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Evaluation of measures used for diagnosis of obstructive sleep apnea in children

Evelyn Constantin, MD FRCPC

Department of Epidemiology and Biostatistics
McGill University
Montréal, Québec

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Your file Votre référence
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To my mother, Jeannette,
my role model

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CONTRIBUTION OF AUTHORS

This thesis centers around two manuscripts.

The first manuscript,

> Evaluation of the OSA-18 quality of life questionnaire in children referred for obstructive sleep apnea. E Constantin, T Tewfik, RT Brouillette,

will be submitted to *Pediatrics*. All authors contributed either to the study conception, statistical analysis or editorial process. I conducted the literature review and with the guidance and support from co-authors, I was primarily responsible for the development of the research questions, study design, data management, and all statistical analyses. I interpreted the results and was responsible for the planning and writing of the manuscript, with the assistance and feedback of the co-authors mentioned above.

For the second manuscript,

> Pulse rate and pulse rate variability decrease following adenotonsillectomy for obstructive sleep apnea. E Constantin, CD McGregor, V Cote, RT Brouillette, Pediatric Pulmonology (Published in *Pediatric Pulmonology:* 2008 May;43(5):498-504),

all authors contributed to the study design, study development and writing the manuscript. With guidance and collaboration from the other authors, I was responsible for the literature review, formulation of hypotheses, and the study design. I conducted thorough chart reviews on the study subjects, collected the raw data and entered all the data for the variables of interest. A co-author (CD McGregor) double-checked all data entries. I was primarily responsible for the data management, all statistical analyses, interpretation of the results, and the writing and preparation of the manuscript for publication.

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ABBREVIATIONS

AAP: American Academy of Pediatrics

AHI: apnea hypopnea index

BMI: body mass index

Bpm: beats per minute

CI: confidence interval

DI_4: number of desaturations ≥4% /hour of study

DI_{90}: number of desaturations to ≤ 90% /hour of study

EKG: electrocardiogram

HR: heart rate

HRV: heart rate variability

HRQOL: health-related quality of life

IQR: interquartile range

MOAHI: mixed obstructive apnea hypopnea index

MOS: McGill Oximetry Score

OSA: obstructive sleep apnea

OSA-18: OSA-18 quality of life questionnaire

OR: odds ratio

PR: pulse rate

PRV: pulse rate variability

PRRI: pulse rate rise index

PSG: polysomnography

REM: rapid eye movement

ROC: receiver operating curve

SD: standard deviation

S_pO_2: oxygen saturation (measured by pulse oximetry)

T&A: adenotonsillectomy

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ABSTRACT

BACKGROUND: In children, sleep-related airway obstruction by large tonsils and adenoids can cause obstructive sleep apnea (OSA). OSA may lead to poor growth, developmental delay, behaviour or learning problems. Recent evidence also suggests that children with OSA may develop cardiovascular complications, the mechanisms perhaps involving hypoxemia, the autonomic nervous system, apneas, and arousals. Surgical removal of tonsils and adenoids (adenotonsillectomy (T&A)) usually cures pediatric OSA. To diagnose OSA at all levels of severity, polysomnography is currently the best approach. The McGill Oximetry Score (MOS) is a validated measure based on nocturnal pulse oximetry. An abnormal MOS has a 97% positive predictive value at detecting moderate-severe OSA. Because the MOS was devised by measuring frequency of desaturations (<90%) and numbers of clusters of desaturations, it is not accurate at detecting OSA in children who do not have such drops in oxygen saturation. Accordingly, other measures applicable to a wider spectrum of children should be assessed. These measures should be simpler, less cumbersome, cheaper, and more accessible than polysomnography.

OBJECTIVES: To study alternative approaches that may be used to identify moderate-severe OSA in children, two studies were conducted. We examined one subjective measure - the OSA-18 parent questionnaire - and two objective measures - pulse rate and pulse rate variability. For the OSA-18 study, the goal was to determine whether it would accurately detect children with moderate-severe OSA as indicated by an abnormal MOS. For the pulse rate and pulse rate variability study, the goal was to determine if either or both would decrease after treatment with T&A for children with moderate-severe OSA.

METHODS: For the OSA-18 study, we used a cross-sectional design that included children 1-18 years old referred to a pediatric sleep laboratory for evaluation of suspected OSA. Alongside data from the OSA-18, we analyzed demographic and medical data (from a parent questionnaire) and information regarding adenotonsillar hypertrophy. We estimated sensitivity, specificity, positive and negative predictive values as well as receiver operating curves of the OSA-18 in detecting an abnormal MOS. We also conducted univariate and multivariate logistic regression analyses, using the MOS as the

dependent variable and the OSA-18 score and others (age, gender, comorbidities, race) as independent variables. For the second study, we used a retrospective before-after design to compare pulse rate and pulse rate variability as measured by nocturnal pulse oximetry pre- and post-T&A of otherwise healthy children 1-18 years old with moderate-to-severe OSA.

RESULTS: For the OSA-18 study, we studied 334 children (58% male, mean age 4.6 ± 2.2 years.) The OSA-18 had a sensitivity of 40% and a negative predictive value of 73% for detecting an abnormal MOS. In addition, the area under the receiver operating curve was 0.611. While controlling for other independent variables in the logistic regression model, for each unit increase in the OSA-18 Score, the odds of having an abnormal MOS were increased by 2%. However, for each increase in age of 1 year, the odds of having an abnormal MOS were decreased by 17%. In the pulse rate and pulse rate variability study, 25 subjects (88% male; mean age 4.3 ± 3.6 years) were enrolled. Following T&A, pulse rate and pulse rate variability decreased in 21 of 25 and 23 of 25 children, respectively. Mean pulse rate dropped from 99.7±11.2 to 90.1±10.7 bpm, $p<0.001$; age-standardized pulse rate (z-score) from 0.8 (0.4, 1.5) to 0.4 (0, 0.9), $p=0.04$). Pulse rate variability, as measured by the standard deviation of the pulse rate decreased from 10.3 ± 2.1 to 8.2 ± 1.6 bpm, $p<0.001$. As well, OSA symptomatology, parental concern about breathing during sleep and the MOS all improved.

CONCLUSIONS: Based on the first study we conclude that among children referred to a sleep laboratory, the OSA-18 does not accurately detect which children will have an abnormal MOS. The OSA-18 should not be used in place of objective testing to identify moderate-severe OSA in children. However, from the second study we conclude that measures of the autonomic nervous system such as pulse rate and pulse rate variability, as measured by pulse oximetry, decreased following surgical treatment of moderate-severe OSA. The results of this study potentially serve as important data for further work that would determine the accuracy of pulse rate and pulse rate variability measures and their diagnostic usefulness for OSA at all levels of severity.

RÉSUMÉ

INTRODUCTION: Chez les enfants, l'obstruction de voies respiratoires durant le sommeil par des amygdales et/ou des adénoïdes hypertrophiés peut conduire à l'apnée obstructive du sommeil (AOS). L'AOS peut conduire à un retard de croissance ou de développement, ainsi qu'à des troubles de comportement ou d'apprentissage. Plus récemment de nouvelles données semblent aussi indiquer que les enfants avec AOS peuvent développer des complications cardiovasculaires, dont l'un des mécanismes pourraient être l'association entre l'hypoxémie, le système nerveux autonomique, l'apnée, et l'éveil. L'ablation chirurgicale des adénoïdes et/ou amygdales (adéno-amygdalectomie (AA)) est le traitement usuel de l'AOS chez les enfants. La polysomnographie est à l'heure actuelle la meilleure méthode pour diagnostiquer l'AOS quelle qu'en soit la sévérité. Le « McGill Oximetry Score » (MOS) est une mesure validée basée sur l'oxymétrie nocturne. Un MOS anormal a une valeur prédictive positive de 97% pour la détection de l'AOS modérée à sévère. Puisque le MOS mesure la fréquence des désaturations importantes (<90%) et la fréquence des périodes ('clusters') de désaturations, le MOS n'est pas une mesure précise pour la détection de l'AOS chez les enfants qui ne présentent pas de désaturations importantes. Il est donc nécessaire d'évaluer d'autres méthodes applicables à un plus grand spectre d'enfants, et en même temps plus simples, moins coûteuses, moins encombrants et plus accessibles que la polysomnographie. **OBJECTIFS :** Pour évaluer d'autres méthodes qui pourraient être utilisés pour identifier les enfants avec l'AOS modérée à sévère, deux études ont été menées. On a examiné une mesure subjective, le questionnaire parental (l'AOS-18), et deux mesures objectives, le pouls et la variabilité du pouls. Le but de l'étude de l'AOS-18 est de déterminer s'il peut identifier de façon précise les enfants à risque de souffrir d'AOS modérée à sévère, telle que diagnostiquée par un MOS anormal. L'étude sur le pouls et sa variabilité a pour but de déterminer si l'une de ces données ou les deux diminueraient après l'AA chez les enfants avec AOS modérée à sévère. **MÉTHODES :** L'étude de l 'AOS était une étude transversale sur des enfants âgés de 1 et 18 ans référés au laboratoire de sommeil pédiatrique pour évaluation d'un diagnostic d'AOS. En plus des données du AOS-18, nous avons analysé les données médicales et démographiques et le degré d'hypertrophie des amygdales et des adénoïdes. On a evalué la sensibilité, la

spécificité, les valeurs de prédiction positive et négative ainsi que les courbes caractéristiques d'opération du récepteur du questionnaire AOS-18 pour détecter un MOS anormal. On a aussi effectué des analyses par régression logistique univariable et multivariable, en utilisant le MOS comme variable dépendante et l 'AOS-18 et d'autres variables (l'âge, le sexe, les comorbidités, la race) comme variables indépendantes. La deuxième étude était une étude rétrospective qui a comparé le pouls et sa variabilité tels que mesurés par oxymétrie nocturne avant et après AA chez des enfants de 1 et 18 ans avec AOS modérée à sévère, mais sans autre morbidité. **RÉSULTATS :** Pour l'étude de l'AOS-18, nous avons étudié 334 enfants (58% de sexe masculin, âge moyen de 4,6± 2,2 ans). Le score AOS-18 avait une sensibilité de 40% et une valeur prédictive négative de 73% pour la détection d'un MOS anormal. De plus, l'aire sous la courbe caractéristique d'opération du récepteur était 0,611. En contrôlant pour les autres variables indépendantes dans le modèle de régression logistique, le risque d'avoir un MOS anormal augmentait de 2% pour chaque augmentation du score AOS-18. Ce risque augmentait de 17% pour chaque année d'âge. Pour l'étude du pouls et de sa variabilité, 25 sujets (88% de sexe masculin; âge moyen de 4,3 ± 3,6 ans) ont été évalués. Après AA, les mesures de pouls et de sa variabilité ont diminué dans 21/25 et 23/25 enfants, respectivement : le pouls moyen de 99,7±11,2 à 90,1±10,7 battements par minute (bpm) ($p<0,001$); le pouls standardisé pour l'âge (scores-z) de 0,8 (0,4 – 1,5) à 0,4 (0 – 0,9), $p=0.04$). La variabilité du pouls telle que mesurée par la déviation standard du pouls a diminué de 10,3±2,1 à 8,2±1,6 bpm, ($p<0,001$). De même, la symptomatologie due à l'AOS, l'inquiétude parentale et le MOS se sont améliorés. **CONCLUSIONS:** La première étude nous montre que, pour les enfants référés au laboratoire du sommeil, l'AOS-18 ne permet pas d'identifer avec précision les enfants qui auraient une oxymétrie nocturne anormale. Cette mesure ne doit pas se substituer aux évaluations objectives de l'AOS modérée à sévère chez les enfants. Cependant, d'après la deuxième étude, nous pouvons conclure que les mesures du système nerveux autonomique telles que le pouls et sa variabilité obtenus par oxymétrie ont diminués après traitement chirurgical de l'AOS modérée à sévère. Les résultats de cette étude servent de base importante pour des travaux ultérieurs qui viseront à déterminer si les mesures de pouls et de sa variabilité peuvent diagnostiquer avec précision les cas d'AOS de toux niveaux de sévérité.

CHAPTER 1. INTRODUCTION

1.1 Overview of the thesis

Childhood obstructive sleep apnea (OSA) is an important and prevalent disorder. OSA in children is a disorder of breathing during sleep usually caused by blockage of the airway from large tonsils, adenoids or both.[1-3] Numerous studies have shown potential links between OSA (particularly severe OSA) and adverse outcomes such as poor growth, developmental delay, cardiovascular complications, metabolic and inflammatory conditions, behaviour, or learning problems.[2-14] For those children who have OSA secondary to adenotonsillar hypertrophy, the most common treatment is surgical removal of the adenoids, tonsils or both (adenotonsillectomy (T&A)).[15] Before taking a decision to operate for OSA, the disorder must ideally be diagnosed to distinguish between snoring and clinically significant OSA.

It has been shown that history and physical examination in isolation or in combination are inaccurate at diagnosing OSA in children.[16,17] Likewise, several questionnaires that have been evaluated have also not proven to be accurate as diagnostic tools for OSA.[5,17,18] Among these, the OSA-18, an OSA-specific quality of life questionnaire[19], is especially widely cited and is used by some otolaryngologists in our institution. It has been proposed by Fischer et al. as a useful diagnostic measure that could replace objective testing, such as polysomnography (PSG).[20] However, the investigators who conducted this study did not compare the OSA-18 against any objective measure of OSA. Therefore we decided to evaluate the accuracy of the OSA-18 in detecting moderate-severe OSA in children, as identified by nocturnal pulse oximetry. (Manuscript #1)

PSG is considered to be the best method for diagnosing OSA in children.[1] A PSG is an overnight laboratory study conducted by a respiratory therapist.[1] Several measures are obtained during a PSG: oxygen saturation using pulse oximetry; heart rate using electrocardiography; and other measures to evaluate sleep and breathing.[1] However, due

to lack of resources or expertise, many children do not have access to PSG. There is thus a need for other forms of testing for OSA in children.

Nocturnal pulse oximetry has been tested and validated against PSG.[21,22] Pulse oximetry is a tool that measures oxygen levels through a pulse signal, usually from the finger or toe. For pediatric studies done in the home, the oximeter probe is placed on the child's toe. Pulse oximetry records two channels: one for oxygen levels, the other for pulse rate. Normal oxygen saturation levels in children are usually between 96-100%.

The McGill Oximetry Score (MOS) is a measure that has been devised using nocturnal pulse oximetry.[22] An abnormal MOS is determined by the number of desaturations below 90% and the number of groups or "clusters" of desaturations. An abnormal MOS has been shown to have a high positive predictive value (97%) to detect moderate-severe OSA in children.[21,22] However, its primary limitation is its low negative predictive value and low sensitivity. This weakness may lead to missed cases. The explanation for this limitation of oximetry is that some children with OSA desaturate at night, while others do not. The clinical practice guideline for OSA from the American Academy of Pediatrics (AAP) has concluded that an abnormal MOS may be a good indicator of an abnormal PSG result and thus may be useful in discriminating between primary snoring and OSA.[15]

Thus far, investigators have only considered the oxygen saturation channel of pulse oximetry in children. Pulse rate and its variability during wake or sleep had not been evaluated. Moreover, changes in both pulse rate and its variability after treatment of OSA had not been studied. Therefore we decided to evaluate if pulse rate and its variability would decrease after T&A for treatment of moderate-severe OSA. (Manuscript #2)

1.2 Relevance for determination of subjective and objective measures for diagnosis of OSA in children

The best method to diagnose OSA in children is PSG. However, PSG is costly, time-consuming, requires specialized expertise, has limited accessibility, and may entail long waiting periods.[23-27] The inaccuracy of oxygen saturation testing alone for the diagnosis of OSA in those children who do not have significant desaturations is also a concern. Accordingly, it is important to develop other diagnostic measures for OSA or to improve those that now exist.

1.3 Objectives

The general objective of my thesis is to study alternative approaches to PSG that may be used to identify moderate-severe OSA in children. Three measures were examined. The first measure is subjective, the OSA-18 (Manuscript #1 (Chapter 3)). This is a parent questionnaire measuring OSA-specific quality of life[19] that has been proposed by at least one group of investigators as a replacement for objective testing (PSG, oximetry) of OSA in children.[20] We aimed to determine how well the OSA-18 identifies children at risk of having moderate-severe OSA, as determined by an abnormal MOS. The two other measures are objective - pulse rate and pulse rate variability, using nocturnal pulse oximetry (Manuscript # 2 (Chapter 4)). We aimed to determine if these measures would decrease after treatment with T&A for children with moderate-severe OSA.

The two studies encompass one theme - evaluation of measures (subjective and objective) for the diagnosis of moderate-severe OSA in children. The approach in each study, however, is different. In the first study, we used a cross-sectional design to estimate the accuracy of the OSA-18 in determining moderate-severe OSA as indicated by an abnormal MOS. For the second study, we used a before-after design to determine the change in pulse rate and pulse rate variability after treatment of moderate-severe OSA as

indicated by an abnormal MOS. These two studies have produced new, interesting and important results regarding diagnostic tools for OSA in children.

1.4 Outline of the thesis

This is a manuscript-based thesis and complies with McGill University thesis guidelines. The thesis includes two manuscripts: one has been published (*Pediatric Pulmonology*), the other is to be submitted to a peer-reviewed journal (*Pediatrics*). Chapter 2 is a literature review on OSA in children, highlighting the pathophysiology, demographics, clinical outcomes, treatment, and a review of diagnostic tools for OSA. A subsection highlights the relationship between the cardiovascular system and OSA, with emphasis on heart rate variability. Subjective tools for evaluation of OSA are also discussed, with a brief review of two questionnaires for OSA (the Pediatric Sleep Questionnaire and the Brouillette OSA Score) and a review of quality of life measurements, specifically the OSA-18. Chapter 3 consists of the first of the two manuscripts. This manuscript focuses on how well the OSA-18 identifies children at risk of having OSA severe enough to cause repeated desaturations. Chapter 4 is the second manuscript presented, which describes how pulse rate and pulse rate variability decrease following treatment of OSA. Chapter 5 summarizes the thesis as a whole. It describes each study's strengths and limitations and emphasizes key and overarching conclusions. Future directions are discussed.

Due to the nature of a manuscript-based thesis, inevitably there is some repetition between the manuscripts and the text of the thesis.

CHAPTER 2. LITERATURE REVIEW

2.1 Obstructive Sleep Apnea (OSA) in Children

2.1.1. Definition of OSA

Obstructive sleep apnea (OSA) is a sleep-related breathing disorder characterized by upper airway obstruction that leads to disrupted sleep with frequent arousals and abnormal respiratory gas exchange.[1-3] It has a reported prevalence of 0.7 to 3 %,[28,29] with the highest prevalence of 3% reported by Gislason and Benedkitsdottir among children 6 months to 6 years old.[29]

2.1.2 Pathophysiology of OSA in children

There are two main components in the pathophysiology of OSA in children – anatomic and physiologic.

2.1.2.1 Anatomic: adenotonsillar hypertrophy

The most common cause of OSA in children is upper airway obstruction from enlarged adenoids, tonsils or both. [30] Other etiologies include craniofacial abnormalities, neuromuscular disorders, genetic disorders (such as Prader-Willi and Down syndromes), and obesity.[31]

Studies have shown that OSA in children most commonly occurs between 2 and 8 years, with a peak prevalence in preschool-aged children.[32] It is during this period that adenoids and tonsils are largest in comparison with the size of the airway.[30]

2.1.2.2 Physiologic: REM hypotonia

Although adenotonsillar hypertrophy is the most common cause of OSA, it has been shown that OSA is due to a combination of structural (i.e., craniofacial abnormalities, adenotonsillar hypertrophy) and neuromuscular components.[31] Studies have shown that obstructive apnea events in children are longer and more frequent during rapid-eye-movement (REM) sleep as compared to non-REM sleep.[33,34] The likely etiology is a REM-related deficit in upper airway and central nervous system function, leading to increased collapsibility of the upper airway causing obstructive events.[31]

2.1.3. Demographics of OSA in children

2.1.3.1 Age

Many differences exist between adult and childhood OSA.[32] As described above (Section 2.1.2), OSA is more common in younger children (ages 2 to 8 years) due to increased adenotonsillar size at that age. Key factors in adults have been summarized in a recent publication by Chung et al.[35] They coined a mnemonic for the key factors in adult OSA called STOP-BANG: **S**noring, **T**iredness, **O**bserved apneas, **P**ressure (hypertension), **B**ody-mass-index (BMI), **A**ge, **N**eck circumference, **G**ender.[35] Of the eight predictive factors, only 2 (snoring, observed apneas) appear to apply to both adults and children.

2.1.3.2 Race and gender

Race may play a role in sleep-disordered breathing and OSA in children.[36-42] Several groups have shown that OSA is more common among black children.[37,38,41,42] Children in Asia also have prevalent sleep-disordered breathing.[40] Chng et al. found that children of Malay descent in Singapore had more habitual snoring than Chinese or Indian children.[40] Generally, there is no significant difference in prevalence of sleep-disordered breathing

between boys and girls,[37] although some studies have shown a higher prevalence in adolescent boys.[43-45]

2.1.3.3 Obesity

Several studies have evaluated snoring and obesity in children and have shown a greater likelihood of sleep-disordered breathing in obese children.[36,37,40,43-47] Obesity may be a more important risk factor in adolescents as compared to younger children.[48] However, some studies are difficult to interpret because the investigators used finite cut-off values for body-mass-index (BMI) for a wide age range, instead of using BMI percentiles.[36,37,45]. Further work needs to be done to more accurately evaluate the relationship between childhood obesity and OSA.

2.1.4 Clinical sequelae

OSA in children may result in morbidity and sequelae.[2-12] In children, death secondary to OSA has been documented in the literature, but is rare.[31]

2.1.4.1 Cardiovascular sequelae

Untreated, severe OSA may lead to right-sided and left-sided heart conditions, notably congestive heart failure, pulmonary hypertension and cor pulmonale, left ventricular hypertrophy, left-ventricular diastolic dysfunction, systemic hypertension, and failure of systemic blood pressure to decrease at night.[4,9,10,49,50] The pathogenesis of these changes remains unknown but may involve inflammatory cytokines and up-regulation of sympathetic nervous stimulation to heart and blood vessels.[9,10] In Section 2.3, I have further elaborated on the cardiovascular system and OSA in children.

2.1.4.2 Growth failure

The association between failure to thrive and OSA has been reported[2,51] and it has been shown that treatment of OSA may lead to growth acceleration.[52] Postulated theories include the fact that children with OSA expend more calories and energy on breathing, whereas some may have reduced caloric intake due to difficulty swallowing with large tonsils. Impaired growth hormone secretion has also been reported.[53] With treatment of OSA, studies have shown improved weight gain and normalization of growth hormone secretion.[52-54]

2.1.4.3 Neurobehavioral outcomes in children with OSA.

A relationship has been reported between sleep-disordered breathing and neurobehavioral or cognitive deficits, or both..[6-8,55-62] Moreover, a few studies have evaluated neurobehavioral outcomes following T&A.[63-67] A recent review article highlights several studies that show an improvement of behaviour, cognition, and quality of life following adenotonsillectomy.[68] One study I previously conducted, however, showed no improvement in behaviour after adenotonsillectomy.[67] In that study, behaviour was measured using the Conners' Parent Rating Scale. This was the first study to show that, according to parental report, behaviour does not change in children with OSA after T&A.[67] Randomized-controlled trials proving a relationship between OSA and neurobehavioural problems need to be conducted.

2.1.5 Treatment of OSA

Adenotonsillectomy (T&A) is the treatment of choice for children with OSA due to adenotonsillar hypertrophy.[15] For most children, complete resolution of OSA is achieved with T&A.[15,24] A metanalysis showed that the success rate was about 85%.[69] Failures may be related to surgical techniques, but more commonly are related to comorbid disorders such as obesity, neuromuscular weakness or craniofacial abnormalities.

Oftentimes before T&A, a trial of nasal steroids with or without antibiotics is conducted. A few studies have shown promise for this option, especially for those with adenoidal hypertrophy as the primary etiology of OSA.[70-72] A recent Cochrane review by Zhang et al. evaluated five randomized-controlled trials of intranasal steroids for airway obstruction in children with adenoidal hypertrophy.[73] Zhang et al. concluded that four of the five trials showed that intranasal corticosteroids may significantly improve symptoms of nasal airway obstruction and reduce adenoid size.[74-77] The conclusions from the Cochrane review were that more robust long-term studies need to be done to make formal recommendations.[73]

Other treatment modalities for OSA have been used, depending on the underlying etiology. These include surgical correction for craniofacial abnormalities,[78] and weight loss for obesity-related OSA.[79-81] Assisted ventilation (CPAP or BIPAP)[82] is used for some patients, including those who are not surgical candidates for T&A, those with persistent OSA despite T&A, or those with neuromuscular disease.

2.1.6 Complications of adenotonsillectomy

T&A is generally safe[83] but children often have painful perioperative courses. T&A has been associated with complications such as post-operative hemorrhage, respiratory difficulties, cardiorespiratory arrest, and anesthetic complications. Brown and coworkers report that children with severe OSA have fewer post-operative complications if they are operated on in the morning rather than in the afternoon[84] and that they require significantly lower doses of postoperative narcotics for adequate pain relief.[85] Risk factors for perioperative respiratory problems include young age (<3 years), an apnea/hypopnea index of > 5, oxygen saturation nadir of < 80% and/or comorbid disorders.[86-88]

2.2 Objective measures for diagnosis of OSA in children

2.2.1 Polysomnography

2.2.1.1 Advantages of Polysomnography

The American Thoracic Society guidelines state that laboratory polysomnography (PSG) is the best diagnostic test of choice (i.e., the gold standard) for OSA in adults and children.[1] PSG involves detailed evaluation of cardiorespiratory and neurological parameters in a pediatric sleep laboratory, including electroencephalography for determination of sleep and arousals, respiratory inductive plethysmography, electromyelography, end-tidal and transcutaneous carbon-dioxide measurements, oxygen measures using pulse oximetry, heart rate metrics using electrocardiography, and audiovisual recording to help determine physical signs of sleep apnea.[1,89-91] All these parameters are used to score the PSG and to establish the frequency of pauses of breathing (apneas) or decreased airflow (hypopneas) per hour of sleep called the mixed obstructive apnea hypopnea index (MOAHI). A MOAHI of more than one per hour is diagnostic of OSA in children.[89-91]

2.2.1.2 Limitations of polysomnography

Although PSG is considered the gold standard, the measure is burdensome, time-consuming, costly, and usually entails long waiting times.[23-27]

PSG is burdensome because it must be done in a sleep laboratory.[23] It is time-consuming with respect to the set-up, the duration of the study, and the scoring of the PSG study – about 14-16 hours in all. One sleep laboratory technician sets up the child in the laboratory, observes the child for the entire night, and then scores the PSG. Pediatric centers have published average costs for each PSG that range from $600US to $2800US. [24-26]

Although sleep medicine services are better developed for adults than children, similar concerns pertain. The waiting times for a patient to obtain a PSG are usually long and can vary among centers. In adults, few studies have looked at wait times.[92] Flemons et al. reported up to 36 months wait time for PSG in Canada and varying times in the United States, United Kingdom and Australia.[92] To date, there have been no formal reviews examining wait times for PSG for children.

At the Montreal Children's Hospital (MCH), we have a two-bed laboratory facility where we evaluate a variety of patients – most commonly, patients with and without comorbidities who are referred for symptoms of snoring and evaluation for OSA. We also evaluate patients for sleep-related movement disorders, those on assisted ventilation for disorders such as neuromuscular conditions, congenital central hypoventilation syndrome, and craniofacial disorders, as well as patients with central sleep apnea (Arnold Chiari malformations, neurological patients). Our wait time for polysomnography is up to 24 months (MCH Sleep Laboratory Annual Report, 2008). However, exceptions are made for patients who require more expedited evaluation.

In many locales, pediatric PSG is simply not available. In Canada, there are only 6 pediatric facilities conducting PSG studies. Their wait times vary but range from 12-24 months.(Personal communication, Canadian Pediatric Sleep Research Network Meeting, Montreal, 2008)

2.2.2 Alternative measures for pediatric OSA

Due to the disadvantages of PSG, other measures may be helpful in the evaluation of OSA in children. Three such tests that have been studied are home PSG, laboratory nap PSG, and nocturnal home oximetry.

2.2.2.1 Home Polysomnography

In adults, home cardiorespiratory monitoring has been recently approved for the evaluation of OSA.[93,94] A review from the American Academy of Sleep Medicine reports that portable monitoring may be an alternative to PSG in adults with a high pretest probability of moderate-severe OSA.[93,94] It would not be appropriate, however, for those with significant comorbidities, nor for general screening.[93,94]

Nasal pressure and thermistor wires are used in home studies in adults and in supervised pediatric laboratory studies. They should not be used in home studies in children because of concern related to the wires around the face and neck disturbing the child's sleep (and thus not providing a comprehensive sleep assessment), and because of the risk of strangulation in an unsupervised setting.[95-99]

It is important to note that while ambulatory monitoring systems (i.e., home PSG) have been used for research studies in older children,[15] these systems are not currently approved for clinical use. The AAP technical report for the diagnosis and management of OSA reported good comparability between one system for home PSG and laboratory PSG. [100] This is based on a study done at the Montreal Children's Hospital in 1995.[23,101] The home PSG set-up included a combination of electrocardiography, pulse rate, hemoglobin saturation, calibrated respiratory inductive plethysmography (thoracic and abdominal excursions), and video and audio recording.[23] These channels were chosen as they were suitable for home recordings and no wires were placed around the face and neck. A trained technician set-up the equipment in the child's home and picked up the equipment in the morning. Jacob et al. showed that the home PSG system had high sensitivity when compared to laboratory PSG,[23] but this system is not commercially available.

Poels et al. conducted a study comparing a home cardiorespiratory recording device to PSG.[102] Few recordings were technically acceptable and successful. One explanation could be that parents were instructed on how to perform the set-up, while in the study by

Jacob et al., a trained technician set-up the equipment in the child's home.[23] Poels et al. concluded that the device was not effective at diagnosing children for OSA. The AAP suggests that more research in this area of home PSG is needed.[15]

2.2.2.2 Nap polysomnography

Nap studies are also not considered acceptable by the AAP for definitive diagnostic testing for OSA.[27,103] This is based on studies that have shown nap PSG to have poor sensitivity and low negative predictive values.[103] Marcus et al. studied forty children (1 month to 16 years old) and showed that nap PSG had a sensitivity of 74%, negative predictive value of only 17%, but the specificity and positive predictive value were 100%. They concluded that nap studies could be useful if abnormal, but that inconclusive nap studies should be followed by a PSG.[103] Saeed et al. conducted a retrospective chart review of 143 children with suspected OSA secondary to adenotonsillar hypertrophy who underwent overnight PSG following normal or mildly abnormal nap studies. The sensitivity of a mildly abnormal nap study at detecting abnormal PSG was 68% and the specificity was 60%.[27] The inaccuracy of brief daytime nap PSG in children may be attributable to the paucity of REM sleep during these naps.[27,103]

2.2.2.3. Audiotaping and videotaping

The accuracy of detecting OSA in children using audiography and videography is variable. Only three studies have been published evaluating these diagnostic tools. The sensitivity of audiotape was 71% and its specificity was 80%[104], while audiotape with history and physical exam had a sensitivity of 92% but specificity was only 29%.[105] Home videotape recordings showed a sensitivity of 94% and a specificity of 68%.[106] The AAP concludes that the use of audiotaping or videotaping without any cardiorespiratory measurements has been inadequately studied.[15]

2.2.3 Nocturnal pulse oximetry

In children, normal oxygen saturation levels are usually between 96-100%. Pulse oximetry measures oxygen levels through a pulse signal using a probe placed around the child's toe. Two channels are recorded: one for oxygen levels, the other for pulse rate.

As mentioned in the Overview section (pg. 13), nocturnal pulse oximetry has been tested and validated against PSG.[21,22] In particular, overnight recordings of oxygen saturation in children with OSA showed desaturations secondary to brief airway obstruction of OSA.[21] In this thesis, I report on new findings from the pulse rate channel of overnight recordings in children with moderate-severe OSA (Chapter 4, Manuscript #2).

2.2.3.1 The McGill Oximetry Score

The McGill Oximetry Score (MOS), devised by Nixon and Brouillette at the Montreal Children's Hospital, is the only score that compares oximetry data to PSG in children.[21,22] The first study, conducted by Brouillette et al., evaluated nocturnal pulse oximetry as a testing modality for OSA in children.[21] They devised criteria for an abnormal study based on the number and depth of drops of oxygen saturation and number of groupings (or "clusters") of desaturation. Clusters of desaturation are important in the designation of OSA in children because it has been shown that obstructive apnea events occur in groups, and predominantly in REM periods.[33,34] Brouillette et al. reviewed patients who were evaluated in the sleep laboratory and for whom no decision regarding adenotonsillectomy was made at the time of referral or at the time of inclusion into the study.[21]

Using the criteria for clusters and abnormal number of desaturations below 90%, the investigators were able to differentiate between normal, inconclusive and abnormal oximetry.[21] The "normal" oximetry group had a median MOAHI of 0.3, those with "inconclusive" oximetries had a median MOAHI of 1.5, and those with abnormal oximetries had a median MOAHI of 16.4. This study showed that in a referral population

of children suspected of having OSA, an abnormal nocturnal pulse oximetry had a 97% positive predictive value for a diagnosis of OSA when compared with PSG. [21]

Nixon et al. later coined the term "McGill Oximetry Score" (MOS) for pediatric OSA. The score ranged from 1 to 4: a score of 1 was inconclusive; scores of 2, 3, and 4 were designated as abnormal (i.e., consistent with a diagnosis of moderate-severe OSA)[22] The MOS was validated against laboratory PSG and showed that abnormal oximetry (MOS of 2-4) was consistent with PSG-documented OSA (MOAHI of 12.6, 13.3, 39.9 respectively), while those with a MOS of 1 had a mean MOAHI of 4.1.[22] (It is important to note that this MOAHI of 4.1 may be an overestimate because the Nixon group evaluated children who were scheduled for T&A and therefore may have been at higher risk. In contrast, the Brouillette study in 2000 evaluated 349 children who were referred to the sleep laboratory but at time of referral and entry into the study, no decision had been made regarding T&A; in that study, children with inconclusive oximetries had a mean MOAHI of 1.5.[21])

These two studies[21,22] demonstrated that nocturnal pulse oximetry can be used to rule in a diagnosis of moderate-severe OSA and thus to prioritize treatment and plan peri-operative management. With its high positive predictive value, the MOS would correctly identify the most severe cases of OSA but the low sensitivity and negative predictive values means that the MOS cannot be used to definitively rule out a diagnosis of OSA.

2.2.3.2 Experience with nocturnal pulse oximetry at the Montreal Children's Hospital

In our sleep laboratory, we perform nocturnal pulse oximetry as the first test to help determine which patients have the most severe desaturations (i.e., abnormal MOS), and thus need expedited evaluation, treatment (T&A), and close perioperative care.

2.2.3.3 Limitations of nocturnal pulse oximetry as a diagnostic tool for OSA in children

First, nocturnal pulse oximetry does not provide as complete information on respiratory, cardiovascular, electroencephalographic and audio/video recordings as does full PSG. Only oxygenation and pulse rate are recorded.

Second, nocturnal pulse oximetry is not a definitive diagnostic test for OSA as it has low sensitivity and poor negative predictive value. When it is deemed inconclusive among children referred for suspected OSA, about 50% are missed. These missed cases are largely due to the fact that some children can have OSA (as detected on polysomnography) without desaturations below 90%. These children have milder forms of OSA than those with greater desaturations.[22] To my knowledge, no studies to date differentiate those patients with OSA with and without important decrements in saturation.

Third, nocturnal pulse oximetry relies on the cooperation of both parent and child, as the oximetry testing is performed by the parent at home.

2.2.3.4 Advantages of nocturnal pulse oximetry testing as a diagnostic tool for OSA in children

First, both Brouillette et al. and Nixon et al. compared oximetry alone to PSG results and showed that patients with abnormal oximetry had high MOAHIs consistent with moderate-severe OSA (97% positive predictive value).[21,22] Those with inconclusive oximetries had much lower indices consistent with either no OSA or mild OSA.

Second, I know of no studies to date showing that continuous values of oxygen saturation could be used in the diagnosis of OSA in children. Urschitz et al. established normative values of nocturnal pulse oximetry in healthy children, specifically for median saturation, numbers of desaturations below 90% per hour (DI_{90}), and number of 4% decrements of saturation per hour (DI_4).[107] They concluded that the DI_{90} and DI_4 are not in "any way

diagnostic of [OSA]."[107] This is likely because examining only the number of desaturations is not as accurate as taking account of both the number of desaturations and clusters of desaturations, which is what the McGill Oximetry Score does.

Third, oximetry testing is much less expensive and less time-consuming than PSG. Oximetry testing is also less burdensome to the parent and child because they do not have to spend 12-14 hours in hospital as they would for PSG.[23-27]

Finally, few tests in the home need to be repeated due to technical problems or poor parental compliance.[21,22] 97% of the oximetry tests in the study by Nixon et al. were of technically good quality.[22] Moreover, the fact that oximetry testing is done in the home may be an advantage, as this familiar setting may allow the child to have better quality and duration of sleep.[23]

2.3 The Cardiovascular System and OSA in Children

At present, other than PSG, there is no other established measure to help diagnose children with OSA who do not desaturate. An improved objective diagnostic measure is needed that could be conducted in the child's home and that would be both highly sensitive and specific for detection of obstructive sleep apnea episodes at all levels of severity, especially for those who do not desaturate.

The second manuscript of my thesis focuses on pulse rate and pulse rate variability in children with moderate-to-severe OSA. We compared nocturnal pulse rate and nocturnal pulse rate variability before and after T&A. We found that both significantly decrease after T&A. This is a new and potentially important contribution to the field of pediatric sleep medicine. Resolution of tachycardia and diminished pulse rate variability after T&A may illustrate the stress that recurrent airway obstruction during sleep places on the cardiovascular system.

Further elaboration on the association between the cardiovascular system and OSA in children is described in this section and in Manuscript #2, with emphasis on cardiac rate and variability in children.

2.3.1 Cardiovascular sequelae of OSA

Traditionally, untreated, severe OSA was thought only to affect the right side of the heart, leading to right heart failure, pulmonary hypertension, and cor pulmonale.[4,49] Recent studies have also noted a strong association between OSA and isolated left-sided heart disease in children, specifically left ventricular hypertrophy, left-ventricular diastolic dysfunction, systemic hypertension, and failure of systemic blood pressure to decrease at night. [9,10,50] The pathogenesis of these changes remains unknown but inflammatory cytokines and up-regulation of sympathetic nervous stimulation to heart and blood vessels have been postulated to play important roles.[9,10]

2.3.2 Cardiovascular changes during normal sleep

In both adults and children, differences exist in cardiovascular regulation during wakefulness as compared with sleep, as well as between sleep states.[108,109] Somers et al. have shown that sympathetic-nerve activity, blood pressure, and heart rate are decreased in normal adults during deep quiet sleep when compared with wakefulness. [108] They also noted that the transition into rapid-eye-movement (REM) sleep was associated with a significant increase in sympathetic drive, with increases in heart rate and blood pressure when compared with quiet sleep. Values during REM sleep were similar to those recorded during wakefulness.[108] In children, normative values during wake and sleep have been established, with a progressive increase in heart rate during the transition from quiet sleep to active REM sleep to wakefulness.[109]

2.3.3 Heart rate variability in children

Fluctuations in heart rate (or heart rate variability) can be measured using electrocardiographic recordings. Heart rate variability represents a non-invasive measure for evaluating the cardiac autonomic nervous system. It reflects the influences of the sympathetic and parasympathetic system on the sinus node in the heart and thus may be useful as a measure of cardiac health status. There is evidence that heart rate and heart rate variability measures change with age, described as a reflection of the progressive maturation of the autonomic nervous system in childhood.[109,110] Finley et al. have established group mean values of heart rate and heart rate variability metrics by age group and sleep stage,[109], and another group demonstrated that in healthy children sleep-stage and age both influence short-term heart rate variability during sleep.[111] Age-based equations for normative values for heart rate and heart rate variability in children have been derived by Massin et al.[110]

2.3.3.1 Interaction between autonomic nervous system, sleep stage and arousals

Some evidence suggests that sympathetic activity is up-regulated in children with obstructive sleep apnea. In these children, there is an increased apnea frequency in REM sleep compared with quiet sleep.[34,112] It should also be noted that the cycle period of these heart rate fluctuations corresponds to the cycle of apnea and arousal. Heart rate variability measures, therefore, may be important in the detection of sleep state, apneas and arousals, independent of oxygenation.

With regard to changes in macrosleep architecture following treatment of OSA, Tal et al. showed that there were no significant changes in duration of any sleep stage (REM and non-REM) before and after T&A in children.[113]

2.3.3.2 Heart rate variability and OSA

Studies have shown that certain characteristics of heart rate variability exist in children with OSA as compared to controls.[114,115] Heart rate variability is known to be elevated in children with OSA.[114,115] To my knowledge, no studies have defined specific measures in heart rate variability in children with severe OSA with desaturations or in those with OSA who do not have desaturations. There are also no studies evaluating changes in both heart rate and heart rate variability in children who have been treated for moderate-severe OSA with T&A.

2.3.3.3 Methods for heart rate variability analysis

There are two methods for analyzing heart rate variability measures: the time-domain method and the frequency-domain method.[116]

i) Time-domain method: This uses the beat-to-beat measure of heart rate (intervals between each beat, i.e., each QRS complex) and is called the normal-to-normal (NN) interval. Using this time-domain method, the most common and simplest variable to measure heart rate variability is the standard deviation of the NN intervals (SDNN) (i.e., the square root of variance). The smaller the standard deviation in beat-to-beat intervals, the lower the heart rate variability.[116]

ii) Frequency-domain method: Frequency measures involve a power spectral analysis of heart rate variability. Power spectral analysis transforms the heart rate variability signal from time to frequency (using a technique called fast Fourier transformation). It does so by representing the signal as a combination of sine and cosine waves with different amplitudes and frequencies. Power spectral density is a measure of how the power of a signal is distributed with frequency (technically, the squared magnitude of the amplitude in each of the frequency components of the signal). A periodogram is a graphical estimate of the power of a signal depicted as a bandwidth and is computed using the fast Fourier transformation technique.

Of particular note, Zamarron et al. found that in adults with OSA (compared to those without), a peak in oxygen saturation and/or pulse rate signal is present in periodograms during the period of 0.010-0.033Hz (equivalent to the period of 30-70 seconds). [117] A peak within this range (30-70 second period) had a high sensitivity (94%) and specificity (82%) for the diagnosis of OSA in adults. [117]

Spectral analysis of heart rate variability thus offers a technique to derive quantitative information on sympathetic and parasympathetic control.[118,119] There are three power components of the heart rate variability spectrum, derived by spectral analysis. High-frequency (HF) variability, better known as respiratory sinus arrhythmia, ranges from 0.15 – 0.40 Hz and is thought to reflect almost exclusively parasympathetic (vagal) activity. Low-frequency (LF) variability ranges from 0.04-0.15 Hz and indicates a variation of both sympathetic and parasympathetic activity.[116] Therefore, the ratio of LF/HF has been used as a surrogate for sympathetic/parasympathetic balance.[116,120] The very low frequency (VLF) spectral component ranges from (0.003-0.05 Hz) and may be related to long-term regulatory mechanisms, including humoral factors, temperature control, and the renin-angiotensin system. [111,121,122]

As described earlier, pulse oximetry not only measures oxygen levels but also measures pulse rate. Pulse rate data are stored from a pulse oximeter at a rate of 0.5 Hz, a rate too slow to accurately reflect high-frequency variability. However, according to the Nyquist formula, data recorded at 0.5 Hz could detect variabilities slower than 0.25 Hz, which is well within the low-frequency variability range.

In summary, it is known that heart rate variability may be increased in children with OSA. There are no studies demonstrating changes in both heart rate and heart rate variability following adenotonsillectomy in children with moderate-severe OSA diagnosed by pulse oximetry. In our study (Manuscript #2), we provided two new contributions to the pediatric literature: 1) evidence that pulse rate and pulse rate variability decrease following T&A for moderate-severe OSA, and 2) support for the

feasibility of pulse oximetry to assess pulse rate and variability. The results of this study potentially serve as preliminary data for further work that would determine the accuracy and diagnostic usefulness of pulse rate and pulse rate variability measures for OSA at all levels of severity, especially in those who may not desaturate during obstructive apnea episodes and are thus missed by oximetry alone. Evaluating both channels of the oximetry study (i.e., oxygen and pulse rate) may improve the accuracy of nocturnal pulse oximetry at detecting all levels of OSA severity in children (from mild to severe).

2.4 Subjective measures for diagnosis of OSA in children

The Montreal Children's Hospital/McGill University Health Centre pediatric sleep laboratory has an extensive database of oximetry data and parental questionnaire data, including data from the OSA-18 (an OSA-specific quality of life questionnaire).[19] In this section of the thesis, I will elaborate on this and other subjective measures used to detect OSA in children.

2.4.1 Clinical history and questionnaires for the evaluation of OSA

Due to lack of resources or expertise, only a small percentage of children have PSG prior to T&A for suspected OSA.[123] Thus, some clinicians are forced to depend on clinical history or questionnaires to evaluate for OSA. Two examples include the Pediatric Sleep Questionnaire[18] and the Brouillette OSA Score[5].

2.4.1.1 The Pediatric Sleep Questionnaire

Chervin and his group validated a 22-item Sleep-Related Breathing Disorder (SRBD) scale, a subscale of the Pediatric Sleep Questionnaire. [18] The questions encompassed symptoms related to OSA, notably snoring, mouth-breathing, observed apneas, and inattention or hyperactivity. They tested 162 subjects – 54 with PSG-confirmed OSA and 108 healthy children recruited from community pediatric clinics. The SRBD scale showed good internal consistency and test-retest reliability for evaluating sleep-related

breathing disorders in a research setting, but it was judged to be "not reliable enough for most individual patients" in a clinical setting.[18,124,125] Accordingly, we do not use this measure in our sleep laboratory and have no data on the SRBD scale from our referral population.

2.4.1.2 The Brouillette OSA Score

The Brouillette OSA Score was derived from questions from parental questionnaires from 92 subjects - 23 with PSG-proved OSA, 23 referred with suspicion of OSA, and 46 age- and sex-matched controls who did not snore.[5] The resulting score was based on the following three-variable equation: OSA score=1.42D + 1.41A + 0.71S – 3.83 (D: difficulty breathing; A: apneas observed; S: snoring). Values for difficulty breathing and snoring were as follows: 0, never; 1, occasionally; 2, frequently; 3, always. Values for apneas were dichotomized (no (0) and yes (1)). A Brouillette OSA score of greater than 3.5 is diagnostic of OSA and score of less than -1 indicates absence of OSA. Scores between -1 and 3.5 were inconclusive.[5] The positive predictive value of the score when compared with controls was 95.7%.[5]

Nevertheless, the Brouillette OSA Score had low accuracy to distinguish snoring from OSA when it was used in other studies.[16,126] Two studies on snoring children reported lower positive predictive values (58.8% and 74.3%).[16,126] Carroll et al. found that the Brouillette OSA Score did not perform well in the clinical setting (sensitivity of 73% and specificity of 83% for detecting OSA).[16] They concluded that it could not differentiate between snoring children with OSA and those without OSA. Thus, this score was also not considered as part of our study design for Manuscript #1 for the following reasons: first, such studies evaluating its diagnostic potential have already been done and have reported poor accuracy, and second, the Brouillette OSA score cannot accurately differentiate between snoring children with and without OSA and thus would not be useful for our patient population, as most of the children who are referred to the sleep laboratory snore.

2.4.2 Quality of life measures

Health-related quality of life (HRQOL) measures have been used extensively in both adult and pediatric research studies. Both generic and specific HRQOL measures exist and both usually include the domains of physical or emotional function.[127,128] Guyatt and his group describe certain criteria that are important to assess the applicability and usefulness of any HRQOL measure: reproducibility, reliability, validity, and interpretability.[127,128]

2.4.2.1 Generic HRQOL instruments

There are advantages and disadvantages to using generic or specific HRQOL measures. One of the main strengths of generic HRQOL measures is that they can be used in healthy or clinical populations at an individual or group level. For research purposes, this makes it feasible to include a comparison group, whereas this may not be possible with a disease-specific HRQOL. Moreover, generic HRQOL instruments presumably provide a more global assessment. One of the most commonly used generic measures is the SF-36. This is a 36-item questionnaire with eight subscales and two global scores.[129] Other generic questionnaires specific to children include the Child Health Questionnaire[130] and the Pediatric Quality of Life Inventory.[131]

2.4.2.2 Specific HRQOL instruments

Specific HRQOL instruments are restricted to a particular disease, a certain population, or a specific function (such as sleep) or problem (such as pain).[127] Although limited in scope, disease-specific QOL instruments presumably provide a more accurate assessment of the impact of a particular illness on a patient's quality of life.

2.4.3 OSA-specific HRQOL instrument: the OSA-18

Three measures, referred to by their authors as 'quality of life' measures, have been devised for children with sleep-disordered breathing: the Obstructive Sleep Apnea-18 (OSA-18),[19] the Obstructive Sleep Disorder-6 (OSD-6)[132] and the Tonsil and Adenoid Health Status Instrument.[133,134] The latter two are not often used whereas the OSA-18[19] has been used in several studies since 2000.[20,135-154]

The OSA-18 was created by Franco and his colleagues.[19] They first devised a 20-item HRQOL questionnaire divided into 5 domains – sleep disturbance, physical symptoms, emotional distress, daytime function and caregiver concerns. Each question was scored on a 7-point ordinal scale (from "none of the time" (a score of 1) to "all of the time" (a score of 7).[19]

After each participant completed the questionnaire they underwent a daytime 90-minute nap polysomnography using a portable system. A respiratory distress index (RDI) was scored using measures of respiratory flow with oral/nasal thermistors, respiratory effort with chest and abdominal pneumobelts, oxygenation with pulse oximetry, electrocardiogram for heart rate and body position. Electroencephalography for measurements of sleep-staging and arousals were not part of their nap polysomnography set-up. Normal/mild OSA was categorized as an RDI of less than or equal to 5; moderate OSA, an RDI of 6-9; and severe OSA, an RDI of greater than or equal to 10. All children had hyperplasia of tonsils or adenoids on physical examination. The validity of the questionnaire was assessed by correlating the results with 3 measures: the RDI, tonsil size and adenoid size. A step-wise multiple linear regression was used to relate the OSA-20 summary score to the RDI, tonsil size, and adenoid size, after controlling for age and BMI.[19]

During a one-year study period, the investigators recruited 61 children who had disrupted sleep and adenotonsillar hypertrophy. The median age was 4 years (range of 1-12) and 85% were Black. Franco et al. report that the physical symptoms subscale of the OSA-18

correlated well with nap PSG parameters consistent with a diagnosis of OSA.[19] However, the more subjective subscales were only weakly correlated (caregiver frustration, discipline problems, social problems). Because of low occurrence rates (67% and 77% reported no social or school problems, respectively) and because of poor correlation of the items with the 3 validity measures (Spearman Rank correlation for each of the three measures were less than 0.20)[19], two items (social problems and school problems) were eliminated from the questionnaire - hence, the designation of the 18-item questionnaire, the OSA-18. The OSA-18 score spans from 18 to 126 (18 refers to no impact on quality of life; 126 refers to a major negative impact).[19]

In their study group, the median OSA-18 score was 70 with a range of 23 to 107. The score was plotted against three categories of RDI (normal/mild, moderate, and severe), but the investigators did not provide values for the median and ranges. The investigators based the OSA-18 cut-off values on the RDI values: less than 60 for the normal/mild OSA group (small impact on QOL); 60-80 for the moderate OSA group (moderate impact); and greater than 80 for the severe OSA group (large impact). [19]

The study by Franco et al., however, has several weaknesses that throw doubt on the accuracy of the OSA-18. First, the questionnaire was validated against 90-minute daytime nap PSG studies using a portable system that measured less parameters than a standard full night PSG. As described in an earlier section (Section 2.2.2.2), nap PSG studies in children have not been shown to be acceptable for definitive diagnosis of OSA.[15] In children, nap studies have poor sensitivity and low negative predictive values for OSA, likely due to the paucity of REM sleep during nap PSGs. It may also be difficult for children to fall asleep during the daytime, especially in an unfamiliar setting.

Second, the small sample did not permit evaluation of the OSA-18 in different age subgroups. Third, the results may not be generalizable because 85% of the children in the study were black. Last, it is unclear if Franco's study population was truly non-obese, as their body mass index (BMI) classifications were erroneous. They classified BMI into three groups: BMI > 30 as obese; BMI between 25 and 30 as overweight; and BMI < 25

as normal. The correct classification for BMI in children is age and gender dependent and should be determined using percentiles, with normal designated as less than 85th percentile, overweight as between the 85th and 95th percentiles, and obese as at or above the 95th percentile for age and gender.[155] For example, a 4 year old child (the median age in their study) with a BMI of 24 should be classified as morbidly obese, as this BMI is much higher than the 97th percentile, according to the standard pediatric growth charts.[155] In the Franco study, this subject would have been classified as normal, according to their criteria stated above.

In spite of these weaknesses, several studies have used the OSA-18[156] and some out-patient otolaryngology clinics use it as part of their clinical assessment for OSA. Because of its popularity and in light of the fact that its accuracy at detecting OSA in children has never been evaluated, the goal for our first study (Manuscript #1) was to evaluate the accuracy of the OSA-18 in detecting moderate-severe OSA as indicated by an abnormal MOS in children referred to a sleep laboratory for evaluation of OSA.

CHAPTER 3. EVALUATION OF THE OSA-18 QUALITY OF LIFE QUESTIONNAIRE IN CHILDREN REFERRED FOR OBSTRUCTIVE SLEEP APNEA

This chapter consists of a manuscript entitled "Evaluation of the OSA-18 quality of life questionnaire in children referred for obstructive sleep apnea" to be submitted for publication in *Pediatrics*.

A particular focus of this study was to evaluate whether the OSA-18, a quality of life questionnaire for pediatric obstructive sleep apnea (OSA), can accurately identify patients at risk of having moderate-severe OSA as determined by an abnormal McGill Oximetry Score (MOS).

3.1 The rationale for evaluating the OSA-18 as a potential diagnostic measure

First, since the development of the OSA-18 score by Franco et al. in 2000, there have been several publications citing the use of the OSA-18 in studies of children with OSA[20,135-154], making it the most widely used quality of life questionnaire in these children.[156]

Second, the OSA-18 questionnaire is used in our institution (both in some ENT clinics and in the sleep laboratory) and the results are included in the MCH Sleep Laboratory database.

Third, the OSA-18 is simple, inexpensive, and takes little time to complete.

Fourth, both the Sleep-Related-Breathing Disorder Scale of the Pediatric Sleep Questionnaire[18] and the Brouillette OSA Score[5] have been deemed inaccurate diagnostic

measures in the clinical setting. These questionnaires are described in detail in Section 2.4.1.

Fifth, the OSA-18 has been proposed by a group of investigators (Fischer et al.) as useful in the diagnosis of OSA and a potential replacement for PSG.[20] This group published a study in 2006 on the long term change in quality of life after adenotonsillectomy in children with OSA. They concluded that the "use of the ...OSA-18 survey should decrease the need for polysomnographic monitoring and facilitate selection of children for T&A."[20] Consequently, this group is promoting the use of the OSA-18 as a diagnostic test in place of objective testing in spite of the fact that Fischer et al. did not compare the OSA-18 to any objective test (oximetry or PSG).

Consequently I decided to evaluate whether the OSA-18 would be useful at detecting children with moderate-severe OSA. I used the McGill Oximetry Score (MOS) as a reference standard for moderate-severe OSA. If the OSA-18 score is accurate at detecting children with moderate-severe OSA (i.e., those with abnormal MOS), then the OSA-18 score should be abnormal in most children with an abnormal MOS. Conversely, if the OSA-18 score is not accurate, then it should not be used for diagnostic purposes.

3.2 Manuscript #1

Evaluation of the OSA-18 quality of life questionnaire in children referred for obstructive sleep apnea

Evelyn Constantin MD

Department of Pediatrics, Montreal Children's Hospital, McGill University, Montreal, Canada

Ted Tewfik MD

Department of Otolaryngology, Montreal Children's Hospital, McGill University, Montreal, Canada

Robert T. Brouillette MD

Department of Pediatrics, Montreal Children's Hospital, McGill University, Montreal, Canada

Author for Correspondence and Reprints:

Dr Evelyn Constantin

Pediatric Sleep Laboratory,

Montreal Children's Hospital

2300 Tupper Street, C508

Montreal, Quebec

H3H 1P3

Email address: evelyn.constantin@muhc.mcgill.ca

Tel: 514 412-4400 ext 24321

Fax: 514 412-4234

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ABSTRACT

Background: The best diagnostic tool for obstructive sleep apnea (OSA) in children is polysomnography (PSG). However, PSG is relatively inaccessible and costly so studies are needed to evaluate other diagnostic approaches to accurately detect OSA in children. **Objective:** To determine how well a quality of life questionnaire, the OSA-18, is able to detect moderate-severe OSA as identified by nocturnal pulse oximetry. **Methods:** We used a cross-sectional study design involving children referred to a sleep laboratory for evaluation of suspected OSA. All had a nocturnal pulse oximetry study, the results of which were interpreted using the McGill Oximetry Score (MOS). The MOS is an ordinal score for which scores of 2, 3, or 4 are considered abnormal and consistent with moderate-severe OSA. We classified those with a score of 2-4 as MOSabn (abnormal) and those with a score of 1 as MOSinc(inconclusive). Alongside data from the OSA-18, we analyzed demographic and medical data (from a parent questionnaire) and information regarding adenotonsillar hypertrophy. We estimated sensitivity, specificity, positive and negative predictive values as well as receiver operating curves of the OSA-18 in detecting an abnormal MOS. We also conducted univariate and multivariate logistic regression analyses, using the MOS as the dependent variable and the OSA-18 score and others (age, gender, comorbidities, race) as independent variables. **Results:** We studied 334 children. The mean age was 4.6 years and 58% were male. The OSA-18 had a sensitivity of 40% and a negative predictive value of 73% for detecting an abnormal MOS. In addition, the area under the receiver operating curve was 0.611. While controlling for other independent variables in the logistic regression model, for each unit increase in the OSA-18 Score, the odds of having an abnormal MOS were increased by 2%. However, for each increase in age of 1 year, the odds of having an abnormal MOS were decreased by 17%. **Conclusions:** Among children referred to a sleep laboratory, the OSA-18 does not accurately detect which children will have an abnormal MOS. The OSA-18 should not be used in place of objective testing to identify moderate-severe OSA in children.

INTRODUCTION

In children, obstructive sleep apnea (OSA) is a sleep-related breathing disorder that is usually caused by adenotonsillar hypertrophy and is characterized by upper airway obstruction that disturbs sleep and disrupts normal respiratory gas exchange[1-3] Childhood OSA has a prevalence of 0.7 to 3%,[4,5] with the highest prevalence of 3% reported by Gislason and Benedkitsdottir among children 6 months to 6 years old.[5] For children with OSA due to adenotonsillar hypertrophy, adenotonsillectomy (T&A) is the treatment of choice.[6] Numerous studies have shown potential links between OSA (particularly severe OSA) and adverse outcomes such as poor growth, developmental delay, cardiovascular complications, metabolic and inflammatory conditions, behaviour, or learning problems.[2,3,7-17]

Laboratory polysomnography (PSG) is considered the best measure of OSA in children.[1] However, PSG involves a detailed, laborious evaluation of cardiorespiratory and neurological parameters in a sleep laboratory and it is, therefore, not widely accessible. PSG is burdensome, time-consuming, costly, and usually entails long waiting times.[18-22] Consequently, some pediatric centers have been using other measures to diagnose OSA.

In our institution, based on a study by Brouillette et al.,[23] we use nocturnal pulse oximetry as a first-pass measure to evaluate oxygenation during sleep. That study showed that in a population of children referred because of suspected OSA, abnormal nocturnal pulse oximetry had a 97% positive predictive value for detecting moderate-severe OSA when compared with PSG.[23] Nixon et al. later devised the McGill Oximetry Score (MOS) for childhood OSA:[24] a MOS of 1 was designated as inconclusive, and children with scores of 2, 3, and 4 were designated as consistent with a diagnosis of moderate-severe OSA based on abnormal PSG-determined mixed/obstructive apnea/hypopnea indices (MOAHI) (12.6, 13.3, and 39.9 respectively).[24] In children, a MOAHI of less than 1 is considered normal.[25-27] Hence, in our institution, children with adenotonsillar hypertrophy suspected of OSA who have an abnormal MOS are scheduled for expedited treatment (T&A).

Some centers may not have access to PSG or oximetry. At these centers, clinicians are forced to depend only on a clinical history to evaluate OSA. To assist in the evaluation, questionnaires are often used, including the Pediatric Sleep Questionnaire[28] and the Brouillette OSA Score[8] Another such measure is the OSA-18 disease-specific quality of life questionnaire (OSA-18) devised by Franco et al.[29]

The Sleep-Related Breathing Disorder Scale of the Pediatric Sleep Questionnaire[28] and the Brouillette OSA Score[8] have been found to be inaccurate diagnostic tools when used in the clinical setting. Although the OSA-18 has been used in several studies on children [30-50], its accuracy at detecting OSA has not been evaluated against objective tests such as PSG or oximetry. Fischer et al. assessed the long-term changes in the OSA-18 following T&A in children and based on this study alone, they have promoted the use of the OSA-18 score to "decrease the need for polysomnographic monitoring and facilitate selection of children for T&A".[41]

The original study by Franco et al. that devised the OSA-18 score has several weaknesses that throw doubt on the accuracy of the OSA-18 questionnaire. First, the validation was against daytime 90-minute nap PSG using a portable system that measured less parameters than a standard full night PSG. Nap PSGs in children have been shown to be inaccurate for definitive diagnosis of OSA because they have poor sensitivity and low negative predictive values for OSA.[6] The inaccuracy of nap studies is thought to be attributable to the paucity of REM sleep. It may also be difficult for children to even fall asleep during the daytime, especially in the unfamiliar setting of a sleep laboratory.

Second, the small sample did not permit an evaluation of the OSA-18 in different age groups. Third, the results may not be generalizable because 85% of the children in the study were black. Last, it is unclear if Franco's study population was truly non-obese, as their body mass index (BMI) classifications were erroneous. They classified BMI into three groups: BMI > 30 as obese; BMI between 25 and 30 as overweight; and BMI < 25 as normal. The correct classification for BMI in children is age and gender dependent and thus should be determined using percentiles, with normal designated as less than 85th

percentile, overweight as between the 85th and 95th percentiles and obese as at or above the 95th percentile for age and gender.[51]

In spite of these weaknesses, many studies have used the OSA-18[30-50,52] and some otolaryngology clinics use it as part of their clinical assessment for OSA. Because of its popularity and in light of the fact that its accuracy at detecting OSA in children has never been evaluated, the goal for our study was to evaluate how well the OSA-18 questionnaire can detect moderate-severe OSA as indicated by an abnormal MOS in children referred to a sleep laboratory for evaluation of OSA. If the OSA-18 is to be useful diagnostically, then it should accurately detect most children with abnormal MOS. Alternatively, if the OSA-18 score is not accurate, then it should not be used for diagnostic purposes.

METHODS

Study Design

We performed a cross-sectional study using an existing clinical database from the pediatric sleep laboratory at the Montreal Children's Hospital. The database included demographic information, past medical history, comorbidities, sleep habits, sleep symptoms, responses to questions from the OSA-18, and oximetry metrics. If the patient is referred by an otolaryngologist, an extra form is attached to the referral for the otolaryngologist to report how much tonsillar hypertrophy (0, 1+, 2+, 3+, 4+), adenoidal hypertrophy (yes, suspected, no, unsure), or both, the child has. Referrals by other physicians (primary care physicians, subspecialists) do not include information on adenotonsillar hypertrophy.

Parents obtain a pulse oximeter and receive a 30-minute instruction session from the sleep laboratory. Parents perform the oximetry study that same night and return the oximeter the next morning. They also complete a web-based questionnaire (PHD Medical, Baie d'Urfe, Quebec) that provides demographic data and information about

their child's past and present medical condition. Included are questions regarding the child's sleep patterns and breathing (number of nights/week of snoring, number of nights/week of difficulty breathing during sleep, presence of observed obstructive apneas during sleep, and the level of parental concern regarding their child's breathing during sleep). The web-based questionnaire also includes the OSA-18. As required by provincial (Quebec) law, our study was given Research Ethics Board approval by the Director of Professional Services of the Montreal Children's Hospital acting on behalf of the Montreal Children's Hospital Research Ethics Board.

Study population

Children between 2 and 10 years old referred for evaluation of possible OSA were included if they had overnight home pulse oximetry done between April 2005 and March 2006. We restricted the sample to this age group for the following reasons: 1) interpretation of the OSA-18 score for children under 2 is difficult; 2) the MOS has only been validated for children 1 year and older; 3) children over 10 may have pubertal changes that may affect the OSA-18 score. Their exclusion also ensures that the questionnaires were only completed by parents or guardians to maintain consistency of the reported data.

Nocturnal Pulse Oximetry

We used nocturnal pulse oximetry as our reference standard for determination of moderate-severe OSA, based on a motion-resistant pulse oximeter set for a two-second averaging time for hemoglobin saturation.(Masimo Radical, Version 4.1.0.0, Irvine, CA).[53] Saturation data were extracted and analyzed using Download 2001 software (version 2.5.0, Stowood Scientific Instruments, Oxford, England). This program provides a detailed report of oxygenation data, including mean oxygen saturation (S_pO_2), minimum S_pO_2, number of decrements of oxygen saturation of ≥4% per hour of study (DI_4), number of desaturations to ≤ 90% /hour of study (DI_{90}), number of decrements of oxygen saturation below 100%, 90%, 85%, 80%, 75%, and 70%, as well as total

recording time and total analyzed time. A computerized algorithm uses the McGill Oximetry Score criteria to interpret the oxygenation data.

OSA-18

The OSA-18 is an 18-item questionnaire that uses a Likert-type scoring system to collect information about five subscales considered to be elements in quality of life: sleep disturbance, physical symptoms, emotional symptoms, daytime function, and caregiver concerns. [29] Based on this information, a summary score is calculated that ranges from 18 to 126 (18 = no impact on quality of life; 126= major negative impact).[29] A value at or above 60 is considered abnormal.[29]

Statistical Analysis

We estimated the sensitivity, specificity, positive and negative predictive values and receiver operator curves of the OSA-18 for the detection of an abnormal MOS. We conducted univariate and multivariate logistic regression analyses. Backward stepwise multivariate logistic regression analyses were performed to determine the final regression model with MOS as the outcome variable. (The MOS was dichotomized into MOS of 1 as inconclusive (MOSinc) and 2-4 as abnormal (MOSabn)). The primary independent variable was the OSA-18 score (a continuous variable with a range from 18-126 units). The other independent variables included gender (male/female), asthma (yes/no), comorbidities (yes/no), race, tonsillar hypertrophy, adenoidal hypertrophy and age. Race was categorized as Caucasian (the reference variable), Black, or Other – the latter included race categories of Amerindian, Asian, Inuit, Latin American and "other". Tonsillar hypertrophy was categorized as "enlarged" (3+, 4+) or "not enlarged" (0, 1+, 2+) and adenoidal hypertrophy was categorized as "enlarged" ("yes/suspected") or "not enlarged" ("unsure/no"). Age was treated as a continuous variable.

Continuous data (age, OSA-18 score) were normally distributed and summarized as means +/- standard deviations. Odds ratios (ORs) and 95% confidence intervals (CIs)

were obtained. A p value of less than 0.05 was considered statistically significant. SPSS 12 for Windows (SPSS Inc, Chicago, Illinois) was used for database management and for statistical analysis.

RESULTS

Demographic characteristics

Table 1 describes the characteristics of the study population as a whole and as divided into two groups based on the MOS (MOSinc and MOSabn). 334 subjects were included in the study. Their mean age was 4.6 years and 58% were boys. The study population was predominantly Caucasian. 99 subjects (30%) had McGill Oximetry Scores of 2, 3, or 4 (61, 21, 17, respectively). Except for age, there were no significant differences between the two groups on any of the variables listed.(Table 1)

Most (77%) were referrals from otolaryngologists. The other referrals were from primary care physicians (20%) or subspecialists (3%). Of the 257 referrals from otolaryngology, 232 had information regarding tonsil and adenoidal size. 89% had adenoidal hypertrophy and 63% had tonsillar hypertrophy. 94% had hypertrophy of tonsils, adenoids, or both.

OSA-18 measure and subscales

The mean OSA-18 score was 52.9 ± 19.0 (mean ± standard deviation). (Table 2) Univariate logistic regression analyses demonstrated that the OSA-18 and four of the five subscales (sleep disturbance, physical symptoms, emotional symptoms, and caregiver concerns) were significantly more abnormal in the MOSabn group than in the MOSinc group.(Table 2).

Sensitivity, specificity and positive and negative predictive values

To evaluate the accuracy of the OSA-18 in detecting an abnormal MOS, we calculated its sensitivity, specificity and positive and negative predictive values. Using a dichotomized OSA-18 score (less than 60; equal to or greater than 60)[29] and a binary MOS variable, we constructed a two-by-two table.(Table 3). Of the 334 subjects, 99 had an abnormal MOS, 40 of whom had an OSA-18 score of 60 or greater. The sensitivity was thus 40.4%. Of the 235 who had an inconclusive MOS, 158 had an OSA-18 score of less than 60, giving a specificity of 67.2%. The positive predictive value of the OSA-18 was 34.2%, while the negative predictive value was 72.8%.(Table 3) Figure 1 illustrates these analyses with a receiver operating curve (ROC). Using the OSA-18 as a continuous variable, the area under the curve is 0.611, (Figure 1) whereas using the OSA-18 as a dichotomous variable, the area under the curve is 0.538.

Post-hoc, we also performed similar analysis for sensitivity and negative predictive value, with stratification of the study population into three age groups of similar size (2-3 years, 4-5 years, and 6-10 years). The sensitivity and negative predictive value for each of these three age groups was equally poor.(Table 4)

Logistic regression analysis

Using the MOS as the dependent variable, univariate logistic regression analyses were completed for the following variables: OSA-18, age, gender, asthma, comorbidities, race, tonsillar or adenoidal hypertrophy, or both.(Table 5). The OSA-18 score and age were the only variables independently associated with an abnormal oximetry score (p-values of 0.001); children with higher OSA-18 scores and younger children were more likely to have an abnormal MOS. (Table 5)

Neither tonsillar or adenoidal hypertrophy was significantly associated with abnormal oximetry (p=0.243, 0.833, respectively). Even combining the two variables (tonsillar and/or adenoidal hypertrophy) did not produce any change in significance.(Table 5)

Other studies have shown that size of adenoids and tonsils are not useful at detecting OSA in children.[54] Our univariate analysis corroborates this finding. Therefore, adenotonsillar hypertrophy was not included as a variable in the multiple regression model. Similarly, our univariate analysis for asthma and the MOS showed no significant association ($p = 0.143$). There is a paucity of literature on the association between asthma and OSA in children. Very few studies have been done with no clear association found.[55,56] Therefore, asthma was also not included in our model.

There is some good evidence that gender, race, and comorbidities may be associated with OSA in children.[57] Although our univariate analyses did not show significant p values for these variables, we included them as potential confounders.

We then performed multivariate logistic regression analyses that included the following independent variables: OSA-18, age, gender, race, and comorbidities. Backward stepwise multiple logistic regression analysis determined that the OSA-18 score and age were both significant ($p=0.004$, 0.003, respectively).(Table 6)

The final regression equation was: Logit(abnormal MOS) = -1.052 + 0.019 OSA-18 Score - 0.188 Age. Thus, for each unit increase in the OSA 18 Score, while keeping all other variables in the model constant, the odds of having an abnormal MOS was increased by 2%. Using a hypothetical clinical example, if two children of the same age, one with an OSA-18 Score of 18 (lowest OSA-18 score) and the other with a score of 60 (OSA-18 cut-off score) were compared using this model, the child with a score of 60 would be 2.3 times as likely to have an abnormal MOS as the child with an OSA-18 Score of 18. For each increase in age of 1 year, the odds of having an abnormal MOS was decreased by 17%, while keeping all other variables in the model constant.

DISCUSSION

Our study demonstrates that although the OSA-18 and its subscales were higher in most of the subjects with abnormal oximetry, the OSA-18 is not able to accurately detect

which children referred to a pediatric sleep laboratory for possible OSA will have an abnormal MOS. If the OSA-18 were to be useful, it should identify most children with OSA severe enough to cause repetitive oxygen desaturations. In fact, the poor sensitivity of the OSA-18 (40%) and its weak negative predictive value (73%) indicate that the OSA-18 does not accurately detect an abnormal MOS in this referral population. The OSA-18 would miss 60% of referred patients who have OSA severe enough to cause desaturations. The negative predictive value of 73% indicates that an OSA-18 score of less than 60 would miss moderate-severe OSA in at least 27% of referred patients.

Our study is the first to determine sensitivity and negative predictive values for the OSA-18 measure as it relates to an objective measure for moderate-severe OSA – the MOS using nocturnal pulse oximetry. Fischer et al. only compared the OSA-18 to other subjective data but not any objective tests.[41] Nonetheless, based on that study, Fischer et al. promote the OSA-18 as a useful measure that could replace PSG.[41] Our results show that the OSA-18 is not accurate at detecting OSA in children and should not be used in place of objective tests. Our findings are new and their importance relates primarily to otolaryngologists and to primary care physicians and specialists who use the OSA-18 to guide referrals or to decide on surgery.

Another strength is that our study involved blinding. The parents were blinded to the results of the oximetry when they completed the OSA-18 because they did so before the oximetry was performed. However, we cannot be certain if the sleep laboratory technicians were also blinded to the OSA-18 score. The technicians who score the oximetry may have been aware if the child was symptomatic for OSA but usually they did not have the results of the OSA-18 when they did the scoring. Nevertheless, the results of the OSA-18 would not influence the MOS, which is computer-generated based on frequency and depth of desaturation events and on clusters of desaturations.

We also examined the relation of oximetry results to age. The logistic regression analysis showing that younger children were more likely to have oximetry results consistent with moderate-severe OSA confirms the association between younger age and OSA.[58] The

increased prevalence in preschool-age children is likely due to the fact that it is during this time that the airway is narrowest because the adenoids and tonsils are at their largest in comparison to the size of the airway.[59] It is not known if age affects the OSA-18 score and this was not part of the Franco et al.'s evaluation.[29]

Limitations

It is important to acknowledge some limitations of this study. One possible limitation is that selection bias on age occurred in our sample. (Table 4) In our study population, there was a higher percentage of younger children who were referred to our sleep laboratory for suspected OSA. In addition, there was a higher percentage of younger children with moderate-severe OSA. These higher percentages may be explained by the known association between younger age and OSA due to the increased ratio of adenotonsillar size to upper airway size in younger children (as described above). As a preliminary attempt to examine this, a stratified analysis by age was performed (2-3 years, 4-5 years and 6-10 years). When we estimated how well the OSA-18 detects an abnormal MOS by age, the OSA-18 had poor sensitivity and weak negative predictive values in all three age subgroups.(Table 4) Therefore, although there remains a possibility that selection bias exists, the results of this analysis suggest the effect would be small.

Another limitation is that the study was not population-based but one that was done in a referred population. Undoubtedly, this study included more cases of OSA than the general population. Although inflated prevalence may result in higher predictive values, this issue may be less important because the predictive values of the OSA-18 were low.

Obesity has been shown to be an important risk factor for OSA in children[60] and might have been an important variable to include in our study. However, because the children themselves were not studied in the laboratory, we did not have information regarding weights and heights of subjects and thus could not determine body mass index percentiles.

The OSA-18 was not evaluated against PSG, but against a reference standard of nocturnal pulse oximetry. Some limitations of nocturnal pulse oximetry are that it relies on parent cooperation, it is not as comprehensive as PSG and is not a definitive diagnostic test. An abnormal MOS has been shown to have a high positive predictive value (97%) to detect moderate-severe OSA in children.[23,24] However, its primary limitation is its low negative predictive value and low sensitivity. This weakness may lead to missed cases. The explanation for these missed cases is that some children with OSA desaturate at night, while others do not. The clinical practice guideline for OSA from the American Academy of Pediatrics has concluded that an abnormal MOS may be a good indicator of an abnormal PSG result and thus may be useful in discriminating between primary snoring and OSA.[6]

The MOS was rigourously derived and validated for the diagnosis of OSA in children. To date, we know of no studies showing that other methods of analyzing oximetry data would be of equal or better diagnostic performance (i.e., mean saturation, minimum saturation, or desaturation indices). Urschitz et al. established normative values of nocturnal pulse oximetry in healthy children, specifically for median saturation, numbers of desaturations below 90% per hour (DI_{90}), and number of 4% decrements of saturation per hour (DI_4).[61] They concluded that the DI_{90} and DI_4 are not in "any way diagnostic of [OSA]."[61] This is because examining only the number of desaturations is not as accurate as taking account of both the number and clusters of desaturations.

Moreover, oximetry testing is much less expensive and less time-consuming than PSG. Oximetry testing is also less burdensome to the parent and child because they do not have to spend 12-14 hours in hospital as they would for PSG. [18-22] Finally, few tests in the home need to be repeated due to technical problems or poor parental compliance.[23,24] 97% of the oximetry tests in the study by Nixon et al. were of technically good quality.[24] The fact that oximetry testing is done in the home may be an advantage, as this familiar setting may allow the child to have better quality and duration of sleep.[18]

If the goal of our study had been to evaluate children with all levels of OSA severity, the ideal reference standard for the OSA-18 evaluation would have been nocturnal PSG. However, our goal was only to determine if the OSA-18 could accurately detect children with *moderate-to-severe OSA*. Accordingly, it was reasonable to use an abnormal MOS as the reference standard for moderate-severe OSA.

Conclusions

Our study shows that in a referral population of children ages 2-10 years old with suspected OSA, the OSA-18 measure has poor sensitivity and weak negative predictive value to detect moderate-severe OSA as indicated by an abnormal McGill Oximetry Score and should not be used in place of objective testing. Due to the obstacles of obtaining PSG for the evaluation of childhood OSA, further studies are needed to evaluate other measures that would accurately detect OSA in children.

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Table 1. Characteristics of the study population, shown as an entire group and by McGill Oximetry Score (MOS) (MOSinc and MOSabn).

	Study population N=334	MOSinc N=235	MOSabn N=99	p**
Age (years)*	4.6 ± 2.2	4.9 ± 2.2	4.0 ± 2.0	0.001
Male	195 (58.4%)	130	65	0.080
Asthma	55 (16.8%)	44	12	0.140
Comorbidities	61 (18.3%)	42	19	0.776
Race				0.100
Caucasian	158 (47.3%)	110	48	0.779
Black	52 (15.6%)	31	21	0.065
Other§	124 (37.1%)	94	30	0.094

* Values expressed as mean ± SD.

** p values calculated comparing MOSinc versus MOSabn

§ Asian (12%), Latin American (6%), Amerindian (1%), Inuit (0.3%), and "Other" (17%)

Table 2. OSA 18 score and its subscales by McGill Oximetry Score (MOS).

	Study population N=334	MOSinc N=235	MOSabn N=99	p**
OSA-18 Score*	52.9±19.0	50.7±18.4	58.3±19.5	0.001
Subscales*				
Sleep disturbance	13.6±6.1	12.9±6.0	15.1±6.1	0.002
Physical symptoms	13.2±5.7	12.6±5.5	14.6±5.9	0.003
Emotional symptoms	8.1±4.6	7.7±4.2	8.9±5.3	0.028
Daytime function	6.7±3.7	6.6±3.5	6.8±3.9	0.731
Caregiver concerns	11.4±6.4	10.8±6.2	12.9±6.6	0.007

* Values expressed as mean ± SD.

** p values calculated comparing MOSinc vs MOSabn

Table 3. Cross-tabulation of the OSA-18 score in two groups (≥60, < 60)) by McGill Oximetry Score (MOS) (two groups (MOSinc, MOSabn)). Sensitivity, specificity, positive predictive and negative predictive values of the OSA-18 score as compared to abnormal MOS were calculated.

	McGill Oximetry Score (MOS)			
OSA 18 Score	MOSabn	MOSinc	Total	
≥60	40	77	117	*PPV=34.2%*
< 60	59	158	217	*NPV=72.8%*
Total	99	235	334	
	Sens=40.4%	*Spec=67.2%*		

Sens: Sensitivity; Spec: Specificity; PPV: Positive predictive value; NPV: Negative predictive value

Table 4. Sensitivity and Negative Predictive Values (NPV) of the OSA-18 for detecting an abnormal MOS by age-group.

Age (years)	2-3	4-5	6-10	Entire Study Group
# in study	126	105	103	334
# with abnormal MOS	49	28	22	99
Sensitivity (%)	45	40	32	40
NPV (%)	63	77	79	73

Table 5. Univariate logistic regression analyses of independent variables compared to abnormal McGill Oximetry Score.

Variable	**Parameter estimate (B)**	**p**	**Odds (95% CI)**
OSA-18 score	0.021	**0.001**	1.022 (1.009, 1.035)
Age	-0.211	**0.001**	0.809 (0.716, 0.915)
Gender	-0.434	0.081	0.648 (0.398, 1.055)
Asthma	-0.513	0.143	0.599 (0.301, 1.190)
Comorbidities	0.087	0.776	1.091 (0.598, 1.991)
Race (Caucasian)*	REF	REF	0
Race (Black)	0.572	0.067	1.772 (0.960, 3.268)
Race (Other)	-0.427	0.095	0.652 (0.395, 1.077)
Tonsillar hypertrophy	0.354	0.243	1.425 (0.786, 2.583)
Adenoidal hypertrophy	-0.096	0.833	0.909 (0.373, 2.216)
Tonsillar and/or adenoidal hypertrophy	-0.030	0.962	0.971 (0.289, 3.263)

CI: Confidence Interval

*Reference category for Race variable was Caucasian (Odds=0)

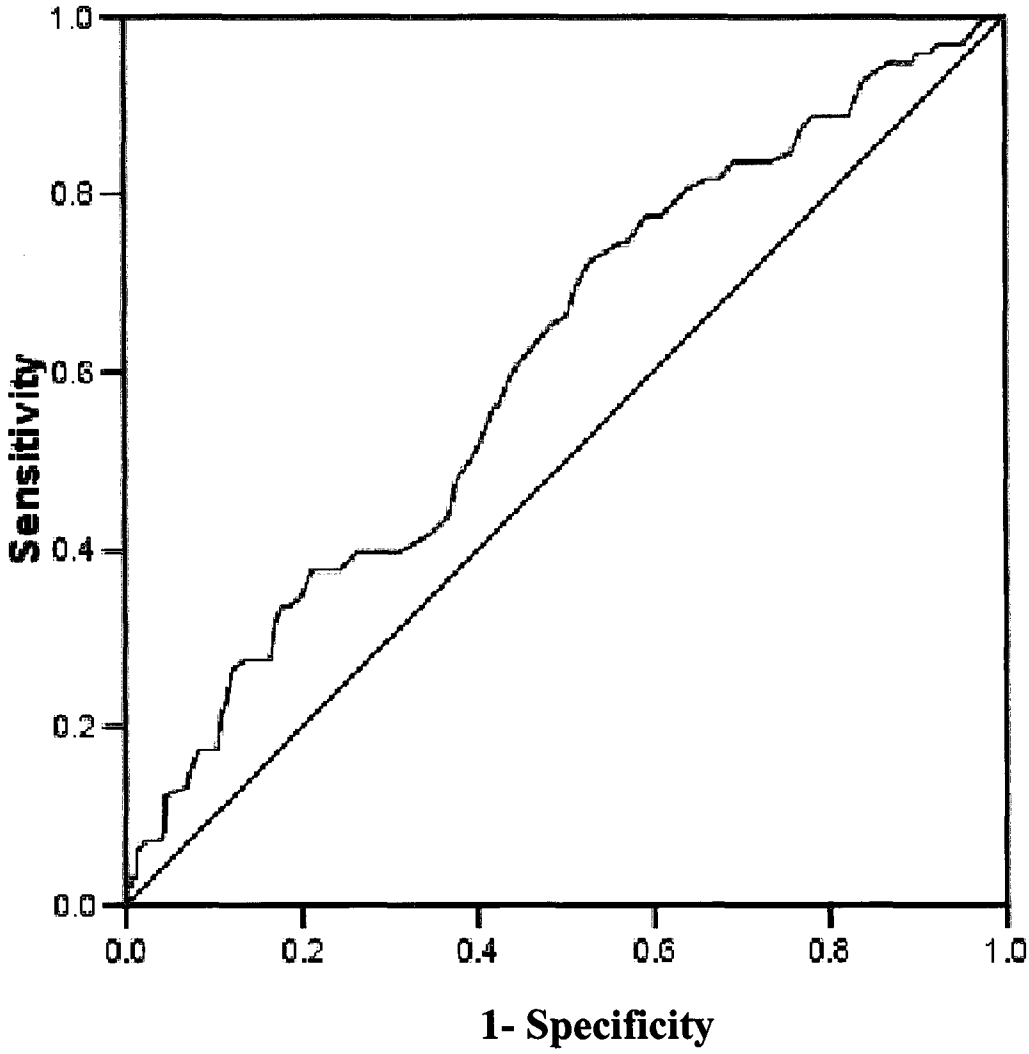
Table 6. Backward stepwise multivariate logistic regression analyses with OSA-18 score and age analyzed against McGill Oximetry Score as the dependent variable.

Variable	Parameter estimate (B)	p	Odds (95% CI)
OSA_18_Score	0.019	0.004	1.019 (1.006, 1.032)
Age	-0.188	0.003	0.828 (0.732, 0.938)

Figure Legend

Figure 1. Receiver operating curve (ROC) using the OSA-18 as a continuous variable illustrating the poor accuracy of the OSA-18 score at detecting an abnormal McGill Oximetry Score. Area under the curve is 0.611 (curved line), which is similar to that of random guess (area under the curve of 0.5, straight line).

Figure 1.



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CHAPTER 4. PULSE RATE AND PULSE RATE VARIABILITY AFTER ADENOTONSILLECTOMY FOR OBSTRUCTIVE SLEEP APNEA IN CHILDREN

A discussion regarding the cardiovascular system and OSA in children is described in Section 2.3 of this thesis. This chapter includes the second manuscript of my thesis, entitled "Pulse rate and pulse rate variability decrease following adenotonsillectomy for obstructive sleep apnea". The manuscript has been recently published in *Pediatric Pulmonology* (Constantin E, McGregor CD, Cote V, Brouillette RT. Pulse rate and pulse rate variability decrease after adenotonsillectomy for obstructive sleep apnea. *Pediatric Pulmonology* 2008 May; 43(5):498-504).

This manuscript focuses on pulse rate and pulse rate variability in children with moderate-severe OSA. We compared nocturnal pulse rate and pulse rate variability before and after adenotonsillectomy (T&A) in children with moderate-severe OSA. We found that pulse rate and pulse rate variability decreased after T&A. No other such studies have reported both pulse rate and pulse rate variability changes in children with moderate-severe OSA.

4.1 Manuscript #2

Pulse rate and pulse rate variability decrease after adenotonsillectomy for obstructive sleep apnea

EVELYN CONSTANTIN MD
Department of Pediatrics, Montreal Children's Hospital, McGill University Health Centre, Montreal, Canada
No conflict of interest

CHRISTINE D. MCGREGOR RRT
Department of Pediatrics, Montreal Children's Hospital, McGill University Health Centre, Montreal, Canada
No conflict of interest

VALERIE COTE MD
Department of Otolaryngology, McGill University Health Centre, Montreal, Canada
No conflict of interest

ROBERT T. BROUILLETTE MD
Department of Pediatrics, Montreal Children's Hospital, McGill University Health Centre, Montreal, Canada
No conflict of interest

Corresponding Author coordinates:
Evelyn Constantin MD
Montreal Children's Hospital
Pediatric Sleep Laboratory
2300 Tupper Street, Room C-508
Montreal, Quebec, Canada H3H 1P3
Phone number: (514) 412-4321
Fax number: (514) 412-4234
evelyn.constantin@muhc.mcgill.ca

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ABBREVIATED TITLE: Pulse rate/pulse rate variability after T&A

SUMMARY

Background: Data suggest that obstructive sleep apnea syndrome (OSA) results in sympathetic stimulation, brady/tachycardia and cardiac stress. Heart rate variability, but not baseline heart rate, is known to be elevated in pediatric OSA. Our patients with moderate to severe OSA (McGill Oximetry Scores of 3 or 4) have been re-evaluated with pulse oximetry after adenotonsillectomy (T&A). We hypothesized that pulse rate (PR) and pulse rate variability (PRV) would decrease after treatment of OSA with T&A. **Methods:** This retrospective before-after study comprised pre- and post-operative oximetries and parental questionnaires of children 1-18 yrs old with moderate to severe OSA from September 2004 to August 2005, inclusive. We excluded patients with significant co-morbidities. **Results:** In 25 subjects, age at surgery was 4.3±3.6 years (mean±SD). OSA symptoms decreased or resolved, saturation metrics improved, and parental concern about breathing during sleep decreased following T&A. PR decreased in 21 of 25 patients after T&A (mean PR from 99.7±11.2 to 90.1±10.7 bpm, $p<0.001$; maximum PR from 150.6±14.5 to 137.4±15.6 bpm, $p<0.001$). PRV, as measured by the standard deviation of the PR, decreased in 23 of 25 patients after T&A (from 10.3±2.1 to 8.2±1.6 bpm, ($p<0.001$)). Pulse accelerations greater than 6, 7, 8 bpm also decreased post-operatively. **Conclusions:** Nocturnal pulse oximetry complements clinical history to document improvement and/or resolution of moderate to severe OSA in children. Resolution of tachycardia and diminished PRV after T&A illustrate the stress that recurrent airway obstruction during sleep places on the cardiovascular system. Further work will be required to determine if PR and PRV as measured by pulse oximetry would be useful in the diagnosis and follow-up of OSA in children.

KEY WORDS

Child, Heart rate, Heart rate variability, Pulse oximetry

ABBREVIATION LIST

OSA: obstructive sleep apnea

PR: Pulse rate

PRV: Pulse rate variability

T&A: Adenotonsillectomy

INTRODUCTION

Obstructive sleep apnea (OSA) is a disorder of breathing during sleep characterized by upper airway obstruction that disturbs sleep and disrupts normal respiratory gas exchange.[1-3] For most children with OSA, adenotonsillectomy (T&A) is the treatment of choice, as adenotonsillar hypertrophy is the most common etiology of OSA in children. Serious consequences of untreated OSA include failure to thrive, behavior and learning problems, and cardiovascular abnormalities.[2-8]

In children, obstructive apneas are often but not always terminated by arousal. [9-11] During the apnea there may be slowing of the heart rate and during the arousal there is an acceleration of heart rate. Such arousals are characterized by an activation of the sympathetic nervous system resulting in brief tachycardia. Electrocardiographic recordings have shown that children with OSA have increased heart rate variability.[12,13]

The most definitive and comprehensive technique for diagnosing OSA in children is polysomnography; however, this technique is expensive and not available in many areas. Even in settings where polysomnography is offered, there is often a prolonged waiting time.[14] We have previously shown that nocturnal pulse oximetry, when abnormal, can confirm a suspicion of OSA in children.[15] Subsequently, we demonstrated that oximetry can be used to prioritize treatment and plan peri-operative management by identifying children with severe and frequent dips in hemoglobin saturation.[16] Although nocturnal pulse oximetry tracings routinely provide data on both hemoglobin saturation and pulse rate, only hemoglobin saturation metrics have been reported from such studies.

The American Academy of Pediatrics recommends that children with moderate to severe OSA and those who do not improve symptomatically be retested after surgery.[17] In our practice, we routinely retest children with moderate to severe OSA, defined as McGill Oximetry Scores of 3 or 4, several months after surgery.[16] In this study, we compared nocturnal pulse rate and nocturnal pulse rate variability before and after T&A in an

available cohort of such children. We hypothesized that after T&A, both pulse rate and pulse rate variability would decrease.

MATERIALS AND METHODS

We conducted a retrospective before-after study, analyzing existing data from our pediatric sleep laboratory. Inclusion criteria for this retrospective study comprised referral to our pediatric sleep laboratory for evaluation of possible OSA, initial evaluation with home pulse oximetry between September 2004 and August 2005, age 1-18 years, an initial McGill Oximetry Score of 3 or 4, treatment by T&A, and availability of a post-operative oximetry test. Patients were excluded if they had conditions that might affect pulse rate or pulse rate variability including congenital/genetic abnormalities, significant cardiorespiratory disease, neurological or neuromuscular conditions and global developmental delay. As required by provincial (Quebec) law, the study was approved by the Director of Professional Services of the Montreal Children's Hospital, who authorized examination and review of existing hospital records.

Inclusion criteria required that subjects have a pre-operative McGill oximetry score of 3 or 4. Subjects with a McGill oximetry score of 3 had at least three clusters of desaturation events and at least four dips in saturation to less than 85%; children with a McGill oximetry score of 4 had at least three clusters of desaturation events and at least four dips in saturation to less than 80%.[16] Our previous study demonstrated that subjects with a McGill Score of 3 had a mean AHI of 13.3, while those with a score of 4 had a mean AHI of 39.9.[16] We could therefore be very confident that all subjects had moderate to severe OSA.[15,16]

Pulse oximetry and parental questionnaire

Both pre-operative and post-operative pulse oximetry were performed as described by Nixon et al.[16] Parents of referred children came to our sleep laboratory and completed a parental questionnaire that included demographic data, information about their child's

past and present medical conditions, and questions regarding their child's sleep and breathing. After the parents received 30 minutes of instruction on oximetry testing, they took the oximeter home, conducted the study that same night, and returned the oximeter the following morning. Parents also completed a sleep log of their child's nocturnal behavior. Study data included age at time of initial oximetry, age at time of surgery, age at time of post-operative oximetry, race, sex, referring doctor and his/her specialty, number of nights/week of snoring, number of nights/week of difficulty breathing during sleep, presence of observed obstructive apneas during sleep, and the level of parental concern regarding their child's breathing during sleep.

We used a motion-resistant pulse oximeter set for a two-second averaging time for hemoglobin saturation. (Masimo Radical, Version 4.1.0.0, Irvine, CA).[18] The pulse oximeter used a fixed seven-second averaging time for pulse rate and stored in memory a new value every two seconds. This seven-second pulse rate averaging did not vary with decreased perfusion, or with motion artifacts. (Personal communication, M. Petterson, Masimo, 2006). Saturation and pulse rate data were extracted and analyzed using software (Download 2001, version 2.5.0, Stowood Scientific Instruments, Oxford, England). This program provided metrics for oxygenation, pulse rate and pulse rate variability: mean oxygen saturation (S_pO_2), minimum S_pO_2, number of decrements in saturation of $\geq$4% /hour of study (DI_4), number of decrements of saturation to $\leq$ 90% /hour of study (DI_{90}), mean, median, minimum, maximum and standard deviation of pulse rate, and the frequency of pulse rate rises per hour of study, above 6, 7 or 8 beats per minute (pulse rate rise index - PRRI-6,-7,-8, respectively). The standard deviation of the pulse rate was used to estimate pulse rate variability over the entire recording. Periods of oximetry recording were excluded from analysis if the oximeter quality signal indicated low signal IQ™ (Masimo), low perfusion, unrecognized, defective or no sensor, interference, and ambient light.

Age-standardization of pulse rate

We calculated age-standardized z-scores for pulse rate to adjust for the wide age range of our cohort (1.5-15.6 years) and the time between oximetry study and surgery. We first calculated each subject's expected mean RR interval during sleep using the formula from Massin et al : mRR = -2.9 * $(age)^2$ + 72.8 * (age) + 479.4.[19] Similarly, we calculated the expected RR interval standard deviation for each subject using Massin's formula: mRR standard deviation = 0.86* $(age)^2$ + 2.3 * (age) + 49.9. RR intervals were transformed into beats per minute (Pulse rate(bpm) = 60000/mean RR (ms)).[19] Z scores for pulse rate were calculated using the following formula: mean PR of patient – expected mean PR/ expected standard deviation of PR. We compared Z scores before and after T&A.

Statistical analysis

We analyzed nominal data (parental questionnaire) using chi square and Fisher exact tests, as indicated. Normally distributed continuous data (hemoglobin saturation as percent and pulse rate as beats per minute) were reported as mean ± standard deviation and analyzed using paired samples t-tests. Age-standardized z-scores for pulse rate were not normally distributed and thus nonparametric-paired analyses (Wilcoxon Rank Sum Test) were performed. Z-scores were expressed as median and interquartile range. Wilcoxon signed-rank test was used for analysis of parental questionnaire responses before and after T&A for frequency of snoring and frequency of difficulty breathing at night, while McNemar test was used to compare parental response of presence or absence of observed apneas and decreased parental concern before and after T&A. A p value of less than or equal to 0.05 was considered statistically significant.

RESULTS

During the study period, 40 children had oximetries with McGill Oximetry Scores of 3 or 4. 15 did not meet inclusion criteria (10 had important comorbidities, 3 were less than 1 year of age, 1 did not have a post-operative oximetry, and 1 did not have

adenotonsillectomy due to parental refusal). In the 25 subjects (3 girls) who met inclusion criteria, ages at both pre-op oximetry and at surgery were 4.3 ± 3.6 years (mean ± standard deviation). In our institution, oximetry is used to help prioritize adenotonsillectomies, with patients with McGill Oximetry Scores of 3 and 4 having surgery soon after an abnormal oximetry result.[16] In this study population, the patients had a median waiting time for adenotonsillectomy of 5 days (IQR 2, 30.5) following abnormal oximetry. Age at post-operative oximetry was 4.8 ± 3.5 years. The time period between the pre-operative and post-operative oximetry studies was 199 days ± 101 days. Most subjects were Caucasian (15); there were 3 African-American children and 7 who were of other or mixed race.

Signs and symptoms of OSA, parental concern, and saturation metrics all improved after T&A. Both pulse rate and pulse rate variability decreased post-operatively (see sections on pulse rate and pulse rate variability below). Figure 1 is an example of one of the study patient's pulse rate trends before and after adenotonsillectomy.(Figure 1)

Parental Questionnaire

Parental report of OSA symptomatology improved or resolved following T&A. Twenty-two of twenty-five parents (88%) reported a decrease in number of nights per week of snoring, $p < 0.001$. Likewise, parents reported less or no difficulty breathing during sleep (18 of 20; 90%, $p < 0.001$) and disappearance of observed apneas (15 of 16; 94%; $p < 0.001$), when those signs were present preoperatively. Parents also reported a decrease in the level of their concern regarding their child's breathing during sleep (19 of 24; 80%; $p < 0.001$).

Hemoglobin saturation

Oximetry metrics significantly improved following T&A in all subjects. Pre-operatively, 10 subjects had a McGill Oximetry Score of 3 and 15 subjects had a score of 4. Mean oxygen saturation (S_pO_2) increased from 96.0±3.9 pre-operatively to 97.8±0.9 post-operatively, $p=0.04$. Minimum S_pO_2 increased from 69.2±12.3 to 86.9±4.7 ($p< 0.001$).

Falls in S_pO_2 to ≤90% per hour (DI_{90}) decreased from 5.1(3.1,19.4) (median (interquartile range)) to 0.2(0,0.4), p=0.03 (normal DI_{90},<0.2).[20] Falls in saturation by ≥4% per hour (DI_4) decreased from 23.8(18.5,48.4) to 5.0(3.7,6.9), p<0.001 (normal DI_4 <3.9).[20]

Pulse rate and pulse rate variability

Pulse rate and /or pulse rate variability decreased in all 25 patients following T&A.

Pulse rate

Following T&A, mean pulse rate decreased in 21 of 25 patients - mean pulse rate decreased from 99.7±11.2 to 90.1±10.7 beats per minute (bpm), p<0.001 (Figure 2; Table 1). Minimum and maximum pulse rate also decreased post-operatively (Table 1). Likewise, age-corrected pulse rate decreased post-operatively (z-scores decreased from 0.8 (0.4,1.5) to 0.4 (0,0.9), p=0.04).

Pulse rate variability

In 23 of 25 patients, the standard deviation of the pulse rate decreased following surgery (Figure 3). Pulse rate standard deviation decreased from 10.3 ± 2.1 bpm pre-operatively to 8.2 ± 1.6 bpm post-operatively (p<0.001). The frequency of pulse rate rises per hour of study above 6, 7 and 8 bpm all decreased significantly after T&A (Table 1).

DISCUSSION

Pulse rate and several measures of pulse rate variability decreased after T&A for children with moderate to severe OSA. As expected, OSA symptoms improved or resolved and hemoglobin saturation metrics also improved post-operatively.

No other such studies have reported both pulse rate and pulse rate variability changes in children with moderate to severe OSA. Stradling and colleagues reported that pulse rate as measured with pulse oximetry was high pre-operatively and normalized post-adenotonsillectomy in children with recurrent tonsillitis and snoring.[21] At least 2 studies have investigated the pulse rate signal from nocturnal pulse oximetry in adults with OSA. Zamarron et al. used spectral analysis to analyze pulse rate variability in 300 patients being evaluated for OSA. They reported that increased power in the frequency band of 30-70 seconds had good sensitivity and specificity for OSA diagnosis.[22] Adachi et al. studied 33 patients being evaluated for OSA and also noted good sensitivity and specificity when using pulse rate rises as surrogates for arousals.[23] An accompanying editorial pointed out that autonomic markers for sleep fragmentation/arousals are practical and can be implemented outside of a highly specialized sleep laboratory.[24]

The post-operative reduction in pulse rate that we observed might be explained by decreased metabolic rate and/or decreased sympathetic nervous system activity. Other investigators have demonstrated that metabolic rate decreases after T&A for OSA. Moreover, it is well known that children compensate for elevated metabolic rate by increasing heart rate rather than stroke volume. In both adults and children with OSA, apneic events are associated with increased sympathetic activity. Somers et al. demonstrated that adults with OSA have increased peripheral sympathetic nerve discharge during apnea and that this activity can be attenuated by Continuous Positive Airway Pressure treatment.[25,26] In children, Tauman et al. found that 92% of obstructive apneas and hypopnea were associated with attenuation of peripheral arterial tonometry, a noninvasive measure of moment to moment sympathetic nerve activity.[27] Loredo et al. showed that adults with obstructive sleep apnea had increased levels of plasma norepinephrine and that these levels correlated with the frequency of movement arousals.[28] Thus, decreases in metabolic rate and/or sympathetic discharge after treatment of OSA could well explain the post-operative decrease we found in pulse rate.

Decreased pulse rate variability

Our data showing reduced pulse rate variability after T&A reinforces prior studies showing increased heart rate variability in children with OSA. Heart rate is modulated by the parasympathetic and sinoatrial sympathetic innervation. High-frequency fluctuations in heart rate, respiratory sinus arrhythmia, occur with a cycle period of 2.5 to 6.7 seconds and are modulated by the parasympathetic system.[29-32] Low frequency heart rate variability occurs with a period of 6.7 to 25 seconds and is modulated by sympathetic and other influences.[29-32]

Previous research has shown that certain characteristic patterns of heart rate variability exist during sleep in children. Some of these patterns, such as increases in the ratio of low frequency to high frequency heart rate variability, may be specific to children with OSA.[12] Because of sample rate considerations, data from a pulse oximeter stored data at 0.5 Hz cannot be used to examine high-frequency variability. However, the variations in pulse rate variability seen in the present preoperative recordings clearly fall in the range of low-frequency variability. Although evidence suggests that sympathetic activity is up regulated in children with obstructive sleep apnea, it should also be pointed out that the cycle period of these pulse rate fluctuations corresponds to the cycle of apnea and arousal. Thus, the decreased pulse rate variability noted in our study may indicate fewer arousals, less sleep fragmentation and thus less sleep disturbance. Another important influence on heart rate variability is sleep state. In children with OSA, there is an increased apnea frequency in REM sleep compared to quiet sleep.[33,34] This fact has been used in our diagnostic algorithm requiring clusters of desaturation for the diagnosis of pediatric OSA by pulse oximetry.[15,16] Examination of our pulse rate graphs demonstrated similar periodic clusters of cardiac accelerations in a time frame consistent with sleep stage cycling (Figure 1).

Traditionally, pediatric OSA was thought to primarily affect the right heart because early reports associated adenotonsillar airway obstruction with congestive heart failure, pulmonary hypertension and cor pulmonale.[4,35] However, recent work by Amin and

colleagues have demonstrated structural changes in the left ventricle, left ventricular diastolic dysfunction and failure of systemic blood pressure to decrease at night.[36,37] The pathogenesis of these changes remains unknown but may involve inflammatory cytokines and up-regulation of sympathetic nervous stimulation to heart and blood vessels.[36,37] The dramatic reductions in pulse rate and pulse rate variability that we report after T&A illustrate the cardiovascular stress that pediatric OSA places on a child night after night.

It is important to acknowledge the limitations of the current study. First, we only report on pre- and post-operative studies in children with OSA significant enough to result in repetitive desaturations to less than 85%. It seems likely that children with more severe OSA would have more frequent arousal and more pronounced sympathetic activation than those with milder disease. Further work will be required to determine if children with less severe OSA also decrease pulse rate and/or pulse rate variability after effective treatment of their airway obstruction. Second, pulse rate variability derived from pulse oximetry tracings cannot be expected to delineate high-frequency variability in the same way that Holter monitoring or other electrocardiographic recordings can. According to the Nyquist formula, a pulse oximeter sampling every 2 seconds could only accurately elucidate pulse rate fluctuations with a period of 4 seconds or more.[38] Important influences on cardiac activity in pediatric OSA, namely sympathetic up-regulation, the apnea arousal cycle, and sleep stage cycling, all occur at periods considerably greater than four seconds. Third, there is no normative data for pulse rate variability using pulse oximetry. Thus, we do not have evidence that pulse rate variability returned to normal. However, we have shown that pulse rate variability decreased compared to pre-operative data. In addition, with only oximetry data, we cannot prove with certainty that adenotonsillectomy completely resolved the children's OSA. Finally, we used a motion-resistant pulse oximeter with a short sampling time; values from other oximeters with different operating characteristics would likely differ for pulse rate variability.[18]

Attention should be paid to pulse rate and pulse rate variability as well as hemoglobin saturation. Resolution of tachycardia and diminished pulse rate variability after T&A illustrate the stress that recurrent airway obstruction during sleep places on the

developing cardiovascular system. The improvement in pulse rate and pulse rate variability that we noted may be associated with fewer arousals and less sleep disturbance, again leading to decreased stress on the cardiovascular system. Further work will be required to determine the sensitivity and specificity of pulse rate and pulse rate variability measures to determine their diagnostic usefulness, especially in those children with OSA who do not desaturate.

ACKNOWLEDGEMENTS

We would like to thank our Sleep Laboratory technicians (Sylvia Ladan, Rebecca Silverberg, Severina Luciano) for their hard work obtaining parental questionnaire data, providing instruction and guidance to the parents for the oximetry testing, and downloading of the oximetry data. We would also like to thank Lina Feliziani and Sofia Bamboulas for assisting with this study.

Table 1. Pulse rate and pulse rate variability decrease following adenotonsillectomy[a]

	Pre-op n=25	Post-op n=25	P
Total Recording Time (hrs)	9.4 ± 2.0	9.4 ± 1.8	0.914
Total Time Analyzed (hrs)[b]	9.1 ± 1.9	8.7 ± 2.1	0.479
Pulse rate (BPM)			
Mean	99.7 ± 11.2	90.1 ± 10.7	<0.001
Minimum	67.7 ± 9.2	63.1 ± 7.7	0.018
Maximum	150.6 ± 14.5	137.4 ± 15.6	<0.001
Pulse rate variability			
Standard deviation of pulse rate (BPM)	10.3 ± 2.1	8.2 ± 1.6	<0.001
PRRI-6[c]	89.0 ± 21.3	68.9 ± 24.1	0.002
PRRI-7[c]	80.2 ± 21.4	59.1 ± 23.0	0.001
PRRI-8[c]	72.6 ± 21.5	50.8 ± 21.1	0.001

[a] Values are expressed as mean ± standard deviation.

[b] Total Time Analyzed (hrs) is defined as duration of valid data in hours.

[c] PRRI-6,-7,-8: Pulse rate rises per hour of study, above 6, 7 and 8 bpm, respectively

FIGURE LEGENDS

Figure 1.a) Pulse rate (PR) from a pre-operative nocturnal pulse oximetry recording of a 6 year old boy with OSA and a McGill Oximetry Score of 4. PR averaged 78 bpm. Note the marked pulse rate variability (PRV) and the clustering of PR rises. The pulse rate rise index-8 (PRRI-8) was 67.5/hr and the standard deviation of the PR was 8.65.

Figure 1.b) Nocturnal PR after T&A decreased by 10 bpm to a mean of 68 bpm. PRV was markedly reduced; the PRRI-8 decreased to 33.1/hr, and the standard deviation of the PR decreased to 6.31.

Figure 2. PR decreased in 21 of 25 subjects following T&A . Boxplots show median, interquartile ranges and 5^{th} and 95^{th} percentiles for PR.

Figure 3. The standard deviation of the PR, a measure of PRV, decreased in 23 of 25 subjects following T&A.

Fig. 1a

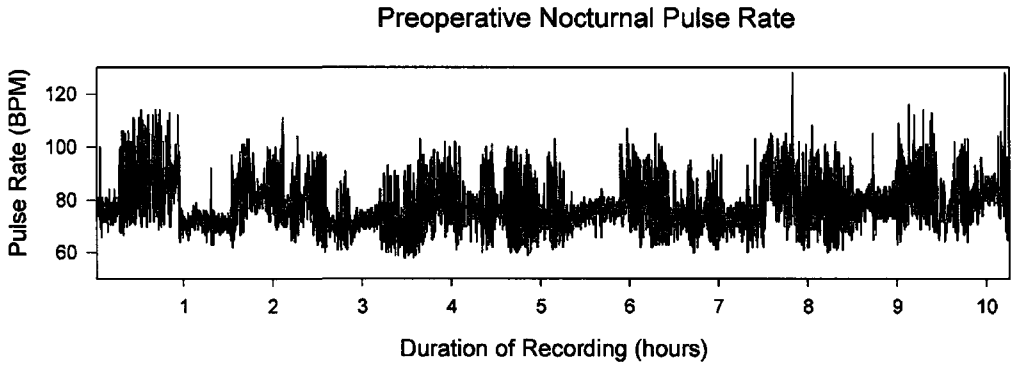

Preoperative Nocturnal Pulse Rate
Pulse Rate (BPM)
120
100
80
60
1
2
3
4
5
6
7
8
9
10
Duration of Recording (hours)

Fig. 1b

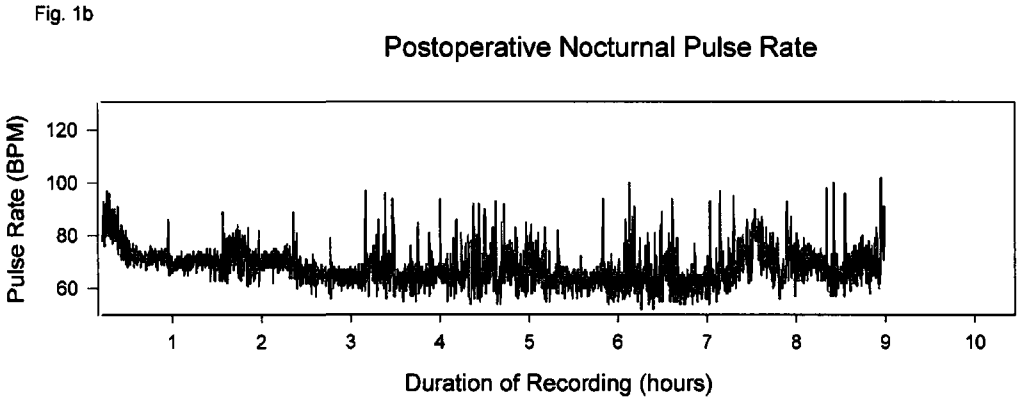

Postoperative Nocturnal Pulse Rate
Pulse Rate (BPM)
120
100
80
60
1
2
3
4
5
6
7
8
9
10
Duration of Recording (hours)

Figure 2

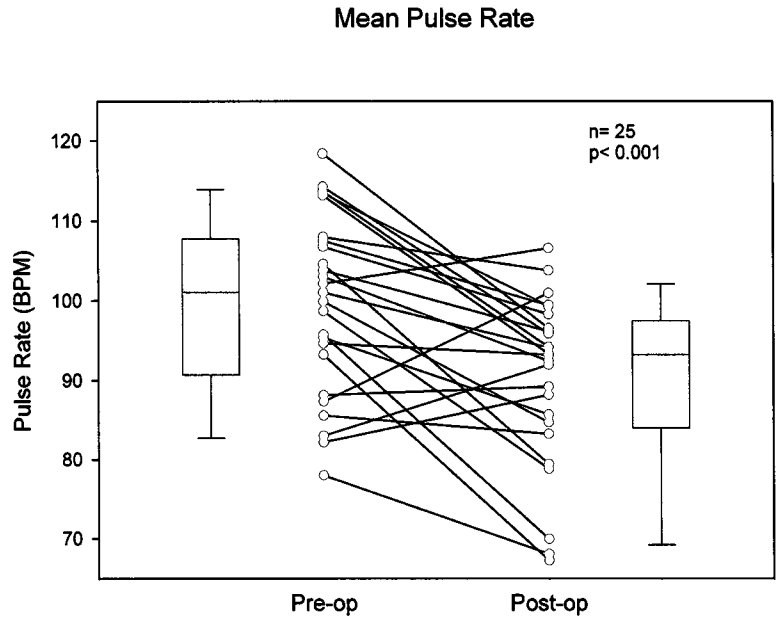
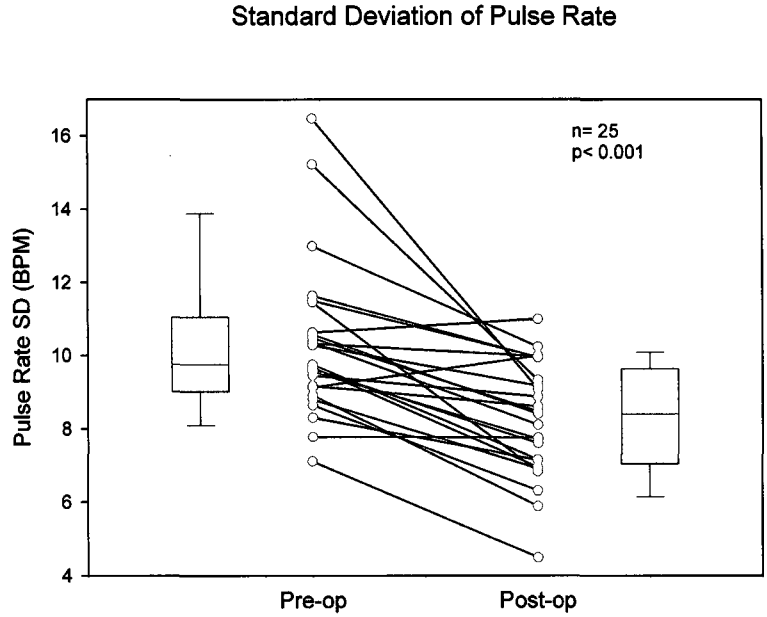

Mean Pulse Rate
n= 25
p< 0.001
Pulse Rate (BPM)
120
110
100
90
80
70
Pre-op
Post-op

Figure 3


Standard Deviation of Pulse Rate
n= 25
p< 0.001
Pulse Rate SD (BPM)
16
14
12
10
8
6
4
Pre-op
Post-op

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CHAPTER 5. CONCLUSIONS

5.1 Summary of contributions

OSA is a prevalent disorder in children and may lead to serious problems in several domains (i.e., cardiovascular, neurobehavioural, or growth). Although PSG is currently the most accurate approach for the diagnosis of OSA, PSG is costly and often not easily accessible. The inadequate availability of pediatric sleep laboratories may contribute to the fact that, prior to T&A for OSA, less than 12% of children have polysomnography.[123] Accordingly, one solution to the broader problem is to somehow find the means to expand the number of sleep laboratories and the capacity of those now in existence to handle more patients.

Realistically, it is unlikely that expansion will occur in the near future and the remaining solution is to find alternative ways to diagnose OSA. Accurate measures for the diagnosis of OSA that are simpler, less expensive, and more accessible than PSG are needed. One such measure was thought to be the OSA-18. This is a widely-used questionnaire that was proposed as a replacement for PSG, but had only been assessed in relation to another subjective measure.[20] Our study reported in the first manuscript of this thesis aimed to evaluate the accuracy of the OSA-18 in detecting moderate-severe OSA as indicated by an objective measure, the McGill Oximetry Score (MOS). In recent years, studies have explored the association between heart rate and its variability and OSA in both adults and children. However, no studies have yet evaluated both pulse rate and its variability in children using nocturnal pulse oximetry. To our knowledge, our study described in this thesis is the first to do so.

In relation to the first measure, we found that the OSA-18 has poor sensitivity and weak negative predictive value (40%, 73%, respectively) in identifying an abnormal MOS. It thus fails to detect over half of those with moderate-severe OSA. These findings are in

keeping with the conclusion of Brietzke et al. that existing questionnaires should not be used to diagnose OSA in children.[17]

In our second study, however, we observed that pulse rate and pulse rate variability decreased following surgical treatment of moderate-severe OSA. The results of this study potentially serve as important data for further work that would determine the accuracy of pulse rate and pulse rate variability and their diagnostic usefulness for OSA at all levels of severity.

5.2 Strengths and Limitations

5.2.1 Manuscript #1: Evaluation of the OSA-18 quality of life questionnaire in children referred for obstructive sleep apnea

One strength of the OSA-18 study is that it is the first to determine sensitivity and negative predictive values for this measure as it relates to an objective measure – the MOS using nocturnal pulse oximetry. Another is that these are potentially important findings. Their importance is related in part to the fact that otolaryngologists have been using the OSA-18 as a diagnostic tool and even some researchers have promoted the OSA-18 as a replacement for oximetry or polysomnography.[20]

Another strength is that our study involved blinding. The parents were blinded to the results of the oximetry when they completed the OSA-18 because they did so before the oximetry was performed. However, we cannot be certain if the sleep laboratory technicians were also blinded to the OSA-18 score. The technicians who score the oximetry may have been aware if the child was symptomatic for OSA but usually they did not have the results of the OSA-18 when they did the scoring. Nevertheless, the results of the OSA-18 would not influence the MOS, which is computer-generated based on frequency and depth of desaturation events and on clusters of desaturations.

Finally, we examined the relation of oximetry results to age. The logistic regression analysis showing that younger children were more likely to have oximetry results consistent with moderate-severe OSA confirms the association between younger age and OSA.[32] The increased prevalence in preschool-age children is likely due to the fact that it is during this time that the airway is narrowest because the adenoids and tonsils are at their largest in comparison to the size of the airway.[30] It is not known if age affects the OSA-18 score and this was not part of the Franco et al.'s evaluation.[19]

One possible limitation is that selection bias on age occurred in our sample. As a preliminary attempt to examine this, a stratified analysis by age was performed (2-3 years, 4-5 years and 6-10 years). (Manuscript #1, Table 4, pg. 58) In our study population, there was a higher percentage of younger children who were referred to our sleep laboratory for suspected OSA. In addition, there was a higher percentage of younger children with moderate-severe OSA. These higher percentages may be explained by the known association between younger age and OSA due to the increased ratio of adenotonsillar size to upper airway size in younger children (as described above). When we estimated how well the OSA-18 detects an abnormal MOS by age, the OSA-18 had poor sensitivity and weak negative predictive values in all three age subgroups.(Manuscript #1, Table 4, pg. 58). Therefore, although there remains a possibility that selection bias exists, the results of this analysis suggest the effect would be small.

Another limitation is that the study was not population-based but one that was done in a referred population. Undoubtedly, this study included more cases of OSA than the general population. Although inflated prevalence may result in higher predictive values, this issue may be less important because the predictive values of the OSA-18 were low.

The OSA-18 was not evaluated against polysomnography, but against a reference standard of nocturnal pulse oximetry. Pulse oximetry should not be considered as a definitive diagnostic test. Oximetry does not provide a comprehensive assessment of sleep and breathing during sleep as does PSG. Most importantly for our study, oximetry has poor sensitivity at detecting OSA associated with repeated desaturations to less than 90%. Conversely, there are some advantages to pulse oximetry. It has a high positive predictive value (97%) for detecting moderate-severe OSA and, unlike continuous oximetry parameters, the MOS was rigourously derived and validated. Finally, oximetry is more widely available, less expensive, and less time-consuming than PSG.

If the goal of the study had been to evaluate children with all levels of OSA severity, the ideal reference standard for the OSA-18 evaluation would have been nocturnal PSG. However, my goal was to determine if the OSA-18 could accurately detect children with *moderate-severe OSA*. Accordingly, it was reasonable to use an abnormal MOS as the reference standard for moderate-severe OSA. If PSG had been used to detect all levels of OSA severity (i.e., not just moderate-severe OSA), due to the low sensitivity of the MOS the sensitivity and negative predictive value could be even worse than what we report in our study. Thus, from the low sensitivity and low negative predictive value of the OSA-18 (40% and 73%, respectively), we concluded that the OSA-18 cannot accurately identify children with moderate-severe OSA.

It is important to highlight that it is difficult to accurately assess the specificity and positive predictive values given the low sensitivity of the MOS as compared to PSG. The specificity and positive predictive value (67% and 34%, respectively) were low when judged against the MOS, but potentially would be higher if tested against PSG. Therefore, these estimates could not be interpreted in our study.

Obesity has been shown to be an important risk factor for OSA in children[47] and might have been an important variable to include. However, because the children themselves were not studied in the laboratory, we did not have information regarding weights and heights of subjects and thus could not determine body mass index percentiles.

Because the OSA-18 remains the most widely-used quality of life questionnaire in pediatric OSA research[156] and at least one research group has promoted its use as a replacement for objective testing for OSA in children,[20] I decided to evaluate whether the OSA-18 could detect children with moderate-severe OSA. If the OSA-18 were to be useful in the detection of OSA in children, one would expect that it would identify most patients with OSA severe enough to cause repetitive oxygen desaturations. Conversely, if the OSA-18 is not accurate, then it should not be used for diagnostic purposes. Through my analyses, I provide evidence against the use of the OSA-18 in place of objective testing in children referred for evaluation of possible OSA.

5.2.2 Manuscript #2 Pulse rate and pulse rate variability decrease after adenotonsillectomy for obstructive sleep apnea

With this conclusion in mind, this second manuscript reports the results of an evaluation of two objective measures to detect abnormal oximetry, i.e., pulse rate and pulse rate variability. We found that both decreased significantly following T&A for moderate-severe OSA. No other such studies have reported both pulse rate and pulse rate variability changes in children following treatment of moderate-severe OSA. Stradling and colleagues reported that pulse rate alone, as measured with pulse oximetry, was high pre-operatively and normalized post-adenotonsillectomy in children with recurrent tonsillitis and snoring.[157]

The limitations of Manuscript #2 are as follows: First, we only report on pre- and post-operative studies in children with OSA significant enough to result in repetitive

desaturations to less than 85%. It seems likely that children with more severe OSA would have more frequent arousals and more pronounced sympathetic activation, and therefore higher pulse rates and more variability, than those with milder disease.

Second, the pulse rate variability measure derived from pulse oximetry tracings cannot delineate high-frequency variability in the same way that Holter monitoring or other electrocardiographic recordings can. According to the Nyquist formula, a pulse oximeter sampling every 2 seconds could only accurately elucidate pulse rate fluctuations with a period of 4 seconds or more.[158] However, important influences on cardiac activity in pediatric OSA, namely sympathetic up-regulation, the apnea-arousal cycle, and sleep stage cycling, all typically occur at periods considerably greater than four seconds.

Third, there are no normative data for pulse rate variability using pulse oximetry. Thus, although we have shown that pulse rate variability decreased compared to pre-operative data, we cannot state that pulse rate variability returned to normal.

Fourth, we used a motion-resistant pulse oximeter with a short sampling time. Pulse rate variability values from other oximeters with different operating characteristics would likely differ.[159]

Finally, we did not use PSG to evaluate OSA in this second study. The oximetry studies that were abnormal pre-operatively were accurate for diagnosis of moderate-severe OSA (as oximetry can accurately detect moderate-severe OSA with a positive predictive value of 97%[21,22]). However, the limitation exists with the interpretation of the oximetries done post-operatively. Due to the fact that oximetry has low sensitivity and low negative predictive value, the post-operative oximetry results could not conclusively demonstrate normal breathing during sleep. On the other hand, all subjects did show improvement in their McGill Oximetry Scores and all improved symptomatically.

5.3 Future directions

Although research in the field of pediatric sleep medicine has substantially increased in the last decade, many gaps remain. In this thesis I present work that has begun to explore unanswered research questions specifically regarding diagnostic testing of OSA in children.

Another gap relates to the need to more closely examine potential adverse outcomes of OSA (neurocognitive, behavioural, metabolic, and cardiovascular) and the mechanisms linking OSA to these outcomes. Short- and long-term outcomes as they relate to different levels of severity of sleep-disordered breathing, from primary snoring to mild OSA to the most severe OSA, should also be studied rigourously.

An understudied group is children with mild OSA. It is unclear what their specific outcomes are and which treatment modality would be most beneficial for them.

Some intervention studies have been done evaluating therapeutic alternatives to T&A (i.e., intranasal steroids, leukotriene receptor antagonists, oral appliances, CPAP).[73,160] However, the short- and long-term outcomes of these measures have not been determined and it is unclear which children, if any, would benefit most from these alternatives.

Finally, studies evaluating characteristics and outcomes of children with OSA who have drops of oxygen saturation compared with those with normal oxygenation would be important.

The two studies comprising this thesis have established a solid foundation for future work. New projects in which I am involved that are logical extensions of this work are currently underway and other projects are being formulated.

1. Heart rate variability as a diagnostic measure for pediatric OSA

My study on pulse rate and pulse rate variability in children has led me to further explore heart rate variability as a diagnostic measure of OSA, either in isolation or in conjunction with the oxygen saturation channel from nocturnal pulse oximetry. Heart rate variability as measured by electrocardiography could potentially serve as such a measure to alert clinicians to patients with OSA who are experiencing significant cardiac stress due to tachycardia and abnormal heart rate variability.

I will be conducting a prospective study to determine if heart rate and heart variability as measured by electrocardiography could accurately detect OSA in children as measured with PSG. This approach may enable a better evaluation of all levels of severity of OSA (mild to severe) and potentially a more accurate evaluation of heart rate variability (i.e., to distinguish between high-frequency and low-frequency variability).

2. Sleep, Obesity and the Metabolic Syndrome

The prevalence of sleep-disordered breathing in obese children reportedly ranges from 13% to 66%.[161-165] Inflammation may have a role in OSA, obesity, and the metabolic syndrome, with studies reporting increased levels of C-reactive protein, inflammatory cytokines and chemokines such as leptin, interlukin-6, and tumour necrosis factor α.[166-171]

Unfortunately, in the studies reported in this thesis, we were unable to study the role of obesity because of lack of weight and height data. As a result, further work is being done to evaluate links between obesity and OSA. Two such studies are currently underway: one is a large prospective study, recently CIHR-funded, aimed at evaluating the association between sleep and childhood obesity by evaluating three pathways: appetite regulating hormones (leptin, ghrelin), the stress response system (cortisol, heart rate variability), and glucose metabolism (glucose, insulin). The other study is focused on the metabolic syndrome in obese children 10 years and older. We postulate that these children compared with those without are at increased risk for asthma, atopy, and OSA.

3. Canadian Pediatric Sleep Research Network

To address the gaps in the field of sleep medicine research in children, ideally the research should be multi-institutional and multi-disciplinary. I am currently involved with the creation of a **Canadian Pediatric Sleep Research Network**. We have submitted a seed grant application for emerging teams and networks (Mother Infant Child and Youth Research Network) and anticipate working together primarily on longitudinal, population-based multi-centred multi-disciplinary studies in healthy, high-risk, and understudied populations. In doing so, we will explore the natural history of sleep-disordered breathing in children and ideally follow these children into adolescence and adulthood.

5.4 Summation

Both manuscripts in this thesis contribute to the knowledge-base for diagnostic testing for OSA in children. The OSA-18 study concludes that the OSA-18 should not be used as a diagnostic measure and cannot replace objective testing for moderate-severe OSA. The evidence in the literature and from my study on the OSA-18 shows that existing subjective measures in the form of questionnaires are not acceptable for the diagnosis of OSA. Therefore, better subjective measures or other objective tests are needed. The study on pulse rate and pulse rate variability after T&A is the first to evaluate differences in both cardiovascular measures using nocturnal pulse oximetry. We concluded that pulse rate and its variability decreased after T&A. These two studies that comprise my thesis provide important data for future work needed to fill the gaps in pediatric sleep medicine research.

APPENDIX I.

REFERENCE LIST FOR NON-MANUSCRIPT SECTIONS

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APPENDIX II.
RESEARCH ETHICS CERTIFICATES

APPENDIX III.
SIGNED WAIVER FROM PUBLISHER (WILEY)