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Porto 2015

To my invaluable support mechanism, my wife

To my son, evidently

Medicine should begin with the patient, continue with the patient and end with the patient.

(William Osler, MD)

ABSTRACT

The specialty of otorhinolaryngology includes both surgical and non-surgical treatment of the upper airway, the expertise required to obtain a proper history and to conduct a proper examination, and the unique ability to assess dysfunctions and disorders of the upper airway. In spite of their diverse expertise and their frequent participation in multidisciplinary teams addressing both adult and pediatric obstructive sleep apnea (OSA), the role of the otorhinolaryngologist in the management of OSA is still subject to debate (both inside and outside the surgical community) due to a lack of reliable evidence supporting the use of otolaryngologic techniques.

Obstructive sleep apnea—also referred to as obstructive sleep apnea-hypopnea—is a sleep disorder that involves cessation or a significant decrease in airflow in the presence of breathing effort. It is the most common type of sleep-disordered breathing and is characterized by recurrent episodes of upper airway collapse during sleep. These episodes are associated with recurrent oxyhemoglobin desaturation and arousal from sleep.

In adults, OSA has an adverse effect on the daytime quality of life. The most frequently experienced symptoms of OSA are intermittent snoring (94%), daytime sleepiness (78%), and diminished intellectual performance (58%). Other symptoms include personality changes (48%), impotence (48%), morning headache (36%), and nocturnal enuresis (30%). Worsening OSA is associated with the development of significant medical co-morbidities, including hypertension, cardiovascular disease, stroke, obesity, and insulin resistance. Furthermore, adults with OSA have an increased risk of motor

vehicle accidents, impaired daytime performance and quality of life, and increased mortality independent of co-morbidities, compared to adults without OSA.

In adults, nasal CPAP therapy is the gold standard treatment for OSA. Unfortunately, the long-term acceptance rate of CPAP therapy is around 70%. The acceptance rate of CPAP therapy is especially low among younger patients, whose subjective ailments improve less with CPAP therapy. Consequently, many patients with moderate or severe OSA are referred to an otorhinolaryngologist for secondary therapy, which is frequently surgical in nature.

Accordingly, one objective of this thesis is to determine the issues that limit evidence-based practice in the area of adult OSA management. Moreover, this thesis reveals serious limitations in the literature regarding the assessment of evidence in sleep surgery practice. Additionally, this thesis considers the evidence base for certain otolaryngologic approaches in CPAP management, specifically the utility of nasal surgery in combination with CPAP therapy, the use of tracheostomy for severely obese OSA patients, and the efficacy of maxillomandibular advancement surgery. Finally, this thesis reviews the evidence for a promising new surgical approach (hypoglossal nerve stimulation), as well as the evidence concerning a non-conventional therapy—myofunctional therapy—as an alternative treatment for both adult and pediatric OSA.

Among pediatric patients, OSA is a common and serious cause of morbidity. OSA affects 1–3% of children aged 2–8 years, although some studies suggest that the rate may be as high as 27%. Major pre-disposing factors for upper airway obstruction include anatomic narrowing, abnormal mechanical linkage between the airway dilating muscles and airway walls, muscle weakness, and abnormal neural regulation. Among pediatric patients, OSA presents with characteristics that differ from those found in adults.

Adenotonsillar hypertrophy is the most frequent underlying condition, although other conditions are also implicated. Complications related to severe OSA among children include cor pulmonale, right ventricular hypertrophy, congestive heart failure, alveolar hypoventilation, pulmonary hypertension, pulmonary edema, and failure to thrive.

This thesis demonstrates that the current diagnostic approach for pediatric OSA, which is based primarily on clinical evaluation, has poor accuracy. Considering the high prevalence of pediatric OSA, it is important to explore new diagnostic pathways. To this end, this thesis shows that unattended multichannel devices are valid tools for identification of OSA among children. Similar results were observed with the development of a clinical decision rule that simplified the diagnosis of pediatric OSA, and may be an alternative in the absence of sleep laboratories or ambulatory devices adapted for pediatric purposes.

In conclusion, this thesis describes novel approaches for assessment and treatment of pediatric and adult OSA. Specifically described are new diagnostic approaches for pediatric OSA patients, and new otorhinolaryngologic treatment techniques for adult OSA patients.

PREFACE

One of the greatest attributes of otorhinolaryngology is its diversity. This is a field that demands excellent medical knowledge, surgical skills, and effective communication.

In 2010, my desire to combine my clinical and surgical experience with rigorous research led me to apply to the Clinical and Health Services Research PhD program. I was admitted as one of the youngest students, as I was only a first year otorhinolaryngology resident.

This PhD program in clinical and health services research is unique in Portugal, and it aims to fill an existing critical gap in our country. The original intent of the program was to respond to the medical community's increasing need and demand for high quality educational offerings and research training opportunities in both clinical research and health services research. In pursuing the PhD program, I established the ideal foundation for my future role as researcher and medical practitioner.

As my career progressed, I developed a keen interest in OSA. Early in my residency, I realized the important role otorhinolaryngology plays in OSA management and adjusted my academic path to add coursework in order to specialize in this area. My initial project was a study of the diagnosis of pediatric OSA. This quickly flourished into a formal research project, which then progressed to this PhD thesis on OSA management through otorhinolaryngology. As I was particularly interested in OSA, I

met with Prof Winck, who became my advisor. We believed that studying the controversy surrounding this topic could provide further scientific evidence in the debate over otorhinolaryngology's role in OSA disease.

To supplement my academic credentials, I sought specific training that would allow me to gain practical experience in the sleep surgery/medicine area. This PhD degree led me to the sleep laboratory at São João Hospital Centre, where I had the privilege to work with my esteemed advisor, Prof Winck. This period provided me with a clearer understanding of sleep pathology in a real practice context and thus strengthened my knowledge.

Following the same objective, I went to Paris, Barcelona, Madrid, Valencia, London, and Hong Kong to assist with courses, meetings and presentations on OSA. I also attempted to expand my comprehension of sleep beyond OSA and sleep surgery by taking courses on oral appliances, PAP, and general sleep disorders.

Over the years, I have worked hard to establish myself in this field, and I have been able to become acquainted with distinguished colleagues that have had a major impact in my academic path. However, one place in particular helped to reinforce my perspective. In 2013, I participated in an observership at Stanford University, where I had the chance to meet and work with one of the world's most brilliant medical teams in sleep medicine/surgery. Since then, I have had opportunities to collaborate with them on several research projects and multiple papers published in high ranking medical journals, for which I am eternally grateful.

Recently, I was invited to be part of the department of Otorhinolaryngology and Sleep Medicine Centre at Hospital CUF – Porto. Under the guidance of Dra Marta Gonçalves, Dr Rui Pratas, and Dr Victor Correia da Silva, I hope to continue to forward my career on this path and to evolve in this field.

This thesis represents a major effort to clarify and assemble the best available evidence to date, and to humbly share my personal views on some topics, based on my continually growing experience.

Porto, June 11th 2015

Victor F. Certal, MD

ACKNOWLEDGMENTS

During this PhD program, I have been privileged to work with and enjoy the support of a vast group of medical colleagues and friends.

I would like to express utmost sincere appreciation and thanks to my esteemed advisor, Prof. João Carlos Winck. You have been a tremendous mentor to me, and it has been a distinct honour and pleasure to be at your service during the completion of my PhD. Your constant motivation was the fuel that energized this project. More than an advisor, you were a friend to me during this journey.

I would like to express my deep gratitude to my co-advisor, Prof. Inês Azevedo, for all her support and help, and for patiently reviewing the entire manuscript. Your experience in pediatric OSA and the generous support you provided were essential for this achievement.

I would also like to thank my co-advisor, Prof. Altamiro Costa-Pereira, for providing a credible and solid platform that allowed many PhD students like me to complete this academic degree. The CINTESIS is a landmark reference in clinical research in Portugal, and this project seems to be just at its beginning. Special thanks to my PhD colleagues for being a source of constant motivation. It was a pleasure to be part of such bright panel.

I am pleased to thank and acknowledge the great help and assistance provided by my colleagues in the Department of Otorhinolaryngology at the Hospital São Sebastião. I would especially like to thank Dr. Carlos Carvalho for his endless patience with me, Dr.

Hélder Silva for his friendship and constant assistance, and Dr. Rui Pratas for being the initial force that started me along this academic path.

Fortunately for me, this thesis is the product of fortuitous encounters overseas with people who have changed the course of my academic career. Had I not made the acquaintances of Dr Macario Camacho and Dr Robson Capasso at Stanford University, this thesis would not have been the same. Thank you for your kind support and for being constant sources of inspiration.

I would also like to express special thanks to my family. Words cannot express how grateful I am to my parents and sister for enabling me to survive during these seemingly endless years of education.

To my lovely son, Vasco; despite being just a baby, he helped me in his own way by being up all night to keep me company as I worked on my thesis, even against my will.

Finally, and most importantly, I would like to express appreciation to my beloved wife Tânia, who was always my support in the moments when no one was available to answer my questions. Your support, encouragement, quiet patience, and unwavering love were undeniably the bedrock upon which the past five years of my life were built. Your tolerance of my occasional foul mood is a testament, in itself, of your unyielding devotion and love.

THESIS OUTLINE

This thesis is organized into 10 chapters. Chapters 2–5 are on pediatric obstructive sleep apnea (OSA), i.e., the controversy surrounding the diagnosis of this disorder. Chapter 2 details the most common diagnostic assessments used in cases with pediatric OSA as well as the findings of study 1, which show the level of accuracy of clinical symptoms and signs in predicting sleep apnea in children. Chapter 3 details the findings of study 2, which tried to evaluate the existing diagnostic alternatives, specifically in unattended sleep studies. Chapter 4 states the findings of study 3 and describes the methodology used to adapt and translate the Pediatric Sleep Questionnaire into Portuguese; this is the most efficient questionnaire that is used during OSA diagnosis. Chapter 5 explores a new and simple method to diagnose pediatric OSA; this is a clinical decision rule. Chapters 6–9 are on adult OSA, namely the controversy surrounding the efficacy and utility of surgical treatment for OSA. Chapter 6 and 7 report the findings of study 5 and 6 that explore the current state of the art regarding surgical therapy of OSA and the debate in the literature via an overview of previous reviews conducted. Chapter 8 provides evidence on three specific surgical approaches: nasal surgery as a complement to continuous positive airway pressure (CPAP) therapy, tracheostomy as an OSA treatment in obese patients and the efficacy of maxillomandibular advancement surgery. Chapter 9 details a new and recent surgical approach known as hypoglossal nerve stimulation and assesses the safety and efficacy of this alternative approach. Chapter 10 reports the findings of a non-conventional therapy called myofunctional therapy, which could be considered as an alternative or complement to

CPAP. Chapter 11 includes a discussion and summary of the thesis as well as suggestions for future directions.

PUBLICATIONS, AWARDS AND RECOMMENDATIONS

a. Publications

1º - "CLINICAL ASSESSMENT OF PEDIATRIC OBSTRUCTIVE SLEEP APNEA: A SYSTEMATIC REVIEW AND META-ANALYSIS"

THE LARYNGOSCOPE

VICTOR CERTAL, EMANUEL CATUMBELA, JOÃO C. WINCK, INÊS AZEVEDO, ARMANDO TEIXEIRA-PINTO; ALTAMIRO COSTA-PEREIRA

2012

(*cf*. Appendix 1)

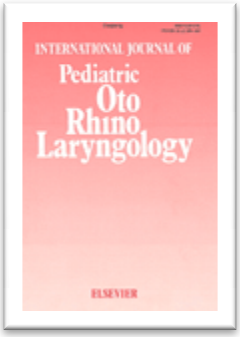
2º - "UNATTENDED SLEEP STUDIES IN PEDIATRIC OSA: A SYSTEMATIC REVIEW AND META-ANALYSIS"

VICTOR CERTAL; MACARIO CAMACHO; ROBSON CAPASSO; INES AZEVEDO; ALTAMIRO COSTA-PEREIRA; JOÃO WINCK

LARYNGOSCOPE

2014

(*cf*. Appendix 2)



3º - "TRANSLATION AND CROSS-CULTURAL ADADPTATION OF THE PEDIATRIC SLEEP QUESTIONNAIRE INTO PORTUGUESE LANGUAGE"

VICTOR CERTAL; FILIPA FLOR DE LIMA; INES AZEVEDO; ALTAMIRO COSTA-PEREIRA; JOÃO WINCK

INTERNATIONAL JOURNAL OF PEDIATRIC OTORHINOLARYNGOLOGY

2014

(*cf*. Appendix 3)

4º - "MODEL FOR PREDICTION OF PEDIATRIC OSA – A CLINICAL DECISION RULE"

VICTOR CERTAL; MACARIO CAMACHO; ROBSON CAPASSO; INÊS AZEVEDO; ALTAMIRO COSTA-PEREIRA; CARLOS CARVALHO; HELDER SILVA; JOÃO WINCK

LARYNGOSCOPE

ACCEPTED FOR PUBLICATION IN JUNE 2015

(*cf*. Appendix 4)

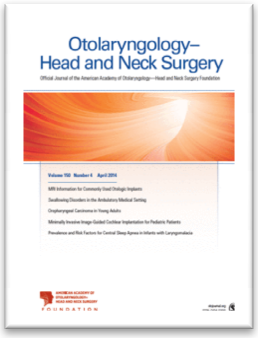
5º - "COMPREHENSIVE REVIEW OF SURGERIES FOR OBSTRUCTIVE SLEEP APNEA SYNDROME"

MACARIO CAMACHO; VICTOR CERTAL; ROBSON CAPASSO

BRAZILIAN JOURNAL OF OTORHINOLARYNGOLOGY

2013

(*cf*. Appendix 5)



6º - "REVIEWING THE SYSTEMATIC REVIEWS IN OSA SURGERY"

VICTOR CERTAL; NAOYA NISHINO; MACARIO CAMACHO; ROBSON CAPASSO

OTOLARYNGOLOGY – HEAD AND NECK SURGERY

2013

(*cf*. Appendix 6)

7º - "THE EFFECT OF NASAL SURGERY ON CONTINUOUS POSITIVE AIRWAY PRESSURE DEVICE USE AND THERAPEUTIC TREATMENT PRESSURES: A SYSTEMATIC REVIEW AND META-ANALYSIS "

MACARIO CAMACHO; MUHAMMAD RIAZ; JOSE ABDULLATIF; SOROUSH ZAGHI; CHAD RUOFF; ROBSON CAPASSO; CLETE KUSHIDA; CHRISTAIN GUILLEMINAULT; VICTOR CERTAL

SLEEP

2014

(*cf*. Appendix 7)

8º - "TRACHEOSTOMY AS TREATMENT FOR ADULT OSA"

MACARIO CAMACHO; VICTOR CERTAL; ROBSON CAPASSO; SCOTT BRIETZKE; JON HOLTY; CHRISTIAN GUILLEMINAULT

LARYNGOSCOPE

2013

(*cf*. Appendix 8)

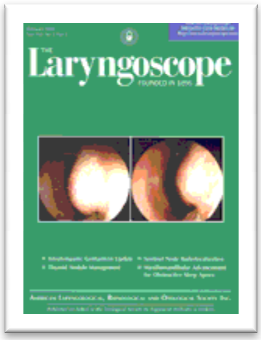
9º - "MAXILLOMANDIBULAR ADVANCEMENT TO TREAT OBSTRUCTIVE SLEEP APNEA: A META-ANALYSIS OF 521 INDIVIDUAL PATIENTS"

SOROUSH ZAGHI; VICTOR CERTAL; NELSON POWELL; JON HOLTY; CHRISTIAN GUILLEMINAULT; MACARIO CAMACHO

JAMA – OTOLARYNGOLOGY – HEAD AND NECK SURGERY

SUBMITTED EN MAY 2015

(*cf.* Appendix 9)



10º - "HYPOGLOSSAL NERVE STIMULATION IN THE TREATMENT OF OSA: A SYSTEMATIC REVIEW AND META-ANALYSIS"

VICTOR CERTAL; MACARIO CAMACHO; ROBSON CAPASSO; CARLOS PINHEIRO; ANTONIO SOUSA VIEIRA; CLETE KUSHIDA

LARYNGOSCOPE

2014

(*cf.* Appendix 10)

11º - "MYOFUNCTIONAL THERAPY TO TREAT OSA: A SYSTEMATIC REVIEW AND META-ANALYSIS "

MACARIO CAMACHO; VICTOR CERTAL; JOSE ABDULLATIF;; CHAD RUOFF; ROBSON CAPASSO; CLETE KUSHIDA

SLEEP

2014

(*cf.* Appendix 11)

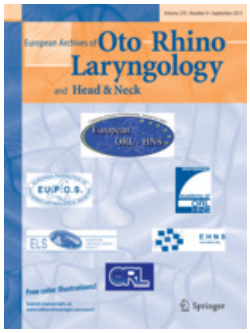
12º - "IN REFERENCE TO REDEFINING SUCCESSFULL THERAPY IN OSA: A CALL FOR ARMS"

VICTOR CERTAL; MACARIO CAMACHO; ROBSON CAPASSO

LARYNGOSCOPE

2014

(*cf.* Appendix 12)



13º - "INTRODUCING A NEW CONCEPT IN OSA: THE *CONTINUUM* OF TREATMENT"

VICTOR CERTAL; MACARIO CAMACHO; ROBSON CAPASSO

EUROPEAN ARCHIVES OF OTORHINOLARYNGOLOGY

SUBMITTED IN APRIL 2015

(*cf*. Appendix 13)

b. Awards, Presentations and Recommendations

I- AWARDS

1. PROJECT AWARD OF PORTUGUESE ENT SOCIETY (MAY 2011)

IN REFERENCE TO: "CLINICAL ASSESSMENT OF PEDIATRIC OSA: A SYSTEMATIC REVIEW AND META-ANALYSIS" (*cf*. Appendix 14)

2. COMMUNICATION AWARD AT PORTUGUESE ENT CONGRESS (MAY 2012)

IN REFERENCE TO: "CLINICAL ASSESSMENT OF PEDIATRIC OSA: A SYSTEMATIC REVIERW AND META-ANALYSIS" (*cf*. Appendix 15)

3. WINNING POSTER AT THE INTERNATIONAL SURGICAL SLEEP SOCIETY MEETING IN DETROIT

IN REFERENCE TO: "MAXILLOMANDIBULAR ADVANCEMENT TO TREAT OBSTRUCTIVE SLEEP APNEA: A META-ANALYSIS OF 521 INDIVIDUAL PATIENTS" (*cf*. Appendix 16)

II- PRESENTATIONS IN INTERNATIONAL CONGRESS

1. POSTER AT FRENCH ENT CONGRESS (OCTOBER 2011) (*cf*. Appendix 17)

INFLUENCE DES DIFFERENTES TECHNIQUES CHIRURGICALES DANS LA SATISFACTION DES PATIENTS AVEC RONFLEMENT – ETUDE RETROSPECTIVE

2. POSTER AT FRENCH ENT CONGRESS (OCTOBER 2012) (*cf*. Appendix 18)

DIAGNOSTIC DU SYNDROME D'APNEE OBSTRUCTIVE DU SOMMEIL CHEZ L´ENFANT PAR AVALIATION CLINIQUE: REVISION SYSTEMATIQUE ET META-ANALYSE

III- RECOMMENDATIONS

ABOUT THE PAPER "CLINICAL ASSESSMENT OF PEDIATRIC OSA: A SYSTEMATIC REVIEW AND META-ANALYSIS":

RECOMMENDED BY F1000 AS BEING OF SPECIAL SIGNIFICANCE IN ITS FIELD

RECOMMENDATION 1 - JOSEPH E DOHAR, CHILDREN'S HOSPITAL OF PITTSBURGH, PA, USA

Few conditions have received more recent medical and community publicity than pediatric obstructive sleep apnea (i.e. OSA). As a consequence of such wide-spread, heightened awareness, the demand for reliable documentation of the presence of the condition has exceeded the supply of sleep laboratories equipped to study children. Given that it is not only impractical but logistically impossible to obtain overnight polysomnography on every at-risk child, a reliance on clinical signs and symptoms to investigate pediatric OSA has emerged as the only reasonable alternative. To assist with this challenge, Certal and colleagues have published a comprehensive, critical and systematic review of the literature and diagnostic medical analysis in the September 2012 edition of Laryngoscope. They specifically analyzed the predictive power and diagnostic accuracy of clinical assessment compared to overnight polysomnography.

Two prior reviews to the one presented arrived at opposite conclusions, reporting high variability in terms of diagnostic accuracy, and employing what these authors considered a 'poor' methodology in systematically reviewing the evidence. This deficiency in the literature supported the need for this study. The investigators found that tonsillar size and snoring were highly sensitive but not specific, in contrast to daytime hypersomnolence, observed apnea, and difficulty breathing while asleep, which were highly specific but insensitive. Unfortunately, despite these authors' attempts to model seven different instruments combining various signs and symptoms, they were only able to achieve moderate sensitivity and specificity, leading them to conclude that neither single nor combined symptoms and signs satisfactorily predict pediatric OSA. Such a discouraging conclusion not withstanding, two very useful clinical outcomes were derived from this study. First, although snoring and tonsillar size were associated with low specificity in predicting pediatric OSA, their very high sensitivity rendered their absence quite valuable in excluding a diagnosis of pediatric OSA. Care must be taken, however, to avoid using these two specific indicators to make the diagnosis of pediatric OSA, as their lack of specificity would most assuredly lead to over diagnosis of the condition. Second, the high specificity of daytime hypersomnolence, observed apnea, and difficulty breathing while asleep rendered this

triad of signs and symptoms useful in identifying pediatric OSA. These two scenarios are quite valuable to a clinician in sub-dividing the entire population of at-risk children.

The article ended with a discussion of diagnostic strategies that may prove viable as alternatives to overnight polysomnography, or at least as low-cost population screens. One such strategy measured morning urinary protein profiles that were differentially expressed in children with OSA versus those without OSA. Putative biomarker combinations resulted in a profile of four proteins, which, if expressed, yielded a diagnostic sensitivity of 100% and specificity of 96.5%. Indeed, if future studies, powered appropriately with larger sample sizes, randomized, blinded, and prospectively controlled, render similar results, the current diagnostic paradigm will be changed considerably. Until then, physicians and healthcare providers must appropriately use the clinical indicators assessed in this study to screen children in determining the need for overnight polysomnography and/or treatment of OSA.

Recommendation 2 - Nico Jonas and Sonna Ifeacho, Great Ormond Street Hospital for Children, UK.

This systematic review and meta-analysis of the diagnostic test accuracy of clinical assessment of obstructive sleep apnoea (OSA) in the paediatric population is an enlightening piece of research.

Full overnight polysomnography is recognised as the gold standard for the diagnosis of OSA, but is not always readily available in units treating this cohort of patients; in addition, when it is accessible, there may be prolonged waiting periods to undergo the test or it may be poorly tolerated by the patient. Hence, it is not in routine use. In light of this, the vast majority of cases of paediatric OSA are diagnosed clinically from a combination of clinical signs and symptoms.

This review pooled the results of 10 studies with comparisons of the diagnosis of paediatric OSA based on clinical tools and polysomnography. Unfortunately, due to the wide variation in study design, data could not be analysed to investigate clinical diagnosis from a combination of clinical signs and symptoms. However, the paper does report the findings of isolated individual signs or symptoms suggestive of OSA.

It was found that parental reports of snoring and large tonsillar size were associated with a high level of sensitivity. Therefore, based on this review's results, children who snore but don't have large tonsils are less likely to have OSA. However, due to the low specificity of these symptoms, a history of snoring associated with large tonsils is likely to produce a high rate of false positive diagnoses of OSA.

The most clinically relevant finding of this review is the high specificity and low sensitivity rates of the following signs and symptoms: excessive daytime somnolence, observed apnoeas and difficulty in breathing while asleep. The high specificity rate supports a diagnosis of OSA when these signs and symptoms are present. Therefore, patients without these signs and symptoms are less likely to have OSA.

The original literature search for this review identified 780 papers, which was whittled down to just 10 for the final review. This highlights the significant amount of ongoing research in this field, but also makes it apparent that more collaborative research would enable the pooling of results for analysis to provide higher quality evidence that can then be incorporated into clinical care.

Recent evidence suggests that particular genes are expressed and proteins produced in those with OSA {1}. In a study by Gozal et al., urine electrophoresis for various proteins was undertaken. Unique sets of these proteins were found to be decreased or increased in the urine of a paediatric OSA population. When a particular group of four proteins were analysed for each patient, sensitivity was 100% sensitivity and specificity was 96.5%. Testing for proteins in this manner may form the basis of future diagnostic testing for OSA and possibly larger scale screening programmes, but this still requires more research.

Recommendation 3 - Manisha Witmans , University of Alberta and Stollery Children's Hospital, AB, Canada.

This is another meta-analysis of the clinical assessment of pediatric obstructive sleep apnea and includes 1525 children: the premise is to try and determine the presence of sleep-disordered breathing using clinical and physical examination to identify children that are likely to have sleep-disordered breathing. Despite modelling and using larger numbers than earlier meta-analyses, history and physical examination are insufficient to diagnose sleep-disordered breathing in children. This is clearly evident from this meta-analysis. This finding has been supported by analyses by several different groups and clinical practice guidelines that have been developed. In conclusion, polysomnography is still required to confirm the diagnosis of sleep-disordered breathing

LIST OF ACRONYMS

AASM	American Association of Sleep Medicine
AHI	Apnea-Hypopnea Index
AUC	Area Under the Curve
BMI	Body Mass Index
CAPSO	Cautery-Assisted Palatal Stiffening Operation
CI	Confidence Interval
CSA	Central Sleep Apnea
DOR	Diagnostic Odd Ratio
CPAP	Continuous Positive Airway Pressure
EDS	Excessive Daytime Sleepiness
EEG	Electroencephalography
EOG	Electrooculography
EKG	Electrocardiography
ESS	Epworth Sleepiness Scale
GA	Genioglossus Advancement
HSA	Hypersomnia Sleep Apnea
HGNS	Hypoglossal Nerve Stimulation
LAUP	Laser Assisted Uvuloplasty
MD	Mean Difference
MMA	Maxillo-Mandibular Advancement
MT	Myofunctional Therapy
NICE	National Institute for Health and Clinical Excelence
NOSE	Nasal Obstruction Symptom Evaluation
NR	Not Reported
ODI	Oxygen Desaturation index
OSA	Obstructive Sleep Apnea
PAP	Positive Airway Pressure
PSQ	Pediatric Sleep Questionnaire

PSG	Polysomnography
QUADAS	Quality Assessment Tool for Diagnostic Accuracy Studies
RCT	Randomized Controlled Trial
RDI	Respiratory Disturbance Index
REM	Rapid Eye Movement
RFA	Radiofrequency Ablation
RME	Rapid Maxillary Expansion
ROC	Receiver Operating Characteristic
SARPE	Surgically-Assisted Rapid Palatal Expansion
SD	Standard Deviation
SMILE	Submucosal Minimally Invasive Lingual Excision
SRBD	Sleep-Related Breathing Disorders
SFORL	Société Française d´Otorhinolaryngologie
SPORL	Sociedade Portuguesa de Otorrinolaringologia
SROC	Summary Receiver Operating Characteristic
TAP	Transpalatal Advancement Pharyngoplasty
TCRFTA	Temperature-Controlled Radiofrequency Tissue Ablation
TORS	Transoral Robotic Surgery
TST	Total Sleep Time
ZPP	Z-palatoplasty

Index

I. INTRODUCTION

1. Rationale

a. Introduction

In modern society, non-restorative sleep is gaining increased awareness. The international classification of sleep disorders includes 95 different diagnoses of possible causes for non-restful sleep. A subgroup with a comparatively high incidence rate is formed by the so-called sleep-related breathing disorders (SRBD). These are further divided into disorders with central sleep apnea (CSA), obstructive sleep apnea (OSA), sleep related hypoventilation syndromes, and other SRBDs. OSA syndromes are separated into adult OSA and pediatric OSA.[1] Pharyngeal collapse during sleep as a consequence of abnormal structural anatomy and loss of muscle tone during sleep is the defining event in OSA, and snoring is its cardinal sign.[2]

b. Adult OSA

Adult obstructive sleep apnea (OSA) is a sleep disorder estimated to affect 2–5% of the population. Although OSA can present at any age, it typically manifests between the ages of 40 and 60 and its prevalence increases with age. Men are twice as likely as women to develop OSA, with an estimated prevalence of 4% and 2% in men and women, respectively.[3] Other high-risk groups include postmenopausal women, who have a two- to three-fold increase in their prevalence of OSA. Obesity and weight gain have also been shown to be important risk factors in the development and progression of OSA in middle-aged adults.[4] However, OSA has been shown to be a gradually progressing disease even in the absence of weight gain. Some have considered this slow progression to be due to upper airway damage characterized by palatal

denervation with localized polyneuropathy and inflammatory cell infiltration of the soft palate. These changes are thought to be caused by snoring-related vibrations and/or large intraluminal pressure oscillations in the area of the obstruction.[5,6]

Snoring is a respiratory sound generated in the upper airway during sleep, and typically occurs during inspiration. Primary snoring occurs without episodes of apnea or hypoventilation. The intensity of snoring may vary and often disturbs the sleep of both the patient and their bed partner. Primary snoring does not cause symptoms of daytime sleepiness or hypersomnia.[7]

In contrast to primary snoring, adult OSA has an adverse effect on the daytime quality of life. The most frequent symptoms of OSA are intermittent snoring (94%), daytime sleepiness (78%), and diminished intellectual performance (58%). Further symptoms are personality changes (48%), impotence in men (48%), morning headaches (36%), and nocturnal enuresis (30%).[8] Worsening OSA has been shown to be associated with the development of significant medical co-morbidities, including hypertension, cardiovascular disease, stroke, obesity, and insulin resistance.[9] Marin et al.[10] showed that the incidence of fatal and non-fatal cardiovascular events in untreated patients with severe obstructive sleep apnea-hypopnea is significantly higher compared to age and BMI matched healthy participants recruited from the general population. Moreover, this association appeared to escalate with disease severity.

Furthermore, the presence of OSA has been linked to an increased risk of motor vehicle accidents, impaired daytime performance and quality of life, and increased mortality independent of co-morbidities.[11]

Table 1. Symptoms of OSA
Adapted from: Sleep Apnea and Snoring: Surgical and Non-surgical Therapy. Michael Friedman. Elsevier Health Sciences, 2009

Nocturnal symptoms	Daytime symptoms
Snoring	Excessive daytime sleepiness
Witnessed apneas	Morning headaches
Dyspnea (choking/gasping)	Neurocognitive impairment:
Drooling	vigilance (secondary impact on
Dry mouth	concentration and memory)
Bruxism	executive functioning
Restless sleep/frequent arousals	motor coordination
Gastroesophageal reflux	Diminished quality of life
Nocturia	Mood and personality changes:
	Depression
	Anxiety
	Irritability
	Sexual dysfunction:
	decreased libido
	impotence
	abnormal menses

The pathogenesis of OSA is traditionally thought to involve a complex interaction of pharyngeal anatomical compromise with state-dependent upper airway dilator muscle dysfunction. Unstable ventilatory control has been implicated in an important role in OSA in the form of high loop gain, i.e., an increased propensity for periodic breathing or cyclical output from the central pattern generator. End-expiratory lung volume and possibly upper airway edema have more recently been suggested as causes. Emerging evidence suggests that OSA mechanisms are variable, with some pathophysiological factors having major roles in some patients but not in others.[12] For example, some patients may have OSA primarily due to anatomical compromise at the velopharynx (amenable to uvulopalatopharyngoplasty), whereas others may primarily have high loop gain (amenable to oxygen) and still others may develop OSA through a combination of abnormalities (requiring a multifaceted therapeutic approach).[13]

Genetically, OSA is a complex disease under a substantial degree of genetic control; it most likely results from multiple interacting, but poorly defined, genetic and

environmental factors. The only published genome-wide linkage scans for OSA within families did not produce strong evidence of linkage to OSA phenotypes. With the exception of these linkage scans, and a small number of genetic association studies, the molecular genetics of OSA in humans remains largely unexplored.[14-16]

The necessary diagnostic work-up for OSA includes anamnesis using standardized questionnaires, a physiological and otolaryngological assessment, and a sleep lab evaluation. According to the American Academy of Sleep Medicine (AASM),[1] when factors inclusive of sensitivity, specificity, likelihood ratios, and strength of evidence are analyzed, four subtypes of sleep-monitoring procedures can be categorized. Type 1 is the gold standard: attended in-laboratory polysomnography (PSG), while the other three include portable monitoring methods inclusive of Type 2 (comprehensive), Type 3 (modified portable sleep apnea testing or cardiorespiratory sleep study), and Type 4 procedures (continuous single recording, such as ambulatory overnight pulse oximetry, or dual bioparameter recording). The AASM considers Type 4 monitoring devices unacceptable for making a diagnosis of obstructive sleep apnea. Type 2 and 3 devices may be helpful in an attended setting if used for patients without significant comorbid conditions, and if manually scored by trained personnel. Type 3 devices have been noted to tend to underestimate the severity of OSA secondary to the absence of EEG monitoring, in that arousals are not scored. Furthermore, the AASM recommends that symptomatic patients with negative ambulatory studies undergo attended PSG for further clarification. According to AASM standards, a full night PSG is routinely indicated for the diagnosis of sleep-related breathing disorders (SRBDs). It is also indicated for continuous positive airway pressure (CPAP) titration in patients with a documented diagnosis of an SRBD, and for whom a PAP test is warranted.

Conservative treatment methods include weight reduction, optimizing sleeping hygiene, conditioning with respect to the avoidance of certain sleep positions, and drug treatments. However, nasal CPAP therapy is considered the gold standard treatment for OSA.[17] With a primary success rate of 98%, CPAP therapy is, alongside tracheotomy, the most successful therapeutic modality available. Indeed, only these two treatment modalities achieve sufficient cure rates in cases of extreme obesity and severe OSA.[18,19] With respect to quality of life and risk of traffic accidents, the cost effectiveness of CPAP therapy was recently corroborated.[20] As one example of many new insights, we refer to the work of Drager et al.[21], which demonstrated that after only 4 months of CPAP therapy (compared to no therapy) significant changes occurred in intima thickness, pulse wave speed, C-reactive protein levels, and serum catecholamine levels. A review recently [22] demonstrated the efficacy of CPAP in comparison to placebo on arterial hypertonia with a combined cohort of 572 patients from 12 randomized studies. Given these successes, all other therapies for OSA should be measured against this method. Unfortunately, the long-term acceptance rate of CPAP therapy is around 70%. The acceptance rate of CPAP therapy is especially low in younger patients, whose subjective ailments also improve less with CPAP therapy. Consequently, many patients with moderate and severe OSA requiring treatment have to be guided into another secondary therapy, which is frequently surgical. [23]

c. Pediatric OSA

Disturbances in sleep can have a dramatic negative impact on children and their families. Sleep disorders in children places them at risk for social problems, failure in school, and accidents.[24] They can also place a burden on families and on parent-child

relationships. The human body has normal sleep-wake cycles and a set of specific stages by which sleep progresses. Newborn infants do not have EEG features that allow characterization of different sleep stages, as is possible in adults and older children.[25] An infant will typically awake every 3 to 4 hours for feeding. Around 3 months of age, identifiable rapid eye movement (REM) sleep periods begin to organize into later sleep cycles and non-REM sleep dominates the earlier segments of sleep. At 6 months of age, sleep will begin with non-REM stages and the inhibition of muscle tone typical for REM sleep will occur. By the end of the first year of life, continuous sleep periods will consolidate so that they predominantly occur during the nighttime hours. The total sleep requirement for a 12 month old is 16 to 18 hours per day, as opposed to approximately 14 to 15 hours per day at term. Between 18 months and 5 years of age, there is a decrease in the amount of daytime napping. Average sleep duration decreases during middle childhood and adolescence but sleep needs do not decline over that time period.[26,27]

Obstructive sleep apnea (OSA) is a common and serious cause of morbidity during childhood. It affects 1–3% of children aged 2–8 years, although some studies suggest that the rate may be as high as 27%.[28] Approximately 40% of children who snore have more significant manifestations of OSA, including obstructive sleep apnea syndrome.[29] Major pre-disposing factors for upper airway obstruction include anatomic narrowing, abnormal mechanical linkage between the airway dilating muscles and airway walls, muscle weakness, and abnormal neural regulation. OSA in children also presents with some characteristics that differ from those in adults.[30] Adenotonsillar hypertrophy is the most frequent causative disease, although other reasons are also implicated [31]:

Table 2. The causative diseases of obstructive sleep dyspnea in children

Adapted from: Sleep Apnea and Snoring: Surgical and Non-surgical Therapy. Michael Friedman. Elsevier Health Sciences, 2009

Hypertrophy of tonsil and adenoid	88.9%
Nasal allergy	2.5%
Sudden infant death syndrome	1.2%
Hunter–Hurler syndrome	1.2%
Niemann–Pick's disease	1.2%
Prader–Willi syndrome	1.2%

Complications related to severe OSAs include cor pulmonale, right ventricular hypertrophy, congestive heart failure, alveolar hypoventilation, pulmonary hypertension, pulmonary edema, and failure to thrive. Affected children are also at risk for permanent neurological damage and even death. [31]

Despite these potential consequences, and the firm recommendation of the American Academy of Pediatrics to conduct PSG for a definitive diagnosis of pediatric OSA, fewer than 10% of children undergo any objective testing before treatment, and fewer than 5% undergo PSG at all. [32]

Current diagnostic approaches range from the exclusive use of clinical presentation and a physical examination to the current standard of PSG. However, while it is clear that the former techniques are fraught with major limitations, the latter is also associated with significant obstacles, such as the relative unavailability of appropriately equipped sleep laboratories and trained personnel, labor-intensive and inconvenient nature of nocturnal PSG, and the high cost of the procedure. Attempts to overcome these limitations through shorter 'nap' studies or home-based monitoring programs are encouraging, but the issues of cost, practicality, and reliable evidence remain.[33-35] Thus,

it is critical to discuss these issues and propose novel ideas for alternative diagnostic methodologies.

The primary surgical approach in children with OSA syndrome and tonsillar hypertrophy is adenotonsillectomy.[36] This procedure is relatively simple with a low complication rate and, unlike the adult presentation, it usually results in a cure. However, the decision to operate should be made not according to the Friedman degree of adenotonsillar hypertrophy, but based on a good observation of the patients' sleep condition, as well as objective monitoring.[37] Mandibular distraction osteogenesis is applicable only for children with craniofacial deformities, for which it has better long-term effects. Tracheotomy is also appropriate for some children with severe obesity and for temporary issues. Nasal CPAP is usually the second-line treatment for children who do not respond to adenoidectomy and tonsillectomy, or when adenoidectomy and tonsillectomy are not indicated. In children with heavy obesity, weight reduction should be tried before surgical treatment. [38,39]

2. Thesis Aims

In determining the appropriate diagnostic method and the best form of treatment for patients with OSA, a broad spectrum of factors must be considered. The opinions of relevant medical and surgical specialists, although recorded in isolation, need to be collectively considered in order to ensure that the patient's best interests are served. Interestingly, despite being frequently part of the multidisciplinary team that addresses both adult and pediatric OSA, the role of otorhinolaryngology remains an area of intense debate, both within and outside of the surgical community itself.

This thesis explores the position of otorhinolaryngology in the management of OSA from childhood to adulthood, and attempts to identify myths and misconceptions in the assessment of OSA by otorhinolaryngologists. The final goal is to provide high-quality evidence in the topics believed to be more controversial in adult and pediatric OSA. While in the case of pediatric OSA, the main debate is about the diagnosis of this treatment (surgical treatment is considered the gold standard of treatment, with a success rate of 80%), in adults, the real debate is about indications and results of surgical therapy (the diagnosis is well established and accessible).

a. Pediatric OSA Aims

Polysomnography (PSG) is the gold standard for diagnosing and quantifying OSA, both in adults and paediatric OSA. Nocturnal PSG recordings provide unbiased and objective information on various sleep-related characteristics such as sleep architecture, cardiac and respiratory patterns, and gas exchange. However, several factors have restricted a more extensive implementation of such diagnostic procedures in children, including the inconvenience of having both parents and children spending the night in the laboratory, the rather onerous and labour-intensive nature of this diagnostic procedure, the relative scarcity of laboratories with expertise in children's sleep disorders, and, as a corollary to this, the extended waiting period between referral and actual testing.

The goal of this thesis is to clarify these diagnostic issues and propose alternative methods to diagnose OSA in children.

b. Adult OSA Aims

Unlike pediatric OSA, the surgical treatment in adult OSA remains an area of intense debate. In many countries, the financial implications of surgical private practice has perhaps contributed to a degree of cynicism regarding the range of available surgical procedures for OSA. Fundamentally, continuous positive airway pressure (CPAP) therapy remains the gold standard for the treatment of OSA; however, surgery may be indicated to improve compliance and outcome in cases in which CPAP is poorly tolerated. Increasing recognition of the multi-level nature of anatomical obstruction consequentially indicates the existence of a large variety of differing surgical techniques used by different surgical specialties in an attempt to address this problem.

In this thesis, we summarize the current range of surgical treatments together with the evidence base for their intervention. The final goal is to create guidelines or algorithms to select the right operation to tackle the individual's specific problem at the correct time.

References

1. American Academy of Sleep Medicine ICSD- International classification of sleep disorders Diagnostic and coding manual. American Academy of Sleep Medicine, 2013: pp 51–59
2. Guilleminault C, van den Hoed J, Mitler MM. The sleep apnea syndrome and its symptoms. In: Guilleminault C, Dement WC (Eds). Sleep apnea syndromes. Alan R Liss, New York, 1978, pp 1–123. Ali NJ, Pitson DJ, Stradling JR. Snoring, sleep disturbance, and behaviour in 4-5 year olds. Arch Dis Child 1993; 68:360–366.
3. Young T, Peppard PE, Gottlieb DJ. Epidemiology of obstructive sleep apnea: a population health perspective.Am. J. Respir. Crit.Care Med.2002;165: 1217–39.
4. Heffner JE, Holgate ST, Chung KFet al.Road ahead to respiratory health: experts chart future research directions.Respirology 2009;14: 625–36.
5. Malhotra A, White DP. Obstructive sleep apnoea.Lancet 2002; 360: 237–45.
6. Chan AS, Phillips CL, Cistulli PA. Obstructive sleep apnoea—an update.Intern. Med. J.2009; 10.1111/j.1445-5994.2009.02069.x.
7. Young T, Palta M, Dempsey Jet al.The occurrence of sleepdisordered breathing among middle-aged adults.N. Engl. J. Med.1993;328: 1230–35.
8. Iber C, Ancoli-Israel S, Chesson Aet al. The AASM Manual for the Scoring of Sleep and Associated Events: Rules, Terminology and Technical Specifications, 1st edn. American Academy of Sleep Medicine, Westchester, IL, 2007.
9. Bradley TD, Floras JS. Obstructive sleep apnoea and its cardiovascular consequences.Lancet2009;373: 82–93.
10. Marin JM, Carrizo SJ, Vicente Eet al.Long-term cardiovascular outcomes in men with obstructive sleep apnoea-hypopnoea with or without treatment with continuous positive airway pressure: an observational

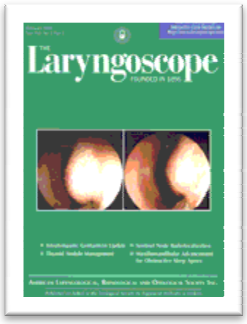
study.Lancet2005;365: 1046–53.9. Bradley TD, Floras JS. Obstructive sleep apnoea and its cardiovascular consequences.Lancet2009;373: 82–93.

11. Ryan S, Taylor CT, McNicholas WT. Systemic inflammation: a key factor in the pathogenesis of cardiovascular complications in obstructive sleep apnoea syndrome? Thorax2009;64: 631–6.
12. Wellman A, Malhotra A, Jordan ASet al. Effect of oxygen in obstructive sleep apnea: role of loop gain.Respir. Physiol. Neurobiol.2008;162: 144–51.
13. Huang Y, White DP, Malhotra A. Use of computational modeling to predict responses to upper airway surgery in obstructive sleep apnea.Laryngoscope2007;117: 648–53.
14. Palmer LJ, Buxbaum SG, Larkin EKet al.A genome-wide search for quantitative trait loci underlying obstructive sleep apnea.Am. J. Respir. Crit. Care Med.2002;165: A419.
15. Palmer LJ, Buxbaum SG, Larkin Eet al.A whole-genome scan for obstructive sleep apnea and obesity.Am. J. Hum. Genet.2003;72:340–50.
16. Bostrom KB, Hedner J, Melander Oet al.Interaction between the angiotensin-converting enzyme gene insertion/deletion polymorphism and obstructive sleep apnoea as a mechanism for hypertension.J. Hypertens.2007;25: 779–83.
17. Mulgrew AT, Fox N, Ayas NTet al.Diagnosis and initial management of obstructive sleep apnea without polysomnography: a randomized validation study.Ann.Intern.Med.2007;146: 157–66.
18. Campos-Rodriguez F, Grilo-Reina A, Perez-Ronchel Jet al.Effect of continuous positive airway pressure on ambulatory BP in patients with sleep apnea and hypertension: a placebocontrolled trial.Chest2006;129: 1459–67.
19. Kohler M, Ayers L, Pepperell JCet al.Effects of continuous positive airway pressure on systemic inflammation in patients with moderate to severe obstructive sleep apnoea: a randomised controlled trial.Thorax2009;64: 67–73.
20. Hillman DR, Murphy AS, Pezzullo L. The economic cost of sleep disorders.Sleep2006;29: 299–305.
21. Drager LF, Bortolotto LA, Figueiredo ACet al.Effects of continuous positive airway pressure on early signs of atherosclerosis in obstructive sleep apnea.Am. J. Respir. Crit. Care Med.2007;176: 706–12.
22. Ishida K, Kato M, Kato Yet al.Appropriate use of nasal continuous positive airway pressure decreases elevated C-reactive protein in patients with obstructive sleep apnea.Chest2009;136: 125–9.
23. Kohler M, Pepperell JC, Casadei Bet al.CPAP and measures of cardiovascular risk in males with OSAS.Eur.Respir.J.2008;32:1488–96.
24. Capp PK, Pearl PL, Lewin D. Pediatric sleep disorders.Prim Care.2005;32(2):549–562.
25. Heraghty JL, Hilliard TN, Henderson AJ,Fleming PJ. The physiology of sleep in infants. Arch Dis Child.2008;93(11): 982–985.
26. Owens J. Classification and epidemiology of childhood sleep disorders.Prim Care Clin Office Pract.2008;35:533–546.
27. Iglowstein I, Jenni OG, Molinari L, et al. Sleep duration from infancy to adolescence: reference values and generational trends. Pediatrics. 2003;111(2):302–307.
28. Goldstein NA, Pugazhendhi V, Rao SM, et al. Clinical assessment of pediatric obstructive sleep apnea.Pediatrics 2004;114:33–43.
29. Marcus CL. Sleep-disordered breathing in children. Curr Opin Pediatr 2000;12:208–212
30. Rembold CM, Suratt PM. Children with obstructive sleep-disordered breathing generate high-frequency inspiratory sounds during sleep. Sleep2004;27:1154–1161.
31. Schechter MS. Technical report: diagnosis and management of childhood obstructive sleep apnea syndrome.Pediatrics2002;109:e69.
32. de Almeida FR, Ayas NT, Otsuka R, et al. Nasal pressure recordings to detect obstructive sleep apnea.Sleep Breath2006;10:62–69.31. Schechter MS. Technical report: diagnosis and management of childhood obstructive sleep apnea syndrome.Pediatrics2002;109:e69.
33. Gozal D, Kheirandish-Gozal L. New approaches to the diagnosis of sleepdisordered breathing in children.Sleep Med2010;11:708–713.
34. Brietzke SE, Katz ES, Roberson DW. Can history and physical examination reliably diagnose pediatric obstructive sleep apnea/hypopnea syndrome? A systematic review of the literature.Otolaryngol Head Neck Surg2004;131:827–832.
35. Messner AH. Evaluation of obstructive sleep apnea by polysomnography prior to pediatric adenotonsillectomy.Arch Otolaryngol Head Neck Surg 1999;125:353–356.
36. Younis RT, Lazar RH. History and current practice of tonsillectomy. Laryngoscope 2002;112:3‐5.
37. Sargi Z, Younis RT. Tonsillectomy and adenoidectomy techniques: Past, present and future. ORL J Otorhinolaryngol Relat Spec 2007;69:331‐5.
38. Piessens P, Hens G, Lemkens N, Schrooten W, Debruyne F, Lemkens P. Effect of adenotonsillectomy on the use of respiratory medication. Int J Pediatr Otorhinolaryngol 2012;76:906‐10.
39. Silva S, Ouda M, Mathanakumara S, Ridyard E, Morar P. Tonsillectomy under threat: Auditing the indications for performing tonsillectomy. J Laryngol Otol 2012;126:609‐11.

Pediatric OSA – Chapter I

Clinical Assessment of Pediatric OSA

I. CLINICAL ASSESSMENT OF PEDIATRIC OSA



(*cf*. Appendix 1)

"CLINICAL ASSESSMENT OF PEDIATRIC OBSTRUCTIVE SLEEP APNEA: A SYSTEMATIC REVIEW AND META-ANALYSIS"

THE LARYNGOSCOPE

VICTOR CERTAL, EMANUEL CATUMBELA, JOÃO C. WINCK, INÊS AZEVEDO, ARMANDO TEIXEIRA-PINTO AND ALTAMIRO COSTA-PEREIRA

2012

2. Introduction

Pediatric OSA is characterized by recurring episodes of complete and/or partial obstruction of the upper airway during sleep, resulting in intermittent hypoxemia and hypercapnia, frequent arousals, and sleep fragmentation.[1, 2] OSA is a severe condition in children and differs from its adult counterpart in its physiology, clinical presentation, polysomnographic characteristics, and outcomes. The estimated prevalence in children is 1–3%[3]; however, the prevalence is difficult to measure because of subdiagnosis.[2, 4] Lack of community awareness about the negative sleep-related effects on the daily functioning of children, together with the parents' underestimation of the problem when they talk to the physician, are factors that contribute to this underestimation.[5, 6]

Polysomnography (PSG) is the gold standard for diagnosing and quantifying OSA.[6-9] Nocturnal PSG recordings provide unbiased and objective information on various sleep-related characteristics such as sleep architecture, cardiac and respiratory patterns, and gas exchange. However, several factors have hampered a more extensive implementation of such diagnostic procedures, including the inconvenience for both

parents and child spending the night in the laboratory, the rather onerous and labor-intensive nature of this diagnostic procedure, the relative scarcity of laboratories with expertise in children's sleep disorders—and as a corollary to this—the extended waiting period between referral and actual testing. Thus, the diagnosis of pediatric OSA is still often made on a clinical basis.[10]

Numerous studies have assessed the accuracy of clinical symptoms and signs in detecting pediatric OSA. The most commonly assessed symptoms and signs include snoring, observed apnea, mouth breathing, excessive daytime somnolence (EDS), and large tonsil size, but the diagnostic accuracy varies significantly for different symptoms and signs, as well as across studies. Two previous reviews addressed this variability.[11, 12] However, both used a poor methodological approach and presented conflicting results.

3. Aims

The aims of this study were to:

- assess the accuracy of clinical symptoms and signs in predicting pediatric OSA
- assess possible sources of heterogeneity
- Define future lines of work in this field

4. Methods

a. Study Design

A systematic review and meta-analysis of studies focusing on the clinical evaluation of pediatric OSA was undertaken. The methodological approach included the

development of selection criteria, definition of search strategies, assessment of the quality of the studies, data abstraction, and statistical data analysis.

b. Selection criteria

For proper identification of studies eligible for the analysis, the study selection criteria were defined before data collection. Only articles whose primary objective was to evaluate the ability of clinical evaluation (i.e., the clinical history and/or physical examination) to accurately diagnose pediatric OSA were selected. Articles that predominantly evaluated other diagnostic modalities (e.g., radiographs, pulse oximetry, electrocardiography, laboratory testing) were excluded. Only articles using full multichannel PSG (with electroencephalography) as the "gold standard" reference test for comparison with clinical evaluation were selected. The included studies provided information such as sensitivity and specificity or sufficient information to allow the construction of the diagnostic 2 × 2 table with 4 cells for true positives, false negatives, false positives, and true negatives.

c. Search strategy

Our primary method to locate potentially eligible studies was a computerized literature search in the MEDLINE database (through PubMed), from inception to August 2011, without any restriction on the language of publication, using the following search keywords and MeSH terms: "sleep apnea OR snoring OR sleep disordered breathing OR obstructive sleep apnea syndrome OR sleep apnea/diagnosis" AND "polysomnography OR sleep monitoring" AND "children OR child." Literature searches were also

undertaken, using the same search keywords, in the following databases: the Cochrane collaboration, SCOPUS, and ProQuest Dissertations & Thesis Database.

In defining the search strategies, we prioritized formats with higher sensitivity, in order to increase the probability of identifying all relevant articles.

Conference proceedings of the American Thoracic Society, Associated Professional Sleep Societies, European Sleep Research Society, and European Respiratory Society for the years 2002–2007 were hand-searched for eligible studies. Reference lists from eligible studies and review articles were cross-checked to identify additional trials. A grey literature research was also performed using OpenSIGLE Database. Both English and non-English studies were considered.

d. Study quality assessment and data abstraction

The titles and abstracts of the retrieved studies were independently screened for relevance by 2 reviewers (VC and EC). As currently recommended for systematic reviews of diagnostic accuracy studies, the reviewers evaluated the methodology of the selected studies using the 14-item Quality Assessment Tool for Diagnostic Accuracy Studies (QUADAS). All disagreements were resolved by consensus.

The data were used to construct 2 × 2 contingency tables, from which sensitivity and specificity were calculated for each study. When the raw data were presented in 3 x 3 or 4 x 4 tables (e.g., when the reference apnea-hypopnea index (AHI) was defined by >2 categories), we reconstructed 2 x 2 contingency tables by considering AHI > 1 as the positive state of pediatric OSA.

Statistical analysis is fully described in the Appendix 1.

5. RESULTS

a. Search and study selection

All database searches were performed in August 2011. A flow chart of the process of study identification and inclusion/exclusion is shown in Figure 1.

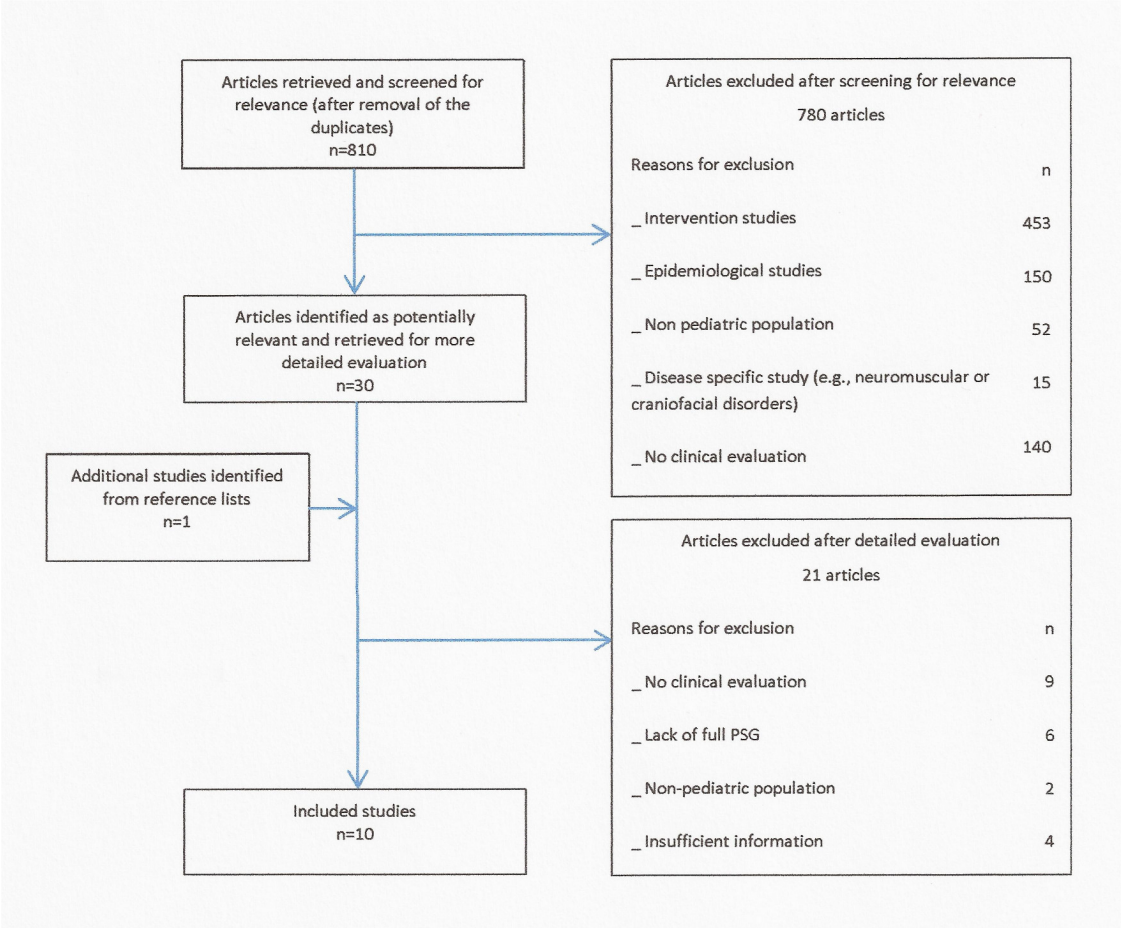


Figure 1 Flow diagram of study identification and selection.

PSG = polysomnography.

In total, 810 articles were identified using the search strategy and sources listed. After the titles and abstracts were screened for relevance, 780 articles were excluded (the reasons for exclusion are presented in Figure 1). The remaining 30 articles were retrieved for more detailed full-paper evaluation, and 21 were excluded for the following reasons: 6 studies[16-21]used a resumed PSG as the reference "gold standard" and thus lacked electroencephalography in their reference PSG; 2 studies included pediatric and adult populations in their results,[8, 22] 4 studies did not provide sufficient information to build 2 x 2 tables;[23-26] and 9 studies evaluated other diagnostic modalities.[27-35] One study[36] was included after a hand-search of references of the included studies. Finally, 10 studies were included in the review.[36-45]

b. Methodological quality of the included studies

The main characteristics of the included studies are presented in Table I. Overall, 1,525 patients were included, with a mean of 152.5 patients per study (range, 30–480 patients).

Despite the American Association of Sleep Medicine (AASM) recommendations,[46] only 6 studies[36-39, 41, 44] defined AHI >1/h as the diagnosis of pediatric OSA (range, 1–15/h). One study[42] did not report any AHI threshold.

All studies satisfied 7 of the 14 items in the QUADAS checklist for the assessment of methodological quality, namely, selection criteria described, complete verification using reference standard, same reference standard used, reference standard independent of the index test, details of execution of the reference standard, similar clinical data available for interpretation of the test as that in practice, and withdrawals

explained (Table II available in appendix 1). The main methodological limitations of the studies were related to poor reporting of items 4 (period between reference standard and index test), 8 (details about the execution of the index test), 10 and 11 (blind interpretation of the reference and index tests), and 13 (reporting of uninterpretable/intermediate test results). In all studies, no explicit criterion for identifying symptoms and signs was presented, and inter-observer agreement was not assessed.

Table I Characteristics of included studies. OSA = obstructive sleep apnea; N.R. = not reported; AHI = apnea/hypopnea index.

Author, year, reference	*Country*	*Setting*	*Sample size n*	*Age, male n (%)*	*Clinical criteria for OSA*	*Polysomnographic criteria for OSA*
Carroll *et al.*, 1995 [37]	USA	Pediatric Sleep and Breathing Disorders Clinic	83	5.4 months — 14,8 years (58)	Individual symptoms and combination of symptoms	AHI>1
Chau *et al.*, 2003 [38]	Singapore	Sleep Clinic	62	2 — 13 years (58)	Individual symptoms	AHI>1
Chervin *et al.*, 2007 [39]	USA	University-Based Sleep Disorders Laboratory	105	5 — 12.9 years (57)	Based on the Pediatric Sleep Questionnaire	AHI>1
Goldstein *et al.*, 1994 [40]	USA	Pediatric Otolaryngology Outpatient Clinic	30	1 — 14 years (60)	Combination of symptoms	AHI>15
Goodwin *et al.*, 2005 [41]	USA	General Population	480	6 — 8 years (50)	Individual symptoms and combination of symptoms	AHI>1
Leach et al., 1991 [42]	USA	Sleep Disorders Center	93	18 months — 12 years (59)	Individual symptoms	N.R.
Li *et al.*, 2006 [43]	China	Sleep Clinic	229	5 — 15 years (65)	Combination of symptoms	AHI>5
Rosen et al., 1999 [36]	USA	Children´s Sleep Laboratory	326	1 — 12 years (56)	Individual symptoms and combination of symptoms	AHI>1
Sproson *et al.*, 2009 [44]	UK	Community hospital	67	3 — 8 years (60)	Based on the Pediatric Sleep Questionnaire	AHI>1
Xu *et al.*, 2006 [45]	China	Sleep Clinic	50	4 — 18 years (76)	Individual symptoms and combination of symptoms	AHI>5

c. Sensitivity and specificity

Sensitivity and specificity for different symptoms and signs varied substantially; this variation was also observed across the studies included (Figure 2). We therefore did not report the pooled sensitivity and specificity of each symptom or sign.

Tonsillar size and snoring reported by parents or caregivers had relatively high sensitivity but low specificity. In contrast, EDS, observed apnea, and difficulty breathing during sleep had relatively high specificity but low sensitivity.

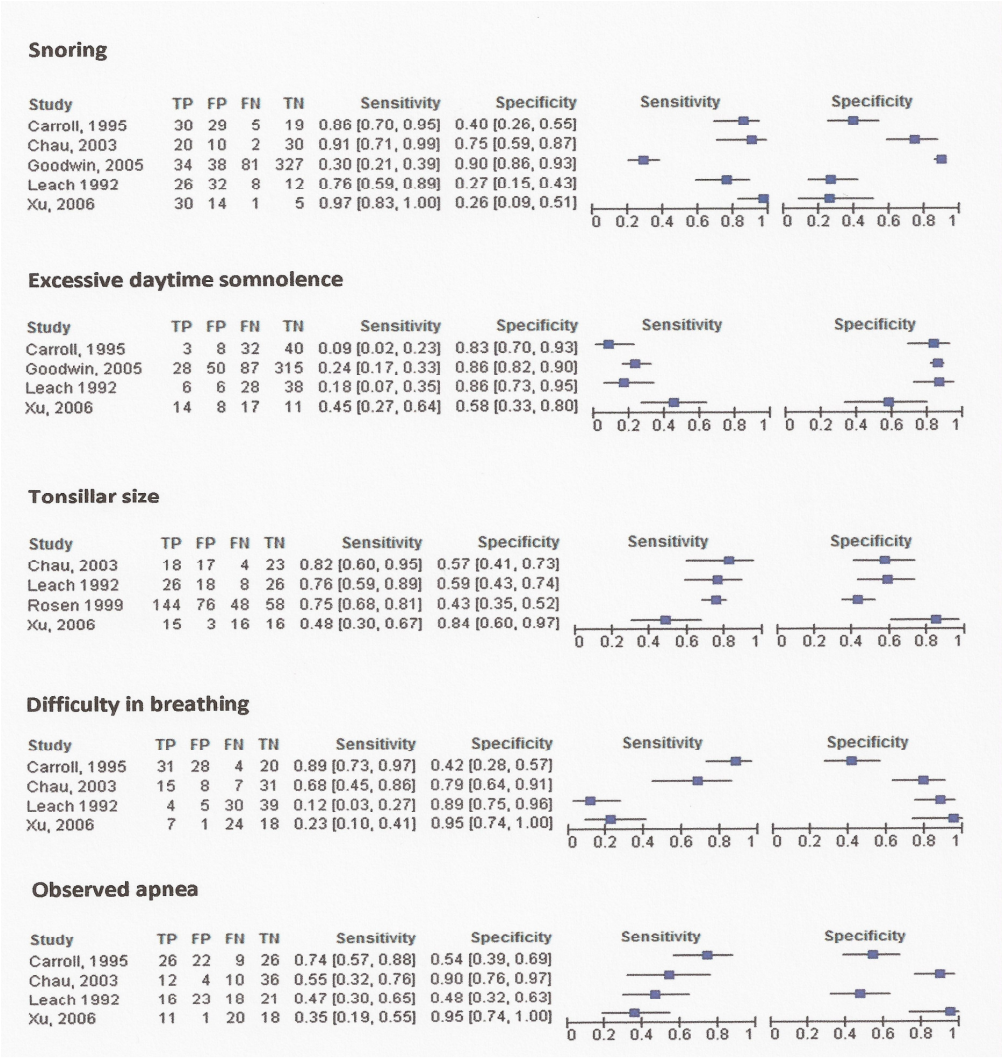


Figure 2 Diagnostic accuracy (sensitivity, specificity and 95%CI) of clinical symptoms and signs from each study.
TP = true-positive; FP = false-positive; FN = false-negative; TN= true-negative; CI = confidence interval.

Several models of combined symptoms and signs were assessed (Table III). Seven models/algorithms presented a moderate sensitivity (range 0.04–0.94) and specificity (range 0.28–0.99): the Pediatric Sleep Questionnaire, the OSA score initially proposed by Brouillette at al.[16] (snoring, difficulty breathing, EDS and behavior, personality or school performance), the modified OSA score of Carroll et al.[37] (observed apnea, difficulty breathing, and parents watching child during sleep), the model of Xu et al.[45](observed apnea, nocturnal enuresis, intrusive naps, mouth breathing, and moderate to severe tonsil hypertrophy), the model of Goldstein et al.[40](snoring, pauses, difficulty breathing, sleep with neck extended, EDS, and adenoid face), and Goodwin et al.[41]presented 2 models of symptoms (snoring and learning problems/snoring and EDS).

Table III Models of combinations of symptoms and signs and their diagnostic accuracy in predicting pediatric OSA. OSA = obstructive sleep apnea; EDS = excessive daytime somnolence.

Models of combinations	*Author, year, reference*	*Sensitivity*	*Specificity*
Pediatric Sleep Questionnaire	Sproson *et al.*, 2009[44]	0.53	0.67
	Chervin *et al.*, 2007[39]	0.78	0.72
Modified OSA score: Observed apnea, difficulty breathing and parents watching child during sleep	Carroll *et al.*, 1995[37]	0.40	0.92
OSA score: Snoring, difficulty in breathing, EDS, and behavior, personality or school performance	Rosen et al., 1999[36]	0.47	0.28
Night sweating, mouth breathing and snoring	Li *et al.*, 2006[43]	0.81	0.57
Observed apnea, nocturnal enuresis, intrusive naps, mouth breathing, and moderate to severe tonsillar hypertrophy	Xu *et al.*, 2006[51]	0.94	0.42
Snoring and learning problems	Goodwin *et al.*, 2005[41]	0.04	0.99
Snoring and EDS	Goodwin *et al.*, 2005[41]	0.09	0.97
Snoring, pauses, difficulty in breathing, sleep with neck extended, EDS, and adenoid face	Goldstein *et al.*, 1994[40]	0.92	0.29

d. Positive likelihood ratio, negative likelihood ratio, and diagnostic odds ratio

Table IV shows the pooled LR+, LR−, and DOR. None of the symptoms or signs had a pooled LR+ > 10, which indicates that the presence of these symptoms and signs may not provide convincing evidence to identify OSA among children. Moreover, none of the symptoms or signs had pooled LR− < 0.1, which suggests that the absence of these symptoms or signs cannot accurately exclude a diagnosis of pediatric OSA. Snoring and observed apnea had a higher pooled DOR than the other symptoms or signs.

Table IV Summary estimates of the diagnostic accuracy of clinical symptoms and signs for pediatric OSA.
DOR = diagnostic odds ratio; CI = confidence interval; LR+ = positive likehood ratio; LR- = negative likehood ratio; OSA = obstructive sleep apnea; EDS = excessive daytime somnolence.

Clinical criteria	*Number of patients (studies)*	*Sensitivity range*	*Specificity range*	*Pooled DOR (95% CI)*	*Pooled LR+ (95% CI)*	*Pooled LR- (95% CI)*
Snoring	753 (5)	0.30 — 0.97	0.26 — 0.90	4.94 (1.93 — 12.64)	1.76 (1.09 — 2.82)	0.36 (0.17 — 0.76)
Observed apnea	273 (4)	0.35 — 0.74	0.48 — 0.95	3.73 (1.21 — 11.54)	2.29 (0.94 — 5.60)	0.61 (0.45 — 0.84)
Difficulty breathing	272 (4)	0.12 — 0.89	0.42 — 0.95	3.62 (1.56 — 8.37)	2.37 (1.49 — 3.76)	0.65 (0.37 — 1.17)
EDS	691 (4)	0.18 — 0.45	0.58 — 0.86	1.59 (1.02 — 2.47)	1.49 (1.01 — 2.06)	0.91 (0.82 — 1.00)
Tonsillar size	516 (4)	0.48 — 0.82	0.43 — 0.84	3.34 (1.97 — 5.66)	1.73 (1.22 — 2.45)	0.52 0.40 — 0.67)

e. Hierarchical summary receiver operating characteristic curves

Figure 3 displays the ROC plots for each of the 5 symptoms and signs assessed by at least 4 studies. The shape of the summary ROC curves differed between symptoms and signs; however, none of the summary ROC curves was close to the upper left corner of the graph, which indicates poor diagnostic performance of the symptoms and signs in predicting OSA among children.

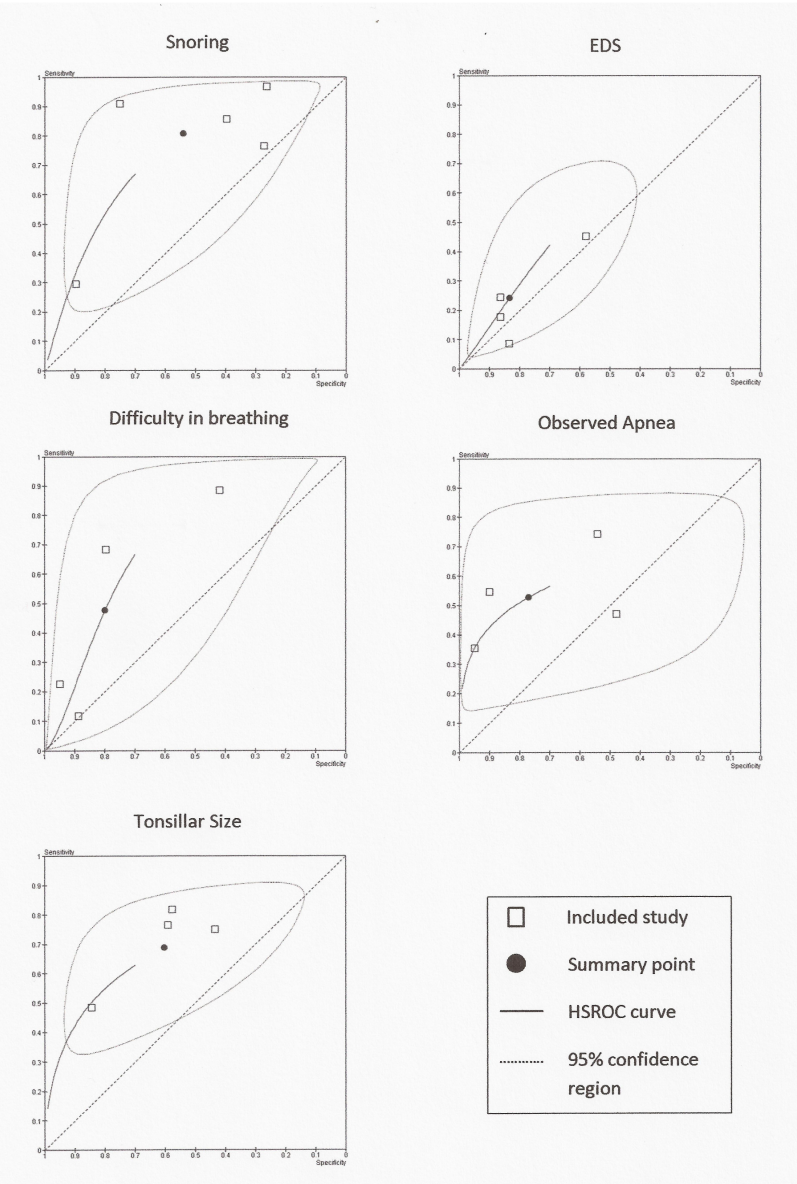


Figure 3 HSROC curves for the diagnostic performance of each symptom and sign.
HSROC = hierarchical summary receiver operating characteristic; EDS = excessive daytime somnolence.

f. Heterogeneity and subgroup analyses

As expected, the forest plots and ROC plots demonstrated substantial heterogeneity across studies, as shown in Figures 2 and 3. No outlier was identified. Because only 2 studies were performed outside sleep centers, no subgroup analysis was possible for the covariate setting (sleep centers vs. general population). The subgroup analysis was only performed for covariate AHI (AHI = 1 vs. AHI > 1); for all symptoms but 1 (difficulty in breathing), no statistical evidence is provided for a difference in the diagnostic accuracy of symptoms and signs according to the AHI threshold.

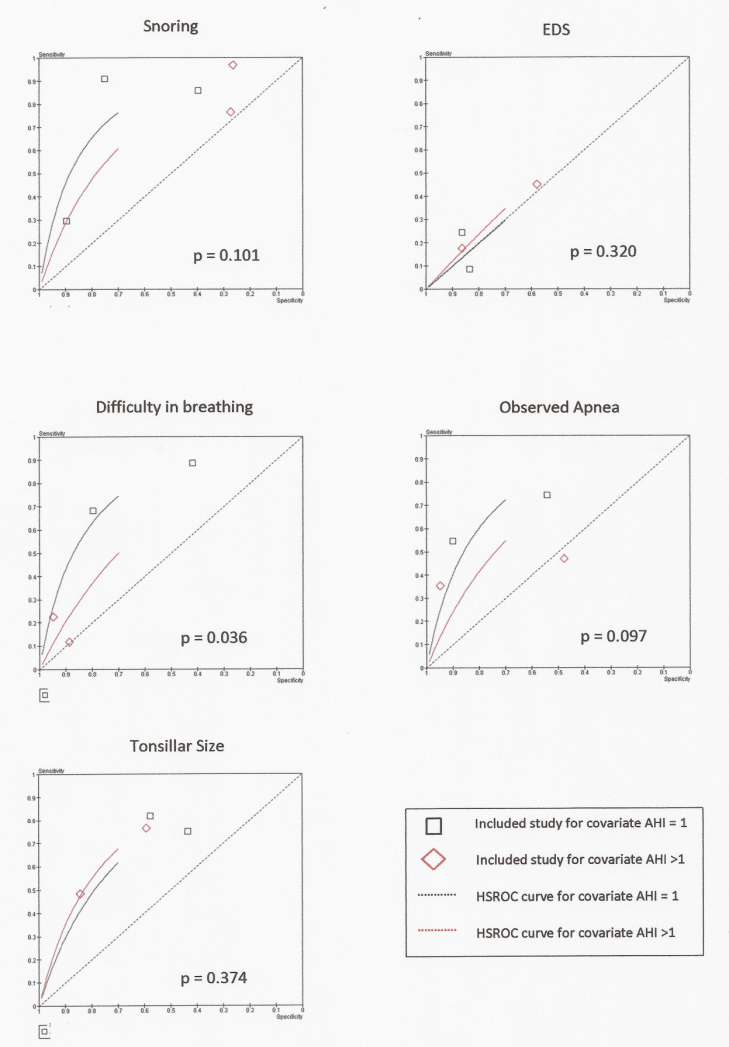


Figure 4 HSROC curves for the diagnostic performance of each symptom and sign for covariate AHI (AHI=1 vs. AHI>1).

6. DISCUSSION

a. Methodological limitations

Some methodological limitations of this review should be considered. First, as expected, there was substantial heterogeneity in results across studies. Several factors could contribute to this situation. In the 2005 edition of the International Classification of Sleep Disorders [46], the AASM defined an AHI greater than 1/h as abnormal in children, but three included studies [40, 43, 45]had other thresholds in their polysomnograph analysis, and one study[42] did not specify any threshold. None of the studies clearly described how to identify symptoms and signs, and it is therefore unclear whether there was a substantial variation across studies with regard to the explicit criteria for the definition of these symptoms and signs. However, a substantial variation in the implicit threshold could be expected among studies, as the test results (presence or absence of symptoms and signs) depend on the perceptions, interpretation, and judgment of observers. In this review, we used the HSROC model for meta-analyses of diagnostic accuracy, which takes threshold effects into account. The subgroup analysis for the covariate AHI (AHI = 1 vs. AHI > 1) did not appear to influence the diagnostic accuracy.

In addition, eight [36-40, 42, 43, 45]of the 10 studies were conducted in sleep clinics or sleep centers, where the prevalence of pediatric OSA is generally higher than in primary health services. A further decrease in the diagnostic yield may thus be expected when clinical symptoms and signs are used to predict pediatric OSA among children in primary care settings.

b. Diagnostic accuracy of symptoms and signs for predicting pediatric OSA

Despite the substantial variation in results among studies, this review demonstrates a poor overall diagnostic accuracy for single symptoms or signs in predicting pediatric OSA. Tonsillar size and snoring reported by parents or caregivers have relatively high sensitivity. Generally, when a test has high sensitivity, a negative result can be used to rule out the target condition. Thus, the absence of these symptoms and signs may be useful for excluding a diagnosis of OSA. However, the low specificity of these symptoms and signs may lead to a large number of false diagnoses of OSA.

In contrast, EDS, observed apnea, and difficulty breathing during sleep have relatively high specificity but low sensitivity. Because a positive result in a high-specificity test can be used to confirm a diagnosis of the target condition, the presence of the above mentioned symptoms or signs may be useful for identifying OSA.

Several models for the combination of symptoms and signs have been proposed; however, the diagnostic performance of these combinations has not yet been well assessed. Eight studies[36,37,39-41,43-45] evaluated the diagnostic accuracy of combined symptoms and signs, and the wide variation in models makes it impossible to pool the results. None of the models present reasonable sensitivity and specificity, and there appears to be substantial variation in the diagnostic performance among these models.

7. CONCLUSION

This meta-analysis provides a comprehensive critical review of the literature to date and a statistical analysis of the current diagnostic accuracy of clinical symptoms and signs for investigating pediatric OSA. The major finding of this study is that both single and combinations of symptoms and signs have poor diagnostic accuracy in predicting pediatric OSA. It is important to critically evaluate the current evidence to appropriately guide future efforts in this research field. High-quality diagnostic studies that address alternative non-invasive methods in the evaluation of pediatric OSA are still necessary.

References

1. Goldstein NA, Pugazhendhi V, Rao SM, et al. Clinical assessment of pediatric obstructive sleep apnea. Pediatrics 2004; 114:33–43.
2. Kotagal S. Sleep disorders in childhood. Neurol Clin 2003; 21:961–981.
3. Ali NJ, Pitson DJ, Stradling JR. Snoring, sleep disturbance, and behaviour in 4-5 year olds. Arch Dis Child 1993; 68:360–366.
4. Marcus CL. Sleep-disordered breathing in children. Curr Opin Pediatr 2000; 12:208–212.
5. Reuveni H, Simon T, Tal A, Elhayany A, Tarasiuk A. Health care services utilization in children with obstructive sleep apnea syndrome. Pediatrics 2002; 110:68–72.
6. Rembold CM, Suratt PM. Children with obstructive sleep-disordered breathing generate high-frequency inspiratory sounds during sleep. Sleep 2004; 27:1154–61.
7. Schechter MS. Technical report: diagnosis and management of childhood obstructive sleep apnea syndrome. Pediatrics 2002; 109:e69.
8. de Almeida FR, Ayas NT, Otsuka R, et al. Nasal pressure recordings to detect obstructive sleep apnea. Sleep Breath 2006; 10:62–69.
9. Morielli A, Ladan S, Ducharme FM, Brouillette RT. Can sleep and wakefulness be distinguished in children by cardiorespiratory and videotape recordings? Chest 1996; 109:680–687.
10. Gozal D, Kheirandish-Gozal L. New approaches to the diagnosis of sleep-disordered breathing in children. Sleep Med 2010; 11:708–713.
11. Brietzke SE, Katz ES, Roberson DW. Can history and physical examination reliably diagnose pediatric obstructive sleep apnea/hypopnea syndrome? A systematic review of the literature. Otolaryngol Head Neck Surg 2004; 131:827–832.
12. Messner AH. Evaluation of obstructive sleep apnea by polysomnography prior to pediatric adenotonsillectomy. Arch Otolaryngol Head Neck Surg 1999; 125:353–356.
13. Rutter CM, Gatsonis CA. A hierarchical regression approach to meta-analysis of diagnostic test accuracy evaluations. Stat Med 2001; 20:2865–2884.
14. Leeflang MM, Deeks JJ, Gatsonis C, Bossuyt PM. Systematic reviews of diagnostic test accuracy. Ann Intern Med 2008; 149:889–897.
15. Brouilette R, Hanson D, David R, et al. A diagnostic approach to suspected obstructive sleep apnea in children. J Pediatr 1984; 105:10–14.
16. Nieminen P, Tolonen U, Lopponen H. Snoring and obstructive sleep apnea in children: a 6-month follow-up study. Arch Otolaryngol Head Neck Surg 2000; 126: 481–486.
17. Otsu SY, Koike Y, Hori Y, Abe K. Hypertrophy of the palatine tonsils and sleep respiratory disorders. Acta Oto-Laryngologica, Supplement 1996; 523:219–221.

18. Preutthipan A, Chantarojanasiri T, Suwanjutha S, Udomsubpayakul U. Can parents predict the severity of childhood obstructive sleep apnoea? Acta Paediatr 2000; 89:708–712.
19. Constantin E, Tewfik TL, Brouillette RT. Can the OSA-18 quality-of-life questionnaire detect obstructive sleep apnea in children? Pediatrics, 2010. 125(1): p. e162–8.
20. Valera FC, Avelino MA, Pettermann MB, et al. OSAS in children: correlation between endoscopic and polysomnographic findings. Otolaryngol Head Neck Surg 2005; 132:268–272.
21. Erdamar B, Suoglu Y, Cuhadaroglu C, Katircioglu S, Guven M. Evaluation of clinical parameters in patients with obstructive sleep apnea and possible correlation with the severity of the disease. Eur Arch Otorhinolaryngol 2001; 258:492–495.
22. Li AM, Wong E, Kew J, Hui S, Fok TF. Use of tonsil size in the evaluation of obstructive sleep apnoea. Arch Dis Child 2002; 87:156–159.
23. Brooks LJ, Stephens BM, Bacevice AM. Adenoid size is related to severity but not the number of episodes of obstructive apnea in children. J Pediatr 1998; 132:682–686.
24. Suen JS, Arnold JE, Brooks LJ. Adenotonsillectomy for treatment of obstructive sleep apnea in children. Arch Otolaryngol Head Neck Surg 1995; 121:525–530.
25. Jain A, Sahni JK. Polysomnographic studies in children undergoing adenoidectomy and/or tonsillectomy. J Laryngol Otol 2002; 116:711–715.
26. Nigro CA, Aimaretti S, Gonzalez S, Rhodius E. Validation of the WristOx 3100™ oximeter for the diagnosis of sleep apnea/hypopnea syndrome. Sleep and Breathing 2009; 13:127–136.
27. Grover SS, Pittman SD. Automated detection of sleep disordered breathing using a nasal pressure monitoring device. Sleep and Breathing 2008; 12:339–345.
28. Griffiths A, Maul J, Wilson A, Stick S. Improved detection of obstructive events in childhood sleep apnoea with the use of the nasal cannula and the differentiated sum signal. J Sleep Res 2005; 14:431–436.
29. Jacob SV, Morielli A, Mograss MA, Ducharme FM, Schloss MD, Brouillette, RT. Home testing for pediatric obstructive sleep apnea syndrome secondary to adenotonsillar hypertrophy. Pediatr Pulmonol 1995; 20:241–252.
30. Gozal D, Kheirandish-Gozal L, Serpero LD, Capdevila OS, Dayyat E. Obstructive sleep apnea and endothelial function in school-aged nonobese children: Effect of adenotonsillectomy. Circulation 2007; 116:2307–2314.
31. Saeed MM, Keens TG, Stabile MW, Bolokowicz J, Davisson-Ward SL. Should children with suspected obstructive sleep apnea syndrome and normal nap sleep studies have overnight sleep studies? Chest 2000; 118:360–365.
32. Sivan Y, Kornecki A, Schonfeld T. Screening obstructive sleep apnoea syndrome by home videotape recording in children. Eur Respir J 1996; 9:2127–2131.
33. Uliel S, Tauman R, Greenfeld M, Sivan Y. Normal polysomnographic respiratory values in children and adolescents. Chest 2004; 125:872–878.
34. Ghaemmaghami H, Abeyratne UR, Hukins C. Normal probability testing of snore signals for diagnosis of obstructive sleep apnea. Conf Proc IEEE Eng Med Biol Soc, 2009. 2009: 5551–5554.
35. Rosen CL. Clinical features of obstructive sleep apnea hypoventilation syndrome in otherwise healthy children. Pediatr Pulmonol 1999; 27:403–409.
36. Carroll JL, McColley SA, Marcus CL, Curtis S, Loughlin GM. Inability of clinical history to distinguish primary snoring from obstructive sleep apnea syndrome in children. Chest 1995; 108:610–618.
37. Chau KW, Ng DK, Kwok CK, Chow PY, Ho JC. Clinical risk factors for obstructive sleep apnoea in children. Singapore Med J 2003; 44:570–573.
38. Chervin RD, Weatherly RA, Garetz SL, et al. Pediatric sleep questionnaire: prediction of sleep apnea and outcomes. Arch Otolaryngol Head Neck Surg 2007; 133:216–222.
39. Goldstein NA, Sculerati N, Walsleben JA, Bhatia N, Friedman DM, Rapoport DM. Clinical diagnosis of pediatric obstructive sleep apnea validated by polysomnography. Otolaryngol Head Neck Surg 1994; 111:611–617.
40. Goodwin JL, Kaemingk KL, Mulvaney SA, Morgan WJ, Quan SF. Clinical screening of school children for polysomnography to detect sleep-disordered breathing--the Tucson Children's Assessment of Sleep Apnea study (TuCASA). J Clin Sleep Med 2005; 1:247–254.
41. Leach J, Olson J, Hermann J, Manning S. Polysomnographic and clinical findings in children with obstructive sleep apnea. Arch Otolaryngol Head Neck Surg 1992; 118:741–744.
42. Li AM, Cheung A, Chan D, et al. Validation of a questionnaire instrument for prediction of obstructive sleep apnea in Hong Kong Chinese children. Pediatric Pulmonology 2006; 41:1153–1160.
43. Sproson EL, Hogan AM, Hill CM. Accuracy of clinical assessment of paediatric obstructive sleep apnoea in two English centres. J Laryngol Otol 2009; 123:1002–1009.
44. Xu Z, Cheuk DK, Lee SL. Clinical evaluation in predicting childhood obstructive sleep apnea. Chest 2006; 130:1765–1771.
45. American Academy of Sleep Medicine. International classification of sleep disorders, 2nd ed: Diagnostic and coding manual, American Academy of Sleep Medicine, Westchester, IL 2005
46. Mason DG, Iyer K, Terrill PI, Wilson SJ, Suresh S. Pediatric Obstructive Sleep Apnea assessment using pulse oximetry and dual RIP bands. Conf Proc IEEE Eng Med Biol Soc 2010; 2010:6154–6157.
47. Okun MN, Hajiangelis N, Green D, Hedli LC, Lee KC, Krieger AC. Acoustic rhinometry in pediatric sleep apnea. Sleep Breath 2010; 14:43–49.

Pediatric OSA – Chapter II

Unattended sleep studies in Pediatric OSA

II. UNATTENDED SLEEP STUDIES IN PEDIATRIC OSA

(*cf.* Appendix 2)

"UNATTENDED SLEEP STUDIES IN PEDIATRIC OSA: A SYSTEMATIC REVIEW AND META-ANALYSIS"

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2014

1. Introduction

Sleep-disordered breathing, including obstructive sleep apnea syndrome (OSA), is increasingly recognized as an important cause of morbidity in children. Clinical symptoms of OSA in children include snoring, nocturnal arousals, restlessness during sleep, enuresis, daytime sleepiness, and hyperactivity.[1,2]

Polysomnography (PSG) is the gold standard for diagnosing and quantifying OSA. Nocturnal PSG recordings provide comprehensive and objective information on various sleep-related characteristics such as sleep architecture, cardiac and respiratory patterns, and gas exchange.[3,4]

However, studying children with laboratory PSG is expensive because of the cost of laboratory use and the relative scarcity of laboratories with expertise in children's sleep disorders. Additionally, parents and their young children, particularly school-aged children, are often hesitant to spend a night in the unfamiliar setting of a sleep laboratory.[5]

In an effort to simplify the diagnostic process and to make this process more accessible and convenient for patients, many unattended multichannel studies have been explored in children.[6]

Ambulatory monitoring with unattended devices is considered reliable for the diagnosis of OSA in particular groups of adult patients, but is not yet recommended for children because of the lack of solid clinical and validation studies.[7]

2. Aims

The aims of this study were to:

- assess the accuracy of unattended sleep studies in predicting pediatric OSA
- assess the practibility and reliability of such instruments

3. Methods

a. Study Design

A systematic review and meta-analysis of studies focusing on unattended multichannel devices for the diagnosis of pediatric OSA was undertaken. The methodological approach included the development of selection criteria, the definition of search strategies, an assessment of study quality, data abstraction, and statistical data analysis.

b. Selection Criteria

For proper identification of studies eligible for the analysis, the study selection criteria were defined before data collection. For the purpose of conducting a systematic review, we assessed all studies in which the primary objective was to evaluate the ability of unattended type 2 or type 3 multichannel devices (according to the American

Academy of Sleep Medicine [AASM] guidelines[8]) to accurately diagnose or monitor OSA. Type 2 monitoring devices can perform full PSG outside of the laboratory. The major difference between type 2 and type 3 devices and type 1 devices is that a technologist is not present with the former types, and these devices are called comprehensive portable devices. Type 3 monitoring devices do not record the signals needed to determine sleep stages or sleep disruption. Typically, the channels include 2 respiratory variables (e.g., respiratory movement and airflow); a cardiac variable (e.g., heart rate or an electrocardiogram), and arterial oxygen saturation. Commonly the same device can perform a type 2 or 3 study, depending only on the number of channels utilized. Articles that evaluated type 4 monitoring devices were excluded. These devices are also called continuous single or dual bioparameter devices. Monitoring devices record 1 or 2 variables and can be used without a technician. The channels typically include arterial oxygen saturation and airflow. Studies including children between 1 and 18 years of age were eligible for inclusion, whereas studies that included adults were excluded. Studies that included subjects with any chronic underlying diseases (i.e., genetic/metabolic disorders, craniofacial malformations, or neurological/neuromuscular disorders) were excluded. For conducting a meta-analysis, only articles using full multichannel PSG (type 1 devices according to AASM guidelines) as the gold standard reference test for comparison with unattended multichannel devices were selected. Further, the included studies had to provide information such as sensitivity and specificity or sufficient information to allow the construction of the diagnostic 2×2 table with 4 cells for true positives, false negatives, false positives, and true negatives for the purpose of conducting a meta-analysis.

c. Search Strategy

Our primary method to locate potentially eligible studies was a computerized literature search in the MEDLINE database (through PubMed) from inception to November 2013. The following search key words and MeSH terms were used: (sleep apnea OR snoring OR sleep disordered breathing OR obstructive sleep apnea syndrome OR sleep apnea/diagnosis) AND (polygraphy OR polysomnography OR sleep monitoring OR portable monitor OR cardiopulmonary) AND (children OR child OR pediatric). Literature searches were also undertaken by using the same search key words in the following databases: the Cochrane collaboration, SCOPUS, and ProQuest Dissertations and Thesis Database.

In defining the search strategies, we prioritized formats with higher sensitivity to increase the probability of identifying all relevant articles. Conference proceedings of the American Thoracic Society, Associated Professional Sleep Societies, European Sleep Research Society, and European Respiratory Society for the years 2005 to 2010 were hand-searched for eligible studies. Reference lists from eligible studies and review articles were crosschecked to identify additional trials. A grey literature search was also performed by using the OpenSIGLE database. Studies meeting the criteria were considered with no language limitation.

d. Study Quality Assessment and Data Abstraction

The titles and abstracts of the retrieved studies were independently screened for relevance by 2 reviewers (VC and MC). As currently recommended for systematic reviews of diagnostic accuracy studies, the reviewers evaluated the methodology of the selected studies by using the 14-item Quality Assessment Tool for Diagnostic Accuracy Studies (QUADAS).[9] All disagreements were resolved by consensus. For the purpose of

conducting a meta-analysis, the data were used to construct 2 × 2 contingency tables, from which sensitivity and specificity were calculated for each study. When the raw data were presented in 3 × 3 or 4 × 4 tables (e.g., when the reference apnea-hypopnea index [AHI] was defined by >2 categories), we reconstructed 2 × 2 contingency tables by considering AHI > 1 as the positive state of pediatric OSA.

Statistical analysis is fully described in the appendix 2.

4. Results

a. Search and Study Selection

All database searches were performed in August 2013. A flow chart of the process of study identification and inclusion/exclusion is shown in Figure 1.

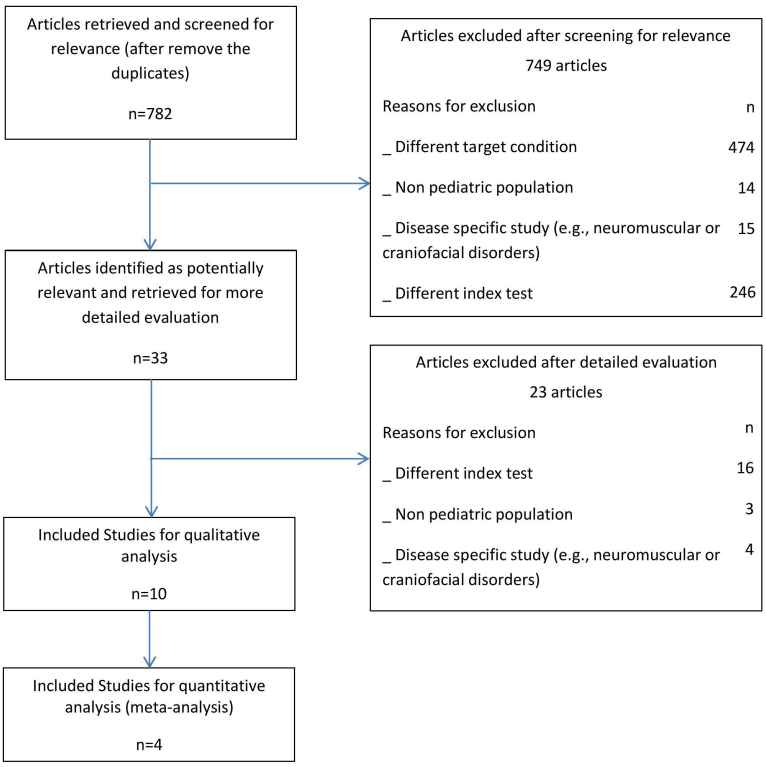


Figure 1 - Flow diagram of study identification and selection.

In total, 782 articles were identified by using the search strategy and sources listed. After the titles and abstracts were screened for relevance, 749 articles were excluded (the reasons for exclusion are presented in Fig. 1). The remaining 33 articles were retrieved for a more detailed full-text evaluation, and 23 were excluded for the following reasons: 16 studies did not use a type 2 or type 3 monitoring device for index test;[12-27] 4 studies included a pediatric population with chronic underlying diseases;[28-31] and 3 studies included an adult population.[32-34] Finally, 10 studies were included in the systematic review (qualitative analysis).[5,35-43] Out of these 10 articles, a total of 4 studies[35-38] performed PSG in all subjects (comparison with the gold standard) and provided sufficient information such as sensitivity and specificity or sufficient information to allow the construction of the diagnostic 2 $\times$ 2 table; therefore, these studies were included in the subsequent meta-analysis (quantitative analysis).

b. **Qualitative Summary (Systematic Review)**

The main characteristics of the included studies are presented in Table I. These studies included a total of 724 patients, with a mean of 72.4 patients per study (range, 12–157 patients). Despite the AASM recommendations, only 3 studies[35,36,42] defined AHI > 1/hour as the diagnosis of pediatric OSA (range, 1–5/hour).

Author, year	*Setting*	*Sample size*	*Age*	*Device (Comparison)*	*Channels evaluated*	*Events scoring*	*OSA criteria*
Alvarez *et al.*, 2008	Sleep-disordered breathing clinic	55	2-14 years	Edentec Monitoring System® (vs. full PSG)	6 channels: oronasal flow using a thermistor, chest movements by impedance plethysmography, body position, snoring, heart rate and SpO2	- Apnea was defined as the absence of oronasal airflow lasting at least 6 seconds - Hypopnea was defined as a decrease of at least 50% in the amplitude of respiratory flow lasting at least 6 seconds, with a decrease in SpO2 of at least 3% or by arousals (in PSG)	AHI>1
Alvarez et al., 2012	Burgos Sleep Unit	100	2-14 years	Edentec Monitoring System® (no comparison)	6 channels: oronasal flow using a thermistor, chest movements by impedance plethysmography, body position, snoring, heart rate and SpO2	- Apnea was defined as the interruption of oronasal flow for at least the time equivalent to two respiratory cycles - Hypopnea was defined as a decrease of at least 50% in the amplitude of oronasal flow during the time equivalent to two respiratory cycles, associated with a drop in oxygen saturation of at least 3%	AHI>4.6
Eguia et al., 2012	Burgos Sleep Unit	150	3.74 years (mean)	Edentec Monitoring System® (no comparison)	6 channels: oronasal flow using a thermistor, chest movements by impedance plethysmography, body position, snoring, heart rate and SpO2	- Apnea was defined as the absence of oronasal airflow lasting at least 6 seconds - Hypopnea was defined as a decrease of at least 50% in the amplitude of respiratory flow lasting at least 6 seconds, with a decrease in SpO2 of at least 3%	AHI>4.6
Goodwin et al., 2001	General population	157	5-12 years	Compumedics PS-2 system® (vs. full PSG in 5 patients)	12 channels: EEG; EOG; bipolar submental electromyogram; thoracic and abdominal displacement; airflow; nasal pressure cannula; oximetry; EKG; snoring (by microphone), body position, and ambient light	- Apneas were scored if the amplitude of the airflow signal decreased below at least 25% of the amplitude of "baseline" breathing, if this change lasted for >6 seconds or two breath cycles. - Hypopneas were designated if the amplitude of any respiratory signal decreased below (approximately) 70% of the amplitude of "baseline", if this change lasted for >6 seconds or two breath cycles.	AHI>5
Hamada et al., 2012	Hospital based	48	2-11 years	Sleeptester ® (no comparison)	5 channels: oronasal airflow, thoracoabdominal effort, snoring, body position, and SpO2	- Apnea was defined as cessation (> 90% reduction) of oronasal airflow lasting for more than 2 breaths. - Hypopnea was defined as > 50% reduction of oronasal airflow with > 3% desaturation for more than 2 breaths	AHI>5

Table I - Characteristics of Included Studies.

PSG = Polysomnography; EKG = Electrocardiography; EEG = Electroencephalography; EOG = Electrooculography; AHI = apnea/hypopnea index; NR: Not reported

Jacob et al., 1995	*Montreal Children´s Hospital*	*21*	*6 months-14years*	*NR (vs. full PSG)*	*7 channels: EKG; pulse rate; SpO2; pulse waveform; thoracic and abdominal; respiratory inductive plethysmograph*	*- Apnea was defined as an 80% or greater decrease in amplitude on the respiratory inductive plethysmograph summation channel with at least 3 seconds* *- Hypopnea was defined as a 50-80% decrease in amplitude of the summation channel and a decrease in saturation of ≥4%*	*AHI>1*
Lesser et al. 2012	Rady Children's Hospital San Diego Sleep Laboratory	25	9-18 years	The ApneaLink Plus® (vs. full PSG)	6 channels: oronasal flow using nasal cannula connected to a pressure transducer, EKG lead, chest and abdominal movements, body position and SpO2	- Apnea was defined as 80% to 100% reduction in airflow associated for 2 respiratory cycles - Hypopnea was defined as 50% to 80% reduction in airflow associated for 2 respiratory cycles	AHI>5
Poels et al., 2003	Hospital Based	24	2-7 years	Embletta PDS® (no comparison)	5 channels: Respiratory movement, nasal airflow, heart rate, oxygen saturation, and body position	- Apnea was defined as a reduction in the airflow signal to below 10% of the reference amplitude for at least 10 seconds. - Hypopnea was defined as a reduction in airflow signal to below 50% of the reference amplitude for at least 10 seconds	AHI>1
Prado et al., 2006	Hospital based	132	8.3 years (mean)	ApnoeScreen® (no comparison)	7 channels: oronasal flow using a thermistor, chest and abdominal movements, body position, snoring, heart rate and SpO2	- Apnea was defined as an 80% or greater decrease in amplitude of the airflow signal if this change lasted for > two breath cycles - Hypopneas were designated if the amplitude of any respiratory signal decreased below 50% if this change lasted for > two breath cycles, and with a O2 dessaturation of ≥4%	AHI>3
Zucconi et al., 2003	Sleep disorders Center	12	3-6 years	Poly-mesam® (vs. full PSG)	7 channels: oronasal flow using a thermistor, laryngeal microphone for snoring, EKG lead, chest and abdominal movements, body position and SpO2	- Apnea was defined as the absence of oronasal airflow lasting at least 8 seconds with a O2 dessaturation of >4% - Hypopnea was defined as a decrease of at least 50% in the amplitude of respiratory flow lasting at least 6 seconds, with a decrease in SpO2 of at least 4%	AHI>5

Table I - Characteristics of Included Studies. (*Continuation)*

PSG = Polysomnography; EKG = Electrocardiography; EEG = Electroencephalography; EOG = Electrooculography; AHI = apnea/hypopnea index; NR: Not reported

The methodological quality of all of the studies included in our analysis was poor. Of the 14 items in the QUADAS checklist for the assessment of methodological quality, all studies satisfied only the following 2 items: item 8, regarding the description of the execution of the index test similar and item 12, regarding the availability of clinical data for interpretation of the test as it would be interpreted in practice (Table II – Available in the Appendix 2). The main methodological limitation of the studies was related to the lack of a reference standard in 6 out of 10 studies. Items 4, 6, 7, 10, and 11 were not applicable in these studies because they did not make a comparison to the full PSG. These 6 articles[5,39-43] were not included in the subsequent meta-analysis. Strong limitations were also found in the definition of selection criteria and in the reporting of uninterpretable/intermediate test results (item 13). Only 3 studies[35,36,42] reported withdrawals in their results.

The 10 selected articles in the systematic review were moderately heterogeneous in terms of the channels of the monitoring device. Most of the studies used a type 3 device with at least 5 channels (range, 5–7 channels) with minor differences. Only 1 study[5] used a type 2 device with 12 analyzed channels. Major heterogeneity was found in the definition of scoring events, with no consensus between the included studies. The definition of apnea in terms of duration in seconds showed major differences across the studies, varying between 3 to 10 seconds. As recommended by AASM guidelines, 5 studies[5,37,39-41] defined apnea as the interruption of oronasal flow for at least the time equivalent to 2 respiratory cycles, with no mention of an objective time frame. Major heterogeneity was even greater for hypopnea scoring, with no consensus between the duration of the event or the definition itself. Most of the included studies defined hypopnea as a decrease of at least 50% in the amplitude of respiratory flow.

Hypopnea was defined as a decrease in the amplitude of any respiratory signal below (approximately) 70% of the amplitude of "baseline" in 1 study[5]. Further, major heterogeneity was found in the definition of the associated minimum desaturation, with 4 studies[35,39,41,43] defining hypopnea as a drop in oxygen saturation of at least 3%, 3 studies[36,38,40] as a drop in oxygen saturation of at least 4%, and 3 studies[5,37,42] did not define any associated desaturation.

Despite the great amount of heterogeneity, most of the included studies in the systematic review concluded that unattended type 2 or type 3 multichannel devices were useful for diagnosing or monitoring pediatric OSA, especially in the comparison of respiratory parameters between pre-operative and post-operative data. The residual rate of disease was high (range, 11.6% to 24.4%) in 3 studies[39,41,43] that analyzed residual OSA after surgical treatment, indicating that such monitoring is important. Two studies[5,42] demonstrated that technically acceptable data could be obtained in most of the children tested, with a high degree of reproducibility and a good diagnostic concordance between clinical and polygraphic post-surgical data.

c. Quantitative Summary (Meta-analysis)

This meta-analysis included 4 articles[35-38] that provided sufficient information for the calculation of diagnostic parameters. Only studies that examined type 3 devices were included in this analysis.

We used sensitivity, specificity, positive (LR+) and negative likelihood ratios (LR−), and the diagnostic odds ratio (DOR) as measures of diagnostic accuracy. The distribution of sensitivity and specificity showed substantial variation across the included studies (Figure 2). The overall pooled results demonstrated a sensitivity of 76% (95% CI: 64–

85%), a specificity of 80% (95% CI: 60–88%), pooled LR+ of 2.78 (95% CI: 0.77–10.07), and a pooled LR - of 0.30 (95% CI: 0.11–0.83) (Table III). The use of any of these measurements alone is not adequate for the purpose of synthetizing the range of data likely to be encountered in a diagnostic accuracy meta-analysis. For this reason, the authors presented the pooled DOR and AUC, which are more likely to be consistent across studies regardless of the diagnostic threshold.[9] Overall, the pooled results for these parameters demonstrated a DOR of 15.18 (95% CI: 3.52–65.43) (Table III) and an AUC of 0.88 (Figure 3). Both values indicated an informative index test with a good overall diagnostic accuracy.

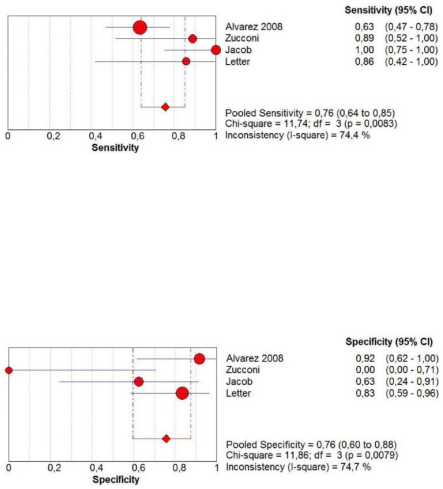


Figure 2 - Diagnostic accuracy (sensitivity, specificity, and pooled results) of unattended sleep studies. CI = confidence interval

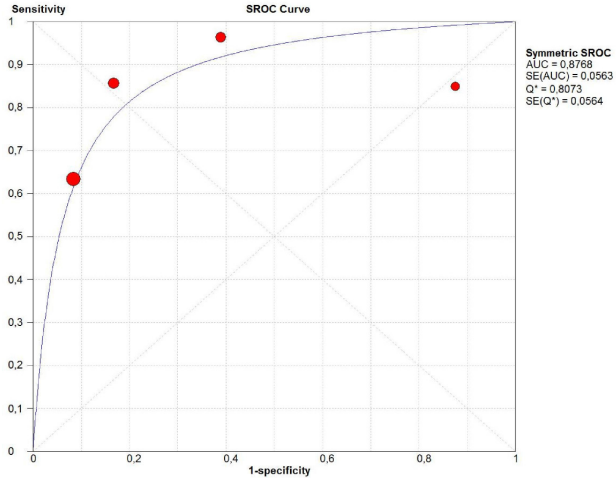


Figure 3 - Hierarchical summary receiver operating characteristic (HSROC) curves for the diagnostic performance of unattended sleep studies.

A sensitivity analysis was carried out based on the AHI criteria used (≤ 1 or > 1 episode/hour). For AHI ≤ 1 (2 studies, 76 patients), the results were as follows: sensitivity, 72% (58–84%); specificity, 80% (56–94%); LR+, 3.42 (1.06–11.06); LR-, 0.2 (0.02–2.02); and DOR, 24.63 (4.21–144.24). For AHI > 1 (2 studies, 37 patients), the results were as follows: sensitivity, 88% (62–98%); specificity, 71% (48–89%); LR+, 2.14 (0.26–17.41); LR-, 0.32 (0.05–1.89); and DOR, 6.06 (0.18–205.81). No significant difference was found between the 2 groups.

Table III - Summary Estimates of the Diagnostic Accuracy and major findings of included studies.
* Included in meta-analysis
DOR = diagnostic odds ratio; CI = confidence interval; LR+ = positive likelihood ratio; LR- = negative likelihood ratio; OSA = obstructive sleep apnea; AHI = apnea/hypopnea index; PSG = polysomnography; ROC = receiver operating characteristic

Author, year	*Aim*	*Main Findings*	*Sensitivity*	*Specificity*	*DOR*	*LR+*	*LR-*
Alvarez et al., 2012	Evaluate the usefulness of respiratory polygraphy to control post-adenotonsillectomy effects in children with OSA	- All of the children who were included completed the study - For AHI >4.6, the post-surgical diagnostic concordance between clinical and polygraphic post-surgical data was 100% in the non-OSA group and 93% in the OSA group	-	-	-	-	-
Eguia et al., 2012	To evaluate the effectiveness of adenotonsillectomy for the treatment of OSA in children by respiratory polygraphy	- There was a significant improvement in all clinical and polygraphic variables six months after adenotonsillectomy - The preoperative RDI was significantly associated with persistent disease - Respiratory polygraphy is useful for monitoring the efficacy of surgical treatment in children with OSA	-	-	-	-	-
Goodwin et al., 2001	Description of the methods used for obtaining and analyzing unattended home polysomnography data	- Technically acceptable studies were obtained in 97% of the children. - Night-to-night variability in key polysomnographic parameters showed a high degree of reproducibility on 2 different nights of study using identical protocols in the same child - In 5 children, polysomnograms done in the home were comparable to those recorded in a sleep laboratory.	-	-	-	-	-
Hamada et al., 2012	Usefulness of respiratory polygraphy by comparing respiratory parameters between pre- and postoperative examinations	- The mean duration of assessable monitoring was 460 ± 172 min (Mean ± S.D.) (range; 90–642 min) in the preoperative test and 471 ± 126 min (range; 184–660 min) in the postoperative test. - The prevalence of OSAS was 93.8% on the basis of the results of preoperative home monitoring when the AHI value of > 5 indicated OSA	-	-	-	-	-
Prado et al., 2006	The aim of this study was to analyze the diagnostic utility of in-home respiratory polygraphy in the diagnosis of OSA	No significant differences were found between the validity of in-home and in-hospital respiratory polygraphy. Likewise, no significant differences were found between AHI/h, SpO2 and in-home and in-hospital respiratory polygraphy.	-	-	-	-	-
Poels et al., 2003	Evaluate the feasibility of using a home cardiorespiratory recording device in children	- Technically acceptable recordings were obtained in 75% of the included children. Only 29% of the recordings were classified as successful. The poorest signal quality was obtained from the nasal cannula.	-	-	-	-	-

Alvarez et al., 2008*	*Evaluate the diagnostic usefulness of respiratory polygraphy in children with clinical suspicion of OSA*	*When ROC curves were calculated for the AHI cutoff points used for the diagnosis of OSA (1, 3, and 5), the best AHI cutoff for all 3 AHI values considered was found to be 4.6*	*0.63*	*0.92*	*19.07*	*7.61*	*0.40*
Jacob et al., 1995*	Comparison of a home-based diagnostic system with standard PSG for the diagnosis of OSA	The device tested is accurate and of practical use in the routine evaluation of OSA in patients with adenotonsillar hypertrophy	1.00	0.62	42.43	2.63	-
Lesser et al. 2012*	Evaluate the diagnostic usefulness of multichannel screening device to screen for OSA in a referral population of obese children and adolescents	- The multichannel screening device is a sensitive screening tool for evaluation of suspected OSAS in obese pediatric patients aged 9-18 years - The specificity improves with increasing AHI cutoffs.	0.86	0.83	30	5.14	0.17
Zucconi et al., 2003*	Comparison of a home-based diagnostic system with standard PSG for the diagnosis of OSA	Both sensitivity and specificity increased with the increase of the AHI cutoff to 10 (sensitivity:1.00/specificity: 0.57)	0.89	0.00	0.81	-	0.78
Pooled results (95% CI)			0.76 (0.64-0.85)	0.76 (0.6-0.88)	15.18 (3.52 – 65.43)	2.78 (0.77-10.01)	0.30 (0.11-0.83)

Table III - Summary Estimates of the Diagnostic Accuracy and major findings of included studies. (*Continuation)*

* Included in meta-analysis

DOR = diagnostic odds ratio; CI = confidence interval; LR+ = positive likelihood ratio; LR- = negative likelihood ratio; OSA = obstructive sleep apnea; AHI = apnea/hypopnea index; PSG = polysomnography; ROC = receiver operating characteristic

5. Discussion

a. Methodological Limitations

Some methodological limitations of this review should be considered. Therefore, although the random-effects model used throughout the analysis should have compensated for these limitations, any conclusions from the pooled diagnostic parameters and their interpretation should be treated with a degree of caution. Several factors could contribute to this situation, beginning with the threshold variability in polysomnography analysis. Only 3 studies[35,36,42] used the recommended criteria for pediatric OSA (AHI > 1/hour) and, despite computing parameters that take this variable into account (DOR and AUC), the statistical power may not have been sufficient to overcome this confounding bias entirely. Moreover, although there is no doubt that PSG recordings provide unbiased and objective information, the recommended criteria for pediatric OSA (AHI>1/hour) lack of consensus because of the relative dichotomy between PSG-derived measures and clinical symptoms.

Another critical fact is the heterogeneity surrounding the event scoring, especially hypopnea scoring, which reiterates that fact that these studies were not entirely comparable. Regarding external validity, it is also important to realize that the participants of the studies may not represent the general population because the majority of the studies were performed in sleep clinics or sleep centers, where the prevalence of pediatric OSA is generally higher. In addition, although unattended devices were similar regarding analyzed channels (with the exception of 1 study[5] that used a type 2 device), it is likely that minor technical differences acted as confounding factors.

Because of these variables, it is difficult to provide general recommendations regarding the clinical utility of unattended multichannel devices. Therefore, despite the good diagnostic accuracy demonstrated in the results of this review, the actual usefulness of these devices must be both systematically investigated and compared to the currently accepted gold standard. Further research is needed to examine the value in clinical decision making, especially for post-treatment follow-up. Moreover, further studies that are carried out in a larger population, perform cost-effectiveness tests, and include patients from primary care settings are necessary.

6. Conclusion

Considering the high prevalence of pediatric OSA, it is important to explore new practicable diagnostic pathways. This meta-analysis provides a comprehensive critical review of the literature to date and a statistical analysis of the current diagnostic accuracy of unattended multichannel devices for investigating pediatric OSA, especially in mild to moderate disease. The major finding of this study is that these devices are useful and valid tools for OSA screening in children. However, high-quality diagnostic studies that address unattended multichannel devices in the evaluation of pediatric OSA are still necessary.

References

1. Gaultier C. Clinical and therapeutic aspects of obstructive sleep apnea syndrome in infants and children. *Sleep*. 1992;15(6 Suppl):S36-S38.
2. Ferber R, Kryger MH. *Principles and Practice of Sleep Medicine in the Child*. Philadelphia: Saunders; 1995.
3. Schechter MS. Technical report: diagnosis and management of childhood obstructive sleep apnea syndrome. *Pediatrics*. 2002;109(4):e69.
4. Guilleminault C, Pelayo R, Leger D, Clerk A, Bocian RC. Recognition of sleep-disordered breathing in children. *Pediatrics.* 1996; 98(5):871-882.
5. Goodwin JL, Enright PL, Kaemingk KL, et al. Feasibility of using unattended polysomnography in children for research—report of the Tucson Children's Assessment of Sleep Apnea study (TuCASA). *Sleep.* 2001; 24(8):937-944.
6. Gozal D, Kheirandish-Gozal L. New approaches to the diagnosis of sleep-disordered breathing in children. *Sleep Med*. 2010; 11(7):708-713.

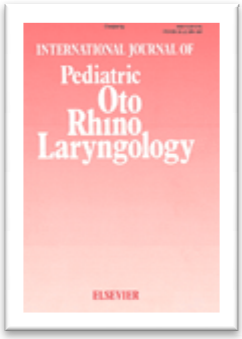
7. Marcus CL, Brooks LJ, Draper KA, et al. Diagnosis and management of childhood obstructive sleep apnea syndrome. *Pediatrics.* 2012; 130(3):e714-755.
8. Collop NA, Anderson WM, Boehlecke B, et al. Clinical guidelines for the use of unattended portable monitors in the diagnosis of obstructive sleep apnea in adult patients. Portable Monitoring Task Force of the American Academy of Sleep Medicine. *J Clin Sleep Med*. 2007; 3(7):737-747.
9. Leeflang MM, Deeks JJ, Gatsonis C, Bossuyt PM, Cochrane Diagnostic Test Accuracy Working G. Systematic reviews of diagnostic test accuracy. *Ann Intern Med*. 2008; 149(12):889-897.
10. Leeflang MM, Bossuyt PM, Irwig L. Diagnostic test accuracy may vary with prevalence: implications for evidence-based diagnosis. *J Clin Epidemiol*. 2009; 62(1):5-12.
11. Zamora J, Abraira V, Muriel A, Khan K, Coomarasamy A. Meta-DiSc: a software for meta-analysis of test accuracy data. *BMC Med Res Methodol*. 2006; 6:31.
12. Foo JY, Bradley AP, Wilson SJ, Williams GR, Dakin C, Cooper DM. Screening of obstructive and central apnoea/hypopnoea in children using variability: a preliminary study. *Acta Paediatr*. 2006; 95(5):561-564.
13. Brouillette RT, Lavergne J, Leimanis A, Nixon GM, Ladan S, McGregor CD. Differences in pulse oximetry technology can affect detection of sleep-disorderd breathing in children. *Anesth Analg*. 2002; 94(1 Suppl):S47-S53.
14. Hyde M, O'Driscoll DM, Binette S, et al. Validation of actigraphy for determining sleep and wake in children with sleep disordered breathing. *J Sleep Res*. 2007; 16(2):213-216.
15. Noehren A, Brockmann PE, Urschitz MS, Sokollik C, Schlaud M, Poets CF. Detection of respiratory events using pulse rate in children with and without obstructive sleep apnea. *Pediatr Pulmonol*. 2010; 45(5):459-468.
16. Sanders MH, Kern NB, Costantino JP, et al. Accuracy of end-tidal and transcutaneous PCO2 monitoring during sleep. *Chest*. 1994; 106(2):472-483.
17. Contencin P, Malorgio E, Noce S, Couloigner V, Vigo A. Questionnaire and nocturnal oxymetry in children with adenotonsillar hypertrophy. *Eur Ann Otorhinolaryngol Head Neck Dis*. 2010; 127(4):137-142.
18. Ghaemmaghami H, Abeyratne UR, Hukins C. *Normal Probability Testing of Snore Signals for Diagnosis of Obstructive Sleep Apnea*. Proceedings of the Annual International Conference of the IEEE Engineering in Medicine and Biology Society IEEE Engineering in Medicine and Biology Society Conference 2009; 2009:5551-5554.
19. Chau Kw, Ng DK, Kwok Kl, et al. Application of videotape in the screening of obstructive sleep apnea in children. *Sleep Med.* 2008; 9(4):442-445.
20. Grover SS, Pittman SD. Automated detection of sleep disordered breathing using a nasal pressure monitoring device. *Sleep Breath.* 2008; 12(4):339-345.
21. Leung LC, Ng DK, Lau MW, et al. Twenty-four-hour ambulatory BP in snoring children with obstructive sleep apnea syndrome. *Chest*. 2006; 130(4):1009-1017.
22. Kirk VG, Bohn SG, Flemons WW, Remmers JE. Comparison of Home Oximetry Monitoring with Laboratory Polysomnography in Children. *Chest*. 2003; 124(5):1702-1708.
23. Marcus CL, Keens TG, Ward SL. Comparison of nap and overnight polysomnography in children. *Pediatr Pulmonol*. 1992; 13(1):16-21.
24. Tong GM, Guo JH, Han F, et al. Screening of sleep apnea syndrome by ECG derived respiration of ambulatory electrocardiogram. *Natl Med J China*. 2006; 86(22):1545-1548.
25. Zhang XW, Li Y, Zhou F, Guo CK, Huang ZT. Comparison of polygraphic parameters in children with adenotonsillar hypertrophy with vs without obstructive sleep apnea. *Arch Otolaryngol Head Neck Surg*. 2007; 133(2):122-126.
26. Brietzke SE, Katz ES, Roberson DW. Pulse transit time as a screening test for pediatric sleep-related breathing disorders. *Arch Otolaryngol Head Neck Surg*. 2007; 133(10):980-984.
27. Nigro CA, Aimaretti S, Gonzalez S, Rhodius E. Validation of the WristOx 3100™ oximeter for the diagnosis of sleep apnea/hypopnea syndrome. *Sleep Breath*. 2009; 13(2):127-136.
28. Amorim A, Sucena M, Winck JC, Almeida J. Home cardiorespiratory sleep study in children. Will it be feasible?. *Rev Port Pneumol*. 2004; 10(6):463-474.
29. Luna-Paredes C, Anton-Pacheco JL, Garcia Hernandez G, Martinez Gimeno A, Romance Garcia AI, Garcia R, Il. Screening for symptoms of obstructive sleep apnea in children with severe craniofacial anomalies: assessment in a multidisciplinary unit. *Int J Pediatr Otorhinolaryngol*. 2012; 76(12):1767-1770.
30. de Miguel-Diez J, Villa-Asensi JR, Alvarez-Sala JL. Prevalence of sleep-disordered breathing in children with Down syndrome: polygraphic findings in 108 children. *Sleep*. 2003; 26(8):1006-1009.
31. Hoch B, Hochban W. Four-year-old girl with Goldenhar-sequence and severe obstructive sleep apnea, symptoms, diagnosis and therapy. *Int J Pediatr Otorhinolaryngol*. 1998; 43(3):277-281.
32. Liu D, Yang X, Wang G, et al. HHT based cardiopulmonary coupling analysis for sleep apnea detection. *Sleep Med*. 2012; 13(5):503-509.
33. Schramm PJ, Thomas RJ. Assessment of therapeutic options for mild obstructive sleep apnea using cardiopulmonary coupling measures. *J Clin Sleep Med*. 2012; 8(3):315-320.
34. Erdamar B, Suoglu Y, Cuhadaroglu C, Katircioglu S, Guven M. Evaluation of clinical parameters in patients with obstructive sleep apnea and possible correlation with the severity of the disease. *Eur Arch Otorhinolaryngol*. 2001; 258(9):492-495.
35. Alonso Álvarez ML, Santos JT, Guevara JAC, et al. Reliability of respiratory polygraphy for the diagnosis of sleep apnea-hypopnea syndrome in children. *Arch Bronconeumol.* 2008; 44(6):318-323.
36. Jacob SV, Morielli A, Mograss MA, Ducharme FM, Schloss MD, Brouillette RT. Home testing for pediatric obstructive sleep apnea syndrome secondary to adenotonsillar hypertrophy. *Pediatr Pulmonol.* 1995; 20(4):241-252.
37. Lesser DJ, Haddad GG, Bush RA, Pian MS. The utility of a portable recording device for screening of obstructive sleep apnea in obese adolescents. *J Clin Sleep Med*. 2012; 8(3):271-277.
38. Zucconi M, Calori G, Castronovo V, Ferini-Strambi L. Respiratory monitoring by means of an unattended device in children with suspected uncomplicated obstructive sleep apnea: a validation study. *Chest*. 2003; 124(2):602-607.
39. Hamada M, Iida M. Home monitoring using portable polygraphy for perioperative assessment of pediatric obstructive sleep apnea syndrome. *Tokai J Exp Clin Med*. 2012; 37(3):66-70.

40. Sardón Prado O, González Pérez-Yarza E, Aldasoro Ruiz A, et al. Diagnostic utility of nocturnal in-home respiratory polygraphy. *An Pediatr (Barc).* 2006; 65(4):310-315.
41. Alonso-Alvarez ML, Navazo-Eguia AI, Cordero-Guevara JA, et al. Respiratory polygraphy for follow-up of obstructive sleep apnea in children. *Sleep Med*. 2012; 13(6):611-615.
42. Poels PJ, Schilder AG, van den Berg S, Hoes AW, Joosten KF. Evaluation of a new device for home cardiorespiratory recording in children. *Arch Otolaryngol Head Neck Surg*. 2003; 129(12):1281-1284.
43. Navazo Eguia AI, Alonso Alvarez ML, de la Mata Franco G, Cordero Guevara J, Teran Santos J, Ordax Carbajo E. Evaluation of the efficacy of adenotonsillectomy for the treatment of obstructive sleep apnea hypopnea syndrome in children using respiratory polygraphy. *An Pediatr (Barc)*. 2013; 78(5):308-313.
44. Jaeschke R, Guyatt GH, Sackett DL. Users' guides to the medical literature. III. How to use an article about a diagnostic test. B. What are the results and will they help me in caring for my patients? The Evidence-Based Medicine Working Group. *JAMA*. 1994; 271(9):703-707.
45. Brietzke SE, Gallagher D. The effectiveness of tonsillectomy and adenoidectomy in the treatment of pediatric obstructive sleep apnea/hypopnea syndrome: a meta-analysis. *Otolaryngol Head Neck Surg.* 2006; 134(6):979-984.

Pediatric OSA – Chapter III

Translation and Cross-Cultural adapation of the Pediatric Sleep Questionnaire into Portuguese Language

III. TRANSLATION AND CROSS-CULTURAL ADAPTATION OF THE PEDIATRIC SLEEP QUESTIONNAIRE INTO PORTUGUESE LANGUAGE



"TRANSLATION AND CROSS-CULTURAL ADAPTATION OF THE PEDIATRIC SLEEP QUESTIONNAIRE INTO PORTUGUESE LANGUAGE"

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(*cf*. Appendix 3)

1. Introduction

Sleep-disordered breathing (SDB), including obstructive sleep apnoea (OSA) syndrome, is acknowledged to be a cause of morbidity in children. Clinical symptoms of OSA among children include snoring, nocturnal arousals, restlessness during sleep, enuresis, daytime sleepiness, and hyperactivity.[1, 2]

As a result of increasing international collaboration in sleep research, the need for culturally appropriate and linguistically accessible instruments for assessing sleep quality among children has expanded.[3] This is particularly true in Portugal, where there are very few of such instruments available. Having these validated tools is very important when evaluating specific sleep treatment outcomes across different countries. Specifically, both methods used by patients and caregivers to describe sleep problems and the assessment of the effects of treatment must be comparable, irrespective of patients' language and cultural background. Recognizing these needs, the International Pediatric Sleep Education Task Force concluded that testing

methodologies and culturally sensitive epidemiologic tools are key components of cross-cultural sleep research.[4]

Despite our recent meta-analysis [5] suggesting that clinical evaluations have poor diagnostic accuracy, especially in regard to OSA, this does not mean that they should not be performed. As a result of a lack of paediatric sleep laboratories, sleep history is frequently the only instrument available to clinicians, especially in Portugal. Thus, sleep history should, and must, be part of routine health care visits as an initial screening tool for children at risk of OSA.

Based on this meta-analysis, the Pediatric Sleep Questionnaire (PSQ) appears to be the only instrument validated by full overnight polysomnography (PSG).[6] Furthermore, using the same gold standard, the PSQ was also tested by Spronson et al.[7] in the UK. Thus, it is the most reliable questionnaire for sleep disorder screening.

2. Aims

The aims of this study were to:

- evaluate a Portuguese language translation of the PSQ by checking the accuracy of the translation
- assess its content validity
- determine whether or not it could be clearly understood when piloted in a sample of children

3. Material and Methods

a. The Pediatric Sleep Questionnaire

The validated PSQ has 22 items documenting the presence or absence of common symptoms such as snoring, observed apnoeas, breathing difficulty during sleep, daytime sleepiness, and inattentive or hyperactive behaviour. Positive responses are scored as 1 and negative responses as 0. Then, the overall score is divided by 22 to provide a final value. Compared with overnight PSG, the PSQ has been reported to have a sensitivity of between 0.81 and 0.85 and a specificity of 0.87 in detecting OSA. A cut-off value of seven positive responses is thought to be most effective in identifying OSA. Subscales within the PSQ include a seven-item sleepiness scale, a nine-item snoring scale, and a six-item behavioural scale.

b. Study design

After obtaining ethical approval from the Institutional Review Board (Appendix 19) and receiving Copyright permission (Appendix 20), an adaptation of the PSQ questionnaire was performed. A written informed consent (Appendix 21) was obtained by all parents. The adaptation process followed internationally recommended steps for translation[3], including back-translation, translation evaluation by a judging committee and pilot testing of the pre-final version. A schematic overview of the linguistic validation process is illustrated in Figure 1.

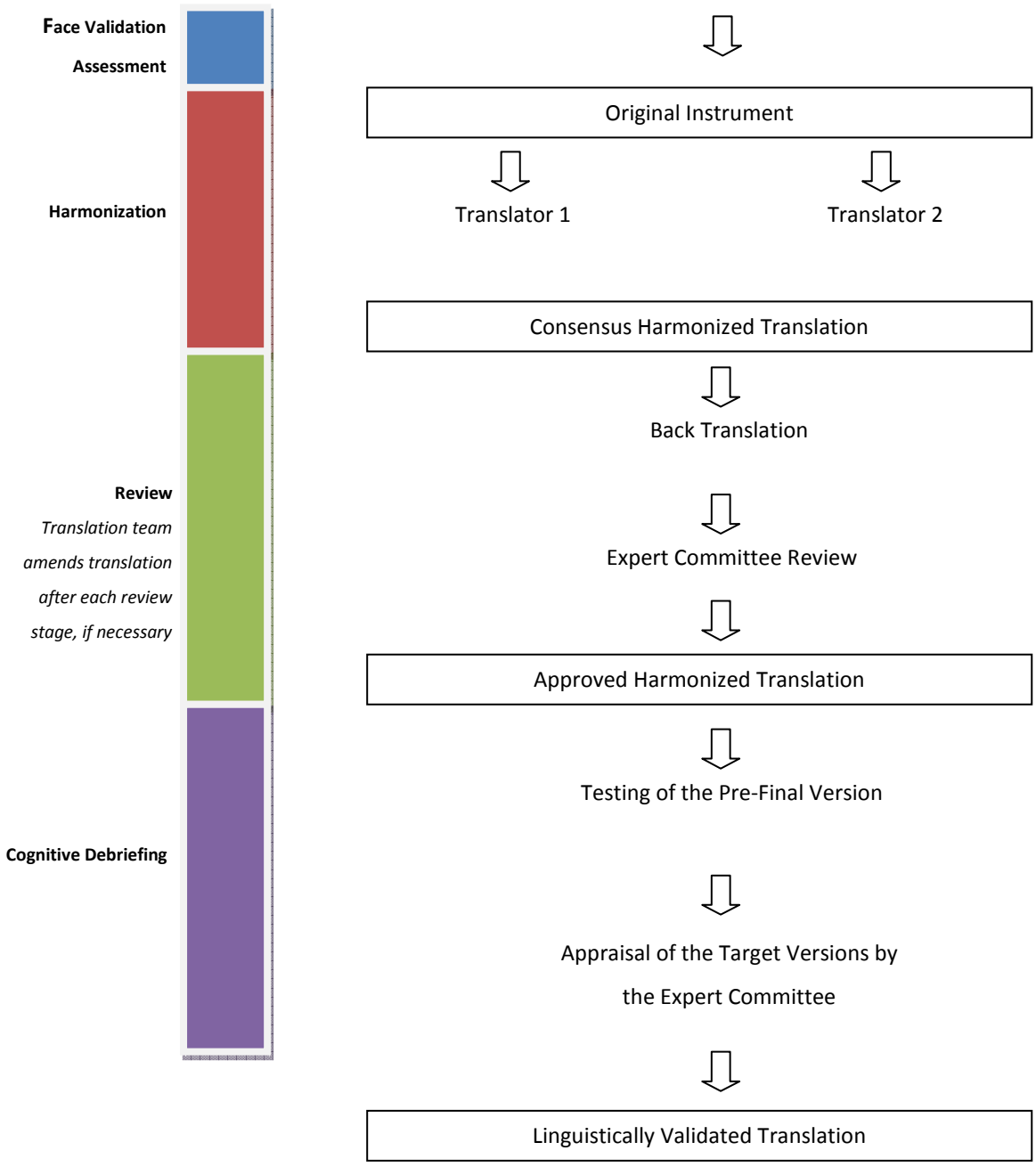

Figure 1. Overview of the linguistic evaluation process

Two translations of the questionnaires from the original language to the target language were conducted. Bilingual translators (VC and FFL) whose first language was the target language independently produced the two translations. Once the two translated versions were created, a consensus version was established by reconciling the differences between the two translated versions. This was achieved through a discussion between the translators and a recording observer. The goal was to enhance cultural sensitivity and appropriate wording of the instrument. The reconciled version was then independently back-translated into the original language by two naive translators whose first language was the source language (English). The primary objective was to ensure that the translated version reflected the same item content as the original. Subsequently, the back-translated versions were reviewed by the research team.

An expert committee was created, and its role was to develop the pre-final version for field-testing. The goal was to achieve semantic, idiomatic, experiential, and conceptual equivalence, which ensured an accurate translation and an appropriate cultural adaptation. This committee comprised health professionals, language professionals, and all the involved translators. The committee reviewed all translations and reached consensus on any discrepancies.

The next step was to test the pre-final version by conducting a pilot study that aimed to assess the clarity, appropriateness, and cultural relevance (i.e. appropriate cultural adaptation) of the target language version. This cognitive debriefing exercise involved the completion of the instrument by a sample of 50 participants. Each subject completed the questionnaire and was subsequently interviewed about the meaning of each item. The responders answered the PSQ twice after at least an interval of 21 days.

Based on the findings of the pilot testing of the pre-final version, further modifications were made to the Portuguese PSQ. The final version of the Portuguese PSQ (Appendix) was applied between June and September 2014, and involved 180 parents of school children aged 4–12 years from a tertiary hospital in Northern Portugal.

Statistical analysis is fully described in the appendix 3.

4. Results

The sample consisted of 180 Caucasian children, including 99 males (55%) and 81 females (45%), with a mean age of 5.5 ± 2.0 years (4–12 years). Based on Graffar's socioeconomic classifications [10], five children belonged to class I (3%), nine to Class II (5%), 117 to Class III (65%), 45 to Class IV (25%) and 4 to Class V (2%). Eighteen caregivers (10%) graduated from university, 11 (6%) graduated from high school or two-year degree programs, 45 (25%) did not complete high school or two-year degree programs and 106 (59%) completed elementary school. The demographic data are shown in Table 1.

TABLE 1. Characteristics of the language validation studied sample

Sex, n (%)	
Male	99 (55)
Female	81 (45)
Age, years	
Mean ± SD	5.5 ± 2.0
Range	4 - 12
Marital status of caregivers, n (%)	
Married/Partnered	126 (70)
Single/Divorced	54 (30)
Graffar classification, n (%)	
Class I	5 (3)
Class II	9 (5)
Class III	117 (65)
Class IV	45 (25)
Class V	4 (2)

The results showed mouth breathing in among 2.9% of patients, loud snoring in 5.8%, and disturbed breathing during sleep in 2.5%, respectively. Sleepiness was reported among 15.3% of the patients, and behavioural problems were reported for 15.4%. There was a moderate correlation between loud snoring and sleepiness (ρ = 0.32) and a weak correlation between loud snoring and behavioural domains (ρ = 0.21). Thirty-one (17.0%) of the 180 participants revealed positive symptoms for SDB.

Reliability analysis was carried out using SPSS based on internal consistency, yielding a Cronbach's alpha of 0.781 of the total items in the study. In terms of the instrument subscales, the snoring domain was α = 0.609, the sleepiness domain was α = 0.612 and the behavioural domain was α= 0.701 (Table 2). Percentages of correct

answers to all items were >90.0%. In addition, results revealed good test-retest reliability for all items (Table 3).

TABLE 2. Internal consistency of the Portuguese PSQ

Variables	*Number of items*	*Cronbach α*
Snoring Domain	9	0.609
Sleepiness Domain	7	0.612
Behavorial Domain	6	0.701
Total	22	0.781

TABLE3. Test-retest reliability of the Portuguese PSQ

SD = Standart Deviation

Items	*Kappa (SD)*	*P*
A1	0.523 (0.165)	<0.001
A2	0.645 (0.103)	<0.001
A3	0.451 (0.165)	<0.001
A4	0.501 (0.201)	<0.001
A5	0.753 (0.251)	<0.001
A6	0.468 (0.101)	<0.001
A7	0.852 (0.095)	<0.001
A8	0.651 (0.084)	<0.001
A9	0.497 (0.099)	<0.001
B1	0.812 (0.111)	<0.001
B2	0.456 (0.093)	<0.001
B3	0.698 (0.201)	<0.001
B4	0.542 (0.165)	<0.001
B5	0.699 (0.302)	<0.001
B6	0.678 (0.165)	<0.001
B7	0.815 (0.198)	<0.001
C1	0.611 (0.165)	<0.001
C2	0.501 (0.143)	<0.001
C3	0.654 (0.164)	<0.001
C4	0.789 (0.213)	<0.001
C5	0.703 (0.197)	<0.001
C6	0.605 (0.163)	<0.001

5. Discussion

With the increase in the number of international research projects, the need to adapt health status measures for use in languages other than the source language is of primary importance. The objective of this study was to translate the PSQ from English into Portuguese by following the international translation guidelines.

Currently, PSG is widely considered to be the gold standard in diagnosing childhood SDB. However, PSG is very expensive, time consuming and not easy to carry out on children. As a result, such cases require simplified methods. In contrast, the PSQ is a quick, easy-to-use, highly reliable and consistent test used to evaluate the subjective aspects of sleep among children with OSA. As confirmed by the high reliability of the Cronbach's alpha (0.791) and significant consistency illustrated by the correlation between individual test items and total scores, this study showed that the Portuguese version of the PSG is an adequate translation and culturally appropriate adaptation.

Translation difficulties encountered as part of this study included the fact that some English words and sentences from the original PSQ were difficult to translate into Portuguese (e.g. question C5 – 'Is your child restless or does he/she behave as if "his/her engine is always running"'?). However, an equivalent translation was identified, and all of the caregivers of children with OSA found the survey questions easy to understand; even those with medium-to-low income levels and low levels of education.

Although sleep history is an essential screening tool, care must be taken when used as a unique tool in this field. In fact, most screening tools rely on clinical evaluation, and in the specific case of paediatric sleep disorders, there are a number of

reasons why sleep history can be misleading: the loudness of snoring does not necessarily correlate with the degree of obstructive apnoea. Thus, children may have very noticeable snoring without apnoea. Children with OSA experience obstruction primarily during rapid eye movement (REM) sleep, which occurs predominantly in the early morning hours when their parents are not observing them. Consequently, there is an underestimation of apnoea. Moreover, some children have a pattern of persistent partial upper airway obstruction associated with gas exchange abnormalities, rather than discrete, cyclic apnoeas ('obstructive hypoventilation'). Since these children will not manifest pauses and gasps in their snoring, the condition may be misdiagnosed as primary snoring.

6. Conclusion

In conclusion, the translation of the PSQ was shown to be linguistically accurate and acceptable for use by Portuguese patients. This Portuguese version of the PSQ is easy to understand, quickly completed, and will potentially be of interest to the Portuguese medical community.

References

1. Gaultier, C., *Clinical and therapeutic aspects of obstructive sleep apnea syndrome in infants and children.* Sleep, 1992. **15**(6 Suppl): p. S36-8.
2. Goldstein, N.A., et al., *Clinical assessment of pediatric obstructive sleep apnea.* Pediatrics, 2004. **114**(1): p. 33-43.
3. Sagheri, D., et al., *Applying principles of good practice for translation and cross-cultural adaptation of sleep-screening instruments in children.* Behav Sleep Med, 2010. **8**(3): p. 151-6.
4. Carter, J.A., et al., *Issues in the development of cross-cultural assessments of speech and language for children.* Int J Lang Commun Disord, 2005. **40**(4): p. 385-401.
5. Certal, V., et al., *Clinical assessment of pediatric obstructive sleep apnea: a systematic review and meta-analysis.* Laryngoscope, 2012. **122**(9): p. 2105-14.
6. Chervin, R.D., et al., *Pediatric sleep questionnaire (PSQ): validity and reliability of scales for sleep-disordered breathing, snoring, sleepiness, and behavioral problems.* Sleep Med, 2000. **1**(1): p. 21-32.
7. Sproson, E.L., A.M. Hogan, and C.M. Hill, *Accuracy of clinical assessment of paediatric obstructive sleep apnoea in two English centres.* J Laryngol Otol, 2009. **123**(9): p. 1002-9.
8. Bonett, D.G. and R.M. Price, *Statistical inference for a linear function of medians: confidence intervals, hypothesis testing, and sample size requirements.* Psychol Methods, 2002. **7**(3): p. 370-83.
9. Landis, J.R. and G.G. Koch, *The measurement of observer agreement for categorical data.* Biometrics, 1977. **33**(1): p. 159-74.
10. Graffar M, *Une methode de classification sociale d´echantillons de population.* Courrier, 1956. **6**(8): p. 455-9.

Questionário Pediátrico do Sono

(Pediatric Sleep Questionnaire - Chervin, 2000) (*cf*. Appendix 22)

Data de Nascimento |__|__| - |__|__| - |__|__|__|__|

Respondido por: ☐Mãe ☐Pai ☐Avó ☐Avô ☐Outro_____

Peso da Criança: _____ **Altura da criança**: _____ **Sexo da Criança:** ☐Masculino ☐Feminino

Este questionário destina-se a avaliar as perturbações respiratórias do sono e alguns dos seus efeitos na saúde das crianças.

Por favor, assinale apenas uma resposta em cada alínea.

Enquanto dorme, o seu filho…	**Sim**	**Não**	**Não sabe**
A1 … ressona mais de metade do tempo?	☐	☐	☐
A2 … ressona sempre?	☐	☐	☐
A3 … ressona alto?	☐	☐	☐
A4 … tem uma respiração pesada ou ruidosa?	☐	☐	☐
A5 … tem dificuldade ou faz um grande esforço para respirar?	☐	☐	☐
Já alguma vez…			
A6 … viu o seu filho parar de respirar durante a noite?	☐	☐	☐
O seu filho…			
A7 … tem tendência a respirar pela boca durante o dia?	☐	☐	☐
A8 … acorda de manhã com a boca seca?	☐	☐	☐
A9 … costuma fazer ocasionalmente xixi na cama?	☐	☐	☐
O seu filho…			
B1 … acorda de manhã com muito sono?	☐	☐	☐
B2 … apresenta sonolência durante o dia?	☐	☐	☐
B3 A professora ou outro responsável comentou que o seu filho parece sonolento durante o dia?	☐	☐	☐
B4 É difícil acordar o seu filho de manhã?	☐	☐	☐
B5 O seu filho acorda com dores de cabeça de manhã?	☐	☐	☐
B6 Alguma vez o seu filho parou de crescer ao ritmo normal desde o nascimento?	☐	☐	☐
B7 O seu filho tem excesso de peso?	☐	☐	☐
O seu filho…			
C1 … parece não ouvir quando estão a falar diretamente com ele	☐	☐	☐
C2 … tem dificuldade em organizar tarefas e atividades	☐	☐	☐
C3 … é facilmente distraído por estímulos externos	☐	☐	☐
C4 … Mexe constantemente com as mãos e os pés e remexe-se na cadeira	☐	☐	☐
C5 … é irrequieto ou comporta-se como se "tivesse sempre as pilhas ligadas"	☐	☐	☐
C6 … interrompe ou intromete-se com os outros (por exemplo, em conversas ou em jogos)	☐	☐	☐

Pediatric OSA – Chapter IV

Model for prediction of pediatric sleep apnea – A clinical decision rule

IV. MODEL FOR PREDICTION OF PEDIATRIC SLEEP APNEA – A CLINICAL DECISION RULE

(*cf*. Appendix 4)

"MODEL FOR PREDICTION OF PEDIATRIC OSA – A CLINICAL DECISION RULE"

VICTOR CERTAL; MACARIO CAMACHO; ROBSON CAPASSO; INÊS AZEVEDO; ALTAMIRO COSTA-PEREIRA; CARLOS CARVALHO; HELDER SILVA; JOÃO WINCK

LARYNGOSCOPE

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1. Introduction

Obstructive sleep apnea (OSA) is frequently diagnosed in children and lacks optimal diagnostic methods. Currently, no definitive set of alternative diagnostic approaches reliably discriminates those children who have OSA and require treatment.[1] Therefore, novel unbiased diagnostic approaches, which are both sensitive and specific, need to be identified in order to permit prospective screening of the large number of children who habitually snore.

There have been advances in the diagnostic methods for this pathology using various modalities, including validated questionnaires and unattended sleep studies.[2-4] However, most of these are unreliable or unavailable to the vast majority of primary care practitioners and pediatricians who provide the major preventive care for children with OSA.[5,6] Clinical decision rules (also called clinical prediction rules, clinical decision guides, predictive indexes, or clinical prediction guides) combine information from several signs, symptoms, and/or tests into a score or algorithm that can be used for accurate diagnosis or predictions of treatment outcomes.[7]

Given the need for a pediatric OSA prediction model that uses multiple risk indicators and is available in most clinical settings, we examined this issue using simple clinical data. We previously reported the results of a review [5] that emphasized clinical symptoms in order to establish potential diagnostic parameters for pediatric OSA. This study aimed to provide patient-level estimates of pediatric OSA with commonly available clinical information.

2. Methods

A prospective cohort study was performed that included both sexes of pre-school aged children aged three to six years of age. The children were consecutively recruited from January 2014 to June 2014. Children who were referred for an otorhinolaryngology consultation at a public tertiary hospital due to clinical suspicion of OSA (i.e., the presence of snoring or pauses in breathing) were included. Exclusion criteria were excluded due to a previous adenotonsillectomy, the presence of severe medical or psychiatric comorbidities, or symptoms suggestive of sleep disorders other than OSA (e.g., parasomnias, narcolepsy, or periodic leg movements). This study was approved by our institutional ethics committee (Appendix 23), and written informed consent (Appendix 24) was obtained from parents of all the children prior to the study.

a. Data Collection

At the first appointment, all variables were assessed and registered through a structured interview and thorough an ear, nose, and throat (ENT) examination. To identify possible OSA predictors, parents were interviewed to collect general demographic data about their children. Demographic data included age, weight, height,

gender, and body mass index (BMI). The Portuguese translation of the Sleep-Related Breathing Disorder scale within the Pediatric Sleep Questionnaire (PSQ) was administered to identify symptoms suggestive of OSA that could act as further predictors. Based on our previous review, the PSQ appears to be the most reliable questionnaire for sleep apnea screening. It is fully translated into Portuguese and is culturally adapted to the Portuguese culture.[8] The validated PSQ has 22 items documenting the presence or absence of common symptoms such as snoring, observed apneas, breathing difficulty during sleep, daytime sleepiness, and inattentive or hyperactive behaviour. A cut-off value of eight positive responses is thought to be most effective in identifying OSA.[9] A physical examination taken into special account on tonsil size was performed by two independent otorhinolaryngologists. Tonsil size was assigned a grade following direct visualization: 0, not visible; 1, extending to the pillars; 2, enlarged beyond the pillars but not meeting the uvula; 3, meeting the uvula; and 4, "kissing" at the midline. Grade ≤2 is considered minor tonsillar hypertrohy and grade 3 or 4 are considered major hypertrophy.

We analyzed the presence of pediatric OSA, as defined by an IAH ≥ 1/h, as the main outcome measure. To confirm or exclude the presence of OSA, respiratory polygraphies were performed in all included children at the patients´ homes using the Nox-T3® Polygraph System, with the accompanying parent sleeping in the same room as the child. The following parameters were measured: airflow through nasal cannula, thoracic and abdominal plethysmograph to measure respiratory effort, body position by sensor position, snoring by microphone, and heart rate and blood oxygen saturation by pulse oximetry. Polygraphy was interpreted by a technician trained in pediatric sleep medicine who was unaware of the clinical findings.

Respiratory events were defined by standard criteria. Apnea was defined as the interruption of oronasal flow for the time equivalent to at least two respiratory cycles, with maintenance of thoracoabdominal effort (obstructive apnea) or without thoracoabdominal effort (central apnea). Hypopnea was defined as a decrease of at least 30% in the oronasal flow amplitude during the time equivalent to two respiratory cycles, with respiratory effort maintenance associated with a drop in oxygen saturation of at least 3%. The Apnea Hypopnea Index (AHI) was defined as the total number of respiratory events (apneas plus hypopneas) divided by the total study time. The interruption of oronasal airflow that frequently follows body movements and artifacts due to movement was not counted in the respiratory polygraphy. The ODI (Oxygen Desaturation Index) was defined as the number of ≥3% arterial desaturations per hour of sleep.

b. Statistical analysis

The risk factor distribution was compared between groups of children with and without OSA. Continuous variables (age, weight, height, BMI, and ODI) were compared using Student's *t*-tests or Mann–Whitney U tests for independent samples according to the distribution of each variable. The remaining dichotomous variables (i.e., PSQ Score, tonsil size and sex) were compared using $\chi 2$ tests. Distribution normality was assessed by evaluating the distribution histogram and applying the Kolmogorov–Smirnov test. Significance was defined as $p < 0.05$.

To develop an optimal prediction model, we: (1) performed a multivariate analysis using logistic regression so that both dichotomous and continuous variables could be considered; (2) used a backwards selection algorithm beginning with a model that

contained all of the variables; and (3) ultimately retained a variable in the final model if its *P* value was ≤ 0.1. To assess the classification accuracy of the final model, we estimated the area under the receiver operating characteristic (ROC) curve of the model. An area under the ROC curve of 0.5 indicated that the test was unable to discriminate between children who did or did not have OSA, whereas values between 0.5 and the maximum value of 1 indicated that the test had utility in distinguishing between children with and without OSA.

All statistical analyses were performed using SPSS version 20.0.

3. Results

Sixty-eight pre-school aged children were included. Three respiratory polygraphies had to be repeated due to inadequate pulse-oximeter operation and/or device malfunction. One child was excluded from the analysis because his/her parents refused to participate in the second repeated sleep study. Consequently, we analyzed 67 children, consisting of 37 (55.2%) boys and 30 girls. General characteristics of the children are summarized in Table 1.

The mean age was 4.5 years (standard deviation [SD] = 0.94), and the mean body mass index was 20.5 (range, 17.0–25.9). Of the 67 children included in this study, 25 (37.3%) subjects were diagnosed with pediatric OSA, meaning that they had an IAH ≥ 1/h (Table 1). Of the 25 children with OSA, five had an IAH ≥ 5/h and four had an IAH ≥ 10/h.

Table 1. Baseline subject characteristics and univariate analysis for prediction of OSA

BMI = Body Mass Index; ODI = Oxygen Desaturation Index; PSQ = Pediatric Sleep Questionnaire; SD = Standard Deviation

	Without OSA	*OSA*	*Odd Ratio (CI)*	*P Value*
n	42	25		
Age	4.12 (0.94)	4.54 (0.96)	0.88 (0.52-1.5)	0.09
Gender Male (%)	56.1	54.2	0.5	0.7
ODI	0.9 (0.61)	4.15 (2.58)	1.55 (1.21-1.99)	0.035
Tonsil Size				
Grade ≤ 2	32	5	0.3 (0.1-0.6)	0.8
Grade 3 or 4	10	20	5.5 (5.22-7.75)	0.056
BMI	20.1 (3.1)	20.9 (2.9)	1.1 (0.7-1.35)	0.51
Height in Centimeters (SD)	107 (12.1)	108 (11.2)	0.9 (0.65-1.3)	0.7
Weight in kilograms (SD)	18.7 (3.5)	19.5 (3.3)	1.04 (0.8-1.6)	0.6
PSQ				
< 8 positive questions	34	4	0.6 (0.4-0.9)	0.8
≥ 8 positive questions	8	21	4.9 (3.5-7.5)	0.044

The following four features were related to a higher risk of pediatric OSA in the univariate analysis: age, PSQ score, ODI and grade 3 or 4 tonsillar hypertrophy. The backward stepwise selection algorithm that considered all variables shown in Table 1 yielded three independent and statistically significant factors in the final pediatric OSA prediction model. One factor (i.e., age) that was significant in the univariate analysis was no longer statistically significant in the multivariate model, and was therefore removed from the model (Table 2).

Table 2. Final multivariable model predicting pediatric OSA

ODI = Oxygen Desaturation Index; PSQ = Pediatric Sleep Questionnaire

	Odd Ratio (CI)	*P Value*	*B Value*
ODI	1.34 (1.0-1.79)	0.046	0.295
Tonsil Size			
Grade 3 or 4	6.7 (3.22-9.75)	0.041	1.909
PSQ			
≥ 8 positive questions	5.12 (3.3.5-6.5)	0.064	1.633

The prediction accuracy of the final multivariable model was evaluated using sensitivity, specificity, and area under the ROC curve (Figure 1). The final decision rule had 88% sensibility and 86% specificity for predicting pediatric OSA. The area under the ROC curve was 0.897 for the diagnostic criteria of IAH ≥ 1/h, which indicates good screening test performance.

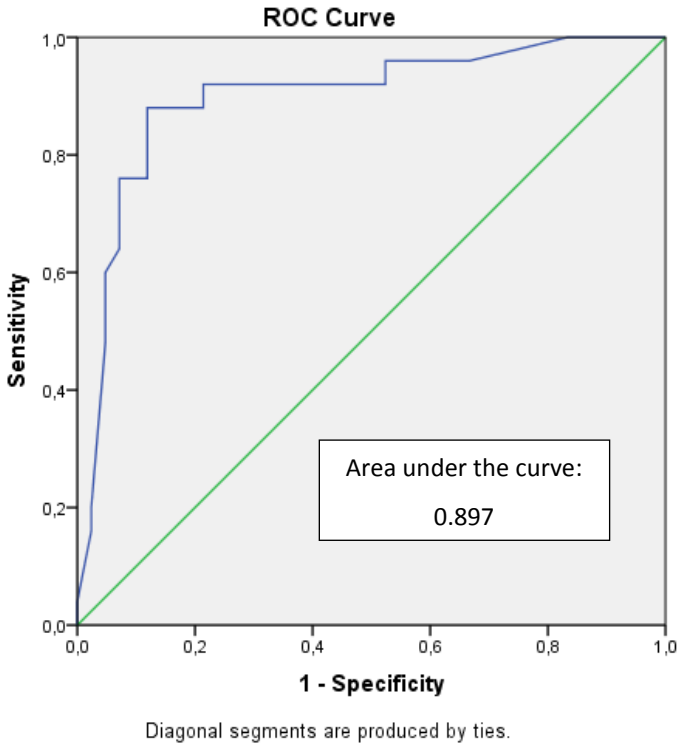

Figure 1. Prediction model ROC curve for pediatric OSA

The logit score X from the logistic regression model was defined as: X = -3.383 + 0.295 × (ODI - Continuous Variable) + 1.633 × (Presence of at least eight positive questions in the PSQ - Dichotomous Variable) + 1.909 × (Presence of tonsillar hypertrophy, grade 3 or 4 - Dichotomous Variable). Therefore, the probability of pediatric OSA (risk score in %) is defined by the equation: [Exp (X)/((1+Exp(X)) x 100]. While providing an accurate estimate, the above equations are quite complex and not practical for point-of-care use by physicians. However, they could be easily programmed into a computer through a spreadsheet or a smartphone application.

4. Discussion

This study evaluated the validity of a logarithmic model to predict pediatric OSA. Logarithmic models are advantageous when compared with simple stratification systems. Knowing the effect of each variable on risk simplifies the detection of risk variables and allows a more personalized diagnostic approach. This decision rule is a promising clinical tool that may help standardize the investigation of pediatric OSA.

Despite the limitations of this study, good overall diagnostic accuracy was observed for the aforementioned decision rule in predicting pediatric OSA, yielding a sensitivity and specificity of 88% and 86%, respectively. The Area Under the Curve (0.897) had good diagnostic accuracy, which confirmed our main finding regarding the utility of this clinical decision rule in pediatric OSA.

Broadly, after evaluating a child suspected with OSA, it seems reasonable to assume three possible actions: (1) for a risk score < 10%, reassure the parents and inform them that the diagnosis is unlikely based on the child's history, physical exam, and initial testing; (2) risk score ≤ 50%, monitor the child and inform the parents that the child

may have pediatric OSA, but that it is too early to know for certain, and further monitoring and periodic testing will be needed; and (3) risk score > 50%, inform the parents that the child is very likely to have pediatric OSA, and that treatment should be initiated (most likely adenotonsillectomy) to prevent progression of the disease. To facilitate calculation of this risk score, the authors have made available a downloadable spreadsheet for its calculation from https://www.dropbox.com/s/gexpkn0xcstnug8/Excel%20CDR.xlsx?dl=0.

Assessing the benefits of any clinical decision rule ultimately determines if the rule should be implemented; therefore, an implementation study with external validation is the next step to determine how a specific decision rule performs in clinical practice, assess the actual effects on patient care and patient outcomes, and conduct a formal economic health analysis. Additional validation of this decision rule in different medical settings could lead to the creation of a smartphone application that could facilitate the diagnostic process.

This study has several potential limitations that should be acknowledged. First, the population studied may represent a biased sample, as this study was performed in a tertiary referral center. The prevalence of OSA in our study (37.3%) was greater than that observed in the general population. Second, the gold standard used in this study (respiratory polygraphy) is not a commonly accepted tool for OSA assessment among children. However, a previous meta-analysis [6] showed that this kind of unattended sleep study could be a valid and solid alternative to overnight polysomnography for diagnosing pediatric OSA, and could be a feasible gold-standard. Third, despite being a relatively inexpensive tool, pediatric oximetry is not available in every medical center. Moreover, PSQ translation and cross-cultural adaptation has officially occurred in only

four languages (i.e., English, Turkish, Malay, and Portuguese); this could limit broader implementation of this clinical decision rule.

Finally, our sample was relatively small and statiscally relevant variables could have been missed due to this fact. Future validation studies should include larger samples of patients with various age groups (as many of the symptoms and signs are age dependent) to improve and optimize the model with the possible inclusion of more variables into the final model.

5. Conclusion

The proposed clinical decision rule, based on three easily available variables, is a promising discriminating instrument for prediction of OSA among children, and his implementation should allow accessible and reliable screening of suspected patients.

References

1. Gozal, D. and L. Kheirandish-Gozal, *New approaches to the diagnosis of sleep-disordered breathing in children.* Sleep Med, 2010. **11**(7): p. 708-13.
2. Brietzke, S.E., E.S. Katz, and D.W. Roberson, *Can history and physical examination reliably diagnose pediatric obstructive sleep apnea/hypopnea syndrome? A systematic review of the literature.* Otolaryngol Head Neck Surg, 2004. **131**(6): p. 827-32.
3. Borgstrom, A., P. Nerfeldt, and D. Friberg, *Questionnaire OSA-18 has poor validity compared to polysomnography in pediatric obstructive sleep apnea.* Int J Pediatr Otorhinolaryngol, 2013. **77**(11): p. 1864-8.
4. Chervin, R.D., et al., *Pediatric sleep questionnaire: prediction of sleep apnea and outcomes.* Arch Otolaryngol Head Neck Surg, 2007. **133**(3): p. 216-22.
5. Certal, V., et al., *Clinical assessment of pediatric obstructive sleep apnea: a systematic review and meta-analysis.* Laryngoscope, 2012. **122**(9): p. 2105-14.
6. Certal, V., et al., *Unattended sleep studies in pediatric OSA: A systematic review and meta-analysis.* Laryngoscope, 2014.
7. Grady, D. and S.A. Berkowitz, *Why is a good clinical prediction rule so hard to find?* Arch Intern Med, 2011. **171**(19): p. 1701-2.
8.
9. Chervin, R.D., et al., *Pediatric sleep questionnaire (PSQ): validity and reliability of scales for sleep-disordered breathing, snoring, sleepiness, and behavioral problems.* Sleep Med, 2000. **1**(1): p. 21-32.

Adult OSA – Chapter I

Surgical approaches in adult OSA – Current state of art

I. SURGICAL APPROACHES IN ADULT OSA: CURRENT STATE OF ART

"COMPREHENSIVE REVIEW OF SURGERIES FOR OBSTRUCTIVE SLEEP APNEA SYNDROME"

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(*cf*. Appendix 5)

1. Introduction

Obstructive sleep apnea syndrome (OSAS) manifests with excessive daytime sleepiness and affected patients can be treated either medically or surgically. Continuous positive airway pressure (CPAP) was first described by Sullivan et al. in 1981 as highly efficacious treatment for OSAS. Although CPAP has high efficacy, the effectiveness of the therapy is limited, as demonstrated by 46%-83% of patients being non-adherent to therapy (defined as > 4 hours of use per night). Patients who fail medical management often seek surgical treatment options. There is debate as to the effectiveness of surgical treatment for OSAS. Surgical treatment, guided by proper patient selection, counseling and realistic expectations increases the likelihood of success and patient satisfaction, respectively.

2. Aims

In this section, the aims were to:

- to review alternative approaches for OSA treatment

- summarise the current range of surgical treatments together with the evidence base for their intervention.

3. Literature review

A literature review was performed for adult obstructive sleep apnea syndrome surgical treatment. A full description of this review is available in Appendix 4.

Table 1 chronologically presents surgeries as they appeared on MedLine or the searched articles' references for the original procedural description. In addition, a total of 11 other articles which are systematic reviews, meta-analyses or comprehensive overviews are also included in this review.

Table 1. The evolution of sleep apnea surgeries.
Listed chronologically based on a MEDLINE search and references from those searches.

Surgical Modality as treatment for OSAS in Adult Patients	*Year described in Medline (or reference)*	*Authors*
Uvulopalatopharyngoplasty	1964 (Snoring)	Ikematsu[26]
	1980 (OSAS-abstract)	Conway, Fujita, Zorick, et al.[27]
	1981 (OSAS-article)	Fujita, Conway, Zorick, Roth[28]
Tracheostomy/Tracheotomy	1965	Valero and Alroy[29]
Tonsillectomy	1975	Sussman, Podoshin, Alroy[30]
Mandibular advancement	1979	Kuo, West, Bloomquist[31]
Genioglossus advancement	1984	Riley, Guilleminault, Powell[32]
Hyoid suspension	1984	Riley, Guilleminault, Powell[32]
Cautery assisted uvuloplasty	1986	Peters and Owens[33]
Maxillomandibular advancement (MMA)	1986	Riley, Powell, Guilleminault, Nino-Murcia[34]
Laser assisted uvuloplasty (LAUP)	1990 (snoring)	Snoring: 2 groups: 1) Kamami,[35] and 2) Haraldsson and Carenfelt[36]
	1994 (OSAS)	OSAS: Kamami[37]
Midline glossectomy	1991	Fujita, Woodson, Clark, Wittig[38]
Aryepiglottic fold reduction	1991	Fujita, Woodson, Clark, Wittig[38]
Epiglottectomy	1991	Fujita, Woodson, Clark, Wittig[38]
Nasal surgery	1992	Series, St. Pierre, Carrier[39]

Transpalatal Advancement Pharyngoplasty (TAP)	1993	Woodson, Toohill[40]
Cautery-assisted uvulopalatoplasty/ Cautery-assisted palatal stiffening operation (CAPSO)	1995 (Snoring) 2000 (OSAS)	Snoring: Blythe, Henrich, Pillsbury[41] OSAS: 2 groups: 1) Wassmuth, Mair, Loube, Leonard[42] and 2) Mair and Day[43]
Epiglottopexy/ Epiglottoplasty	1998	Chabolle, Wagner, Sequert, Lachiver, Coquille, Fleury, Blumen[44]
Radiofrequency ablation of the soft palate	1998	Powell, Riley, Troell, Li, Blumen, Guilleminault[45]
Rapid maxillary expansion (RME)/Surgically-assisted rapid palatal expansion (SARPE)	1996 (case report) 1998 (case series)	Case report: Palmisano, Wilcox, Sullivan, Cistulli[46] Case series: Cistulli and Palmisano[47]
Radiofrequency ablation of the tongue	1999	Powell, Riley, Guilleminault[48]
Tongue stabilization/ Tongue Suspension	2000	DeRowe, Gunther, Fibbi, Lehtimaki, Vahatalo, Maurer, Ophir[49]
Hypoglossal nerve stimulator/implant (HGNS)	2001	Schwartz AR, Bennett ML, Smith PL, De Backer W, Hedner J, Boudewyns A, Van de Heyning P, Ejnell H, Hochban W, Knaack L, Podszus T, Penzel T, Peter JH, Goding GS, Erickson DJ, Testerman R, Ottenhoff F, Eisele DW[50]
Mandibular distraction	2002	Li, Powell, Riley, Guilleminault[51]
Lateral pharyngoplasty	2003	Cahali[52]
Palatal implant	2004	Ho, Wei, Chung[53]
Z-palatoplasty (ZPP)	2004	Friedman,Ibrahim, Vidasagar, Pomeranz, Joseph[54]
Tongue base coblation	2005 2006 (with microlaryngoscopy) 2006 (with endoscopes)	He, Chen, Jin, He, Su, Fan, Yu[55] Robinson, Ettema, Brusky, Woodson[56] Maturo and Mair[57]
Submucosal minimally invasive lingual excision (SMILE)	2006 (peds) 2008 (adults)	Maturo and Mair[58] Friedman, Soans, Gurpinar, Lin, Joseph
Expansion sphincter pharyngoplasty	2007	Pang, Woodson[59]
Transoral Robotic Surgery (TORS)	2010	Vicini, Dallan, Canzi, Frassineti, La Pietra, Montevecchi[60]

Table 1. The evolution of sleep apnea surgeries. (*Continuation)*

a. Nasal surgeries

Hoijer et al described 7 patients with OSAS and nasal obstruction, who improved from an apnea index of 18 to 6.4/h after using nasal dilators.[61] Series et al described 20 adults in 1992 who had undergone nasal surgery, with significant improvement in nasal resistance, but minimal improvement in RDI from 39.8±6.1 to

36.8±5.9.[39] Friedman et al in 2000 demonstrated an improvement in patients' breathing in 98%, decreased snoring in 34%, increased energy levels in 78%, but no improvement in the respiratory disturbance indices.[62] A recent meta-analysis by Li et al, analyzing 9 articles with pooled AHI results demonstrating a decrease from 35.2±22.6/h to 33.5±23.8/h, with a total success rate of 16.7%.[21] Although nasal procedures do have a statistically significant improvement in isolated treatment for OSAS, they do improve nasal breathing and can help improve CPAP compliance and reduce CPAP pressures from a mean of 11.9 down to 9.2.[63]

b. Palatal surgeries

a. Uvulopalatopharyngoplasty (UPPP)

UPPP is one of the most commonly performed procedures for obstructive sleep apnea syndrome, comprising 93.8% of sleep surgeries performed in the US annually.[64] Ikematsu et al first began performing uvulopalatopharyngoplasties in 1952, and subsequently published a series of his results of the procedure as treatment of snoring in 1964.[26,65] Over the years, several modifications have been described.[52,54,59,66-75] Initial techniques described removal of larger amounts of palatal tissue and subsequently had increased risks for foreign body sensation, dry throat, globus sensation, lower fundamental frequency of speech, problems with phlegm, velopharyngeal insufficiency and nasopharyngeal stenosis.[52-55] However, newer descriptions have been modified in a manner that re-organizes and preserves tissue.[67] Systematic reviews of UPPP surgeries have demonstrated wide variability among polysomnography results.[14] Caples et al pooled data from 15 studies demonstrating a pre-operative AHI of 40.3 /h, and post-operative AHI of 29.8 /h for a 33% reduction.[14] Elshaug et al pooled 7 studies

and demonstrated a 51.5% success rate of 50% reduction in AHI and/or ≤20 /h.[16] Franklin et al assessed complications and found 30 deaths in six studies between 1989 and 2004.[17]

b. Cautery assisted uvuloplasty

Blythe et al first described palatal stiffening utilizing cauterization under local anesthesia as treatment for snoring.[41] Local anesthetic is used and the tongue is retracted inferiorly, the uvula is grasped and the mucosa is removed from the anterior oral surface of the palate and the uvula is usually removed.[41] Franklin et al demonstrated one death from sepsis, difficulty swallowing (27%), globus sensation (27%), voice changes, smell disturbances, taste disturbances and velopharyngeal stenosis.[17]

c. Laser assisted uvuloplasty (LAUP)

Stiffening of the palate as treatment for snoring was then applied as treatment for sleep apnea.[35,37] Kamami, then Haraldsson and Carenfelt reported their initial experiences with LAUP in 1990, as a form that is more easily performed under local anesthesia.[35,36] Caples et al assessed 2 randomized controlled trials and 6 observational studies, with a pooled decrease of 32% in the AHI.[14] Elshaug et al demonstrated a pooled success rate of 48.8%/h (CI 37.6-60).[16] One issue with the LAUP is that patients often require several treatments, Kamami described that on average patients were treated with 4 individual sessions.[35,37] Herford et al in 2000 described a single stage CO_2 laser assisted uvuloplasty, with significant improvement in snoring frequency, snoring loudness, overall sleep, and energy.[76]

d. Transpalatal advancement pharyngoplasty (TAP)

Because the results of UPPP procedures were inconsistent, Woodson and Toohill developed the TAP as a way to advance the palate anteriorly with more consistency.[40] The technique involves a gothic arch incision from posterior to the alveolus and continued forward in the palatoglossal fold, the hamulus is exposed and fractured, the posterior hard palate is removed, redundant mucosa is excised and lateral flaps are advanced and sutured to the alveolar mucoperiosteum.[40] The response from the initial study in 6 patients demonstrated a mean decrease from 69.3±32.1 to 26.6±25.3/h.[40] Shine and Lewis describe a modification of the TAP, which utilizes a "propeller incision" which has a lower incidence of oronasal fistula.[77] Shine and Lewis describe patients who underwent the traditional Gothic arch incision compared to the newer propeller incision and found a 31% improvement in success rate with the propeller incision.[78]

e. Cautery-assisted uvulopalatoplasty/Cautery-assisted palatal stiffening operation (CAPSO)

Initially described as a simple, inexpensive single stage clinic procedure for snoring, the procedure was subsequently described as treatment for OSAS.[41-43,79] When performed for snoring treatment, Blythe et al describe that 83% of spouses reported either resolution or significant improvement in the patients' snoring.[41] Mair and Day reported treating 200 consecutive patients over an 18-month period with success rates of 92% initially, and a slight decrease to 77% after 1 year.[43] Wassmuth et al demonstrated a decrease in AHI from 25±12.9 to 16.6±15.0 (p=0.01).[80] Pang an Terris'

modification involves performing a uvulectomy, removing a horizontal strip of mucosa from the anterior aspect of the soft palate and the creation of vertical trenches into the soft palate bilaterally.[79] The modified CAPSO reports an improvement in their patients' AHI form 12.3 to 5.2/h ($p<0.05$).[79]

f. Radiofrequency ablation (RFA) of the soft palate

RFA of the soft palate was described by Powell et all in a group of 22 healthy men in 1998.[45] This initial study demonstrated that procedure was effective for treatment of snoring (snoring scores decreased by 77%), and improvement in AHI and only mild patient discomfort.[45] Caples et al reviewed 7 observational studies and showed a mean change in AHI from 23.4 to 14.2 /h.[14] Elshaug demonstrated a 60% success rate in the two studies evaluated (95% CI 37.6-60).[16]

g. Lateral pharyngoplasty

Cahali described treatment of OSAS by performing a bilateral tonsillectomy, elevation of the superior pharyngeal constrictor muscle within the tonsillar fossa, superior traction is placed on the upper palatopharyngeus muscle, and a palatine flap is created laterally, a subtotal resection of the palatopharyngeus muscle is made and the flaps are closed in a z-plasty fashion.[52] Results demonstrated an improvement in AHI from 41.2 to 9.5 ($p = 0.009$).[52]

h. Palatal implants

There was one double-blinded, randomized, placebo-controlled trial which demonstrated a modest reduction in AHI, from 23.8 to 15.9 /h for the palatal implant arm vs 20.1 to 21.0 /h for the placebo group, demonstrating a statistically significant difference in the two groups, p<0.001.[81] Choi et al pooled data from 7 studies and demonstrated a statistically significant reduction in AHI with and SMD, -0.378; 95% CI, 0.619 to -0.138, p=0.02.[82] The meta-analysis data also demonstrated a 9.3% extrusion rate.[82]

i. Z-palatoplasty (ZPP)

The ZPP was described by Friedman et al for treatment of patients with OSAS who have previously undergone a tonsillectomy.[54] In this technique the mucosa over the anterior soft palate and uvula are removed, exposing the underlying muscle, followed by bisection of the uvula and inferior soft palate with a cold knife, the flaps are then rotated laterally over the soft palate and are sutured into position.[54] This study demonstrated improved results compared to standard UPPP (25 patients in each arm), with ZPPP decreasing AHI from 41.8±26.4 down to 20.9±19.3/h.[54]

j. Expansion sphincter pharyngoplasty

Pang and Woodson describe a technique in which a horizontal incision is made in the palatopharyngeus muscle (after tonsillectomy), superolateral incisions are made on the soft palate, in the inferior aspect of the palatopharyngeus muscle is then suspended superolaterally.[59] The 45 patients had a BMI <30 kg/m^2, were Friedman

stage 2 or 3, Type 1 Fujita and had lateral pharyngeal wall collapse, with an AHI improvement from 44.2±10.2 to 12.0±6.6/h ($p<0.005$).[59]

c. Tonsillectomy

Whereas, in children there is a significant amount of data, in adults, tonsillectomy studies as treatment for OSAS is limited. Sussman et al describe performing a tonsillectomy in two obese patients who also had significant tonsillar hypertrophy, and had resolution of their sleepiness after the tonsillectomy.[30] One study by Stow et al of 13 patients who underwent tonsillectomy (11 with additional nasal surgeries) as treatment for OSAS and found a significant reduction in the AHI from 31.7 to 5.5 ($p=0.0002$).[83] The effectiveness of this procedure is dependent on several factors to include: the anatomy of the patients, the BMI, neck circumference, tongue size, and the anatomical location of the apneic obstruction during sleep.

d. Tongue

a. Radiofrequency ablation (RFA) of the tongue

After radiofrequency ablation of the palate had successful outcomes, Powell et al piloted a study on 18 patients with sleep disordered breathing to assess the effectiveness for the RFA to the tongue in 1999.[48] This study found a mean reduction in AHI from 39.6 to 17.8/h, with no change in speech or swallowing, and only one infection.[48] Kezirian and Goldberg reviewed 11 studies on results of RFA of the tongue and demonstrated a wide range of successful AHI outcomes, ranging from 20% to 83% successful.[20] Most studies demonstrate decreased daytime hypersomnolence, improved quality of life and improvement in the lowest oxygen saturation.[20]

b. Tongue stabilization/Tongue suspension

DeRowe et al described the Repose system in 2000 as a new, minimally invasive procedure in which there is suspension of the base of tongue to reduce tongue-base collapse.[49] This initial study on 16 patients demonstrated a mean RDI improvement from 35 to 17/h (p = 0.001) and 14/16 bed-partners reported improvement in snoring.[49] Kezirian and Goldberg reviewed 6 studies and found 20% to 57% success rates.[20]

c. Tongue base coblation

He et al studied UPPP with tongue base coblation in 112 patient with OSAS and at 12 months post-operatively, demonstrated 24 patients being cured (21.4%), 52 patients had notable improvement (46.4%), 16 had improvement (14.2%), and 20 patients had no effect.[55] Robinson et al described lingual tonsillectomies in 18 patients with massive (10) and modest (8) lingual tonsillar hypertrophy, with moderate pain (7-10 d), mean of 20 mL of blood loss during the procedure and only two requiring revision.[56] Robinson et al describe using microlaryngoscopy with an operating microscope during the procedure, while Maturo and Mair in a letter to the editor described coblation lingual tonsillectomy utilizing a rubber bite block and a 70 degree sinus endoscope placed per-orally, which is the current technique used in many institutions.[56,57]

d. Submucosal minimally invasive lingual excision (SMILE)

Maturo and Mair described this technique for use in children with good results.[58] The first article to evaluate the effectiveness in adults was Friedman et al, in

2008, in which they demonstrated a 64.6% success rate (p=0.024), however, there was a higher necessity for narcotic pain control (3.8±3.8 d vs 2.4±3.5 d) and a longer time to return to a normal diet (4.9±4.5 d vs 2.9±4.1 d) when compared to patients who underwent radiofrequency ablation of the tongue, respectively.[88]

e. Transoral robotic surgery (TORS)

McLeod and Melder presented a case report of the use of the da Vinci Surgical System for removal of a vallecular cyst in 2005.[89] Since this case report, transoral robotic surgery (TORS) has been utilized mostly for neoplasms.[90,91] In 2010, Vicini et al described their outcomes utilizing TORS for OSAS.[60] The study reports 10 patients with a mean preoperative AHI of 38.3/h which decreased to 20.6/h with surgery of the tongue base and epiglottis using the transoral robotic surgery.[92] Since the first study, there have been five additional studies focusing on TORS as treatment for OSAS, each demonstrating an improvement in AHI.[93-97] The most dramatic improvement is seen in Friedman et al's 2012 publication which demonstrated a reduction in AHI from 54.6/h to 18.6/h (p<0.001) and a success rate of 66.7% and cure rate of 18%.[97]

e. Hyoid suspension

Resistance of airflow is directly proportional to the length of the airway, therefore, a decrease in airway length will provide a decrease in resistance. The decrease in airway length can be accomplished by performing a hyoid suspension, which was described in 1984 by Riley et al.[32] Bowden et al found a low success rate (17%) among the 29 patients who underwent the procedure in combination with a

UPPP and tonsillectomy.[98] Kezirian and Goldberg evaluated 4 studies' data and found that when the hyoid suspension is performed at the same time as another surgery, then there are better outcomes with 71% successful outcomes in the multiple procedures surgery, however, when performed in isolation after previous unsuccessful surgery, then there is a 35% success rate.[20]

f. Multiple procedures

Because obstructive apneic events during sleep occur in multiple locations in the airway, the treatment options are therefore more successful if those areas of obstruction are addressed, rather than performing single site surgery. A common anatomical site of obstruction is hypopharynx and supraglottic region, therefore, removal or reduction of tissue in this area can help reduce obstructive events. Fujita et al described removal of midline glossectomy in 12 patients with simultaneously performed laser lingual tonsillectomy (N=7), reduction in aryepiglottic folds (N=10), partial epiglottectomy (N=5) and all received a temporary tracheostomy.[38] Fujita et al's results demonstrated an RDI decrease from 60.6 to 14.5/h in responders (42%) and a decrease from 62.6 to 48.4/h in non-responders (N=7).[38] There have not been studies for isolated aryepiglottic fold reduction or isolated epiglottectomy. Kezirian and Goldberg reviewed 5 studies in which multiple procedures were performed and demonstrated a range of success (25-83%).[20] Results for epiglottopexy and epiglottoplasty are not generally performed as isolated procedures, rather are described as part of multiple procedures.[38,99,100]

Lin et al pooled 58 studies in which multiple procedures were performed, with 1,978 patients, mean age of 46.2, with a pre-operative AHI of 48 and found a 60.3% reduction in the AHI, which corresponds to a 66.4% success rate.[22]

g. Skeletal surgeries

a. Mandibular advancement

Kuo et al first described the mandibular advancement surgery in 1979 as treatment for hypersomnia sleep apnea (HSA), which is now called obstructive sleep apnea syndrome (OSAS).[31] Kuo et al describe three cases of traumatically induced mandibular retrognathism which caused sleep apnea with daytime hypersomnia, and each had resolution after the mandibular advancement.[101] It is the mandibular advancement procedure which would was the groundwork for future movement of the maxillomandibular complex in patients who did not have retrognathia, as treatment for OSAS.

b. Genioglossus advancement

This procedure is often combined with other procedures such as a hyoid suspension, or uvulopalatopharyngoplasty. Initially described by Riley et al, in combination with the hyoid suspension as a new treatment for a 24 year old male with a BMI of 36.1 kg/m^2 who had failed previous tonsillectomy and septoplasty.[32] Kezirian and Goldberg demonstrated a pooled success rate of >60%, with the AHI decreasing from 60 to 29/h.[20] Two key factors influencing the outcomes were the BMI <30 kg/m^2 (64% successful) compared with BMI >30 kg/m^2 (41% successful).[20] A preoperative AHI <50/h was successful in 71% of patients, while those with an AHI >50/h was successful in 32%.[20]

c. Maxillomandibular advancement (MMA)

MMA involves the creation of a LeForte 1 osteotomy to the maxilla and a bilateral split sagittal osteotomy to the mandible. This procedure was first described with simultaneously performed hyoid suspension as treatment for OSAS by Riley et al in 1986.[34] Holty and Guilleminault performed a meta-analysis in 2012 demonstrating a mean AHI decrease from 63.9 to 9.5/h, $p<0.001$, with a surgical success rate of 86% and cure rate of 43.2%. It was noted that younger age, lower preoperative weight and AHI, and a maxillary advancement >10 mm and a mandibular advancement more than 11.3 mm improved the likelihood of success.[19] The procedure has also demonstrated an 81% success rate among patients with a BMI >40 kg/m^2.[102] Pirklbauer et al's systematic review and analysis of data recommends a grade of A to B with regard to levels of evidence based medicine.[23]

d. Rapid maxillary expansion (RME)/Surgically-assisted rapid palatal expansion (SARPE)

An initial case report by Palmisano and Cistulli, followed by a case series by Cistulli et al, has been performed on adults, and demonstrated an improvement in AHI from 19±4/h to 7±4/h. [46,47] When performed in patients with transverse maxillary insufficiency, as was performed in these patients, then the success rate is 90% and the cure rate is 70%.[47]

e. Mandibular distraction osteogenesis

There is limited data on mandibular distraction osteogenesis as treatment for OSAS in adults. One study by Li et al performed mandibular distractions on 5 healthy

adults and after 12 months, found a mean improvement in AHI from 49 to 7/h.[51] In this study, the distraction osteogenesis advanced the mandibles between 5.5 to 12.5 mm, mean 8.1 mm.[51]

h. Tracheostomy/tracheotomy

There are tubed, tubeless and permanent tracheostomies performed for obstructive sleep apnea syndrome.[103-105] Valero and Alroy demonstrated the effectiveness of tracheostomy as treatment for obstructive sleep apnea in a patient with acquired micrognathia (1965).[29] Since this article, several studies have demonstrated the effectiveness of tracheostomies in treating OSAS.[106-120] Holty and Guilleminault pooled 9 studies and found that the apnea index decreased from 88.4 to 0.5/h ($p<0.001$), AHI during REM decreased from 63.8 to 26.2/h ($p<0.001$) and AHI during NREM decreased from 98.9 to 21.6/h ($p<0.001$).[18] Tracheostomies were previously performed frequently in the 1970's to 1990's, but as other surgical options became available, patients and surgeons began selecting against this procedure.[106,112-114,116-118,121-123] Tracheostomies are associated with significant morbidities such as stomal granulation tissue formation, stomal stenosis, bleeding from granulation tissue, tracheoinnominate fistulas, mucous plugging, aspiration and pneumonia.[103,105,124-131] Despite the morbidity from the surgery, the patients who have had long term tracheostomies have had a significant decrease in mortality.[114,116] Partinen et al evaluated 198 patients treated with either a tracheostomy (N=71) or weight loss (127), and had no deaths after five years in the tracheostomy group and 14 deaths in those in the weight loss group.[116]

Discussion

Despite having several different types of surgery used on an annual basis to treat obstructive sleep apnea syndrome ($35,000/year - USA), the surgeries most often performed in the United States are palatal surgeries, at an estimated $33,000/year.[64] Other procedures described herein are much less frequently performed on an annual basis, but include hypopharyngeal surgeries ($6500), genioglossus advancement ($5100), maxillomandibular advancement ($1400) and hyoid suspension ($675).[64] However, each surgeon must continue to review newer techniques which may improve patient outcomes. The experience at Stanford has seen the development or application of several techniques for treatment of OSAS to include maxillomandibular advancement, mandibular distraction, genioglossus advancement, hyoid suspension, radiofrequency ablation, each of which have been modified or expanded by other colleagues around the country and around the world.[32,34,45,48,51,67,102,132-135] Innovation and technology are also providing improved outcomes as demonstrated by the application of radiofrequency, coblation and transoral robotic surgery.[45,48] In addition to the challenges of keeping up with the current literature and technology, there will be patients who fail sleep surgery. In order to maximize success and cure rates, multiple procedures are often necessary. Some patients may fail soft tissue surgeries and may be candidates for either maxillomandibular advancements or tracheostomies.[34,135]

4. Conclusion

There is a large amount of variability in outcomes for sleep surgeries, however, in order to maximize success and cure rates, multiple procedures are most often necessary. Technology is changing, and sleep surgeons must keep up with current

literature and participate in multi-disciplinary care in order to maximize outcomes for patients.

References

1. Shepard JW, Jr. Hypertension, cardiac arrhythmias, myocardial infarction, and stroke in relation to obstructive sleep apnea. *Clinics in chest medicine.* Sep 1992;13(3):437-458.
2. Madani M, Madani F. Epidemiology, pathophysiology, and clinical features of obstructive sleep apnea. *Oral and maxillofacial surgery clinics of North America.* Nov 2009;21(4):369-375.
3. Loke YK, Brown JW, Kwok CS, Niruban A, Myint PK. Association of obstructive sleep apnea with risk of serious cardiovascular events: a systematic review and meta-analysis. *Circulation. Cardiovascular quality and outcomes.* Sep 1 2012;5(5):720-728.
4. Jennum P, Sjol A. Snoring, sleep apnoea and cardiovascular risk factors: the MONICA II Study. *International journal of epidemiology.* Jun 1993;22(3):439-444.
5. Gottlieb DJ, Whitney CW, Bonekat WH, et al. Relation of sleepiness to respiratory disturbance index: the Sleep Heart Health Study. *American journal of respiratory and critical care medicine.* Feb 1999;159(2):502-507.
6. Gottlieb DJ, Yenokyan G, Newman AB, et al. Prospective study of obstructive sleep apnea and incident coronary heart disease and heart failure: the sleep heart health study. *Circulation.* Jul 27 2010;122(4):352-360.
7. Newman AB, Nieto FJ, Guidry U, et al. Relation of sleep-disordered breathing to cardiovascular disease risk factors: the Sleep Heart Health Study. *American journal of epidemiology.* Jul 1 2001;154(1):50-59.
8. Punjabi NM, Shahar E, Redline S, Gottlieb DJ, Givelber R, Resnick HE. Sleep-disordered breathing, glucose intolerance, and insulin resistance: the Sleep Heart Health Study. *American journal of epidemiology.* Sep 15 2004;160(6):521-530.
9. Redline S, Yenokyan G, Gottlieb DJ, et al. Obstructive sleep apnea-hypopnea and incident stroke: the sleep heart health study. *American journal of respiratory and critical care medicine.* Jul 15 2010;182(2):269-277.
10. Walsleben JA, Kapur VK, Newman AB, et al. Sleep and reported daytime sleepiness in normal subjects: the Sleep Heart Health Study. *Sleep.* Mar 15 2004;27(2):293-298.
11. Young T, Shahar E, Nieto FJ, et al. Predictors of sleep-disordered breathing in community-dwelling adults: the Sleep Heart Health Study. *Archives of internal medicine.* Apr 22 2002;162(8):893-900.
12. Sullivan CE, Issa FG, Berthon-Jones M, Eves L. Reversal of obstructive sleep apnoea by continuous positive airway pressure applied through the nares. *Lancet.* Apr 18 1981;1(8225):862-865.
13. Weaver TE, Grunstein RR. Adherence to continuous positive airway pressure therapy: the challenge to effective treatment. *Proceedings of the American Thoracic Society.* Feb 15 2008;5(2):173-178.
14. Caples SM, Rowley JA, Prinsell JR, et al. Surgical modifications of the upper airway for obstructive sleep apnea in adults: a systematic review and meta-analysis. *Sleep.* Oct 2010;33(10):1396-1407.
15. Choi JH, Kim SN, Cho JH. Efficacy of the Pillar implant in the treatment of snoring and mild-to-moderate obstructive sleep apnea: a meta-analysis. *The Laryngoscope.* Jan 2013;123(1):269-276.
16. Elshaug AG, Moss JR, Southcott AM, Hiller JE. Redefining success in airway surgery for obstructive sleep apnea: a meta analysis and synthesis of the evidence. *Sleep.* Apr 2007;30(4):461-467.
17. Franklin KA, Anttila H, Axelsson S, et al. Effects and side-effects of surgery for snoring and obstructive sleep apnea--a systematic review. *Sleep.* Jan 2009;32(1):27-36.
18. Holty JE, Guilleminault C. Surgical options for the treatment of obstructive sleep apnea. *The Medical clinics of North America.* May 2010;94(3):479-515.
19. Holty JE, Guilleminault C. Maxillomandibular advancement for the treatment of obstructive sleep apnea: a systematic review and meta-analysis. *Sleep medicine reviews.* Oct 2010;14(5):287-297.
20. Kezirian EJ, Goldberg AN. Hypopharyngeal surgery in obstructive sleep apnea: an evidence-based medicine review. *Archives of otolaryngology--head & neck surgery.* Feb 2006;132(2):206-213.
21. Li H, Wang PC, Chen YP, Lee LA, Fang TJ, Lin HC. Critical appraisal and meta-analysis of nasal surgery for obstructive sleep apnea. *American journal of rhinology & allergy.* Dec 17 2010.
22. Lin HC, Friedman M, Chang HW, Gurpinar B. The efficacy of multilevel surgery of the upper airway in adults with obstructive sleep apnea/hypopnea syndrome. *The Laryngoscope.* May 2008;118(5):902-908.
23. Pirklbauer K, Russmueller G, Stiebellehner L, et al. Maxillomandibular advancement for treatment of obstructive sleep apnea syndrome: a systematic review. *Journal of oral and maxillofacial surgery : official journal of the American Association of Oral and Maxillofacial Surgeons.* Jun 2011;69(6):e165-176.
24. Sarkhosh K, Switzer NJ, El-Hadi M, Birch DW, Shi X, Karmali S. The impact of bariatric surgery on obstructive sleep apnea: a systematic review. *Obesity surgery.* Mar 2013;23(3):414-423.
25. Sher AE, Schechtman KB, Piccirillo JF. The efficacy of surgical modifications of the upper airway in adults with obstructive sleep apnea syndrome. *Sleep.* Feb 1996;19(2):156-177.
26. Ikematsu T. Study of snoring. 4th report. *J Jpn Otol Rhinol Laryngol Soc.* 1964;64:434-435.
27. Conway W, Fujita S, Zorick F. Uvulo-palato-pharyngoplasty in treatment of upper airway sleep apnea [abstract]. *The American review of respiratory disease.* 1980;121.
28. Fujita S, Conway W, Zorick F, Roth T. Surgical correction of anatomic azbnormalities in obstructive sleep apnea syndrome: uvulopalatopharyngoplasty. *Otolaryngology--head and neck surgery : official journal of American Academy of Otolaryngology-Head and Neck Surgery.* Nov-Dec 1981;89(6):923-934.
29. Valero A, Alroy G. Hypoventilation in Acquired Micrognathia. *Archives of internal medicine.* Mar 1965;115:307-310.

30. Sussman D, Podoshin L, Alroy G. The Pickwickian syndrome with hypertrophy of tonsils: a re-appraisal. *The Laryngoscope.* Mar 1975;85(3):565-569.

31. Kuo PC, West RA, Bloomquist DS, McNeil RW. The effect of mandibular osteotomy in three patients with hypersomnia sleep apnea. *Oral surgery, oral medicine, and oral pathology.* Nov 1979;48(5):385-392.

32. Riley R, Guilleminault C, Powell N, Derman S. Mandibular osteotomy and hyoid bone advancement for obstructive sleep apnea: a case report. *Sleep.* 1984;7(1):79-82.

33. Peters GE, Owens J. Refinements in the use of the electrocautery in tonsillectomy and uvulopalatopharyngoplasty. *The Laryngoscope.* Feb 1986;96(2):216.

34. Riley RW, Powell NB, Guilleminault C, Nino-Murcia G. Maxillary, mandibular, and hyoid advancement: an alternative to tracheostomy in obstructive sleep apnea syndrome. *Otolaryngology--head and neck surgery : official journal of American Academy of Otolaryngology-Head and Neck Surgery.* Jun 1986;94(5):584-588.

35. Kamami YV. Laser CO2 for snoring. Preliminary results. *Acta oto-rhino-laryngologica Belgica.* 1990;44(4):451-456.

36. Haraldsson PO, Carenfelt C. Laser uvulopalatoplasty in local anaesthesia. A safe approach in the treatment of habitual snoring. *Rhinology.* Mar 1990;28(1):65-66.

37. Kamami YV. Outpatient treatment of sleep apnea syndrome with CO 2 laser, LAUP: laser-assisted UPPP results on 46 patients. *Journal of clinical laser medicine & surgery.* Aug 1994;12(4):215-219.

38. Fujita S, Woodson BT, Clark JL, Wittig R. Laser midline glossectomy as a treatment for obstructive sleep apnea. *The Laryngoscope.* Aug 1991;101(8):805-809.

39. Series F, St Pierre S, Carrier G. Effects of surgical correction of nasal obstruction in the treatment of obstructive sleep apnea. *The American review of respiratory disease.* Nov 1992;146(5 Pt 1):1261-1265.

40. Woodson BT, Toohill RJ. Transpalatal advancement pharyngoplasty for obstructive sleep apnea. *The Laryngoscope.* Mar 1993;103(3):269-276.

41. Blythe WR, Henrich DE, Pillsbury HC. Outpatient uvuloplasty: an inexpensive, single-staged procedure for the relief of symptomatic snoring. *Otolaryngology--head and neck surgery : official journal of American Academy of Otolaryngology-Head and Neck Surgery.* Jul 1995;113(1):1-4.

42. Wassmuth Z, Mair E, Loube D, Leonard D. Cautery-assisted palatal stiffening operation for the treatment of obstructive sleep apnea syndrome. *Otolaryngology--head and neck surgery : official journal of American Academy of Otolaryngology-Head and Neck Surgery.* Jul 2000;123(1 Pt 1):55-60.

43. Mair EA, Day RH. Cautery-assisted palatal stiffening operation. *Otolaryngology--head and neck surgery : official journal of American Academy of Otolaryngology-Head and Neck Surgery.* Apr 2000;122(4):547-556.

44. Chabolle F, Wagner I, Sequert C, et al. [Tongue base reduction with hyoid-epiglottoplasty. A surgical alternative in severe sleep apnea syndromes]. *Annales d'oto-laryngologie et de chirurgie cervico faciale : bulletin de la Societe d'oto-laryngologie des hopitaux de Paris.* Dec 1998;115(6):322-331.

45. Powell NB, Riley RW, Troell RJ, Li K, Blumen MB, Guilleminault C. Radiofrequency volumetric tissue reduction of the palate in subjects with sleep-disordered breathing. *Chest.* May 1998;113(5):1163-1174.

46. Palmisano RG, Wilcox I, Sullivan CE, Cistulli PA. Treatment of snoring and obstructive sleep apnoea by rapid maxillary expansion. *Australian and New Zealand journal of medicine.* Jun 1996;26(3):428-429.

47. Cistulli PA, Palmisano RG, Poole MD. Treatment of obstructive sleep apnea syndrome by rapid maxillary expansion. *Sleep.* Dec 15 1998;21(8):831-835.

48. Powell NB, Riley RW, Guilleminault C. Radiofrequency tongue base reduction in sleep-disordered breathing: A pilot study. *Otolaryngology--head and neck surgery : official journal of American Academy of Otolaryngology-Head and Neck Surgery.* May 1999;120(5):656-664.

49. DeRowe A, Gunther E, Fibbi A, et al. Tongue-base suspension with a soft tissue-to-bone anchor for obstructive sleep apnea: preliminary clinical results of a new minimally invasive technique. *Otolaryngology--head and neck surgery : official journal of American Academy of Otolaryngology-Head and Neck Surgery.* Jan 2000;122(1):100-103.

50. Schwartz AR, Bennett ML, Smith PL, et al. Therapeutic electrical stimulation of the hypoglossal nerve in obstructive sleep apnea. *Archives of otolaryngology--head & neck surgery.* Oct 2001;127(10):1216-1223.

51. Li KK, Powell NB, Riley RW, Guilleminault C. Distraction osteogenesis in adult obstructive sleep apnea surgery: a preliminary report. *Journal of oral and maxillofacial surgery : official journal of the American Association of Oral and Maxillofacial Surgeons.* Jan 2002;60(1):6-10.

52. Cahali MB. Lateral pharyngoplasty: a new treatment for obstructive sleep apnea hypopnea syndrome. *The Laryngoscope.* Nov 2003;113(11):1961-1968.

53. Ho WK, Wei WI, Chung KF. Managing disturbing snoring with palatal implants: a pilot study. *Archives of otolaryngology--head & neck surgery.* Jun 2004;130(6):753-758.

54. Friedman M, Ibrahim HZ, Vidyasagar R, Pomeranz J, Joseph NJ. Z-palatoplasty (ZPP): a technique for patients without tonsils. *Otolaryngology--head and neck surgery : official journal of American Academy of Otolaryngology-Head and Neck Surgery.* Jul 2004;131(1):89-100.

55. He M, Chen H, Jin W, et al. [Uvulopalatopharyngoplasty and tongue base coblation treat the 112 cases of severe obstructive sleep apnea -hypopnea syndrome]. *Lin chuang er bi yan hou ke za zhi = Journal of clinical otorhinolaryngology.* Dec 2005;19(23):1061-1062.

56. Robinson S, Ettema SL, Brusky L, Woodson BT. Lingual tonsillectomy using bipolar radiofrequency plasma excision. *Otolaryngology--head and neck surgery : official journal of American Academy of Otolaryngology-Head and Neck Surgery.* Feb 2006;134(2):328-330.

57. Maturo SC, Mair EA. Coblation lingual tonsillectomy. *Otolaryngology--head and neck surgery : official journal of American Academy of Otolaryngology-Head and Neck Surgery.* Sep 2006;135(3):487-488.

58. Maturo SC, Mair EA. Submucosal minimally invasive lingual excision: an effective, novel surgery for pediatric tongue base reduction. *The Annals of otology, rhinology, and laryngology.* Aug 2006;115(8):624-630.

59. Pang KP, Woodson BT. Expansion sphincter pharyngoplasty: a new technique for the treatment of obstructive sleep apnea. *Otolaryngology--head and neck surgery : official journal of American Academy of Otolaryngology-Head and Neck Surgery.* Jul 2007;137(1):110-114.

60. Vicini C, Dallan I, Canzi P, Frassineti S, La Pietra MG, Montevecchi F. Transoral robotic tongue base resection in obstructive sleep apnoea-hypopnoea syndrome: a preliminary report. *ORL; journal for oto-rhino-laryngology and its related specialties.* 2010;72(1):22-27.

61. Hoijer U, Ejnell H, Hedner J, Petruson B, Eng LB. The effects of nasal dilation on snoring and obstructive sleep apnea. *Archives of otolaryngology--head & neck surgery.* Mar 1992;118(3):281-284.

62. Friedman M, Tanyeri H, Lim JW, Landsberg R, Vaidyanathan K, Caldarelli D. Effect of improved nasal breathing on obstructive sleep apnea. *Otolaryngology--head and neck surgery : official journal of American Academy of Otolaryngology-Head and Neck Surgery.* Jan 2000;122(1):71-74.

63. Poirier J, George C, Rotenberg B. The effect of nasal surgery on nasal continuous positive airway pressure compliance. *The Laryngoscope.* Apr 10 2013.

64. Kezirian EJ, Maselli J, Vittinghoff E, Goldberg AN, Auerbach AD. Obstructive sleep apnea surgery practice patterns in the United States: 2000 to 2006. *Otolaryngology--head and neck surgery : official journal of American Academy of Otolaryngology-Head and Neck Surgery.* Sep 2010;143(3):441-447.

65. Crestinu JM. Intrapalatine resection (IPR) in the treatment of sleep apnea and snoring. *Plastic and reconstructive surgery.* Mar 1991;87(3):467-469.

66. Sulsenti G, Palma P. [Carbon dioxide laser uvulopalatopharyngoplasty (UPPP). Part I. Surgical technique]. *Acta otorhinolaryngologica Italica : organo ufficiale della Societa italiana di otorinolaringologia e chirurgia cervico-facciale.* Jan-Feb 1993;13(1):53-62.

67. Powell N, Riley R, Guilleminault C, Troell R. A reversible uvulopalatal flap for snoring and sleep apnea syndrome. *Sleep.* Sep 1996;19(7):593-599.

68. Clarke RW, Yardley MP, Davies CM, Panarese A, Clegg RT, Parker AJ. Palatoplasty for snoring: a randomized controlled trial of three surgical methods. *Otolaryngology--head and neck surgery : official journal of American Academy of Otolaryngology-Head and Neck Surgery.* Sep 1998;119(3):288-292.

69. Fairbanks DN. Operative techniques of uvulopalatopharyngoplasty. *Ear, nose, & throat journal.* Nov 1999;78(11):846-850.

70. Hultcrantz E, Johansson K, Bengtson H. The effect of uvulopalatopharyngoplasty without tonsillectomy using local anaesthesia: a prospective long-term follow-up. *The Journal of laryngology and otology.* Jun 1999;113(6):542-547.

71. Wolford LM, Mehra P. Modified uvulopalatopharyngoplasty: the lateral inversion flap technique. *Journal of oral and maxillofacial surgery : official journal of the American Association of Oral and Maxillofacial Surgeons.* Oct 2001;59(10):1242-1243.

72. Li HY, Li KK, Chen NH, Wang PC. Modified uvulopalatopharyngoplasty: The extended uvulopalatal flap. *American journal of otolaryngology.* Sep-Oct 2003;24(5):311-316.

73. Labra A, Huerta-Delgado AD, Gutierrez-Sanchez C, Cordero-Chacon SA, Basurto-Madero P. Uvulopalatopharyngoplasty and uvulopalatal flap for the treatment of snoring: technique to avoid complications. *Journal of otolaryngology - head & neck surgery = Le Journal d'oto-rhino-laryngologie et de chirurgie cervico-faciale.* Apr 2008;37(2):256-259.

74. Shin SH, Ye MK, Kim CG. Modified uvulopalatopharyngoplasty for the treatment of obstructive sleep apnea-hypopnea syndrome: resection of the musculus uvulae. *Otolaryngology--head and neck surgery : official journal of American Academy of Otolaryngology-Head and Neck Surgery.* Jun 2009;140(6):924-929.

75. Komada I, Miyazaki S, Okawa M, Nishikawa M, Shimizu T. A new modification of uvulopalatopharyngoplasty for the treatment of obstructive sleep apnea syndrome. *Auris, nasus, larynx.* Feb 2012;39(1):84-89.

76. Herford AS, Finn R. Single-stage CO2 laser assisted uvuloplasty for treatment of snoring and mild obstructive sleep apnoea. *Journal of cranio-maxillo-facial surgery : official publication of the European Association for Cranio-Maxillo-Facial Surgery.* Aug 2000;28(4):213-216.

77. Shine NP, Lewis RH. The "Propeller" incision for transpalatal advancement pharyngoplasty: a new approach to reduce post-operative oronasal fistulae. *Auris, nasus, larynx.* Sep 2008;35(3):397-400.

78. Shine NP, Lewis RH. Transpalatal advancement pharyngoplasty for obstructive sleep apnea syndrome: results and analysis of failures. *Archives of otolaryngology--head & neck surgery.* May 2009;135(5):434-438.

79. Pang KP, Terris DJ. Modified cautery-assisted palatal stiffening operation: new method for treating snoring and mild obstructive sleep apnea. *Otolaryngology--head and neck surgery : official journal of American Academy of Otolaryngology-Head and Neck Surgery.* May 2007;136(5):823-826.

80. !!! INVALID CITATION !!!

81. Friedman M, Schalch P, Lin HC, Kakodkar KA, Joseph NJ, Mazloom N. Palatal implants for the treatment of snoring and obstructive sleep apnea/hypopnea syndrome. *Otolaryngology--head and neck surgery : official journal of American Academy of Otolaryngology-Head and Neck Surgery.* Feb 2008;138(2):209-216.

82. Choi JH, Kim SN, Cho JH. Efficacy of the pillar implant in the treatment of snoring and mild-to-moderate obstructive sleep apnea: A meta-analysis. *The Laryngoscope.* Aug 2 2012.

83. Stow NW, Sale PJ, Lee D, Joffe D, Gallagher RM. Simultaneous tonsillectomy and nasal surgery in adult obstructive sleep apnea: a pilot study. *Otolaryngology--head and neck surgery : official journal of American Academy of Otolaryngology-Head and Neck Surgery.* Aug 2012;147(2):387-391.

84. Guilleminault C, Hill MW, Simmons FB, Dement WC. Obstructive sleep apnea: electromyographic and fiberoptic studies. *Experimental neurology.* Oct 1978;62(1):48-67.

85. Eisele DW, Smith PL, Alam DS, Schwartz AR. Direct hypoglossal nerve stimulation in obstructive sleep apnea. *Archives of otolaryngology--head & neck surgery.* Jan 1997;123(1):57-61.

86. Fairbanks DW, Fairbanks DN. Neurostimulation for obstructive sleep apnea: investigations. *Ear, nose, & throat journal.* Jan 1993;72(1):52-54, 57.

87. Kezirian EJ, Boudewyns A, Eisele DW, et al. Electrical stimulation of the hypoglossal nerve in the treatment of obstructive sleep apnea. *Sleep medicine reviews.* Oct 2010;14(5):299-305.

88. Friedman M, Soans R, Gurpinar B, Lin HC, Joseph N. Evaluation of submucosal minimally invasive lingual excision technique for treatment of obstructive sleep apnea/hypopnea syndrome. *Otolaryngology--head and neck surgery : official journal of American Academy of Otolaryngology-Head and Neck Surgery.* Sep 2008;139(3):378-384; discussion 385.

89. McLeod IK, Melder PC. Da Vinci robot-assisted excision of a vallecular cyst: a case report. *Ear, nose, & throat journal.* Mar 2005;84(3):170-172.

90. O'Malley BW, Jr., Weinstein GS, Snyder W, Hockstein NG. Transoral robotic surgery (TORS) for base of tongue neoplasms. *The Laryngoscope.* Aug 2006;116(8):1465-1472.

91. de Almeida JR, Genden EM. Robotic surgery for oropharynx cancer: promise, challenges, and future directions. *Current oncology reports.* Apr 2012;14(2):148-157.

92. Vicini C, Frassineti S, La Pietra MG, De Vito A, Dallan I, Canzi P. Tongue Base Reduction with Thyro-Hyoido-Pexy (TBRTHP) vs. Tongue Base Reduction with Hyo-Epiglottoplasty (TBRHE) in mild-severe OSAHS adult treatment. Preliminary findings from a prospective randomised trial. *Acta otorhinolaryngologica Italica : organo ufficiale della Societa italiana di otorinolaringologia e chirurgia cervico-facciale.* Jun 2010;30(3):144-148.

93. Vicini C, Montevecchi F, Dallan I, Canzi P, Tenti G. Transoral robotic geniohyoidpexy as an additional step of transoral robotic tongue base reduction and supraglottoplasty: feasibility in a cadaver model. *ORL; journal for oto-rhino-laryngology and its related specialties.* 2011;73(3):147-150.

94. Vicini C, Dallan I, Canzi P, et al. Transoral robotic surgery of the tongue base in obstructive sleep Apnea-Hypopnea syndrome: anatomic considerations and clinical experience. *Head & neck.* Jan 2012;34(1):15-22.

95. Lin HS, Rowley JA, Badr MS, et al. Transoral robotic surgery for treatment of obstructive sleep apnea-hypopnea syndrome. *The Laryngoscope.* Apr 2 2013.

96. Lee JM, Weinstein GS, O'Malley BW, Jr., Thaler ER. Transoral robot-assisted lingual tonsillectomy and uvulopalatopharyngoplasty for obstructive sleep apnea. *The Annals of otology, rhinology, and laryngology.* Oct 2012;121(10):635-639.

97. Friedman M, Hamilton C, Samuelson CG, et al. Transoral robotic glossectomy for the treatment of obstructive sleep apnea-hypopnea syndrome. *Otolaryngology--head and neck surgery : official journal of American Academy of Otolaryngology-Head and Neck Surgery.* May 2012;146(5):854-862.

98. Bowden MT, Kezirian EJ, Utley D, Goode RL. Outcomes of hyoid suspension for the treatment of obstructive sleep apnea. *Archives of otolaryngology--head & neck surgery.* May 2005;131(5):440-445.

99. Li KK. Hypopharyngeal airway surgery. *Otolaryngologic clinics of North America.* Aug 2007;40(4):845-853.

100. Marcus CL, Crockett DM, Ward SL. Evaluation of epiglottoplasty as treatment for severe laryngomalacia. *The Journal of pediatrics.* Nov 1990;117(5):706-710.

101. Berger KI, Fagondes SC, Giugliani R, et al. Respiratory and sleep disorders in mucopolysaccharidosis. *Journal of inherited metabolic disease.* Mar 2013;36(2):201-210.

102. Li KK, Powell NB, Riley RW, Zonato A, Gervacio L, Guilleminault C. Morbidly obese patients with severe obstructive sleep apnea: is airway reconstructive surgery a viable treatment option? *The Laryngoscope.* Jun 2000;110(6):982-987.

103. Akst LM, Eliachar I. Long-term, tube-free (permanent) tracheostomy in morbidly obese patients. *The Laryngoscope.* Aug 2004;114(8):1511-1512; author reply 1512-1513.

104. Clayman GL, Adams GL. Permanent tracheostomy with cervical lipectomy. *The Laryngoscope.* Apr 1990;100(4):422-424.

105. Fee WE, Jr., Ward PH. Permanent tracheostomy: a new surgical technique. *The Annals of otology, rhinology, and laryngology.* Sep-Oct 1977;86(5 Pt 1):635-638.

106. <2002 Defatting tracheostomy.pdf>.

107. Browaldh N, Markstrom A, Friberg D. Elective tracheostomy is an alternative treatment in patients with severe obstructive sleep apnoea syndrome and CPAP failure. *Acta oto-laryngologica.* Oct 2009;129(10):1121-1126.

108. Case RC, Schweinfurth J. Efficacy of a conservative weight loss program in the long-term management of chronic upper airway obstruction. *International journal of otolaryngology.* 2009;2009:396523.

109. Eliashar R GA, Gross M, Sischel JY. A perment tube-free tracheostomy in a mobrbidly obese patient with severe obstructive sleep apnea syndrome. *The Israel Medical Association Journal.* 2002;4(12):1156-1157.

110. Fletcher EC. Recurrence of sleep apnea syndrome following tracheostomy. A shift from obstructive to central apnea. *Chest.* Jul 1989;96(1):205-209.

111. Fletcher EC, Miller J, Schaaf JW, Fletcher JG. Urinary catecholamines before and after tracheostomy in patients with obstructive sleep apnea and hypertension. *Sleep.* Feb 1987;10(1):35-44.

112. Guilleminault C, Simmons FB, Motta J, et al. Obstructive sleep apnea syndrome and tracheostomy. Long-term follow-up experience. *Archives of internal medicine.* Jul 1981;141(8):985-988.

113. Haapaniemi JJ, Laurikainen EA, Halme P, Antila J. Long-term results of tracheostomy for severe obstructive sleep apnea syndrome. *ORL; journal for oto-rhino-laryngology and its related specialties.* May-Jun 2001;63(3):131-136.

114. He J, Kryger MH, Zorick FJ, Conway W, Roth T. Mortality and apnea index in obstructive sleep apnea. Experience in 385 male patients. *Chest.* Jul 1988;94(1):9-14.

115. Motta J, Guilleminault C, Schroeder JS, Dement WC. Tracheostomy and hemodynamic changes in sleep-inducing apnea. *Annals of internal medicine.* Oct 1978;89(4):454-458.

116. Partinen M, Jamieson A, Guilleminault C. Long-term outcome for obstructive sleep apnea syndrome patients. Mortality. *Chest.* Dec 1988;94(6):1200-1204.

117. Rapoport DM, Garay SM, Epstein H, Goldring RM. Hypercapnia in the obstructive sleep apnea syndrome. A reevaluation of the "Pickwickian syndrome". *Chest.* May 1986;89(5):627-635.

118. Sugita Y, Wakamatsu H, Teshima Y, et al. Therapeutic effects of tracheostomy in two cases of hypersomnia with respiratory disturbance during sleep. *Folia psychiatrica et neurologica japonica.* 1980;34(1):17-25.

119. Weitzman ED, Kahn E, Pollak CP. Quantitative analysis of sleep and sleep apnea before and after tracheostomy in patients with the hypersomnia-sleep apnea syndrome. *Sleep.* 1980;3(3-4):407-423.

120. Kumar A, Camacho M, Capasso R. Quantitative Assessment of an Obstructive Sleep Apnea Patient Before and After Tracheostomy: A Case Study. *J Otol Rhinol.* 2013;2(2).

121. Afzelius LE, Elmqvist D, Hougaard K, Laurin S, Nilsson B, Risberg AM. Sleep apnea syndrome--an alternative treatment to tracheostomy. *The Laryngoscope.* Feb 1981;91(2):285-291.

122. Timmis HH. Tracheostomy: an overview of implications, management and morbidity. *Advances in surgery.* 1973;7:199-233.

123. Guilleminault C, Cummiskey J. Progressive improvement of apnea index and ventilatory response to CO2 after tracheostomy in obstructive sleep apnea syndrome. *The American review of respiratory disease.* Jul 1982;126(1):14-20.

124. Biderman P, Weinbroum AA, Rafaeli Y, et al. Retrosternal percutaneous tracheostomy: an approach for predictably impossible classic tracheostomy. *Critical care research and practice.* 2010;2010:397270.

125. Byard RW, Gilbert JD. Potentially lethal complications of tracheostomy: autopsy considerations. *The American journal of forensic medicine and pathology.* Dec 2011;32(4):352-354.

126. Conway WA, Victor LD, Magilligan DJ, Jr., Fujita S, Zorick FJ, Roth T. Adverse effects of tracheostomy for sleep apnea. *JAMA : the journal of the American Medical Association.* Jul 24-31 1981;246(4):347-350.

127. Engels PT, Bagshaw SM, Meier M, Brindley PG. Tracheostomy: from insertion to decannulation. *Canadian journal of surgery. Journal canadien de chirurgie.* Oct 2009;52(5):427-433.

128. Halum SL, Ting JY, Plowman EK, et al. A multi-institutional analysis of tracheotomy complications. *The Laryngoscope.* Jan 2012;122(1):38-45.

129. Heyrosa MG, Melniczek DM, Rovito P, Nicholas GG. Percutaneous tracheostomy: a safe procedure in the morbidly obese. *Journal of the American College of Surgeons.* Apr 2006;202(4):618-622.

130. Jin K, Okabe S, Chida K, et al. Tracheostomy can fatally exacerbate sleep-disordered breathing in multiple system atrophy. *Neurology.* May 8 2007;68(19):1618-1621.

131. Khoo SG, Rajaretnam N. Surgical tracheostomy in morbidly obese patients: technical considerations and a two-flap technique for access. *The Journal of laryngology and otology.* Apr 2012;126(4):435-438.

132. Li KK, Riley RW, Powell NB, Troell RJ. Obstructive sleep apnea surgery: genioglossus advancement revisited. *Journal of oral and maxillofacial surgery : official journal of the American Association of Oral and Maxillofacial Surgeons.* Oct 2001;59(10):1181-1184; discussion 1185.

133. Powell N, Guilleminault C, Riley R, Smith L. Mandibular advancement and obstructive sleep apnea syndrome. *Bulletin europeen de physiopathologie respiratoire.* Nov-Dec 1983;19(6):607-610.

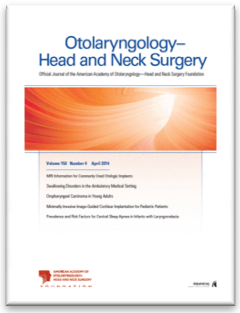
134. Riley RW, Powell NB, Guilleminault C. Inferior sagittal osteotomy of the mandible with hyoid myotomy-suspension: a new procedure for obstructive sleep apnea. *Otolaryngology--head and neck surgery : official journal of American Academy of Otolaryngology-Head and Neck Surgery.* Jun 1986;94(5):589-593.

135. Riley RW, Powell NB, Guilleminault C. Obstructive sleep apnea syndrome: a surgical protocol for dynamic upper airway reconstruction. *Journal of oral and maxillofacial surgery : official journal of the American Association of Oral and Maxillofacial Surgeons.* Jul 1993;51(7):742-747; discussion 748-749.

Adult OSA – Chapter II

Surgical Treatment of Adult OSA – The debate around his efficacy

VII. SURGICAL TREATMENT OF ADULT OBSTRUCTIVE SLEEP APNEA: THE DEBATE AROUND HIS EFFICACY (STUDY 5)



"REVIEWING THE SYSTEMATIC REVIEWS IN OSA SURGERY"
VICTOR CERTAL – NAOYA NISHINO – MACARIO CAMACHO – ROBSON CAPASSO
OTOLARYNGOLOGY – HEAD AND NECK SURGERY
2013

(*cf.* Appendix 6)

1. Introduction

Obstructive sleep apnea (OSA) is a condition characterised by recurring episodes of increase in upper airway resistance and decreased airflow due to upper airway collapse or narrowing during sleep.[1] Common symptoms include loud snoring, breathing interruptions, excessive daytime sleepiness and cognitive impairment. Its association with an increased risk of cardiovascular complications is well described.[2]

The primary course of treatment for OSA is therapy with continuous positive airway pressure (CPAP) devices. However, CPAP compliance is often low, and in cases where effectiveness is not optimal, surgery is often utilized as an alternative after medical management has failed.[3] Nasal surgeries may be used to improve CPAP compliance in patients with nasal obstruction.[4]

Several procedures may be used to increase upper airway patency or to decrease its collapsibility, anywhere from the nasal cavity down to the hypopharynx, including the neck and the maxillomandibular complex. These procedures are often combined as part of a multiple procedures instead of an isolated procedure.[5]

2. Aims

The aims of this study were to:

- provide an overview of systematic reviews
- assess its content validity
- discuss the strength of the various conclusions.

3. Methods

a. Selection Criteria

For proper identification of studies eligible for the analysis, the study selection criteria were defined before data collection. Only systematic reviews whose primary objective was to evaluate the efficacy of surgery to treat OSA on adults were selected. Reviews that predominantly evaluated other treatment modalities (e.g. oral appliances, positive airway pressure devices, positional therapy, or adjunctive treatment modalities) or focused on pediatric population were excluded. Authors sought to identify and include only those papers that met standard criteria for systematic reviews. This required that the review had to have used and described adequate methods to search for, appraise, and describe the included studies. No restrictions in the inclusion criteria of the identified reviews were applied regarding participants, details of the interventions, or outcomes of interest.

b. Search Strategy

Our primary method to identify potentially eligible studies was by utilizing a computerized literature search in the MEDLINE database from inception to April 2013, without any restriction on the language of publication. The following search keywords and MeSH terms were used: 'sleep apnea', 'surgery', 'nose', 'palate', 'tongue', 'tongue base', 'hypopharynx', 'hyoid', 'epiglottis', 'genioglossus', 'radiofrequency', 'advancement', 'glossectomy', 'suspension', and 'stabilization'; the following terms were used for systematic reviews: 'systematic review' and 'meta-analysis'. Literature searches were also undertaken, using the same search keywords, in the following databases: the Cochrane collaboration and SCOPUS database. To minimize the risk of missing relevant reviews, a manual search of key journals and of the reference lists of reviews captured by the initial searches was performed.

c. Study Quality Assessment and Data Abstraction

The titles and abstracts of the retrieved studies were independently screened for relevance by 2 reviewers (V.C. and N.N.). As currently recommended for overviews of reviews[6], the reviewers evaluated the quality of included studies at 2 levels: the methodological quality (AMSTAR) and the quality of the evidence (GRADE). For both assessments, the criteria were applied independently. All disagreements were resolved by consensus.

The AMSTAR checklist is validated as a means to assess the methodological quality of systematic reviews and was used in overview of reviews to determine if the potentially eligible reviews met minimum requirements on the basis of quality.[7]

The GRADE approach for appraisal of the quality of the evidence suggests the initial separate consideration of 4 categories of reasons for rating down the quality of evidence, and 3 categories for rating up, with a yes/no decision regarding rating up or down in each case. The GRADE approach results in an assessment of the quality of a body of evidence as high, moderate, low, or very low.

The primary outcome measures included apnea-hypopnea index (AHI), Epworth Sleepiness Scale (ESS), and snoring improvement. Secondary outcome measures included any other outcome measures evaluated. To reduce heterogeneity among findings, whenever it was feasible, authors grouped results by the surgical approach type: single procedure or multiple simultaneous procedures (occasionally called multilevel surgery). In the case of MMA, authors presented results separately, as it is skeletal surgery and quite commonly it is preceded by previous upper airway surgeries for OSA.

4. RESULTS

All database searches were performed in March 2013. A flow chart of the process of study identification is shown in Figure 1.

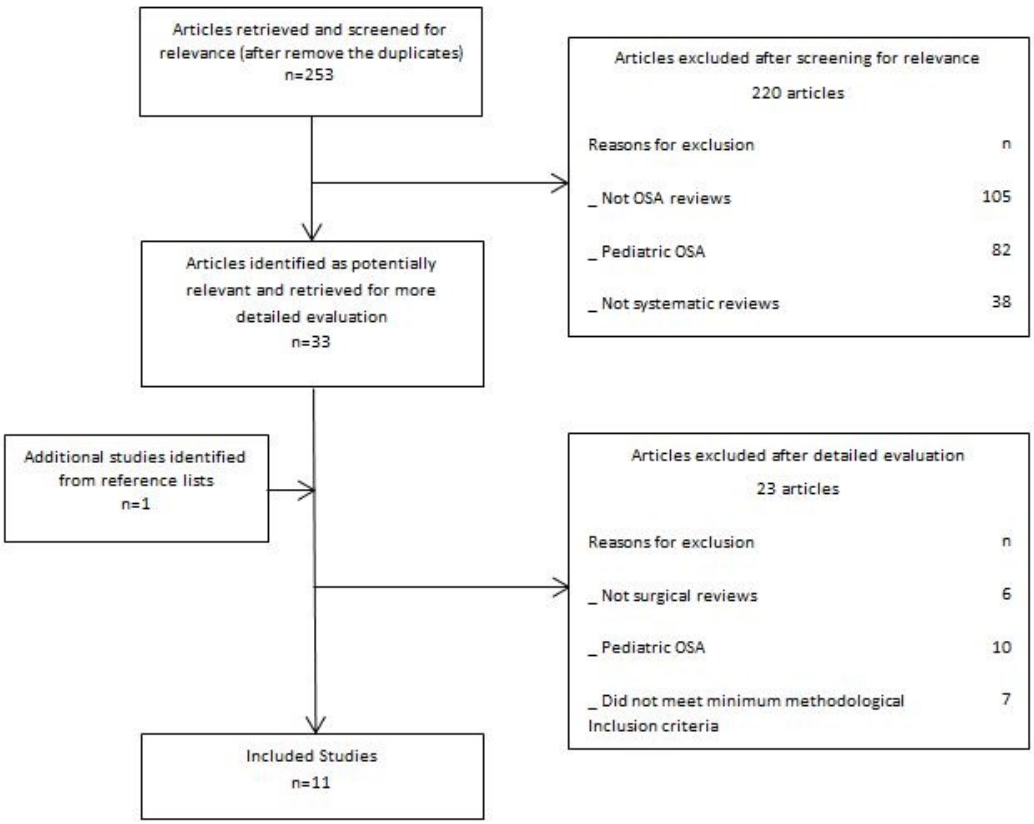


Figure 1 Flow diagram of study identification and selection.
OSA = Obstructive Sleep Apnea

Two hundred fifty-three articles were identified using the search strategy and sources listed previously. After the titles and abstracts were screened for relevance, 220 articles were excluded. The remaining 33 articles were retrieved for more detailed full-text evaluation, and 23 were excluded for the following reasons: seven were not surgical reviews[8-14], 10 focused on pediatric OSA[15-19], six were not actually systematic reviews and did not meet minimum methodological inclusion criteria.[20-25] One study[26]

was included after a manual search of references of the included studies. A total of 11 reviews[1,3,5,26-33] were included in the final overview.

a. Description of Included Reviews

The included reviews contained a total of 378 primary studies. Four systematic reviews analysed only single procedures, one review analyzed only multiple procedures, one review presented results for single and multiples procedures, three reviews presented results for single- and/or multiple procedures together with MMA surgery, and two reviews analyzed only MMA surgery results. Substantial heterogeneity was found in methodological inclusion criteria, but most of the included reviews did not have any study design limitation.

b. Methodological and Evidence Quality of Included Reviews

The main characteristics of the included studies are presented in Table 1.

Author	*Aim*	*Search Database*	*Type of surgery*	*Number of studies*	*Total of participants*	*Study design*
Caples et al. 2010[27]	Provide a basis for standards of practice recommendations on surgical modifications of the upper airway for treatment of OSA	- Medline - Embase - Current Contents - Cochrane	- Single procedure (LAUP; UPP; UPPP; TCRAFTA; Palatal implant; MMA) - Multiples procedures	- Total: 79 studies - Single procedure: 47 studies - Multiples procedures: 32 studies	3913 participants	Randomized and non-randomized controlled trials, cohort studies and case series (sample size > 1)
Choi et al., 2012[28]	Efficacy of Pillar implants on OSA and Snoring	- Medline - LILACS - Scopus - Cochrane	Single procedure: Pillar implants	7 studies	174 participants	No study design limitation No randomized trials were identified
Elshaug G. et al. 2006[29]	Highlight how surgical "success" rates decrease when contemporary, evidence-based criteria of effectiveness are applied	Medline	Single or multiples procedures (UPPP, Genioplasty, MMA, GA, LAUP, TCRFTA, hyoid suspension)	Phase I Procedures: 14 studies Phase II Procedures: 4 studies	Phase I Procedures:347 patients Phase II Procedures: 38 patients	No study design limitation
Franklin et al. 2009[30]	Efficacy and adverse effects of surgery for snoring and OSA	- PubMed - Cochrane	Only single procedure (LAUP; UPP; UPPP; TCRAFTA)	Efficacy: 4 studies Adverse effects: 45 studies	Efficacy: 145 participants Adverse effects: 6016 participants (3130 enrolled in 1 study)	Efficacy: Only RCT´s of medium and high quality Adverse effects: Randomized, controlled studies and observational studies of medium and high quality
Holty JC and Guilleminault C. 2010[3]	Clinical efficacy and safety of MMA in treating OSA	Medline	- MMA as single procedure (33% of participants) - MMA with previous or concurrent phase-I surgery (67% of participants)	22 studies	627 participants	No study design limitation No randomized trials were identified
Kezirian et al., 2006[31]	Review of hypopharyngeal surgery outcomes in OSA	Medline	Single procedure: GA; Mortised genioplasty; Tongue radiofrequency;	36 studies	973 participants	No study design limitation 94% were case series

			Midline glossectomy; Hyoid suspension; Tongue stabilization Multiples procedures			
Li et al., 2011[32]	Analyse the efficacy of nasal surgery in the treatment of OSA	Medline	Single procedure: nasal surgery	13 studies	474 participants	Prospective/retrospective clinical trial, controlled, and randomized
Lin et al., 2008[5]	Efficacy of multiples procedures for OSA patients	PubMed Cochrane Database MEDLINE	Multiples procedures	49 studies	1978 participants	No study design limitation
Pirklbauer et al. 2011[33]	Review the published data and evaluate the effectiveness of MMA for OSA.	PubMed	MMA	39 studies	1213 patients	No study design limitation
Sher et al., 1996[26]	Efficacy of surgery for OSA patients	Medline	Single procedure: nasal procedures, UPPP, Tongue procedures Multiples procedures: GA with hyoid myotomy and suspension MMA	54 studies	1707 participants	No study design limitation
Sundaram S. et al. 2013[1]	Assess the effects of any type of surgery for the treatment of the symptoms of OSA	Cochrane Central MEDLINE EMBASE CINAHL	Single procedure: TCRFTA; LAUP; UPPP; Palatal implants;	12 studies	709 participants	Only RCT´s were included

Table I General Characteristics of included systematic reviews

GA = genioglossus advancement UPP = uvulopalatoplasty; UPPP = uvulopalatopharyngoplasty; LAUP = Laser-assisted uvulopalatoplasty; TCRFTA = temperature-controlled radiofrequency tissue ablation; MMA = Maxillomandibular advancement; RCT = Randomized controlled trial; OSA = obstructive sleep apnea

The systematic reviews were mostly graded as low quality (Table 2 and 3 – Available in Appendix 5). The Cochrane review[1] scored higher, partly because of standardized reporting and greater word allowances, relative to peer-reviewed journals, to allow for greater detail, which permitted us to more completely evaluate methods and risk of biases. The other non-Cochrane reviews were low-quality reviews mostly based on non-randomized studies. All but one[28] of the included reviews failed to perform any kind of publication bias evaluation. Publication bias is a systematic underestimate or an overestimate of the underlying beneficial or harmful effect due to the selective publication of studies. In the included systematic reviews, it is unclear how the authors managed the extent to which they were uncertain about the magnitude of the effect due to selective publication of studies. For example, Franklin et al.[30] used different inclusion criteria for searching primary studies, according to the outcomes of interest (only RCT´s for evaluation of efficacy and minor study design limitation for the evaluation of potential harm of surgery). The combination of these factors limit the ability to assess the external validity of the studies included in the reviews.

All studies satisfied 4 or more of the 11 items in the AMSTAR checklist (table 3) for the assessment of methodological quality and were therefore considered low to moderate quality. The major methodological limitations include the lack of assessment of the scientific quality of the included studies and the lack publication bias evaluation. Also, 6 included reviews based their comprehensive literature searching on only one database, which could have led to a source-selection bias

c. Outcomes

Findings are summarized in Table 4. All the included reviews presented substantial variation in the outcome definition and in the presentation of results. We, therefore, did not report any pooled result or perform statistical analysis other than that already performed by the authors, and presented individual main results and range of effect for each outcome according to the outcome definition in each review.

d. Apnea–hypopnea index

The results regarding the impact on AHI were reported in all the included reviews. Heterogeneity of this impact was evident; even categorizations such as single-level, multiples procedures, and MMA showed significant differences among reviews. Most of the reviews[5,26,27,29,31,33] presented their results as overall success (defined by AHI <20 events/hr and 50% reduction from baseline, pre surgical state), but some reviews[1,3,28,32] reported AHI reduction or did not provide any numeric data to support surgical success.[30] Elshaug et al.[29] used different definitions of surgical success thereby showing a substantial degree of heterogeneity according to the variation of the success criteria (Phase I procedures or soft tissue procedures: from 13% to 55% and Phase II procedures or skeletal procedures: from 43% to 86%.) and suggested that all surgical articles should report 'objective cure' rates with success based on AHI outcomes of ≤5 and/or ≤10. Lin et al.[5] showed an average success rate (excluding MMA) of 59.2% and advocated multiple procedures as the standard procedure in sleep surgery because it produced superior results.

Author	*Effect on AHI*	*Effect on ESS*	*Effect on Snoring*	*Other findings*
Caples et al.2010[27]	- **Single procedure:** Reduction of AHI variable (range from 21% to 33% AHI reduction) - **Multiples procedures**: Overall mean success range [40% to 78.3%] defined by AHI < 20 and 50% reduction. - **MMA**: overall reduction in AHI of 87% with a mean postoperative AHI of 7.7	- **Single procedure**: Improvement in Sleepiness (no measure stated) - **Multiples procedures:** 61% of patients were deemed successfully treated - **MMA:** Reduction from 17.8 to 4.7	- **Single procedure**: significant reduction - **Multiples procedures**: N.R. - **MMA**: N.R.	- Improvements in blood pressure 6 months after MMA - Data on non-respiratory sleep outcomes, quality of life, and cardiovascular/systemic interactions are sparse
Choi et al., 2012[28]	- **Single procedure (Pillar implants):** Substantial degree of heterogeneity. (range from - 17% to 50% AHI reduction). Significant overall standardized mean difference of -0.378 (CCI, -0.619 to -0.138, P = .002)	Substantial degree of heterogeneity. (range from 5% to 43% ESS reduction)	Range from 25% to 52% snoring reduction on visual analogue scale	- Extrusion rate of 9.3%
Elshaug G. et al. 2006[29]	- **Single procedure**: Overall mean success range [48.8% to 60.8%] defined by AHI < 20 and 50% reduction. - **Multiples procedures:** Overall mean success of 55% defined by AHI < 20 and 50% reduction. - **MMA:** Overall mean success of 86% defined by AHI < 20 and 50% reduction.	N.R.	N.R.	- Authors proposed that all surgical audits should report "objective cure" rates with success based on AHI outcomes of ≤ 5 and/or ≤ 10 - Substantial degree of heterogeneity according to the definition of success. **Phase I Procedures (overall success):** from 13% to 55% **Phase II Procedures (overall success):** from 43% to 86%.
Franklin et al. 2009[30]	- **Single procedure:** Conflicting results (reduced in one trial after laser-assisted uvulopalatoplasty but not in another trial)	No significant effect	Significant effect	- No effect on quality of life (through the Calgary Sleep Apnea Quality of Life Index) - Persistent side-effects occurred after UPPP and UPP in about half the patients and difficulty in swallowing, globus sensation and voice changes were especially common
Holty JC and Guilleminault C. 2010[3]	- **MMA**: Significant reduction (mean AHI decreased from 63.9/h to 9.5/h)	- **MMA**: Significant reduction (mean ESS decreased from 13.2 to 5.1)	N.R.	- Significant improvement in all domains of the functional outcomes of sleep questionnaire - Reduction in reported symptoms of depression, irritability, morning headaches, memory loss and impaired concentration. - Statistically and clinically relevant improvements in blood pressure - Younger age, lower preoperative weight and AHI, and greater degree of

Table IV Summary of findings

				maxillary advancement were predictive of increased surgical success - Low complication rate
Kezirian et al., 2006[31]	**- Single procedure**: Overall mean success range [35% to 62%] defined by AHI < 20 and 50% reduction. **- Multiples procedures*:** Overall mean success range [22% to 77%] defined by AHI < 20 and 50% reduction.	Significant improvement	N.R.	- Significant improvement in quality of life - Several factors such as the body mass index apnea-hypopnea index, Friedman stage, and SNB angle on lateral cephalogram have been associated with surgical outcomes
Li et al., 2011[32]	**- Single procedure (nasal procedures):** Non-significant reduction (mean AHI decreased from 35.2/h to 33.5/h)	Mean ESS scores decreased significantly from 10.6 to 7.1	Significant in bedpartner's snoring VAS	
Lin et al., 2008[5]	**- Multiples procedures:** Overall redefined success*** rate was 66.4%. The redefined success*** rate (excluding MMA) was 59.2% - The weighted average percentage change of AHI showed a significant 60.3% improvement after multiple procedures	- the weighted average percentage change improved by 43.0% postoperatively	- 65.1% decrease in bedpartner's snoring VAS	- 8.8% increase in quality of life - The percentage changes of weighted average on mO2 and BMI revealed no significant difference after surgery - The recalculated success rates with a meta-analysis using the commonly agreed upon criteria (postoperative AHI of 50% or more and an AHI of less than 20) were 56.5% for mild/moderate disease and 69.3% for severe disease, respectively.
Pirklbauer et al. 2011[33]	**- MMA:** Mean success rates ranged from 65% to 100%, depending on the criteria defined by the investigators	Reduced after MMA in all studies	N.R.	- The Functional Outcomes of Sleep Questionnaire showed improvement in quality of life in patients with OSA treated with MMA - Long-term success rates of 80% during an observation period of 24 months
Sher et al., 1996[26]	**Single procedure**: Nasal procedures: no significant differences between baseline and postoperative values in AI UPPP: Overall mean success rate defined by 50% decrease in AI: range from 18.2% to 90% Tongue procedures: Overall mean success rate defined by 50% decrease in AI: range from 41.7% to 77% **Multiples procedures**: Overall mean success rate defined by 50% decrease in AI: range from 67% to 79.2% **MMA**: Overall success rate defined by 50% decrease	N.R.	N.R.	- The site of pharyngeal narrowing or collapse, although identified by different and unvalidated methods, has a marked effect on the probability of success of uvulopalatopharyngoplasty - Patients who achieve a favorable response with uvulopalatopharyngoplasty tend to have less severe obstructive sleep apnea than those who do not.

Table IV Summary of findings *(Continuation)*

	in AI: range from 77.8% to 97.8%			
Sundaram S. et al. 2013[1]	**Single procedure**: TCRFTA**: No significant difference LAUP**: 21% reduction in mean AHI UPPP**: No significant differences were observed between the two groups Palatal implants**: Mean change in AHI was significantly greater when compared with placebo	TCRFTA**: mean difference in change: -1.1. Significant greater reduction in symptoms in favor of TCRFTA compared with placebo LAUP**: No significant difference UPPP**: A significant difference was observed in favor of surgery over conservative management Palatal implants**: ESS scores improved more with implants than placebo	N.R.	TCRFTA**: *Quality of life:* There was a significantly greater improvement on the Functional Outcomes of Sleep Questionnaire (FOSQ) in favor of TCRFTA LAUP**: There was no significant difference between LAUP and control in Calgary Sleep Apnoea Quality of Life Index (SAQLI) scores. Palatal implants**: Surgery led to better quality of life when compared with placebo (SF-36 - Short Form 36 Health Survey)

Table IV Summary of findings *(Continuation)*

UPP = uvulopalatoplasty; UPPP = uvulopalatopharyngoplasty; LAUP = Laser-assisted uvulopalatoplasty; TCRFTA = temperature-controlled radiofrequency tissue ablation; MMA = Maxillomandibular advancement; RCT = Randomized controlled trial; OSA = obstructive sleep apnea; AHI = Apnea-hypopnea índex; ESS = Epworth Sleepiness Scale; BMI = Body mass índex N.R. = Not reported

* The patient populations, on average, were overweight or obese

* Compared with conservative management or placebo

** the definition of success used by the authors of the various papers reviewed was not consistent. Linet al.[5] redefined the success rate to be consistent with the commonly agreed upon criteria—namely "a reduction in AHI of 50% or more and an AHI of less than 20

e. Sleepiness

The results regarding the impact on Epworth Slepiness Scale (ESS) or other psychometric validated tool such as the Stanford Sleepiness Scale were not reported in all the included reviews. Two reviews[26,29] did not provide any information about this outcome, and substantial variation was found in the presentation of results. However, despite this heterogeneity, only 1 review[30] found no significant reduction in ESS outcome, and 1 subgroup (LAUP subgroup) of Sundaram's review[1] also failed to show any effect on sleepiness.

f. Snoring

Five reviews[5,27,28,30,32] contained data regarding improvement in snoring. Although there was considerable heterogeneity in the criteria for snoring improvement, all the reviews reported significant reduction.

g. Other outcomes

Seven reviews[1,3,5,27,30,31,33] contained data regarding the quality of life. Only 1 review[30] found no significant improvement in quality of life, and 1 subgroup (LAUP subgroup) of Sundaram's review[1] also failed to show any effect on this outcome. In one review, MMA surgery showed positive results in several outcomes such as improvement in blood pressure and reduction of symptoms of depression, irritability, morning headaches, memory loss, and impaired concentration.[3]

5. Discussion

The reviews present conflicting results regarding not only methods and indications of OSA surgery, but also definition of a successful surgery.

The different inclusion/exclusion criteria used in different reviews may have influenced the respective results and conclusions. Franklin et al.[30] only included RCTs for the evaluation of the efficacy of surgical treatment, leading to the exclusion of most of the published surgical literature, thus limiting included studies to minimally invasive treatments, which by nature are less comprehensive treatments for OSA and some are not meant for OSA surgical procedures. These facts not only weaken their conclusions but also strongly affect the external validity of the results. There is debate about the feasibility of RCTs for surgical interventions[34] and the superiority of RCTs over non-RCTs or observational designs.[35] In reality, experimental and observational studies contribute to complementary evidence; as it is the research question that dictates the appropriate study design. Solomon et al.[36] performed a systematic review of treatment evaluation questions and concluded that only 40% of treatment questions involving surgical procedures could have been evaluated by an RCT. It is important to recognize the value of evidence from non-RCTs which evaluate OSA surgical interventions when the conduct of RCTs is impractical or unethical, which could apply to the sleep-surgery field. Relying exclusively on RCTs may have led to a set of reports that were not representative of all the relevant literature that would have been identified through a search with no study-design restriction.

Half of the included reviews based their research on only 1 database, which could have led to a source-selection bias. A search of MEDLINE alone is not considered adequate.

A systematic review showed that only 30% to 80% of all known published randomized trials were identifiable using MEDLINE. Going beyond MEDLINE is important not only to ensure that as many relevant studies as possible are identified but also to minimize selection bias for those that are found.

The findings of this overview support that sleep apnea surgeries are associated with improved outcomes, but the level and quantity of evidence reviews remain low, because of the following factors: difficulty in standardizing procedures (the surgical approaches seem to vary according to the upper airway anatomy), experience of the study center with all surgical procedures[38,39] (few surgical centers have the experience to perform all available techniques) and lack of long-term follow-ups.

The commonly accepted criteria for 'success' is a 50% or more reduction in AHI from baseline pre-operative values, with an AHI of less than 20 with an associated improvement in the condition of the patient. Others maintain that 'success' should be defined as a post-operative AHI of less than 5 or 10. When applying the latter definition of 'success' to multiple procedures, there is a significant decrease in the percentage of overall surgical success rates; however, it is the authors opinion that this should not be used as an argument to rule out the utility and value of surgical treatment. The goal of surgery is not solely to cure OSA but to control symptoms and minimize ongoing multi-system damage for those who cannot or will not accept CPAP therapy. For instance, most of the reviews indicate that sleepiness, snoring, and even quality of life improve with many various surgical treatments, even if OSA is not cured.

In addition, the surgeries can also lead to higher CPAP compliance by allowing the patient to reduce the amount of pressure required to operate the device, resulting in

less discomfort.[40] Another major complication of OSA is its association with cardiovascular disease[41,42], and the AHI, which is commonly thought to be the more reliable parameter in sleep medicine, is commonly used to determine OSA severity, and determine this association. However, great variation is exists whenever this metric is used.[43,44]

The variation in AHI scoring and results can be attributed to a number of factors such as intra-individual variability of a single-night recording, as well as scoring variability between PSG technologists and sleep laboratories due to different scoring criteria and/or disparity in interpretation of the rules.[43] In addition, the AHI depends largely on hypopnea scoring, which is not entirely correlated with cardiovascular disease risk. By varying the criteria for defining hypopnea, Punjabi et al.[45] showed that hypopneas associated with desaturations are independently associated with cardiovascular disease, but no association was observed between cardiovascular disease and arousals. As one of the purposes of surgery in OSA should be the improvement of cardiovascular disease risk, the oxygen desaturation index (ODI) might provide a more consistent metric for appraisal of surgical treatment.[46]

a. Limitations and research perspectives

The limitations of the overview are due to the heterogeneity in the presentation of the results and methodological limitations in the reviews themselves. Most of the reviews were based on case series, and the AMSTAR results reflect a lack of thoroughness in the methodology of the investigations. Future reviews would benefit from consistency in AHI scoring (eg, hypopnea definition), inclusion of ODI outcomes, standardized definitions of surgical success, and a greater focus on improvement in clinical

outcomes. Also, the evidence presented here suggests that further research should be performed using a more robust methodological approach to create systematic reviews and perform primary studies with higher quality.

6. Conclusion

This overview of reviews suggests that the majority of the literature reviews targeting surgical treatment for obstructive sleep apnea present deficient quality assessment of evidence, with conflicting results not only on metrics, methods and indications, but also in the definition of a successful OSA surgery. The level and quality of the evidence provided in the reviews remain low, and it is unclear how these reviews reflect OSA surgery literature overall

References

1. Sundaram S, Bridgman SA, Lim J, Lasserson TJ. Surgery for obstructive sleep apnoea. *Cochrane Database Syst Rev*. 2005:CD001004.
2. Marin JM, Carrizo SJ, Vicente E, Agusti AG. Long-term cardiovascular outcomes in men with obstructive sleep apnoea-hypopnoea with or without treatment with continuous positive airway pressure: an observational study. *Lancet*. 2005; 365:1046-1053.
3. Holty JE, Guilleminault C. Maxillomandibular advancement for the treatment of obstructive sleep apnea: a systematic review and meta-analysis. *Sleep Med Rev*. 2010; 14:287-297.
4. Powell NB, Zonato AI, Weaver EM et al. Radiofrequency treatment of turbinate hypertrophy in subjects using continuous positive airway pressure: a randomized, double-blind, placebo-controlled clinical pilot trial. *Laryngoscope*. 2001; 111:1783-1790.
5. Lin HC, Friedman M, Chang HW, Gurpinar B. The efficacy of multiple procedures of the upper airway in adults with obstructive sleep apnea/hypopnea syndrome. *Laryngoscope*. 2008; 118:902-908.
6. Higgins JPT, Green S, Cochrane Collaboration. *Cochrane handbook for systematic reviews of interventions*. Chichester, England ; Hoboken, NJ: Wiley-Blackwell, 2008.
7. Shea BJ, Hamel C, Wells GAet al. AMSTAR is a reliable and valid measurement tool to assess the methodological quality of systematic reviews. *J Clin Epidemiol.* 2009; 62:1013-1020.
8. Alsufyani NA, Al-Saleh MA, Major PW. CBCT assessment of upper airway changes and treatment outcomes of obstructive sleep apnoea: a systematic review. *Sleep Breath.* 2013.
9. Georgalas C, Garas G, Hadjihannas E, Oostra A. Assessment of obstruction level and selection of patients for obstructive sleep apnoea surgery: an evidence-based approach. *J Laryngol Otol*. 2010; 124:1-9.
10. Moyer CA, Sonnad SS, Garetz SL, Helman JI, Chervin RD. Quality of life in obstructive sleep apnea: a systematic review of the literature. *Sleep Med*. 2001; 2:477-491.
11. Vasu TS, Grewal R, Doghramji K. Obstructive sleep apnea syndrome and perioperative complications: a systematic review of the literature. *J Clin Sleep Med*. 2012; 8:199-207.
12. Panossian LA, Veasey SC. Daytime sleepiness in obesity: mechanisms beyond obstructive sleep apnea--a review. *Sleep*. 2012; 35:605-615.

13. Rocke D, Sharp S, Wiener D, Puscas L, Lee WT. Effectiveness of a postoperative disposition protocol for sleep apnea surgery. *Am J Otolaryngol.* 2013.
14. Thomasouli MA, Brady EM, Davies MJet al. The impact of diet and lifestyle management strategies for obstructive sleep apnoea in adults: a systematic review and meta-analysis of randomised controlled trials. *Sleep Breath*. 2013.
15. Marcus CL, Brooks LJ, Draper KA et al. Diagnosis and management of childhood obstructive sleep apnea syndrome. *Pediatrics*. 2012; 130:e714-755.
16. Nolan J, Brietzke SE. Systematic review of pediatric tonsil size and polysomnogram-measured obstructive sleep apnea severity. *Otolaryngol Head Neck Surg*. 2011; 144:844-850.
17. Valrie CR, Bromberg MH, Palermo T, Schanberg LE. A systematic review of sleep in pediatric pain populations. *J Dev Behav Pediatr*. 2013; 34:120-128.
18. Khan AM. Adenotonsillectomy outcomes in treatment of obstructive sleep apnea and children: a multicenter retrospective study. *Am J Respir Crit Care Med.* 2011; 183:826; author reply 826-827.
19. Friedman M, Wilson M, Lin HC, Chang HW. Updated systematic review of tonsillectomy and adenoidectomy for treatment of pediatric obstructive sleep apnea/hypopnea syndrome. *Otolaryngol Head Neck Surg*. 2009; 140:800-808.
20. Aurora RN, Casey KR, Kristo D et al. Practice parameters for the surgical modifications of the upper airway for obstructive sleep apnea in adults. *Sleep*. 2010; 33:1408-1413.
21. Li KK. Surgical therapy for adult obstructive sleep apnea. *Sleep Med Rev*. 2005; 9:201-209.
22. Ephros HD, Madani M, Yalamanchili SC. Surgical treatment of snoring & obstructive sleep apnoea. *Indian J Med Res*. 2010; 131:267-276.
23. Kao YH, Shnayder Y, Lee KC. The efficacy of anatomically based multiple procedures for obstructive sleep apnea. *Otolaryngol Head Neck Surg*. 2003; 129:327-335.
24. Holty JE, Guilleminault C. Surgical options for the treatment of obstructive sleep apnea. *Med Clin North Am*. 2010; 94:479-515.
25. Blumen M, Crampette L, Fischler M et al. Surgical treatment of obstructive sleep apnea syndrome. *Rev Mal Respir*. 2010; 27 Suppl 3:S157-165.
26. Sher AE, Schechtman KB, Piccirillo JF. The efficacy of surgical modifications of the upper airway in adults with obstructive sleep apnea syndrome. *Sleep*. 1996; 19:156-177.
27. Caples SM, Rowley JA, Prinsell JR et al. Surgical modifications of the upper airway for obstructive sleep apnea in adults: a systematic review and meta-analysis. *Sleep*. 2010; 33:1396-1407.
28. Choi JH, Kim SN, Cho JH. Efficacy of the Pillar implant in the treatment of snoring and mild-to-moderate obstructive sleep apnea: a meta-analysis. *Laryngoscope*. 2013; 123:269-276.
29. Elshaug AG, Moss JR, Southcott AM, Hiller JE. Redefining success in airway surgery for obstructive sleep apnea: a meta analysis and synthesis of the evidence. *Sleep*. 2007; 30:461-467.
30. Franklin KA, Anttila H, Axelsson S et al. Effects and side-effects of surgery for snoring and obstructive sleep apnea--a systematic review. *Sleep*. 2009; 32:27-36.
31. Kezirian EJ, Goldberg AN. Hypopharyngeal surgery in obstructive sleep apnea: an evidence-based medicine review. *Arch Otolaryngol Head Neck Surg*. 2006; 132:206-213.
32. Li HY, Wang PC, Chen YP, Lee LA, Fang TJ, Lin HC. Critical appraisal and meta-analysis of nasal surgery for obstructive sleep apnea. *Am J Rhinol*. 2011; 25:45-49.
33. Pirklbauer K, Russmueller G, Stiebellehner L et al. Maxillomandibular advancement for treatment of obstructive sleep apnea syndrome: a systematic review. *J Oral Maxillofac Surg*. 2011; 69:e165-176.
34. Fu WK. Randomized controlled trials in surgery: an essential component of scientific progress (Spine 1999; 24:2553-5). *Spine*. 2000; 25:2002-2004.
35. Concato J. Observational versus experimental studies: what's the evidence for a hierarchy? *NeuroRx.* 2004; 1:341-347.
36. Solomon MJ, McLeod RS. Should we be performing more randomized controlled trials evaluating surgical operations? *Surgery*. 1995; 118:459-467.
37. Dickersin K, Scherer R, Lefebvre C. Identifying relevant studies for systematic reviews. *BMJ*. 1994; 309:1286-1291.
38. Tuncel U, Inancli HM, Kurkcuoglu SS, Enoz M. A comparison of unilevel and multiple procedures in obstructive sleep apnea syndrome. *Ear Nose Throat J*. 2012; 91:E13-18.
39. Shen T, Shimahara E, Cheng J, Capasso R. Sleep medicine clinical and surgical training during otolaryngology residency: a national survey of otolaryngology residency programs. *Otolaryngol Head Neck Surg*. 2011; 145:1043-1048.
40. Kezirian EJ, Hussey HM, Brietzke SE et al. Hypopharyngeal surgery in obstructive sleep apnea: practice patterns, perceptions, and attitudes. *Otolaryngol Head Neck Surg*. 2012; 147:964-971.
41. Poirier J, George C, Rotenberg B. The effect of nasal surgery on nasal continuous positive airway pressure compliance. *Laryngoscope*. 2013.
42. Bixler EO, Vgontzas AN, Lin HM et al. Association of hypertension and sleep-disordered breathing. *Arch Intern Med*. 2000; 160:2289-2295.
43. Shahar E, Whitney CW, Redline S et al. Sleep-disordered breathing and cardiovascular disease: cross-sectional results of the Sleep Heart Health Study. *Am J Respir Crit Care Med*. 2001; 163:19-25.
44. Aarab G, Lobbezoo F, Hamburger HL, Naeije M. Variability in the apnea-hypopnea index and its consequences for diagnosis and therapy evaluation. *Respiration*. 2009; 77:32-37.
45. Newell J, Mairesse O, Verbanck P, Neu D. Is a one-night stay in the lab really enough to conclude? First-night effect and night-to-night variability in polysomnographic recordings among different clinical population samples. *Psychiatry Res*. 2012; 200:795-801.
46. Punjabi NM, Newman AB, Young TB, Resnick HE, Sanders MH. Sleep-disordered breathing and cardiovascular disease: an outcome-based definition of hypopneas. *Am J Respir Crit Care Med*. 2008; 177:1150-1155.
47. Oeverland B, Skatvedt O, Kvaerner KJ, Akre H. Pulseoximetry: sufficient to diagnose severe sleep apnea. *Sleep Med*. 2002; 3:133-138.

Adult OSA – Chapter III

Evidence-based practice in Sleep Apnea Surgery: Filling the gaps

III. EVIDENCE-BASED PRACTICE IN SLEEP APNEA SURGERY: FILLING THE GAPS

(*cf.* Appendix 7)

"THE EFFECT OF NASAL SURGERY ON CONTINUOUS POSITIVE AIRWAY PRESSURE DEVICE USE AND THERAPEUTIC TREATMENT PRESSURES: A SYSTEMATIC REVIEW AND META-ANALYSIS "

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SLEEP

2014

I. The Effect of Nasal Surgery on Continuous Positive Airway Pressure Device Use and Therapeutic Treatment Pressures

1. Introduction

Nasal continuous positive airway pressure (CPAP) was introduced by Sullivan et al.[1] in 1981 as treatment for obstructive sleep apnea (OSA) and treatment has been shown to have a mortality benefit.[2] Although CPAP is highly efficacious, the non-adherence rate (<4 h of nightly use 70% of nights) is between 46–83%.[3] CPAP side effects include insomnia, claustrophobia, nocturnal awakenings, irritation of the upper airway, sneezing, nasal dryness, rhinitis, rhinorrhea, laryngitis, and epistaxis.[4-7] Nasal obstruction is a common complaint among CPAP users, with an estimated prevalence of 25–45%.[4,7,8] Decreased cross-sectional area and reduced volume of the nasal airway is associated with patients being less compliant with CPAP therapy.[9] Increased nasal resistance has also been associated with decreased CPAP therapy adherence.[10] Studies demonstrate that isolated nasal surgery in patients with nasal obstruction reduces

therapeutic CPAP pressures and/or improves CPAP acceptance, compliance, tolerance, adherence, or use.[5,10-26]

2. Aims

In this section, the aims were to:

- assess the effect of isolated nasal surgery on therapeutic CPAP device

- assess the effect of isolated nasal surgery on CPAP use in adults with OSA

3. Methods

a. Search strategy

A search of four databases (MEDLINE, Scopus, Web of Science, and The Cochrane Library) was performed from inception through September 1, 2013, with an update through July 15, 2014. Keywords, MeSH terms, and phrases searched included combinations of: “continuous positive airway pressure,” “nasal obstruction,” “nasal surgery,” “nose surgery,” “rhinoplasty,” “septoplasty,” “septorhinoplasty,” “septoturbinoplasty,” “sleep apnea,” “sleep apnea syndromes,” “surgery,” “turbinate reduction,” “turbinectomy,” and “turbinoplasty”. An example of a search on MEDLINE is: ((("Continuous Positive Airway Pressure"[MeSH]) OR (“Sleep Apnea, Obstructive”[MeSH])) AND ((“Nasal Obstruction/surgery*”[MeSH]) OR (“Nasal Septum/surgery*”[MeSH]) OR “nasal surgery” OR (“Nasal Surgical Procedures*”[MeSH]) OR “nose surgery” OR “rhinoplasty” OR (“Rhinoplasty/methods*”[MeSH]) OR “septoplasty” OR “septorhinoplasty” OR

"septoturbinoplasty" OR "turbinate reduction" OR ("Turbinates/surgery"[MeSH]) OR "turbinectomy" OR "turbinoplasty")).

The titles and abstracts for each of the results were reviewed for relevance. The full text versions of relevant articles were obtained for complete evaluation. The references of the obtained articles were also reviewed and any relevant studies in the reference lists were also obtained and included if they met criteria. As an additional step, each time a relevant article was encountered during the review of titles and abstracts, the "related citations/articles" and "cited by" features of the four databases and Google Scholar were searched to identify any additional potentially relevant articles.

b. Study Selection

Inclusion criteria for the studies consisted of adult patients with OSA who were treated with CPAP and underwent isolated nasal surgery. Additionally, the included studies needed to report quantitative outcomes data comparing prenasal and postnasal surgery therapeutic CPAP pressures and/or prenasal and postnasal surgery CPAP acceptance, compliance, tolerance, adherence, or use after nasal surgery, without regard to follow-up length. All languages and study designs were included. Exclusion criteria consisted of studies reporting qualitative data only and studies on children. If a study reported individual patient data for nasal surgeries and non-nasal surgeries, then the nasal surgery data were abstracted and included in this review.

c. Data Abstractions and Study Quality Assessment

Two authors (VC and MC) performed a literature search and screened titles and abstracts, and retrieved articles for further review. Data collected included the ages,

body mass indices (BMI), therapeutic CPAP device pressures, and CPAP use data. After the data were collected, the National Institute for Health and Clinical Excellence (NICE) quality assessment tool, consisting of eight items for each study, was used to evaluate the quality of each of the included studies. Data were placed into an Excel 2013 spreadsheet. Authors of studies in which there were insufficient data reported (e.g., study means, standard deviations [SD], etc.) to include in the meta-analysis were contacted via email or phone, in an attempt to obtain these additional data. The corresponding authors were contacted for the following studies: Bican et al.,[19] Friedman et al.,[16] Nakata et al.,[10] Park et al.,[26] Pniak et al.,[24] Poirier et al.,[11] and Powell et al.[25] The raw data were no longer available for studies by Friedman et al. or Powell et al. Means and SD for CPAP pressures and use were provided by Rotenberg (Poirier et al. study). There was no reply from corresponding authors for Park et al., Bican et al., Nakata et al., and Pniak et al.

A full description of the statistical analysis is available in Appendix 6.

4. Results

The search identified a total of 792 articles after removal of duplicates. After the preliminary review of the titles and abstracts, a total of 29 studies were agreed to as being relevant and the full text was downloaded for further evaluation. Review of the articles' reference lists identified an additional 7 articles, which were also obtained. Of these 36 articles, a total of 18 were excluded for the following reasons: no quantitative CPAP data prenasal and postnasal surgery were presented in the article,[31,32] non-nasal surgeries were performed (i.e. uvulopalatopharyngoplasties, pillar implants or multilevel surgeries)[33-41] or no nasal surgery was performed.[4,7,9,42-45] Zonato et al.[13]

reported individual data for nasal surgeries and multilevel surgeries; therefore, the data for nasal surgeries could be separated and included as part of the review. A total of 18 articles were included in this study, with a total of 279 patients identified within those articles, who underwent isolated nasal surgery and had quantitative data available.[5,10-25] Figure 1 demonstrates the flow diagram for the article selection. The mean patient age was 52.5 ± 8.7 y and the mean BMI was 29.5 ± 4.0 kg/m^2.

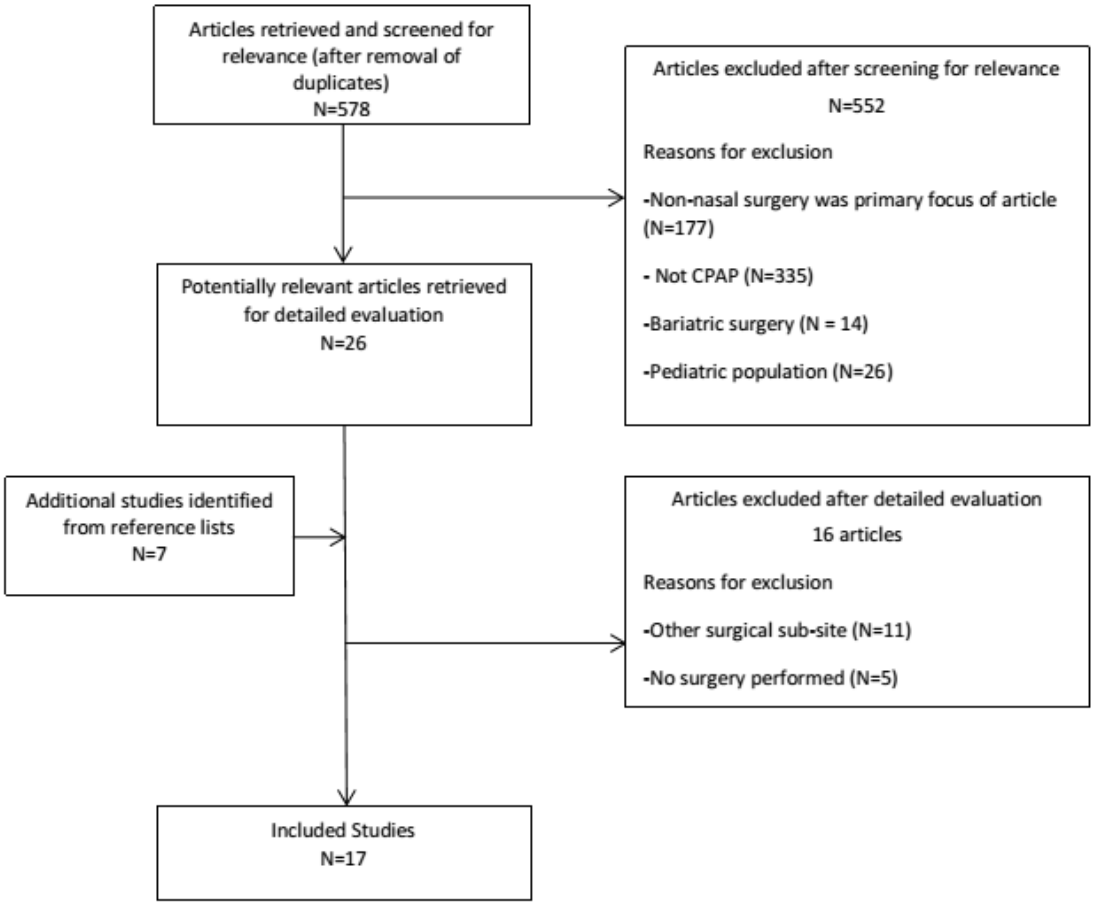

Figure 1. Literature search and study selection. CPAP = continuous positive airway pressure; N = number of studies.

a. Methodological Quality of the Included Studies

The studies included in this review were all either retrospective or prospective case series (Level 4 evidence), except for one study by Powell et al.[25] that was a randomized, double-blind, placebo-controlled clinical trial (RCT), which is Level 1 evidence. The NICE quality assessment tool demonstrated that the included studies satisfied between three to six of the eight items, with most satisfying more than four items (presented in Table S1 – Available in Appendix 7). The main limitations in general are that none of the studies were multicenter, patients were not recruited consecutively, and there was only one randomized controlled trial and the remaining studies were case series.

b. Therapeutic CPAP Pressures

A total of 10 studies (135 patients) described therapeutic CPAP device pressures as an outcome after isolated nasal surgery.[5,10-16,20,21,24] Two studies reported the mean difference (MD) of the therapeutic pressures (Balcerzak et al.[20] reported a MD of -2.7 cwp and Ripberger and Pirsig[21] reported a MD of -5 cwp), but lacked the SD, therefore, were excluded from meta-analysis. Friedman et al.[16] reported the therapeutic CPAP means prenasal and postnasal surgery, but did not report the SD; therefore, the study was excluded from pooled meta-analysis calculations.[16] The remaining 7 studies (82 patients) reported both preoperative and postoperative therapeutic CPAP device pressures and SD, which were provided in the article or were obtained by contacting the authors of the original studies.[5,10-15]

With regard to determination of the therapeutic CPAP device pressures, Park et al.,[6] Poirier et al.,[11] and Mayer-Brix et al.[5] reported the therapeutic pressures based on the patients' CPAP devices, whereas in the remaining 5 studies in the meta-analysis reported therapeutic pressures based upon the in-laboratory polysomnography titrations.[5,10-15] Hypopnea scoring criteria for the studies included ≥ 10 sec for the hypopnea duration, in combination with: ≥ 3% oxygen desaturation with a 50% decrease in thermistor for Sufioglu et al.,[12] ≥ 3% oxygen desaturation or arousal associated with a hypopnea for Nakata et al.,[10] > 4% oxygen desaturation for Nowak et al.,[14] ≥ 4% oxygen desaturation with a ≥ 50% decreased effort to breathe for Katsantonis et al.,[46] whereas the remaining studies did not specify which hypopnea scoring criteria was used.[5,11,13,15,26]

The combined data for the 7 studies demonstrated a prenasal and postnasal surgery therapeutic CPAP device pressure that reduced from a mean ± SD of 11.6 ± 2.2 to 9.5 ± 2.0 centimeters of water pressure (cwp), with results shown in Table 1. The pooled random effects analysis (Figure 2) demonstrated a statistically significant reduction in the mean pressures, with a MD of -2.66 cwp (95% CI, -3.65 to -1.67; overall effect: Z score = 5.27 ($P < 0.00001$)). The I^2 (82%) and Cochran Q statistic ($P < 0.00001$) suggest significant heterogeneity across included studies, and therefore justified the need for a random-effects model. A sensitivity analysis showed that removing the Sufioglu et al.[12] study resulted in a low level of heterogeneity (I^2 = 27% and Cochran Q statistic = 0.23) but did not significantly affect the summarized effect size (MD: -3.00 cwp; 95% CI: -3.56 to -2.43, Z score = 10.39, and $P < 0.00001$). The study by Sufioglu et al.[12] states that a postoperative CPAP titration was not performed in five patients who

were cured of OSA (apnea-hypopnea index [AHI] < 5/h).[12] Visual inspection of the funnel plot also demonstrated that the study by Sufioglu et al.[12] was slightly outlying when compared to the remaining studies.

Study authors, year	*N*	*Mean Age (years)*	*BMI (kg/m²)*	*Nasal surgery sub-site*	*Mean CPAP cwp pre-nasal surgery*	*Mean CPAP cwp post-nasal surgery*	*p-value**
Poirier et al, 2013	18	52	31.8	ST	11.9±0.9	9.2±0.7	p=0.062
Sufioglu et al, 2012	28	53± 9.6	30.3±4.1	E, R, S, T, ST	11.2±1.2	10.4±1.4	p=0.062
Zonato et al, 2006	13	49±9	30±4	ST, T	11.9±2.7	10.1±2.3	p=0.009*
Nakata et al, 2005	5	54.2±9.2	26±2.8	ST, T	16.8±1.2	12.0±1.9	p<0.045*
Nowak et al, 2003	10	55.8±3.6	27.4±0.7	S, ST, T	10.0±0.6	7.1±1.2	p<0.05*
Dorn et al, 2001	5	50.4±9.1	31.9±5.1	E, R, S, ST	11.8±3.9	8.5±1.6	p=0.055
Friedman et al, 2000	22	-	35.7	ST	9.3	6.7	p<0.01*
Mayer-Brix et al, 1989	3	-	-	ST	9.7±0.6	6.0±1.0	p=0.032*
Total**	104	52.5±8.7	29.5±4.0		11.6±2.2	9.5±2.0	p<0.00001*

Table 1. Patient demographics and pre and post-nasal surgery therapeutic mean CPAP pressure data. Abbreviations: cwp = centimeters of water pressure; E = endoscopic sinus surgery; N= number of patients; R = septorhinoplasty; S = septoplasty; ST = septoturbinoplasty; T = turbinoplasty. *Denotes a statistically significant p-value based on either the reported study value or a paired samples t-test and the calculated 2-tailed significance for the paired difference.

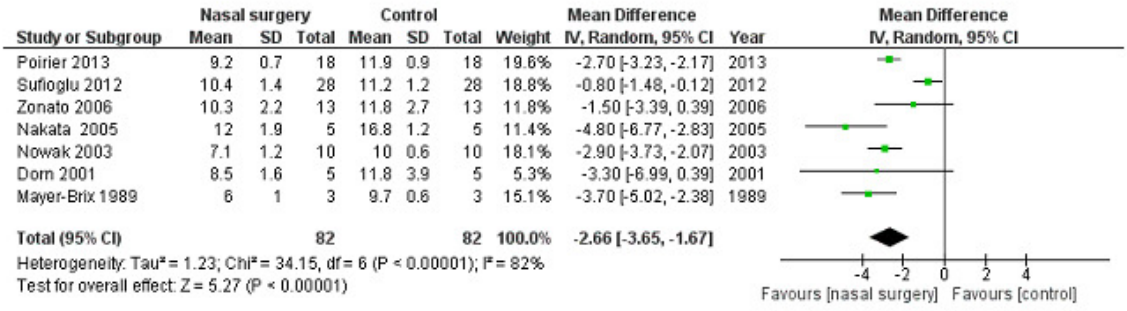

Figure 2. Prenasal and postnasal surgery random effects analysis.

A subgroup analysis was performed for studies that specifically stated in the article that nasal mask interfaces were used (studies did not specify nasal pillows versus nasal triangle masks), which resulted in the exclusion of studies by Sufioglu et al.[12] and Nakata et al.[10,12] When pooling the data from the remaining five studies (49 patients), the nasal CPAP pressures decreased from 11.3 ± 2.0 to 8.8 ± 1.9 cwp.[5,11,13-15] There was no heterogeneity across these studies, demonstrated by an I^2 of 0% and Cochran Q statistic of P = 0.54. The fixed effects analysis for this subgroup demonstrated a statistically significant decrease in the mean pressure with MD of -2.81 cwp (95% CI, -3.22 to -2.40; overall effect: Z score = 13.46, P < 0.00001 [see Figure 3]).

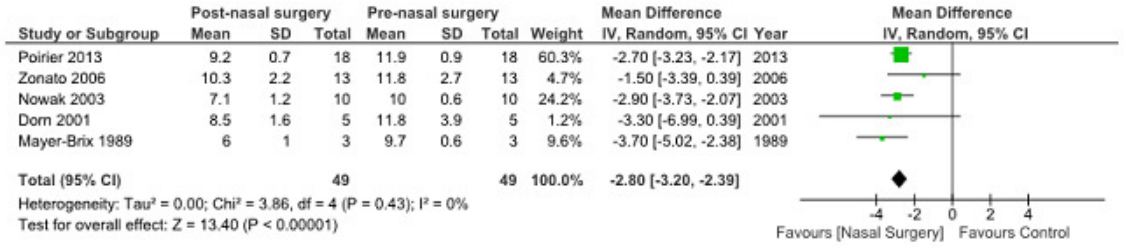

Figure 3. Subgroup analysis for studies in which continuous positive airway pressure (CPAP) was delivered by a nasal mask interface, prenasal and postnasal surgery. .

Individual patient therapeutic CPAP pressure data were reported for 20 patients, overall 85% (17 patients) decreased, 5% (one patient) remained the same, and 10% (two patients) increased their therapeutic CPAP pressures.[5,13,15]

c. Type of Nasal Surgery Performed and the Effect on Therapeutic CPAP Pressures

Data analyses were performed for the specific nasal surgery subsites: (1) septoplasty, (2) turbinoplasty, (3) septoplasty with turbinoplasty, and (4) unspecified; there were four studies[10,12,14,15] during which multiple procedures such as septoplasties, turbinoplasties, rhinoplasties, and sinus surgeries, were performed but

did not list individual patient data. Therefore the data are presented in the category of "unspecified." Overall, 2 studies reported individual patient data and the specific sub-site,[5,13] and Poirier et al.[11] performed the same procedure in all patients, and therefore could be included in individual subsite data analyses. Outcomes for the combined nasal surgery subsites are presented in Table 2.

Nasal surgery performed	*Study authors Number of patients in individual studies (N)*	*N*	*Mean CPAP pressure pre-nasal surgery (cwp)*	*Mean CPAP pressure post-nasal surgery (cwp)*	*Mean difference*	*p-value*
Septoplasty	Zonato et al.	1	10.0	8.0	-2.0 cwp	-
Turbinoplasty	Zonato et al.	8	12.4±3.3	10.2±2.5	-2.2±2.6 cwp	p-value = 0.048*
Septoplasty with turbinoplasty	Poirier et al. (N=18) Zonato et al. (N=4) Mayer-Brix et al. (N=3)	25	11.6±1.1	9.0±1.5	-2.60 cwp (CI -1.87, -3.33)	p-value <0.00001*
Unspecified**	Sufioglu et al. (N=28) Nakata et al. (N=5) Nowak et al. (N=10) Dorn et al. (N=5)	48	11.6±2.4	9.7±2.1	-1.90 cwp (CI -1.00, -2.80)	p-value = 0.0001*

Table 2. Pre and post-nasal surgery therapeutic mean CPAP pressure data stratified by nasal surgical sub-sites. Abbreviations: cwp = centimeters of water pressure; N= number of patients. *Denotes a statistically significant p-value. Note: only three studies provided individual patient data that allow sub-site analyses. **Denotes the 4 nasal surgery studies that did not report individual patient data, however, the articles reported that septoplasties, turbinoplasties, rhinoplasties and/or sinus surgeries were performed.

The largest MD was observed in the septoplasty with turbinoplasty group (25 patients), demonstrating a MD of -2.60 cwp (95% CI -3.33, -1.87); overall effect: Z score = 5.52, P < 0.00001. The MD for the remaining nasal surgery sub-sites included: (1) unspecified (48 patients), -1.90 cwp (95% CI -2.80, -1.00); overall effect: Z score = 2.99, P = 0.0001; (2) turbinoplasty (8 patients), -2.2 cwp; paired *t* test P = 0.048; and (3) septoplasty (one patient), -2.0 cwp.

d. CPAP Use After Nasal Surgery

Eleven studies (153 patients) evaluated CPAP acceptance, compliance, tolerance, adherence, or use before and after nasal surgery.[10,11,17-19,21-25] Three studies (n = 40) reported objective data from the CPAP devices themselves,[11,25,26] three studies (n = 49) reported subjective, patient self-reported use,[19,21,25] and six studies (n = 81) did not specify whether objective or subjective data was collected (Note: Powell et al. reported both objective and subjective data for all patients).[10,17,18,22-24]

The percentage of patients regularly using CPAP prior to nasal surgery was 38.7% (36 of 93 patients) and the percentage of patients who were adherent (synonymous with compliant), accepting, or tolerating CPAP after nasal surgery was 90.2% (92 of 102 patients). A subgroup analysis demonstrated that 89.1% (57 of 64 patients) who were not using CPAP prior to nasal surgery subsequently accepted, adhered to, or tolerated CPAP after nasal surgery. There were differences in the inclusion criteria between studies (i.e., six studies included patients not tolerating CPAP prior to nasal surgery,[10,11,18,22,24,26] two studies included patients already using CPAP, but with nasal obstruction present,[17,25] and three studies did not specify[19,21,23]). The

CPAP device downloaded data for prenasal surgery hours of CPAP use mean and SD were 3.0 ± 3.1 h and postnasal surgery were 5.5 ± 2.0 h. The calculated treatment effect of nasal surgery based on Powell et al.'s RCT (difference between the treatment group and placebo controls) at 1 mo was 32 min (95% CI -21, 84), P = 0.22.[25] Table 3 summarizes prenasal and postnasal surgery objective and subjective CPAP use data.

Study authors, Study Year, Follow-up duration	*# Pts*	*Pre-Nasal Surgery: # Pts regularly using CPAP*	*Post-Nasal Surgery: # Pts adherent, accepting or tolerating CPAP*	*Pre-Nasal Surgery: Objective hours of use*	*Post-Nasal Surgery: Objective hours of use*	*Pre-Nasal Surgery: Subjective hours of use*	*Post-Nasal Surgery: Subjective hours of use*	*Additional information*
Park et al.* 2014, 2 mo	7	0/7	7/7	0.0	≥4	-	-	RCS. Pressures reduced in 6 out of 7 patients.
Poirier et al.* 2013, 6 mo	16	0/16	16/16	0.5±0.73	5.0±2.37	-	-	PCS. 2 of 18 patients were cured.
Powell et al.*, 2001, 1 mo**	17	17/17	17/17	5.77±2.08	5.97±1.43	-	-	RCT. Treatment group used CPAP 32 min more at 1 mo compared to placebo controls.
Pniak et al.* 2012, 3-6 mo**	8	0/8	3/8	-	-	-	-	RCS. Improved subjective nasal patency.
Bican et al. 2010, 2.5-6.5 mo**	20	12/20	20/20	-	-	-	-	RCS. Tolerating CPAP device was easier. Mean post-op pressure: 8.5 cwp.
Nakata et al.* 2005, -**	12	0/12	12/12	-	-	-	-	RCS: Nasal resistance decreased from 0.57±0.31 to 0.16±0.03 Pa/cm³/sec (p-value <0.01).
Esteller et al.* 2004, >12 mo**	9	-	8/9	-	-	-	-	PCS. Tolerance was easier, and adherence increased (5 hours a day, 5 nights a week).
Biermann et al.* 2001, 36 mo**	39	-	-	-	-	-	6.7±1.4	RCC. Treatment group used CPAP 48 min more at 3 years compared to control group.
Hollandt et al.* 1997, 21 mo**	6	0/6	2/6	-	-	0.0	5.85±2.90	PCS. Two patients accepted PAP therapy after nasal surgery.
Ripberger et al. 1994, 18 mo**	12	-	-	-	-	-	-	PCS. Pressure decreased by an average of 5 cwp and the CPAP acceptance increased.
Series et al.* 1992, 3 mo**	7	0/7	7/7	-	-	-	-	RCS. 7 pts intolerant to CPAP due to discomfort, became tolerant after nasal surgery.
Total	153	36/93 (38.7%)	92/102 (90.2%)	3.0±3.1	5.5±2.0	-	-	57/64 pts (89.1%) not using CPAP subsequently accepted, adhered to or tolerated it after surgery.

Table 3. Data regarding pre and post-nasal surgery acceptance, adherence, tolerance, or use. Note: Poirier et al's results exclude two patients who were cured of OSA. Abbreviations: * = objective CPAP device data reported, ** = subjective, patient-reported data, *** = study did not specify if objective or subjective use data was reported, # = number, cwp = cm of water pressure, mo = months, PCS = prospective case series, Pts = patients, RCC = retrospective case-control, RCS = retrospective

5. Discussion

There are five main findings in this study. First, there is a statistically significant relationship between nasal surgery and therapeutic CPAP pressures. Poiseuille's Law has demonstrated that resistance to airflow is directly proportional to the length and is inversely proportional to the fourth-power of the radius.[47] Therefore, a 10% increase in the cross-sectional area of the nasal airway can result in an increase of 21% of nasal airflow.[25] Thus, decreasing the size of the inferior turbinates or decreasing other sources of nasal obstruction (deviated septums, septal spurs, polyps, etc.) can provide a reduction in the nasal airway resistance, and therefore may lead to a decreased therapeutic CPAP pressure. In this meta-analysis, the pooled data for 82 patients demonstrates a MD of -2.66 cwp with a range of -0.8 to -4.8 cwp. The sensitivity analysis identified the study by Sufioglu et al.[12] as the source of heterogeneity, which is possibly caused by not performing a postoperative CPAP titration in five patients who were cured of OSA (AHI < 5/h), therefore the prenasal and postnasal CPAP device pressure MD is potentially smaller (0.8 cwp) than it would have been had those cured patients undergone a postoperative CPAP titration. The remaining studies' MD decreased by at least 1.5 cwp. Additionally, the visual inspection of the funnel plot for therapeutic CPAP device pressures demonstrated that the study by Sufioglu et al.[12] was slightly outlying when compared to the remaining studies. One difference in this study compared to the others is that this study reported the use of thermistors whereas the other studies did not specify whether thermistors or nasal cannulas were used.[12] Despite this difference, a similar MD prenasal and postnasal surgery would be expected because the same technique was used within the same study group. Because of

publication bias against negative studies, it is possible that additional studies demonstrating minimal or no difference in CPAP device pressures after nasal surgery never made it to publication and therefore the study by Sufioglu et al.[12] would not be an outlier in that situation.[28]

Second, regardless of the nasal surgery subsite, there is at least a MD of -1.9 cwp between preoperative and postoperative CPAP device pressures (as outlined in Table 2). The greatest difference was seen in patients undergoing a combined septoplasty with turbinoplasty (MD of -2.6 cwp). It must be pointed out that only the study by Zonato et al.[13] reported outcomes for isolated septoplasty (one patient) and isolated turbinoplasty (eight patients). Additionally, only three of seven studies reported both preoperative and postoperative means and SD and also had individual patient data or performed the same procedure in all patients, which allowed the subsite data to be combined (34 patients). A significant limitation in the ability to subanalyze the data for the remaining four studies (48 patients) was that multiple procedures were listed in these studies, without individual patient data. Therefore, it is possible that other procedures such as endoscopic sinus surgery for nasal polyposis or a functional rhinoplasty combined with septoplasty and turbinoplasty could be as effective or more effective in reducing CPAP device pressures; however, without stratified data, these conclusions cannot be made. Given that the currently published literature reporting outcomes for individual patient data is limited, we recommend that future researchers report outcomes for individual patients stratify the data for isolated subsites (i.e. septoplasty, turbinoplasty, etc.).

Third, overall CPAP use increased after nasal surgery and was demonstrated by 11 studies (153 patients). It should be noted that the patients in these studies were motivated enough to reattempt CPAP therapy. Two issues exist: first, only three studies specified that objective device data was used, whereas the remaining eight studies either reported subjective outcomes or did not specify. Second, one of the challenges in combining the "use" data is that studies refer to "use" by different terminology, such as: acceptance, compliance, adherence, tolerance, and use. We reviewed each of the study descriptions of "use" in order to organize the results into appropriate categories. The hours of use in each study reporting it varied significantly because of the differences in the inclusion criteria between studies, which ranged from including patients not tolerating CPAP prior to nasal surgery,[10,11,18,22,24] to including patients already using CPAP, but with complaints of nasal obstruction significant enough to warrant surgery.[17,25] Despite the differences in the inclusion criteria, there was an increase in objective and subjective CPAP use after surgery and there was a progressive increase in hours of use as the duration of follow-up from nasal surgery increased. There can be significant nasal crusting and edema after nasal surgery, and the healing phase may last 2–6 w. Therefore, studies reporting on pressure reduction and hours of use, should follow patients for 3–6 mo after surgery to ensure the healing is complete and the edema has resolved, because this can affect the results of CPAP use and therapeutic CPAP device pressures.

Fourth, in order to facilitate future research, we would like to recommend standardized terminology. Regarding the term "use", studies have demonstrated that self-reported CPAP usage overestimates the actual usage by approximately 1 h when

compared to the CPAP device download data[8,48-50]; therefore, we recommend reporting the device download data as "use". The terms "adherence" and "compliance" have been used interchangeably,[3,50] and have been previously defined as "using CPAP for ≥ 4 h per night.[3,48,51]" When reporting the percentage of nights that patients are adherent, 70% is often used as a cutoff "regularly using" CPAP therapy.[48,51] The term "tolerance", as related to CPAP and nasal surgery, has been defined by the use of a visual analog scale (10 cm) with anchors 0 cm = "unable to tolerate or use" and 10 cm = "easily tolerated and use all 7 nights per week."[25] The term "acceptance", if used, should be defined by the authors reporting it to avoid ambiguity.

Fifth, there is a need for additional high-quality studies to allow for additional data analyses and to increase the power to draw more definitive conclusions. Most of the studies in this review were retrospective case series, with only five prospective case series and one randomized controlled trial. The study by Powell et al.,[25] which was very well planned, can serve as an example for future randomized, double-blind, placebo-controlled clinical trials. Two limitations with the study by Powell et al. were that only 22 patients were included, and the follow-up was short (1 mo, which is within the window of healing). When planning a study on nasal surgery and CPAP, important data to collect includes: the total number of nights of CPAP use versus nonuse, the percentage of nights with CPAP use versus nonuse, the percentage of nights with usage ≥ 4 h per night versus < 4 h per night, the average usage on nights CPAP was used and the average usage on all nights.[52] Additional important information to report includes: the 95th percentile leak, Epworth Sleepiness Scale questionnaire data,[53] the effect of treatment on quality of life, inferior turbinate sizes before and after surgery,[54] and

information on nasal obstruction, which can be assessed with the Nasal Obstruction Symptom Evaluation (NOSE) scale questionnaire.[55]

6. Conclusion

Isolated nasal surgery in patients with OSA with nasal obstruction reduces therapeutic CPAP device pressures, and the currently published literature's objective and subjective data consistently suggest that it also increases CPAP use in select patients.

8º - "TRACHEOSTOMY AS TREATMENT FOR ADULT OSA: A SYSTEMATIC REVIEW AND METRA-ANALYSIS"

MACARIO CAMACHO; VICTOR CERTAL; ROBSON CAPASSO; SCOTT BRIETZKE; JON HOLTY; CHRISTIAN GUILLEMINAULT

LARYNGOSCOPE

2013

(*cf.* Appendix 8)

II. Tracheostomy as treatment for adult OSA: a systematic review and meta-analysis

1. Introduction

In 1965, Valero et al described resolution of hypersomnia by way of tracheostomy in a patient with significant traumatic micrognathia who was observed to have apneas during a hospital admission.[1] In 1969, Kuhlo et al were the first to describe treating a Pickwickian or OSA patient (BMI of 32.7 kg/m^2), successfully with a tracheostomy.[2] Lugaresi demonstrated increased pulmonary and systemic arterial pressures during apneic events. Later, Lugaresi et al and Coccagna et al described tracheostomy in patients with hypersomnia and periodic breathing, and demonstrated complete resolution of hypersomnia and normalization of systemic and pulmonary pressures as well as blood gas values.[3,4] Since these early studies, there have been several other case reports and case series which have demonstrated the effectiveness of tracheostomies as treatment for obstructive sleep apnea (OSA).[5-17] Additional benefits of tracheostomy include improvement in control of hypertension, diabetes mellitus, hyperlipidemia and reversal of cardiac arrhythmias.[15,18,19]

Between the late 1960's to early 1980's tracheostomies were the primary surgical modality utilized to treat OSA subjects failing previous medical

management.[2,6,14,16,19] Beginning in the 1980's other surgical modalities were introduced such as uvulopalatopharyngoplasty, hypopharyngeal surgeries and maxillomandibular advancement.[20-26] Studies have reported that these newer surgical modalities (other than maxillomandibular advancement) are less effective in treating morbidly obese patients (i.e. BMI >40 kg/m^2).[27,28] Obesity and sedentary lifestyles are becoming national and worldwide pandemic.[29,30] Given the increase in obesity, traditional surgical modalities are less effective as surgical treatment options.[27] Tracheostomies are used to treat OSA patients with obesity and those who have failed other surgical modalities or in non-obese patients who are not surgical candidates for other surgical techniques.[24] Tracheostomy is perceived as a highly effective surgical option in treating OSA and associated daytime sleepiness.[6,7,9-11,13,14,16,17,19,31] Thus, we performed a systematic review and meta-analysis of tracheostomy studies to critically evaluate the effectiveness in the treatment for OSA.

2. Aims

In this section, the aims were:

- evaluate the effectiveness of tracheostomy in the treatment od OSA

- evaluate his value in obese patients

3. Methods

a. Search Strategy and selection criteria

A MEDLINE, Scopus and Cochrane search was performed (from inception to-October 2012 with an update May, 2013) with the words tracheotomy or tracheostomy

and sleep with the following search keywords and MeSH terms: obstructive sleep apnea, Pickwickian, obese, obesity, apnea index, apnea hypopnea index, oxygen desaturation index, mortality, vascular, sleepiness, hypersomnolence and Epworth Sleepiness Scale. References of all relevant articles, review articles, and relevant non-electronic literature were manually searched to identify additional relevant studies. The authors of studies not reporting sufficient data were contacted to request additional information.

Authors included adult studies of tracheostomies or tracheotomies for the treatment of OSA, with the outcomes for apnea index (AI), apnea-hypopnea index (AHI), oxygen desaturation index (ODI), mortality benefit, or effect on daytime sleepiness. English studies that evaluated these outcomes quantitatively were included. All studies that did not include the selected polysomnogram (PSG) data were excluded.

b. Data Abstraction, Study Quality Assessment, and Statistical Analysis

Two reviewers (MC and VC) independently extracted data from the included studies. The basic data included the following study characteristics: year of publication, author(s), study site, length of follow-up, sample size, body mass index (BMI) and outcomes analyzed.

Case series studies may be affected by various types of biases related to selection, detection, performance, attrition, reporting, and publication. For these reasons, we employed a quality appraisal tool from National Institute for Health and Clinical Excellence (NICE) to assess methodological quality of included case series studies. NICE includes 8-items per case series study in its quality assessment. Means and 95% confidence interval (CI) for change in post-tracheotomy outcomes compared

with pre-operative status was calculated from mean difference (after - before) and standard deviation (SD). A P-value < 0.05 was considered statistically significant. When pooling study level data, we excluded studies with less than two subjects in the calculations or with incomplete or missing pre- or post-tracheotomy data. If heterogeneity existed, data was analyzed using a random effects model. In the absence of heterogeneity, a fixed effects model was used. We graphically inspected Forest plots, and calculated the Q statistic ($p \leq 0.01$) and I^2 statistic to assess heterogeneity. A sensitivity analysis was performed by excluding each of the studies from the overall analysis one at a time to measure whether the relevant estimates were strongly influenced by any single study. The data processing and statistical analyses were performed using the Cochrane Collaboration's Review Manager Software version 4.2, and the Statistical Package for Social Sciences software (SPSS version 20.0).

4. Results

We identified 493 titles of potentially relevant articles from our computerized and manual search strategies (Figure 1). We excluded 448 articles based on our preliminary title and abstract screening. The remaining 45 articles were retrieved for full-text evaluation, and excluded an additional 30 articles which were excluded for the following reasons: 13 failed to provide complete pre or post-operative PSG data, 5 evaluated other surgical modalities (i.e. not tracheotomy) and 11 were not sleep apnea related studies. Two studies identified from our hand search were added to the review. Overall, 17 studies were included describing 286 patients with a mean age of 49.4±10.9 years (N=146), and a mean BMI of 35.5±8.5 kg/m^2 (N=91).

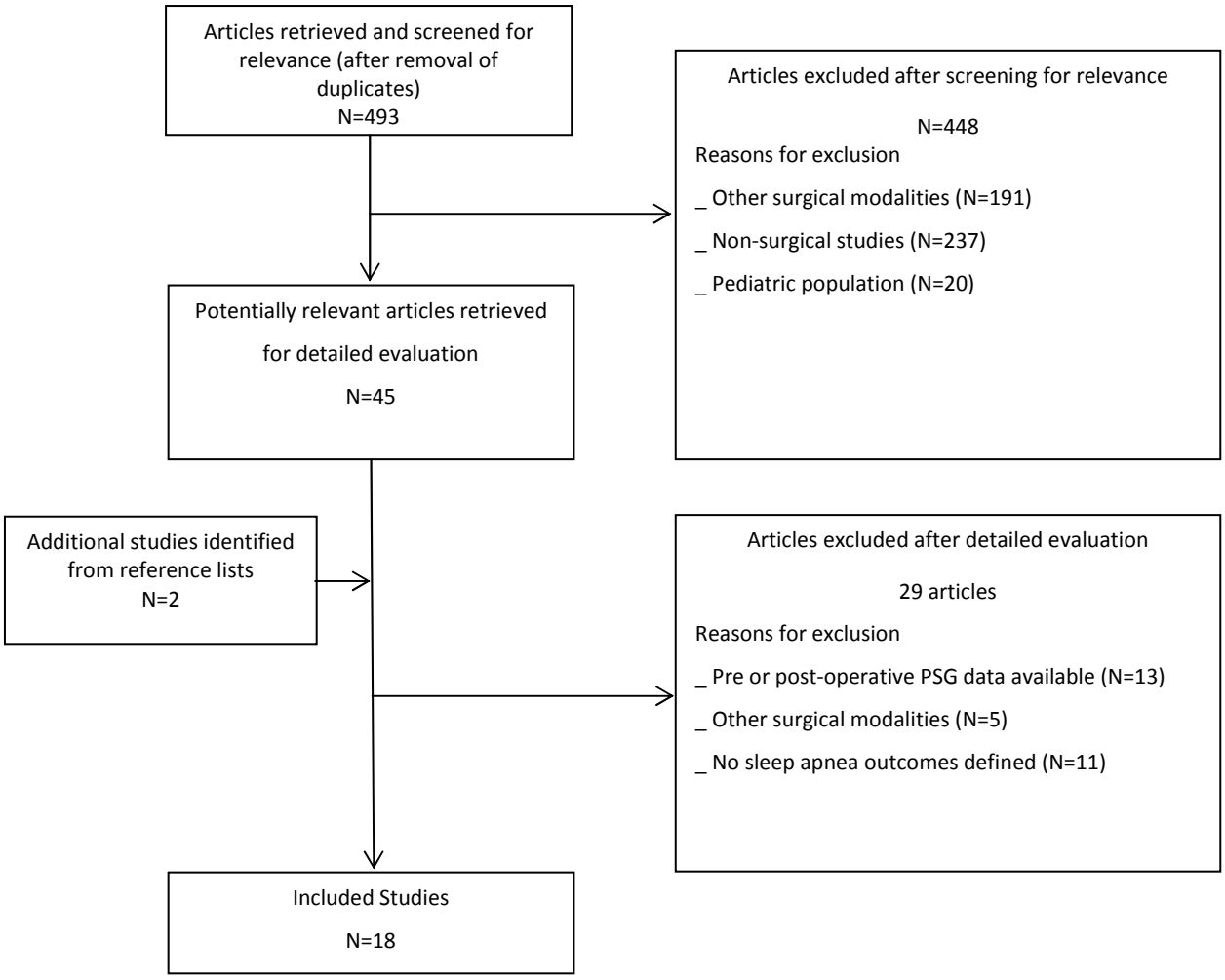

Figure 1. Literature search and selection. PSG = polysomnography.

Methodological quality of included studies

Most included studies were retrospective case series and three were case reports (Table 1). Study quality was generally poor with most included studies satisfying only 3 of the 8 items on the NICE quality assessment tool for case series studies. The primary methodological limitation of the included studies was related to the definition of inclusion and exclusion criteria, the lack of prospective design, and stratification of outcomes. No study had a multi-center design and none explicitly stated that subjects were recruited consecutively. Methodological quality appraisal was not performed for the case report studies.

Table 1. General characteristics and quality criteria of included studies

	General Characteristics					*Quality assessment of included studies**							
Author, Year	**Study site**	**N**	**Follow-up**	**BMI**	**Outcomes analyzed**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**
Kumar et al., 2013[17]	USA	1	3 mos	40	AI, AHI, EDS, O_2 sat, ODI, $tcCO_2$	NA	NA	NA	NA	NA	NA	NA	NA
Browaldh et al., 2009[32]	Sweden	10	5 yrs	31 to 50	Clinical outcomes, EDS, ODI	No	Yes	Yes	Yes	No	No	Yes	Yes
Haapaniemi et al., 2001[7]	Finland	7	2.5-9 yrs	34 to 60	O_2 sat, quality of life	No	Yes	No	Yes	No	No	Yes	Yes
Kim et al., 1998[31]	USA	28	NA	N.R.	ABG data, AHI, O_2 sat	No	Yes	No	Yes	No	No	Yes	Yes
Fletcher, 1989[9]	USA	1	4 yrs	NR	AI, hemo. parameters	NA	NA	NA	NA	NA	NA	NA	NA
Hastie et al, 1989[18]	England	1	6 mos	46.7	AI, AHI, CV, hemo. Parameters, O_2 sat	NA	NA	NA	NA	NA	NA	NA	NA
He et al., 1988[8]	USA	33	8 yrs	33.6+/-8.5	AI, mortality	No	Yes	No	Yes	No	No	Yes	Yes
Ledereich et al., 1988[33]	USA	30	5 yrs	34.6+/-8.4	EDS, snoring	No	Yes	No	Yes	Yes	No	Yes	No
Fletcher et al., 1987[10]	USA	13	6-12 mos	NR	AI, BP, urinary catecholamines	No	Yes	No	Yes	Yes	No	Yes	No
Rapoport et al., 1986[13]	USA	7	16-60 mos	NR	ABG values, AI, O_2 sat	No	Yes	No	Yes	Yes	No	Yes	No
Fletcher et al, 1985[34]	USA	10	2-26 mos	NR	ABG values, AI, O_2 sat, PF	No	Yes	No	Yes	No	No	Yes	Yes
Partinen et al., 1982[12]	USA	71	5-7 yrs	34+/-7.7	Mortality	No	Yes	Yes	Yes	Yes	No	Yes	Yes
Guilleminault et al., 1982[5]	USA	5	12-24 wks	NR	AI, O_2 sat, PF	No	Yes	No	Yes	Yes	No	Yes	Yes
Guilleminault et al., 1981[6]	USA	50	0.75-6 yrs	NR	AI, hemo. parameters	No	Yes	No	Yes	No	No	Yes	Yes
Sugita et al., 1980[14]	Japan	2	4 and 6 yrs	20.9 21.7	Respiration, sleep disturbances, EDS	No	No	No	No	No	No	Yes	No
Weitzman et al., 1980[16]	USA	10	2-3 yrs	NR	Apnea, sleep patterns	No	Yes	No	Yes	Yes	No	Yes	Yes
Weitzman et al., 1978[19]	USA	1	15 days	NR	AI, hemo. parameters	NA	NA	NA	NA	NA	NA	NA	NA
Motta et al., 1978[11]	USA	6	1-16 mos	NR	Hemo. parameters, O_2 tension	No	Yes	No	Yes	Yes	No	Yes	Yes

Polysomnography results:

Apnea Index (AI), Apnea-Hypopnea Index (AHI) and Oxygen Desaturation Index (ODI):

Obstructive apnea index:

Eight of nine studies (37 subjects) reported a reduction in the obstructive AI post tracheostomy with a pooled post-operative AI of 0.5±2.7events/h ($p<0.001$; **Tables 2** and **3**). Pooled random effects analysis demonstrated a statistically significant improvement in AI (mean difference (MD), -78.35; 95% CI, -63.15 to -93.56; $p< 0.0001$). The Q ($p<0.01$) and I^2 (86%) statistics from the random effects model suggested statistically significant heterogeneity existed in AI between studies, although all included studies in this analysis showed a clinically significant AI improvement after tracheotomy. To evaluate the stability of the estimated effect sizes, we conducted a sensitivity analysis by removing each study sequentially and then evaluating the associations in the remaining data. The overall estimates ranged from -83.64 (95% CI: -106.37, -62.13) to -71.86 (95% CI: -84.76, -58.95) (data not shown). The results did not change significantly when we omitted any single study from the overall analysis.

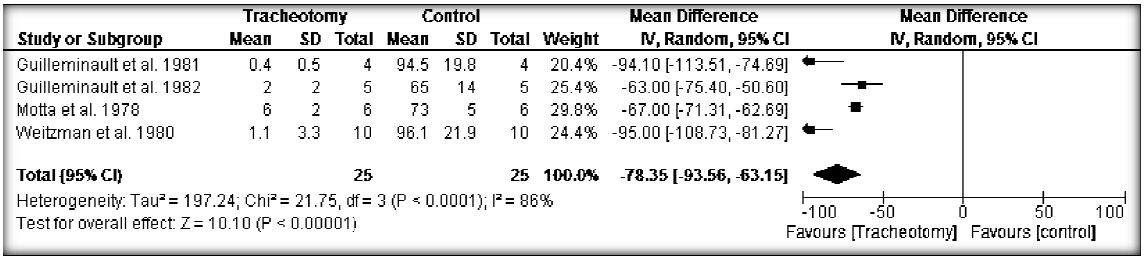

Table 3. The pooled analysis of random effects showed a statistically significant improvement in apnea index (mean difference, -78.35; 95% CI, -63.15 to -93.56; p< 0.0001).

Table 2. Obstructive apnea indices pre and post-tracheostomy.
*Note the significant decrease in obstructive apnea index, p<0.0001.
Abbreviations: N = Number of patients, b = BMI = Body mass index (kg/m²), - Denotes that the information was not available from the study.

Study year	*Study authors*	*N*	*Mean Age*	*Mean BMI[b]*	*Follow-up in months*	*Pre-Trach Total Apnea Index*	*Post-Trach Obstructive Apnea Index*
2013	Kumar et al[17]	1	27	40	1.0	0.0	0.0
1990	Partinen et al[12,35]	71	48.8±11	34±7.7	≤1.0	69±23	0.0
1989	Fletcher[9]	1	-	-	51.0	114.0	0.0
1989	Hastie[18]	1	32	46.7	6.3	25.3	1.1
1987	Fletcher[10]	8	55.4±6.8	-	9.0±3.2	84.6±38.7	0.0
1985	Fletcher[34]	11	56.5±7.4	-	(2-26)	69.6±36.1	0.0
1982	Guilleminault[5]	5	45.8	27.7	3.0+	65±14	2.0±2.0
1981	Guilleminault[6]	4	-	-	30.0±6.9	94.5±19.8	0.4±0.5
1980	Sugita[14]	1	40	20.9	3.0	77.0	0.0
1980	Weitzman[16]	10	47.5±2.4	-	0.3±0.4	96.1±21.9	1.1±3.3
1978	Motta[11]	6	47.0±4.0	-	7.5±6.3	73.0±12.2	0.0
1978	Weitzman[19]	1	67	-	0.5	96.7	4.1
Total		*120*	*49.4±10.1*	*34.0±7.8*	*9.1±12.4*	*73.0±27.1*	*0.2±1.2*

Central apnea index

Guilleminault et al's 1982 case series (5 patients) reported central apneas of 30/h at 2-3 days, 45/h at 2-3 weeks, 10/h at 12-14 weeks and 0.8±0.4h at 16-24 weeks.[5] Most of the studies reporting central apnea indices demonstrated increased indices initially for several weeks, with subsequent significantly decreased indices, and all published studies demonstrated a mean central apnea indices ≤4/h after 14 weeks, with a mean of 2±3.2/h.[5,9-11] Table 4 demonstrates the data for pre-tracheostomy total AI, pre-tracheostomy central AI and post-tracheostomy central AI (listed by post-operative follow-up duration).

Study Year	*Study authors*	*N*[a]	*Mean Age*	*Pre-Trach Total AI*	*Post-Trach Central AI <1 week*	*Post-Trach Central AI 1-4 weeks*	*Post-Trach Central AI >4-14 weeks*	*Post-Trach Central AI >14 weeks*
2013	Kumar et al[17]	1	27	0.0	-	5.4	0.7	-
1989	Fletcher[9]	1	-	114.0	0.0	0.0	-	0
1989	Hastie[18]	1	32	25.3	-	-	-	0
1987	Fletcher[10]	8	55.4±6.8	84.6±38.7	-	-	-	≤3.0*
1982	Guilleminault[5]	5	45.8	65±14	30	45	10	0.8±0.4
1980	Sugita[14]	1	40	77.0	-	-	0.0	-
1980	Weitzman[16]	10	47.5±2.4	96.1±21.9	7.1±6.9 (N=9)	-	27.3 (N=1)	-
1978	Motta[11]	6	47.0±4.0	73.0±12.2	-	8.5±2.1 (N=2)	-	4±4.7 (N=4)
Total		*33*	*48.1±8.0*	*80.1±29.3*	-	-	-	*2.1±3.5***

Table 4. Central apnea indices post-tracheostomy, categorized by time intervals.
Abbreviations: a = N = Number of patients, - Denotes that the information was not available from the study,
*Calculation excludes Fletcher's 1987 case series as it did not give a mean or SD, the article stated "no subject had >3 central apneas/h."

Apnea-Hypopnea Index:

Four studies reported apnea hypopnea indices which were sub-categorized into NREM sleep, REM sleep and/or total AHI.[13,16,17,31] The pooled post-operative mean AHI was 17.3 ±20.5 events/h which is an improvement from a preoperative AHI of 92.0 ±34.8 events/h (**Table 5**). Pooled random effects analysis demonstrated a statistically

significant improvement in AHI (mean difference, -79.82; 95% CI, -63.74 to -95.90; p< 0.0001) compared with pre-operative values. We were unable to assess heterogeneity with respect to AHI given that only two case studies reported any given parameter.

Apnea-Hypopnea Index (AHI) Pre and Post-Tracheostomy

Year	*Study Authors*	*N*[a]	*Mean Age*	*Follow-up in mo.*	*Pre-Trach AHI during NREM*[b]	*Post-Trach AHI during NREM*[b]	*Pre-Trach AHI during REM*[c]	*Post-Trach AHI during REM*[c]	*Pre-Trach Total AHI*	*Post-Trach Total AHI*
2013	Kumar et al[17]	1	27	1	35.1	35.5	57.1	36.3	39.6	35.7
1998	Kim et al[31]	23	47.0±12.4	-	92.5±39.0	19.8±26.3	58.5±34.1	26.0±31.2	-	-
1986	Rapoport et al[13]	7	56.0±8.0	-	-	-	-	-	74.3±36.6	3.6±5.6
1980	Weitzman et al[16]	10	47.5±2.4	0.3±0.4	113.7±23.0	25.8±25.4	79.0±18.6	26.5±25.2	109.6±22.4	25±22.9
Total		*41*	*48.2*±10.9	*0.4±0.5*	*97.0*±37.1	*22.0±25.5*	*64.5±40.0*	*26.5±28.7*	*92.0±34.8*	*17.3±20.5*

Table 5. Apnea-hypopnea index pre and post-tracheostomy with a mean difference, -79.82; 95% CI, -63.74 to -95.90; p< 0.0001. Note: Although there was a statistically significant decrease in the patient's apnea-hypopnea index, most subjects had residual hypopneas after the tracheostomy.
Abbreviations: a = N = Number of patients, b = NREM = Non-rapid eye movement sleep, c = REM = Rapid eye movement sleep, - Denotes that the information was not available from the study.

Oxygen Desaturation Index (ODI) Pre and Post-Tracheostomy:

The pre-tracheostomy 4% oxygen desaturation index (ODI) of 78.2 ±25.8 events/h was reduced to 20.8 ±25.5 events/h postoperatively (**Table 6**). The effectiveness of tracheostomy in improving ODI was found to be associated with a preoperative BMI less than 45 kg/m^2 (p=0.16, **Figure 2**). In subjects with a preoperative BMI <45 kg/m^2, the mean ODI went from 87.7 events/h preoperatively to 8.4 events/h post-tracheostomy. The post-operative BMI was not listed in the studies as related to the ODIs. Given the limited number of included studies reporting pre and post-surgery ODI, pooled random-effect analysis was not performed. The transcutaneous carbon dioxide was reported in Kumar et al's study which demonstrated that the patient had obesity

hypoventilation syndrome as a co-morbidity, and required post-tracheostomy average volume assured pressured support to normalize his AHI.

Year of Study	*Study authors*	*N[a]*	*Mean Age*	*Mean BMI[b]*	*Follow-up in months*	*Pre-Trach ODI[c]*	*Post-Trach ODI[c]*
2013	Kumar et al[17]	1	27	40	1	33.0	34.4
2009	Browaldh et al[32]	10	53.2±13.5	38.8±6.3	5.6±6.3	82.7±22.1	24.5±31.7
2001	Haapaniemi et al[7]	7	53.4±9.8	46.0±9.7	60.9±30.7	-	14.2*±16.9*
Total		*18*	*51.8±13.0*	*41.7±8.2*	*26.8±33.7*	*78.2±25.8*	*20.8±25.5*

Table 6: Oxygen Desaturation Index Pre and Post-Tracheostomy.
Abbreviations: a = N = Number of patients; b = BMI = Body mass index (kg/m²); c = ODI = Oxygen desaturation index; - Denotes that the information was not available from the study

Mortality:

Two studies compared outcomes for tracheostomy, one compared it to medical management (7-year follow-up) and the other to CPAP (8-year follow-up).[8,12,35] Partinen et al retrospectively evaluated 198 OSA subjects between 1972 and 1980 who underwent tracheostomy (N=71) compared with a historical control group (conservative measures such as weight loss, N=127).[12] Mortality in the tracheostomy group (2.8%) vs. the conservatively treated group (17.3%) was statistically significant with respect to vascular death ($p<0.031$) and total number of deaths ($p<0.006$).[12,35] The follow-up study at 7-years demonstrated The conservatively treated group had a lower mean preoperatively AI of 43 events/h and a lower mean BMI of 31 kg/m^2 compared with 69 events/h ($p<0.001$) and 34 kg/m^2 ($p=0.011$) for the surgical group. There was [12]

He et al performed a retrospective chart review of 385 adult male OSA subjects (AI ≥20/h) treated with either tracheostomy (N=33), CPAP (N=25), uvulopalatopharyngoplasty (N=60) or no therapy (N=104). Mortality was assessed by mailed questionnaire (324 of 709 did not return).[8] Overall mortality at eight years was 10.6% for those receiving no therapy compared with 0% in those treated with

tracheostomy (p=0.051) and the unadjusted five-year survival rate was 0.87 in tracheostomy treated subjects compared to untreated (p<0.01).[8] Pooled random effects analysis revealed a statistically and clinically significant reduction in mortality between those treated with tracheostomy (1.7%) compared with untreated OSA subjects (13.8%, p=0.019; risk difference -11.8%, CI -8.2 to -15.3%).

Sleepiness:

Four studies evaluated daytime sleepiness post-tracheostomy.[7,17,32,33] Ledereich et al, reported that 24% of post-tracheostomy OSA subjects reported excessive daytime sleepiness compared with 59% in the control group (p<0.01).[33] Only 3% of the tracheostomy group vs. 46% of the control group answered that they were either 'more than' or 'just as' sleepy compared to sleepiness prior to the treatment (p<0.001).[33]

Haapaniemi et al, utilized a questionnaire in six patients regarding the impact of the tracheostomy on several aspects of general health, sleep quality or depression.[7] Outcomes were assessed by a Likert scale defined as 1 = much poorer, 2 = poorer, 3 = similar, 4 = better and 5 = much better. Five patients answered the question on the effect of the tracheostomy on daytime sleepiness with a mean response of 3.6 suggesting an overall improvement compared to pre-tracheostomy.[7]

Browaldh et al, evaluated ten subjects (mean age of 53.2±13.6 years old, mean BMI of 38.8±6.3 kg/m²) with a mean pre-tracheostomy Epworth Sleepiness Scale (ESS) of 16.8±5.1 and a mean post-tracheostomy ESS of 4.0±2.8.[32] Kumar et al, reported a single patient with an ESS of 22 pre-tracheostomy and ESS of 5 post-tracheostomy.[17]

Table 7 includes all studies (N=4) that assessed sleepiness quantitatively. Regardless of the system utilized to assess the post-tracheostomy sleepiness outcomes, most subjects reported decreased sleepiness post-tracheostomy.

Table 7: Combined Sleepiness Outcome Table Pre and Post-Tracheostomy. In all cases, patient demonstrated decreased sleepiness.
a = N = Number of patients
b = Epworth Sleepiness Scale (0-24), 10 denotes excessive daytime sleepiness warranting further evaluation
c = Grading Scale by Haapaniemi et al, 1 to 5 scale (1=much poorer, 2=poorer, 3=similar, 4=better and 5=much better)
d = Ledereich et al, when asked, "Do you have debilitating, uncontrollable or excessive daytime sleepiness?" 24% of the tracheostomy group responded yes, therefore, 76% of patients post-tracheostomy are without excessive daytime sleepiness.

Year of Study	*Study authors*	*N*[a]	*Follow-up in months*	*Pre-Trach ESS*[b]	*Post-Trach ESS*	*Grading scale 1-5*[c]	*Post-Trach Without Excessive Sleepiness*[d]
2013	Kumar et al[17]	1	1	22	5	-	-
2009	Browaldh et al[32]	10	5.6±6.3	16.8±5.1	4.0±2.8	-	-
2001	Haapaniemi et al[7]	7	60.9±30.7	-	-	3.6±1.1	-
1988	Ledereich et al[33]	30	79.3±8.9	-	-	-	76%
Total		48	59.6±33.4	17.3±5.1	4.1±2.7	3.6±1.1	76%

5. Discussion

This systematic review and meta-analysis of 16 studies of tracheostomy for the treatment of OSA reveals three key findings. First, tracheostomies appear highly effective with a clinically and statistically significant decrease in the observed mean AI from 74.8±39.6 events/h to 0.7±2.0/h for obstructive events post-surgery. Post-tracheostomy, there was a development of central apneas, however, the central AI demonstrated near normalization after 14 weeks to a mean of 2±3.2/h. Hypopneas may persist or even increase (in some patients) post-tracheostomy with the mean AHI decreasing from 92.0±34.8 events/h to 17.3 ±20.5 events/h. Similarly, the ODI decreased from 78.2±25.8/h to 20.8±25.5/h. Second, despite a residual mean AHI and ODI, the overall postoperative observed mortality appears improved compared with historical untreated OSA subjects with a benefit similar to CPAP.[8] Finally, subjective sleepiness improves after tracheostomy with a mean decrease in the ESS from 17.3±5.1 to 4.1±2.7 (normal ESS <11).[17,32]

Despite the effectiveness of tracheostomy in treating OSA, it is usually a surgery of last resort. Reasons for patient and physician reluctance to pursue or perform a tracheostomy include: inability to swim, unsightly appearance, frequent coughing up of mucous, formation of granulation tissue, mucous plugging of the tracheostomy tube, aspiration, pneumonia, vocal cord paralysis and tracheoinnominate fistula.[7,36]

Ideal tracheostomy candidates are patients who have failed medical management, are not candidates for soft tissue surgery, and refuse a maxillomandibular advancement surgery. Patients who undergo a tracheostomy, should undergo post-operative polysomnography (with CO_2 monitoring as appropriate)

to assess surgical effectiveness, as some patients may have post-operative central apneas, hypopneas, and/or obesity hypoventilation syndrome that could warrant positive airway pressure therapy through the tracheostomy.[6,7,9,17]

Limitations

This systematic review has several potential limitations primarily due to the inclusion of case reports (level 5 evidence) and case series (level 4 evidence) limited to the English language literature with poor methodological quality, which is common to systematic reviews. Further studies with higher methodological quality are needed to better quantify AI, AHI, ODI, mortality benefit and sleepiness benefit as well as other outcomes after tracheostomies for the treatment of OSA.

6. Conclusion

Tracheostomies significantly decrease apnea index, oxygen desaturation index, sleepiness and mortality in OSA subjects.

8º - "MAXILLOMANDIBULAR ADVANCEMENT TO TREAT OBSTRUCTIVE SLEEP APNEA: A META-ANALYSIS OF 521 INDIVIDUAL PATIENTS"

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JAMA – OTOLARYNGOLOGY HEAD AND NECK SURGERY

SUBMITTED EN MAY 2015

(*cf*. Appendix 9)

III. Maxillomandibular Advancement to Treat Obstructive Sleep Apnea: A Meta-Analysis of 521 Individual Patients

1. Introduction

Maxillomandibular advancement (MMA) is a highly effective surgical option in the treatment of obstructive sleep apnea (OSA) that hasemerged as a promising alternative for patients who have difficulty tolerating continuous positive airway pressure (CPAP) and have been refractory to other surgical modalities (Li, 2003). MMA achieves enlargement of the nasopharyngeal, retropalatal, and hypopharyngeal airway by physically expanding the facial skeletal framework,which places tension on the soft tissue, thereby increasing measurements in both themedial-lateral dimensions and anteroposterior dimensions. Advancements of the maxilla and mandible by approximately 10 mm via Le Fort I maxillary and sagittal split mandibular osteotomies induces significant increases in the total airway volume and the transverse dimensions of all airway subsites (Gokce et al., 2014, Hsieh et al., 2014). A previous meta-analysis of 22 studies by Holty and Guilleminault from 1985-2009 described MMA for OSA and demonstrated a mean AHI decrease from 63.9/h to 9.5/h with a pooled surgical success rate of 86.0% and OSA cure rate of 43.2% using study-level data (Holty and Guilleminault, 2010). Despite a large number of studies reporting outcomes data on the cohort level, baseline individual parameters that might be predictive of surgical success

or OSA cure by MMA remain to be elucidated. Individual studies reported in the literature have been limited in this respect due tosmall sample sizes insufficient for multivariate analysis.

2. Aims

- To provide a 5-year update to a prior meta-analysis
- to use individual patient-level data for multivariate analysis to assess whether there are any baseline pre-operative (pre-op) factors that might be predictive of post-operative (post-op) AHI and RDI outcomes, surgical success, and/or OSA cure.

3. Methods

Three co-authors (M.C., V.C. and J.A.) independently performed a literature search to identify potentially relevant studies viasearch of MEDLINE, Scopus, Web of Science and the Cochrane Library. The authors came to a consensus as to which studies met the inclusion criteria and submitted these to the first author (S.Z.) who then independently reviewed each article to ensure that they did in fact meet the inclusion and exclusion criteria.

Search Strategy: The Cochrane Library, Scopus, Web of Science, and PubMed were searched through November 1, 2014. MeSH, keywords and phrases searched included: “maxillomandibular advancement,” “orthognathic surgery,” “maxillary osteotomy,” “mandibular advancement,” “sleep apnea,” “surgical,” “surgery,” “sleep apnea syndrome,” and “obstructive sleep apnea”. One example of a search performed on MEDLINE is: ((("Mandibular advancement"[MeSH]) AND "Sleep Apnea

Syndromes"[MeSH]) OR (("Orthognathic Surgery"[MeSH]) AND "Sleep Apnea Syndromes"[MeSH]) OR (("Maxillary osteotomy"[MeSH]) AND "Sleep Apnea Syndromes"[MeSH]) OR ("maxillomandibular advancement" AND "sleep apnea")). Study inclusion criteria included: 1) Adult patients (age>18 years) who underwent maxillomandibular advancement with or without separate osteotomies for advancement of the genial turbercle as treatment for OSA, 2) reporting of both pre-operative and postoperative quantitative outcomes for either the apnea-hypopnea index (AHI) and/or respiratory disturbance index (RDI), (3) individual patient data needed to be reported, 4) all languages were included. Exclusion criteria: Patients who underwent adjunctive procedures at the time of MMA (including tonsillectomy, uvulopalatopharyngoplasty, septoplasty, turbinate reduction, partial glossectomy) were individually excluded from the analysis.

Methodological quality of included studies: 1239 MMA studies were screened for potential relevance, and 117 non-duplicated articles were downloaded for detailed evaluation. Five additional articles were added based on review of references. After reviewing the full-text versions of 122 manuscripts, a final total of 45 studies met the inclusion and exclusion criteria. One of these was a randomized control trial (Vicini et al., 2010). These are the reasons that the other articles were excluded: animal study (n=1), children (n=1), does not qualify as MMA surgery (n=5), no AHI or RDI outcomes reported (n=17), individual patient data not available (n=40), review or editorial (n=9), combined case of MMA + glossectomy (n=1), combined reports of single stage UPPP + MMA (n=3).

Data abstraction: Individual patient data from each article was abstracted into an Excel

spreadsheet. Abstracted data included: age, gender,prior OSA surgery, body mass index (BMI), apnea index (AI), apnea-hypopnea index(AHI), oxygen desaturation index (ODI), lowest oxygen saturation (SpO2 nadir), respiratory disturbance index (RDI), Epworth Sleepiness Score (ESS), posterior airway space (PAS), length of maxilla advancement, length of mandible advancement, sella-nasion-Point A angle (SNA), sella-nasion-Point B angle (SNB). All articles werereviewed at least three times to ensure accurate transposition of the data.

Statistical analysis: Meta-analysis was performed to assess for heterogeneity of the studies included and to assess the overall effect size of the MMA intervention. Heterogeneity was assessed by three methods: 1) Graphical inspection of forest plots, 2) the I2 statistic was reviewed with cutoffs being: low = 25%, moderate = 50% and high = 75%, and 3) the Cochran Q statistic was reviewed with a heterogeneity cutoff p-value ≤0.10. Funnel plots were reviewed by visual assessment as part of the evaluation for publication bias. Univariate and multivariate analyses of the individual patient data was performed to assess for pre-operative factors that could be predictive of differences in patients'outcomes. The Preferred Reporting Items for Systematic Reviews and MetaAnalysis (PRISMA) statement was followed as much aspossible throughout the article (Moher et al., 2009).

4. Results

Individual data from a total of 521 patients was extracted from 45 studies that met the inclusion criteria. The vast majority of patients were males (83.1%). The mean age was 45.5 +/-10.0 years with a mean pre-op BMI of 31.5 +/- 7.5 (mean +/-SD). Prior surgery for obstructive sleep apnea (including turbinate reduction, septoplasty, tonsillectomy,

uvulopalatopharyngoplasty, partial glossectomy, and/or genioplasty) was performed in 73.5% of patients prior to evaluation for MMA surgery.

The average pre-op ESS score was 13.5 +/- 5.2 (mean +/- SD). The mean pre-op AHI was 53.0 +/- 24.7 and the mean pre-op RDI was 66.9 +/- 26.9 (mean +/-SD). The median minimum follow up time was 6 months with a range of 2-6 months reported as the minimum follow up time by studies included in the series. Mean post-operative change in AHI and RDI scores after MMA were ΔAHI= -43.4 +/-23.9 and ΔRDI= -53.0 +/- 28.6, respectively (mean +/-SD). The average percent change in AHI and RDI scores were -78.1 +/- 2.5% and -73.9 +/- 3.9% (mean+/- SE), respectively. See Table 1 for post-operative BMI, polysomnography, and ESS outcomes, as well as for baseline and post-operative cephalometric data.

The overall combined standardized mean difference for the AHI and RDI outcomes was -1.8 +/- 1.0 (SMD +/- SD). Standardized mean difference (SMD)= ΔAHI/ SD or ΔRDI/SD. SMD is used as a summary statistic in meta-analysis when the studies all assess the same outcome but measure it in a varietyof ways (i.e., ΔAHI and ΔRDI). In this circumstance, each 1 unit SMD corresponded to a ΔAHI of 23.9 events/hr and ΔRDI of 28.6 events/hr.

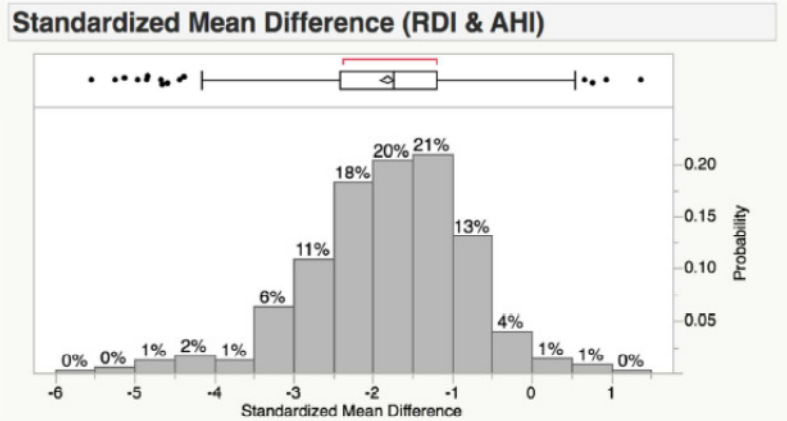
Table 1. Summary of Individual Patient Data Results

Age (Years)	N	330	Pre-Op AHI (events/hr)	N	336
	Mean	45.5		Mean	53.0
	Std Dev	10.0		Std Dev	24.7
Gender	N	339	Post-Op AHI (events/hr)	N	336
	Males	282 (83.1%)		Mean	9.57
	Females	57 (16.8%)		Std Dev	11.3
Prior Surgery for OSA	N	268	Δ AHI (events/hr)	N	336
	Yes	197 (73.5%)		Mean	-43.4
	No	71 (26.5%)		Std Dev	23.9
Pre-Op BMI (kg/m^2)	N	248	% Change AHI	N	336
	Mean	31.5	*p< 0.0001**	Mean	-78.1%
	Std Dev	7.5		Std Error	2.5%
Post-Op BMI (kg/m^2)	N	82	Pre-Op RDI (events/hr)	N	200
	Mean	32.8		Mean	66.9
	Std Dev	9.4		Std Dev	26.9
% Change BMI	N	82	Post-Op RDI (events/hr)	N	200
*p= 0.0004**	Mean	-2.6%		Mean	13.9
	Std Error	0.7%		Std Dev	15.1
Maxilla Advancement (mm)	N	218	Δ RDI (events/hr)	N	200
	Mean	9.0		Mean	-53.0
	Std Dev	1.6		Std Dev	28.6
Mandible Advancement (mm)	N	237	% Change RDI	N	330
	Mean	10.0	*p< 0.0001**	Mean	-73.9%
	Std Dev	1.8		Std Error	3.9%
Pre-Op SNA (degrees)	N	107	Standardized Mean Difference (ΔRDI & ΔAHI)	N	521
	Mean	80.0		Mean	-1.826
	Std Dev	3.9		Std Dev	0.992
Post-Op SNA (degrees)	N	107		Std Error	0.043
	Mean	84.7	Pre-Op SpO2% Nadir	N	218
	Std Dev	3.9		Mean	68.9
% Change SNA	N	107		Std Dev	15.6
*p< 0.0001**	Mean	6.1 %	Post-Op SpO2% Nadir	N	186
	Std Error	0.4%		Mean	87.0
Pre-Op SNB (degrees)	N	137		Std Dev	5.2
	Mean	74.9	Δ SpO2% Nadir	N	186
	Std Dev	4.7	*p< 0.0001**	Mean	17.0

Post-Op SNB (degrees)	N	107		Std Dev	14.7
	Mean	80.9		Std Error	1.08
	Std Dev	4.4	Pre-op ESS (0-24)	N	113
% Change SNB	N	107		Mean	13.5
*p< 0.0001**	Mean	7.9 %		Std Dev	5.2
	Std Error	0.4%	Post-op ESS (0-24)	N	111
Pre-op PAS (mm)	N	124		Mean	3.2
	Mean	5.5		Std Dev	3.1
	Std Dev	2.8	Δ ESS	N	111
Post-op PAS (mm)	N	124		Mean	-10.3
	Mean	11.5		Std Dev	6.3
	Std Dev	3.4	% Change ESS	N	110
% Change PAS	N	124	*p< 0.0001**	Mean	-72.0%
*p< 0.0001**	Mean	157.3%		Std Error	2.9%
	Std Error	13.0 %			

Table 1. Summary of Individual Patient Data Results (Continuation)

Figure 1 shows a distribution of the standardized mean difference for the 521 patients included in this study. The distribution approximates a normal curve with a mean of -1.8 and standard deviation of 1.0. The figure demonstrates that 98.8% of patients (517/521) have negative values for the SMD; a negative value represents a net decrease in the post-operative AHI or RDI outcome for each patient. This means that all but 6 patients in the series experienced at least some degree of improvement in AHI or RDI outcomes after the MMA surgery. Moreover, 81% of patients had improvements that exceeded -1.0 SMD units.



Quantiles

100.0%	maximum	1.375
99.5%		0.83605
97.5%		-0.0438
90.0%		-0.6667
75.0%	quartile	-1.2083
50.0%	median	-1.7448
25.0%	quartile	-2.4126
10.0%		-3.0392
2.5%		-4.1573
0.5%		-5.1717
0.0%	minimum	-5.5417

Summary Statistics

Mean	-1.826126
Std Dev	0.9923101
Std Err Mean	0.0434739
Upper 95% Mean	-1.74072
Lower 95% Mean	-1.911532
N	521

Figure 1. **Standardized Mean Difference (RDI and AHI).** Distribution of the standardized mean difference for the 521 patients included in this study.

The overall rate of surgical success and cure using the AHI Criteria and RDI criteria is shown in Table 2.

	Surgical Success: >50% reduction and AHI < 20/h	*>50% reduction and AHI < 15/h*	*>50% reduction and AHI < 10/h*	*Surgical Cure: >50% reduction and AHI <5/h*
Numbers	Yes: 280	Yes: 266	Yes: 218	Yes: 138
Total =336	No: 56	No: 70	No: 118	No: 198
Yes (Percent Total)	83.3%	79.1 %	64.8%	41.1%
Std Error	2.0%	2.2%	2.6%	2.7%
	Surgical Success: >50% reduction and RDI < 20/h	**>50% reduction and RDI < 15/h**	**>50% reduction and RDI < 10/h**	**Surgical Cure: >50% reduction and RDI <5/h**
Numbers	Yes:	Yes: 266	Yes: 218	Yes: 138
Total =200	No: 56	No: 70	No: 118	No: 198
Yes (Percent Total)	80.5%	73.5 %	51.0%	25.5%
Std Error	2.8%	3.1%	3.5%	3.0%

Table 2. Rates of Surgical Success and Cure After MMA: AHI and RDI Criteria**.**

Surgical success is defined as Post-Op AHI< 20/h and a >50% reduction in the AHI or Post-Op RDI< 20/h and a >50% reduction in the RDI. Surgical cure is defined as Post-Op AHI< 5/h and a >50% reduction in the AHI or PostOp RDI< 5/h and a >50% reduction in the RDI. The data are presented according to recommendations by Kezirian et al. 2011 (Kezirian et al., 2011) to include a subgroup analysis of patients who experienced a reduction ofat least 50% in the AHI to levels below 20, 15, 10, and 5 events/h. There is wide variation in terms of grading of RDI values with OSA severity, but by consensus (Epsteinet al., 2009) RDI is categorized on the same severity scale as that for the AHI: Normal: 0 to <5; Mild Sleep Apnea: 5 to <15; Moderate Sleep Apnea: 15 to <30; Severe Sleep Apnea: 30 or more. As such, we also provide subgroup analysis of patients who

experienced a reduction of at least 50% in the RDI to levels below 20, 15, 10, and 5 events/hr. Rates of surgical success in this series were 83.3 +/- 2.0% (AHI) and 80.5% +/- 2.8%(RDI). Rates of surgical cure were 41.1% +/-2.7% (AHI) and 25.5 +/- 3.0% (RDI). Univariate analysis revealed the following baseline pre-operative factors to be associated with larger ΔRDI, ΔAHI, and standardizedmean difference post-operative outcomes, respectively: pre-op BMI (higher BMI patients responded more favorably; p=0.0002*, p<0.0001*, p<0.0001*), gender (female patients responded more favorably; p=0.1595, p=0.2061, p=0.0451*), pre-op AHI (higher pre-op AHI responded more favorably, p<0.0001*, p=0.0211*, p<0.0001*), pre-opRDI (higher pre-op RDI responded more favorably, p<0.0001*, p=0.0008*, p<0.0001*), pre-op SpO2 nadir (lower pre-op SpO2 nadir responded more favorably, p=0.0827, p=0.0277*, p=0.0126*), and pre-op ESS (higher pre-op ESS responded more favorably, p=0.4741, p=0.0338*, p=0.0138*). Age, Pre-Op SNA, Pre-Op SNB, and Pre-Op Posterior Airway Space were not significantly associated with differences in post-operative effect size for ΔRDI, ΔAHI, and standardized mean difference outcomes. On multivariate analysis using Standard Least Squares- Effect Leverage Model, pre-op RDI was found to be the only significant pre-operative predictor of outcome effect-size for ΔRDI and standardized mean difference (RDI & AHI), p<0.0001 and p=0.0044. Pre-Op AHI was found to be the only significant predictor of ΔAHI, p=0.0045. There wasa direct linear correlation between pre-op AHI and ΔAHI (R2=0.79, p<0.0001), as well as for pre-op RDI and ΔRDI R2=0.72, p<0.0001). Patients with more severe pre-op AHI and RDI values experienced the greatest magnitude of reduction in the post-op AHI and RDI values. See figure 2.

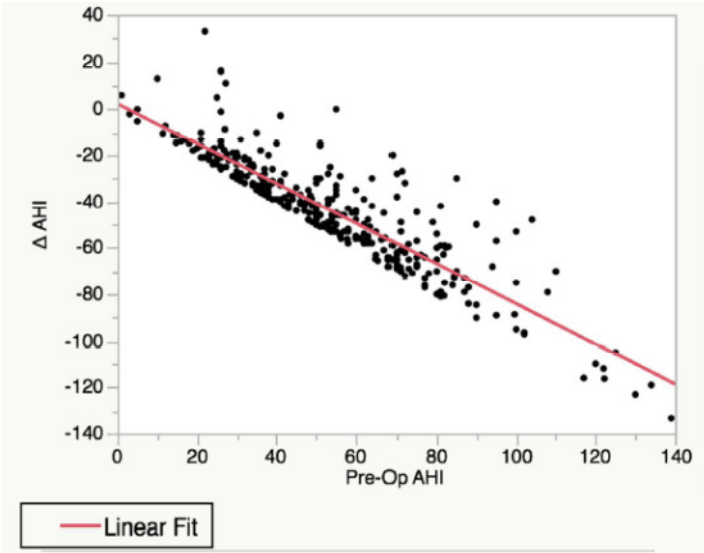


Figure 2a. Linear Fit of (a) ΔAHI by Pre-Op AHI and (b) ΔRDI by Pre-Op RDI.

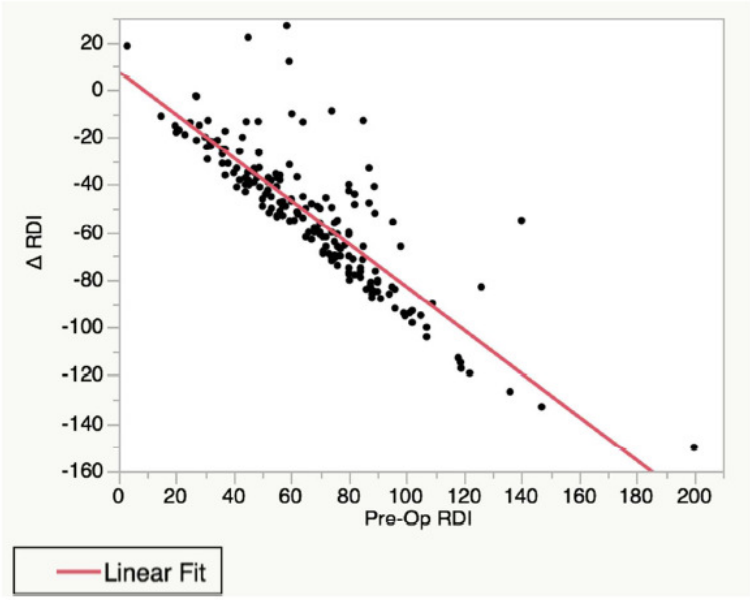


Figure 2b. Linear Fit of (a) ΔAHI by Pre-Op AHI and (b) ΔRDI by Pre-Op RDI.

With respect to baseline pre-operative factors andodds of surgical success and cure: univariate logistic fit analysis revealed that pre-op AHI was significantly associated with Success-AHI Criteria (Yes/No); lower pre-op AHI was modestly more likely to be associated with Surgical Success (Odds Ratio 0.9832+/- SE 0.006 per unit AHI, p=0.0032*). Univariate analysis revealed the following pre-operative factors to be associated with Cure with AHI Criteria (Yes/No): Age (p=0.0053*), Pre-Op AHI (p< 0.0001*), and Pre-Op ESS (p=0.0136*). Using multivariate analysis with Nominal Logistic Model, Pre-Op AHI (Odds Ratio 0.9741 +/- SE 0.007 per unit AHI, p<0.0001*) was found to be the only independent predictor for odds of surgical cure using the AHI Criteria. None of the pre-operative factors were significantly associated with odds of Surgical Success or Cure using the RDI criteria. These findings show that patients with higher AHI are at a modest clinical disadvantage with respect to their chance to achieve "surgical success" and "cure." Figure 3 demonstrates these findings graphically with a subgroup analysis of rates of surgical success or cure by AHI cohorts. Patients in the highest pre-op AHI cohort (75-139 events/hr) had the lowest rates of surgical success (66%), whereas patients with lower pre-op AHI (1-75events/hr) had higher rates of surgical success (81-95%). A similar trend is observed for rates of surgical cure.

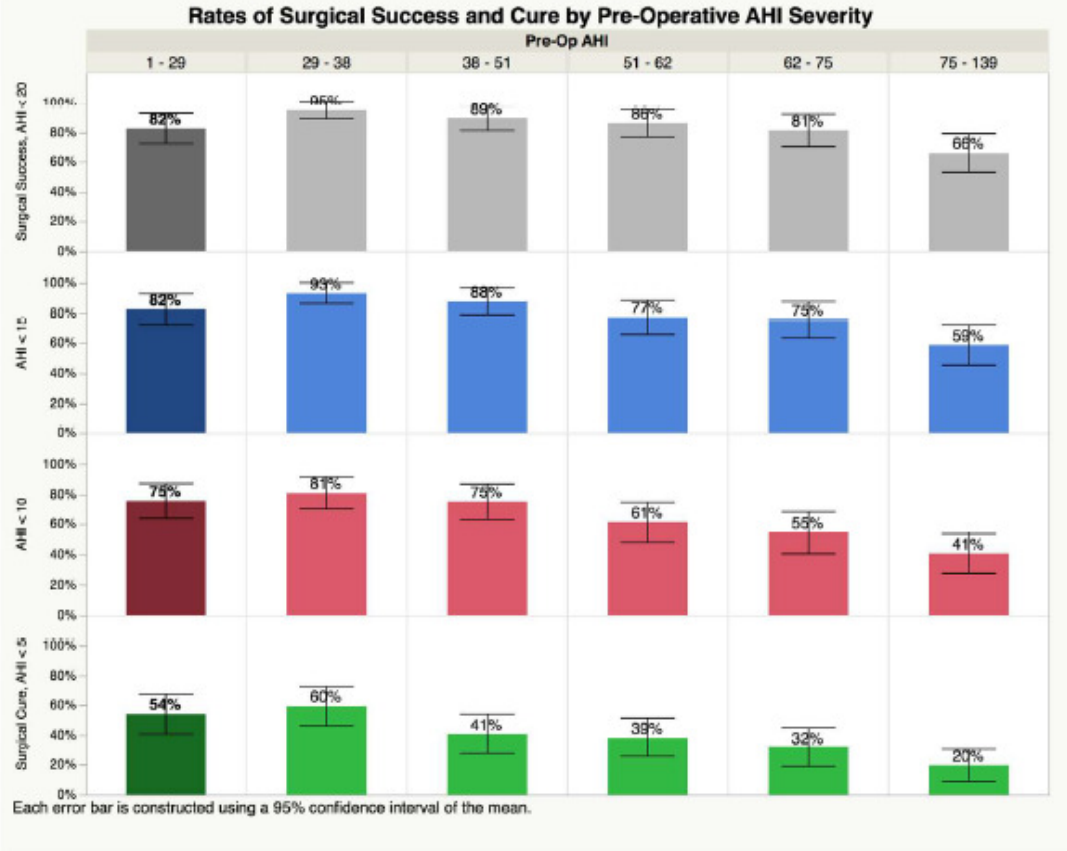


Figure 3. Rates of Surgical Success or Cure by Pre-Operative AHI Severity**.**

Among the 521 cases of MMA included in this study,174/521 (33.3%) included genial tubercle advancement at the time of MMA surgery. Cases of MMA which included UPPP, tonsillectomy, septoplasty, partial glossectomy, or other such interventions at the time of MMA surgery were not included in the data abstraction. Patients who underwent MMA + genial tubercle advancement (GTA) were significantly different from patients who underwent MMA alone only with respect to the following baseline measures on univariate analysis: Pre-op BMI (Mean +/- SE, MMA+GTA: 28.3 +/- 0.9 vs. MMA: 32.7 +/- 0.5, p<0.0001*), Pre-op SPO2 Nadir (MMA+GTA: 50.8+/-2.7 vs. MMA: 68.5 +/- 1.8, p<0.0001*), and Pre-op ESS(MMA+GTA: 14.8 +/- 0.7 vs. MMA: 12.5 +/- 0.6, p=0.0133*). There was an apparent selection bias towards lower BMI patients with more severe SpO2 Nadir and Pre-Op ESSScores to undergo MMA+GTA. MMA+GTA patients were otherwise well matched with respect to age, gender, pre-op AHI, pre-op RDI, pre-op SNA, pre-Op SNB, pre-op PAS. The two post-operative outcome measures that were significantly different between the two groups were %Change SNA (MMA+GTA: 7.1 +/- 0.4 % vs. MMA: 4.1 +/- 0.5 %, p<0.0001*) and %Change ESS (MMA+GTA: 91.5 +/- 3.8 % vs. MMA: 57.5 +/- 3.2%, p<0.0001). On multivariate analysis of pre-operative baseline andpost-operative outcomes using Standard Least Square-Effect Leverage, %Change SNAwas the only factor that remained statistically significant for a differencebetween the two groups, p=0.0241*. Because the degree of change for SNA is known to bea direct surgical consequence of the addition of GTA to the MMA procedure, and because we determined that the other differences in pre-operative differences and outcome measures were most likely due to chance random distribution as per multivariate analysis, we felt justified in combining the two interventions for all

other statistical analyses reported in this study, using change in ΔSNA as a proxy to control for the differences in MMA+GTA vs. MMA interventions.

Forest Plot for the meta-analysis of MMA studies for RDI, AHI, and Standardized Mean Difference Outcomes is shown in Figure 4.

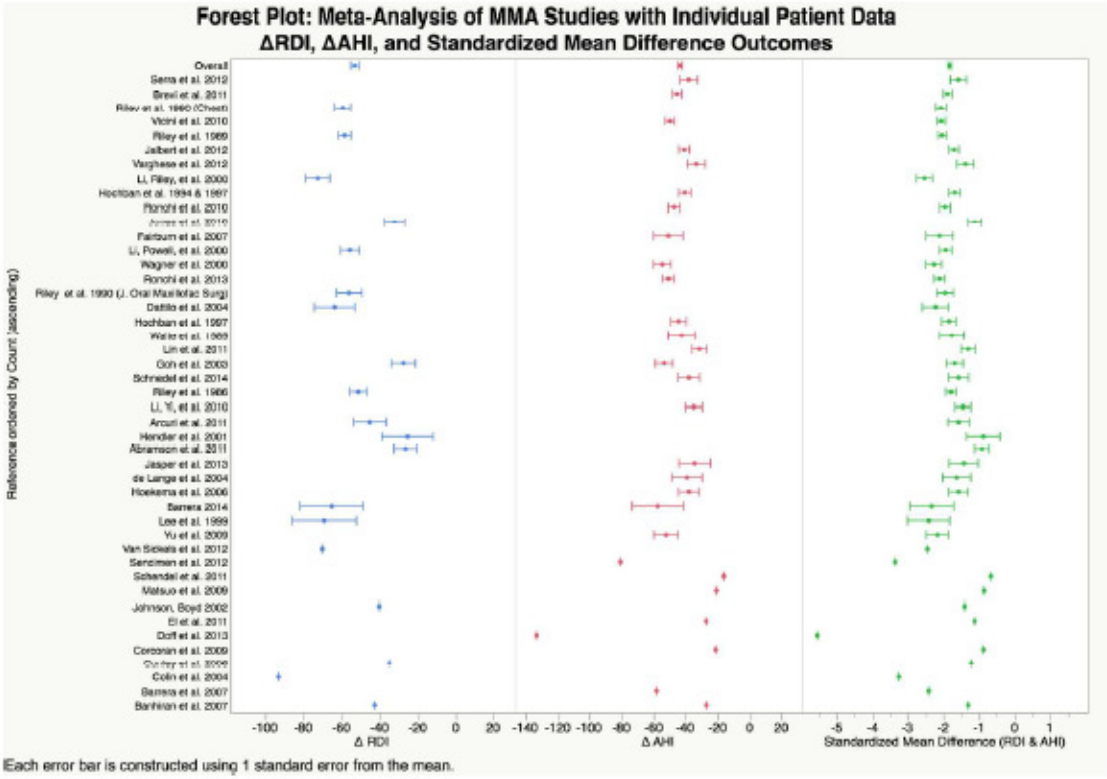


Figure 4. Forest Plot- Meta-Analysis of MMA Studies with Individual Patient Data: ΔRDI, ΔAHI, and Standardized Mean Difference Outcomes.

The figure shows a symmetric inverted funnel shape and reflects a data set for which publication bias has been minimized. There was an overall moderate level of heterogeneity among the studies included in the meta-analysis. See table 3.

	Overall Percent Success or Cure	Std Err	Cochran Q	P	DF	I^2
Success- AHI	83.3%	2.0%	78.248	<0.0001	28	64.2%
Success- RDI	80.5 %	2.8%	73.913	<0.0001	18	75.6%
Cure- AHI	41.1%	2.7%	95.347	<0.0001	28	70.6%
Cure- RDI	25.5%	3.0%	21.460	0.2569	18	16.1%

Table 3. Heterogeneity Analysis of Surgical Success and OSA Cure Rates

A random effects model was assumed to control for the moderately high level of heterogeneity among the studies included in the analysis. Appropriateness of the random effects model was confirmed via analysis of variance, which revealed a significant degree of heterogeneity between the studies for the following baseline factors: age ($p<0.0001^*$), pre-op BMI ($p<0.0001^*$), pre-op RDI ($p<0.0075^*$), pre-op AHI($p<0.0001^*$), pre-op SpO2 Nadir ($p<0.0001^*$), pre-op ESS ($p<0.0001^*$), pre-op SNA ($p<0.0006^*$), pre-op SNB ($p<0.0006^*$), pre-op PAS ($p<0.0001^*$). Graphs of "study reference" vs. each individual baseline factor was visually inspected: there were no significant outliers in the data series and as such all of the 45 studies were included in the meta-analysis.

5. Discussion

MMA is a highly effective treatment modality for OSA that is associated with substantial improvements to AHI and RDI polysomnogram outcomes. Among the 521

patients, 98.8% of patients experienced at least some degree of improvement in outcomes (2 patients had no reported change from pre-op to post-op and 4 patients had worse polysomnography outcomes post-operatively (Fairburn et al., 2007), (Serra et al., 2012) (Goh and Lim, 2003) (Jones et al., 2010) (Waite et al., 1989). The average AHI improved from 53.0 +/- 24.7 (pre-op, mean +/- SD) to 9.6 +/- 11.3 (post-op, mean +/- SD) for studies included in this meta-analysis. Similarly, the average RDI improved from 66.9 +/- 26.9 (pre-op, mean +/- SD) to 13.9 +/- 15.1 (post-op, mean +/- SD). This represents improvements of 78.1 +/- 2.5% and 73.9 +/- 3.9%, respectively for AHI and RDI outcomes (mean +/- SE). There were also significant improvements to the post-op SpO2% Nadir and ESS outcomes.

The results here are promising as they show a veryrobust response to surgical intervention by means of MMA. Indeed, MMA has been demonstrated to physically expand the pharyngeal airway (Gokce et al., 2014, Hsieh et al., 2014), so it is not surprising that the vast majority of patients wouldexperience some degree of improvement to upper airway obstruction. However, there is a wide variety in the range of reported outcomes. Post-op AHI in this series ranges from 0 to 55 events/hr and post-op RDI ranges from 0 to 85.3 events/hr.

Because some degree of improvement is nearly universal but not all patients experience a degree of improvement that is satisfactory, alternative outcomes measures have been developed to assess the efficacyof interventions for OSA- namely that of surgical success and cure. In this report, we used criteria for surgical success and cure developed by Sher et al. (Sher et al., 1996) and further advocated by Kezirian 2011 et al. (Kezirian et al., 2011) defined as >50%reduction and Post-Op AHI<20/h for

surgical success and >50% reduction and Post-Op AHI<5/h for surgical cure. If RDI was reported, > 50% RDI reduction and post-op RDI <20/hwas used as a measure of surgical success for the "RDI Criteria" and surgical cure was defined as RDI > 50% RDI reduction and post-op RDI <5/h. There is wide variation in terms of grading of RDI values with OSA severity in the literature (Hochbanet al., 1994) (Waite et al., 1989); we selected parameters that were agreed upon with the consensus by (Epstein et al., 2009) to grade RDI severity on the same scale as AHI severity. This includes: Normal: 0 to <5; Mild Sleep Apnea: 5 to <15; Moderate Sleep Apnea: 15 to <30; Severe Sleep Apnea: 30 or more.

Here we report surgical success rates of 83.3 +/- 2.0% and 80.5 +/- 2.8% (mean +/- SE; AHI and RDI, respectively) and cure rates of 41.1 +/- 2.7% and 25.0 +/- 3.0% (mean +/- SE; AHI and RDI, respectively). Our findings show that there was a direct linear relationship between pre-op AHI and pre-op RHI vs. magnitude of post-operative improvement (ΔAHI and ΔRDI). Patients with higher pre-operative OSA severity were most likely to experience the greatest magnitude ofbenefit from surgery (Figure 2). However, patients with lower pre-operative OSA severity were more likely to achieve the previously defined constructs of "surgical success" and "cure."

Holty and Guillminault performed a prior meta-analysis including twenty-two studies reporting AHI outcomes describing 627 adults undergoing MMA to treat OSA (Holty and Guilleminault, 2010). Most subjects wereobese (mean BMI 30.4 +/- 5.5 kg/m2) men (88%) with a mean age of 44.4 +/- 9.4 years-with a similar demographic to the present study. They report a significant reduction in the AHI (63.9 +/- 26.7/h vs. 9.5 +/- 10.7/h; $p < 0.001$) and improvement in the lowest nocturnal oxyhemoglobin saturation

(71.9 +/- 14.8% vs. 87.7 +/- 4.8%; p < 0.001) at a mean follow-up of 5.3 months after MMA with a surgical success rate of 86.0%. The percent of subjects with an AHI <15, <10 and <5/h after MMA was 77.6%, 63.4%and 43.2%, respectively.

Patient characteristics and clinical factors predictive of surgical success in the analysis by Holty et al. (Holty and Guilleminault, 2010) included age, preoperative BMI, and AHI. This present meta-analysis differs from the prior report by Holty et al. 2010 in that here we only considered studies that reported individual patient data. In addition, here we also included studies that report RDI without AHI data. Moreover, the prior meta-analysis did not exclude individual patients in published series who underwent adjunctive procedures at the time of MMA (septoplasty, UPPP, tongue reduction). The results of our present meta-analysis is similar to that of Holty et al 2010, except for a few notable differences. In this study, pre-op RDI and pre-op AHI were found to be the only significant pre-operative predictors of outcome effect-size for ΔRDI and ΔAHI outcomes. With our large sample of individual patient data, we were able to perform multivariate analysis to show that the other pre-operative factors previously reported to have an association with outcome (including age andBMI) were confounders dependent on AHI and RDI severity. Moreover, here we show a positive linear relationship between pre-op RDI and AHI severity vs. magnitude of post-operative improvement. Patients with higher pre-op RDI and AHI experienced the greatest magnitude of improvement, even though they did havelowest chance of conventionally defined “surgical success” and “cure” as has been previously reported by others (Riley et al., 1993) (Pirklbauer et al., 2011) (Holty and Guilleminault, 2010).

One important limitation of this meta-analysis is that we only included studies that reported individual patient data- as such, this mayhave introduced selection bias by systematically excluding studies with very large sample sizes. The following are some notable studies that did not meet the inclusion criteria due to lack of reported individual patient data: Riley et al. 1993 n= 306 (Riley et al., 1993); Prinsell et al. 1999, n=50 (Prinsell, 1999); Li et al. 2000, n=175 (Li et al.,2000a); Bettega et al. 2000 n=51; (Bettega et al., 2000). Results for these studies from centers with greater experience and sample size actually shows even higher levels of success than that which is reported here. For example, Li et al. (n=175) report a 95% overall success rate (Li et al., 2000), mean RDI 69.6 +/- 27.9 to 7.7 +/- 5.3,n= 175. Prisnell et al. report a 100% success rate, mean apnea-hypopnea index (59.2 +/- 28.4 to 4.7 +/- 5.9, respectively), n= 50. We show a moderate to high level of heterogeneity for studies included in this present meta-analysis; this reflects a broad range of experiences among different practitioners and populations with respect to use of the surgical technique. However, we were also limited by the heterogeneity in that there was inconsistency in terms of the variables reported between the studies.

MMA is a highly invasive surgical procedure with risks including pain, swelling, malocclusion, poor cosmetic result, facial numbness, tingling, jaw stiffness, postsurgical relapse of advancement. Minor hemorrhage, local infection, and extrusion of hardware has also been reported (Pirklbauer et al.,2011) (Li, 2003) (Riley et al., 2000) (Hochban et al., 1997) (Goh and Lim, 2003) (Holty and Guilleminault, 2010). Facial paresthesia due to stretching or injury to the inferior alveolar nerve is universally common (100% of patients) but has been reported to resolve in 85-90% of patients by between 6 and 12

months postoperatively (Van Sickels et al., 2002) (Li et al., 2000a). Patient perception of facial aesthetics has been generally positive after MMA; modified MMA techniques such as using counter-clockwise rotation and pre- or post-surgical orthodontics have been developed to prevent maxillary protrusion and improve facial aesthetics (Li et al., 2000b). The mean duration of surgery (from tracheostomy and intermaxillary fixation to the final imaging in operating room) according to one study was 6.0 ± 1.0 SD hours (Vicini et al., 2010). After undergoing MMA surgery, subjects require an average of 3.5 days of hospitalization. Most patients are able to return to their regular functional status within two to ten weeks after surgery (Prinsell, 1999, Bettega et al., 2000). Major complications are rare (~1%) and are associated with older age and pre-op medical comorbidity (Holty and Guilleminault, 2010). Because many OSA patients undergoing MMA are obese (mean BMI 30.2 kg/m2) with compromised airways, careful post-operative care is warranted includingpostoperative evaluation by nasopharyngolaryngoscopy. (Li et al., 2000c). To our knowledge no deaths attributable to or related to MMA have been published; however, this does not exclude the possibility that there may have been deaths during or in the immediate post-operative period.

This meta-analysis shows that MMA is a highly effective treatment for OSA. The vast majority of patients with OSA do indeed benefit from MMA (despite prior surgical treatments) and there is trend for those with the most severe measures of disease to benefit to the greatest degree; patients with less severe measures of disease demonstrate a lower degree of change in AHI or RDI post-operatively, but they conversely have a greater chance for both surgical success and cure. Future studies are

in progress to further sub-classify patients with respect to their likelihood to benefit from surgery.

6. Conclusion

MMA is a highly effective treatment for OSA. Pre-op severity of OSA disease is the most reliable predictor of outcome effect-size and likelihood of surgical success and cure among patients who underwent MMA for the treatment of OSA. Patients with high residual RDI and AHI scores (despite prior treatments by means of UPPP, partial glossectomy, and/or nasal surgery) are highly likely to benefit from management of OSA by means of maxillary mandibular advancement. Future studies will provide additional insights to help optimize patient selection for this treatment option.

References I

1. Valero A, Alroy G. Hypoventilation in Acquired Micrognathia. *Archives of internal medicine.* Mar 1965;115:307-310.

2. Kuhlo W, Doll E, Franck MC. [Successful management of Pickwickian syndrome using long-term tracheostomy]. *Deutsche medizinische Wochenschrift.* Jun 13 1969;94(24):1286-1290.

3. Coccagna G, Mantovani M, Brignani F, Parchi C, Lugaresi E. Tracheostomy in hypersomnia with periodic breathing. *Bulletin de physio-pathologie respiratoire.* Sep-Oct 1972;8(5):1217-1227.

4. Lugaresi E, Coccagna G, Mantovani M, Brignani F. [Effects of tracheotomy in hypersomnia with periodic respiration]. *Revue neurologique.* Oct 1970;123(4):267-268.

5. Guilleminault C, Cummiskey J. Progressive improvement of apnea index and ventilatory response to CO2 after tracheostomy in obstructive sleep apnea syndrome. *The American review of respiratory disease.* Jul 1982;126(1):14-20.

6. Guilleminault C, Simmons FB, Motta J, et al. Obstructive sleep apnea syndrome and tracheostomy. Long-term follow-up experience. *Archives of internal medicine.* Jul 1981;141(8):985-988.

7. Haapaniemi JJ, Laurikainen EA, Halme P, Antila J. Long-term results of tracheostomy for severe obstructive sleep apnea syndrome. *ORL; journal for oto-rhino-laryngology and its related specialties.* May-Jun 2001;63(3):131-136.

8. He J, Kryger MH, Zorick FJ, Conway W, Roth T. Mortality and apnea index in obstructive sleep apnea. Experience in 385 male patients. *Chest.* Jul 1988;94(1):9-14.

9. Fletcher EC. Recurrence of sleep apnea syndrome following tracheostomy. A shift from obstructive to central apnea. *Chest.* Jul 1989;96(1):205-209.

10. Fletcher EC, Miller J, Schaaf JW, Fletcher JG. Urinary catecholamines before and after tracheostomy in patients with obstructive sleep apnea and hypertension. *Sleep.* Feb 1987;10(1):35-44.

11. Motta J, Guilleminault C, Schroeder JS, Dement WC. Tracheostomy and hemodynamic changes in sleep-inducing apnea. *Annals of internal medicine.* Oct 1978;89(4):454-458.

12. Partinen M, Jamieson A, Guilleminault C. Long-term outcome for obstructive sleep apnea syndrome patients. Mortality. *Chest.* Dec 1988;94(6):1200-1204.

13. Rapoport DM, Garay SM, Epstein H, Goldring RM. Hypercapnia in the obstructive sleep apnea syndrome. A reevaluation of the "Pickwickian syndrome". *Chest.* May 1986;89(5):627-635.

14. Sugita Y, Wakamatsu H, Teshima Y, et al. Therapeutic effects of tracheostomy in two cases of hypersomnia with respiratory disturbance during sleep. *Folia psychiatrica et neurologica japonica.* 1980;34(1):17-25.

15. Tilkian AG, Guilleminault C, Schroeder JS, Lehrman KL, Simmons FB, Dement WC. Sleep-induced apnea syndrome. Prevalence of cardiac arrhythmias and their reversal after tracheostomy. *The American journal of medicine.* Sep 1977;63(3):348-358.

16. Weitzman ED, Kahn E, Pollak CP. Quantitative analysis of sleep and sleep apnea before and after tracheostomy in patients with the hypersomnia-sleep apnea syndrome. *Sleep.* 1980;3(3-4):407-423.

17. Kumar A, Camacho M, Capasso R. Quantitative Assessment of an Obstructive Sleep Apnea Patient Before and After Tracheostomy: A Case Study. *J Otol Rhinol.* 2013;2(2).

18. Hastie SJ, Prowse K, Perks WH, Atkins J, Blunt VA. Obstructive sleep apnoea during pregnancy requiring tracheostomy. *The Australian & New Zealand journal of obstetrics & gynaecology.* Aug 1989;29(3 Pt 2):365-367.

19. Weitzman ED, Pollack CP, Borowiecki B. Hypersomnia-sleep apnea due to micrognathia. Reversal by tracheoplasty. *Archives of neurology.* Jun 1978;35(6):392-395.

20. Fujita S, Conway W, Zorick F, Roth T. Surgical correction of anatomic azbnormalities in obstructive sleep apnea syndrome: uvulopalatopharyngoplasty. *Otolaryngology--head and neck surgery : official journal of American Academy of Otolaryngology-Head and Neck Surgery.* Nov-Dec 1981;89(6):923-934.

21. Fujita S, Conway WA, Zorick FJ, et al. Evaluation of the effectiveness of uvulopalatopharyngoplasty. *The Laryngoscope.* Jan 1985;95(1):70-74.

22. Conway W, Fujita S, Zorick F, et al. Uvulopalatopharyngoplasty. One-year followup. *Chest.* Sep 1985;88(3):385-387.

23. Zorick F, Roehrs T, Conway W, Fujita S, Wittig R, Roth T. Effects of uvulopalatopharyngoplasty on the daytime sleepiness associated with sleep apnea syndrome. *Bulletin europeen de physiopathologie respiratoire.* Nov-Dec 1983;19(6):600-603.

24. Riley RW, Powell NB, Guilleminault C. Obstructive sleep apnea syndrome: a surgical protocol for dynamic upper airway reconstruction. *Journal of oral and maxillofacial surgery : official journal of the American Association of Oral and Maxillofacial Surgeons.* Jul 1993;51(7):742-747; discussion 748-749.

25. Riley RW, Powell NB, Guilleminault C. Inferior sagittal osteotomy of the mandible with hyoid myotomy-suspension: a new procedure for obstructive sleep apnea. *Otolaryngology--head and neck surgery : official journal of American Academy of Otolaryngology-Head and Neck Surgery.* Jun 1986;94(5):589-593.

26. Powell N, Guilleminault C, Riley R, Smith L. Mandibular advancement and obstructive sleep apnea syndrome. *Bulletin europeen de physiopathologie respiratoire.* Nov-Dec 1983;19(6):607-610.

27. Friedman M, Tanyeri H, La Rosa M, et al. Clinical predictors of obstructive sleep apnea. *The Laryngoscope.* Dec 1999;109(12):1901-1907.

28. Friedman M, Ibrahim H, Joseph NJ. Staging of obstructive sleep apnea/hypopnea syndrome: a guide to appropriate treatment. *The Laryngoscope.* Mar 2004;114(3):454-459.

29. Manson JE, Skerrett PJ, Greenland P, VanItallie TB. The escalating pandemics of obesity and sedentary lifestyle. A call to action for clinicians. *Archives of internal medicine.* Feb 9 2004;164(3):249-258.

30. Swinburn BA, Sacks G, Hall KD, et al. The global obesity pandemic: shaped by global drivers and local environments. *Lancet.* Aug 27 2011;378(9793):804-814.

31. Kim SH, Eisele DW, Smith PL, Schneider H, Schwartz AR. Evaluation of patients with sleep apnea after tracheotomy. *Archives of otolaryngology--head & neck surgery.* Sep 1998;124(9):996-1000.

32. Browaldh N, Markstrom A, Friberg D. Elective tracheostomy is an alternative treatment in patients with severe obstructive sleep apnoea syndrome and CPAP failure. *Acta oto-laryngologica.* Oct 2009;129(10):1121-1126.
33. Ledereich P, Thorpy M, Lovinsky P. Five-year follow-up of daytime sleepiness and snoring after tracheotomy in patients with obstructive sleep apnea. *Chronic Rhonchopathy.* 1988:354-357.
34. Fletcher EC, Brown DL. Nocturnal oxyhemoglobin desaturation following tracheostomy for obstructive sleep apnea. *The American journal of medicine.* Jul 1985;79(1):35-42.
35. Partinen M, Guilleminault C. Daytime sleepiness and vascular morbidity at seven-year follow-up in obstructive sleep apnea patients. *Chest.* Jan 1990;97(1):27-32.
36. Engels PT, Bagshaw SM, Meier M, Brindley PG. Tracheostomy: from insertion to decannulation. *Canadian journal of surgery. Journal canadien de chirurgie.* Oct 2009;52(5):427-433.

References II

1. Sullivan CE, Issa FG, Berthon-Jones M, Eves L. Reversal of obstructive sleep apnoea by continuous positive airway pressure applied through the nares. *Lancet.* Apr 18 1981;1(8225):862-865.
2. Martinez-Garcia MA, Campos-Rodriguez F, Catalan-Serra P, et al. Cardiovascular mortality in obstructive sleep apnea in the elderly: role of long-term continuous positive airway pressure treatment: a prospective observational study. *American journal of respiratory and critical care medicine.* Nov 1 2012;186(9):909-916.
3. Weaver TE, Grunstein RR. Adherence to continuous positive airway pressure therapy: the challenge to effective treatment. *Proceedings of the American Thoracic Society.* Feb 15 2008;5(2):173-178.
4. Hoffstein V, Viner S, Mateika S, Conway J. Treatment of obstructive sleep apnea with nasal continuous positive airway pressure. Patient compliance, perception of benefits, and side effects. *The American review of respiratory disease.* Apr 1992;145(4 Pt 1):841-845.
5. Mayer-Brix J, Becker H, Peter JH. [Nasal high pressure ventilation in obstructive sleep apnea syndrome. Theoretical and practical otorhinolaryngologic aspects]. *Laryngo- rhino- otologie.* May 1989;68(5):295-298.
6. Constantinidis J, Knobber D, Steinhart H, Kuhn J, Iro H. Fine-structural investigations of the effect of nCPAP-mask application on the nasal mucosa. *Acta oto-laryngologica.* Mar 2000;120(3):432-437.
7. Brander PE, Soirinsuo M, Lohela P. Nasopharyngeal symptoms in patients with obstructive sleep apnea syndrome. Effect of nasal CPAP treatment. *Respiration; international review of thoracic diseases.* 1999;66(2):128-135.
8. Pepin JL, Leger P, Veale D, Langevin B, Robert D, Levy P. Side effects of nasal continuous positive airway pressure in sleep apnea syndrome. Study of 193 patients in two French sleep centers. *Chest.* Feb 1995;107(2):375-381.
9. Li HY, Engleman H, Hsu CY, et al. Acoustic reflection for nasal airway measurement in patients with obstructive sleep apnea-hypopnea syndrome. *Sleep.* Dec 2005;28(12):1554-1559.
10. Nakata S, Noda A, Yagi H, et al. Nasal resistance for determinant factor of nasal surgery in CPAP failure patients with obstructive sleep apnea syndrome. *Rhinology.* Dec 2005;43(4):296-299.
11. Poirier J, George C, Rotenberg B. The effect of nasal surgery on nasal continuous positive airway pressure compliance. *The Laryngoscope.* Apr 10 2013.
12. Sufioglu M, Ozmen OA, Kasapoglu F, et al. The efficacy of nasal surgery in obstructive sleep apnea syndrome: a prospective clinical study. *European archives of oto-rhino-laryngology : official journal of the European Federation of Oto-Rhino-Laryngological Societies.* Feb 2012;269(2):487-494.
13. Zonato AI, Bittencourt LR, Martinho FL, Gregorio LC, Tufik S. Upper airway surgery: the effect on nasal continuous positive airway pressure titration on obstructive sleep apnea patients. *European archives of oto-rhino-laryngology : official journal of the European Federation of Oto-Rhino-Laryngological Societies.* May 2006;263(5):481-486.

14. Nowak C, Bourgin P, Portier F, Genty E, Escourrou P, Bobin S. [Nasal obstruction and compliance to nasal positive airway pressure]. *Annales d'oto-laryngologie et de chirurgie cervico faciale : bulletin de la Societe d'oto-laryngologie des hopitaux de Paris.* Jun 2003;120(3):161-166.

15. Dorn M, Pirsig W, Verse T. [Postoperative management following rhinosurgery interventions in severe obstructive sleep apnea. A pilot study]. *Hno.* Aug 2001;49(8):642-645.

16. Friedman M, Tanyeri H, Lim JW, Landsberg R, Vaidyanathan K, Caldarelli D. Effect of improved nasal breathing on obstructive sleep apnea. *Otolaryngology--head and neck surgery : official journal of American Academy of Otolaryngology-Head and Neck Surgery.* Jan 2000;122(1):71-74.

17. Biermann E. Nasal CPAP therapy in obstructive sleep apnea syndrome: Does functional rhinosurgery improve compliance? [Nasale CPAP-therapie beim obstruktiven schlafapnoe-syndrom: Verbessert funktionelle rhinochirurgie die compliance?]. *Somnologie.* 2001;5(2):59-64.

18. Series F, St Pierre S, Carrier G. Effects of surgical correction of nasal obstruction in the treatment of obstructive sleep apnea. *The American review of respiratory disease.* Nov 1992;146(5 Pt 1):1261-1265.

19. Bican A, Kahraman A, Bora I, Kahveci R, Hakyemez B. What is the efficacy of nasal surgery in patients with obstructive sleep apnea syndrome? *The Journal of craniofacial surgery.* Nov 2010;21(6):1801-1806.

20. Balcerzak J, Niemczyk K, Arcimowicz M, Gotlib T. [The role of functional nasal surgery in the treatment of obstructive sleep apnea syndrome]. *Otolaryngologia polska. The Polish otolaryngology.* 2007;61(1):80-84.

21. Ripberger R, Pirsig W. [Nasal positive pressure ventilation (nCPAP) in therapy of obstructive sleep apnea: acceptance by 50 patients]. *Laryngo- rhino- otologie.* Nov 1994;73(11):581-585.

22. Hollandt JH, Kuhl S, Siegert R. [Therapy with nasal CPAP (continuous positive airway pressure) in patients with obstructive sleep apnea syndrome (OSAS). I: Long-term acceptance of nasal CPAP]. *Laryngo- rhino- otologie.* Sep 1997;76(9):550-553.

23. Esteller E, Matino E, Segarra F, Sanz JJ, Adema JM, Estivill E. [Adverse effects of continuous positive airway pressure therapy and its relation to the nose]. *Acta otorrinolaringologica espanola.* Jan 2004;55(1):17-22.

24. Pniak T, Matousek P, Strympl P, Novak V, Kominek P. Obstructive Sleep Apnoe and CPAP - is it Reasonable to Solve Nasal Patency? . *Cesk Slov Neurol N.* 2012;75(108):222-226.

25. Powell NB, Zonato AI, Weaver EM, et al. Radiofrequency treatment of turbinate hypertrophy in subjects using continuous positive airway pressure: a randomized, double-blind, placebo-controlled clinical pilot trial. *The Laryngoscope.* Oct 2001;111(10):1783-1790.

26. Park CY, Hong JH, Lee JH, et al. Clinical effect of surgical correction for nasal pathology on the treatment of obstructive sleep apnea syndrome. *PloS one.* 2014;9(6):e98765.

27. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ (Clinical research ed.).* Sep 6 2003;327(7414):557-560.

28. Lau J, Ioannidis JP, Schmid CH. Quantitative synthesis in systematic reviews. *Annals of internal medicine.* Nov 1 1997;127(9):820-826.

29. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS medicine.* Jul 21 2009;6(7):e1000097.

30. Stroup DF, Berlin JA, Morton SC, et al. Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group. *JAMA : the journal of the American Medical Association.* Apr 19 2000;283(15):2008-2012.

31. Lasters F, Mallegho C, Boudewyns A, et al. Nasal symptoms in patients with obstructive sleep apnea and their impact on therapeutic compliance with continuous positive airway pressure. *Acta clinica Belgica.* Apr 2014;69(2):87-91.

32. Sato K. [Continuous positive airway pressure therapy in multidisciplinary treatment]. *Nihon Jibiinkoka Gakkai kaiho.* Feb 2005;108(2):150-156.

33. Seemann R, DiToppa JC, Holm MA, Hanson J. Combination surgical and mechanical therapy for refractory cases of obstructive sleep apnea. *The Journal of otolaryngology.* Apr 2002;31(2):85-88.

34. Mortimore IL, Bradley PA, Murray JA, Douglas NJ. Uvulopalatopharyngoplasty may compromise nasal CPAP therapy in sleep apnea syndrome. *American journal of respiratory and critical care medicine.* Dec 1996;154(6 Pt 1):1759-1762.

35. Han F, Song W, Li J, Zhang L, Dong X, He Q. Influence of UPPP surgery on tolerance to subsequent continuous positive airway pressure in patients with OSAHS. *Sleep & breathing = Schlaf & Atmung.* Mar 2006;10(1):37-42.

36. Gillespie MB, Wylie PE, Lee-Chiong T, Rapoport DM. Effect of palatal implants on continuous positive airway pressure and compliance. *Otolaryngology--head and neck surgery : official journal of American Academy of Otolaryngology-Head and Neck Surgery.* Feb 2011;144(2):230-236.

37. Chandrashekariah R, Shaman Z, Auckley D. Impact of upper airway surgery on CPAP compliance in difficult-to-manage obstructive sleep apnea. *Archives of otolaryngology--head & neck surgery.* Sep 2008;134(9):926-930.

38. Bertoletti F, Indelicato A, Banfi P, Capolunghi B. Sleep apnoea/hypopnoea syndrome: combination therapy with the Pillar palatal implant technique and continuous positive airway pressure (CPAP). A preliminary report. *B-Ent.* 2009;5(4):251-257.

39. Friedman M, Soans R, Joseph N, Kakodkar S, Friedman J. The effect of multilevel upper airway surgery on continuous positive airway pressure therapy in obstructive sleep apnea/hypopnea syndrome. *The Laryngoscope.* Jan 2009;119(1):193-196.

40. Lin Z, Wang T, Fan X. [Continuous positive airway pressure therapy after uvulopalatopharygoplasty]. *Zhonghua er bi yan hou ke za zhi.* Apr 1999;34(2):100-102.

41. Masdon JL, Magnuson JS, Youngblood G. The effects of upper airway surgery for obstructive sleep apnea on nasal continuous positive airway pressure settings. *The Laryngoscope.* Feb 2004;114(2):205-207.

42. Hollandt JH, Mahlerwein M. Nasal breathing and continuous positive airway pressure (CPAP) in patients with obstructive sleep apnea (OSA). *Sleep & breathing = Schlaf & Atmung.* Jun 2003;7(2):87-94.

43. Morris LG, Setlur J, Burschtin OE, Steward DL, Jacobs JB, Lee KC. Acoustic rhinometry predicts tolerance of nasal continuous positive airway pressure: a pilot study. *American journal of rhinology.* Mar-Apr 2006;20(2):133-137.

44. Sugiura T, Noda A, Nakata S, et al. Influence of nasal resistance on initial acceptance of continuous positive airway pressure in treatment for obstructive sleep apnea syndrome. *Respiration; international review of thoracic diseases.* 2007;74(1):56-60.

45. Mayer-Brix J, Muller-Marschhausen U, Becker H, Peter JH. [How frequent are pathologic ENT findings in patients with obstructive sleep apnea syndrome?]. *Hno.* Dec 1989;37(12):511-516.

46. Katsantonis GP, Friedman WH, Krebs FJ, 3rd, Walsh JK. Nasopharyngeal complications following uvulopalatopharyngoplasty. *The Laryngoscope.* Mar 1987;97(3 Pt 1):309-314.

47. Susarla SM, Thomas RJ, Abramson ZR, Kaban LB. Biomechanics of the upper airway: Changing concepts in the pathogenesis of obstructive sleep apnea. *International journal of oral and maxillofacial surgery.* Dec 2010;39(12):1149-1159.

48. Kribbs NB, Pack AI, Kline LR, et al. Objective measurement of patterns of nasal CPAP use by patients with obstructive sleep apnea. *The American review of respiratory disease.* Apr 1993;147(4):887-895.

49. Engleman HM, Asgari-Jirhandeh N, McLeod AL, Ramsay CF, Deary IJ, Douglas NJ. Self-reported use of CPAP and benefits of CPAP therapy: a patient survey. *Chest.* Jun 1996;109(6):1470-1476.

50. Rauscher H, Formanek D, Popp W, Zwick H. Self-reported vs measured compliance with nasal CPAP for obstructive sleep apnea. *Chest.* Jun 1993;103(6):1675-1680.

51. Weaver TE, Sawyer AM. Adherence to continuous positive airway pressure treatment for obstructive sleep apnoea: implications for future interventions. *The Indian journal of medical research.* Feb 2010;131:245-258.

52. Schwab RJ, Badr SM, Epstein LJ, et al. An official American Thoracic Society statement: continuous positive airway pressure adherence tracking systems. The optimal monitoring strategies and outcome measures in adults. *American journal of respiratory and critical care medicine.* Sep 1 2013;188(5):613-620.

53. Johns MW. A new method for measuring daytime sleepiness: the Epworth sleepiness scale. *Sleep.* Dec 1991;14(6):540-545.

54. Camacho M, Zaghi S, Certal V, et al. Inferior Turbinate classification system, grades 1 to 4: Development and validation study. *The Laryngoscope.* 2014.

55. Stewart MG, Witsell DL, Smith TL, Weaver EM, Yueh B, Hannley MT. Development and validation of the Nasal Obstruction Symptom Evaluation (NOSE) scale. *Otolaryngology--head and neck surgery : official journal of American Academy of Otolaryngology-Head and Neck Surgery.* Feb 2004;130(2):157-163.

References III

1. Serra MM, Greenburg D, Barnwell M, Fallah D, Keith K, Mysliwiec V. Maxillomandibular advancement as surgical treatment for obstructive sleep apnea in active duty military personnel: a retrospective cohort. Military medicine. Nov 2012;177(11):1387-1392.
2. Brevi BC, Toma L, Pau M, Sesenna E. Counterclockwise rotation of the occlusal plane in the treatment of obstructive sleep apnea syndrome. *Journal of oral and maxillofacial surgery : official journal of the American Association of Oral and Maxillofacial Surgeons.* Mar 2011;69(3):917-923.
3. Riley RW, Powell NB, Guilleminault C. Maxillofacial surgery and nasal CPAP. A comparison of treatment for obstructive sleep apnea syndrome. *Chest.* Dec 1990;98(6):1421-1425.
4. Vicini C, Dallan I, Campanini A, et al. Surgery vs ventilation in adult severe obstructive sleep apnea syndrome. *American journal of otolaryngology.* Jan-Feb 2010;31(1):14-20.
5. Riley RW, Powell NB, Guilleminault C. Maxillofacial surgery and obstructive sleep apnea: a review of 80 patients. Otolaryngology--head and neck surgery : official journal of American Academy of Otolaryngology-Head and Neck Surgery. Sep 1989;101(3):353-361.
6. Jalbert, F., Lacassagne, L., Bessard, J., Dekeister, C., Paoli, J. R., & Tiberge, M. (2012). [Oral appliances or maxillomandibular advancement osteotomy for severe obstructive sleep apnoea in patients refusing CPAP]. Revue de stomatologie et de chirurgie maxillo-faciale, 113(1), 19-26.
7. Varghese, R., Adams, N. G., Slocumb, N. L., Viozzi, C. F., Ramar, K., & Olson, E. J. (2012). Maxillomandibular advancement in the management of obstructive sleep apnea. International journal of otolaryngology, 2012.
8. Li KK, Riley RW, Powell NB, Gervacio L, Troell RJ, Guilleminault C. Obstructive sleep apnea surgery: patient perspective and polysomnographic results. *Otolaryngology--head and neck surgery : official journal of American Academy of Otolaryngology-Head and Neck Surgery.* Nov 2000;123(5):572-575.
9. Hochban W, Brandenburg U, Peter JH. Surgical treatment of obstructive sleep apnea by maxillomandibular advancement. *Sleep.* Oct 1994;17(7):624-629.
10. Hochban W, Conradt R, Brandenburg U, Heitmann J, Peter JH. Surgical maxillofacial treatment of obstructive sleep apnea. *Plastic and reconstructive surgery.* Mar 1997;99(3):619-626; discussion 627-618.
11. Ronchi P, Novelli G, Colombo L, et al. Effectiveness of maxillo-mandibular advancement in obstructive sleep apnea patients with and without skeletal anomalies. *International journal of oral and maxillofacial surgery.* Jun 2010;39(6):541-547.
12. Jones R, Badlani J, Jones C. Maxillary, mandibular and chin advancement surgery for the treatment of obstructive sleep apnoea. *Australian dental journal.* Sep 2010;55(3):314-321.
13. Fairburn SC, Waite PD, Vilos G, et al. Three-dimensional changes in upper airways of patients with obstructive sleep apnea following maxillomandibular advancement. *Journal of oral and maxillofacial surgery : official journal of the American Association of Oral and Maxillofacial Surgeons.* Jan 2007;65(1):6-12.
14. Li KK, Powell NB, Riley RW, Zonato A, Gervacio L, Guilleminault C. Morbidly obese patients with severe obstructive sleep apnea: is airway reconstructive surgery a viable treatment option? *The Laryngoscope.* Jun 2000;110(6):982-987.
15. Wagner I, Coiffier T, Sequert C, Lachiver X, Fleury B, Chabolle F. [Surgical treatment of severe sleep apnea syndrome by maxillomandibular advancing or mental tranposition]. *Annales d'oto-laryngologie et de chirurgie cervico faciale : bulletin de la Societe d'oto-laryngologie des hopitaux de Paris.* Jun 2000;117(3):137-146.

16. Ronchi, P., Cinquini, V., Ambrosoli, A., & Caprioglio, A. (2013). Maxillomandibular advancement in obstructive sleep apnea syndrome patients: a restrospective study on the sagittal cephalometric variables. Journal of oral & maxillofacial research, 4(2).
17. Riley RW, Powell NB, Guilleminault C. Maxillary, mandibular, and hyoid advancement for treatment of obstructive sleep apnea: a review of 40 patients. *Journal of oral and maxillofacial surgery : official journal of the American Association of Oral and Maxillofacial Surgeons.* Jan 1990;48(1):20-26.
18. Dattilo, David J., and Scott A. Drooger. "Outcome assessment of patients undergoing maxillofacial procedures for the treatment of sleep apnea: comparison of subjective and objective results." Journal of oral and maxillofacial surgery 62.2 (2004): 164-168.
19. Waite PD, Wooten V, Lachner J, Guyette RF. Maxillomandibular advancement surgery in 23 patients with obstructive sleep apnea syndrome. *Journal of oral and maxillofacial surgery : official journal of the American Association of Oral and Maxillofacial Surgeons.* Dec 1989;47(12):1256-1261; discussion 1262.
20. Lin CH, Liao YF, Chen NH, Lo LJ, Chen YR. Three-dimensional computed tomography in obstructive sleep apneics treated by maxillomandibular advancement. *The Laryngoscope.* Jun 2011;121(6):1336-1347.
21. Goh YH, Lim KA. Modified maxillomandibular advancement for the treatment of obstructive sleep apnea: a preliminary report. *The Laryngoscope.* Sep 2003;113(9):1577-1582.
22. Schendel, Stephen A., Joseph A. Broujerdi, and Richard L. Jacobson. "Three-dimensional upper-airway changes with maxillomandibular advancement for obstructive sleep apnea treatment." American Journal of Orthodontics and Dentofacial Orthopedics 146.3 (2014): 385-393.
23. Riley RW, Powell NB, Guilleminault C, Nino-Murcia G. Maxillary, mandibular, and hyoid advancement: an alternative to tracheostomy in obstructive sleep apnea syndrome. *Otolaryngology--head and neck surgery : official journal of American Academy of Otolaryngology-Head and Neck Surgery.* Jun 1986;94(5):584-588.
24. Li, Y., Yi, B., Wang, X., Li, Z. L., Liang, C., & Wang, X. X. (2010). [Clinical study on modified maxillomandibular advancement for the treatment of obstructive sleep apnea syndrome]. Beijing da xue xue bao. Yi xue ban= Journal of Peking University. Health sciences, 42(5), 570-574.
25. Arcuri F, Brucoli M, Benech R, Giarda M, Benech A. Maxillomandibular advancement in obstructive sleep apnea syndrome: a surgical model to investigate reverse face lift. *The Journal of craniofacial surgery.* Nov 2011;22(6):2148-2152.
26. Hendler BH, Costello BJ, Silverstein K, Yen D, Goldberg A. A protocol for uvulopalatopharyngoplasty, mortised genioplasty, and maxillomandibular advancement in patients with obstructive sleep apnea: an analysis of 40 cases. *Journal of oral and maxillofacial surgery : official journal of the American Association of Oral and Maxillofacial Surgeons.* Aug 2001;59(8):892-897; discussion 898-899.
27. Abramson Z, Susarla SM, Lawler M, Bouchard C, Troulis M, Kaban LB. Three-dimensional computed tomographic airway analysis of patients with obstructive sleep apnea treated by maxillomandibular advancement. *Journal of oral and maxillofacial surgery : official journal of the American Association of Oral and Maxillofacial Surgeons.* Mar 2011;69(3):677-686.
28. Jaspers GW, Booij A, de Graaf J, de Lange J. Long-term results of maxillomandibular advancement surgery in patients with obstructive sleep apnoea syndrome. *The British journal of oral & maxillofacial surgery.* Apr 2013;51(3):e37-39.
29. de Lange, J., et al. "[Treatment of snoring and sleep apnea. Maxillo-mandibular advancement osteotomy]." Nederlands tijdschrift voor tandheelkunde 111.7 (2004): 287-290.
30. Hoekema A, de Lange J, Stegenga B, de Bont LG. Oral appliances and maxillomandibular advancement surgery: an alternative treatment protocol for the obstructive sleep apnea-hypopnea syndrome. *Journal of oral and maxillofacial surgery : official journal of the American Association of Oral and Maxillofacial Surgeons.* Jun 2006;64(6):886-891.
31. Barrera, Jose E. "Virtual surgical planning improves surgical outcome measures in obstructive sleep apnea surgery." The Laryngoscope 124.5 (2014): 1259-1266.
32. Lee NR, Givens CD, Jr., Wilson J, Robins RB. Staged surgical treatment of obstructive sleep apnea syndrome: a review of 35 patients. *Journal of oral and maxillofacial surgery : official journal of the American Association of Oral and Maxillofacial Surgeons.* Apr 1999;57(4):382-385.

33. Yu CC, Hsiao HD, Lee LC, et al. Computational fluid dynamic study on obstructive sleep apnea syndrome treated with maxillomandibular advancement. *The Journal of craniofacial surgery.* Mar 2009;20(2):426-430.
34. Van Sickels JE, Wallender A. Closure of anterior open bites with mandibular surgery: advantages and disadvantages of this approach. *Oral and maxillofacial surgery.* Dec 2012;16(4):361-367.
35. Sencimen, M., Bayar, G. R., Akcam, T., Altug, H. A., Altug, H., Gulses, A., & Ozkan, A. (2012). Management of Obstructive Sleep Apnea by Maxillomandibular Advancement Surgery in an Edentulous Patient. Journal of Craniofacial Surgery, 23(6), e582-e585.
36. Schendel S, Powell N, Jacobson R. Maxillary, mandibular, and chin advancement: treatment planning based on airway anatomy in obstructive sleep apnea. *Journal of oral and maxillofacial surgery : official journal of the American Association of Oral and Maxillofacial Surgeons.* Mar 2011;69(3):663-676.
37. Matsuo A, Nakai T, Toyoda J, Takahashi H, Suzuki I, Chiba H. Good esthetic results after modified maxillomandibular advancement for obstructive sleep apnea syndrome. *Sleep & Biological Rhythms.* 2009;7(1):3-10.
38. Johnson JD, Boyd, SB. Obstructive sleep apnea: a case report. The Journal of the Tennessee Dental Association 02/2002; 82(3):48-51.
39. El AS, El H, Palomo JM, Baur DA. A 3-dimensional airway analysis of an obstructive sleep apnea surgical correction with cone beam computed tomography. *Journal of oral and maxillofacial surgery : official journal of the American Association of Oral and Maxillofacial Surgeons.* Sep 2011;69(9):2424-2436.
40. Doff MH, Jansma J, Schepers RH, Hoekema A. Maxillomandibular advancement surgery as alternative to continuous positive airway pressure in morbidly severe obstructive sleep apnea: a case report. *Cranio : the journal of craniomandibular practice.* Oct 2013;31(4):246-251.
41. Corcoran S, Mysliwiec V, Niven AS, Fallah D. Development of central sleep apnea after maxillofacial surgery for obstructive sleep apnea. *Journal of clinical sleep medicine : JCSM : official publication of the American Academy of Sleep Medicine.* Apr 15 2009;5(2):151-153.
42. Conley RS, Legan HL. Correction of severe obstructive sleep apnea with bimaxillary transverse distraction osteogenesis and maxillomandibular advancement. American journal of orthodontics and dentofacial orthopedics : official publication of the American Association of Orthodontists, its constituent societies, and the American Board of Orthodontics. Feb 2006;129(2):283-292.
43. Colin WB. Comprehensive reconstructive surgery for obstructive sleep apnea. *The Journal of the Kentucky Medical Association.* Apr 2004;102(4):154-162.
44. Barrera JE, Powell NB, Riley RW. Facial skeletal surgery in the management of adult obstructive sleep apnea syndrome. *Clinics in plastic surgery.* Jul 2007;34(3):565-573.
45. Banhiran W, Vachiramon A, Metheetrairut C, Chierakul N, Tubpentha Y. Maxillomandibular Advancement (MMA) for the Treatment of Severe Obstructive Sleep Apnea Syndrome (OSAS): The first case report in Thailand. *Siriraj Med J.* 2007;59:369-372.

Adult OSA – Chapter IV

Future Surgical Approach in Adult OSA:

The Hypoglossal Nerve Stimulation

IV. FUTURE SURGICAL APPROACH IN ADULT OBSTRUCTIVE SLEEP APNEA: THE HYPOGLOSSAL NERVE STIMULATION

"HYPOGLOSSAL NERVE STIMULATION IN THE TREATMENT OF OSA: A SYSTEMATIC REVIEW AND META-ANALYSIS"

VICTOR CERTAL; SOROUSH ZAGHI; MUHAMMAD RIAZ; CARLOS PINHEIRO; ANTONIO VIEIRA; CLETE KUSHIDA; MACARIO CAMACHO; ROBSON CAPASSO

LARYNGOSCOPE

2014

(*cf*. Appendix 10)

1. Introduction

Obstructive sleep apnea (OSA) is a serious, potentially life-threatening disorder characterized by recurrent episodes of upper-airway collapse during sleep that often lead to hypoxemia and hypercapnia.[1]

Common symptoms include loud snoring, breathing interruptions, excessive daytime sleepiness, and cognitive impairment. Its association with an increased risk of cardiovascular complications is well described.[2]

The primary course of treatment for OSA is therapy with continuous positive airway pressure (CPAP) devices. Despite efforts to improve adherence, only 40% to 60% of patients continue to use CPAP longterm or as prescribed, and many others do not seek medical attention. In cases where the effectiveness is not optimal, alternative therapies are often utilized after medical management has failed.[3]

In 1978, Remmers et al.[4] were the first to report the direct relationship between loss of genioglossus muscle activation during sleep and upper airway closure in patients with

OSA. This finding led to early attempts to treat the disorder by electrical stimulation of the pharyngeal muscles with transcutaneous, intraoral, and intramuscular electrodes.[5-7] Several subsequent projects since then have attempted to prove the usefulness of chronic hypoglossal nerve stimulation (HNS) as a novel therapeutic approach to sleep apnea. Selective HNS is less likely to produce arousal than direct intramuscular stimulation, which is associated with sensory stimulation, because the nerve is purely motor. Although the potential feasibility and efficacy of this approach has been demonstrated in studies dating back to at least 1994, the technology was never successfully developed to a point that allowed its use in routine practice. However, interest in this treatment modality has been re-emerging during the last decade because of significant technological advances in this area, targeting patients with moderate-to-severe obstructive sleep apnea and difficulty accepting or adhering to CPAP treatment.[8,9]

2. Aims

In this section, the aims were to:

- assess the efficacy and safety of HNS in the treatment of OSA

- assess the safety of HNS in the treatment of OSA

3. Methods

a. Search strategy

A comprehensive literature search was performed initially on April 1, 2014 with an update September 5, 2014 using electronic databases to include the Cochrane Library,

SCOPUS, and PubMed. To achieve maximum sensitivity, we combined the following keywords and MeSH terms: “Hypoglossal Nerve/surgery”; “Hypoglossal Nerve/therapy”; “hypoglossal nerve stimulation”; “Hypoglossal nerve”; “Electric stimulation therapy”; and “sleep apnea.” No language restriction was applied. To minimize the risk of missing relevant data, we also reviewed the references of all relevant articles, and searched abstracts and conference proceedings of recent relevant congresses and scientific forums from 2010 to 2013 by hand.

b. Selection criteria, data abstraction, and study quality assessment

Only studies with a primary objective of evaluating the efficacy of HNS to treat OSA in adults were selected. Studies included were those that provided quantitative outcomes pre- and post-implantation of a hypoglossal nerve device for, at minimum, the apnea-hypopnea index (AHI), the oxygen desaturation index (ODI), and the Epworth Sleepiness Scale (ESS). All studies that did not include these outcomes, polysomnogram (PSG) data, or those that were focused on pediatric populations were excluded.

Data were abstracted by two independent reviewers (M.R. and S.Z.) in a blinded manner, and discrepancies were resolved by a third reviewer (V.C.). Case series studies may be affected by various types of bias. Thus, we employed a quality appraisal tool from the National Institute for Health and Clinical Excellence (NICE) to assess the methodological quality of included case series studies.

The primary outcome measures included AHI, ODI, and ESS data. The secondary outcome measures included all other outcomes or complications described in the included studies.

A full description of the statistical analysis is available in Appendix 8.

4. Results

a. Search and study selection

A flow chart of the process of study identification is shown in Figure 1.

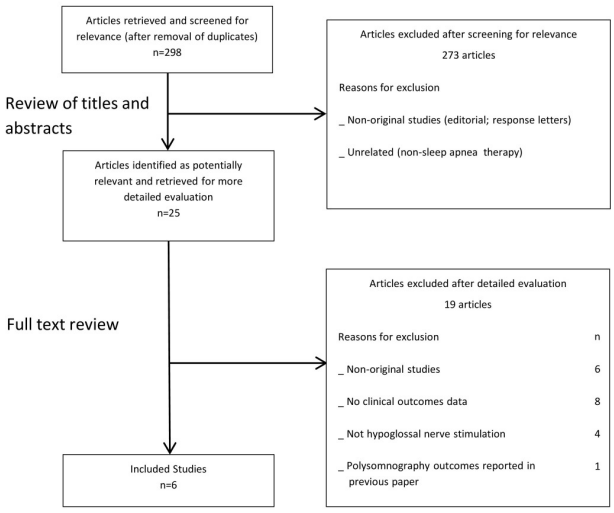


Figure 1 Flow diagram of study identification and selection

A total of 298 articles were identified using the search strategy and sources listed. After screening titles and abstracts for relevance, 273 articles were excluded (the reasons for exclusion are presented in Figure 1). The remaining 25 articles were retrieved for more detailed full-paper evaluation and 19 were excluded for the following reasons: 6 studies[9,11-15] were not original studies; 8 studies [8,16-22] did not provide sufficient clinical outcomes (AHI, ODI and ESS), 1 study's[23] polysomnography outcomes were reported in

their previously published article, and 4 studies [5,7,24,25] evaluated other electrical stimulation modalities (submental and intraoral stimulation). The final selection included 6 studies[26-31] in the review, describing 200 patients with a mean age of 53.9 ± 10.1 years and a follow-up period ranging from 6 to 12 months (Table 1 – Available in Appendix 8).

b. Methodological quality of included studies

Most included studies were prospective case series and one was a case report (Table 1 – Available in Appendix 8). There was no randomized trial identified in the literature search. The evidence was level 5 (case report) and level 4 (case series). All of the included studies were of generally high quality and satisfied the majority of the eight items on the NICE quality-assessment tool for case series studies. The primary methodological limitation of the included studies was related to the lack of explicit statement that participants were recruited consecutively. Otherwise, most of the studies were high quality prospective case series. Methodological quality appraisal was not performed for the case report.

c. Technical characteristics of included hypoglossal nerve stimulation systems

Three types of HNS systems were analyzed in the included studies: the HGNS® System (Apnex Medical, Inc., St. Paul, MN, USA), the Aura6000™ system (ImThera Medical, Inc., San Diego, CA, USA), and the Inspire II® Upper Airway Stimulation device (Inspire Medical Systems, Inc., Maple Grove, MN, USA).

Both the HGNS® System and the Inspire II® Upper Airway Stimulation device consist of implantable single electrode neurostimulators that deliver an electrical current to the hypoglossal nerve by a stimulation lead.[26,30] This stimulation is intermittent and is synchronized with respiration-sensing leads that measure changes in breathing. The Aura6000™ system consists of an implanted pulse generator and a multi-electrode lead (six stimulating electrodes) that is in contact with the body of the proximal hypoglossal nerve.[28] The stimulation via the multi-electrode lead is continuous, obviating the need for respiration-sensing leads

d. Primary outcome measures

The findings are summarized in Table 2. There was substantial variation in the follow-up length and in the presentation of results among the included studies. In order to further clarify the results, we performed a sub-group analysis according to duration of follow-up (3, 6, and 12 months) for each primary outcome.

e. Apnea-Hypopnea Index (AHI)

The results regarding the impact on AHI at 3, 6, and 12 months are presented in Figure 2.

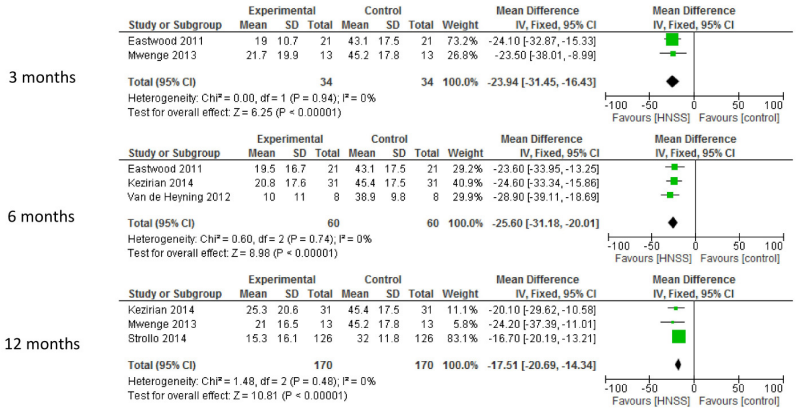


Figure 2 Results and pooled analysis of mean differences for the AHI outcome

The pooled fixed effects analysis demonstrated statistically significant reductions in AHI mean difference (MD) at 3, 6, and 12 months of −23.94 (95% confidence interval (CI), −31.45 to −16.43; P < .001), −25.60 (95% CI, −31.18 to −20.01; P < .001), and −17.51 (95% CI, −20.69 to −14.34; P < .001), respectively.

At 3, 6 and 12 months, the AHI improved from 43.90 ± 17.61/hr to 20.03 ± 14.15/hr, 43.73 ± 16.55/hr to 18.91 ± 16.47/hr, and 35.45 ± 13.26/hr to 17.55 ± 16.94/hr, respectively. The overall reduction in AHI was 54% at 3 months, 57% at 6 months and 50% at 12 months.

Despite the comparisons of results for different hypoglossal nerve stimulators in each sub-group analysis, no significant heterogeneity was found in any of the comparisons, suggesting equivalent efficacy in AHI reduction.

f. Oxygen Desaturation Index (ODI)

The results regarding the impact on ODI at 3, 6, and 12 months are presented in Figure 3.

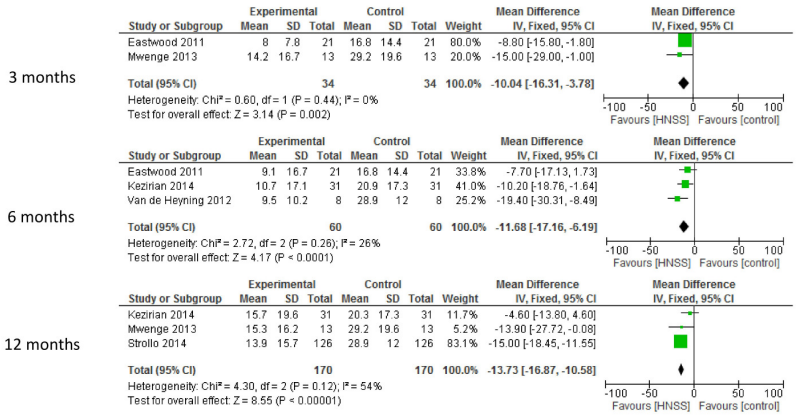


Figure 3 Results and pooled analysis of mean differences for the ODI

The pooled fixed effects analysis demonstrated statistically significant reductions in ODI MD at 3, 6, and 12 months of −10.04 (95% CI, −16.31 to −3.78; P < .01), −11.68 (95% CI, −17.16 to −6.19; P < .001), and −13.73 (95% CI, −16.87 to −10.58; P < .001), respectively.

At 3, 6 and 12 months, the ODI improved from 21.54 ± 16.35/hr to 10.37 ± 11.14/hr, 20.53 ± 15.91/hr to 9.8 ± 16.40/hr, and 27.35 ± 13.50/hr to 14.34 ± 16.43/hr, respectively. The overall reduction in ODI was 52% at 3 months, 52% at 6 months and 48% at 12 months.

No significant heterogeneity was found in any of the comparisons, suggesting equivalent efficacy in ODI reduction.

g. Epworth Sleepiness Scale (ESS)

The results regarding the impact on ESS at 3, 6, and 12 months are presented in Figure 4.

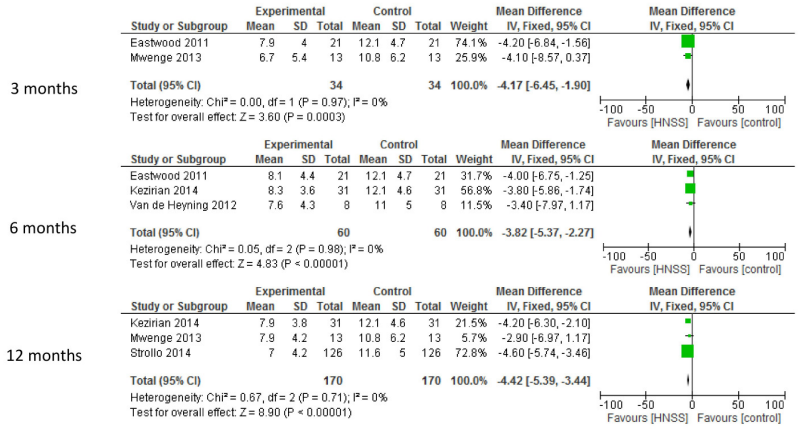


Figure 4 Results and pooled analysis of mean differences for the ESS outcome at 3, 6 and 12 months.

At 3, 6, and 12 months, the pooled fixed effects analysis demonstrated statistically significant reductions in ESS MD of −4.04 (95% CI, −6.45 to −1.90; P < .001), −3.82 (95% CI, −5.37 to −2.27; P < .001), and −4.42 (95% CI, −5.39 to −3.44; P < .001), respectively.

At 3, 6 and 12 months, the ESS improved from 11.60 ± 5.26/hr to 7.44 ± 4.53/hr, 11.95 ± 4.68/hr to 8.14 ± 3.97/hr, and 11.63 ± 5.01/hr to 7.23 ± 4.13/hr, respectively.

No significant heterogeneity was found in any of the comparisons, suggesting equivalent efficacy in ESS reduction.

h. Secondary outcome measures

Four included studies[26,27,29,30] contained data regarding the Functional Outcomes of Sleep Questionnaire, and all studies showed significant improvement, which was independent of the follow-up length (Table 2). Other subjective scales of quality of life were analyzed. Two included studies[26,27] reported significant improvements in Sleep Apnea Quality of Life Index, Pittsburgh Sleep Quality Index, and Beck Depression Index, and one study[28] showed significant improvement in the Fatigue Severity Scale (Table 2 – Available in Appendix 8).

Three studies[26,27,31] reported data regarding therapy utilization that showed high rates of compliance and therapy adherence, with use on more than 85% of nights (range, 86–96%) at an elevated number of hours per night (range, 5.4–7.5 h) (Table 2 – Available in Appendix 8).

Regarding sleep architecture, one study[26] reported that total sleep time was unchanged from baseline, while sleep latency was decreased at 6 months. Significant improvement

was noticed in sleep efficiency at 3 months and 6 months. At 3 months, the percent of total sleep time in stage N1 sleep was reduced (P < .001), and time in REM sleep was increased (P < .001). These changes were sustained at 6 months. The time in stage N2 and N3 sleep was unchanged from baseline values.

i. Safety

None of the included studies described any serious adverse events, defined as any complication resulting in life-threatening illness or injury or permanent impairment of body structure or function, and no deaths were reported. All of the included studies described minor complications such as tongue weakness, tongue soreness, pain/swelling at the neck incision, fever, and lack of tongue response to stimulation (Table 2 – Available in Appendix 8). These complications were in most cases temporary and did not interfere with the subsequent activation of the device. Of the 200 patients included in this review, 9 had serious device-related adverse events that led to removal of the stimulator (rate of 4.5% of the total).

5. Discussion

This systematic review and meta-analysis of 6 studies evaluating HNS for the treatment of OSA indicates that this treatment may be a safe and effective alternative for improving OSA outcomes in individuals with moderate to severe OSA who have failed medical treatment. The results analyzed in this review demonstrated clinically and significant decreases in observed mean AHI, ODI, and ESS, combined with improvements in several quality of life scales. Moreover, these results seemed to be stable through a 12-month follow-up period, with high rates of compliance/adherence

to therapy. Although definite indications are still needed, the majority of literature defines the ideal candidate as having BMI≤32 kg/m^2, AHI between 20 and 50/hr, and without complete concentric collapse at the level of soft palate. Also, patients with a relatively larger tongue tended to have a larger response.[32]

One interesting finding was that regardless of the type of hypoglossal stimulation device, the results in terms of improvement of OSA outcomes appear to be consistent. Three types of devices were analyzed, although at present, there are only two systems still in development (Apnex Medical Inc., the producer of HGNS®, ceased its activity in March 2013). Certain technical differences should be noted, particularly regarding the Aura6000®, which utilizes a silicone cuff multi-electrode that targets only the desired portions of the hypoglossal nerve, allowing a high degree of specificity. Targeted activation of the genioglossus muscle obviates the need to synchronize stimulation with the respiratory cycle and may reduce some of the costs related to the estimated surgery time.

a. Clinical implication of the findings

Overall, HNS seems to be a promising therapy in the treatment of OSA in select subjects. Its safety combined with its stable outcome results over 12 months of follow-up should sustain further research in this particular area. However, the cost impact of these devices must be taken into account when considering this therapy, because the estimated cost of some of these systems is reported as US $30,000 with a 15-year estimated lifetime. A cost-utility analysis performed by Imthera Medical® concluded that the therapy is a highly cost-effective intervention for OSA from a health system

perspective and 'dominant' from a societal perspective. Nevertheless, this cost-utility analysis may be optimistic given the limitations of the available evidence data.

Finally, the evidence presented here suggests that further research should be performed to compare HNS with other conventional therapies (i.e., CPAP, oral appliance, and other surgical procedures) using a robust methodological approach to create unbiased randomized controlled trials and cost-effectiveness studies. Research in the future should also concentrate on the definition of subgroups of patients for whom introduction of HNS could be combined in a multi-level surgery procedure, as the hypoglossal nerve devices target only a part of the upper airway tract, or subgroups of patients for whom bilateral stimulation may be more effective.

b. Study limitations

This study has several limitations that should be acknowledged. First, the findings of this study are based on a limited number of case series/case reports, which are, by definition, subject to confounding. Second, the results of the included studies are from a few highly experienced centers and therefore do not necessarily represent "real-world practice." The implantation requires some surgical skills although, as Mwenge et al.[28] observe, surgeons well trained in otorhynolaryngology, or maxillofacial surgery should be able to perform this procedure without any problem. Third, the duration of clinical follow-up was limited to 6 to 12 months in the included studies. The shortage of long-term data beyond one year limits the provision of evidence-based guidelines and recommendations, and thus more long-term data are required. Fourth, the inclusion and exclusion criteria for the included studies were generally highly specific, which lead

to a carefully selected population and may not be representative of the population with moderate to severe OSA. Fifth, like most phamarcologic and medical device therapies, HNS must be titrated to achieve optimal degrees of pharyngeal opening during sleep, and none of the included studies trully address this issue. Lastly, the HNS involved a heterogeneous group of systems, and thus, any conclusions from the pooled results and their interpretation should be treated with a degree of caution. However, the final mechanism in all the systems is basically similar (HNS, which provides protrusion of the tongue) despite the technical differences. Moreover, none of the comparisons performed showed significant heterogeneity, and the outcomes measures presented in this review were very consistent, regardless of the system in use.

6. Conclusion

Despite possible limitations, the results of this review should provide a rationale to consider therapy with HNS for selected patients with obstructive sleep apnea who have difficulties with CPAP therapy. The selective stimulation of the hypoglossal nerve during sleep may provide a physiological approach to treatment of OSA based on the restoration or improvement of upper airway dilator muscle activity during sleep.

References

1. Sundaram S, Bridgman SA, Lim J, Lasserson TJ. Surgery for obstructive sleep apnoea. The Cochrane database of systematic reviews 2005:CD001004.
2. Marin JM, Carrizo SJ, Vicente E, Agusti AG. Long-term cardiovascular outcomes in men with obstructive sleep apnoea-hypopnoea with or without treatment with continuous positive airway pressure: an observational study. Lancet 2005; 365:1046-1053.
3. Holty JE, Guilleminault C. Maxillomandibular advancement for the treatment of obstructive sleep apnea: a systematic review and meta-analysis. Sleep medicine reviews 2010; 14:287-297.
4. Remmers JE, deGroot WJ, Sauerland EK, Anch AM. Pathogenesis of upper airway occlusion during sleep. Journal of applied physiology: respiratory, environmental and exercise physiology 1978; 44:931-938.
5. Steier J, Seymour J, Rafferty GFet al. Continuous transcutaneous submental electrical stimulation in obstructive sleep apnea: a feasibility study. Chest 2011; 140:998-1007.

6. Smith PL, Eisele DW, Podszus Tet al. Electrical stimulation of upper airway musculature. Sleep 1996; 19:S284-287.
7. Randerath WJ, Galetke W, Domanski U, Weitkunat R, Ruhle KH. Tongue-muscle training by intraoral electrical neurostimulation in patients with obstructive sleep apnea. Sleep 2004; 27:254-259.
8. Schwartz AR, Bennett ML, Smith PLet al. Therapeutic electrical stimulation of the hypoglossal nerve in obstructive sleep apnea. Archives of otolaryngology--head & neck surgery 2001; 127:1216-1223.
9. Kezirian EJ, Boudewyns A, Eisele DWet al. Electrical stimulation of the hypoglossal nerve in the treatment of obstructive sleep apnea. Sleep medicine reviews 2010; 14:299-305.
10. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. BMJ 2009; 339:b2535.
11. Kuna ST. Back to the future or forward to the past? Sleep 2011; 34:1455-1456.
12. Barbe F, Masa JF. Hypoglossal neurostimulation for obstructive sleep apnoea. The European respiratory journal 2013; 41:257-258.
13. Akinnusi M, Saliba R, El-Solh AA. Emerging therapies for obstructive sleep apnea. Lung 2012; 190:365-371.
14. Chwiesko-Minarowska S, Minarowski L, Kuryliszyn-Moskal A, Chwiesko J, Chyczewska E. Rehabilitation of patients with obstructive sleep apnea syndrome. International journal of rehabilitation research Internationale Zeitschrift fur Rehabilitationsforschung Revue internationale de recherches de readaptation 2013; 36:291-297.
15. Oliven A. Treating obstructive sleep apnea with hypoglossal nerve stimulation. Current opinion in pulmonary medicine 2011; 17:419-424.
16. Eisele DW, Schwartz AR, Smith PL. Tongue neuromuscular and direct hypoglossal nerve stimulation for obstructive sleep apnea. Otolaryngologic clinics of North America 2003; 36:501-510.
17. Eisele DW, Smith PL, Alam DS, Schwartz AR. Direct hypoglossal nerve stimulation in obstructive sleep apnea. Archives of otolaryngology--head & neck surgery 1997; 123:57-61.
18. Schwartz AR, Barnes M, Hillman Det al. Acute upper airway responses to hypoglossal nerve stimulation during sleep in obstructive sleep apnea. American journal of respiratory and critical care medicine 2012; 185:420-426.
19. Oliven R, Tov N, Odeh Met al. Interacting effects of genioglossus stimulation and mandibular advancement in sleep apnea. J Appl Physiol (1985) 2009; 106:1668-1673.
20. Knaack L, Podszus T. Electric stimulation of the upper airway muscle. Current opinion in pulmonary medicine 1998; 4:370-375.
21. Goding GS, Jr., Tesfayesus W, Kezirian EJ. Hypoglossal nerve stimulation and airway changes under fluoroscopy. Otolaryngology--head and neck surgery : official journal of American Academy of Otolaryngology-Head and Neck Surgery 2012; 146:1017-1022.
22. Guilleminault C, Powell N, Bowman B, Stoohs R. The effect of electrical stimulation on obstructive sleep apnea syndrome. Chest 1995; 107:67-73.
23. Safiruddin F, Vanderveken OM, de Vries Net al. Effect of upper-airway stimulation for obstructive sleep apnoea on airway dimensions. The European respiratory journal 2014.
24. Miki H, Hida W, Chonan T, Kikuchi Y, Takishima T. Effects of submental electrical stimulation during sleep on upper airway patency in patients with obstructive sleep apnea. The American review of respiratory disease 1989; 140:1285-1289.
25. Mann EA, Burnett T, Cornell S, Ludlow CL. The effect of neuromuscular stimulation of the genioglossus on the hypopharyngeal airway. The Laryngoscope 2002; 112:351-356.
26. Eastwood PR, Barnes M, Walsh JHet al. Treating obstructive sleep apnea with hypoglossal nerve stimulation. Sleep 2011; 34:1479-1486.
27. Kezirian EJ, Goding GS, Jr., Malhotra Aet al. Hypoglossal nerve stimulation improves obstructive sleep apnea: 12-month outcomes. Journal of sleep research 2014; 23:77-83.
28. Mwenge GB, Rombaux P, Dury M, Lengele B, Rodenstein D. Targeted hypoglossal neurostimulation for obstructive sleep apnoea: a 1-year pilot study. The European respiratory journal 2013; 41:360-367.

29. Strollo PJ, Jr., Soose RJ, Maurer JTet al. Upper-airway stimulation for obstructive sleep apnea. The New England journal of medicine 2014; 370:139-149.
30. Van de Heyning PH, Badr MS, Baskin JZet al. Implanted upper airway stimulation device for obstructive sleep apnea. The Laryngoscope 2012; 122:1626-1633.
31. Eastwood PR WJ, Maddison K. Treatment Of Obstructive Sleep Apnea With Unilateral Hypoglossal Nerve Stimulation. American journal of respiratory and critical care medicine 2010; 181.
32. Dotan Y, Golibroda T, Oliven Ret al. Parameters affecting pharyngeal response to genioglossus stimulation in sleep apnoea. The European respiratory journal 2011; 38:338-347.

Adult OSA - Chapter V

An alternative method to treat both adult and pediatric OSA: The Myofunctional therapy

V. AN ALTERNATIVE METHOD TO TREAT ADULT AND PEDIATRIC OSA: THE MYOFUNCTIONAL THERAPY

"MYOFUNCTIONAL THERAPY TO TREAT OSA: A SYSTEMATIC REVIEW AND META-ANALYSIS "

MACARIO CAMACHO; VICTOR CERTAL; JOSE ABDULLATIF; SOROUSH ZAGHI; CHAD RUOFF; ROBSON CAPASSO; CLETE KUSHIDA

ACCEPTED IN SLEEP

2014

(*cf*. Appendix 11)

1. Introduction

Several medical and surgical treatment modalities exist as treatment for obstructive sleep apnea (OSA).[1–3] Four pathophysiological traits seen in patients with OSA are: the passive critical closing pressure of the upper airway (Pcrit), arousal threshold, loop gain, and muscle responsiveness (PALM) with categories of 1, 2, 2a, 2b, and 3.[4] It has been demonstrated that patients in four of five PALM categories will benefit from anatomic interventions.[4] Because the dilator muscles of the upper airway play a critical role in maintaining an open airway during sleep, researchers have explored exercises and other airway training (singing, didgeridoo, instrument playing) that target oral cavity and oropharyngeal structures as a method to treat OSA.[5–7] Myofunctional therapy (MT) and proper tongue positioning in the oral cavity has been described since 1918 to improve mandibular growth, nasal breathing, and facial appearance.[8] Guimaraes has proposed MT as a treatment for OSA since the 1990s.[9] MT is composed of isotonic and isometric exercises that target oral (lip, tongue) and oropharyngeal structures (soft palate, lateral pharyngeal wall).[7,10] There have been an

increasing number of studies evaluating the effect of MT in the form of case studies, case series, and most recently, two randomized controlled trials.[7,10–13]

The most comprehensive MT exercises are described by Guimaraes et al.[7] and involve the soft palate, tongue, and facial muscles and address stomatognathic functions. For soft palate exercises, patients pronounce oral vowel sounds either continuously (isometric exercises) or intermittently (isotonic exercises).[7] Tongue exercises include moving the tongue along the superior and lateral surfaces of the teeth, positioning the tongue tip against the anterior aspect of the hard palate, pressing the entire tongue against the hard and soft palate, and forcing the tongue onto the floor of the mouth.[7] Facial exercises address the lip (i.e., contraction and relaxation of the orbicularis oris), buccinators (i.e., suction movements and application of intraoral finger pressure against the buccinator muscles), and jaw muscles (i.e., lateral jaw movements).[7] In addition, stomatognathic functions are addressed by instructing patients to inhale nasally and exhale orally without and then with balloon inflation, and performing specific swallowing and chewing exercises (i.e., swallowing with the teeth clenched together, tongue positioned in the palate and without contraction of perioral muscles; alternating chewing sides).[7] A newer study describes a device that conditions and strengthens oral and tongue muscles.[12]

2. Aims

In this section, the aims were to:

- Evaluate myofunctional therapy or oral/oropharyngeal exercises as treatment for OSA in both children and adults
- Evaluate effect on the available polysomnographic and sleepiness data.

3. Methods

a. Search Strategy

A search was performed on Web of Science, Scopus, MEDLINE, and The Cochrane Library, initially January 18, 2014, with an update on June 18, 2014. MeSH terms and keywords used for the search included various combinations of the following: "myofascial reeducation," "myofunctional therapy," "obstructive sleep apnea," "orofacial myotherapy," "oral myotherapy," "oropharyngeal exercises," "sleep," "sleep apnea syndromes," "speech therapy," "upper airway exercises," and "upper airway remodeling." One example of a MEDLINE search is: ((("Myofunctional Therapy"[MeSH]) AND "Sleep Apnea Syndromes"[MeSH])) OR ("sleep" AND ("myofascial reeducation" OR "myofunctional therapy" OR "orofacial myotherapy" OR "oral myotherapy" OR "oropharyngeal exercises" OR "speech therapy" OR "upper airway exercises" OR "upper airway remodeling")).

For each of the searches, the titles and abstracts were screened and the full text versions of articles that met criteria were downloaded. Full texts were reviewed and any referenced articles that were not already obtained were ordered and obtained. "Related citations" were also reviewed during the searches, and the "cited by" function on Google Scholar was also used to identify any additional studies.

b. Study Selection

Criteria for inclusion included peer-reviewed studies (published articles or abstracts) evaluating oral or oropharyngeal MT as an isolated treatment for either adult or pediatric OSA; studies needed to report quantitative polysomnographic, snoring, and/or sleepiness data pretreatment and posttreatment or they needed to report the

percentage of difference between pretreatment and posttreatment outcomes. All languages were included. Exclusion criteria included studies evaluating singing, instrument playing, and studies without quantitative data. If individual patient data were reported and patients lost 10% or more of their body weight, then those patients were excluded. Studies in which the MT patients also underwent additional interventions such as continuous positive airway pressure therapy, mandibular advancement device therapy, sleep apnea surgery, allergy management, weight loss management, or any other intervention that could also contribute to improved sleep apnea outcomes were excluded (unless the additional interventions were performed in control groups and the data were provided separately for both MT and control groups).

c. Data Abstraction and Study Quality Assessment

Authors MC, JA, and SZ independently performed a search of the literature and screened titles and abstracts and downloaded the articles for inclusion. The decision to include the articles was made by consensus, and if necessary the final decision was made by author MC. Data collected included patient age, body mass index (BMI), polysomnographic data (AHI, lowest oxygen saturation), snoring, and sleepiness data. If data were missing from the articles, then the corresponding author was contacted in an attempt to obtain the data. The corresponding author of the study by Suzuki et al.[12] was contacted and confirmed that the reported oxygen saturation data were for lowest oxygen saturation and that tongue training was involved as part of the MT device training.

The National Institute for Health and Clinical Excellence (NICE) quality assessment tool was used to evaluate the quality of the included studies. The instrument consists of eight items that are assessed for each individual study.

A full statistical analysis is available in Appendix 10.

4. Results

A total of 226 studies were screened for relevance, and 204 were excluded. After identification of 22 potentially relevant studies, they were downloaded and the reviews of the reference lists yielded an additional 6 studies, for a total of 28 studies.[7–13,17–36] Nine were review articles,[8,20,22,27,30,32–34,36] two reported no intervention,[24,31] two studied lip exercises and the effect on lip thickness,[21,37] one reported breathing exercises not involving oral cavity or oropharyngeal structures,[28] one was a letter to the editor,[11] and two studies were abstracts in which data were later reported in the authors' journal articles.[19,25] Eleven studies met criteria and were included in this review. Individual patient data were reported by one pediatric study[35] and one adult study,[12] whereas the remaining nine studies reported outcomes with means and standard deviations.[7,9,10,13,17,18,23,26,29] Figure 1 summarizes the flow for study selection.

a. Methodological Quality of the Included Studies

The studies included in this review included one abstract,[26] one retrospective case report,[23] three retrospective case series,[9,10,18] three prospective case series,[12,17,29] one randomized trial,[35] and two randomized controlled trials.[7,13] Most of the studies satisfied four to six of the eight NICE quality assessment tool items (presented in Table

S1 of supplemental material). The main limitations were that the total number of patients in most studies was low, the studies were at single institutions (except one that was multicentered) and most studies did not explicitly state that patients were consecutive.

b. **Adult Studies**

A total of nine adult studies (120 patients, age 44.5 ± 11.6 y, BMI 28.9 ± 6.2 kg/m^2) reported polysomnography and/or sleepiness outcomes (Table 1).

Study Authors Year Study Design	*N*	*Age (years)*	*BMI (kg/m²)*	*Pre-MT AHI (events/h)*	*Post-MT AHI (events/h)*	*Pre-MT low O2 (%)*	*Post-MT low O2 (%)*	*Pre-MT ESS*	*Post-MT ESS*
Suzuki et al.* 2013 PCS	6	22.0± 0.5	23.8± 1.8	15.1± 3.4	9.2± 1.5	90.0± 2.9	96.8± 0.8	-	-
Kronbauer et al. 2013 PCS	8	(40-65)	-	-	-	-	-	11.75	4.25
Diaferia et al. 2013 RCT	27	45.2± 13.0	25.0± 7.4	28.0± 22.7	13.9± 18.5	83.7± 7.7	84.9± 8.8	13.7± 3.2	7.5± 3.7
Baz et al. 2012 PCS	30	44.1± 7.5	33.6± 2.0	22.3± 4.5	11.5± 5.4	84± 4	87± 5	16.4± 2.0	9.3± 2.9
Guimaraes et al. 2009 RCT	16	51.5± 6.8	29.6± 3.8	22.4± 4.8	13.7± 8.5	83± 6	85± 7	14± 5	8± 6
de Paula Silva et al. 2007 RCR	1	60	23.3	44	3	83	92	-	-
Berreto et al. 2007 RCS	2	46± 12.7	24.2± 2.9	44.5± 5.7	6.0± 3.7	78± 1.4	85± 2.8	12.5± 0.7	4.5± 3.5
Guimaraes et al. 2003 ABS	10	-	-	36.1	11.3	-	-	11	7.6
Guimaraes et al. 1999 RCS	20	(33-55)	-	-	-48%	-	-	-	-
Total	120	44.5± 11.6	28.9± 6.2	24.5± 14.3	12.3± 11.8	83.9± 6.0	86.6± 7.3	14.8± 3.5	8.2± 4.1

Table 1. Adult pre- and post-myofunctional therapy outcomes. Abbreviations: - = not reported, % = percent, ABS = abstract, AHI = apnea-hypopnea index, BMI = body mass index, ESS = Epworth Sleepiness Scale, events/h = events per hour, kg/m^2 = kilograms per meter squared, low O2 = lowest oxygen saturation, MT = myofunctional therapy, N = number of myofunctional therapy patients in the study, PCS = prospective case series, RCR = retrospective case report, RCS = retrospective case series, RCT = randomized controlled trial, *Study authors confirmed the reported oxygen saturation data was for lowest oxygen saturation.

Baz et al.[17] reported using American Academy of Sleep Medicine (AASM) scoring criteria but did not specify which year, Diaferia et al.[13] and Guimaraes et al.[7] reported using 1999 AASM scoring criteria, Suzuki et al.[12] scored based on the 2005 update to AASM scoring criteria, and the remaining five studies did not specify which polysomnography scoring criteria were used.[9,18,23,26,29]

The pre- and post-MT AHI mean ± standard deviation (M ± SD; 82 patients) decreased from 24.5 ± 14.3/h to 12.3 ± 11.8/h, with a mean difference (MD) of -14.26 [95% CI -20.98, -7.54], Z score of 4.16 (P < 0.0001) (Figure 2). Both the I^2 statistic (91%) and the Q statistic (value of < 0.00001) demonstrated significant heterogeneity; therefore, studies were individually excluded to identify the source(s). Exclusion of the studies by Suzuki et al.[12] and Berreto et al.[18] resulted in no heterogeneity in the remaining 73 patients, with the I^2 statistic = 0% and the Q statistic value of 0.6. The mean difference for the remaining studies was -10.49 26 [95% CI -12.67, -8.31]. In adult studies in which MT was performed for at least 3 mo, the mean AHI reduced from 25.2 ± 14.6/h to 12.6 ± 12.2/h, which is a 50% reduction.

The lowest oxygen saturation improved in 82 patients from 83.9 ± 6.0% to 86.6 ± 7.3%, MD of 4.19 [95% CI 1.85, 6.54], with an overall Z score of 3.5 (P = 0.0005); see Figure 3. Both the I^2 statistic (59%) and the Q statistic (value of 0.05) demonstrated significant heterogeneity, therefore, studies were individually excluded to identify the source(s). Exclusion of the studies by Suzuki et al.[12] and Berreto et al.[18] resulted in no heterogeneity in the remaining 73 patients, with the I^2 statistic = 0% and the Q statistic value of 0.56. Oxygen desaturation index was reported by one study, and demonstrated a reduction from 14.53 ± 5.04 to 9.27 ± 4.27, pre- and post-MT,

respectively.[17] Sleepiness decreased in all studies reporting the outcome. The Epworth Sleepiness Scale (ESS)[38] decreased in 75 patients from 14.8 ± 3.5 to 8.2 ± 4.1, MD of -6.81 [95% CI -7.79, -5.82], with an overall Z score of 13.55 (P < 0.00001); see Figure 4. Both the I^2 statistic (0%) and the Q statistic (value of 0.8) demonstrated no heterogeneity.

c. Snoring

Snoring changes were evaluated by 4 studies, Baz et al.,[17] Berreto et al.,[18] de Paula Silva et al.[23] and Guimaraes et al.[7]; see Table 2.

Study Authors Year	*N*	*Subjective Snoring Pre-MT*	*Subjective Snoring Post-MT*	*PSG %TST Snoring Pre-MT*	*PSG %TST Snoring Post-MT*
Baz et al. 2012	30	Yes = 30 No = 0	Yes = 16 No = 14	14.05± 4.89%	3.87± 4.12%
Guimaraes et al. 2009	16	Very loud	Similar to breathing	-	-
de Paula Silva et al. 2007	1	Snoring	Decreased snoring	-	-
Berreto et al. 2007	2	Disturbs bedpartner	Light snoring	-	-

Table 2. Snoring outcomes based on mean values pre and post-myofunctional therapy.
Abbreviations: MT = myofunctional therapy, %TST = percentage of total sleep time. Note: snoring outcomes are based on quantified definitions pre- and post-myofunctional therapy by all studies except de Paula Silva et al (case report).

Baz et al.[17] reported that 30 patients snored before therapy and 16 snored after therapy, P = 0.008 (yes versus no; article did not specify if patient or bed partner was asked) and the polysomnography demonstrated that the percent of total sleep time spent snoring decreased from 14.05 ± 4.89% to 3.87 ± 4.12% (before and after, respectively), P < 0.001.[17] Guimaraes et al.[7] found snoring frequency decreased by 25%

(article did not specify if patient or bed partner was asked) from 4 to 3 (based on 0 = never to 4 = everyday), P = 0.001, and the snoring intensity decreased by 66% from 3 to 1 (based on 1 = similar to breathing and 3 = very loud) with P = 0.001; whereas the control groups had no change in snoring frequency or intensity. The case study by de Paula Silva et al.[23] demonstrated a decrease in snoring intensity after 8 sessions. Berreto et al.[18] described two patients who decreased from a (bed partner) snoring score of 3 down to 2 (0 = snoring absence, 1 = heavy breathing, 2 = light snoring, 3 = snoring that disturbs the bed partner and 4 = snoring that can be heard outside the bedroom).

d. Pediatric Studies

A total of two pediatric studies (25 patients, age 8.4 ± 3.1 y) reported polysomnography and/or sleepiness outcomes. Both pediatric studies reported using 2007 AASM scoring criteria, and Guilleminault et al.[10] also specified that hypopneas were scored with a 50% reduction in nasal cannula curve and an associated 3% or more reduction in oxygen saturation and/or with associated arousals, while Villa et al.[35] did not specify the hypopnea scoring criteria. The study by Villa et al.[35] was a prospective randomized controlled trial in which postadenotonsillectomy patients were randomized to either oropharyngeal exercises or control group. The treatment group in this study consisted of 14 patients and the pre- and post-MT AHI was evaluated after 2 mo of oropharyngeal exercises. The AHI M ± SD reduced from 4.87 ± 3.0/h to 1.84 ± 3.2/h, P = 0.004 (a 62% reduction).[35] The control group had minimal change in AHI during the 2-mo period (4.56/h down to 4.11/h).[35] The study by Guilleminault et al.[10] was a retrospective chart review, evaluating 24 children who were cured by the

combination of adenotonsillectomy and palatal expansion (AHI 0.4 ± 0.3); and 11 of the children received MT (intervention group) and 13 children did not receive MT (controls).[10] At the 4-y follow-up, the children who practiced MT over the long term remained cured of OSA (AHI 0.5 ± 0.4), compared to children who were never trained to perform the exercises and subsequently had a recurrence of OSA (AHI 5.3 ± 1.5/h).[10] Although both pediatric MT studies compared the intervention groups to control groups, neither study reported pretreatment and posttreatment lowest oxygen saturation or sleepiness outcomes.

5. Discussion

This systematic review and meta-analysis of nine adult and two pediatric studies evaluating the effect of MT on OSA has five main findings. First, MT provides a reduction in AHI of approximately 50% in adults and 62% in children. The pre- and post-MT AHI for adults decreased from 24.5 ± 14.3/h to 12.3 ± 11.8/h, MD of -14.26 [95% CI -20.98, -7.54] ($P < 0.0001$). For pediatric patients, the pre- and post-MT M ± SD for AHI decreased from 4.87 ± 3.0/h to 1.84 ±3.2/h, $P = 0.004$. Additionally, the study by Guilleminault et al.[10] reported that 11 children remained cured of OSA (AHI of 0.5 ± 0.4/h) after continuing MT for 4 y. There was heterogeneity, and the studies by Suzuki et al.[12] and Berreto et al.[18] were shown to be the sources. The study by Suzuki et al. [12] had six patients, who used an oral exercise device to help train, but the length of time between polysomnography was 2 mo, whereas the remaining adult studies reporting AHI had a follow-up duration of at least 3 mo between polysomnography. Had the study been extended to 3 mo, there may have been additional improvement in AHI. In studies with control groups, there was little to no improvement in the AHI for the

control groups compared to improvement in the MT intervention group. There is also a clear improvement in lowest oxygen saturation by approximately 3–4%, with the meta-analysis of 81 patients demonstrating a mean difference pre- and post-MT of 4.19%, [95% CI 1.85, 6.54]. The oxygen desaturation index (ODI) was only reported by Baz et al.,[17] demonstrating a 36% reduction, but the article did not specify whether the ODI in the study was based on 3% or 4% desaturation.

Second, MT decreases snoring both subjectively and objectively. Four studies compared the pre- and post-MT outcomes and it was noted that snoring decreased after therapy (three of four studies quantified the snoring). The polysomnography demonstrated a 72.4% reduction in snoring pre- versus post-MT (14.05 ± 4.89% to 3.87 ± 4.12%, before and after, respectively), $P < 0.001$.[17] With regard to subjective improvement in snoring intensity, the three studies quantifying the outcomes reported that during posttreatment there was a decrease in snoring to either light snoring, or the sound was similar to normal breathing.

Third, subjective sleepiness also improves post-MT as demonstrated by a clear reduction in ESS score for the 93 patients in which it was administered, with a reduction from 14.8 ± 3.5 to 8.2 ± 4.1 (in 75 patients in whom M ± SDs were reported).[7,13,17,18,26,29] The posttreatment ESS is below the threshold for hypersomnia, which is generally considered to be 11 or higher on the scale.[39] Additionally, the 1999 study by Guimaraes[9] reported a subjective reduction in sleepiness; however, the use of a validated sleepiness scale was not specified.[9]

Fourth, despite the heterogeneity in oral and oropharyngeal exercises, overall the improvements in polysomnographic outcomes and sleepiness were consistent. MT

was performed for as little as 5 min, twice daily, 4 days a week for 2 mo[12] to as many as 10 min, three to five times daily for 3 mo.[17] The longest published experience with MT for adult OSA has been that of Guimaraes,[9] which is 6 mo. Guimaraes[9] has also published thorough instructions for performing the exercises that involve the soft palate, tongue, facial muscles, and stomatognathic functions to be performed 30 min a day.[7]

Fifth, future research is needed to help explain the pathophysiology and mechanism of action of MT as treatment for OSA. It can be hypothesized that the exercises improve oral and/or oropharyngeal muscle tone and also may decrease the amount of fatty deposition of the tongue, but this has not been proven. It can be recommended that future researchers consider using the standardized exercises, which have been developed and used over a period of several years by Guimaraes et al.[7] because they have the most experience with the therapy. As pointed out by Guimaraes et al.,[7] because MT is based on an integrative approach with several exercises, it is not possible to determine the effects of specific exercises to determine which ones contribute the most to improvement in outcomes[7]; therefore, future studies could consider exploring the effect of individual exercises. Individual patient data were not available for most studies; therefore, a subanalysis could not be performed for BMI, AHI, age, etc. based on the current literature. However, with regard to BMI, Guimaraes et al.[7] and Baz et al.[17] had significant reductions in AHI in overweight (BMI M ± SD 29.6 ± 3.8) and obese patients (BMI M ± SD 33.6 ± 2.0). With regard to age, the MT has been shown effective in children and adults of all ages studied thus far, ranging from 3 to 60y.

a. Limitations

A total of 145 patients (including 25 children) were included in this meta-analysis; however, the magnitude of the effects was highly significant. Although there were nine adult studies, a significant limitation for pediatric studies is that currently only two articles have been published. Additionally, long-term follow-up for more than 6 mo is limited. Except the study by Guilleminault et al,[10] which followed patients for 4 y, all of the other studies spanned 2 to 6 mo. The study by Guilleminault et al.[10] demonstrates a long-term (4 y) maintenance of reduction in AHI and alleviation of OSA symptoms in patients who continued to perform MT exercises, compared to the control group that had recurrence of symptoms and recurrence of an elevated AHI at 4-y follow-up.[10] Because this is the only study that has reported outcomes longer than 6 mo after initiation of MT exercises, additional long-term studies are needed to demonstrate the lasting effects of continued MT. Questions that have not been addressed that could be studied in the future include whether there is a relationship with the tongue exercises and changes in the tongue and palatal muscle tone and/or strength, tongue size (tongue fat), and overall upper airway volume changes pretreatment and posttreatment.

6. Conclusion

Current literature demonstrates that myofunctional therapy decreases AHI by approximately 50% in adults and 62% in children. Lowest oxygen saturation, snoring, and sleepiness outcomes improve in adults. Myofunctional therapy could serve as an adjunct to other OSA treatments.

References

1. Sullivan CE, Issa FG, Berthon-Jones M, Eves L. Reversal of obstructive sleep apnoea by continuous positive airway pressure applied through the nares. Lancet 1981;1:862–5.

2. Camacho M, Certal V, Capasso R. Comprehensive review of surgeries for obstructive sleep apnea syndrome. Braz J Otorhinolaryngol 2013;79:780–8.

3. Randerath WJ, Verbraecken J, Andreas S, et al. Non-CPAP therapies in obstructive sleep apnoea. Eur Respir J 2011;37:1000–28.

4. Eckert DJ, White DP, Jordan AS, Malhotra A, Wellman A. Defining phenotypic causes of obstructive sleep apnea. Identification of novel therapeutic targets. Am J Crit Care Med 2013;188:996–1004.

5. Puhan MA, Suarez A, Lo Cascio C, Zahn A, Heitz M, Braendli O. Didgeridoo playing as alternative treatment for obstructive sleep apnoea syndrome: randomised controlled trial. BMJ 2006;332:266–70.

6. Wardrop PJ, Ravichandran S, Hair M, Robertson SM, Sword D. Do wind and brass players snore less? A cross-sectional study of snoring and daytime fatigue in professional orchestral musicians. Clin Orolaryngol 2011;36:134–8.

7. Guimaraes KC, Drager LF, Genta PR, Marcondes BF, Lorenzi-Filho G. Effects of oropharyngeal exercises on patients with moderate obstructive sleep apnea syndrome. Am J Respir Crit Care Med 2009;179:962–6.

8. Rogers AP. Exercises for the development of muscles of face with view to increasing their functional activity. Dental Cosmos LX 1918;59:857–76.

9. Guimaraes KC. [Soft tissue changes of the oropharynx in patients with obstructive sleep apnea]. J Bras Fonoaudiol 1999;1:69–75.

10. Guilleminault C, Huang YS, Monteyrol PJ, Sato R, Quo S, Lin CH. Critical role of myofascial reeducation in pediatric sleep-disordered breathing. Sleep Med 2013;14:518–25.

11. Steele CM. On the plausibility of upper airway remodeling as an outcome of orofacial exercise. Am J Respir Crit Care Med 2009;179:858–9.

12. Suzuki H, Watanabe A, Akihiro Y, et al. Pilot study to assess the potential of oral myofunctional therapy for improving respiration during sleep. J Prosthodont Res 2013;57:195–9.

13. Diaferia G, Badke L, Santos-Silva R, Bommarito S, Tufik S, Bittencourt L. Effect of speech therapy as adjunct treatment to continuous positive airway pressure on the quality of life of patients with obstructive sleep apnea. Sleep Med 2013;14:628–35.

14. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. BMJ 2003;327:557–60.

15. Lau J, Ioannidis JP, Schmid CH. Quantitative synthesis in systematic reviews. Ann Intern Med 1997;127:820–6.

16. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS Med 2009;6:e1000097.

17. Baz H, Elshafey M, Elmorsy S, Abu-Samra M. The role of oral myofunctional therapy in managing patients with mild to moderate obstructive sleep apnea. PAN Arab J Rhinol 2012;2:17–22.

18. Berreto e Silva Pitta D, Farias Pessoa A, Sampaio AL, Nonato Rodrigues R, Guiot Tavares M, Tavares P. Oral myofunctional therapy applied on two cases of severe obstructive sleep apnea. Intl Arch Otorhinolaryngol 2007;11:350–4.

19. Brasili L, Martella S, Vitelli O, et al. Myofunctional treatment of sleep disordered breathing in children [Abstract]. Eur Respir Soc Annu Congress 2013;42:992.

20. Cooper A. Orofacial myology and myofunctional therapy for sleep telated breathing disorders. Sleep Med Clin 2010;5:109–13.

21. Das UM, Beena JP. Effectiveness of circumoral muscle exercises in the developing dentofacial morphology in adenotonsillectomized children: an ultrasonographic evaluation. J Indian Soc Pedod Prev Dent 2009;27:94–103.

22. De Dios JA, Brass SD. New and unconventional treatments for obstructive sleep apnea. Neurotherapeutics 2012;9:702–9.

23. de Paula Silva LM, dos Santos Aureliano FT, Rodrigues Motta A. [Speech therapy in the obstructive sleep apnea-hypopnea syndrome: case report]. Revista CEFAC 2007;9:490–6.

24. Diaféria G, Truksinas E, Haddad FLM, et al. Phonoaudiological assessment of patients with obstructive sleep apnea. Sleep Sci 2011;4:1–7.

25. Guimaraes KC, Drager LF, Marcondes BF, Lorenzi Filho G. Treatment of obstructive sleep apnea with oro-pharyngeal exercises: a randomized study [abstract]. Am J Respir Crit Care Med 2007:A755.

26. Guimaraes KC, Protetti HM. The phonoaudiological work at obstructive sleep apnea [abstract]. Sleep 2003;26:A209.

27. Huang YS, Guilleminault C. Pediatric obstructive sleep apnea and the critical role of oral-facial growth: evidences. Front Neurol 2012;3:184.

28. Khaleghipour S, Masjedi M, Kelishadi R. The effect of breathing exercises on the nocturnal enuresis in the children with the sleep-disordered breathing. Iran Red Crescent Med J 2013;15:e8986.

29. Kronbauer KF, Trezza PM, Gomes CF. [Speech therapy proposals to the snoring patient]. Distúrbios da Comunicação 2013;25:119–27.

30. Moeller JL. Orofacial myofunctional therapy: why now? Cranio 2012;30:235–6.

31. Sauer C, Schluter B, Hinz R, Gesch D. Childhood obstructive sleep apnea syndrome: an interdisciplinary approach A prospective epidemiological study of 4,318 five-and-a-half-year-old children. J Orofac Orthop 2012;73:342–58.

32. Valbuza JS, de Oliveira MM, Conti CF, Prado LB, de Carvalho LB, do Prado GF. Methods for increasing upper airway muscle tonus in treating obstructive sleep apnea: systematic review. Sleep Breath 2010;14:299–305.

33. Valbuza JS, Oliveira MM, Conti CF, Prado LB, Carvalho LB, Prado GF. Methods to increase muscle tonus of upper airway to treat snoring: systematic review. Arq Neuropsiquiatr 2008;66:773–6.

34. Verma SK, Maheshwari S, Sharma NK, Prabhat KC. Role of oral health professional in pediatric obstructive sleep apnea. Natl J Maxillofac Surg 2010;1:35–40.

35. Villa MP, Brasili L, Ferretti A, et al. Oropharyngeal exercises to reduce symptoms of OSA after AT. Sleep Breath 2014.

36. Moeller JL, Paskay LC, Gelb ML. Myofunctional therapy: A novel treatment of pediatric sleep-disordered breathing. Sleep Med Clin 2014;9:235–43.

37. Kumar TV, Kuriakose S. Ultrasonographic evaluation of effectiveness of circumoral muscle exercises in adenotonsillectomized children. J Clin Pediatr Dent 2004;29:49–55.

38. Johns MW. A new method for measuring daytime sleepiness: the Epworth sleepiness scale. Sleep 1991;14:540–5.

39. Johns M, Hocking B. Daytime sleepiness and sleep habits of Australian workers. Sleep 1997;20:844–9.

Discussion, Conclusions and Suggestions for future work

1. Summary of thesis aims and findings

This thesis examines the role of otorhinolaryngologists in the management of obstructive sleep apnea (OSA) from childhood to adulthood, and provides high-quality evidence on controversial topics in adult and pediatric OSA. The specialty of otorhinolaryngology includes both surgical and non-surgical treatment of the upper airway, the expertise to obtain a proper history and to conduct a proper examination, and the unique ability to assess dysfunctions and disorders of the upper airway. In spite of this diverse expertise, the role of the otorhinolaryngologist in the management of OSA is still subject to debate because of the lack of reliable evidence. Therefore, an aim of this thesis was to investigate the range of issues that have limited evidence-based practice in this specialty. Furthermore, this thesis sought new insight into the assessment and treatment of both pediatric and adult OSA, namely new diagnostic approaches for pediatric OSA and new solutions for the treatment of adult OSA.

This thesis concludes that the current diagnostic approach in pediatric OSA, which is based primarily on clinical evaluation, has poor accuracy in diagnosing this pathology. Considering the high prevalence of pediatric OSA, it is important to explore new practicable diagnostic pathways. To this end, the use of unattended multichannel devices appears to be a useful and valid solution for OSA screening in children. Similar results were observed in the development of a clinical decision rule that simplified the diagnostic method of pediatric OSA, and that may be an alternative in the absence of sleep laboratories or ambulatory devices adapted for pediatric purposes.

In adult OSA, this thesis exposes serious limitations in the literature regarding the assessment of the outcomes in sleep surgery, and provides evidence that was lacking in some surgical approaches, namely the utility of nasal surgery in combination with CPAP therapy and tracheostomy for severely obese OSA patients and non-compliant to CPAP. Finally, this thesis reviews the evidence for a new promising surgical approach (hypoglossal nerve stimulation) and the evidence concerning a non-conventional therapy, myofunctional therapy, as an alternative treatment for both adult and pediatric OSA.

This chapter provides a summary of the findings followed by a discussion of the significance of the findings for clinical practice. Future research is also discussed.

a. Summary of key findings in pediatric OSA

Study 1 was conducted to assess the accuracy of clinical symptoms and signs in predicting pediatric OSA. The rationale behind Study 1 was the empiric knowledge that clinical evaluation may not be sufficient to diagnose OSA consistently in children. Results confirmed that single and combined symptoms and signs do not have satisfactory diagnostic reliability. Tonsillar size and snoring reported by parents or caregivers have relatively high sensitivity, but low specificity, whereas EDS, observed apnea, and difficulty breathing during sleep, have relatively high specificity, but low sensitivity. Another finding of this study was that the Pediatric Sleep Questionnaire (PSQ) appears to be the only instrument validated by full overnight polysomnography (PSG). Compared with overnight PSG, the PSQ has been reported to have a sensitivity

between 0.81 and 0.85 and a specificity of 0.87 in detecting OSA. Thus, the PSQ is the most reliable questionnaire for sleep disorder screening and is available for medical and research settings in the Portuguese language (Study 3). Following this line of reasoning, the rationale behind Study 3 was the need for less cumbersome methods to assess sleep apnea without requiring investigator-attended overnight monitoring to acquire quality data. Despite significant heterogeneity, Study 3 demonstrated that unattended type 2 or type 3 multichannel devices are useful for diagnosing or monitoring pediatric OSA, especially in the comparison of respiratory parameters between pre-operative and post-operative data. Overall, the pooled results demonstrated a DOR of 15.18 (95% CI; range, 3.52–65.43) and an area under the curve (AUC) of 0.88. These values indicate an informative index test with a good overall diagnostic accuracy, and suggest that they are suitable for identifying OSA in children. Finally, the last study regarding pediatric OSA investigated a new method to simplify and integrate multiple variables using a clinical decision rule model. This tool, despite the need to be fully tested in daily practice, proved to be a solid way to overcome some of the aforementioned issues regarding the diagnosis of pediatric OSA, yielding a sensibility of 88% and specificity of 86%. Moreover, the AUC (0.897) demonstrated the utility of such instrument in the diagnosis of pediatric OSA.

b. Summary of key findings in adult OSA

The first and second study of adult OSA assessed the extensive list of surgical procedures available to treat OSA and focused on the intense debate around their efficacy. The results showed that future surgical strategies need to be targeted based

on the underlying mechanism and to move beyond a single level approach. A single procedure or a combination of surgeries is unlikely to cure apnea using a "one-size fits all" approach. However, individualized therapy based on the patient's underlying anatomy is likely to be more effective in the treatment of adult OSA. In the early years after the description of OSA, tracheostomies were the primary surgical modality utilized to treat OSA subjects who had failed previous medical treatments. Despite being an effective treatment, the use of tracheostomies in clinical practice has decreased significantly after the emergence of newer procedures that show greater acceptance, but generally less effective treatment outcomes. Given the increase in obesity, traditional surgical modalities are even less effective, and the findings of this thesis revealed that tracheostomy should be considered in selected patients, including obese patients who have failed medical management, are not candidates for soft tissue surgery, and refuse a maxillomandibular advancement surgery or bariatric surgery.

An interesting debate is emerging in the literature. Instead of deciding between non-surgical and surgical options in the treatment of OSA, there is evidence that some surgical modalities, such as nasal procedures, might complement non-surgical treatments. Isolated nasal surgery in patients with OSA with nasal obstruction reduces the required pressure of therapeutic CPAP devices, and the current literature's objective and subjective data suggest that it also increases CPAP use in select patients, suggesting that a multi-disciplinary approach is advantageous in cases of adult OSA.

Despite being identified since the 1980s, a new surgical approach has been proposed progressively in recent years as a viable option in the management of adult OSA: hypoglossal nerve stimulation. Selective stimulation of the hypoglossal nerve during sleep may provide a physiological approach to the treatment of OSA based on the restoration or improvement of upper airway dilator muscle activity during sleep. The results demonstrate clinically significant decreases in the observed mean AHI, ODI, and ESS, combined with improvements in several quality of life scales. Moreover, these results seem to be stable through a 12-month follow-up period, with high rates of compliance/adherence to therapy.

Among new non-invasive treatments, myofunctional therapy appears to be an option for some patients. Because the dilator muscles of the upper airway play a critical role in maintaining an open airway during sleep, researchers have explored exercises and other airway training (singing, didgeridoo, instrument playing) that target oral cavity and oropharyngeal structures as methods to treat OSA. Despite the heterogeneity in oral and oropharyngeal exercises, overall improvements in polysomnographic outcomes and sleepiness were consistent, and current literature demonstrates that myofunctional therapy decreases AHI by approximately 50% in adults and 62% in children, and may serve as an adjunct to other OSA treatments.

2. Implications for Clinical Practice

a. Pediatric OSA

The results of this thesis indicate that single and combined symptoms and signs do not have a satisfactory diagnostic performance in predicting pediatric OSA. These results, taken together with the findings from a previous review[1], suggest that the diagnosis of pediatric OSA should be based on more reliable non-invasive methods. In recent years, several diagnostic tools have been developed that possess some degree of predictability in the detection of OSA and some of its consequences. However, such tools have not been evaluated extensively beyond the program in which they were developed, and their validity has not been assessed across different countries or settings (i.e., community versus referral populations). This thesis explores new diagnostic approaches and investigates the use of sleep devices without requiring investigator-attended overnight monitoring to acquire quality data. Despite the substantial heterogeneity, the results of this systematic review and meta-analyses suggest that unattended multichannel devices have a satisfactory overall diagnostic accuracy when compared with the gold standard of full PSG-tested type 1 devices. These devices possess a moderate sensitivity, which indicates that they can be used to rule out the target condition, and a moderate specificity pooled value, which indicates that they are suitable for identifying OSA in children. Using a cut-off of AHI > 1, the results showed a high sensitivity and a moderate specificity, which suggests that these devices may be more useful in cases of mild to moderate pediatric OSA. However, the results for both the LR+ and LR- were unsatisfactory when the analysis was expanded to LRs. Although the interpretation of LRs depends on the pre-test probability and clinical

context, an LR+ > 10 or LR− < 0.1 is considered convincing diagnostic evidence. Since diagnostic parameters are interdependent, independent weighting may yield spurious results and biased estimates. To overcome the interdependence problem and the threshold effect, we computed the summary receiver operating characteristic curve (SROC) with the associated AUC. The AUC pooled in the quantitative summary demonstrated a good diagnostic accuracy, which confirmed the main findings of all of the studies included in this thesis regarding the practicality of unattended multichannel devices in pediatric OSA. These results are of interest because an ambulatory technique, in contrast to conventional PSG, may be ubiquitously accessible and more cost-effective. Another notable finding in study 2 is that four of the included studies[2-5] advocated that unattended multichannel devices are important for managing the treatment of OSA and, thus, for the early detection of cases of residual or persistent OSA after a surgical procedure. This last item is crucial because the success rate of surgical treatment varies between 70% and 80%, leaving a substantial number of children with residual OSA.[6] Therefore, while the gold standard for OSA diagnosis remains attended laboratory PSG, unattended sleep studies should be used as a viable alternative. One suggested piece of equipment that has been put into practice in our medical setting is the overnight respiratory polygraphy (Nox-T3® in our studies). The exam is conducted at the patient´s home, with the accompanying parent sleeping in the same room with the child. The following parameters are measured: airflow through the nose, thoracic and abdominal plethysmograph to measure respiratory effort, and pulse oximetry. Polygraphy results are interpreted by a technician trained in pediatric sleep medicine.

Despite being an attractive solution, it should be noted that any simplified model of diagnosis must be evaluated with an understanding of the limitations of the simplified test, the patient population being tested, and careful consideration of the clinical issues of the child by a health professional trained in pediatric sleep medicine.

Although there have been technical advances in sleep devices, in a vast majority of medical settings, there may be no sleep equipment access at all. In such a situation, most physicians must rely on clinical symptoms and signs for identifying possible OSA patients who require further treatment. Understanding this issue, this thesis offers a solution through a clinical decision rule that takes into account some simple and practical parameters available in most medical settings. In the specific case of Portugal, the use of a validated questionnaire should bring more precision and confidence to future clinical and research projects.

b. **Adult OSA**

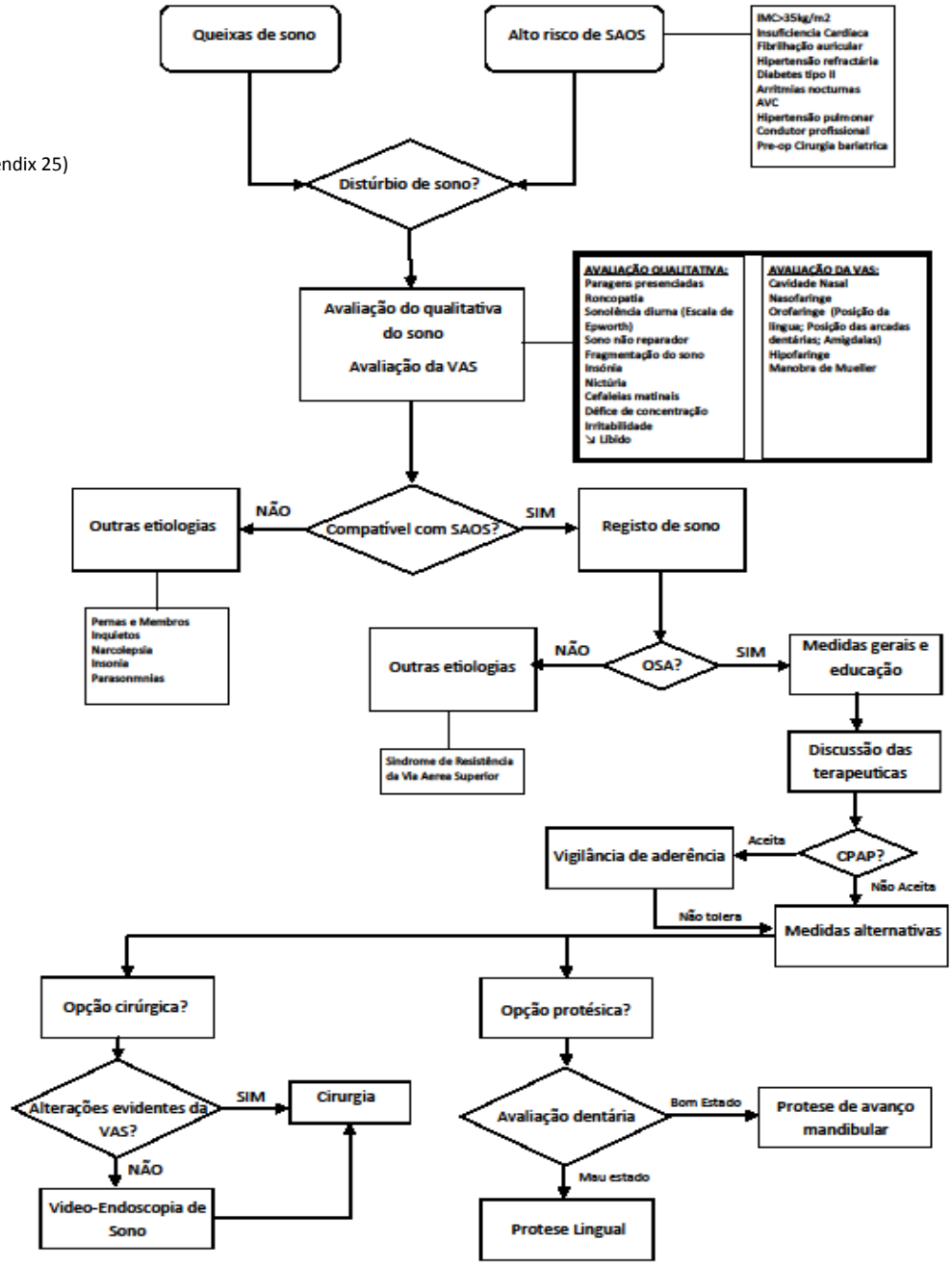
For many years, otorhinolaryngology surgeons, assuming only two sites of obstruction, pursued a concept that may be too mechanistic. For example, Fujita classified OSA patients into those with an obstruction solely behind the soft palate (type I), those with an obstruction solely behind the tongue (type II), and those with an obstruction behind both the soft palate and tongue (type III).[7]

This thesis demonstrates that characterizing surgical candidates is essential. Surgery treats anatomic abnormalities, and there is substantial evidence suggesting that surgical outcomes depend on the pattern of upper airway obstruction. In general, incorporating surgical procedures to treat regions or structures responsible for obstruction in an individual patient improves outcomes. Unfortunately, there is no gold standard for evaluation. Most available techniques are limited by being static examinations and/or performed during wakefulness; they have not proven adequate for characterizing sleep-related patterns of obstruction for most patients. Drug-induced sleep endoscopy is a promising technique because it defines dynamic airway examination under sedation (albeit not natural sleep), but this technique is not well understood and has its own limitations including cost.[8]

In the light of the variability in the manifestation of OSA in patients and the gaps in our knowledge about which patients will suffer cardiovascular consequences of this disease, significant controversy exists with respect to the selection of patients for OSA treatment. Proper evaluation and diagnosis of patients with OSA are critical for

determining a suitable treatment plan. Clearly, a patient whose depression is misdiagnosed as OSA or, conversely, a patient whose OSA is misdiagnosed as depression will receive a treatment plan inappropriate for his clinical condition. In the evaluation of a patient with suspected sleep-disordered breathing, the history and physical examination, as well as various adjunctive studies and consultations are helpful to correctly diagnose and, therefore treat the patient. In order to simplify this process, the authors proposed the followed algorithm:

(*cf.* Appendix 25)



Another misconception in daily practice is that surgical and non-surgical options are opposing treatments. In the literature, the concept of *continuum* of disease is used frequently. The level of disease in an individual patient can improve or worsen, with the patient moving up or down this continuum both over time and on a night-to-night basis. In this thesis, we introduce the concept of *continuum* of treatment. OSA treatment can be viewed as a *continuum* from CPAP to surgical treatment or oral appliances at a different time points during the disease or different patient expectations. None of the treatments exclude the previous or the future treatment, and the *continuum* of treatment adapts to the *continuum* of disease.

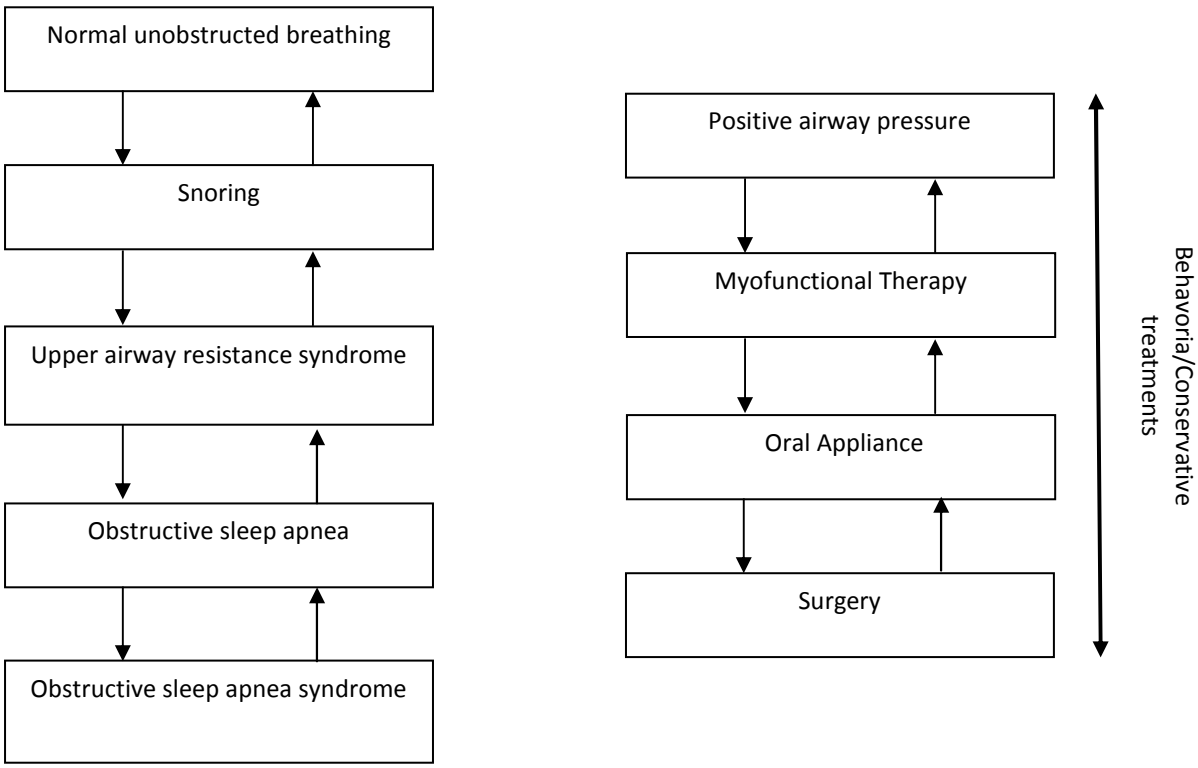


Figure – The concept of continuum of disease and continuum of treatment

Parameters such as weight loss, patient preferences, compliance to treatment, and efficacy could move the therapy up or down this new *continuum*, requiring long-term monitoring by professionals from the various specialties involved in the treatment of OSA. In addition, in the case of nasal surgery, these parameters may complement treatment compliance to both CPAP and oral appliances. Moreover, behavioral/conservative treatments such as weight reduction, optimizing of sleeping hygiene, avoidance of certain sleep positions, and drug treatment can work synergistically with these other options. Despite the controversy in literature, the results of this thesis reinforced the role of surgery in this *continuum*, and this role is now based on solid evidence.

3. Future Directions

a. Pediatric OSA

This thesis aimed to resolve problems regarding the diagnosis of pediatric OSA and proposed some models to overcome issues related to this specific pathology. However, the proposed tools should be established and validated in various age groups, as many of the symptoms and signs are age dependent. Further studies should define explicit criteria for identifying symptoms and signs, interpret the index tests (symptoms and signs) and reference tests blindly, and include patients from primary care settings.

Multiple sites can be narrowed in children with OSA, including the retropalatal and retrolingual areas. Moreover, the obstruction patterns of the upper airway when a patient is awake may differ from those during sleep. Therefore, an ideal diagnostic

method for OSA patients should evaluate both the structural component and the dynamic changes in the upper airway during sleep.[9]

MRI is a noninvasive imaging technique that avoids ionizing radiation and has provided valuable insights into understanding upper airway anatomy and function in patients with OSA syndrome. MRI sleep studies have been shown to be a useful tool in the evaluation of children with OSA [10,11] and in assisting surgical planning in these patients. The most common identified entities include recurrent enlargement of the adenoids and tonsils, enlargement of the lingual tonsils, abnormal soft palate, glossoptosis, and hypopharyngeal collapse.[12]

For sleep study, the MRI protocol should include a 3D volumetric MR acquisition of the upper airways (e.g. flash gradient echo sequence) for the posterior 3D reconstruction and a cine-MRI sequence to demonstrate a reproduction of physiological airway motion.[13]

The use and implementation of MRI to study OSA patients routinely in Portugal would be innovative and of great interest for otorhinolaryngologists and pediatricians. The Cincinnati Children's Hospital Medical Center is the only institution with a history of the clinical use of MRI to assess OSA patients[14]. Therefore, sleep MRI appears to be an interesting tool for OSA screening and should be a topic for further investigation.

Another possible line of research in this field is the impulse oscillometry. The forced oscillation technique (FOT) was developed in 1956 to measure the impedance of the respiratory system through application of small pressure oscillations at the mouth during normal breathing. FOT systems use pseudorandom noise signals to enable the simultaneous measurement of respiratory resistance (Rrs) and reactance (Xrs).[15] The impulse oscillometry system (IOS) is a type of FOT but with 2 important differences; rectangular wave form impulses are applied instead of pseudorandom noise signals, and the IOS has a different set of data outputs. In short, rectangular mechanical impulses containing the whole frequency spectrum are applied to the respiratory system through a mouthpiece while the patient is breathing quietly. The resulting pressure and flow signals are analyzed for amplitude, and the impedance (Z) represents the total mechanical load of the subject's respiratory system from which the resistance (R) and the reactance (X) of the respiratory system can be derived. The frequency range of the signal was from 5 to 35 Hz.[16] In IOS, the impedance at 5 Hz (Z5) represents the impedance of the total respiratory system, while those at frequencies ≥20 Hz (Z20) are thought to be damped out before reaching the peripheral airways, which could be an indirect way to evaluate the upper airway resistance (UAR).[17] Increased UAR was shown to play a role in the pathogenesis of OSA through the association with increased susceptibility of airway narrowing and collapse. In children, enlarged tonsils and adenoids play a major role in OSA. In addition to anatomic obstruction, upper airway patency is regulated by neuromotor input. During sleep, muscle tone decreases continuously with increased stage of sleep, reaching a nadir during REM when muscle activity is barely detectable.[18] Chemoreceptors sense changing levels of CO2 and

oxygen, resulting in a compensatory increase in respiratory muscle activity. In a recent study[19], pressure-flow values were used to assess the upper airway neuromotor response in sleep apnea patients versus control subjects. The airway neuromotor response to induced hypercapnia and decreased pressure were measured. Non-OSA patients were noted to have a 90% increase in airflow for a given pressure when exposed to hypercapnia compared with only 27% in the OSA patients. Thus, the upper airway dynamic response is reduced in patients with OSA, possibly due to habituation or mechanical damage, leading to an increase upper airway resistance. Also, this instrument has the advantage of being convenient, noninvasive and requiring minimal cooperation of the patient (approved for child > 2 years).

Therefore, impulse oscilometry appears to be an interesting tool on OSA screening, but have not been yet fully tested in the pediatric population.

b. Adult OSA

The current diagnostic methods for OSA include in-laboratory polysomnography (PSG) and home portable monitoring, both of which report the apnea–hypopnea index (AHI) as the primary metric of OSA severity. Furthermore, the effectiveness of surgical treatments for OSA is almost exclusively on reported changes in AHI. However, by focusing almost exclusively on the AHI leads to missed opportunities to better risk-stratify patients by using other OSA related variables.

The role of surgery in patients with OSA has been the object of great debate over the years. Our overview of reviews (Appendix 6) showed that reporting the results of surgery based almost exclusively on changes of AHI could lead to conflicting results regarding not only efficacy but also indications and definitions for successful surgeries.

The AHI is commonly used to determine OSA severity, and consequently, its association with cardiovascular disease[20,21]; however, there is significant subjectivity, variability, and discrepancy in AHI scoring criteria. The AHI depends largely on hypopnea scoring, which is a subject of great controversy as mentioned in the latest Deliberations of the Sleep Apnea Definitions Task Force of the American Academy of Sleep Medicine report. Factors affecting AHI scoring include intraindividual (patient) AHI variability from night to night, variability between scorers, and last, sleep laboratories that vary in scoring criteria and/or interpretation of the rules.

Punjabi et al.[22] demonstrated that hypopneas associated with desaturations are independently associated with cardiovascular disease; however, no association was observed between cardiovascular disease and hypopneas associated with arousals (no desaturations). Because improvement of cardiovascular disease risk is considered one of the purposes of surgery for OSA, the oxygen desaturation index may provide a more consistent metric for appraisal of surgical treatment. Kendzerska et al.[23] demonstrated that other polysomnography outcomes such as time with oxygen saturation below 90%, degree of sleep fragmentation, and total sleep time were associated with worse cardiovascular outcomes, whereas AHI was not.

The real goal of surgery is not solely to cure OSA in terms of AHI reduction but to control symptoms and minimize ongoing multisystem damage. It is important to include both subjective and objective measures of disease burden. Someday, the definition of OSA may need to be revised, to reflect not simply the AHI but the actual physiologic (degree and length of oxygen desaturation, heart rate variability changes,

sleep fragmentation, sleep deprivation, and sympathetic activation) and patient-centered consequences (quality of life, patient perception of disease) that occur.

3. Concluding Remarks

This thesis represents a major effort to bring together consistent evidence pertaining to both pediatric and adult OSA. Many challenges exist in this field. Successful treatment requires a minimum of three steps: accurate diagnosis, correct selection of therapy, and rigorous application and monitoring.

In the field of pediatric OSA, it remains unanswered whether the level of complexity of a laboratory PSG is required for routine diagnosis of pediatric OSA. Polysomnographies can be difficult to perform and analyze; sleep measurements using EEG, electrooculograms, and electromyograms are largely responsible for this complexity. Despite our results demonstrating the utility of simpler diagnostic methods, EEG measurement during sleep can be important in certain situations, such as in the detection of nocturnal seizure disorders. Thus, any simplified diagnostic model must be backed by an understanding of its limitations. In addition, knowledge about the patient population being tested, and careful consideration of their clinical features by a health professional trained in sleep medicine is essential.

In adults, surgical treatment of OSA is the most controversial, confusing, and frustrating procedure performed by otolaryngologists. As demonstrated by this thesis, surgery does not have a single role in the treatment of disease. In fact, with regard to sleep-

disordered breathing, it could prevent or cure the disease, reduce disease severity resulting from the failure of other treatments, or serve as an ancillary treatment to augment the benefits of other therapies. Currently, the opportunities to cure or prevent disease are infrequent. Surgery is more frequently performed to improve function following treatment failure or to supplement other therapies. As sleep-disordered breathing is a chronic, presumably life long condition, the need to adjust and modify therapies is inescapable. Therefore, in the future, surgery should aim to provide reconstructive techniques for lifelong airway management.

References

1. Morielli A, Ladan S, Ducharme FM, Brouillette RT. Can sleep and wakefulness be distinguished in children by cardiorespiratory and videotape recordings Chest 1996;109:680–687.
2. Jacob SV, Morielli A, Mograss MA, Ducharme FM, Schloss MD, Brouillette RT. Home testing for pediatric obstructive sleep apnea syndrome secondary to adenotonsillar hypertrophy.Pediatr Pulmonol 1995;20:241–252.
3. Hamada M, Iida M. Home monitoring using portable polygraphy for perioperative assessment of pediatric obstructive sleep apnea syndrome. Tokai J Exp Clin Med 2012;37:66–70.
4. Alonso-Alvarez ML, Navazo-Eguia AI, Cordero-Guevara JA, et al. Respiratory polygraphy for follow-up of obstructive sleep apnea in children. Sleep Med 2012;13:611–615.
5. Navazo Eguia AI, Alonso Alvarez ML, de la Mata Franco G, Cordero Guevara J, Teran Santos J, Ordax Carbajo E. Evaluation of the efficacy of adenotonsillectomy for the treatment of obstructive sleep apnea hypopnea syndrome in children using respiratory polygraphy. An Pediatr (Barc) 2013;78:308–313.
6. Brietzke SE, Gallagher D. The effectiveness of tonsillectomy and adenoidectomy in the treatment of pediatric obstructive sleep apnea/hypopnea syndrome: a meta-analysis.Otolaryngol Head Neck Surg 2006;134:979–984
7. Fujita S . UPPP for sleep apnea and snoring . Ear Nose Throat J 1984 ; 63 : 227 – 35 .
8. Abdullah VJ , van Hasselt CA . Video sleep nasendoscopy . In: Surgical Management of Sleep Apnea and Snoring. Terris DJ , Goode RL , eds . Boca Raton, FL : Taylor & Francis ; 2005 , pp. 143 – 54 .
9. Lee CH, Won TB, Cha W, Yoon IY, Chung S, Kim JW. Obstructive site localization using multisensor manometry versus the Friedman staging system in obstructive sleep apnea.Eur Arch Otorhinolaryngol2008;265:171–177.
10. Suto Y, Inoue Y. Sleep apnea syndrome: examination of pharyngeal obstruction with high-speed MR and polysomnography.Acta Radiol1996;37:315–320.
11. Donnelly LF, Surdulescu V, Chini BA, Casper KA, Poe SA, Amin RS. Upper airway motion depicted at cine MR imaging performed during sleep: comparison between young patients with and those without obstructive sleep apnea. Radiology 2003;227:239–245.
12. Bradley TD, Brown IG, Grossman RF, et al. Pharyngeal size in snorers, nonsnorers, and patients with obstructive sleep apnea. N Engl J Med 1986;315:1327–1331.
13. Donnelly LF: Obstructive sleep apnea in pediatric patients: Evaluation with cine MR sleep studies. Radiology 236:768-778, 2005
14. Donnelly LF, Surdulescu V, Chini BA, et al: Upper airway motion depicted at cine MR imaging performed during sleep: Comparison between young patients with and those without obstructive sleep apnea. Radiology 227:239-245, 2003
15. Cao J, Que C, Wang G, He B (2009) Effect of posture on airway resistance in obstructive sleep apnea–hypopnea syndrome by means of impulse oscillation. Respiration 77:38–43
16. Vogel J, Smidt U. Impulse oscillometry: analysis of lung mechanics in general practice and the clinic, epidemiological and experimental research. Frankfurt am Main; Moskau; Sennwald; Wien: pmi-Verl.-Gruppe, 1994.
17. Schmekel B, Smith HJ. The diagnostic capacity of forced oscillation and forced expiration techniques in identifying asthma by isocapnic hyperpnoea of cold air. Eur Respir J 1997;10:2243-9
18. Heraghty JL, Hilliard TN, Henderson AJ, Fleming PJ. The physiology of sleep in infants. Arch Dis Child.2008;93(11):982–985.
19. Cao J, Que C, Wang G, He B (2009) Effect of posture on airway resistance in obstructive sleep apnea–hypopnea syndrome by means of impulse oscillation. Respiration 77:38–43

20. Bixler EO, Vgontzas AN, Lin HM, et al. Association of hypertension and sleep-disordered breathing. Arch Intern Med 2000;160:2289–2295.
21. Shahar E, Whitney CW, Redline S, et al. Sleep-disordered breathing and cardiovascular disease: cross-sectional results of the Sleep Heart Health Study.Am J Respir Crit Care Med 2001;163:19–25.
22. Punjabi NM, Newman AB, Young TB, Resnick HE, Sanders MH. Sleep-disordered breathing and cardiovascular disease: an outcome-based definition of hypopneas.Am J Respir Crit Care Med 2008; 177:1150–1155.
23. Kendzerska T, Gershon AS, Hawker G, Leung RS, Tomlinson G. Obstructive sleep apnea and risk of cardiovascular events and all-cause mortality: a decade-long historical cohort study. PLoS Med 2014; 11:1001599.

Appendix