risk of stroke[17,18]. However, there is also the important social factor of snoring in that it can increase the chances of the bed partner having insomnia and depression.[19,20]

1.1.1. Diagnosis

Obstructive Sleep Apnea (OSA) can lead to an increased risk of motor vehicle crashes and cardiovascular morbidity.[4] Therapy for sleep apnea effectively treats many of these adverse consequences, thus stressing the importance of prompt diagnosis of the disease. In-laboratory overnight polysomnography (PSG) is the best test to confirm the presence of OSA and assess its severity.[21] PSG can also distinguish OSA from other sleep disorders that may have similar clinical symptoms such as central apneas, narcolepsy or periodic limb movement disorder.[11] Although PSG is the current standard diagnostic test for OSA, it is costly and cumbersome. In some centres, waiting lists to obtain a PSG can be over a year, leading to delays in diagnosis and treatment.

PSG usually consists of electroencephalography (EEG), electrooculography (EOG), submental and tibial electromyography (EMG), electrocardiography (ECG), chest and abdominal pletysmography, arterial oxygen saturation and

airflow. Cessation or reduction of the airflow of a magnitude greater than 80% for a period of ten seconds or more is the definition of an apnea, while hypopneas are defined as a decrease in flow of more than 50% with a drop in oxygen saturation greater than 3% for at least ten seconds. OSAS is defined by the sum of apneas and hypopneas per hour of sleep, the apnea and hypopnea index (AHI), and associated symptoms such as excessive daytime sleepiness.[11]

1.1.2. Management of OSA

Until the early 1980's the only treatment approach available for OSA was the tracheostomy[22]. Since then, there have been huge advances in the knowledge of sleep, sleep apnea and its treatments modalities. The treatment of OSA focuses on the decrease in daytime excessive somnolence and diminish the consequences of OSA such as hypertension and stroke by increasing the oxygen saturation and decreasing the AHI during sleep. The current available treatments for OSA can be divided into behavioral, pharmacological, medical, surgery, positive airway pressure and oral appliances[22].

The behavioral approach for OSA treatment can be applied to many sleep apnea patients and, according to the disease severity and patient individuality, a specific therapy should be customized. Obesity is related to sleep apnea, and weight loss is proven to decrease sleep apnea severity.[23] The use of alcohol and sedatives should be avoided since they have been proven to decrease pharyngeal muscle tone and therefore cause or intensify sleep apnea.[24] A supine sleeping position also has a negative effect on sleep apnea, and different approaches have been proven to alleviate this condition.[25] Although the long-term effectiveness of the behavioral management of OSA is still under discussion, it should always be addressed to facilitate the effectiveness of other therapies.

The pharmacological therapies proposed for OSA have been widely discussed; it is tempting to use a medication to cure such a complex disease. However, most treatments proposed such as medroxy progesterone, clonidine, buspirone, aminophylline, theophylline or sabeluzole showed no beneficial effects for OSA treatment.[26] Estrogen replacement seems to alleviate the symptoms of OSA in post-menopausal women but more studies in this field are still needed.[27] Most recently, the use of a wake-promoting agent, Modafenil, has been employed for patients in which excessive sleepiness remains after proper reduction of the AHI and improvement of oxygen saturation with nasal continuous positive airway pressure (nCPAP).[28] The medical assessment of hypothyroidism with thyroid replacement as a treatment for OSA is controversial. Such medications seems to have some effect on sleep apnea severity, but mostly there remains the need of an adjunctive therapy for the total reduction of the apneas.[29]

Surgical management of snoring and OSA first started with tracheostomy, but because of its intrusive nature and long-term management issues, it is currently seldom used. Adenotonsillectomy and nasal surgery, although effective in children,[30] are usually unsuccessful in the treatment of the OSA adult population.[31] In 1985, uvulopalatopharyngoplasty (UPPP) was first described by Fujita.[32] In the following years, different approaches to this procedure were developed which became very popular, all of which used the same concept of diminishing the uvula and soft palate[33] (uvulopalatal flap, laser assisted UPPP[34] and radiofrequency reduction of tissue). Since the response to the various types of UPPP decreases progressively over the years after surgery,[35,36] with some 36% success[37] in the treatment of OSA, this type of therapy has often been used for primary snoring. Although these procedures might not be totally successful for OSA, they could be complimentary to other treatments, correcting anatomical abnormalities and facilitating other interventions. With the use of more invasive jaw surgery

techniques, the effectiveness of the OSA treatment increases,[38] but because of the scope of this surgery, associated morbidity, mortality and cost, these procedures are often reserved for patients with severe OSA who are non-compliant to any other types of therapy.

Since the development of nCPAP,[39] this therapy modality has been the reference treatment for OSA and the most common form of therapy. It consists of an application of positive pressure into the patient's upper airway through a nasal, oral or oro-nasal mask. It is non-invasive and highly effective, but it is intrusive, cumbersome and there is resistance and intolerance to nCPAP use, which compromises its long-term efficacy.[40] The literature suggests failure rates for complying with treatment which range between 25 and 50%[41] and it appears that only 60% of the patients use nCPAP on a daily basis.[42] Rosenthal and collaborators[43] reported that in mild cases, only 17% of the patients opted for CPAP and 39% of those withdrew treatment after only one week. Side effects are mostly related to the mask, such as pressure sores, mask dislodgement, claustrophobia, air leakage and eye discomfort, and occur in up to 50% of OSA patients. Nasal problems such as nasal congestion, dripping and mucosal drying were observed in 15 to 45% of patients,[44] this can be corrected by heated humidifier. Still, nCPAP if worn is effective in most of the patients, normalizing the oxygen saturation, AHI and sleep architecture as well as the consequences of OSA such as daytime hypersomnolence, neurocognitive performance and hypertension.[45]

1.2. Oral Appliances

The use of oral appliances (OAs) has dramatically increased for the treatment of snoring and OSA patients. OAs are a non-invasive, simple, well

tolerated, and efficient therapy which does not require a power source. The development of this therapy represented an important step in the management of OSA.[46] A number of imaging studies using cephalometry,[47-49] videoendoscopy,[50,51] computed tomography (CT)[52] and/or magnetic resonance imaging (MRI)[53] have shown that OAs enlarge the volume and change the curvature of the upper airway by advancing the mandible forward[48,49]. OAs used as a therapeutic treatment for OSA have proven over the past 15 years to effectively treat sleep apnea patients, reducing the apnea and hypopnea index (AHI),[45,50,54-59] improving oxygen saturation during sleep, reducing snoring, and, more recently, reducing arterial blood pressure.[45,55]

1.2.1. Types of Appliances

The OAs currently used can be divided into two separate groups, the tongue retaining devices (TRDs) and the mandibular repositioners (MRs). The mechanism of the TRD is mainly repositioning the tongue in a forward position with the use of an anterior bulb, which through suction holds the tongue in a forward position. The TRD reduces the genioglossus muscle activity,[60,61] but the mechanism and significance of this effect is still unknown. This type of appliance was first described in 1982 by Cartwright and Samelson[62] and there are a few different modifications of the first TRD currently in the market: the Tongue Stabilizing Device,[63] Tongue Locking Device and the original Tongue Retaining Device. The TRD has proven to decrease the AHI from a mean of 27.4 to 11.4/h[64] and a non-significant reduction of 11/h in the AHI was seen with the Tongue Stabilizing Device.[63] Although there is only one small clinical trial comparing the TRD with mandibular repositioners,[65] it was reported that TRDs are less effective than titratable mandibular repositioners.[61,65]

The mandibular repositioner device is the most studied and frequently used type of OA. This category of appliance can be subdivided according to how they are manufactured (pre-fabricated or custom made); if they are adjustable or not (single jaw position or titratable); the material they are fabricated out of; the type of retention (only to the maxilla or both mandible and maxilla); the amount of vertical opening; and the design. With all of these variables, there are more than 80 different types of OAs on the market today. The Klearway™ appliance is the appliance most commonly used in the projects of this thesis; it is a custom-made, titratable appliance made of a thermo-sensitive resin, with retention in the mandible and maxilla and with the anterior vertical opening kept to a minimum.

1.2.2. Efficacy

A large number of studies have assessed the efficacy OAs as a treatment for OSA, eleven of those[35,45,50,54,66-72] are randomized well-designed trials. OA treatment for OSA has shown, in short term studies, to significantly reduce the severity of OSA, to improve the oxygen saturation during the night, to improve sleep architecture, to abolish or reduce snoring, [50,54,56,57,70] to decrease daytime hypersomnolence,[54,66,68] to improve neurocognitive function,[45,54] to improve the quality of life, and even to decrease arterial blood pressure.[45,55] OA use has been recommended as an alternative to nCPAP for moderate and severe OSA patients who refuse or are unable to tolerate nCPAP and as a primary treatment for mild OSA, upper airway resistance syndrome and snoring.[73] There is a tendency to stop treatment over long-term periods,[74] which decreases the effectiveness of OAs, although the efficacy, in terms of AHI reduction, does not seem to change over the years.[75] Still, an improvement in the effectiveness of OA is needed and there are

mainly two pathways; first is to find the most effective jaw position and second to improve the compliance rate over long-term periods.

1.2.3. Compliance

OA compliance might differ depending on the type of appliance, disease severity and perhaps patient management. Fransson and collaborators[76] used a one-piece appliance and reported that, after a 2 year period, 84% of the patients were still wearing the OA and 85% of those used it every night. Clark and collaborators[77] found that only 48% of patients were still wearing a two-piece appliance (Herbst) after two years, and most of those who quit did so in the first three months. McGown and collaborators,[78] using the same type of appliance, found a compliance rate of 55% over a mean period of 22 months. Pantin and collaborators[79] investigated a two-piece appliance and reported a 76% rate of compliance after 2.6 years, while Ringqvist and collaborators[74] described a decrease from 82 to 62% in compliance over a period of 2 to 4 years. Absence of primary compliance, described as less than 3 months of OA use, was described in 10.9% of the patients and body mass index was the only variable found to be correlated with compliance.[80] The main reasons for discontinuing treatment were reported to be insufficient reduction of snoring and the presence of side effects. More recently, Marklund and collaborators[75] reported a 76% compliance rate for a one-piece, titratable appliance in 630 patients. Amongst patients with non-supine dependent sleep apneas, women showed a greater treatment success when compared to men. In order to improve compliance, an increased understanding of the long-term efficacy, compliance and long-term risks of the side effects is essential to better understand this therapy and to develop a specific clinical protocol to monitor treatment over time.

1.2.4. Titration

Recently, the ability to titrate OAs over time seems to improved their efficacy.[81] This fact may be related to a dose-dependent enlargement of the UA,[47] augmentation of UA muscle activity[82] and improvement of minimum oxygen saturation (SaO_2)[83] due to mandibular protrusion. Respiratory as well as sleep variables also demonstrate a dose-dependent improvement. However, the acceptable range of mandibular advancement for each patient is not well understood, although it was reported that the maximal protrusion of the mandible enlarges the airway most.[47,84] A maximum forward mandibular position is not adequate since it can cause temporomandibular joint (TMJ) and/or muscle discomfort. Clinically, for most of the patients OSA symptoms disappear as the mandible is advanced and each patient has a comfortable forward mandibular position in which reduction or cessation of OSA symptoms is reported.

Although it is still not fully understood, there is some evidence that the amount of mandibular protrusion correlates with the efficacy of OA treatment.[71,83,85-88] There have been some attempts to titrate OAs during a one night PSG[85,88,89] but the technology is not clinically available at this point. Fleury and colleagues[86] found that the combination of oximetry and clinical evaluation improved the OA effectiveness in the follow-up PSG. Because regular clinical OA titration is still dependent mainly on subjective evaluation such as sleepiness, bed-partner reports of snoring and witnessed apneas,[90] patients often undergo more than two PSGs in order to find the therapeutic mandibular position. There can be a delay in the diagnosis of poor mandibular advancement and treatment failures. Repeated PSG recordings are the ideal method to properly titrate an OA but they are too complex and expensive.[87] Therefore the use of simple sleep apnea and

snoring monitor devices could have an important role to more rapidly assess titration and treatment outcome in OA treatment protocols.

1.2.5. Side Effects

Short-term side effects of OAs are usually described as mild and transient. Subjective side effects include dry mouth, excessive salivation, tooth discomfort, muscle tenderness and jaw stiffness, but none of those symptoms appear to lead patients to abandon treatment.[74,77,79,91-93] Problems such as pain and occlusal changes were related to discontinuation of OA use in 7.5-25% of cases.[77,79] Interestingly, a much higher percentage of tooth movement and occlusal change has been seen in objective measurements after one to four years of follow-up, but these changes were not reported as being related to treatment withdrawal.[74-76,94,95]

Several OA trials for the treatment of OSA have evaluated the possible development of temporomandibular disorders (TMD) related to the use of OAs.[77,79,96] Some authors[50,66,96-103] did not observe TMD in their studies, while other trials mentioned the appearance of TMD characterized by pain or discomfort in the TMJ region and/or chewing muscles in a small number of cases in which OA treatment was discontinued.[79,89,104-107] De Almeida[87] evaluated the TMJ with MRI over a mean period of 11.5 months and found no changes related to OA use. There is great concern with possible osteoarticular problems, pain, dental malocclusion, articular cavity and condyle deformities as a result of the mandibular advancement secondary to the use of an OA.

In a short-term analysis of adverse events during the first year of oral appliance use, Tegelberg[96] found that neither mandibular movements nor the occlusion had changed. Subjective changes in the dental occlusion were reported in 12 to 19.2% of patients.[77,79,91] Using a cephalometric analysis, various authors

evaluated craniofacial changes induced by OA use for an average of 2 to 3 years. Significant changes were reported such as a more downward[94] and forward[94,95] mandibular position, a decrease in overbite and overjet,[79,92-95] a retroclination of the upper incisors,[92,93,95] a proclination of the lower incisors,[92,95,108] an increase in the lower facial height[94,95,109] and a change in the molar relationship.[93] OA use also changes the upper airway configuration: a decrease in the palatal length and an increase in the pharyngeal area, probably related to a loss of the edema caused by snoring and repetitive apneas, have been reported.[95,110] OA therapy may be a lifelong treatment. Even though a limited number of studies have investigated OA use and their long-term side effects, a better understanding of the possible side effects and consequences is very important to improve clinical protocols and OA effectiveness.

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CHAPTER 2

HYPOTHESES AND OBJECTIVES

2.1. Long Term Compliance and Subjective Side Effects

Although a limited number of studies have investigated OA use and their long-term side effects, OAs may be a life-long treatment and a follow-up of compliance and side effects after more than five years of treatment has not yet been completed. Despite technological advances in the field, there are inadequate efforts to improve compliance and there is still a need to develop appropriate follow-up protocols for OA therapy (Chapter 3). We hypothesize that the OA compliance is good and side effects are different between patients that uses OAs and those who stop using it. Our objective is to understand of the long-term efficacy, compliance and long-term risks of the side effects could increase the comprehension of this therapy and lead to the development of a specific clinical protocol to monitor treatment over time. Therefore the objective of the first study (Chapter 3) was to utilize a mail survey to evaluate the reported compliance and side effects in snoring and OSA patients who had been treated with an OA for more than five years.

2.2. Titration Procedures

OA compliant patients had their snoring and fatigue better controlled and their bed partners were more satisfied with treatment than non-compliant patients (Chapter 3), which suggests that the compliance is related to a better treatment outcome. According to this rationale, the proper titration of an OA together with a patient's awareness of the problem could probably improve the compliance, the efficacy and therefore the effectiveness of the OA therapy. OAs are currently titrated based on clinical symptoms, but we know that clinical evaluation alone is not accurate. There have been several studies showing reasonable accuracy with

portable monitors; several of them have already been commercialized by dentists who work in the sleep apnea field, most of the time without having the accuracy formally assessed.

2.2.1. Nasal pressure recordings

Sleep Check (IM Systems Inc. Baltimore), is an example of a one channel unattended device which measures the apneas and hypopneas through a nasal cannula (Chapter 4). Preliminary studies with SleepCheck (see Chapter 4) included only a small number of patients and consequently the accuracy of this home monitor device has not yet been fully evaluated. We hypothesize that the SleepCheck accurately measures the apneas and hypopneas throughout the night. Therefore, the primary objective of the study, included in Chapter 4, was to prospectively evaluate the accuracy of this simple device, the SleepCheck, to evaluate OSA as compared to the current standard, the in-laboratory PSG.

2.2.2.Snoring Evaluation

Snoring is the most consistent sign of upper airway narrowing leading to apnea and hypopnea events. It has been widely used for the titration of OAs. Once the snoring is greatly diminished, the OA is not advanced further and a medical follow-up assessment is recommended. The PTAF Screening (Chapter 5), is another example of a one channel unattended device which measures the snoring through a nasal cannula pressure transducer (PTAF2, Protech Services, WA). The reliability of the snoring information captured in this fashion has not been rigorously compared to that obtained with sound intensity either from an ambient noise level meter or tracheal sound analysis. We hypothesized that filtering the

high frequencies from the nasal cannula could provide a precise measurement of snoring. As a potential monitor to improve OA titration, the objective of the study, included in Chapter 5, was to assess the accuracy of the snoring recorded from a nasal cannula signal compared to the snoring measured through a noise level meter and to correlate it with the apnea and hypopnea indices obtained from simultaneous in-hospital sleep studies.

2.3. Long-Term Sequelae

Another problem, which emerged from the study in Chapter 3, was that more and more patients appear to be wearing their OAs for longer periods of time. Currently, side effects have only been evaluated over relatively short time periods and a long-term clinical approach to evaluate the types of changes may be highly relevant. Using a cephalometric and study model analysis, previous authors have evaluated dental and craniofacial changes induced by OA use for an average of two to three years. These changes include a decrease in overbite and overjet, a retroclination of the upper incisors, a proclination of the lower incisors, an increase in the lower facial height and a change in the molar relationship. Although these changes were present after the two to three year time period, they did not appear to be clinically relevant. We hypothesize that adverse sequelae might be more evident with longer follow-up.

2.3.1. Cephalometric Analyses

A cephalometric radiograph is an excellent diagnostic tool and critical in the monitoring of dental and craniofacial changes. We hypothesize that the longer use of OAs could cause greater changes in the patient's craniofacial structures which could be clinically relevant. Therefore, the objective of the study in Chapter 6 was to evaluate, using cephalometric data in a sample of OSA patients, the

skeletal, dental and occlusal changes subsequent to OA therapy after five or more years of wear.

2.3.2.Study Models Analyses

The evaluation of study models is essential to assess anteroposterior and transverse changes of the dental arches and to understand the clinical relevance of the changes, such as favorable or unfavorable tooth movements. We hypothesize that longer use of an OA will cause greater changes in a patient's dentition and that for a particular set of patients, these changes might not necessarily be negative. Therefore, the objective of the study presented in Chapter 7 was to evaluate, with the use of study model analysis, occlusal changes and the type of changes (favorable or unfavorable) induced by OA therapy after more than five years.

A better understanding of the compliance, titration methods and possible side effects is highly relevant. We propose that with all of the gathered information considered together, an improved clinical protocol (Chapter 10), with specific follow-up assessments, could become more specific and relevant to actual OA wear.

CHAPTER 3

LONG TERM COMPLIANCE AND SIDE EFFECTS

OF ORAL APPLIANCES USED FOR THE TREATMENT

OF SNORING AND OBSTRUCTIVE SLEEP APNEA

3.1. Introduction

Obstructive Sleep Apnea (OSA) is a common sleep disorder affecting 4-19% of the middle-aged populations.[1,2] OSA is a progressive disease and is associated with excessive daytime sleepiness and long-term cardiovascular morbidity.[3] Oral appliance (OA) use is one successful treatment available and it has been recommended as an alternative to nasal Continuous Positive Airway Pressure (nCPAP) for moderate and severe OSA patients who refuse or are unable to tolerate nCPAP and as a primary treatment for mild OSA, upper airway resistance syndrome and snoring.[4] OA use reduces apneas as the device advances the mandible and enlarges the upper airway.[5] Randomized trials documented significant decreases in the Respiratory Disturbance Index (RDI) and sleepiness, confirming the effectiveness of this therapy for OSA.[6-13] Recently, two studies have reported that OAs significantly improve oxygen desaturation and reduce systemic blood pressure in OSA patients.[14,15]

CPAP is the most common form of therapy and is highly effective for OSA but there is resistance and intolerance to CPAP use, which compromises its long-term efficacy.[16] The literature suggests failure rates for complying with treatment that range between 25 and 50%[17,18] and it appears that only 60% of the patients use CPAP on a daily basis.[19] Rosenthal and collaborators[20] reported that in mild cases, only 17% of the patients opted for CPAP and 39% of those withdrew treatment after only one week. Side effects such as pressure sores, mask dislodgement, claustrophobia, air leakage and eye discomfort occur in up to 50% of OSA patients. Nasal problems such as nasal congestion, dripping and mucosal drying were observed in 15 to 45% of patients.[21]

OA treatment also exhibits problems with compliance and side effects. OA compliance might differ depending on the type of the appliance, disease severity

and perhaps patient management. Within a period of approximately two years compliance rates with OA ranged from 48 to 84%[22-28]. A greatest percentage of non-compliant patients were revealed in the first three months[22] with 82 to 62% reductions in compliance over a period of 2 to 4 years[26]. The main reasons for discontinuing treatment were reported to be insufficient reduction of snoring and the presence of side effects[22-27]. Neither supine-dependent sleep apnea, age, obesity, gender or sleepiness seem to be related to OA tolerability.[28]

Short-term side effects of OAs are usually described as mild and transient. Subjective side effects include dry mouth, excessive salivation, tooth discomfort, muscle tenderness and jaw stiffness, but none of those symptoms appear to lead patients to abandon treatment.[23-25,29] Problems such as pain and occlusal changes were related to discontinuation of OA use in 7.5-25% of cases.[23,25] Interestingly, a much higher percentage of tooth movement and occlusal change has been seen in objective measurements after one to four years of follow-up, but these changes were not reported as being related to treatment withdrawal.[22,26,30-32]

Although a limited number of studies have investigated OA use and their long-term side effects, OAs are a life-long treatment and a follow-up of side effects after more than five years of treatment has not yet been completed. An increased understanding of the long-term efficacy, compliance and long-term risks of the side effects is essential to better understand this therapy and to develop a specific clinical protocol to monitor treatment over time. The purpose of this study was to utilize a mail survey to evaluate the reported compliance and side effects in snoring and Obstructive Sleep Apnea patients who had been treated with an OA for more than five years.

3.2. Methods

This was a questionnaire-based survey developed to evaluate long-term OA treatment. All 544 patients who had been treated with an OA for snoring and/or OSA at The University of British Columbia or in the orthodontic practice of one of the authors (AAL), between February 1989 and June 2001, were included in this study. One copy of the questionnaire was sent by mail to each patient (see Appendix A). In the cover letter, it was explained that their participation in the study was entirely voluntary and that the patient could refuse to answer without any consequences to their continuing medical or dental care. A postage-paid, self-addressed reply envelope was included. If the patients did not answer, a second and a third copy were sent after one month intervals. Patients were asked to identify themselves at the end of the survey if they wished. The study was approved by the Behaviour Research Ethics Committee of The University of British Columbia.

Within the period mentioned above, the family and/or sleep doctors had primarily referred patients for OA therapy if the patient was a snorer or had mild sleep apnea without associated comorbidities such as sleepiness or health related issues, or moderate to severe patients who were not compliant with CPAP therapy. The Sleep Apnea Dental Clinic always required a physician's referral prior to OA insertion, and then treated these patients according to certain protocols which included: selecting the proper type of OA, titrating into the optimum jaw position as evaluated subjectively by the dentist and bed-partner, and then referring the patient back to the physician for follow-up. Depending on the severity of each case and the accessibility of PSG, patients were reassessed with overnight PSG or oximetry only. If there was a positive but insufficient reduction in the AHI, attempts were made to further titrate the OA with one more follow-up evaluation.

This clinical protocol requires 2 to 10 months depending upon the patient, and they were encouraged to return after their doctor's post-titration evaluation of treatment and every two years after this date. There were no systematic follow-up letters or procedures.

A specially-designed self-reported questionnaire was created with select questions from previous studies.[23-25] From the patient's chart, a database was compiled and objective information on gender, age, body mass index (BMI), baseline and OA Respiratory Disturbance Index (RDI) was collected. RDI was defined as the apnea and hypopnea index from full night polysomnography or an oxygen desaturation index greater than 4% per hour from an overnight oximetry study. The disease severity was categorized following the standards proposed by AASM[33] as snorer for an RDI < 5, mild OSA for $5 \leq$ RDI <15, moderate for $15 \leq$ RDI < 30 and severe for RDI $\geq$ 30. Compliance for OA therapy was divided into the number of nights per week and percentage of each night of OA use. If patients stopped wearing their appliance, they were asked the number of months they had used the appliance for and to specify the reasons why they had stopped. The date of first appliance insertion and the type of the current or last appliance used was added to the data analysis. Questions regarding sleepiness (Epworth Sleepiness Scale[34]) before and under OA therapy, amount of change in the snoring, apneas, daytime fatigue and bed partner's subjective satisfaction were also included.

A 14 symptom questionnaire for the evaluation of possible side effects while under OA therapy was initially scored as present, or not present, and then according to frequency as rarely (1), sometimes (2) or often (3) and in terms of severity as mild (1), moderate (2) or severe (3). The maximum score per question was then 6 and the total maximum score per patient was 84 (14 questions x 6). If the patients answered any of the questions in this section, the blank ones were considered as an absence of the symptom (score 0), but if the whole section was

left blank it was considered as missing data. A questionnaire for TMJ symptoms was included with 13 questions and each absent symptom was scored as a zero (0) and each present symptom scored as one (1), the maximum score then being 13. All data was entered into a template; questions with multiple answers were scored under the "worst case scenario" and written answers were interpreted and converted into a code by one of the authors (FA). Gender differences were evaluated according to age, BMI, baseline and post-titration RDI, improvement of snoring, and amount of general and TMJ side effects.

Statistics analysis was performed using SPSS software program (Chicago, IL). Data was presented as percentages or as means ± standard deviation (SD). To assess statistical significance before and after treatment, a paired Student's t-test was used. To compare the non-returned, users and non-user groups, an analysis of variance (ANOVA) was conducted. Changes of symptoms before and during treatment were analysed with a Wilcoxon's paired matched test or a Yates Corrected Chi-square test. Differences between users and non-users were evaluated using the Fisher exact two-tail test. Correlations (r) were carried out with Pearson correlation tests for parametric variables and Spearman correlation tests for non-parametric variables. A P value of <0.05 was considered significant.

3.3. Results

All patients were referred for OA treatment by sleep physicians, otolaryngologists or family physicians because of a confirmed diagnosis of OSA and/or disturbing snoring. Of the 544 surveys mailed, 251 (46.1%) of the patients returned the questionnaire. Of the non-returned surveys (53.7%), 0.9% had deceased, 15% were returned with an invalid address and 37.8% were not returned. Out of the group that returned the questionnaire, 161 (64.1%) were still

wearing their OA (users) and 90 patients (35.9%) had stopped treatment (non-users). The mean and standard deviation time period between oral appliance insertion and the return date of these surveys was 5.7 ± 3.5 years (range 0.11-16.5 y). This interval was significantly smaller for the users (3.8 ± 3.2 y) (range 0.19-16.5 y) than the non-users (6.2 ± 3.3 y) (range 0.21–13.2 y) and the non-returned group (6.7 ± 3.4 y) (range 0.11–13.2 y). Of the initial 544 patients, 80.5% were male and 19.5% female; the gender distribution (male/female) for the non-returned, users and non-users groups were 80.3/19.7%, 84.2/15.8% and 74.7/25.3%, respectively. The mean age of the entire sample was 49.7 years and the mean BMI was 29.0 kg/m^2; both characteristics presented similar values in the non-returned, users and non-users groups. We did not have access to 34 of the 544 polysomnography (PSG) or oximetry studies performed prior to the beginning of treatment. The baseline RDI of the entire sample was 29.2 ± 20/h; the non-returned group showed a mean baseline RDI of 30.2 ± 20.4/h while users and non-users showed baseline RDIs of 28.6 ± 19.2/h and 31.9 ± 19.7/h, respectively. The distribution according to disease severity showed a greater percentage of patients at baseline in the moderate to severe range (Figure 3.1). None of the groups were significantly different from each other with regards to sleep apnea severity, age, BMI, baseline and post-titration RDI or gender. The RDI with OA use significantly improved in all groups. The demographic data of these groups is provided in Table 3.1.
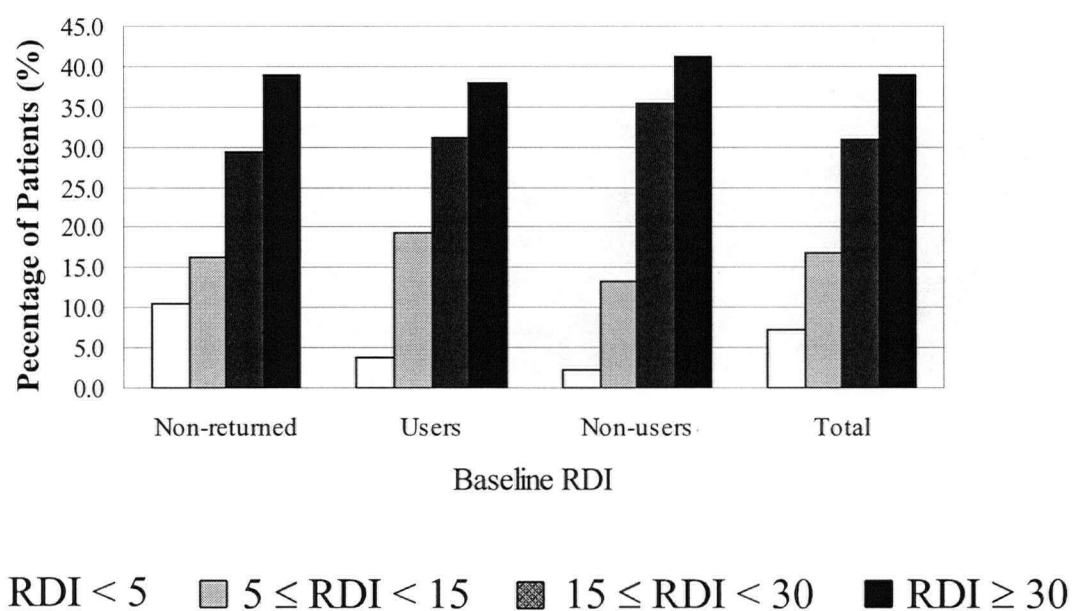
Figure 3.1. Baseline RDI severity (%) in the non-returned, user and non-user groups. There was no statistically significant difference between the severity distribution

Table 3.1. Baseline demographic characteristics for the total sample, non-returned, user and non-user groups. There was a significant difference between baseline and post-titration RDI (* p<0.05), but no differences within the sub-groups.

	Total Sample	Non-Returned	Users	Non-users
n	544	293	161	90
Age (years)	49.7 ± 10.6	48.8 ± 11.1	50.6 ± 9.7	51.5 ± 10.2
BMI (kg/m^2)	29.0 ± 5.2	29.1 ± 5.2	29.0 ± 5.5	28.6 ± 4.6
Baseline RDI (/hr)	29.2 ± 20.0	30.2 ± 20.4	28.6 ± 19.2	31.9 ± 19.7
Post-titration RDI (/hr)	16.3 ± 14.9 *	16.1 ±15.4 *	15.4 ±13.9 *	19.8 ±16.6 *

Within the users, 82.3% reported wearing the OA every night and 10.3% used it 4-6 nights/week. Some 90.3% wore it for the whole night and 9.7% for more than half of each night. Some 18% of the non-users stopped wearing their appliance during the first month, 32% in the following 6 months and another 22% before the end of the first year. The remaining 27% of non-users withdrew treatment after 1 to 4 years of use as illustrated in Figure 3.2. As shown in Table 3.2, the most frequent reasons why patients discontinued wearing the OA were that it was uncomfortable (44.9%), had little or no effect (36.0%), switched to nasal Continuous Positive Airway Pressure (23.6%) or had experienced a dry mouth (20.2%). A higher BMI was related to the choice to switch to CPAP, but it was not correlated to baseline or follow-up RDI. Reasons such as uncomfortable and inconvenient were present more frequently in patients who stopped treatment within six months of OA use and changes in occlusion was more frequently pointed out by patients who used their appliance for periods longer than 6 months. Some 18% underwent some form of surgery for snoring or OSA. Regarding the type of OA, 52 patients (9.4%) received an appliance other than Klearway™ in the entire sample; 17 of those were TRD and 25 were other mandibular repositioners (MRs). In the users group, there were 3 TRD, 3 MRs and 154 Klearway™ appliances; in the non-users groups there were 9 TRD, 15 MRs and 66 Klearway™ appliances. The number of appliances used other than Klearway™ was statistically higher in the non-user group.

Table 3.2. Percentage of patients that indicated specific reasons to discontinue OA use.

	% of patients
Discomfort/cumbersome	44.9
No/little effect	36.0
Started CPAP	23.6
Mouth became too dry	20.2
Inconvenient to use	18.0
Painful	15.7
Dental work changed	15.7
Occlusion/jaw changes	12.4
Appliance doesn't fit any more	7.9
Lost weight, apnea lessened	7.9
Claustrophobic	5.6
Could not swallow	5.6
Apnea worsened	2.2
Lost the appliance	1.1
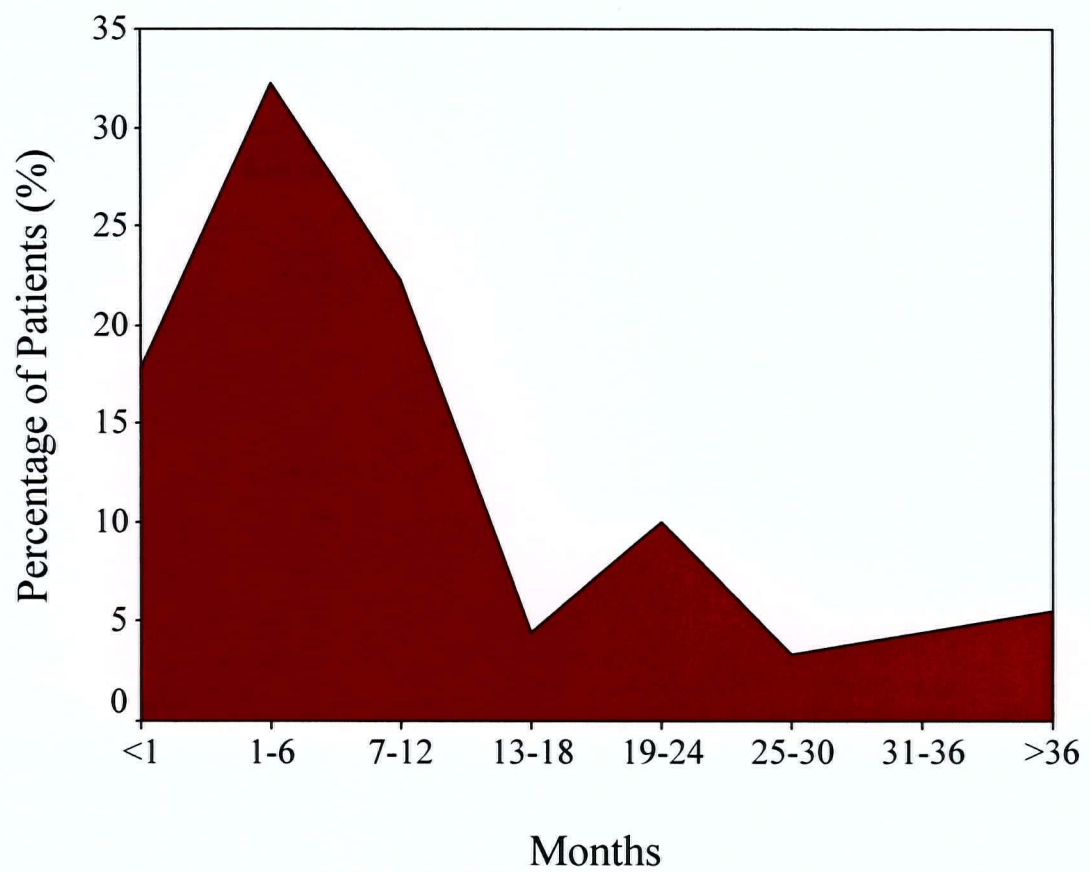
Figure 3.2. Percentage of patients who discontinued OA use according to duration (months) of wear.

At the time of this survey, 69.3% of users and 36.2% of non-users had a PSG or oximetry with the OA in place. The interval between the baseline and follow-up PSG varied from 5 months to 4 years. We had access to follow-up records in 43% of users, 20% of non-users and 26% of the non-returned group. The mean RDI with the OA in place was significantly reduced in all groups from 28.6 ± 19.2/h to 15.4 ± 13.9/h for users, from 31.9 ± 19.7/h to 19.9 ± 16.6/h for non-users and from 30.2 ± 20.4/h to 16.1 ± 15.4/h for the non-returned group. The baseline RDI was significant correlated with the Epworth Sleepiness Scale (ESS) from the pre-treatment questionnaire ($p<0.001$). ESS scores for users and non-users before treatment were similar (Table 3.3). A significant improvement in ESS was found in both groups and there was no improvement difference between the groups. The snoring was satisfactorily controlled in 75.6% of users and it was statistically less controlled in non-users (43.2%). Similar significant results were reported regarding subjective improvement of apnea and fatigue; satisfactorily controlled in 59.4 and 71.2% of users and 26.7 and 25.5% of non-users, respectively. Bed partner's satisfaction with the treatment outcome was significantly higher in users ($p<0.05$). A subjective assessment of the sleep apnea and related symptoms are provided in Table 3.3.

Table 3.3. Subjective treatment outcome
characteristics of user and non-user groups.
* p<0.05

	Users	Non-users
Baseline ESS	11.0	11.1
ESS with OA	7.0	8.1
% of patients snoring controlled	75.6	43.2*
% of patients apnea improved	59.4	26.7*
% of patients fatigue improved	71.2	25.5*
% of bed partners satisfied	82.2	46.4*

With all side effects plotted together, 46% of the users and 59.1% of the non-users reported the presence of one or more side effects (Table 3.4). From a total of 14 side effects, the mean number of side effects present per patient was statistically higher in the non-users when compared to users: 9.1 ± 4.3 and 6.6 ± 3.3 side effects, respectively. A significantly greater percentage of the users, when compared to the non-users, experienced less side effects such as difficulty chewing with the back teeth; dry mouth; morning headaches; teeth apart in the morning; tongue discomfort; jaw discomfort; gum discomfort; sense of suffocation; movement of one or more teeth; and movement of the teeth so that the upper and lower jaws no longer meet properly. Side effects such as dry mouth and tooth and/or jaw discomfort were more frequent in non-users. Non-users scored higher for the following side effects: tongue discomfort, sense of suffocation and movement of one or more teeth (p<0.05). After OA therapy, 42.7% of the patients in the non-users group classified their side effects as moderate to severe, compared to 32.8% of the users. The incidence of TMJ symptoms was calculated as less than one symptom per patient in the pre-treatment evaluation and it changed significantly for users and non-users while under OA therapy, but there was no difference between the groups.

The percentage of males who stopped using the OA out of the males who returned the questionnaire was 32.8% while for females this percentage was 46.8%. In the assessment of OSA, men were statistically more severe at baseline than women. Women reported a significantly smaller reduction in their snoring and showed higher scores in the evaluation of the side effects related to OA use (p<0.05) (Table 3.5). There were no significant gender differences according to the percentage who stopped using the OA, age, BMI, post-titration RDI, baseline and an increase in TMJ symptoms.

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Table 3.4. Differences between OA users (U) and non-users (NU) expressed as percentage of patients who never experienced a specific side effect and the frequency and severity of those who did report side effects. *p<0.05

	Never		Frequency						Severity					
			Rarely		Sometimes		Often		Mild		Moderate		Severe	
	U	NU	U	NU	U	NU	U	NU	U	NU	U	NU	U	NU
a. Difficulty chewing in the morning (%)	45.8	37.1	18.1	5.6	13.5	6.7	18.7	11.2	24.0	10.1	14.3	7.9	5.8	4.5
b. Difficulty in chewing with back teeth (%)	51.6	36.0 *	14.8	6.7	15.5	6.7	14.2	12.4	20.0	9.0	13.5	9.0	5.8	5.6
c. Excessive salivation (%)	31.0	31.8	14.2	11.4	28.4	11.4	20.0	9.1	24.5	12.4	20.6	9.0	3.2	3.4
d. Dry mouth (xerostomia) (%)	36.1	18.2 *	20.6	13.6	22.6	17.0	14.2	20.5 *	23.2	11.2	16.8	18.0	3.2	10.1 *
e. Morning headaches (%)	59.4	39.3 *	16.8	5.6	16.1	10.1	2.6	2.2	18.1	11.2	9.0	6.7	0.6	0.0
f. Tooth discomfort (%)	26.5	18.0	24.5	6.7	28.4	19.1	14.8	22.5 *	40.0	5.6	13.5	25.8	1.9	9.0 *
g. Teeth apart in the morning (%)	52.3	25.0 *	13.5	6.8	5.8	8.0	12.3	11.4	16.2	10.1	7.8	9.0	2.6	3.4
h. Tongue discomfort (%)	58.7	33.0 *	14.2	6.8	16.1	9.1	5.8	8.0	16.1	3.4	8.4	14.6	2.6	4.5 *
i. Jaw discomfort (%)	33.5	16.9 *	26.5	6.7	28.4	28.1	8.4	19.1 *	29.7	13.6	15.5	25.0	3.9	11.4 *
j. Gum discomfort (%)	51.3	32.6 *	27.3	11.2	11.0	10.1	2.6	1.1	21.3	7.9	11.0	5.6	0.6	2.2
k. A sense of suffocation (%)	74.8	42.7 *	10.3	6.7	8.4	7.9	0.6	3.4	11.6	4.5	3.9	9.0	0.0	2.2 *
l. Movement of one or more teeth (%)	59.6	31.5 *	13.1	5.6	9.2	4.5	9.2	12.4	14.8	2.3	7.1	9.1	3.9	3.4 *
m. Movement of the teeth so that upper and lower jaws no longer meet properly (%)	47.7	29.2 *	10.5	3.4	9.2	9.0	17.0	12.4	16.8	7.9	8.4	9.0	7.1	7.9

Table 3.5. Gender differences in the returned sample. *p<0.05

	Male	Female
Stopped treatment (%)	32.8	46.8
Age (years)	50.9	50.7
BMI (kg/m^2)	28.3	31.9
Baseline RDI (/h)	31.8	21.3 *
OA RDI (/h)	17.6	9.3
Snoring controlled (% patients)	68.8	51.2 *
Side Effects (frequency+severity 0-84)	16.2	20.6 *
Baseline TMJ symptoms (score 0-13)	0.8	1.4
Increase TMJ symptoms (score 0-13)	1.3	1.9

3.4. Discussion

This questionnaire-based study presented a response rate of 46.7%. The returned and non-returned groups had no differences with respect to apnea severity, sex, age or type of appliance used, and therefore the 251 snoring and/or sleep apnea patients who returned this survey were analyzed as being representative of our clinic population. After a mean of 5.7 years, 35.9% of the patients stopped OA treatment (non-users); 72% of those did so during the first year of treatment. All groups showed a significant reduction in RDI and sleepiness. OA users had their snoring and fatigue better controlled and their bed partners were more satisfied with treatment than non-users.

We anticipated lower compliance among the severe cases due to the possible reduced efficacy of the OA in those cases, but the present results demonstrate that neither disease severity nor baseline sleepiness were predictors of OA compliance. When compared to CPAP studies, the OSA severity of patients in our study is less severe, although 69% of the patients were in the moderate to severe range. OAs are effective for snoring and mild cases, but for moderate and severe cases the success rate ranges only from 35 to 60%.[14,35] The percentage of patients referred for OA therapy with an RDI less than <20/hour has been reported to be as high as 59 to 72%.[25,28] In contrast, our sample showed that only 36.4% of the patients had an RDI <20/hour, which suggests that most were CPAP failures. In this sense our sample was biased, since these patients were already in a second type of treatment approach. This could be related to a more symptomatic population and/or patients with a greater understanding of the present disease consequences. Because of the expertise of the UBC group in the OA field, the referrals to OA therapy in this setting might be biased toward more complicated cases and the greater percentage of patients complaining of the lack of OA

efficacy in the present study could be explained by the severity of the patients evaluated. Marklund and collaborators[28] evaluated a less severe population and reported that 22% of the patients who discontinued treatment reported a poor effect on snoring. Patients tended to discontinue OA treatment in this report not only due to side effects, but also because some 35% of the non-users reported little or no effect of the OA. The rate of non-compliance was not correlated to the baseline OSA severity or sleepiness similar to data described by McGown and collaborators.[24] Since there are different devices that have been used by different clinicians, the generalizability of these results towards more severe sleep apnea populations should be interpreted with caution, and further studies with less population bias are still needed.

Failure to comply with CPAP treatment has been reported to be 83% in mild apneics[20] and resistance to this type of therapy has been described to be as high as 25 to 50% in the general sleep apnea population.[17,18] Although the present study was based on self-reported compliance, users reported good compliance for more hours per night (90.3% use it all night) and more days per week (82.3% use it every night). McGown and collaborators[24] found similar results with patients using the OA for a mean period of 6.6 hours after a 22 month period. The treatment compliance rate after a mean period of 5.7 years in this study was 64.1%, which appears to be a well-accepted treatment modality for this type of disease. The present study results are in agreement with previous reports in which the compliance rates for the first year range from 48-84%[22,23] and drop after more than 4 years to 62%-76%.[26,30] Since this is survey data, all the non-returned questionnaires could be interpreted as compliance failures and then the compliance rate of the OA should drop to 29.3%. However, we did rely on a representative response of the questionnaires, and since there were no differences between the returned and non-returned questionnaires regarding apnea severity, sex, age or

type of appliance used, we have considered the OA compliance to be 64.1%. Our study relied on subjective questionnaires with obvious limitations, which could be an overestimation of OA use. With the use of a temperature-sensitive compliance monitor, a mean OA use of 6.8 hours/night was documented,[35] but long-term objective OA compliance data is still unavailable. Low levels of compliance have been suggested to decrease the effectiveness of CPAP.[36] It is still unclear whether OAs, even though less effective than CPAP, could achieve the same effectiveness if used for more hours per night. Although the majority of our moderate to severe cases were CPAP failures, 23% of non-users did switch back to CPAP after the OA trial. From our analysis, the higher the BMI, the more likely the patient was to accept CPAP treatment after OA failure, but there was no correlation with RDI.

In the group that discontinued treatment (non-users), 27% wore an appliance other than Klearway™ compared to 1.5% in the users group. Even though the number of patients wearing an OA other than Klearway™ was small, we found a statistically better tolerance with this appliance. Pitsis and collaborators,[37] in a randomized controlled trial, reported that patients had a higher preference for OAs with a smaller degree of opening. The degree of mandibular advancement has a positive correlation with the efficacy of the OA.[38,39] Appliances with a design similar to Klearway™ have shown comparable compliance rates,[22,23] but there is still a need for longer clinical trials with the same clinical management to compare different types of OAs. Although there are no large clinical trials comparing TRD with mandibular repositioners, it was reported that TRD are less effective than titratable mandibular repositioners.[40,41] TRDs may be more difficult to wear and tolerate, as evidenced by the 75% of the TRD patients in this study who discontinued treatment.

Although our study was retrospective, it is interesting to evaluate side effects at different intervals of OA use. As shown previously, we also found that,

when compared to users, non-users reported a significantly greater number of side effects per patient,[24] more frequent and severe dry mouth, tooth and/or jaw discomfort, and more severe tongue discomfort, sense of suffocation and movement of teeth, also excessive salivation is a short-term side effect which tends to improve over time.[23,29,30] In the evaluation of non-users, our data suggests that patients who feel uncomfortable with the appliance and experience more side effects tend to stop using it sooner. Patients who are able to use it for longer periods might have experienced milder problems, which encouraged them to get used to wearing the appliance. Otsuka and collaborators[42] reported an objective decrease in occlusal contact and bite force in the morning after OA use. Interestingly, our patients reported that difficulty chewing with the back teeth or in the morning decreased with the longer use of an OA. According to patient reports, subjective benefits of OA therapy outweigh these side effects and patients did not perceive most tooth movements unless their dentist brought it to their attention.[29] As expected, with only a subjective evaluation of the side effects, the current study found less dental changes than the above-mentioned authors. For non-users, occlusal changes given as a reason to discontinue treatment showed a positive correlation with increasing length of OA use and appear to be an important reason only after a year of OA use. We hypothesize that some patients adapt to this type of side effect, changing their eating habits in the morning or their masticatory pattern, because it is unlikely that such a side effect would decrease over time. Of the 14 side effects investigated in this survey, 50% of users and 54% of non-users reported no side effects. The difference in long-term use seems to be related not only to the number of side effects[24] but also to the impact of the side effects, since non-users experienced more frequent and more severe side effects, as shown by reporting their side effects to be more in the moderate to severe categories.

TMJ symptoms increased with OA use but were not related to the discontinuation of treatment or gender. In contrast to previous studies,[23,25] we could not find a higher incidence of TMJ discomfort in early treatment, but this could be because of the retrospective nature of this study. Similar to TMJ disorder incidence studies,[43,44] women in our sample had more TMJ complaints, but OA use did not show any different increase in those symptoms when compared to men. Since the questionnaire used for the TMJ assessment had some questions that represent common side effects of OAs as well as TMJ symptoms, we interpret the increase of a mean of 1.3 symptoms to be potentially related only to occlusal changes with respect to OA use.

Females experienced more side effects and seem to have a greater tendency to abandon treatment than males as 46.8% of the females who answered the survey had discontinued use it compared to 32.8% of males. Although women are more likely to have treatment success,[28] we discovered that a higher percentage of women discontinued treatment. Considering no differences between genders according to age, BMI or sleepiness, women's non-compliance may be related to a greater perception or presence of side effects.

The present study has several potential limitations. The response sample was considered representative and it may have resulted in a sample bias in favour of a good response to OA therapy. As a retrospective study, we have to consider that the data was collected from different patients at different time intervals, and longer and larger-sample prospective studies on OA use are required. With regards to the different OA types, the expertise of the dental staff in this study was higher with the Klearway™ appliance and cross-over studies could be more reliable. As a retrospective study, we did not have access to polysomnography records for all subjects, but this might be representative of the majority of clinics dealing with sleep apnea patients. A questionnaire-based survey always evaluates subjective

symptoms since it is the nature of such protocol, but it is still of great importance in the assessment of a large number of patients to gain an overall understanding of compliance and side effects. Despite the numerous types of OAs and the new development of titratable appliances, dentists in the sleep field may not be fully aware of the need for educational intervention and to include, based on this study, a more aggressive follow-up protocol to improve compliance, reduce side effects and consequently increase the effectiveness of OA therapy.

3.5. Acknowledgements

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CHAPTER 4

NASAL PRESSURE RECORDINGS TO DETECT

OBSTRUCTIVE SLEEP APNEA

Nasal Pressure Recordings to Detect Obstructive Sleep Apnea. Almeida FR, Lowe AA, Otsuka R, Hamilton P, Ryan CF, Ayas N.

4.1. Introduction

Obstructive Sleep Apnea (OSA) is a commonly under-diagnosed disorder characterized by repetitive collapse of the upper airway during sleep leading to nocturnal desaturation, sleep fragmentation, daytime sleepiness, an increased risk of motor vehicle crashes and cardiovascular morbidity. Therapy for sleep apnea effectively treats many of these adverse consequences, thus stressing the importance of prompt diagnosis of the disease. In-laboratory overnight polysomnography (PSG) is the best test to confirm the presence of OSA and assess its severity.[1] A PSG can also discriminate OSA from other sleep disorders that might have similar clinical symptoms such as central apneas, narcolepsy or periodic limb movement disorder.[2] A PSG is the gold standard diagnostic test for OSA, however it is costly and cumbersome. In some countries, waiting lists to obtain a PSG can be over a year, leading to delays in diagnosis and treatment. Therefore, there is a clear need for less expensive ambulatory devices that can accurately diagnose OSA.

A variety of ambulatory devices to diagnose OSA have been developed. There have been several studies showing reasonable accuracy of portable monitors classified according to the AASM task force[2] as type 4 (includes only one or two channels of physiologic signals and generally uses only one channel, either SaO2 or airflow, to define a sleep disordered breathing event; no EEG signals are monitored). Each of the methods used a different methodology to evaluate the severity of sleep apnea, such as oximetry;[3-5] oximetry and nasal airflow[6-9] (Autoset™, ResMed, Sydney, Australia); peripheral arterial tonometry, oximetry and actigraphy[10,11] (Watch-PAT); airflow, body position, wrist actimetry, pulse rate and oxygen desaturation[12] (Apnoescreen-I); oral and nasal thermistor[13] (SleepStrip™); microphone and nasal airflow[14] (SNAP); or tracheal sound

analysis.[15] These screening modalities are feasible for an ambulatory setting in which physicians treat sleep-related breathing disorders. Most of them require a computer to analyze the data, and while some are disposable, they still involve a high complexity in the interpretation of the results and are also expensive. For most dentists who treat OSA patients in their private practice settings, such types of sleep apnea evaluation may not be realistic.

A most important role of these screening devices has been to more rapidly assess titration and/or treatment efficacy. Several of these devices have already been commercialized to dentists who work with sleep apnea, often without having their accuracy formally assessed. One example is the SleepCheck (IM Systems Inc. Baltimore); it is classified as a type 4 unattended device which records one channel.[2] It uses an algorithm that relies on nasal pressure fluctuations to detect the apnea and hypopnea events (these events are counted during the recording period). The liquid crystal display (LCD) display on the SleepCheck indicates the total number of events, the number of events for each hour of sleep, and the total number of events during the entire recording period. SleepCheck measures the airflow through an oro-nasal cannula, runs on one 1.5 volt AAA battery, has a size similar to a pager and is user-friendly.

Although the device has been approved by the FDA, prior studies with SleepCheck were done with a small number of patients and in abstract form only.[16-18] The primary objective of this study was to prospectively evaluate the accuracy of the SleepCheck, to evaluate OSA as compared to the in-laboratory PSG.

4.2. Methods

Consecutive patients referred to a full-night, in-laboratory PSG with suspected sleep-related breathing disorders were invited to participate in this

study. To reduce possible bias, all consecutive individuals that were eligible underwent their sleep study in a designated bedroom of the Sleep Laboratory. Patients from outside the Lower Mainland that were referred for a split night study with CPAP or a follow-up study using any type of therapy were excluded from the study.

A full night diagnostic in-laboratory PSG was conducted for each patient. Standard measurements included electroencephalography (EEG), electrooculography (EOG), submental and tibial electromyography (EMG), electrocardiography (ECG), chest and abdominal inductance plethysmography (Respitrace; Ambulatory Monitoring Systems, Ardsley, NY), arterial oxygen saturation (pulse oximeter built into Sandman Sleep Diagnostic System) and airflow with an oro-nasal cannula attached to a "Y" tube, with one of the tube endings connected to the PSG through a pressure transducer (PTAF2, Protech Services, WA) and the other ending connected to the SleepCheck.

The SleepCheck has a solid-state air pressure transducer that measures the nasal flow signal which is digitized and traced continuously. It monitors the airflow signal and starts a ten second timer when the signal decreases by 50% of the baseline. The baseline is defined as the average signal value of the last eight inhale-exhale cycles. Apneas and hypopneas are then scored when the signal amplitude drops below the baseline. The SleepCheck had, custom-made for this study, a DC output cable connected to an accessory channel of the PSG; it exported a signal of 0 V for normal breathing and a 1 V signal lasting 1 second for apnea and hypopnea events recorded on one PSG channel. Concomitantly, the SleepCheck recorded in its memory the number of events, number of events in each hour and number of events per recording time; these measurements were shown in an LCD display on the monitor. If the SleepCheck recorded four or more consecutive minutes of low signal, it was interpreted as a low signal error (LSE).

If less than three LSEs occur, or if less than twelve total minutes of LSE occur, the data for the hour is considered valid. If there are three or more LSEs, or twelve or more minutes of LSE, the data for the hour is invalid and that hour was not included in the total RDI. In the PSG marker, there was no indication of low signal errors. The display readings were always completed by one of the authors (FRA).

Sleep staging, and apnea and hypopnea characterization were scored manually by the same technologist, following the parameters of "Rechtschafen & Kales"[19] and the American Academy of Sleep Medicine.[2] The sleep technologist (PH) that scored the data was blinded to the SleepCheck marker channel and to the display readings. We performed the following analysis:

a) the RDI calculated by the SleepCheck algorithm (LCD display reading);

b) the RDI counted manually as all apneas and hypopneas marked by the SleepCheck in the PSG, divided by the total recording period. For this evaluation one of the authors (FRA) analysed the PSG in epochs of 120 seconds blinded to the apneas and sleep staging;

c) the assessment of sensitivity and positive predictive value; a subgroup of patients was defined as the first consecutive 15 patients. The PSG was the gold standard and true positive was considered if there was temporal agreement or desynchronization of less than 5 seconds. The analysis included identity of the SleepCheck marker to the manual PSG scoring (true positive), false positive and false negative scorings. The same author (FRA) assessed the apnea and hypopnea scorings of both methods in epochs of 30 seconds. The duration of the apneas were not measured by the SleepCheck; if there was an apnea event that lasted 30 seconds and the SleepCheck marked two events, one of them was considered false positive. Apneas and hypopneas were not discriminated and marked equally;

d) for comparative purposes, the respiratory events from the PSG were scored from flow signals and oximetry only, with the technician blinded to EEG, EOG, EMG, EKG, SleepCheck marker and previous scoring; this analysis was performed by the same technician one month after the initial full PSG scoring. This scoring followed the same criteria described by the American Academy of Sleep Medicine (1999), but without sleep staging and arousals input;

e) visual qualitative analysis of the discordance in identifying the apneas and hypopneas was also assessed by the authors (FRA and NA).

Patients were included in the study only if they signed a consent form. This study was approved by the Ethics Committee at UBC and by the Vancouver Coastal Health Authority.

4.2.1. Statistical analysis

The results were analyzed with a statistical package (SPSS software program, Chicago, IL). To evaluate statistical correlation, Pearson correlation coefficient and the linear regression equation was used to define the "best fit" line through the data. The Bland-Altman method of concordance plot[20] was used to do the comparison between diagnostic measurements. To assess the sensitivity and specificity of the SC for the diagnosis of sleep apnea, a receiver operating characteristics (ROC) curve was plotted and the area under the curve (AUC) was calculated.

4.3. Results

Of 35 consecutive patients, 30 agreed to participate in the study. In the comparison of the RDI calculated by the SleepCheck algorithm (LCD display reading) and the RDI counted manually from the SleepCheck marker in the PSG (total number of events / total recording time), we found that the SleepCheck algorithm and error detection slightly improved the detection of the apneas and hypopneas. The correlations between the manual counting and LCD display RDI to the PSG AHI was $r=0.79$ and $r=0.80$ respectively. Because of these results, the display data on the 30 patients was used to evaluate this portable device. Table 4.1 shows the demographic data, confirming a wide distribution of OSA severity, with 18 patients with an AHI less than 15/h and 12 patients with an AHI greater than 15/h. With a cut-off point of AHI<5, the prevalence of OSA in the studied population was 73.3%. Following the AASM classification of apnea severity, there were eight snorer patients, all males with a mean age and body mass index (BMI) of 34.4 years and 26.2 kg/m^2, respectively. For this group, the mean difference and standard deviation of RDI minus AHI was 25.4 ± 11.9 events per hour. There were six males and four females in the mild group, mean age 47.5 years and mean BMI 31.7 kg/m^2, and the RDI/AHI difference was 34.2 ± 11.7 events per hour. Six patients were classified as moderate; four males and 2 females were in this group, with a mean age of 44.5 years and a mean BMI of 34.5 kg/m^2. The mean difference of the scored events (RDI-AHI) was 30.5 ± 10.8 events per hour. An AHI greater than 30, was recorded in five males and one female with a mean age of 51.3 years and a mean BMI of 33.5 kg/m^2. The mean overscoring of the tested screening (RDI-AHI) was 15.5 ± 13.5 events per hour.

Table 4.1. Characteristics of the subjects within each sleep apnea severity group and the entire sample, expressed as mean and standard deviation (SD) values.

PSG	n	Gender	PSG AHI		SC RDI		Age, ys		BMI	
			Mean	SD	Mean	SD	Mean	SD	Mean	SD
AHI < 5	8	0F/8M	1.7	1.5	27.2	12.4	34.4	8.7	26.2	2.8
AHI 5-15	10	4F/6M	7.8	2.3	42.0	12.7	47.5	6.2	31.7	10.7
AHI 15-30	6	2F/4M	22.4	4.4	52.8	11.6	44.5	19.2	34.5	8.3
AHI >30	6	1F/5M	55.1	22.5	70.7	10.6	51.3	9.9	33.5	4.5
ALL	30	7F/23M	18.6	22.1	45.9	19.2	44.2	12.3	31.1	8

For the analysis of the PSG, one of the authors (FRA) evaluated the apnea and hypopnea markers of SleepCheck in the PSG. In this analysis, the display RDI and the low signal error were not included. The sensitivity and positive predictive value of the SC marker in detecting apneas and hypopneas in each of the 15 patients assessed for this purpose are shown, in order of OSA severity, in Table 4.2. In this evaluation, there were two snorers, four mild, five moderate and four severe sleep apnea patients. The sensitivity ranged from 0.27 to 1.00, with a mean value of 0.81, and the positive predictive value ranged from 0.01 to 0.80, with a mean value of 0.32. Figure 4.1 shows the scatter plot that illustrates the significant correlation between SleepCheck RDI and PSG AHI ($r=0.803$, $p<0.001$, $n=30$), and illustrated the tendency of the SleepCheck to overscore apneas, since the best fitted line crosses the "y" axis at the 33.0 index.

The Bland-Altman plot of the differences between the SleepCheck RDI and the PSG AHI versus the corresponding average of the PSG AHI and SleepCheck RDI is provided in Figure 4.2. The SleepCheck showed a systematic overscoring tendency and, as suggested by Bland & Altman,[20] the mean difference was then adjusted by transforming the SleepCheck RDI values by -27.4. After the adjustment, the mean value was -0.04 and the 95% confidence interval of the bias was 4.8 and -4.8, the limits of agreement was 26.6 and -26.6, the 95% confidence interval for the upper limit of agreement was 35.1 and 18.0 and for the lower limit of agreement was -18.0 and -35.1. The SleepCheck RDI shows a tendency to overscore the events in snorers, mild and moderate sleep apnea and less, but still overscoring, for the severe cases. With the aim of assessing the sensitivity and specificity of the SleepCheck, we established different ROC curves, with thresholds of AHI of 5, 10, 15 and 20 events per hour; the respective optimum combinations of sensitivity and specificity were 86.4/75.0, 85.7/87.5, 83.5/83.5 and 88.9/81.0 and the corresponding area under the curve (AUC) was 0.886,

0.915, 0.898 and 0.910. Figure 4.3 shows the ROC curves for the AHI cut-off points of 10 and 20 events per hour.

Table 4.2. Assessment of sensitivity [true positive / (true positive + false negative)] and positive predictive value (PPV) [true positive / (true positive + false positive)].

PSG AHI	SC RDI	true positive	false positive	false negative	sensitivity	PPV
0.1	22.6	1	182	0	1.00	0.01
3.3	44.2	21	333	5	0.81	0.06
6.4	36.4	35	225	8	0.81	0.13
7.4	35.7	13	254	36	0.27	0.05
9.5	32.3	41	201	5	0.89	0.17
11.9	68.6	62	328	9	0.87	0.16
18.9	63.3	140	336	1	0.99	0.29
24.6	38.4	123	144	19	0.87	0.46
26.1	63.6	133	338	54	0.71	0.28
28	42.2	126	137	41	0.75	0.48
29.2	57.1	158	211	20	0.89	0.43
30.3	34.3	101	176	109	0.48	0.36
45.9	63.4	225	203	51	0.82	0.53
47.9	74.8	378	248	7	0.98	0.60
75.7	75.5	468	117	5	0.99	0.80
Mean 24.3	50.2	135.0	228.9	24.7	0.81	0.32
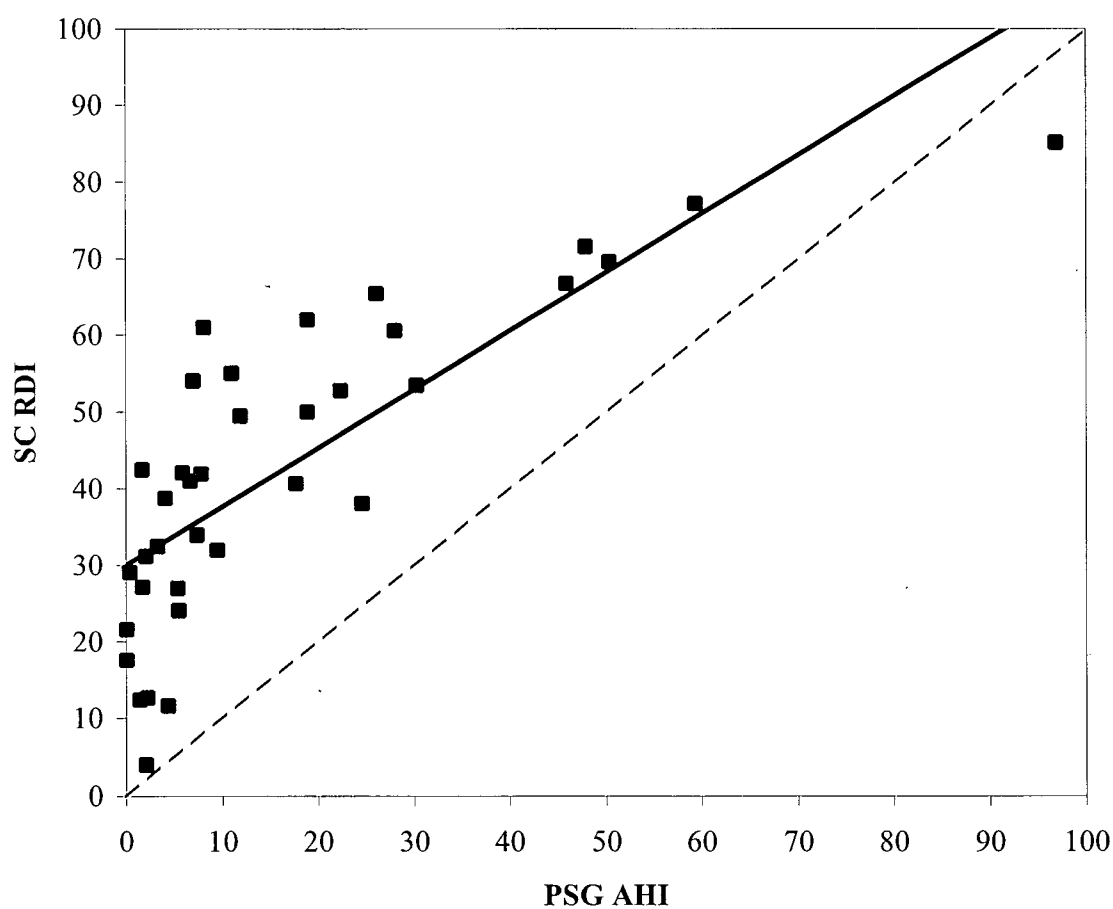
Figure 4.1. Scatter plot of the PSG AHI versus SleepCheck RDI.   Pearson correlation coefficient was r = 0.805, p < 0.001, n = 30 and the linear regression equation was calculated as y = 0.6961x + 33.002.
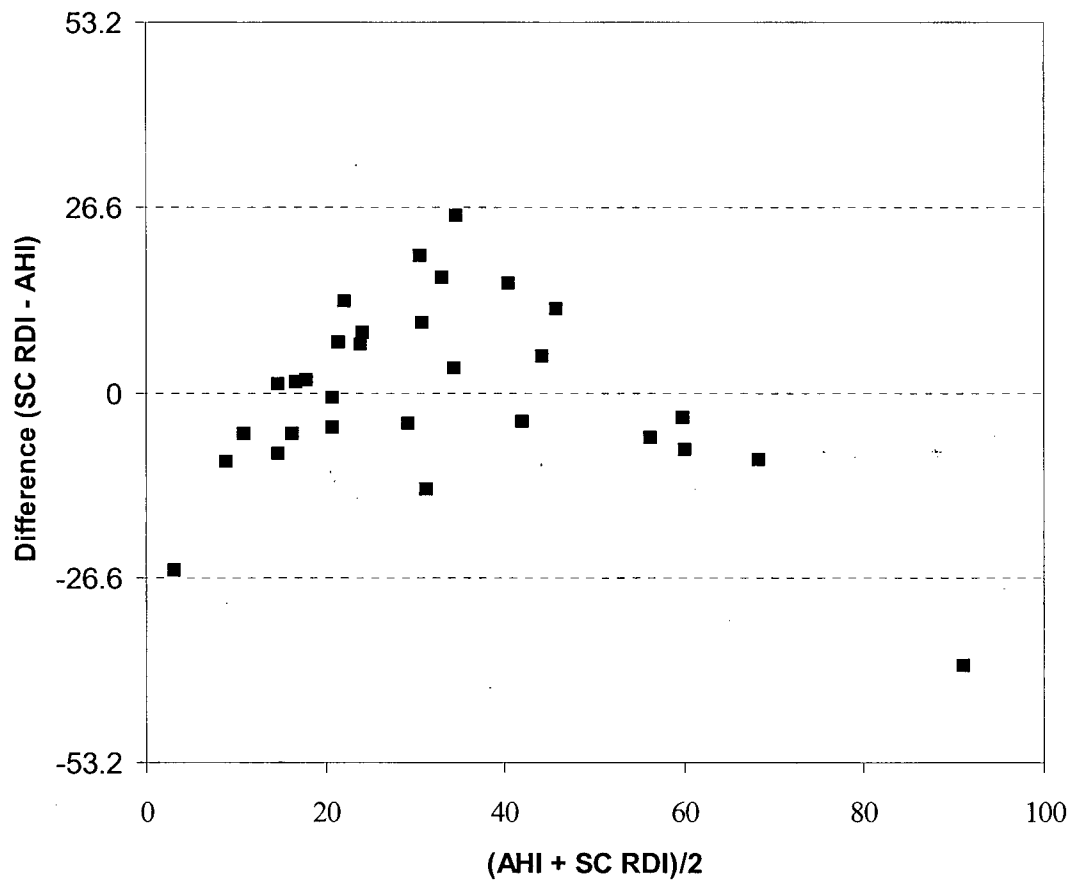
Figure 4.2. Bland-Altman plot illustration the agreement between SleepCheck RDI and PSG AHI after adjusting for the systematic overscoring bias of 27.4. Limits of agreement were 26.6 and -26.6, corresponding to ± 1.96 standard deviations.
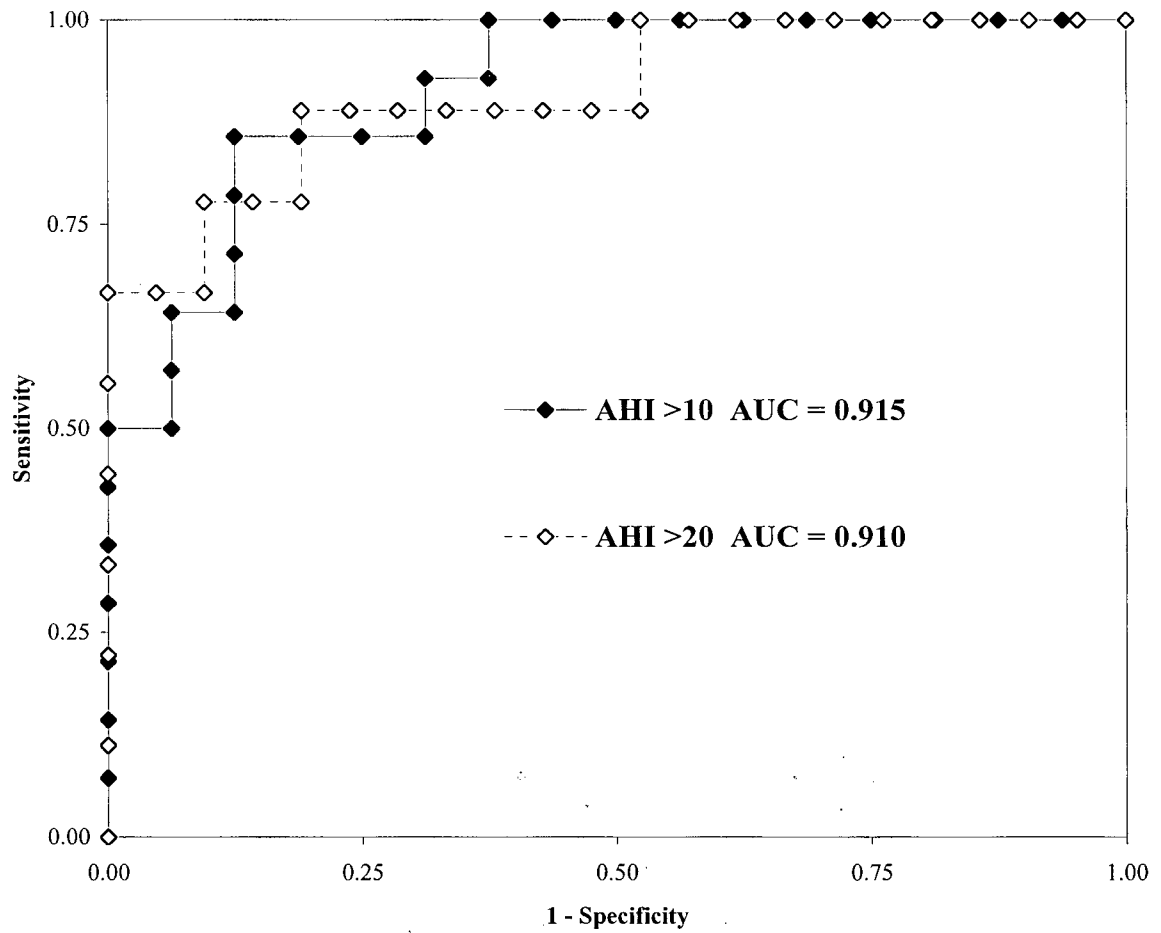
Figure 4.3. Representative ROC curves for PSG AHI threshold of greater than 10 and greater than 20 events per hour.

For the analysis of the PSG scored with flow and oximetry only, there was a correlation of r=0.94 with the full PSG. When this method of RDI was compared to the SleepCheck RDI, the correlation was r=0.814 (p<0.001). In the qualitative analysis of four patients, one snorer, one mild, one moderate and one severe sleep apnea, there was a marked overscoring in REM sleep as shown in Figure 4.4. Although there was no desaturation or arousal, the decrease in flow detected has no clinical implication, being part of the normal physiology of REM sleep. Another systematic overscoring occurred after arousals and periodic limb movements, illustrated in Figure 4.5. Since patients after such kinds of events normally present an irregularity of breathing, this physiological breath recovery was wrongly scored by the SleepCheck. In some epochs, though, we found a decrease in flow followed by an arousal that was scored by the SleepCheck but not by the sleep technician. These events do follow the criteria of a respiratory event related to arousal that was missed in the normal PSG analysis, as shown in Figure 4.6.
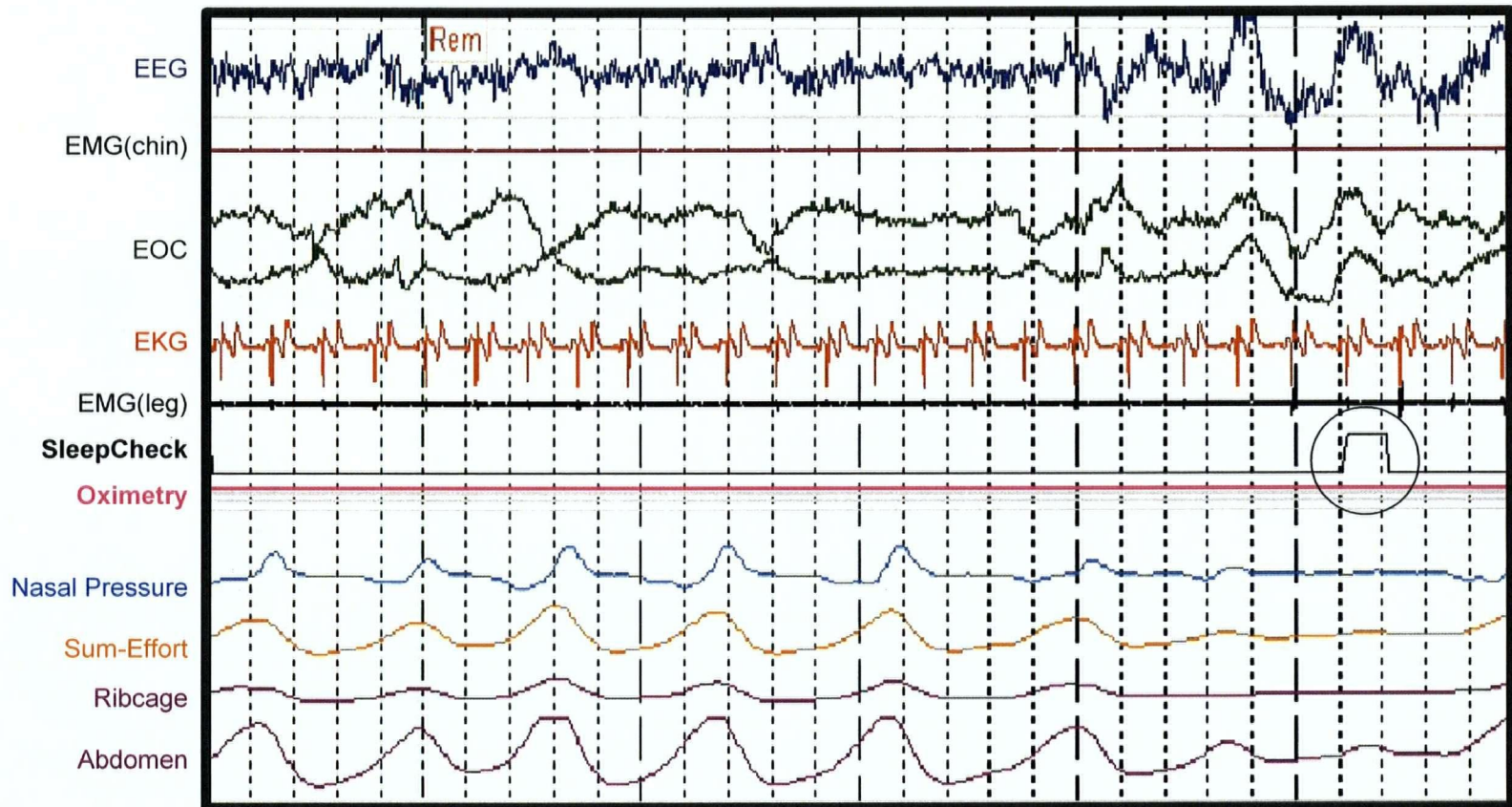
Figure 4.4. Example of a 30 seconds PSG epoch, with the SleepCheck signal which illustrates a variation in ventilation that occurs commonly during REM sleep and was scored as an apnea by SleepCheck (in circle).
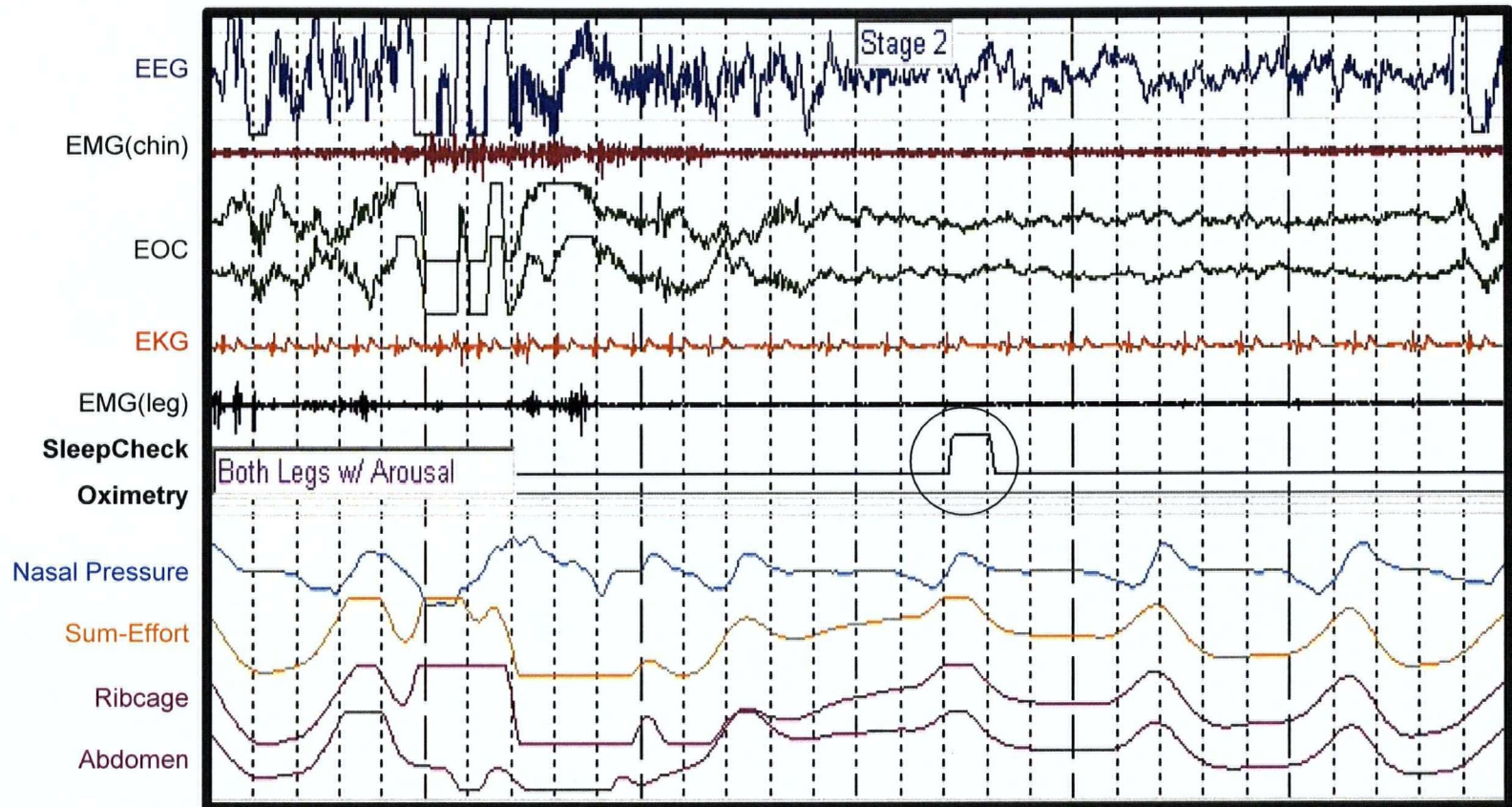
Figure 4.5. Example of a 30 seconds PSG, an event scored by the SleepCheck (circle) related to a normal decrease in flow after arousal from a leg movement.
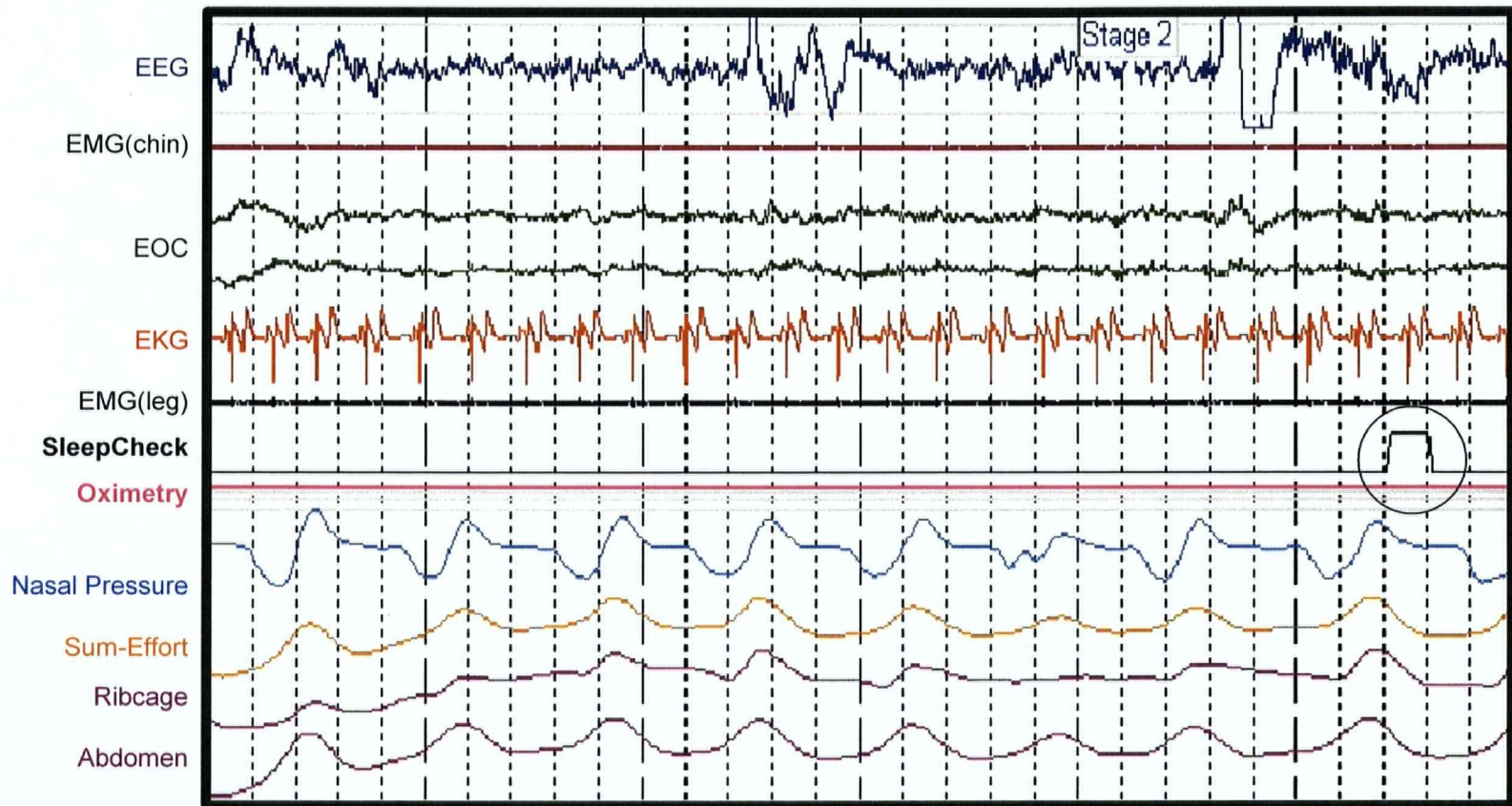
Figure 4.6. Example of a 30 seconds PSG, the SleepCheck scored an event with paradoxical ribcage/abdominal movement followed by an arousal. This may represent a respiratory effort related arousal.

4.4. Discussion

Although the present tested portable monitor gives a number that should be comparable to the AHI, it differs from oximetry that could be interpreted with various desaturation thresholds. Even though oximetry is the bio-parameter mostly used in Type 4 portable monitors for OSA, the present monitor showed a similar ROC curve and the AUC of 0.915 was comparable to more sophisticated devices, such as the three-channel WP100[11] (AUC 0.87) and the five-channel Apnoescreen I[12] (AUC=0.89). In the evaluation of the Bland-Altman plot, we first had to adjust it to a consistent bias of overscoring by the present monitor. Second, although comparable to other more complex monitors, [6,12,21] we believe that the limits of agreement found in this study are wide and caution should be taken in the interpretation of the results of this and other portable monitors.

The portable monitor used in the present study showed a large overscoring and some disagreement with the PSG results. The automatic scoring of the apneas are compromised since the airflow measured might vary according to patient breathing patterns, such as intermittent oral breathing and nasal anatomy. [22] We found that it falsely detected as apneas events of decreases in flow related to REM sleep and decreases of flow following periodic limb movements and arousals. These events have no clinical implication and therefore should not be scored. However, this is a limitation of a single channel device, since there was an actual decrease in flow, but because normal breathing can vary in different phases of sleep and as a response to different physiological events, they can only be properly scored with a simultaneous oximetry and EEG. Still, we found that it did score several events of decreases of flow preceding an arousal that was not detected in the PSG and could be interpreted as a respiratory effort related to arousal, and therefore it is more precise than the PSG in the evaluation of such kinds of

respiratory events. The overscoring bias of the device was reported to the manufacturer and, as a consequence of our results, they decreased the sensitivity of the SleepCheck by decreasing the gain of the nasal cannula flow analysis. This new version was not tested in the present study. We hypothesize that the differences within the same patients should be minimal, only representing the night-to-night variability of the AHI.[23] Following this methodology, two measurements should be assessed when using this type of devices: first, a baseline with the SleepCheck in which the quantity of overscoring could be evaluated; and, after or during titration and/or treatment, a follow-up measurement to appraise the optimization of the treatment should take place. Further study is still required to test this hypothesis.

Although this evaluation took place in a supervised setting, the monitor utilized is fairly simple to use and so the rate of lost data in an unsupervised environment is expected to be minimal. Training patients for the correct placement of the cannula and to turn on the machine prior to the testing are the only requirements for this technique. The SleepCheck is small and it stays clipped to the patient's pyjamas through the night, avoiding the displacement of the cannula or restricting patients from their preferred sleep position. It also saves clinical time in the evaluation in that it is simply turning the machine on and registering a couple of numbers that stand for the total number of apneas and the RDI for the total recording period and for each hour of recording time. Since it does not register EEG or any other interpretation of sleep[10] (actigraphy for example), a diary of the night is probably useful and certain hours of recording could be excluded and the index recalculated. A strong characteristic of the present study was that it was recorded simultaneously with the PSG and used the same methodology in recording airflow, the pressure transducer. Studies that compare PSG to home monitoring could lead to misinterpretation of the data because of the

night-to-night variability of the AHI[23] and also a comparison of in-laboratory with home assessment does induce an error based on patient sleep position, reported as being more supine at the sleep lab.[22] Previous studies showed loss rates of 10 to 14% in studies using a nasal cannula associated with oximetry,[24] but there is still a need to evaluate the performance of the present monitor in an unattended setting.

The mean sensitivity of the SleepCheck in 15 patients was 0.81 but the positive predictive value was small, confirming the overestimate bias of about 27 events per hour. Some of the false positive apneas could be excluded if the machine software was used, since when patients unplug the nasal cannula to go to the washroom in the middle of the night, the SleepCheck marker counts it as apneas, but the software would detect an LSE (Low Signal Event) and would remove that hour in the calculation of the RDI. However, this is one of the few studies on Type 4 portable monitors[7] to evaluate the synchronism of the apnea events of the tested portable monitor to the PSG, and the comparison of these results with the literature is therefore compromised. We could confirm that apneas and hypopneas were detected without differences, which was expected by the nature of the nasal pressure analysis.[22] However, continuous efforts should persist to get a better algorithm associated with this machine that could reduce the false positive detection of apneas and hypopneas.

The complexity and cost of PSG are always cited as a reason to search for new diagnostic systems[22] and similarly are an impediment to OA titration studies, especially if repeated PSGs are requested. Although the results of this study show a good correlation, there was a high overscoring tendency with the tested machine. We believe that such type of monitors should be used in the monitoring of OSA treatment approaches only after a baseline PSG has been accomplished. In this sense, a simpler approach would not misinterpret sleep apnea severity or other sleep disorders such as narcolepsy, periodic limb movement and upper airway

resistance syndrome. Sleep laboratories prioritize primarily diagnostic PSGs, but follow-up assessments mostly require a long waiting period. OAs, surgery and behavioural therapies can reduce snoring and also might have a placebo effect[25] and therefore a home monitor could be important. SleepCheck could be used to reduce the treatment period in which a certain therapy was not fully efficacious and the patients could be referred to an alternative therapy earlier. Still, in mild to severe sleep apnea, symptomatic or high cardiovascular risk patients, a clinical assessment by a sleep doctor is recommended and a possible follow-up PSG might be required.

Fleury and colleagues[26] showed the combination of home oximetry and patient's subjective evaluation did improve the effectiveness of OA therapy. OAs are currently titrated based on clinical symptoms, but we know that clinical evaluation alone may not be accurate. In the OA field, multi comparisons of the SleepCheck measurement together with clinical evaluation might optimize the mandibular titration procedure. As oximetry is still relatively expensive and requires a physician's interpretation, we consider that SleepCheck could have an important role in the OA titration field. We anticipate that the measurements within the same subject could be comparable and a decrease of 50% in the RDI of the SleepCheck could correlate with a 50% decrease of PSG AHI. However, this is only a hypothesis and needs to be tested. Furthermore, we should also acknowledge that simple devices are more feasible and do save time and expense, but there is a trade-off with the amount of information that can be extracted from it against its simplicity. Therefore the limitations of this device have to be considered and its practical use has some limitations.

This study has several limitations such as being an in-laboratory study without home assessment, and although there is still a need for in-home assessment, we believe that because of the simplicity of the device, the rate of lost

data should be minor. The small sample size is also a limitation, but because the data was collected on consecutive patients, there was less bias and patients were distributed fairly equally according to OSA severity; our sample was biased because all the patients were actually referred to the sleep lab with some symptom of sleep disturbance breathing, but there were 8 patients with an AHI smaller than 5, which could be interpreted as the non-apneic population in the present study.

In conclusion, the use of SleepCheck in a sleep apnea population might be simple, less costly and reasonably easy to use by different professionals especially if compared with baseline PSG and used for titration. The home monitor evaluated in the present study showed acceptable accuracy for the diagnosis of OSA when adjusted for the overscoring bias. However prior to the use of SleepCheck for the assessment of different treatment modalities, further studies are still necessary. According to our results, the use of Type 4 portable monitors for primary diagnosis of sleep apnea should be evaluated with caution.

4.5. Acknowledgements

4.6. Bibliography

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CHAPTER 5

SNORING EVALUATION BASED ON A

NASAL CANNULA PRESSURE TRANSDUCER

5.1. Introduction

Snoring is the earliest and most consistent sign of upper airway dysfunction leading to Obstructive Sleep Apnea (OSA)[1] and can be a useful indicator of increased negative inspiratory effort and upper airway resistance syndrome.[2] Even without hypoxemia or apnea, chronic snorers may present significant sleep fragmentation,[3] thereby causing disruptive sleep architecture. Epidemiological studies have found snoring to be a risk factor in the development of daytime hypertension,[4-6] coronary artery disease[7] and stroke.[8] There is current evidence[9] that non-apneic snorers do present reduced baroreflex sensitivity prior to other cardiovascular alterations, which can be restored with the use of nasal continuous positive airway pressure (CPAP). Snoring is an acoustic phenomenon generated by upper airway structure vibration during sleep.[10] Its sound intensity is related to clinical and polysomnographic findings of sleep apnea patients.[10,11] There are different treatment modalities such as oral appliances and uvulopalatopharyngoplasty (UPPP), which are also designed to treat primary snoring, but the evaluation of these therapies is difficult if the patient does not have any sleep abnormalities other than snoring itself. Since the perpetuation of snoring can lead to health problems, the treatment of snoring is not cosmetic. However, the effectiveness of such treatment approaches is currently based on subjective evaluation of the snoring by a bed partners.[13,14]

The current standard measurement of snoring is often expressed as the sound intensity in decibels. With a microphone positioned in front of the patient's head,[10,15] the snoring is detected if the noise exceeds a certain threshold, usually about 50 to 55 decibels.[16] Recently, a nasal cannula pressure transducer (PTAFlite, Protech Services, Seattle, WA) has been manufactured to determine snoring from the nasal flow. As recommended by American Academy of Sleep Medicine

(AASM) Task Force Report,[17] the nasal cannula pressure transducer has replaced the nasal thermistor in the measurement of airflow during sleep, after studies proved this measurement to be more sensitive. The nasal cannula measures and quantifies airflow, including a better dynamic response due to flow changes by recognizing increases of upper airway resistance through pressure fluctuations caused by inspiration and expiration.[18-20] With the use of high frequency filters, the snoring component of the flow is extracted, but the reliability of the snoring information captured in this fashion has not been rigorously compared to that obtained with sound intensity either from an ambient noise level meter or tracheal sound analysis. Currently, some polysomnography (PSG) software, such as ProFusion PSG Sleep Analysis (Compumedics, MN) and level 3 home monitoring devices (includes a minimum of four channels and must monitor at least two channels of respiratory movement or respiratory movement and airflow to define an event; generally no EEG signals are monitored) such as Embletta (Medcare, NY) use the nasal cannula pressure transducer high frequency filter to quantify snoring. Since the nasal cannula is currently standard equipment during sleep studies to record airflow, it is tempting to evaluate the snoring signal obtained from the same cannula.

We hypothesized that filtering the high frequencies from the nasal cannula could provide a precise measurement of snoring which could play an interesting role in the sleep laboratories and in the evaluation of the effectiveness of snoring treatment approaches. Accordingly, the objective of this study was to assess the accuracy of the snoring recorded from a nasal cannula signal compared to the snoring measured through a noise level meter and also to attempt to correlate it to the apnea and hypopnea indices obtained from simultaneous in-hospital sleep studies.

5.2. Methods

Fifty consecutive patients referred to the Sleep Laboratory of the University of British Columbia for snoring or suspected OSA and currently not receiving any kind of treatment were invited to participate in this study. A full-night diagnostic in-laboratory PSG was conducted for every patient. Standard measurements included: electroencephalography (EEG), electrooculography (EOG), submental and tibial electromyography (EMG), electrocardiography (ECG), chest and abdominal pletysmography (Respitrace; Ambulatory Monitoring Systems, Ardsley, NY), arterial oxygen saturation (pulse oximeter built in Sandman Sleep Diagnostic System), and airflow with an oro-nasal cannula connected to the PSG through a pressure transducer (PTAF2, Protech Services, WA). Sandman Elite® Sleep Diagnostic Software (Nellcor Puritan Bennett Ltd., ON) equipment was used. The sound was recorded in audible decibels (dBA) during an entire night in the same room of the UBC Sleep Lab using a noise level meter (±2 dBA) (CEL-281). A microphone connected to the noise level meter was mounted in the Sleep Laboratory and was located adjacent to the patient's head. The signal was sent simultaneously to the Sleep Lab through a DC output from the noise level meter to a DC input from the PSG. The noise level meter was regularly calibrated to a mean dBA level, with a sampling rate of 51.2Hz, and was exported. The 40 dBA signal were converted to zero (0) volts and 100 dBA to one (1) volt through the PSG software. In the analysis of snoring through this methodology, 50 decibels was set as the minimum intensity of the sound required to be scored as snoring, which corresponded to 0.16 volts, as suggested in a previous study.[3] The other snoring signal was captured through a nasal and oral cannula (Braebon Medical Corporation, ON) connected to a pressure transducer (PTAFlite transducer,

Protech Services, WA) with the high frequency filter output (snore filter) connected to a DC channel (51.2 Hz) of the sleep study software (Sandman).

After collection of the data, the PSG was manually scored. The primary evaluation counted the number of snores measured by the noise level meter and by the nasal cannula pressure transducer. For the analysis of snoring, both snoring channels and the sum of the effort signals were exported in volts to software specifically developed for this study. To export the data, the last awake stage before the first stage 1 sleep of the night was selected as the first epoch exported; if there was background noise or fluctuations in flow or snoring signal, the first "quiet" stage 1 epoch was selected. This software converted the files exported from the PSG software into a graphical format identical to the original PSG. For the analysis of the noise level meter snoring, the threshold was set at 50 dBA[3] and any sound that crossed this threshold in the ascending direction was counted as one snore. The total number of snores was then divided by the total period analyzed.

Since there are no standard criteria to evaluate the nasal cannula snore waveform, we evaluated the snore signal from five patients who exhibited good snoring signals, with visible changes in the snore waveform during snoring episodes and then developed software quantified the snoring. This software analyzed this signal as follows:

a) it evaluated the first 30 seconds exported (1,548 points) chosen as non-snoring and non-background noise), finding an average and standard deviation of the baseline snoring signal;

b) it rectified the data using the average as the zero point;

c) a moving time average smoothed both snoring signals to exclude transient surges;

d) it analyzed the snores as the number of times that it exceeded the two standard deviation threshold for at least 1 second; if the signal dropped for more than 0.10 volts and raised again, it was then counted as one more episode of snoring.

e) the total number of snores were then counted and divided by the total analyzed period.

For the visual qualitative analysis of the discordance of the snoring signal extracted from both methods, the software plotted the graph together with the sum of the abdominal and chest effort signals and for each inspiration that the snoring was identified, the snoring from the noise level meter was established as the standard reference.

5.3. Results

Of the 50 patients contacted, a total of 46 agreed to participate in the study. Two patients were not included in the analysis because of problems with the noise level meter; in one case it was not turned on and in the other, the battery ran out after one hour of recording. The apnea severity of the 44 patients was equally distributed and the mean values of age, BMI and AHI within these severity groups and the whole sample are provided in Table 5.1. There was no significant difference between the apnea severity groups according to age or BMI.

Table 5.1. Characteristics of the subjects within each sleep apnea severity group
and the entire sample, expressed as mean and standard deviation (SD) values.

	n	Gender	Age, ys		BMI		PSG AHI	
			Mean	SD	Mean	SD	Mean	SD
AHI < 5	11	1F/10M	42.6	12.7	27.7	3.7	2.1	1.3
5≤AHI<15	12	5F/7M	46.7	7.1	34.1	10.4	8.4	2.4
15≤AHI<30	10	2F/8M	46.9	16.7	31.7	7.7	23.2	5.0
AHI≥30	11	1F/10M	52.8	9.9	31.1	3.7	49.1	15.2
ALL	44	9F/35M	48.4	12	31.4	7.2	21.8	19.9

The correlation of the snore index measured through the noise level meter and nasal cannula pressure transducer was significant (r = 0.51, p < 0.001) as shown in Figure 5.1.A. The Bland-Altman plot of the differences between these snoring indexes versus the corresponding average of these snore indexes are shown in Figure 5.1.B. The bias was -44.7 snores per hour and the limits of agreement were calculated as 310.1 and -399.7 snores per hour. The nasal cannula snore analysis showed a tendency to overscore the mild cases and, as the severity progressed, there was no consistency in either overscoring or underscoring. To evaluate the correlation between the snoring and the apnea severity, both snoring indexes were plotted against the AHI as illustrated in Figure 3.2. The noise level meter showed a significant correlation to AHI (r = 0.49, p < 0.001) while the nasal cannula pressure snore index had no correlation as the trendline was almost parallel to the "X" axis (r = -0.05).

The total number of snores and the snoring index for each of the snoring measurement analyses were then divided according to PSG AHI severity as provided in Table 5.2. For the noise level meter analysis, there was an increasing snore index as the AHI increased, but the total number of snores did not change from moderate to severe cases. In the nasal cannula snore evaluation, the number of snores and snoring index were similar with the exception of the severe sleep apnea group. In this subset of patients, the snoring index of the severe cases decreased to an index similar to the snorer group. As we calculated the mean percentage of overscoring of the nasal cannula pressure ([nasal cannula index – noise level meter index] / [noise level meter index] x 100), there was a decrease in the overscoring from snorer to moderate cases, and in the severe group the nasal cannula underscored the number of snores. The distribution of the snoring index measured with both instruments according to the sleep apnea severity is illustrated in Figure 5.3.
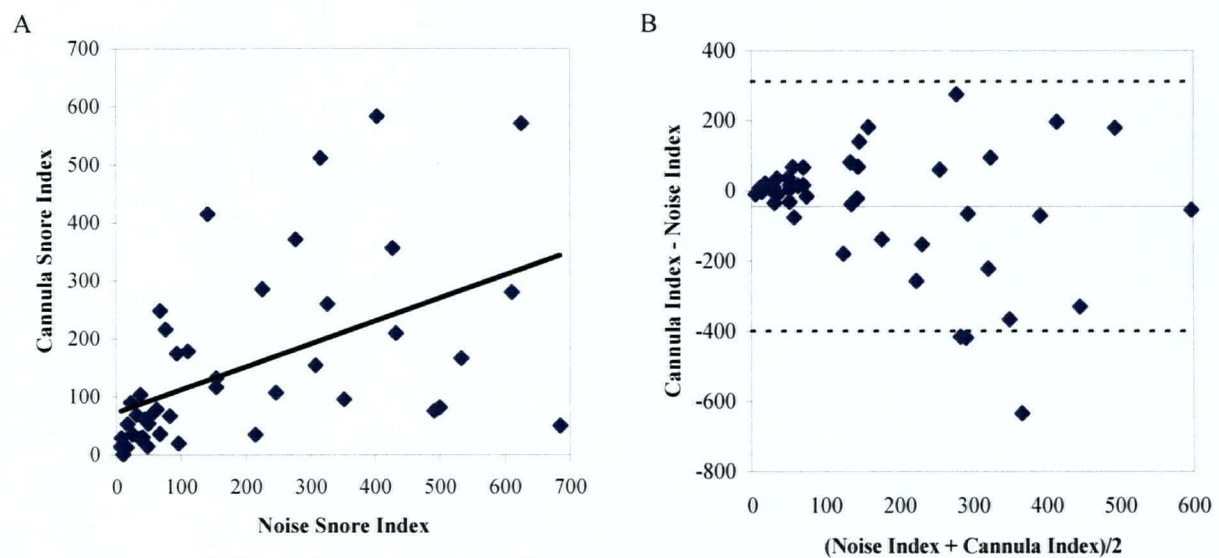
Figure 5.1.A. Correlation between the snore indexes measured by the noise level meter and by the nasal cannula pressure filter. Pearson correlation was r = 0.51, p<0.001, n = 44 and the linear regression equation was calculated as y = 0.40x + 72.0.

Figure 5.1.B. Bland-Altman plot illustration of the agreement between the noise level meter and the nasal cannula pressure snore indexes. The solid line represents the bias of - 44.7 and the limits of agreement are 310.1 and -399.6 snores per hour (n = 44).
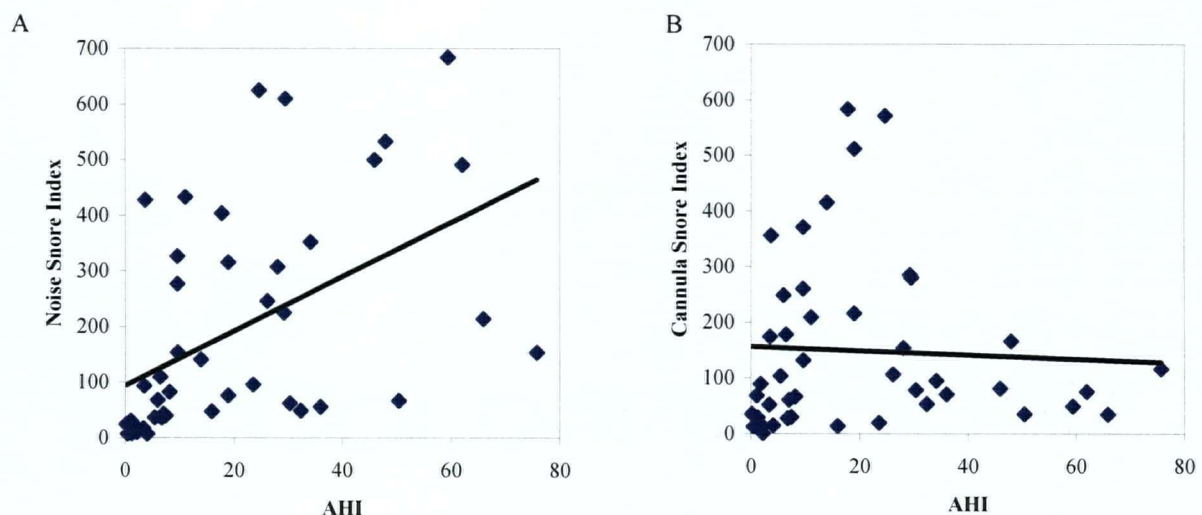
Figure 5.2.A. Correlation between the noise level meter snore index and PSG AHI. Pearson correlation was r = 0.49, p<0.001, n = 44 and the linear regression equation was calculated as y = 4.9x + 94.0.

Figure 5.2.B. Correlation between the nasal cannula snore index and PSG AHI. Pearson correlation was r = -0.05, p>0.05.

Table 5.2. Characteristics of the number of snores per night within each sleep apnea severity group and the entire sample, expressed as mean and standard deviation (SD) values.

	Noise level (#/night)		Noise level (/hour)		Cannula (#/night)		Cannula (/hour)		% Overscoring	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
AHI < 5	348.1	643.6	60.0	124.1	471.4	565.9	76.9	104.9	104.6	127.5
AHI 5-15	964.0	886.9	145.3	130.9	1172.4	945.7	175.2	129.5	52.5	104.9
AHI 15-30	2132.2	1560.3	294.9	204.5	1966.1	1639.8	274.1	215.5	-0.01	82.2
AHI >30	2095.8	1747.3	287.2	232.6	578.7	333.3	77.8	38.4	-45.1	46.6
ALL	1446.7	1449.1	193.5	197.9	1083.5	1110.5	148.8	152.9	25.1	108.3
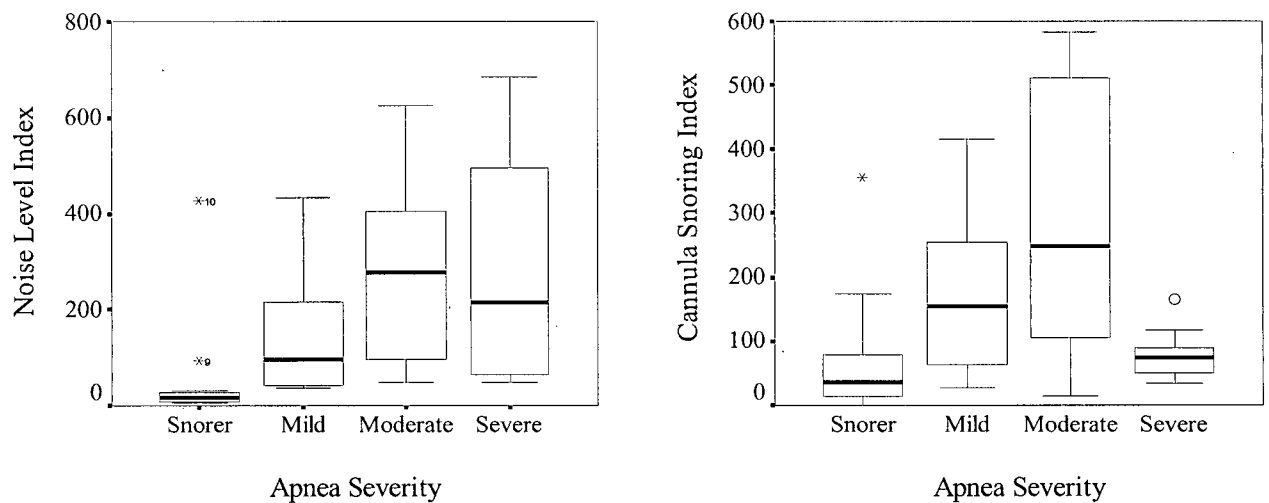
Figure 5.3. Noise level meter and Nasal Cannula Snoring indexes in the different sleep apnea severity groups. The heavier line represents the median, the box represents the middle 50% of the data and the whiskers the range. * and ° identifies the outliers.

As the severe sleep apnea group showed the greatest discrepancy between the measurements, we re-analyzed the data including only the patients with an AHI smaller than 30/h. The correlation between the snoring indexes increased from 0.51 to 0.77 and, according to the Bland-Altman plot, the bias turned out to be positive 10.2/h and the limits of agreement became narrower at 248.1 and 227.7/h, as illustrated in Figure 5.4. The correlation of the noise level meter snore index to the PSG AHI increased from 0.49 to 0.63, and the nasal cannula snore index became significantly correlated with the AHI (r = 0.47) as seen in Figure 5.5.

For the graphic qualitative analysis of the rectified averaged data, we simultaneously analyzed effort, nasal cannula and noise level meter snoring waveforms. For some patients, the nasal cannula snore signal had a high sensitivity, and mild snorers exhibited great changes in the amplitude of that signal, as illustrated in Figure 5.6. In a subset of patients, the response of both signals to the patient's snore was very similar, showing a compatible wave form as seen in Figure 5.7, but there were other patients in which the nasal cannula snore signal showed only some background noise and no correlation with the snore measured by the noise level meter, as illustrated in Figure 5.8; this subset of patients was not different in terms of sleep apnea severity or BMI.
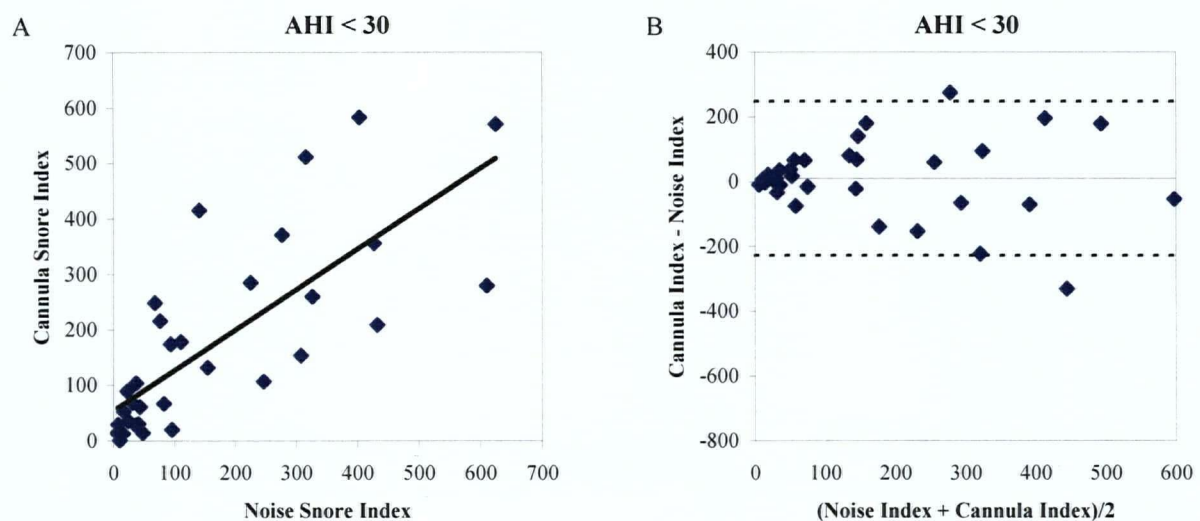
A   **AHI < 30**

B   **AHI < 30**

Figure 5.4.A. Analysis of snorers, mild and moderate sleep apneas (AHI<30, n=33). Correlation between the snore indexes measure by the noise level meter and by the nasal cannula pressure filter. Pearson correlation was r = 0.77, p<0.001, n = 33 and the linear regression equation was calculated as y = 0.73x + 54.2.

Figure 5.4.B. Blan-Altman plot illustration of the agreement between the noise level meter and the nasal cannula pressure snore indexes. The solid line represents the bias of 10.2 and the limits of agreement are 248.1 and -227.7 snores per hour.
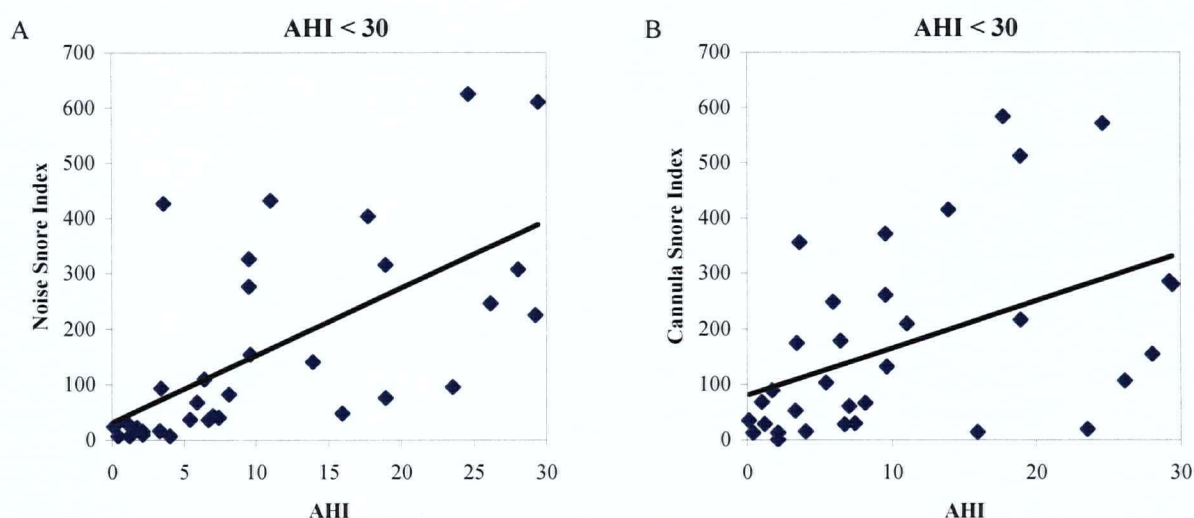
Figure 5.5.A. Analysis of snorers, mild and moderate sleep apneas (AHI<30, n=33). Correlation between the noise level meter snore index and PSG AHI. Pearson correlation was r = 0.63, p<0.001, n = 33 and the linear regression equation was calculated as y = 12.1x + 31.5.

Figure 5.5.B. Correlation between the nasal cannula snore index and PSG AHI. Pearson correlation was r = 0.47, p<0.001, n = 33 and the linear regression equation was calculated as y = 8.5x + 81.0.
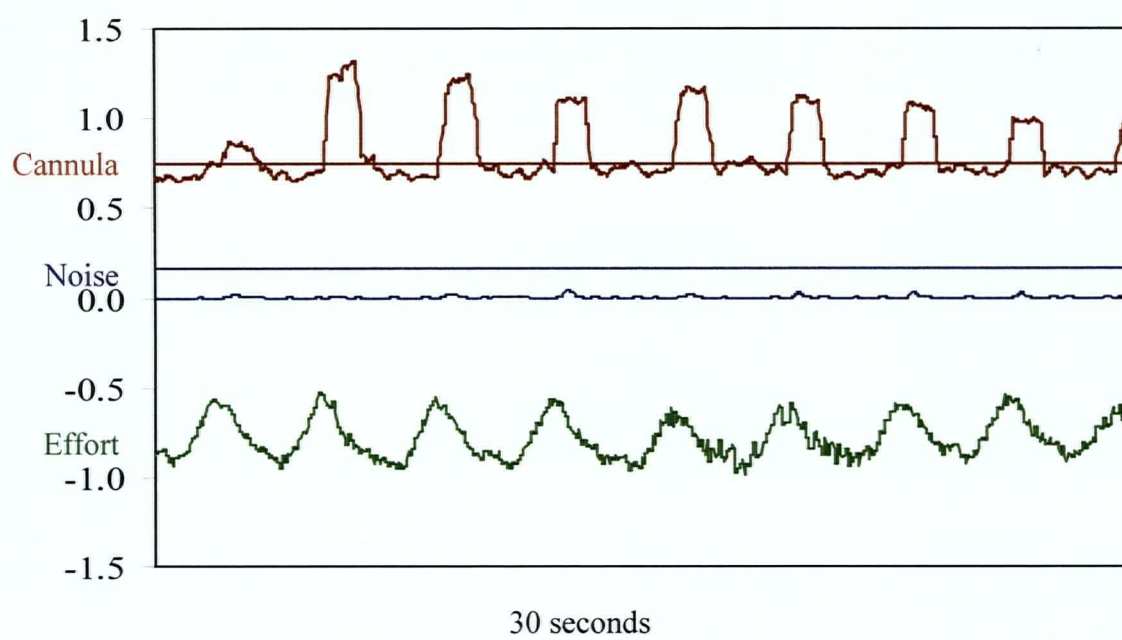
Figure 5.6. Graph of the rectified and averaged nasal cannula snore signal showing a response to the nasal cannula snoring not corresponding to any production of snore measured through the dosimeter (noise level meter) wave does not increase in the same intensity.
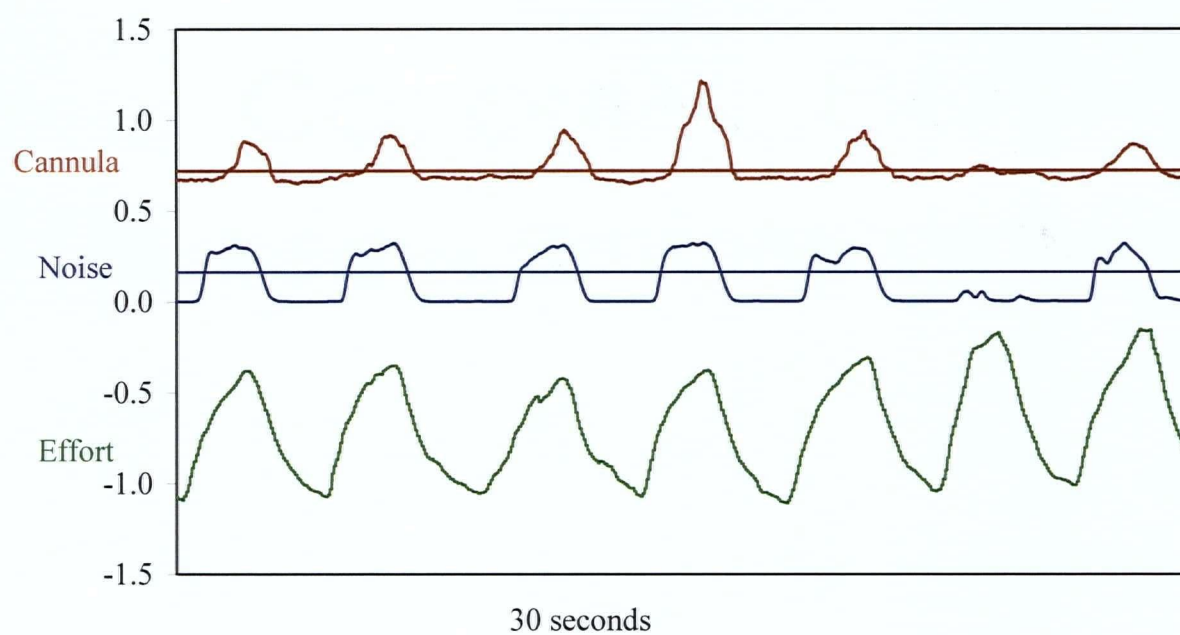
Figure 5.7. Graph of the rectified and averaged nasal cannula snore signal showing good correlation between the two measurements of snore analyzed.
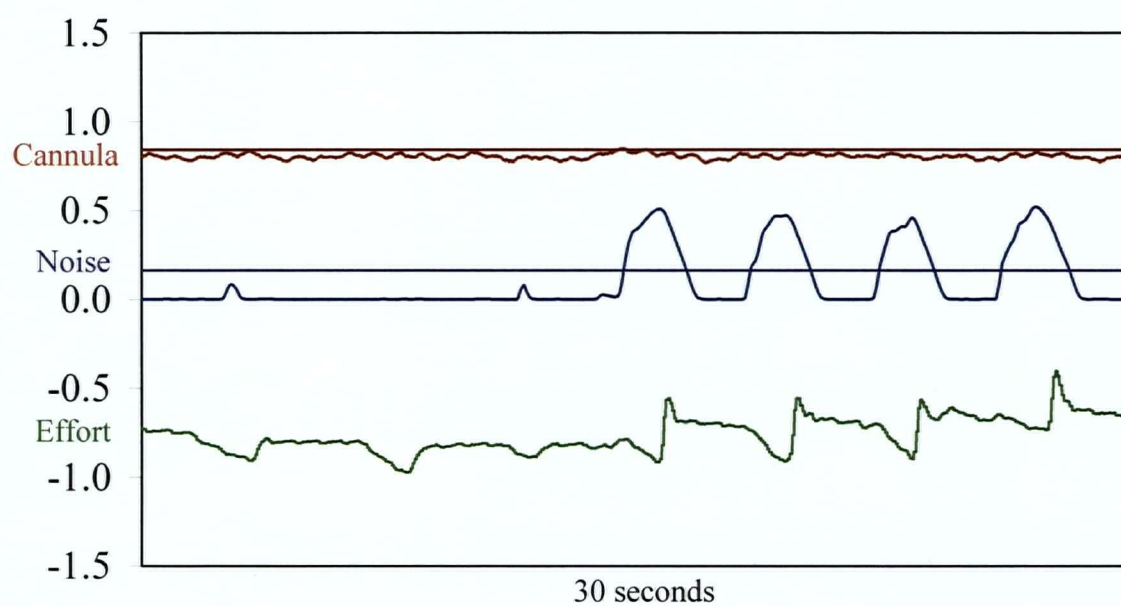
Figure 5.8. Graph of the rectified and averaged nasal cannula snore signal showing only background noise on the cannula snore channel not related to snoring measured in decibels.

5.4. Discussion

Based on this evaluation of the nasal cannula snore analysis, we concluded that, sleep laboratories should be cautious when interpreting snoring as recorded from the nasal pressure transducer. The nasal cannula pressure transducer presented a reasonably good correlation with the noise level meter only in patients with an AHI smaller than 30. The present method of analysis of the snoring signal obtained from the nasal cannula pressure transducer is unique to this study. Although the waveform was changed, all values being positive, the capability of identifying whether or not there was an increase in the amplitude of the snoring signal value did not change. The threshold was chosen as two standard deviations based on mathematical concepts in the evaluation of five patients, which presented as a visible increase in the waveform during snoring episodes. The application of a time moving average to construct a smooth curve and ignore transient peaks has been previously used for the analysis of tracheal sound for the diagnosis of sleep apnea.[11] Even though the analysis used was new, we do believe that there are patients whose snore is not perceived through the nasal pressure transducer, as seen in Figure 8. We believe that with the results found in the present study, more caution should be taken in the analysis of snoring through the nasal cannula pressure transducer.

Since the evaluation of snoring is more important in non-apneic and mild sleep apnea patients, it could be argued that nasal cannula pressure transducer snore analysis had a good correlation with the estimation of snoring addressed by the noise level meter. The correlation of the snore indexes was 0.77 for patients with an AHI smaller than 30/h, with a bias of 10.2 snores per hour. However, for patients with a higher number of snore events, we found that the limits of agreement, even in this set of patients, were too wide.

One hypothesis as of the reason why the nasal cannula failed in detecting the snoring in patients with an AHI greater than 30/h is the frequency of mouth snoring. According to Dalmasso and collaborators[1] the snoring generated through the mouth only has a frequency of 50Hz. The filters from the pressure transducer for the snoring are setted at 70Hz, which could have eliminated those events from being captured.

In the present study, we evaluated only the loudness of the snoring, which is related to the annoyance and bed partner's hearing, but the detailed analysis of snoring is much more complex. Previous studies[1,11] found a better correlation of snoring and the severity of sleep apnea disease when the power spectrum evaluation of the snoring was added. Since the purpose of this study was not to correlate the snoring with the AHI, but to assess the accuracy of this new snoring measurement in the identification of snore episodes, the reference standard would be the human ear and brain,[3] and from a previous study, sounds that exceed 50 decibels are the nearest threshold that can be compared to human hearing limit for snoring description. However, we acknowledge that this is one of the limitations of the present study, since the flow analysis could have more similarities to a power spectrum evaluation; a future approach to more closely evaluate the nasal cannula snoring extraction should include such an evaluation.

The placement of the microphone varies from attached to the neck over the trachea,[11] on the forehead just above the level of the nasion[3] or on the bedside table.[21] In the present study, we have placed the microphone adjacent to the patient's head. There was a brick wall on the opposite side of the bed which reflected the sound with minor absorption, minimizing differences in the snoring level according to the patient's body position. The temporary response of the noise level meter to the patient's snoring was minimal as well, since there was less than one meter distance and the timing delay is calculated as a three millisecond delay.

There are also differences between oral and nasal snorers, and although there are no significant changes in the evaluation of the nasal flow with a nasal cannula, we did use an oro-nasal cannula to diminish the low signal during oral breathing.

Despite some weaknesses in the present study, the nasal cannula pressure transducer did not prove to be reliable in all patients, especially in the severe sleep apnea cases. Since there are sleep laboratories and ambulatory home monitors that currently rely on this method of snoring evaluation, there are no consequences for a gross evaluation of snoring in non-apneic, mild and moderate sleep apnea patients. However, for the assessment of snoring therapies, the counting of snores through the nasal cannula pressure transducer should not be considered accurate specially for those subjects who have AHI greater than 30.

5.5. Acknowledgements

5.6. Bibliography

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CHAPTER 6

LONG-TERM SEQUELAE OF ORAL APPLIANCE THERAPY

IN OBSTRUCTIVE SLEEP APNEA PATIENTS

PART 1. CEPHALOMETRIC ANALYSIS

6.1. Introduction

Obstructive Sleep Apnea (OSA) symptoms such as snoring and daytime somnolence are common in the population. Snoring appears to affect 35 to 40% of the adult population and is related to OSA, which has a prevalence of 4 to 19% depending upon the definitions used.[1,2] The treatment of OSA has a great impact on the patient's quality of life.[3-5] Oral appliance (OA) use as a therapeutic treatment for OSA has proven over the past 10 years to effectively treat sleep apnea patients, reducing the apnea and hypopnea index (AHI)[4-10] improving oxygen saturation during sleep, reducing snoring, and more recently, reducing arterial blood pressure.[11,12] A myriad of image techniques have been used to investigate the aetiology of OSA such as cephalometrics, videofluoroscopy, tomography and magnetic resonance imaging (MRI).[13-15] The cephalometric method (two-dimensional, simple and widely established in dentistry) has been used to assess craniofacial and upper airway characteristics and predictors of sleep apnea.[16,17] Important findings recently correlate cephalometric characteristics and OA treatment outcomes.[7,18-21] The Academy of Dental Sleep Medicine suggested cephalograms as one diagnostic aid for the initial dental examination for every patient involved in OA treatment.[14,22]

Side effects due to OA use include symptoms such as dry mouth, excessive salivation, tooth and jaw discomfort, myofascial pain, tooth grinding and stiffness of the jaw, but these are frequently reported as mild, acceptable and transient.[7,23-27] In a short-term analysis of adverse events during the first year of oral appliance use, Tegelberg and collaborators[28] found that neither mandibular movements nor the occlusion had changed in patients with a mean age of 49 years. De Almeida and collaborators[29] evaluated the temporomandibular joint (TMJ) with MRI over a mean period of 11.5 months, in a sample of patients with mean age of 46, and

found no changes in the TMJ related to OA use. Otsuka and collaborators[30] revealed that over an average period of 6.5 months, the occlusal contact area and bite force decreased with the use of an OA. Subjective changes in the dental occlusion were reported in 12 to 19.2% of patients.[26, 27, 31] Using cephalometric analyses, various authors evaluated craniofacial changes induced by OA use for an average of 2 to 3 years. Significant changes were reported such as a more downward[32] and forward[32,33] mandibular position, a decrease in overbite and overjet,[24,27,32-34] a retroclination of the upper incisors, [24,33, 34] a proclination of the lower incisors,[33-35] an increase in the lower facial height[32,33,35] and a change in the molar relationship[24]. OA use also changes the upper airway configuration: a decrease in the palatal length and an increase in the pharyngeal area, probably related to a loss of the edema caused by snoring and repetitive apneas, have been reported.[33, 35]

OA therapy may be a lifelong treatment. Hence, a better understanding of the possible side effects and consequences are highly important for the design of a follow-up protocol. We postulate that longer use of OAs could cause greater changes in the patient's craniofacial structures. Therefore, the purpose of this study was to evaluate, using cephalometric data in a sample of OSA patients, the skeletal, dental and occlusal changes subsequent to OA therapy after five or more years of wear.

6.2. Methods

Patients who have been wearing an oral appliance for at least five years were identified and invited to participate in this study.[25] Patients who came to the Dental Sleep Apnea Clinic at The University of British Columbia, or to one of the authors' (AAL) private practices, for a regular follow-up of their oral appliance

and were currently using their appliance for four or more days a week on a consistent basis and had been doing so for more than five years were recruited. All patients had been treated with a mandibular advancement device for snoring and/or OSA. Even though some patients did start with a different appliance, all were currently using Klearway™ (Figure 6.1), and all of the patients were titrated until the optimal anteroposterior mandibular position was achieved as described previously.[36] The vertical opening was kept to a minimum to prevent downward rotation of the mandible. Patients were excluded if they had a missing or poor quality diagnostic upright cephalometric film. The study was approved by The University of British Columbia Ethics Committee.

The sample consisted of 71 OSA subjects, 8 females and 63 males, mean age 49.7 ± 9.7 years, with a pre-treatment respiratory disturbance index (RDI) of 28.9 ± 17.0 per hour and a body mass index (BMI) of 29.3 ± 5.9 kg/m^2. A post-treatment upright cephalogram in centric occlusion was taken for the 71 patients. Initial cephalograms in the upright centric occlusion, demographic data and sleep studies were also used to evaluate possible correlations and changes in the skeletal and dental structures. RDI was defined as the apnea and hypopnea index from a full night polysomnography or an oxygen desaturation index greater than 4% per hour from an overnight oximetry study. Demographic data used in the correlations were collected before OA insertion. The period of OA use was calculated as the interval between the date of the first appliance insertion and the date that the new cephalogram was collected. All lateral cephalometric radiographs were taken with the same cephalostat (Counterbalance Cephalometer Model W-105, BF Wehmer Co.), with the patient in the upright position, with natural head posture, in centric occlusion and at the end of tidal expiration. Tracings were constructed for each lateral head film; landmarks and traditional contours of the anatomical structures were digitized.[14,37,38] The position of the teeth, maxilla and mandible were

examined, which included: measurements of the angulations of incisors and molars (U1toSN°, U1toPP°, U6toSN°, U6toPP°, L1toMP°, L6toMP°); molar heights (MXMH, MDMH); relationship between upper and lower incisors (OB, OJ, IIA°); relationship between upper and lower molars (U6L6SN); relationship between maxilla and mandible (ANB°); size and position of the maxilla (ANS-PNS, SNA°, SNPP°); size and position of the mandible (MDUL, SNB°, SNMP°, PPMP°, SNPg°); and facial height (TFH, LFH, UFH/LFH%). In addition, we evaluated the upper airway size with tongue height (TGH) and area (TNGXA); soft palate length (PNS-P) and area (SPXA); nasopharynx area (NASOXA); oropharynx area (OROXA); hypopharynx area (HYPOXA); and vertical airway length (VAL). The condilion position was measured as previously described[33]. The points, lines, angles, distances and areas used in the cephalometric analysis of this study are provided in Figures 6.2 and 6.3. The same orthodontist (JOS) traced and digitized each cephalometric radiograph.
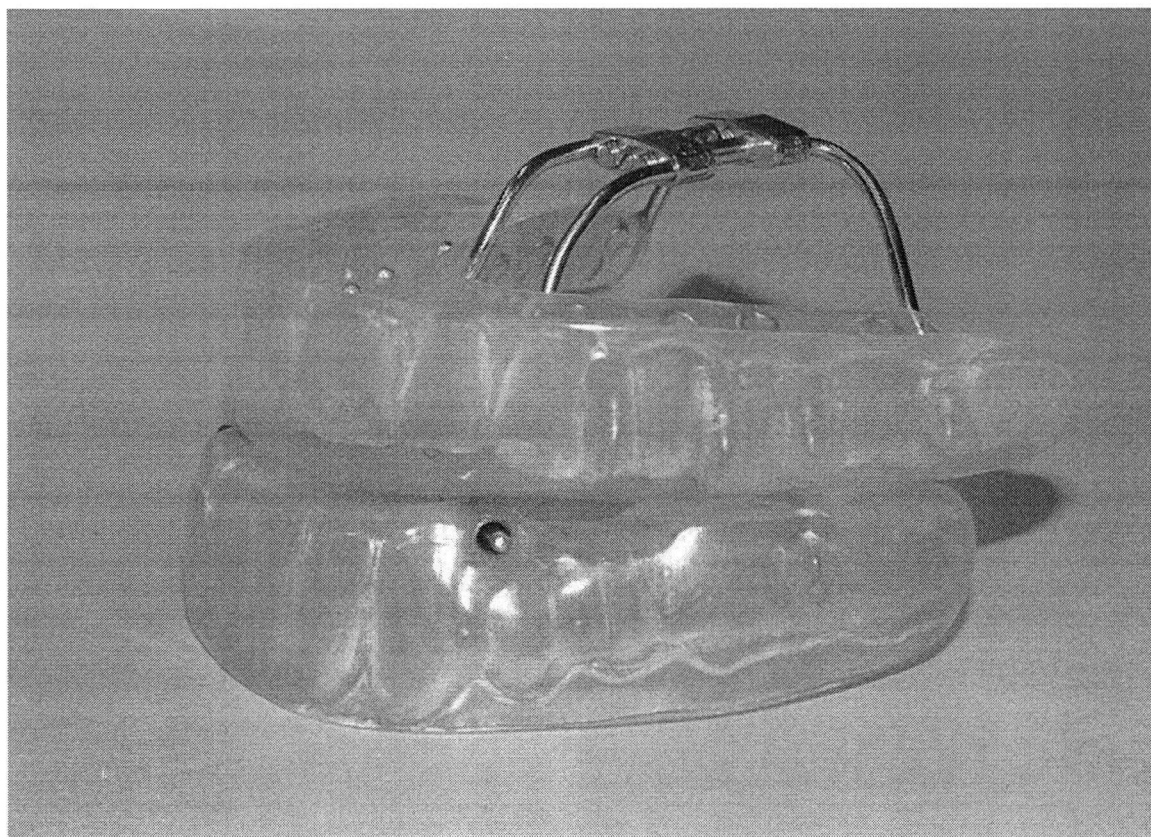
Figure 6.1. Titratable oral appliance (Klearway^{TM}·). The palatal screw enables 44 advancements of the mandible in 0.25 mm increments.
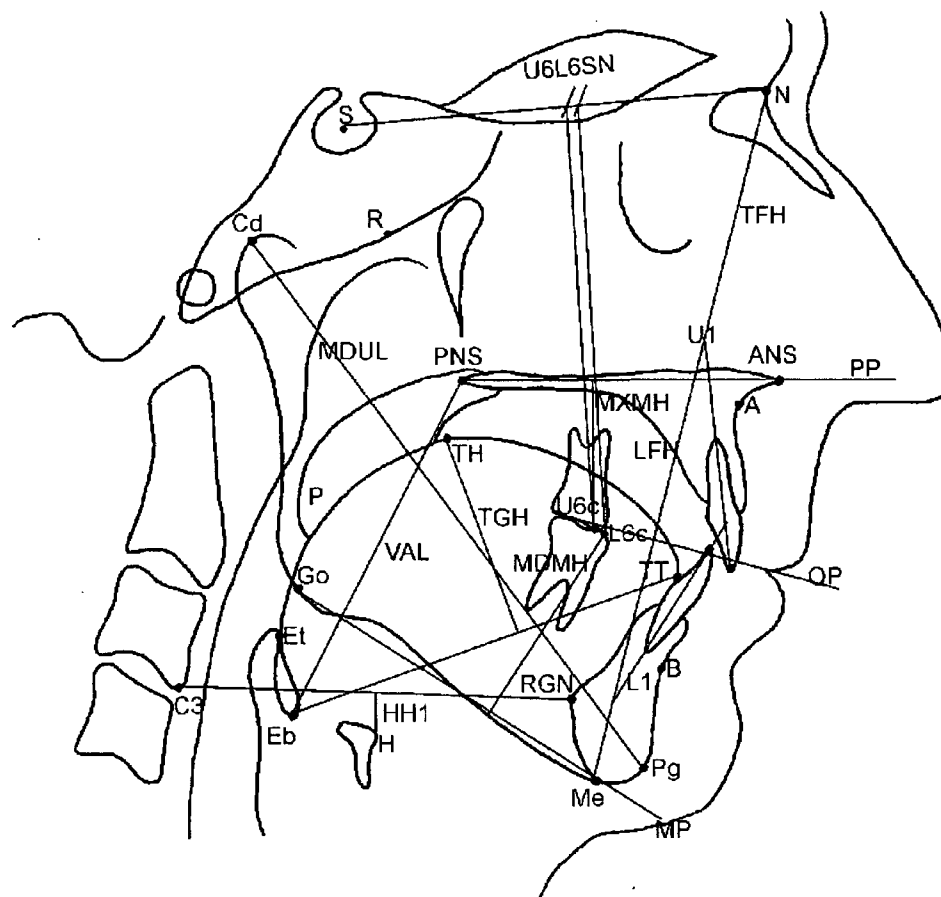
Figure 6.2. Diagrammatic representation of landmarks and variables. **POINTS**: S, sella; N, nasion; ANS, anterior nasal spine; PNS, posterior nasal spine; A, point A; B, point B; Pg, pogonio; Me, menton; RGN, retrognation; Go, gonion; Cd, condilion; U1i, upper incisor edge; U6c, upper molar mesial cusp tip; L1i, lower incisor edge; L6c, lower molar mesial cusp tip; Eb, base of epiglottis; Et, tip of epiglottis; H1, hyoid point; C3, third vertebra point; TT, tongue tip; TH, superior tongue curve point; P, tip of soft palate; R, roof of the pharynx as the point on posterior pharyngeal wall constructed by line PNS to cross-sectional point of

cranial base and lateral pterygoid plate. **PLANES**: SN, anterior cranial base, MP mandibular plane (Me-Go); PP, palatal plane (ANS-PNS); OP, occlusal plane (midpoint between maxillary and mandibular incisor edges to the midpoint between maxillary and mandibular molar mesial cusps); U1, upper incisor (connects the incisor edge to root apex); L1, lower incisor (connects the incisor edge to root apex); U6, upper molar (connects the U6c to its mesial root apex); L6, lower molar (connects the L6c to its mesial root apex). **LINEAR MEASUREMENTS** (in milimeters): MXMH, maxillary molar height (U6c $\perp$ PP); MDMH, mandibular molar height (L6c $\perp$ MP); OB, overbite (maxillary incisal edge to mandibular incisal edge on the occlusal plane); OJ, overjet (maxillary incisal edge to mandibular incisal edge on a line $\perp$ to occlusal plane); U6L6SN, maxillary molar (U6c) distance to mandibular molar (L6c) projected on S-N plane; MDUL, mandibular length (Cd-Pg); LFH, lower facial height (Me-PP on the N-Me line); TFH, total facial hight (N-Me); HH1, vertical position of hyoid (H1$\perp$ C3-RGN); TGH, tongue hight (TH $\perp$ TT-Eb); VAL, vertical airway length (PNS-Eb). **ANGULAR MEASUREMENTS**: maxillary incisor angle (U1toSN°, U1toPP°); maxillary molar angle (U6toSN°, U6toPP°); mandibular incisor angle (L1toMP°); mandibular molar angle (L6toMP°); interincisor angle (IIA°); anteroposterior position of the maxilla (SNA°); anteroposterior position of the mandible (SNB°); palatal plane angle (SNPP°); mandibular plane angle to the base of the cranium (SNMP°); mandibular plane angle to the palatal plane (PPMP°); chin position relative to cranium (SNPg°).

Figure 6.3. Diagrammatic representation of landmarks and contours used to identify tongue, soft palate, upper airway and cross-sectional areas. (1) TNGXA, tongue cross-sectional area; (2) SPXA, soft palate cross-sectional area; (3) NASOXA, nasopharynx cross-sectional area; (4) OROXA, oropharynx cross-sectional area; (5) HYPOXA, hypopharynx cross-sectional area. R, roof of the pharynx; P, tip of soft palate; Eb, base of epiglottis; Et, tip of epiglottis; H1, hyoid point; C3, third vertebra point; TT, tip of tongue; PNS, posterior nasal spine; ANS, anterior nasal spine; RGN, retrognation.

Figure 6.3. Diagrammatic representation of landmarks and contours used to identify tongue, soft palate, upper airway and cross-sectional areas. (1) TNGXA, tongue cross-sectional area; (2) SPXA, soft palate cross-sectional area; (3) NASOXA, nasopharynx cross-sectional area; (4) OROXA, oropharynx cross-sectional area; (5) HYPOXA, hypopharynx cross-sectional area. R, roof of the pharynx; P, tip of soft palate; Eb, base of epiglottis; Et, tip of epiglottis; H1, hyoid point; C3, third vertebra point; TT, tip of tongue; PNS, posterior nasal spine; ANS, anterior nasal spine; RGN, retrognation.

6.3. Data Analysis

After digitization, the results of the cephalometric analysis were transferred to a statistical package (SPSS software program, Chicago, IL). Data is presented as means ± standard deviation (SD). To assess statistically significant changes in the measurements before and during OA treatment, a paired Student's t-test was used. Bonferroni's inequality corrections for significance levels were used when multiple comparisons were made. Differences between subgroups of patients were first tested with analyses of variance (ANOVA) followed by the post-hoc Tukey test. Correlations (r) were carried out with Pearson correlation tests for parametric variables.

6.4. Results

The 71 patients included in this study had been wearing an OA for a minimum of 4 nights a week and usually for the night. The majority of the patients wore this appliance every night since without regular wear, experience of morning headaches and excessive daytime sleepiness were reported. These patients had been using an OA for 7.3 ± 2.1 years by the time the follow-up evaluation was completed. A team of five orthodontists evaluated pre- and post-treatment models and reached consensus on Angle Classification[39] for each case. The mean cephalometric changes according to craniofacial type before treatment and after long-term use of an OA for the whole sample are shown in Table 6.1. Of the 71 patients, 49 exhibit Class I, 10 had Class II Division 1, 10 had Class II Division 2, and 2 had Class III molar relationships.

For the total sample, the maxilla revealed a significant retroclination of the upper incisors (ΔU1toSN° and ΔU1toPP° equal to -3.1° and -3.5°, respectively), the

molars tipped distally (ΔU6SN° and ΔU6PP° equal to -2.3° and -2.6°, respectively) and extruded (ΔMXMH = 0.5 mm). In the mandible there was a significant downward rotation of the mandible (ΔSNMP° and ΔPPMP° equal to 0.7° and 1.0°, respectively), proclination of the lower incisors (ΔL1toMP° = 6.6°), the molars tipped mesially (ΔL6MP° = 3.4°) and also extruded (ΔMDMH = 0.7 mm). There was no significant difference in the chin position relative to cranium (SNPg°) or in the mandibular length measurement (MDUL) or in the condylion (Cd) vertical and horizontal position. The relationship between maxillary and mandibular incisors significantly changed, a decrease in OB (ΔOB = -2.8 mm), a decrease in overjet (ΔOJ = -2.6 mm), a decrease in the interincisor angle (ΔIIA° = -4.1°) and an increase in basal bone relation (ΔANB° = 0.5°). There was mesial tendency in the follow-up molar relationship (ΔU6L6SN = -1.8 mm). There was a significant increase in total facial height (ΔTFH = 1.8 mm) and lower facial height (ΔLFH = 1.8 mm), with a greater component of changes in the lower facial height since there was a decrease in the proportion of upper facial height to lower facial height (ΔUFHLFH% = -1.9%). In the analysis of the upper airway, there was an increase in vertical airway length (ΔVAL = 1.8 mm), tongue height (ΔTGH = 1.5 mm) and tongue cross-sectional area (ΔTNGXA = 119.4 mm^2). For the Class I subgroup, the only variables that were not statistically significant, in comparison to the whole sample, were the maxillary molar height (MXMH) and the basal bone relations (ANB°). In the Class II Division 1 subgroup, there were significant changes observed: proclination of lower incisor (ΔL1toMP° = 7.0°), decrease in overjet (ΔOJ = -2.4 mm) and a mesial tendency in the molar relationship (ΔU6L6SN = -2.1 mm). In the Class II Division 2 subgroup, only the upper incisors (ΔU6SN° = -3.0°) and the tongue cross-sectional area (ΔTNGXA = 150.5 mm^2) changed significantly. Although different variables became significant for

the different intermaxillary relation groups, there was no statistical difference within different craniofacial types. In this analysis, the two patients with a Class III malocclusion were excluded from the statistics because of the small sample size.

Table 6.1. Cephalometric variables that changed significantly after the use of an OA for the entire sample and for the skeletal subgroups.

	Total Sample			Class I			Class II Div 1			Class II Div 2		
	Mean	SD		Mean	SD		Mean	SD		Mean	SD	
Maxilla												
U1toSN°	-3.1	4.8	**	-3.6	4.8	**	-4.3	5.6	ns	-0.1	3.5	ns
U1PP°	-3.5	4.7	**	-4.1	4.3	**	-3.9	6.8	ns	-0.7	3.8	ns
U6toSN°	-2.3	4.4	**	-2.5	4.7	**	-1.2	4.7	ns	-3.0	2.7	**
U6PP°	-2.6	4.7	**	-3.0	4.8	**	-0.8	5.5	ns	-3.4	3.3	ns
MXMH(mm)	0.5	1.5	**	0.6	1.6	ns	0.6	1.2	ns	0.5	1.2	ns
Mandible												
SNMP°	0.7	1.9	**	0.8	2.0	**	0.7	2.1	ns	-0.1	1.8	ns
PPMP°	1.0	0.8	**	1.2	1.8	**	-0.1	1.9	ns	0.5	2.0	ns
SNPg°	-0.4	1.4	ns	-0.5	1.5	ns	-0.5	1.1	ns	0.2	1.2	ns
MDUL(mm)	0.5	2.3	ns	0.3	2.2	ns	0.6	2.5	ns	1.7	1.3	ns
L1toMP°	6.6	5.2	**	7.3	5.0	**	7.0	6.2	**	3.7	4.8	ns
L6toMP°	3.4	6.2	**	3.3	5.7	**	4.5	9.8	ns	2.4	4.9	ns
MDMH(mm)	0.7	1.5	**	0.8	1.6	**	0.8	1.5	ns	0.7	1.6	ns
Intermaxillary relationships												
OB(mm)	-2.8	2.5	**	-3.3	2.5	**	-1.6	1.7	ns	-1.9	2.1	ns
OJ(mm)	-2.6	1.9	**	-2.9	1.9	**	-2.4	1.8	**	-1.5	1.6	ns
IIA°	-4.1	6.3	**	-4.4	6.2	**	-3.5	8.3	ns	-3.6	5.6	ns
ANB°	0.5	1.2	**	0.4	1.3	ns	0.8	1.4	ns	0.4	0.9	ns
U6L6SN(mm)	-1.8	2.2	**	-1.8	2.4	**	-2.1	1.8	**	-1.5	1.6	ns
TFH(mm)	1.8	2.4	**	2.1	2.5	**	1.4	1.7	ns	1.5	2.4	ns
LFH(mm)	1.8	1.9	**	2.1	1.7	**	1.5	1.9	ns	1.6	1.5	ns
UFHLFH %	-1.9	2.8	**	-2.2	2.7	**	-1.7	2.8	ns	-1.8	2.6	ns
Upper airway												
VAL(mm)	1.8	4.1	**	1.9	4.3	**	0.5	3.9	ns	2.6	2.7	ns
TGH(mm)	1.5	3.6	**	2.0	3.8	**	0.0	2.9	ns	0.6	3.1	ns
TNGXA(mm^2)	119.4	233	**	132.2	246	**	60.8	180	ns	150.5	129	**

Variables that showed statistical significance **$p < 0.01$. SD = standard deviation. Changes expressed as post- minus pre-treatment values.

In relation to the initial overbite, as shown in Figure 6.4, the sample was divided into shallow OB (OB less than 1 mm), normal OB (1 to 4 mm) and deep overbite (OB greater than 4 mm). The deep overbite group experienced statistical significant changes in OB, OJ, LFH, PPMP°, IIA°, U1toSN°, U6SN°, L1MP° and L6MP°. The group defined as having a normal OB showed significant changes similar to the deep overbite group with exception of IIA° and L6toMP°. The lower incisor angulation (L1toMP°) was the only variable that changed significantly in the shallow bite group. There was a significant difference between the shallow OB compared to the deep overbite group regarding the overbite changes. Subjects with a deep bite (greater than 4 mm) before OA use tended to have a greater change in bite depth over time (Figure 6.4).

With respect to the duration of OA use, the sample was divided in the three subgroups: less than 6 years; 6 to 8 years; and more than 8 years of OA use, and further subdivided according to skeletal type (Table 6.2). In the analysis of the entire sample, there was a significant difference between subgroups 6 to 8 years and more than 8 years, evaluated as a smaller extrusion of maxillary molars (MXMH), less proclination of the mandibular incisor (L1toMP°) and smaller decrease in the interincisor angle in the 6 to 8 years group. The hyoid progressively increased its vertical position (HH1), showing a significant difference between the subgroups less than 6 years and more than 8 years. In the Class I subgroup, there was a significant change between the subgroups less than 6 years and more than 8 years, showing a progressive decrease in SNA°, increase in mandibular plane (SNMP°), backward position of pogonion (SNPg°) and an increase in total facial height (TFH). The OB change increased significantly between the subgroups less than 6 years and 6 to 8 years. Within the Class II subgroup, the hyoid progressively increased its vertical position (HH1) and there was smaller extrusion of mandibular molars (MDMH) (Table 6.2).
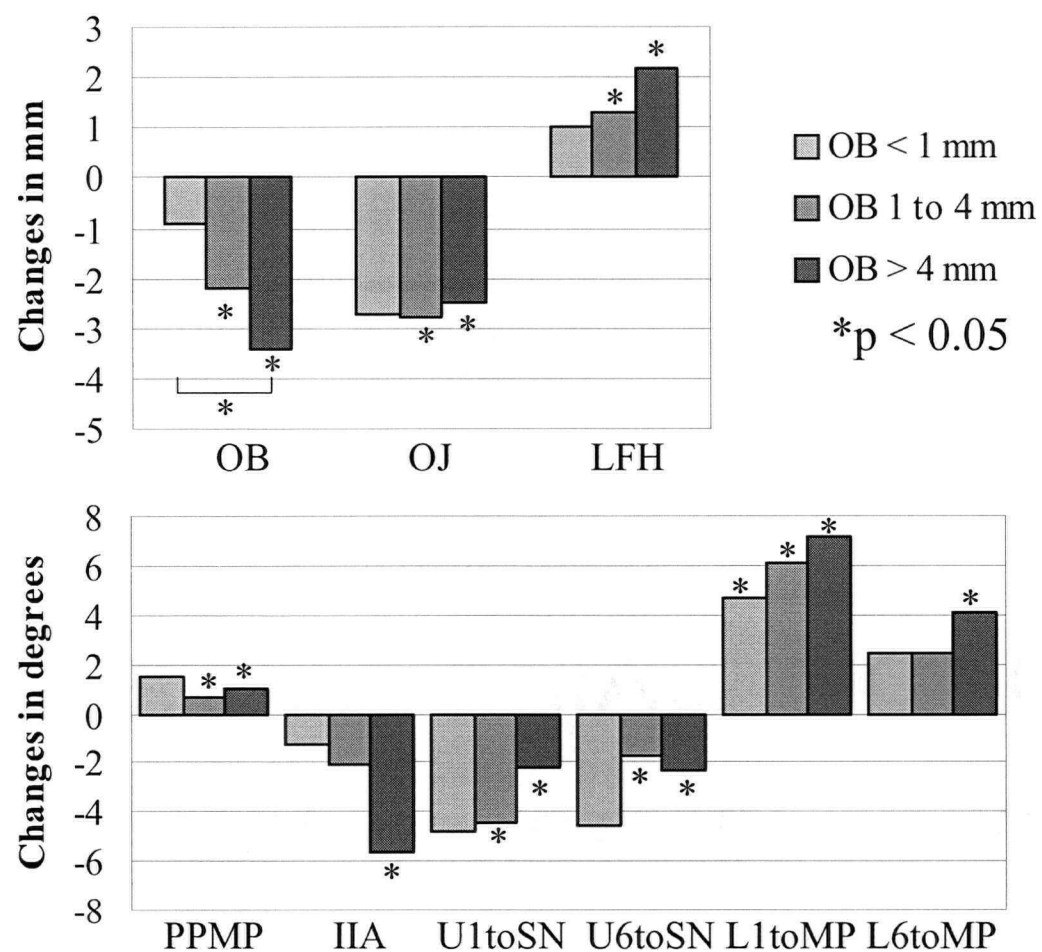
Figure 6.4. Cephalometric changes divided by initial overbite measurements.

Table 6.2. Duration of oral appliance use and amount of change.

	All (n=71)			Class I (n=49)			Class II (n=20)		
Years	< 6	6 - 8	> 8	< 6	6 - 8	> 8	< 6	6 - 8	> 8
# of patients	25	21	25	18	15	16	7	6	7
Maxilla									
SNA°	0.8	0.0	-0.3	0.9	-0.1*	-0.8	0.4	0.1	0.9
MXMH(mm)	0.7	1.1*	0.0	0.94	0.89	-0.1	0.0	1.7	0.2
Mandible									
SNMP°	0.3	0.4	1.2	-0.1	0.7*	1.9	1.2	-0.3	-0.2
SNPG°	0.1	-0.5*	-0.8	0.2	-0.6	-1.2	-0.4	-0.4	0.3
L1toMP°	6.3	8.9	5.0	6.5	9.3*	6.2	5.8	7.7*	2.8
MDMH(mm)	0.3	0.7*	1.1	0.1	0.8	1.5	1.0	0.4*	0.8
HH1(mm)	-0.5	1.3	2.5	0.3	1.5	2.7	-2.4	0.7	2.7
Intermaxillary Relationships									
OB(mm)	-2.0	-3.7	-2.8	-2.1	-4.4*	-3.8	-1.8	-2.0	-1.5
IIA °	-3.6	-6.9*	-2.4	-3.0	-7.1	-3.5	-5.0	-6.5	0.6
TFH(mm)	1.3	2.1	2.0	1.0	2.2*	3.2	2.0	1.9	0.5

* $p < 0.05$. Changes expressed as post minus pre treatment values.

Several variables showed significant correlations when analyzed with Pearson correlation. An initial deep overbite correlates with a greater reduction in the OB ($R^2 = 0.13$) and with a greater increase in LFH ($R^2 = 0.08$). An initial proclined upper incisor correlates with a greater increase in ANB° ($R^2 = 0.08$) and a greater decrease in U1toSN° ($R^2 = 0.08$). An initial steep mandibular plane correlates with more retroclination of the upper incisors ($R^2 = 0.09$). Longer use of an OA and increasing patient age correlates with a more retropositioned pogonion (Pg) ($R^2 = 0.07$ and $R^2 = 0.07$, respectively). Longer use of an OA also correlates with a more vertical position of the hyoid bone ($R^2 = 0.14$). A more severe baseline AHI correlates with a greater decrease in ANB ($R^2 = 0.13$). Apnea severity, duration of OA use and BMI did not appear to influence the OB change.

6.5. Discussion

This study demonstrates that oral appliances used for a mean period of 7.3 years have a significant impact on occlusal and dental structures, such as a 2.8 mm decrease in OB and a 2.6 mm decrease in OJ. Changes observed in the craniofacial structures were mainly related to significant tooth movements. Although some of these changes might be described as undesirable in a subset of patients, we believe that the effective treatment of a life-threatening disease, such as OSA, surpasses the concept that maintenance of baseline occlusion is mandatory. Even if major tooth movements are seen, the discontinuation of OA treatment should only occur if the patient accepts another treatment modality, such as continuous positive airway pressure. Since the greatest changes are seen in the anterior teeth, studies of OA designs with less force or pressure on the labial surface of the

maxillary incisors and on the lingual surface of mandibular incisors are indicated to evaluate whether such changes could be reduced.

This is the first study on the side effects of OAs used for periods longer than five years. In previous studies, only 12 to 19.2% of patients were reported to have occlusal changes,[26,27,31] but, as demonstrated by previous authors,[27,31,34] their perception does not correlate with objective measurements unless those changes were brought to the patient's attention by their general dentist. One study evaluated the general untreated population and found dental arch changes during life,[40] but those changes, although sometimes significant, were small, and the OB and OJ were reported to be stable during adulthood. Evaluating the literature on OAs, their side effects are very similar, are not influenced by the type of appliance, and are of greater magnitude than in the general population. OAs do impose a significant pressure on dental structures, having to hold the mandible and subsequently the tongue in a forward position. Our findings were expected, although not of this magnitude, as a result of these forces. In a review article, Aelbers & Dermault[41] concluded that most orthopedic appliances move teeth, but not craniofacial structures, and only Herbst appliances showed a significant decrease in ANB° and increase in SNB° and CdPg in children. In the orthodontic literature, it is common clinical conjecture that removable orthopedic appliances have minor effects on the adult dentition, but seldom do those appliances apply such jaw displacement forces with such a great commitment by the patients to the treatment as that seen in the OSA population.

According to our results, OAs induced tooth movements but not craniofacial skeletal changes. Actually, the changes found in this study are in the opposite direction of the findings with a Herbst appliance in a growing child population.[42] We found an increase in ANB°, a tendency for SNB° to decrease, and

no change in CdPg, which could be interpreted as a downward rotation of the mandible, seen as an increase in SNMP° related to the decrease in OB and OJ without mandibular growth. A downward rotation of the mandible without forward displacement, the absence of mandibular growth, and changes limited to dental positions found in this study confirms previous findings,[24,27,33,35,43] with the exception of Bondenmark and collaborators[32], who found an increase in mandibular length and forward rotation of the mandible. Still, these findings challenge a paradigm in orthodontics as a significant amount of tooth movement was achieved with the OA in the adult population. Although it was not measured in the present study, Marklund and collaborators[34] and Bondemanrk and collaborators[32] reported no changes between centric relation and centric occlusion before and after OA use, which also suggests that the occlusal changes found in this study are related to tooth movement and not to a neuromuscular adaptation.

As a consequence of the proclination of lower incisors, retroclination of upper incisors and molar extrusion, a rotation of the mandible, an increase in interincisal angle and an increase in lower facial height were observed. But these were not the only measurements found to be statistically significant in our study; the lower molar extruded and tipped forward as the upper molar rotated distally and extruded. This was confirmed by the mesial tendency in the molar relationship, indicating a more forward position of the lower arch (U6L6SN), also reported by Fritsch and collaborators[24] and Marklund and collaborators.[34] We interpreted that the tooth movements occurring amongst these patients are movements of the entire arch. OAs have a full-arch occlusal coverage and therefore the mechanical loading force is applied to all teeth, which could explain the mesial movement of the lower molar (L6) and distal movement of the upper molar (U6). If the incisors move, all the supporting dental structures may move as a response to this change; perhaps transceptal fibers also have an important role in

this phenomenon. A healthy periodontium is in continuous remodeling in order to maintain equilibrium and function.[44] Molar extrusion findings have not been described previously. In contrast, Rose and collaborators[31] hypothesized that intrusion of molars (seen as an increase in the posterior open-bite) is related to a vertical opening greater than 8 to 12 mm induced by the appliance. However, there were no cephalometric measurements of molar height to confirm molar intrusion in that report.

With objective cephalometric measurements, a decrease in OB and OJ is in agreement with previous studies,[24, 27,31-34] except for the results of Ringqvist and collaborators,[43] who found a decrease in OB and OJ that did not reach statistical significance. Although our study is cross-sectional and therefore there are different patients in each duration-of-use subgroup, we found that changes in OB tend to continue as long as OAs are used and this could explain why we found greater changes than previous, shorter studies. Changes in OB and OJ seem to be totally related to incisor angulation changes, which have been described as smaller but similar in preceding papers.[24,27,31-35,43]

Although studies in children show that changes related to orthodontic treatment can be predicted in part by the characteristics of the initial malocclusion, the present study found no statistical difference between the amount of dental and occlusal changes and the different malocclusion groups, which confirms previous findings.[27,31,34] Although significant levels were not achieved, we observed differences between Class I, Class II Division 1, and Class II Division 2 subjects (Table I). The OB change in Class I was -3.3 mm and in Class II Division 1 and Class II Division 2 was -1.6 and -1.9 mm, respectively. Another interesting finding was a much smaller proclination of lower incisors and retroclination of upper incisors in Class II Division 2 subjects. Even though these changes are smaller and did not achieve statistical significance, because of the intermaxillary relationships

in Class II Division 2 subjects, they may have clinical relevance, producing an anterior edge-to-edge bite. Such peculiarity may be related to our traditional concept of significant vertical muscle forces in Class II Division 2 patients. However, our sample may have been too small to find significant differences between these skeletal subgroups.

Regarding the amount of mandibular advancement, most of the patients included in this study had used one to six appliances during the period that the side effects occurred, and so the amount of advancement may have varied during treatment. Over time, the severity of OSA worsens and further advancements of the mandible may be required. As a clinical protocol for treatment with the Klearway™ appliance, mandibular advancement starts at two-thirds of maximum protrusion (6-10 mm) and further advancement is required if there is persistent snoring and/or sleep apnea symptoms. De Almeida and collaborators[29] reported that an increase in mandibular advancement was correlated to a decrease in the RDI. Marklund and collaborators[34] also found a greater efficacy of appliances with 75% advancement in comparison to 50% advancement. Although we could not ascertain the amount of advancement from the patient records, it was always greater than 6 mm. The accurate measurement of the amount of advancement and the subsequent side effects over a period of five years are still necessary to understand the mechanisms involved. Several authors reported that orthodontic changes were not related to OA design or mandibular advancement.[24,27,31] Robertson and collaborators,[33] postulated that changes in OB could be reduced with a smaller vertical opening of the appliance. Marklund and collaborators[34] reported no relationship between the amount of vertical opening and OJ change and between mandibular advancement and the amount of OB change, but reported that with a mandibular advancement greater than 6 mm, a soft elastomeric appliance had a greater risk of OJ changes than a hard acrylic appliance. However,

in the comparison of both groups, the patients who used the hard acrylic appliances experienced greater changes in OB and OJ. The Klearway™ appliance is a titratable appliance made of thermo-sensitive acrylic. We believe that the orthodontic side effects found in our and most similar studies are related to the mandibular advancement and not to differences in appliance design or material. Nonetheless, a prospective random study with two groups with different appliances is needed, including a cephalometric study in centric occlusion before treatment followed by one with the appliance in the titrated position more than five years later, to confirm the possible differences.

A particular strength of this study was the duration of OA use. This was the first study to evaluate long-term side effects over a mean time period of 7.3 years, but there are some potential limitations to this report. Patient compliance was not objectively measured. There is no commercially-available compliance monitor since the appliance must function in intraorally, without a power supply.[36] As a cross-sectional study, findings over a period of time are actually verified in different patients, and not in the same patient over time, and this could result in error. A cephalometric prospective study over a determined periodicity is required. Some patients changed the type of OA used during the time period being studied. De Almeida and collaborators[29] reported no TMJ changes with the use of an OA, but a long-term assessment of the TMJ was not accomplished in the present study, although we did not find cephalometric evidence of mandibular growth, jaw displacement or TMJ changes. For the measurements of the condylion position, there was no significant difference either in the vertical or horizontal position of condylion, in contrast to an earlier study[33] in which a significant downward displacement of condylion was seen. Condylion measurements should be interpreted with caution, since only a careful TMJ assessment, based on tomography or MRI could properly evaluate the position of the TMJ and possible

changes related to OA usage. The population in need of OAs is usually older than 40 years of age, a time during which periodontal disease tends to increase, and so a prospective study with a detailed periodontal assessment is required to evaluate this possible important predictor of tooth movement. The prevalence of sleep apnea is greater amongst men and in our clinic, over 80% of the patients are male. In a previous study,[25] females experienced more side effects and showed a greater tendency to abandon treatment when compared to men.

Dividing our sample into groups with different durations of OA use, we found that most of the changes tended to continue over time. These results are especially important because OAs may be a life-long treatment therapy and the changes in the alveolar bone over time may affect the amount of tooth movements. When the apical surface of a tooth impinges on the cortical bone, the remodeling process is no longer possible and there is a risk of root resorption or bone fenestration.[45,46] Actual measurement of alveolar bone width and shape for upper and lower incisors were not evaluated and further studies in this field are required. The consequences of OA use over 20 or 30 years is totally unknown and a careful follow-up of these patients is imperative.

From a clinical perspective, it would be useful to find good predictors of OA side effects. The present study found that patients with a baseline OB greater than 4 mm had a greater change in OB than patients with an initial OB smaller than 1 mm. The greater the initial overbite, the greater was the decrease in OB. We found other correlations, none of which were strong, but we hypothesize that there are several characteristics involved, each with a different weight of influence. A more proclined upper incisor at baseline was correlated with a greater decrease in the U1toSN angle. Another interesting finding was that the older the patient, the greater the retroposition of the mandible that was observed. Marklund and collaborators[34] found similar results and this may be related to the diminished

periodontal health in the elderly that would favor the decrease in OJ and consequent increase in SNPg°. Sleep apnea tends to worsen with age[2] and, as life expectancy increases, there may be an increased demand in the geriatric population for OA therapy. A lower hyoid position is one characteristic of OSA severity[37] and obesity is another.[47] Although we could not find a statistical difference in the hyoid position before and after treatment, we did identify that the longer a patient uses an OA, the larger the HH1 distance. Increases were also found by Robertson and collaborators[33] after one year of treatment and by Fransson and collaborators[35] after two years of treatment. We hypothesize that a greater inferior hyoid displacement could be age related since Nelson and collaborators,[48] in a longitudinal study, identified an increase in hyoid position and vertical airway length (VAL). These factors may be related to the tendency of patients to get worst with age, which might suggest the need for greater mandibular advancements over time. A larger tongue is related to a more severe apnea and to greater body mass index.[37,47] Although it was not measured, the patients studied might have gained weight and/or their apnea might have been exacerbated over the years of OA use.

6.6. Conclusions

The results of this study showed that craniofacial side effects do occur after long term OA use, which may have clinical implications. With the use of a mandibular advancement appliance over a mean duration of 7.3 years, we found significant and progressive changes in the dentition. Since OAs are a life-long treatment approach for OSA, and the changes appeared to continue over time, the

collection of cephalometric radiographs, study models, and intra-oral photographs before and during treatment should be encouraged in all clinical OA protocols.

6.7. Acknowledgements

6.8. Bibliography

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CHAPTER 7

LONG-TERM SEQUELAE OF ORAL APPLIANCE THERAPY

IN OBSTRUCTIVE SLEEP APNEA PATIENTS

PART 2. STUDY MODEL ANALYSIS

7.1. Introduction

Obstructive Sleep Apnea (OSA) is a life-threatening disease that demands treatment. Many patients receive Continuous Positive Airway Pressure (CPAP) treatment, but the acceptability of this type of therapy is compromised because of related side effects and its intrusive nature. Oral appliance (OA) therapy is accepted as a first choice treatment for patients with primary snoring and mild apnea or for moderate to severe OSA patients who are intolerant or refuse treatment with CPAP.[1] Oral appliances protrude the mandible and hold it in a forward and downward position. As a consequence, the upper airway enlarges antero-posteriorly[2] and laterally,[3,4] improving the stability of the airway.[5] The efficacy of OAs is related to adequate retention and the amount of mandibular protrusion.[6,7]

Recent studies have evaluated cephalometric side effects related to long-term use of OAs.[8-16] Most of the craniofacial side effects found were classified as orthodontic changes, interpreted mainly as tooth movements. In the analysis of study models, some authors[9,12,14] confirmed the decrease in OJ and OB found in the cephalometric analyses; there was also a significant mesial shift of the mandible. Marklund and collaborators[12] found different changes in arch width depending on the appliance used, but the mandibular intermolar distance increased with both appliances. Rose and collaborators[14] found a significant increase in mandibular arch length. All the study model changes were considered minor and clinically irrelevant within the period evaluated.

OA therapy is considered a life-long treatment and an understanding of the possible side effects and their clinical consequences is highly important for the design of a follow-up protocol. Currently, side effects have only been evaluated over relatively short time periods and a long term clinical approach to evaluate the

types of changes from study models may be relevant. We postulate that longer use of an OA will cause greater changes in a patient's dentition. Therefore, the purpose of this study was to evaluate, with the use of study model analysis, occlusal changes induced by OA therapy after more than five years.

7.2. Methods

Patients were invited to participate in this study if they had been using an OA for at least five years. Patients were recruited by telephone after being identified in a previous study[17] or as they came to the Dental Sleep Apnea Clinic at The University of British Columbia or to one of the authors (AAL) private practice for a regular follow-up of their oral appliance. All subjects were currently using the appliance for four or more days a week and had been doing so on a consistent basis for more than five years. Patients who had been treated with an appliance other than a mandibular advancement device (eg. tongue retaining device) for snoring and/or OSA were excluded. Even though some patients did start with a different appliance, all were currently using Klearway™ as described previously.[18,19] Patients were excluded if diagnostic study models were missing or of poor quality. The University of British Columbia Ethics Committee approved the design of this study.

This study sample consisted of 70 subjects, 7 females and 63 males, mean age 50.0 ± 9.7 years, with a pre-treatment Respiratory Disturbance Index (RDI) of 28.0 ± 14.9 per hour and a Body Mass Index of 29.3 ± 5.8 kg/m^2. Baseline and treatment follow-up study models in centric occlusion were obtained for all patients. Initial study models, demographic data and sleep studies were also used to evaluate possible correlations and changes in the dental structures and occlusion. RDI was defined as the apnea and hypopnea index from a full night

polysomnography or an oxygen desaturation index greater than 4% per hour from the overnight oximetry. Demographic data used in the correlations was always collected before OA insertion. The period of OA use was calculated as the interval between the date of the first appliance insertion and the date that the new study models were collected. All the measurements on the study models were taken by one orthodontist (MF) and reviewed by another (SF).

Angle's classification of malocclusion was used to identify the antero-posterior relationship of maxillary and mandibular first molars and canines. Class I molar was defined as the mesiobuccal cuspid of the maxillary first permanent molar falling within the groove between the mesial and middle cuspid of the mandibular first permanent molar. Class II molar was defined as the occurrence of a distal (posterior) relationship of the mandibular molar, mesial (anterior) relationship of the maxilla, or a combination of the two where the mesiobuccal cuspid of the maxillary first molar occludes mesially to the buccal groove of the mandibular molar. Class III molar was defined as the mesial (anterior) relationship of the mandibular first molar to the maxilla, a retruded relationship of the maxillary first molar to the mandible, or a combination of the two where the mesiobuccal cuspid of the maxillary first molar occludes near the embrasure between the mandibular first and second molars. Class I canine was defined as the maxillary canine occluding between the mandibular canine and first bicuspid. Class II canine was defined as the maxillary canine occluding mesially of the contact between mandibular canine and first bicuspid. Class III canine was defined as the maxillary canine occluding distally of the contact between mandibular canine and first bicuspid. For statistical purposes, to follow a linearity of positions, Class II (canine and molar) was coded as 1, Class I (canine and molar) as zero (0) and Class III (canine and molar) as -1. Mesial shifts of mandibular molar and canine were expressed with negative values.

A sliding caliper to the nearest 0.05 mm was used to measure overjet, overbite, arch length, intermolar and intercanine distances. The overjet (OJ) was measured as a horizontal projection of the midpoint to the labial surface of the maxillary teeth beyond the labial surface of the mandibular teeth, measured parallel to the occlusal plane, at the level of the edge of the maxillary incisor. This measurement (mm) was made for each of the anterior teeth (left and right central incisor, lateral incisor and canine). The anterior overjet was calculated as the mean of the OJ between the maxillary central incisors (11 and 21). Overbite (OB) was defined as the vertical overlapping of the edge of the maxillary teeth over the buccal surface of the mandibular teeth, measured perpendicular to the occlusal plane for all anterior teeth (left and right central, lateral and canine). The anterior overbite was calculated as the mean of the OBs between the maxillary central incisors (11 and 21). Arch length was measured as the millimeter distance, through the general alignment of contact points, from the mesial contact surface of one permanent first molar to the mesial contact surface of the contra-lateral permanent first molar. If the first permanent molars were missing, second molars were used. Intermolar distance was the width between the mesio-lingual cusp of the first permanent molar to the mesio-lingual cusp of the contra-lateral molar; it was measured for the maxillary and mandibular molars. If the first permanent molars were missing, second molars were used. Intercanine distance was measured as the width between the centers of the cuspid of the permanent canine to the contra-lateral canine. If the canines were missing, it was considered missing data unless the first premolar was in the space of the canine and functioned as a canine before and after treatment. In relation to the initial overbite, the sample was divided into shallow OB (less than 1 mm), normal OB (1 to 4 mm) and deep OB (greater than 4 mm).

Other assessments of tooth movements and occlusion were accomplished by visual analysis. Changes in crowding, appearance of interproximal open spaces within the upper or lower arch, tipping and rotations, occlusal contacts, size of occlusal contacts, and anterior and posterior crossbites were evaluated. Crowding was defined as an altered tooth position caused by inadequate space in the alveolar arch, and classified as increased, decreased or no change after treatment. Evaluation of interproximal open spaces was done for the upper and lower arches by examining the study models and looking at the anteroposterior contact surfaces of the teeth before and after treatment. Only open spaces created after treatment were counted; tipping was recorded as tooth movement, either spontaneous or therapeutic. Tipping was recorded as mesial, distal, buccal/labial or lingual on individual teeth after treatment. Rotation (torsiversion) was interpreted as tooth malposition in which the tooth became rotated around its long axis, resulting in the actual contact point with the proximal teeth being different from the optimal anatomic contact point orientation. Rotations were recorded if they occurred after treatment as mesiolingual and distobuccal rotations.

Occlusal contacts (the relationship of the maxillary and mandibular teeth as they were brought into functional contact) were recorded before and after treatment, using articulating paper and by the number of teeth in contact were determined. Size of occlusal contacts were classified as increased, decreased or no change with the articulating paper.

Crossbite or edge-to-edge was an abnormal relationship of a tooth or teeth to the opposing teeth in which normal buccolingual relationships were either in edge-to-edge relation or reversed relation, mandibular teeth more buccally than maxillary teeth. Both anterior (33 to 43) and posterior (38 to 34 and 44 to 48) evaluations were done separately and, if one or more teeth were in crossbite, the number of mandibular teeth in crossbite was recorded. In the posterior openbite

assessment, the number of maxillary teeth that lost contact with the mandibular teeth was counted.

Five orthodontists first evaluated the type of malocclusion (Class I, Class II Division 1, Class II Division 2 or Class III) and then, with all the baseline and follow-up study models, these same orthodontists (blinded to all actual study model measurements) determined if there was no change, if the change was favorable or unfavorable, and to what degree (small, intermediate or large). For this assessment, the following definitions were used: no change if there was no or a very small movement that was not clinically relevant; a favorable change if there was a correction of Class II molar, correction of Class II canine, reduced OJ or OB, reduced palatal impingement or reduced mandibular incisor crowding; an unfavorable change if there was a change to edge-to-edge incisors, reverse OJ or OB, vertical openbite, reduced interarch contacts or a posterior crossbite.

7.3. Data Analysis

The results of the study models analysis were evaluated with a statistical package (SPSS software program, Chicago, IL). Data is presented as percentage or means ± standard deviation (SD). To assess the statistical significance of changes in the measurements before and during OA treatment, a paired Student's t-test was used for parametric variables while non-parametric changes (molar relation, canine relation, type of change, size of contact area and crowding) were analyzed with Wilcoxon's paired matched test or Yates Corrected Chi-square. Differences between subgroups of patients were first tested with analyses of variance (ANOVA) followed by the post-hoc Tukey test. Correlations (r) were carried out with Pearson correlation tests for parametric variables or with Spearman tests for the non-parametric variables. A P value of <0.05 was considered significant.

7.4. Results

After the use of an OA for a mean of 7.4 ± 2.2 years, a study model evaluation was completed in 70 patients. As shown in Table 7.1, five orthodontists found that 48 patients were initially Class I, 10 patients were Class II Division 1, 10 patients were Class II Division 2, and 2 patients were Class III Angle relationship. A dental or occlusion change was verified visually in 85.7% of the patients. In the assessment of these types of changes that were induced by the OA, the orthodontists found no clinical change in 10 patients (14.3%), favorable changes in 29 patients (41.4%) and unfavorable changes in 31 patients (44.3%). Favorable and unfavorable changes were then further subdivided into small, intermediate and large and separated according to skeletal subtype. The unfavorable group included more Class I individuals while the favorable included more Class II in the pre-treatment Angle relationship evaluation.

Table 7.1. Occlusal changes according to skeletal subtype.

		Cl I	Cl II Div1	Cl II Div2	Cl III	Total
No change (14.3%)		6	1	2	1	10
Favorable (41.4%)	Small	6	5	2	0	13
	Intermediate	6	1	6	0	13
	Large	0	3	0	0	3
Unfavorable (44.3%)	Small	8	0	0	0	8
	Intermediate	14	0	0	1	15
	Large	8	0	0	0	8
Total		48	10	10	2	70
%		69%	14%	14%	3%	100%

When evaluating the mandible to maxilla relationship, there was a significant mesial shift of mandibular canines and molars. For the right side molar relationship, there were 5 Class II that turned into Class I, 7 Class I that turned into Class III, and 1 Class II that turned into Class III. On the left side, there were 7 Class II that turned into Class I, 10 Class I that turned into Class III, and 2 Class II that turned into Class III.

Differences between the skeletal subtypes according to the type of change revealed several differences in their pre-treatment craniofacial structures, in their follow-up evaluation, and in the amount of change as indicated in Table 7.2. In the pre-treatment evaluation, the unfavorable group included more Class I individuals while the favorable included more Class II subjects. The pre-treatment left mandibular canine was more mesially positioned in the unfavorable group compared to the favorable, while on the right side a similar significant difference was found between the no change and favorable subgroups. The initial OB and OJ was significantly smaller pre-treatment in the unfavorable group compared to the favorable one. In the post-treatment measurements, the unfavorable group was statistically different from the favorable group and from the no change group, showing a more mesial and Class III canine relation, and smaller OB and OJ. The no change group was statistically different from the unfavorable group in their canine relation (right and left), anterior and posterior crossbite, OB and OJ. The no change group was different from the favorable group changes in OB and OJ. These calculations revealed a significant difference between the unfavorable and favorable groups for canine mesialization, number of teeth per patient that changed into an edge-to-edge or crossbite in the anterior and posterior segments, and the number of teeth per patient that changed into an edge-to-edge or posterior open-bite relationship (Table 7.2).

Table 7.2. Differences between the skeletal subgroups according to the type of change.

	Unfavorable n = 31	No Change n = 10	Favorable n = 29
Pre-treatment		**	
Molar Type [a]	0.97	1.40	1.86
Canine Relation R [b]	0.29	0.00 *	0.62
Canine Relation L [b]	0.29	0.60 **	0.79
OB (mm)	2.70	4.46 **	4.47
OJ (mm)	2.12	2.75 **	3.95
Post-treatment		*	
Canine Relation R [b]	-0.34	-0.10 **	0.31
Canine Relation L [b]	-0.33 *	0.50 **	0.62
OB (mm)	0.46 **	3.87 **	2.52
OJ (mm)	0.45 **	2.90 **	2.72
Changes		* *	
Canine Relation R [b]	-0.65	-0.10	-0.31
Canine Relation L [b]	-0.67 *	-0.10 **	-0.17
Anterior Crossbite [c]	3.57 **	0.00 **	0.66
Posterior Crossbite [c]	2.53 *	0.40 **	0.80
Posterior Openbite [d]	0.20	0.10 *	0.04
OB (mm)	-2.29 **	-0.58 *	-1.90
OJ (mm)	-1.75 **	0.17 *	-1.20

All values are expressed as means.

$*$ $p<0.05$ and $**$ $p<0.01$.

[a] Class I = 1, Class II Div 1 = 2, Class II Div 2 = 3 and Class III = 0.

[b] Class I = 0, Class II = 1 and Class III = -1. Negative changes are related to a mesial shift of the mandible.

[c] Number of teeth per patient in edge-to-edge or crossbite.

[d] Number of teeth per patient in that condition.

The interarch relation revealed a decrease in OB and OJ in the entire anterior segment (see Figure 7.1). An OB decrease of more than 1 mm occurred in 68.6% of the patients and an OJ decrease of more than 1 mm occurred in 50% of the patients. A schematic of OB and OJ changes in the different craniofacial subgroups is provided in Figure 5.1. The Class I and Class II Division 1 patients showed a significantly smaller OB and OJ in the post-treatment measurements while the Class II Division 2 subjects demonstrated differences in the OB but not in the OJ.

CLASS I

CLASS II Division 1

CLASS II Division 2
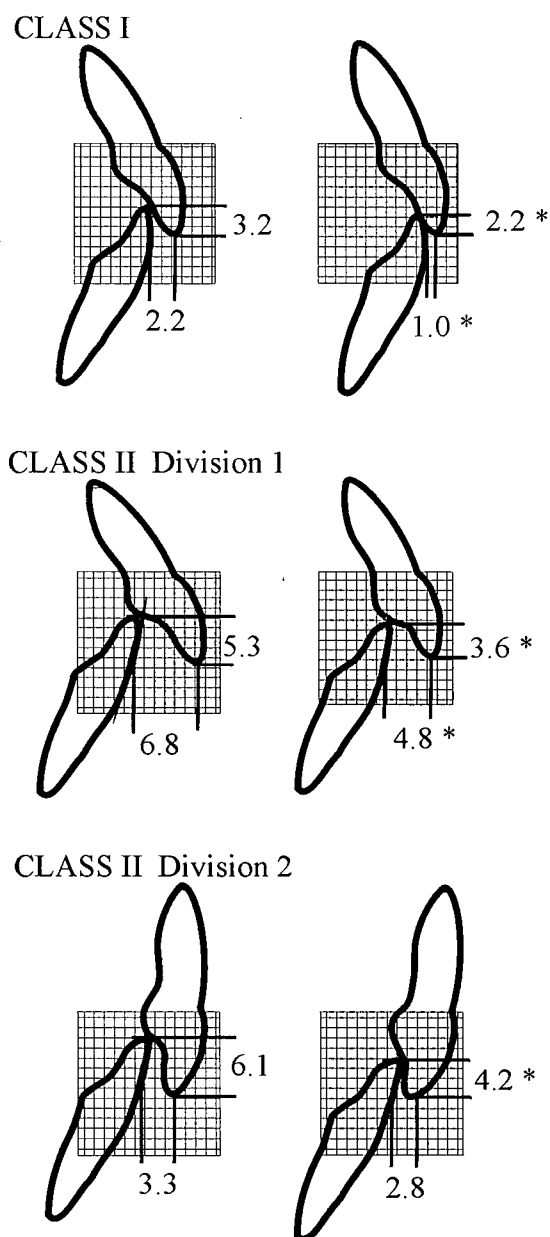
Figure 7.1. Schematic representation of the mean changes in OB and OJ according to the type of malocclusion. *Significant changes (p<0.05).

All of the mean changes and standard deviations for the study model variables divided according to skeletal type are provided in Table 7.3. Evaluating all of the patients combined, there were significant changes in the number of interproximal open spaces in the maxilla; in the mandible there were significant increases in intercanine, intermolar and arch length distances as well as in the number of interproximal open spaces. For the assessment of interarch relations, there were changes in OB, OJ, OB and OJ measured in each specific anterior tooth, a more mesial molar and canine relation on the right and left sides, a decrease of the number of teeth per patient in contact with the opposing teeth, and an increase in the number of teeth per patient in anterior and posterior crossbites. After we evaluated the Class I craniofacial subgroup separately, the same variables described above changed significantly. Class II Division 1 subjects demonstrated significant changes and in almost all anterior teeth OB and OJ, with the exception of the OJ measured on teeth 12 and 23. The Class II Division 2 subjects showed significant alterations in OB, and in OB of each anterior tooth, while the OJ only changed significantly on tooth 13. Class I subjects, in comparison to Class II Division 1 and Class II Division 2 subjects, demonstrated a greater change in the canine mesialization (left and right) and in the number of teeth per patient in anterior crossbite. Class II Division 1 differed from the Class II Division 2 patients, showing a greater decrease on the OJ measured on tooth 22 and 23.

Table 7.3. Study model measurements, expressed values are follow-up minus initial measurement.

Variables	Total Sample (n=70)			Class I (n=48)			Class II Div 1 (n=10)			Class II Div 2 (n=10)		
	Mean	SD	p	Mean	SD	p	Mean	SD	p	Mean	SD	p
Maxillar												
Intercanine, mm	-0.09	0.59	ns	-0.17	0.62	ns	-0.07	0.34	ns	0.28	0.59	ns
Intermolar, mm	0.16	0.79	ns	0.14	0.83	ns	0.01	0.79	ns	0.46	0.69	ns
Arch length, mm	0.07	1.19	ns	0.07	1.32	ns	-0.05	1.04	ns	0.18	0.88	ns
Interprox. open spaces [a]	0.43	0.94	**	0.48	0.92	**	0.40	0.70	ns	0.10	1.20	ns
Crowding [b]	0.03	0.38	ns	0.08	0.35	ns	0.00	0.47	ns	-0.20	0.42	ns
Mandible												
Intercanine, mm	0.40	0.66	**	0.42	0.66	**	0.59	0.76	ns	0.18	0.66	ns
Intermolar, mm	0.57	0.78	**	0.65	0.75	**	0.44	0.87	ns	0.41	0.56	ns
Arch length, mm	0.50	0.93	**	0.52	0.94	**	0.75	1.15	ns	0.25	0.73	ns
Interprox. open spaces [a]	0.77	0.36	**	0.88	1.33	**	0.60	1.26	ns	0.60	1.78	ns
Crowding [b]	-0.03	0.59	ns	0.04	0.62	ns	-0.30	0.48	ns	-0.20	0.42	ns
Interarch relation												
Overbite, mm	-1.91	1.53	**	-2.03	1.71	**	-1.67	1.31	**	-1.87	0.44	**
Overjet, mm	-1.24	1.52	**	-1.23	1.50	**	-1.97	1.56	**	-0.48	1.21	ns
OB 13, mm	-2.00	1.82	**	-2.16	2.01	**	-1.93	1.53	**	-1.52	0.86	**
OB 12, mm	-1.99	1.78	**	-2.21	2.00	**	-1.47	1.25	**	-1.83	0.70	**
OB 11, mm	-1.93	1.59	**	-2.08	1.79	**	-1.56	1.22	**	-1.94	0.54	**
OB 21, mm	-1.88	1.53	**	-1.99	1.66	**	-1.79	1.53	**	-1.79	0.56	**
OB 22, mm	-1.81	1.41	**	-1.99	1.53	**	-1.50	1.14	**	-1.51	1.06	**
OB 23, mm	-1.96	1.83	**	-2.28	2.02	**	-1.25	1.14	**	-1.49	1.03	**
OJ 13, mm	-1.07	1.24	**	-1.23	1.42	**	-0.61	0.41	**	-0.70	0.52	**
OJ 12, mm	-1.45	1.51	**	-1.34	1.36	**	-1.96	1.99	ns	-1.04	1.41	ns
OJ 11, mm	-1.28	1.57	**	-1.23	1.54	**	-2.05	1.81	**	-0.63	1.16	ns
OJ 21, mm	-1.20	1.54	**	-1.21	1.52	**	-1.88	1.46	**	-0.32	1.29	ns
OJ 22, mm	-1.39	1.51	**	-1.31	1.42	**	-2.35	1.90	**◇	-0.69	1.10	ns
OJ 23, mm	-1.27	1.56	**	-1.17	1.18	**	-2.65	2.57	ns ◇	-0.23	0.80	ns
Molar relation R [c]	-0.26	0.49	**	-0.34	0.54	**	-0.11	0.33	ns	-0.14	0.38	ns
Molar relation L [c]	-0.39	0.56	**	-0.47	0.61	**	-0.20	0.42	ns	-0.17	0.41	ns
Canine relation R [c]	-0.43	0.58	**	-0.50	0.55	** †	-0.30	0.67	ns	-0.30	0.67	ns
Canine relation L [c]	-0.38	0.57	**	-0.47	0.58	** †	-0.20	0.63	ns	-0.10	0.32	ns
Size of contact area [b]	-0.47	0.74	**	-0.48	0.77	**	-0.40	0.70	ns	-0.40	0.70	ns
Tooth in contact [a]	-3.01	4.60	**	-3.58	5.00	**	-1.80	3.19	ns	-1.20	2.66	ns
Anterior crossbite [a]	1.81	2.36	**	2.46	2.46	** †	0.20	0.42	ns	0.10	0.32	ns
Posterior crossbite [a]	1.49	2.06	**	1.69	2.20	**	1.00	1.76	ns	0.60	1.58	ns

** p< 0.01, ns stands for not significant, variables shown as mean changes and standard deviation (SD).

† Changes significantly different from the other groups (Class II Division 1 and Class II Division 2).

◇ Changes significantly different from Class II Division 2.

[a] Number of teeth per patient in that condition.

[b] Means are calculated from the scores: decrease = -1, no change = 0 and increase = +1.

[c] Means are calculated from the scores: Class I = 0, Class II = 1 and Class III = -1.

Negative changes are related to a mesial shift of the mandible.

As to the number of teeth that had lost contact with the opposite arch, there was a mean decrease of three teeth per patient. This change varied from the worst case, where 13 teeth lost contact to the best case, where 6 teeth gained contact. The contact area increased in 10 patients, did not change in 17 patients and decreased in 43 patients. In the estimate of anterior and posterior openbite, most of the patients showed a combination of two or more teeth in the edge-to-edge or open-bite relation. After we calculated the percentage of patients that showed specific teeth changing into an edge-to-edge or open-bite relationship, the premolars were most common in this relationship (over 14%). The buccolingual relationships measured as changing into an edge-to-edge relationship or cross-bite varied depending on the amount of teeth that came into this relationship. For the anterior segment, 39 patients (55.7%) showed no change while 10 patients (14.3%) showed all six anterior teeth with abnormal labiolingual relationships. For the posterior segment, 35 patients (50%) showed no change, while no one showed all eight posterior teeth with abnormal buccolingual relationships; all of the percentages of patients with 0 to 8 teeth under such conditions are shown in Table 7.4.

Table 7.4. Frequency and percentages of total number of teeth per patient that changed into an edge-to-edge or crossbite relationship.

	Anterior (13-23)		Posterior (18-14,24-28)	
	Frequency	%	Frequency	%
0	39	55.7	35	50.0
1	4	5.7	11	15.7
2	3	4.3	6	8.6
3	2	2.9	5	7.1
4	9	12.9	6	8.6
5	3	4.3	2	2.9
6	10	14.3	2	2.9
7	n/a	n/a	3	4.3
8	n/a	n/a	0	0.0

n/a = not applicable

With regards to tooth tipping and rotation, 7 patients did not reveal such changes. Mesial tipping appeared in 19 patients, affecting one to six teeth per patient, mostly in the lower arch. Distal tipping only appeared in the upper arch of three patients (1 or 2 teeth). Buccal/labial tipping occurred in 73.9% of the patients within the range of 1 to 12 teeth and mostly in the mandibular anterior teeth. Lingual tipping appeared in 21.1% of the patients, mainly in the maxillary anterior incisors. Mesiolingual and distobuccal rotations were predominant in the lower arch and appeared in 27.1% and 35.7% of the patients, respectively.

With respect to the initial overbite subgroups, the deep overbite group experienced a significantly greater change in OB when compared to the shallow OB group (p=0.008). Analyzed with Pearson or Spearman correlations, the following variables showed significant correlations. A longer use of the OA correlated with more interproximal open spaces in the maxilla (r=0.267) and less change in the mandibular intermolar distance (r = -0.302). The older the patient at the beginning of treatment, the greater the change in OB (r = -0.270). An initial deep overbite correlated with a more favorable change (r = 0.362), less anterior crossbite (r = -0.351) and greater reduction in the OB (r = -0.321). The greater the initial OJ, the more favorable change (r = 0.397), less anterior crossbite (r = -0.276) and greater the decrease in OJ (r = -0.306).

7.5. Discussion

Even though OAs have been used to treat snoring and sleep apnea for the past 15 years, their side effects over periods longer than five years are still uncertain. The present study is the first one to demonstrate that oral appliance use for a mean period of 7.4 years affects occlusal and dental structures, such as an increase in mandibular arch length, a mesial shift of the mandibular teeth, a

decrease in OB and a decrease in OJ. In contrast to previous studies, we found significant orthodontic side effects in 85.7% of the patients and suggest that tooth movement increases with the longer use of OAs.

OA mechanisms of action on the dentition may be very similar to functional appliances, such as Herbst or twin-block appliances, but OAs are used in non-growing adults and for only 6 to 8 hours a day. Unlike an orthodontic setting, the treatment plan for snoring and OSA does not attempt tooth movement. Although some tooth movement was expected, we found that in 41.4% of the patients, these changes were actually favorable for the patient's occlusion; this is the first study to acknowledge that not all tooth movements are clinically undesirable. Important findings in the difference between unfavorable (44.3%) and favorable (41.4%) changes are relevant to the initial clinical assessment of patients referred for OA treatment. The favorable occlusal changes cases, as determined by the initial dental evaluation, were more likely to be in Class II Division 1 or Class II Division 2 subjects, with a more distal mandibular canine position and a greater initial OB and OJ. Most patients who presented with an unfavorable change were Class I at the beginning of treatment. The unfavorable cases significantly changed their occlusion more into an edge-to-edge or anterior and posterior crossbite as well as openbite position. In previous papers, the authors pointed out that the side effects induced by OAs were small[12] and clinically irrelevant.[14] However, minimal or no change conditions were found in only 14.3% of our patients, the no change group. This group that did not show any changes had only one characteristic that significantly differed from the favorable group in the initial evaluation, the right side canine relationship. The differentiation between the groups was done blinded to all measurements, and after the study model analysis was concluded, we could find some measurement changes in the "no change" group, but because they were

minor, they were probably not detected clinically. There was no correlation with the period of OA use, but patient compliance was not objectively measured.

The present study and the study from Rose and collaborators[14] found changes in the maxilla that did not achieve statistical significance. In contrast, Marklund and collaborators[12] found a decrease in the maxillary inter-canine distance (0.3 mm) with a hard acrylic device and an increase in the mandibular molar width (0.2 mm) with an elastomeric device. In our results, we could not find statistical differences in maxillary inter-canine and inter-molar distances, arch length or crowding. In a small section of our sample, the Class II Division 2, the maxillary canine and molar widths increased by 0.28 and 0.46 mm, respectively. Although it was not specified by Marklund and collaborators,[12] the different skeletal subgroups characteristics might be an explanation for the differences in the results. It appears that the maxilla is more stable during adulthood than the mandible[20] and may be less prone to changes over time.

Interestingly, the mandible showed an increase in canine and molar widths, arch length and the number of interproximal open spaces. It has been shown that the mandibular incisors are proclined with the use of OAs,[10] possibly causing an enlargement of the mandibular arch length. An increase in the arch length and anterior spaces[14] or an increase in the intermolar distance[12] was previously found. This is the first study which could determine if all of these measurements, as well as the intercanine distance, changed significantly. Although the mandibular arch can experience changes over the years in adults, the changes found in the present study are in the opposite direction to the changes found in untreated patients.[20] In snoring and OSA patients, OA induced changes occur in the same direction as that observed with functional appliances.[21] The time period of OA use in the present study was longer than in previous studies and so we hypothesize that some of these tooth movements do continue with longer use of the appliance. The forces

induced by the appliance in an artificial forward position may explain the increase in intermolar distance, or there might be a tongue posture change as the upper airway is enlarged, with a more anterior position of the tongue during the night. During the day, the tongue might be slightly more anteriorly positioned, which would apply forces in the lateral directions of the molars. As confirmed by previous cephalometric analysis,[19] the mandibular molars do extrude, and during this extrusion movement, the molar might be more susceptible to buccal tipping, thus widening the arch.

OB and OJ changed significantly in our sample, in accordance with previous reports of a similar and regular pattern of tooth movement induced by OA use.[8-15] Although there was no significant difference between different malocclusion groups for OB and OJ, there were significant differences between Class II Division 1 and Class II Division 2 subjects for the OJ change of teeth 22 and 23. The OJ did change significantly except in Class II Division 2 subjects, which was expected orthodontically, since Class II Division 2 patients present with a deeper initial overbite associated with retroclination of maxillary incisors, greater muscle activity, more hypertonic lower lips and therefore appear to be more difficult to treat orthodontically.[22] The amount of change in OB and OJ was not significantly different between favorable and unfavorable groups; this finding is important in the interpretation that OAs do change the anterior teeth relationship but, depending on the initial teeth position, the changes may or may not be favorable.

There were some differences between right and left side changes. The forces imposed on the teeth by the OA are reciprocal to the forces of the muscles that try to bring the mandible to a centric relationship. The OA used in the present study has a full-arch occlusal coverage and the bite registration midline was obtained at two thirds of full protrusion according to the patient's repeatable path

of comfortable protrusion. Therefore, the mechanical loading was applied to all teeth in protrusion. We hypothesize that the forces of the mandible during chewing, speech and bruxism do not follow a centered straight line, but instead are directed to the preferred chewing side or to the side with the greater condyle displacement. The distribution of chewing side preference in the population seems to be related to hemispheric laterality and does not change depending on missing teeth, implants or restorations; the right side is predominantly used for chewing, ranging from 73.3 to 85% of subjects.[23] The right and left condyle displacement with the OA in place was described as equal or with the right side in a more forward position.[6] Based on chewing side preference and condyle position, the forces of the mandible would be backward and to the right, and consequently the force applied by the appliance on the teeth would be forward and angulated to the left (see Figure 7.2). Because of the arch shape, the force vectors in each tooth are different. Our findings support this angled force theory since, on the right side, the forces on the canine have a greater mesial vector direction, and we found a greater change in the canine relationship on the right side (mesial movement); on the opposite side, the force vector had a labial (buccal) direction, which would explain the smaller mesial movement and the greater decrease in OJ. The forces on the right molar are mesial, towards the premolar, and encountering this resistance in the arch produced less molar relation changes, while on the left side, the forces were mesial and buccal, and hence the left molars would be more prone to move buccally and mesially, which explains the greater change in molar relationship on this side (see Table 7.3 and Figure 7.2).
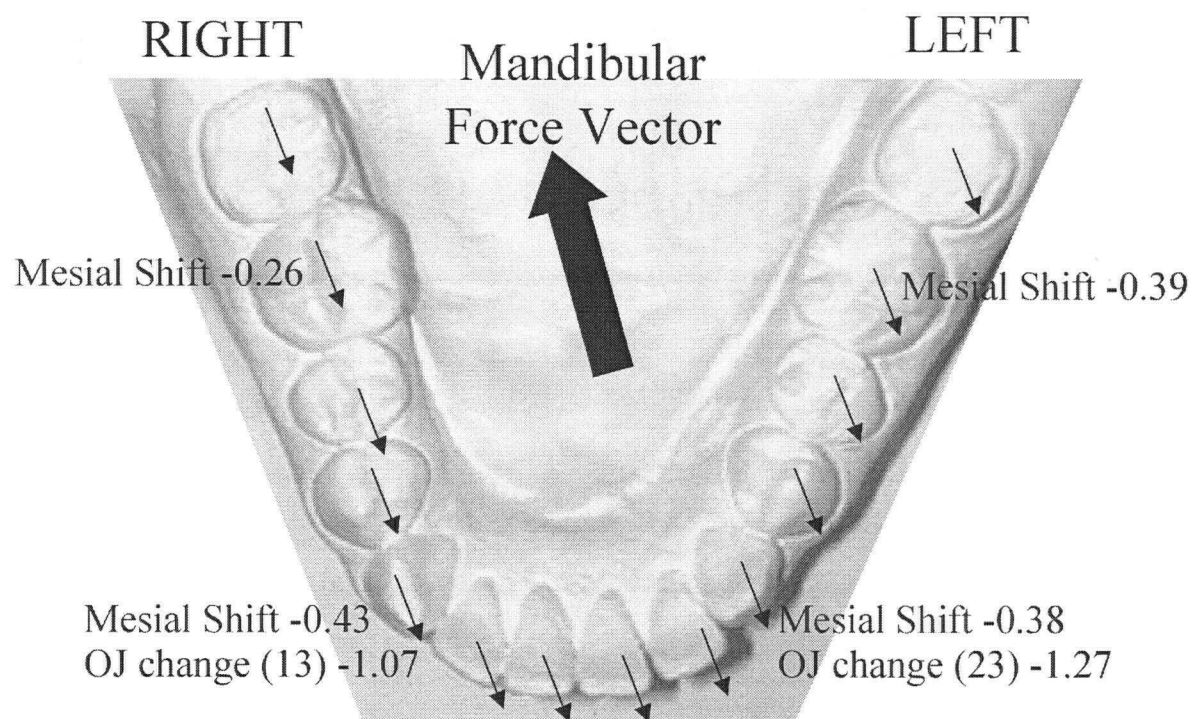
Figure 7.2. Hypothetical forces of the mandible in a right-sided chewer and the forces, represented with small arrows, that the OA may apply to each individual tooth.

This is the first study to quantify tooth rotation and tipping movements after long term OA use. Even though the OA used in this study has a full occlusal coverage, we should not exclude such analysis, as OAs appear to move teeth in an uncontrolled environment. All the anterior and posterior open bites of our patients changed significantly, similar to a prior study,[14] and we found that the premolars appeared in edge-to-edge or openbite relationships in up to 14% of our patients while the molars showed a slightly lower frequency of up to 11% (Figure 7.2). Once a patient shows this kind of change, there is often a combination of more than one tooth in an edge-to-edge or openbite condition.

From a clinical perspective, it is important to determine useful predictors of OA side effects in snoring and OSA patients. We have found some correlations, none of which were very strong, but we hypothesize that there are several characteristics involved, each with a different weight of influence. A deeper OB correlated with a greater reduction in the OB and the greater the initial OJ, the greater the reduction in OJ. There is also a correlation between a greater OB and OJ and a more favorable change and lower incidence of anterior crossbite. There was a correlation between older age and a decrease in OB; Marklund and collaborators[12] also found more movements in the older population. These results might be related to periodontal health in the elderly population, since this population is more likely to have more severe sleep apnea. This population is increasing in the dental setting and a more careful assessment and further research regarding these issues are needed.

A particular strength of this study was the duration of OA use. This was the first study to evaluate long-term side effects over an interval greater than five years. Nonetheless, the present study had several limitations. Patient compliance was not objectively measured since there is no commercially-available compliance monitor. Molar and canine relationships were only evaluated in categories instead

of actual millimeters. The classification of favorable or unfavorable, although based on objective standards, was subjective, and for the minimum bias, we included the evaluation of five orthodontists at one setting for all study models. Further studies with computerized superimposition of three dimensional coordinates of the maxilla, mandible and the dentition, before and during treatment, are required to better quantify these side effects and eliminate part of the subjectiveness of the follow-up evaluation.

7.6. Conclusions

The use of a mandibular advancement appliance over a mean duration of 7.4 years induced significant occlusal changes in 85.7% of the patients in the present study. Interestingly, for almost half of these patients, the tooth movement was considered favorable. The group with unfavorable changes presented a significantly smaller OB and OJ in the pre-treatment measurements and unfavorable changes were more likely to happen in the Class I craniofacial subgroup. The mandible showed significant changes in arch length and intercanine and intermolar distances as the maxilla was more stable. OA therapy is a life-long treatment of a disease that tends to worsen with age, and careful monitoring of the common side effects elucidated in this study is mandatory, not only by cephalometric evaluation, but also with study models. Additional studies are required to assess the forces imposed by the appliance on each tooth with various mandibular advancements, amongst individuals with right and left chewing preferences, and to analyze TMJ displacement with the appliance in place.

7.7. Acknowledgements

7.8. Bibliography

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CHAPTER 8

GENERAL DISCUSSION

8.1. Long Term Compliance and Subjective Side Effects

OAs appear to be effective for snoring and mild cases, but for moderate and severe cases the reported success rates range only 35 to 60%.[1,2] Due to the perceived limitations of OA therapy, most patients referred for this type of treatment are generally less severe, but perhaps because of the expertise of The University of British Columbia (UBC) group in the OA field, the referrals to OA therapy in this setting often include more complicated cases. Therefore a more rigorous protocol, probably including an objective titration monitor, is needed. Marklund and collaborators[3] evaluated a less severe population and reported that 22% of the patients who discontinued treatment reported a poor effect on snoring. In our questionnaire-based study (Chapter 3), patients tended to discontinue OA treatment not only due to side effects, but also because some 35% of the non-compliant patients reported little or no effect of the OA. The rate of non-compliance was not correlated to the baseline OSA severity or sleepiness. This is similar to data described by McGown and collaborators,[4] which suggested the need for some generous protocols for the entire sleep apnea dental field. However the lack of efficacy may also be a limitation of OA therapy.

Although Chapter 3 was based only on self-reported compliance, users reported good compliance for more hours per night (90.3% use it all night) and more days per week (82.3% use it every night) when compared to CPAP.[5-7] McGown and collaborators[4] found similar results with patients using the OA for a mean period of 6.6 hours after a 22 month period. The treatment compliance rate after a mean period of 5.7 years in this study was 64.1%, which appears to be a well-accepted treatment modality for this type of disease. The present study results are in agreement with previous reports in which the compliance rates for the first year range from 48-84%[8,9] and drop after more than 4 years to 62%-76%.[10,11] Still,

the current study relied on subjective questionnaires with obvious limitations, which could be an overestimation of OA use. Long-term effectiveness studies of OA use compared to CPAP are still lacking. Low levels of compliance have been suggested to decrease the effectiveness of CPAP.[12] It is still unclear whether OAs, even though less effective than CPAP, could achieve the same effectiveness if used for more hours per night. Other than CPAP, there are no reports on psychological management as motivation or ongoing education and patient support; such factors could be related to the patient management skills of each attending dentist.

Regarding the type of OA, we found a statistically better tolerability with Klearway™ than other appliances used in our clinic. Pitsis and collaborators,[13] in a randomized controlled trial, reported that patients had a higher preference for OAs with a smaller degree of opening. Klearway™ has been designed to have an interincisal opening of 2 mm or less and to allow a slow and gradual mandibular advancement of up to 11 mm from the 65% initial advancement. The protocol in the UBC clinic is to advance the mandible until subjective symptoms of sleep apnea are solved. The degree of mandibular advancement has a positive correlation with the efficacy of the OA.[14,15] Most of the mandibular repositioners other than Klearway™ used in our clinic were not adjustable and some of them had a greater vertical opening.

With OA use after a mean period of 5.7 years, 35.9% of the patients stopped OA treatment; 72% of those did so during the first year of treatment. Compliant and non-compliant groups showed a significant reduction in RDI and sleepiness. OA users had their snoring and fatigue better controlled and their bed partners were more satisfied with treatment than non-compliant subjects. An improvement in the clinical protocol and in the titration of OA have become evident needs of the field.

Considering subjective side effects, in our questionnaire-based survey (Chapter 3), it was interesting to evaluate side effects at different intervals of OA use. As shown previously,[4] there was a significantly greater number of side effects per non-compliant patient, such as more frequent and severe dry mouth, tooth and/or jaw discomfort, more severe tongue discomfort, sense of suffocation and movement of teeth. Excessive salivation is a short-term side effect which tends to improve over time.[3,9,16] Otsuka and collaborators[17] reported an objective decrease in occlusal contact and bite force in the morning after OA use. According to patient reports, subjective benefits of OA therapy outweigh these side effects and patients did not perceive most tooth movements unless their dentist brought it to their attention.[16] As expected, with only a subjective evaluation of the side effects, the current study found less dental changes than the above-mentioned authors. For non-compliant patients, occlusal changes given as a reason to discontinue treatment showed a positive correlation with increasing length of OA use and appear to be a significant reason only after a year of OA use.

TMJ symptoms increased with OA use but were not related to the discontinuation of treatment or gender. In contrast to previous studies,[9,18] we could not find a higher incidence of TMJ discomfort in early treatment, but this may be due to the retrospective nature of this study. Although women are more likely to have treatment success,[19] we discovered that a higher percentage of women discontinued treatment. Females experienced more side effects and seem to have a greater tendency to abandon treatment than males since 46.8% of the females who answered the survey had discontinued using it compared to 32.8% of males. Considering that no differences between genders according to age, BMI or sleepiness could be identified, women's non-compliance may be related to a greater perception of, or susceptibility to, side effects. In the evaluation of non-compliant patients, our data suggests that patients who feel uncomfortable with the

appliance and experience more side effects tend to stop using it sooner. Patients who are able to use it for longer periods might have experienced milder problems, which encouraged them to get used to wearing the appliance. Therefore, the recognition, quantification and specific approaches to the specific side effects cited above during the first year of treatment could have a great impact on OA compliance.

This questionnaire-based study has several potential limitations. The response sample was considered representative and it may have resulted in a sample bias in favor of a good response to OA therapy. As a retrospective study, we have to consider that the data was collected from different patients at different time intervals, and longer and larger-sample prospective studies on OA use are required. With regards to the different OA types, the expertise of the dental staff in this study was higher with the Klearway™ appliance and cross-over studies could be more reliable. As a retrospective study, we did not have access to polysomnography records for all subjects, but this might be representative of the majority of clinics dealing with sleep apnea patients. A questionnaire-based survey always evaluates subjective symptoms since it is the nature of such protocol, but it is still of great importance in the assessment of a large number of patients to gain an overall understanding of compliance and side effects.

8.2. Titration Procedures

In our first study (Chapter 3), although there was a significant improvement in the daytime sleepiness, which is one of the mostly used subjective symptom of OSA, there was still a lack of OA efficacy for some non-compliant patients, which elucidates the need for objective measurements to titrate OAs. Fleury and colleagues[20] showed the combination of home oximetry and patient's subjective

evaluation did improve the effectiveness of an OA. OAs are currently titrated based on clinical symptoms, but we know that clinical evaluation alone is not accurate. The complexity and cost of PSG is always cited as a reason to search for new diagnostic systems[21] and similarly is an impediment to OA titration studies, especially if repeated PSGs are requested. Still, we believe that portable home monitors should be used in the monitoring of OSA treatment approaches, but only after a baseline diagnostic PSG has been performed. In this sense, a more simple approach would not misinterpret sleep apnea severity or other sleep disorders such as narcolepsy, periodic limb movement and upper airway resistance syndrome. Sleep laboratories prioritize primarily diagnostic PSGs, but follow-up assessments often have a long waiting period. OAs, surgery and behavioral therapies may not be as effective as CPAP, but can reduce snoring and also may have a placebo effect[22] and therefore a home monitor could be important.

There are some limitations in the studies on OA titration included in this thesis. Since there were no previous studies on simple monitor devices, which in our evaluation were feasible for the OA field, this thesis assessed the accuracy of two devices, but did not undertake a clinical trial phase. Therefore, the routine use of these devices in a clinical setting is not yet recommended.

8.2.1. Nasal Pressure Recordings

The SleepCheck used in Chapter 4 could be used to reduce the treatment period in which a certain therapy was not fully efficacious and the patient could be referred, if necessary, to an alternative therapy earlier. Still, in mild to severe sleep apnea, symptomatic or high cardiovascular risk patients, a clinical assessment by a sleep doctor is recommended and a possible follow-up PSG might be required. SleepCheck showed a large overscoring and some disagreement with the PSG

results. The automatic scoring of the apneas are compromised since the airflow measured might vary according to patient breathing patterns, such as intermittent oral breathing and nasal anatomy.[21] Also we found that it falsely detected as apneas events of decreases in flow related to REM sleep and decreases of flow following periodic limb movements and arousals. These events have little clinical implication and therefore should not be scored. However, this is a limitation of a single channel device, since there was an actual decrease in flow, but because normal breathing can vary in different phases of sleep and as a response to different physiological events, apneic events can only be properly scored with a simultaneous oximetry and EEG. Still, we found that SleepCheck did score several events in decreases of flow preceding an arousal that was not detected in the PSG and could be interpreted as a respiratory effort related to arousal, and therefore it is more precise than the PSG in the evaluation of such kinds of respiratory events.

The overscoring bias of the device was reported to the manufacturer and, as a consequence of our results, they increased the sensitivity of the SleepCheck by increasing the gain of the nasal cannula flow analysis. This new version was not tested in the present study. We hypothesize that the differences within the same patients should be minimal, only representing the night-to-night variability of the AHI.[23]

This evaluation of SleepCheck has several limitations such as being an in-laboratory study without home assessment. Although there is still a need for in-home assessment, we believe that because of the simplicity of the device, the rate of lost data should be minor. The small sample size is also a limitation, but because the data was collected on consecutive patients, there was less bias and patients were distributed fairly equally according to OSA severity. Our sample was biased because all the patients were actually referred to the sleep lab with some symptom of sleep disturbance breathing, but there were eight patients with

an AHI smaller than 5, which could be interpreted as the non-apneic population in the present study.

In the OA field, multi-comparisons of the SleepCheck together with clinical evaluation might optimize the mandibular titration procedure. As oximetry is still relatively expensive and requires a physician's interpretation, we believe that some monitors may have an important role in the OA titration field. Furthermore, we acknowledge that simple devices are more feasible and do save time and expenses, but there is a trade-off with the amount of information that can be obtained. Therefore, the limitations of these devices have to be considered and their practical use has some definite limitations.

8.2.2. Snoring Evaluation

The nasal cannula pressure transducer, used to evaluate snoring in Chapter 5, presented a reasonably good correlation with the noise level meter in patients with an AHI smaller than 30/h. Even though the analysis used was new, we do believe that there are patients whose snore is not perceived through the nasal pressure transducer. We evaluated only the loudness of the snoring, which is related to the annoyance and bed partner's hearing, but the detailed analysis of snoring is much more complex. Previous studies[24,25] found a better correlation of snoring and the severity of OSA when the power spectrum evaluation of the snoring was added. Since the purpose of the study was not to correlate the snoring with the AHI, but to assess the accuracy of this new snoring measurement in the identification of snore episodes, the reference standard would be the human ear and brain, and from a previous study,[26] sounds that exceed 50 decibels are the nearest that a machine can achieve when compared to human hearing. There are sleep laboratories and ambulatory home monitors that currently rely on this

method of snoring evaluation, for a gross evaluation of snoring in non-apneic, mild and moderate sleep apnea patients. However, for the assessment of snoring therapies, the counting of snores through the nasal cannula pressure transducer should not be considered accurate at the present time specially for those subjects who have AHI greater than 30/h.

8.3. Long Term Sequelae

In Chapter 3, we observed that, of the non-compliant patients, 12.4% identified occlusal changes as a reason to discontinue treatment. If we analyse the data more rigorously, movement of the teeth so that the upper and lower jaws no longer meet properly never occurred in 47.7% and 29.2% of the compliant and non-compliant patients, respectively. Although some occlusal changes are not permanent, an objective assessment of the occlusal side effects was felt to be imperative. In previous studies, only 12 to 19.2% of patients were reported to have occlusal changes,[9,18,27] but, as demonstrated in earlier reports,[3,9,18,27] their perception does not correlate with objective measurements unless those changes were also brought to the patient's attention by their dentist. OAs do impose a significant pressure on dental structures, having to hold the mandible and subsequently the tongue in a forward position.

The following studies on the assessment of long-term sequelae of OAs, presented some common limitations. These studies are cross-sectional and there are different patients in each duration-of-use subgroup, therefore a longitudinal study is necessary to confirm the data. Still, since the changes in the groups with a longer period of OA use were similar to previous studies,[3,10,16,18,27-30] we believe that the extent of side effects induced by the OA are correlated with the duration of OA use. Another limitation of these studies is in the assessment of the amount

of mandibular advancement. Since most of the patients used more than one appliance, and during the treatment period there were further mandibular advancements as required by the recurrence of OSA symptoms, we were unable to quantify the total mandibular advancement, or to correlate mandibular advancements and amount of side effects.

8.3.2. Cephalometric Analysis

In Chapter 6, some cephalometric changes induced by OA use after a mean period of 7.3 years were expected although not in the magnitude observed. In the orthodontic literature, it is common clinical conjecture that removable orthopedic appliances have minor effects on the adult dentition, but seldom do those appliances apply such jaw displacement forces with such a great commitment by the patients to the treatment as that seen in the OSA population.

According to our results, OAs induced tooth movements but not craniofacial skeletal changes. As a consequence of the proclination of lower incisors, retroclination of upper incisors and molar extrusion, a rotation of the mandible, an increase in interincisal angle and an increase in lower facial height were observed. A downward rotation of the mandible without forward displacement, the absence of mandibular growth, and changes limited to dental positions found in this study confirms previous findings,[10,16,18,30,31] with the exception of Bondenmark and collaborators,[28] who found an increase in mandibular length and forward rotation of the mandible. Still, these findings challenge a paradigm in orthodontics as a significant amount of tooth movement was achieved with the OA in the adult population.

We interpreted that the tooth movements occurring amongst these patients are movements of the entire arch. OAs have a full-arch occlusal coverage and

therefore the mechanical loading force is applied to all teeth, which could explain the mesial movement of the lower molar (L6) and distal movement of the upper molar (U6). If the incisors move, all of the supporting dental structures may move as a response to this change; perhaps transceptal fibers have an important role in this phenomenon. A healthy periodontium is in continuous remodeling in order to maintain equilibrium and function.[32] A decrease in overbite (OB) and overjet (OJ) is in agreement with previous studies,[3,16,18,27,28,30] except for the results of Ringqvist and collaborators,[10] who found a decrease in OB and OJ that did not reach statistical significance. Although our study is cross-sectional and therefore there are different patients in each duration-of-use subgroup, we found that changes in OB tend to continue as long as OAs are used and this could explain why we found greater changes than previous, shorter term studies. Changes in OB and OJ seem to be totally related to incisor angulation changes, which have been described as smaller but similar in preceding papers. [3,10,16,18,27,28,30,31]

Dividing our sample into groups with different durations of OA use, we found that most of the changes tended to continue over time. These results are especially important because OAs may be a life-long treatment therapy and the changes in the alveolar bone over time may affect the amount of tooth movement. When the apical surface of a tooth impinges on the cortical bone, the remodeling process may not be possible and there is a risk of root resorption or bone fenestration.[33,34]

8.3.3. Study Models Analysis

Analyses of study models are an excellent way we have to compare the actual clinical consequences of the use of OAs. Although tooth movement as a consequence of OA use was not done deliberately, we found that in 41.4% of the

patients (Chapter 7), these changes were actually favorable for the patient's occlusion; this was the first study to acknowledge that not all tooth movements are clinically undesirable. Important findings in the difference between unfavorable (44.3%) and favorable (41.4%) changes were related to the initial clinical assessment of patients referred for OA treatment. The favorable occlusal changes cases, as determined by the initial dental evaluation, were more likely to be in Class II Division 1 or Class II Division 2 subjects, with a more distal mandibular canine position and a greater initial OB and/or OJ. Most patients who presented with an unfavorable change were Class I at the beginning of treatment. The unfavorable cases significantly changed their occlusion into more of an edge-to-edge or anterior and posterior crossbite or openbite position.

In previous papers, the authors pointed out that the side effects induced by OAs were small[3] and clinically irrelevant.[27] However, minimal or no change conditions were found in only 14.3% of our patients, the no change group. This group that did not show any changes had only one characteristic that significantly differed from the favorable group in the initial evaluation, the right side canine relationship. From a clinical perspective, it is important to determine useful predictors of OA side effects in snoring and OSA patients. We have found some correlations, none of which were very strong, but we hypothesize that there are several characteristics involved, each with a different weight of influence. A deeper OB correlated with a greater reduction in the OB and the greater the initial OJ, the greater the reduction in OJ. There is also a correlation between a greater OB and OJ and a more favorable change and lower incidence of anterior crossbite. There was a correlation between older age and a decrease in OB; Marklund and collaborators[3] also found more movements in the older population. These results might be related to periodontal health in the elderly population, which is more likely to have more severe sleep apnea. This population is increasing in the dental

setting and a more careful assessment and further research regarding these issues are needed.

With respect to the occlusal side effects, measured either from cephalometric radiographs or study models, we hypothesize that some patients adapt to this type of side effect, changing their eating habits or their masticatory pattern. Although some of these changes might be described as undesirable in a subset of patients, we believe that the effective treatment of a life-threatening disease, such as OSA, surpasses the concept that maintenance of baseline occlusion is mandatory. Even if major tooth movements are seen, the discontinuation of OA treatment should only occur if the patient concurs with their sleep physician and accepts another treatment modality, such as nCPAP.

Since OAs are a life-long treatment approach for OSA, and the changes appeared to continue over time, the use of the revised OA clinical protocol (as proposed in Chapter 10), should be encouraged and the collection of study models and cephalometric radiographs before and during treatment be undertaken for all patients treated with an OA.

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CHAPTER 9

GENERAL SUMMARY & CONCLUSIONS

9.1. Long Term Compliance and Subjective Side Effects

The questionnaire-based study (Chapter 3) presented a response rate of 46.7%. The group that returned the questionnaire and the group that did not return it had no differences with respect to apnea severity, sex, age or type of appliance used. From a total of 251 snoring and/or sleep apnea patients analyzed after a mean of 5.7 years, some 35.9% of the patients stopped OA treatment; 72% of those did so during the first year of treatment. All the groups showed a significant reduction in RDI and sleepiness. OA compliant patients had their snoring and fatigue better controlled and their bed partners were more satisfied with treatment than non-compliant patients. Within the compliant patients, 93.7% used the OA more than 4 nights/week, 100% wore it more than half of each night, and 95% were satisfied with the treatment. The most frequent reasons why patients discontinued use were uncomfortable (44.4%), had little or no effect (33.6%), or switched to nCPAP (23.3%). Snoring was satisfactorily controlled in 75.6% of compliant and 43.2% of non-compliant patients. Side effects, such as dry mouth and tooth and/or jaw discomfort, were more frequent and more severe in the non-users ($p<0.05$). With OA usage, both compliant and non-compliant patients reported an increase in TMJ symptoms but there was no difference in the degree of change. In conclusion, subjects who were compliant with OA therapy reported long periods of use, adequately controlled snoring and a lower incidence of side effects.

9.2. Titration Procedures - Nasal pressure recordings

In an attempt to find a good titration monitor for OAs, the SleepCheck (Chapter 4) was not fully accurate when compared to the full-night PSG. This was

because there was a systematic bias in overscoring the data by a mean of 27.4 ± 13.3 events per hour. The overscoring was mostly related to decreases in flow either during REM sleep, after an arousal or limb movements, or even after changes in the wave form of the nasal flow signal. Still, it revealed a good correlation value of 0.805 (p<0.001) with the AHI. In the calculation of receiver operating characteristic (ROC) curves at threshold values of AHI of 10 and 20/hour, the areas under the curves were 0.915 and 0.910, respectively. Optimum combinations of sensitivity and specificity for these thresholds were calculated as 86.4/75.0 and 88.9/81.0. The Bland-Altman graph revealed that the limits of agreement were -26.6 to 26.6 AHI after an adjustment for the consistent bias. It is simpler, more convenient and affordable than most of the ambulatory monitors, reasonably easy to use by different professionals and probably more accurate than subjective bed partner reports. In conclusion, this study suggests that the SleepCheck could have a relatively good performance in monitoring titration of OAs and is a potential titration device in patients who have OSA. Therefore after a diagnostic PSG, a baseline SleepCheck RDI may be obtained to verify the amount of overscoring for that patient and to later compare the RDI at different jaw positions and the post-titration RDI. If a marked improvement in RDI is seen, patients could then be referred back for a PSG to confirm efficacy of the OA. Prior to the routine clinical use of SleepCheck for the assessment of OA titration, further studies are still necessary.

9.3. Titration Procedures - Snoring Evaluation

From this preliminary evaluation of the nasal cannula pressure transducer snore analysis (Chapter 5), we concluded that for the evaluation of the number of snores, in patients with an AHI smaller than 30, it presented a reasonably good

correlation with the noise level meter snore index. For patients with an AHI smaller than 30/h, the correlation of the snore indexes was 0.77; according to the Bland-Altman plot the bias was 10.2/h and the limits of agreement 248.1 and 227.7/h. If the patients with an RDI greater than 30/h were added to the analysis, there was a noticeable decrease in the applicability of this type of measurement. Since the evaluation of snoring is more important in non-apneic and mild sleep apnea patients, the nasal cannula pressure transducer snore analysis had a good correlation with the estimation of snoring addressed by the noise level meter, with some advantages over regular noise level meters. In conclusion, the use of this portable monitor in non-severe sleep apnea patients could probably identify the cessation of snoring without the influence of environmental noises such as background noise, the bed partner's snore and the dog's bark, for example, and have an important role in the titration of OAs. Still, a clinical trial with this measurement for the titration of OA is necessary prior to routine clinical use.

9.4. Long-Term Sequelae - Cephalometric Analysis

The study of cephalometric analyses after long-term OA use (Chapter 6) revealed significant ($p<0.01$) changes in a myriad of variables including increases in mandibular plane and ANB°; decreases in overbite and overjet; retroclined upper incisors and proclined lower incisors and increased lower facial height; and maxillary molars tipped distally while mandibular molars tipped mesially and erupted. The initial deep OB group showed a significantly greater decrease in OB. Duration of OA use correlated positively with variables such as a decrease in OB and an increase in mandibular plane angle, and changes in the dentition appeared to be progressive over time. After long-term use, OAs appear to change tooth positions, which also may affect mandibular posture.

9.5. Long-Term Sequelae - Study Model Analysis

With visual evaluation of the study models presented in Chapter 7, we identified that 14.3% of the patients exhibited no occlusal change, 41.4% had favorable changes and 44.3% had unfavorable changes. Significant changes in a myriad of variables were found. Patients with a higher initial OB and Class II Division 1 and Class II Division 2 malocclusions were more likely to have favorable or no change. A more favorable change in OB occurred in subjects with a large baseline OB. A greater baseline OJ and more distal mandibular canine relationship were correlated with favorable changes. A greater initial OJ was correlated with a more favorable change, a decrease in mandibular crowding, a smaller change in anterior crossbite and a greater change in OJ. OA use after a mean of 7.3 years induces clinically relevant changes in the dental arch and occlusion.

OA therapy may be a life-long treatment of a disease that tends to worsen with age. The results of these studies (Chapter 6 and 7) showed that occlusal side effects do occur after long-term OA use, which may have clinical implications. With the use of a mandibular advancement appliance over a mean duration of 7 years, we found significant and progressive changes in the dentition. Therefore careful monitoring, with cephalometric and study models evaluation of the common side effects elucidated in these studies appears to be essential.

In conclusion, compliance is related to a smaller efficacy of the OA and higher incidence of side effects, the compliance could probably be improved with the utilization of titration procedures involving apnea and/or snoring evaluation. The prevalence of noticeable side effects is much higher than previous thought and

the implementation of specific follow-up assessments could probably improve the effectiveness and understanding of the OA therapy.

CHAPTER 10

FINAL COMMENTS & FUTURE DIRECTIONS

Based on the findings reported in this thesis, there is an obvious necessity to establish a revised OA protocol for the initial evaluation, titration and periodic follow-up. An ideal protocol for the assessment of patients with snoring or OSA who seek OA therapy might include:

a) **Initial Records**: Based on the studies in Chapters 4 and 5, specific information is needed to monitor possible occlusal changes, such as radiographs, (cephalometric radiographs in centric occlusion, panoramic and probably periapicals of the incisors), dental study models with a registration of the occlusion in centric occlusion and intra-oral photographs in occlusion.

b) **Initial Consent Form**: Since we identified that most of the patients will experience some change in their occlusion over a period of five years, every patient could be advised of this reality and examples and explanations of such anticipated changes could be given at the time of insertion. To avoid further problems, informed consent could be in a written format and the patient could sign and consent to treatment knowing these potential long-term side effects.

c) **Titration Evaluation**: Based on the questionnaire data, poor efficacy is associated with compliance failure. In order to both improve the efficacy and make the patient more conscious of the titration procedure, a titration protocol with some objective measurement of snoring and/or sleep apnea could be added to the protocol. Based on the findings of this thesis with the identified limitations, SleepCheck could be a useful tool in the titration of OA in sleep apnea patients and the nasal cannula pressure transducer could be useful for snorers and mild sleep apnea patients.

d) **Follow-up Questionnaire**: A standard questionnaire could be applied every month during the first six months of treatment, in which the frequency and severity of the most common side effects could be evaluated. From the questionnaire-based study (Chapter 1), we could probably anticipate compliance

failure because of side effects, and deal with these issues as soon as they arise to subsequently improve compliance.

e) **Regular Follow-up**: Every year, the patient could be seen for a follow-up examination. As sleep apnea is a disease that worsens with age, OA may become less effective over time. Such evaluation might also include some kind of home monitor. During this appointment, side effects should be evaluated in a questionnaire format as well as by records and/or intraoral clinical examination. Based on the studies in Chapters 4 and 5, definite information is needed to monitor possible occlusal changes. A cephalometric radiograph, dental study models with a good registration of the occlusion, and intra-oral photographs, all in occlusion, could be taken. If there are any changes, the patient should be informed.

The field of OA used for the treatment of snoring and OSA is still relatively new and many future research directions can be identified. Determining the correct jaw position in a timely manner is difficult to accomplish with existing clinical protocols. Currently, the appliance is titrated until the patient's bed partner reports a cessation of snoring and/or the patient reports a reduction in symptoms. However, not all patients report excessive daytime somnolence or have a partner to monitor the snoring. Reports from bed partners are very unreliable tools to evaluate titration success due to a variety of factors. In addition, about 5% of patients treated with an OA may reveal an increase in the AHI. This could result either from an atypical anatomy, poor titration of the OA or other unknown variables. A clinical trial of different types of monitors versus the current protocol is required to improve OA effectiveness. We have tested the SleepCheck (Chapter 4) and a snoring measurement (Chapter 5) as possible tools to titrate OAs. We hypothesize that the SleepCheck measurements within the same subject could be comparable such that, for example, a decrease in 50% of the SleepCheck RDI could correlate with a 50% decrease of PSG AHI. Since the evaluation of snoring

is more important in non-apneic and mild sleep apnea patients, we believe that for those cases an evaluation of the snoring should be more reliable and closer to the patient's expectations. But still these are only hypotheses that need to be tested further. The objectives of a future prospective clinical trial might be to evaluate these measurements as objective and simple methods to titrate OAs through the assessment of snoring and/or apneas on different nights in patients with OSA. A research protocol to correlate subjective and objective snoring measurements as well as to elucidate the correlation between different amounts of mandibular advancement and the subsequent decrease in snoring and apneas is required.

A most important study for the future is an ongoing measurement of occlusal changes after long-term wear at the 10, 15 or even 20 year time intervals. Occlusal function and the progressive impact of the side effects on the patient's masticatory system should be carefully evaluated. Further studies with computerized superimposition of three-dimensional co-ordinates of the maxilla, mandible and the dentition, as well as larger studies with measurements of bite force and area, before and during treatment, are indicated to better quantify these side effects and eliminate part of the subjectiveness of the follow-up evaluation. Another evaluation of the side effects is the actual measurement of width and shape of the alveolar bone. With the incisor angulation changes seen in these studies, and with the uncertainties of what these changes are going to occur in 20 or 30 years, further studies in this field are essential. Since the greatest impact seems to be related to the anterior teeth, studies on different OA designs which apply less force to the labial surface of the maxillary incisors and the lingual surface of the mandibular incisors are required to clarify if there could be a decrease in some of the effects on the anterior dentition. There is also a need for longer clinical trials with identical clinical management protocols to compare different types of OAs including TRDs.

There are some reports, although not a high number, of patients who tended to use OAs as a short-term treatment alternative when CPAP treatment is inconvenient, particularly when away from home. A prospective study is needed to measure the efficacy and safety of the oral appliance as a short-term treatment for moderate and severe OSA patients. Such a study could determine the feasibility of a new role for oral appliances – that of an adjunct to therapy in patients previously established on nCPAP. The combination of therapies, if tolerated, will allow greater flexibility of treatment and opportunity for ongoing compliance in circumstances where nCPAP cannot be used.

In summary, OAs continue to be used as a major therapeutic option in subjects with snoring and/or OSA. Our knowledge of patient compliance and long term side effects as well as our ability to effectively titrate these appliances have both improved but many unanswered questions remain in the field

CHAPTER 11

APPENDICES

11.1. Questionnaire

Effects and Long Term Compliance of Oral Appliances Used for the Treatment of Snoring and Obstructive Sleep Apnea

1. Are you still wearing your oral appliance (OA)?

If ☐ **Yes** answer here: If ☐ **No** answer here:
⇓   ⇓

2a. How many nights do you use it? ☐ Every night ☐ 4 to 6 nights a week ☐ 1 to 3 nights a week ☐ Less than once a week	**2b. How long did you use the oral appliance?** _____ Years _____ Months
3a. How much of the night do you use it? ☐ All night ☐ More than half of the night ☐ Half of the night ☐ Less than half of the night	3b. Have you undergone any other treatment for snoring or apnea? ☐ No ☐ Yes If Yes, which? _____ When? _____ Year _____ Month
4a. How satisfied are you with the OA? ☐ Very satisfied ☐ Moderately satisfied ☐ Moderately dissatisfied ☐ Very dissatisfied	4b. When did you stop using the oral appliance? _____ Year _____ Month

5a. What is the frequency of complications related to the appliance?	5b. Why did you stop wearing the OA? Mark all that apply to you.
☐ None ☐ Less than once a month ☐ Once a month ☐ Every second week ☐ 1 to 3 times a week ☐ 4 to 6 times a week ☐ Every day	☐ No/little effect ☐ Occlusion/jaw changes ☐ Uncomfortable/cumbersome ☐ Painful ☐ Inconvenient to use ☐ Dental work changed ☐ Appliance doesn't fit any more ☐ Apnea worsened ☐ Lost weight, apnea lessened ☐ Started CPAP ☐ Lost the appliance ☐ Claustrophobic ☐ Could not swallow ☐ Mouth became too dry ☐ Other (Please Specify)

6. Do you/did you experience any of these side effects while wearing the oral appliance?

Side Effect	Frequency = How Often				Severity = How Much		
	Never	Rarely	Some times	Often	Mild	Moderate	Severe
a. Difficulty chewing in the morning							
b. Difficulty in chewing on your back teeth							
c. Excessive salivation							
d. Dry mouth (xerostomia)							
e. Morning headaches							
f. Tooth discomfort							
g. Teeth apart in the morning							
h. Tongue discomfort							
i. Jaw discomfort							
j. Gum discomfort							
k. A sense of suffocation							
l. Movement of one or more teeth							
m. Movement of the teeth so upper & lower jaws no longer meet properly							
n. Other (Please specify)							

7. Do you/did you experience any of these situations while wearing the oral appliance?

Situation	Before		After	
	Yes	No	Yes	No
a. Difficulty and/or pain e.g. when yawning?				
b. Does your jaw get "stuck", "lock", or "go out"?				
c. Difficulty closing your jaw after it is open?				
d. Difficulty and/or pain when using your jaws (chewing/ talking)?				
e. Difficulty eating chewy foods (breads, meats)				
f. Difficulty biting into hard foods (raw vegetables, apples)?				
g. Noises coming from the jaw joints?				
h. Stiff, tight or tired feeling jaws?				
i. Pain in or around ears, temples or cheeks?				
j. Frequent headaches, neck aches or tooth aches?				
k. An injury to your head, neck or jaw?				
l. Changes in your bite?				
m. Have you been treated for a jaw joint problem?				

8. How likely are you/were you to doze off or fall asleep in the following situations, in contrast to just feeling tired? Even if you have not done some of these things recently, try to work out how they would have affected you.

Please use the following scale to choose the most appropriate number for each situation:

0 = would never doze
1 = slight chance of dozing
2 = moderate chance of dozing
3 = high chance of dozing

Situation	Before Appliance	With Appliance
a. Sitting and reading		
b. Watching TV		
c. Sitting, inactive in a public place (theatre, meeting)		
d. As a passenger in a car for an hour without a break		
e. Lying down to rest in the afternoon when circumstances permit		
f. Sitting and talking to someone		
g. Sitting quietly after a lunch without alcohol		
h. In a car, while stopped for a few minutes in traffic		

9. How satisfied is/was your partner with the use of the appliance?

☐ Very satisfied ☐ Moderately satisfied ☐ Moderately dissatisfied ☐ Very dissatisfied
          ☐ Not Applicable

10. How would you classify your side effects?

☐ None ☐ Mild   ☐ Moderate   ☐ Severe

11. Did you return to the sleep specialist to have a repeat overnight study with the appliance in place?

☐ No   ☐ Yes   When? _____Year _____ Month

12. Did you return to the sleep specialist to have a repeat home oximetry test with the appliance in place?

☐ No   ☐ Yes   When? _____Year _____ Month

13. How common is/was your breath cessation (apneas)?

a. Before Appliance	b. With Appliance
☐ None/ Not Applicable	☐ No change
☐ Mild	☐ Totally controlled
☐ Moderate	☐ Satisfactorily controlled
☐ Severe	☐ Not satisfactorily controlled
☐ I don't know	☐ I don't know

14. How significant is/was your sleepiness (fatigue)?

a. Before Appliance	b. With Appliance
☐ None/ Not Applicable	☐ No change
☐ Mild	☐ Totally controlled
☐ Moderate	☐ Satisfactorily controlled
☐ Severe	☐ Not satisfactorily controlled
☐ I don't know	☐ I don't know

15.How significant is/was your snoring?

a. Before Appliance	b. With Appliance
☐ None/ Not Applicable ☐ Mild ☐ Moderate ☐Severe ☐ I don't know	☐ No change ☐ Totally controlled ☐ Satisfactorily controlled ☐ Not satisfactorily controlled ☐ I don't know

16. Were there any other problems with your oral appliance? Do you have any additional comments?

_____

_____

_____

_____

We need to calculate your body mass index as a predictor of sleep apnea severity, and to do so we require both your current height and weight.

Height: _____ ft _____in   or   _____cm
Weight: _____lbs   or   _____kg

Your Name: _____ Date:_____

THANK YOU

APPENDIX 2

ETHICAL APPROVALS